(*Z*)-4-(TRIMETHYLSTANNYL)-1,3-BUTADIENES: PREPARATION AND USES IN ORGANIC SYNTHESIS

By

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October 1990

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ABSTRACT

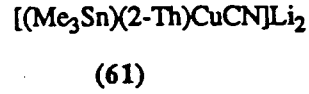
This thesis is divided into three parts. Part 1 describes the chemistry of dilithium (trimethylstannyl)(2-thienyl)(cyano) cuprate (**61**). This higher order cuprate reagent efficiently transfers the trimethylstannyl group, in a conjugate sense, to a variety of α,β-unsaturated carbonyl compounds. Also, it reacts with α,β-acetylenic esters **43** to give, stereoselectively, (*Z*)-β-trimethylstannyl α,β-unsaturated esters **46**.

Part 2 describes the stereoselective preparation of (*Z*)-β-trimethylstannyl α,β-unsaturated aldehydes/ketones **151** via the Pd(0)-catalyzed reactions of α,β-acetylenic aldehydes and ketones **115** with hexamethylditin. Compounds **151** were converted into stannyldienes **166** via Wittig olefinations. The aldehydes **151** (R^1=H) undergo Wittig-Horner olefination. For example, reaction of **154** with the sodio-phosphonate reagent prepared from diisopropyl *tert*-butylphosponoacetate **179**, afforded **180**. The stannyldienes **166** are synthetic equivalents of the diene donor synthon **183**. For example, transmetallation of **169** with methyllithium, followed by alkylation of the resulting alkenylithium species with ethylene oxide, provided **187**.

The third section describes the synthesis of 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hexan-2-ones **237** (R^1=H) from stannyldienes **250**. The stannyldienes **250** were converted into the corresponding iodo dienes **249**, which undergo Pd(0)-catalyzed cross coupling with the reagent **246** to give the diene esters **241**. Compounds **241** were converted into diene diazoketones **240** which, upon reaction with an appropriate transition metal catalyst, provided, stereospecifically, the ketones **237** (R^1=H).

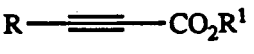
The ketones **237** (R^1=H) are excellent precursors to functionalized, substituted 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hex-2-enes **215** (R^1=H). The *cis* divinylcyclopropanes **215** undergo facile, clean and efficient Cope rearrangement to the bicyclo[3.2.1]octa-2,6-dienes **216** (R^1=H). The rates of a number of these Cope rearrangements were measured at

43°C using ^{1}H nmr spectroscopy. The effects of different substituents on the rate of Cope rearrangement were rationalized in terms of steric and/or electronic factors.



[(Me$_3$Sn)(2-Th)CuCN]Li$_2$

(61)



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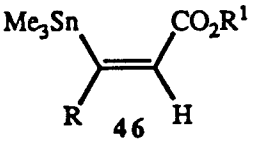

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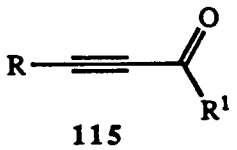

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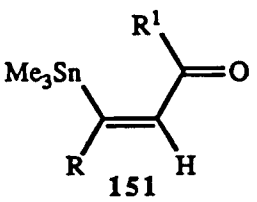

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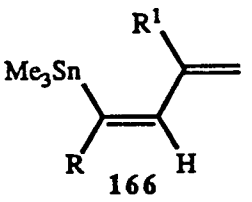

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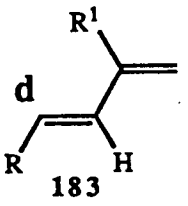

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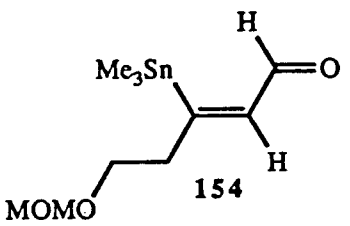
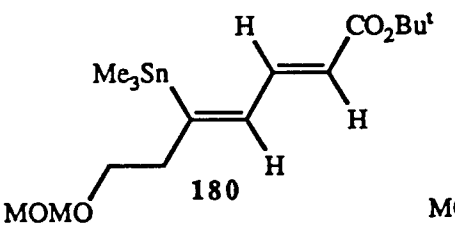


154

(Pr^{i}O)$_2$P(O)CH$_2$CO$_2$Bu^t

179



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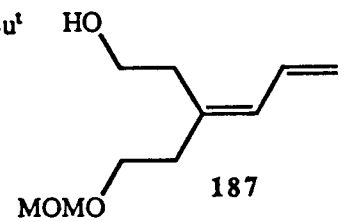

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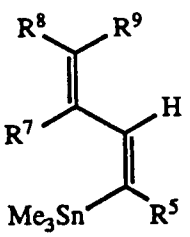

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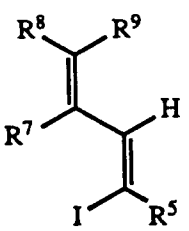

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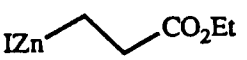

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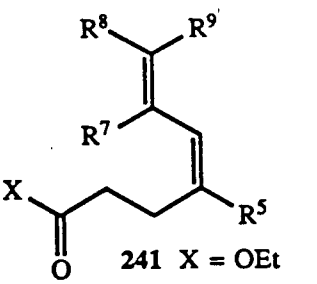
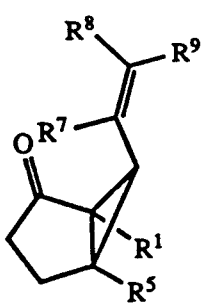


241 X = OEt

240 X = CHN$_2$



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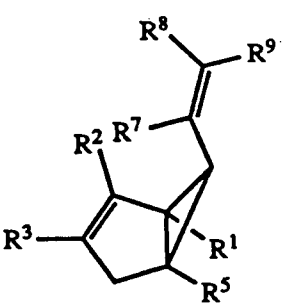

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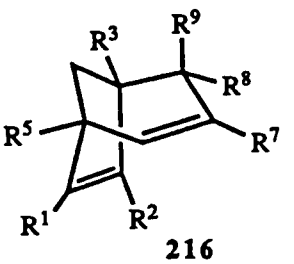

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LIST OF GENERAL PROCEDURES

LIST OF ABBREVIATIONS

acac	-	acetylacetonate
Ac_2O	-	acetic anhydride
ADD	-	1,1'-(azodicarbonyl)dipiperidine
approx.	-	approximately
br	-	broad
n-Bu	-	*n*-butyl
Bu^t	-	*tert*-butyl
calcd.	-	calculated
cims	-	chemical ionization mass spectrometry
COSY	-	(homonuclear) correlation spectroscopy
d	-	doublet
DIBAL	-	diisobutylaluminum hydride
DMA	-	*N*,*N*-dimethylacetamide
DME	-	dimethoxyethane
DMF	-	dimethylformamide
equiv.	-	equivalent(s)
Et	-	ethyl
glc	-	gas-liquid chromatography
h	-	hour(s)
HOAc	-	acetic acid
HMPA	-	hexamethylphosphoramide
ir	-	infrared
LDA	-	lithium diisopropylamide
Me	-	methyl

m	-	multiplet
min	-	minute(s)
MOM	-	methoxymethyl
mp	-	melting point
NMO	-	*N*-methylmorpholine *N*-oxide
nmr	-	nuclear magnetic resonance
nOe	-	nuclear Overhauser enhancement
PCC	-	pyridinium chlorochromate
PDC	-	pyridinium dichromate
Ph	-	phenyl
PhH	-	benzene
Pr^i	-	isopropyl
q	-	quartet
s	-	singlet
t	-	triplet
TBDMS	-	*tert*-butyldimethylsiloxy
Tf	-	trifluoromethanesulphonyl
2-Th	-	2-thienyl
THF	-	tetrahydrofuran
tlc	-	thin layer chromatography
TPAP	-	tetra-*n*-propylammonium perruthenate

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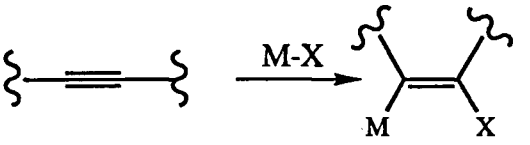
GENERAL INTRODUCTION

The development of new reagents and reactions and the improvement of existing synthetic methods are fundamental aspects of synthetic organic chemistry. Despite the vast amount of literature that is concerned with these topics, it is fair to say that efficient, general methodologies are still required in all areas of organic synthesis. One such area is that of carbon-carbon double bond formation. Most, if not all, planned synthetic pathways to a given structurally complex target molecule will involve the construction of one or more carbon-carbon double bonds. Usually, it is required that these units be synthesized with a specific geometry and in a highly stereoselective manner. For example, if the geometry of the carbon-carbon double bond determines the stereochemical outcome of a later synthetic transformation, the alkene of correct geometry (and high isomeric purity) must be available, so that the desired product is obtained stereoselectively. Examples of such reactions include Diels-Alder reactions, Claisen rearrangements, Cope rearrangements and cyclopropanations.

There has been an enormous amount of literature dedicated to the stereoselective synthesis of olefinic compounds, covering a wide range of reaction types. A particularly useful approach is based on the reactions of organometallic reagents with acetylenic compounds. These reactions can be divided into four general categories: a) hydrometallation; b) halometallation; c) carbometallation; and d) bismetallation (Scheme 1).

To be a useful synthetic method the reaction must possess a number of characteristics. It should be efficient. It should be both regioselective (i.e. produce one of the alkenylmetal regioisomers exclusively or predominantly) and stereoselective (i.e. produce one of the alkenylmetal stereoisomers exclusively or predominantly). The reaction should be compatible with a wide range of functionality in the acetylenic starting material. Finally, the alkenylmetal species produced by the reaction must be easily transformed (stereospecifically) into an

alkene by replacement of the metal by other groups, such as H, alkyl, aryl, alkenyl, halogens, acyl, other metals, and so forth.

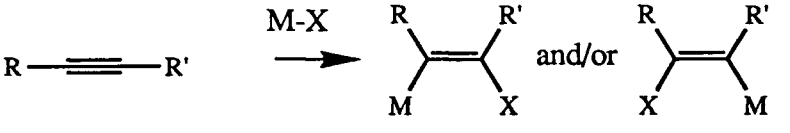


M = metal, X = H: hydrometallation

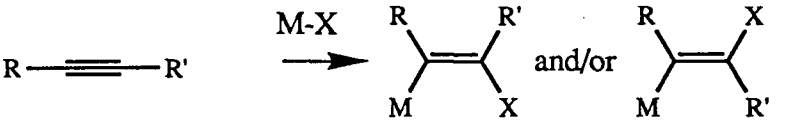
M = metal, X = halogen: halometallation

M = metal, X = alkyl: carbometallation

M = metal, X = metal: bismetallation



REGIOISOMERS

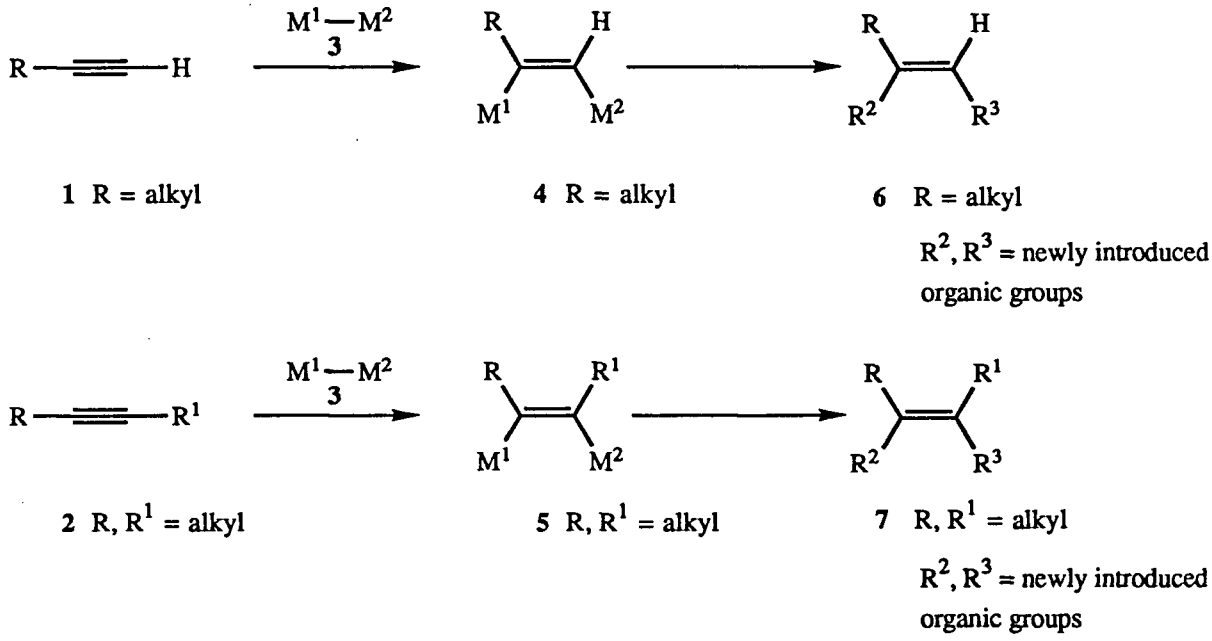


STEREOISOMERS

Scheme 1

Numerous successful, general methodologies for the synthesis of stereodefined substituted alkenes have been developed based on hydrometallation,[1-7] carbometallation,[5, 8-13] and halometallation[14-16] of acetylenic compounds and these subjects have been well reviewed. However, there are fewer general methods of alkene synthesis based on bismetallation reactions. Some of the available bismetallation methodology is briefly discussed in this introduction.

The reaction of terminal acetylenes **1** and internal acetylenes **2** with bimetallic reagents (depicted as **3**) usually results in the formation of bismetallated alkenes of general structures **4** and **5** respectively (Scheme 2). In order to be a synthetically useful process the reaction must fulfill the requirements mentioned above. Additionally, it is necessary to be able to perform chemistry at one alkenylmetal site in compounds **4** or **5**, without affecting the other alkenylmetal site. Successive replacement of the alkenylmetal moieties in **4** or **5** by organic groups results in the stereoselective synthesis of trisubstituted alkenes **6**, and tetrasubstituted alkenes **7**, respectively.



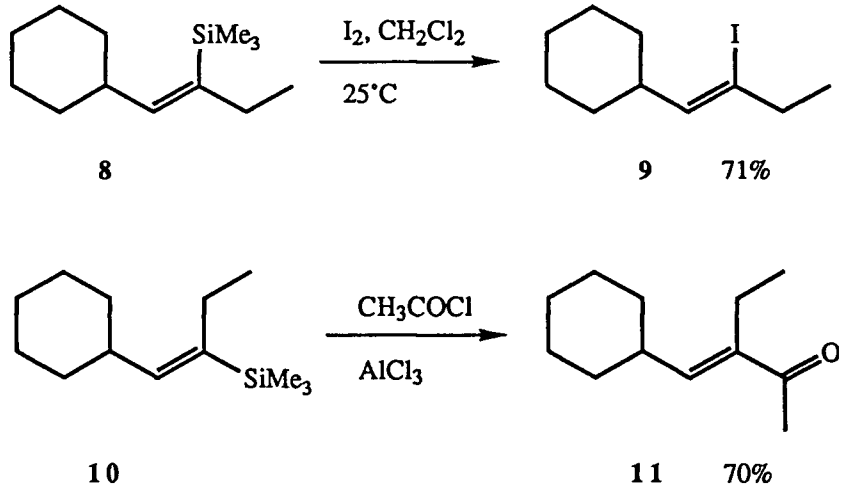
Scheme 2

Most of the bismetallation methodology reported to date involves the regio- and stereoselective preparation of alkenylsilanes or alkenylstannanes. These compounds may subsequently be converted into stereodefined substituted alkenes.

1. The preparation of alkenylsilanes via bismetallation of acetylenic compounds, and the conversion of these compounds into stereodefined alkenes

Alkenylsilanes may be converted into stereodefined alkenes in a number of ways. For example, they react with iodine to give alkenyl iodides. These reactions usually proceed stereospecifically, with retention of carbon-carbon double bond geometry. For example,[17] the alkenylsilane **8** reacts with iodine to give the alkenyl iodide **9** (Scheme 3).

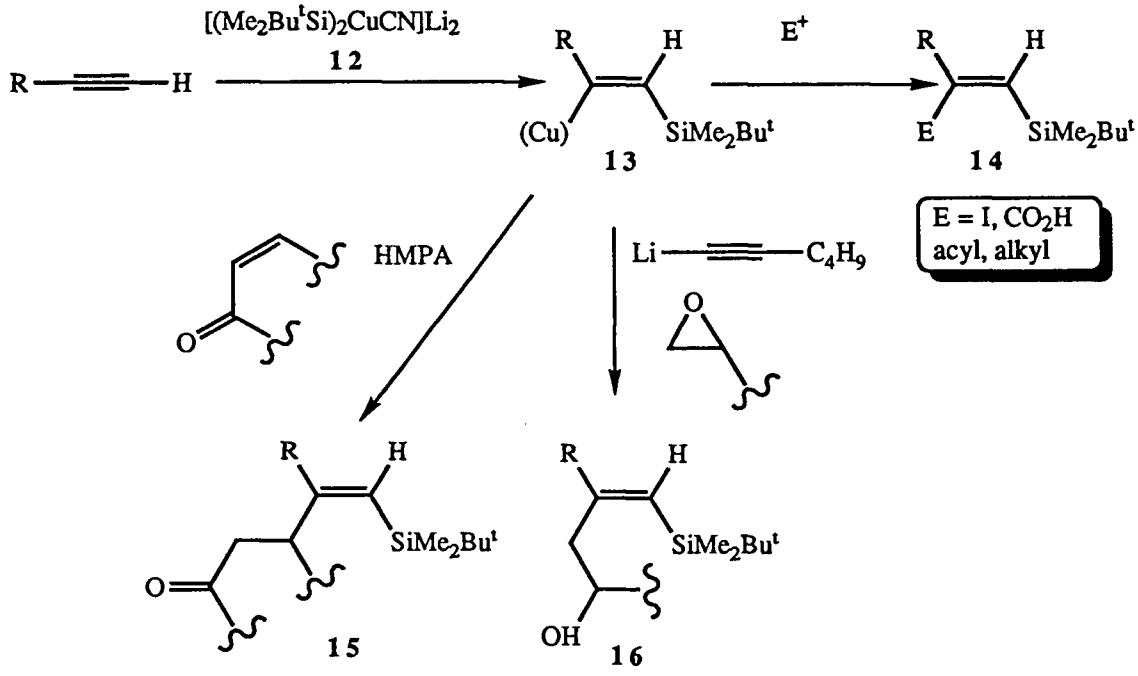
Alkenylsilanes also react efficiently with acyl halides, in the presence of Lewis acids, to give α,β-unsaturated ketones in a highly stereospecific manner. For example,[17] the alkenylsilane **10** reacts with acetyl chloride in the presence of aluminum trichloride, to give the unsaturated ketone **11** (Scheme 3).



Scheme 3

Regarding the preparation of alkenylsilanes, Fleming *et al.*[18] have reported that terminal acetylenes react with the higher order silylcuprate reagent **12** (Scheme 4) regio- and stereoselectively, to give alkenylsilane/alkenylcopper intermediates of general structure **13**. The reaction is also applicable to symmetrical internal acetylenes, but with unsymmetrical internal acetylenes it does not proceed with high regioselectivity. It was shown that the

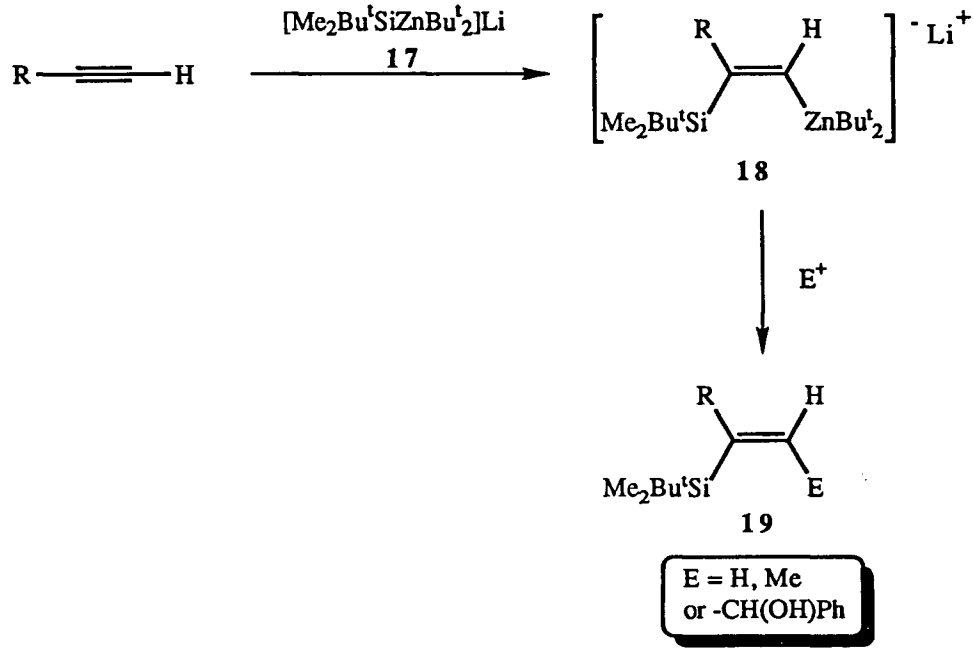
alkenylcopper moieties of intermediates **13** can be replaced stereospecifically by other groups, without affecting the alkenylsilane sites (Scheme 4). For example, the intermediates **13** react directly with a variety of electrophiles[18] (e.g. I_2, CO_2, acyl chlorides, and MeI) to give alkenylsilanes of general structure **14**. They also react with α,β-unsaturated ketones[18] to give the conjugate adducts **15**, and with epoxides[18] (in the presence of a lithium acetylide), to give the alkenylsilanes/homoallylic alcohols **16**.



Scheme 4

Oshima and coworkers[19-21] have developed several reagents that effect silylmetallation of acetylenic compounds. Some of these reagents add to terminal acetylenes regio- and stereoselectively, giving alkenylsilanes similar to those obtained via the silylcupration methodology discussed above. However, the silylzincate[21] reagent **17** reacts with terminal acetylenes to give alkenylsilane/alkenylzincate intermediates of general structure **18** (Scheme 5). The alkenylzincate moiety of intermediates **18** may be reacted with electrophiles (e.g. protons, MeI or PhCHO), to give alkenylsilanes of general structure **19**.

The alkenylsilanes **19** obtained via this methodology are regiochemically different from the alkenylsilanes **14** obtained via silylcupration. These processes are, therefore, complementary.



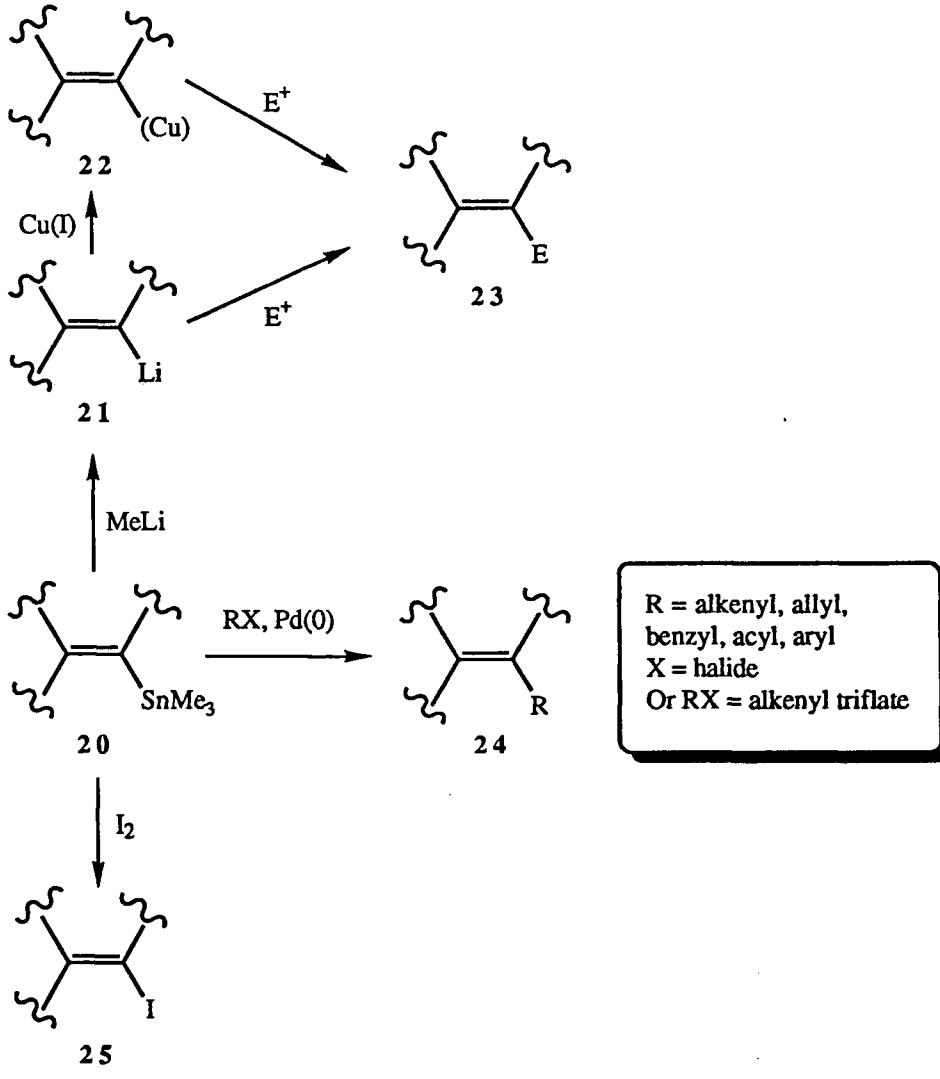
Scheme 5

2. <u>The preparation of alkenylstannanes via bismetallation of acetylenic compounds and the conversion of these compounds into stereodefined alkenes</u>

Alkenylstannanes are extremely versatile synthetic intermediates, as there are many methods available for the conversion of these compounds into substituted alkenes. For example, alkenyltrimethylstannanes depicted generally as **20** usually react cleanly with MeLi[22a] to give alkenyllithium species of general type **21**(Scheme 6), although the efficiency of the transmetallation process is dependant on the substitution pattern of the alkene.[23] The

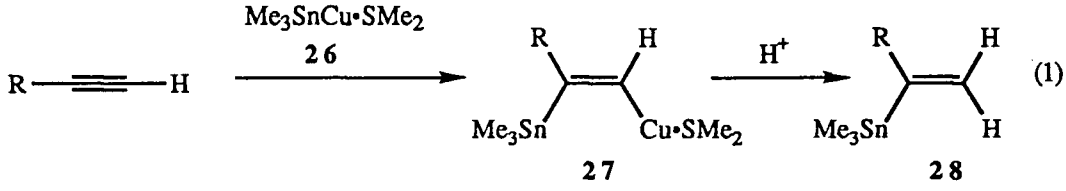
alkenyllithium reagents **21** may be reacted with electrophiles directly,[23,24] or via the corresponding organocopper (I) reagents[23,25] **22** to give substituted alkenes **23**.

Furthermore, the alkenylstannanes **20** may be cross coupled[26] (in the presence of a Pd(0) catalyst) with a wide range of aryl, allyl, alkenyl, benzyl, and acyl halides, as well as with alkenyl triflates[27] to give, stereospecifically, alkenes of general structure **24** (Scheme 6). Additionally, alkenylstannanes **20** react with iodine[22b] to give the corresponding alkenyl iodides **25** in a highly stereospecific manner (Scheme 6).



Scheme 6

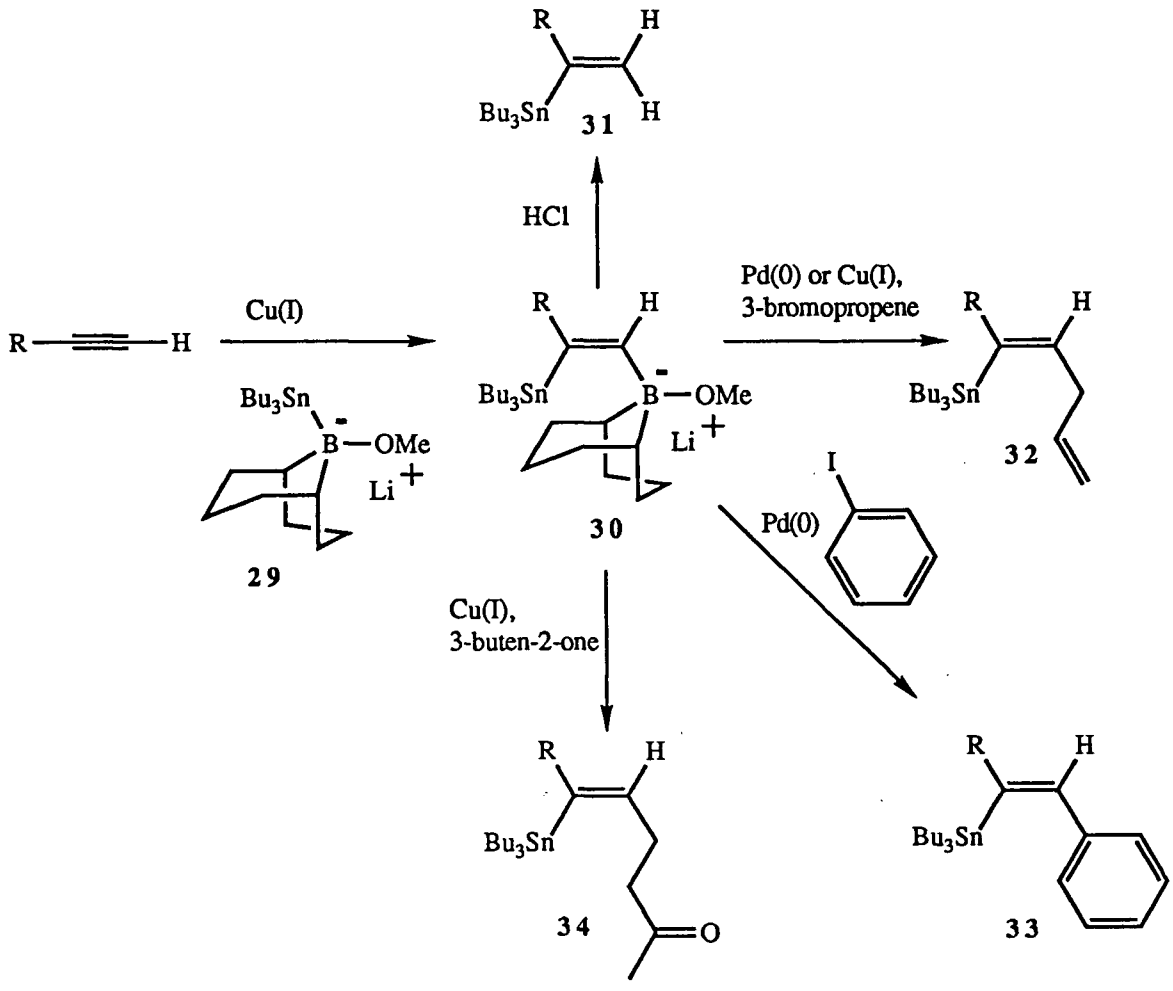
Regarding the synthesis of alkenylstannanes, Piers and Chong[28,29] have shown that the trimethylstannylcopper(I) reagent **26** reacts with terminal acetylenes efficiently and both regio- and stereoselectively, to give alkenylstannane/alkenylcopper intermediates of general structure **27** (equation 1). Several types of functional groups, such as halides, hydroxyls, and ethers are compatible with the reaction conditions. Unfortunately, the alkenylcopper moiety of the intermediates **27** does not react with electrophiles other than proton. In fact, an *in situ* proton source is required in these reactions in order to achieve complete consumption of the acetylene by the organocopper(I) reagent. Therefore, this methodology is limited to the synthesis of alkenylstannanes of general structure **28**.



(1)

Oehlschlager and Sharma[30] have reported that the stannylborate reagent **29** reacts with terminal acetylenes (in the presence of a Cu(I) catalyst) to give, regio- and stereoselectively, alkenylstannane/alkenylborate intermediates of general structure **30** (Scheme 7). The alkenylborate moiety of intermediates **30** may be selectively replaced by a proton or by a variety of organic groups. For example, protonation of intermediates **30** gives alkenylstannanes of general structure **31**. The intermediates **30** react with 3-bromopropene (in the presence of a Cu(I) salt or a Pd(0) catalyst) to give the substituted alkenylstannanes **32**. They also react with iodobenzene (in the presence of a Pd(0) catalyst) to give substituted alkenylstannanes **33** and with 3-buten-2-one (in the presence of a Cu(I) salt) to give the alkenylstannanes **34** (Scheme 7).

A novel approach to the preparation of substituted alkenylstannanes has been reported by Wang *et al.*[25] It was shown acetylenic triethylborates of general structure **35** (prepared

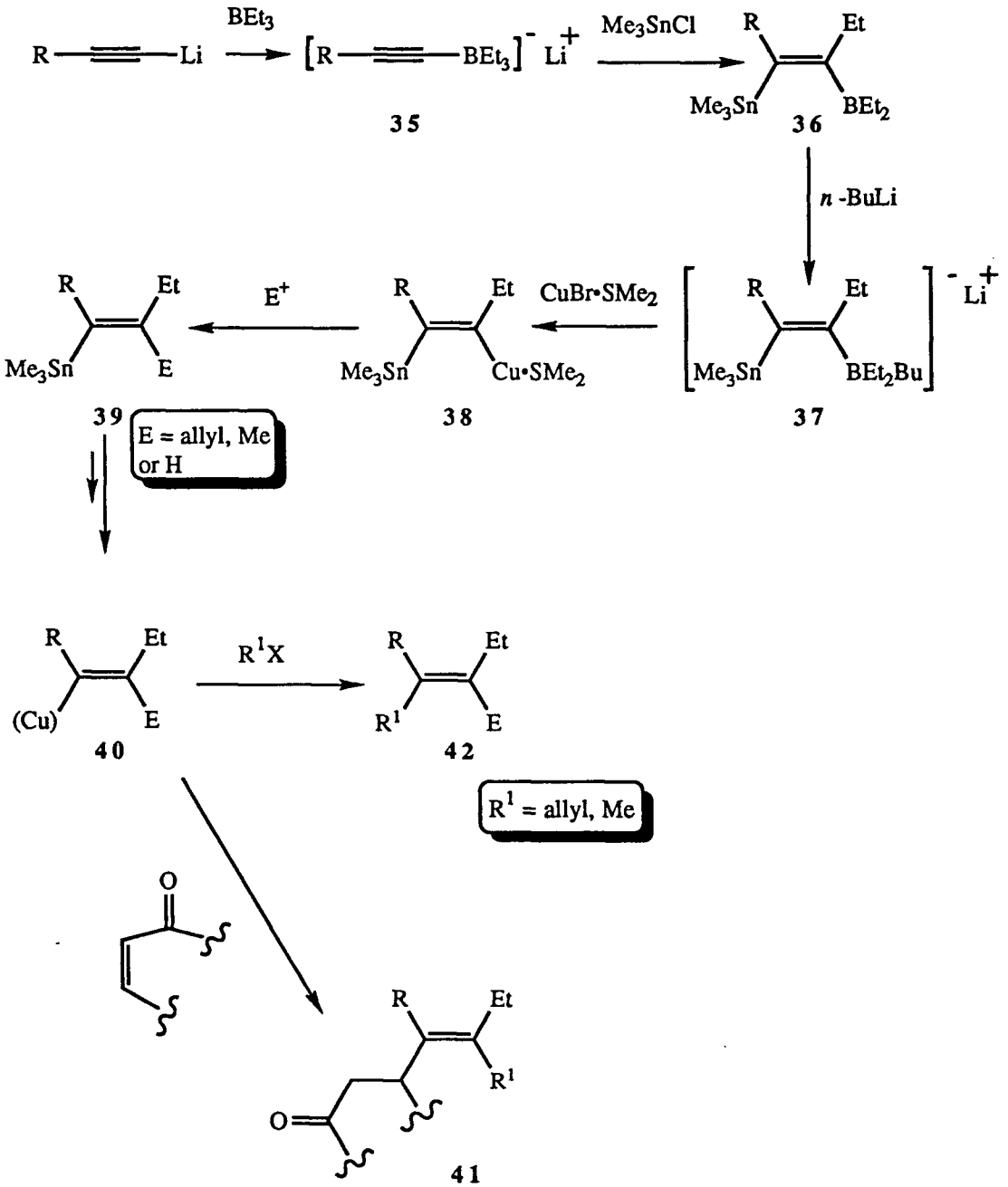


Scheme 7

via reaction of the appropriate lithium acetylides with triethylborane) react with trimethyltin chloride to give alkenylstannanes/alkenylboranes of general structure **36** (Scheme 8). Presumably, these compounds arise via migration of an ethyl group from boron to carbon, induced by electrophilic attack of trimethylstannyl chloride on the carbon-carbon triple bond of borates **35**.

Interestingly, treatment of compounds **36** with *n*-BuLi gives the corresponding alkenylborates **37** (without destruction of the alkenylstannane moiety), which react with copper(I) bromide-dimethyl sulphide complex to give alkenylcopper/alkenylstannane intermediates of general structure **38**. These alkenylcopper intermediates may be trapped

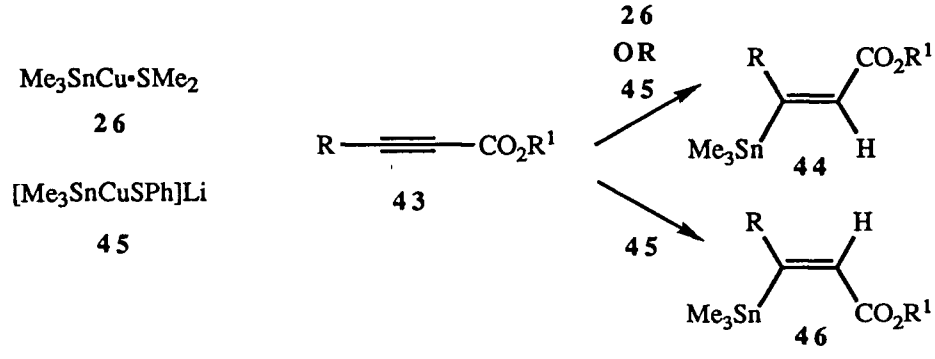
with reactive electrophiles such as 3-bromopropene, 2,3-dibromopropene, MeI or MeOH, to give stereodefined alkenylstannanes of general structure **39** (Scheme 8).



Scheme 8

Alkenylstannanes **39** are readily converted into stereodefined alkenylcopper(I) reagents **40**. These reagents react with α,β-unsaturated ketones to give stereodefined tetrasubstituted alkenes **41**, or react with alkylating agents to give stereodefined tetrasubstituted alkenes of general structure **42**.

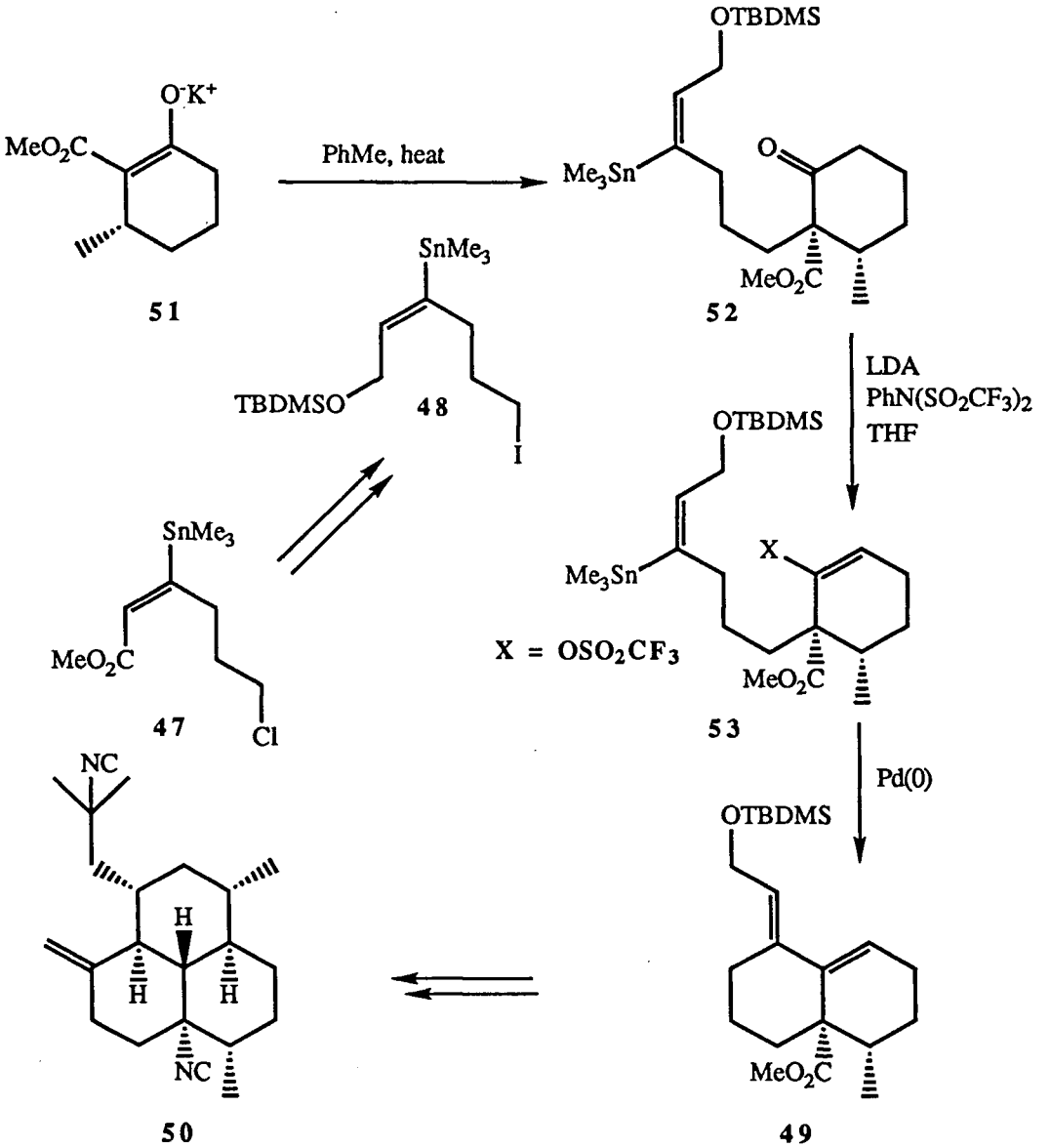
The bismetallation methodology described so far has involved the preparation of alkenylstannanes (or alkenylsilanes) from terminal acetylenes. Sometimes, regio- and stereoselective bismetallation reactions can be achieved using α,β-acetylenic esters as starting materials. For example, Piers *et al.*[31-33] have reported that the stannylcopper reagent **26** reacts with α,β-acetylenic esters **43** to give (upon protonation of the reaction intermediates) alkenylstannanes of general structure **44**. On the other hand, the stannylcuprate reagent **45** reacts with acetylenic esters to give, depending on the reaction conditions, alkenylstannanes of general structures **44** or **46** (Scheme 9). A wide range of functional groups, such as halides, ethers and carbon-carbon double bonds, are compatible with the reaction conditions. This stannylcupration methodology is discussed in detail in the introduction to Part 1 of this thesis.



Scheme 9

Alkenylstannanes of general structure **44** are exceptionally useful synthetic intermediates. For example, the compound **47** (prepared via stannylcupration of methyl

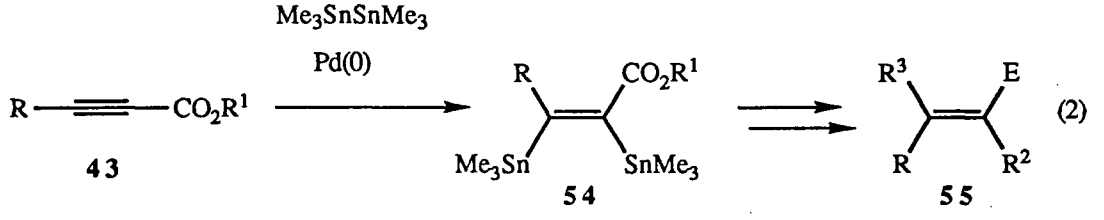
6-chloro-2-hexynoate) is readily converted into the alkenylstannane **48**. This compound was used for the preparation of the bicyclic diene **49**, which was a key intermediate in the total synthesis of (±)-8,15-diisocyano-11(20)-amphilectene **50** reported by Piers and Llinas-Brunet[34] (Scheme 10). Thus, alkylation of the potassium enolate **51** with compound **48**



Scheme 10

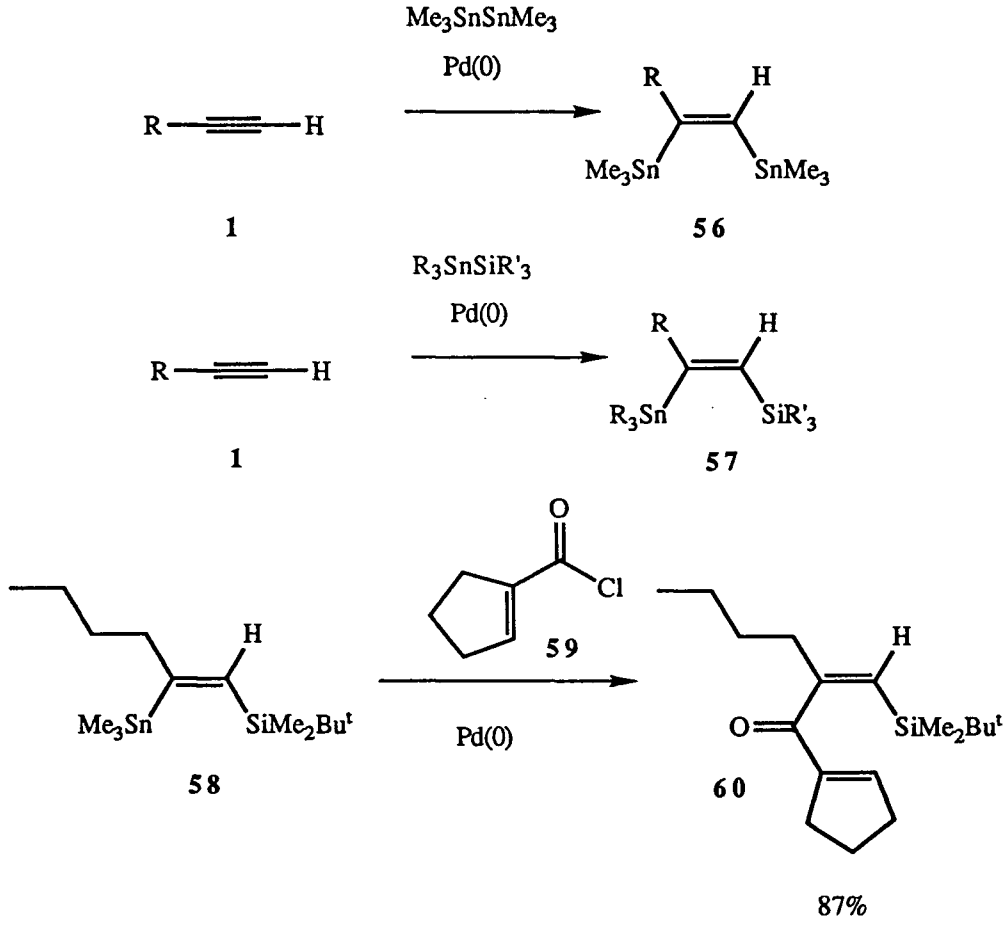
gave the ketone **52**. The desired bicyclic diene **49** was prepared from ketone **52** in a one-pot operation, involving formation of the enol triflate **53**, followed by Pd(0)-catalyzed intramolecular cross coupling between the alkenylstannane and alkenyl triflate[35,36] moieties of this compound.

It has also been shown that α,β-acetylenic esters **43** react with hexamethylditin in the presence of a Pd(0) catalyst to give (Z)-2,3-bis(trimethylstannyl)-2-alkenoates of general structure **54** (equation 2).[37] These bismetallation reactions are both efficient and stereoselective, and a variety of functional groups, including halides, ethers, and carbon-carbon double bonds are compatible with the reaction conditions. The distannyl alkenoates **54** are excellent precursors to stereodefined tetrasubstituted alkenes of general type **55**, since it is possible to sequentially replace the alkenylstannyl moieties of these compounds by organic groups.[23] This methodology is described in detail in the introduction to Part 2 of this thesis.



Pd(0)-catalyzed bismetallation reactions similar to those described above have been performed using terminal acetylenes **1** as starting materials. For example Mitchell *et al.*[38] reported that terminal acetylenes **1** react with hexamethylditin (in the presence of a Pd(0) catalyst) to give bis(trimethylstannyl) alkenes of general structure **56** (Scheme 11). Also, Chenard and Van Zyl[39] and Mitchell *et al.*[40] have independently reported that trialkylsilyl

trialkylstannanes react with terminal acetylenes (in the presence of a Pd(0) catalyst) to give, highly regio- and stereoselectively, alkenylsilanes/alkenylstannanes of general structure **57** (Scheme 11). It was shown that the alkenylstannane moiety of compounds **57** can sometimes be manipulated without affecting the alkenylsilane moiety. For example,[41] compound **58** was coupled efficiently and stereospecifically with the acid chloride **59**, in the presence of a Pd(0) catalyst, to give the alkenylsilane **60** (Scheme 11).



Scheme 11

The chemistry described in this general introduction has shown that bismetallation of acetylenic compounds is an exceptionally useful approach to the regio- and stereoselective preparation of alkenylsilanes and alkenylstannanes, which are precursors to stereodefined

substituted alkenes. However, at the time that the work described in this thesis was initiated, it appeared that there was certainly room for the development of new methodology in this area.

The work described in the first two sections of this thesis is concerned primarily with the development of new bismetallation methodology for the preparation of stereodefined alkenylstannanes. Each section contains a brief introduction to the existing methodologies as well as an outline of the proposed research.

The first section deals with stannylcupration reactions. In particular, the chemistry of a new, higher order trimethystannylcuprate reagent, dilithium (trimethylstannyl) (2-thienyl)(cyano)cuprate, is described.

The second section is concerned with the Pd(0)-catalyzed reactions of hexamethylditin with α,β-acetylenic aldehydes and ketones, and the subsequent preparation and general synthetic uses of (Z)-4-(trimethylstannyl)-1,3-butadienes.

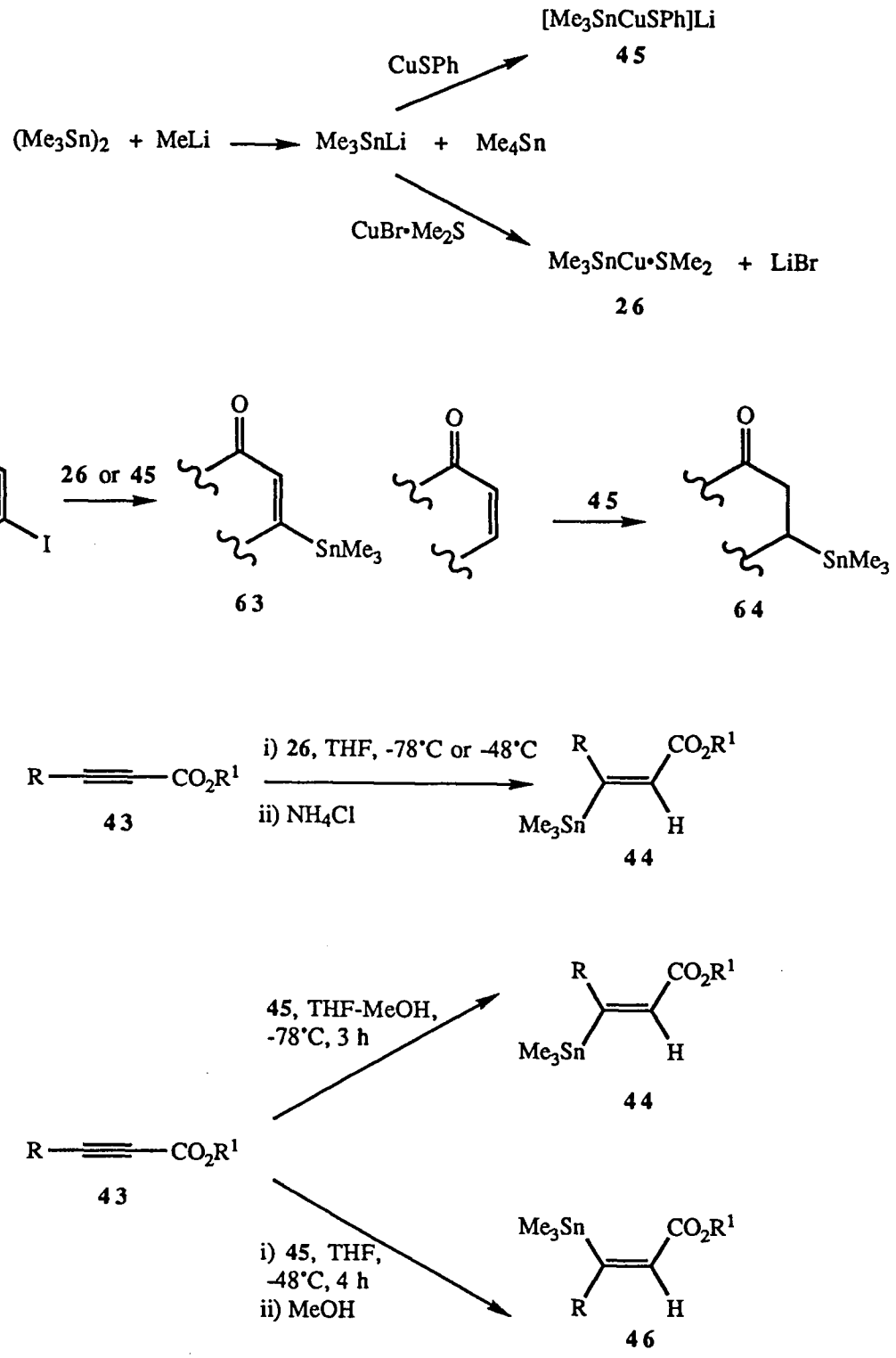
The final section involves the use of these stannyldienes in the construction of 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hex-2-enes, and a study of the Cope rearrangements of these compounds to highly substituted bicyclo[3.2.1]octa-2,6-dienes. A brief introduction to these topics is included.

PART 1. **The chemistry of dilithium (trimethylstannyl)(2-thienyl)(cyano) cuprate (61).**

I. Introduction

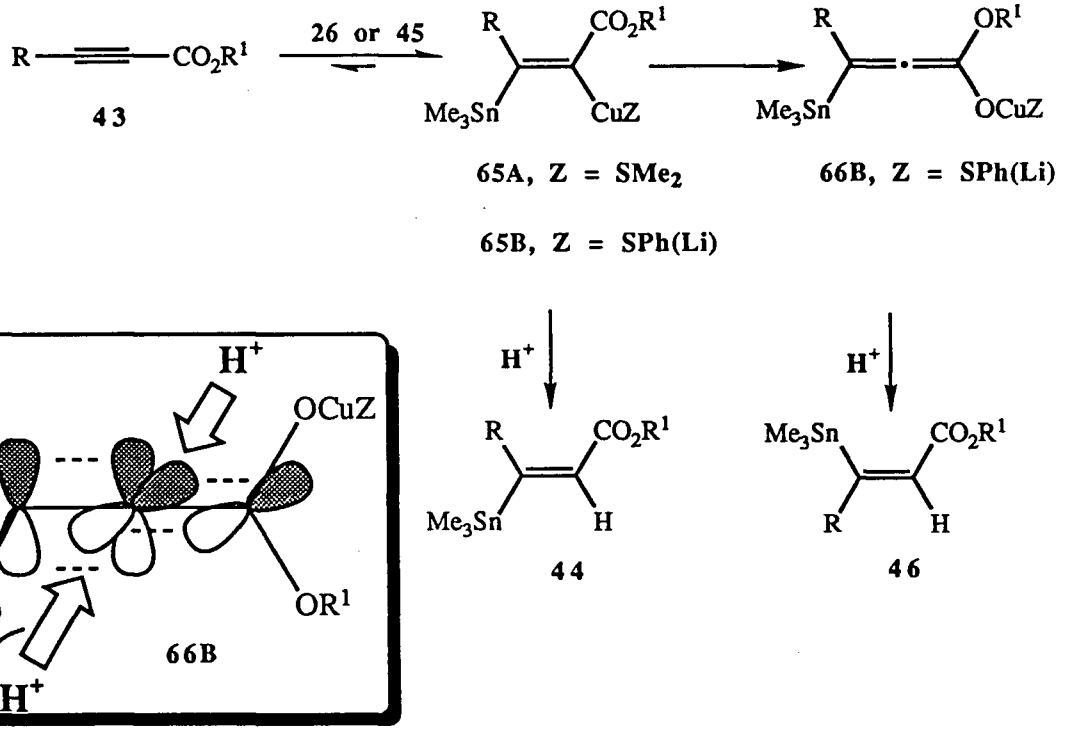
Previous work carried out in this laboratory has demonstrated the viability and synthetic utility of several (trimethylstannyl)copper(I) reagents.[28,29,31,32,33,42] These reagents are easily prepared and transfer the trimethylstannyl moiety to a variety of organic substrates. For example, both the (trimethylstannyl)copper(I) reagent **26** (prepared from equimolar amounts of trimethylstannyllithium and cuprous bromide-dimethyl sulphide complex) and the phenylthio(trimethylstannyl)cuprate reagent **45** (prepared from equimolar amounts of trimethylstannyllithium and phenylthiocopper) react with β-iodo α,β-unsaturated ketones of general structure **62** to give β-trimethylstannyl α,β-unsaturated ketones of general structure **63** (Scheme 12).[42] Also, the cuprate reagent **45** reacts with α,β-unsaturated ketones to give β-trimethylstannyl ketones of general structure **64**, whereas reagent **26** does not effect this transformation efficiently.[42]

Reagents **26** and **45** react efficiently and both regio- and stereoselectively with α,β-acetylenic esters **43**.[31,32,33] In particular, the (trimethylstannyl)copper(I) reagent **26** reacts with acetylenic esters either at -78°C or at -48°C to give (after protonation of the reaction intermediates) (*E*)-β-trimethylstannyl α,β-unsaturated esters of general structure **44** (Scheme 12). The (trimethylstannyl)cuprate reagent **45** reacts with acetylenic esters at -78°C in the presence of a proton source to give compounds **44** stereoselectively. Alternatively, **45** reacts with acetylenic esters at -48°C to give (*Z*)-β-trimethylstannyl α,β-unsaturated esters of general structure **46** (Scheme 12). A wide range of functional groups, including ethers, halides, and carbon-carbon double bonds, are compatible with all of the above reaction conditions.


[Me3SnCuSPh]Li
45
CuSPh
(Me3Sn)2 + MeLi
Me3SnLi + Me4Sn
CuBr•Me2S
Me3SnCu•SMe2 + LiBr
26
26 or 45
SnMe3
62
63
45
64
i) 26, THF, -78°C or -48°C
ii) NH4Cl
R
CO2R1
43
Me3Sn
H
44
45, THF-MeOH,
-78°C, 3 h
i) 45, THF,
-48°C, 4 h
ii) MeOH
46

Scheme 12

The stereochemical outcomes of these reactions may be rationalized in the following manner (Scheme 13). Reaction of either **26** or **45** with acetylenic esters probably involves reversible *cis* stannylcupration of the carbon-carbon triple bond to give alkenylcopper intermediates depicted as **65A** or **65B**, respectively. The alkenylcopper intermediates **65A** are, apparently, stable at -78°C or at -48°C and protonation provides, stereoselectively, the (*E*)-alkenylstannanes **44** (Scheme 13). It is proposed that alkenylcopper intermediates **65B**, on the other hand, isomerize to copper allenoate intermediates of general structure **66B**. This isomerization occurs quite readily at -48°C and, after 4 hours at this temperature, the allenoates **66B** are, apparently, formed predominantly. Protonation of **66B** occurs in the plane of the groups attached to the β-carbon, from the side opposite the bulky trimethylstannyl group, to give the (*Z*)-alkenylstannanes of general structure **46**

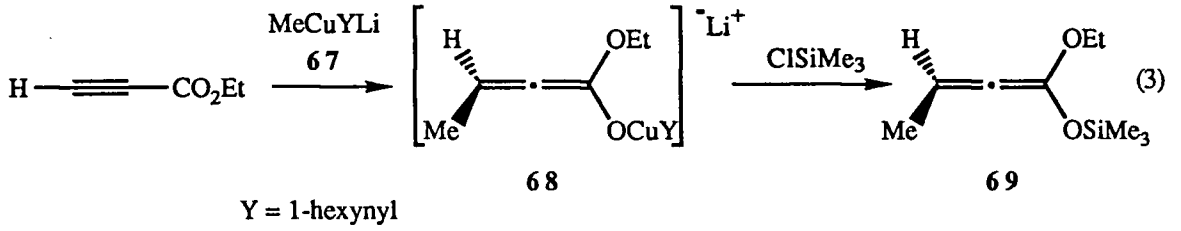


Scheme 13

(Scheme 13). The alkenylcopper-copper allenoate isomerization may proceed even at -78°C,[33] but if an *in situ* proton source is used at this temperature, the alkenylcopper intermediates **65B** are protonated before any isomerization to the allenoates can occur and the (*E*)-alkenylstannanes **44** are obtained stereoselectively.

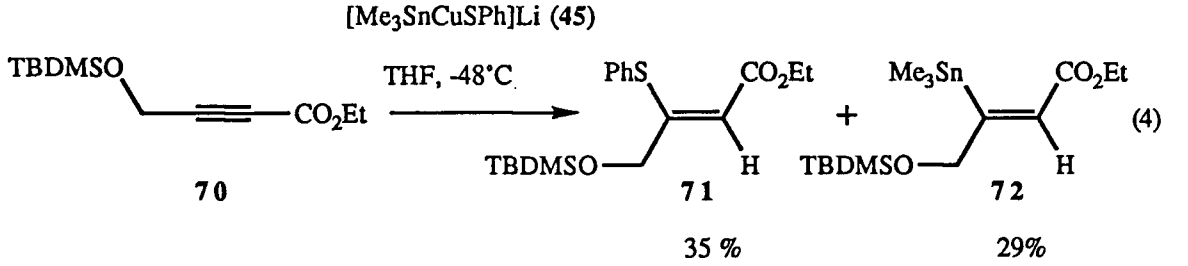
It is not clear why the alkenylcopper intermediates **65B** readily isomerize to the corresponding copper allenoates **66B**, whereas the alkenylcopper intermediates **65A** are stable species. The reasons must be related to the nature of Z and, therefore, to the actual structures of **65A** and **65B**, which are at present unknown.

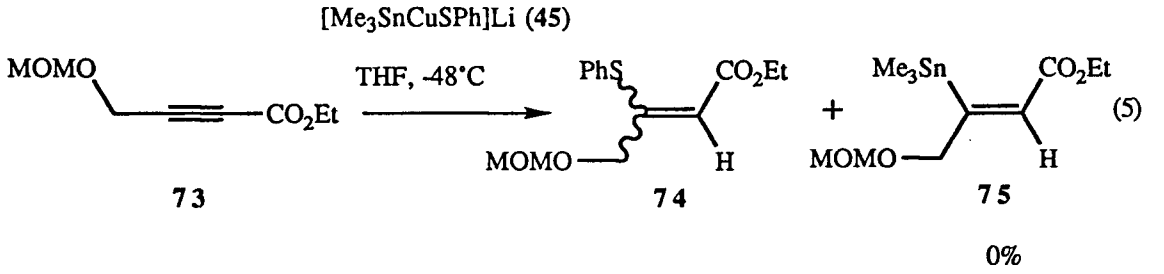
It should be emphasized that the above arguments are presented purely on the basis of the observed stereochemical outcomes of these stannylcupration reactions. Very little is known about the actual structures of the reaction intermediates, and it is not even certain that allenoate intermediates are involved. However, other workers have suggested that allenoate species are intermediates in reactions of alkylcuprates with acetylenic esters[43-46] and some evidence has been presented to support this. For example, Marino and Lindermann[43,44] have reported that the reaction of the mixed cuprate **67** with ethyl propynoate results in the formation of an allenoate intermediate **68**, which can be trapped as the allenic compound **69** by addition of trimethylsilyl chloride to the reaction mixture (equation 3).



Regardless of these mechanistic considerations, the stannylcupration of acetylenic esters with reagents **26** and **45** constitutes a general, efficient, stereoselective method for the synthesis of stereodefined, disubstituted alkenylstannanes. There are, however, some problems associated with this methodology.

The (trimethylstannyl)cuprate reagent **45** reacts anomalously with acetylenic esters which possess an ether function at the γ position. For example, **45** reacts with the acetylenic ester **70** to give compound **71** as the major product, along with a low yield of the expected alkenylstannane **72** (equation 4).[33] Additionally, **45** reacts with the acetylenic ester **73** to give compounds **74** and none of the expected alkenylstannane **75** (equation 5).





In these reactions, the cuprate reagent **45** preferentially transfers the phenylthio group (rather than the trimethylstannyl group) to the substrate. This is somewhat surprising, since phenylthiocuprates are generally reluctant to release the phenylthio moiety from copper[47] (although examples of this have been reported[48]). The reasons for the anomalous behavior of reagent **45** in these reactions are not clear, although they are likely related to the presence of an electron withdrawing group close to the carbon-carbon triple bond in substrates **70** and **73**. It is interesting to note that the reagent Me3SnCu•SMe2 (**26**) reacts efficiently with the acetylenic esters **70** and **73** to give the expected γ-alkoxy-(*E*)-β-trimethylstannyl α,β-unsaturated esters. Therefore, only γ-alkoxy-(Z)-β-trimethylstannyl α,β-unsaturated esters are not available via the existing stannylcupration methodology.

The intermediates formed in the reactions of either reagent **26** or **45** with acetylenic esters do not react efficiently with electrophiles other than proton.[49,50] In attempted intermolecular conjugate addition/alkylation reactions, the products obtained are those due to protonation of the reaction intermediates (i.e. alkenylstannanes of general structures **44** and **46**). Apparently, the reaction intermediates (alkenylcopper species or copper allenoates) are unreactive towards alkylating agents and, therefore, remain unchanged until a proton source is added during workup. In attempts to trap reaction intermediates with iodine, a highly reactive electrophile, only the protonated products **44** and **46** are obtained, along with variable amounts of the acetylenic ester starting material. In these cases, it appears that the iodine reacts preferentially with the (trimethylstannyl)copper(I) or cuprate reagent, driving the reversible stannylcupration reaction to the left and resulting in regeneration of the acetylenic ester.

II. Proposals

Organometallic reagents derived from copper(I) can be broadly classified into three groups:

1) Organocopper(I) reagents.

These are prepared from equimolar amounts of a copper(I) halide and an organolithium or Grignard reagent. Reagent **26** is, therefore, a trimethylstannyl version of an organocopper(I) reagent.

$$RLi + CuX \longrightarrow RCu + LiX$$

$$Me_3SnLi + CuBr{\cdot}SMe_2 \rightarrow \underset{\mathbf{26}}{Me_3SnCu{\cdot}SMe_2} + LiBr$$

2) Lower order cuprate reagents.

Lower order cuprates are represented generally by the stoichiometric formula R^1R^2CuM, in which R^1 and R^2 are organic ligands and M is a metal counter ion, usually Li^+ (or $MgBr^+$). Lower order cuprates in which R^1 and R^2 are the same are generally referred to as Gilman reagents, and may be prepared via reaction of two equivalents of an organolithium or Grignard reagent with one equivalent of a copper(I) halide. Lower order cuprates in which R^1 and R^2 are different are generally termed "mixed" cuprates. In these reagents, one of the organic groups attached to copper is necessarily a non-transferable ligand or "dummy" ligand, meaning that the other group will be transferred preferentially to the substrate by the cuprate reagent. Synthetically useful "mixed" lower order cuprate reagents have been developed using 1-alkynyl,[51] cyano,[52] phenylthio,[47] dicyclohexylamido,[53,54] and dicyclohexylphosphido[55] groups as non-transferable ligands. These reagents can be derived from the reaction of an alkyllithium reagent (which provides the transferable ligand) with an organocopper(I) reagent (which contains the non-transferable ligand). The phenylthiocuprate reagent **45** is a trimethylstannyl analogue of a "mixed" lower order cuprate.

The use of mixed cuprates (rather than Gilman type reagents) in organic synthesis is preferred if the transferable organic group is available only via multistep synthesis or is derived from an expensive reagent. Gilman type reagents, derived from two equivalents of the transferable group, usually transfer only one of these groups to the organic substrate, resulting in wastage of the other.

$$2RLi + CuX \longrightarrow R_2CuLi + LiX$$ GILMAN TYPE REAGENTS

$$RLi + CuR^{NT} \longrightarrow RR^{NT}CuLi$$

$$Me_3SnLi + CuSPh \longrightarrow Me_3SnCuSPhLi$$

} MIXED LOWER ORDER CUPRATES

45

R^{NT} = NON -TRANSFERABLE LIGAND

3) Higher order cuprates.

The most common higher order cuprate reagents[56] are those represented by the general formula $[R^1R^2CuCN]Li_2$. These higher order cyanocuprates are, therefore, different from lower order reagents in that there are three (rather than two) groups attached to copper, making these complexes formally dianionic. In these reagents, the cyano group[57] is a non-transferable ligand, and the two organic groups attached to copper may either be the same or different ("mixed" cuprates). In higher order "mixed" cyanocuprates,[58] one of the organic groups attached to copper must be a non-transferable ligand so that the remaining organic group may be transferred selectively by the cuprate. Lipshutz *et al.*[59,60] have shown that the

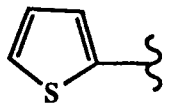
$$2RLi + CuCN \longrightarrow [R_2CuCN]Li_2$$ HIGHER ORDER CYANO CUPRATES

$$RLi + R^{NT}Li + CuCN \longrightarrow [RR^{NT}CuCN]Li_2$$ MIXED HIGHER ORDER CYANO CUPRATES

R^{NT} = NON-TRANSFERABLE LIGAND

2-thienyl ligand is not usually transferred easily from copper and that higher order mixed cyanocuprates **76** are conveniently prepared via addition of an organolithium reagent (the transferable ligand) to the lower order thienyl cyanocuprate **77** (equation 6).

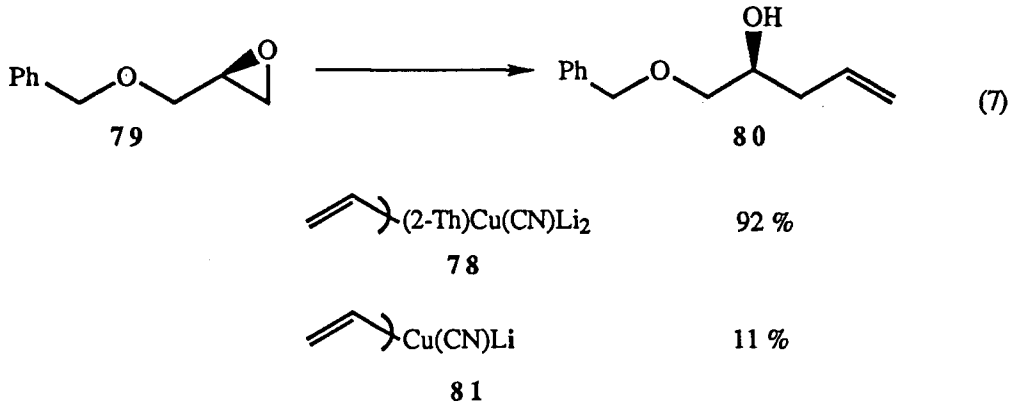
$$2\text{-ThLi} + CuCN \longrightarrow \underset{\mathbf{77}}{2\text{-ThCuCNLi}} \xrightarrow{RLi} \underset{\mathbf{76}}{R(2\text{-Th})CuCNLi_2} \qquad (6)$$



= 2-Th

Alkyl higher order cuprates are generally superior reagents compared with their lower order analogues. For example, the higher order mixed cuprate reagent **78** reacts with the

epoxide **79** (2.5 h at 0°C) to give a 92 % yield of the alcohol **80**. The lower order reagent **81** reacts with the epoxide **79** under identical conditions to give an 11% yield of the same alcohol (equation 7).[60]



(7)

On the basis of previous results reported in the literature regarding alkylcuprate reagents, as summarized above, it was envisaged that a higher order (trimethylstannyl)cuprate reagent should exhibit reactivity somewhat different from that of the lower order cuprates **26** and **45**. Thus, it seemed possible that a higher order (trimethylstannyl)cuprate might serve as a useful alternative to these well established reagents.

The aim of this project was, therefore, to investigate the chemistry of a higher order (trimethylstannyl)cuprate reagent. Initially, we wanted to determine the reactivity of such a reagent, relative to **26** and **45**, with typical organic substrates, such as α,β-unsaturated carbonyl compounds. However, the main objective was to investigate the reactions of this type of reagent with α,β-acetylenic esters **43**. Several questions needed to be addressed regarding these reactions. Firstly, would the reagent transfer the trimethylstannyl group efficiently to these acetylenic esters, and if so, what would be the stereochemical outcome in these reactions? Also, would the reagent react "normally" with α,β-acetylenic esters that have an ether function at the γ position (e.g. compounds **70** and **73**)? Finally, would the intermediates formed in the reactions of acetylenic esters with the higher order cuprate reagent

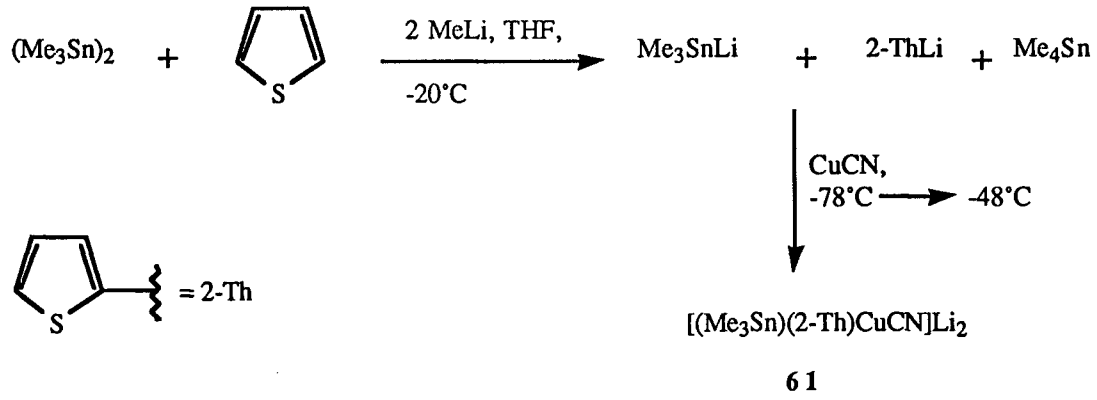
be amenable to trapping with electrophilic reagents (e.g. alkylating reagents) other than proton?

III. Results and discussion

At the outset of this project there were no reports regarding the preparation and reactions of higher order (trimethylstannyl)cuprates, although a number of such reports[61-63] appeared in the literature during the course of our work and since the publication of our results. Due to the high cost of hexamethylditin (which is used to prepare trimethylstannyllithium), the decision was made to investigate the chemistry of a mixed cuprate reagent rather than a bis(trimethylstannyl) species. Therefore, based on the methodology developed by Lipshutz *et al.*[59] in connection with alkylcuprate chemistry, we decided to prepare a higher order mixed cyanocuprate reagent composed of 1 equivalent of trimethylstannyllithium (the transferable ligand), 1 equivalent of 2-thienyllithium (the non-transferable ligand), and 1 equivalent of copper(I) cyanide.

3.1. Preparation of dilithium (trimethylstannyl)(2-thienyl)(cyano)cuprate (**61**)[64]

It was found that a reagent of the required stoichiometry could be conveniently prepared by the following procedure. To a cold (-20°C), stirred solution (argon atmosphere) of Me_6Sn_2 and thiophene (1 equivalent each) in dry THF was added a solution of MeLi (2 equivalents) in ether. After the mixture had been stirred at -20°C for 50 min, it was cooled to -78°C and solid copper(I) cyanide was added, giving a bright yellow solution which contained undissolved CuCN. On warming to -48°C the solids dissolved to give a clear, homogeneous, yellow solution of the cuprate reagent **61** (Scheme 14).



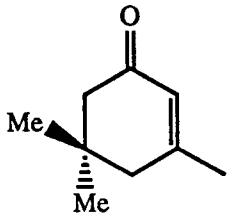
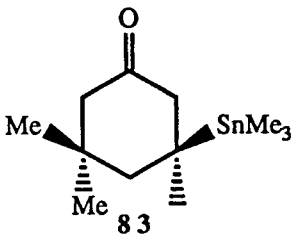
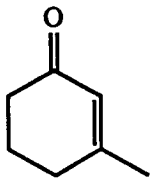
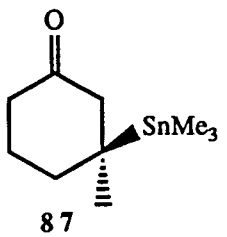
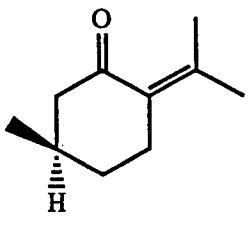
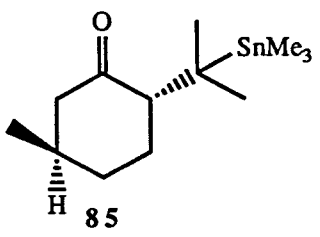
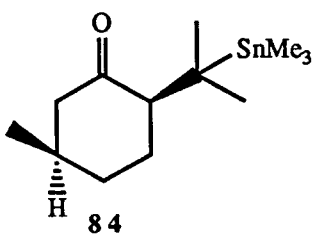
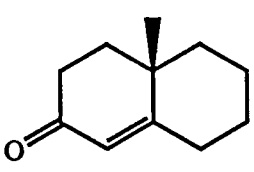
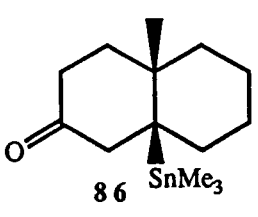
Scheme 14

3.2. Reactions of the higher order cuprate **61** with α,β-unsaturated carbonyl compounds

With a simple, reproducible preparation of reagent **61** in hand, it was now possible to determine its reactivity with simple organic substrates, such as α,β-unsaturated carbonyl compounds. Of particular concern was the ability of reagent **61** to transfer the trimethylstannyl group to these substrates selectively and efficiently, without competitive transfer of the thienyl residue. In connection with this, it is known that some higher order (alkyl)(thienyl) cyanocuprates preferentially transfer the thienyl group[60] (in a 1,2 sense) to sterically hindered β,β-disubstituted α,β-unsaturated ketones, although this problem may be avoided by the use of Lewis acid additives.

The substrates chosen for this study were sterically hindered β,β-disubstituted α,β-unsaturated ketones, namely 3-methyl-2-cyclohexen-1-one, 3,5,5-trimethyl-2-cyclohexen-1-one, and pulegone, which are commercially available, and the bicyclic enone **82**.[65] The reaction conditions and results are summarized in Table 1. Several important points regarding these reactions should be noted. In all cases, the reactions proceeded smoothly and in reasonable reaction times, using 1.5 equivalents of **61**, to give good isolated yields of the products. In no case was any material isolated which was derived from the transfer of the thienyl group to the organic substrate. Therefore, the higher order cuprate **61**

Table 1. Reactions of reagent **61** with α,β-unsaturated ketones

Entry	Substrate	Conditions	Product	Yield[1]
1		THF, -78°C, 5 min; -20°C, 4 h	 **83**	87 %
2		THF, -78°C, 5 min; -20°C, 4h	 **87**	90 %
3		THF, -78°C, 5 min; -20°C, 2 h	 **85**	69 %
			 **84**	20 %
4	 **82**	THF, -78°C, 10 min; -20°C, 3 h	 **86**	70 %

[1] Isolated yield of distilled product

appears to be a viable reagent for the selective transfer of the trimethylstannyl group to organic substrates. In fact, the yield (87%) of compound **83** obtained from the reaction of **61** with 3,5,5-trimethyl-2-cyclohexen-1-one (entry 1) compares favorably with that obtained (69%) using the lower order reagent **45**.[42]

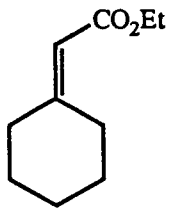
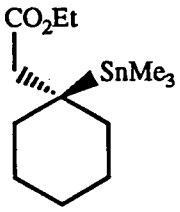
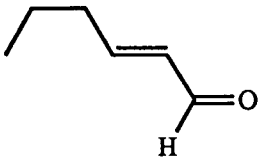
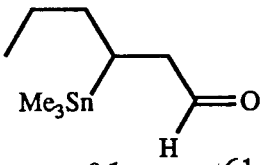
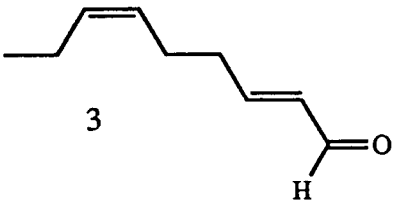
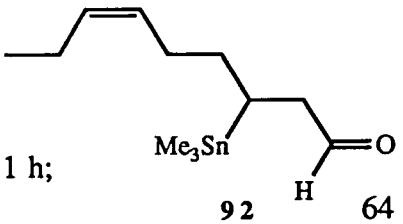
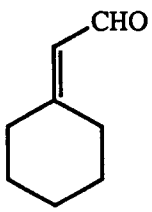
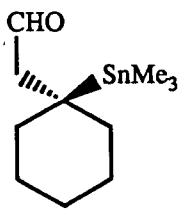
The spectral data for the reaction products shown in Table 1 were consistent with the proposed structures. Compound **83** exhibited spectral data identical with those reported for the same compound prepared by previous workers in this laboratory.[42]

Regarding the reaction of the higher order cuprate **61** with pulegone, a mixture of two products, in a ratio of 3:1 (glc analysis), was obtained. The two products were easily separated by flash chromatography. The stereochemistry of the minor component was confirmed to be *cis* by the treatment of this compound with NaOMe/MeOH at room temperature. The pure *cis* isomer **84** was thus converted into an 88:12 mixture (by glc analysis) of the *trans* isomer **85** and the *cis* isomer **84**, respectively.

Regarding the reaction of the cuprate reagent **61** with the bicyclic enone **82**, a single product **86** was obtained. The relative stereochemistry at the ring fusion in this compound was assumed to be *cis*, based on the known reactions of enone **82** with alkylcuprates.[66,67] Despite attempts to confirm this relative stereochemistry by nOe difference experiments, no conclusive evidence was obtained to support our assignment. The lack of an nOe effect between the angular methyl group and the trimethylstannyl group is most likely due to the long carbon-tin bond. As a result of this, the protons of the trimethylstannyl group and the protons of the methyl group at the ring fusion are apparently too far away from each other for an nOe effect to be observed between these groups.

The reactions of the higher order cuprate reagent **61** with other types of α,β-unsaturated carbonyl compounds were investigated next. The substrates chosen for this brief study were (*E*)-2-hexenal and (2*E*, 6*Z*)-2,6-nonadienal, which are commercially available, the aldehyde **88**,[68] and the ester **89**.[69] The conditions employed for these reactions and the results are presented in Table 2.

Table 2. Reactions of reagent **61** with α,β-unsaturated aldehydes and esters

Entry	Substrate	Conditions	Product	Yield[1]
1	 **89**	THF, -78°C, 1 h; -20°C, 30 min	 **90**	91 %
2		THF, -78°, 1 h; -20°C, 1 h	 **91**	61 %
3		THF, -78°, 1 h; -20°C, 1 h	 **92**	64 %
4	 **88**	THF, -78°C, 1 h; -20°C, 1 h	 **93**	62 %

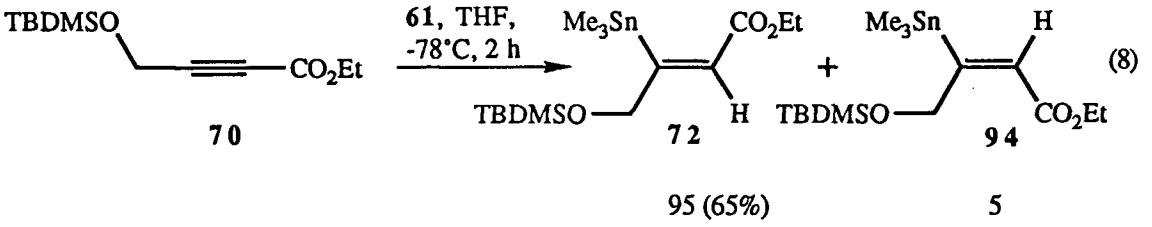
[1] Isolated yield of distilled product

Several comments must be made regarding the reactions summarized in Table 2. Firstly, the reactions of the cuprate reagent **61** (1.5 equivalents) with these substrates were complete within reasonable lengths of time, and gave respectable to very good yields of products. Secondly, it was pleasing to find that **61** reacted efficiently with the β,β-disubstituted ester **89** (entry 1) to give the conjugate addition product **90** in high yield. It had been shown previously[42] that the lower order phenylthiocuprate reagent **45** does not react with this substrate at all. Additionally, the higher order cuprate reagent **61** reacted with α,β-unsaturated aldehydes to give reasonable yields of the corresponding conjugate addition products, even in the case of the sterically hindered β,β-disubstituted aldehyde **88** (entry 4). These results are of particular note since it is known that tri-*n*-butylstannyllithium[70] reacts with β-substituted α,β-unsaturated aldehydes, in THF, to give mainly the products of 1,2-addition. Finally, the spectral data for the products shown in Table 2 were in full accord with the assigned structures.

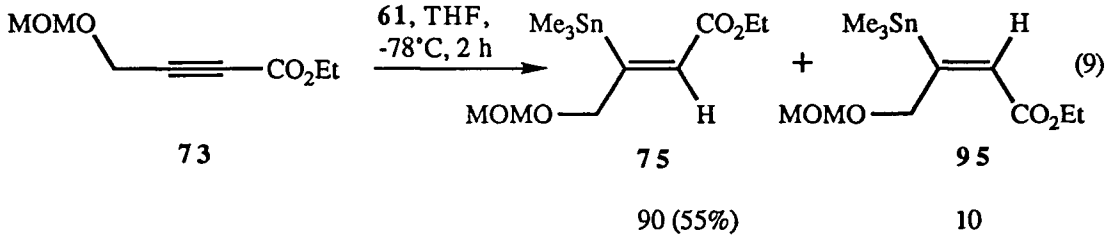
3.3. Reactions of the higher order cuprate **61** with α,β-acetylenic esters

The substrates used in this brief study were the α,β-acetylenic esters **70** and **73**. As mentioned earlier, the lower order phenylthiocuprate **45** reacts with these substrates to give, predominantly, products resulting from phenylthio transfer. The reasons for this anomalous behaviour are linked to the presence of an ether function at the γ position of compounds **70** and **73**.

The cuprate reagent **61** was allowed to react with the acetylenic ester **70** for 2 hours at -78°C. After appropriate workup, glc analysis of the crude reaction product showed the presence of the (*Z*)- and (*E*)-alkenylstannanes **72** and **94** in a ratio of 95:5 respectively (equation 8). The crude reaction mixture was purified by flash chromatography to give a 65% yield (after distillation) of the pure (*Z*)-alkenylstannane **72**, which was spectroscopically identical with the same substance prepared previously.[33]



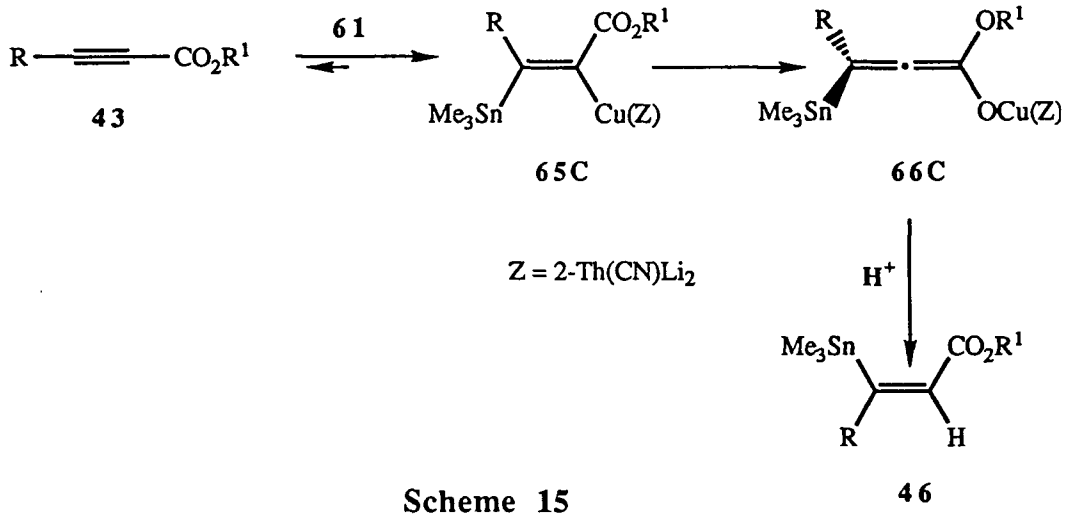
In an identical procedure, the cuprate reagent **61** was allowed to react with the acetylenic ester **73**. After appropriate workup, glc analysis of the crude product showed the presence of the (*Z*)- and (*E*)-alkenylstannanes **75** and **95**, in a ratio of 9:1 respectively, as well as some other minor unidentified products (equation 9). The (*Z*)-alkenylstannane **75** was isolated in 55 % yield after flash chromatography and distillation.



The isolated yields of compounds **72** and **75** in these reactions are much better than those obtained previously by reaction of the acetylenic esters **70** and **73** with the lower order phenylthiocuprate **45** (65 % and 55 %, respectively, compared with 29 % and 0 %, respectively). However, they are not as high as would have been expected from the very clean glc analyses of the crude reaction mixtures. The presence of baseline material by tlc analyses suggested that some polar, high molecular weight compounds may have been formed, but the nature of this material was not investigated.

The above results show that the higher order cuprate **61** can be used effectively for the stereoselective preparation of (*Z*)-β-trimethylstannyl α,β-unsaturated esters **46** from acetylenic esters, and is therefore a useful alternative to the lower order reagent **45**. The stereochemical outcomes in these reactions may be rationalized using arguments similar to

those presented earlier. Thus, it may be proposed that the higher order reagent **61** reacts with acetylenic esters regio- and stereoselectively to give alkenylcopper intermediates of general structure **65C** (Scheme 15). Apparently, the alkenylcopper intermediates **65C** undergo isomerization (even at -78°C) to the corresponding copper allenoates **66C**. Upon workup, protonation of the allenoates **66C** takes place from the less hindered face to give, stereoselectively, (Z)-alkenylstannanes of general structure **46**. It is not immediately clear why the alkenylcopper intermediates **65C** isomerize so readily to the corresponding allenoates **66C**. As suggested earlier for the reactions of the lower order reagents **26** and **45** with acetylenic esters, the nature of Z affects the stability of the alkenylcopper intermediates, and it appears that the intermediate **65C** is somewhat more prone to isomerization than **65B** (Z=SPh(Li)).



Scheme 15

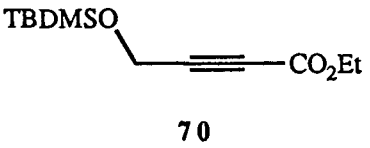
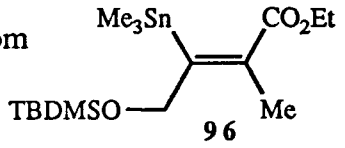
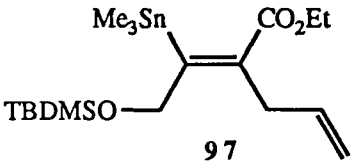
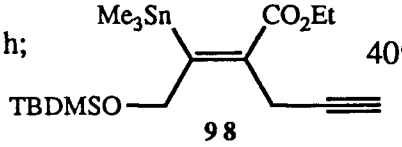
The next objective was to investigate the possibility of trapping the intermediates formed in these stannylcupration reactions with alkylating agents. For this study, it was decided to use the acetylenic ester **70** as the starting material, since the conditions for reaction of **61** with this substrate had been determined and the reaction was known to proceed cleanly.

Interestingly, it was found that the intermediate formed in this reaction could be smoothly alkylated with methyl iodide under the following conditions. A solution of the cuprate reagent **61** (1.5 equivalents) and the acetylenic ester **70** (1 equivalents) in dry THF was stirred at -78°C for 1 hour and at -20°C for 30 min. Hexamethylphosphoramide (excess, 10 equivalents) and MeI (excess) were added successively and the resulting mixture was stirred at -20°C for 30 min and at room temperature for 1 hour. After appropriate workup, glc analysis of the crude product showed one major peak attributable to the alkylated product **96**. Flash chromatography of the crude product gave the compound **96** in 65 % yield (after distillation) (Table 3). The ^{1}H nmr spectrum of this material showed no signal due to an olefinic proton, but did show a 3-proton singlet at δ 1.93 ($^{4}J_{Sn\text{-}H}$ = 7.1 Hz) due to the vinyl methyl group. The ^{13}C nmr spectrum of this compound showed signals at δ 169.47 (-$\underline{C}O_2Et$), and at 163.06 and 134.53 (olefinic carbons). The proposed double bond geometry (which is that expected from approach of the alkylating agent to the less hindered face of an allenoate intermediate (**66C**) in a manner similar to that described earlier) was confirmed by nOe difference experiments. Thus, irradiation of the signal at δ 1.93 (vinyl methyl) resulted in the expected enhancement of the signal at δ 4.40 (-SiOC$\underline{H}_2$-) and *vice versa.*

Similar trapping experiments were carried out successfully using other reactive alkylating agents. The conditions for these reactions and the results are summarized in Table 3. Several points should be made in connection with these reactions.

Regarding the reaction using 3-iodopropene as the alkylating agent, glc analysis of the crude product showed one major peak, attributable to the desired alkylated product **97**. The crude product was readily purified by flash chromatography (followed by distillation) to give the alkylated product **97** in 60% yield. The ^{1}H nmr spectrum of this material showed 1-proton multiplets at δ 4.93, 4.98, and 5.77, corresponding to the olefinic protons of the propenyl group, as well as a 2-proton multiplet at δ 3.14 (bis-allylic methylene). The ^{13}C

Table 3. Reaction of the acetylenic ester **70** with the reagent **61** and trapping of the intermediate with alkylating reagents.

Substrate	Alkylating Conditions	Product	Yield[1]
 **70**	HMPA, MeI, -20°C, 30 min; room temp, 1 h	 **96**	65%
	HMPA, 3-iodo-propene,-20°C, 30 min	 **97**	60%
	HMPA, 3-bromo-propyne, -78°C, 1 h; -20°C, 1 h	 **98**	40%

[1] Isolated yield of distilled, stereochemically pure material

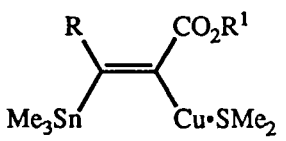
nmr spectrum showed signals at δ 168.92 (-CO_2Et) and at δ 164.93, 136.12, 135.72 and 115.13 (olefinic carbons). The proposed double bond geometry was confirmed by nOe difference experiments. Thus, irradiation of the signal at δ 3.14 (bis-allylic methylene) resulted in signal enhancement at δ 4.39 (-SiOCH_2-) and *vice versa.*

Regarding the reaction using 3-bromopropyne as the electrophile, glc analysis of the crude product showed the presence of the expected alkylated product **98** along with a significant amount (approx. 25 % by glc analysis) of the products **72** and **94**, which resulted from protonation of the reaction intermediates. The crude product was purified by careful

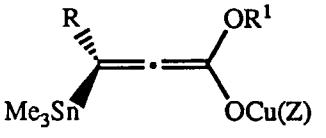
flash chromatography (followed by distillation) to give the alkylated product **98** in 40% yield. The infrared spectrum of this material showed signals at 2121 cm^{-1} and 3312 cm^{-1} attributable to the carbon-carbon and carbon-hydrogen stretching frequencies, respectively, of the terminal acetylene function. The ^1H nmr spectrum showed a 1-proton triplet (J = 2.8 Hz) at δ 1.94 (acetylenic H) and a 2-proton doublet (J = 2.8 Hz) at δ 3.31 (allylic-propargylic methylene). The proposed double bond geometry was confirmed by nOe difference experiments. Thus, irradiation of the signal at δ 3.31 (allylic-propargylic methylene) caused signal enhancement at δ 4.49 (-SiOC<u>H</u>$_2$-) and *vice versa.*

Although the (allenoate) intermediate formed by reaction of the acetylenic ester **70** with the higher order cuprate reagent **61** may be trapped using highly reactive alkylating agents, it was found that none of the desired products were obtained when less reactive alkylating agents (e.g. 1-iodobutane or 4-bromo-1-butene) were used. In these cases, glc analyses of the crude reaction products showed the presence of compounds **72** and **94**, which result from protonation of the reaction intermediate.

Although these conjugate addition/alkylation reactions appear to be of limited scope, they do constitute the first successful stereoselective intermolecular alkylation reactions of intermediates formed in the reactions of stannylcuprates with acetylenic esters. It appears from the success of these trapping reactions that the allenoate intermediates **66C** are more reactive than both the allenoate intermediates **66B** and the alkenylcopper intermediates **65A** which are obtained from the reactions of the lower order reagents **45** and **26**, respectively, with acetylenic esters.

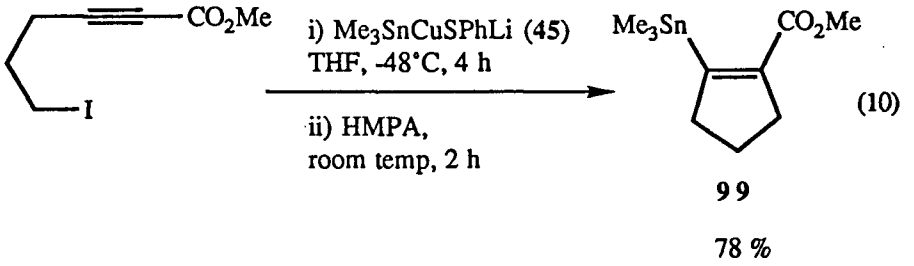


65A



66B Z=SPh(Li)
66C Z=(2-Th)(CN)Li_2

As mentioned earlier, the intermediates formed by reaction of the lower order reagents **26** or **45** with acetylenic esters cannot be trapped by electrophiles (other than proton) in an intermolecular sense. On the other hand, intramolecular alkylations[33] of such intermediates are feasible. For example, reaction of methyl 6-iodo-2-hexynoate with the phenylthiocuprate reagent **45** at -48°C, followed by addition of HMPA and warming of the reaction mixture to room temperature, gives the cyclic alkenylstannane **99** in 78% yield (equation 10).

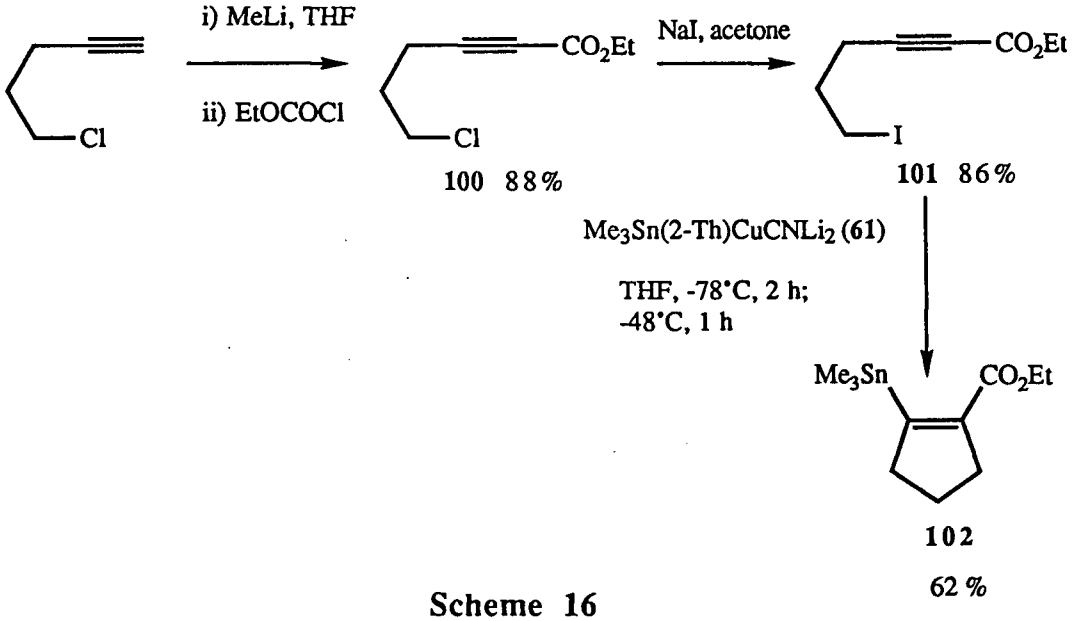


99

78 %

(10)

In order to test our new higher order reagent **61**, a similar reaction was performed using ethyl 6-iodo-2-hexynoate (**101**), which was prepared from commercially available 5-chloro-1-pentyne in two steps (Scheme 16). It was found that the higher order cuprate reagent reacted smoothly with this acetylenic ester in the absence of HMPA to give the cyclized compound **102** in 62 % yield (Scheme 16).



102

62 %

Scheme 16

3.4. Conclusions

It has been shown that the higher order cuprate formulated as **61** is an easily prepared, synthetically useful reagent. It reacts efficiently with α,β-unsaturated ketones, esters, and aldehydes, transferring the trimethylstannyl group to these substrates in a conjugate sense. The cuprate also reacts cleanly with α,β-acetylenic esters **43**. In particular, **61** reacts with substrates possessing an ether function at the γ position (e.g. **70** and **73**) to give the γ-alkoxy-(*Z*)-β-trimethylstannyl α,β-unsaturated esters (**72** and **75**) stereoselectively and in reasonable yields. Furthermore, the intermediates formed in the reaction of the higher order cuprate **61** with the acetylenic ester **70** may be trapped by highly reactive alkylating agents to give the corresponding (*Z*)-trisubstituted alkenylstannanes (**96**, **97** and **98**) stereoselectively and in reasonable yields.

This brief study of the chemistry of the higher order stannylcuprate reagent **61** has shown that, like alkyl higher order cuprate reagents, it is generally more reactive towards organic substrates than its lower order analogues **26** and **45**. Reagent **61** can be used effectively for the preparation of a variety of organotin compounds and is a useful alternative to reagents **26** and **45**.

IV. Experimental

4.1. General

Melting points (uncorrected) were determined using a Fisher-Johns melting point apparatus. Distillation temperatures (uncorrected) quoted for the compounds described in the experimental procedures were recorded as air bath temperatures required for bulb-to-bulb (Kugelrohr) distillations. Infrared (ir) spectra were obtained either as liquid films (NaCl plate) or as KBr disks, using a Perkin Elmer model 1710 spectrophotometer (internal

calibration). The ir signals quoted for each compound in the experimental procedures are the characteristic absorptions for the compound and/or the most prominent signals. Proton nuclear magnetic resonance (^{1}H nmr) spectra were recorded on deuteriochloroform solutions (unless otherwise stated), using a Bruker WH-400 or a Varian XL-300 spectrometer. Carbon nuclear magnetic resonance (^{13}C nmr) and phosphorus nuclear magnetic resonance (^{31}P nmr) were recorded on deuteriochloroform solutions (unless otherwise stated), using a Bruker AM-200 or a Varian XL-300 spectrometer. Signal positions for ^{1}H nmr spectroscopy are given in δ units and were measured relative to the chloroform signal (δ 7.25)[71a] (or the pentadeuteriobenzene signal δ 7.20).[71a] The multiplicity, number of protons, assignments (where possible) and coupling constants are indicated in parenthesis. Tin-hydrogen coupling constants (J_{Sn-H}) are given as an average of the ^{117}Sn and ^{119}Sn values. In some cases, the proton assignments were supported by decoupling, nOe difference, and/or COSY experiments. These experiments were carried out using a Bruker WH-400 spectrometer. Variable temperature studies were carried out on hexadeuteriobenzene solutions using a Varian XL-300 spectrometer. For ^{13}C nmr spectroscopy δ was measured relative to the deuteriochloroform signal (δ 77.0)[71b] (or hexadeuteriobenzene δ 128.0).[71b] Mass spectra were recorded with AEI MS9 (low resolution) or Kratos MS50 (low and high resolution) mass spectrometers. Chemical ionization mass spectra were recorded with a Delsi-Nermag R-10-10 quadrupole mass spectrometer. Molecular mass determinations (high resolution mass spectrometry) in cases of compounds with trimethylstannyl groups were based on ^{120}Sn and were made on the (M^{+}-Me) peak.[72] Elemental analyses were provided by the UBC microanalytical laboratory.

Gas-liquid chromatography (glc) analyses were performed on Hewlett-Packard models 5880 or 5890 capillary gas chromatographs, using 25 m x 0.21 mm fused silica columns coated with cross-linked SE-54, and equipped with flame ionization detectors.

Thin layer chromatography (tlc) analyses were done on commercial aluminium backed silica gel plates (E. Merck, Type 5554). Visualization was accomplished with ultraviolet

light, iodine, or staining with 5% ammonium molybdate - 10% aqueous sulphuric acid, or phospomolybdic acid. Flash chromatography[73] was done on 230-400 mesh silica gel. The approximate amounts of silica gel used for chromatography are quoted in each experimental procedure.

All compounds that were subjected to high resolution mass spectrometry and elemental analysis were homogeneous by tlc and glc analyses.

Unless otherwise stated, all reactions were carried out under an atmosphere of dry argon using glassware that had been thoroughly flame dried. Glass syringes and metal syringe needles used for solvents and reagents were oven dried (approx. 140°C). Plastic syringes were dried at room temperature under reduced pressure (0.5 Torr).

Cooling baths used for various reactions were obtained as follows: ice-acetone (-10°C), 27 g $CaCl_2$/100 mL H_2O - CO_2 (-20°C), 46 g $CaCl_2$/100 mL H_2O - CO_2 (-48°C), acetone-CO_2 (-78°C).

4.2. Solvents and reagents

Solvents and reagents were purified and dried using well known procedures.[74] Diethyl ether and THF were distilled from sodium benzophenone ketyl. Methylene chloride, triethylamine, diisopropylamine, *N,N*-diisopropylethylamine, HMPA, DMF, hexane and benzene were distilled from calcium hydride. *N,N*-dimethylacetamide was distilled from BaO and stored over 4Å molecular sieves. Petroleum ether refers to the fraction boiling between 30-60°C. Acetic acid was fractionally distilled using a Vigreux column. Acetic anhydride was stirred over calcium carbide for several days and then was distilled.

Hexamethylditin was obtained from Organometallics Inc., while tetrakis(triphenylphosphine)palladium(0) was obtained from either Aldrich Chemical Co.,

Inc., or from Morton Thiokol, Inc. (Alfa Products). These materials were used without further purification.

Solutions of methyllithium (lithium bromide complex (this was generally used), or low halide) in diethyl ether, *n*-butyllithium in hexane, and diisobutylaluminium hydride in hexane were obtained from Aldrich Chemical Co., Inc. and the former two reagents were standardized using diphenylacetic acid as primary standard.[75]

Copper(I) cyanide was available from Aldrich Chemical Co., Inc., and was dried under reduced pressure (room temperature, 0.5 Torr). Copper(I) bromide-dimethyl sulphide complex was prepared by the method of House,[76] after washing commercial copper(I) bromide with methanol.[77] Copper(II) acetylacetonate (commercial) was recrystallized from absolute ethanol. Rhodium(II) acetate was prepared according to the method of Wilkinson and coworkers.[78] Tetra *n*-propylammonium perruthenate was available from the Aldrich Chemical Co., Inc., and was used without further purification.

Aqueous ammonium chloride (pH 8) was prepared by the addition of 50 mL of aqueous ammonium hydroxide (58%) to 1 L of saturated aqueous ammonium chloride.

A solution of lithium diisopropylamide in THF (0.3 M) was prepared by the addition of a solution of *n*-butyllithium in hexane to a solution of diisopropylamine (1 equiv.) in dry THF at -78°C. The resulting colourless solution was stirred at -78°C for 15 min and at 0°C for 10 min before being used.

Activated 4Å molecular sieves were prepared by flame drying powdered 4Å molecular sieves under vacuum (approx 0.5 Torr) for several minutes.

4.3. Experimental procedures

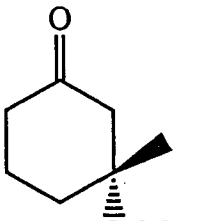
Preparation of $Me_3SnCu(2\text{-}Th)(CN)Li_2$ (**61**).

To a cold (-20°C), stirred solution of $(Me_3Sn)_2$ (164 mg, 0.5 mmol) in 10 mL of dry THF (argon atmosphere) was added, successively, thiophene (42 mg, 0.5 mmol) and a solution of MeLi (1.0 mmol) in Et_2O. After the pale yellow solution had been stirred at -20°C for 50 min, it was cooled to -78°C and CuCN (45 mg, 0.5 mmol) was added. The resulting suspension was stirred for 5 min at -78°C and for 10 min at -48°C to provide a bright yellow solution of the cuprate reagent **61**. The solution was cooled to -78°C and used immediately.

General Procedure A. Reaction of the cuprate reagent **61** with α,β-unsaturated aldehydes, ketones and esters.

To a cold (-78°C), stirred solution of the cuprate reagent **61** (0.5 mmol) in 10 mL of dry THF (argon atmosphere) was added the α,β-unsaturated carbonyl compound (0.33 mmol). After the solution had been stirred at -78°C (5 min -1 h) and at -20°C (1-4 h), it was treated with saturated aqueous NH_4Cl-NH_4OH (pH 8) (10 mL) and Et_2O (10 mL). The vigorously stirred mixture was exposed to air and allowed to warm to room temperature. The phases were separated and the aqueous phase was extracted with Et_2O (3x10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The resultant oils were purified by flash chromatography, followed by distillation.

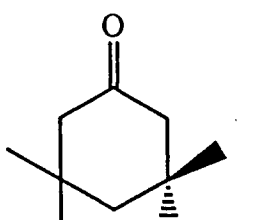
Preparation of 3-methyl-3-trimethylstannylcyclohexanone (87).



87

Following general procedure A, 37 mg (0.33 mmol) of 3-methyl-2-cyclohexen-1-one was allowed to react with the cuprate reagent **61** (0.5 mmol) for 5 min at -78°C and 4 h at -20°C. Flash chromatography (1:4 Et_2O - petroleum ether; 24 g of silica gel) of the crude product, followed by distillation of the oil thus obtained (90-100°C/2.0 Torr), gave 83 mg (90%) of the ketone **87**, a colourless oil which exhibited ir (neat): 1713, 1452, 1224, 768 cm^{-1}; ^1H nmr (300 MHz) δ: 0.06 (s, 9H, -Sn<u>Me</u>3, $^2J_{Sn-H}$ = 50 Hz), 1.20 (s, 3H,-<u>Me</u>, $^3J_{Sn-H}$ = 60 Hz), 1.55-2.60 (m, 10H). *Exact Mass* calcd. for $C_9H_{17}OSn$ (M^+-Me) : 261.0301; found: 261.0306.

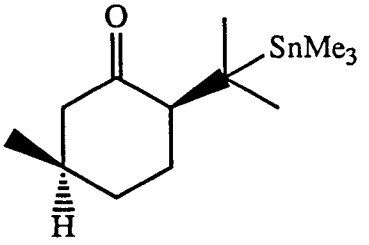
Preparation of 3,5,5 - trimethyl -3-trimethylstannylcyclohexanone (83).



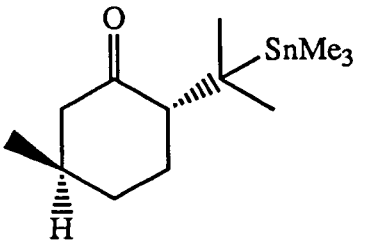
83

Following general procedure A, 46 mg (0.33 mmol) of isophorone (3,5,5-trimethyl-2-cyclohexen-1-one) was allowed to react with the cuprate reagent **61** for 5 min at -78°C and 4 h at -20°C. Flash chromatography (1:4 Et_2O - petroleum ether; 24 g of silica gel) of the crude product, followed by distillation of the oil thus obtained (90-95°C/2.0 Torr), gave 88 mg (87%) of the ketone **83**, a colourless oil that was spectrally identical with the same substance prepared previously.[42]

Preparation of the ketones 84 and 85.



84



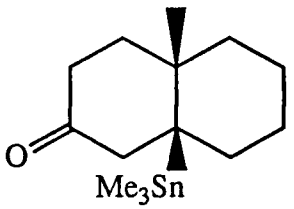
85

Following general procedure A, 51 mg (0.33 mmol) of pulegone was allowed to react with the cuprate reagent **61** for 5 min at -78°C and 2 h at -20°C. Flash chromatography (3:97 Et_2O - petroleum ether; 24 g of silica gel) of the crude product, followed by distillation of the oils thus obtained (90-100°C/2.0 Torr), gave 74 mg (69%) of the ketone **85** and 21 mg (20%) of the ketone **84**. The *trans* isomer **85** was a colourless oil which exhibited ir (neat): 1705, 1457, 764 cm^{-1}; ^1H nmr (300 MHz) δ: 0.00 (s, 9H, -Sn<u>Me</u>3, $^2J_{Sn-H}$ = 48 Hz), 1.00 (d, 3H, CH<u>Me</u>, J = 6 Hz), 1.03, 1.07 (s, s, 3H each, C<u>Me</u>2, $^3J_{Sn-H}$ = 65 Hz for each signal), 1.32 (br t, 2H), 1,70 - 2.05 (m, 3H), 2.15 (m, 2H), 2.30 (m, 1H); ^{13}C nmr

(75.4 MHz) δ: -8.52, 22.38, 24.75, 25.00, 28.56, 28.21, 34.40, 36.05, 51.02, 61.51, 213.85. *Exact Mass* calcd. for $C_{12}H_{23}OSn$ (M^+-Me): 303.0771; found : 303.0763.

The *cis* isomer **84** was a colourless oil which exhibited ir (neat): 1704, 1467, 763 cm^{-1}; ^1H nmr (300 MHz) δ: 0.00 (s, 9H, -SnMe3, $^2J_{Sn-H}$ = 49 Hz), 0.90 (d, 3H, CHMe, *J* = 6 Hz), 1.03, 1.06 (s, s 3H each, CMe2, $^3J_{Sn-H}$ = 65 Hz for each signal), 1.56 - 1.65 (m, 2H), 1.82 - 2.23 (m, 4H), 2.4 - 2.55 (m, 2H). *Exact Mass* calcd. for $C_{12}H_{23}OSn$ (M^+-Me): 303.0771; found: 303.0765. Treatment of pure **84** with MeONa in MeOH (room temperature, overnight), resulted in an 88:12 mixture of **85** and **84** respectively.

Preparation of the ketone **86.**

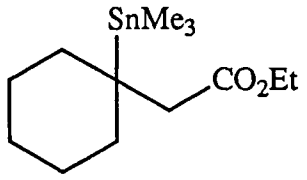


86

Following general procedure A, 55 mg (0.33 mmol) of the bicyclic enone **82** was allowed to react with the cuprate reagent **61** for 10 min at -78°C and 3 h at -20°C. Flash chromatography (1:4 Et_2O - petroleum ether; 24 g of silica gel) of the crude product, followed by distillation of the oil thus obtained (150-160°C/2.0 Torr), gave 77 mg (70%) of the ketone **86**, a colourless oil which exhibited ir (neat) : 1708, 1158, 765 cm^{-1}; ^1H nmr (300 MHz) δ: 0.08 (s, 9H, -SnMe3, $^2J_{Sn-H}$ = 48 Hz), 1.04 (s, 3H, Me), 1.16 - 1.87 (m, 10H), 2.05 - 2.75 (m, 4H); ^{13}C nmr (75.4 MHz) δ: -5.94, 15.09, 21.17, 24.66, 33.23,

36.59, 37.79, 38.42, 40.20, 45.32, 49.76, 210.83. *Exact Mass* calcd. for $C_{13}H_{28}OSn$ (M^+-Me): 315.0768; found: 315.0767.

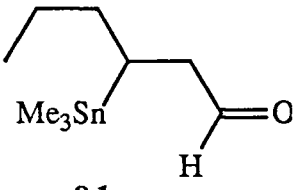
Preparation of the ester **90.**



90

Following general procedure A, 42 mg of the α,β-unsaturated ester **89** (0.33 mmol) was allowed to react with the cuprate reagent **61** at -78°C for 1 h and -20°C for 30 min. Flash chromatography (3:97 Et_2O - petroleum ether; 24 g of silica gel) of the crude product, followed by distillation of the oil thus obtained (120-125°C/2.0 Torr), gave 76 mg (91%) of the ester **90**, a colourless oil which exhibited ir (neat): 1729, 1186, 1163, 766 cm^{-1}; ^1H nmr (300 MHz) δ : 0.04 (s, 9H, $SnMe_3$, $^2J_{Sn-H}$ = 49 Hz), 1.22 (t, 3H, $-OCH_2CH_3$, J = 8 Hz), 1.30 (m, 5H), 1.60 (m, 3H), 1.85 (m, 2H), 2.45 (s, 2H, $-CH_2CO_2Et$, $^3J_{Sn-H}$ = 72 Hz), 4.07 (q, 2H, $-OCH_2CH_3$, J = 8 Hz); ^{13}C nmr (75.4 MHz) δ: -8.62, 14.27, 23.69, 26.35, 32.41, 36.67, 45.27, 60.13, 173.33. *Exact Mass* calcd. for $C_{12}H_{23}O_2Sn$ (M^+-Me): 319.0720; found: 319.0718.

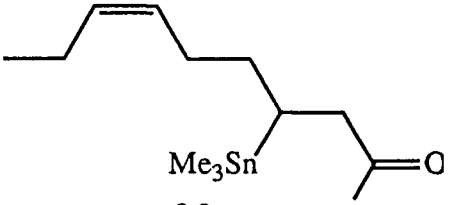
Preparation of 3-trimethylstannylhexanal (**91**).



91

Following general procedure A, 33 mg (0.33 mmol) of (*E*)-2-hexenal was allowed to react with the cuprate reagent **61** for 1 h at -78°C and 1 h at -20°C. Flash chromatography (1:4 Et_2O - petroleum ether; 24 g of silica gel) of the crude product, followed by distillation of the oil thus obtained (50-55°C/2.0 Torr), gave 54 mg (61%) of the aldehyde **91**, a colourless oil which exhibited ir (neat): 2718, 1723, 1186, 764 cm^{-1}; ^1H nmr (300 MHz) δ: 0.04 (s, 9H, -Sn<u>Me</u>3, $^2J_{Sn-H}$ = 51 Hz), 0.87 (t, 3H, -$CH_2C\underline{H}_3$, J = 8 Hz), 1.38 - 1.70 (m, 5H), 2.65 (dd, 2H, -$C\underline{H}_2CHO$, J = 6 Hz, J = 1.5 Hz, $^3J_{Sn-H}$ = 62 Hz), 9.74 (t, 1H, -C<u>H</u>O, J = 1.5 Hz); ^{13}C nmr (75.4 MHz) δ: -9.86, 14.12, 19.42, 23.14, 35.63, 47.94, 203.34. *Exact Mass* calcd. for $C_8H_{17}OSn$ (M^+-Me): 249.0301; found: 249.0304.

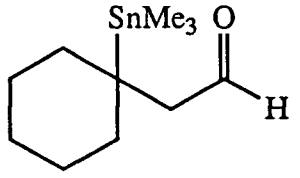
Preparation of (Z)-3-trimethylstannyl-6-nonenal (**92**).



92

Following general procedure A, 46 mg (0.33 mmol) of (2*E* ,6*Z*)-2,6-nonadienal was allowed to react with the cuprate reagent **61** for 1 h at -78°C and 1 h at -20°C. Flash chromatography (1:4 Et_2O - petroleum ether; 24 g of silica gel) of the crude product, followed by distillation of the oil thus obtained (75-80°C/2.0 Torr), gave 65 mg (64%) of the aldehyde **92**, a colourless oil which exhibited ir (neat) : 2715, 1724, 1187, 767 cm^{-1}; ^1H nmr (300 MHz) δ: 0.05 (s, 9H, -Sn<u>Me</u>3, $^2J_{Sn-H}$ = 50 Hz), 0.93 (t, 3H, -$CH_2C\underline{H}_3$, *J* = 7 Hz), 1.4-1.75 (m, 3H), 1.85-2.15 (m, 4H, both allylic C<u>H</u>2), 2.68 (dd, 2H, -C<u>H</u>2CHO, *J* = 6.5 Hz, *J* = 1.3 Hz, $^3J_{Sn-H}$ = 62 Hz), 5.33 (m, 2H, olefinic H), 9.75 (t, 1H, -C<u>H</u>O, *J* = 1.3 Hz); ^{13}C nmr (75.4 MHz) δ: -9.82, 14.36, 19.18, 20.58, 27.42, 33.39, 47.83, 128.28, 132.06, 203.11. *Exact Mass.* calcd. for $C_{11}H_{21}OSn$ (M^+-Me): 289.0614 ; found: 289.0617.

<u>Preparation of the aldehyde **93**.</u>



93

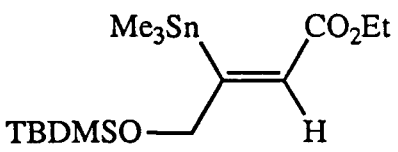
Following general procedure A, 41 mg (0.33 mmol) of the α,β-unsaturated aldehyde **88** was allowed to react with the cuprate reagent **61** for 1 h at -78°C and 1 h at -20°C. Flash chromatography of the crude product (1:4 Et_2O - petroleum ether ; 24 g of silica gel), followed by distillation of the oil thus obtained (120-125°C/2.0 Torr), gave 60 mg (62%) of the aldehyde **93**, a colourless oil which exhibited ir (neat) : 2722, 1720, 1450, 896,

767 cm^{-1}; ^1H nmr (300 MHz) δ: 0.05 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn-H}$ = 49 Hz), 1.15-1.44 (m, 5H), 1.76-2.04 (m, 2H), 2.60 (d, 2H, -C<u>H</u>$_2$CHO, J = 1.6 Hz, $^3J_{Sn-H}$ = 67 Hz), 9.77 (t, 1H, -C<u>H</u>O, J = 1.6 Hz); ^{13}C nmr (75.4 MHz) δ: -8.66, 23.95, 26.23, 31.40, 36.85, 55.74, 203.05. *Exact Mass* calcd. for $C_{10}H_{19}OSn$ (M^+-Me): 275.0458; found: 275.0457.

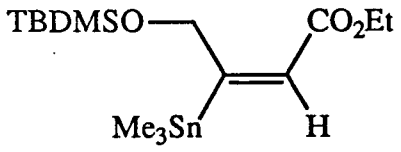
<u>General Procedure B. Reaction of the cuprate reagent **61** with α,β-acetylenic esters.</u>

To a cold (-78°C), stirred solution of the cuprate reagent **61** (0.5 mmol) in 10 mL of dry THF (argon atmosphere) was added a solution of the α,β-acetylenic ester (0.38 mmol) in 0.5 mL of dry THF. After the mixture had been stirred for 2 h at -78°C, saturated aqueous NH_4Cl-NH_4OH (pH 8) (10 mL) was added and the vigorously stirred mixture was exposed to air and allowed to warm to room temperature. The phases were separated and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. The crude product thus obtained was purified by flash chromatography, followed by distillation.

<u>Preparation of ethyl (Z)-4-*tert*-butyldimethylsilyoxy-3-trimethylstannyl-2-butenoate (**72**).</u>



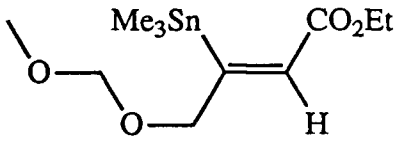
72



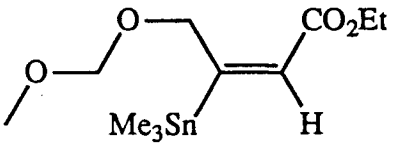
94

Following general procedure B, 93 mg (0.38 mmol) of the α,β-acetylenic ester **70**[33] was allowed to react with the cuprate reagent **61**. Glc analysis of the crude product showed that it consisted of a 95:5 mixture of compounds **72** and **94**, respectively. Flash chromatography (3:97 Et_2O - petroleum ether ; 30 g of silica gel) of the crude mixture, followed by distillation of the oil thus obtained (110-120°C/2.0 Torr), gave 102 mg (65%) of the ester **72**, a colourless oil which exhibited spectra identical with those of the same substance reported previously.[33]

Preparation of ethyl (Z)-4-(methoxymethoxy)-3-trimethylstannyl-2-butenoate (**75**).



75



95

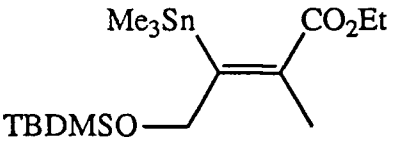
Following general procedure B, 65 mg (0.38 mmol) of the α,β-acetylenic ester **73**[64] was allowed to react with the cuprate reagent **61**. Glc analysis of the crude product showed that it consisted of a 9:1 mixture of compounds **75** and **95**, respectively. Flash chromatography (3:97 Et_2O - petroleum ether; 30 g of silica gel) of the crude mixture, followed by distillation of the oil thus obtained (130-135°C/2.0 Torr), gave 72 mg (55%) of the ester **75**, a colourless oil which exhibited ir (neat): 1703, 1608, 1198, 1040,775 cm^{-1}; ^1H nmr (300 MHz) δ: 0.2 (s, 9H, -SnMe3, $^2J_{Sn-H}$ = 56 Hz), 1.29 (t, 3H, -OCH_2CH_3, J = 8 Hz), 3.40 (s, 3H, -OMe), 4.22 (q, 2H, -OCH_2CH_3, J = 8 Hz), 4.39 (d, 2H, -OCH_2-, J = 3 Hz, $^3J_{Sn-H}$ = 30 Hz), 4.69 (s, 2H, -OCH_2O-), 6.69 (t, 1H, vinyl H, J = 3 Hz,

$^3J_{Sn-H}$ = 108 Hz). *Exact Mass* calcd. for $C_{10}H_{19}O_4Sn$ (M^+-Me): 323.0305; found: 323.0298.

General Procedure C. Reaction of the cuprate reagent **61** with the α,β-acetylenic ester **70**, and trapping of the reaction intermediate with alkylating agents.

To a cold (-78°C), stirred solution of the cuprate reagent **61** (0.5 mmol) in 10 mL of dry THF (argon atmosphere) was slowly added a solution of the α,β-acetylenic ester **70** (81 mg, 0.33 mmol) in 0.5 mL of dry THF. After the mixture had been stirred at -78°C for 1 h and at -20°C for 30 min, HMPA (3.3 mmol) and the appropriate alkylating agent (excess) were added successively. The solution was stirred at -20°C for 30 min and at room temperature (0-1 h). Saturated aqueous NH_4Cl-NH_4OH (pH 8) (10 mL) and Et_2O (10 mL) were added and the vigorously stirred mixture was exposed to air. The phases were separated and the deep blue aqueous phase was extracted with Et_2O (4 x 10 mL). The combined organic extracts were washed with saturated aqueous $CuSO_4$ (3 x 10 mL) and brine (2 x 10 mL) and were then dried ($MgSO_4$) and concentrated. The crude product thus obtained was purified by chromatography, followed by distillation.

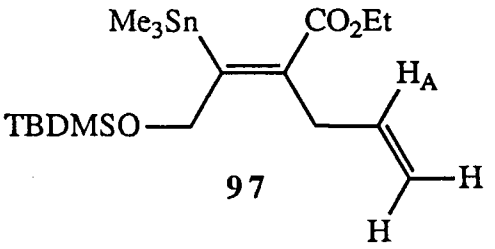
Preparation of ethyl (*Z*)-4-*tert*-butyldimethylsiloxy-2-methyl-3-trimethylstannyl-2-butenoate (**96**).



96

Following general procedure C, the α,β-acetylenic ester **70** (81 mg, 0.33 mmol) was allowed to react with the cuprate reagent **61**. After addition of HMPA (3.3 mmol) and MeI (8 mmol) the mixture was stirred at -20°C for 30 min and at room temperature for 1 h. Flash chromatography (3:97 Et_2O - petroleum ether; 30 g of silica gel) of the crude product, followed by distillation of the oil thus obtained (130-135°C/2.0 Torr), gave 91 mg (65%) of the ester **96**, a colourless oil which exhibited ir (neat): 1702, 1599, 1176, 838, 776 cm^{-1}; ^1H nmr (300 MHz) δ: 0.04 (s, 6H, -Si$\underline{Me_2}$), 0.11 (s, 9H, -Sn$\underline{Me_3}$, $^2J_{Sn-H}$ = 55 Hz), 0.87 (s, 9H, -Si$\underline{Bu^t}$), 1.28 (t, 3H, -OCH$_2$C$\underline{H_3}$, J = 7 Hz), 1.93 (s, 3H, vinyl Me, $^4J_{Sn-H}$ = 7.1 Hz), 4.17 (q, 2H, -OC$\underline{H_2}$CH$_3$, J = 7 Hz), 4.40 (s, 2H, -SiOC$\underline{H_2}$-, $^3J_{Sn-H}$ = 48 Hz). In nOe difference experiments, irradiation at δ 1.93 (vinyl Me) caused signal enhancement at δ 4.40 (-SiOC$\underline{H_2}$-), while irradiation at δ 4.40 (-SiOC$\underline{H_2}$-) caused signal enhancement at δ 1.93 (vinyl Me) and δ 0.11 (-SnMe$_3$); ^{13}C nmr (75.4 MHz) δ: -5.99, -5.19, 14.26, 14.60, 18.28, 25.95, 61.04, 64.26, 134.53, 163.06, 169.47. *Exact Mass* calcd. for $C_{15}H_{31}O_3SiSn$ (M^+-Me): 407.1072; found: 407.1064.

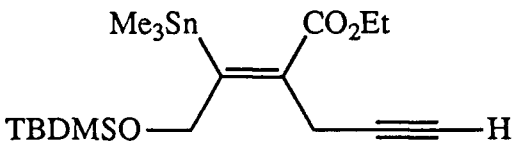
Preparation of ethyl (*Z*)-4-*tert*-butyldimethylsiloxy-2-(2-propenyl)-3-trimethylstannyl-2-butenoate (97).



97

Following general procedure C, the α,β-acetylenic ester **70** (81 mg, 0.33 mmol) was allowed to react with the cuprate reagent **61**. After addition of HMPA (3.3 mmol) and 3-iodopropene (5.5 mmol) the mixture was stirred at -20°C for 30 min. Flash chromatography (3:97 Et_2O - petroleum ether; 30 g of silica gel) of the crude product, followed by distillation of the oil thus obtained (115-120°C/2.0 Torr), gave 91 mg (60%) of the ester **97**, a colourless oil which exhibited ir (neat): 3080, 1703, 1639, 1154, 1073, 776 cm^{-1}; ^1H nmr (300 MHz) δ: 0.03 (s, 6H, -Si<u>Me</u>2), 0.13 (s, 9H, -Sn<u>Me</u>3, $^2J_{Sn-H}$ = 54 Hz), 0.86 (s, 9H, -Si<u>Bu</u>^{t}), 1.26 (t, 3H, -$OCH_2C\underline{H}_3$, J = 8 Hz), 3.14 (m, 2H, bis-allylic CH_2), 4.16 (q, 2H, -$OC\underline{H}_2CH_3$ J = 8 Hz), 4.39 (s, 2H, -$SiOC\underline{H}_2$-, $^3J_{Sn-H}$ = 49 Hz), 4.93 (m, 1H), 4.98 (m, 1H), 5.77 (m, 1H, $\underline{H}_A$). In nOe difference experiments, irradiation of the signal at δ 3.14 (bis-allylic CH_2) caused signal enhancement at δ 4.39 (-$SiOC\underline{H}_2$-) and δ 5.77 ($\underline{H}_A$), while irradiation of the signal at δ 4.39 (-$SiOC\underline{H}_2$-) caused signal enhancement at δ 3.14 (bis-allylic CH_2), and δ 0.13 (-Sn<u>Me</u>3); ^{13}C nmr (75.4 MHz) δ: -5.93, -5.21, 14.21, 18.27, 25.94, 32.91, 61.04, 64.11, 115.13, 135.72, 136.12, 164.93, 168.92. *Exact Mass* calcd. for $C_{17}H_{33}O_3SiSn$ (M^+-Me): 433.1221; found: 433.1216.

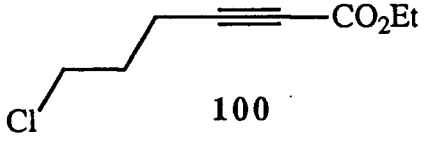
<u>Preparation of ethyl (Z)-4-*tert*-butyldimethylsiloxy-2-(2-propynyl)-3-trimethylstannyl-2-butenoate (98).</u>



98

Following a procedure similar to general procedure C, the α,β-acetylenic ester **70** (81 mg. 0.33 mmol) was allowed to react with the cuprate reagent **61** for 2 h at -78°C. HMPA (3.3 mmol) and 3-bromopropyne (1.67 mmol) were added successively and the mixture was stirred at -78°C for 1 h and at -20°C for 1 h. The crude product consisted of a 3:1 mixture of compound **98** (glc analysis) and the corresponding protonation products **72** and **94**. Flash chromatography (3:97 Et_2O - petroleum ether; 30 g of silica gel), followed by distillation of the oil thus obtained (140-145°C/2.0 Torr), gave 59 mg (40%) of compound **98**, a colourless oil which exhibited ir (neat): 3312, 2121, 1704, 1599, 1206, 1043, 839, 779 cm^{-1}; ^1H nmr (300 MHz) δ: 0.06 (s, 6H, -SiMe2), 0.15 (s, 9H, -SnMe3, $^2J_{Sn-H}$ = 56 Hz), 0.87 (s, 9H, -SiBu^t), 1.30 (t, 3H, $-OCH_2CH_3$, J = 7 Hz), 1.94 (t, 1H, acetylenic H, J = 2.8 Hz), 3.31 (d, 2H, allylic-propargylic CH_2, J = 2.8 Hz), 4.22 (q, 2H, $-OCH_2CH_3$, J = 7 Hz), 4.49 (s, 2H, $-SiOCH_2-$, $^3J_{Sn-H}$ = 44 Hz). In nOe difference experiments, irradiation of the signal at δ 4.49 ($-SiOCH_2-$) caused signal enhancement at δ 3.31 (allylic-propargylic CH_2) and δ 0.15 (-SnMe3), while irradiation of the signal at δ 3.31 (allylic-propargylic CH_2) caused signal enhancement at δ 4.49 ($-SiOCH_2-$). *Exact Mass* calcd. for $C_{17}H_{31}O_3SiSn$ (M^+-Me): 431.1064; found: 431.1059.

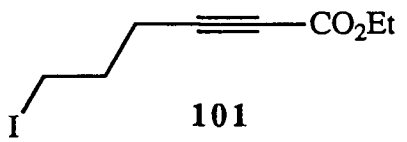
Preparation of ethyl 6-chloro-2-hexynoate (100).



100

To a cold (-78°C), stirred solution of 5-chloro-1-pentyne (2 g, 19.5 mmol) in 100 mL of dry THF (argon atmosphere) was added a solution of MeLi (19.5 mmol) in Et_2O. After the mixture had been stirred at -78°C for 10 min and at -20°C for 45 min, EtOCOCl (3.15 g, 29 mmol) was added and stirring was continued at -20°C for 1 h and at room temperature for 1 h. Saturated aqueous $NaHCO_3$ (30 mL) and Et_2O (50 mL) were added and the phases were separated. The aqueous phase was extracted with Et_2O (2 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Distillation (85-90°C/2.0 Torr) of the crude product gave 3.0 g (88%) of the ester **100** , a colourless oil which exhibited ir (neat): 2243, 1717, 1447, 1084 cm^{-1}; ^1H nmr (300 MHz) δ: 1.26 (t, 3H, $-OCH_2C\underline{H}_3$, J = 8 Hz), 2.00 (quintet, 2H, $-CH_2C\underline{H}_2CH_2$, J = 7 Hz), 2.52 (t, 2H, $-C\underline{H}_2CH_2CH_2Cl$, J = 7 Hz), 3.64 (t, 2H, $-CH_2CH_2C\underline{H}_2Cl$, J = 7 Hz), 4.18 (q, 2H, $-OC\underline{H}_2CH_3$, J = 8 Hz). *Exact Mass* calcd. for $C_8H_{11}{}^{35}ClO_2$ (M^+): 174.0448; found: 174.0456.

Preparation of ethyl 6-iodo-2-hexynoate (**101**).

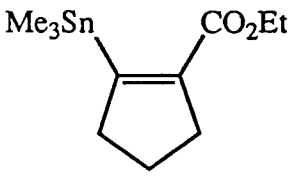


101

To a solution of NaI (17.2 g, 115 mmol) in dry acetone (150 mL) (argon atmosphere) was added a solution of the chloro ester **100** (2 g, 11.5 mmol) in 10 ml of dry acetone, and the mixture was refluxed overnight. Most of the solvent was removed and water (50 mL) and Et_2O (50 mL) were added to the residue. The phases were separated and the aqueous phase was extracted with Et_2O (2 x 20 mL). The combined extracts were dried ($MgSO_4$) and

concentrated. Distillation (100-110°C/2.0 Torr) of the crude product gave 2.62 g (86%) of the iodo ester **101**, a colourless oil which exhibited ir (neat): 2237, 1703, 1273, 1078 cm^{-1}; ^1H nmr (300 MHz) δ: 1.26 (t, 3H, $-OCH_2C\underline{H}_3$, J = 8 Hz), 2.02 (quintet, 2H, $-CH_2C\underline{H}_2CH_2I$, J = 8 Hz), 2.45 (t, 2H, $-C\underline{H}_2CH_2CH_2I$, J = 8 Hz), 3.24 (t, 2H, $-CH_2CH_2C\underline{H}_2I$, J = 8 Hz), 4.17 (q, 2H, $-OC\underline{H}_2CH_3$, J = 8 Hz). *Exact Mass* calcd. for $C_8H_{11}IO_2$ (M^+): 265.9804; found: 265.9815.

Preparation of ethyl 2-trimethylstannyl-1-cyclopentenecarboxylate (**102**).



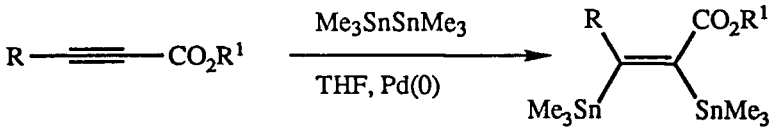
102

Following a procedure very similar to general procedure B, the iodo ester **101** (102 mg, 0.38 mmol) was allowed to react with the cuprate reagent **61** for 2 h at -78°C and 1 h at -48°C. Flash chromatography (3:97 Et_2O - petroleum ether; 30 g of silica gel) of the crude product, followed by distillation of the oil thus obtained (110-115°C/2.0 Torr), gave 73 mg (62%) of the ester **102**, a colourless oil which exhibited ir (neat): 1699, 1592, 1187, 768 cm^{-1}; ^1H nmr (400 MHz) δ: 0.17 (s, 9H, $-Sn\underline{Me}_3$, $^2J_{Sn-H}$ = 50 Hz), 1.27 (t, 3H, $-OCH_2C\underline{H}_3$, J = 6 Hz), 1.90 (m, 2H, $-CH_2C\underline{H}_2CH_2$), 2.49 (br t, 4H, both allylic CH_2), 4.18 (q, 2H, $-OC\underline{H}_2CH_3$, J = 6 Hz). *Exact Mass* calcd. for $C_{10}H_{17}O_2Sn$ (M^+-Me): 289.0250; found: 289.0252.

PART 2. **The preparation of (Z)-β-trimethylstannyl α,β-unsaturated aldehydes and ketones via the Pd(0)-catalyzed reaction of hexamethylditin with α,β-acetylenic aldehydes and ketones. The preparation and synthetic uses of (Z)-4-(trimethylstannyl)-1,3-butadienes.**

I. Introduction

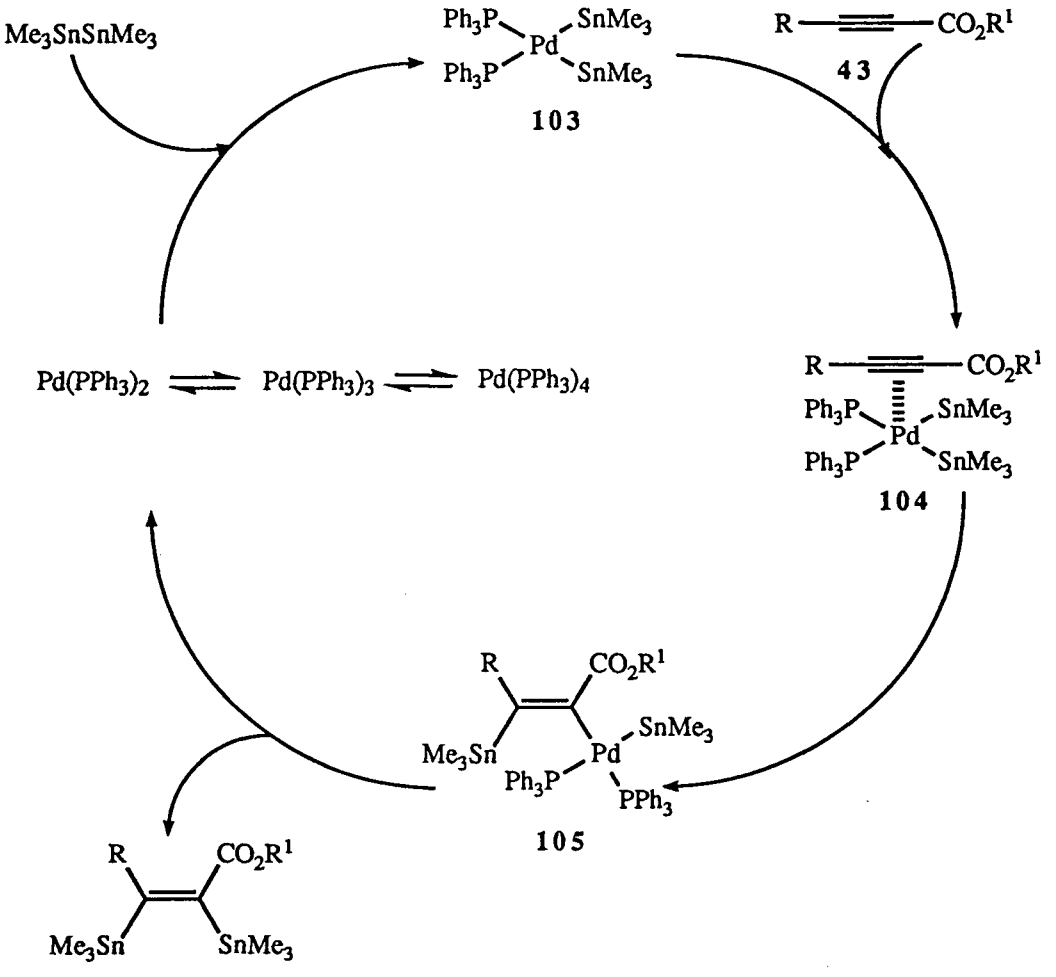
Recently, it was shown[37] that α,β-acetylenic esters of general structure **43** react with equimolar amounts of hexamethylditin (THF, room temperature or reflux) in the presence of a Pd(0) catalyst to give alkyl (Z)-2,3-bis(trimethylstannyl)-2-alkenoates of general structure **54** (equation 11). These bismetallation reactions are both efficient and stereoselective, and a wide range of functional groups in R, including halides, ethers, and carbon-carbon double bonds, are compatible with the reaction conditions.



43 **54** (11)

A possible pathway for the formation of compounds **54** in these reactions is shown in Scheme 17. It is known that, in solution, $Pd(PPh_3)_4$ is in equilibrium[79,80] with the co-ordinatively unsaturated species $Pd(PPh_3)_3$ and $Pd(PPh_3)_2$. It is generally accepted that the active catalyst in Pd(0)-catalyzed cross coupling reactions is $Pd(PPh_3)_2$. Oxidative addition of the tin-tin bond of hexamethylditin to $Pd(PPh_3)_2$ would result in an intermediate square planar bis(trimethylstannyl) Pd(II) species **103**. Co-ordination of the acetylenic ester **43** with **103** could give the intermediate Pd(II) complex **104**, which could then lead, via stannylpalladation of the carbon-carbon triple bond, to the intermediate **105**. If the

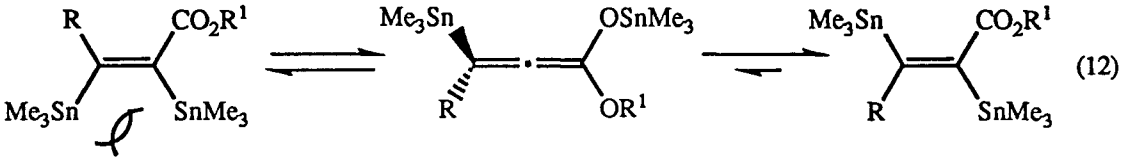
intermediate **105** has *cis* geometry (as depicted in Scheme 17), reductive elimination[81] could occur to give the alkyl (Z)-2,3-bis(trimethylstannyl)-2-alkenoate **54**, with concomitant regeneration of the Pd(0) catalyst. If, however, the complex **105** has *trans* geometry, then a *trans* to *cis* isomerization is required before reductive elimination can take place.[81,82]



Scheme 17

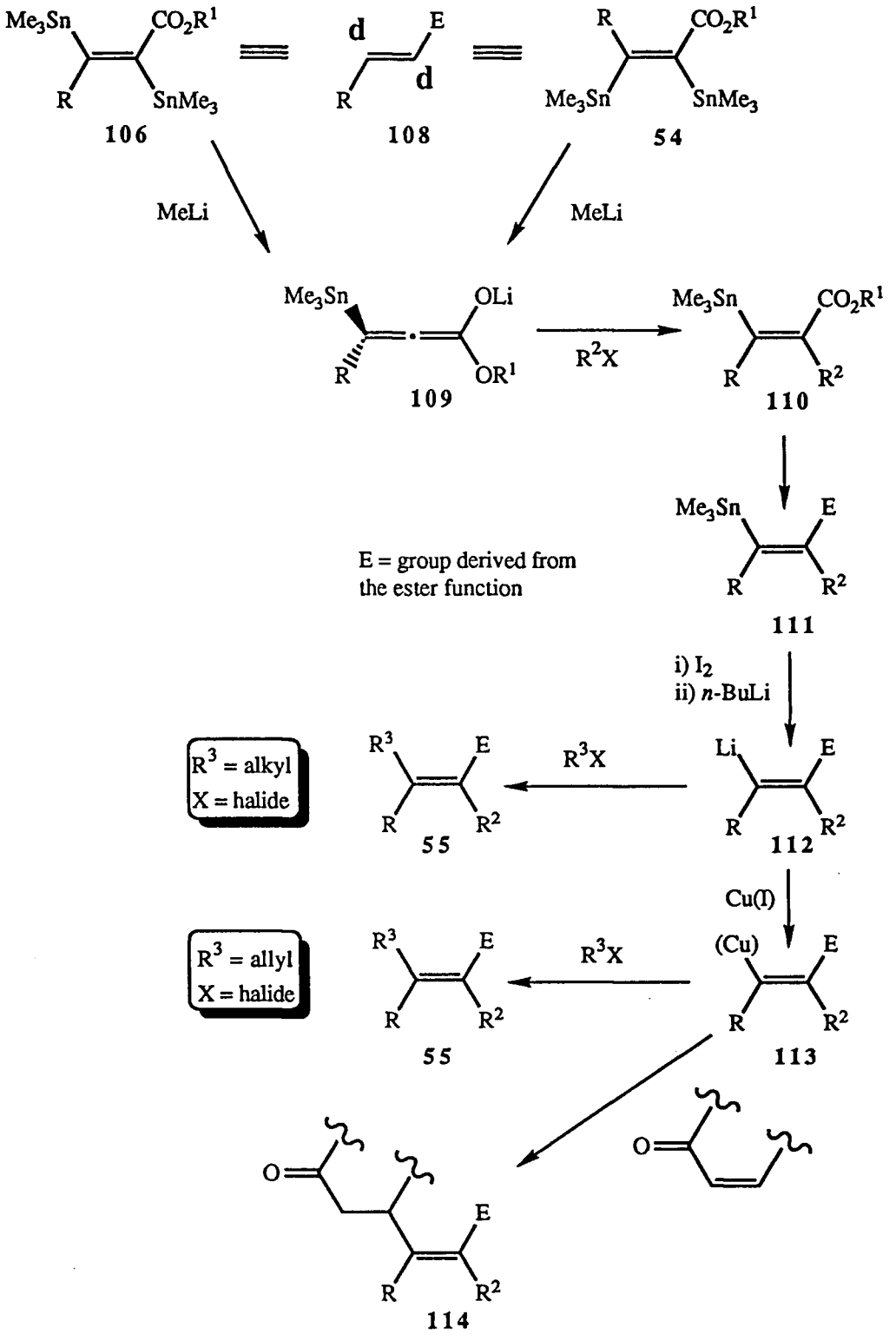
Although there is as yet no direct evidence to support the participation of this catalytic cycle in these reactions, it is appropriate to consider this proposed pathway as a working model to account for the formation of the observed products **54**. Other workers have used similar arguments to explain the Pd(0)-catalyzed reactions of disilanes with acetylenic compounds.[83]

Interestingly, it was found that the alkyl (Z)-2,3-bis(trimethylstannyl)-2-alkenoates **54** may be thermally rearranged (at 75-95°C) to the corresponding (*E*)-isomers **106** in a clean, efficient manner.[37] A possible route by which this isomerization could occur is shown in equation 12. Thus, it is proposed that at elevated temperatures the compounds **54** are in equilibrium with their (*E*)-isomers **106** via trimethylstannyl allenoates of general structure **107**. The equilibrium position apparently lies far to the right, favoring the (*E*)-isomers **106**, due primarily to steric interactions between the trimethylstannyl groups in compounds of structure **54**.



54 **107** **106** (12)

The synthetic utility of alkyl 2,3-bis(trimethylstannyl)-2-alkenoates was described very briefly in the general introduction of this thesis, where it was stated that they serve as precursors to stereodefined tetrasubstituted alkenes.[23] In fact, both compounds **54** and **106** are synthetic equivalents of the *trans* (d, d) synthon of general structure **108** (Scheme 18). Thus, reaction of either compounds **54** or **106** with MeLi results in tin-lithium exchange at the trimethylstannyl group adjacent to the ester function to give, presumably, lithium allenoate intermediates of general structure **109**. Alkylation of the allenoates **109** occurs from the least hindered face, that is, opposite the bulky trimethylstannyl group, to give the (*Z*)-β-trimethylstannyl α,β-unsaturated esters of general structure **110** efficiently and stereoselectively. It is important to emphasize that since the isomeric alkyl 2,3-bis(trimethylstannyl)-2-alkenoates (**54** and **106**) give identical products in these transmetallation/alkylation sequences, this methodology can only be used for the preparation of compounds of structure **110**. The isomeric (*E*)-β-trimethylstannyl α,β-unsaturated esters cannot be prepared in this manner.


Me3Sn
CO2R1
R
SnMe3
106
d
E
d
108
R
CO2R1
Me3Sn
SnMe3
54
MeLi
MeLi
Me3Sn
OLi
R
OR1
109
R2X
Me3Sn
CO2R1
R
R2
110
Me3Sn
E
R
R2
111
E = group derived from
the ester function
i) I2
ii) n-BuLi
R3 = alkyl
X = halide
R3
E
R
R2
55
R3X
Li
E
R
R2
112
Cu(I)
R3 = allyl
X = halide
R3
E
R
R2
55
R3X
(Cu)
E
R
R2
113
O
E
R
R2
114
O

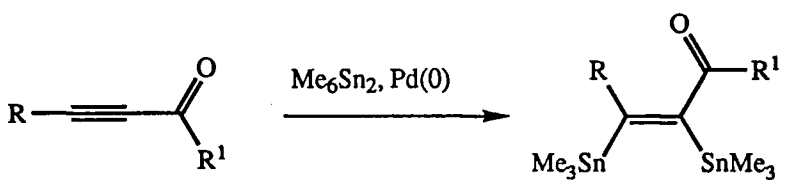
Scheme 18

After conversion of the ester function of compounds **110** into a group that is stable to alkyllithium reagents (e.g. alkoxymethyl), the resulting alkenylstannanes of general structure **111** are readily converted, stereospecifically, into alkenyllithium species of general structure **112**. These may be alkylated directly to give stereodefined tetrasubstituted alkenes of general structure **55** (R^3=alkyl). Alternatively, they may be converted into the corresponding alkenylcopper species **113**, which react with allylic halides or with α,β-unsaturated ketones to give stereodefined tetrasubstituted alkenes of general structures **55** (R^3=allyl) or **114**, respectively.

II. Proposals

Other Pd(0)-catalyzed bis-stannylation reactions similar to those described above have been reported using either α,β-acetylenic amides[37] or terminal acetylenes[38] as starting materials. However, Mitchell *et al.*[38] have reported that this methodology cannot be applied to internal unactivated acetylenes. We were, therefore, interested in extending the bis-stannylation methodology to other types of acetylenic compounds, especially to activated substrates such as α,β-acetylenic aldehydes and ketones.

Thus, the immediate aims of this project were to examine the reactions of acetylenic aldehydes and ketones of general structure **115** with hexamethylditin under Pd(0) catalysis. The expected products in these reactions were bis(trimethylstannyl) compounds of general structure **116** (equation 13), which were considered to be potentially useful precursors to stereodefined substituted alkenes.



(13)

115

115A R^1=H
115B R^1=Alkyl

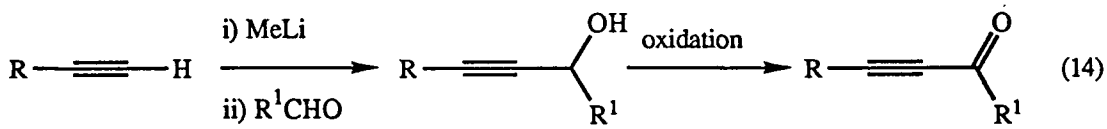
116

116A R^1=H
116B R^1=Alkyl

III. Results and discussion

A series of diversely functionalized α,β-acetylenic aldehydes of general structure **115A** and α,β-acetylenic ketones of general structure **115B** were required for this study. Two methods were used for the preparation of these materials.

A) The first method involved the reaction of lithium acetylides (derived from the appropriate terminal acetylenes **1**) with aldehydes, followed by oxidation of the resulting propargylic alcohols of general structure **117** (equation 14).

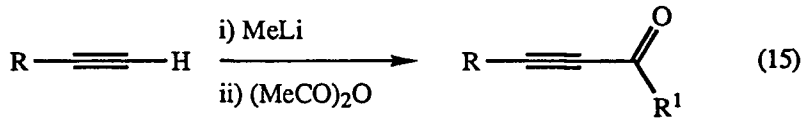


(14)

1 **117** **115**

117A R^1=H **115A** R^1=H
117B R^1=Alkyl **115B** R^1=Alkyl

B) The second method, leading specifically to acetylenic methyl ketones **115B** (R^1=Me), involved the reaction of lithium acetylides with acetic anhydride (equation 15).

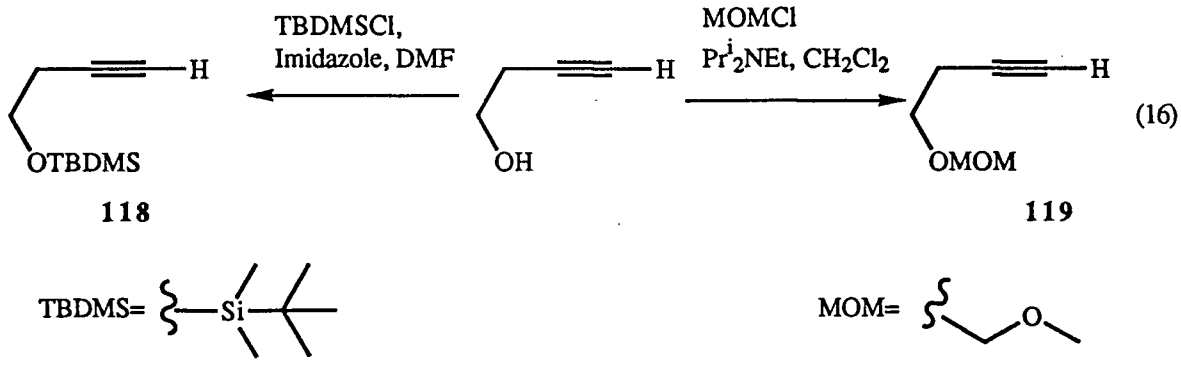


(15)

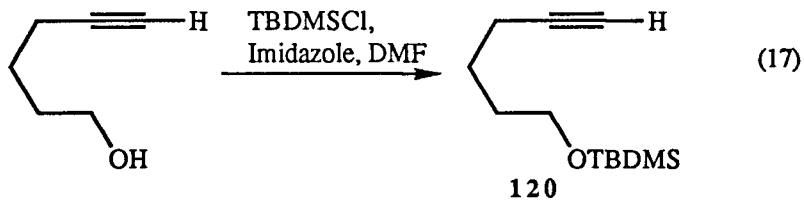
1 **115B** (R^1 = Me)

3.1. The preparation of terminal acetylenes **1**

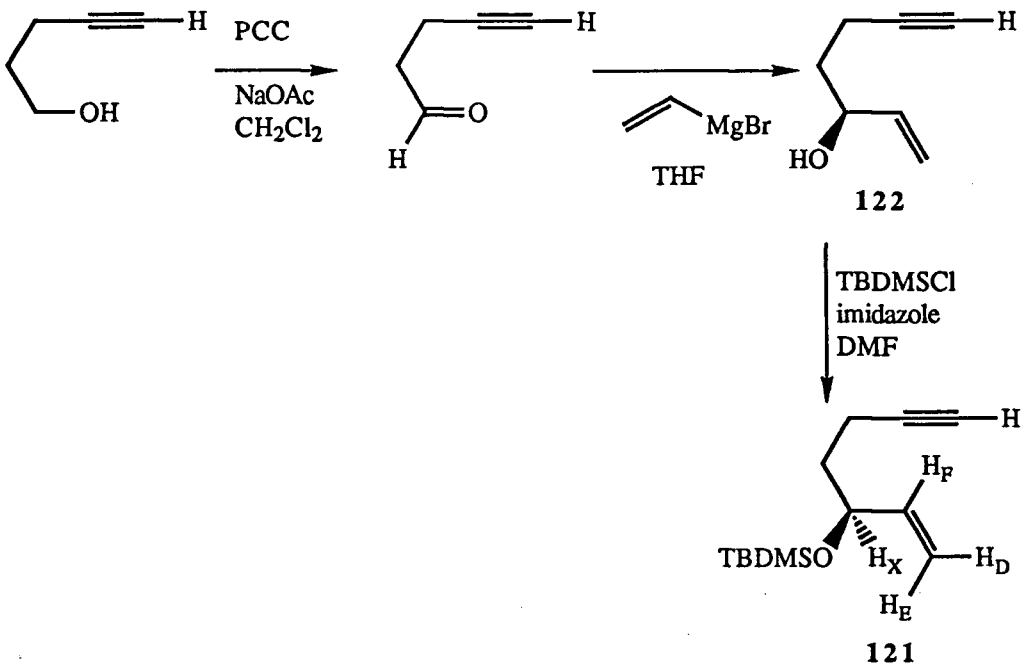
The terminal acetylenes 4-*tert*-butyldimethylsiloxy-1-butyne (**118**) and 4-methoxymethoxy-1-butyne (**119**), were prepared from commercially available 3-butyn-1-ol using standard literature methods (equation 16).[84,85]



The terminal acetylene 6-*tert*-butyldimethylsiloxy-1-hexyne (**120**) was prepared from commercially available 5-hexyn-1-ol via a procedure identical with that used for the preparation of **118** (equation 17).



The terminal acetylene **121** was prepared in three steps from 4-pentyn-1-ol, as shown in Scheme 19. Thus, 4-pentyn-1-ol (in dry CH_2Cl_2, argon atmosphere) was allowed to react with pyridinium chlorochromate[86] (1.5 equivalents) and NaOAc (0.3 equivalents) for two hours at room temperature. After appropriate workup, the solvent was removed by atmospheric pressure distillation to give a crude, volatile oil containing 4-pentynal. This oil was dissolved in dry THF and was then treated with excess vinyl magnesium bromide (-78°C, then room temperature). After appropriate workup, the solvent was removed by atmospheric pressure distillation to give a crude, volatile oil containing the alcohol **122**. This oil was dissolved in dry DMF and the resulting solution was treated with TBDMSCl and imidazole, using a procedure similar to that reported in the literature.[84] After workup, the crude reaction product was purified by flash chromatography and distillation to give the

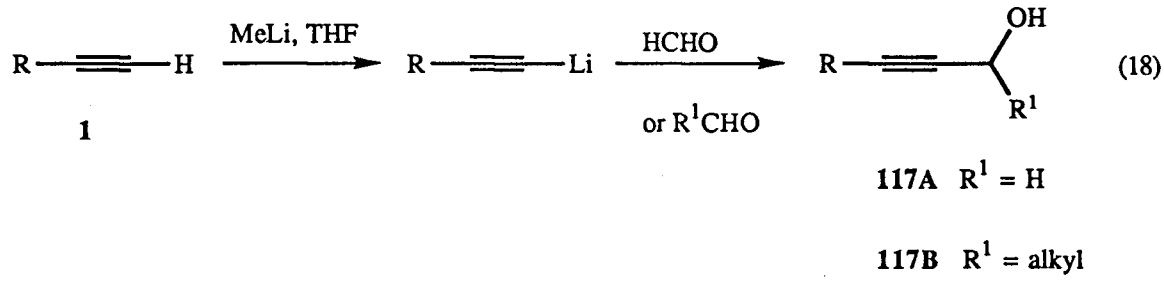


Scheme 19

terminal acetylene **121** in an overall yield of 31%. This material exhibited spectral data which were fully consistent with the proposed structure. For example, the infrared spectrum showed absorbances at 3314 cm^{-1} and 2121 cm^{-1} attributable to the carbon-hydrogen and carbon-carbon stretching frequencies, respectively, of the terminal acetylene function. The ^1H nmr spectrum of **121** showed a 6-proton singlet at δ 0.02 and a 9-proton singlet at δ 0.89 due to the TBDMS group, as well a 1-proton triplet at δ 1.92 (J = 4 Hz) due to the acetylenic proton. Also, a 1-proton doublet of doublet of doublets at δ 5.78 (J = 16 Hz, J = 10 Hz, J = 6 Hz), a 1-proton doublet of doublet of doublets at δ 5.17 (J = 16 Hz, J = 2 Hz, J = 2 Hz), a 1-proton doublet of doublet of doublets at δ 5.05 (J = 10 Hz, J = 2 Hz, J = 2 Hz), and a 1-proton multiplet at δ 4.22 were assigned to H_F, H_E, H_D, and H_X, respectively.

3.2. The preparation of propargylic alcohols **117**

Lithium acetylides (derived from terminal acetylenes **1**) react readily with formaldehyde[87a] to give primary propargyl alcohols **117A**, and with other aldehydes to give secondary propargyl alcohols **117B** (equation 18).[87b]



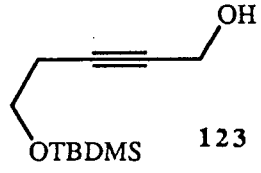
1

117A $R^1 = H$

117B R^1 = alkyl

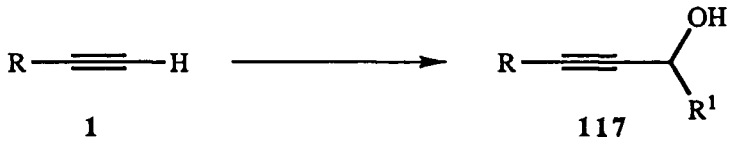
In a typical procedure, ethereal MeLi (1 equivalents) was added to a solution of the terminal acetylene **1** in dry THF at -78°C and the resulting mixture was stirred at -78°C for 10 min and at -20°C for 1 hour. The appropriate aldehyde (excess) was added and the reaction mixture was allowed to warm to room temperature. After appropriate workup, the crude product was purified by flash chromatography, followed by distillation, to give the pure propargyl alchohol **117**.

A series of propargyl alcohols **117** were prepared in this manner. The conditions used in these reactions and the results are summarized in Table 4. A few points should be noted regarding the data in Table 4. Firstly, the reactions were generally very clean. In most cases, tlc analysis of the crude reaction product showed the presence of the desired product **117** and very minor amounts of other materials. Secondly, the products obtained in these reactions exhibited spectral data which were in full accord with the assigned structures. For example, the infrared spectrum of compound **123** showed a strong broad absorption at 3394 cm^{-1} attributable to the oxygen-hydrogen stretching frequency of the hydroxyl group, as well as a weak absorption at 2227 cm^{-1} attributable to the carbon-carbon stretching frequency of the internal acetylene function. The ^1H nmr spectrum of **123** showed a 1-proton broad multiplet at δ 1.8-1.95 (-OH) which disappeared upon addition of D_2O, and



123

Table 4. The preparation of propargylic alcohols **117**



1 **117**

Entry	**1**	R	R^1	**117**	Conditions[1]	Yield[2] %
1	**118**	$CH_2CH_2OTBDMS$	H	**123**	A	74
2	**120**	$(CH_2)_4OTBDMS$	H	**124**	A	81
3	**119**	CH_2CH_2OMOM	H	**125**	A	80
4	**118**	$CH_2CH_2OTBDMS$	Me	**126**	B	92
5	**120**	$(CH_2)_4OTBDMS$	Me	**127**	B	90
6		$(CH_2)_3CCH$	Me	**128**	C	60
7		$(CH_2)_3Cl$	Me	**129**	B	85
8		Bu^t	C_6H_{13}	**130**	D	96
9	**118**	$CH_2CH_2OTBDMS$	Pr^i	**131**	E	85

[1]Conditions. A) i) MeLi (1 equiv.), THF, -78°C, 10 min; -20°C, 1 h: ii) HCHO (4 equiv.), warmed to room temp; room temp, 30 min.

B) i) as A: ii) cooled to -78°C, CH_3CHO added (2 equiv.), -78°C, 10 min; warmed to room temp.

C) as B except 5 equiv. of acetaldehyde was used.

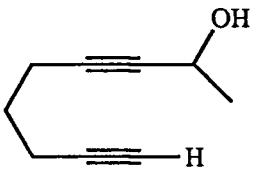
D) i) as A: ii) cooled to -78°C, heptanal (1.5 equiv.) added, -78°C, 10 min; warmed to room temp.

E) i) as A: ii) cooled to -78°C, 2-methylpropanal added (1.5 equiv.), -78°C, 10 min; warmed to room temp.

[2] Isolated yield of distilled product.

a 2-proton broad singlet at δ 4.24 (-CH_2OH) which sharpened to a triplet (J = 2 Hz) upon addition of D_2O.

Regarding the reaction of the lithium acetylide of 1, 6-heptadiyne with acetaldehyde (entry 6), tlc analysis of the crude reaction product showed the presence of two compounds. These compounds were easily separated by flash chromatography. The less polar (and major) product was assigned the structure **128**, on the basis of its spectral data. In particular, the infrared spectrum showed an absorption at 2247 cm^{-1} attributable to the carbon-carbon stretching frequency of the internal acetylene function, and an absorption at



128

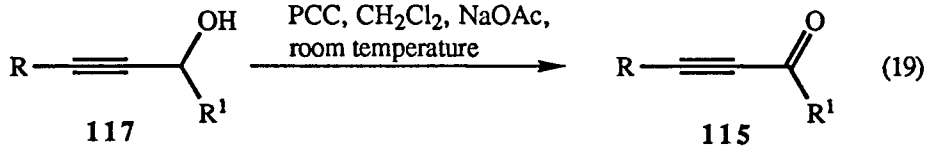
3301 cm^{-1}, attributable to the oxygen-hydrogen stretching frequency of the hydroxyl group. Also present were absorptions at 2118 cm^{-1} and 3350 cm^{-1} attributable to the carbon-carbon and carbon-hydrogen stretching frequencies, respectively, of the terminal acetylene function. The ^1H nmr spectrum of this compound showed a 1-proton triplet at δ 1.95 (J = 2.5 Hz) due to the acetylenic proton. The more polar (and minor) compound was not characterized but it was assumed to be the diol arising from reaction at both terminal acetylene functions of the starting material.

3.3. The oxidation of propargylic alcohols **117** to α,β-acetylenic aldehydes and ketones **115**

Pyridinium chlorochromate (PCC), an oxidizing reagent developed by Corey and Suggs,[86] was chosen for our initial studies. Although pyridinium chlorochromate is slightly

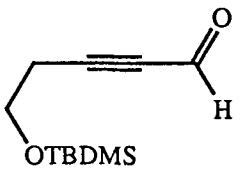
acidic, it may be used as a reagent for the oxidation of alcohols containing acid sensitive functional groups (such as TBDMS ethers) to the corresponding aldehydes or ketones, providing that the reactions are buffered by NaOAc.[86,88]

It was found that PCC reacts with the propargylic alchohols **117** (CH_2Cl_2, room temperature) in the presence of NaOAc to give the corresponding α,β-acetylenic carbonyl compounds **115** in reasonable yield (equation 19).



117 **115** (19)

The conditions used in these reactions and the results are presented in Table 5. Several comments should be made regarding these data. Firstly, the crude reaction products were generally very clean (as judged by glc analysis). The pure compounds **115** were readily obtained by flash chromatography of the crude reaction products, followed by distillation. Secondly, the spectral data derived from the products obtained in these reactions were in full accord with the proposed structures. The spectral data exhibited by compound **133** are typical of those exhibited by the acetylenic aldehydes. The infrared spectrum of **133** showed an absorbance at 2740 cm^{-1} attributable to the carbon-hydrogen stretching frequency of the aldehyde function, as well as absorbances at 1673 cm^{-1} and 2207 cm^{-1} attributable to the carbon-oxygen and carbon-carbon stretching frequencies, respectively, of the conjugated acetylenic aldehyde function. The ^1H nmr spectrum of **133** showed a 1-proton singlet at δ 9.15 (-CHO).



133

Table 5. The oxidation of propargylic alcohols **117**

117 **115**

Entry	**117**	R	R^1	**115**	Conditions[1]	Yield[2] %
1	**123**	$CH_2CH_2OTBDMS$	H	**133**	A	72
2	**124**	$(CH_2)_4OTBDMS$	H	**134**	A	74
3	**125**	CH_2CH_2OMOM	H	**135**	A	57
4	**126**	$CH_2CH_2OTBDMS$	Me	**136**	B	74
5	**127**	$(CH_2)_4OTBDMS$	Me	**137**	B	76
6	**128**	$(CH_2)_3CCH$	Me	**138**	B	55
7	**129**	$(CH_2)_3Cl$	Me	**139**	B	74
8	**130**	Bu^t	C_6H_{13}	**140**	B	72
9	**131**	$CH_2CH_2OTBDMS$	Pr^i	**141**	B	81
10	**132**	Pr^i	Me	**142**	C	56

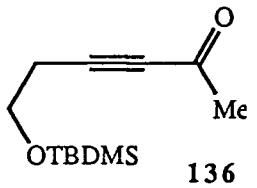
[1]Conditions. A) PCC (1.5 equiv.), NaOAc (0.3 equiv.), CH_2Cl_2, room temp, 2 h

B) PCC (2.5 equiv.), NaOAc (0.3 equiv.), CH_2Cl_2, room temp, 2.5 h

C) This compound was prepared from isopropyl acetylene without purification of the propargyl alcohol **132** formed in the first step. See text.

[2] Isolated yield of distilled product.

The spectral data exhibited by compound **136** are typical of those exhibited by the acetylenic ketones. The infrared spectrum of **136** showed strong absorbances at 1680 cm^{-1} and 2214 cm^{-1} attributable to the carbon-oxygen and carbon-carbon stretching frequencies, respectively, of the conjugated acetylenic ketone function. The ^{1}H nmr spectrum of **136** showed a 3-proton singlet at δ 2.30 (-C(O)C<u>H</u>3).

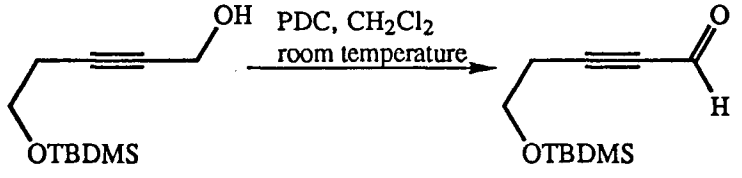


136

Finally, the preparation of compound **142** requires special mention, since a slightly different procedure was used in this case. Reaction of the lithium acetylide of isopropyl acetylene with acetaldehyde, in the usual manner, provided the propargyl alcohol **132**. Since this material was volatile, attempts were not made to remove all traces of solvent from it. Thus, after appropriate workup, most of the solvent was removed by atmospheric pressure distillation and the residual oil, containing **132**, was carried on to the next step. Oxidation of this material, using PCC, proceeded cleanly and efficiently to give the acetylenic ketone **142**. After appropriate workup, the solvent was removed by atmospheric pressure distillation to give a crude, volatile oil containing the product. This oil was distilled to give the pure compound **142** in an overall yield of 56%.

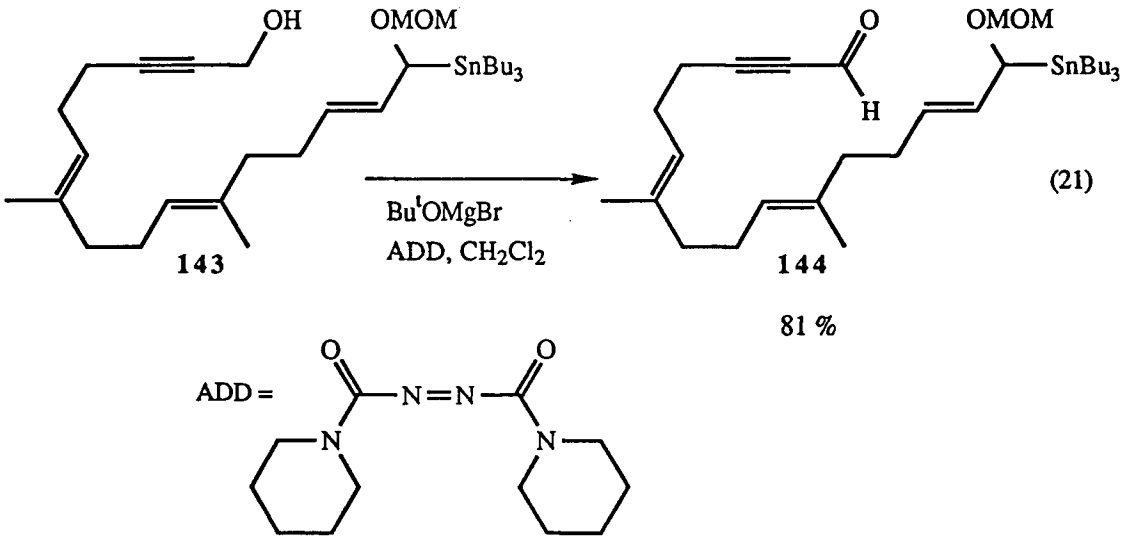
The data presented in Table 5 show that pyridinium chlorochromate is a suitable reagent for the oxidation of propargylic alcohols **117** to the corresponding acetylenic aldehydes and ketones **115**. The reagent is commercially available and inexpensive. Also, the reactions are convenient and fairly efficient, and the products are readily purified. Nevertheless, the decision was made to investigate some oxidation methods to determine whether better yields could be obtained for the conversion of propargylic alcohols **117** to the acetylenic carbonyl compounds **115**.

Pyridinium dichromate (PDC), an oxidizing reagent developed by Corey and Schmidt,[89] is known to oxidize alcohols to aldehydes or ketones efficiently and under neutral conditions. However, when the propargyl alcohol **123** was allowed to react with PDC according to the reported procedure,[89] only a 50 % yield of the acetylenic aldehyde **133** was obtained (equation 20).



123 50% **133** (20)

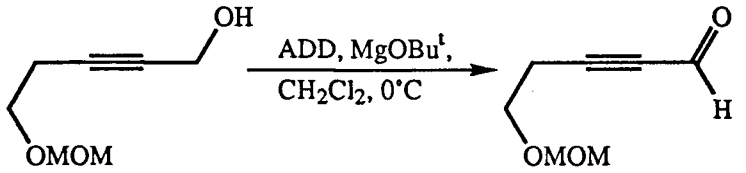
Marshall *et al.*[90] have recently reported that the propargylic alcohol **143** (equation 21) reacts with 1,1'-(azodicarbonyl)dipiperidine (ADD)[91] in the presence of *tert*-butoxymagnesium bromide to give the acetylenic aldehyde **144** in 81% yield. This aldehyde was a key intermediate in a cembranolide total synthesis.



143 **144** 81 % (21)

The propargyl alcohol **125** was readily oxidized to the acetylenic aldehyde **135** using a similar procedure (equation 22). Thus, a solution of the alcohol **125** in dry CH_2Cl_2 was

added to a solution of *tert*-butoxymagnesium bromide (1.5 equivalents) and ADD (1.5 equivalents) in dry CH_2Cl_2 at 0°C (argon atmosphere), and the resulting mixture was stirred



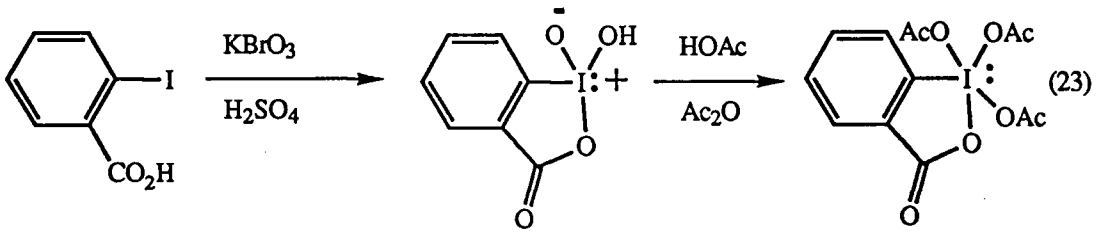
125 81% 135 (22)

for 15 min at this temperature. After workup, the crude reaction product was purified by flash chromatography, followed by distillation, to give the aldehyde **135** in 81% yield. This material was spectrally identical with the same substance prepared earlier (using PCC as oxidant). This oxidation method appears to be superior to that employing PCC, at least for the oxidation of alcohol **125** to the aldehyde **135** (81 % compared to 57% with PCC), but suffers from one major disadvantage. Commercially available ADD costs approximately 70 cents per mmol (compared to approximately 2 cents per mmol for PCC), which means that large scale oxidations can be very expensive. However, the cost of ADD is reduced significantly if it is prepared in the laboratory from piperidine and diethyl azodicarboxylate.[92]

The periodinane reagent **145**, developed by Dess and Martin,[93] has been used for the oxidation of highly functionalized and/or sensitive alcohols to the corresponding carbonyl compounds.[94] It was, therefore, expected that this reagent would be suitable for the oxidation of propargyl alcohols **117** to acetylenic aldehydes/ketones **115**.

The reagent **145** was prepared, via the reported procedure, in two steps from commercially available 2-iodobenzoic acid (equation 23). Thus, 2-iodobenzoic acid was allowed to react with acidic potassium perbromate to give the compound **146**, which was then treated with a mixture of hot (140°C) acetic anhydride and acetic acid to give **145**. The reagent **145** is a white, moisture sensitive solid and was found to contain traces of acetic acid

even after being stored under high vacuum for several days. Therefore, it was always prewashed with anhydrous ether (under an argon atmosphere) immediately prior to use.



146 145

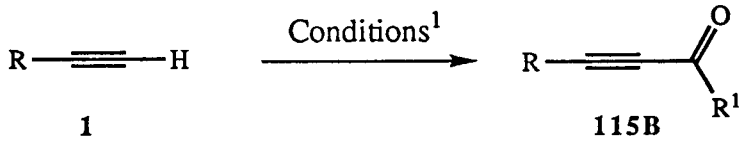
In a typical oxidation procedure, a solution of the substrate alcohol in dry CH_2Cl_2 was added to a solution/suspension of (prewashed) reagent **145** (1.3 equivalents) in dry CH_2Cl_2 at room temperature (argon atmosphere), and the resulting mixture was stirred for 15 minutes. After appropriate workup, the crude product was distilled to give the pure acetylenic carbonyl compound. In this manner, the alcohols **123** and **124** were oxidized to the aldehydes **133** and **134** in 88 and 86% yields, respectively. These materials were spectroscopically identical with the same materials prepared earlier, via PCC oxidation. This oxidation method appears to be superior to the PCC oxidation procedure in terms of yield, ease of workup, and purification of products.

3.4. The preparation of α,β-acetylenic methyl ketones **115B** (R^1=Me) via direct acylation of lithium acetylides.

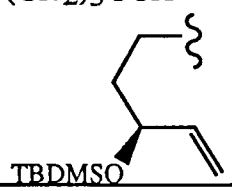
It was found that acetylenic methyl ketones may be prepared in reasonable yield via reaction of lithium acetylides (derived from the appropriate terminal acetylenes **1**) with acetic anhydride, using a procedure developed by Brandsma and coworkers.[95] Typically, an ethereal solution of the terminal acetylene **1** was allowed to react with MeLi (1 equivalents) for 10 min at -78°C and for 1 hour at -20°C. The ethereal solution of the lithium acetylide

thus obtained was added, via cannula, into a cold (-78°C) ethereal solution of acetic anhydride (2 equivalents) and the resulting mixture was stirred at -78°C for 10 min and then at -48°C for 30 min. After appropriate workup, the crude product was purified by flash chromatography, followed by distillation, to give the pure acetylenic methyl ketone **115B**. Several terminal acetylenes were converted into acetylenic methyl ketones in this manner and the results are summarized in Table 6.

Table 6. The preparation of α,β-acetylenic methyl ketones **115B** (R^1=Me).



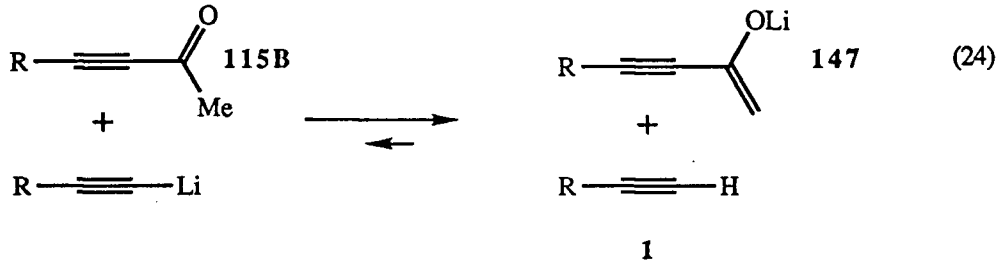
1 **115B**

Entry	**1**	R	**115B**	Yield[2] %
1	**118**	$CH_2CH_2OTBDMS$	**136**	50
2		$(CH_2)_3Cl$	**139**	54
3		$(CH_2)_3CCH$	**138**	50
4	**121**		**148**	63

[1]Conditions. i)MeLi (1 equiv.), Et_2O, -78°C, 10 min; 20°C, 1h: ii) Ac_2O (2 equiv.), Et_2O, -78°C, 10 min; -48°C, 30 min: iii) NH_4Cl-NH_4OH (pH 8).

[2] Isolated yield of distilled product.

A few comments should be made regarding these reactions. Firstly, in each case, it was shown (by glc analysis) that significant amounts of terminal acetylene were present after workup. Hence, it is concluded that the lithium acetylide reacts with the product acetylenic ketone **115B** (R^1=Me) in competition with the acylation reaction, to give the lithium enolate of general structure **147** and the starting terminal acetylene (equation 24). This type of proton exchange should be thermodynamically favorable since there is a reasonable difference in acidity between a methyl ketone function (pKa approximately 20) and a terminal acetylene function (pKa approximately 25). Upon workup, the enolate **147** is protonated, and the acetylenic ketone **115B** (R^1=Me) is obtained, along with unreacted terminal acetylene.



(24)

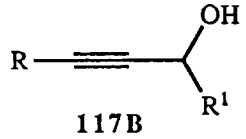
Secondly, when 1,6 heptadiyne was used as the starting material (entry 3), glc analysis of the crude reaction mixture showed the presence of the expected product **138** plus a small amount of a higher molecular weight material. This material was not characterized but was assumed to be the diacylated material, formed via reaction at both terminal acetylene functions of the starting material. Interestingly, the yield (50%) of the mono-acylated material **138** obtained in this reaction is better than that obtained via the two step procedure described earlier (33%).

Finally, the products obtained in these reactions were spectroscopically identical with the same materials prepared by the two step route outlined previously. As well, the acetylenic ketone **148**, prepared only via the present method, exhibited spectral data which were in full accord with the assigned structure. For example, the infrared spectrum of this material

showed absorbances at 2211 cm^{-1} and 1681 cm^{-1}, attributable to the carbon-carbon and carbon-oxygen stretching frequencies, respectively, of the conjugated acetylenic ketone function. The ^1H nmr spectrum of **148** showed a 3-proton singlet at δ 2.31(-C(O)C<u>H</u>3).

In summary, the synthesis of acetylenic aldehydes and ketones **115** is readily accomplished via a two step sequence involving the preparation and oxidation of propargyl alcohols **117**. In connection with this, PCC is an efficient, convenient oxidizing reagent, although superior yields of α,β-acetylenic aldehydes may be obtained using either ADD or the periodinane reagent **145** as oxidant.

The direct acylation of lithium acetylides with acetic anhydride, as described above, is a useful method for the preparation of α,β-acetylenic methyl ketones. However, although it is more convenient than the two step procedure involving the preparation and PCC oxidation of propargyl alcohols **117B** (R^1=Me), it is generally less efficient.

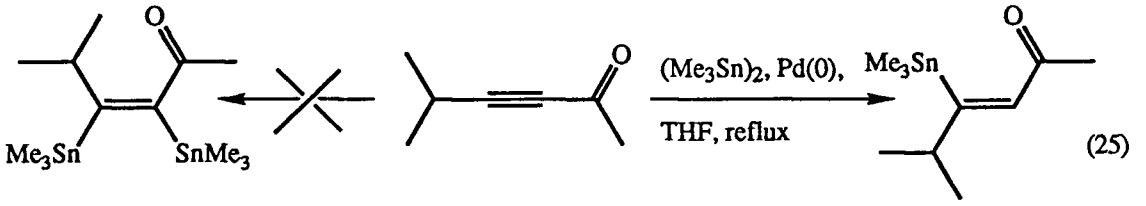


117B

3.5. <u>The Pd(0)-catalyzed reaction of α,β-acetylenic aldehydes and ketones with hexamethylditin.</u>[96]

With convenient, reliable procedures available for the preparation of functionalized acetylenic aldehydes and ketones **115**, it was now possible to examine in detail the reactions of these compounds with hexamethylditin under Pd(0) catalysis. The initial experiment was performed using the acetylenic ketone **142** as substrate. Thus, using a procedure similar to that reported previously in connection with the Pd(0)-catalyzed reaction of hexamethylditin with α,β-acetylenic esters,[37] Pd(PPh3)4 (5 mol %) was added to a stirred solution of the ketone **142** (1 equivalent) and hexamethylditin (1 equivalent) in dry THF under an argon

atmosphere. The concentration of **142** in THF was approximately 0.6 M. The resulting mixture was refluxed and the progress of the reaction was monitored periodically by tlc analysis. After 5 hours at reflux, tlc analysis of the reaction mixture showed that all of the acetylenic ketone **142** had been consumed. In fact, a major component was present which was less polar than the starting material (by tlc analysis), was uv active, and stained heavily with ammonium molybdate and with iodine. Also present were small amounts of hexamethylditin, triphenylphosphine, and minor amounts of some more polar components. Most of the solvent was removed and the residual dark brown oil was purified by flash chromatography and distillation, to give the pure major product. The infrared spectrum of this material indicated that it could be the expected bis(trimethylstannyl) adduct **149** (equation 25). For example, there were strong absorbances at 1682 cm^{-1} and 1568 cm^{-1} attributable to the carbon-oxygen and carbon-carbon stretching frequencies, respectively, of an α,β-unsaturated ketone function. Also present was an absorbance at 770 cm^{-1} attributable to the tin-methyl rocking vibration of a trimethylstannyl group. However, upon inspection of the ^1H nmr spectrum of this material it was immediately obvious that the product was not the expected bis(trimethylstannyl) adduct **149**, but was actually the (*Z*)-β-trimethylstannyl α,β-unsaturated ketone **150** (equation 25). The 300 MHz ^1H nmr spectrum for this



(25)

149 **142** **150**

compound is shown in Figure 1. This spectrum shows a 9-proton singlet at δ 0.09 ($^2J_{Sn-H}$ = 54 Hz) due to the trimethylstannyl group, as well as a 6-proton doublet at δ 1.03 (J = 6.5 Hz) and a 1-proton septet of doublets at δ 2.75 (J = 6.5 Hz, J = 1.5 Hz) due to the

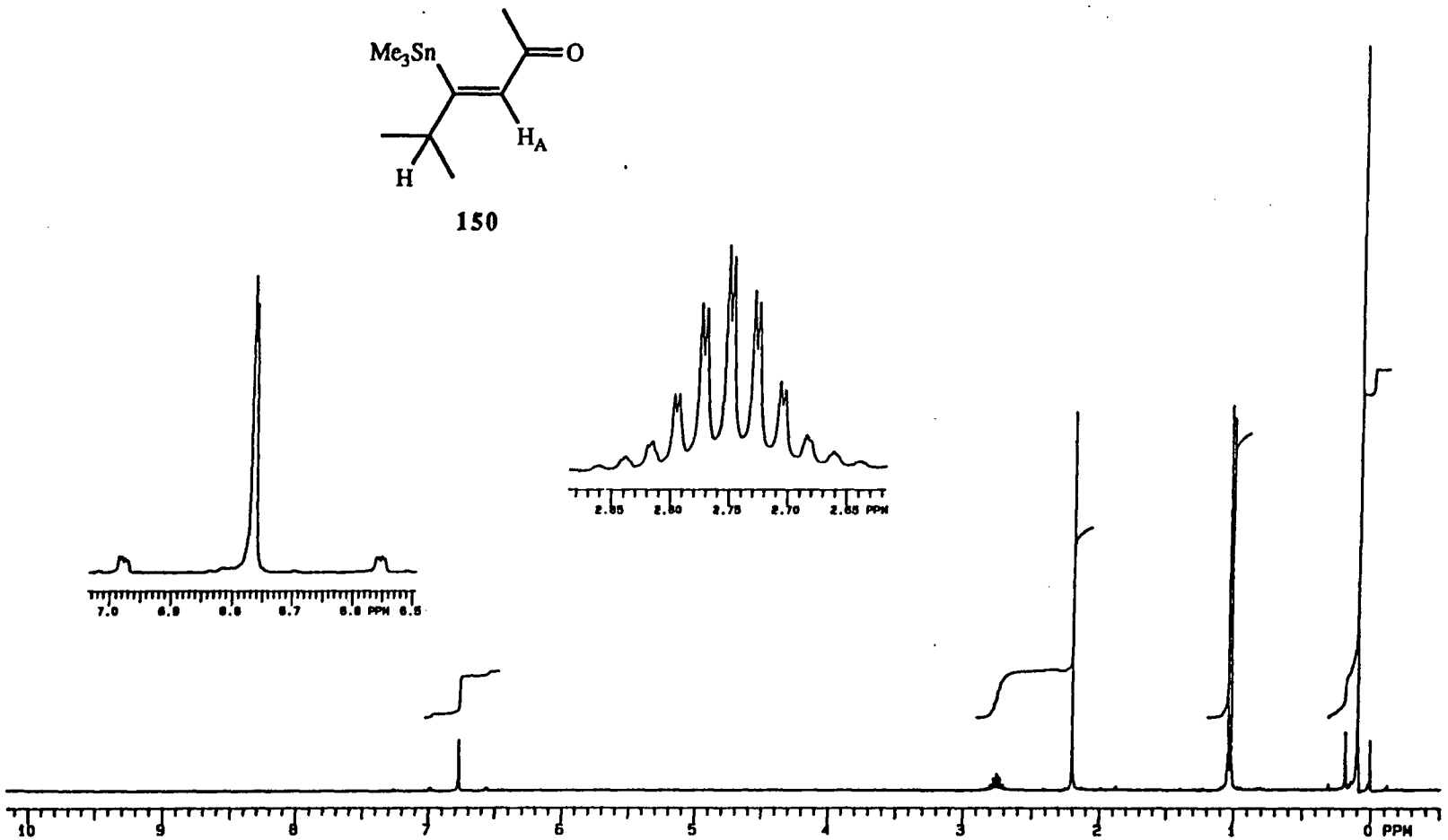
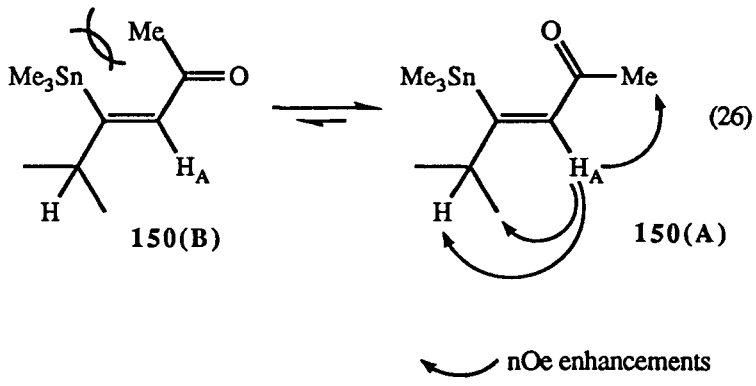


Figure 1. 300 MHz ^{1}H nmr spectrum of compound **150**

isopropyl group. Also, there is a 3-proton singlet at δ 2.20 due to the methyl ketone group and a 1-proton doublet at δ 6.77 (J = 1.5 Hz, $^3J_{Sn\text{-}H}$ = 127 Hz) due to H_A. The magnitude of the tin-hydrogen coupling constant for H_A is characteristic of coupling between tin and a proton that are *trans* to each other on a carbon-carbon double bond.[97] This *trans* relationship was confirmed by nOe difference experiments, in which irradiation of the signal at δ 6.77 (H_A) caused signal enhancements at δ 2.75 (-C<u>H</u>Me$_2$), 1.03 (-CH<u>Me</u>$_2$) and 2.20 (methyl ketone). This last enhancement indicates that compound **150** exists preferentially in the cisoid conformation **150(A)** (equation 26). Presumably, **150(A)** is the preferred conformation primarily because the transoid conformation **150(B)** suffers from steric interactions between the methyl group of the methyl ketone function and the trimethylstannyl group.



(26)

There are several important features associated with this reaction. Firstly, the compound **150** was produced in high yield (80%). Additionally, this material was stereochemically homogeneous. If any of the (*E*)-isomer was formed in this reaction, it was present in extremely minor amounts and did not contaminate the product after chromatography. Finally, there was no evidence obtained which indicated the presence of any bis(trimethylstannyl) compounds such as **149** in the reaction mixture. In fact, the only other compounds isolated from the crude reaction mixture were hexamethylditin and triphenylphosphine. Although the expected product **149** was not obtained in this reaction,

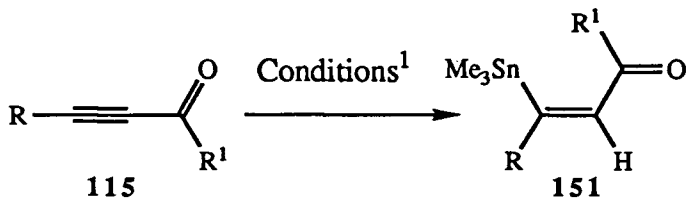
the efficient, stereoselective formation of compound **150** was an interesting and potentially useful result. It was, therefore, decided to determine whether this transformation could be achieved using a variety of α,β-acetylenic aldehydes and ketones **115** as substrates.

It was pleasing to find that this reaction is indeed general. Good to excellent yields of (*Z*)-β-trimethylstannyl α,β-unsaturated ketones **151B** and (*Z*)-β-trimethylstannyl α,β-unsaturated aldehydes **151A** were obtained from a variety of α,β-acetylenic ketones **115B** and aldehydes **115A**, respectively. The conditions used in these reactions and the results are summarized in Table 7.

Several points should be made regarding the data in Table 7. Firstly, the reactions were carried out at concentrations (of the acetylenic carbonyl compound in dry THF) ranging between 0.3M and 0.6M, and were generally complete within reasonable lengths of time. The products were easily isolated by flash chromatography of the crude oil obtained after removal of the solvent from the reaction mixture. Secondly, the products obtained in these reactions exhibited spectral data which were in full accord with the proposed structures. Some of the important infrared and ^{1}H nmr data for these compounds is presented in Table 8. Thus, the infrared spectrum of each of these compounds showed absorbances attributable to the carbon-carbon and carbon-oxygen stretching frequencies of the α,β-unsaturated carbonyl function. The ^{1}H nmr spectrum of each of these compounds showed a 1-proton signal due to H_A. The magnitude of the three bond tin-hydrogen coupling constant for this signal was, in each case, consistent with the proton and tin being *trans* to each other on the carbon-carbon double bond.[97] It is interesting to note that the values of $^3J_{Sn\text{-}H}$ associated with H_A are consistently lower for the aldehydes **152-154** than for the ketones **150** and **155-161.**

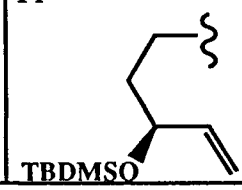
Some of the reactions listed in Table 7 deserve extra comment. Regarding the reaction using the acetylenic ketone **140** as the substrate (entry 8), it was found that starting materials were present even after a reaction time of 24 hours. It was decided to stop the

Table 7. The preparation of β-trimethylstannyl α,β-unsaturated aldehydes and ketones **151**.



115 **151**

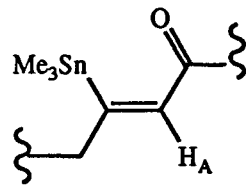
151A R^1=H
151B R^1=Alkyl

Entry	115	R	R^1	151	Time/h	Yield[2] %
1	**133**	$CH_2CH_2OTBDMS$	H	**152**	2	87
2	**134**	$(CH_2)_4OTBDMS$	H	**153**	2	88
3	**135**	CH_2CH_2OMOM	H	**154**	2	76
4	**136**	$CH_2CH_2OTBDMS$	Me	**155**	2	90
5	**137**	$(CH_2)_4OTBDMS$	Me	**156**	2	83
6	**138**	$(CH_2)_3CCH$	Me	**157**	4	69
7	**139**	$(CH_2)_3Cl$	Me	**158**	3	81
8	**140**	Bu^t	C_6H_{13}	**159**	24	48
9	**141**	$CH_2CH_2OTBDMS$	Pr^i	**160**	5	94
10	**142**	Pr^i	Me	**150**	5	80
11	**148**		Me	**161**	8	95

1. Conditions: $Me_3SnSnMe_3$ (1 equiv.), Pd(0) (5 mol%), THF, reflux.

2 Isolated yield of distilled product.

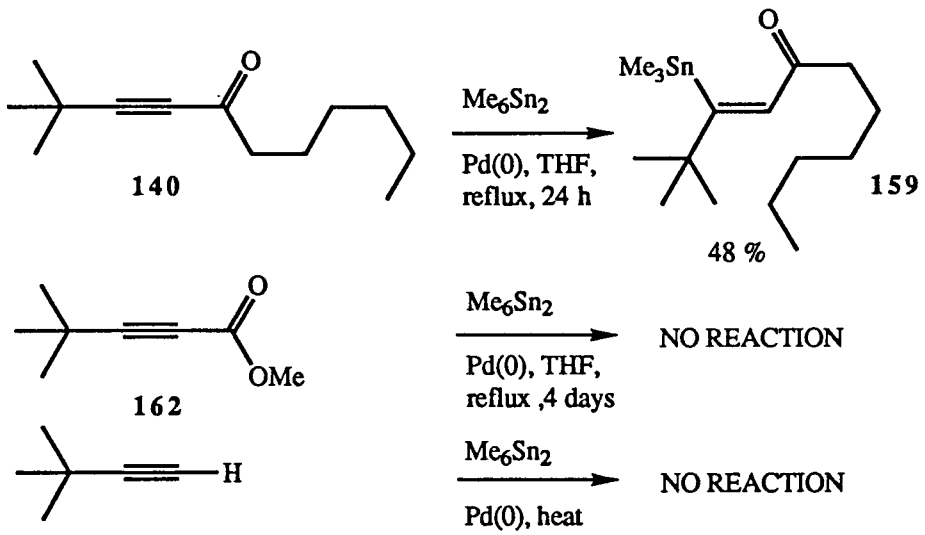
Table 8. Selected spectral data for (Z)-β-trimethylstannyl α,β-unsaturated aldehydes and ketones **151**



151

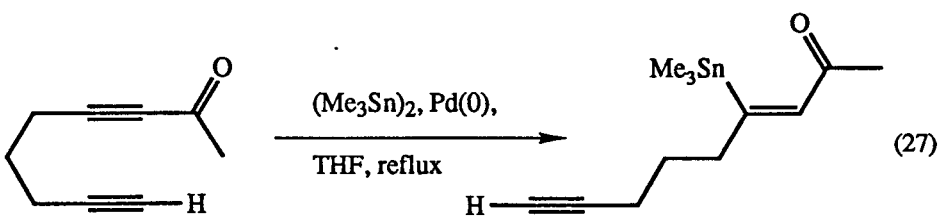
151	ν(C=O) (cm^{-1})	ν(C=C) (cm^{-1})	δ (H_A)	$^3J_{Sn-H}$(Hz)
152	1685	1563	6.68	114
153	1685	1562	6.62	115
154	1683	1562	6.72	113
155	1682	1573	6.82	121
156	1682	1572	6.79	122
157	1681	1571	6.62	120
158	1682	1572	6.82	120
159	1685	1562	6.75	130
160	1678	1572	6.88	127
150	1682	1568	6.77	127
161	1682	1571	6.80	124

reaction at this point, since tlc and glc analyses indicated that the reaction mixture was becoming progressively more messy as time went on. The expected product **159** was isolated in 48% yield (Scheme 20). The sluggish nature of the reaction with the substrate **140** is consistent with results obtained by previous workers (Scheme 20). It was shown that neither the acetylenic ester **162**[98] nor 3,3-dimethyl-1-butyne[38] reacts with hexamethylditin in the presence of a Pd(0) catalyst, even after prolongued heating of the reaction mixtures (Scheme 20). Therefore, it is reasonable to conclude that the rates of bis-metallation reactions of this type are sensitive to the size of the groups attached to the carbon-carbon triple bond.



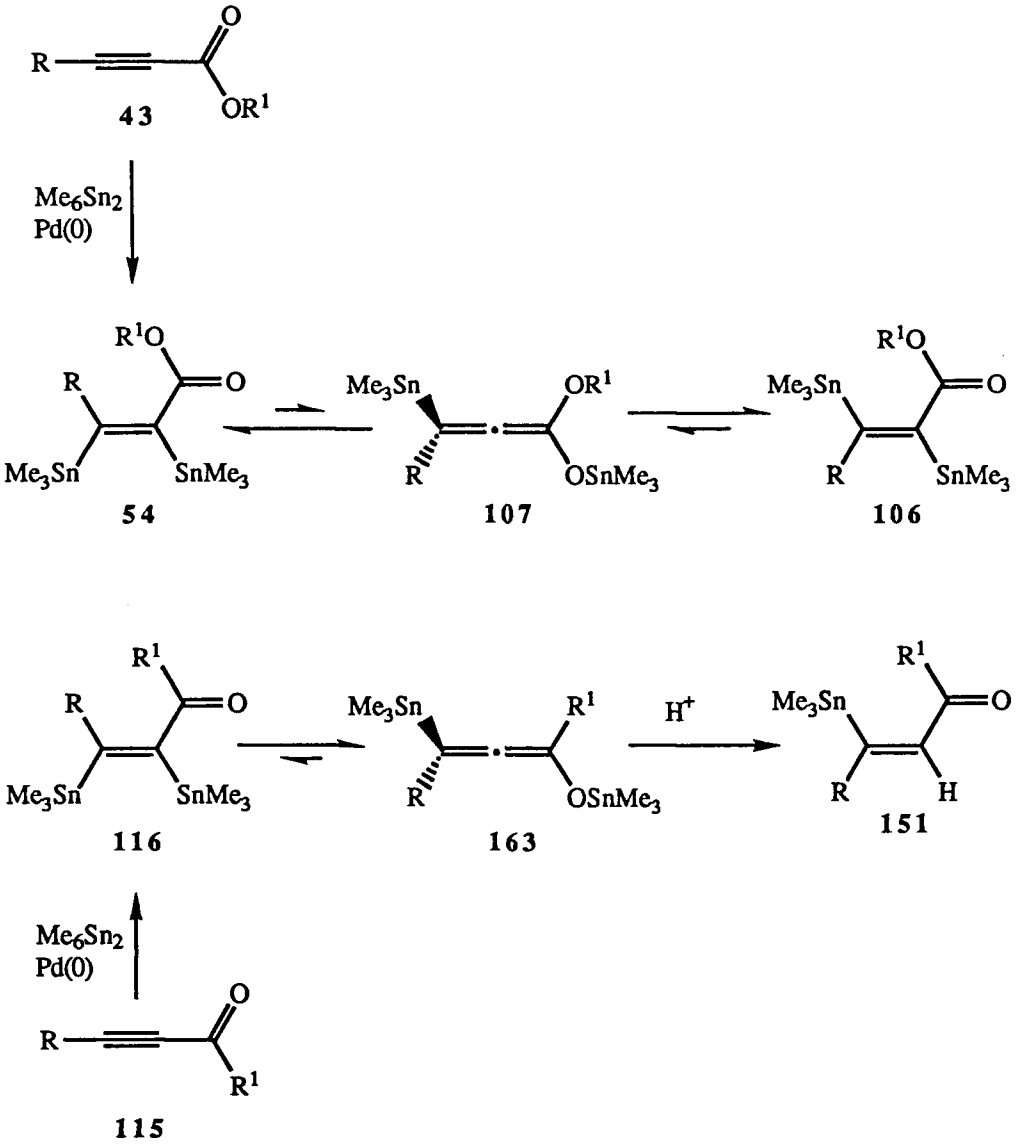
Scheme 20

Regarding the reaction using the acetylenic ketone **138** as starting material (Table 7, entry 6), it was found that the (Z)-β-trimethylstannyl α,β-unsaturated ketone **157** was obtained in (an unoptimized) 69% yield (equation 27). The fact that the terminal acetylene functions present in compounds **138** and **157** do not interfere with the "observed" reaction is particularly noteworthy, since it is known[38] that terminal acetylenes may be bis-stannylated under conditions similar to those used here. It is clear, therefore, that the Pd(0)-catalyzed reactions of terminal acetylenes with hexamethylditin are slower than the similar reactions involving α,β-acetylenic aldehydes and ketones.



The observation that α,β-acetylenic aldehydes/ketones **115** react with hexamethylditin in the presence of a Pd(0) catalyst to give (Z)-β-trimethylstannyl

α,β-unsaturated aldehydes/ketones **151**, whilst similar reactions involving α,β-acetylenic esters **43** afford the bis(trimethylstannyl) adducts **54** may be rationalized by the following arguments (Scheme 21). It was proposed earlier that the thermal isomerization of alkyl (Z)-2,3-bis(trimethylstannyl)-2-alkenoates **54** to the corresponding (*E*)-isomers **106** proceeds via trimethylstannyl allenoates of general structure **107**. However, in the Pd(0)-catalyzed reactions of acetylenic esters with hexamethylditin, the initally formed products **54** are stable and, apparently, the allenoates **107** are not produced (Scheme 21).



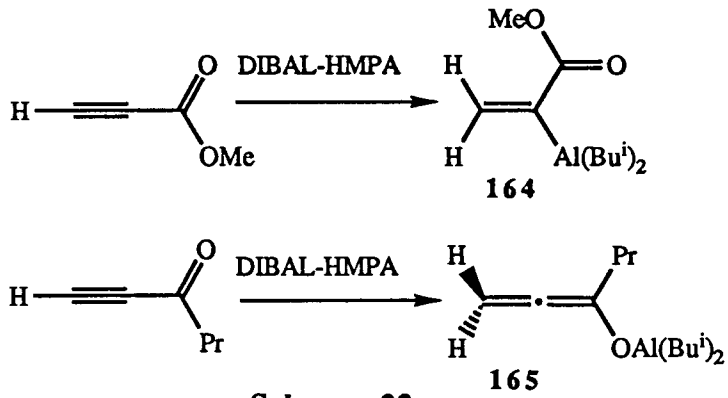
Scheme 21

In a similar fashion, it is proposed that bis(trimethylstannyl) compounds of general structure **116** (which were the expected products in the Pd(0)-catalyzed reactions of α,β-acetylenic aldehydes/ketones with hexamethylditin) may isomerize to the corresponding allenolates **163** (Scheme 21). Apparently, the tendency to form allenolates **163** from compounds **116** is greater than the tendency to form allenoates **107** from the distannyl alkenoates **54**. Thus, it is proposed that the initial products from the Pd(0)-catalyzed reactions of α,β-acetylenic aldehydes/ketones **115** with hexamethylditin are the expected bis(trimethylstannyl) adducts **116**, which, under the conditions of the reaction, readily isomerize to the trimethylstannyl allenolates **163** (Scheme 21). Protonation of **163**, presumably during silica gel chromatography, occurs from the face opposite the bulky trimethylstannyl group to give the (*Z*)-β-trimethylstannyl α,β-unsaturated aldehydes/ketones **151** stereoselectively (Scheme 21).

It must be emphasized that this proposed pathway is intended only as a hypothetical rationalization of the results observed from the Pd(0)-catalyzed stannylation reactions of α,β-acetylenic esters on one hand and α,β-acetylenic aldehydes/ketones on the other. Nothing as yet is known about the intermediates in these reactions. However, the arguments presented above are supported by some observations made recently by Saegusa and coworkers.[99] It was reported that reaction of α,β-acetylenic carbonyl compounds with DIBAL produces organoaluminum intermediates which are both thermally stable and identifiable. Interestingly, the structures of these intermediates are dependant on the nature of the carbonyl group in the starting material. For example, methyl propynoate gives rise to the alkenylalane **164**, whilst 2-hexyn-3-one gives rise to the aluminum allenolate **165** (Scheme 22). The similarities between these results and those presented above are striking.

In summary, regardless of the pathway by which the products are formed, the Pd(0)-catalyzed reaction of α,β-acetylenic aldehydes and ketones **115** with hexamethylditin constitutes a general method for the synthesis of (*Z*)-β-trimethylstannyl α,β-unsaturated aldehydes and ketones **151**. The reaction proceeds in high yield and with excellent regio-

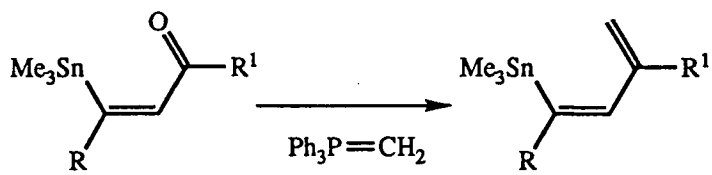
and stereoselectivity, and a wide variety of functional groups in the substrate, such as halides, ethers, allylic ethers and terminal acetylenes are compatible with the reaction conditions.



Scheme 22

3.6. The preparation of (Z)-4-(trimethylstannyl)-1,3-butadienes **166**

The readily available (Z)-β-trimethylstannyl α,β-unsaturated aldehydes and ketones **151** are potentially useful intermediates in organic synthesis. For example, these compounds should readily undergo Wittig olefination reactions to give a variety of substituted stannyldienes of general structure **166** (equation 28). A few stannyldienes of type **166A** have been prepared by previous workers in this laboratory via Wittig olefination of aldehydes of structure **151A**.[31] However, at the time of this study the ketones of general structure **151B** were not readily available and therefore the olefination reactions of these compounds had not been investigated.

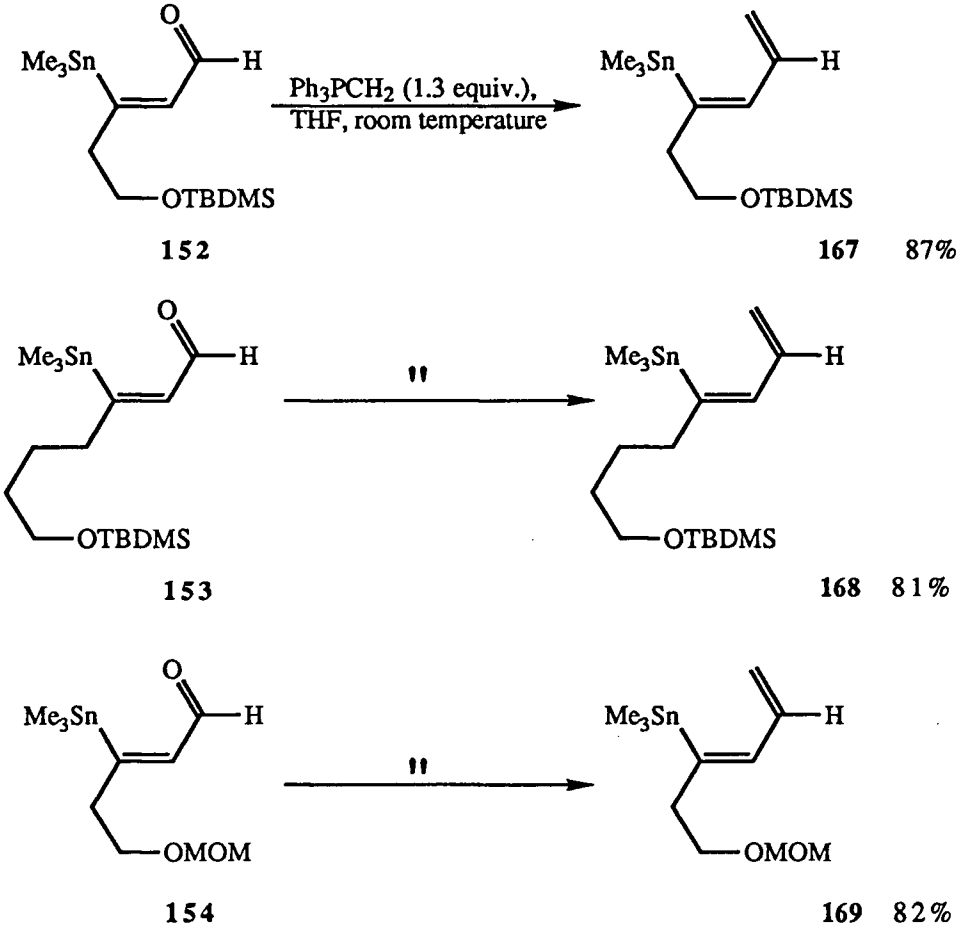


(28)

151 **166**

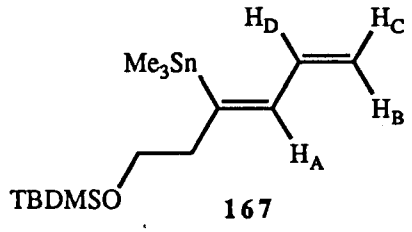
151A R^1=H **166A** R^1=H
151B R^1=Alkyl **166B** R^1=Alkyl

It was found that the (*Z*)-β-trimethylstannyl α,β-unsaturated aldehydes **152-154** react with methylenetriphenylphosphorane to give the corresponding stannyldienes in a clean and efficient manner (Scheme 23). Typically, a solution of the aldehyde in dry THF was added to a slight excess of methylenetriphenylphosporane (prepared from *n*-BuLi and methyltriphenylphosphonium bromide) in dry THF at room temperature. The resulting mixture was stirred at room temperature until the reaction was complete (as judged by glc analysis). After appropriate workup, the crude product was purified by flash chromatography followed by distillation.



Scheme 23

The products obtained from these reactions exhibited spectral data which were in full accord with the assigned structures. For example, the ^1H nmr spectrum of compound **167** showed a series of signals due to the diene unit. Thus, a 1-proton doublet of doublets at δ 5.10 (J = 11 Hz, J = 1.5 Hz), a 1-proton doublet of doublets at δ 5.15 (J = 16 Hz, J = 1.5 Hz), a 1-proton multiplet at δ 6.30, and a one proton broad doublet at δ 6.64 (J = 11 Hz, $^3J_{Sn-H}$ = 131 Hz) were assigned to H_C, H_B, H_D and H_A, respectively. The ^{13}C nmr spectrum of **167** showed signals at δ 117.07, 137.67, 142.63, and 147.33 due to the olefinic carbons. The spectral data for the dienes **168** and **169** exhibited similar features (see the Experimental section).

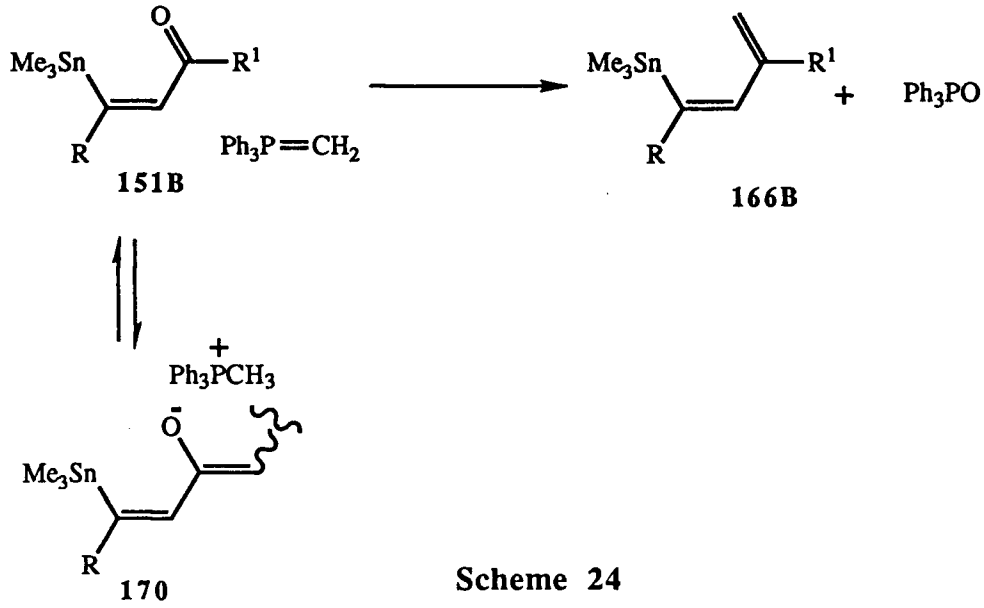


167

The (*Z*)-β-trimethylstannyl α,β-unsaturated ketones of general structure **151B** may also be converted into the corresponding stannyldienes using the procedure described above. However, in these cases complete conversion of the starting materials into products was not achieved, even after reaction times of several hours at room temperature. Also, after long reaction times the reaction mixtures were generally messy and the isolated yields of stannyldienes were low. In fact, only the ketone **150** was converted into the corresponding stannyldiene in satisfactory yield using this method (See Table 9, entry 6).

The unsatisfactory nature of these transformations might be the result of a competition between the olefination process and the (reversible) formation of the enolate of general structure **170** (Scheme 24). Since the olefination reaction is irreversible it should, in principle, be possible to achieve complete conversion of starting material into product. However, side reactions (presumably due to the presence of the enolate **170**) apparently

compete with the olefination reaction and low yields of stannyldienes **166B** are generally the result.



Scheme 24

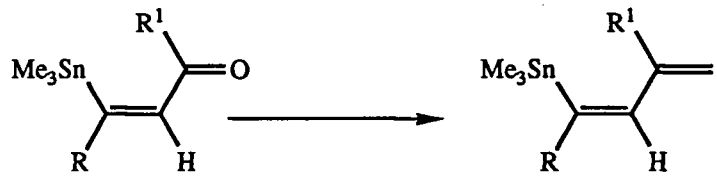
Since most of the β-trimethylstannyl α,β-unsaturated ketones **151B** gave disappointingly low yields of the stannyldienes **166B** under these conditions ($Ph_3P=CH_2$, THF, room temperature) an alternative method was sought which might effect this transformation more efficiently.

It has been reported[100,101] that reaction of enolizable ketones with a mixture of sodium 2-methyl-2-butoxide and methyltriphenylphosphonium bromide in dry benzene at room temperature, provides the corresponding olefins in a highly efficient manner.

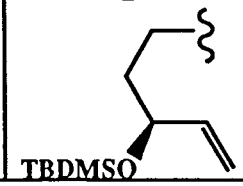
It was found that the (*Z*)-β-trimethylstannyl α,β-unsaturated ketones **151B** were smoothly converted into the corresponding stannyldienes **166B** via this method. Typically, a solution of the ketone **151B** in dry benzene was added to a mixture of sodium 2-methyl-2-butoxide (2.5 equivalents) and methyltriphenylphosphonium bromide (2.5 equivalents) in dry benzene, at room temperature under an argon atmosphere. The mixture was stirred at room temperature until the reaction was complete (as judged by glc and tlc analyses). After

appropriate workup, the crude product was purified by flash chromatography, followed by distillation, to give the pure stannyldiene **166B**. The conditions used in these reactions and the results are summarized in Table 9.

Table 9. The preparation of (Z)-4-(trimethylstannyl)-1,3-butadienes **166**.



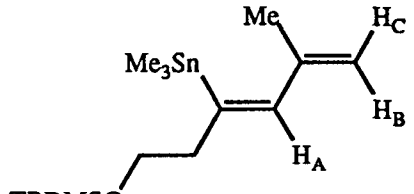
151B **166B**

Entry	**151B**	R	R^1	**166B**	Conditions[1]	Yield[2] %
1	**155**	$CH_2CH_2OTBDMS$	Me	**171**	B	86
2	**156**	$(CH_2)_4OTBDMS$	Me	**172**	B	75
3	**157**	$(CH_2)_3CCH$	Me	**173**	B	83
4	**158**	$(CH_2)_3Cl$	Me	**174**	B	57
5	**159**	Bu^t	C_6H_{13}	**175**	B	81
6	**150**	Pr^i	Me	**176**	A	87
7	**160**	$CH_2CH_2OTBDMS$	Pr^i	**177**	C	64
8	**161**		Me	**178**	B	85

[1]Conditions. A) Ph_3PCH_2 (1.5 equiv.), THF, room temp, 5 h; B) $MePPh_3^+Br^-$ (2.5 equiv.), Sodium 2-methyl-2-butoxide (2.5 equiv.), benzene, room temp, 30 min; C) as B) except 15 min at room temp.

[2] Isolated yield of distilled product.

The stannyldienes **166B** which were obtained in these reactions exhibited spectral data which were in full accord with the assigned structures. For example, the ^1H nmr spectrum of compound **171** showed a series of signals due to the substituted 1,3-butadiene unit. Thus, 1-proton broad singlets at δ 4.75 and 4.79 could be assigned to H_B and H_C (or *vice versa*) while a 1-proton broad singlet at δ 6.53 ($^3J_{Sn-H}$ = 137 Hz) was attributed to H_A. The ^{13}C nmr spectrum of this compound showed signals at δ 112.91, 141.78, 144.95 and 146.61 (olefinic carbons).



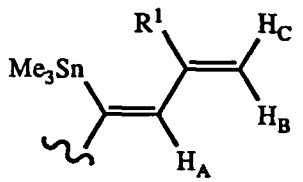
171

The spectral data derived from the other stannyldienes **166B** exibited features similar to those mentioned above. Some important ^1H nmr data for these compounds are listed in Table 10. Regarding the data in Table 10, it should be noted that the 3-bond tin hydrogen coupling constants associated with H_A are consistently larger for compounds **166B** than for the precursor unsaturated carbonyl compounds **151B** (see Table 8).

The results presented in Scheme 23 and in Table 9 show that (*Z*)-4-(trimethylstannyl)-1,3-butadienes of general structure **166** are readily prepared from the (*Z*)-β-trimethylstannyl α,β-unsaturated aldehydes **151A** and ketones **151B** via Wittig olefination reactions. It was subsequently shown that the (*Z*)-β-trimethylstannyl α,β-unsaturated aldehydes **151A** readily undergo Wittig-Horner olefination reactions.[102] For example, the aldehyde **154** reacted with the sodio-phosphonate reagent, derived from the reaction of *tert*-butyl diisopropylphosphonacetate **179** with NaH, to give the α,β-unsaturated ester **180** (equation 29). In a similar manner, the aldehyde **152** reacted with the sodio-phosphonate reagent, derived from the reaction of trimethylphosphonoacetate **181** with NaH,

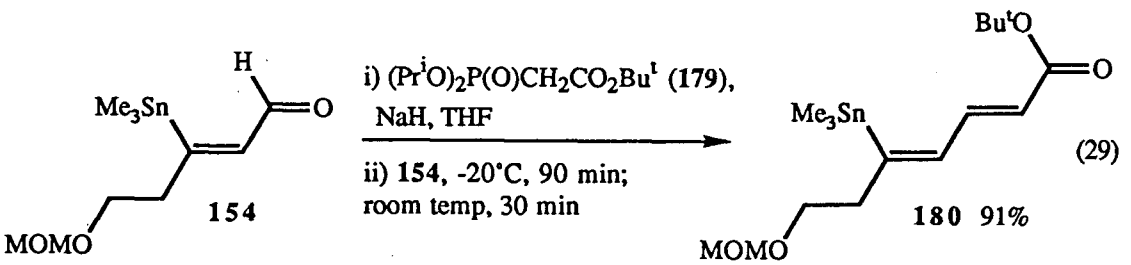
to give the α,β-unsaturated ester **182** (equation 30). Both of these reactions proceed in high yield and with excellent stereoselectivity.

Table 10. Selected ^{1}H nmr data for stannyldienes **166B**

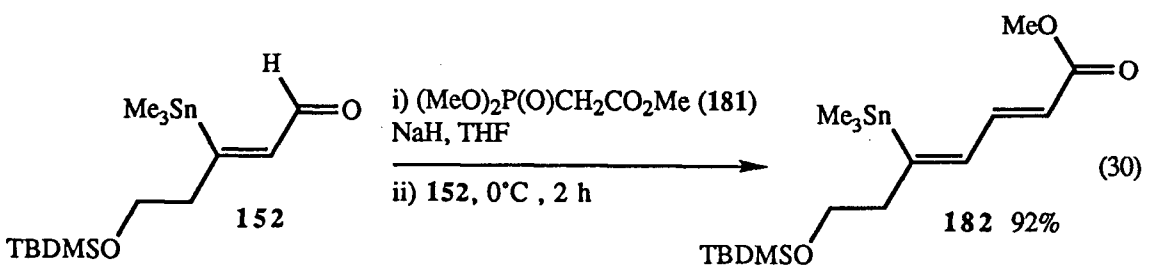


166B

166B	δ (H_A)	$^3J_{Sn\text{-}H(H_A)}$ (Hz)	δ (H_B/H_C)
171	6.53	137	4.75, 4.79
172	6.47	139	4.74, 4.79
173	6.51	139	4.75, 4.79
174	6.52	136	4.76, 4.80
175	6.49	151	4.72, 4.77
176	6.45	144	4.74, 4.78
177	6.60	140	4.71, 4.80
178	6.50	139	4.76, 4.80

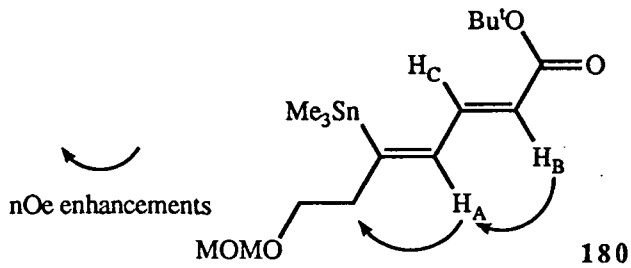


(29)



(30)

The products obtained from these reactions exhibited spectral data which were in full accord with the assigned structures. For example the infrared spectrum of compound **180** showed an absorbance at 1703 cm^{-1}, attributable to the carbonyl stretching frequency of the α,β-unsaturated ester function. The 400 MHz ^1H nmr spectrum of **180** is shown in Figure 2. This spectrum shows a 9-proton singlet at δ 0.25 ($^3J_{Sn-H}$ = 52 Hz) due to the trimethylstannyl group, a 9-proton singlet at δ 1.48 (-$CO_2\underline{Bu^t}$), a 2-proton broad triplet at δ 2.64 (-$OCH_2\underline{CH_2}$-, J = 7 Hz, $^3J_{Sn-H}$ = 49 Hz), a 3-proton singlet at δ 3.33 (-O$\underline{Me}$), a 2-proton triplet at δ 3.54 (-$OCH_2\underline{CH_2}$-, J = 7 Hz), and a 2-proton singlet at δ 4.58 (-OCH_2O-). Also, a 1-proton broad doublet at δ 5.72 (J = 15 Hz), a 1-proton broad doublet at δ 6.74 (J = 11 Hz, $^3J_{Sn-H}$ = 120 Hz), and a 1-proton doublet of doublets at δ 7.21 (J = 15 Hz, J = 11 Hz, $^4J_{Sn-H}$ = 7 Hz), were assigned to H_B, H_A, and H_C, respectively. The magnitude of the 3-bond tin-hydrogen coupling constant for H_A indicates that H_A and the trimethylstannyl group are located *trans* to each other on the carbon-carbon double bond. This stereochemical configuration, along with that of the α,β-unsaturated ester function, were confirmed by nOe difference experiments. Thus, irradiation of the signal at δ 6.74 (H_A) caused signal enhancements at δ 5.72 (H_B) and 2.64 (-$OCH_2\underline{CH_2}$-) whilst irradiation at δ 5.72 (H_B) caused signal enhancement at δ 6.74 (H_A).



180

The spectral data derived from compound **182** exhibited similiar features to those exhibited by compound **180** (see Experimental section).

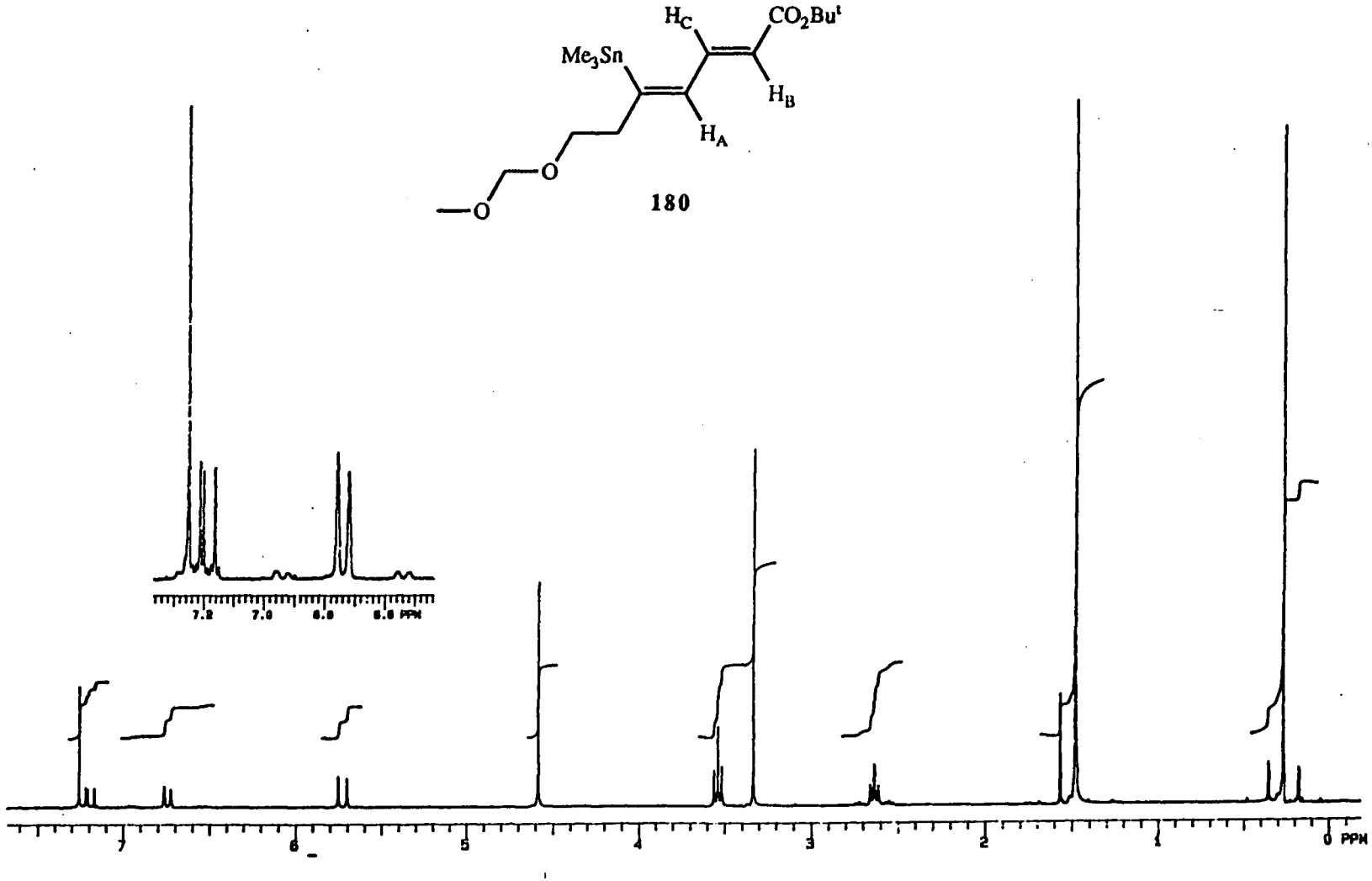
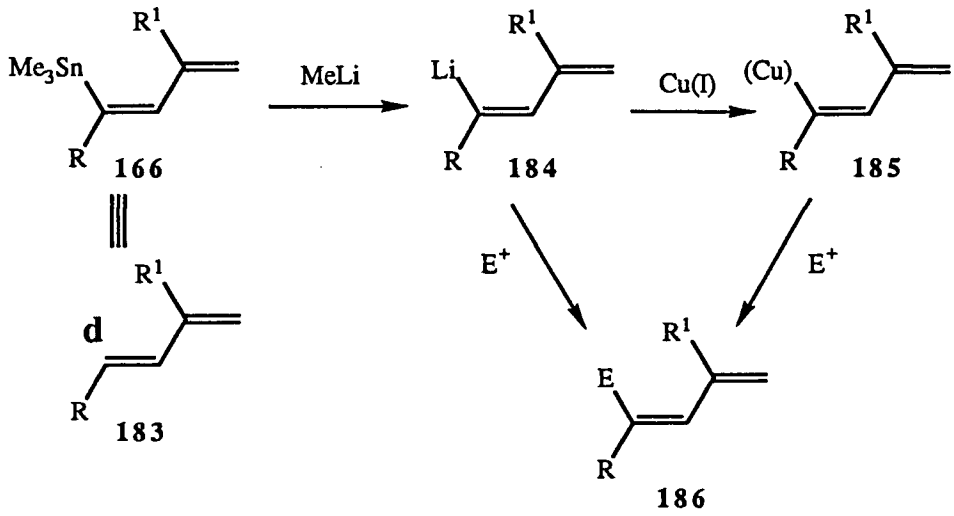


Figure 2. 400 MHz ^{1}H nmr spectrum of compound **180**

3.7. Synthetic uses of (Z)-4-(trimethylstannyl)-1,3-butadienes **166**

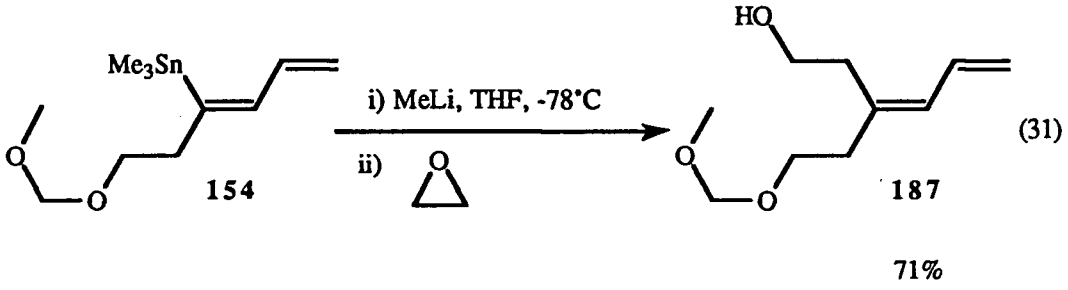
With simple convenient methodology available for the preparation of stannyldienes **166**, it was our next objective to demonstrate the synthetic utility of these substances. It was anticipated that these stannyldienes could serve effectively as synthetic equivalents of the donor synthon **183** (Scheme 25).[23, 31] In other words, treatment of compounds **166** with MeLi should result in transmetallation of the alkenylstannane moiety to give alkenyllithium species of general structure **184**. These reagents should react with electrophiles, either directly or via the corresponding alkenylcopper(I) species **185**, to give substituted 1,3-butadienes of general structure **186** (Scheme 25).



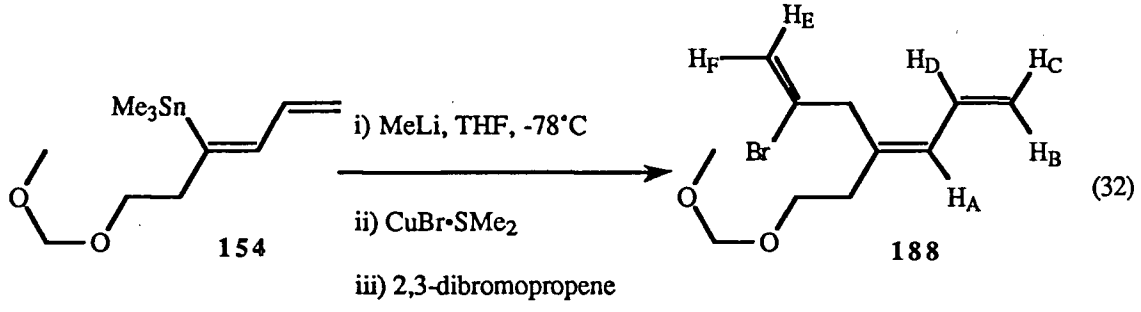
Scheme 25

It was found that reaction of the stannyldiene **154** with MeLi (1.1 equivalents) for 45 min at -78°C, in THF, resulted in clean transmetallation of the alkenylstannane moiety (as judged by glc analysis of an aliquot taken from the reaction mixture). Reaction of the dienyllithium so formed with excess ethylene oxide gave, after purification of the crude product by flash chromatography and distillation, the homoallylic alcohol **187** in 71% yield

(equation 31). This compound exhibited spectral data which were in full accord with the assigned structure (see Experimental section).



Additionally, the stannyldiene **154** was converted into the corresponding alkenyllithium species, as described above, which was then treated with $CuBr{\bullet}SMe_2$ (1.1 equivalents) to give the corresponding alkenylcopper(I) reagent. This species, upon reaction with 2,3-dibromopropene gave the compound **188** in 83 % yield (equation 32). The 400 MHz ^1H nmr spectrum for **188** is shown in Figure 3. This spectrum shows a 2-proton



triplet at δ 2.38 (-$OCH_2\underline{CH_2}$-, J = 6 Hz), a 5-proton broad singlet at δ 3.35 (-O<u>Me</u> and the bis-allylic methylene), a 2-proton triplet at δ 3.62 (-OCH_2CH_2-) and a 2-proton singlet at δ 4.60 (-OCH_2O-). Also present are broad singlets at δ 5.48 and 5.62 due to H_E and H_F (or *vice versa*). Additionally, a 1-proton doublet of doublets at δ 5.12 (J = 11 Hz, J = 1.5 Hz), a 1-proton doublet of doublets at δ 5.20 (J = 17 Hz, J = 1.5 Hz), a 1-proton broad doublet at

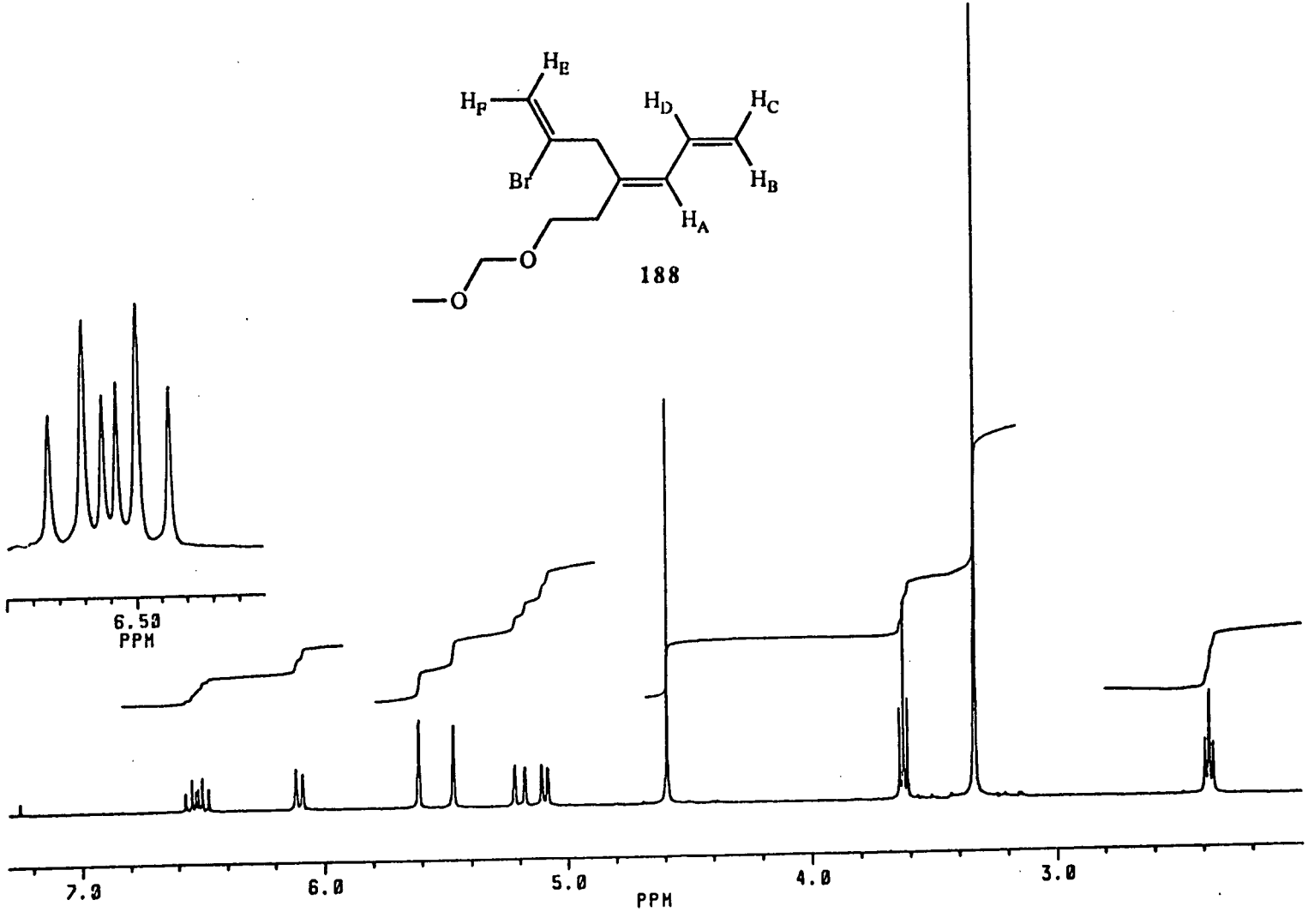
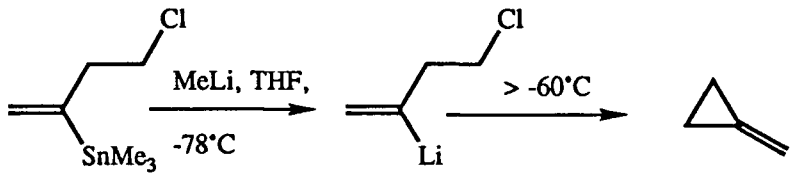


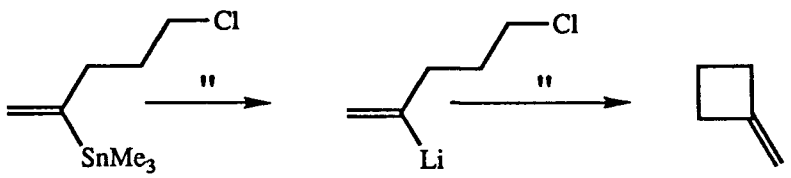
Figure 3. 400 MHz ^{1}H nmr spectrum of compound **188**

δ 6.13 (J = 11 Hz), and a 1-proton doublet of doublets of doublets at δ 6.54 (J = 17 Hz, J = 11 Hz, J = 11 Hz), may be assigned to H_C, H_B, H_A and H_D, respectively.

Previous workers in this laboratory have shown that the alkenylstannanes **189**[103] and **190**[104] are readily transmetallated with MeLi in THF at low temperatures to form the corresponding alkenyllithium species **191** (equation 33) and **192** (equation 34), respectively. These alkenyllithium species are stable below approximately -60°C. However, at slightly higher temperatures **191** reacts, via intramolecular displacement of the chloride by the nucleophilic alkenyllithium moiety, to give methylenecyclopropane **193**. Compound **192** likewise reacts to give methylenecyclobutane **194**.



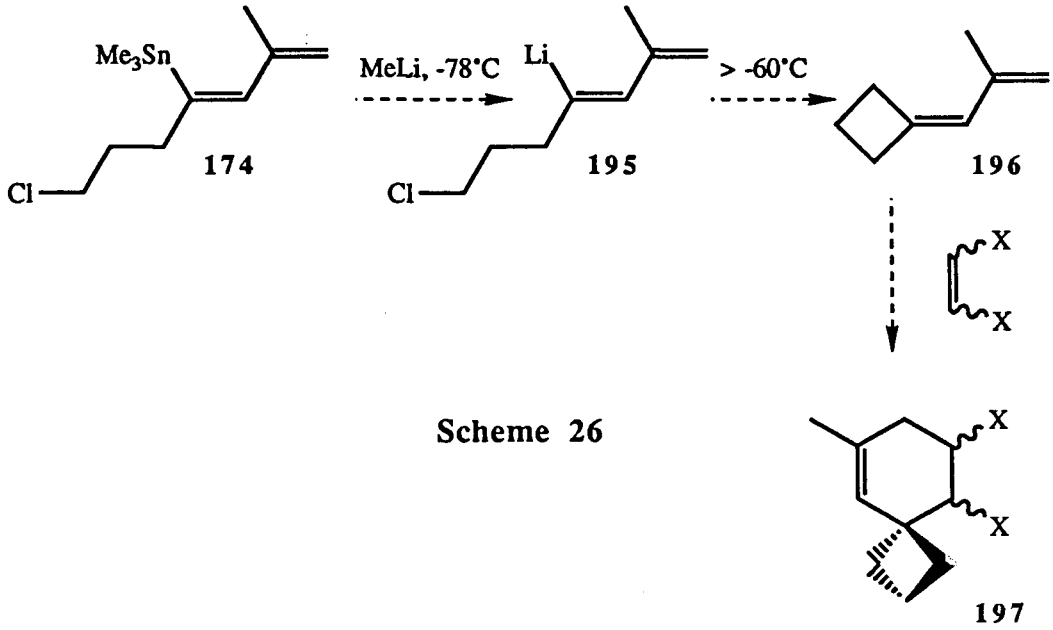
189 **191** **193** (33)



190 **192** **194** (34)

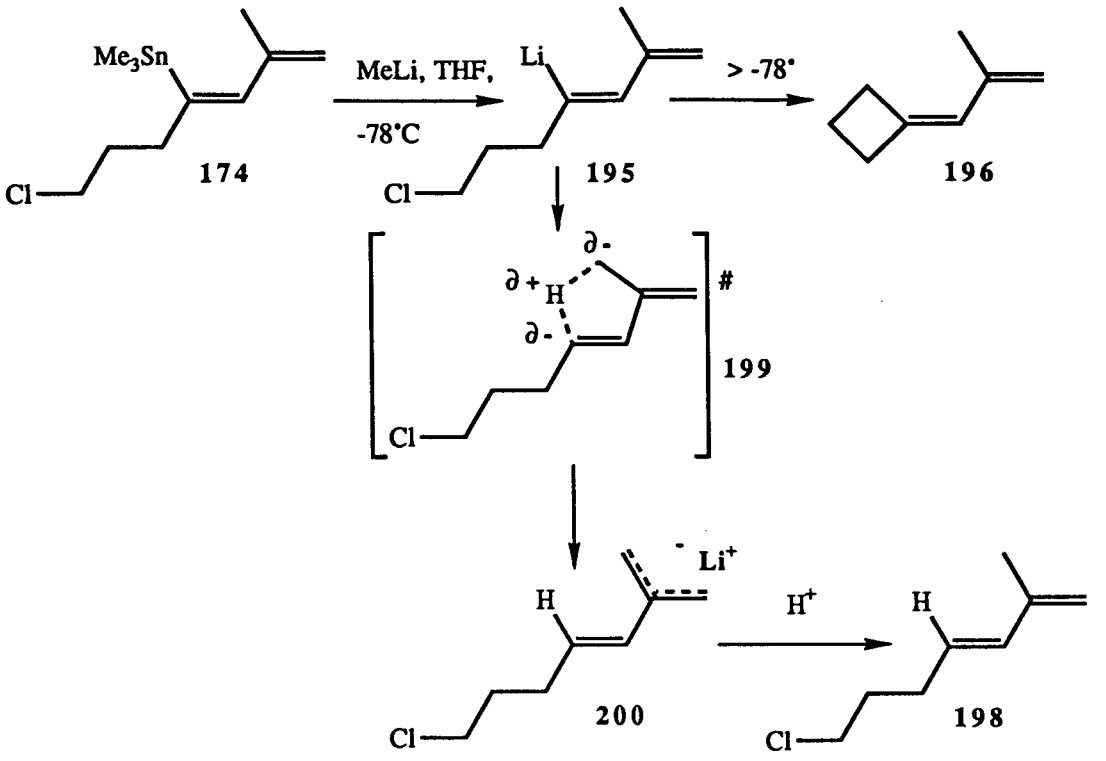
The stannyldiene **174** (which is readily prepared from the acetylenic ketone **139** via the chemistry described earlier in this section of the thesis; see Table 7, entry 7 and Table 9, entry 4) is structurally similar to the alkenylstannane **190**. On the basis of the chemistry of **190** described above it was anticipated that the alkenyllithium species **195**, derived from reaction of **174** with MeLi, would be a stable reagent at low temperature (Scheme 26). However, upon warming, it was expected that **195** should undergo intramolecular alkylation to give the strained cyclobutyl diene **196**. This diene should, in principle, undergo Diels-

Alder reactions with suitable dienophiles to give interesting, structurally novel spirocyclobutanes of general structure **197** (Scheme 26).



Scheme 26

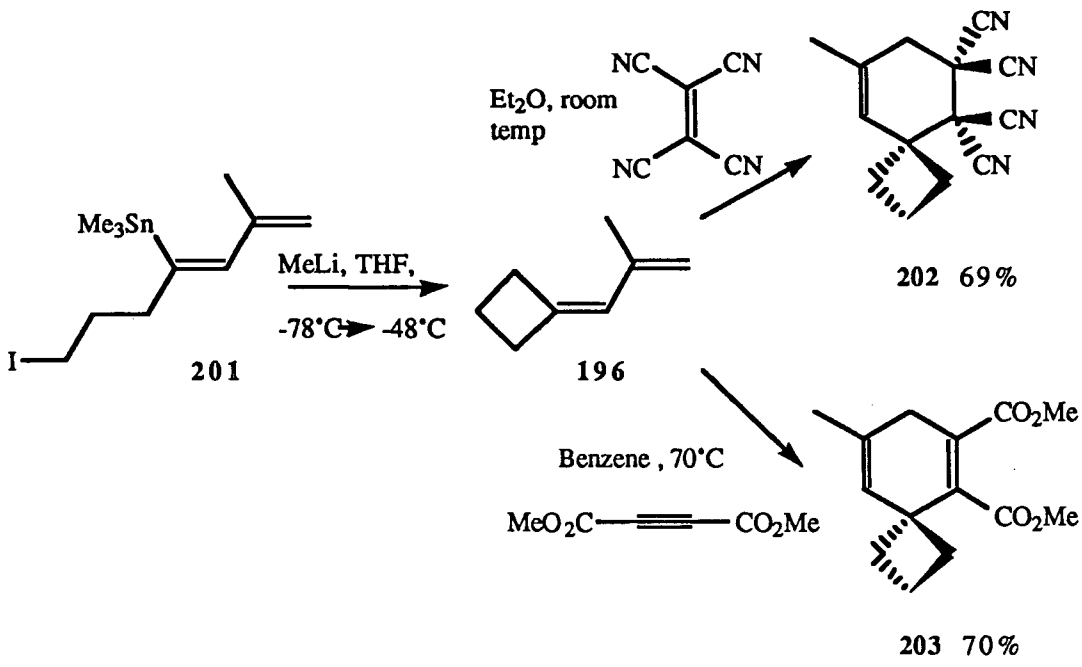
Unfortunately, it was found that the transmetallation/intramolecular alkylation reactions of the stannyldiene **174** did not proceed cleanly under any of the reaction conditions that were employed. Glc analyses of the crude reaction products always showed the presence of two major compounds, which were assumed to be (based on glc retention times) the desired cyclobutyl diene **196** and the transmetallated but uncyclized compound **198** (Scheme 27). The ratio of these materials obtained in these reactions depended on the reaction conditions, and at best was approximately 6:1 in favour of **196**. These products could be derived from the dienyllithium **195** via competing intramolecular cyclization and intramolecular proton transfer (Scheme 27). This proton transfer could proceed via a 5-membered ring transition state **199** to give an allyllithum species **200**, which cannot undergo intramolecular alkylation due to geometrical constraints. Upon workup, the allyllithium **200** would be protonated to give the compound **198**.



Scheme 27

On the basis of the above proposed reaction pathway it was expected that the desired cyclobutyl diene **196** would be more readily prepared via transmetallation/intramolecular alkylation reaction using the iodide **201** as starting material (Scheme 28). The alkenyllithium species derived from **201** would be expected to undergo intramolecular alkylation must faster than the alkenyllithium species **195** (derived from the chloride **174**). Therefore, it was hoped that the intramolecular proton transfer mode of reaction would be suppressed.

The iodide **201** was prepared from the chloride **174** via reaction with NaI in acetone (see Experimental section). Fortunately, when a solution of compound **201** in dry THF was treated with MeLi at -78°C and the solution was warmed to -48°C, glc analysis of the reaction mixture after workup showed the presence of one compound, which was assumed to be the desired cyclized product **196** (based on its glc retention time). Due to the volatility of this compound attempts to isolate it free of solvent were not carried out. Instead, it was treated,



Scheme 28

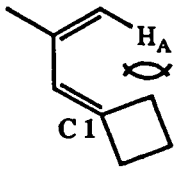
in situ, with the highly reactive dienophile tetracyanoethylene (Scheme 28). Thus, to the ethereal solution (argon atmosphere, room temperature) of the crude diene **196** obtained after extractive workup, was added, in batches, tetracyanoethylene. Upon addition of each batch, the solution became bright red and then was decolourized immediately. When the reaction was complete, as judged by glc analysis, the crude reaction product was purified by flash chromatography to give (after recrystallization) the compound **202** in 69 % yield (Scheme 28).

In a manner similar to that described above, a solution of the crude cyclobutyl diene **196** was treated with excess dimethylacetylene dicarboxylate to give the corresponding Diels-Alder adduct **203** in 70 % overall yield (Scheme 28). However, the use of excess dienophile and prolongued heating was required in order for this reaction to proceed to completion.

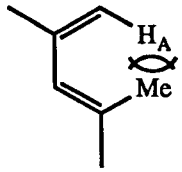
The success of these Diels-Alder reactions might be attributable primarily to two factors. Firstly, the diene **196** should be able to adopt the required cisoid conformation fairly easily. Comparison of molecular models of **196** and the similar diene **204** indicates that the steric interaction between H_A and the protons on the four-membered ring in compound **196**

(cisoid conformation) is less severe than that between H_A and the methyl group in compound **204** (cisoid conformation).

Secondly, there is release of some strain in the four-membered ring upon formation of the Diels-Alder adducts from the diene **196**. Carbon 1 is sp^2 hybridized in compound **196** and becomes sp^3 hybridized in the products. This release in angle strain should be "felt" by the transition state for the Diels-Alder reaction.

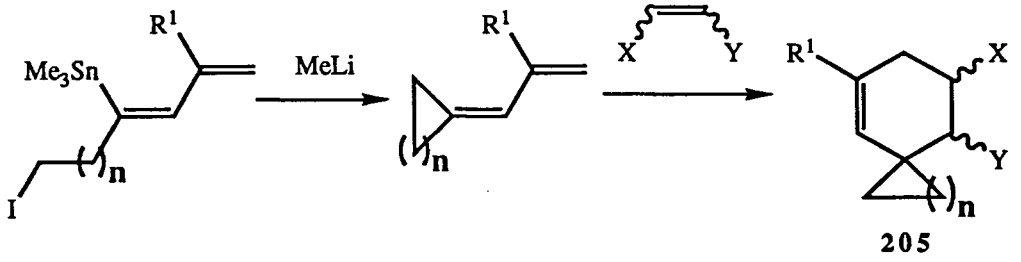


196



204

The reactions described above constitute a novel method for the preparation of spirocyclic cyclobutanes. It is quite possible that this methodology could be extended to the preparation of a variety of spirocyclic compounds of general structure **205**, by appropriate choices of stannyldienes for the transmetallation/intramolecular alkylation reaction, and dienophiles for the Diels-Alder reaction (equation 35).



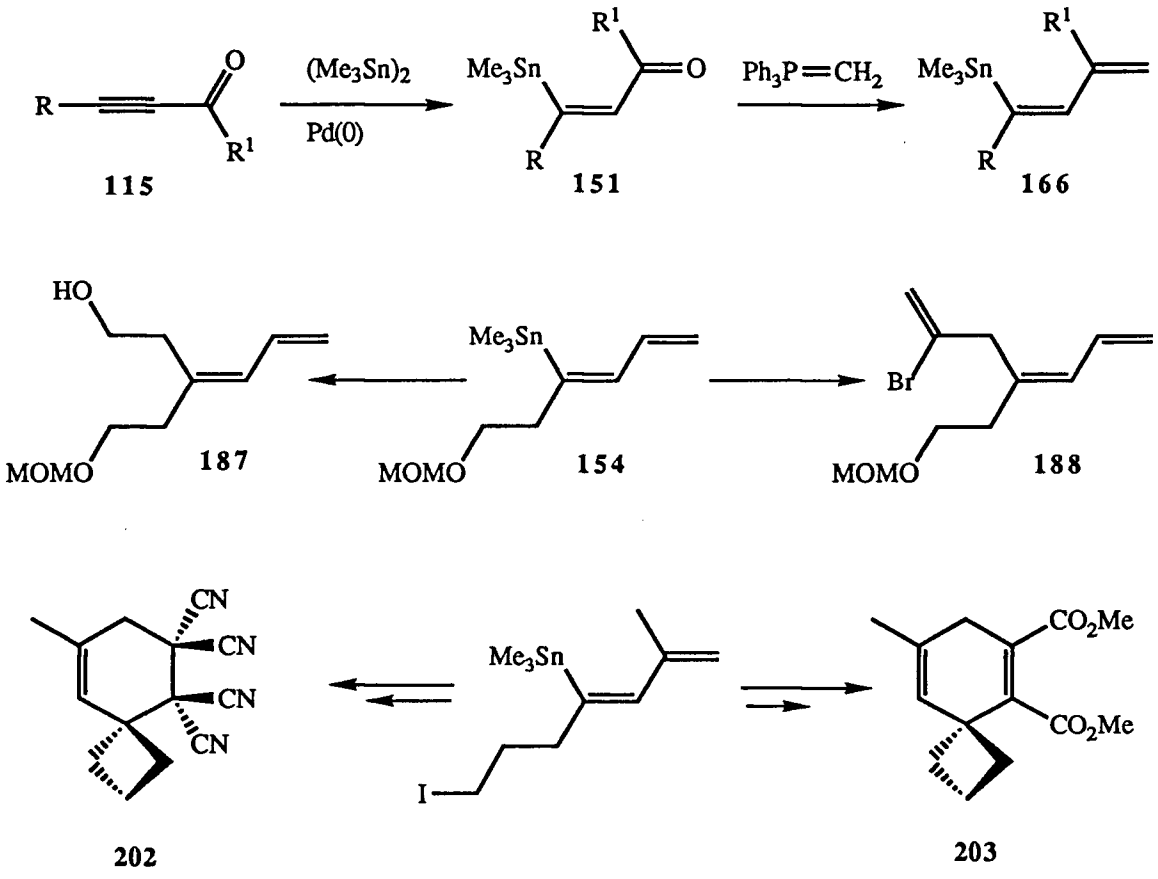
(35)

205

3.8. Conclusions

It was shown in this section of the thesis that α,β-acetylenic aldehydes and ketones **115** are efficiently and stereoselectively converted into the corresponding

(*Z*)-β-trimethylstannyl α,β-unsaturated aldehydes and ketones **151**, by reaction with hexamethylditin under Pd(0) catalysis (Scheme 29). These unsaturated carbonyl compounds are excellent precursors to a variety of (*Z*)-4-(trimethylstannyl)-1,3-butadienes **166**, by way of Wittig olefination reactions. The synthetic utility of functionalized stannyldienes of general structure **166** was demonstrated by the efficient preparation of compounds **187** and **188** (via the transmetallation/alkylation reactions of compound **154**). It was also shown that the stannyldiene **201** may be converted in a simple, efficient manner into the spirocyclic cyclobutanes **202** and **203**. The synthetic applications of the stannyldienes **166** are again exemplified in the next section of this thesis, where these compounds are used as the starting materials for the preparation of highly substituted bicyclo[3.2.1]octa-2,6-dienes.

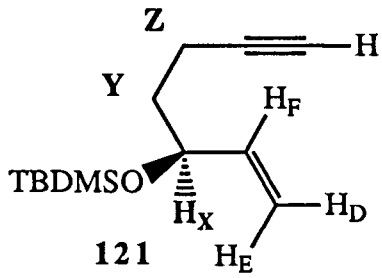


Scheme 29

IV. Experimental

For General experimental details and "Solvents and reagents", see Experimental section for Part 1 of this thesis.

Preparation of the terminal acetylene **121.**



121

To a stirred solution of 4-pentyn-1-ol (3 g, 35.7 mmol) in dry CH_2Cl_2 (100 mL) (argon atmosphere) was added NaOAc (860 mg, 0.3 equiv.) and PCC (11.6 g, 1.5 equiv.). After the mixture had been stirred for 2 h at room temperature, dry Et_2O (approx 100 mL) was added and the mixture was filtered through Florisil® (approx. 100 g), using ether as the eluant. The material remaining in the reaction vessel was rinsed (and sonicated) thoroughly with Et_2O, and the washings were also passed through the Florisil® column. The combined eluate was dried ($MgSO_4$) and most of the solvent was removed by atmospheric pressure distillation using a long Vigreux column (50 cm x 2 cm). The crude product thus obtained was immediately dissolved in dry THF (100 mL) (argon atmosphere) and the solution was cooled to -78°C. A solution of vinyl magnesium bromide [2 equiv. (based on 35.7 mmol of 4-pentyn-1-ol)] in THF was added at -78°C and then the mixture was allowed to warm to room temperature. Saturated aqueous NH_4Cl (approx. 50 mL) and Et_2O (approx. 50 mL)

were added, and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 50 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated by atmospheric pressure distillation, using a long Vigreux column (50 cm x 2 cm). The remaining volatile oil was carried on to the next step without further purification.

To a stirred solution of the crude oil in dry DMF (80 mL) (argon atmosphere) was added imidazole (6.07 g, 2.5 equiv. (based on 35.7 mmol of 4-pentyn-1-ol)) and TBDMSCl (8.07 g, 1.5 equiv.). The mixture was stirred at room temperature overnight. Saturated aqueous $NaHCO_3$ (approx 50 mL) and Et_2O (approx 50 mL) were added, and the aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic extracts were washed with brine (2 x 50 mL) and then were dried ($MgSO_4$) and concentrated. Flash chromatography of the crude reaction product (2:98 Et_2O - petroleum ether; 180 g of silica gel), followed by distillation of the oil thus obtained (80-90°C/0.5 Torr), gave 2.5 g (31%) of the acetylene **121**, a colourless oil which exhibited ir (neat): 3314, 3081, 2121, 1254, 838 cm^{-1}; ^1H nmr (400 MHz) δ: 0.02 (s, 3H, -SiMe), 0.06 (s, 3H, -SiMe), 0.89 (s, 9H, -SiBu^t), 1.68 (m, 2H, methylene **Y**), 1.92 (t, 1H, acetylenic H, J = 4 Hz), 2.22 (m, 2H, methylene **Z**), 4.22 (m, 1H, H_X), 5.05 (ddd, 1H, H_D, J = 10 Hz, J = 2 Hz, J = 2 Hz), 5.17 (ddd, 1H, H_E, J = 16 Hz, J = 2 Hz, J = 2 Hz), 5.78 (ddd, 1H, H_F, J = 16 Hz, J = 10 Hz, J = 6 Hz). *Exact Mass* calcd. for $C_{13}H_{24}OSi$ (M^+): 224.1597; found: 224.1593.

General Procedure D. The preparation of primary propargyl alcohols **117A.**

To a cold (-78°C) stirred solution of the terminal acetylene (1 equiv.) in dry THF (argon atmosphere) was added a solution of MeLi (1 equiv.) in Et_2O. After the mixture had been stirred at -78°C for 10 min and at -20°C for 1 h, solid paraformaldehyde (4 equiv.) was added and the mixture was allowed to warm to room temperature. After the mixture had been

stirred for 30 min at room temperature, saturated aqueous $NaHCO_3$ and Et_2O were added. The phases were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography, followed by distillation.

Preparation of the alcohol **123**.

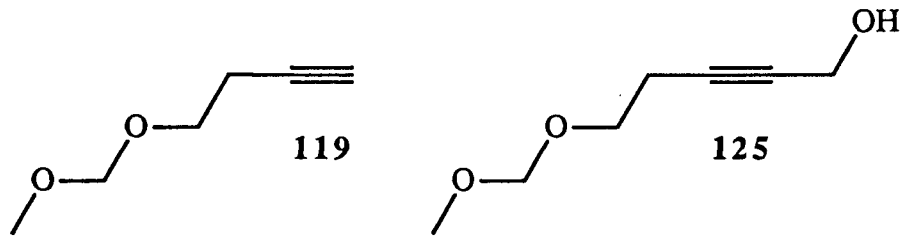
118 **123**

Following general procedure D, the terminal acetylene **118** (2.8 g, 15.22 mmol; in 75 mL of dry THF) was converted into the corresponding lithium acetylide, which was allowed to react with paraformaldehyde (1.85 g, 4 equiv.). Flash chromatography of the crude reaction product (3:7 Et_2O - petroleum ether; 130 g of silica gel), followed by distillation of the oil thus obtained (75-80°C/0.5 Torr), gave 2.4 g (74%) of the alcohol **123**, a colourless oil which exhibited ir (neat): 3394, 2227, 1473, 1109 cm^{-1}; ^1H nmr (300 MHz) δ: 0.06 (s, 6H, -Si$\underline{Me_2}$), 0.89 (s, 9H, -Si$\underline{Bu^t}$), 1.8-1.95 (br m, 1H, -O$\underline{H}$), 2.43 (tt, 2H, -SiOCH$_2$C$\underline{H_2}$-, J = 7 Hz, J = 2 Hz), 3.72 (t, 2H, -SiOC$\underline{H_2}$-, J = 7 Hz), 4.24 (br s, 2H, -C$\underline{H_2}$OH). On addition of D_2O, the signal at δ 1.8-1.95 (-O$\underline{H}$) disappeared, and the signal at δ 4.24 (-C$\underline{H_2}$OH) sharpened to a t (J = 2 Hz). *Exact Mass* calcd. for $C_7H_{13}O_2Si$ (M^+-Bu^t): 157.0685; found: 157.0679; cims (negative ion detection, NH_3): 213 (M^--H).

Preparation of the alcohol **124.**

Following general procedure D, the terminal acetylene **120** (2 g, 9.43 mmol; in 50 mL of dry THF) was converted into the corresponding lithium acetylide, which was allowed to react with paraformaldehyde (1.2 g, 4 equiv.). Flash chromatography of the crude reaction product (3:7 Et_2O - petroleum ether; 85 g of silica gel), followed by distillation of the oil thus obtained (100-110°C/0.5 Torr), gave 1.85 g (81%) of the alcohol **124**, a colourless oil which exhibited ir (neat): 3362, 2230, 1256, 1107, 838 cm^{-1}; ^1H nmr (300 MHz) δ: 0.04 (s, 6H, -Si<u>Me</u>2), 0.86 (s, 9H, -Si<u>Bu</u>^{t}), 1.57 (m, 4H, -SiOCH2C<u>H2</u>C<u>H2</u>-), 1.78 (br s, 1H, -O<u>H</u>), 2.23 (m, 2H, -SiOCH2CH2CH2C<u>H2</u>-), 3.61 (t, 2H, -SiOC<u>H2</u>-, J = 7 Hz), 4.24 (br t, 2H, -C<u>H2</u>OH, J = 2 Hz). On addition of D_2O, the signal at δ 1.78 (-O<u>H</u>) disappeared. *Exact Mass* calcd. for $C_9H_{27}O_2Si$ (M^+-Bu^t): 185.0998; found: 185.0997; cims (negative ion detection, NH_3): 241 (M^--H).

Preparation of the alcohol **125.**

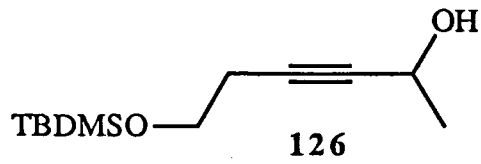


Following general procedure D, the terminal acetylene **119** (8.46 g, 74.2 mmol; in 200 mL of dry THF) was converted into the corresponding lithium acetylide, which was allowed to react with paraformaldehyde (8.9 g, 4 equiv.). Flash chromatography of the crude reaction product (65:35 Et_2O - petroleum ether; 280 g of silica gel), followed by distillation of the oil thus obtained (110-120°C/0.5 Torr), gave 8.60 g (80%) of the alcohol **125**, a colourless oil which exhibited ir (neat): 3424, 2227, 1151, 1111, 1029 cm^{-1}; ^1H nmr (400 MHz) δ: 0.75-0.9 (br m, 1H, -OH), 1.52 (tt, 2H, $-OCH_2\underline{CH_2}-$, J = 6.5 Hz, J = 2 Hz), 3.38 (s, 3H, -OMe), 3.65 (t, 2H, $-OC\underline{H_2}CH_2-$, J = 6.5 Hz), 4.24 (dt, 2H, $-C\underline{H_2}OH$, J = 6 Hz, J = 2 Hz), 4.64 (s, 2H, $-OC\underline{H_2}O-$). On addition of D_2O, the signal at δ 0.75-0.9 (-OH) disappeared, and the signal at δ 4.24 ($-C\underline{H_2}OH$) collapsed to a br s. *Exact Mass* calcd. for $C_5H_7O_2$ ($M^+-C_2H_5O$): 99.0446; found: 99.0446.

General Procedure E. The preparation of secondary propargyl alcohols **117B.**

To a cold (-78°C), stirred solution of the terminal acetylene (1 equiv.) in dry THF (argon atmosphere) was added a solution of MeLi (1 equiv.) in Et_2O. After the mixture had been stirred at -78°C for 10 min and at -20°C for 1 h, it was re-cooled to -78°C and the aldehyde (1.5-5 equiv.) (freshly distilled) was added. The mixture was stirred at -78°C for 10 min and was then allowed to warm to room temperature. Saturated aqueous $NaHCO_3$ and Et_2O were added, the phases were separated, and the aqueous phase was extracted with Et_2O. The combined organic extracts were dried ($MgSO_4$) and concentrated. The crude product was purified by flash cromatography, followed by distillation.

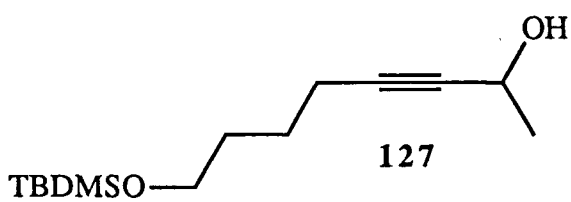
Preparation of the alcohol **126.**



126

Following general procedure E, the terminal acetylene **118** (1.5 g, 8.15 mmol, 1 equiv.; in 50 mL of dry THF) was converted into the corresponding lithium acetylide, which was allowed to react with acetaldehyde (0.72 g, 2 equiv.). Flash chromatography of the crude reaction product (3:7 Et_2O - petroleum ether; 80 g of silica gel), followed by distillation of the oil thus obtained (80-90°C/0.5 Torr), gave 1.71 g (92%) of the alcohol **126**, a colourless oil which exhibited ir (neat): 3368, 2250, 1256, 818 cm^{-1}; ^1H nmr (300 MHz) δ: 0.04 (s, 6H, -Si<u>Me</u>2), 0.86 (s, 9H, -Si<u>Bu</u>^{t}), 1.39 (d, 3H, -<u>Me</u>, J = 8 Hz), 2.25 (br s, 1H, -O<u>H</u>), 2.38 (td, 2H, -OCH2C<u>H</u>2-, J = 7 Hz, J = 2 Hz), 3.68 (t, 2H, -OC<u>H</u>2CH2-, J = 7 Hz), 4.49 (m, 1H, -C<u>H</u>OH-). On addition of D_2O, the signal at δ 2.25 (-O<u>H</u>) disappeared, and the signal at δ 4.49 (-C<u>H</u>OH-) simplified to a br q (J = 8 Hz). *Exact Mass* calcd. for $C_8H_{15}O_2Si$ (M^+-Bu^t): 171.0842; found: 171.0834; cims (negative ion detection, NH_3): 227 (M^--H).

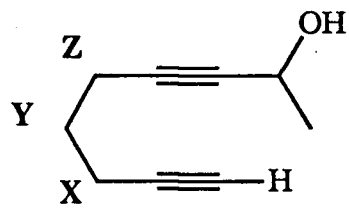
Preparation of the alcohol **127.**



127

Following general procedure E, the terminal acetylene **120** (2 g, 9.43 mmol, 1 equiv.; in 50 mL of dry THF) was converted into the corresponding lithium acetylide, which was allowed to react with acetaldehyde (830 mg, 2 equiv.). Flash chromatography of the crude reaction product (3:7 Et_2O - petroleum ether ; 80 g of silica gel), followed by distillation of the oil thus obtained (110-120°C/0.5 Torr), gave 2.17 g (90%) of the alcohol **127**, a colourless oil which exhibited ir (neat): 3353, 2248, 1256 cm^{-1}; ^1H nmr (300 MHz) δ: 0.03 (s, 6H, -Si<u>Me</u>2), 0.87 (s, 9H, -Si<u>Bu</u>^{t}), 1.40 (d, 3H, -<u>Me</u>, J = 8 Hz), 1.56 (m, 4H, -$OCH_2C\underline{H}_2C\underline{H}_2CH_2$-), 1.74-1.80 (br m, 1H, -O<u>H</u>), 2.22 (m, 2H, -$OCH_2CH_2CH_2C\underline{H}_2$-), 3.60 (t, 2H, -$OC\underline{H}_2CH_2CH_2CH_2$-, J = 6 Hz), 4.50 (m, 1H, -C<u>H</u>Me-). On addition of D_2O, the signal at δ1.74-1.80 (-O<u>H</u>) disappeared, and the signal at δ 4.50 (-C<u>H</u>Me-) simplified to a br q (J = 8 Hz). *Exact Mass* calcd. for $C_{10}H_{19}O_2Si$ (M^+-Bu^t): 199.1155; found: 199.1156; cims (negative ion detection, NH_3): 255 (M^--H).

<u>Preparation of the alcohol **128**.</u>

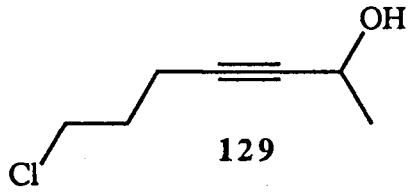


128

Following general procedure E, 1,6-heptadiyne (1 g, 10.87 mmol, 1 equiv.; in 50 mL of dry THF) was converted into the corresponding lithium acetylide, which was allowed to react with acetaldehyde (2.39 g, 5 equiv.). Flash chromatography of the crude product (35:65 Et_2O - petroleum ether; 65 g of silica gel), followed by distillation of the oil thus

obtained (80-85°C/0.5 Torr), gave 883 mg (60%) of the alcohol **128**, a colourless oil which exhibited ir (neat): 3301, 2247, 2118, 1154, 1013, 882 cm^{-1}; ^1H nmr (400 MHz) δ: 1.41 (d, 3H, -CHMe-, *J* = 6.5 Hz), 1.65-1.75 (m, 3H , -OH and methylene **Y**), 1.95 (t, 1H, acetylenic H, *J* = 2.5 Hz), 2.25-2.40 (m, 4H, methylenes **X** and **Z**), 4.49 (m, 1H, -CHMe-). On addition of D_2O, the signal at δ 1.65-1.75 (-OH and H_Y) collapsed to a quintet (2H, H_Y, *J* = 7 Hz), and the signal at 4.49 (-CHMe-) simplified to a br q (*J* = 6.5 Hz). *Exact Mass* calcd. for $C_9H_{11}O$ (M^+-H): 135.0810; found: 135.0815.

Preparation of the alcohol **129.**

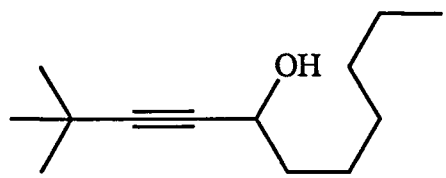


129

Following general procedure E, 5-chloro-1-pentyne (4 g, 39 mmol, 1 equiv.; in 100 mL of dry THF) was converted into the corresponding lithium acetylide, which was allowed to react with acetaldehyde (3.43 g, 2 equiv.). Flash chromatography of the crude reaction product (3:7 Et_2O - petroleum ether; 150 g of silica gel), followed by distillation of the oil thus obtained (65-70 °C/0.5 Torr), gave 4.85 g (85%) of the alcohol **129**, a colourless oil which exhibited ir (neat): 3372, 1089, 1050, 881 cm^{-1}; ^1H nmr (300 MHz) δ: 1.36 (d, 3H, -Me, *J* = 8 Hz), 1.80 (quintet, 2H, $ClCH_2CH_2CH_2$-, *J* = 8 Hz), 2.33 (td, 2H, $ClCH_2CH_2CH_2$-, *J* = 8 Hz, *J* = 2 Hz), 2.75 (br s, 1H, -OH), 3.59 (t, 2H, $ClCH_2CH_2CH_2$-, *J* = 8 Hz), 4.46 (m, 1H, -CHMe-). On addition of D_2O, the signal at

δ 2.75 (-O<u>H</u>) disappeared, and the signal at δ 4.46 (-C<u>H</u>Me-) simplified to a br q (J = 8 Hz). *Exact Mass* calcd. for $C_7H_{11}{}^{35}ClO(M^+)$: 146.0499; found: 146.0504.

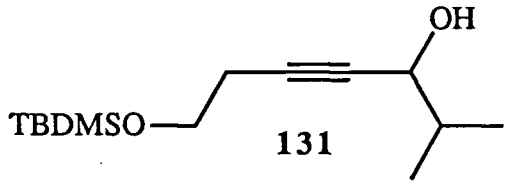
<u>Preparation of the alcohol **130**</u>



130

Following general procedure E, 3,3-dimethyl-1-butyne (3.5 g, 42.68 mmol, 1 equiv.; in 120 mL of dry THF) was converted into the corresponding lithium acetylide, which was allowed to react with heptanal (7.3 g, 1.5 equiv.). Flash chromatography of the crude reaction product (3:7 Et_2O - petroleum ether; 250 g of silica gel), followed by distillation of the oil thus obtained (80-85°C/0.5 mmol), gave 8.05 g (96%) of the alcohol **130**, a colourless oil which exhibited ir (neat): 3342, 2238, 1460, 1265 cm^{-1}; ^1H nmr (300 MHz) δ: 0.87 (m, 3H, -$CH_2C\underline{H}_3$), 1.20 (s, 9H, -$\underline{Bu}^t$), 1.25-1.70 (m, 10H), 2.85 (br s, 1H, -O<u>H</u>), 4.33 (br t, 1H, -C<u>H</u>OH-, J = 8 Hz). On addition of D_2O, the signal at δ 2.85 (-O<u>H</u>) disappeared. *Exact Mass* calcd. for $C_{13}H_{24}O$ (M^+): 196.1828; found: 196.1819.

Preparation of the alcohol **131**.



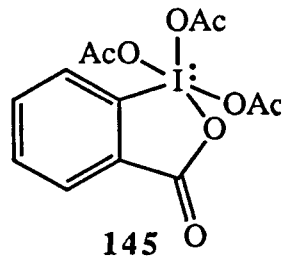
Following general procedure E, the terminal acetylene **118** (8.212 g, 44.6 mmol, 1 equiv.; in 120 mL of dry THF) was converted into the corresponding lithium acetylide, which was allowed to react with 2-methylpropanal (4.82 g, 1.5 equiv.). Flash chromatography of the crude reaction product (3:7 Et_2O - petroleum ether; 300 g of silica gel), followed by distillation of the oil thus obtained (110-120°C/0.5 Torr), gave 9.70 g (85%) of the alcohol **131**, a colourless oil which exhibited ir (neat): 3368, 2218, 1256, 1113, 836, 777 cm^{-1}; ^1H nmr (400 MHz) δ: 0.06 (s, 6H, -Si$\underline{Me}_2$), 0.89 (s, 9H, -Si$\underline{Bu}^t$), 0.96, 0.98 (2 doublets, 6H, $\underline{Me}_2$CH-, J = 6 Hz, J = 6 Hz), 1.70 (br d, 1H, -O$\underline{H}$, J = 4 Hz), 1.82 (m, 1H, -C$\underline{H}Me_2$), 2.42 (td, 2H, -$OCH_2C\underline{H}_2$-, J = 8 Hz, J = 2 Hz), 3.70 (t, 2H, -$OC\underline{H}_2CH_2$-, J = 8 Hz), 4.13 (br m, 1H, -C$\underline{H}$OH-). On addition of D_2O, the signal at δ 1.70 (-O$\underline{H}$) disappeared, and the signal at δ 4.13 (-C$\underline{H}$OH-) simplified to a br d (J = 6 Hz). *Exact Mass* calcd. for $C_{11}H_{21}O_2Si$ (M^+-Pr^i): 213.1311; found: 213.1318; cims (positive ion detection, NH_3): 257 (M^++H).

General Procedure F. The oxidation of propargyl alcohols **117** to α,β-acetylenic aldehydes and ketones **115**

A mixture of the propargyl alcohol (1 equiv.), NaOAc (0.3 equiv) and PCC (1.5 - 2.5 equiv.) in dry CH_2Cl_2 (argon atmosphere) was stirred (2 - 2.5 h) at room temperature. Dry

Et_2O (approx. the same volume as that of solvent used for the reaction) was added and the mixture was filtered through a column of Florisil® (approx. 30 g of Florisil® per g of propargyl alcohol), using ether as the eluant. The material remaining in the reaction vessel was rinsed (and sonicated) thoroughly with Et_2O, and the washings were also passed through the Florisil® column. The combined eluate was dried ($MgSO_4$) and concentrated. The crude reaction product was purified by flash chromatography, followed by distillation.

General Procedure G. The oxidation of primary propargyl alcohols **117A** to α,β-acetylenic aldehydes **115A**

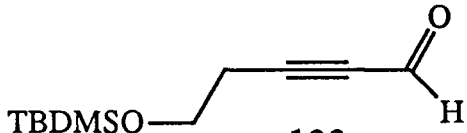


145

To a stirred suspension of the Dess-Martin periodinane reagent **145**[93] (1.3 equiv.) (prewashed with dry Et_2O) in dry CH_2Cl_2 (approx. 5 mL per mmol of the periodinane) (argon atmosphere) was added a solution of the propargyl alcohol (1 equiv.) in dry CH_2Cl_2 (approx 3 mL per mmol of the propargyl alcohol). After the mixture had been stirred for 15 min at room temperature, it was diluted with Et_2O (approx. the same volume as that of solvent used in the reaction) and then was poured into saturated aqueous $NaHCO_3$ (approx. the same volume as the volume of solvent used for the reaction) containing 7 equiv. of $Na_2S_2O_3$. The mixture was stirred vigorously until all solids had dissolved (approx. 10 min). The phases were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with saturated aqueous $NaHCO_3$ and with water,

and were then dried ($MgSO_4$) and concentrated. The crude reaction product was purified by distillation.

Preparation of the aldehyde **133**.

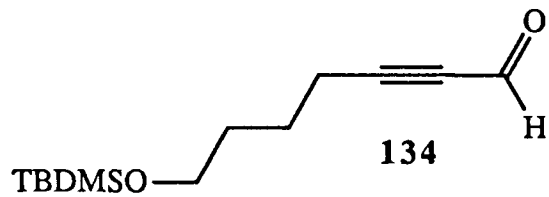


133

Following general procedure F, the propargyl alcohol **123** (3.6 g, 16.82 mmol, 1 equiv.; in 120 mL of dry CH_2Cl_2) was allowed to react with NaOAc (404 mg, 0.3 equiv.) and PCC (5.44 g, 1.5 equiv.) for 2 h at room temperature. Flash chromatography of the crude reaction mixture (15:85 Et_2O - petroleum ether; 140 g of silica gel), followed by distillation of the oil thus obtained (75-85°C/0.5 Torr), gave 2.55 g (72%) of the aldehyde **133**, a colourless oil which exhibited ir (neat): 2740, 2207, 1673, 1257 cm^{-1}; ^1H nmr (300 MHz) δ: 0.05 (s, 6H, -Si<u>Me</u>$_2$), 0.87 (s, 9H, -Si<u>Bu</u>^{t}), 2.60 (t, 2H, -OCH$_2$C<u>H</u>$_2$-, J = 8 Hz), 3.77 (t, 2H, -OC<u>H</u>$_2$CH$_2$-, J = 8 Hz), 9.15 (s, 1H, -C<u>H</u>O). *Exact Mass* calcd. for $C_7H_{11}O_2Si$ (M^+-Bu^t): 155.0528; found: 155.0532; cims (negative ion detection, NH_3): 211 (M^--H).

Following general procedure G, the propargyl alcohol **123** (2.4 g, 11.2 mmol, 1 equiv.) was allowed to react with the Dess-Martin periodinane reagent (6.2 g, 1.3 equiv.) for 15 min at room temperature. Distillation of the crude reaction product gave 2.1 g (88%) of the aldehyde **133**.

Preparation of the aldehyde **134.**

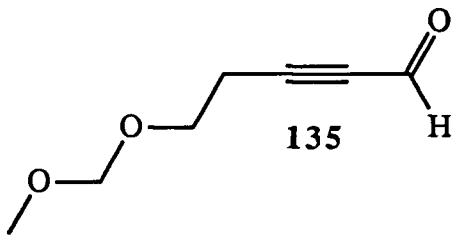


134

Following general procedure F, the propargyl alcohol **124** (1 g, 4.13 mmol, 1 equiv.; in 50 mL of dry CH_2Cl_2) was allowed to react with NaOAc (100 mg, 0.3 equiv.) and PCC (1.34 g, 1.5 equiv.) for 2 h at room temperature. Flash chromatography of the crude reaction product (15:85 Et_2O - petroleum ether; 60 g of silica gel), followed by distillation of the oil thus obtained (95-100°C/0.5 Torr), gave 730 mg (74%) of the aldehyde **134**, a colourless oil which exhibited ir (neat): 2742, 2202, 1673, 1107, 838 cm^{-1}; ^1H nmr (300 MHz) δ: 0.05 (s, 6H, -Si<u>Me</u>2), 0.9 (s, 9H, -Si<u>Bu</u>^{t}), 1.65 (m, 4H, -OCH2C<u>H2</u>C<u>H2</u>CH2-), 2.46 (t, 2H, -OCH2CH2CH2C<u>H2</u>-, J = 8 Hz), 3.63 (t, 2H, -OC<u>H2</u>CH2CH2CH2-, J = 6 Hz), 9.18 (s, 1H, -C<u>H</u>O). *Exact Mass* calcd. for $C_9H_{15}O_2Si$ (M^+-Bu^t): 183.0842; found: 183.0834; cims (negative ion detection, NH_3): 239 (M^--H).

Following general procedure G, the propargyl alcohol **124** (900 mg, 3.7 mmol, 1 equiv.) was allowed to react with the Dess-Martin periodinane reagent (2.05 g, 1.3 equiv.) for 15 min at room temperature. Distillation of the crude reaction product gave 768 mg (86%) of the aldehyde **134.**

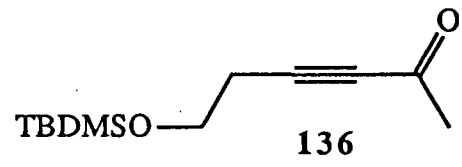
Preparation of the aldehyde **135.**



135

Following general procedure F, the propargyl alcohol **125** (3.55 g, 24.65 mmol, 1 equiv.; in 150 mL of dry CH_2Cl_2) was allowed to react with NaOAc (600 mg, 0.3 equiv.) and PCC (8.0 g, 1.5 equiv.) for 2 h at room temperature. Flash chromatography of the crude reaction product (6:4 Et_2O - petroleum ether; 120 g of silica gel), followed by distillation of the oil thus obtained (90-95°C/0.5 Torr), gave 1.90 g (57%) of the aldehyde **135**, a colourless oil which exhibited ir (neat): 2827, 2207, 1669, 1151, 1111, 963 cm^{-1}; ^1H nmr (400 MHz) δ: 2.72 (t, 2H, -OCH_2CH_2-, J = 7 Hz), 3.38 (s, 3H, -OMe), 3.72 (t, -OCH_2CH_2-, J = 7 Hz), 4.64 (s, 2H, -OCH_2O-), 9.18 (s, 1H, -CHO). *Exact Mass* calcd. for $C_7H_9O_3$ (M^+-H): 141.0551; found: 141.0546.

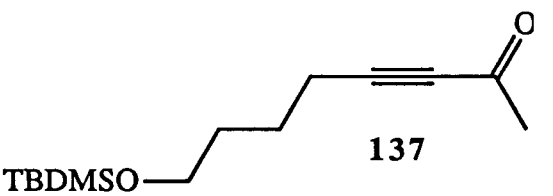
Preparation of the ketone **136.**



136

Following general procedure F, the propargyl alcohol **126** (200 mg, 0.88 mmol, 1 equiv.; in 8 mL of dry CH_2Cl_2) was allowed to react with NaOAc (21 mg, 0.3 equiv.) and PCC (472 mg, 2.5 equiv.) for 2.5 h at room temperature. Flash chromatography of the crude reaction product (1:9 Et_2O - petroleum ether; 45 g of silica gel), followed by distillation of the oil thus obtained (70-80°C/0.5 Torr), gave 146 mg (74%) of the ketone **136**, a colourless oil which exhibited ir (neat): 2214, 1680, 1113, 839 cm^{-1}; ^1H nmr (300 MHz) δ: 0.08 (s, 6H, -SiMe2), 0.89 (s, 9H, -SiBu^t), 2.30 (s, 3H, -Me), 2.56 (t, 2H, -OCH_2CH_2-, J = 8 Hz), 3.76 (t, 2H, -OCH_2CH_2-, J = 8 Hz). *Exact Mass* calcd. for $C_8H_{13}O_2Si$ (M^+-Bu^t): 169.0685; found: 169.0684.

Preparation of the ketone **137.**

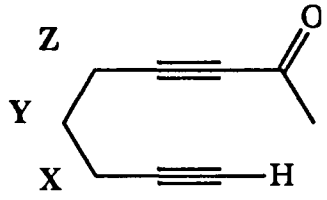


137

Following general procedure F, the propargyl alcohol **127** (1 g, 3.9 mmol, 1 equiv.; in 40 mL of dry CH_2Cl_2) was allowed to react with NaOAc (96 mg, 0.3 equiv.) and PCC (2.10 g, 2.5 equiv.) for 2.5 h at room temperature. Flash chromatography of the crude reaction product (1:9 Et_2O - petroleum ether; 75 g of silica gel), followed by distillation of the oil thus obtained (95-100°C/0.5 Torr), gave 755 mg (76%) of the ketone **137**, a colourless oil which exhibited ir (neat): 2212, 1680, 1360, 1104 cm^{-1}; ^1H nmr (300 MHz) δ: 0.04 (s, 6H, -SiMe2), 0.88 (s, 9H, -SiBu^t), 1.62 (m, 4H, -$OCH_2CH_2CH_2CH_2$-), 2.30 (s, 3H, -Me), 2.38 (t, 2H, -$OCH_2CH_2CH_2CH_2$-, J = 7 Hz), 3.62 (t, 2H, -$OCH_2CH_2CH_2CH_2$-, J

= 6 Hz). *Exact Mass* calcd. for $C_{10}H_{17}O_2Si$ (M^+-Bu^t): 197.0998; found: 197.1006; cims (negative ion detection, NH_3): 253 (M^--H).

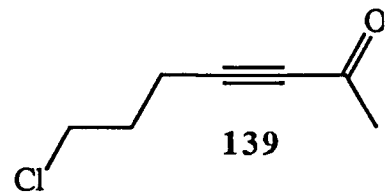
Preparation of the ketone **138.**



138

Following general procedure F, the propargyl alcohol **128** (130 mg, 0.96 mmol, 1 equiv.; in 8 mL of dry CH_2Cl_2) was allowed to react with NaOAc (23 mg, 0.3 equiv.) and PCC (515 mg, 2.5 equiv.) for 2.5 h at room temperature. Flash chromatography of the crude reaction mixture (1:9 Et_2O - petroleum ether; 35 g of silica gel), followed by distillation of the oil thus obtained (120-130°C/6.0 Torr), gave 70 mg (55%) of the ketone **138**, a colourless oil which exhibited ir (neat): 2215, 1680, 1231 cm^{-1}; ^1H nmr (400 MHz) δ: 1.79 (quintet, 2H, methylene **Y**, J = 7 Hz), 1.98 (t, 1H, acetylenic H, J = 2.5 Hz), 2.31 (s, 3H, -Me), 2.32 (td, 2H, methylene **X**, J = 7 Hz, J = 2.5 Hz), 2.50 (t, 2H, methylene **Z**, J = 7 Hz). *Exact Mass* calcd. for C_9H_9O (M^+-H): 133.0653; found: 133.0651.

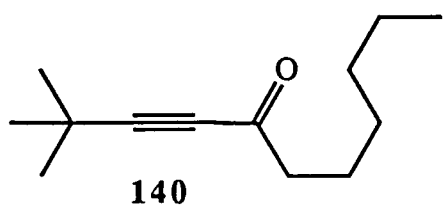
Preparation of the ketone **139.**



139

Following general procedure F, the propargyl alcohol **129** (1.5 g, 10.24 mmol, 1 equiv.; in 100 mL of dry CH_2Cl_2) was allowed to react with NaOAc (252 mg, 0.3 equiv.) and PCC (5.52 g, 2.5 equiv.) for 2.5 h at room temperature. Flash chromatography of the crude reaction product (1:9 Et_2O - petroleum ether; 80 g of silica gel), followed by distillation of the oil thus obtained (60-65°C/0.5 Torr), gave 1.09 g (74%) of the ketone **139**, a colourless oil which exhibited ir (neat): 2215, 1677, 1232, 734 cm^{-1}; ^1H nmr (300 MHz) δ: 2.0 (quintet, 2H, -$ClCH_2\underline{CH_2}CH_2$-, J = 7 Hz), 2.30 (s, 3H, -Me), 2.54 (t, 2H, -$ClCH_2CH_2\underline{CH_2}$-, J = 7 Hz), 3.51 (t, 2H, -$Cl\underline{CH_2}CH_2CH_2$-, J = 7 Hz). *Exact Mass* calcd. for $C_7H_9{}^{35}ClO$ (M^+): 144.0343; found: 144.0343.

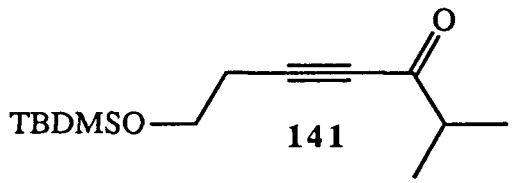
Preparation of the ketone **140**



140

Following general procedure F, the propargyl alcohol **130** (4.0 g, 20.41 mmol, 1 equiv.; in 130 mL of dry CH_2Cl_2) was allowed to react with NaOAc (500 mg, 0.3 equiv.) and PCC (11 g, 2.5 equiv.) for 2.5 h at room temperature. Flash chromatography of the crude reaction product (1:9 Et_2O - petroleum ether; 150 g of silica gel), followed by distillation of the oil thus obtained (75-80°C/0.5 Torr), gave 2.85 g (72%) of the ketone **140**, a colourless oil which exhibited ir (neat): 2213, 1675, 1263, 1142 cm^{-1}; ^1H nmr (300 MHz) δ: 0.87 (m, 3H, -CH_2CH_3), 1.28 (br s, 15H), 1.63 (m, 2H), 2.50 (t, 2H, -C(O)CH_2-, J = 7 Hz). *Exact Mass* calcd. for $C_{13}H_{22}O$ (M^+): 194.1672; found 194.1680.

Preparation of the ketone **141.**

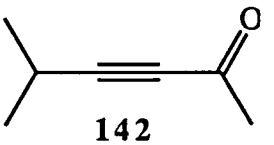


141

Following general procedure F, the propargyl alcohol **131** (2.92 g, 11.41 mmol, 1 equiv.; in 80 mL of dry CH_2Cl_2) was allowed to react with NaOAc (280 mg, 0.3 equiv.) and PCC (6.15 g, 2.5 equiv.) for 2.5 h at room temperature. Flash chromatography of the crude reaction product (1:9 Et_2O - petroleum ether; 150 g of silica gel), followed by distillation of the oil thus obtained (95-105°C/0.5 Torr), gave 2.35 g (81%) of the ketone **141**, a colourless oil which exhibited ir (neat): 1676, 2214, 1118, 779 cm^{-1}; ^1H nmr (400 MHz) δ: 0.08 (s, 6H, -$SiMe_2$), 0.90 (s, 9H, -$SiBu^t$), 1.18 (d, 6H, -$CHMe_2$, J = 8 Hz), 2.58-2.68 (m, 3H, -$CHMe_2$ and -OCH_2CH_2-), 3.80 (t, 2H, -OCH_2CH_2-, J = 6 Hz). *Exact Mass* calcd. for

$C_{10}H_{17}O_2Si$ (M^+-Bu^t): 197.0998; found: 197.1003; cims (positive ion detection, CH_4): 255 (M^++H).

Preparation of the ketone **142.**



142

To a cold (-78°C), stirred solution of 3-methyl-1-butyne (3 g, 44 mmol, 1 equiv.) in dry THF (150 mL) (argon atmosphere) was added a solution of MeLi (1 equiv.) in Et_2O. After the mixture had been stirred at -78°C for 10 min and at -20° for 1 h, it was re-cooled to -78°C and acetaldehyde (2.52 g, 1.3 equiv.) was added. The mixture was stirred at -78°C for 10 min and then was allowed to warm to room temperature. Saturated aqueous $NaHCO_3$ (50 mL) and Et_2O (50 mL) were added. The phases were separated and the aqueous layer was extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried ($MgSO_4$) and most of the solvent was removed by atmospheric pressure distillation using a long Vigreux column (50 cm x 2 cm). Distillation of the residual oil thus obtained (80-90°C/10 Torr) gave 4.6 g of a crude oil, which was carried on to the next step without further purification.

To a solution of this crude oil in dry CH_2Cl_2 (200 mL) (argon atmosphere), was added NaOAc (1.08 g, 0.3 equiv. (based on 44 mmol of 3-methyl-1-butyne)) and PCC (14.22 g, 1.5 equiv.). After the mixture had been stirred at room temperature for 3 h, dry Et_2O (approx 100 mL) was added and the mixture was filtered through a column of Florisil®

(approx 150 g), using Et_2O as the eluant. The material remaining in the reaction vessel was thoroughly rinsed (and sonicated) with Et_2O, and the washings were also passed through the Florisil® column. The combined eluate was dried ($MgSO_4$) and most of the solvent was removed by atmospheric pressure distillation using a long Vigreux column (50 cm x 2 cm). Distillation of the crude oil thus obtained (80-90°C/10 Torr) gave 2.7 g (56%) of the ketone **142**, a colourless oil which exhibited ir (neat): 2208, 1679, 1228 cm^{-1}; ^1H nmr (300 MHz) δ: 1.20 (d, 6H, -CH<u>Me</u>$_2$, J = 8 Hz), 2.29 (s, 3H,- <u>Me</u>), 2.68 (septet, 1H, -C<u>H</u>Me$_2$, J = 8 Hz). *Exact Mass* calcd. for $C_7H_{10}O$ (M^+): 110.0732; found: 110.0726.

<u>General Procedure H. The preparation of α,β-acetylenic methyl ketones from the corresponding terminal acetylenes</u>[95]

To a cold (-78°C), stirred solution of the terminal acetylene (1 equiv.) in dry Et_2O (argon atmosphere) was added a solution of MeLi (1 equiv.) in Et_2O. After the reaction mixture had been stirred at -78°C for 10 min and at -20°C for 1 h, it was re-cooled to -78°C and then was transferred slowly (over approx.10 min, via cannula) into a cold (-78°C), stirred solution of Ac_2O (2 equiv.) in Et_2O. After the mixture had been stirred for 10 min at -78°C and 30 min at -48°C, saturated NH_4Cl-NH_4OH (pH 8) (approx. the same volume as that of solvent used for the reaction) was added and the vigorously stirred mixture was allowed to warm to room temperature. The phases were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with saturated aqueous NH_4Cl, dried ($MgSO_4$) and concentrated. The crude reaction product was then purified by flash chromatography, followed by distillation.

Preparation of the ketone **136**

Following general procedure H, the terminal acetylene **118** (3.26 g, 17.7 mmol, 1 equiv.; in 80 mL of dry Et_2O) was converted into the corresponding lithium acetylide, which was added to Ac_2O (3.61 g, 2 equiv.; in 30 mL of dry Et_2O). Flash chromatography of the crude reaction product (1:9 Et_2O - petroleum ether; 130 g of silica gel), followed by distillation of the oil thus obtained (70-80°C/0.5 Torr), gave 2.0 g (50%) of the ketone **136**.

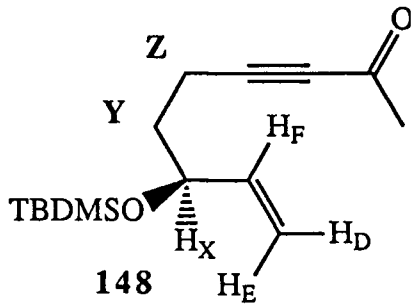
Preparation of the ketone **138.**

Following general procedure H, 1,6-heptadiyne (3 g, 32.56 mmol, 1 equiv.; in 100 mL of dry Et_2O) was converted into the corresponding lithium acetylide, which was added to Ac_2O (6.65 g, 2 equiv.; in 50 mL of dry Et_2O). Flash chromatography of the crude reaction product (15:85 Et_2O - petroleum ether; 150 g of silica gel), followed by distillation of the oil thus obtained (120-130°C/6.0 Torr), gave 2.18 g (50%) of the ketone **138**.

Preparation of the ketone **139.**

Following general procedure H, 5-chloro-1-pentyne (3 g, 29.27 mmol; in 100 mL of dry Et_2O) was converted into the corresponding lithium acetylide, which was added to Ac_2O (6 g , 2 equiv.; in 40 mL of dry Et_2O). Flash chromatography of the crude reaction product (1:9 Et_2O - petroleum ether; 150 g of silica gel), followed by distillation of the oil thus obtained (60-65°C/0.5 Torr), gave 2.31 g (54%) of the ketone **139**.

Preparation of the ketone **148.**



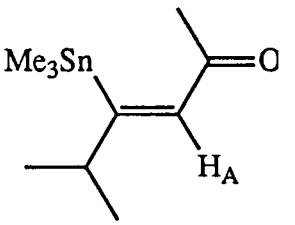
Following general procedure H, the terminal acetylene **121** (441 mg, 1.97 mmol, 1 equiv.; in 10 mL of dry Et_2O) was converted into the corresponding lithium acetylide, which was added to Ac_2O (402 mg, 2 equiv.; in 4 mL of dry Et_2O). Flash chromatography of the crude reaction product (1:9 Et_2O - petroleum ether; 50 g of silica gel), followed by distillation of the oil thus obtained (90-100°C/0.5 Torr), gave 330 mg (63%) of the ketone **148**, a colourless oil which exhibited ir (neat): 3082, 2211, 1681, 1228, 838 cm^{-1}; ^1H nmr (400 MHz) δ: 0.03 (s, 3H, -SiMe), 0.06 (s, 3H, -SiMe), 0.89 (s, 9H, -SiBu^t), 1.74 (m, 2H, methylene **Y**), 2.31 (s, 3H, -Me), 2.41 (m, 2H, methylene **Z**), 4.22 (m, 1H, H_X), 5.08 (ddd, 1H, H_D, J = 10 Hz, J = 2 Hz, J = 2 Hz), 5.19 (ddd, 1H, H_E, J = 17 Hz, J = 2 Hz, J = 2 Hz), 5.77 (ddd, 1H, H_F, J = 17 Hz, J = 10 Hz, J = 6 Hz). *Exact Mass* calcd. for $C_{11}H_{17}O_2Si$ (M^+-Bu^t): 209.0998; found: 209.0995; cims (positive ion detection, CH_4): 267 (M^++H).

General Procedure I. The Pd(0)-catalyzed reaction of α,β-acetylenic aldehydes and ketones with hexamethylditin[96]

To a stirred solution of the α,β-acetylenic aldehyde or ketone (1 equiv.) in dry THF (argon atmosphere) was added $(Me_3Sn)_2$ (1 equiv.) and $Pd(PPh_3)_4$ (5 mol%). The mixture

was allowed to reflux (2-24 h), and the progress of the reaction was monitored by tlc. When the reaction was complete, the solvent was removed and the viscous residual oil was purified by chromatography, followed by distillation.

Preparation of the ketone **150.**

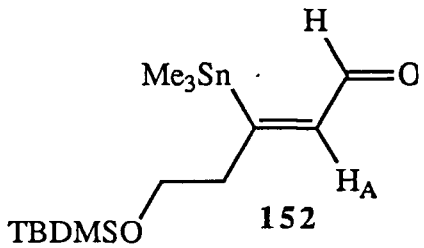


150

Following general procedure I, a solution of the ketone **142** (200 mg, 1.82 mmol), $(Me_3Sn)_2$ (600 mg) and $Pd(PPh_3)_4$ (105 mg, 5 mol %) in dry THF (3 mL) was allowed to reflux for 5 h. Flash chromatography of the crude product (2:98 Et_2O - petroleum ether; 45 g of silica gel) followed by distillation of the oil thus obtained (70-75°C/0.5 Torr), gave 400 mg (80%) of the ketone **150**, a colourless oil which exhibited ir (neat): 1682, 1568, 1203, 770 cm^{-1}; ^1H nmr (300 MHz): 0.09 (s, 9H, -Sn<u>Me</u>3, $^2J_{Sn-H}$ = 54 Hz), 1.03 (d, 6H, -CH<u>Me</u>2, J = 6.5 Hz), 2.20 (s, 3H, -<u>Me</u>), 2.75 (septet of d, -C<u>H</u>Me2, J = 6.5 Hz, J = 1.5 Hz, $^3J_{Sn-H}$ = 54 Hz), 6.77 (d, 1H, <u>H</u>A, J = 1.5 Hz, $^3J_{Sn-H}$ = 127 Hz). In nOe difference experiments, irradiation at δ 6.77 (<u>H</u>A) caused signal enhancement at δ 2.75 (-C<u>H</u>Me2), δ 1.03 (-CH<u>Me</u>2) and δ 2.20 (-<u>Me</u>), while irradiation at δ 2.75 (-C<u>H</u>Me2) caused signal enhancement at δ 1.03 (-CH<u>Me</u>2) and δ 6.77 (<u>H</u>A). ^{13}C nmr (75.4 MHz) δ: -6.86,

21.68, 30.13, 36.17, 130.66, 183.04, 197.94. *Exact Mass* calcd. for $C_9H_{17}OSn$ (M^+-Me): 261.0301; found: 261.0297.

Preparation of the aldehyde **152.**

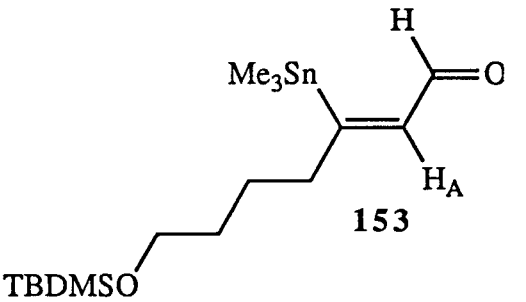


152

Following general procedure I, a solution of the aldehyde **133** (1.50 g, 7.08 mmol), $(Me_3Sn)_2$ (2.33 g) and $Pd(PPh_3)_4$ (410 mg, 5 mol %) in dry THF (12 mL) was allowed to reflux for 2 h. Flash chromatography of the crude product (5:95 Et_2O - petroleum ether; 100 g of silica gel), followed by distillation of the oil thus obtained (110-120°C/0.5 Torr), gave 2.33 g (87%) of the aldehyde **152**, a colourless oil which exhibited ir (neat): 2743, 1685, 1563, 1099, 776 cm^{-1}; ^1H nmr (300 MHz) δ: 0.04 (s, 6H, -SiMe2), 0.26 (s, 9H, -SnMe3, $^2J_{Sn-H}$ = 54 Hz), 0.86 (s, 9H, -SiBu^t), 2.69 (td, 2H, -OCH_2CH_2-, J = 6.5 Hz, J = 1.3 Hz, $^3J_{Sn-H}$ = 46 Hz), 3.69 (t, 2H, -OCH_2CH_2-, J = 6.5 Hz), 6.68 (dt, 1H, H_A, J = 5.5 Hz, J = 1.3 Hz, $^3J_{Sn-H}$ = 114 Hz), 9.56 (d, 1H, -CHO, J = 5.5 Hz, $^4J_{Sn-H}$ = 5.5 Hz). In nOe difference experiments, irradiation at δ 6.68 (H_A) caused signal enhancement at δ 2.69 (-OCH_2CH_2-) and δ 9.59 (-CHO); irradiation at δ 9.59 (-CHO) caused signal enhancement at δ 6.68 (H_A); irradiation at δ 2.69 (-OCH_2CH_2-) caused signal enhancement at δ 6.68 (H_A) and δ 3.69 (-OCH_2CH_2-). ^{13}C nmr (75.4 MHz) δ: -7.17,

-5.21, 18.40, 25.95, 43.70, 62.18, 140.31, 178.18, 192.37. *Exact Mass* calcd. for $C_{13}H_{27}O_2SnSi$ (M^+-Me): 363.0802; found: 363.0806.

Preparation of the aldehyde **153**.

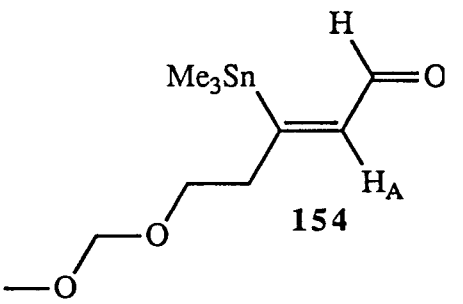


153

Following general procedure I, a solution of the aldehyde **134** (300 mg, 1.25 mmol), $(Me_3Sn)_2$ (413 mg) and $Pd(PPh_3)_4$ (72 mg, 5 mol %) in dry THF (2 mL) was allowed to reflux for 2 h. Flash chromatography of the crude product (5:95 Et_2O - petroleum ether; 30 g of silica gel), followed by distillation of the oil thus obtained (120-130°C/0.5 Torr), gave 448 mg (88%) of the aldehyde **153**, a colourless oil which exhibited ir (neat): 2742, 1685, 1562, 1256, 1106, 775 cm^{-1}; ^1H nmr (300 MHz) δ: 0.02 (s, 6H, -SiMe2), 0.25 (s, 9H, -SnMe3, $^2J_{Sn-H}$ = 55 Hz), 0.87 (s, 9H, -SiBu^t), 1.48 (m, 4H, $-OCH_2CH_2CH_2CH_2-$), 2.49 (br t, 2H, $-OCH_2CH_2CH_2CH_2-$, J = 6.5 Hz, $^3J_{Sn-H}$ = 47 Hz), 3.59 (t, 2H, $-OCH_2CH_2CH_2CH_2-$, J = 6 Hz), 6.62 (dt, 1H, H_A, J = 6 Hz, J = 1.3 Hz, $^3J_{Sn-H}$ = 115 Hz), 9.55 (d, 1H, -CHO, J = 6 Hz, $^4J_{Sn-H}$ = 5.5 Hz). In nOe difference experiments, irradiation at δ 6.62 (H_A) caused signal enhancement at δ 9.55 (-CHO) and δ 2.49 ($-OCH_2CH_2CH_2CH_2-$); irradiation at δ 9.55 (-CHO) caused signal enhancement at δ 6.62 (H_A); irradiation at δ 2.49 ($-OCH_2CH_2CH_2CH_2-$) caused signal enhancement at

δ 6.62 ($\underline{H}_A$). ^{13}C nmr (300 MHz) δ: -7.30, -5.17, 18.40, 25.33, 26.01, 32.37, 41.01, 62.68, 138.59, 181.87, 192.57. *Exact Mass* calcd. for $C_{15}H_{31}O_2SiSn$ (M^+-Me): 391.1115; found: 391.1112.

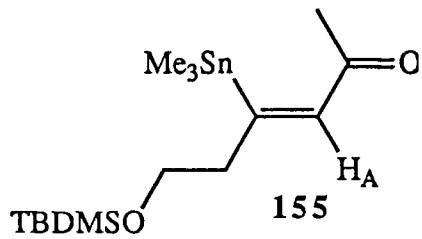
Preparation of the aldehyde **154.**



154

Following general procedure I, a solution of the aldehyde **135** (1.897 g, 13.36 mmol), $(Me_3Sn)_2$ (4.41 g) and $Pd(PPh_3)_4$ (772 mg, 5 mol %) in dry THF (45 mL) was allowed to reflux for 2 h. Flash chromatography of the crude product (35:65 Et_2O - petroleum ether; 120 g of silica gel), followed by distillation of the oil thus obtained (100 - 105°C/0.5 Torr), gave 3.12 g (76%) of the aldehyde **154**, a colourless oil which exhibited ir (neat): 1683, 1562, 1151, 1043, 776 cm^{-1}; ^1H nmr (400 MHz) δ: 0.25 (s, 9H, -Sn$\underline{Me}_3$, $^2J_{Sn-H}$ = 54 Hz), 2.77 (td, 2H, -$OCH_2C\underline{H}_2$-, J = 6.5 Hz, J = 1.3 Hz, $^3J_{Sn-H}$ = 44 Hz), 3.61 (t, 2H, -$OC\underline{H}_2CH_2$-, J = 6.5 Hz), 4.58 (s, 2H, -$OC\underline{H}_2O$-), 6.72 (dt, 1H, $\underline{H}_A$, J = 5.5 Hz, J = 1.3 Hz, $^3J_{Sn-H}$ = 113 Hz), 9.59 (d, 1H, -C$\underline{H}$O, J = 5.5 Hz, $^4J_{Sn-H}$ = 5.5 Hz). *Exact Mass* calcd. for $C_9H_{17}O_3Sn$ (M^+-Me): 293.0199; found: 293.0201.

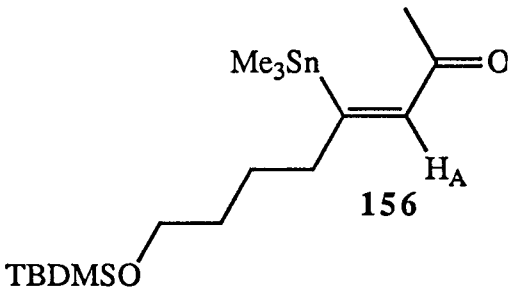
Preparation of the ketone **155.**



155

Following general procedure I, a solution of the ketone **136** (130 mg, 0.58 mmol, 1 equiv.), $(Me_3Sn)_2$ (190 mg) and $Pd(PPh_3)_4$ (33 mg, 5 mol %) in dry THF (2 mL), was allowed to reflux for 2 h. Flash chromatography of the crude reaction product (4:96 Et_2O - petroleum ether; 30 g of silica gel), followed by distillation of the oil thus obtained (110-120°C/0.5 Torr), gave 204 mg (90%) of the ketone **155**, a colourless oil which exhibited ir (neat): 1682, 1573, 1192, 1095, 776 cm^{-1}; ^1H nmr (300 MHz) δ: 0.00 (s, 6H, -Si<u>Me</u>2), 0.10 (s, 9H, -Sn<u>Me</u>3, $^2J_{Sn-H}$ = 54 Hz), 0.84 (s, 9H, -Si<u>Bu</u>^{t}), 2.19 (s, 3H, -<u>Me</u>), 2.63 (td, 2H, -OCH2C<u>H2</u>-, J = 6.5 Hz, J = 1.3 Hz, $^3J_{Sn-H}$ = 49 Hz), 3.62 (t, 2H, -OC<u>H2</u>CH2-, J = 6.5 Hz), 6.82 (br s, 1H, <u>HA</u>, $^3J_{Sn-H}$ = 121 Hz). In nOe difference experiments, irradiation at δ 6.82 (<u>HA</u>) caused signal enhancement at δ 2.63 (-OCH2C<u>H2</u>-) and δ 2.19 (-<u>Me</u>); irradiation at δ 2.63 (-OCH2C<u>H2</u>-) caused signal enhancement at δ 3.62 (-OC<u>H2</u>CH2-) and δ 6.82 (<u>HA</u>); irradiation at δ 2.19 (-<u>Me</u>) caused signal enhancement at δ 6.82 (<u>HA</u>). ^{13}C nmr (75.4 MHz) δ: -7.42, -5.31, 18.23, 25.88, 30.01, 42.51, 61.97, 136.69, 172.45, 197.29. *Exact Mass* calcd. for $C_{14}H_{29}O_2SiSn$ (M^+-Me): 377.0959; found: 377.0966.

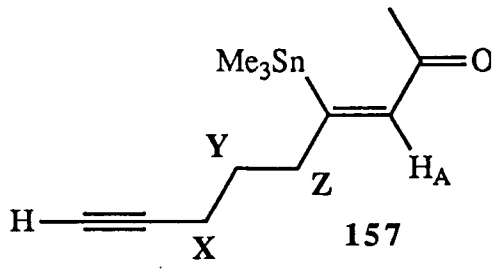
Preparation of the ketone **156.**



156

Following general procedure I, a solution of the ketone **137** (160 mg, 0.63 mmol), $(Me_3Sn)_2$ (208 mg) and $Pd(PPh_3)_4$ (36 mg, 5 mol %) in dry THF (2 mL) was allowed to reflux for 2 h. Flash chromatography of the crude product (4:96 Et_2O - petroleum ether; 35 g of silica gel), followed by distillation of the oil thus obtained (120-130°C/0.5 Torr), gave 265 mg (83%) of the ketone **156**, a colourless oil which exhibited ir (neat): 1682, 1572, 1103, 776 cm^{-1}; ^1H nmr (300 MHz) δ: 0.04 (s, 6H, -Si<u>Me</u>$_2$), 0.12 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn-H}$ = 53 Hz), 0.88 (s, 9H, -Si<u>Bu</u>^{t}), 1.35-1.55 (m, 4H, -$OCH_2\underline{CH_2}\underline{CH_2}CH_2$-), 2.22 (s, 3H, -<u>Me</u>), 2.44 (br t, 2H, -$OCH_2CH_2CH_2\underline{CH_2}$-, J = 6.5 Hz, $^3J_{Sn-H}$ = 49 Hz), 3.60 (t, 2H, -$O\underline{CH_2}CH_2CH_2CH_2$-, J = 6.5 Hz), 6.79 (br s, 1H, <u>H_A</u>, $^3J_{Sn-H}$ = 122 Hz). In nOe difference experiments, irradiation at δ 6.79 (<u>H_A</u>) caused signal enhancement at δ 2.44 (-$OCH_2CH_2CH_2\underline{CH_2}$-) and δ 2.22 (-<u>Me</u>); irradiation at δ 2.22 (-<u>Me</u>) caused signal enhancement at δ 6.79 (<u>H_A</u>); irradiation at δ 2.44 (-$OCH_2CH_2CH_2\underline{CH_2}$-) caused signal enhancement at δ 6.79 (<u>H_A</u>). ^{13}C nmr (75.4 MHz) δ: -7.48, -5.30, 18.31, 25.55, 25.91, 30.09, 32.46, 39.67, 62.91, 134.68, 176.80, 197.59. *Exact Mass* calcd. for $C_{16}H_{33}O_2SiSn$ (M^+-Me): 405.1272; found: 405.1266.

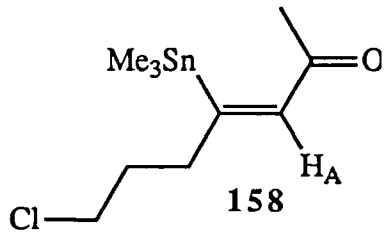
Preparation of the ketone **157**.



157

Following general procedure I, a solution of the ketone **138** (175 mg, 1.31 mmol), $(Me_3Sn)_2$ (431 mg) and $Pd(PPh_3)_4$ (75 mg, 5 mol %) in 4 mL of dry THF was allowed to reflux for 4 h. Flash chromatography of the crude product (5:95 Et_2O - petroleum ether; 35 g of silica gel), followed by distillation of the oil thus obtained (70-80°C/0.5 Torr), gave 270 mg (69%) of the ketone **157**, a colourless oil which exhibited ir (neat): 3308, 2119, 1681, 1571, 772 cm^{-1}; ^1H nmr (400 MHz) δ: 0.12 (s, 9H, -Sn<u>Me</u>3, $^2J_{Sn-H}$ = 54 Hz), 1.63 (quintet, 2H, methylene **Y**, J = 7.5 Hz), 1.97 (t, 1H, acetylenic H, J = 2.5 Hz), 2.19 (td, 2H, methylene **X**, J = 7.5 Hz, J = 2.5 Hz), 2.22 (s, 3H, -<u>Me</u>), 2.54 (td, 2H, methylene **Z**, J = 7.5 Hz, J = 1.3 Hz, $^3J_{Sn-H}$ = 48 Hz), 6.62 (br s, 1H, <u>H</u>A, $^3J_{Sn-H}$ = 120 Hz). In nOe difference experiments, irradiation at δ 6.62 (<u>H</u>A) caused signal enhancement at δ 2.54 (methylene **Z**) and δ 2.22 (-<u>Me</u>); irradiation at δ 2.54 (methylene **Z**) caused signal enhancement at δ 6.62 (<u>H</u>A) and δ 1.63 (methylene **Y**); irradiation at δ 2.22 (-<u>Me</u>) caused signal enhancement at δ 6.62 (<u>H</u>A). *Exact Mass* calcd. for $C_{11}H_{17}OSn$ (M^+-Me): 285.0302; found: 285.0302.

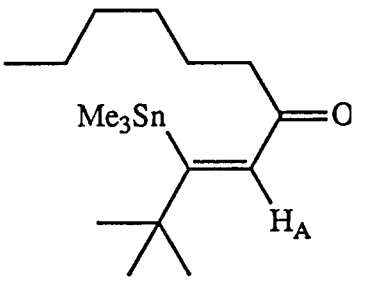
Preparation of the ketone **158**



158

Following general procedure I, a solution of the ketone **139** (800 mg, 5.54 mmol), $(Me_3Sn)_2$ (1.83 g) and $Pd(PPh_3)_4$ (320 mg, 5 mol %) in dry THF (9 mL) was allowed to reflux for 3 h. Flash chromatography of the crude product (5:95 Et_2O - petroleum ether; 75 g of silica gel), followed by distillation of the oil thus obtained (100-105°C/0.5 Torr), gave 1.40 g (81%) of the ketone **158**, a colourless oil which exhibited ir (neat): 1682, 1572, 1202, 774 cm^{-1}; ^1H nmr (300 MHz) δ: 0.12 (s, 9H, -Sn<u>Me</u>3, $^2J_{Sn-H}$ = 54 Hz), 1.85 (br quintet, 2H, $ClCH_2C\underline{H}_2CH_2$-, J = 7 Hz), 2.23 (s, 3H, -<u>Me</u>), 2.59 (br t, 2H, $ClCH_2CH_2C\underline{H}_2$-, J = 7 Hz, $^3J_{Sn-H}$ = 48 Hz), 3.50 (t, 2H, $ClC\underline{H}_2CH_2CH_2$-, J = 7 Hz), 6.82 (br s, 1H, <u>H_A</u>, $^3J_{Sn-H}$ = 120 Hz). In nOe difference experiments, irradiation at δ 6.82 (<u>H_A</u>) caused signal enhancement at δ 2.59 ($ClCH_2CH_2C\underline{H}_2$-) and δ 2.23 (-<u>Me</u>), while irradiation at δ 2.59 ($ClCH_2CH_2C\underline{H}_2$-) caused signal enhancement at δ 1.85 ($ClCH_2C\underline{H}_2CH_2$-), δ 3.50 ($ClC\underline{H}_2CH_2CH_2$-) and δ 6.82 (<u>$H_A$</u>). ^{13}C nmr (75.4 MHz) δ: -7.41, 30.19, 31.60, 36.55, 44.10, 135.59, 174.63, 197.53. *Exact Mass* calcd. for $C_9H_{16}{}^{35}ClOSn$ (M^+-Me): 294.9912; found: 294.9912.

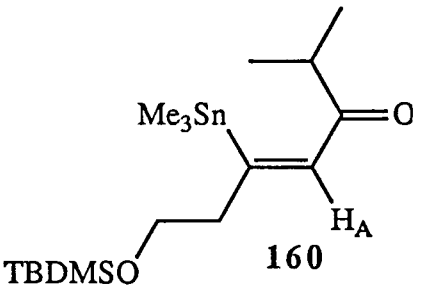
Preparation of the ketone **159.**



159

Following general procedure I, a solution of the ketone **140** (1g, 5.15 mmol), $(Me_3Sn)_2$ (1.70 g) and $Pd(PPh_3)_4$ (300 mg, 5 mol %) in dry THF (8 mL) was allowed to reflux for 24 h. Flash chromatography of the crude product (3:97 Et_2O - petroleum ether; 75 g of silica gel), followed by distillation of the oil thus obtained (120-130°C/0.5 Torr), gave 900 mg (48%) of the ketone **159**, a colourless oil which exhibited ir (neat): 1685, 1562, 779, 532 cm^{-1}; ^1H nmr (300 MHz) δ: 0.16 (s, 9H, -SnMe3, ^2J Sn-H = 53 Hz), 0.86 (m, 3H, -Me), 1.13 (s, 9H, -Bu^t), 1.27 (br s, 6H), 1.5-1.67 (m, 2H, $-C(O)CH_2CH_2-$), 2.49 (t, 2H, $-C(O)CH_2-$, J = 7.5 Hz), 6.75 (s, 1H, H_A, ^3J Sn-H = 130 Hz). In nOe difference experiments, irradiation at δ 6.75 (H_A) caused signal enhancement at δ 1.13 (Bu^t) and δ 2.49 ($-C(O)CH_2-$); irradiation at δ 2.49 ($-C(O)CH_2-$) caused signal enhancement at δ 6.75 (H_A) and δ 1.5-1.67 ($-C(O)CH_2CH_2-$); irradiation at δ 1.13 (-Bu^t) caused signal enhancement at δ 6.75 (H_A). ^{13}C nmr (75.4 MHz) δ: -3.61, 14.11, 22.58, 24.29, 28.99, 29.65, 31.62, 39.97, 43.43, 130.30, 184.93, 200.97. *Exact Mass* calcd. for $C_{15}H_{29}OSn$ (M^+-Me): 345.1241; found: 345.1237.

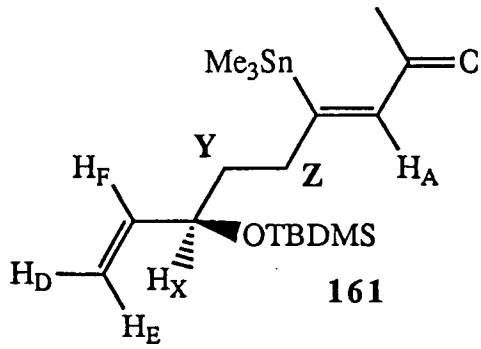
Preparation of the ketone **160.**



160

Following general procedure I, a solution of the ketone **141** (2.34 g, 9.23 mmol), $(Me_3Sn)_2$ (3.04 g) and $Pd(PPh_3)_4$ (533 mg, 5 mol%) in dry THF (15 mL) was allowed to reflux for 5 h. Flash chromatography of the crude product (5:95 Et_2O - petroleum ether; 140 g of silica gel), followed by distillation of the oil thus obtained (130-135°C/0.5 Torr), gave 3.64 g (94%) of the ketone **160**, a colourless oil which exhibited ir (neat): 1678, 1572, 1256, 1098, 777 cm^{-1}; ^{1}H nmr (400 MHz) δ: 0.04 (s, 6H, -SiMe2), 0.12 (s, 9H, -SnMe3, $^2J_{Sn-H}$ = 55 Hz), 0.87 (s, 9H, -SiBu^t), 1.12 (d, 6H, -CHMe2, J = 7 Hz), 2.66 (m, 3H, -CHMe2 and -OCH_2CH_2-), 3.66 (t, 2H, -OCH_2CH_2-, J = 6.5 Hz), 6.88 (br s, 1H, H_A, $^3J_{Sn-H}$ = 127 Hz). In nOe difference experiments, irradiation at δ 6.88 (H_A) caused signal enhancement at δ 2.66 (-CHMe2 and -OCH_2CH_2-), while irradiation at δ 2.66 (-CHMe2 and -OCH_2CH_2-) caused signal enhancement at δ 6.88 (H_A). *Exact Mass* calcd. for $C_{16}H_{33}O_2SnSi$ (M^+-Me): 405.1272; found: 405.1269.

Preparation of the ketone **161.**



161

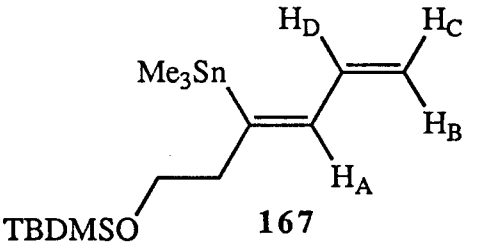
Following general procedure I, a solution of the ketone **148** (840 mg, 3.16 mmol), $(Me_3Sn)_2$ (1.04 g) and $Pd(PPh_3)_4$ (182 mg, 5 mol %) in dry THF (10 mL) was allowed to reflux for 8 h. Flash chromatography of the crude product (5:95 Et_2O - petroleum ether; 75 g of silica gel), followed by distillation of the oil thus obtained (130-135°C/0.5 Torr), gave 1.29 g (95%) of the ketone **161**, a colourless oil which exhibited ir (neat): 1682, 1571, 837, 776 cm^{-1}; ^1H nmr (400 MHz): 0.02 (s, 3H, -SiMe), 0.05 (s, 3H, -SiMe), 0.12 (s, 9H, -$SnMe_3$, $^2J_{Sn-H}$ = 54 Hz), 0.89 (s, 9H, -$SiBu^t$), 1.45-1.65 (m, 2H, methylene **Y**), 2.21 (s, 3H, -Me), 2.35-2.60 (m, 2H, methylene **Z**), 4.10 (m, 1H, H_X), 5.05 (ddd, 1H, H_D, J = 10 Hz, J = 2 Hz, J = 2 Hz), 5.14 (ddd, 1H, H_E, J = 18 Hz, J = 2 Hz, J = 2 Hz), 5.80 (ddd, 1H, H_F, J = 18 Hz, J = 10 Hz, J = 6 Hz), 6.80 (br s, 1H, H_A, $^3J_{Sn-H}$ = 124 Hz). *Exact Mass* calcd. for $C_{17}H_{33}O_2SiSn$ (M^+-Me): 417.1272; found: 417.1270.

General Procedure J. The preparation of (Z)-4-(trimethylstannyl)-1,3-butadienes **166**

To a cold (0°C), stirred suspension of methyltriphenylphosphonium bromide (1.8-2.0 equiv.) in dry THF (argon atmosphere) was added a solution of *n* -BuLi in hexane (1.3-1.5

equiv.). After the resulting yellow solution/suspension had been stirred for 10 min at 0°C and for 30 min at room temperature, a solution of the aldehyde (or ketone) (1 equiv.) in dry THF was added. After the reaction mixture had been stirred at room temperaure for 30 min-5 h, H_2O (approx. 0.5 mL per mL of reaction solution) and Et_2O (approx. 0.5 mL per mL of reaction solution) were added and the phases were separated. The aqueous phase was extracted with ether and the combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography, followed by distillation.

Preparation of the diene **167.**

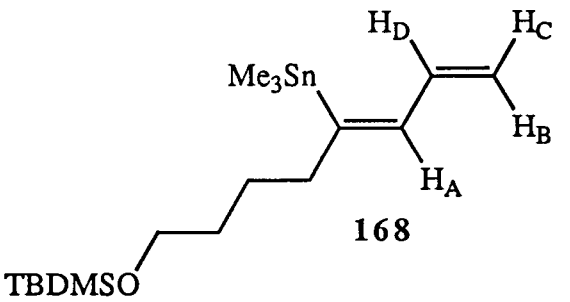


167

Following general procedure J, a solution of the aldehyde **152** (2.72 g, 7.2 mmol, 1 equiv.) in dry THF (15 mL) was added to the Wittig reagent (prepared by the addition of a solution of *n*- BuLi (1.3 equiv.) in hexane to a suspension of methyltriphenylphosphonium bromide (4.63 g, 1.8 equiv.) in 50 mL of dry THF) and the mixture was stirred at room temperature for 30 min. Flash chromatography of the crude product (2:98 Et_2O - petroleum ether; 120 g of silica gel), followed by distillation of the oil thus obtained (105-110°C/0.5 Torr), gave 2.35 g (87 %) of the diene **167**, a colourless oil which exhibited ir (neat): 3087, 3049, 1621, 1574, 1100, 774 cm^{-1}; ^1H nmr (300 MHz) δ: 0.04 (s, 6H, -SiMe2),

0.21 (s, 9H, -Sn<u>Me</u>3, $^{2}J_{Sn-H}$ = 53 Hz), 0.88 (s, 9H, -Si<u>Bu</u>^{t}), 2.49 (br t, 2H, -OCH2C<u>H2</u>-, J = 7 Hz, $^{3}J_{Sn-H}$ = 55 Hz), 3.57 (t, 2H, -OC<u>H2</u>CH2-, J = 7 Hz), 5.10 (dd, 1H, <u>HC</u>, J = 11 Hz, J = 1.5 Hz), 5.15 (dd, 1H, <u>HB</u>, J = 16 Hz, J = 1.5 Hz), 6.30 (m, 1H, <u>HD</u>), 6.64 (br d, 1H, <u>HA</u>, J = 11 Hz, $^{3}J_{Sn-H}$ = 131 Hz). ^{13}C nmr (75.4 MHz) δ: -8.01, -5.09, 18.44, 26.04, 43.61, 63.60, 117.07, 137.67, 142.63, 147.33. *Exact Mass* calcd. for $C_{14}H_{29}OSiSn$ (M^{+}-Me): 361.1010; found: 361.1018. *Anal.* calcd. for $C_{15}H_{32}OSiSn$: C 48.02, H 8.60; found: C 48.00, H 8.70.

<u>Preparation of the diene **168**.</u>

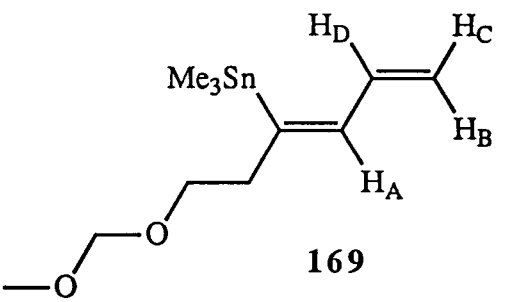


168

Following general procedure J, a solution of the aldehyde **153** (100 mg, 0.25 mmol, 1 equiv.) in dry THF (2 mL) was added to the Wittig reagent (prepared by the addition of a solution of *n*- BuLi (1.3 equiv.) in hexane to a suspension of methyltriphenylphosphonium bromide (160 mg, 1.8 equiv.) in 3 mL of dry THF) and the mixture was stirred at room temperature for 30 min. Flash chromatography of the crude product (2:98 Et2O - petroleum ether; 30 g of silica gel), followed by distillation of the oil thus obtained (110-115°C/0.5 Torr), gave 81 mg (81 %) of the diene **168**, a colourless oil which exhibited ir (neat): 3086, 1622, 1574, 1255, 1105, 775 cm^{-1}; ^{1}H nmr (300 MHz) δ: 0.04 (s, 6H, -Si<u>Me2</u>), 0.20 (s,

9H, -Sn<u>Me</u>$_3$, $^2J_{Sn-H}$ = 53 Hz), 0.88 (s, 9H, -Si<u>Bu</u>^{t}), 1.30-1.55 (m, 4H, -OCH$_2$C<u>H$_2$</u>C<u>H$_2$</u>CH$_2$-), 2.28 (br t, 2H, -OCH$_2$CH$_2$CH$_2$C<u>H$_2$</u>-, J = 7 Hz, $^3J_{Sn-H}$ = 56 Hz), 3.59 (t, 2H, -OC<u>H$_2$</u>CH$_2$CH$_2$CH$_2$-, J = 6 Hz), 5.06 (dd, 1H, <u>H$_C$</u>, J = 10 Hz, J = 1.5 Hz), 5.13 (dd, 1H, <u>H$_B$</u>, J = 16 Hz, J = 1.5 Hz), 6.31 (m, 1H, <u>H$_D$</u>), 6.59 (br d, 1H, <u>H$_A$</u>, J = 11 Hz, $^3J_{Sn-H}$ = 136 Hz). ^{13}C nmr (75.4 MHz) δ: -8.12, -5.15, 18.43, 26.07, 26.53, 32.51, 40.60, 62.07, 116.52, 137.83, 140.26, 152.05. *Exact Mass* calcd. for $C_{16}H_{33}OSnSi$ (M^+-Me): 389.1323; found: 389.1329.

<u>Preparation of the diene **169**.</u>

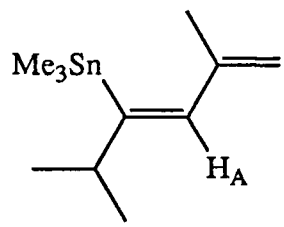


169

Following general procedure J, a solution of the aldehyde **154** (5.84 g, 18.96 mmol, 1 equiv.) in dry THF (25 mL) was added to the Wittig reagent (prepared by the addition of a solution of *n*- BuLi (1.3 equiv.) in hexane to a suspension of methyltriphenylphosphonium bromide (10.84 g, 1.6 equiv.) in 120 mL of dry THF) and the mixture was stirred at room temperature for 30 min. Flash chromatography of the crude product (1:9 Et$_2$O - petroleum ether; 230 g of silica gel), followed by distillation of the oil thus obtained (95-105°C/0.5 Torr), gave 4.76 g (82 %) of the diene **169**, a colourless oil which exhibited ir (neat): 3086, 1149, 1045, 771 cm^{-1}; ^{1}H nmr (300 MHz) δ: 0.02 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn-H}$ = 53 Hz),

2.55 (br t, 2H, -$OCH_2C\underline{H}_2$-, J = 6 Hz, $^3J_{Sn\text{-}H}$ = 53 Hz), 3.24 (s, 3H, -O$\underline{Me}$), 3.50 (t, 2H, -$OC\underline{H}_2CH_2$-, J = 6 Hz), 4.60 (s, 2H, -$OC\underline{H}_2O$-), 5.10 (br d, 1H, $\underline{H}_C$, J = 10 Hz), 5.15 (br d, 1H, $\underline{H}_B$, J = 17 Hz), 6.30 (m, 1H, $\underline{H}_D$), 6.66 (br d, 1H, $\underline{H}_A$, J = 11 Hz, $^3J_{Sn\text{-}H}$ = 125 Hz). ^{13}C nmr (75.4 MHz) δ: -8.20, 40.33, 55.01, 67.83, 96.22, 117.28, 137.62, 142.36, 147.68. *Exact Mass* calcd. for $C_{10}H_{19}O_2Sn$ (M^+-Me): 291.0407; found: 291.0406.

Preparation of the diene **176.**



176

Following general procedure J, a solution of the ketone **150** (3.6 g, 13.04 mmol, 1 equiv.) in dry THF (20 mL) was added to the Wittig reagent (prepared by the addition of a solution of *n*-BuLi (1.5 equiv.) in hexane to a suspension of methyltriphenylphosphonium bromide (9.4 g, 2 equiv.) in 100 mL of dry THF) and the mixture was stirred at room temperature for 5 h. Flash chromatography of the crude product (petroleum ether; 150 g of silica gel), followed by distillation of the oil thus obtained (90-105°C/10 Torr), gave 3.10 g (87 %) of the diene **176**, a colourless oil which exhibited ir (neat): 3083, 1632, 1602, 1188, 769 cm^{-1}; ^1H nmr (300 MHz) δ: 0.14 (s, 9H, -Sn$\underline{Me}_3$, $^2J_{Sn\text{-}H}$ = 52 Hz), 1.03 (d, 6H, -CH$\underline{Me}_2$, J = 7 Hz), 1.77 (s, 3H, -$\underline{Me}$), 2.51 (septet of d, 1H, -C$\underline{H}Me_2$, J = 7 Hz, J = 1.5 Hz, $^3J_{Sn\text{-}H}$ = 60 Hz), 4.74 (br s, 1H), 4.78 (br s, 1H), 6.45 (br s, 1H, $\underline{H}_A$,

$^3J_{Sn-H}$ = 144 Hz). ^{13}C nmr (75.4 MHz) δ: -6.34, 22.70, 23.05, 36.88, 112.55, 138.52, 147.21, 152.94. *Exact Mass* calcd. for $C_{10}H_{19}Sn$ (M^+-Me): 259.0509; found: 259.0512.

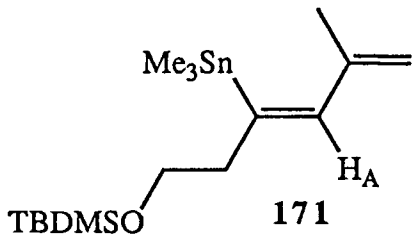
The preparation of a solution of sodium 2-methyl-2-butoxide in benzene[100]

To a stirred suspension of sodium wire (41.4 g, 1.8 mol) in dry benzene (750 mL) at room temperature (argon atmosphere) was added, slowly, 2-methyl-2-butanol (132.2 g, 1.5 mol) (freshly distilled from Mg (activated by I_2)). The mixture was allowed to gently reflux overnight. The solution was cannulated from the reaction vessel into an airtight container, and was stored in the refrigerator. The solution (2 ml in 5 mL of 95% EtOH) was titrated with 1M HCl, using phenolphthalein as indicator and was found to be 1.75 M.

General Procedure K. The preparation of (Z)-4-(trimethylstannyl)-1,3-butadienes **166**

To a stirred suspension of methyltriphenylphosphonium bromide (2.5 equiv.) in dry benzene (room temperature, argon atmosphere) was added a solution (1.75 M) of sodium 2-methyl-2-butoxide (2.5 equiv.) in dry benzene. After the mixture had been stirred for 20 min at room temperature, a solution of the ketone (1 equiv.) in dry benzene was added, and stirring was continued for 15-30 min. Water (approx. 0.5 mL per mL of reaction solution) and Et_2O (approx. 1 mL per mL of reaction solution) were added and the phases were separated. The aqueous phase was extracted with Et_2O, and the combined organic extracts were washed with brine, dried ($MgSO_4$) and concentrated. The crude product was purified by flash chromatography, followed by distillation.

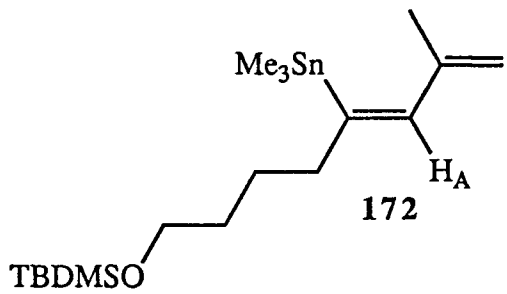
Preparation of the diene **171.**



171

Following general procedure K, a solution of the ketone **155** (200 mg, 0.51 mmol, 1 equiv.) in dry benzene (2 mL) was added to the Wittig reagent (prepared by the addition of a solution of sodium 2-methyl-2-butoxide in dry benzene (1.75 M, 0.73 mL, 2.5 equiv.) to a suspension of methyltriphenylphosphonium bromide (456 mg, 2.5 equiv.) in dry benzene (4 mL)) and the mixture was stirred at room temperature for 30 min. Flash chromatography of the crude product (2:98 Et_2O - petroleum ether; 35 g of silica gel), followed by distillation of the oil thus obtained (105-110°C/0.5 Torr), gave 172 mg (86%) of the diene **171**, a colourless oil which exhibited ir (neat): 3083, 1633, 1604, 1572, 1255, 774 cm^{-1}; ^1H nmr (300 MHz) δ: 0.04 (s, 6H, -Si<u>Me</u>2), 0.13 (s, 9H, -Sn<u>Me</u>3, $^2J_{Sn-H}$ = 53 Hz), 0.88 (s, 9H, -Si<u>Bu</u>^{t}), 1.76 (s, 3H, -<u>Me</u>), 2.45 (td, 2H, -OCH2C<u>H2</u>-, J = 7 Hz, J = 1.3 Hz, $^3J_{Sn-H}$ = 55 Hz), 3.56 (t, 2H, -OC<u>H2</u>CH2-, J = 7 Hz), 4.75 (br s, 1H), 4.79 (br s, 1H), 6.53 (br s, 1H, <u>HA</u>, $^3J_{Sn-H}$ = 137 Hz). ^{13}C nmr (75.4 MHz) δ: -7.20, -5.20, 18.40, 22.68, 26.02, 43.56, 63.67, 112.91, 141.78, 144.95, 146.61. *Exact Mass* calcd. for $C_{15}H_{31}OSiSn$ (M^+-Me): 375.1166; found: 375.1161.

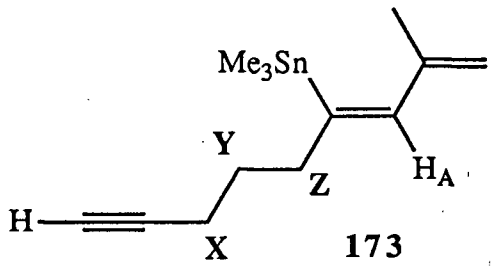
Preparation of the diene **172**.



172

Following general procedure K, a solution of the ketone **156** (155 mg, 0.37 mmol, 1 equiv.) in dry benzene (2 mL) was added to the Wittig reagent (prepared by the addition of a solution of sodium 2-methyl-2-butoxide in dry benzene (1.75 M, 0.53 mL, 2.5 equiv.) to a suspension of methyltriphenylphosphonium bromide (330 mg, 2.5 equiv.) in dry benzene (3 mL)) and the mixture was stirred at room temperature for 30 min. Flash chromatography of the crude product (3:97 Et_2O - petroleum ether; 30 g of silica gel), followed by distillation of the oil thus obtained (110-115°C/0.5 Torr), gave 116 mg (75%) of the diene **172**, a colourless oil which exhibited ir (neat): 3081, 1572, 1562, 1255, 1103, 775 cm^{-1}; ^1H nmr (300 MHz) δ: 0.03 (s, 6H, -Si<u>Me</u>2), 0.12 (s, 9H, -Sn<u>Me</u>3, $^2J_{Sn-H}$ = 52 Hz), 0.88 (s, 9H, -Si<u>Bu</u>^{t}), 1.29-1.55 (m, 4H, -$OCH_2C\underline{H}_2C\underline{H}_2CH_2$-), 1.76 (s, 3H, -<u>Me</u>), 2.24 (br t, 2H, -$OCH_2CH_2CH_2C\underline{H}_2$-, J = 7 Hz, $^3J_{Sn-H}$ = 55 Hz), 3.59 (t, 2H, -$OC\underline{H}_2CH_2CH_2CH_2$-, J = 6 Hz), 4.74 (br s, 1H), 4.79 (br s, 1H), 6.47 (br s, 1H, <u>H</u>A, $^3J_{Sn-H}$ = 139 Hz). ^{13}C nmr (75.4 MHz) δ: –7.41, –5.27, 18.33, 22.71, 25.98, 26.50, 32.38, 40.40, 60.13, 112.62, 142.48, 146.21, 146.60. *Exact Mass* calcd. for $C_{17}H_{35}OSn$ (M^+-Me): 403.1479; found: 403.1472.

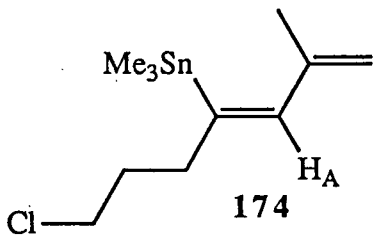
Preparation of the diene **173**



173

Following general procedure K, a solution of the ketone **157** (1.22 g, 4.07 mmol, 1 equiv.) in dry benzene (8 mL) was added to the Wittig reagent (prepared by the addition of a solution of sodium 2-methyl-2-butoxide in dry benzene (1.75 M, 5.8 mL, 2.5 equiv.) to a suspension of methyltriphenylphosphonium bromide (3.63 g, 2.5 equiv.) in dry benzene (15 mL)) and the mixture was stirred at room temperature for 30 min. Flash chromatography of the crude product (petroleum ether; 65 g of silica gel), followed by distillation of the oil thus obtained (70-80°C/0.5 Torr), gave 1.01 g (83%) of the diene **173**, a colourless oil which exhibited ir (neat): 3312, 3082, 2120, 897, 770 cm^{-1}; ^1H nmr (400 MHz) δ: 0.13 (s, 9H, -SnMe3, $^2J_{Sn-H}$ = 53 Hz), 1.57 (quintet, 2H, methylene **Y**, J = 7 Hz), 1.76 (s, 3H, -Me), 1.94 (t, 1H, acetylenic H, J = 2.6 Hz), 2.16 (td, 2H, methylene **X**, J = 7 Hz, J = 2.6 Hz), 2.34 (td, 2H, methylene **Z**, J = 7 Hz, J = 1.3 Hz, $^3J_{Sn-H}$ = 55 Hz), 4.75 (br s, 1H), 4.79 (br s, 1H), 6.51 (br s, 1H, H_A, $^3J_{Sn-H}$ = 139 Hz). ^{13}C nmr (75.4 MHz) δ: -7.3, 17.77, 22.71, 28.83, 39.38, 68.42, 84.39, 112.86, 143.46, 144.93, 146.55. *Exact Mass* calcd. for $C_{12}H_{19}Sn$ (M^+-Me): 283.0509; found: 283.0510.

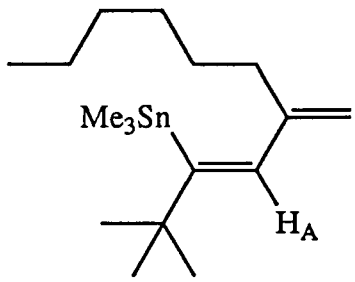
Preparation of the diene **174.**



174

Following general procedure K, a solution of the ketone **158** (288 mg, 0.73 mmol, 1 equiv.) in dry benzene (3 mL) was added to the Wittig reagent (prepared by the addition of a solution of sodium 2-methyl-2-butoxide in dry benzene (1.75 M, 1.05 mL, 2.5 equiv.) to a suspension of methyltriphenylphosphonium bromide (656 mg, 2.5 equiv.) in dry benzene (5 mL)) and the mixture was stirred at room temperature for 30 min. Flash chromatography of the crude product (2:98 Et_2O - petroleum ether; 35 g of silica gel), followed by distillation of the oil thus obtained (85-90°C/0.5 Torr), gave 128 mg (57%) of the diene **174**, a colourless oil which exhibited ir (neat): 3082, 1632, 1605, 897 cm^{-1}; ^1H nmr (300 MHz) δ: 0.14 (s, 9H, -Sn<u>Me</u>3, $^2J_{Sn-H}$ = 53 Hz), 1.77 (s, 3H, -<u>Me</u>), 1.81 (quintet, 2H, $ClCH_2C\underline{H_2}CH_2$-, J = 7 Hz), 2.38 (td, 2H, $ClCH_2CH_2C\underline{H_2}$-, J = 7 Hz, J = 1.3 Hz, $^3J_{Sn-H}$ = 54 Hz), 3.50 (t, 2H, $ClC\underline{H_2}CH_2CH_2$-, J = 7 Hz), 4.76 (br s, 1H), 4.80 (br s, 1H), 6.52 (br s, 1H, <u>H</u>A, $^3J_{Sn-H}$ =136 Hz). *Exact Mass* calcd. for $C_{10}H_{18}{}^{35}ClSn$ (M^+-Me): 293.0119; found: 293.0114.

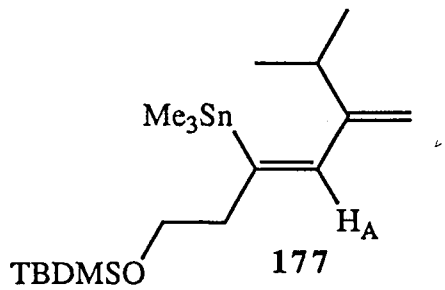
Preparation of the diene **175.**



175

Following general procedure K, a solution of the ketone **159** (110 mg, 0.31 mmol, 1 equiv.) in dry benzene (2 mL) was added to the Wittig reagent (prepared by the addition of a solution of sodium 2-methyl-2-butoxide in dry benzene (1.75 M, 0.44 mL, 2.5 equiv.) to a suspension of methyltriphenylphosphonium bromide (273 mg, 2.5 equiv.) in dry benzene (3 mL)) and the mixture was stirred at room temperature for 30 min. Flash chromatography of the crude product (2:98 Et_2O - petroleum ether; 35 g of silica gel), followed by distillation of the oil thus obtained (105-110°C/0.5 Torr), gave 89 mg (81%) of the diene **175**, a colourless oil which exhibited ir (neat): 3038, 1630, 899, 770 cm^{-1}; ^1H nmr (300 MHz) δ: 0.15 (s, 9H, -SnMe3, $^2J_{Sn-H}$ = 52 Hz), 0.88 (m, 3H, $CH_3CH_2CH_2CH_2CH_2CH_2$-), 1.07 (s, 9H, Bu^t), 1.30 (br s, 6H, $CH_3CH_2CH_2CH_2CH_2CH_2$-), 1.42 (m, 2H, $CH_3CH_2CH_2CH_2CH_2CH_2$-), 2.01 (br t, 2H, $CH_3CH_2CH_2CH_2CH_2CH_2$-, J = 8 Hz), 4.72 (br s, 1H), 4.77 (br s, 1H), 6.49 (br s, 1H, H_A, J = 151 Hz). ^{13}C nmr (75.4 MHz) δ: -3.60, 14.19, 22.77, 27.66, 29.41, 30.74, 31.84, 37.07, 38.91, 111.22, 137.32, 151.34, 156.63. *Exact Mass* calcd. for $C_{16}H_{31}Sn$ (M^+-Me): 343.1448; found: 343.1453.

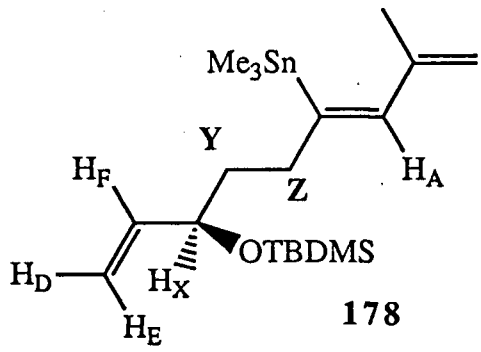
Preparation of the diene **177**



177

Following general procedure K, a solution of the ketone **160** (174 mg, 0.41 mmol, 1 equiv.) in dry benzene (2 mL) was added to the Wittig reagent (prepared by the addition of a solution of sodium 2-methyl-2-butoxide in dry benzene (1.75 M, 0.6 mL, 2.5 equiv.) to a suspension of methyltriphenylphosphonium bromide (370 mg, 2.5 equiv.) in dry benzene (4 mL)) and the mixture was stirred at room temperature for 15 min. Flash chromatography of the crude product (3:97 Et_2O - petroleum ether; 35 g of silica gel), followed by distillation of the oil thus obtained (110-115°C/0.5 Torr), gave 111 mg (64%) of the diene **177**, a colourless oil which exhibited ir (neat): 3090, 1461, 1255, 1007, 775 cm^{-1}; ^1H nmr (400 MHz) δ: 0.04 (s, 6H, -SiMe2), 0.12 (s, 9H, -SnMe3, $^2J_{Sn-H}$ = 53 Hz), 0.87 (s, 9H, -SiBu^t), 1.02 (d, 6H, -CHMe2, J = 7 Hz), 2.27 (br septet, 1H, -CHMe2, J = 7 Hz), 2.48 (br t, 2H, -OCH_2CH_2-, J = 7 Hz, $^3J_{Sn-H}$ = 53 Hz), 3.56 (t, 2H, -OCH_2CH_2-, J = 7 Hz), 4.71 (br s, 1H), 4.80 (br s, 1H), 6.60 (br s, 1H, HA, $^3J_{Sn-H}$ = 140 Hz). ^{13}C nmr (75.4 MHz) δ: -7.07, -5.17, 18.41, 21.60, 26.03, 34.0, 43.74, 63.77, 108.94, 143.40, 143.44, 156.40. *Exact Mass* calcd. for $C_{17}H_{35}OSiSn$ (M^+-Me): 403.1479; found: 403.1474.

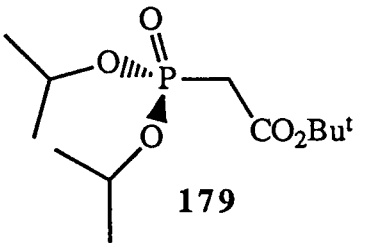
Preparation of the diene **178.**



178

Following general procedure K, a solution of the ketone **161** (92 mg, 0.21 mmol, 1 equiv.) in dry benzene (2 mL) was added to the Wittig reagent (prepared by the addition of a solution of sodium 2-methyl-2-butoxide in dry benzene (1.75 M, 0.3 mL, 2.5 equiv.) to a suspension of methyltriphenylphosphonium bromide (190 mg, 2.5 equiv.) in dry benzene (3 mL)) and the mixture was stirred at room temperature for 30 min. Flash chromatography of the crude product (3:97 Et_2O - petroleum ether; 30 g of silica gel), followed by distillation of the oil thus obtained (125-130°C/0.5 Torr), gave 78 mg (85%) of the diene **178**, a colourless oil which exhibited ir (neat): 3081, 1253, 1084, 775 cm^{-1}; ^1H nmr (400 MHz) δ: 0.04 (s, 3H, -SiMe), 0.06 (s, 3H, -SiMe), 0.14 (s, 9H, -SnMe3, $^2J_{Sn-H}$ = 52 Hz), 0.90 (s, 9H, -SiBu^t), 1.40-1.60 (m, 2H, methylene **Y**), 1.78 (s, 3H, -Me), 2.19-2.40 (m, 2H, methylene **Z**), 4.10 (br m, 1H, HX), 4.76 (br s, 1H), 4.80 (br s, 1H), 5.03 (ddd, 1H, HD, J = 10 Hz, J = 2 Hz, J = 2 Hz), 5.14 (ddd, 1H, HE, J = 17 Hz, J = 2 Hz, J = 2 Hz), 5.81 (ddd, 1H, HF, J = 17 Hz, J = 10 Hz, J = 6 Hz), 6.50 (br s, 1H, HA, $^3J_{Sn-H}$ = 139 Hz). ^{13}C nmr (50 MHz) δ: -7.28, -4.76, -4.32, 18.23, 22.72, 25.92, 36.40, 38.86, 73.60, 112.69, 113.72, 141.75, 142.56, 145.89, 146.66. *Exact Mass* calcd. for $C_{18}H_{35}OSiSn$ (M^+-Me): 415.1480; found: 415.1478.

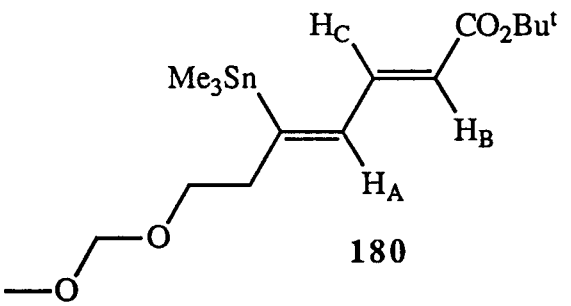
Preparation of the phospononate reagent **179**



179

A mixture of triisopropyl phosphite (3.2 g, 15.38 mmol, 1 equiv.) and *tert*-butyl bromoacetate (3 g, 1 equiv.) (argon atmosphere) was heated at 125°C for 1.5 h. Distillation of the oil thus obtained (fraction collected between 110-115°C/0.5 torr) gave 3.50 g (81%) of the phosphonate **179**, a colourless oil which exhibted ir (neat): 1730, 1289, 1107, 991 cm^{-1}; ^1H nmr (400 MHz) δ: 1.27 (d, 6H, $\underline{Me_2}CHO$-, J = 7 Hz), 1.29 (d, 6H, $\underline{Me_2}CHO$, J = 7 Hz), 1.42 (s, 9H, -$CO_2\underline{Bu^t}$), 2.77 (d, 2H, -$C\underline{H_2}CO_2Bu^t$, $^2J_{P-H}$ = 22 Hz), 4.68 (m, 2H, $Me_2C\underline{H}O$-). ^{13}C nmr (75.4 MHz) δ: 23.76 (d, $\underline{Me_2}CHO$-, $^3J_{P-C}$ = 5 Hz), 23.93 (d, $\underline{Me_2}CHO$-, $^3J_{P-C}$ = 4 Hz), 27.82, 36.62 (d, -$\underline{C}H_2CO_2Bu^t$, $^1J_{P-C}$ = 134 Hz), 70.88 (d,$Me_2\underline{C}HO$-, $^2J_{P-C}$ = 6 Hz), 81.60, 164.94 (d,-$CH_2\underline{C}O_2Bu^t$, $^3J_{P-C}$ = 6 Hz). ^{31}P nmr (122 MHz) δ: 16.20 (tt, J = 22 Hz, J = 8 Hz).

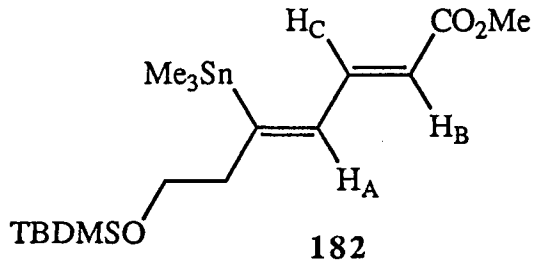
Preparation of the diene **180**.



180

A 60% dispersion of NaH (260 mg, 6.4 mmol, 1.7 equiv.) in mineral oil was washed with dry THF (3 x 2 mL) (argon atmosphere), and to the residual oil-free solid was added 25 mL of dry THF. The stirred suspension was cooled to 0°C and a solution of the phosphonate reagent **179** (1.79 g, 6.4 mmol, 1.7 equiv.) in 10 mL of dry THF was added slowly (over a period of approx. 5 min). After the mixture had been stirred at 0°C for 5 min and at room temperature for 20 min it was cooled to -20°C and a solution of the aldehyde **154** (1.17 g, 3.8 mmol, 1 equiv.) in 10 mL of dry THF was added. The mixture was stirred at -20°C for 1.5 h and was then allowed to warm to room temperature (30 min). Water (approx. 20 mL) and Et_2O (approx. 40 mL) were added and the phases were separated. The aqueous phase was extracted with Et_2O (2 x 20 mL) and the combined organic extracts were washed with brine (20 mL), dried ($MgSO_4$), and concentrated. Flash chromatography of the crude product (1:4 Et_2O - petroleum ether; 65 g of silica gel), followed by distillation of the oil thus obtained (190-210°C/0.5 Torr), gave 1.4 g (91%) of the diene **180**, a colourless oil which exhibited ir (neat): 1703, 1626, 1368, 1045, 770 cm^{-1}; ^1H nmr (400 MHz) δ: 0.25 (s, 9H, -Sn$\underline{Me}_3$, $^2J_{Sn-H}$ = 52 Hz), 1.48 (s, 9H, -$CO_2\underline{Bu^t}$), 2.64 (br t, 2H, -$OCH_2\underline{CH_2}$-, J = 7 Hz, $^3J_{Sn-H}$ = 49 Hz), 3.33 (s, 3H, -O$\underline{Me}$), 3.54 (t, 2H, -$OCH_2\underline{CH_2}$-, J = 7 Hz), 4.58 (s, 2H, -$OCH_2\underline{O}$-), 5.72 (br d, 1H, $\underline{H_B}$, J = 15 Hz), 6.74 (br d, 1H, $\underline{H_A}$, J = 11 Hz, $^3J_{Sn-H}$ = 120 Hz), 7.21 (dd, 1H, $\underline{H_C}$, J = 15 Hz, J = 11 Hz, $^4J_{Sn-H}$ = 7 Hz). In nOe difference experiments, irradiation at δ 6.74 ($\underline{H_A}$) caused signal enhancement at δ 5.72 ($\underline{H_B}$) and δ 2.64 (-$OCH_2\underline{CH_2}$-); irradiation at δ 2.64 (-$OCH_2\underline{CH_2}$-) caused signal enhancement at δ 3.54 (-$OCH_2\underline{CH_2}$-) and δ 6.74 ($\underline{H_A}$); irradiation at δ 5.72 ($\underline{H_B}$) caused signal enhancement at δ 6.74 ($\underline{H_A}$). ^{13}C nmr (75.4 MHz) δ: -7.80, 28.21, 40.95, 55.27, 67.45, 80.08, 96.39, 123.22, 139.47, 144.19, 160.52, 166.50. Exact Mass calcd. for $C_{15}H_{27}O_4Sn$ (M^+-Me): 391.0931; found: 391.0938. *Anal.* calcd. for $C_{16}H_{30}O_4Sn$: C 47.42, H 7.47; found: C 47.59, H 7.39.

Preparation of the diene **182.**

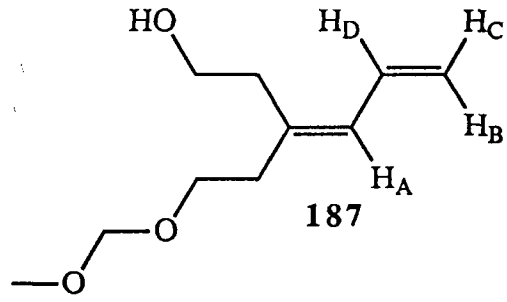


182

A 50% dispersion of NaH (1.02 g, 21.25 mmol, 1.5 equiv.) in mineral oil was washed with dry THF (3 x 5 mL) (argon atmosphere), and to the residual oil-free solid was added 100 mL of dry THF. The stirred suspension was cooled to 0°C and trimethylphosphonoacetate (**181**) (3.87 g, 21.25 mmol, 1.5 equiv.) was added dropwise (over a period of approx. 5 min). The resultant slurry was stirred at 0°C for 5 min and at room temperature for 20 min. The mixture was then re-cooled to 0°C and a solution of the aldehyde **152** (5.35 g, 14.15 mmol, 1 equiv.) in 25 mL of dry THF was added. The resulting suspension was stirred at 0°C for 2 h. Water (approx. 50 mL) and Et_2O (approx. 50 mL) were added and the phases were separated. The aqueous phase was extracted with Et_2O (2 x 40 mL) and the combined organic extracts were washed with brine (40 mL), dried ($MgSO_4$) and concentrated. Flash chromatography of the crude product (6:94 Et_2O - petroleum ether; 250 g of silica gel), followed by distillation of the oil thus obtained (140-150°C/0.5 Torr), gave 5.65 g (92%) of the diene **182**, a colourless oil which exhibited ir (neat): 1723, 1626, 1268, 1100, 776 cm^{-1}; ^1H nmr (400 MHz) δ: 0.03 (s, 6H, -Si$\underline{Me}_2$), 0.27 (s, 9H, -Sn$\underline{Me}_3$, $^2J_{Sn-H}$ = 54 Hz), 0.87 (s, 9H, -Si$\underline{Bu}^t$), 2.57 (br t, 2H, -$OCH_2\underline{CH}_2$-, J = 7 Hz, $^3J_{Sn-H}$ = 50 Hz), 3.62 (t, 2H, -$O\underline{CH}_2CH_2$-, J = 7 Hz), 3.73 (s, 3H, -O$\underline{Me}$), 5.80 (br d, 1H, $\underline{H}_B$, J = 15 Hz), 6.73 (br d, 1H, $\underline{H}_A$, J = 11 Hz, $^3J_{Sn-H}$ = 122 Hz), 7.30 (dd, 1H, $\underline{H}_C$, J = 15 Hz, J = 11 Hz, $^4J_{Sn-H}$ = 7 Hz). In nOe difference experiments, irradiation at δ 2.57 (-$OCH_2\underline{CH}_2$-) caused signal enhancement at δ 6.73 ($\underline{H}_A$)

and δ 3.62 (-OCH2CH2-); irradiation at δ 5.80 (HB) caused signal enhancement at δ 6.73 (HA); irradiation at δ 6.73 (HA) caused signal enhancement at δ 5.80 (HB) and δ 2.57 (-OCH2CH2-). *Exact Mass* calcd. for $C_{16}H_{31}O_3SnSi$ (M^+-Me): 419.1065; found: 419.1070.

Preparation of the alcohol **187**

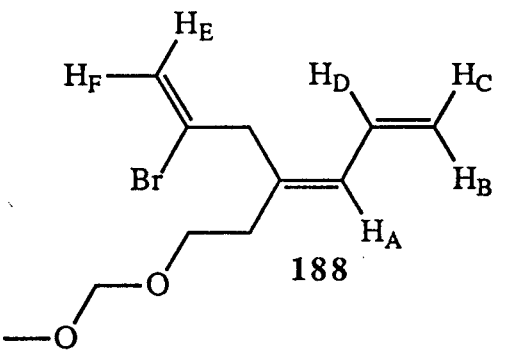


187

To a cold (-78°C), stirred solution of the stannyldiene **169** (870 mg, 2.84 mmol) in dry THF (50 mL) (argon atmosphere) was added a solution of MeLi (1.1 equiv.) in Et2O. After the mixture had been stirred for 45 min at -78°C, ethylene oxide (excess, approx. 2.5 g, 20 equiv.) was added via syringe (the barrel of the syringe was cooled, using a piece of dry ice, in order to facilitate the transfer of the volatile liquid). The resulting mixture was stirred at -78°C for 5 min and at -20°C for 20 min and was then allowed to warm to room temperature (30 min). Saturated aqueous NaHCO3 (10 mL) and Et2O (30 mL) were added, the phases were separated and the aqueous phase was extracted with Et2O (3 x 20 mL). The combined organic extracts were washed with brine (20 mL) and then dried and concentrated. Flash chromatography of the crude product (6:4 Et2O - petroleum ether; 40 g of silica gel), followed by distillation of the oil thus obtained (110 -120°C/0.5 Torr), gave 375 mg (71%)

of the alcohol **187**, a colourless oil which exhibited ir (neat): 3401, 3085, 1150, 1109, 1039 cm^{-1}; ^1H nmr (400 MHz) δ: 1.74 (br s, 1H, -O<u>H</u>), 2.39 (br t, 2H, -OCH$_2$C<u>H</u>$_2$-, J = 6.5 Hz), 2.49 (t, 2H, -C<u>H</u>$_2$CH$_2$OH, J = 6.5 Hz), 3.34 (s, 3H, -O<u>Me</u>), 3.67 (t, 2H, -OC<u>H</u>$_2$CH$_2$-, J = 6.5 Hz), 3.70 (br m, 2H, -C<u>H</u>$_2$OH), 4.61 (s, 2H, -OC<u>H</u>$_2$O-), 5.05 (dd, 1H, <u>H</u>$_C$, J = 10 Hz, J = 1.5 Hz), 5.15 (dd, 1H, <u>H</u>$_B$, J = 17 Hz, J = 1.5 Hz), 6.06 (br d, 1H, <u>H</u>$_A$, J = 11 Hz), 6.60 (ddd, 1H, <u>H</u>$_D$, J = 17 Hz, J = 11 Hz, J = 10 Hz). On addition of D_2O the signal at δ 3.70 (-C<u>H</u>$_2$OH) sharpened to a t (J = 6.5 Hz) and the signal at δ 1.74 disappeared. ^{13}C nmr (75.4 MHz) δ: 34.44, 37.06, 55.34, 61.16, 66.53, 96.37, 116.80, 129.91, 132.54, 136.27. *Exact Mass* calcd. for $C_{10}H_{16}O_2$ (M^+-H_2O): 168.1151; found: 168.1152. *Anal.* calcd. for $C_{10}H_{18}O_3$: C 64.49, H 9.74; found: 64.49, H 9.88.

<u>Preparation of the triene **188**</u>

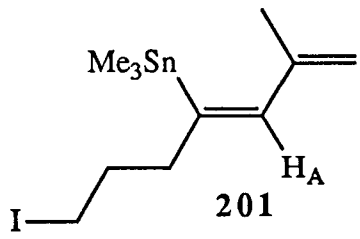


188

To a cold (-78°C), stirred solution of the stannyldiene **169** (346 mg, 1.13 mmol) in dry THF (5 mL) (argon atmosphere) was added a solution of MeLi (1.1 equiv.) in Et_2O. After the mixture had been stirred for 45 min at -78°C, CuBr.Me_2S (256 mg, 1.1 equiv.) was added. The resulting bright pink solution/suspension was stirred at -78°C for 5 min and

at -48°C for 15 min. To the resulting bright orange-red solution was added 2,3-dibromopropene (excess, 1.5 g, 6.7 equiv.) and the resulting colourless solution was stirred at -48°C for 45 min. Saturated NH_4Cl-NH_4OH (pH 8) (5 mL) and Et_2O (10 mL) were added and the vigorously stirred mixture was allowed to warm to room temperature. The phases were separated and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with brine (10 mL), dried ($MgSO_4$), and concentrated. Flash chromatography of the crude product (1:9 Et_2O - petroleum ether; 40 g of silica gel), followed by distillation (100-110°C/0.5 Torr) of the oil thus obtained, gave 244 mg (83%) of the triene **188**, a colourless oil which exhibited ir (neat): 3086, 1150, 1072, 917 cm^{-1}; ^1H nmr (400 MHz) δ: 2.38 (br t, 2H, -$OCH_2\underline{CH_2}$-, J = 6 Hz), 3.35 (br s, 5H, -O<u>Me</u> and bis-allylic $C\underline{H_2}$), 3.62 (t, 2H, -$OC\underline{H_2}CH_2$-, J = 6 Hz), 4.60 (s, 2H, -$OC\underline{H_2}O$-), 5.12 (dd, 1H, $\underline{H_C}$, J = 11 Hz, J = 1.5 Hz), 5.20 (dd, 1H, $\underline{H_B}$, J = 17 Hz, J = 1.5 Hz), 5.48 (br s, 1H, $\underline{H_E}$ or $\underline{H_F}$), 5.62 (br s, 1H, $\underline{H_E}$ or $\underline{H_F}$), 6.13 (br d, 1H, $\underline{H_A}$, J = 11 Hz), 6.54 (ddd, 1H, $\underline{H_D}$, J = 17 Hz, J = 11 Hz, J = 11 Hz). ^{13}C nmr (75.4 MHz) δ: 36.55, 42.76, 55.23, 66.1, 96.34, 117.53, 117.82, 130.43, 130.89, 132.35, 134.56. *Exact Mass* calcd. for $C_9H_{12}{}^{79}BrO$ (M^+-C_2H_5O): 215.0072; found: 215.0064. *Anal.* calcd. for $C_{11}H_{17}BrO_2$: C 50.59, H 6.56; found: C 50.85, H 6.58.

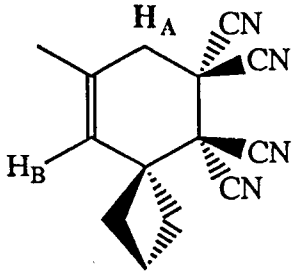
<u>Preparation of the diene **201**</u>



201

To a stirred solution of NaI (1.80 g, 11.8 mmol) in dry acetone (7 mL) (room temperature, argon atmosphere) was added a solution of the stannyldiene **174** (364 mg, 1.18 mmol) in dry acetone (3 mL). The mixture was allowed to reflux overnight. Most of the acetone was removed, Et_2O (20 mL) and H_2O (10 mL) were added to the residue, and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic extracts were washed with H_2O (10 mL) and then dried ($MgSO_4$) and concentrated. Flash chromatography of the crude product (5:95 Et_2O - petroleum ether; 35 g of silica gel), followed by distillation of the oil thus obtained (100-110°C/0.5 Torr), gave 406 mg (86%) of the diene **201**, a colourless oil which exhibited ir (neat): 3080, 1215, 896, 769 cm^{-1}; ^1H nmr (400 MHz) δ: 0.16 (s, 9H, -Sn<u>Me</u>$_3$, $^2J_{Sn-H}$ = 56 Hz), 1.78 (s, 3H, -<u>Me</u>), 1.87 (quintet, 2H, $ICH_2C\underline{H_2}CH_2$-, J = 7 Hz), 2.34 (br t, 2H, $ICH_2CH_2C\underline{H_2}$-, J = 7 Hz, $^3J_{Sn-H}$ = 54 Hz), 3.15 (t, 2H, $IC\underline{H_2}CH_2CH_2$-, J = 7 Hz), 4.76 (br s, 1H), 4.80 (br s, 1H), 6.54 (s, 1H, <u>H_A</u>, $^3J_{Sn-H}$ = 132 Hz). ^{13}C nmr (50 MHz) δ: -7.28, 6.15, 22.66, 33.62, 40.82, 113.015, 143.77, 143.99, 146.45. *Exact Mass* calcd. for $C_{10}H_{18}ISn$ (M^+-Me): 384.9477; found: 384.9476.

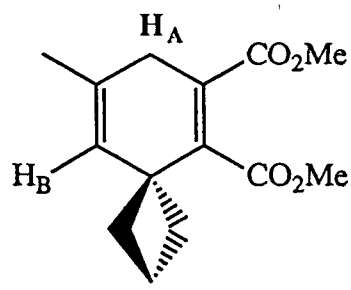
<u>Preparation of the spirocyclic compound 202</u>



202

To a cold (-78°C), stirred solution of the stannyldiene **201** (186 mg, 0.47 mmol) in dry THF (2 mL) (argon atmosphere) was added a solution of MeLi (1.1 equiv). in Et_2O. After the mixture had been stirred for 10 min at -78°C and 20 min at -48 °C, H_2O (0.5 mL) and Et_2O (2 mL) were added, and the mixture was allowed to warm to room temperature. The phases were separated, the aqueous phase was extracted with Et_2O (2 x 2 mL), and the combined organic extracts were dried ($MgSO_4$). The ethereal solution of the crude reaction product exhibited essentially one (non-solvent) peak by glc analysis and was used immediately in the next step. To the ethereal solution of the crude reaction product (argon atmosphere) was added (in portions of 5 mg) tetracyanoethylene (50 mg), until the reaction was shown to be complete (by glc analysis). The solvent was removed and the white solid thus obtained was dissolved in a minimum amount of Et_2O. Flash chromatography of this solution (1:1 Et_2O - petroleum ether; 25 g of silica gel) and recrystallization of the white solid thus obtained (petroleum ether) , gave 75 mg (69%) of the spirocyclic compound **202**, a white solid which exhibited, mp 166-167°C; ir (KBr disk): 2253, 1440, 883, 696 cm^{-1}; ^1H nmr (400 MHz) δ: 1.88 (br s, 3H, -Me), 2.08-2.10 (m, 1H), 2.17-2.24 (m, 3H), 2.73-2.75 (m, 2H), 2.95 (br s, 2H, H_A), 5.99 (br s, 1H, H_B). *Exact Mass* calcd. for $C_{14}H_{12}N_4$ (M^+): 236.1062; found: 236.1056.

Preparation of the spirocyclic compound 203



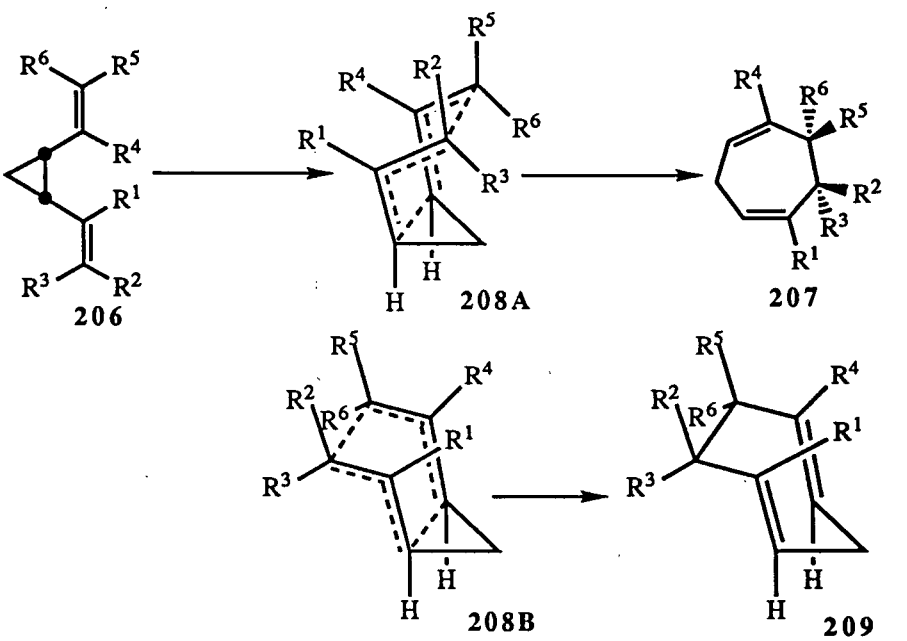
203

To a cold (-78°C), stirred solution of the stannyldiene **201** (170 mg, 0.43 mmol) in dry THF (2 mL) (argon atmosphere) was added a solution of MeLi (1.1 equiv.) in Et_2O. After the mixture had been stirred for 10 min at -78°C and 20 min at -48°C, H_2O (0.5 mL) and benzene (2 mL) were added, and the mixture was allowed to warm to room temperature. The phases were separated, the aqueous phase was extracted with benzene (3 x 1 mL), and the combined organic extracts were dried ($MgSO_4$). To the solution of the crude product (in a sealable reaction vessel, argon atmosphere) was added dimethylacetylene dicarboxylate (360 mg, 6 equiv.). The vessel was sealed and the mixture was heated at 70°C for 36 h. After the solvent had been removed the residual oil was purified by flash chromatography (1:1 Et_2O - petroleum ether; 30 g of silica gel), followed by distillation (100-110°C/0.5 Torr), to give 74 mg (70%) of the spirocyclic compound **203**, a colourless oil which crystallized on standing. Recrystallization of this material from pentane produced white crystals, which exhibited mp 55-56 °C; ir (KBr disk): 1724, 1635, 1440, 1267, 1051, 754 cm^{-1}; ^1H nmr (400 MHz) δ: 1.72 (br s, 3H, -Me), 1.72-1.80 (m, 1H), 1.92-1.96 (m, 3H), 2.58-2.59 (m, 2H), 2.82 (br s, 2H, H_A), 3.73 (s, 3H, -OMe), 3.88 (s, 3H, -OMe), 5.73 (br s, 1H, H_B). *Exact Mass* calcd. for $C_{14}H_{18}O_4$ (M^+): 250.1205; found: 250.1203.

PART 3. The preparation of 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hex-2-enes and the thermal Cope rearrangement of these compounds into substituted bicyclo[3.2.1]octa-2,6-dienes.

I. Introduction

Cis divinylcyclopropanes of general structure **206** can undergo thermal [3,3]-sigmatropic (Cope) rearrangement to give 1,4-cycloheptadienes of general structure **207**.[105-108] There are several important features associated with this type of rearrangement. Firstly, it is usually a facile process since it is accompanied by opening of the highly strained cyclopropane ring (the strain energy of a cyclopropane is approximately 27.5 kcal mol^{-1}).[107] Also, the rearrangement is completely stereospecific, in that the geometries of the carbon-carbon double bonds in the divinylcyclopropane **206** determine the relative stereochemistry of the substituents in the product **207**. Thus, the substituents R^3 and R^6 in the divinylcyclopropane **206** end up *cis* to each other in the product **207**, as do R^2 and R^5

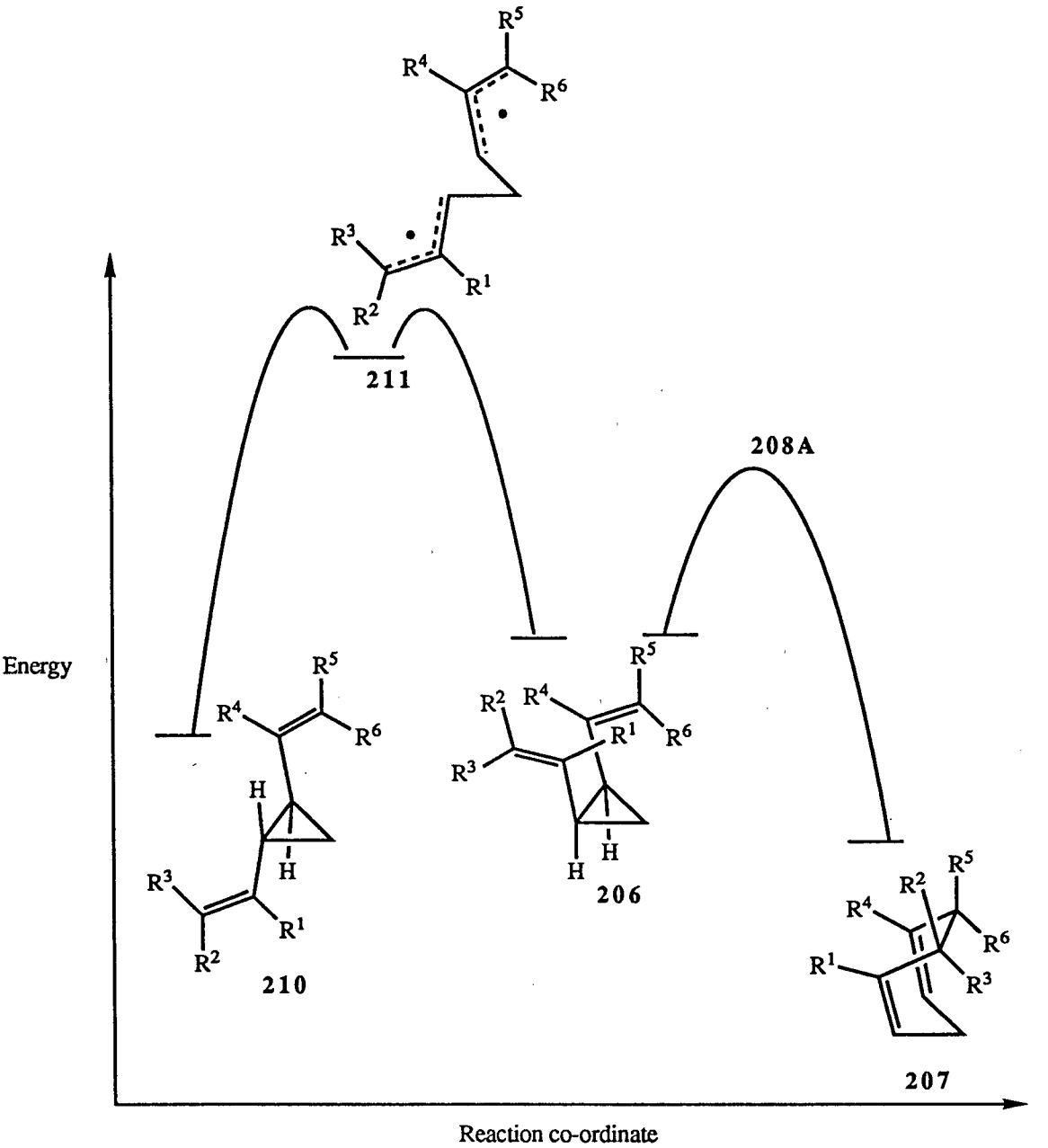


Scheme 30

(Scheme 30). Finally, the mechanism of the reaction is generally described as a concerted bond reorganization via a boat-like transition state **208A**, in which the two vinyl groups hang over the cyclopropyl ring (Scheme 30).[105] The alternative, chair-like, transition state of type **208B** is assumed to be much higher in energy than **208A** since it would lead to highly strained 1,4-cycloheptadienes **209** which have two *trans* carbon-carbon double bonds.

Trans divinylcyclopropanes of general structure **210** cannot attain the transition state **208A** for Cope rearrangement due to geometric reasons (Scheme 31). However, at high temperatures *trans* divinylcyclopropanes **210** often rearrange, cleanly and efficiently, to give the 1,4-cycloheptadienes **207**.[106,109-112] In these cases, it is generally accepted that the *trans* divinylcyclopropane **210** is first isomerized, via a diradical intermediate **211**, to the *cis* isomer **206**, which then undergoes the Cope rearrangement.[106,113] This *trans* to *cis* isomerization is generally (but not always) rate determining and, therefore, once formed, the *cis* divinylcyclopropane **206** usually rearranges rapidly, via the transition state **208A**, to the 1,4-cycloheptadiene **207** (Scheme 31). The Cope rearrangements of *trans* divinylcyclopropanes are completely stereospecific. Therefore, if the *trans* to *cis* isomerization involves a diradical intermediate **211**, it apparently re-closes to either the *cis* divinylcyclopropane **206** or the *trans* isomer **210** without allowing for bond rotation within either allyl unit.

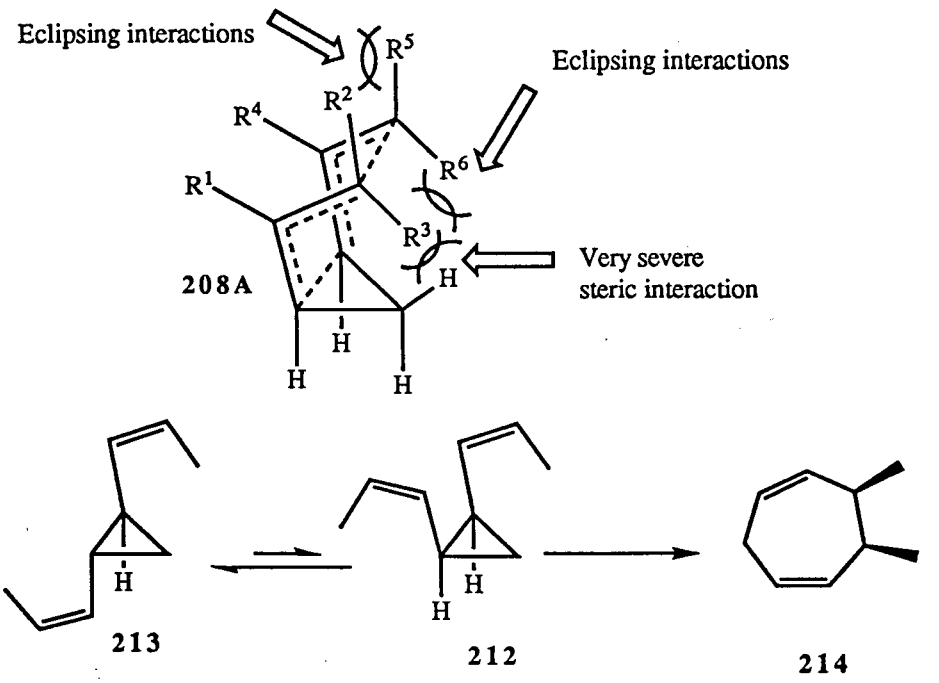
The effects of substituents on the rate of Cope rearrangement of *cis* divinylcyclopropanes of general structure **206** have not been thoroughly investigated. However, it has been shown that *cis* divinylcyclopropanes **206** which have alkyl groups attached to the termini of the vinyl groups undergo Cope rearrangement more slowly than those which are unsubstituted at these positions.[114] These effects are readily rationalized in terms of steric interactions between substituents in the transition state **208A**, as shown in Scheme 32. For example, *trans* substituents (i.e. R^2 and/or R^5=alkyl) cause moderate rate



Scheme 31

retardation, presumably due to eclipsing interactions between these groups in the boat-like transition state **208A** (Scheme 32). On the other hand, *cis* substituents (R^3 and/or R^6=alkyl) cause drastic reductions in the rate of Cope rearrangement. In these cases, the transition states **208A** are destabilized by eclipsing interactions involving R^3 and/or R^6 as well as by

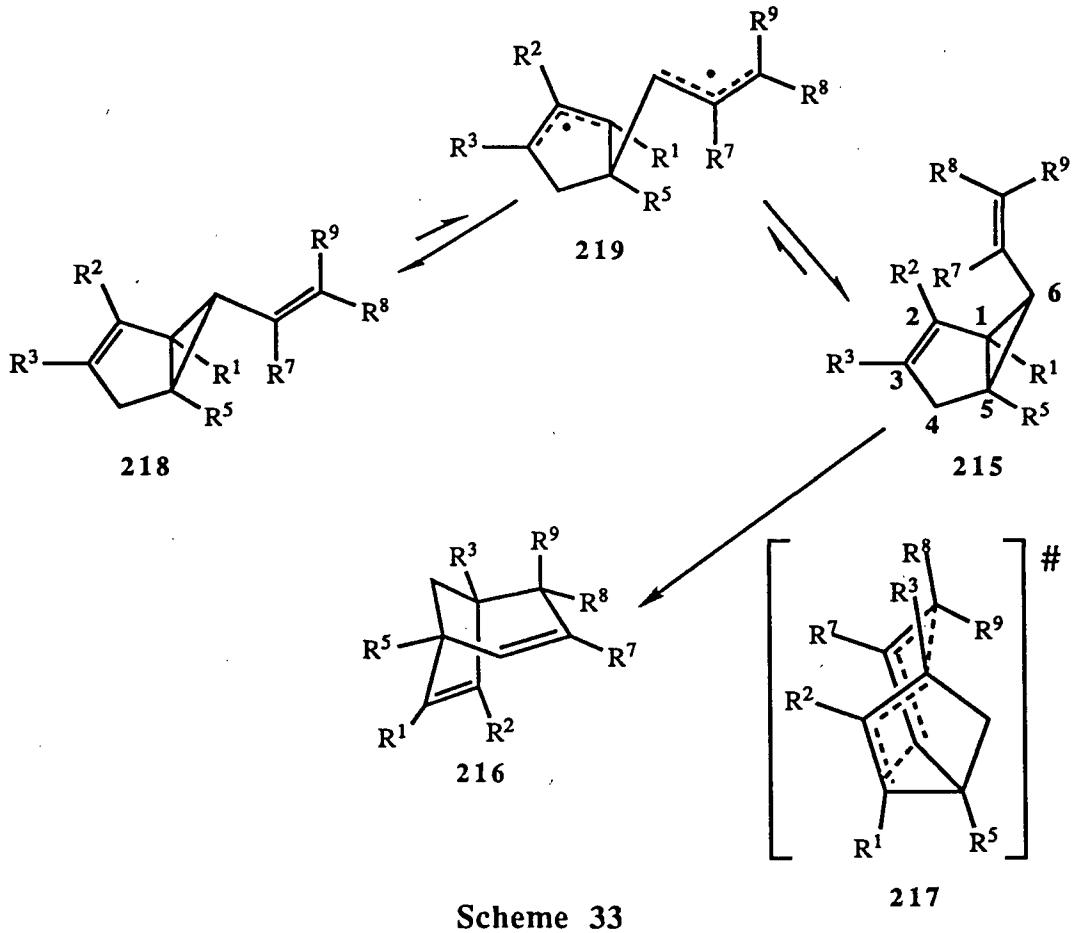
severe steric interactions between R^3 and/or R^6 and the cyclopropyl ring, as shown in Scheme 32. In fact, Schneider and Rau[114], and Baldwin and Ullenius[113] have reported that, upon thermolysis, the *cis* divinylcyclopropane **212** (which has a *cis* methyl group attached to the terminus of each vinyl group) equilibrates with the *trans* divinylcyclopropane **213** faster than it undergoes Cope rearrangement. Only minor amounts of the 1,4-cycloheptadiene **214** are produced even after prolonged heating. Apparently, the transition state for this Cope rearrangement is sufficiently congested to be of higher energy than the transition states associated with interconversion of the *trans* isomer **213** and the *cis* isomer **212** (via a diradical intermediate).



Scheme 32

The thermal [3,3]-sigmatropic (Cope) rearrangement of *cis* divinylcyclopropanes of general structure **215** (i.e. 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hex-2-enes) provides substituted bicyclo[3.2.1]octa-2,6-dienes of general structure **216** (Scheme 33).[115-117] The rearrangement is stereospecific and presumably proceeds via a transition state of general

structure **217**. The corresponding *trans* divinylcyclopropanes **218** (i.e. 6-*exo*-(1-alkenyl)bicyclo[3.1.0]hex-2-enes) may also undergo Cope rearrangement to give the bicyclic products **216**.[118-120] However, high temperatures are required to effect this transformation, since the 6-*exo*-(1-alkenyl)bicyclo[3.1.0]hex-2-enes **218** must first be isomerized to the *endo* isomers **215**, before the Cope rearrangement can take place (Scheme 33).[121] This *exo-endo* isomerization is usually rate limiting and probably involves a diradical intermediate of general structure **219** (Scheme 33).

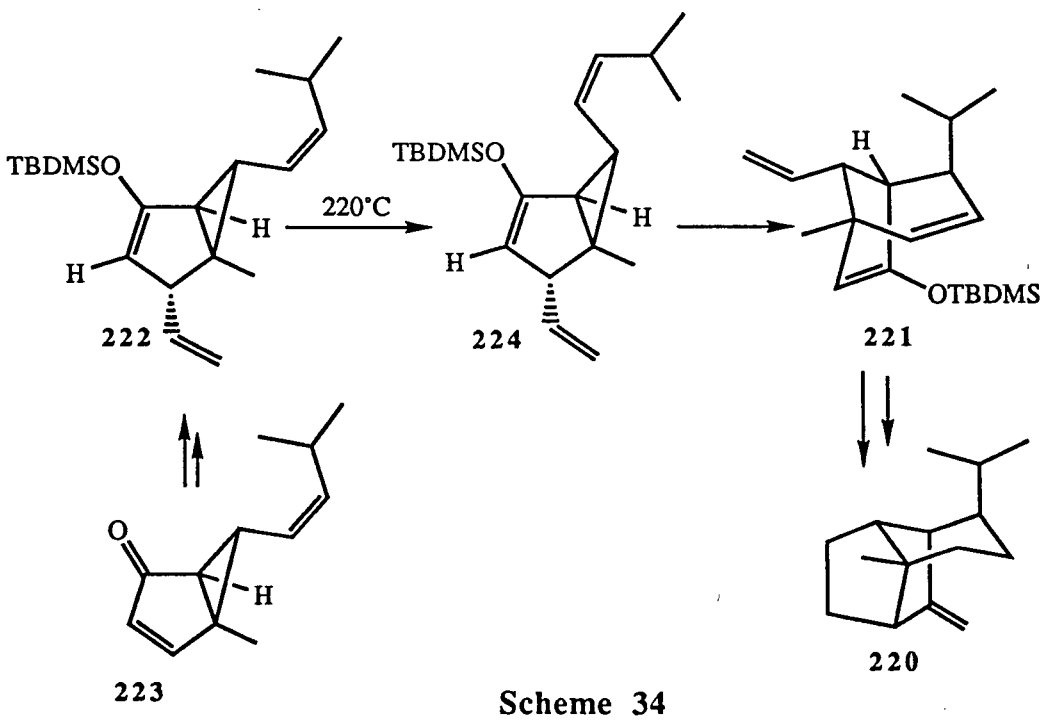


Scheme 33

Since, in principle, either the *endo*-(1-alkenyl)bicyclo[3.1.0]hex-2-enes **215** or the *exo* isomers **218** can undergo the Cope rearrangement, it should be possible to prepare the desired bicyclo[3.2.1]octa-2,6-dienes **216** from either isomer or a mixture of both isomers.

In practice, however, the high temperatures required to effect Cope rearrangement of the *exo* isomers **218** may result in alternative modes of reaction and/or substrate decomposition. In these cases, the desired products are available only via Cope rearrangement of the *endo* isomers **215** which, therefore, must be synthesized stereoselectively. These points are well illustrated by the following examples.

In a recent synthesis of sinularene **220** (Scheme 34),[122] the key bicyclic intermediate **221** was prepared in 86% yield via thermolysis (220°C, 4.5 hours) of the *exo*-(1-alkenyl)bicyclo[3.1.0]hex-2-ene **222**, which was derived from the α,β-unsaturated ketone **223**. The reaction probably proceeds via rate limiting isomerization of **222** to the *endo* isomer **224** which then undergoes Cope rearrangement. Apparently, alternative modes of reaction which could be available to **222**, such as a [1,5] sigmatropic hydrogen shift, do not compete with *exo* to *endo* isomerization or Cope rearrangement under these conditions.

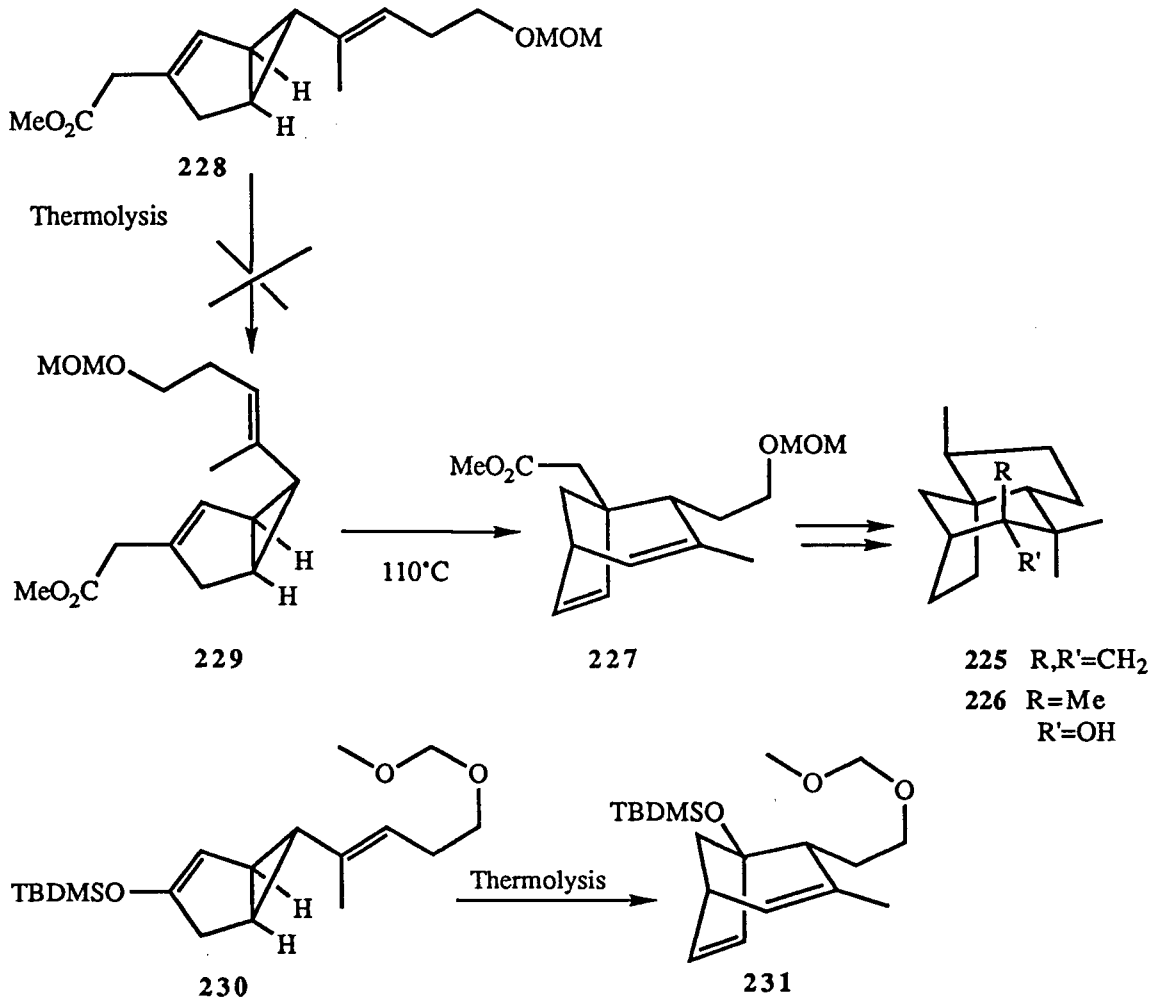


222 **224** **221** **223** **220**

Scheme 34

In the total syntheses of (±)-prezizaene **225** and (±)-prezizanol **226** recently carried out in this laboratory,[123] the key intermediate **227** was expected to be available via Cope

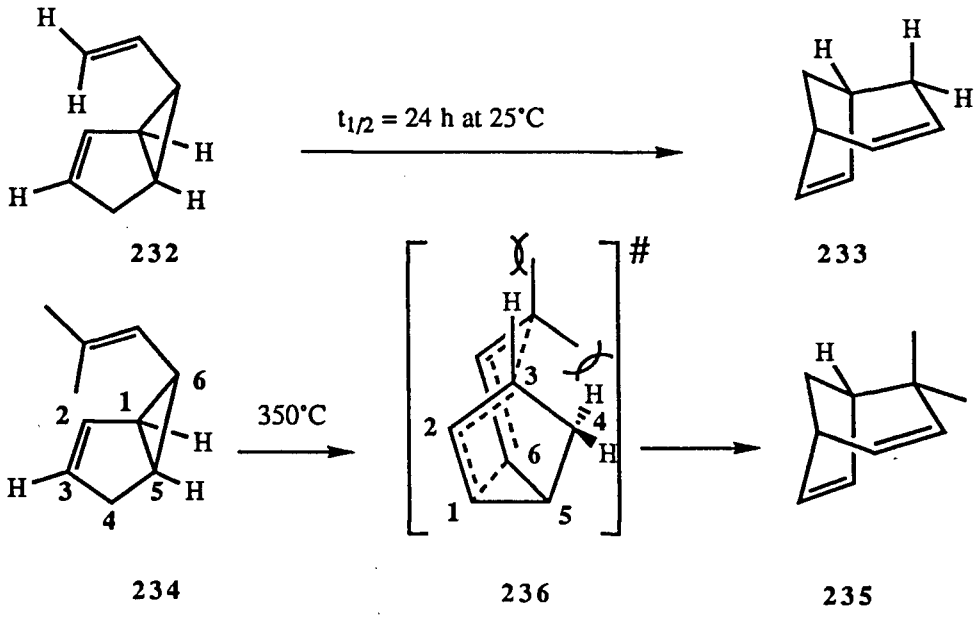
rearrangement of the *exo*-(1-alkenyl)bicyclo[3.1.0]hex-2-ene **228**. However, it was found that thermolysis of **228** produced a mixture of many products and only minor amounts of **227**. Evidently, the high temperature required for isomerization of **228** to the *endo* isomer **229**, which must precede the Cope rearrangement, results in substrate decomposition. In fact, it was shown that the β,γ-unsaturated ester function present in **228** is responsible for its thermal instability, since thermolysis of the structurally similar compound **230** gives the expected Cope rearrangement product **231** cleanly and efficiently (Scheme 35).[124] The key



Scheme 35

intermediate **227** was subsequently prepared via stereoselective synthesis and facile Cope rearrangement of the *endo*-(1-alkenyl)bicyclo[3.1.0]hex-2-ene **229** (Scheme 35). Compound **227** was readily converted into the target molecules **225** and **226**.

There is very little quantitative data available regarding the effects of substituents on the rates of Cope rearrangement of 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hex-2-enes of general structure **215**. Generally, it appears that substituents attached to the termini of the vinyl groups in **215** cause rate retardation in a manner similar to that described earlier (Scheme 32) for the "simple" *cis* divinylcyclopropanes **206**. For example,[125] compound **232** (Scheme 36) rearranges to bicyclo[3.2.1]octa-2,6-diene (**233**) with a half life of approximately 1 day at 25°C, whereas the diene **234** is stable at room temperature. However, upon flash vacuum pyrolysis at 350°C, **234** rearranges to the bicyclo[3.2.1]octa-2,6-diene **235**.[126] Presumably, this Cope rearrangement proceeds via a boat-like transition state **236** in which there is an eclipsing interaction between the *trans* vinyl methyl group and the hydrogen attached to C3, as well as a severe interaction between the *cis* vinyl methyl group and the hydrogen attached to C4 (Scheme 36).

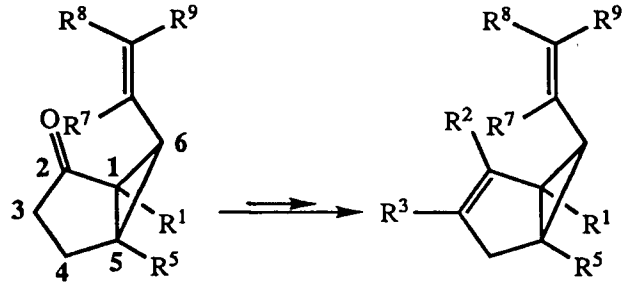


Scheme 36

II. Proposals

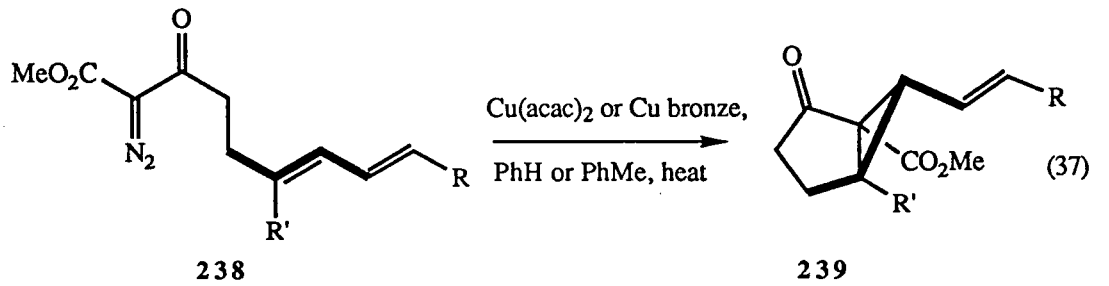
Although bicyclo[3.2.1]octa-2,6-dienes **216** may often be prepared efficiently via Cope rearrangement of 6-*exo*-(1-alkenyl)bicyclo[3.1.0]hex-2-enes **218**, the high temperatures that are required to effect this transformation may limit its utility as a general synthetic method. The Cope rearrangement of the corresponding 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hex-2-enes **215** is a more reliable process, yet has not been greatly exploited primarily due to the lack of general methods available for the stereoselective preparation of these compounds. The main objective of this project was, therefore, to develop a general synthesis of functionalized, substituted 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hex-2-enes **215** and to convert these compounds (via Cope rearrangement) into the corresponding bicyclo[3.2.1]octa-2,6-dienes. It was envisaged that the availability of a wide range of functionalized compounds of general structure **215** would provide an excellent opportunity to observe the effects of different substituents and substitution patterns on the rate of Cope rearrangement.

It was anticipated that 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hexan-2-ones of general structure **237** would be excellent precursors to a variety of 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hex-2-enes **215** (equation 36).[118,119,122] The ketone function in compounds **237** was expected to serve as a "handle" for incorporation of a number of different alkyl substituents or functional groups at C3 as well as for introduction of the C2-C3 double bond (equation 36). The ketones **237** were, therefore, our initial synthetic targets.



237 **215** (36)

Workers in this group[118,119,122] and in others[127,128] have shown that compounds related to **237** may be prepared via intramolecular transition metal-catalyzed cyclopropanation reactions of molecules containing a diene unit and a diazoketone function. For example,[118] it was shown that diene diazoketones of general structure **238** undergo chemoselective and stereoselective intramolecular cyclopropanation in the presence of a copper(II) or copper(0) catalyst to give 6-*exo*-(1-alkenyl)bicyclo[3.1.0]hexan-2-ones of general structure **239** (equation 37). The geometry of the diene unit determines the relative stereochemistry of the cyclopropane ring, as indicated by the bold lines in structures **238** and **239**.

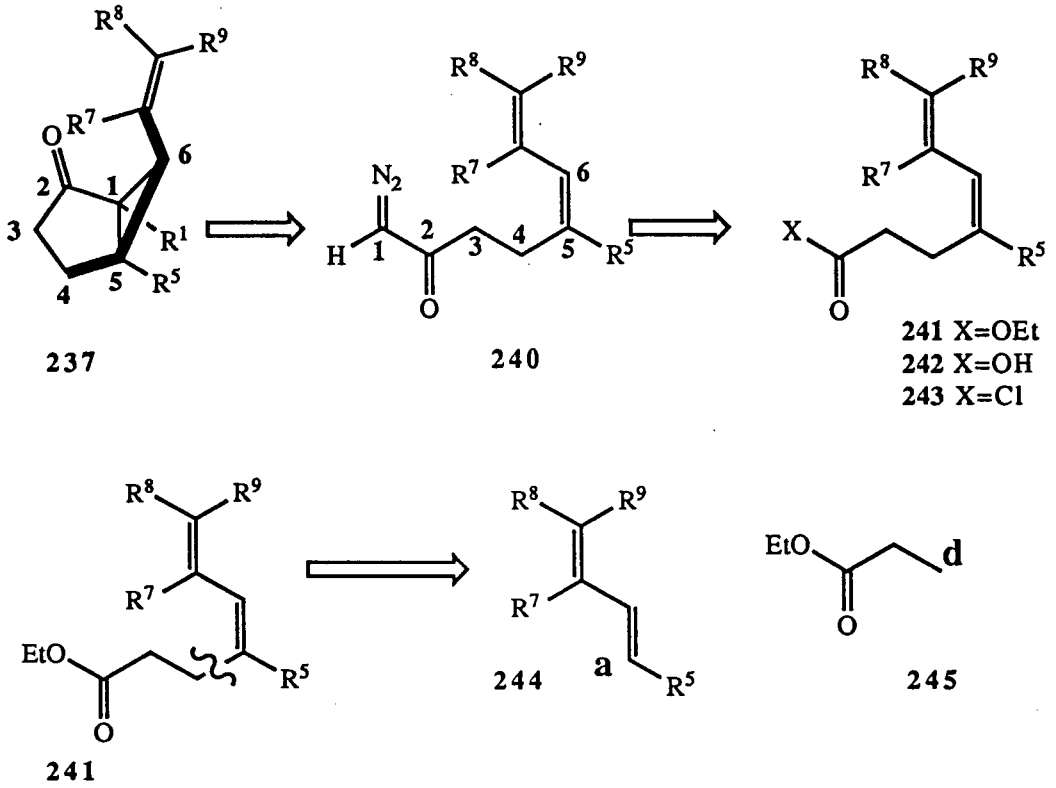


238 **239**

It was envisaged that 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hexan-2-ones **237** (in which R^1=H) would be available via intramolecular transition metal-catalyzed cyclopropanation reactions involving diene diazoketones of appropriate geometry (i.e. compounds of general structure **240**) (Scheme 37). Retrosynthetically, the diene diazoketones **240** could be derived from the diene esters of general structure **241** via functional group manipulation.[122,128] In particular, it was expected that the esters **241** could be hydrolyzed to give the corresponding carboxylic acids **242**, which could then be converted into the corresponding acid chlorides **243**. Reaction of the acid chlorides **243** with diazomethane should provide the desired diene diazoketones **240**.

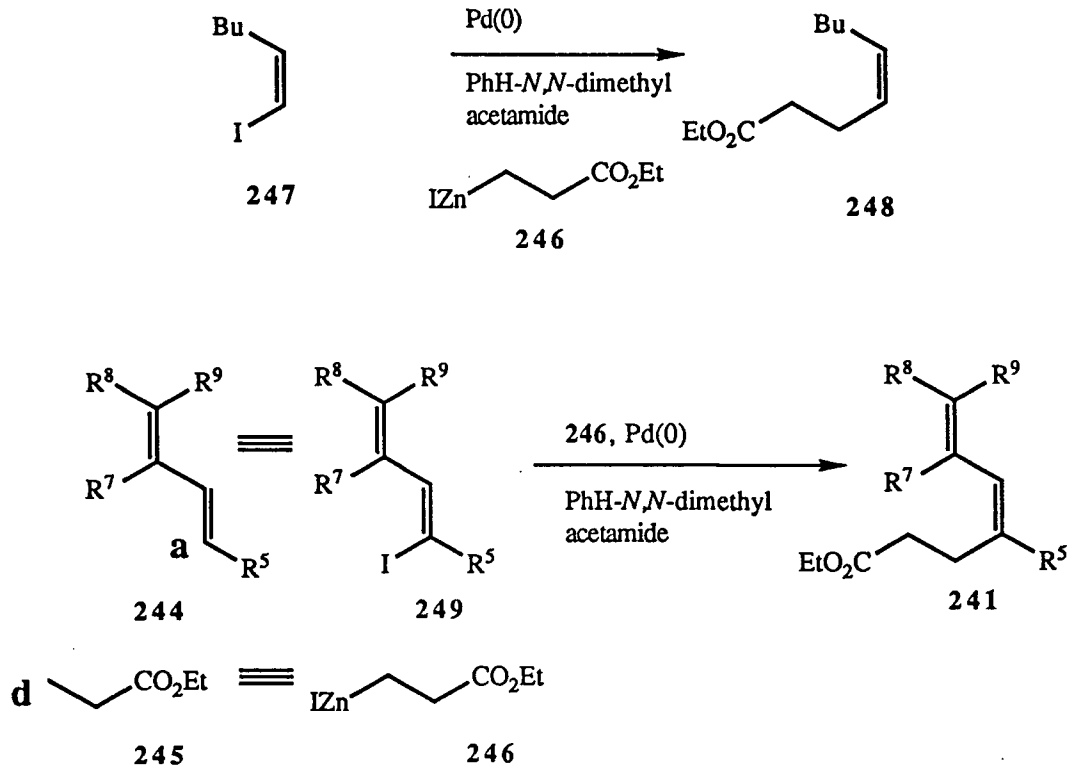
Although there are many ways of dissecting the diene esters **241** retrosynthetically, disconnection of the C4-C5 bond to give a substituted diene acceptor synthon **244** and a

three carbon donor synthon **245** (Scheme 37) seemed particularly attractive, for the



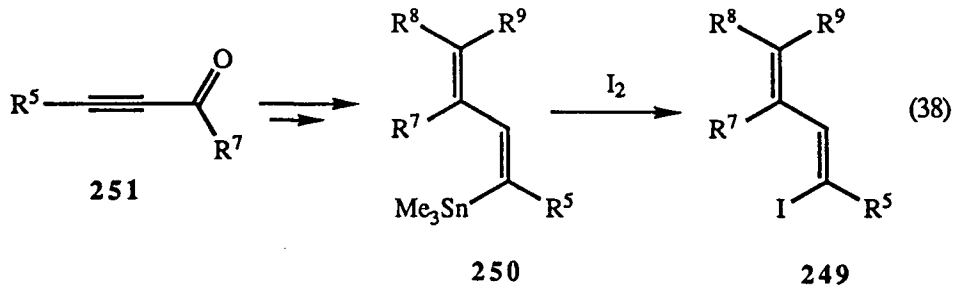
Scheme 37

following reasons. Firstly, Yoshida and coworkers[129] recently reported that the organozinc reagent **246** (which is actually a zinc homoenolate reagent) undergoes Pd(0)-catalyzed cross coupling reactions with alkenyl iodides or enol triflates. For example, the reagent **246** reacts with the alkenyl iodide **247** in the presence of a catalytic amount of $Pd(PPh_3)_4$ to give, stereoselectively, the cross coupled product **248** (Scheme 38). It was, therefore, expected that **246** would react with iodo dienes of general structure **249**, in the presence of a Pd(0) catalyst, to give the desired diene esters **241** (Scheme 38). In this type of reaction the organozinc reagent **246** would be a synthetic equivalent of the donor synthon **245**, whilst the iodo dienes **249** would be synthetic equivalents of the diene acceptor synthon **244**.



Scheme 38

Secondly, iodo dienes **249** should be readily available via reaction of the corresponding stannyldienes **250** with iodine (equation 38).[22b] Stannyldienes similar to those of general structure **250** can be prepared from α,β-acetylenic aldehydes or ketones **251** in a highly efficient and stereoselective manner , via the methodology described in the part 2 of this thesis.[96]

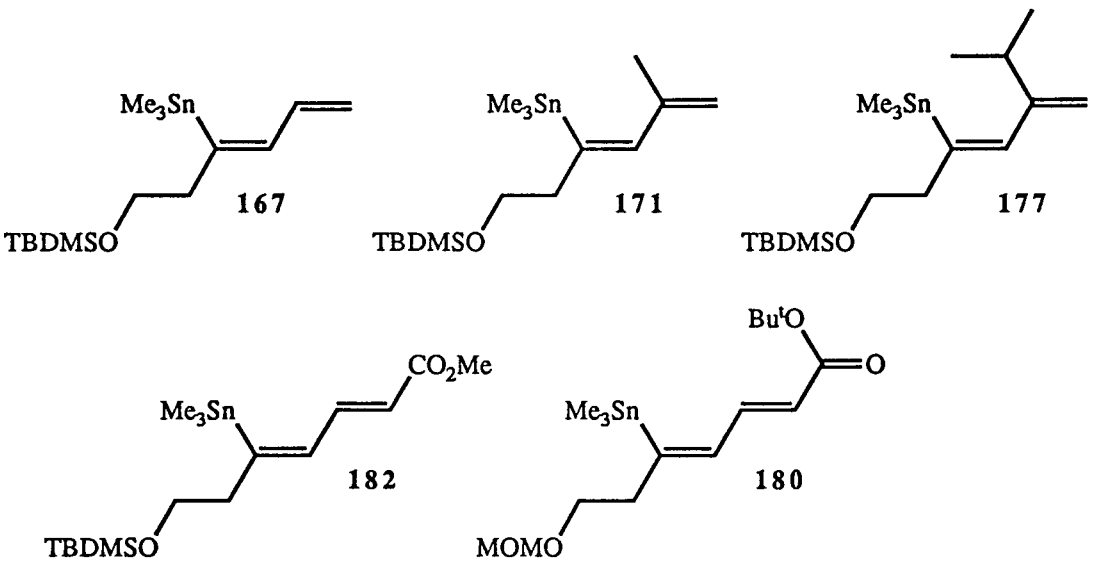


(38)

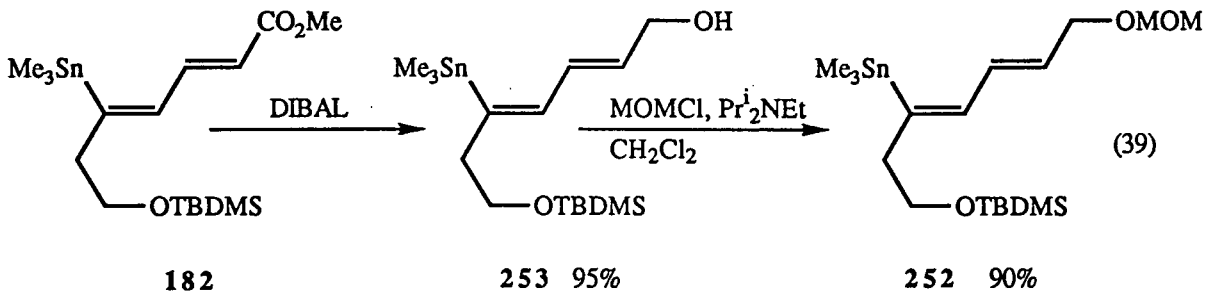
III. Results and discussion

3.1. The preparation of the stannyldienes

The starting materials used in this project were the stannyldienes **167**, **171**, **177**, **180** and **182**, which were prepared efficiently and stereoselectively as described in Part 2 of this thesis.



The stannyldiene **252** was prepared from **182** in two steps, as shown in equation 39. Thus, reaction of **182** with DIBAL provided the alcohol **253** in 95% yield. The alcohol **253** was then converted into compound **252** in 90% yield via reaction with chloromethyl methyl ether and *N,N*-diisopropylethylamine, following a standard literature procedure (equation 39).[85]

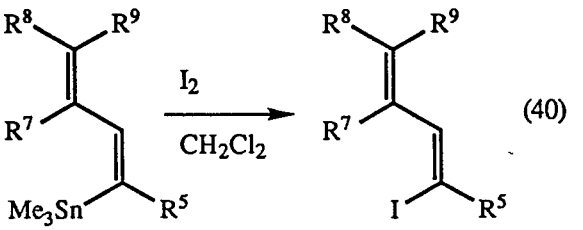


182 **253** 95% **252** 90%

3.2. The preparation of the iodo dienes **249**

Alkenylstannanes may be converted into the corresponding alkenyl iodides via reaction with iodine.[22b] This transformation is usually both highly efficient and stereospecific, and generally proceeds with retention of carbon-carbon double bond geometry.

It was found that stannyldienes **250** were readily converted into the corresponding iodo dienes **249** by reaction with iodine in CH_2Cl_2 (equation 40). These reactions were



(40)

250 **249**

carried out either at -78°C or at 0°C, and essentially involved titration of a solution of the stannyldiene **250** in CH_2Cl_2 with a solution of I_2 in CH_2Cl_2. The end point was reached when the reaction mixture maintained a permanent yellow-orange colour, due to the presence of excess iodine. After appropriate workup, the iodo dienes **249** were readily obtained in high yield and stereochemical purity by flash chromatography of the crude reaction product, followed by distillation. The iodo dienes obtained from these reactions and the yields are shown in Chart 1.

These compounds exhibited spectral data which were in full accord with the proposed structures. For example, the ^1H nmr spectrum of **254** showed a 1-proton doublet of doublets at δ 5.30 (J = 10 Hz, J = 1.5 Hz), a 1-proton doublet of doublets at δ 5.41 (J = 17 Hz, J = 1.5 Hz), a 1-proton broad doublet at δ 6.23 (J = 10 Hz), and a 1-proton doublet of doublets of doublets at δ 6.44 (J = 17 Hz, J = 10 Hz, J = 10 Hz), which were assigned to

H_C, H_B, H_A, and H_D respectively. The low resolution chemical ionization mass spectrum of **254** showed a molecular ion (M^++H) at m/z 339 corresponding to $C_{12}H_{24}OISi$.

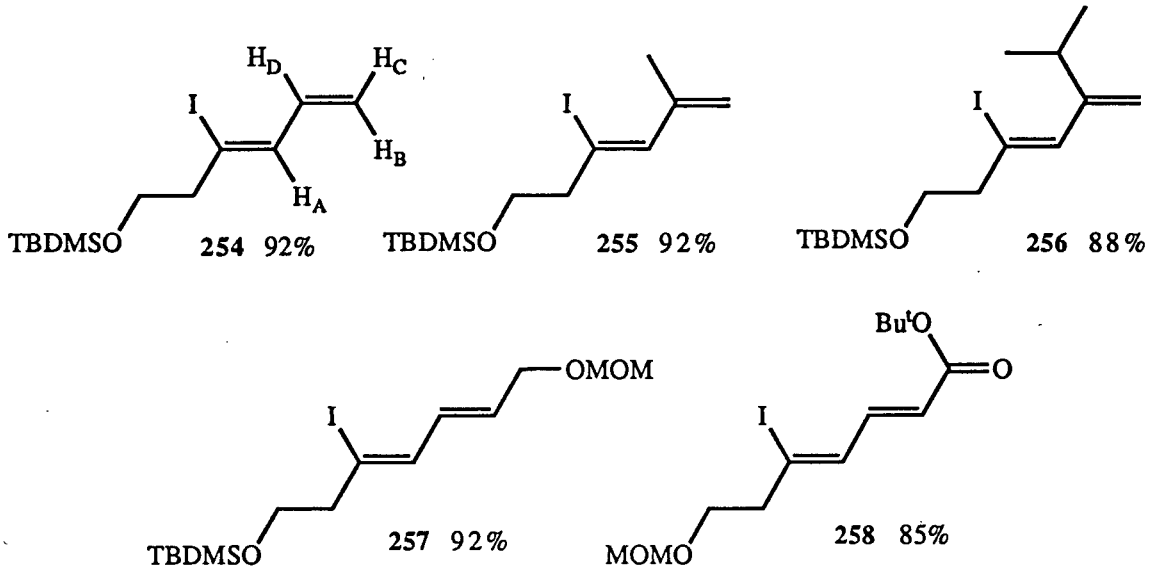
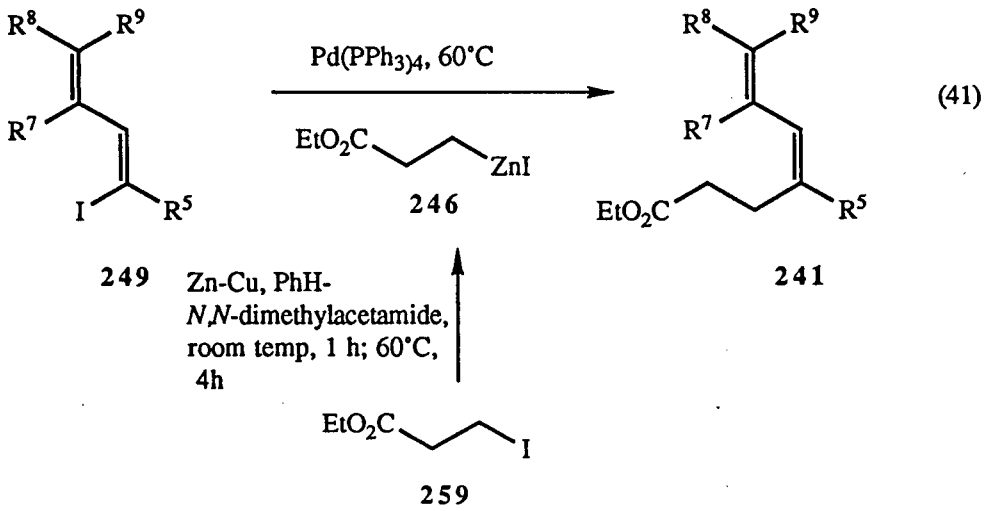


Chart 1

3.3. The preparation of the diene esters **241**

The diene esters of general structure **241** were prepared via Pd(0)-catalyzed cross coupling reactions between the iodo dienes **249** and the organozinc reagent **246** (equation 41).[129] The cross coupling reactions were carried out in a manner similar to that reported in the literature. Typically, a mixture of ethyl 3-iodopropanoate (**259**)[130] (1.5 equivalents) and zinc-copper couple[131] (2.3 equivalents) in dry benzene-DMA (15:1)(argon atmosphere) was stirred at room temperature for 1 hour and at 60°C for 4 hours (equation 41). Tetrakis(triphenylphosphine)palladium(0) (5 mol%) was added and the mixture was stirred at 60°C for 5 minutes. Then, a solution of the iodo diene **249** in dry benzene was added quickly and the resulting mixture was stirred at 60°C for 15 minutes. The reaction mixture was cooled and diluted with diethyl ether, and the resulting mixture was filtered through a

plug of Florisil®, using ether as eluant. The crude reaction product thus obtained was purified by flash chromatography, followed by distillation, to give the diene ester **241**.

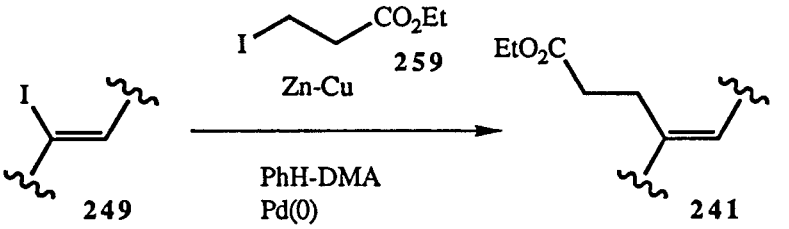


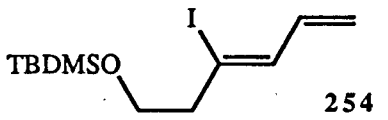
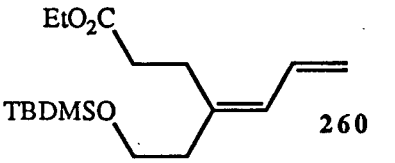
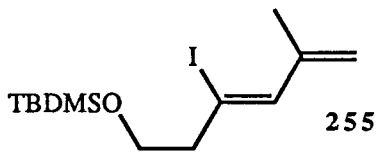
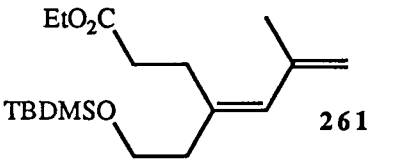
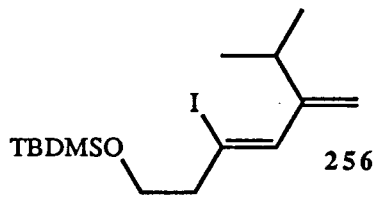
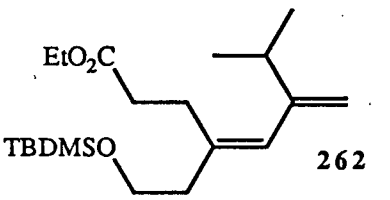
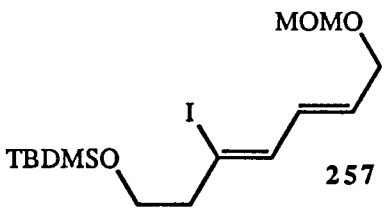
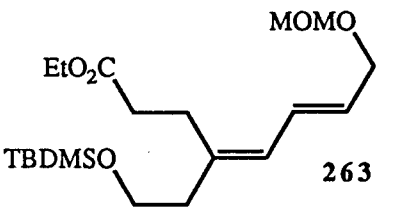
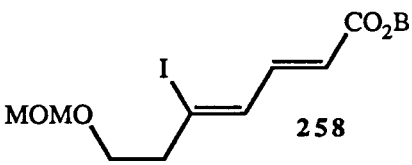
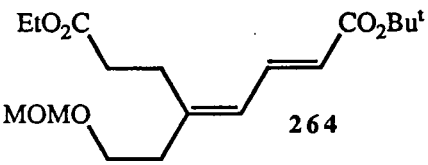
(41)

The amounts of reagents used in these reactions and the results are summarized in Table 11. There are several points which should be mentioned regarding the data in Table 11. Firstly, in some cases it was found that more than 1.5 equivalents of the organozinc reagent **246** was required in order to achieve clean and complete consumption of the iodo diene substrate (entries 1, 4, 5).

Secondly, the workup procedure described above was adopted for all of the reactions listed in Table 11. The reported workup procedure,[129] which involves addition of hydrochloric acid to the reaction mixture, was avoided since most of the substrates used in these reactions have acid sensitive functional groups (such as TBDMS ethers). In most cases, glc analysis of the crude reaction mixture showed the presence of one major peak, which was attributable to the diene ester product. Flash chromatography of the crude reaction product followed by distillation, provided the desired, stereochemically homogeneous diene ester in high purity.

Table 11. The preparation of the diene esters **241**

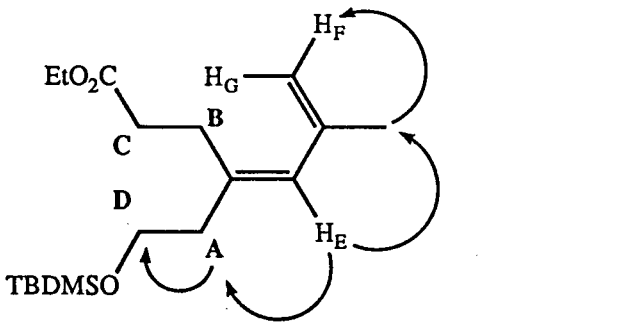


Entry	**249**	Reagent quantities[1]	**241**	Yield[2]%
1	 **254**	B	 **260**	87
2	 **255**	A	 **261**	77
3	 **256**	A	 **262**	74
4	 **257**	B	 **263**	65
5	 **258**	C	 **264**	87

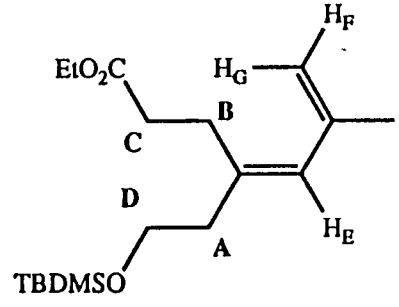
[1] Reagent quantities: A) 1.5 equiv. **259**, 2.3 equiv. Zn-Cu; B) 1.9 equiv. **259**, 2.9 equiv. Zn-Cu; C) 1.7 equiv. **259**, 2.7 equiv. Zn-Cu.

[2] Isolated yield of distilled product.

Finally, the spectral data for these compounds were in full accord with the assigned structures, and are exemplified by those derived from compound **261**. Thus, the infrared spectrum of **261** showed an absorbance at 1736 cm^{-1} attributable to the carbonyl stretching frequency of the ester function. The 400 MHz ^1H nmr spectrum (C_6D_6) of this compound is shown in Figure 4. This spectrum shows a 6-proton singlet at δ 0.09 and a 9-proton singlet at 1.00 due to the TBDMS ether group, a 3-proton triplet at δ 0.99 (J = 8 Hz) and a 2-proton quartet at δ 3.99 (J = 8 Hz) due to the ethyl ester group, and a 3-proton singlet at δ 1.81 (vinyl methyl). A 2-proton broad triplet at δ 2.24 (J = 7 Hz), a 2-proton triplet at δ 3.66 (J = 7 Hz), a 2-proton multiplet at δ 2.41, and a 2-proton triplet at δ 2.75 (J = 7 Hz) were assigned to the methylene groups **A**, **D**, **B**, and **C**, respectively. Also, a 1-proton broad singlet at δ 4.95, a 1-proton broad singlet at δ 4.97, and a 1-proton broad singlet at δ 5.80 were assigned to H_F, H_G and H_E, respectively. The stereochemistry of the diene unit of **261** was confirmed by nOe difference experiments. Thus, irradiation of the signal at δ 5.80 (H_E) caused signal enhancements at δ 2.24 (methylene **A**) and 1.81 (vinyl Me), whilst irradiation at δ 2.24 (methylene **A**) caused signal enhancement at δ 5.80 (H_E) and 3.66 (methylene **D**). Also, irradiation at δ 1.81 (vinyl methyl) caused signal enhancement at δ 5.80 (H_E) and 4.97 (H_F). The observed nOe enhancements also confirm the signal assignments, and indicate that the diene is in the cisoid conformation, as shown below.



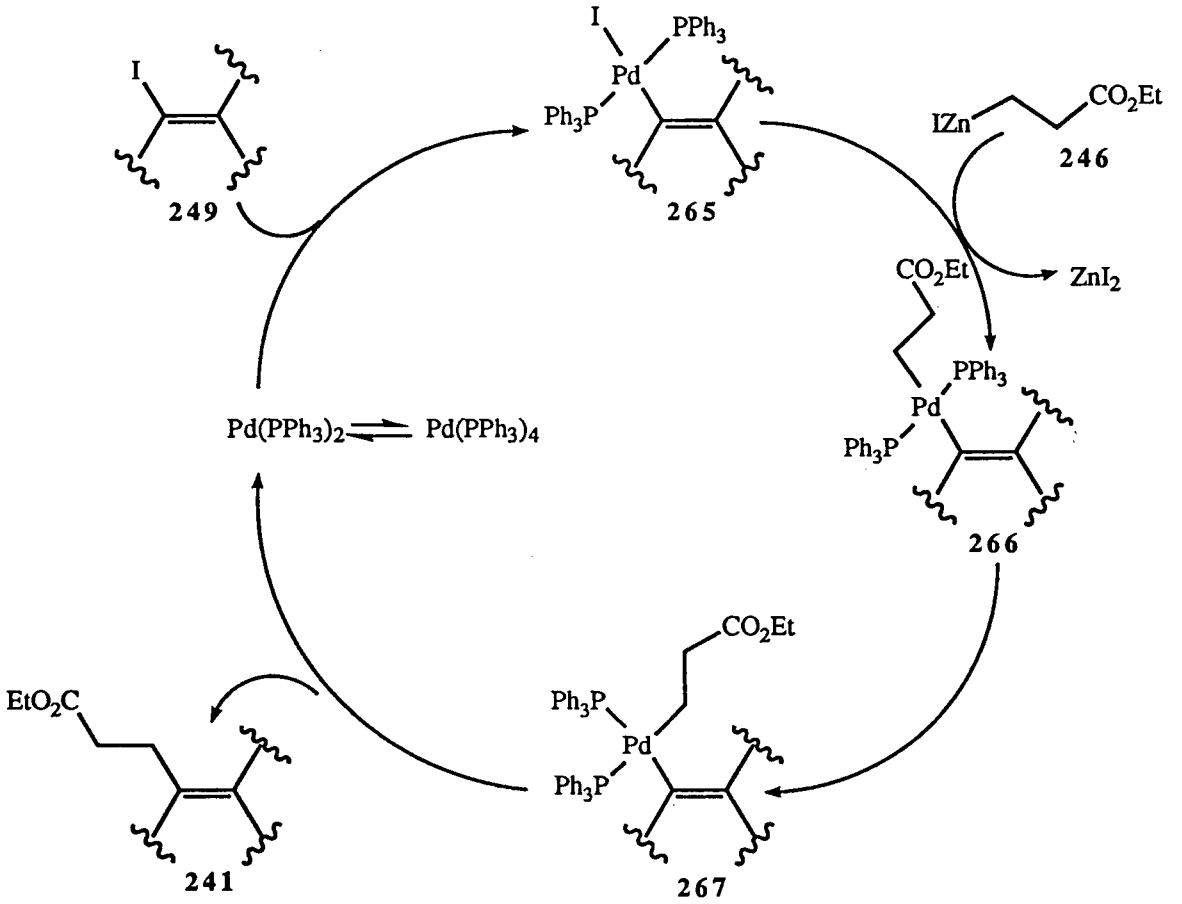
261 nOe enhancements



261

Figure 4 400 MHz ^1H nmr spectrum (C_6D_6) of compound **261**

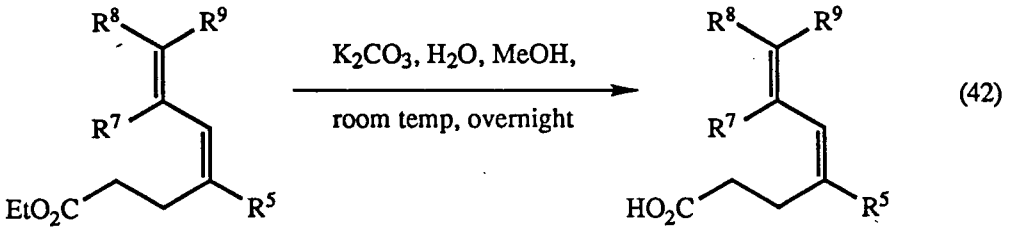
A possible pathway for the formation of diene esters **241** in these cross coupling reactions is summarized in Scheme 39. Firstly, oxidative addition of the iodo diene **249** to the active Pd(0) catalyst would provide a *trans* Pd(II) square planar complex of general structure **265**. Reaction of **265** with the organozinc reagent **246** would result in transmetallation, to give a di-organopalladium(II) complex of general structure **266**. The intermediate **266** could then isomerize to the *cis* complex **267** which may then undergo reductive elimination to give the diene ester **241**, with concomitant regeneration of the Pd(0) catalyst.



Scheme 39

3.4. The preparation of the diene acids 242.

The diene esters of general structure **241** were hydrolyzed to the corresponding carboxylic acids **242** via reaction with a mixture of aqueous K_2CO_3 and methanol at room temperature (equation 42). It was found that the hydrolysis reactions proceeded at a reasonable rate only if the reaction mixtures were completely homogeneous. Thus, the



241 **242** (42)

hydrolysis solution was prepared via dropwise addition of water to a 1:1 mixture of saturated aqueous K_2CO_3 and MeOH, until the mixture was homogeneous. Upon addition of the hydrolysis solution to the diene ester **241** a two phase mixture was formed, so MeOH was added dropwise, while stirring, until the droplets of substrate dissolved in the reaction medium. If the addition of MeOH resulted in precipitation of K_2CO_3, a few drops of water were added to redissolve it. The mixture was stirred at room temperature until the reaction was complete (as judged by tlc analysis). After appropriate workup, all traces of solvent were removed from the product to give the carboxylic acid **242** in a highly pure state. The carboxylic acids **242** which were obtained in these reactions, along with their yields, are listed in Chart 2. These compounds exhibited spectral data which were in full accord with the assigned structures. For example, the infrared spectrum of compound **269** showed a broad intense absorption at 2400-3400 cm^{-1} attributable to the oxygen-hydrogen stretching frequency of the carboxylic acid function, and an absorption at 1713 cm^{-1} attributable to the carbonyl stretching frequency of the carboxylic acid function. The ^1H nmr spectrum of **269**

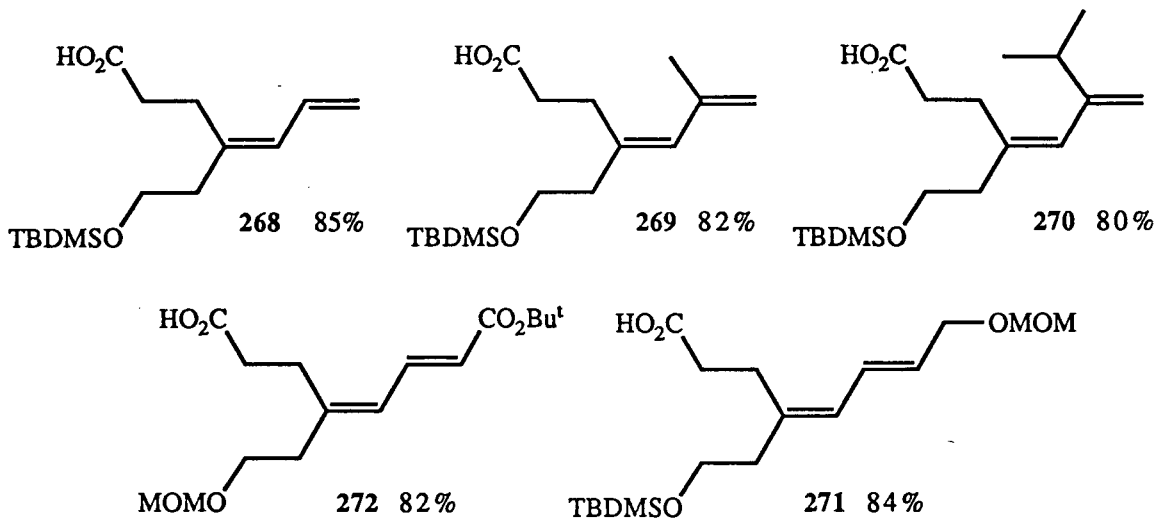
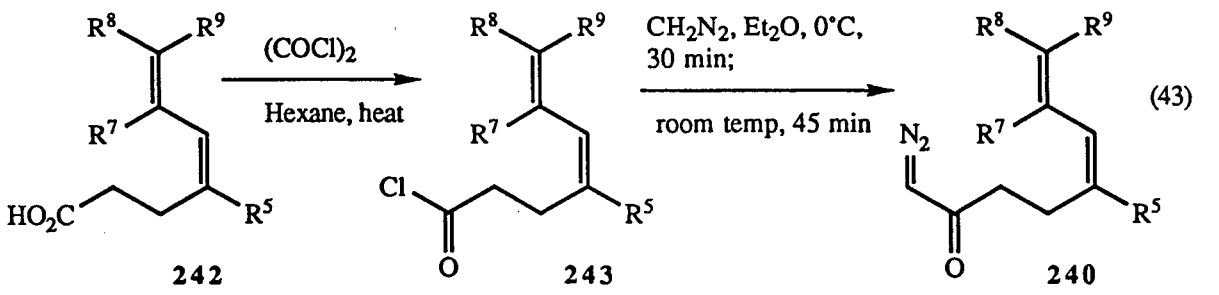


Chart 2

showed very similar features to those already discussed for the precursor ester **261** except that the resonances due to the ethyl ester function were not present. Also, the signal due to the carboxylic acid proton was not visible. The low resolution chemical ionization mass spectrum of **269** showed a peak at m/z 299 (M^++H) corresponding to the molecular formula $C_{16}H_{31}O_3Si$.

3.5. The preparation of the diene diazoketones **240**

The requisite diene diazoketones of general structure **240** were prepared from the appropriate carboxylic acids **242** using a procedure similar to that reported by previous workers.[122,128] Thus, the carboxylic acids **242** were converted into the corresponding acid chlorides **243** via reaction with oxalyl chloride in refluxing hexane. Reaction of the crude acid chlorides **243** with diazomethane provided the diazoketones **240** (equation 43).



(43)

In a typical procedure, a mixture of the carboxylic acid **242** and oxalyl chloride (3 equivalents) in dry hexane (argon atmosphere) was refluxed for 2 hours. Removal of solvent and volatile material from the crude reaction mixture, under reduced pressure (0.5 Torr, room temperature), provided the crude acid chloride **243**. A solution of the crude acid chloride **243** in anhydrous ether was added slowly, via cannula, to an ethereal solution of diazomethane in dry ether at 0°C. Immediate and rapid effervescence was observed. The mixture was stirred at 0°C for 30 min and at room temperature for 45 min. Then, excess diazomethane was removed from the reaction mixture by bubbling argon through the solution for approximately 30 min. The crude reaction product was purified by flash chromatography to give the essentially pure (as judged by tlc analysis) diazoketone **240** , a bright yellow viscous oil. These compounds were committed to the next step without further purification or characterization. However, it was found that the diazoketones **240** are stable in a freezer in the dark for several months. The diazoketones which were prepared in this manner, along with their yields, are listed in Chart 3.

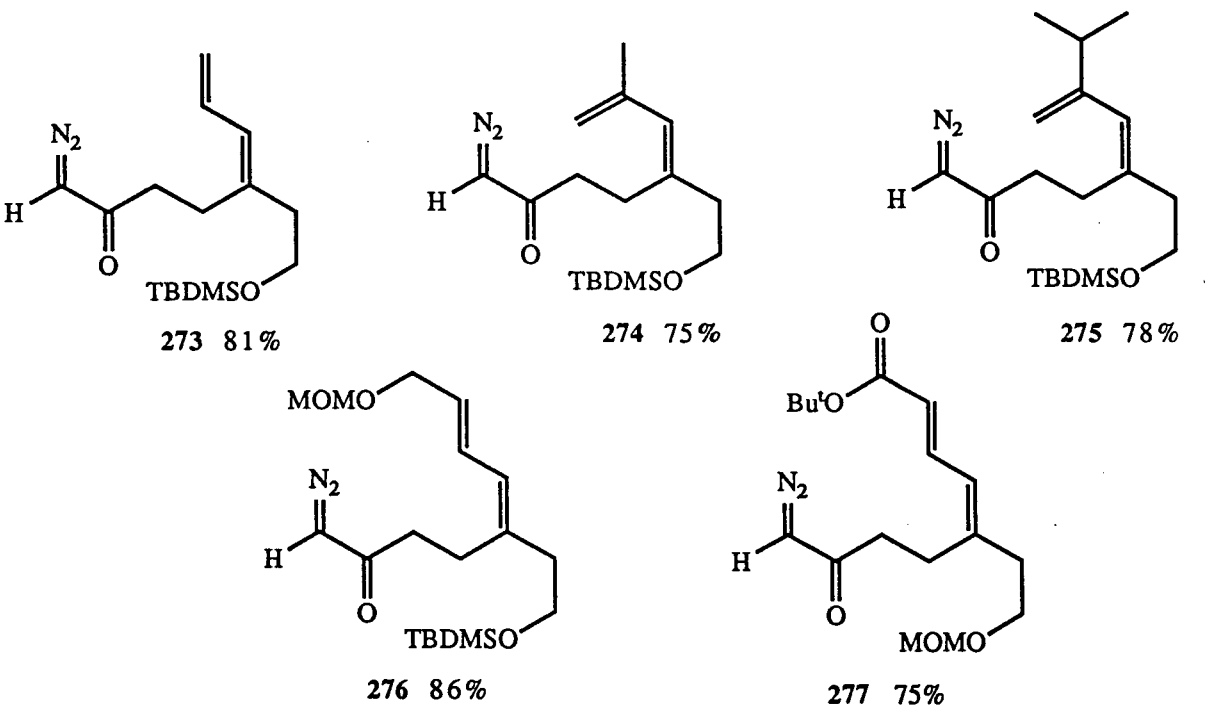
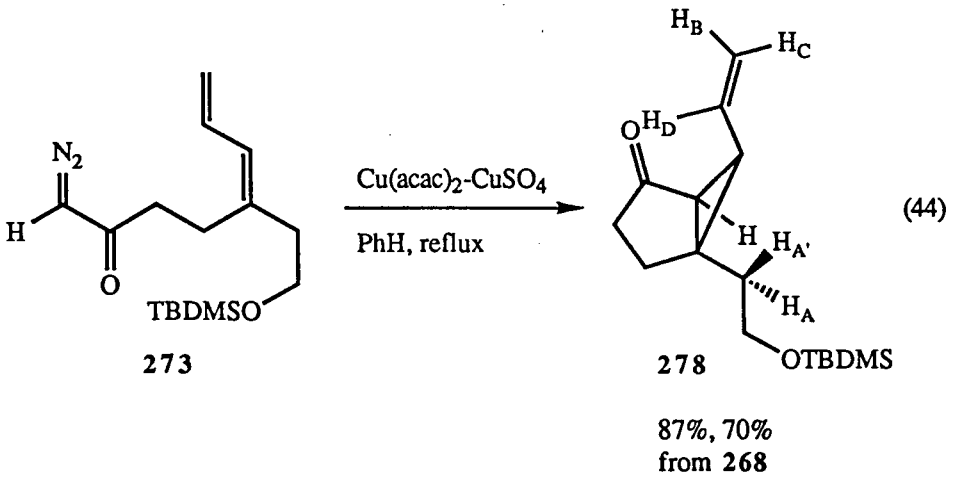


Chart 3

3.6. The transition metal-catalyzed intramolecular cyclopropanation reactions of the diene diazoketones **240**. The preparation of the 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hexan-2-ones **237** (R^1=H).

The initial experiments were carried out using the diazoketone **273** as substrate. It was found that **273** was smoothly converted into the desired 6-*endo*-vinylbicyclo[3.1.0]hexan-2-one **278**, via reaction with a mixture of copper(II) sulphate and copper(II) acetylacetonate in refluxing benzene (equation 44).[132] Thus, a 0.1M (approximately) solution of the diazoketone **273** in dry benzene was added slowly (over approximately 30 min), via syringe pump, to a suspension of copper(II) sulphate (1 equivalent) and copper(II) acetylacetonate (10 weight percent relative to copper(II) sulphate) in the same volume of refluxing anhydrous benzene. The resulting mixture was refluxed for a further 15 min and was then cooled to room temperature. Glc analysis of the crude reaction mixture showed the presence of only one compound, which was assumed to be the desired ketone **278**. Tlc analysis of the crude reaction mixture showed that all of the diazoketone **273** had been consumed and that one major product was formed. The crude product was passed through a short column of Florisil® and was then purified by flash chromatography followed by distillation, to give **278** in 87% yield, an overall yield of 70% from the carboxylic acid **268**.



273 **278** (44)

87%, 70%
from **268**

Compound **278** exhibited spectral data which were entirely consistent with the proposed structure. Thus, the infrared spectrum of **278** showed a strong absorbance at 1719 cm^{-1}, attributable to the carbon-oxygen stretching frequency of the ketone function. The ^1H nmr spectrum (400 MHz, C_6D_6) of **278** is shown in Figure 5. Although this spectrum contains many overlapping multiplets, several characteristic features can be readily identified. Thus, there is a 6-proton singlet at δ 0.06 and a 9-proton singlet at δ 0.99 due to the TBDMS group. There is a 2-proton triplet at δ 3.48 (J = 6 Hz, -$CH_2C\underline{H_2}O$-), as well as a doublet of triplets at δ 1.22 (J = 14 Hz, J = 6 Hz) and a doublet of triplets at δ 1.59 (J = 14 Hz, J = 6 Hz) due to H_A and $H_{A'}$. Also, a 1-proton doublet of doublets of doublets at δ 5.08 (J = 10 Hz, J = 2 Hz, J = 1 Hz), a 1-proton doublet of doublets of doublets at δ 5.24 (J = 16 Hz, J = 2 Hz, J = 1 Hz) and a 1-proton doublet of doublets of doublets at δ 5.51 (J = 16 Hz, J = 10 Hz, J = 6 Hz) were assigned to H_B, H_C and H_D respectively.

The relative stereochemistry of compound **278** was not proven spectroscopically, but the vinyl group was assumed to be in the *endo* orientation on the basis of the known stereospecificity[118,119,122,127,128] of transition metal catalyzed cyclopropanation reactions involving α-diazocarbonyl compounds. This relative stereochemistry was later confirmed since divinylcyclopropanes derived from **278** were found to undergo extremely facile Cope rearrangement. This would not be the case if the vinyl group was in the *exo* orientation.

Reaction of the diazoketone **276** with $CuSO_4$-$Cu(acac)_2$ in refluxing benzene, using a procedure very similar to that described above, afforded the ketone **279** in 90% yield, an overall yield of 78% from the carboxylic acid **271** (equation 45).

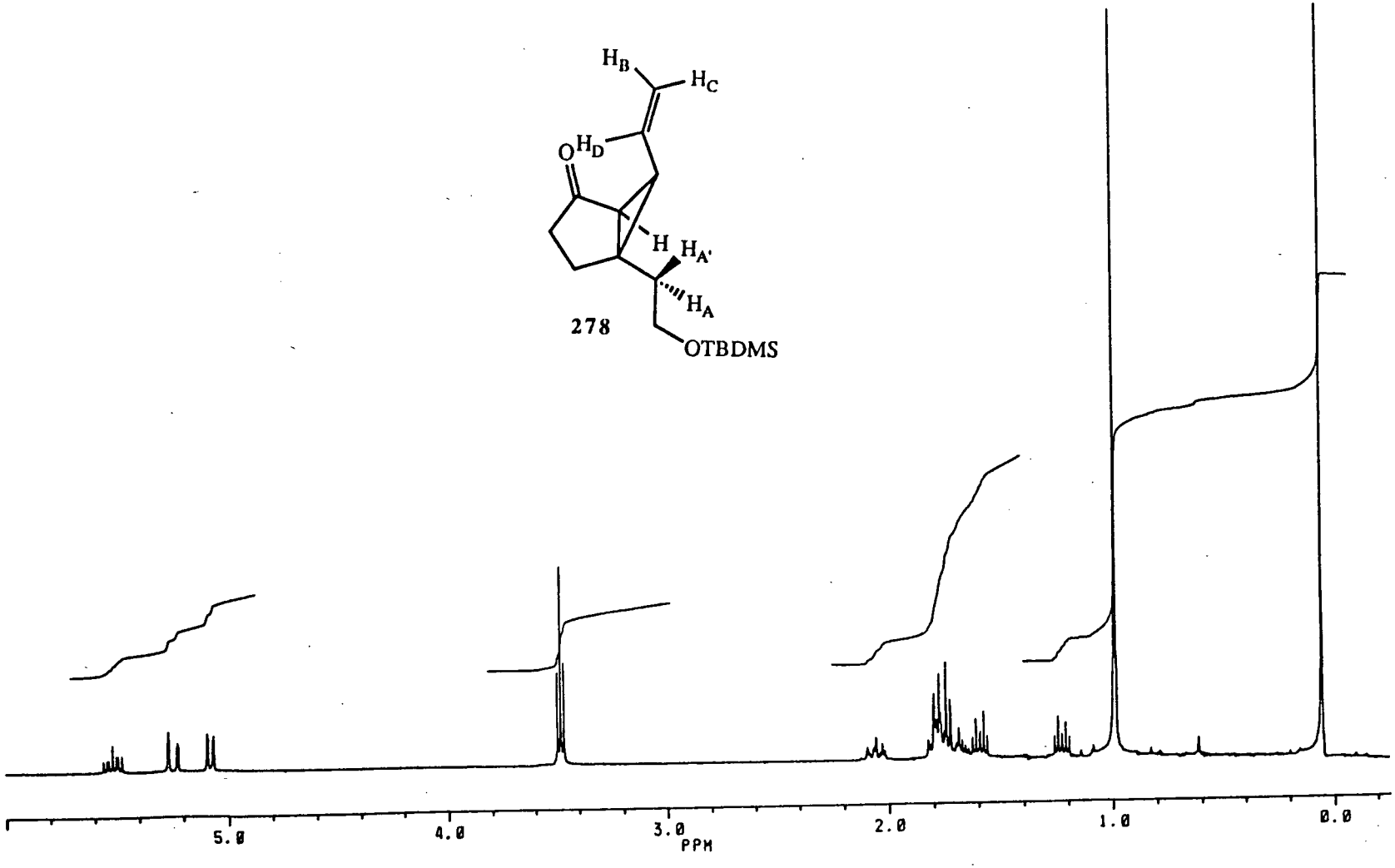
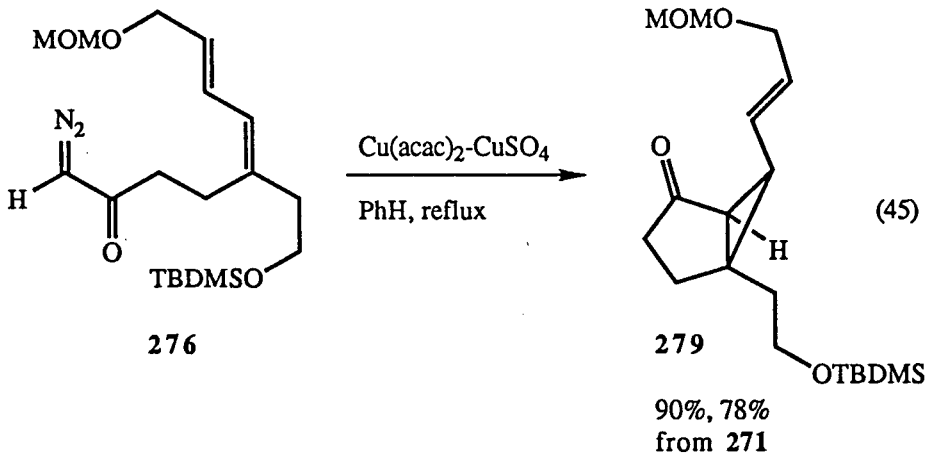


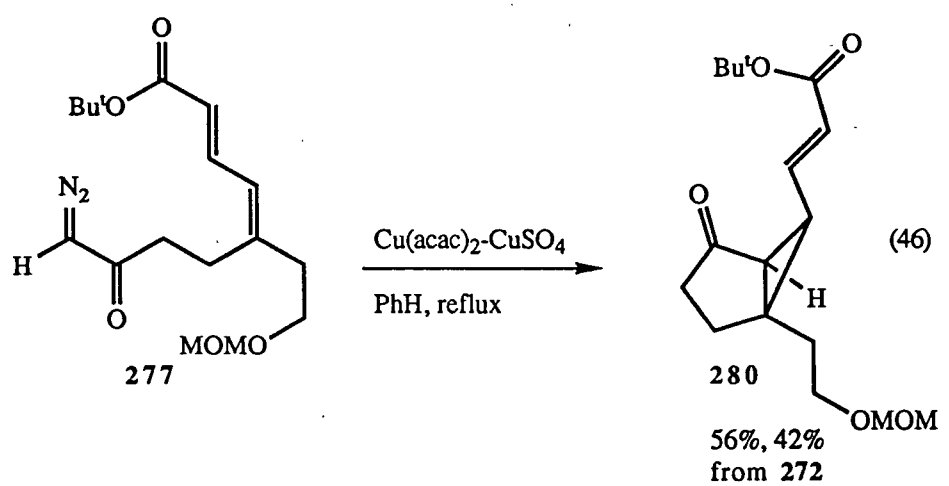
Figure 5 400 MHz ^{1}H nmr spectrum (C_6D_6) of compound **278**



276 279 (45)

90%, 78% from 271

The diazoketone **277** was converted into the ketone **280** via reaction with $CuSO_4$-Cu(acac)2 in refluxing benzene (equation 46), using a procedure similar to that described above. However, this reaction was neither as clean nor as efficient as those involving the diazoketones **273** and **276**. Glc analysis of the crude reaction mixture showed the presence of several compounds, the major component being the desired product **280**. Flash chromatography of the crude product followed by distillation provided the ketone **280** in 56% yield (42% from the carboxylic acid **272**) (equation 46).

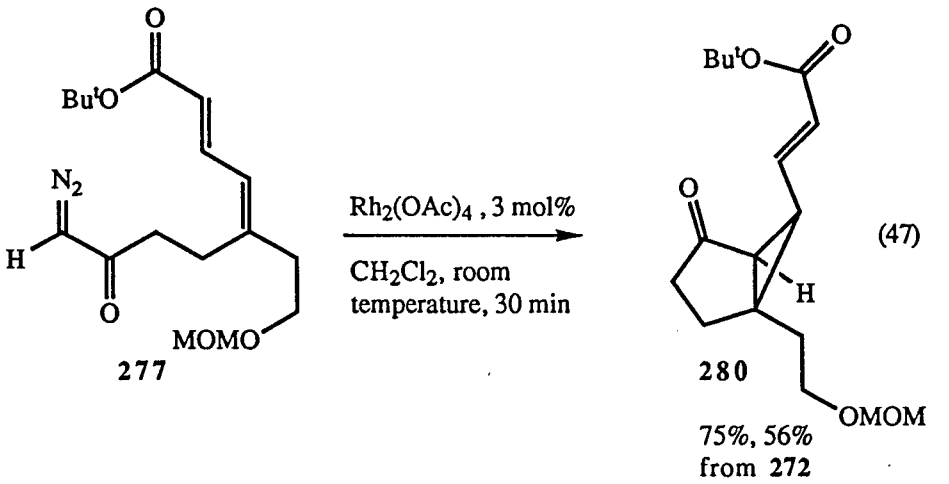


277 280 (46)

56%, 42% from 272

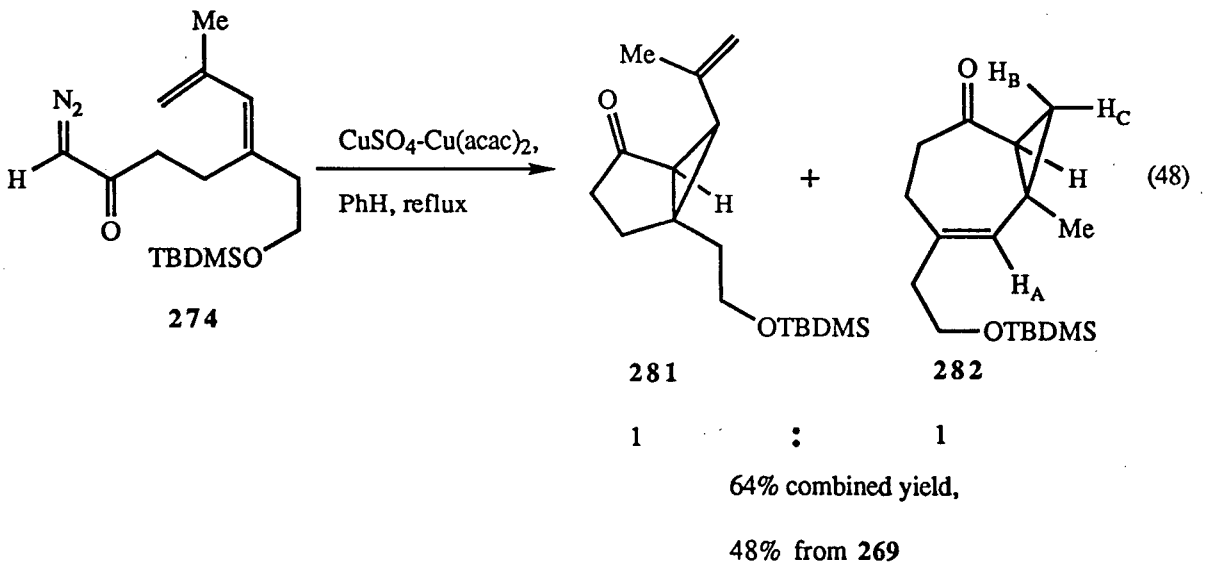
It was found that the cyclopropanation reaction proceeded much more cleanly when $Rh_2(OAc)_4$ was used as the catalyst (equation 47). Thus, reaction of the diazoketone **277**

with $Rh_2(OAc)_4$ (3 mol%) in dry CH_2Cl_2 at room temperature, for 30 min, provided **280** in 75% yield, an overall yield of 56% from the carboxylic acid **272**.



(47)

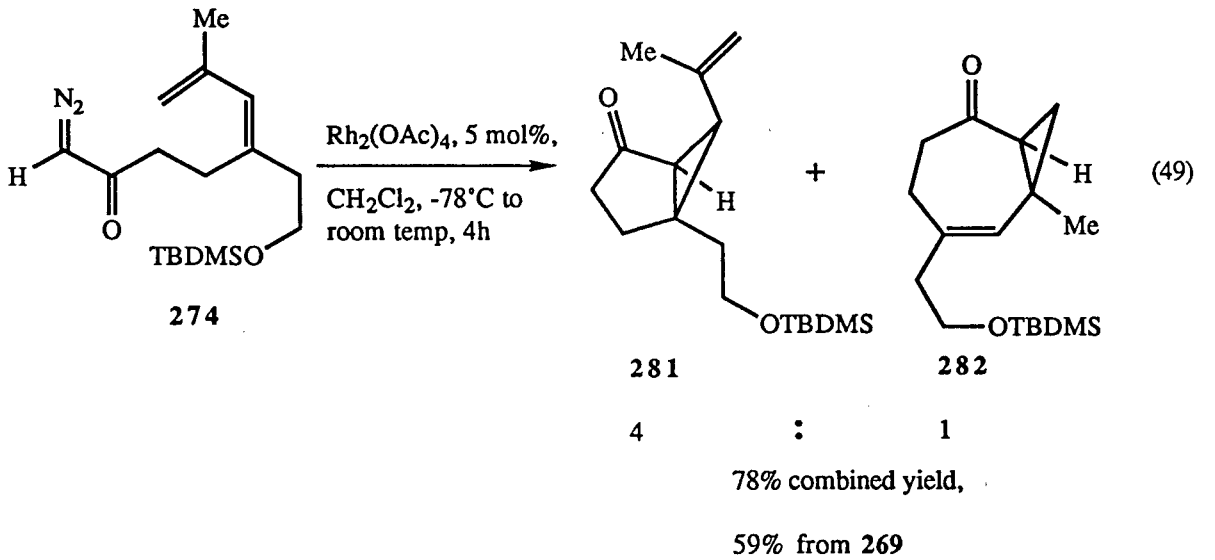
Reaction of the diazoketone **274** with $CuSO_4$-$Cu(acac)_2$ in refluxing benzene via a procedure similar to that described earlier, provided a 1:1 mixture of two compounds, which were inseparable by silica gel flash chromatography. One of the compounds was the expected product **281** (equation 48). This was confirmed later by comparison of the ^1H nmr spectrum of the mixture of products with that of a pure sample of compound **281**. The other product was assigned the structure **282** based on the ^1H nmr spectrum of the mixture.



(48)

Thus, the ^1H nmr spectrum of the mixture showed, as well as peaks due to the desired product **281**, a 1-proton broad singlet at δ 5.41, a 1-proton doublet of doublets at δ 0.74 (J = 8 Hz, J = 4 Hz), and a 3-proton singlet at δ 0.98, which were assigned to H_A, H_B (or H_C) and the angular methyl group, respectively, of compound **282**.

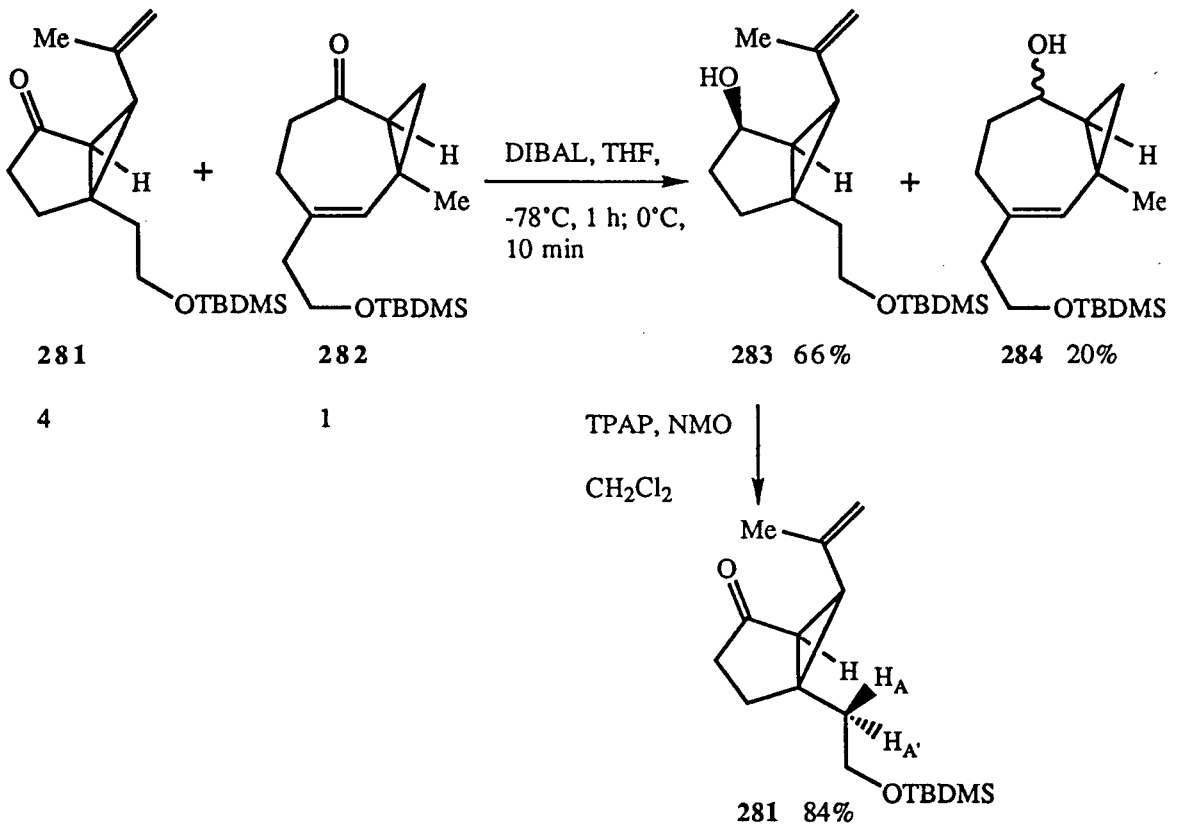
The ketones **281** and **282** are derived from the diazoketone **274** by cyclopropanation taking place at different carbon-carbon double bonds of the diene unit. The lack of chemoselectivity in this cyclopropanation reaction was an interesting but undesirable result. Therefore it was decided to investigate different cyclopropanation conditions to determine whether the chemoselectivity could be improved. Fortunately, it was found that reaction of the diazoketone **274** with $Rh_2(OAc)_4$ (5 mol%) in dry CH_2Cl_2 (-78°C to room temperature, 4 hours) provided a 4:1 mixture of the ketones **281** and **282**, respectively, in 78% yield (an overall yield of 59% from the carboxylic acid **269**) (equation 49).



(49)

Since **281** and **282** were inseparable by silica gel chromatography, later synthetic transformations were carried out on mixtures of the two compounds. However, a pure sample of **281** was required for full characterization and was obtained in the following manner (Scheme 40). Reaction of a 4:1 mixture of ketones **281** and **282** (respectively) with

DIBAL in THF afforded a mixture of products, consisting of the alcohol **283** and the alcohols **284**. Flash chromatography of this mixture provided the alcohol **283** in 66% yield and the alcohols **284** in 20% yield. The ^1H nmr spectrum of **283** indicated that it was stereochemically homogeneous. Although the orientation of the hydroxyl group was not determined, it was assumed to be *endo* (as shown in Scheme 40) since the bulky reducing agent (DIBAL) would be expected to react with the ketone **281** from the less hindered, convex face of the molecule.

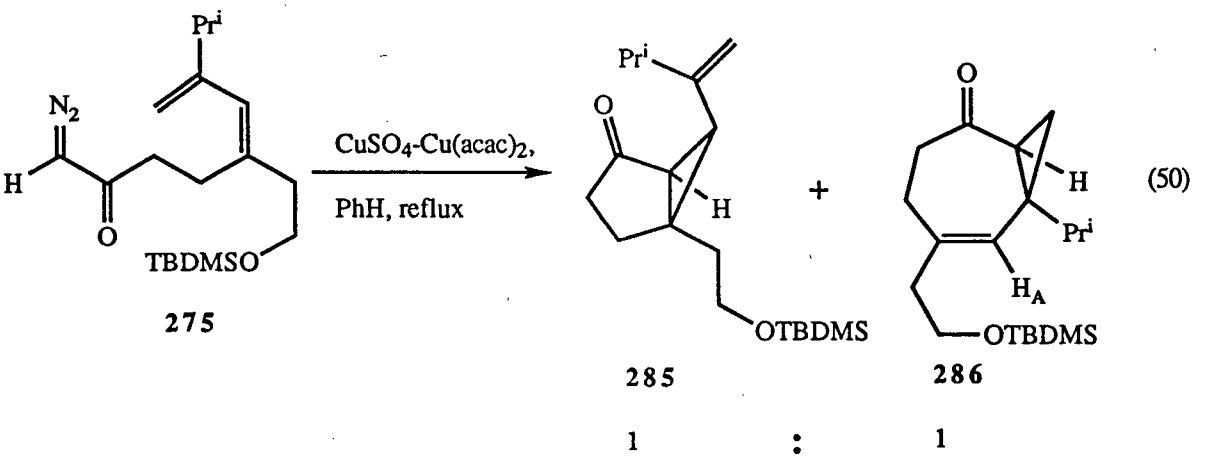


Scheme 40

The pure alcohol **283** was oxidized to the ketone **281** using a procedure developed by Griffith and Ley.[133] Thus, to a solution of the alcohol **283** in dry CH_2Cl_2 was added freshly activated molecular sieves and *N*-methylmorpholine *N*-oxide (NMO) (2.5

equivalents). After the resulting mixture had been stirred for 10 min at room temperature tetra-*n*-propylammonium perruthenate (TPAP) (5 mol%) was added, and stirring was continued until the reaction was complete (as judged by tlc analysis). After appropriate workup, the crude reaction product was purified by flash chromatography, followed by distillation, to give the pure ketone **281** in 84% yield. This compound exhibited spectral data which were in full accord with the assigned structure. For example, the infrared spectrum of **281** showed an absorbance at 1723 cm^{-1}, attributable to the carbon-oxygen stretching frequency of the ketone function. The 400 MHz ^1H nmr spectrum of this compound is shown in Figure 6. Several features are readily discernible from this spectrum. There is a 6-proton singlet at δ 0.06 and a 9-proton singlet at δ 1.00 due to the TBDMS ether function, a 1-proton doublet of triplets at δ 1.18 (J = 13 Hz, J = 6 Hz) due to either H_A or $H_{A'}$ and a 2-proton triplet at δ 3.52 (J = 6 Hz, $-CH_2\underline{CH_2}O-$). Also, there are 1-proton broad singlets at δ 4.85 and 4.98 due to the olefinic protons.

Reaction of the diazoketone **275** with $CuSO_4$-$Cu(acac)_2$ in refluxing benzene afforded two products in a 1:1 ratio, which were inseparable by silica gel chromatography. One of the products was readily identified as the ketone **285** (equation 50) by comparison of



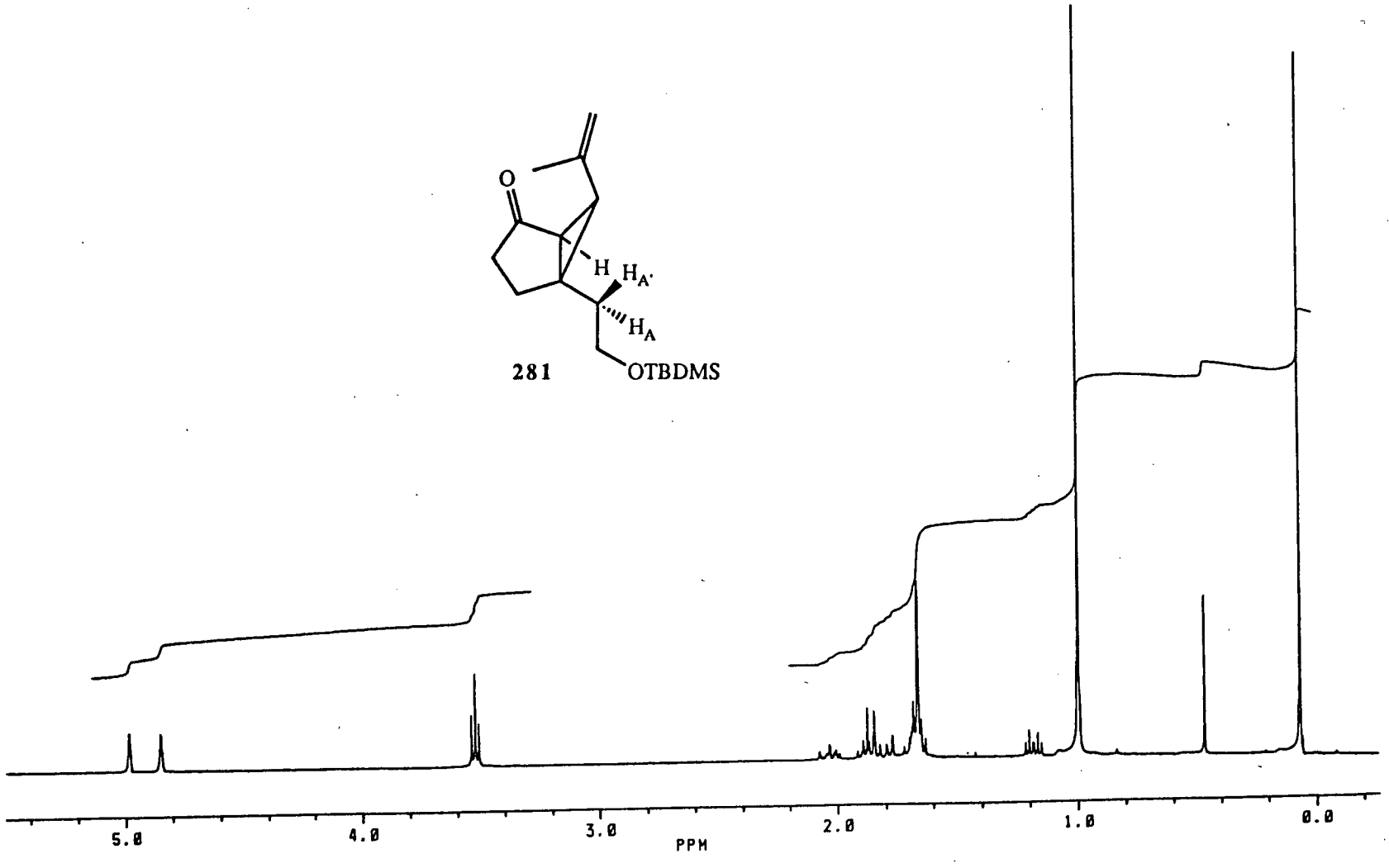
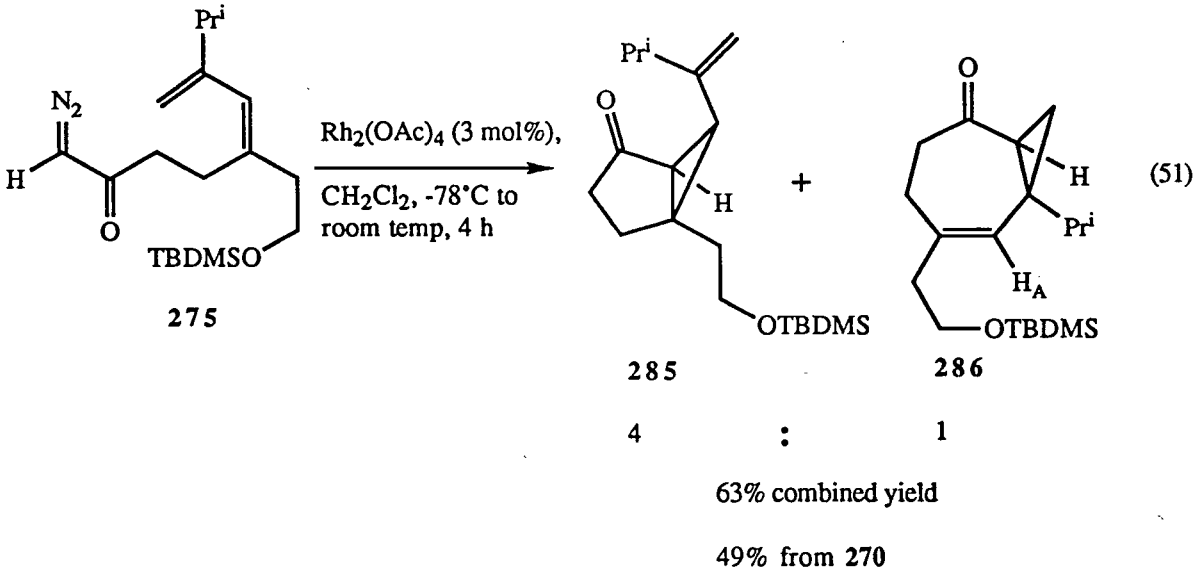


Figure 6 400 MHz ^{1}H nmr spectrum (C_6D_6) of compound **281**

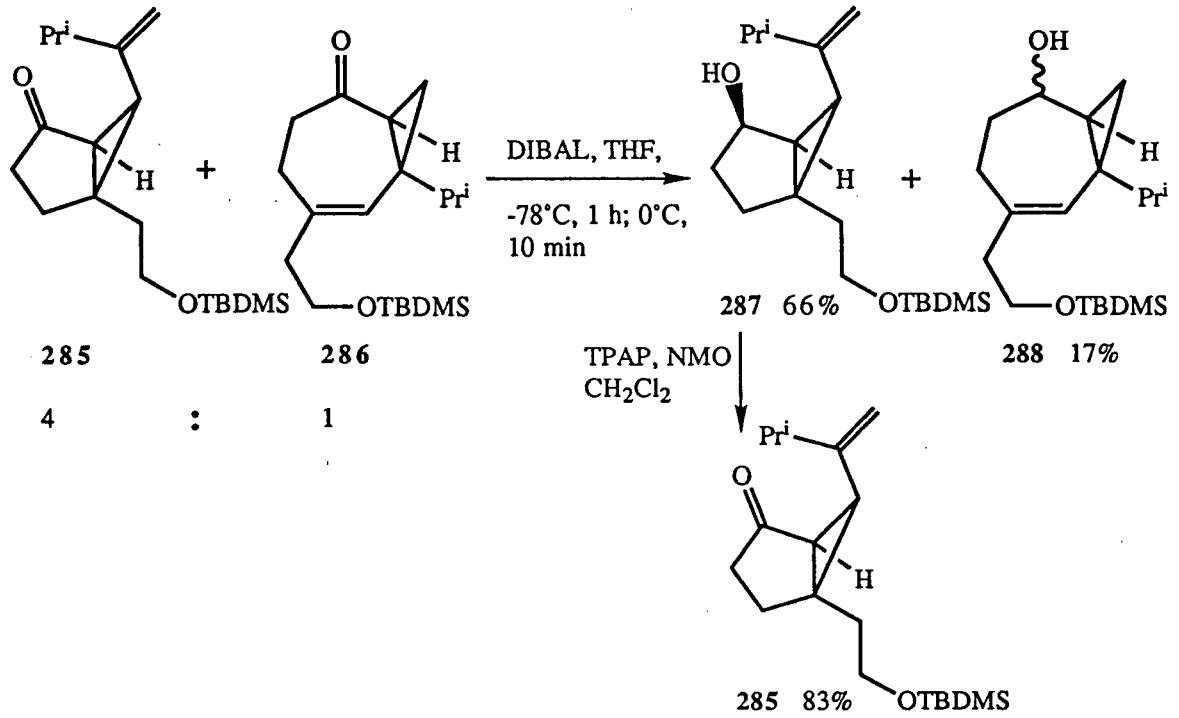
the ^1H nmr spectrum of the crude reaction mixture with that of a pure sample of **285** (the preparation of which is described later). The presence of a 1-proton broad singlet at δ 5.49 (H_A) in the ^1H nmr spectrum of the crude reaction mixture indicated that the other product was compound **286** (equation 50).

It was found that the chemoselectivity of the intramolecular cyclopropanation reaction could be improved by using $Rh_2(OAc)_4$ as catalyst. Thus, reaction of the diazoketone **275** with $Rh_2(OAc)_4$ (3 mol%) in CH_2Cl_2 (-78°C to room temperature, 4 hours) gave a 4:1 ratio of **285** and **286**, respectively, in 63% yield (an overall yield of 49% from the carboxylic acid **270**) (equation 51).



Since these compounds were inseparable by silica gel chromatography, later synthetic transformations were carried out using mixtures containing both compounds. However, a pure sample of **285** was required for spectral characterization and was prepared from the mixture of ketones **285** and **286** (Scheme 41) via a reduction-separation-oxidation sequence very similar to that described earlier, in connection with preparation of pure compound **281**. Thus, DIBAL reduction of a 4:1 mixture of **285** and **286** (respectively) provided, after chromatographic separation of the products, the pure alcohol **287** in 66% yield and the

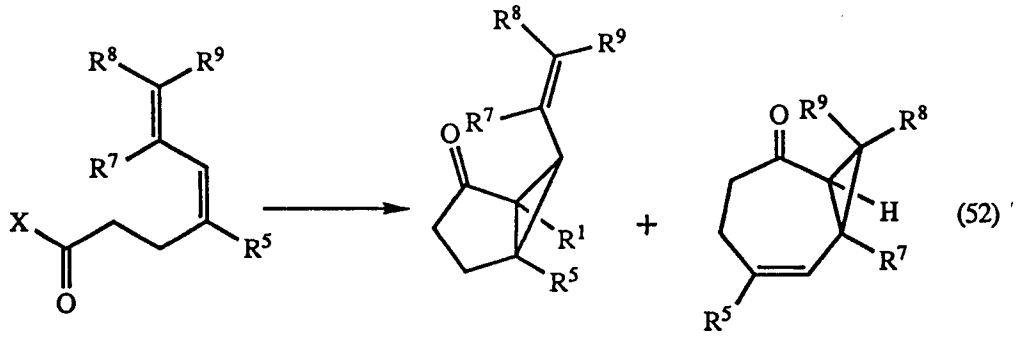
alcohols **288** (in 17% yield). Oxidation of **287** using TPAP and NMO proceeded cleanly, to give the pure ketone **285** in 83% yield. This material exhibited spectral data entirely consistent with the proposed structure.



Scheme 41

There are several general comments that should be made regarding the transition metal-catalyzed intramolecular cyclopropanation reactions of diene diazoketones of general structure **240**. Firstly, with the correct choice of catalyst, these reactions proceed cleanly and efficiently to give good overall yields of the cyclopropyl ketones **237** (R^1=H) and/or **289** from the corresponding carboxylic acids **242** (equation 52).

Secondly, the reactions are completely stereospecific, providing the 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hexan-2-ones of general structure **237** (R^1=H) and none of the corresponding *exo* isomers. However, the chemoselectivity of this process appears to be dependant on the substitution pattern of the diene unit of diazoketones **240**. In particular, the reactions are completely chemoselective when R^7=H, but when R^7=alkyl both five and seven



242 X = OH

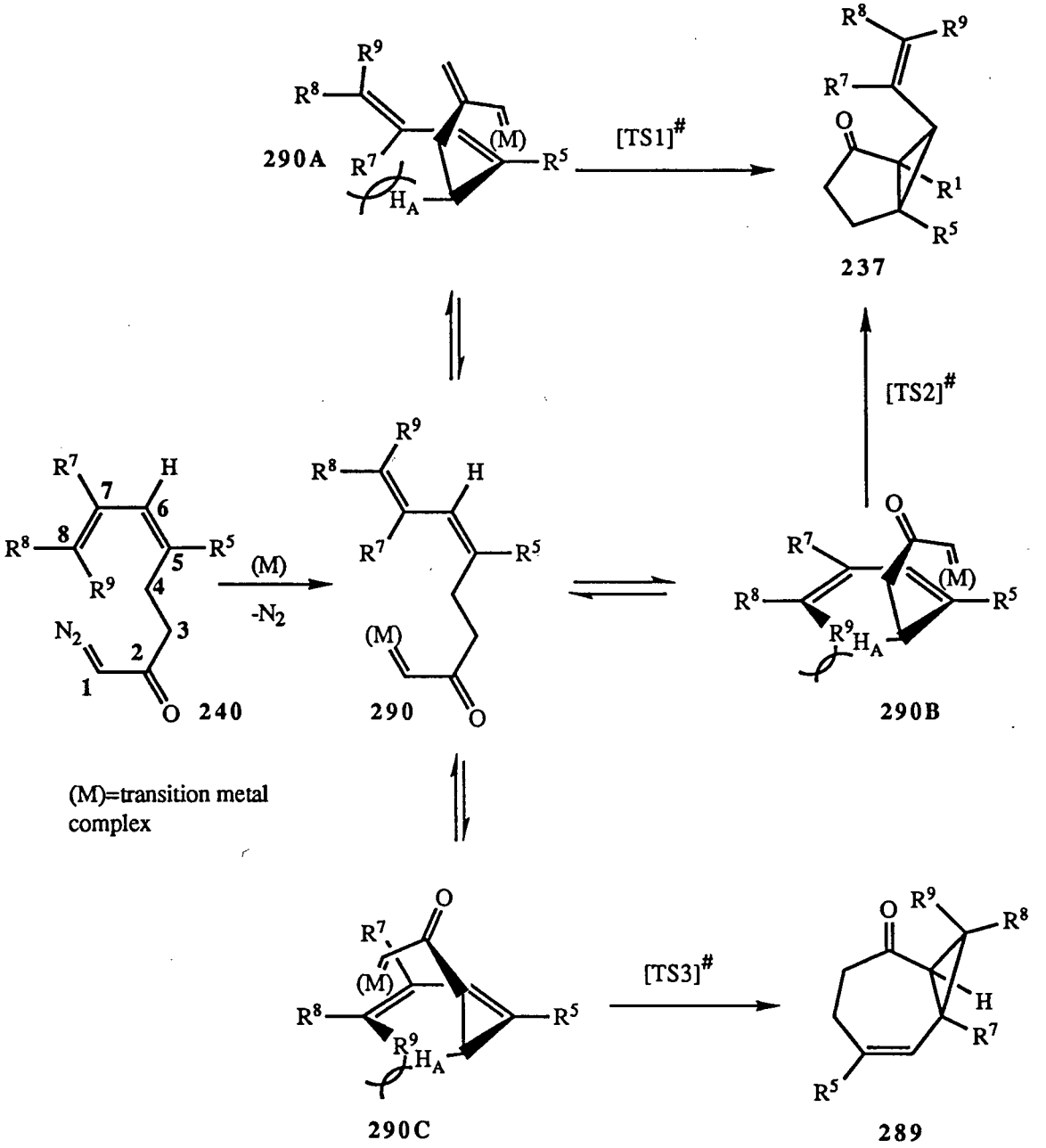
240 X = CHN_2

237

289

(52)

membered ring ketones [**237** (R^1=H) and **289**] are formed. These results may be rationalized using the following arguments (Scheme 42). It is likely that the first step in this process involves reaction of the diazoketone function in compounds **240** with the transition metal catalyst to give a transition metal carbene complex, represented by **290**.[134,135] Presumably, the carbenoid site of intermediates **290** interacts with one of the carbon-carbon double bonds of the diene unit, resulting in cyclopropanation with concomitant regeneration of the catalyst. How readily either carbon-carbon double bond of the diene unit in **290** is cyclopropanated should depend primarily on how accessible it is to the metal carbenoid site. Examination of a molecular model representing **290** indicates that the carbenoid site can readily approach the C5-C6 double bond when the diene unit is either in the transoid conformation or the cisoid conformation, but can approach the C7-C8 double bond only when the diene unit is cisoid. Therefore, it is proposed that formation of five membered ring ketones **237** (R^1=H) may take place either via a transition state [TS1]$^{\#}$ derived from a conformer of general structure **290A** (diene unit transoid) or via a transition state [TS2]$^{\#}$ derived from a conformer of general structure **290B** (diene unit cisoid). Additionally, formation of the seven membered ring ketones **289** is possible only via a transition state [TS3]$^{\#}$ derived from a conformer of general structure **290C** (diene unit cisoid) (Scheme 42). The differences in free energy between these transition states should determine the chemoselectivity of the cyclopropanation reaction.



Scheme 42

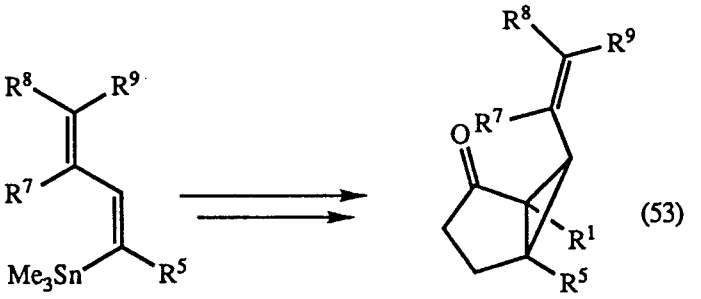
It would be expected that formation of five membered ring products **237** (R^1=H) (via either [TS1]# or [TS2]#) is inherently favoured over formation of seven membered ring products **289** (via [TS3]#), primarily due to entropy effects. However, steric effects might also be important in these reactions. The transition state [TS1]# would experience a steric

interaction between H_A and R^7, whereas the transition states [TS2]$^{\#}$ and [TS3]$^{\#}$ would experience a steric interaction between H_A and R^9. The substituent R^8 should not cause unfavourable steric interactions in any of the possible transition states.

For each of the diene diazoketones **273**, **276** and **277**, R^9=H and R^7=H. Regarding the cyclopropanation reactions involving these substrates, the steric interaction in the transition state [TS1]$^{\#}$ appears to be less severe than the steric interaction in the transition states [TS2]$^{\#}$ and [TS3]$^{\#}$. It is, therefore, proposed that these reactions proceed preferentially via [TS1]$^{\#}$ to give five membered ring products **237** (R^1=H)

For the diene diazoketones **274** and **275**, R^9=H and R^7=alkyl. Regarding the cyclopropanation reactions involving these substrates, the steric interaction in the transition state [TS1]$^{\#}$ appears to be more severe than the steric interaction in the transition states [TS2]$^{\#}$ and [TS3]$^{\#}$. Therefore, it is proposed that these reactions proceed primarily via [TS2]$^{\#}$ and [TS3]$^{\#}$ to give both the five and seven membered ring products **237** (R^1=H) and **289**, respectively. Although the ketones **237** (R^1=H) would still be expected to be formed more readily than the seven membered ring products **289**, the low (or lack of) chemoselectivity in these reactions must be a result of a subtle balance between steric and entropic effects. The ratio of **237** (R^1=H) to **289** formed in these reactions is somewhat dependant on the reaction conditions (e.g. the nature of the catalyst) which suggests that other factors may also be involved in determining the chemoselectivity.

In summary, an efficient, stereoselective synthesis of functionalized 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hexan-2-ones of general structure **237** (R^1=H) has been developed, employing stannyldienes of general structure **250** as starting materials (equation 53). The compounds which were prepared via this general synthetic route, and the overall yields, are presented in Table 12. In principle, it should be possible to prepare many other ketones **237** (R^1=H) via this methodology.

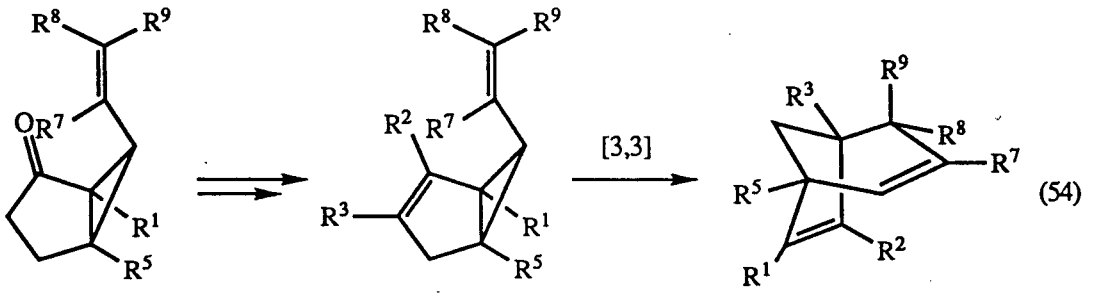


(53)

250 **237**

3.7. The preparation and Cope rearrangement of 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hex-2-enes **215**. The synthesis of bicyclo[3.2.1]octa-2,6-dienes **216**.

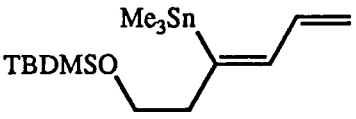
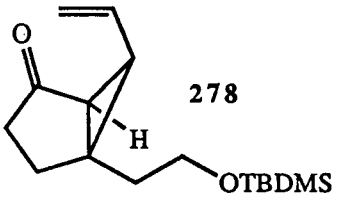
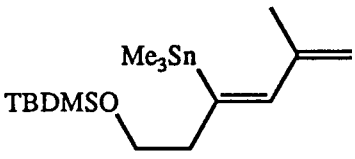
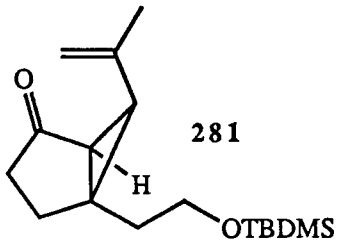
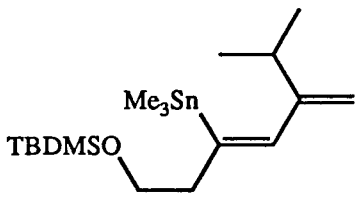
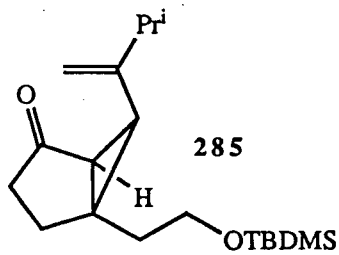
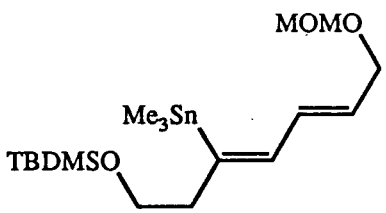
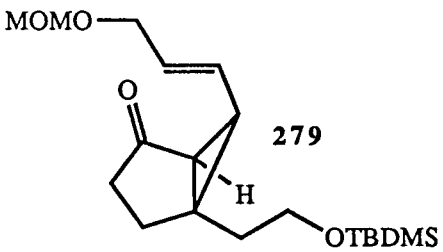
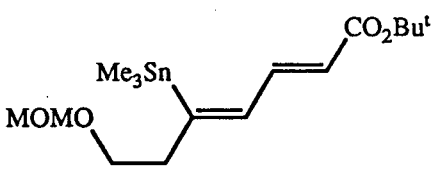
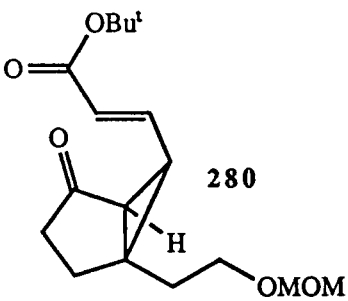
The 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hexan-2-ones **237** (R^1=H) were readily converted, via simple manipulation of the ketone function, into functionalized 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hex-2-enes of general structure **215** (R^1=H) (equation 54). These *cis* divinylcyclopropanes were found to undergo facile Cope rearrangement, to give the corresponding bicyclo[3.2.1]octa-2,6-dienes **216** (R^1=H) cleanly and efficiently (equation 54). It was found that the overall transformation of the ketones **237** into the bicyclic compounds **216** could be achieved conveniently without full purification of the intermediate *cis* divinylcyclopropanes **215**. The Cope rearrangements were effected either by distillation of the crude *cis* divinylcyclopropane **215**, or by warming a solution of (crude) **215** in benzene (in which case the products were purified by flash chromatography).



(54)

237 **215** **216**

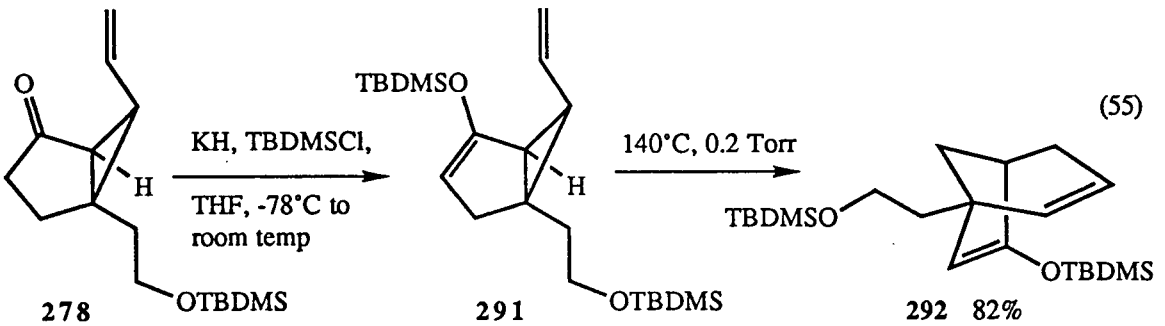
Table 12. The preparation of 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hexan-2-ones **237**

Entry	**250**	Notes[1]	**237**	Yield[2]%
1	 **167**		 **278**	48
2	 **171**	A	 **281**	34
3	 **177**	A	 **285**	26
4	 **252**		 **279**	39
5	 **180**		 **280**	34

[1] Notes. A) Product contaminated by approx. 20% of the corresponding seven membered ring ketone **289**.

[2] Overall yield of product from the appropriate stannyldiene

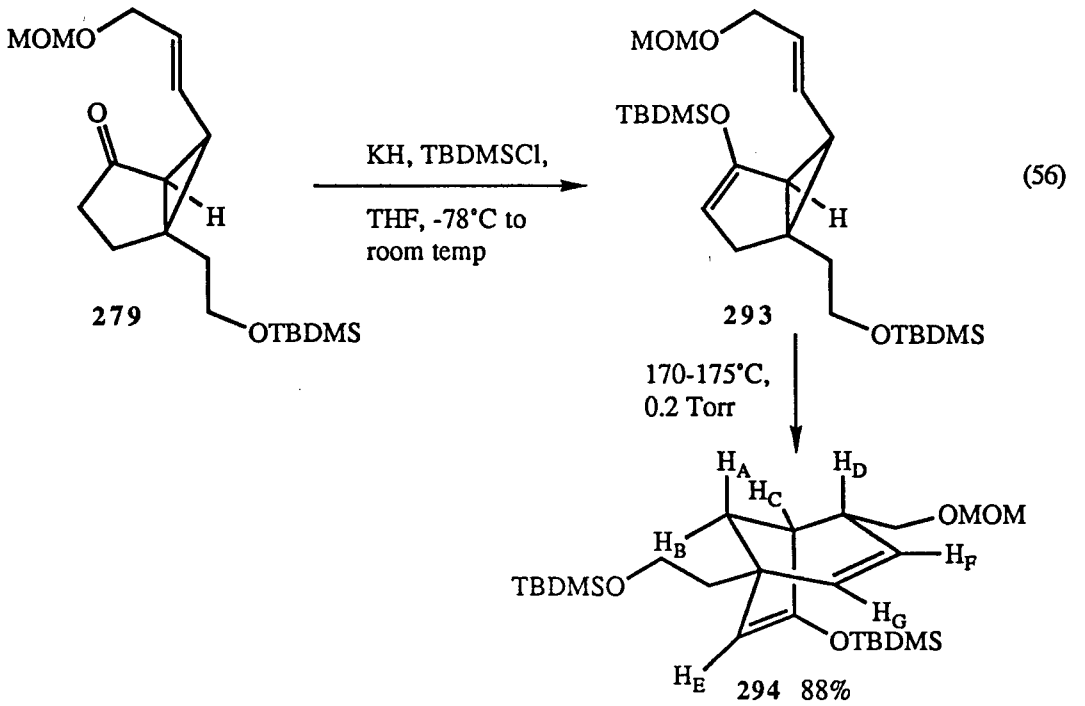
It was found that the 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hex-2-enes **215** are readily available from the ketones **237** via formation of the corresponding enol silyl ethers. For example, the ketone **278** was converted into the silyl enol ether **291** via reaction with KH and TBDMSCl, using a procedure very similar to that reported in the literature (equation 55).[136] Thus, a suspension of KH (approximately 5 equivalents) in dry THF was added to a mixture of **278** and TBDMSCl (1.5 equivalents) in dry THF at -78°C. The resulting mixture was allowed to warm to room temperature and was stirred until the reaction was complete. After appropriate workup, glc analysis of the crude reaction mixture showed the presence of one major product. Distillation of this material under reduced pressure (140°C/0.2 Torr) afforded the pure bicyclo[3.2.1]octa-2,6-diene **292** in 82% yield (equation 55).



278 291 292 82% (55)

The ketone **279** was converted into the enol silyl ether **293** via reaction with KH and TBDMSCl using a procedure identical with that described above (equation 56). Distillation of the crude reaction product under reduced pressure (170-175°C/0.2 Torr) afforded the pure bicyclo[3.2.1]octa-2,6-diene **294** in 88% yield (equation 56).

The ^{1}H nmr spectrum for **294** is shown in Figure 7. This spectrum shows 6-proton singlets at δ 0.11 and 0.17 as well as 9-proton singlets at δ 1.00 and 1.03, due to the TBDMS ether functions. There is a 3-proton singlet at δ 3.25 (-OMe), a 2-proton multiplet at δ 3.57-3.72 (-CH$_2$OMOM), a 2-proton triplet at δ 3.76 (J = 6 Hz, -OCH$_2$CH$_2$-), 1-proton



(56)

doublets at δ 4.59 and 4.66 (J = 7 Hz for each signal, -OC<u>H</u>$_2$O-), and a 1-proton singlet at δ 5.12, due to <u>H</u>$_E$. The remaining signals were assigned using a combination of decoupling and COSY experiments (see Experimental section). Thus, the 1-proton doublet of doublets of doublets at δ 2.11 (J = 10 Hz, J = 5 Hz, J = 1.5 Hz), the 1-proton doublet of doublets of doublets at δ 5.58 (J = 10 Hz, J = 2 Hz, J = 2 Hz), and the 1-proton broad doublet at δ 6.24 (J = 10 Hz) were assigned to H_B, H_F, and H_G, respectively. Also, the 2-proton multiplet at δ 2.70-2.80 was assigned to H_C and H_D whilst the 3-proton multiplet at δ 1.70-1.90 was assigned to H_A and -OCH$_2$C<u>H</u>$_2$-. Several points should be made regarding these assignments. Firstly, H_G and H_F were readily distinguished since there is a long range ("W") coupling between H_B and H_G (J = 1.5 Hz) but no observable coupling between H_B and H_F. Secondly, H_B and H_A were readily distinguished on the basis of multiplicity and coupling constants. Thus, the signal due to H_B appears as a doublet of doublets of doublets (at δ 2.11) due to coupling to H_A (J_{BA} = 10 Hz), H_C (J_{BC} = 5 Hz) and H_G (J_{BG} = 1.5 Hz). Irradiation at δ 3.76 (-CH$_2$C<u>H</u>$_2$O-) enabled identification the signal due to H_A as a

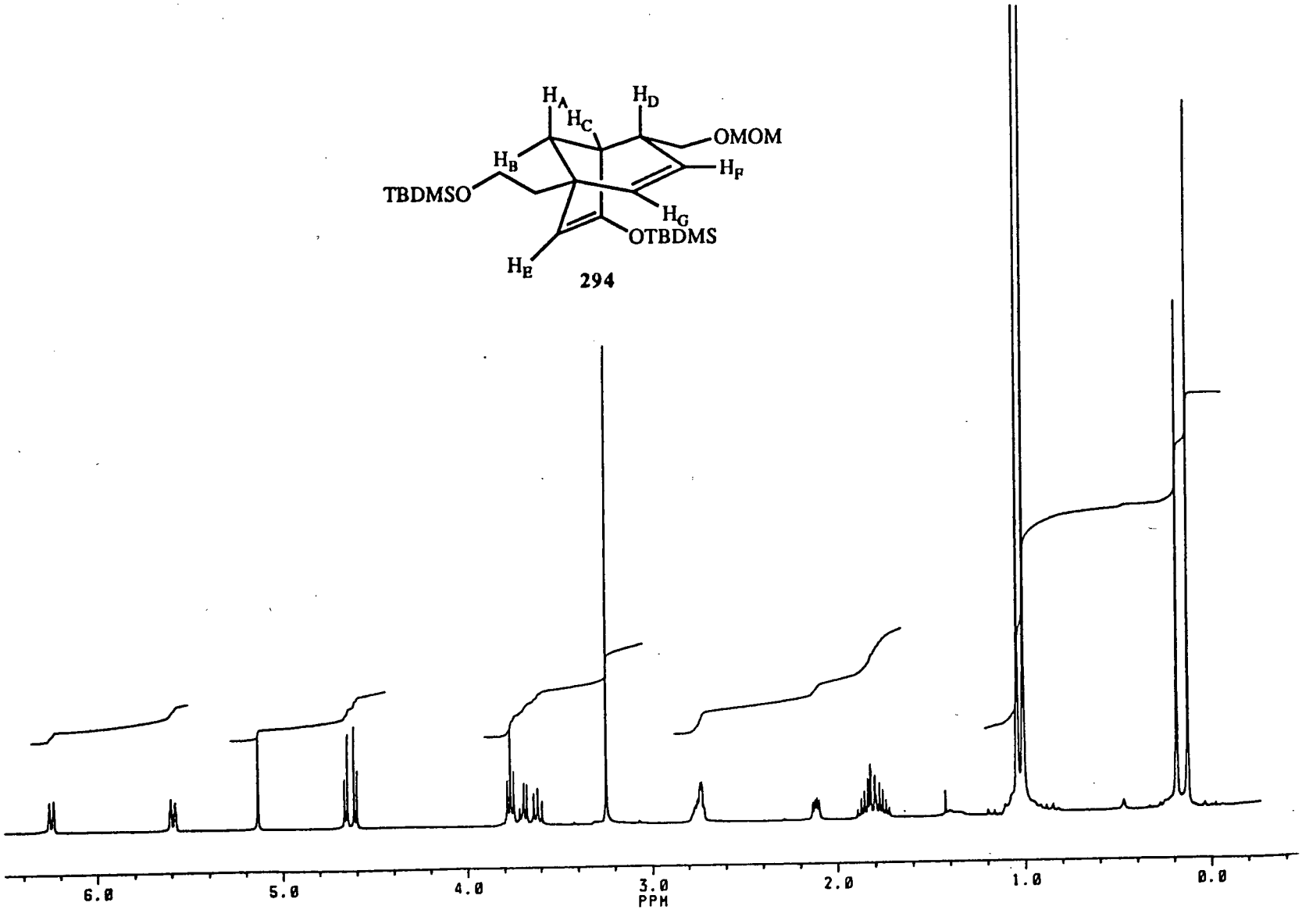
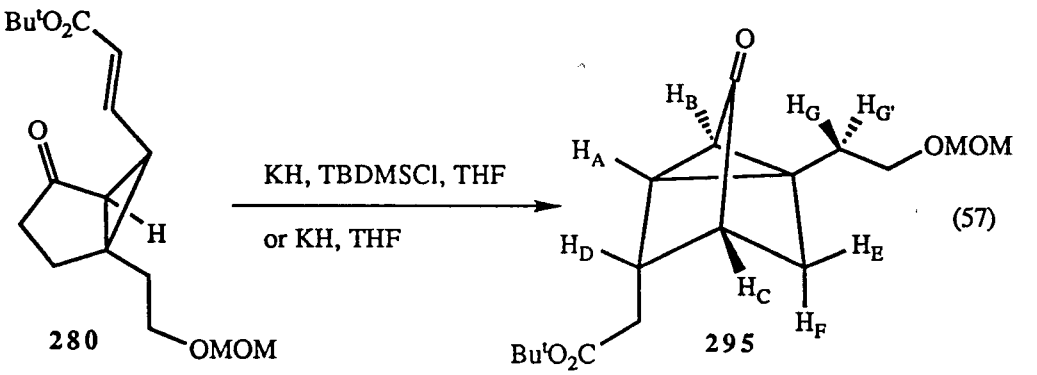


Figure 7 400 MHz ^{1}H nmr spectrum (C_6D_6) of compound **294**

doublet at δ 1.81 (J_{AB} = 10 Hz). The observation that H_A couples weakly, if at all, to H_C is fully consistent with the 90° dihedral angle which exists between these protons (as indicated by molecular models).

The ketone **280** could not be converted into its enol silyl ether using the procedure described above. In fact, it was found that reaction of **280** with KH and TBDMSCl provided, after aqueous workup, a single product which was assigned the structure **295** (equation 57). Reaction of the ketone **280** with KH in THF (without TBDMSCl) also provided **295** (in 87% yield) (equation 57). This compound is the product of an intramolecular Michael reaction involving the potassium enolate derived from the ketone **280**.



(57)

The spectral data derived from **295** were in full accord with the proposed structure. For example, the infrared spectrum of **295** showed strong absorbances at 1752 cm^{-1} and 1729 cm^{-1} attributable to the carbonyl stretching frequencies of the ketone and ester functions, respectively. The ^1H nmr spectrum (400 MHz, C_6D_6) of **295** is shown in Figure 8. This spectrum shows a 9-proton singlet at δ 1.39 (-CO_2Bu^t), a 3-proton singlet at δ 3.19 (-OMe), a 2-proton triplet at δ 3.32 (J = 6 Hz, -OCH_2CH_2-), a 2-proton multiplet at δ 2.00 (-CH_2CO_2Bu^t) and 1-proton doublets at δ 4.41 and 4.42 (J = 6 Hz for each signal, -OCH_2O-). The remaining signals were assigned using a COSY experiment (see Experimental section). Thus, the 1-proton broad doublet at δ 1.18 (J = 6 Hz), the 1-proton

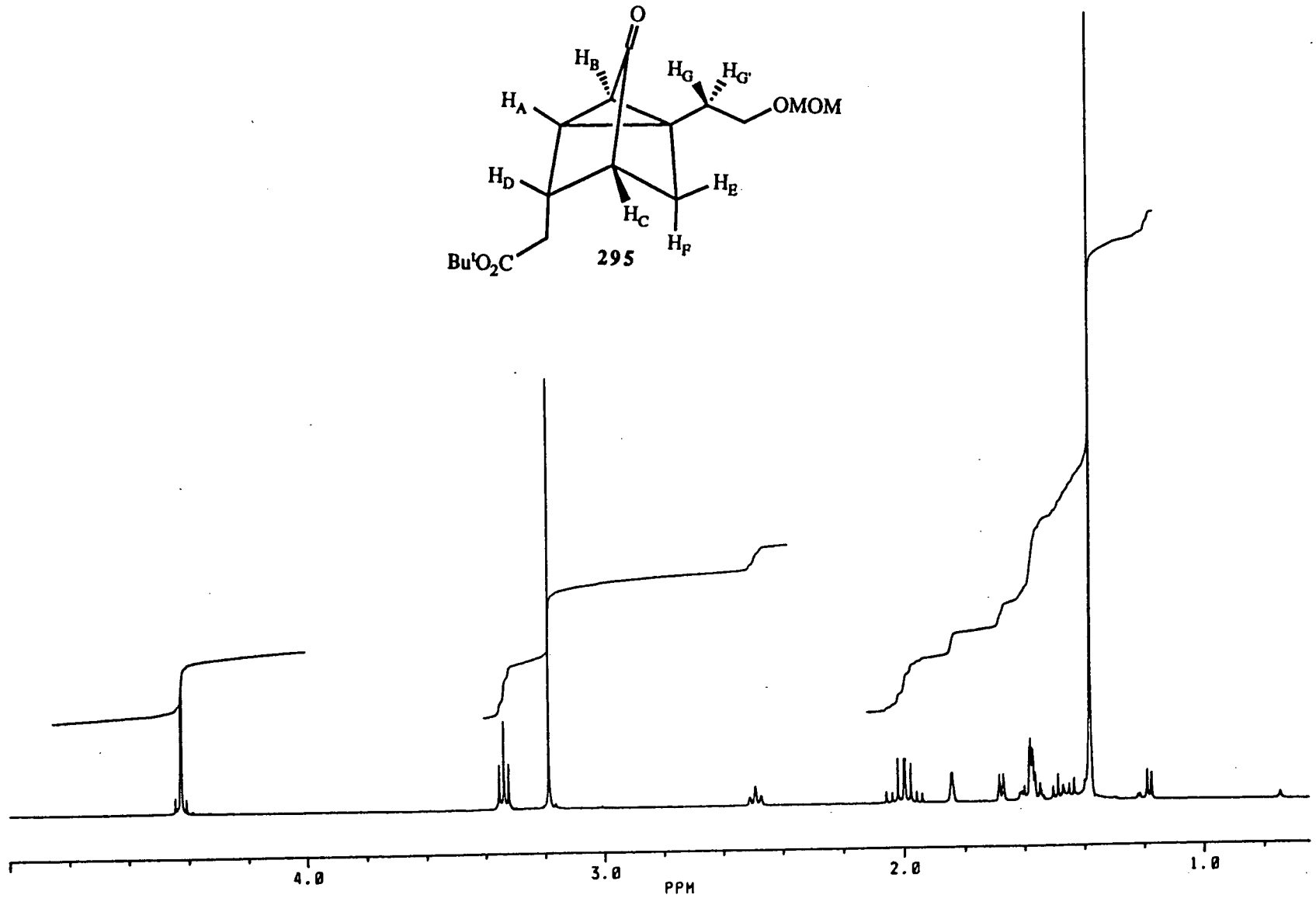
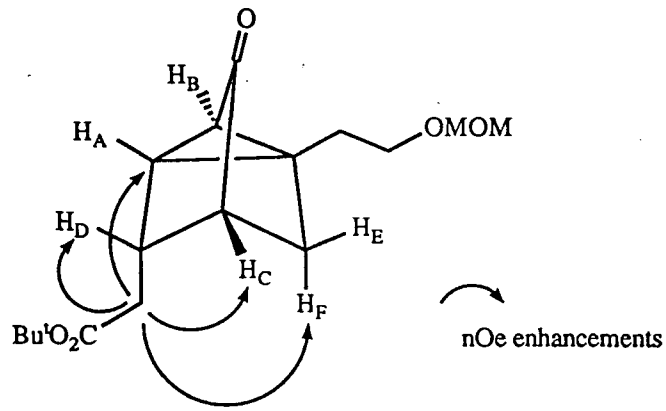


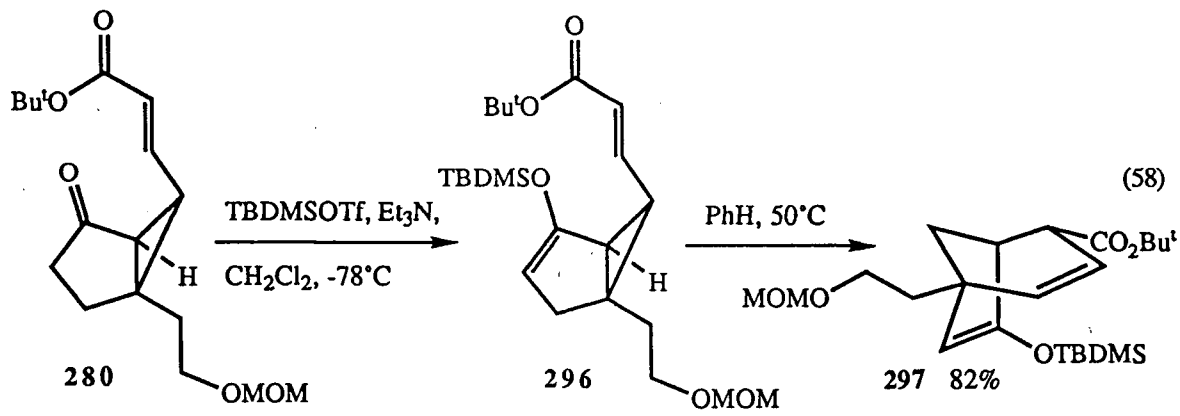
Figure 8 400 MHz ^1H nmr spectrum (C_6D_6) of compound **295**

broad doublet at δ 1.67 (J = 6 Hz), the 1-proton broad singlet at δ 1.84, and the 1-proton broad triplet at δ 2.49 (J = 6 Hz), were assigned to H_B, H_A, H_C, and H_D, respectively. Also, the 1-proton multiplet at δ 1.41-1.51 was assigned to H_G or $H_{G'}$ and the 3-proton multiplet at δ 1.52-1.62 was assigned to H_G or $H_{G'}$, H_E and H_F.

The relative stereochemistry of **295** was confirmed by nOe difference experiments. In particular, irradiation at δ 2.00 (-C<u>H</u>$_2$CO$_2$Bu^t) resulted in signal enhancement at δ 1.58 (which was assigned to H_F), 2.49 (H_D), 1.67 (H_A), and δ 1.84 (H_C).

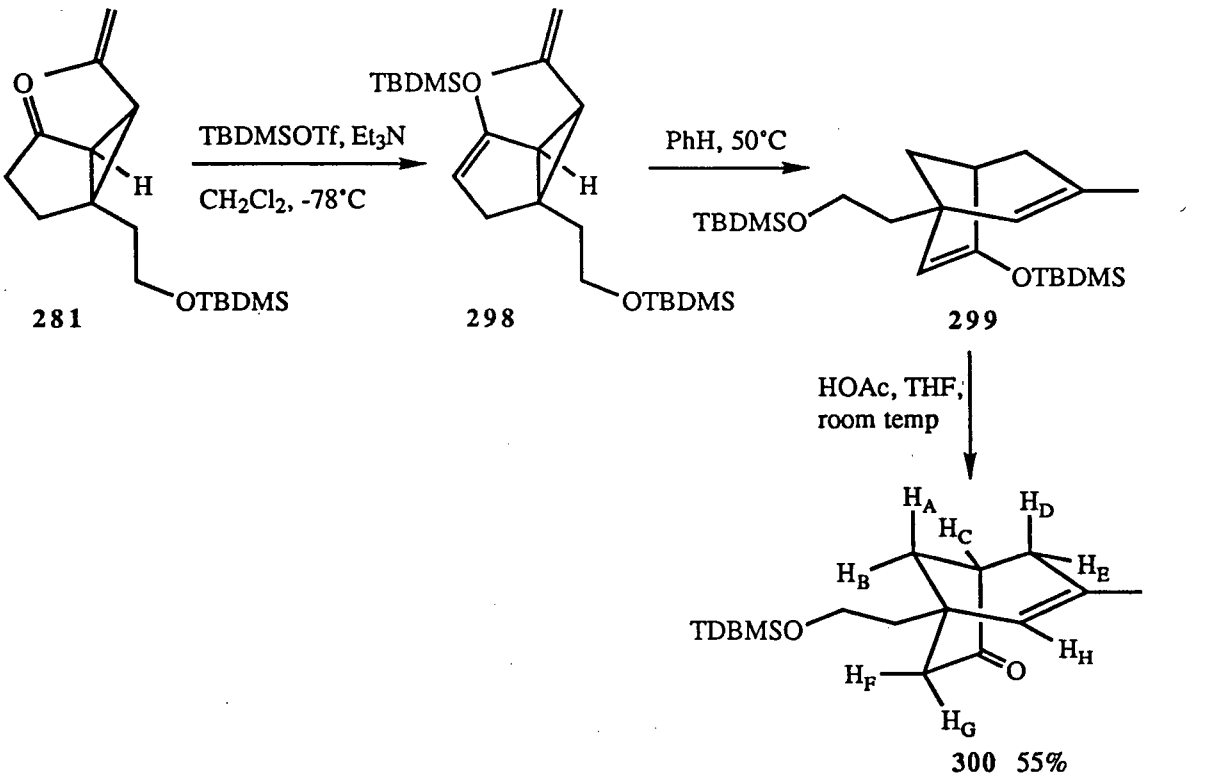


It was found that the ketone **280** could be converted into the corresponding enol silyl ether **296** via reaction with TBDMSOTf and Et$_3$N, using a procedure very similar to that reported by Mander and Sethi (equation 58).[137] Thus, TBDMSOTf (1.5 equivalents) was



added to a mixture of **280** and Et_3N (3 equivalents) in dry CH_2Cl_2 at -78 °C, and the resulting mixture was stirred at -78 °C for 30 min. After appropriate workup, glc analysis of the crude reaction product showed the presence of a single compound. The crude product was dissolved in dry benzene and the resulting solution was warmed to 50°C overnight. Flash chromatography of the material thus obtained provided the bicyclo[3.2.1]octa-2,6-diene **297** in 82% yield (equation 58).

The ketone **281** (which was contaminated with approximately 20% of the seven membered ring ketone **282**) was converted into the silyl enol ether **298** via reaction with TBDMSOTf and Et_3N, following a procedure very similar to that which was described above (Scheme 43). After appropriate workup, glc analysis of the crude product showed the



Scheme 43

presence of two products, in a ratio of approximately 4:1. The crude material was dissolved in dry benzene and the resulting solution was warmed to 50°C overnight. The crude mixture of enol silyl ethers (containing the bicyclo[3.2.1]octa-2,6-diene **299**) thus obtained was treated with HOAc in THF at room temperature to give a readily separable mixture of products containing the bicyclo[3.2.1]oct-2-en-6-one **300** (Scheme 43). Flash chromatography of this mixture, followed by distillation, afforded the pure bicyclo[3.2.1]oct-2-en-6-one **300** in 55% yield.

The spectral data derived from the ketone **300** were fully consistent with the assigned structure. For example, the infrared spectrum of **300** showed a strong absorbance at 1747 cm^{-1} attributable to the carbon-oxygen stretching frequency of the ketone function. The ^1H nmr spectrum of **300** (400 MHz, C_6D_6) is shown in Figure 9. This spectrum shows a 6-proton singlet at δ 0.07 and a 9-proton singlet at δ 1.01 due to the TBDMS group, a 3-proton singlet at δ 1.41 (vinyl methyl group), a 2-proton multiplet at δ 3.61 (-OC$\underline{H_2}$CH_2-) and a 1-proton broad singlet at δ 5.44, due to H_H. The remaining signals were assigned using decoupling experiments (see Experimental section). Thus, the 3-proton broad multiplet at δ 1.53-1.67 was assigned to H_A and -C$\underline{H_2}$CH_2O-, whilst the 1-proton broad doublet of doublets at δ 1.51 (J = 11 Hz, J = 5.5 Hz), the 1-proton doublet of doublets at δ 2.27 (J = 17 Hz, J = 3 Hz), and the 1-proton doublet at δ 1.87 (J = 17 Hz) were assigned to H_B, H_G, and H_F, respectively. Also, the 1-proton multiplet at δ 2.42, the 1-proton broad doublet of doublets at δ 1.97 (J = 17 Hz, J = 5 Hz), and the 1-proton broad doublet at δ 2.05 (J = 17 Hz) were assigned to H_C, H_D and H_E, respectively. Two points should be made regarding these data. Firstly, H_B shows coupling to H_C (J_{BC} = 5.5 Hz) whereas H_A couples weakly, if at all to H_C. This observation is fully consistent with the 90° dihedral angle which exists between H_A and H_C (as indicated by molecular models). Similarly, H_E couples weakly (if at all) to H_C, which is consistent with the 90° dihedral angle which exists between these protons, whereas H_D does show coupling to H_C (J_{DC} = 5 Hz). Secondly,

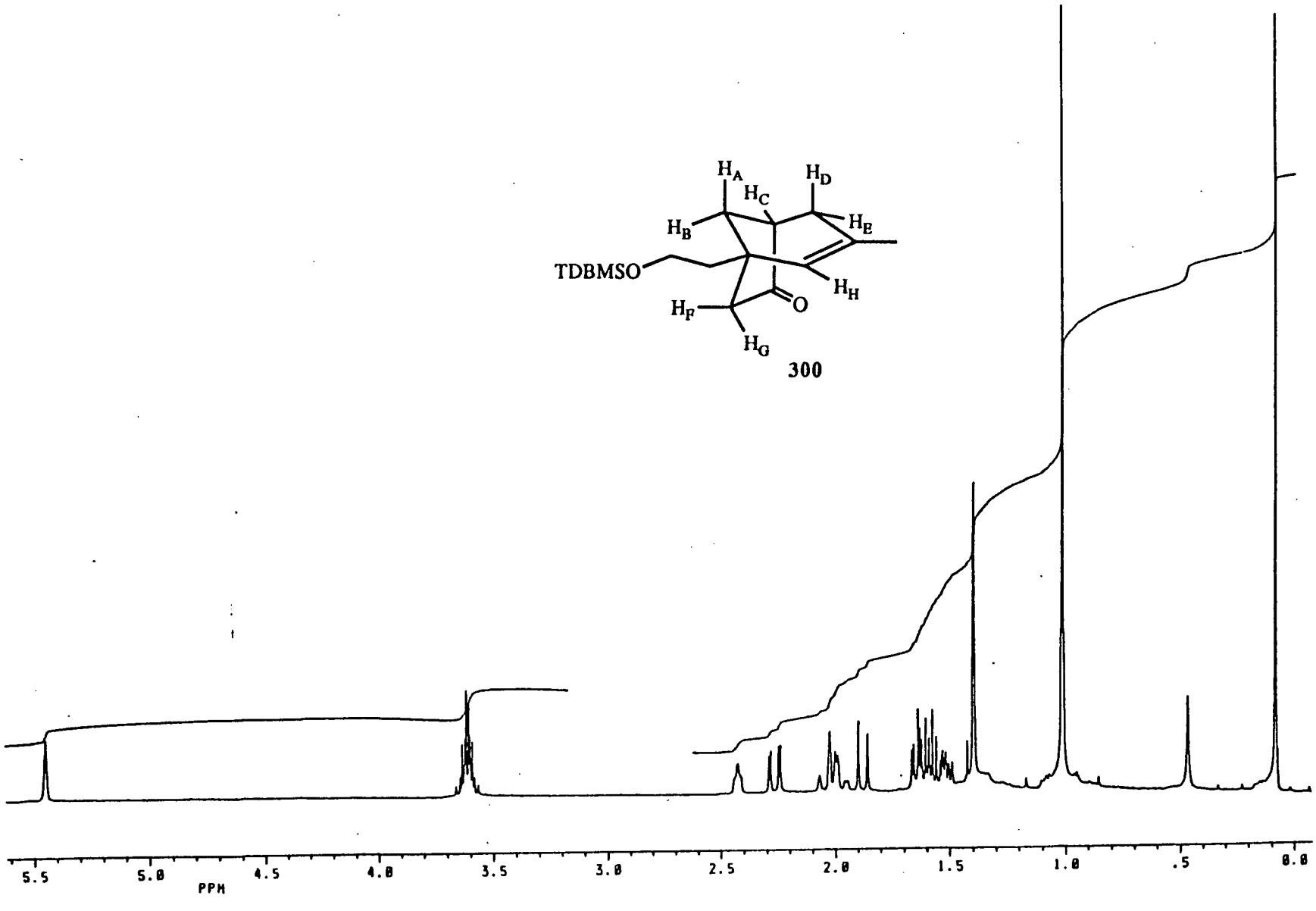
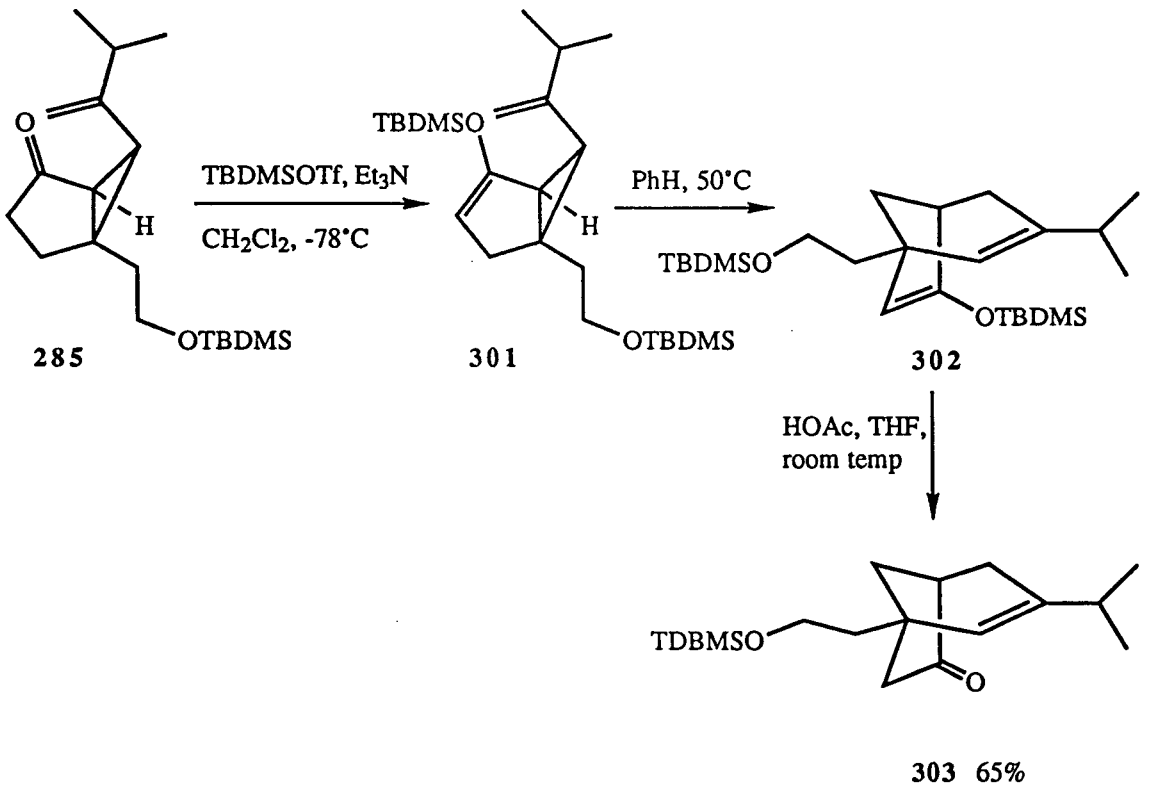


Figure 9 400 MHz ^{1}H nmr spectrum (C_6D_6) of compound **300**

H_G and H_F are readily distinguished since H_A shows a long range ("W") coupling to H_G (J = 3 Hz) but does not show coupling to H_F.

The ketone **285** (which was contaminated with approximately 20% of the ketone **286**) was converted into the silyl enol ether **301** via reaction with TBDMSOTf and Et_3N (Scheme 44). Using a procedure similar to that described earlier, a benzene solution of crude **301** was warmed to 50°C overnight and the resulting mixture of products (containing the bicyclo[3.2.1]octa-2,6-diene **302**) was treated with HOAc in THF (Scheme 44). Flash chromatography of the crude reaction product thus obtained, followed by distillation, provided the bicyclo[3.2.1]oct-2-en-6-one **303** in 65% yield.



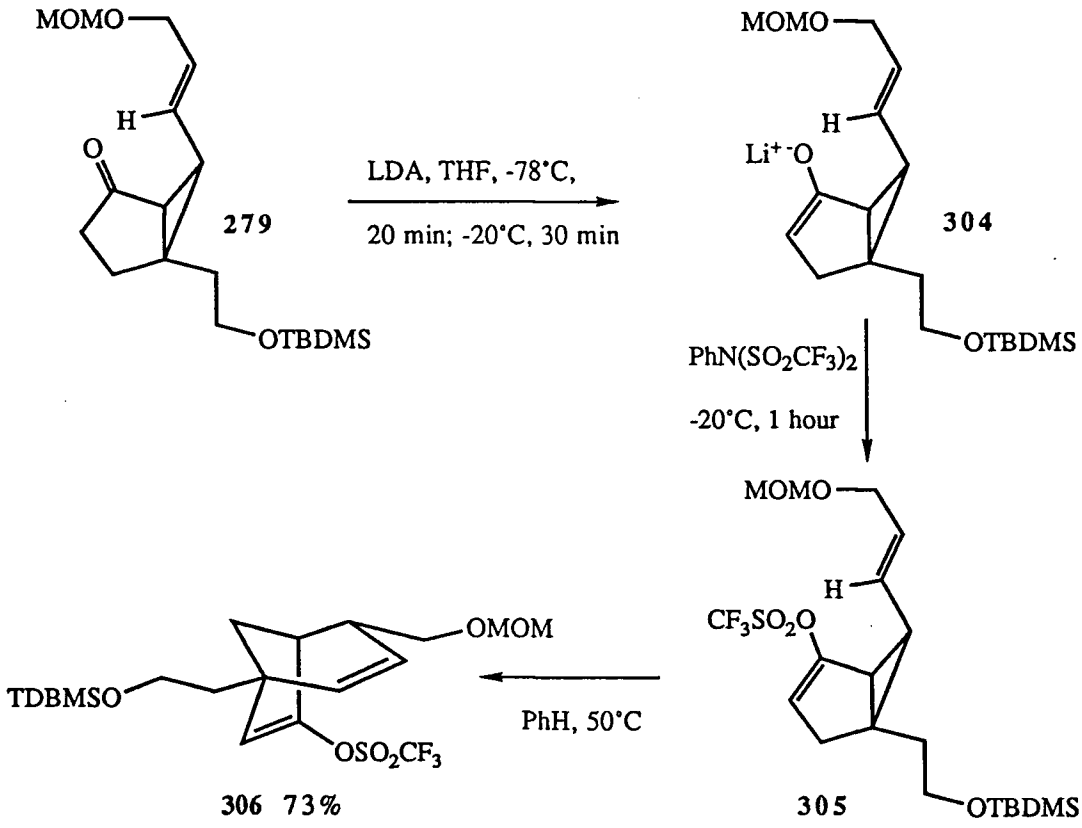
285 **301** **302**

303 65%

Scheme 44

The 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hexan-2-ones of general structure **237** were converted into functionalized 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hex-2-enes **215** in several other ways, as described below.

Thus, reaction of the ketone **279** with lithium diisopropylamide (LDA) in THF provided the corresponding lithium enolate **304** (Scheme 45). Reaction of the enolate **304** with *N*-phenyltrifluoromethanesulfonimide[138] (excess) at -20°C for 1 hour, provided the enol triflate **305**. After appropriate workup, the crude product was partially purified by flash chromatography. The material thus obtained was dissolved in dry benzene and the resulting solution was warmed to 50°C overnight. Flash chromatography of the resulting mixture afforded the bicyclo[3.2.1]octa-2,6-diene **306** in 73% overall yield.



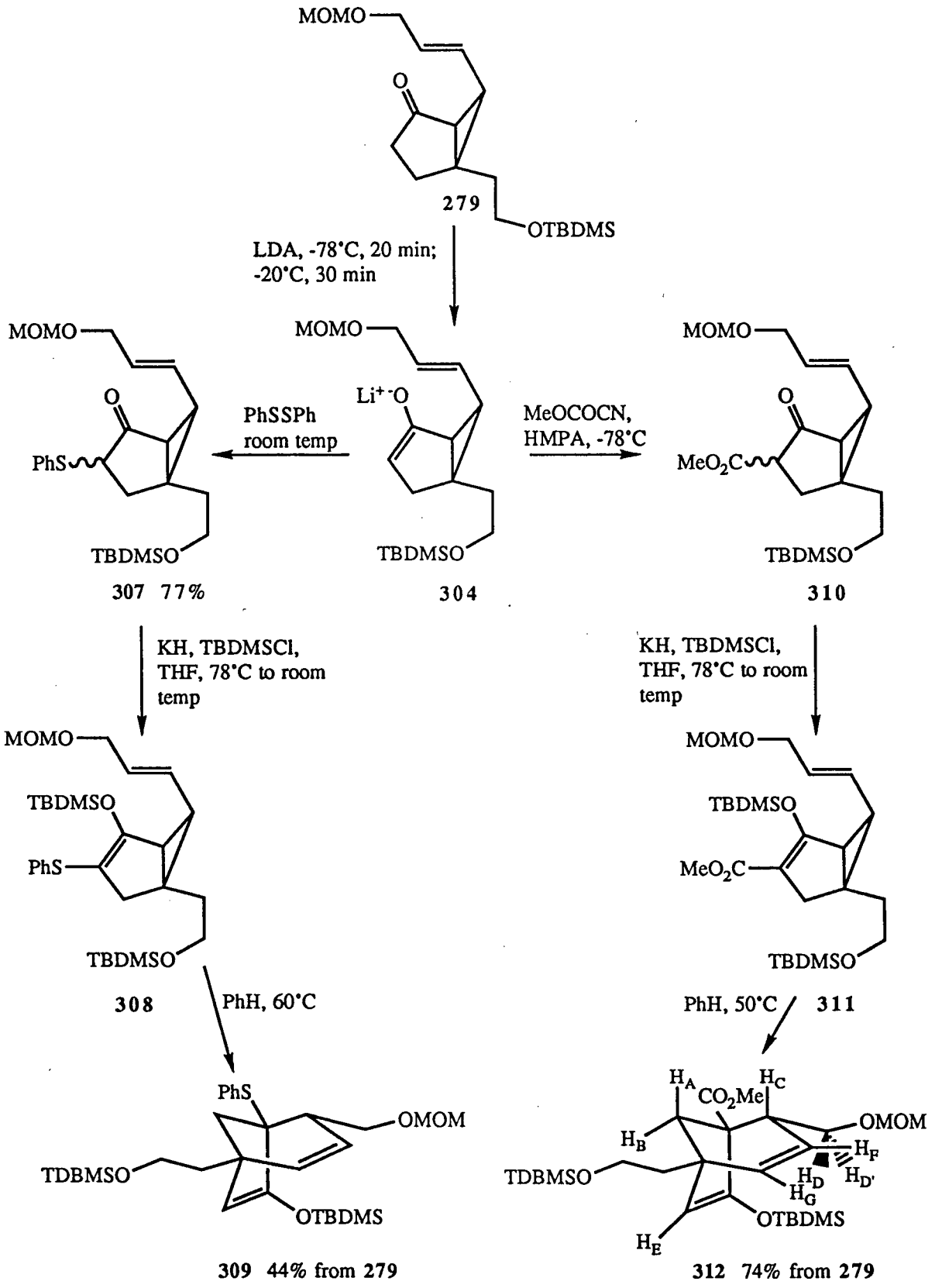
Scheme 45

Also, reaction of the lithium enolate **304** with excess diphenyldisulphide[139] (PhSSPh) at room temperature (1.5 hours) afforded the α-phenylthio ketones **307** in 77% yield (after flash chromatography) (Scheme 46). Compounds **307** were converted into the silyl enol ether **308** via reaction with KH and TBDMSCl in THF, following a procedure

which was very similar to that described earlier. After appropriate workup, the crude silyl enol ether was dissolved in dry benzene and the resulting solution was warmed to 60°C overnight. Flash chromatography of the mixture thus obtained provided the bicyclo[3.2.1]octa-2,6-diene **309** in 44% overall yield from the ketone **279** (Scheme 46).

Additionally, reaction of the lithium enolate **304** with methyl cyanoformate (MeOCOCN)[140] at -78°C, in the presence of hexamethylphosporamide (HMPA), afforded the β-ketoesters **310** (Scheme 46). Reaction of the crude product (containing **310**) with TBDMSCl and KH, in THF, provided the silyl enol ether **311**. After appropriate workup, the crude oil containing **311** was dissolved in dry benzene and the resulting solution was warmed to 50°C overnight. Flash chromatography of the reaction mixture afforded the bicyclo[3.2.1]octa-2,6-diene **312** in 74% yield from the ketone **279** (Scheme 46).

The spectral data derived from the bicyclo[3.2.1]octa-2,6-dienes **309** and **312** were in full accord with the assigned structures. For example, the infrared spectrum of **312** showed a strong absorbance at 1737 cm^{-1}, attributable to the carbonyl stretching frequency of the ester function, and an absorbance at 1627 cm^{-1}, attributable to the carbon-carbon stretching frequency of the enol ether function. The ^1H nmr spectrum (400 MHz, C_6D_6) of **312** is shown in Figure 10. This spectrum shows a 6-proton singlet at δ 0.11, a 3-proton singlet at δ 0.18, a 3-proton singlet at δ 0.21, a 9-proton singlet at δ 0.97 and a 9-proton singlet at δ 1.02, which are attributable to the TBDMS ether functions. Also, there is a 2-proton multiplet at δ 1.68-1.85 (-$OCH_2C\underline{H_2}$-), a 3-proton singlet at δ 3.24 (-O<u>Me</u>), a 3-proton singlet at δ 3.50 (-O<u>Me</u>), a 2-proton multiplet at δ 3.71 (-$OC\underline{H_2}CH_2$-) and 1-proton doublets at δ 4.61 and 4.67 (J = 6 Hz, -$OC\underline{H_2}O$-). The remaining signals were assigned using decoupling and COSY experiments (see Experimental section). Thus, the 1-proton doublet at δ 1.93 (J = 9 Hz) and the 1-proton broad doublet at δ 2.50 (J = 9 Hz) were assigned to H_A and H_B, respectively. The 1-proton singlet at δ 5.08, the 1-proton doublet of doublets at δ 5.97 (J = 10 Hz, J = 2 Hz), and the 1-proton broad doublet at δ 6.18 (J =


MOMO
O
279
OTBDMS
LDA, -78°C, 20 min;
-20°C, 30 min
MOMO
Li+ -O
TBDMSO
304
PhSSPh
room temp
MeOCOCN,
HMPA, -78°C
MOMO
O
PhS
TBDMSO
307 77%
MOMO
O
MeO2C
TBDMSO
310
KH, TBDMSCl,
THF, 78°C to room
temp
KH, TBDMSCl,
THF, 78°C to room
temp
MOMO
TBDMSO
PhS
TBDMSO
308
PhH, 60°C
MOMO
TBDMSO
MeO2C
TBDMSO
PhH, 50°C
311
PhS
OMOM
TDBMSO
OTBDMS
309 44% from 279
HA
CO2Me
HC
OMOM
HB
HF
TDBMSO
HD
HD'
HG
OTBDMS
HE
312 74% from 279

Scheme 46

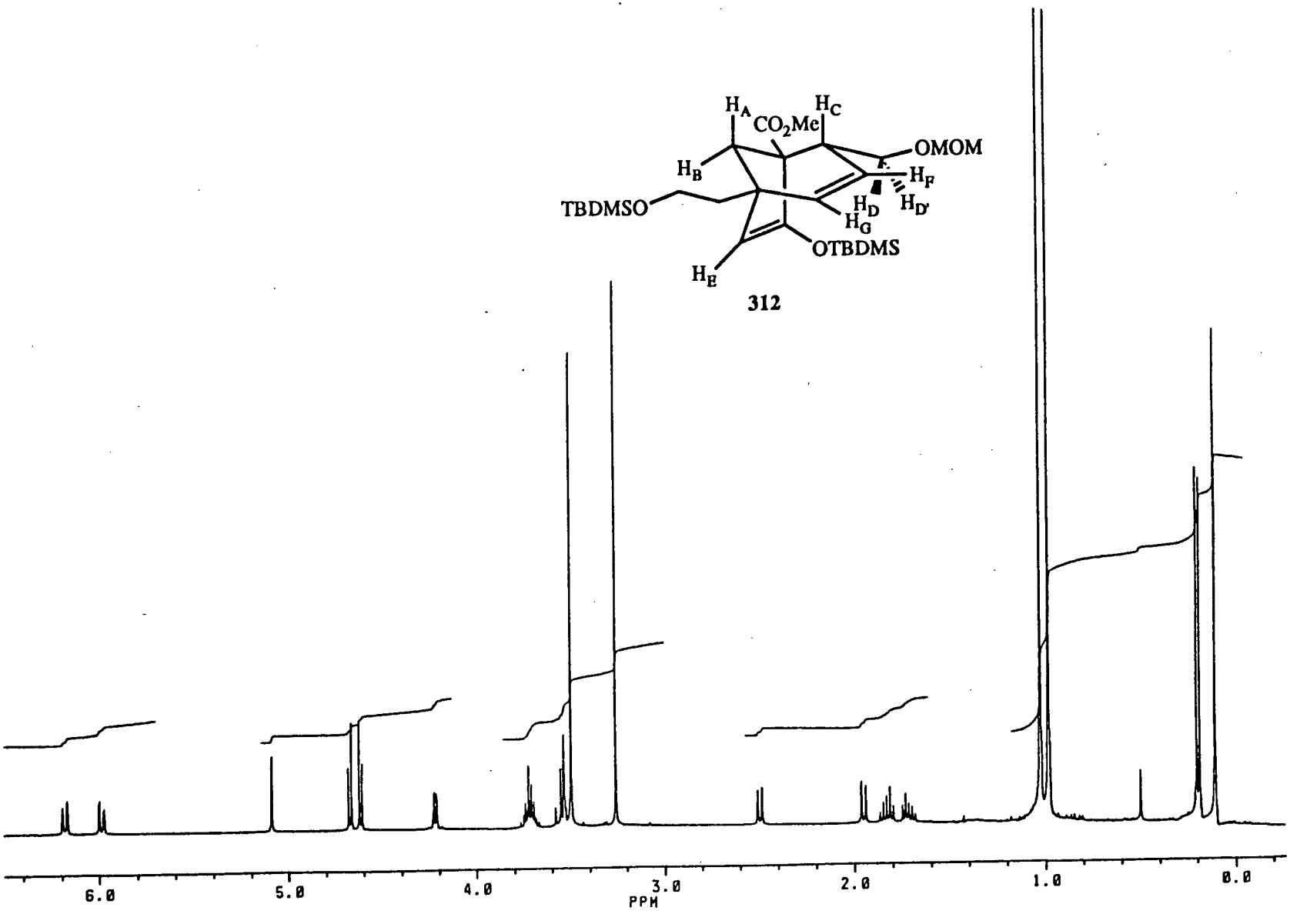
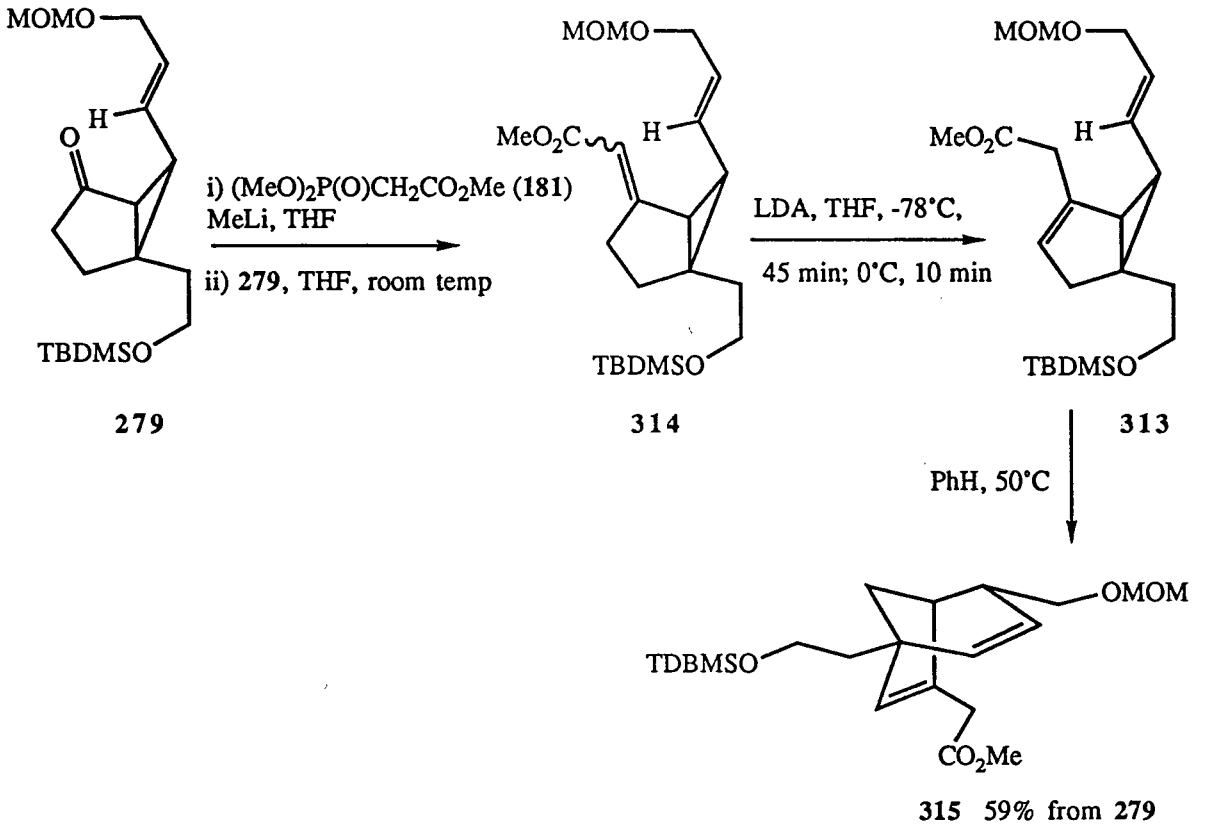


Figure 10 400 MHz ^{1}H nmr spectrum (C_6D_6) of compound **312**

10 Hz) were assigned to H_E, H_F, and H_G, respectively. Finally, the 2-proton multiplet at δ 3.50-3.58 was assigned to H_C plus H_D or $H_{D'}$, whilst the 1-proton multiplet at δ 4.22 was assigned to H_D or $H_{D'}$. Two points should be made regarding these data. Firstly, the signals due to H_A and H_B could easily be assigned, since irradiation at δ 2.50 (H_B) caused the signal at δ 6.18 (H_G) to sharpen to a doublet of doublets (J_{GF} = 10 Hz, J_{GC} = 1.5 Hz), whereas irradiation at δ 1.93 (H_A) did not affect the signal at δ 6.18 (H_G). The long range coupling between H_B and H_G is fully consistent with the "W" relationship which exists between these protons (as indicated by molecular models). Secondly, the assignment of the 2-proton multiplet at δ 3.50-3.58 to H_C plus H_D or $H_{D'}$, was confirmed by decoupling. Thus, irradiation at δ 3.50-3.58 caused the signal at δ 4.22 (H_D or $H_{D'}$) to collapse to a singlet, whilst the signal at δ 5.97(H_F) collapsed to a doublet (J_{FG} = 10 Hz).

The ketone **279** was converted into the 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hex-2-ene **313** in two steps, as shown in Scheme 47. Thus, a mixture of **279** and an excess of the lithio phosphonate reagent (which was prepared via reaction of trimethylphosponoacetate (**181**) with MeLi) in THF was stirred overnight at room temperature. After appropriate workup, flash chromatography of the crude reaction mixture provided the α,β-unsaturated esters **314** (a 1:1 ratio of geometrical isomers, by glc analysis). A solution of this material in dry THF was cooled to -78°C, LDA was added, and the resulting mixture was stirred at -78°C for 45 min and at 0°C for 10 min. The mixture was then transferred, via cannula, into a cold (-78°C) mixture of HOAc and THF (1:1), and the resulting mixture was stirred for 10 min at -78°C. After appropriate workup, glc analysis of the crude reaction product showed the presence of one compound. The crude product was dissolved in dry benzene and the resulting solution was warmed to 50°C overnight. Flash chromatography of the crude product afforded the bicyclo[3.2.1]octa-2,6-diene **315** in 59% overall yield from the ketone **279** (Scheme 47).

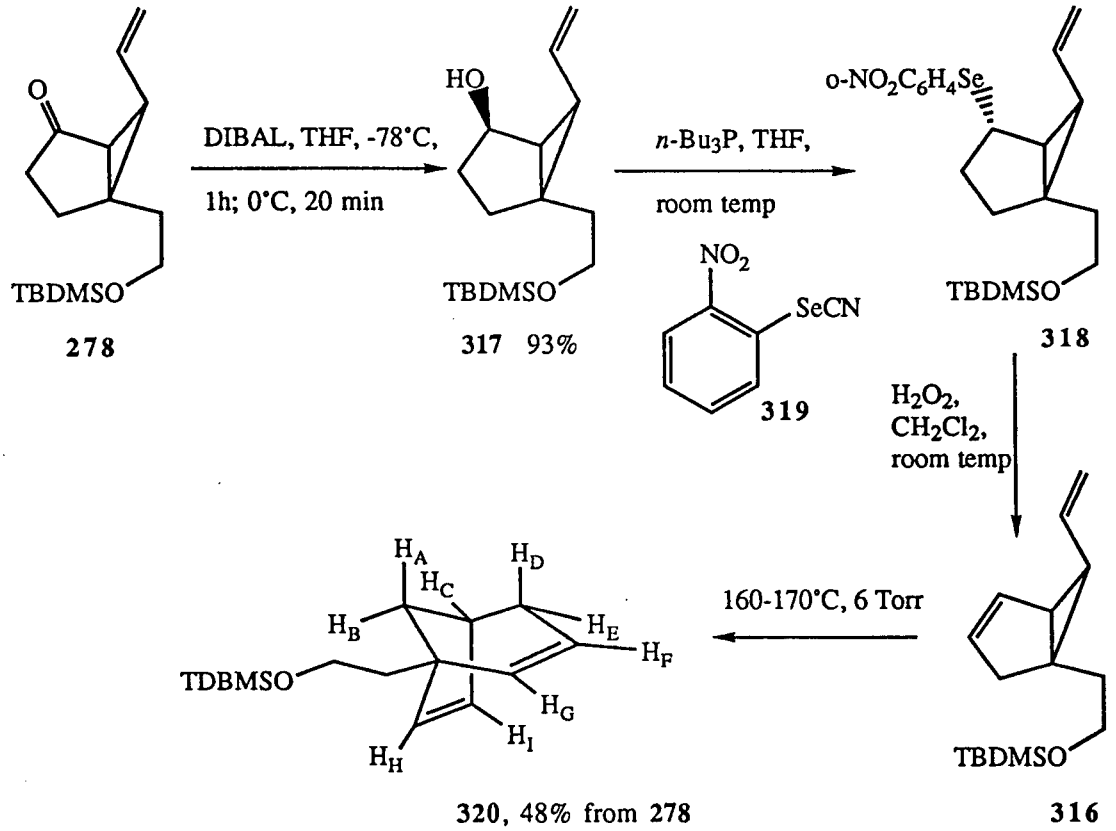


Scheme 47

Another approach to the synthesis of 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hex-2-enes **215** involves reduction of the carbonyl group in the ketones of general structure **237** followed by dehydration. For example, the ketone **278** was converted into the 6-*endo*-vinylbicyclo[3.1.0]hex-2-ene **316** via the reaction sequence shown in Scheme 48. Thus, the carbonyl group of **278** was reduced with DIBAL to give the alcohol **317** in 93% yield. The ^{1}H nmr spectrum of this compound indicated that it was stereochemically homogeneous. Although the orientation of the hydroxyl group in **317** was not proven, it was assumed to be endo (as shown) since the bulky reducing agent (DIBAL) would be expected to react with **278** from its more open, convex face. The alcohol **317** was converted into the selenide **318** via reaction with *n*-Bu3P and *o*-nitrophenylselenocyanate **319** (THF, room temp), according to the procedure reported by Grieco (Scheme 48).[141] The crude reaction product was purified by flash chromatography, to give **318**, which was contaminated by a small amount

of *n*-Bu3P. The relative stereochemistry of this material was assumed to be that shown in Scheme 48, since this substitution reaction would be expected to proceed with inversion of configuration.

The selenide **318** was subjected to an oxidation-selenoxide elimination procedure.[142, 143] Thus, a solution of **318** in CH_2Cl_2 was treated with 30% aqueous H_2O_2 (excess) at room temperature. The two-phase mixture was stirred vigorously, until the reaction was complete. After appropriate workup, the crude reaction product was purified by flash chromatography to give the 6-*endo*-vinylbicyclo[3.1.0]hex-2-ene **316**. Distillation (160-170°C/6 Torr) of this material afforded the bicyclo[3.2.1]octa-2,6-diene **320** in 48% overall yield from the ketone **278** (Scheme 48).



Scheme 48

The ^1H nmr spectrum (400 MHz, C_6D_6) of **320** is shown in Figure 11. This spectrum shows a 6-proton singlet at δ 0.1 and a 9-proton singlet at δ 1.02, due to the TBDMS ether group, and a 2-proton multiplet at δ 3.73 (-OC$\underline{H_2}$CH_2-). The remaining signals were assigned using a combination of decoupling and COSY experiments (see Experimental section). Thus, the 1-proton doublet of doublets of doublets of doublets at δ 5.25 (J = 10 Hz, J = 3 Hz, J = 2.5 Hz, J = 1.5 Hz), the 1-proton doublet of doublets at δ 5.61 (J = 6 Hz, J = 3 Hz), the 1-proton multiplet at δ 5.98 and the 1-proton doublet at δ 6.09 (J = 6 Hz) were assigned to H_F, H_I, H_G, and H_H, respectively. Also, the 1-proton multiplet at δ 2.61 and the 1-proton doublet of doublets of doublets of doublets at δ 2.17 (J = 18 Hz, J = 5 Hz, J = 3 Hz, J = 2.5 Hz) were assigned to H_C and H_D, respectively. Finally, the 5-proton multiplet at δ 1.65-1.95 was assigned to H_A, H_B, H_E and -OCH_2C$\underline{H_2}$-. A few points should be made regarding these assignments. Firstly, the signal at δ 2.17 was assigned to H_D (and not H_E), since irradiation at δ 2.61 (H_C) caused the signal at δ 2.17 (H_D) to collapse to a doublet of doublets of doublets (J = 18 Hz, J = 3 Hz, J = 2.5 Hz), removing a 5 Hz coupling constant. Therefore, H_D couples to H_C fairly strongly (J_{CD} = 5 Hz), whereas H_E would be expected to couple with H_C very weakly (if at all) due to the 90°C dihedral angle which exists between these protons.

Secondly, H_F and H_G were readily distinguished since H_C couples to H_F (J_{FC} = 1.5 Hz) but not to H_G. This is shown by irradiation at δ 2.61 (H_C), which caused the signal at δ 5.25 (H_F) to collapse to a doublet of doublets of doublets (J = 10 Hz, J = 3 Hz, J = 2.5 Hz), whereas the signal at δ 5.98 (H_G) was unaffected.

The ketone **281** (which was contaminated with approximately 20% of the ketone **282**) was converted into the 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hex-2-ene **321** via a sequence identical with that described above (Scheme 49). Reduction of a mixture of **281** and **282** with DIBAL, as described earlier gave, after separation of the products by flash chromatography, the alcohol **283** in 66% yield. The alcohol was then converted into the

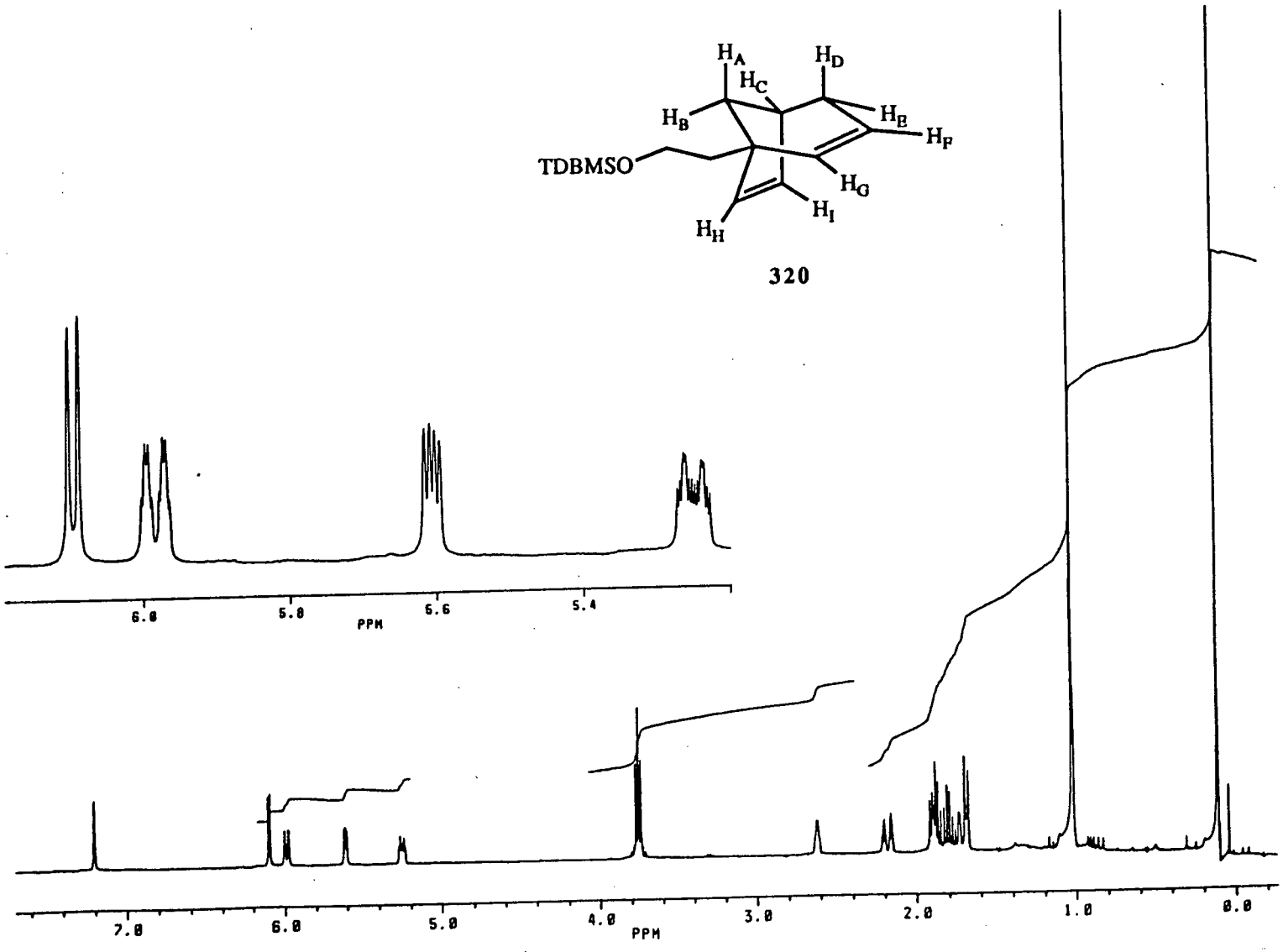
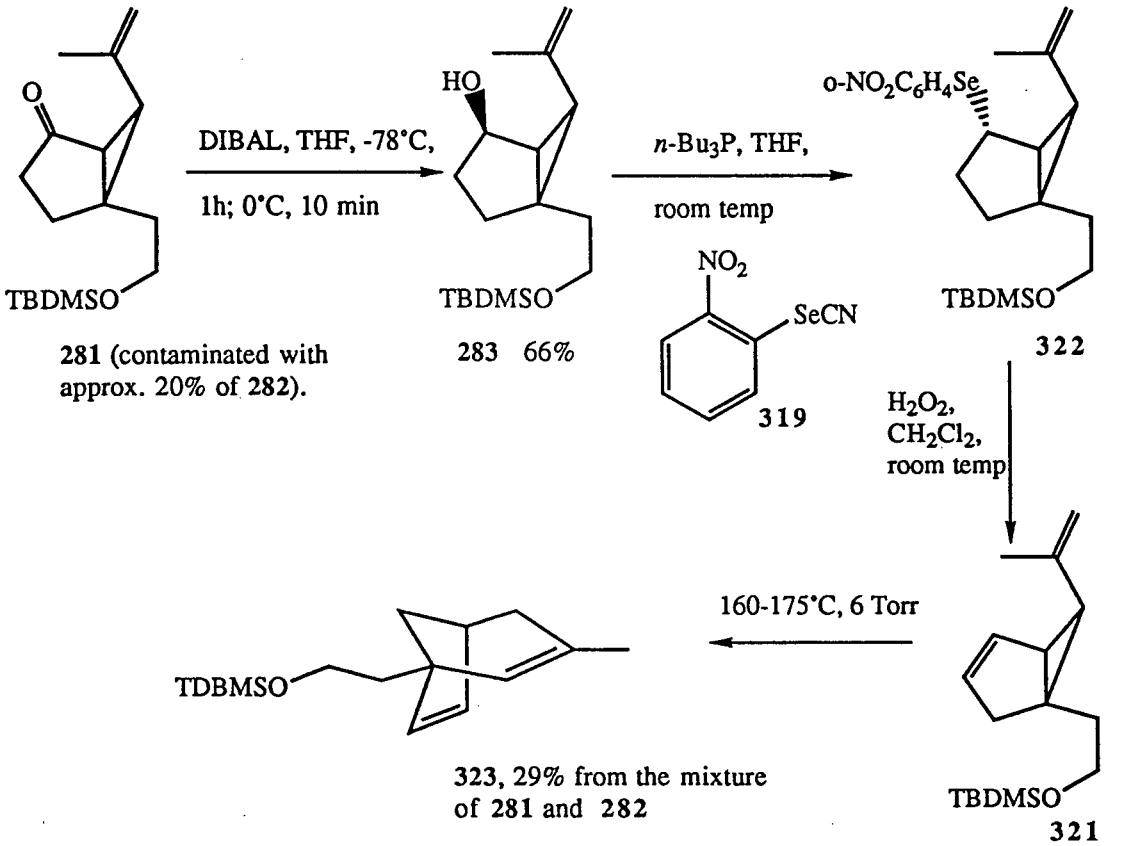


Figure 11 400 MHz ^{1}H nmr spectrum (C_6D_6) of compound **320**

selenide **322** via reaction with *n*-Bu3P and *o*-nitrophenylselenocyanate (**319**). Reaction of the selenide **322** with H_2O_2 provided, after flash chromatography of the crude reaction product, the 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hex-2-ene **321**. Distillation of this material (160-175°C, 6 Torr) afforded the bicyclo[3.2.1]octa-2,6-diene **323** in 29% overall yield from the mixture of ketones **281** and **282** (Scheme 49).



281 (contaminated with approx. 20% of **282**).

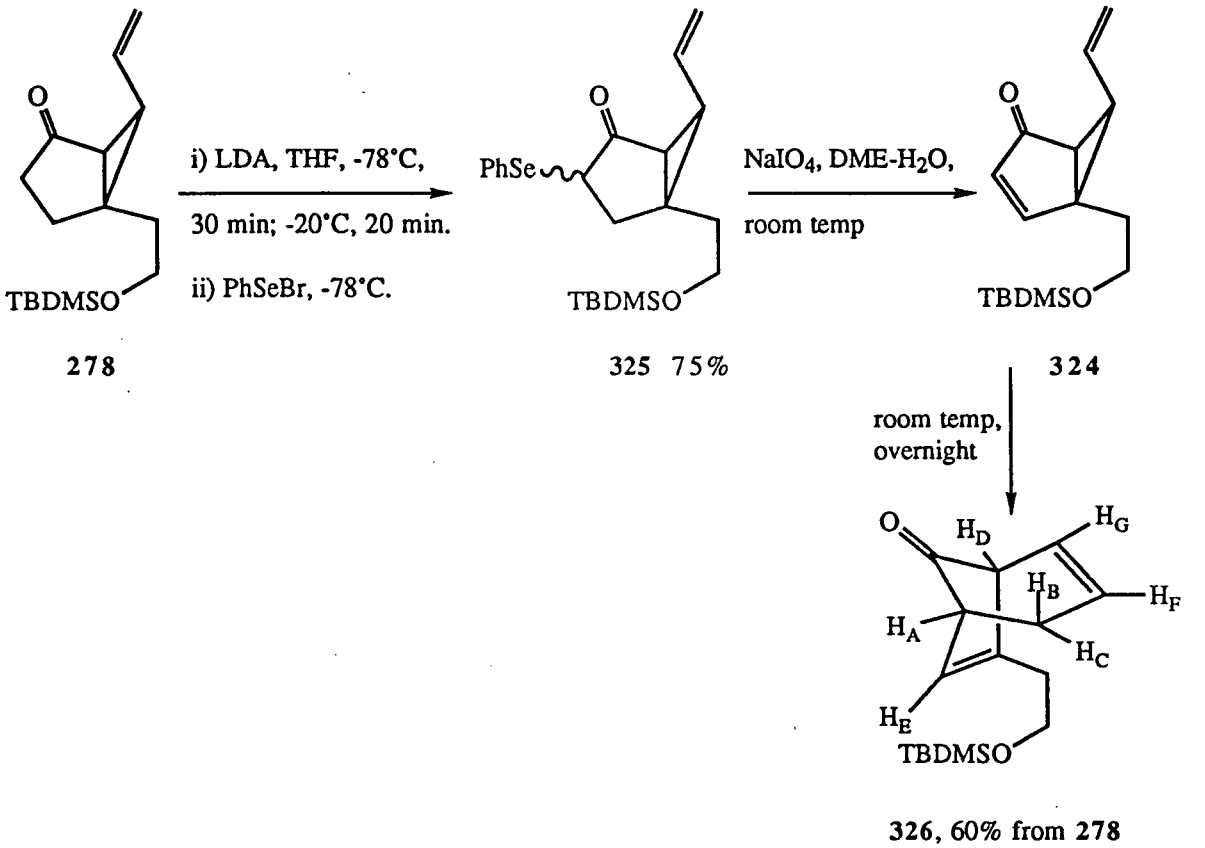
283 66%

323, 29% from the mixture of **281** and **282**

Scheme 49

Finally, it was shown that 6-*endo*-(1-alkenyl)bicyclo[3.1.]hexan-2-ones **237** may be converted into *cis* divinylcyclopropanes by conversion of the ketone function to an α,β-unsaturated ketone function. Thus, the ketone **278** was converted into the α,β-unsaturated ketone **324** via the selenylation-oxidation-selenoxide elimination sequence shown in Scheme 50.[143] To a solution of the ketone **278** in THF was added a solution of

LDA (2 equivalents) in THF and the resulting mixture was stirred for 30 min at -78°C and for 20 min at -20°C. Excess PhSeBr (prepared by reaction of PhSeSePh with Br_2) was added to the reaction mixture at -78°C, via cannula, and the resulting mixture was stirred at -78°C for 20 min. After appropriate workup, the crude reaction product was purified by flash chromatography, to give the selenides **325** in 75% yield (Scheme 50). This material was



Scheme 50

carried on to the next step without further purification. The selenides **325** were subjected to an oxidation-selenoxide elimination procedure similar to that reported by Clive.[144] Thus, a mixture of **325** and $NaIO_4$ (excess) in aqueous dimethoxyethane (DME) was stirred at room temperature overnight. After appropriate workup, the crude reaction product was purified by flash chromatography, to give the bicyclo[3.2.1]octa-2,6-diene **326** in 80% yield (60% from

the ketone **278**). Apparently, the *cis* divinylcyclopropane **324**, formed in this manner, undergoes Cope rearrangement at room temperature to give the observed product **326** (Scheme 50).

This compound exhibited spectral data which were in full accord with the assigned structure. For example, the infrared spectrum of **326** showed a strong absorbance at 1770 cm^{-1} attributable to the carbon-oxygen stretching frequency of the ketone function. The ^1H nmr spectrum (400 MHz, C_6D_6) of **326** is shown in Figure 12. This spectrum shows a 6-proton singlet at δ 0.05 and a 9-proton singlet at δ 0.99, due to the TBDMS group, as well as a 2-proton triplet of doublets at δ 2.03 (J = 6 Hz, J = 1.5 Hz, -$OCH_2C\underline{H}_2$-), a 2-proton multiplet at δ 3.43 (-$OCH_2C\underline{H}_2$-), and 1-proton multiplets at δ 1.62 and 2.27, attributable to H_B and H_C (although these signals were not individually assigned). The 1-proton multiplet at δ 2.98 and the 1-proton broad doublet at δ 4.44 (J = 6.5 Hz) were assigned to H_A and H_D, respectively. Finally, the 1-proton multiplet at δ 5.15, the 1-proton doublet of multiplets at δ 5.32 (J = 6.5 Hz) and the 1-proton multiplet at δ 5.82, were assigned to H_F, H_E, and H_G, respectively. These signal assignments were supported by decoupling experiments (see Experimental section). For example, irradiation at δ 2.98 (H_A) caused the signal at δ 5.32 (H_E) to collapse to a multiplet, whilst the signal at δ 5.15 (H_F) sharpened to a doublet of doublets of doublets of doublets (J = 11 Hz, J = 3.5 Hz, J = 3.5 Hz, J =1 Hz). Also, irradiation at δ 4.44 (H_D) caused the signal at δ 5.82 (H_G) to sharpen to a doublet of doublets of doublets (J =11 Hz, J = 2 Hz, J = 2 Hz), whilst the signal at δ 5.15 (H_F) sharpened to a doublet of doublets of doublets of doublets (J = 11 Hz, J = 3.5 Hz, J = 3.5 Hz, J = 1.5 Hz), and the signal at δ 5.32 (H_E) sharpened to a doublet of triplets (J = 6.5 Hz, J = 1.5 Hz). Finally, irradiation at δ 2.03 (-$OCH_2C\underline{H}_2$-) caused the signal at δ 5.32 (H_E) to sharpen to a doublet of doublets (J = 6.5 Hz, J = 1.5 Hz), whilst the signal at δ 3.43 (-$OC\underline{H}_2CH_2$-) collapsed to a singlet.

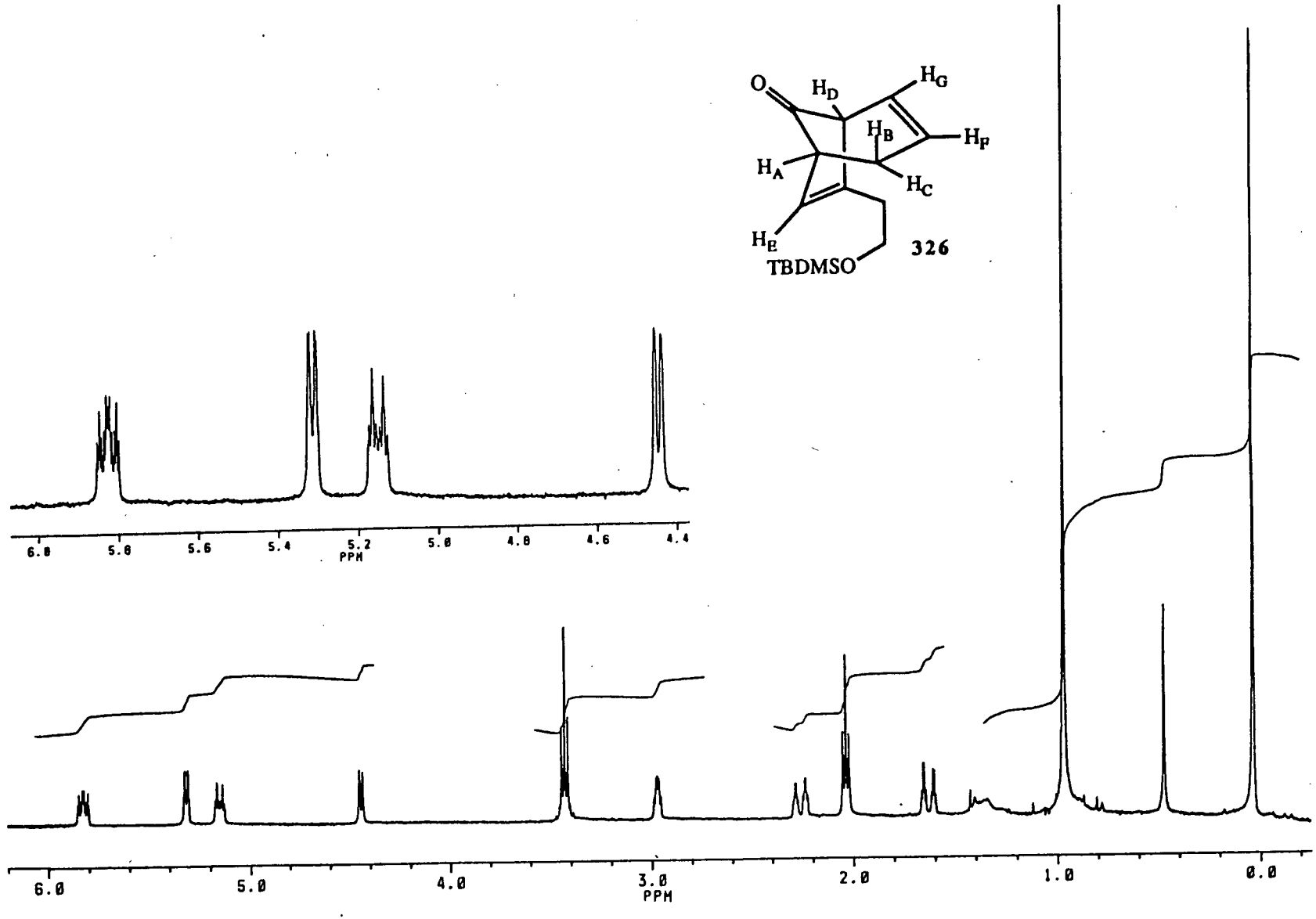
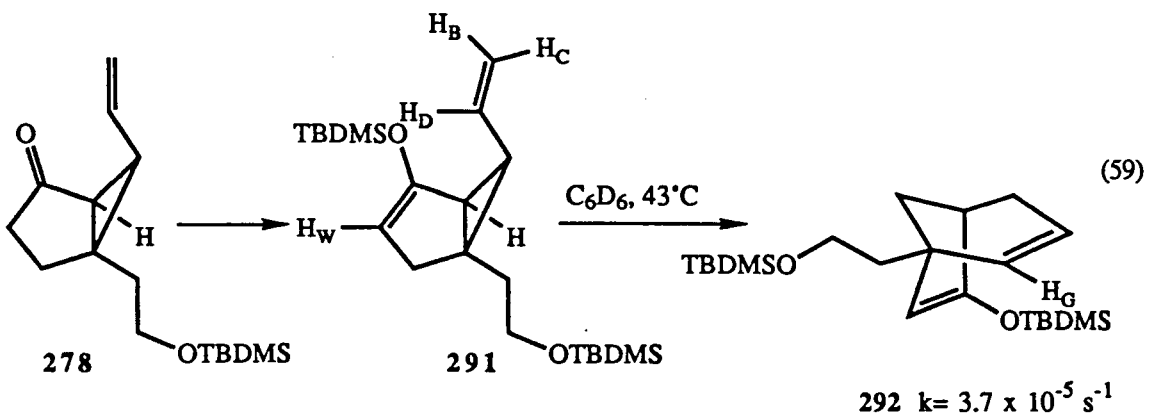


Figure 12 400 MHz ^{1}H nmr spectrum (C_6D_6) of compound **326**

3.8. The preparation of 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hex-2-enes **215** and the Cope rearrangement of these compounds into bicyclo[3.2.1]octa-2,6-dienes **216**. The effects of substituents on the rates of these Cope rearrangements.

Although the 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hex-2-enes **215**, which were prepared as described in the previous section, were found to undergo facile Cope rearrangement to the corresponding bicyclo[3.2.1]octa-2,6-dienes **216**, these rearrangements generally proceed slowly at room temperature. Since the compounds **215** were prepared from the appropriate precursors under mild conditions (i.e. at or below room temperature), it was usually possible to isolate these materials before significant Cope rearrangement had occurred. As a result, we had the opportunity to observe and, therefore, measure the rates of the Cope rearrangement of these compounds by ^{1}H nmr spectroscopy. The general procedure which was used for the kinetic studies is described below for the preparation and Cope rearrangement of compound **291** (equation 59). Thus, the ketone **278** was converted into the 6-*endo*-vinylbicyclo[3.1.0]hex-2-ene **291** via reaction with KH and TBDMSCl as described earlier. After appropriate workup, the solvent was removed by rotary evaporation at room temperature. Any remaining volatile material was removed under vacuum (room temp,



(59)

0.5 Torr) to provide the essentially pure compound **291**, approximately 15 mg (38 μmol) of which was dissolved in enough dry benzene-d_6 (approximately 0.8 mL) to fill a 5mm (base washed) nmr tube to 3 cm. The solution was transferred to the nmr tube, which was then placed in the nmr spectrometer probe (Varian XL-300 spectrometer) at room temperature, and a spectrum was recorded. The olefinic region of this spectrum is shown in Figure 13a. There is a 1-proton singlet at δ 4.48, a 1-proton doublet of doublets at δ 5.20 (J = 10 Hz, J = 2 Hz), a 1-proton doublet of doublets at δ 5.40 (J = 16 Hz, J = 2 Hz) and a 1-proton doublet of doublets of doublets at δ 5.88 (J = 16 Hz, J = 10 Hz, J = 10 Hz), which are assigned as H_W, H_B, H_C, and H_D, respectively. There are no signals present which are due to the rearranged product **292**. This spectrum represented the situation at t = 0. The probe temperature was set at 40°C (although this actually achieves a temperature of 43°C, as determined by calibration using ethylene glycol as standard) and the time was noted. Although the required temperature (43°C) was reached after a few seconds, thermal equilibration of the solution in the nmr tube probably takes several minutes. The time taken for thermal equilibration of the solution was neglected since it is small in comparison to the time taken for the overall experiment. Spectra were then recorded at time intervals.

The rearrangement of **291** to **292** proved to be fairly slow at 43°C. After 1.5 hours (at 43°C), some signals due to the rearranged product **292** were readily discernible. The olefinic region of this spectrum is shown in Figure 13b. Thus, as well as signals due to **291**, there is a 1-proton broad doublet at δ 6.17 (J = 10 Hz) and a 1-proton singlet at δ 5.14, attributable to H_G (**292**) and H_H (**292**), respectively. The signal due to H_F (**292**) is at approximately δ 5.30, but is overlapped by the signal due to H_C (**291**).

The progress of the Cope rearrangement was measured by observation of the growth of the signal at δ 6.17 (H_G, **292**) and the decay of the signal at δ 5.86 (H_D, **291**) (see Figures 13a-f) since these appear to be the most well dispersed signals in this region. Integration of these signals (using Varian XL-300 software, keeping the vertical scale of the

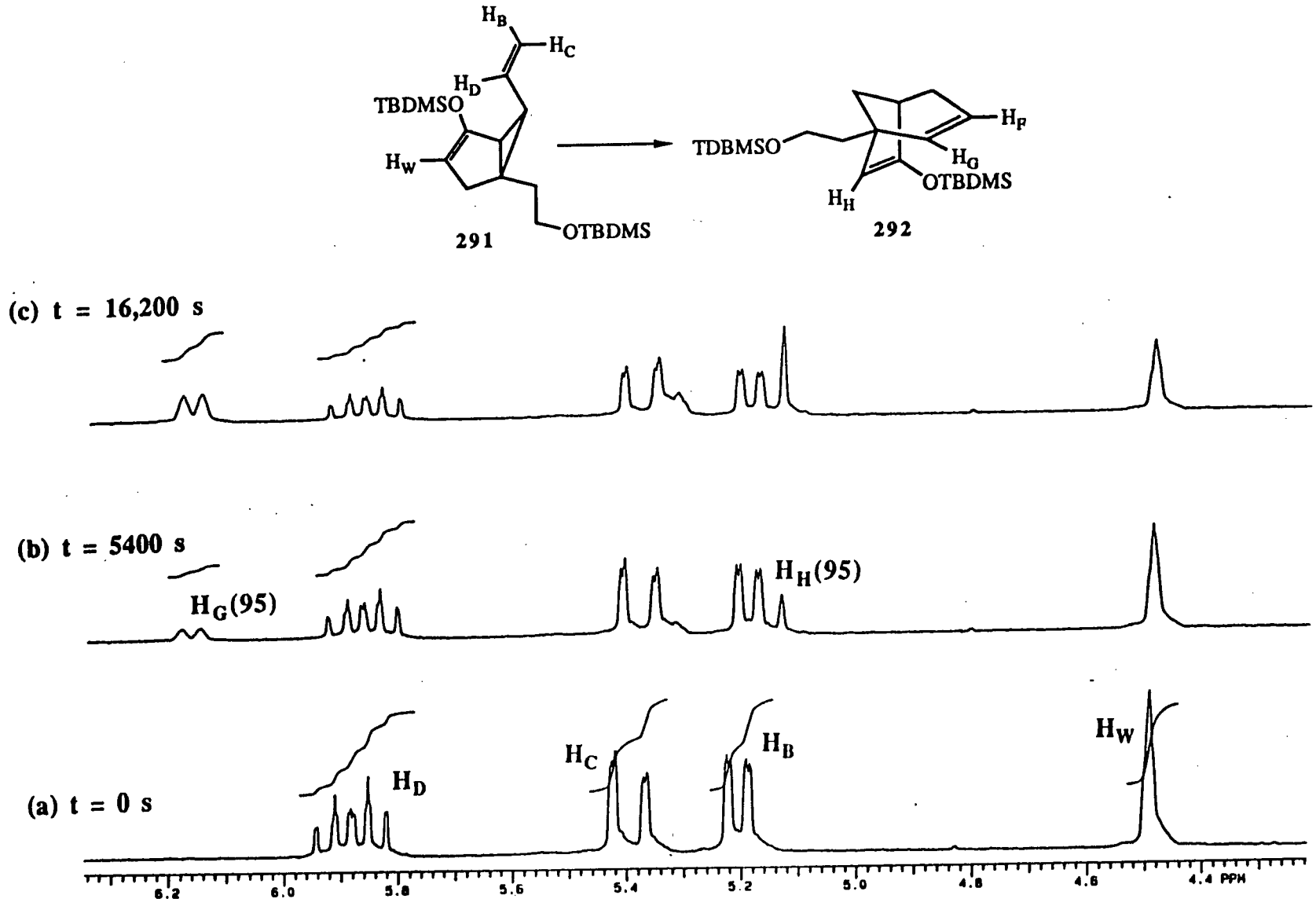


Figure 13 The rearrangement of compound **291** to **292** at 43°C in C_6D_6. Spectra recorded at 300 MHz.

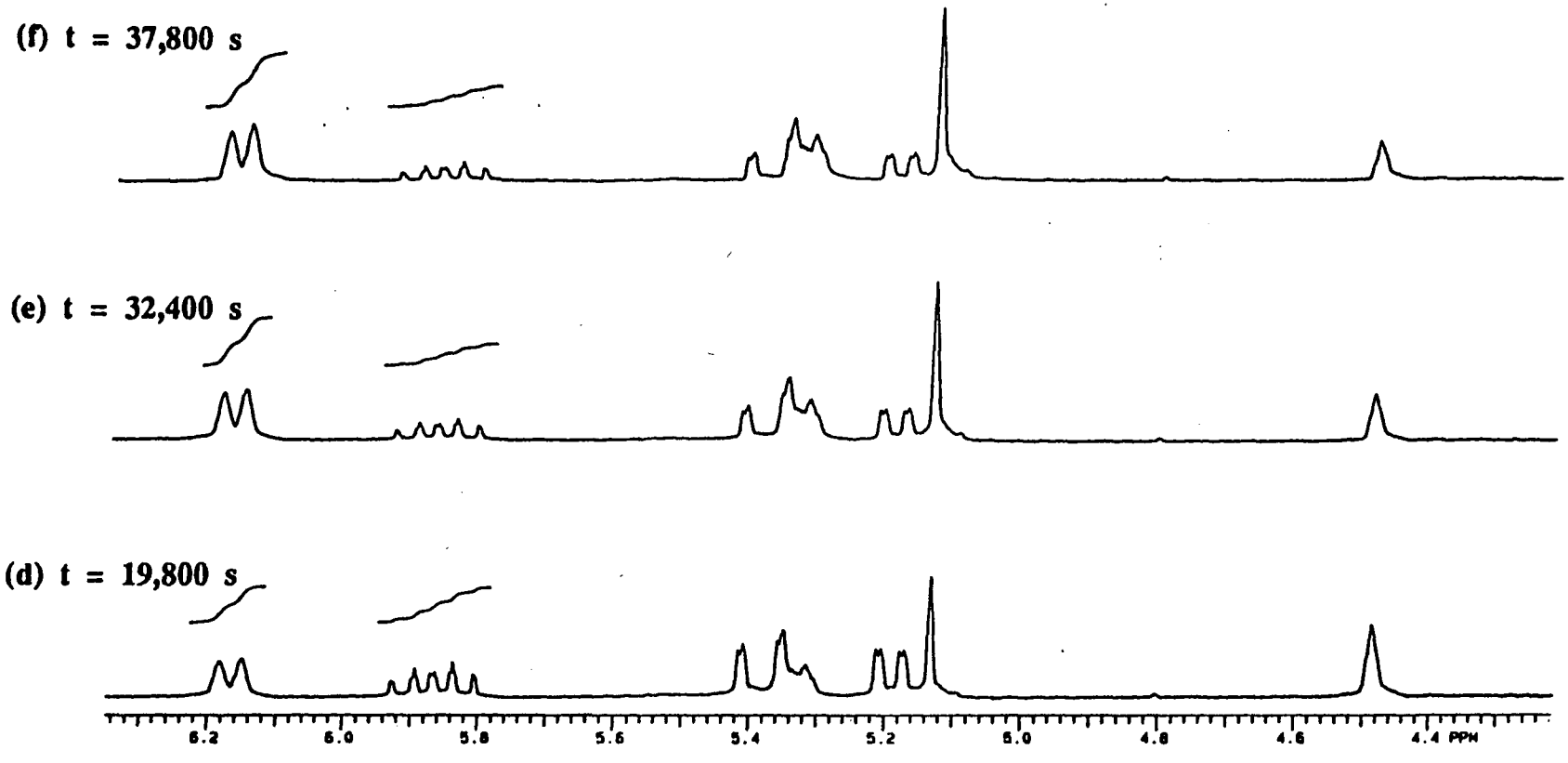


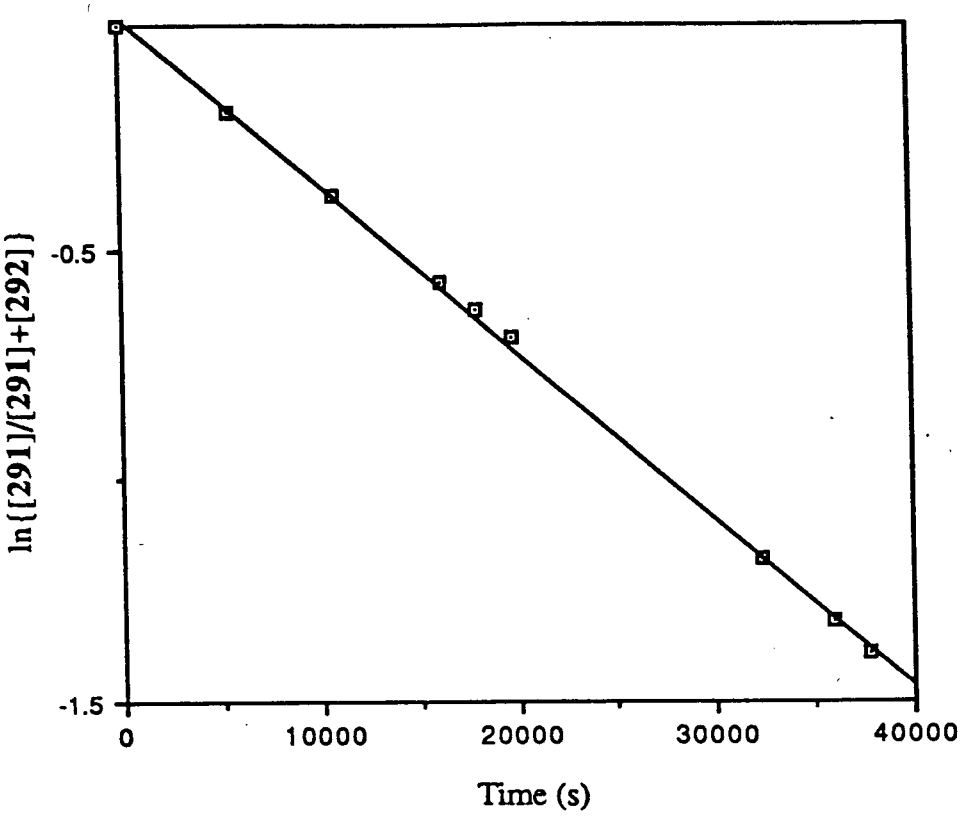
Figure 13, continued. The rearrangement of compound **291** to **292** at 43°C in C_6D_6. Spectra recorded at 300 MHz.

spectrum constant and the integral scale constant) provided the ratios of **291** to **292** which existed after periods of time (measured in seconds) at 43°C. The fractions of **291** remaining after time t seconds were calculated from the integral number for H_D **(291)** divided by the sum of the integral numbers for H_D**(291)** and H_G**(292)**. These data are listed in Table 13. A plot[145] of ln{[**291**]/[**291**]+[**292**]} versus time [where [**291**] = integration number for H_D **(291)**, and [**292**] = integration number for H_G**(292)**], using the data in Table 13, produces series of points which best fit a straight line of slope -3.7×10^{-5} s^{-1} (Figure 14). This corresponds to a rate constant for rearrangement of **291** to **292** of 3.7×10^{-5} s^{-1}.

When this rearrangement reaction was repeated, a similar plot generated a rate constant of 3.4×10^{-5} s^{-1}. The difference in size between these rate constants suggests that an error of approximately 10% is associated with these experiments.

Table 13. Kinetic data for the rearrangement of **291** into **292** at 43°C.

Time, s	[**291**]/[**291**]+[**292**]	ln{[**291**]/[**291**]+[**292**]}
0	1	0
5,400	0.83	-0.19
10,800	0.68	-0.38
16,200	0.56	-0.57
18,000	0.53	-0.63
19,800	0.50	-0.69
32,400	0.31	-1.18
36,000	0.27	-1.32
37,800	0.25	-1.39



[291] = integration number for H_D (291)

[292] = integration number for H_G (292)

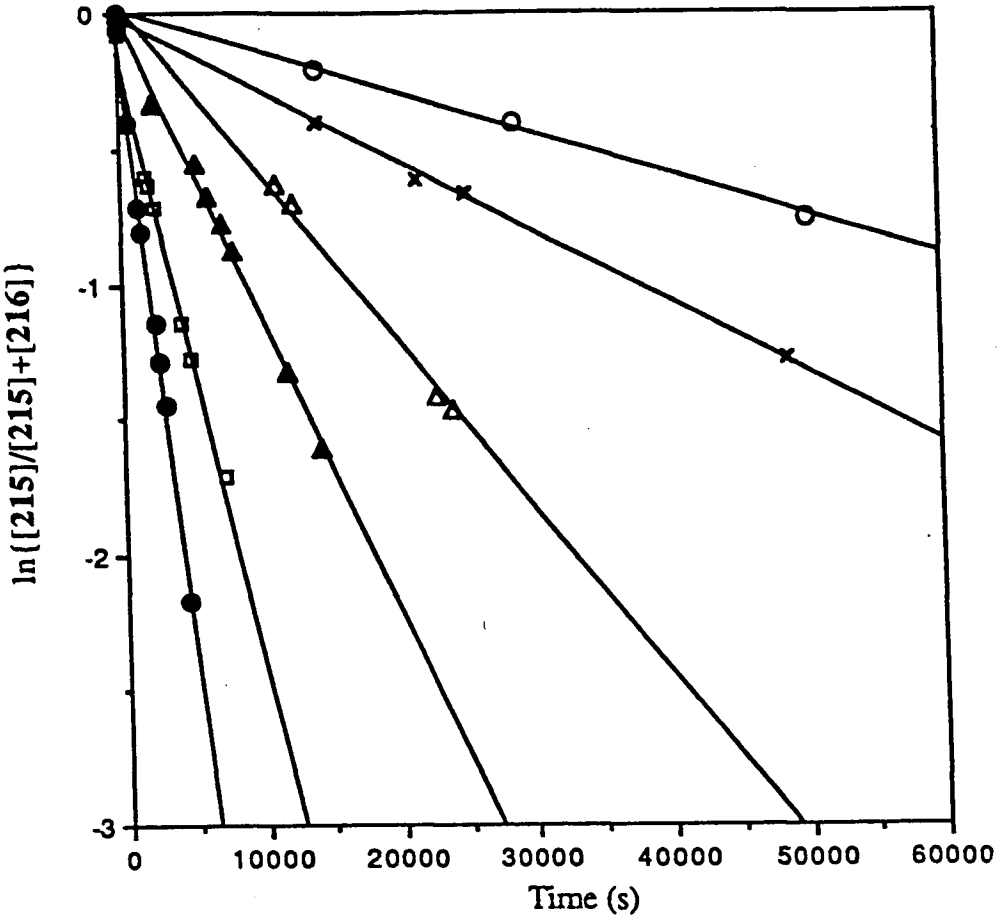
Slope = -3.7×10^{-5} s^{-1}

Figure 14. Plot of the kinetic data for the Cope rearrangement of **291** to **292.**

The rates of Cope rearrangement for other *cis* divinylcyclopropanes **215** were determined in a similar manner. Each compound was prepared from the appropriate precursor, as described in the previous section of this thesis, and the Cope rearrangement was observed by ^{1}H nmr spectroscopy at 43°C. The progress of the rearrangement was monitored by integration of well dispersed signals due to the unrearranged and rearranged products. These experiments and the kinetic data are presented in the Experimental section, and the log plots corresponding to these data are shown in Figures 15 and 16. The rate constants for these Cope rearrangements are summarized in Table 14.

Several points should be made regarding the data given in Table 14. Firstly, each kinetic run was repeated, and the rate constant obtained was, in each case, very similar (within ± 10%) to that obtained originally. There are several potential sources of experimental error associated with these kinetic experiments. For example, there is a time period in which the sample warms to 43°C in the nmr probe and equilibrates at this temperature, so the sample does not initially experience a uniform temperature. The major source of error in the data, however, arises from the integration of the ^{1}H nmr signals. Firstly, it must be decided where the integration curve for a particular signal begins and finishes. Therefore, in each case the integration limits were kept constant throughout the experiment. Secondly, any signals due to minor (unknown) impurities could be a source of error in the integration if these signals were to be very close to or underneath those due to the divinylcyclopropane and/or the rearranged product. It was felt that this problem was minimized by integration of well defined, well dispersed signals for these measurements.

The data in Table 14 show some general trends with respect to the effect of substituents on the rates of Cope rearrangement of 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hex-2-enes **215**. For example, increasing the size of the substituent R^7 increases the rate of Cope rearrangement. This is exemplified by comparison of entries 3, 4 and 5, in which replacement of R^7=H by R^7=Me causes a three-fold rate increase and replacing R^7=H by R^7= Pr^i causes a 12.5 fold rate increase. This effect is also shown by comparison of entries



[215] = integration number for signal representing **215** (1 proton)

[216] = integration number for signal representing **216** (1 proton)

× Rearrangement of **293** to **294**. See entry 7, Table 14. Slope = -2.6×10^{-5} s^{-1}.

□ Rearrangement of **296** to **297**.[a] See entry 6, Table 14. Slope = -2.3×10^{-4} s^{-1}.

▲ Rearrangement of **298** to **299**. See entry 4, Table 14. Slope = -1.1×10^{-4} s^{-1}.

● Rearrangement of **301** to **302**. See entry 5, Table 14. Slope = -4.5×10^{-4} s^{-1}.

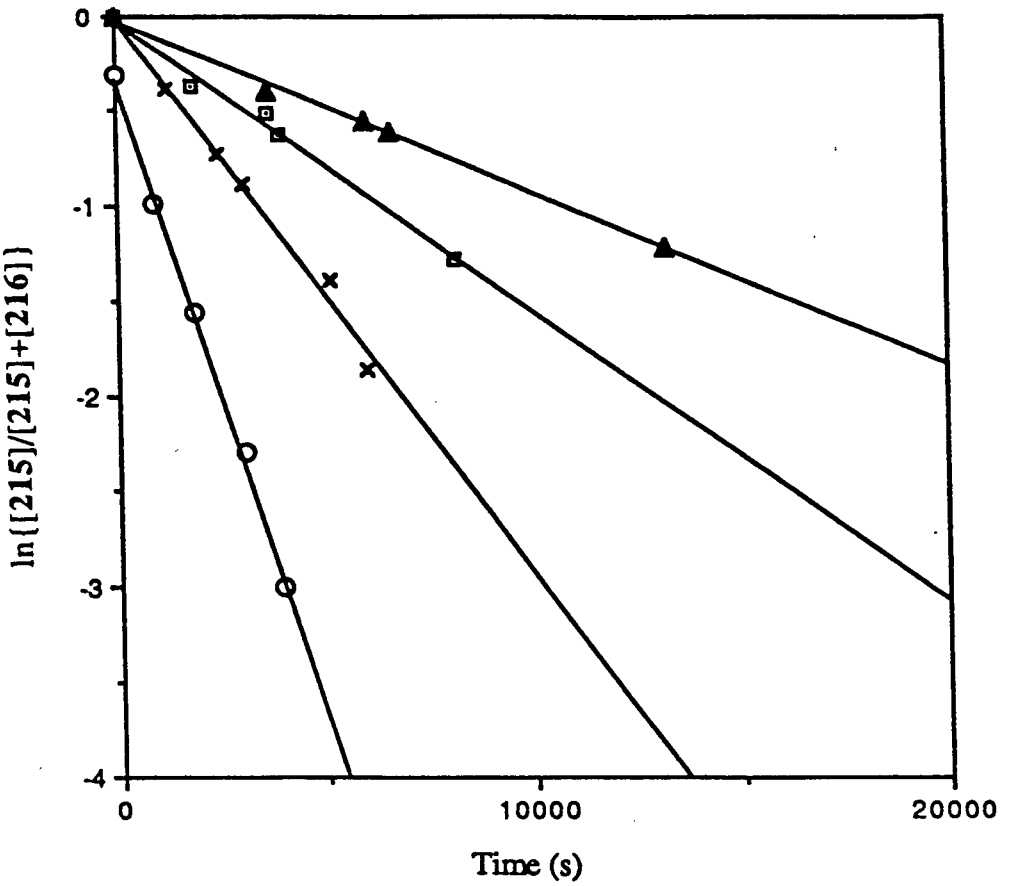
○ Rearrangement of **308** to **309**. See entry 9, Table 14. Slope = -1.5×10^{-5} s^{-1}.

△ Rearrangement of **311** to **312**. See entry 8, Table 14. Slope = -6.2×10^{-5} s^{-1}

---

[a] The progress of the rearrangement was measured by integration of 2-proton signals corresponding to the starting material and product. See Experimental section.

Figure 15. Plots of kinetic data for Cope rearrangements of the 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hex-2-enes **293**, **296**, **298**, **301**, **308** and **311**.



[215] = integration number for signal representing **215** (1 proton)

[216] = integration number for signal representing **216** (1 proton)

× Rearrangement of **305** to **306**. See entry 10, Table 14. Slope = -2.9×10^{-4} s^{-1}.

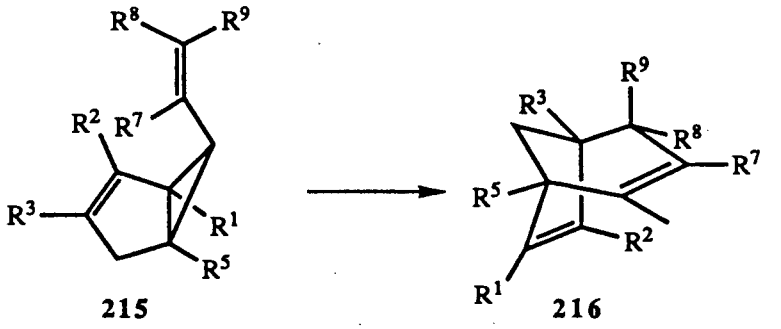
▫ Rearrangement of **313** to **315**. See entry 11, Table 14. Slope = -1.5×10^{-4} s^{-1}.

▲ Rearrangement of **316** to **320**. See entry 1, Table 14. Slope = -9.0×10^{-5} s^{-1}.

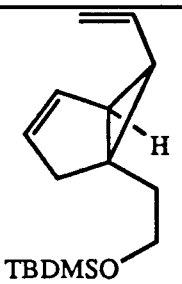
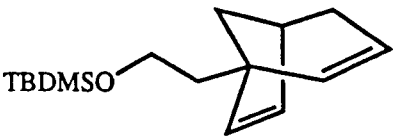
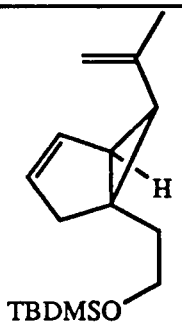
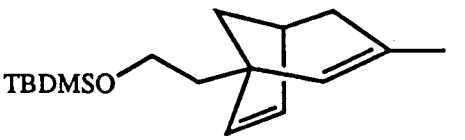
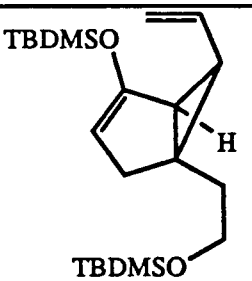
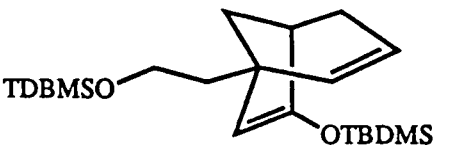
○ Rearrangement of **321** to **323**. See entry 2, Table 14. Slope = -6.8×10^{-4} s^{-1}.

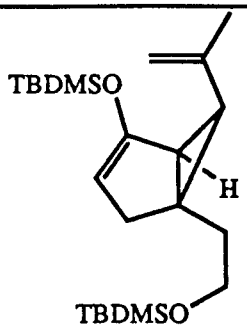
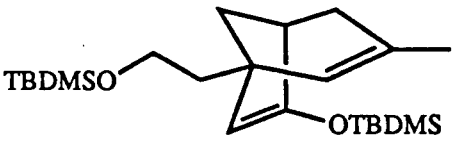
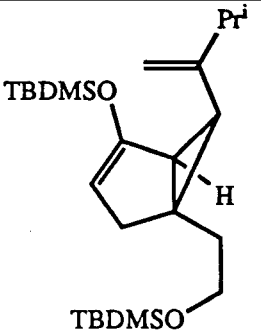
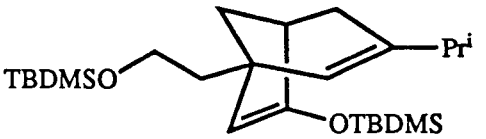
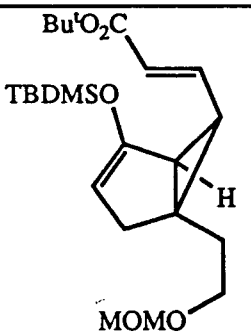
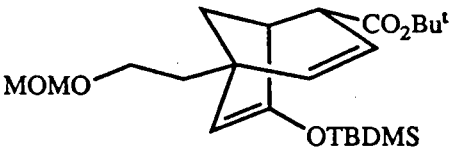
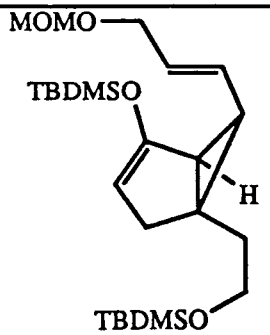
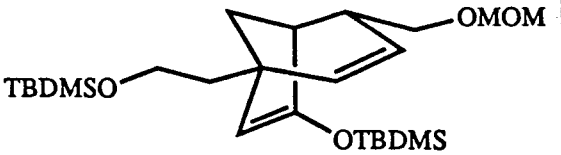
Figure 16. Plots of kinetic data for Cope rearrangements of the 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hex-2-enes **305**, **313**, **316** and **321**.

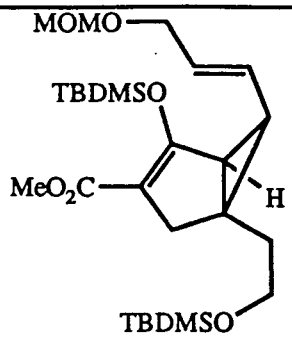
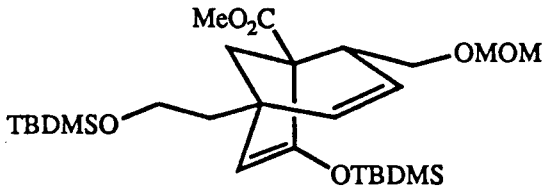
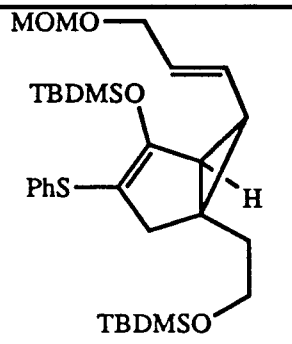
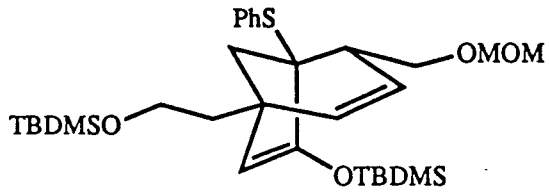
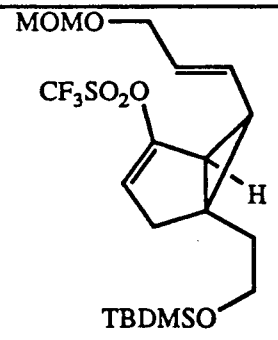
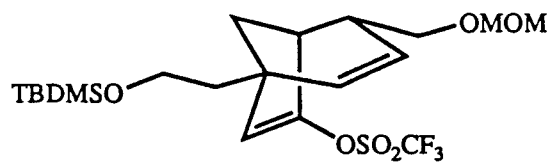
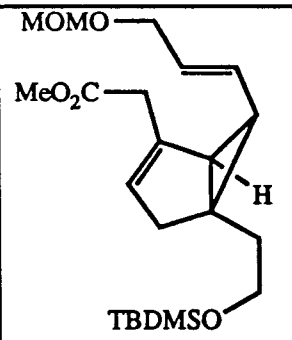
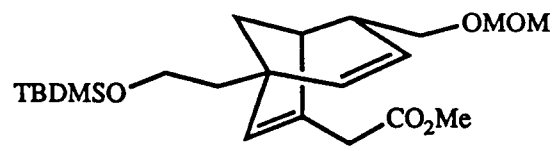
Table 14. The rates of Cope rearrangement of functionalized 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hex-2-enes **215** (R^1=H) into bicyclo[3.2.1]octa-2,6-dienes **216** (R^1=H).



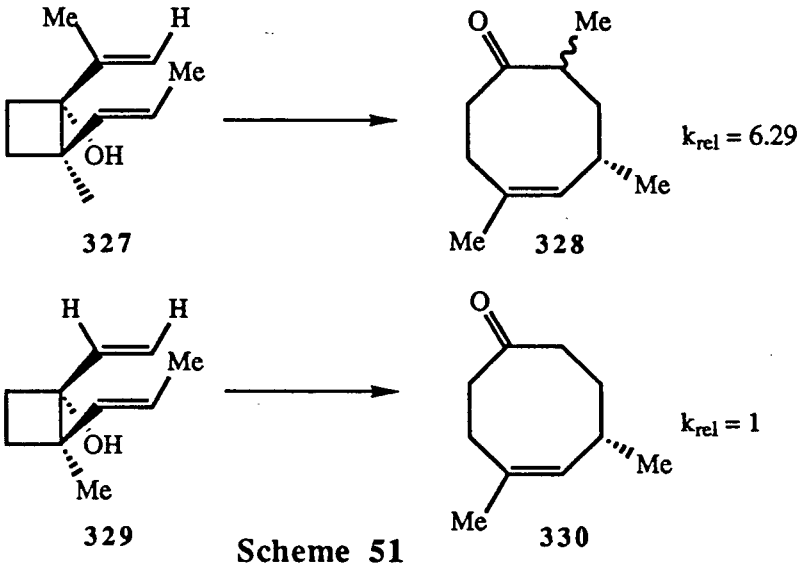
215 **216**

Entry	**215**	**216**	k_{rel}
1	 **316**	 **320** $k = 9.0 \times 10^{-5}\ s^{-1}$	1
2	 **321**	 **323** $k = 6.8 \times 10^{-4}\ s^{-1}$	7.6
3	 **291**	 **292** $3.7 \times 10^{-5}\ s^{-1}$	0.4

4	 **298**	 **299** $k = 1.1 \times 10^{-4}\ s^{-1}$	1.2
5	 **301**	 **302** $k = 4.5 \times 10^{-4}\ s^{-1}$	5.0
6	 **296**	 **297** $k = 2.3 \times 10^{-4}\ s^{-1}$	2.6
7	 **293**	 **294** $2.6 \times 10^{-5}\ s^{-1}$	0.3

8	 **311**	 **312** $k = 6.2 \times 10^{-5}\ s^{-1}$	0.7
9	 **308**	 **309** $k = 1.5 \times 10^{-5}\ s^{-1}$	0.2
10	 **305**	 **306** $2.9 \times 10^{-4}\ s^{-1}$	3.2
11	 **313**	 **315** $k = 1.5 \times 10^{-4}\ s^{-1}$	1.7

1 and 2, in which replacing R^7=H by R^7=Me causes a 7.6 fold increase in rate of Cope rearrangement. Very similar effects have been observed in other types of Cope rearrangement. In particular, Miller and Gadwood[146] reported that the *cis* divinylcyclobutane **327** rearranges to the cyclooctenone **328** approximately six times faster than **329** rearranges to **330** (Scheme 51). These results were attributed to the greater electron donating nature of the methyl substituent in compound **327** relative to H in compound **329**. In our cases, the observed rate enhancements might be related to an increase in +I inductive effect associated with the substituent R^7, on going from R^7=H to -Me to -Pr^i.



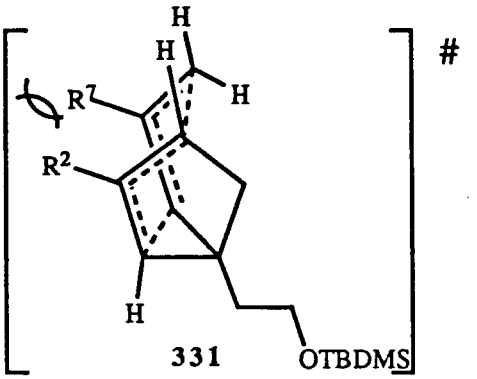
327 **328**

329 **330**

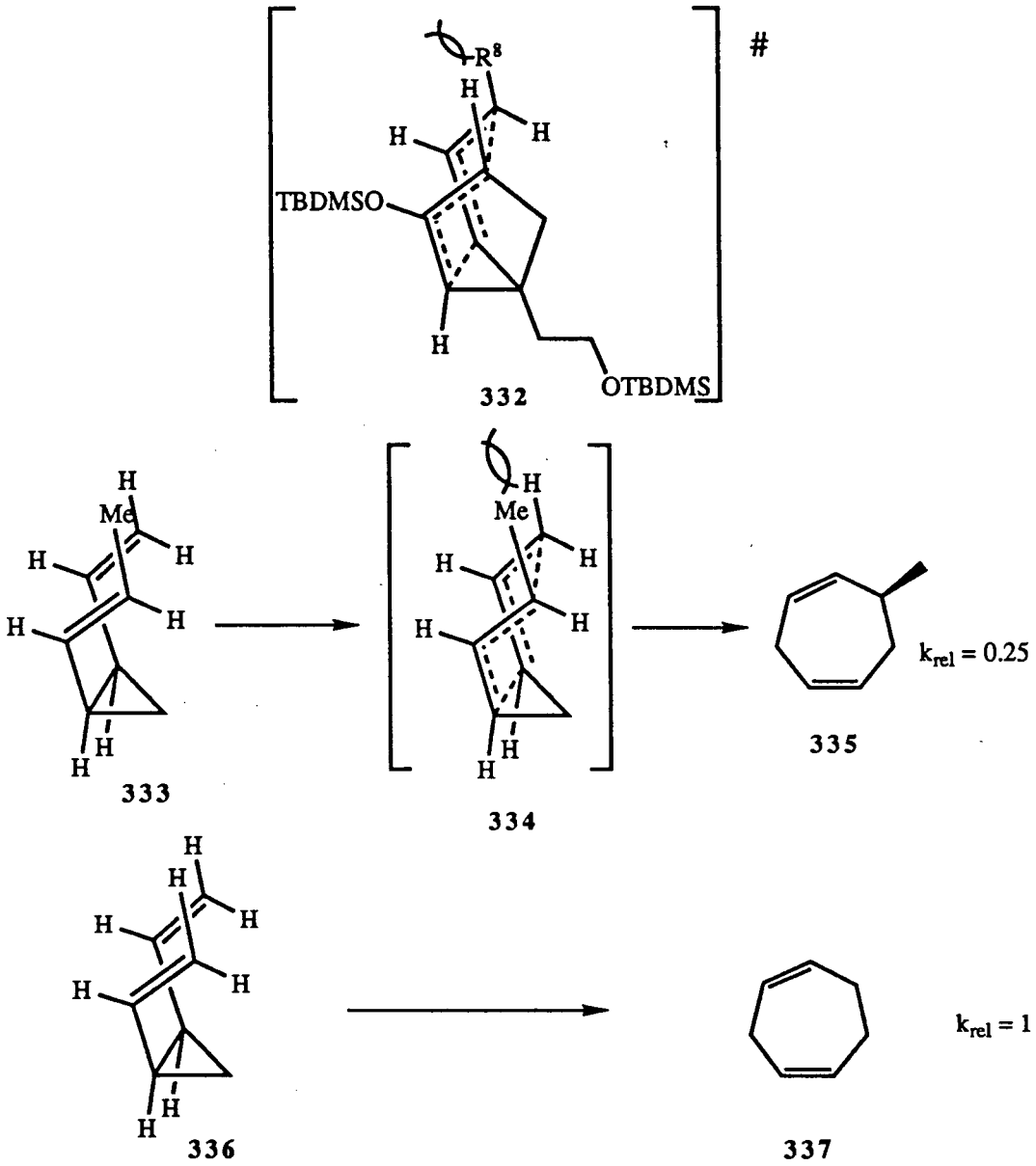
Scheme 51

Replacement of R^2=H by R^2=OTBDMS causes a reduction in rate of Cope rearrangement. This is shown by comparison of entry 3 and entry 1, in which there is a 2.5 fold reduction in rate upon replacement of R^2=H by R^2=OTBDMS, and by comparison of entry 4 and entry 2, in which there is a 6.3 fold reduction in rate upon replacement of R^2=H by R^2=OTBDMS. Since, in the former case (R^2=H or OTBDMS, R^7=H), only minor steric interactions would exist between R^2 and R^7 in the transition states **331** for Cope rearrangement, the observed rate reduction might be the result of an electronic effect. However, in the latter case, the steric interaction between R^2=OTBDMS and R^7=Me in the

transition state **331** for Cope rearrangement would be significantly larger than the steric interaction in **331** between R^2=H and R^7=Me. The observed rate reduction could, therefore, be due to a combination of electronic and steric factors.



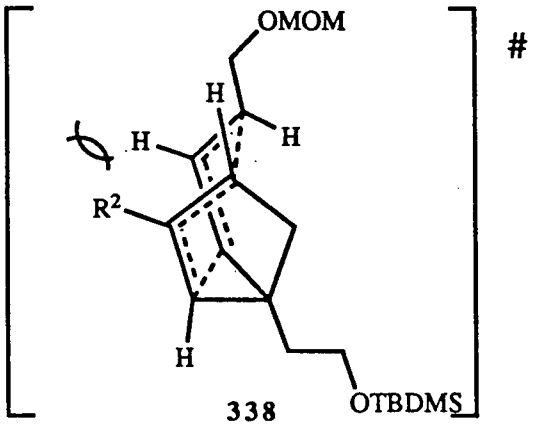
A comparison of entry 3 with entry 6 shows that there is a 6.5 fold increase in the rate of Cope rearrangement upon replacement of R^8=H by R^8=CO_2Bu^t. This effect is most likely electronic in nature and, apparently, outweighs the eclipsing interaction that would exist in the transition state **332** for Cope rearrangement, between R^8=CO_2Bu^t and the proton at C3 (Scheme 52). In light of this observation, it is interesting to note that replacement of R^8=H by R^8=CH_2OMOM causes a 1.3 fold reduction in the rate of rearrangement (a comparison of entries 3 and 7). This result may be rationalized by the presence of an eclipsing interaction in the transition state **332** for Cope rearrangement, between R^8=CH_2OMOM and the proton at C3 (Scheme 52). However, such an eclipsing interaction would be expected to cause a larger rate retardation than is actually observed. In a related study, Schneider and Rau[114] reported that the *cis* divinylcyclopropane **333** rearranges, via a transition state **334**, to the 1,4-cyclohexadiene **335** approximately four times slower than *cis* divinylcyclopropane (**336**) rearranges to 1,4-cyclohexadiene (**337**) (Scheme 52). Therefore, in our case it appears that the eclipsing interaction in the transition state **332** is partially balanced by the electron withdrawing nature of the substituent (CH_2OMOM).



Scheme 52

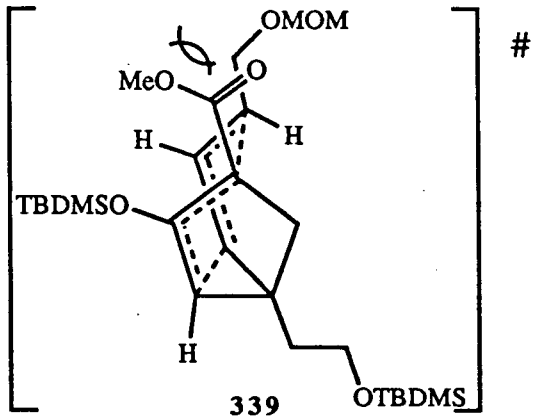
A comparison of entries 7 and 10 shows that replacement of R^2=OTBDMS by R^2=OSO_2CF_3 causes a 10.7 fold increase in the rate of Cope rearrangement, whilst a comparison of entries 7 and 11 shows that replacement of R^2=OTBDMS by R^2=CH_2CO_2Me causes a 5.7 fold increase in rate. These effects are most likely due to the greater electron withdrawing ability of both R^2=OSO_2CF_3 and R^2=CH_2CO_2Me, compared

to R^2=OTBDMS since, in each case, the steric interactions involving R^2 in the transition state **338** for Cope rearrangement should be of similar magnitude.



338

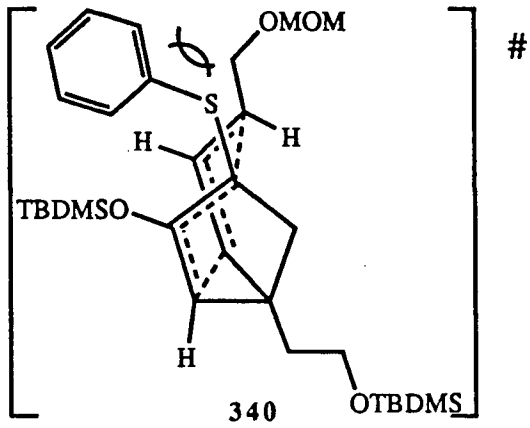
A comparison of entries 7 and 8 shows that replacement of R^3=H by R^3=CO_2Me causes a 2.3 fold increase in the rate of Cope rearrangement. It is concluded that this effect is electronic in nature and is large enough to outweigh the significant eclipsing interaction that would exist in the transition state **339** for Cope rearrangement, as shown below.



339

Finally, a comparison of entries 7 and 9 shows that replacement of R^3=H by R^3=SPh causes a 1.5 fold reduction in rate of Cope rearrangement. This could be a result of the eclipsing interaction that would exist in the transition state **340** for Cope rearrangement.

However, since the SPh group is potentially electron donating (via a resonance effect), an electronic contribution to this rate reduction cannot be ruled out.



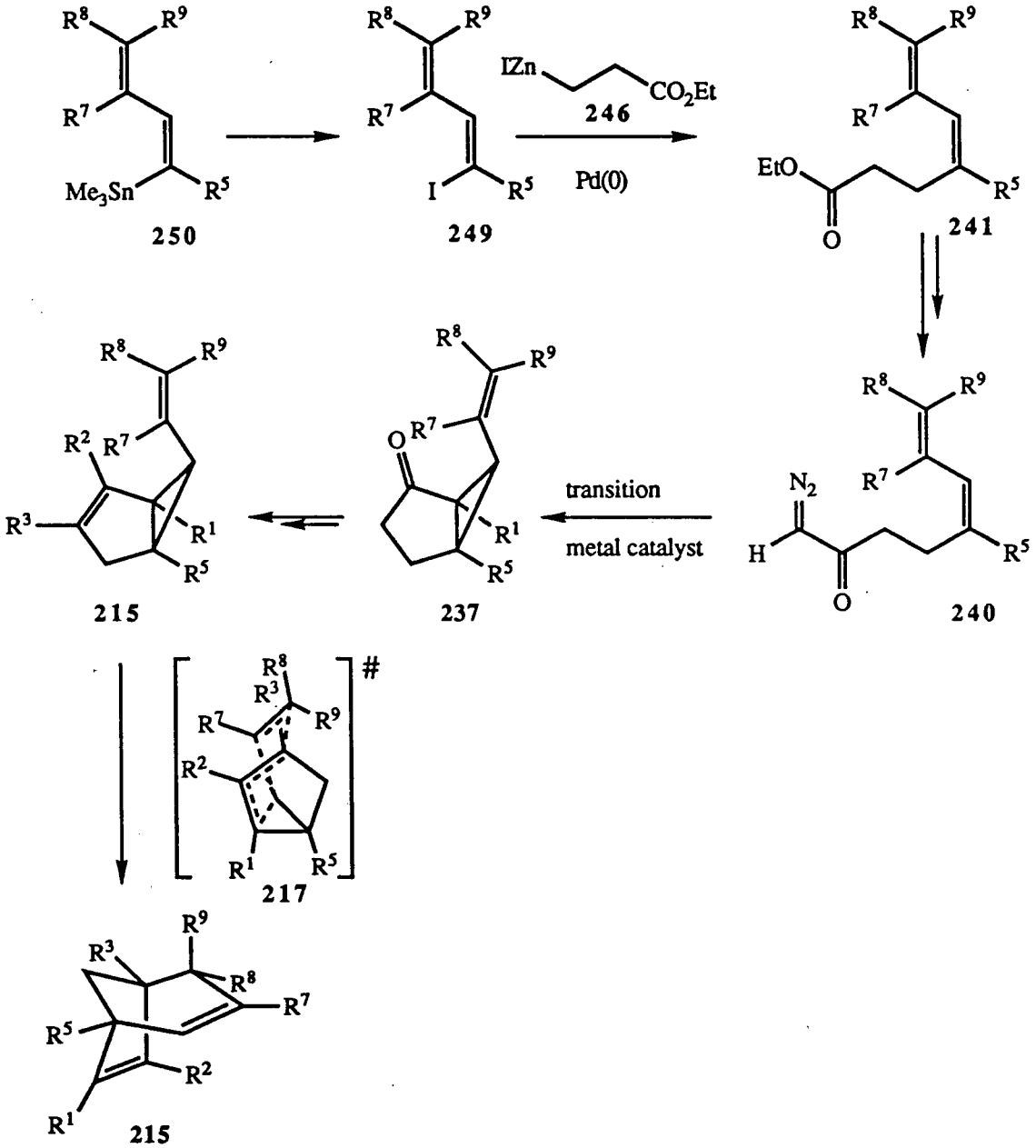
340

In summary, it has been shown that the rate of Cope rearrangement of 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hex-2-enes **215** depends on the nature of the substituents and the substitution pattern. Although previous workers[113,114] have rationalized substituent effects in terms steric interactions in the transition state for Cope rearrangement, this study has shown that the electron donating or withdrawing nature of the substituent is also important. In fact, in some cases it appears that the electronic effects outweigh the steric effects. The results presented in Table 14 and discussed above certainly indicate that the transition state for Cope rearrangement of 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hex-2-enes has some polar character. However, no further conclusions can be made regarding the exact nature of the transition state.

3.9. Conclusions

A general, efficient, stereoselective synthesis of 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hexan-2-ones of general structure **237** (R^1=H) was developed, using the readily available stannyldienes of general structure **250** as starting materials

(Scheme 53). The key steps of this synthesis involve the preparation of diene esters **241** via Pd(0)-catalyzed cross coupling reaction between iodo dienes of general structure **249** and the organozinc reagent **246**, and the transition metal-catalyzed intramolecular cyclopropanation reactions of diene diazoketones **240** (Scheme 53).



Scheme 53

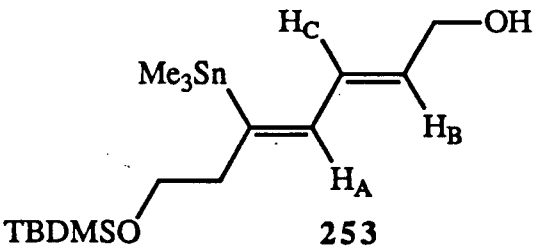
The ketones **237** (R^1=H) were readily converted into a variety of functionalized 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hex-2-enes of general structure **215** (R^1=H) via simple synthetic manipulation of the carbonyl group. Distillation, or warming benzene solutions of the *cis* divinylcyclopropanes **215** (R^1=H) provided the bicyclo[3.2.1]octa-2,6-dienes **216** (R^1=H) cleanly and efficiently. This overall synthetic sequence, therefore, constitutes a general, reliable methodology for the preparation of functionalized bicyclo[3.2.1]octanes.

The rates of Cope rearrangement of a number of the *cis* divinylcyclopropanes **215** (R^1=R^9=H) were measured by ^{1}H nmr spectroscopy (43°C, C_6D_6). The effects of substituents on the rate of Cope rearrangement of these *cis* divinylcyclopropanes were attributed to either steric or electronic effects. In some cases, the electronic effects appear to outweigh the steric interactions between substituents in the transition state for Cope rearrangement **217**.

IV. Experimental

For General experimental details and "Solvents and reagents", see Experimental section for Part 1 of this thesis.

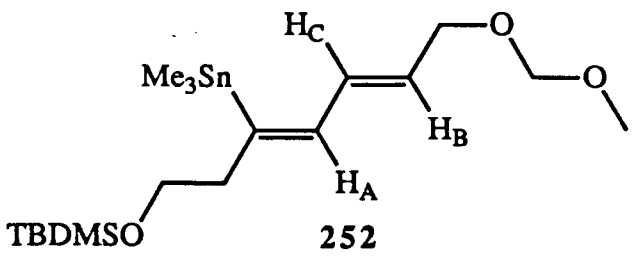
Preparation of the alcohol **253**.



253

To a cold (-78°C), stirred solution of the ester **182** (5.65 g, 13.02 mmol) in dry Et_2O (100 mL) was added a solution of diisobutylaluminium hydride (2.5 equiv.) in hexane. After the mixture had been stirred at -78°C for 1h and at 0°C for 1 h, saturated aqueous NH_4Cl (5 mL) was added and the mixture was exposed to air and allowed to warm to room temperature. After approx. 30 min at room temperature a heavy gelatinous white precipitate had formed. Et_2O (50 mL) and $MgSO_4$ were added and the mixture was suction filtered through a short pad of Florisil® (7 cm x 7 cm), using Et_2O as eluant. The eluate was concentrated and the crude reaction product was purified by flash chromatography (1:3 Et_2O - petroleum ether; 180 g of silica gel). Distillation (145-150°C/0.5 Torr) of the oil thus obtained gave 5.02 g (95%) of the alcohol **253**, a colourless oil which exhibited ir (neat): 3332, 1472, 1098, 837, 775 cm^{-1}; ^1H nmr (400 MHz, C_6D_6) δ: 0.11 (s, 6H, -Si$\underline{Me}_2$), 0.31 (s, 9H, -Sn$\underline{Me}_3$, $^2J_{Sn-H}$ = 53 Hz), 0.64 (t, 1H, -O$\underline{H}$, J = 5.5 Hz), 1.02 (s, 9H, -Si$\underline{Bu}^t$), 2.64 (br t, 2H, -$OCH_2C\underline{H}_2$-, J = 7 Hz, $^3J_{Sn-H}$ = 55 Hz), 3.69 (t, 2H, -$OC\underline{H}_2CH_2$-, J = 7 Hz), 3.90 (ddd, 2H, -$C\underline{H}_2OH$, J = 5.5 Hz, J = 5.5 Hz, J = 1.5 Hz), 5.66 (dt, 1H, $\underline{H}_B$, J = 15 Hz, J = 5.5 Hz), 6.45 (ddt, 1H, $\underline{H}_C$, J = 15 Hz, J = 11 Hz, J = 1.5 Hz), 6.80 (br d, 1H, $\underline{H}_A$, J = 11 Hz, $^3J_{Sn-H}$ = 130 Hz). On addition of D_2O the signal at δ 0.64 (-O$\underline{H}$) disappeared and the signal at 3.90 (-$C\underline{H}_2OH$) collapsed to a br d (J = 5.5 Hz). *Exact Mass* calcd. for $C_{15}H_{31}O_2SiSn$ (M^+-Me): 391.1115; found: 391.1114.

Preparation of the diene **252.**



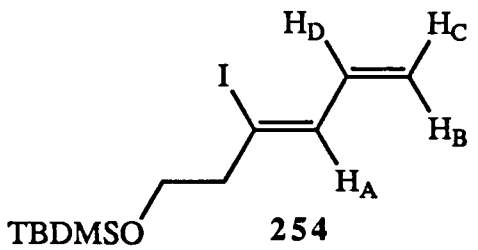
252

To a cold (0°C), stirred solution of the alcohol **253** (5.30 g, 13.05 mmol) in dry CH_2Cl_2 (80 mL) (argon atmosphere) was added, successively, dry *N,N*-diisopropylethylamine (freshly distilled) (3.37 g, 2 equiv.) and chloromethyl methyl ether (1.98 g, 1.9 equiv.). After the mixture had been stirred overnight at room temperature, saturated aqueous $NaHCO_3$ (30 mL) and Et_2O (50 mL) were added. The phases were separated and the aqueous phase was extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed with H_2O (30 mL) and brine (30 mL) and were then dried ($MgSO_4$) and concentrated. Flash chromatography of the residual oil (7:93 Et_2O - petroleum ether; 200 g of silica gel), followed by distillation of the oil thus obtained (130-140°C/0.5 Torr), gave 5.29 g (90%) of the stannyldiene **252**, a colourless oil which exhibited ir (neat): 1472, 1255, 1103, 838, 776 cm^{-1}; ^1H nmr (400 MHz, C_6D_6) δ: 0.1 (s, 6H, -SiMe2), 0.30 (s, 9H, -SnMe3, $^2J_{Sn-H}$ = 53 Hz), 1.01 (s, 9H, -SiBu^t), 2.62 (br t, 2H, -OCH_2CH_2-, J = 7 Hz, $^3J_{Sn-H}$ = 55 Hz), 3.21 (s, 3H, -OMe), 3.67 (t, 2H, -OCH_2CH_2-, J =7 Hz), 4.08 (dd, 2H, -CH_2O-, J = 5.5 Hz, J = 1.5 Hz), 4.55 (s, 2H, -OCH_2O-), 5.72 (dt, 1H, H_B, J = 15 Hz, J = 5.5 Hz), 6.53 (ddt, 1H, H_C, J = 15 Hz, J = 11 Hz, J = 1.5 Hz), 6.80 (br d, 1H, H_A, J = 11 Hz, $^3J_{Sn-H}$ = 130 Hz). In nOe difference experiments, irradiation at δ 6.80 (H_A) caused signal enhancement at δ 5.72 (H_B) and at δ 2.62 (-OCH_2CH_2-); irradiation at δ 2.62 (-OCH_2CH_2-) caused signal enhancement at δ 3.67 (-OCH_2CH_2-) and at δ 6.80 (H_A); irradiation at δ 6.53 (H_C) caused signal enhancement at δ 4.08 (-CH_2O-); irradiation at δ 5.72 (H_B) caused signal enhancement at δ 6.80 (H_A) and at δ 4.08 (-CH_2O-). ^{13}C nmr (75.4 MHz, C_6D_6) δ: -8.13, -5.07, 18.55, 26.14, 44.08, 55.88, 64.00, 67.20, 95.59, 130.15, 133.01, 142.10, 146.92. *Exact Mass* calcd. for $C_{17}H_{35}O_3SiSn$ (M^+-Me): 435.1378; found: 435.1377.

General Procedure L. The preparation of the iodo dienes **249**.

To a cold (0°C or -78°C), stirred solution of the stannyldiene in dry CH_2Cl_2 (argon atmosphere), was added, via syringe, a solution of I_2 in CH_2Cl_2 (prepared by dissolving 1.05 equiv. of solid I_2 in a minimum amount of dry CH_2Cl_2). When enough of the solution had been added (as shown by the persistent yellow orange colour of the solution, as well as by glc analysis), 10% aqueous $Na_2S_2O_3$ (approx. 0.5 mL per mL of reaction solvent) and Et_2O (approx. 0.5 mL per mL of reaction solvent) were added, and the vigorously stirred mixture was allowed to warm to room temperature. The phases were separated and the aqueous phase was extracted with Et_2O. The combined organic extracts were washed with 10% aqueous $Na_2S_2O_3$ and with brine and were then dried ($MgSO_4$) and concentrated. The crude reaction product was purified by flash chromatography, followed by distillation.

Preparation of the iodo diene **254**

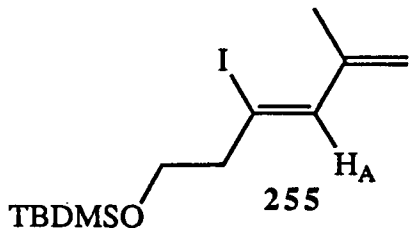


254

Following general procedure L, the stannyldiene **167** (2.94 g, 7.82 mmol; in 50 mL of dry CH_2Cl_2), was allowed to react with a solution of I_2 in dry CH_2Cl_2, at -78°C. Flash chromatography of the crude product (3:97 Et_2O - petroleum ether; 70 g of silica gel),

followed by distillation of the oil thus obtained (85-90°C/0.5 Torr), gave 2.43 g (92%) of the iodo diene **254**, a pale yellow oil which exhibited ir (neat): 3089, 1632, 1413, 836 cm^{-1}; ^1H nmr (300 MHz) δ: 0.08 (s, 6H, -Si<u>Me</u>$_2$), 0.92 (s, 9H, -Si<u>Bu</u>^{t}), 2.79 (br t, 2H, -OCH$_2$C<u>H</u>$_2$-, J = 6.5 Hz), 3.77 (t, 2H, -OC<u>H</u>$_2$CH$_2$-, J = 6.5 Hz), 5.30 (dd, 1H, <u>H</u>$_C$, J = 10 Hz, J = 1.5 Hz), 5.41 (dd, 1H, <u>H</u>$_B$, J = 17 Hz, J = 1.5 Hz), 6.23 (br d, 1H, <u>H</u>$_A$, J = 10 Hz), 6.44 (ddd, 1H, <u>H</u>$_D$, J = 17 Hz, J = 10 Hz, J = 10 Hz). *Exact Mass* calcd. for $C_{11}H_{20}IOSi$ (M^+-Me): 323.0329; found: 323.0333; cims (positive ion detection, NH_3): 339 (M^++H). *Anal.* calcd. for $C_{12}H_{23}IOSi$: C 42.60, H 6.85; found: 42.40, H 6.77.

<u>Preparation of the iodo diene **255**.</u>

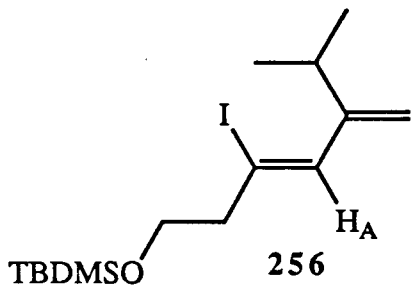


255

Following general procedure L, the stannyldiene **171** (2.96 g, 7.59 mmol; in 60 mL of dry CH_2Cl_2), was allowed to react with a solution of I_2 in dry CH_2Cl_2, at -78°C. Flash chromatography of the crude product (2:98 Et_2O - petroleum ether; 70 g of silica gel), followed by distillation of the oil thus obtained (95-100°C/0.5 Torr), gave 2.47 g (92%) of the iodo diene **255**, a pale yellow oil which exhibited ir (neat): 3086, 1256, 1107, 837 cm^{-1}; ^1H nmr (400 MHz) δ: 0.06 (s, 6H, -Si<u>Me</u>$_2$), 0.88 (s, 9H, -Si<u>Bu</u>^{t}), 1.88 (s, 3H, -<u>Me</u>), 2.75 (br t, 2H, -OCH$_2$C<u>H</u>$_2$-, J = 6.5 Hz), 3.74 (t, 2H, -OC<u>H</u>$_2$CH$_2$-, J = 6.5 Hz), 5.06 (br s,

1H), 5.07 (br s, 1H), 6.14 (br s, 1H, $\underline{H}_A$). *Exact Mass* calcd. for $C_{11}H_{16}IOSi$ (M^+-Bu^t): 295.0017; found: 295.0018; cims (positive ion detection, NH_3): 353 (M^++H).

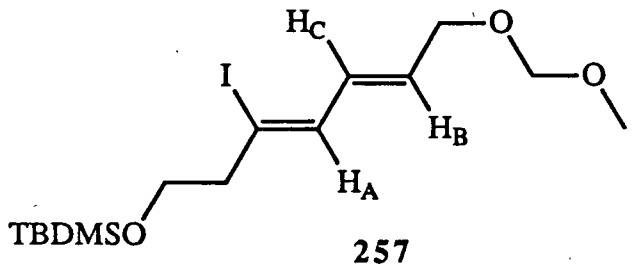
Preparation of the iodo diene **256.**



256

Following general procedure L, the stannyldiene **177** (1.376 g, 3.29 mmol; in 30 mL of dry CH_2Cl_2), was allowed to react with a solution of I_2 in dry CH_2Cl_2, at -78°C. Flash chromatography of the crude product (3:97 Et_2O - petroleum ether; 40 g of silica gel), followed by distillation of the oil thus obtained (105-110°C/0.5 Torr), gave 1.102 g (88%) of the iodo diene **256**, a pale yellow oil which exhibited ir (neat): 1472, 1256, 1109, 837, 776 cm^{-1}; ^1H nmr (300 MHz) δ: 0.05 (s, 6H, $Si\underline{Me}_2$), 0.88 (s, 9H, -$Si\underline{Bu}^t$), 1.02 (d, 6H, -$CH\underline{Me}_2$, J = 6 Hz), 1.35 (br septet, 1H, -$C\underline{H}Me_2$, J = 6 Hz), 2.74 (br t, 2H, -$OCH_2C\underline{H}_2$-, J = 6 Hz), 3.75 (t, 2H, -$OC\underline{H}_2CH_2$-, J = 6 Hz), 5.01 (br s, 1H), 5.03 (br s, 1H), 6.01 (br s, 1H, $\underline{H}_A$). *Exact Mass* calcd. for $C_{15}H_{29}IOSi$ (M^+): 380.1034; found: 380.1046.

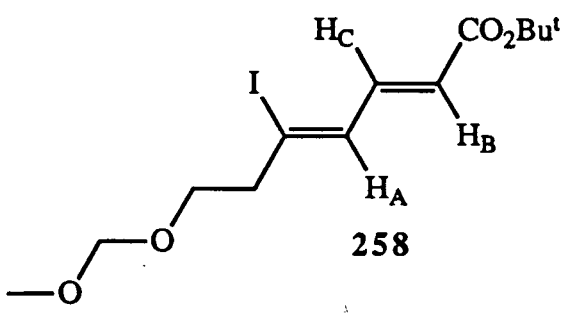
Preparation of the iodo diene **257**.



257

Following general procedure L, the stannyldiene **252** (2.80 g, 6.2 mmol; in 40 mL of dry CH_2Cl_2), was allowed to react with a solution of I_2 in dry CH_2Cl_2, at -78°C. Flash chromatography of the crude product (8:92 Et_2O - petroleum ether; 70 g of silica gel), followed by distillation of the oil thus obtained (120-130°C/0.5 Torr), gave 2.28 g (92%) of the iodo diene **257**, a pale yellow oil which exhibited ir (neat): 1461, 1105, 1043, 837 cm^{-1}; ^1H nmr (400 MHz, C_6D_6) δ: 0.08 (s, 6H, -Si<u>Me</u>$_2$), 0.98 (s, 9H, -Si<u>Bu</u>^{t}), 2.64 (br t, 2H, -OCH$_2$C<u>H</u>$_2$-, J = 7 Hz), 3.19 (s, 3H, -O<u>Me</u>), 3.67 (t, 2H, -OC<u>H</u>$_2$CH$_2$-, J = 7 Hz), 3.95 (dd, 2H, -C<u>H</u>$_2$O-, J = 5 Hz, J = 1.5 Hz), 4.50 (s, 2H, -OC<u>H</u>$_2$O-), 5.82 (dt, 1H, <u>H</u>$_B$, J = 16 Hz, J = 5 Hz), 6.08 (br d, 1H, <u>H</u>$_A$, J = 10 Hz), 6.63 (ddt, 1H, <u>H</u>$_C$, J = 16 Hz, J = 10 Hz, J = 1.5 Hz). *Exact Mass* calcd. for $C_{15}H_{29}IO_3Si$ (M^+): 412.0932; found: 412.0937.

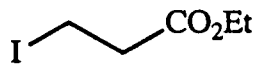
Preparation of the iodo diene **258**.



258

Following general procedure L, the stannyldiene **180** (1.80 g, 4.43 mmol; in 30 mL of dry CH_2Cl_2), was allowed to react with a solution of I_2 in dry CH_2Cl_2, at 0°C. Flash chromatography of the crude product (1:4 Et_2O - petroleum ether; 50 g of silica gel), followed by distillation of the oil thus obtained (190-200°C/0.5 Torr), gave 1.39 g (85%) of the iodo diene **258**, a pale yellow oil which exhibited ir (neat): 1708, 1260, 1137, 1063; ^1H nmr (400 MHz) δ: 1.50 (s, 9H, -$CO_2\underline{Bu}^t$), 2.88 (br t, 2H, -$OCH_2\underline{CH_2}$-, J = 7 Hz), 3.33 (s, 3H, -O$\underline{Me}$), 3.70 (t, 2H, -$OCH_2\underline{CH_2}$-, J = 7 Hz), 4.60 (s, 2H, -OCH_2O-), 5.96 (br d, 1H, $\underline{H_B}$, J = 16 Hz), 6.36 (br d, 1H, $\underline{H_A}$, J = 11 Hz), 7.28 (dd, 1H, $\underline{H_C}$, J = 16 Hz, J = 11 Hz). *Exact Mass* calcd. for $C_{13}H_{21}IO_4$ (M^+): 368.0486; found: 368.0483. *Anal.* calcd. for $C_{13}H_{21}IO_4$: C 42.41, H 5.75; found: C 42.26, H 5.67.

Preparation of ethyl 3-iodopropanoate (259)



259

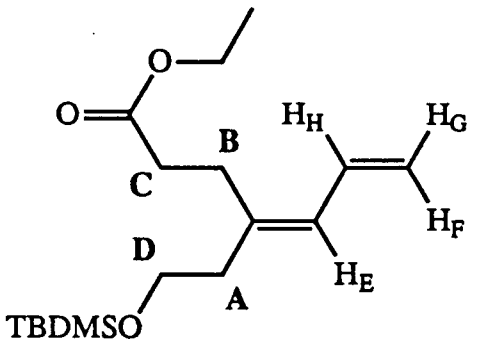
To a stirred solution of NaI (26 g, 8 equiv.) in dry acetone (150 mL) (argon atmosphere) was added ethyl 3-chloropropanoate (3g, 1 equiv.) and the mixture was allowed to reflux overnight. Most of the solvent was removed and Et_2O (50 mL) and H_2O (50 mL) were added to the residue. The phases were separated and the aqueous phase was extracted with Et_2O (3 x 30 mL). The combined organic extracts were washed with H_2O (2 x 20 mL) and then dried ($MgSO_4$) and concentrated. Flash chromatography (3:7 Et_2O - petroleum ether; 130 g of silica gel), followed by distillation of the oil thus obtained (100-110°C/6.0

Torr), gave 4.38 g (87%) of ethyl 3-iodopropanoate (**259**), a colourless oil which exhibited ir (neat): 1736, 1214, 1019 cm^{-1}; ^1H nmr (400 MHz) δ: 1.27 (t, 3H, $-OCH_2\underline{CH_3}$, J = 8 Hz), 1.96 (t, 2H, $-\underline{CH_2}CO_2Et$, J = 8 Hz), 3.32 (t, 2H, $I\underline{CH_2}-$, J = 8 Hz), 4.18 (q, 2H, $-O\underline{CH_2}CH_3$, J = 8 Hz). *Exact Mass* calcd. for $C_5H_9IO_2$ (M^+): 227.9649; found: 227.9647. This reagent decomposes slowly at room temperature and is also light sensitive. It can be stored for several months in a freezer, in the dark. The reagent was always purified immediately before use, by passing it through a short plug of silica gel (in a Pasteur pipette), followed by distillation.

General Procedure M. The preparation of the diene esters **241**[129]

A mixture of Zn-Cu couple (2.3-2.9 equiv.) and ethyl 3-iodopropanoate (1.5-1.9 equiv.) in dry benzene (2 mL per mmol of ethyl 3-iodopropanoate) and dry *N,N*-dimethylacetamide (0.133 mL per mmol of ethyl 3-iodopropanoate) (argon atmosphere) was stirred at room temperature for 1 h and at 60°C for 4 h. $Pd(PPh_3)_4$ (5 mol%) was added and stirring was continued for 5 min at 60°C. A solution of the iodo diene (1 equiv.) (freshly distilled) in dry benzene was added quickly, via syringe (the material remaining in the syringe was washed in to the reaction mixture with a small amount of dry benzene), and the resulting mixture was stirred at 60°C for 15 min. The mixture was cooled to room temperature and Et_2O (approx. 1 mL per mL of reaction solvent) was added. The mixture was filtered through a short column of Florisil® (approx. 20 g per g of iodo diene) using Et_2O as eluant. The eluate was concentrated and the residual crude oil was purified by flash chromatography, followed by distillation.

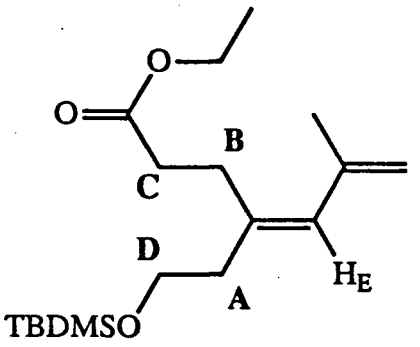
Preparation of the ester **260.**



260

Following general procedure M, ethyl 3-iodopropanoate (2.1 g, 9.2 mmol, 1.9 equiv.; in 18.5 mL of dry benzene and 1.25 mL of dry *N,N*-dimethylacetamide) was allowed to react with Zn-Cu couple (921 mg, 2.9 equiv.). To the reagent thus formed was added, successively, $Pd(PPh_3)_4$ (280 mg, 5 mol%) and a solution of the iodo diene **254** (1.63 g, 4.82 mmol, 1 equiv.) in dry benzene (4 mL initially, plus 3 mL for washings). Flash chromatography of the crude reaction product (6:94 Et_2O - petroleum ether; 70 g of silica gel), followed by distillation of the oil thus obtained (115-125°C/0.5 Torr), gave 1.313 g (87%) of the ester **260**, a colourless oil which exhibited ir (neat): 3085, 1737, 1473, 1256, 1098, 837 cm^{-1}; ^1H nmr (400 MHz, C_6D_6) δ: 0.09 (s, 6H, -SiMe2), 1.02 (s, 9H, -SiBu^t), 1.02 (t, 3H, $-OCH_2CH_3$, J = 8 Hz), 2.24 (br t, 2H, methylene **A**, J = 7 Hz), 2.34 (m, 2H, methylene **B**), 2.58 (br t, 2H, methylene **C**, J = 7 Hz), 3.63 (t, 2H, methylene **D**, J = 7 Hz), 4.01 (q, 2H, $-OCH_2CH_3$, J = 8 Hz), 5.03 (dd, 1H, HG, J = 10 Hz, J = 2 Hz), 5.16 (dd, 1H, HF, J = 16 Hz, J = 2 Hz), 5.98 (br d, 1H, HE, J = 10 Hz), 6.65 (ddd, 1HH, J = 16 Hz, J = 10 Hz, J = 10 Hz). *Exact Mass* calcd. for $C_{17}H_{32}O_3Si$ (M^+): 312.2121; found: 312.2115. *Anal.* calcd. for $C_{17}H_{32}O_3Si$: C 65.33, H 10.32; found: C 65.50, H 10.50.

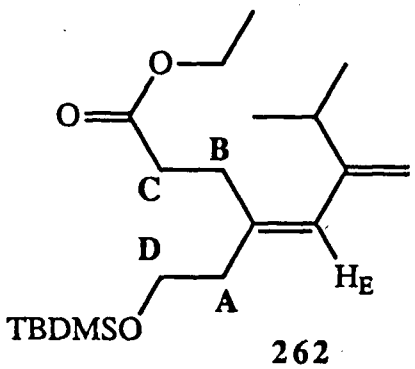
Preparation of the ester **261**.



261

Following general procedure M, ethyl 3-iodopropanoate (1.65 g, 7.24 mmol, 1.5 equiv.; in 14.5 mL of dry benzene and 1 mL of dry *N,N*-dimethylacetamide) was allowed to react with Zn-Cu couple (720 mg, 2.3 equiv.). To the reagent thus formed was added, successively, $Pd(PPh_3)_4$ (280 mg, 5 mol%) and a solution of the iodo diene **255** (1.70 g, 4.83 mmol, 1 equiv.) in dry benzene (4 mL initially, plus 3 mL for washings). Flash chromatography of the crude reaction product (8:92 Et_2O - petroleum ether; 70 g of silica gel), followed by distillation of the oil thus obtained (125-135°C/0.5 Torr), gave 1.22 g (77%) of the ester **261**, a colourless oil which exhibited ir (neat): 3083, 1736, 1473, 1095, 838 cm^{-1}; ^1H nmr (400 MHz, C_6D_6) δ: 0.09 (s, 6H, -SiMe2), 0.99 (t, 3H, -OCH_2CH_3, J = 7 Hz), 1.00 (s, 9H, -SiBu^t), 1.81 (s, 3H, -Me), 2.24 (br t, 2H, methylene **A**, J = 6.5 Hz), 2.41 (m, 2H, methylene **B**), 2.75 (br t, 2H, methylene **C**, J = 8 Hz), 3.66 (t, 2H, methylene **D**, J = 6.5 Hz), 3.99 (q, 2H, -OCH_2CH_3, J = 7 Hz), 4.95 (br s, 1H, H_G), 4.97 (br s, 1H, H_F), 5.80 (br s, 1H, H_E). In nOe difference experiments, irradiation at δ 5.80 (H_E) caused signal enhancement at δ 2.24 (methylene **A**) and at δ 1.81 (vinyl Me); irradiation at δ 2.24 (methylene **A**) caused signal enhancement at δ 5.80 (H_E) and at δ 3.66 (methylene **D**); irradiation at δ 1.81 (vinyl Me) caused signal enhancement at δ 5.80 (H_E) and at δ 4.97 (H_F). *Exact Mass* calcd. for $C_{18}H_{34}O_3Si$ (M^+): 326.2277; found: 326.2277.

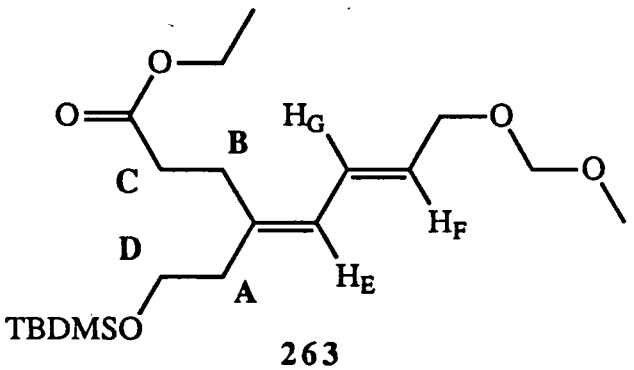
Preparation of the ester **262**.



262

Following general procedure M, ethyl 3-iodopropanoate (1.04 g, 4.56 mmol, 1.5 equiv.; in 9 mL of dry benzene and 0.6 mL of dry *N,N*-dimethylacetamide) was allowed to react with Zn-Cu couple (457 mg, 2.3 equiv.). To the reagent thus formed was added, successively, $Pd(PPh_3)_4$ (176 mg, 5 mol%) and a solution of the iodo diene **256** (1.16 g 3.05 mmol, 1 equiv.) in dry benzene (3 mL initially, plus 2 mL for washings). Flash chromatography of the crude reaction product (6:94 Et_2O - petroleum ether; 60 g of silica gel), followed by distillation of the oil thus obtained (140-150°C/0.5 Torr), gave 800 mg (74%) of the ester **262**, a colourless oil which exhibited ir (neat): 3088, 1737, 1099, 837 cm^{-1}; ^1H nmr (400 MHz, C_6D_6) δ: 0.10 (s, 6H, -Si<u>Me</u>2), 1.00 (t, 3H, -OCH2C<u>H</u>3, *J* = 7 Hz), 1.01 (s, 9H, -Si<u>Bu</u>^{t}), 1.04 (d, 6H, -CH<u>Me</u>2, *J* = 7 Hz), 2.26-2.30 (m, 3H, -C<u>H</u>Me2 and methylene **A**), 2.44 (m, 2H, methylene **B**), 2.77 (br t, 2H, methylene **C**, *J* = 8 Hz), 3.70 (t, 2H, methylene **D**, *J* = 6.5 Hz), 3.99 (q, 2H, -OC<u>H</u>2CH3, *J* = 7 Hz), 4.91 (br s, 1H), 5.02 (br s, 1H), 5.84 (br s, 1H, <u>H</u>E). *Exact Mass* calcd. for $C_{20}H_{38}O_3Si$ (M^+): 354.2590; found: 354.2597. *Anal.* calcd. for $C_{20}H_{38}O_3Si$: C 67.74, H 10.80; found: C 67.99, H 10.79.

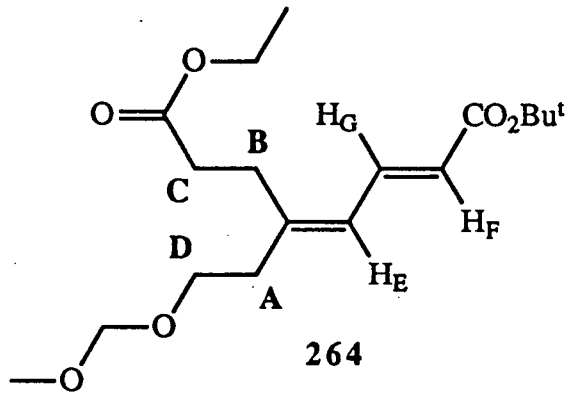
Preparation of the ester **263**.



263

Following general procedure M, ethyl 3-iodopropanoate (1.452 g, 6.37 mmol, 1.9 equiv.; in 13 mL of dry benzene and 0.9 mL of dry *N,N* -dimethylacetamide) was allowed to react with Zn-Cu couple (640 mg, 2.9 equiv.). To the reagent thus formed was added, successively, $Pd(PPh_3)_4$ (200 mg, 5 mol%) and a solution of the iodo diene **257** (1.40 g, 3.40 mmol, 1 equiv.) in dry benzene (3 mL initially, plus 3 mL for washings). Flash chromatography of the crude reaction product (1:4 Et_2O - petroleum ether; 60 g of silica gel), followed by distillation of the oil thus obtained (140-150°C/0.5 Torr), gave 860 mg (65%) of the ester **263**, a colourless oil which exhibited ir (neat): 1737, 1150, 1103, 838 cm^{-1}; ^1H nmr (400 MHz, C_6D_6) δ: 0.08 (s, 6H, -SiMe2), 1.01 (t, 3H, $-OCH_2\underline{CH_3}$, J = 8 Hz), 1.10 (s, 9H, -SiBu^t), 2.25 (br t, 2H, methylene **A**, J = 7 Hz), 2.35 (br t, 2H, methylene **B**, J = 8 Hz), 2.60 (br t, 2H, methylene **C**, J = 8 Hz), 3.23 (s, 3H, -OMe), 3.65 (t, 2H, methylene **D**, J = 7 Hz), 4.00 (q, 2H, $-OC\underline{H_2}CH_3$, J = 8 Hz), 4.09 (br d, 2H, $-C\underline{H_2}O-$, J = 6 Hz), 4.57 (s, 2H, $-OC\underline{H_2}O-$), 5.75 (dt, 1H, HF, J = 16 Hz, J = 6 Hz), 5.98 (br d, 1H, HE, J = 10 Hz), 6.67 (ddt, 1H, HG, J = 16 Hz, J = 10 Hz, J = 1.5 Hz). *Exact Mass* calcd. for $C_{19}H_{35}O_5Si$ (M^+-Me): 371.2254; found: 371.2248; cims (positive ion detection , NH_3): 387 (M^++H).

Preparation of the ester **264**.



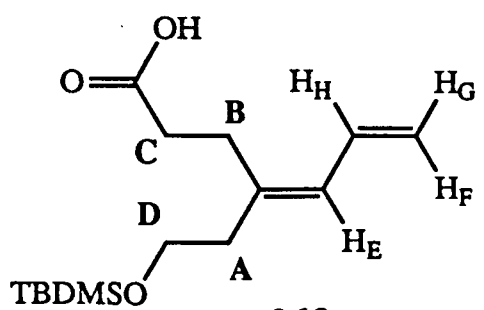
264

Following general procedure M, ethyl 3-iodopropanoate (631 mg, 2.76 mmol, 1.75 equiv.; in 5.5 mL of dry benzene and 0.4 mL of dry *N,N*-dimethylacetamide) was allowed to react with Zn-Cu couple (277 mg, 2.7 equiv.). To the reagent thus formed was added, successively, $Pd(PPh_3)_4$ (91 mg, 5 mol%) and a solution of the iodo diene **258** (580 mg, 1.58 mmol, 1 equiv.) in dry benzene (2 mL initially, plus 1.5 mL for washings). Flash chromatography of the crude reaction product (3:7 Et_2O - petroleum ether; 40 g of silica gel), followed by distillation of the oil thus obtained (190-200°C/0.5 Torr), gave 470 mg (87%) of the ester **264**, a colourless oil which exhibited ir (neat): 1736, 1708, 1636, 1110 cm^{-1}; ^1H nmr (400 MHz, C_6D_6) δ: 1.02 (t, 3H, $-OCH_2\underline{CH_3}$, J = 7 Hz), 1.49 (s, 9H, $-CO_2\underline{Bu^t}$), 2.18 (br t, 2H, methylene **A**, J = 7 Hz), 2.21 (br t, 2H, methylene **B**, J = 7 Hz), 2.50 (br t, 2H, methylene **C**, J = 7 Hz), 3.14 (s, 3H, -O<u>Me</u>), 3.42 (t, 2H, methylene **D**, J = 7 Hz), 3.96 (q, 2H, $-OC\underline{H_2}CH_3$, J = 7 Hz), 4.43 (s, 2H, $-OC\underline{H_2}O-$), 5.93 (br d, 1H, $\underline{H_E}$, J = 11 Hz), 5.95 (d, 1H, $\underline{H_F}$, J = 16 Hz), 7.89 (dd, 1H, $\underline{H_G}$, J = 16 Hz, J = 11 Hz). *Exact Mass* calcd. for $C_{18}H_{30}O_6$ (M^+): 342.2042; found: 342.2040. *Anal.* calcd. for $C_{18}H_{30}O_6$: C 63.14, H 8.83; found: C 63.34, H 8.80.

General Procedure N. The preparation of the diene acids **242**

A mixture of saturated aqueous K_2CO_3 and MeOH (1:1 v:v) was made homogeneous by dropwise addition of H_2O. Addition of this solution to the ester (approx. 8 mL per mmol of the ester) at room temperature, gave a heterogeneous mixture, which was made homogeneous by the addition of MeOH (and H_2O, to re-dissolve any K_2CO_3 which may precipitate). The solution thus obtained was stirred at room temperature until the reaction was complete (by tlc analysis). Et_2O and H_2O were added, until a two-phase mixture was obtained. The phases were separated and the ethereal layer was extracted with H_2O. The combined aqueous extracts were washed with Et_2O and were then cooled (using a -20°C cooling bath). Aqueous HCl (10%) was added, dropwise, to the cold, stirred solution, until it was neutral. The aqueous solution was then extracted exhaustively with Et_2O. The combined organic extracts were washed with H_2O and then dried and concentrated. The residual oil thus obtained contained some MeOH, which was removed at reduced pressure (0.5 Torr, room temperature), to give the essentially pure carboxylic acid.

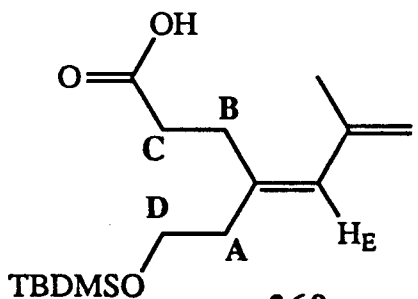
Preparation of the acid **268.**



268

Following general procedure N, a mixture of aqueous K_2CO_3 and MeOH (30 mL) was added to the ester **260** (1.313 g, 4.21 mmol) and the resulting heterogeneous mixture was made homogeneous by the addition of MeOH and H_2O. The mixture was stirred overnight at room temperature to give, after workup, 1.015 g (85%) of the carboxylic acid **268**, a colourless oil which exhibited ir (neat): 2400-3700, 1713, 1099, 837, 777 cm^{-1}; ^1H nmr (400 MHz, C_6D_6) δ: 0.07 (s, 6H, -Si<u>Me</u>2), 0.99 (s, 9H, -Si<u>Bu</u>^{t}), 2.17 (br t, 2H, methylene **A**, J = 6.5 Hz), 2.28 (m, 2H, methylene **B**), 2.48 (br t, 2H, methylene **C**, J = 8 Hz), 3.59 (t, 2H, methylene **D**, J = 6.5 Hz), 5.02 (dd, 1H, <u>H</u>G, J = 10 Hz, J = 2 Hz), 5.14 (dd, 1H, <u>H</u>F, J = 17 Hz, J = 2 Hz), 5.94 (br d, 1H, <u>H</u>E, J = 11 Hz), 6.58 (ddd, 1H, <u>H</u>H, J = 17 Hz, J = 11 Hz, J = 10 Hz). *Exact Mass* calcd. for $C_{15}H_{28}O_3Si$ (M^+): 284.1808; found: 284.1800. *Anal.* calcd. for $C_{15}H_{28}O_3Si$: C 63.33, H 9.92; found: C 63.28, H 9.87.

<u>Preparation of the acid 269</u>

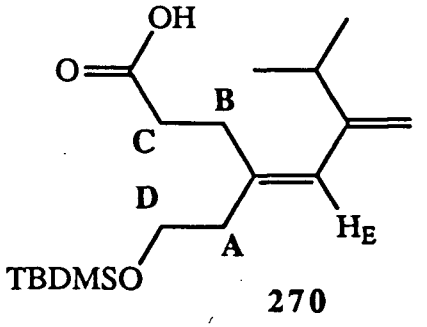


269

Following general procedure N, a mixture of aqueous K_2CO_3 and MeOH (5 mL) was added to the ester **261** (200 mg, 0.61 mmol) and the resulting heterogeneous mixture was made homogeneous by the addition of MeOH and H_2O. The mixture was stirred

overnight at room temperature to give, after workup, 150 mg (82%) of the carboxylic acid **269**, a colourless oil which exhibited ir (neat): 2400-3400, 1713, 1099, 837 cm^{-1}; ^1H nmr (400 MHz, C_6D_6) δ: 0.08 (s, 6H, -SiMe2), 1.00 (s, 9H, -SiBu^t), 1.78 (br s, 3H, -Me), 2.18 (br t, 2H, methylene **A**, *J* = 6.5 Hz), 2.35 (br t, 2H, methylene **B**, *J* = 8 Hz), 2.67 (br t, 2H, methylene **C**, *J* = 8 Hz), 3.63 (t, 2H, methylene **D**, *J* = 6.5 Hz), 4.90 (br s, 1H), 4.96 (br s, 1H), 5.78 (br s, 1H, H_E). *Exact Mass* calcd.for $C_{12}H_{21}O_3Si$ (M^+-Bu^t): 241.1260; found: 241.1258; cims (positive ion detection, CH_4): 299 (M^++H). *Anal.* calcd. for $C_{16}H_{30}O_3Si$: C 64.38, H 10.13; found: C 64.50, H 10.18.

Preparation of the acid **270**

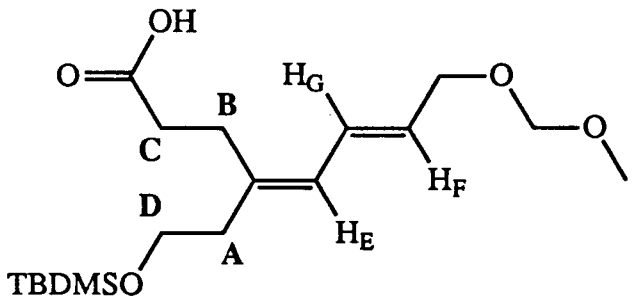


270

Following general procedure N, a mixture of aqueous K_2CO_3 and MeOH (10 mL) was added to the ester **262** (433 mg, 1.22 mmol) and the resulting heterogeneous mixture was made homogeneous by the addition of MeOH and H_2O. The mixture was stirred overnight at room temperature to give, after workup, 318 mg (80%) of the carboxylic acid **270**, a colourless oil which exhibited ir (neat): 2400-3600, 1713, 1463, 1288, 899, 777 cm^{-1}; ^1H nmr (400 MHz, C_6D_6) δ: 0.10 (s, 6H, -SiMe2, 1.02 (s, 9H, -SiBu^t), 1.04 (d, 6H, -CHMe2, *J* = 7 Hz), 2.20 -2.35 (m, 3H, -CHMe2 and methylene **A**), 2.38 (m, 2H,

methylene **B**), 2.70 (br t, 2H, methylene **C**, J = 8 Hz), 3.68 (t, 2H, methylene **D**, J = 6.5 Hz), 4.85 (br s, 1H), 5.01 (br s, 1H), 5.82 (br s, 1H, $\underline{H}_E$). *Exact Mass* calcd. for $C_{18}H_{34}O_3Si$ (M^+): 326.2277; found: 326.2272. *Anal.* calcd. for $C_{18}H_{34}O_3Si$: C 66.21, H 10.50; found: C 66.20, H 10.61.

Preparation of the acid **271**.

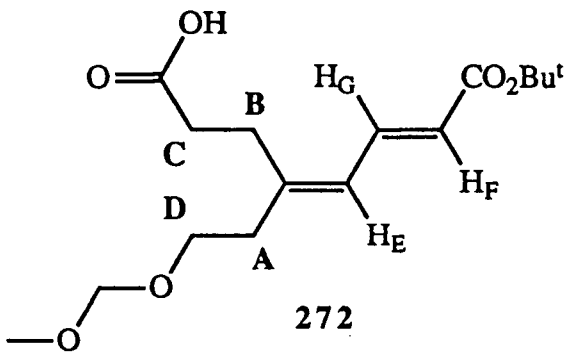


271

Following general procedure N, a mixture of aqueous K_2CO_3 and MeOH (5 mL) was added to the ester **263** (250 mg, 0.65 mmol) and the resulting heterogeneous mixture was made homogeneous by the addition of MeOH and H_2O. The mixture was stirred overnight at room temperature to give, after workup, 196 mg (84%) of the carboxylic acid **271**, a colourless oil which exhibited ir (neat): 2400-3400, 1708, 1256, 1150, 778 cm^{-1}; ^1H nmr (400 MHz, C_6D_6) δ: 0.08 (s, 6H, -Si$\underline{Me}_2$), 1.00 (s, 9H, -Si$\underline{Bu}^t$), 2.19 (br t, 2H, methylene **A**, J = 6.5 Hz), 2.26 (br t, 2H, methylene **B**, J = 8 Hz), 2.50 (br t, 2H, methylene **C**, J = 8 Hz), 3.21 (s, 3H, -O$\underline{Me}$), 3.61 (t, 2H, methylene **D**, J = 6.5 Hz), 4.07 (dd, 2H,-C$\underline{H}_2$O-, J = 6 Hz, J = 1.5 Hz), 4.58 (s, 2H, -OC$\underline{H}_2$O-), 5.71 (dt, 1H, $\underline{H}_F$, J = 16 Hz, J = 6 Hz), 5.96 (br d, 1H, $\underline{H}_E$, J = 11 Hz), 6.64 (ddd, $\underline{H}_G$, J = 16 Hz, J = 11 Hz, J = 1.5 Hz). *Exact Mass* calcd. for $C_{16}H_{29}O_3Si$ (M^+-$C_2H_5O_2$): 297.1886; found:

297.1891; cims (positive ion detection, NH_3): 395 (M^++H). *Anal.* calcd. for $C_{18}H_{34}O_5Si$: C 60.30, H 9.56; found: C 60.18, H 9.70.

Preparation of the acid **272**



272

Following general procedure N, a mixture of aqueous K_2CO_3 and MeOH (5 mL) was added to the ester **264** (210 mg, 0.61 mmol) and the resulting heterogeneous mixture was made homogeneous by the addition of MeOH and H_2O. The mixture was stirred overnight at room temperature to give, after workup, 158 mg (82%) of the carboxylic acid **272**, a colourless oil which exhibited ir (neat): 2500-3600, 1708, 1636, 1146, 1038 cm^{-1}; ^1H nmr (400 MHz, C_6D_6) δ: 1.49 (s, 9H, -$CO_2\underline{Bu^t}$), 2.15 (br t, 2H, methylene **A**, J = 6 Hz), 2.23 (br t, 2H, methylene **B**, J = 8 Hz), 2.51 (br t, 2H, methylene **C**, J = 8 Hz), 3.18 (s, 3H, -O<u>Me</u>), 3.43 (t, 2H, methylene **D**, J = 6 Hz), 4.44 (s, 2H, -OC<u>H</u>$_2$O-), 5.94 (br d, 1H, <u>H</u>$_E$, J = 11 Hz), 5.97 (br d, 1H, <u>H</u>$_F$, J = 16 Hz), 7.91 (dd, 1H, <u>H</u>$_G$, J = 16 Hz, J = 11 Hz). *Exact Mass* calcd. for $C_{11}H_{14}O_5$ (M^+-$C_5H_{12}O$): 226.0841; found: 226.0846; cims (positive ion detection, CH_4): 315 (M^++H).

Preparation of an ethereal solution of diazomethane[147]

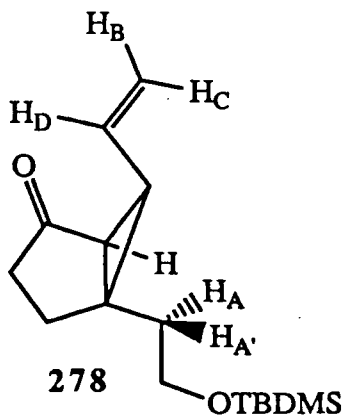
This preparation was carried out in a specially designed apparatus (available from Aldrich Chemical Co.), that has no ground glass joints. The reaction was performed in a fume hood and the apparatus was set up behind a blast shield. To a stirred mixture of Et_2O (5 mL) , diethylene glycol monomethyl ether (17 mL) and a solution of KOH (3 g) in H_2O (5 mL) at 70°C (using a water bath as heat source) was added slowly (over approx. 30 min), via dropping funnel, a solution of Diazald® (10.7 g) in Et_2O (65 mL). During this period, a yellow ethereal solution of diazomethane distilled into a cooled (0°C) round-bottom flask. Diethyl ether (approx. 20 mL) was added to the stillpot mixture (via dropping funnel), until no more diazomethane was generated (at this point the distillate was colourless). The yellow distillate was dried (Na_2SO_4 - this is the only drying agent that should be used) and was used immediately. The amount of diazomethane generated by this procedure was approx. 1.5 g (i.e. approx. 33 mmol in approx. 85 mL of Et_2O).

General Procedure O. The preparation of the diene diazoketones **240**

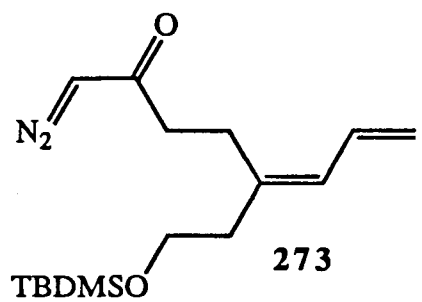
To a stirred solution of the carboxylic acid (1 equiv.) in dry, freshly distilled hexane (argon atmosphere, room temperature) was added oxalyl chloride (3 equiv.). After the mixture had been refluxed for 2 h, it was allowed to cool to room temperature and the solvent was removed. Any remaining volatile material was removed under reduced pressure (0.5 Torr, room temperature), and then dry Et_2O was added to the residue (argon atmosphere). The solution of the acid chloride thus obtained was used immediately. To a

cold (0°C), stirred solution of diazomethane (excess) in Et_2O (argon atmosphere) was added a small amount of drying agent (Na_2SO_4). To this solution was added slowly, via cannula, the solution of the acid chloride in Et_2O, resulting in rapid effervescence. Stirring was continued at 0°C for 30 min and at room temperature for 45 min. Excess diazomethane was removed from the mixture by bubbling argon through the solution for approx. 30 min (using a flame polished pasteur pipette as gas inlet). The solution was dried ($MgSO_4$) and concentrated, to give the crude diazoketone, a viscous bright yellow oil. The diazoketone was purified by rapid chromatography (silica gel). The diazoketones were stable in a freezer (in the dark) for several weeks, although they were generally used immediately.

Preparation of the diazoketone **273**. The conversion of **273** into the ketone **278**.



278



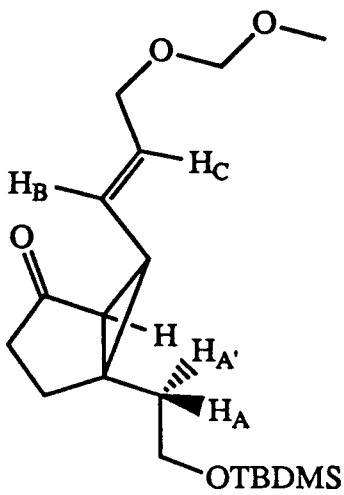
273

Following general procedure O, the carboxylic acid **268** (700 mg, 1 equiv., 2.46 mmol) in dry hexane (14 mL) was allowed to react with oxalyl chloride (0.94 g, 3 equiv.). A solution of the resulting crude acid chloride in dry Et_2O (approx. 15 mL, including washings) was added to a solution of diazomethane in Et_2O (approx. 50 mL,

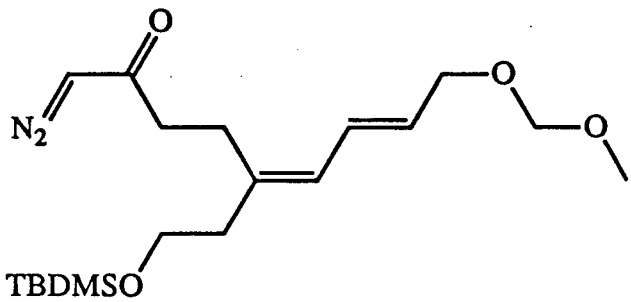
approx. 8 equiv.). The crude product thus obtained was purified by rapid chromatography (35:65 Et_2O - petroleum ether; 35 g of silica gel), to give 611 mg (81%) of essentially pure (tlc analysis) diazoketone **273**. This compound was used immediately.

A solution of the diazoketone **273** (611 mg, 1.98 mmol, 1 equiv.) in dry benzene (15 mL) was added slowly (over approx. 30 min) via syringe pump to a refluxing suspension of $CuSO_4$ (1 equiv., 317 mg) and $Cu(acac)_2$ (32 mg) in dry benzene (15 mL) (argon atmosphere). After the mixture had been refluxed for 15 min, it was allowed to cool to room temperature and then most of the benzene was removed. The residue was passed through a short column of Florisil® (15 g), using Et_2O as eluant. The combined eluate was concentrated and the crude oil thus obtained was purified by flash chromatography (3:7 Et_2O - petroleum ether; 40 g of silica gel). Distillation of the oil thus obtained (115-120°C/0.5 Torr) gave 481 mg (87%; 70% from the acid **268**) of the ketone **278**, a colourless oil which exhibited ir (neat): 3084, 3045, 1719, 1472, 1099, 776 cm^{-1}; ^1H nmr (400 MHz, C_6D_6) δ: 0.06 (s, 6H, -Si$\underline{Me}_2$), 0.99 (s, 9H, -Si$\underline{Bu}^t$), 1.22 (dt, 1H, $\underline{H}_A$ or $\underline{H}_{A'}$, J = 14 Hz, J = 6 Hz), 1.59 (dt, 1H, $\underline{H}_A$ or $\underline{H}_{A'}$, J = 14 Hz, J = 6 Hz), 1.64-1.84 (overlapping m, 5H), 2.07 (m, 1H), 3.48 (t, 2H, -OC$\underline{H}_2$CH_2-. J = 6 Hz), 5.08 (ddd, 1H, $\underline{H}_B$, J = 10 Hz, J = 2 Hz, J = 1 Hz), 5.24 (ddd, 1H, $\underline{H}_C$, J = 16 Hz, J = 2 Hz, J = 1 Hz), 5.51 (ddd, 1H, $\underline{H}_D$, J = 16 Hz, J = 10 Hz, J = 6 Hz). *Exact Mass* calcd. for $C_{18}H_{28}O_2Si$ (M^+): 280.1858; found: 280.1859. *Anal.* calcd. for $C_{16}H_{28}O_2Si$: C 68.53, H 10.07; found: C 68.80, H 9.93.

Preparation of the diazoketone **276**. The conversion of **276** into the ketone **279**.



279



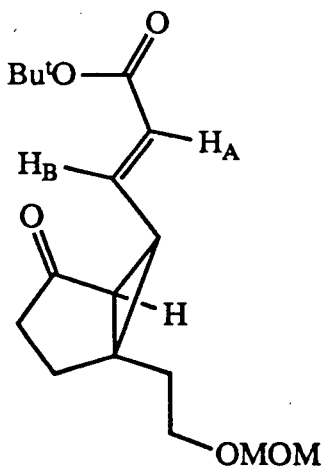
276

Following general procedure O, the carboxylic acid **271** (194 mg, 1 equiv., 0.54 mmol) in dry hexane (5 mL) was allowed to react with oxalyl chloride (207 mg, 3 equiv.). A solution of the resulting crude acid chloride in dry Et_2O (approx. 5 mL, including washings) was added to a solution of diazomethane in Et_2O (approx. 12 mL, approx. 8 equiv.). The crude product thus obtained was purified by rapid chromatography (1:1 Et_2O - petroleum ether; 30 g of silica gel), to give 179 mg (86%) of essentially pure (tlc analysis) diazoketone **276**. This compound was used immediately.

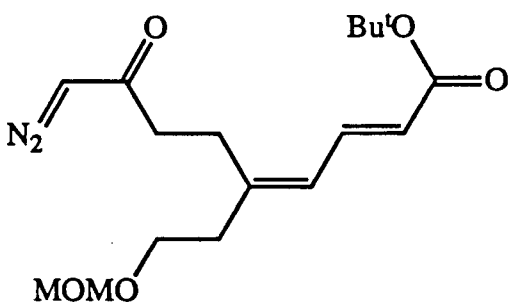
A solution of the diazoketone **276** (179 mg, 0.47 mmol, 1 equiv.) in dry benzene (4 mL) was added slowly (over approx. 30 min) via syringe pump, to a refluxing suspension of $CuSO_4$ (1 equiv., 75 mg) and $Cu(acac)_2$ (8 mg) in dry benzene (4 mL) (argon atmosphere). After the mixture had been refluxed for 15 min it was allowed to cool to room temperature, and most of the benzene was removed. The mixture was passed through a plug of Florisil® (5 g), using Et_2O as eluant. The combined eluate was concentrated and the crude oil thus obtained was purified by flash chromatography (35:65 Et_2O - petroleum ether;

30 g of silica gel). Distillation of the oil thus obtained (160-170°C/0.5 Torr) gave 150 mg (90% ; 78% from the acid **271**) of the ketone **279**, a colourless oil which exhibited ir (neat): 1719, 1472, 1256, 1151, 837, 778 cm^{-1}; ^1H nmr (400 MHz, C_6D_6) δ: 0.07 (s, 6H, -SiMe2), 1.00 (s, 9H, -SiBu^t), 1.27 (dt, 1H, H_A or H_A', J = 14 Hz, J = 6 Hz), 1.62 (dt, 1H, H_A or H_A', J = 14 Hz, J = 6 Hz), 1.66-1.93 (m, 5H), 2.09 (m, 1H), 3.21 (s, 3H, -OMe), 3.51 (t, 2H, -OCH2CH2-, J = 6 Hz), 3.96 (br d, 2H, -CH2O-, J = 6 Hz), 4.52 (s, 2H, -OCH2O-), 5.58 (br dd, 1H, H_B, J = 16 Hz, J = 6 Hz), 5.84 (dtd, 1H, H_C, J = 16 Hz, J = 6 Hz, J = 1 Hz). *Exact Mass* calcd. for $C_{19}H_{34}O_4Si$ (M^+): 354.2227; found; 354.2231. *Anal.* calcd. for $C_{19}H_{34}O_4Si$: C 64.36, H 9.67; found: C 64.42, H 9.76.

Preparation of the diazoketone **277**. The conversion of **277** into the ketone **280**.



280



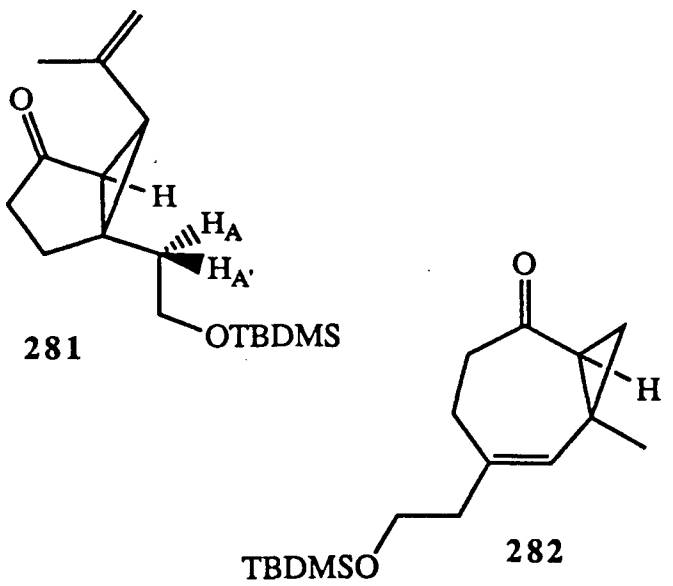
277

Following general procedure O, the carboxylic acid **272** (257 mg, 1 equiv., 0.82 mmol) in dry hexane (8 mL) was allowed to react with oxalyl chloride (312 mg, 3 equiv.). A solution of the resulting crude acid chloride in dry Et2O (approx. 8 mL,

including washings) was added to a solution of diazomethane in Et_2O (approx. 15 mL, approx. 8 equiv.). The crude product thus obtained was purified by rapid chromatography (3:1 Et_2O - petroleum ether; 30 g of silica gel), to give 207 mg (75%) of essentially pure (tlc analysis) diazoketone **277**. This compound was used immediately.

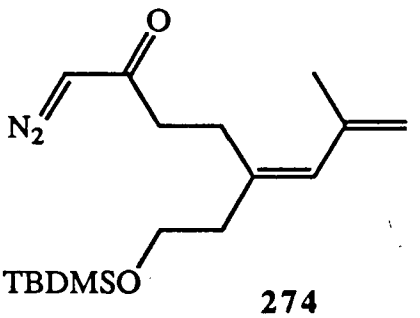
To a cold (0°C), stirred solution of the diazoketone **277** (100 mg, 0.30 mmol) in dry CH_2Cl_2 (8 mL) (argon atmosphere) was added $Rh_2(OAc)_4$ (4 mg, 3 mol%). After the mixture had been stirred at 0°C for 5 min and at room temperature for 30 min, the solvent was removed and the residual oil was purified by flash chromatography (3:7 Et_2O - petroleum ether; 25 g of silica gel). Distillation of the oil thus obtained (190-200°C/0.5 Torr), gave 69 mg (75%, 56 % from the acid **272**) of the ketone **280**, a colourless oil which exhibited ir (neat): 1718, 1640, 1148, 1109 cm^{-1}; ^1H nmr (400 MHz, C_6D_6) δ: 1.20 (m, 1H), 1.43 (s, 9H, $-CO_2\underline{Bu}^t$), 1.45-1.57 (m, 2H), 1.58-1.70 (m, 2H), 1.78-1.88 (m, 2H), 1.97 (m, 1H), 3.15 (s, 3H, -O<u>Me</u>), 3.28 (t, 2H, $-OC\underline{H}_2CH_2-$, J = 6 Hz), 4.38 (s, 2H, $-OC\underline{H}_2O-$, 6.08 (d, 1H, $\underline{H}_A$, J = 15 Hz), 6.87 (dd, 1H, $\underline{H}_B$, J = 15 Hz, J = 8 Hz). *Anal.* calcd. for $C_{17}H_{26}O_5$: C 65.78, H 8.44; found: C 65.58, H 8.60.

<u>Preparation of the diazoketone **274**. The conversion of **274** into the ketones **281** and **282**.</u>



281

282



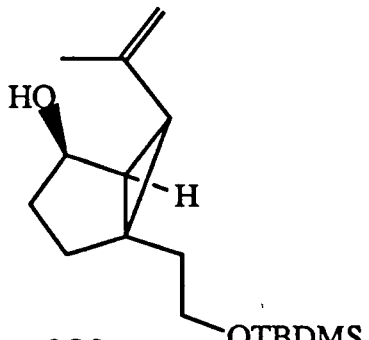
274

Following general procedure O, the carboxylic acid **269** (198 mg, 1 equiv., 0.66 mmol) in dry hexane (4 mL) was allowed to react with oxalyl chloride (253 mg, 3 equiv.). A solution of the resulting crude acid chloride in dry Et_2O (approx. 5 mL, including washings) was added to a solution of diazomethane in Et_2O (approx. 15 mL, approx. 8 equiv.). The crude product thus obtained was purified by rapid chromatography (35:65 Et_2O - petroleum ether; 30 g of silica gel), to give 160 mg (75%) of essentially pure (tlc analysis) diazoketone **274**. This compound was used immediately.

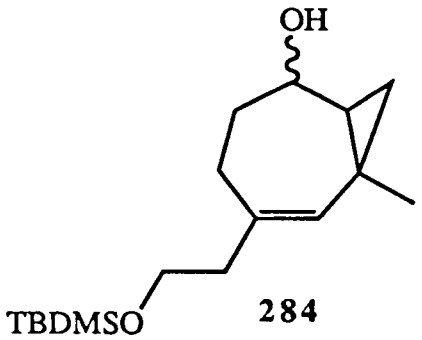
(a) A solution of the diazoketone **274** (160 mg, 0.50 mmol, 1 equiv.) in dry benzene (4 mL) was added slowly (over approx. 30 min) via syringe pump, to a refluxing suspension of $CuSO_4$ (1 equiv., 80 mg) and $Cu(acac)_2$ (8 mg) in dry benzene (4 mL) (argon atmosphere). After the mixture had been refluxed for 15 min, it was allowed to cool to room temperature, and then most of the benzene was removed. The mixture was passed through a plug of Florisil® (5 g), using Et_2O as eluant. The combined eluate was concentrated and the residual oil was purified by flash chromatography (3:7 Et_2O - petroleum ether; 30 g of silica gel). Distillation of the oil thus obtained (130-135°C/0.5 Torr) gave 93 mg (64% ; 48% from the acid **269**) of a mixture (1:1 by glc analysis) of the ketones **281** and **282**, which was inseparable by column chromatography.

(b) To a cold (-78°C), stirred solution of the diazoketone **274** (62 mg, 0.19 mmol) in dry CH_2Cl_2 (3 mL) (argon atmosphere) was added $Rh_2(OAc)_4$ (4 mg, 5 mol%). After the mixture had been stirred at -78°C for 10 min it was allowed to warm to room temperature, over 4 h. The solvent was removed and the residual oil was purified by flash chromatography (3:7 Et_2O - petroleum ether; 25 g of silica gel). Distillation of the oil thus obtained gave 44 mg (78%, 59 % from the acid **269**) of a mixture of the ketones **281** and **282** (4:1 respectively, by glc analysis).

Characterization of the ketone **281**



283

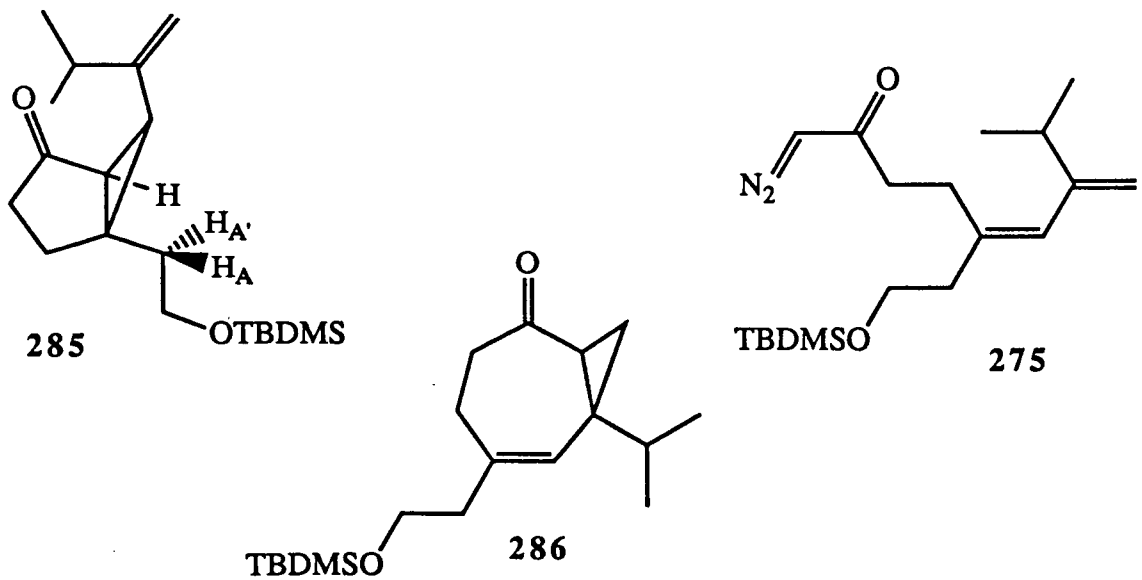


284

To a cold (-78°C), stirred solution of the mixture of ketones **281** and **282** (45 mg, 0.15 mmol, 4:1 by glc analysis) in dry THF (2 mL) (argon atmosphere) was added a solution of diisobutylaluminium hydride (2 equiv.) in hexane. After the mixture had been stirred for 1 h at -78°C and for 10 min at 0°C, saturated aqueous NH_4Cl (approx. 0.2 mL) was added and the vigorously stirred mixture was exposed to air and was allowed to warm to room temperature. To the resulting suspension was added diethyl ether (approx. 1 mL) and drying agent ($MgSO_4$) and the mixture was suction filtered through a short pad (3 g) of Florisil®, using Et_2O as eluant. The combined eluate was concentrated and the resulting oil was purified by flash chromatography (3:7 Et_2O - petroleum ether; 25 g of silica gel), to give 32 mg (66%) of the alcohol **283** (traces of solvent were removed under reduced pressure; 0.5 Torr/25°C), and 9 mg (20%) of the alcohols **284** (traces of solvent were removed under reduced pressure; 0.5 Torr/25°C). The alcohol **283** was a colourless oil which exhibited ir (neat): 3389, 1255, 1064, 837 cm^{-1}; ^1H nmr (400 MHz, C_6D_6), 0.11 (s, 6H, -Si<u>Me</u>$_2$), 1.04 (s, 9H, -Si<u>Bu</u>^{t}), 1.21 (m, 1H), 1.30-1.48 (m, 3H), 1.59-1.79 (m, 2H), 1.80-1.88 (m, 1H), 2.01 (m, 1H), 2.08 (br s, 3H, -<u>Me</u>), 3.70 (m, 2H, -OC<u>H</u>$_2$CH$_2$-), 4.48 (m, 1H, -C<u>H</u>OH), 4.98 (br s, 1H), 5.24 (br s, 1H). *Exact mass* calcd. for $C_{17}H_{30}O_2Si$ (M^+): 296.2171; found: 296.2165.

To a stirred solution of the alcohol **283** (30 mg, 0.1 mmol) in dry CH_2Cl_2 (2 mL) (argon atmosphere, room temperature) was added *N*-methylmorpholine *N* -oxide (30 mg, 2.5 equiv.) and activated 4Å molecular sieves. The resulting suspension was stirred for 10 min at room temperature and then TPAP[133] (4 mg, 5 mol%) was added. After the mixture had been stirred for 45 min at room temperature it was filtered through a short column of Florisil® (approx. 5 g) using Et_2O as eluant. The combined eluate was concentrated and the resulting oil was purified by flash chromatography (1:4 Et_2O - petroleum ether; 20 g of silica gel). Distillation (130-135°C/0.5 Torr) of the oil thus obtained gave 25 mg (84%) of the ketone **281**, a colourless oil which exhibited ir (neat): 1723, 1100, 837, 777 cm^{-1}; ^1H nmr (400 MHz, C_6D_6) δ: 0.06 (s, 6H, -Si$\underline{Me}_2$), 1.00 (s, 9H, -Si$\underline{Bu}^t$), 1.18 (dt, 1H, $\underline{H}_A$ or $\underline{H}_{A'}$, J = 13 Hz, J = 6 Hz), 1.60-1.72 (m, 6H), 1.75-1.93 (m, 3H), 2.23 (m, 1H), 3.52 (t, 2H, -OC$\underline{H}_2$CH_2-, J = 6 Hz), 4.85 (br s, 1H), 4.98 (br s, 1H). *Anal.* calcd. for $C_{17}H_{30}O_2Si$: C 69.34, H 10.28; found: C 69.72, H 10.41.

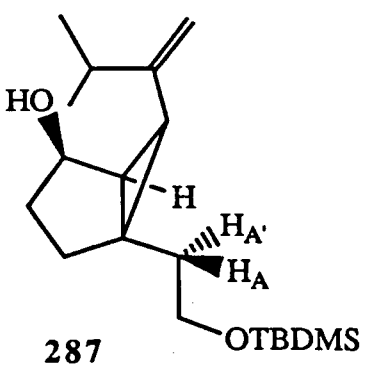
Preparation of the diazoketone **275**. The conversion of **275** into the ketones **285** and **286**



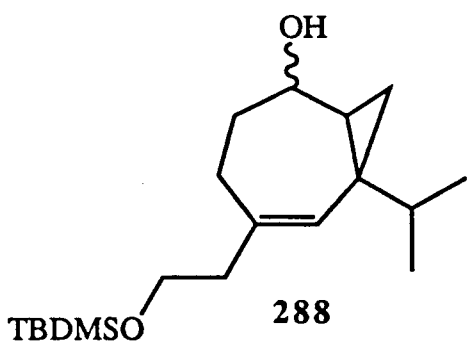
Following general procedure O, the carboxylic acid **270** (314 mg, 1 equiv., 0.93 mmol) in dry hexane (7 mL) was allowed to react with oxalyl chloride (356 mg, 3 equiv.). A solution of the resulting crude acid chloride in dry Et_2O (approx. 8 mL, including washings) was added to a solution of diazomethane in Et_2O (approx. 20 mL, approx. 8 equiv.). The crude product thus obtained was purified by rapid chromatography (35:65 Et_2O - petroleum ether; 30 g of silica gel), to give 264 mg (78%) of essentially pure (tlc analysis) diazoketone **275**. This compound was used immediately.

To a cold (-78°C), stirred solution of the diazoketone **275** (173 mg, 0.48 mmol) in dry CH_2Cl_2 (10 mL) (argon atmosphere) was added $Rh_2(OAc)_4$ (6 mg, 3 mol%). After the mixture had been stirred at -78°C for 10 min it was allowed to warm to room temperature, over 4 h. The solvent was removed and the residual oil was purified by flash chromatography (3:7 Et_2O - petroleum ether; 35 g of silica gel). Distillation of the oil thus obtained (140-150°C/0.5 Torr), gave 100 mg (63%, 49% from the acid **270**) of a mixture of the ketones **285** and **286** (4:1 respectively, by glc analysis).

Characterization of the ketone **285**



287



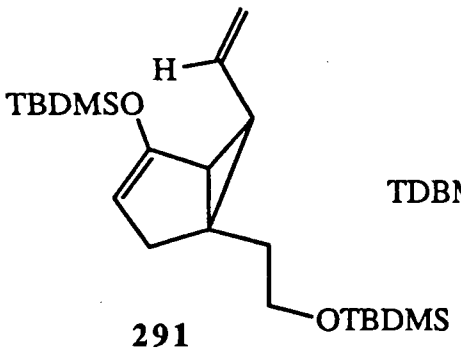
288

To a cold (-78°C), stirred solution of the mixture of ketones **285** and **286** (60 mg, 0.19 mmol, 4:1 by glc analysis) in dry THF (3 mL) (argon atmosphere) was added a solution of diisobutylaluminium hydride (2 equiv.) in hexane. After the mixture had been stirred for 1 h at -78°C and for 10 min at 0°C, saturated aqueous NH_4Cl (approx. 0.2 mL) was added and the vigorously stirred mixture was exposed to air and was allowed to warm to room temperature. Diethyl ether (approx. 1 mL) and drying agent ($MgSO_4$) were added to the suspension thus formed, and the mixture was suction filtered through a short pad (3 g) of Florisil®, using Et_2O as eluant. The combined eluate was concentrated and the resulting oil was purified by flash chromatography (3:7 Et_2O - petroleum ether; 30 g of silica gel), to give 40 mg (66%) of the alcohol **287** (traces of solvent were removed at reduced pressure; 0.5 Torr/25°C), and 10 mg (17%) of the alcohols **288** (traces of solvent were removed at reduced pressure; 0.5 Torr/25°C). The alcohol **287** was a colourless oil which exhibited ir (neat): 3406, 1254, 1067, 836 cm^{-1}; ^1H nmr (400 MHz, C_6D_6), 0.11 (s, 6H, -Si<u>Me</u>$_2$), 1.03 (s, 9H, -Si<u>Bu</u>^{t}), 1.19 (d, 3H, -CH<u>Me</u>-, J = 6 Hz), 1.22 (d, 3H, -CH<u>Me</u>-, J = 6 Hz), 1.21-1.35 (m, 2H), 1.44 (dt, 1H, <u>H</u>$_A$ or <u>H</u>$_A$', J = 13 Hz, J = 6 Hz), 1.56 (br d, 1H, J = 8 Hz), 1.60-1.73 (m, 2H), 1.83 (dt, 1H, <u>H</u>$_A$ or <u>H</u>$_A$'. J = 13 Hz, J = 6 Hz), 1.96 (m, 1H), 2.88 (br septet, 1H, -C<u>H</u>Me$_2$, J = 6 Hz), 3.70 (t, 2H, -OC<u>H</u>$_2$CH$_2$-, J = 6 Hz), 4.46 (m, 1H, -C<u>H</u>OH), 5.02 (br s, 1H), 5.27 (br s, 1H). *Exact Mass* calcd. for $C_{19}H_{36}O_2Si$ (M^+): 324.2484; found: 324.2477.

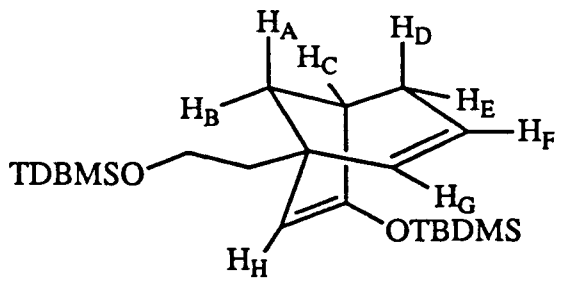
To a stirred solution of the alcohol **287** (35 mg, 0.11 mmol) in dry CH_2Cl_2 (2 mL) (argon atmosphere, room temperature) was added *N*-methylmorpholine-*N*-oxide (32 mg, 2.5 equiv.) and activated 4Å molecular sieves. The resulting suspension was stirred for 10 min at room temperature and then TPAP[133] (4 mg, 5 mol%) was added. After the mixture had been stirred for 45 min at room temperature it was filtered through a short column of Florisil® (approx. 5 g) using Et_2O as eluant. The combined eluate was concentrated and the resulting oil was purified by flash chromatography (1:4 Et_2O - petroleum ether; 20 g of silica gel). Distillation (140-150°C/0.5 Torr) of the oil thus obtained gave 29 mg (83%) of the

ketone **285**, a colourless oil which exhibited ir (neat): 1719, 1256, 1099, 837, 777 cm^{-1}; ^1H nmr (400 MHz, C_6D_6) δ: 0.06 (s, 6H, -SiMe$_2$), 0.98 (d, 3H, -CHMe-, J = 8 Hz), 1.00 (s, 9H, -SiBu^t), 1.02 (d, 3H, -CHMe-, J = 8 Hz), 1.25 (dt, 1H, H_A or $H_{A'}$, J = 13 Hz, J = 6 Hz), 1.63-1.79 (m, 3H), 1.80-1.95 (m, 3H), 2.04 (m, 1H), 2.18 (br septet, 1H, -CHMe$_2$, J = 8 Hz), 3.55 (t, 2H, -OCH$_2$CH$_2$-, J = 6 Hz), 4.92 (br s, 1H), 5.05 (br s, 1H). *Exact Mass* calcd. for $C_{19}H_{34}O_2Si$ (M^+): 322.2328; found: 232.2330. *Anal.* calcd. for $C_{19}H_{34}O_2Si$: C 70.76, H 10.63; found: C 70.62, H 10.49.

The preparation of compound **291** and the thermal rearrangement of this compound into the bicyclo[3.2.1]octa-2,6-diene **292**.



291

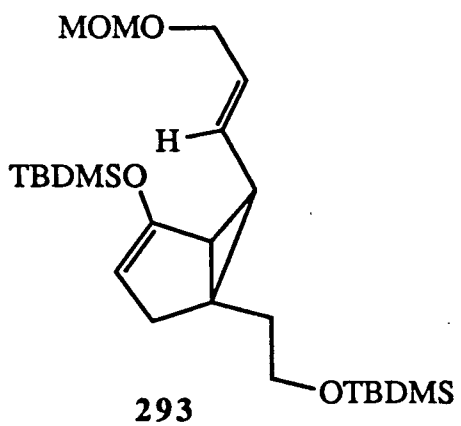


292

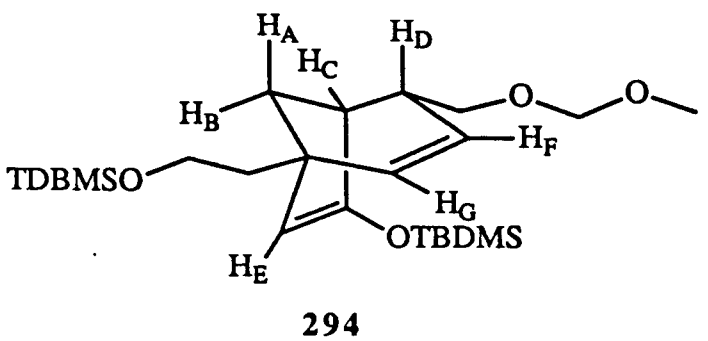
To a cold (-78°C), stirred solution of the ketone **278** (70 mg, 0.25 mmol) and TBDMSCl (57 mg, 1.5 equiv.) in dry THF (2 mL) (argon atmosphere) was added quickly, via Pasteur pipette, a suspension of KH (approx. 150 mg of a 35% dispersion of KH in mineral oil, 5 equiv.; pre-washed with dry THF) in dry THF (approx. 1 mL). The mixture was stirred for 5 min at -78°C and was then allowed to warm to room temperature. The progress of the reaction was monitored by tlc. When all of the ketone had reacted (after

45 min at room temperature) the mixture was cooled to -78°C and saturated aqueous $NaHCO_3$ (2 mL) and Et_2O (5 mL) were added. The vigorously stirred mixture was exposed to air and was allowed to warm to room temperature. The phases were separated and the aqueous phase was extracted with Et_2O (2 x 5 mL). The combined organic extracts were washed with brine (5 mL) and were then dried ($MgSO_4$) and concentrated, to give the crude compound **291**. Distillation of this crude oil (140-145°C/0.2 Torr) gave 81 mg (82%) of the compound **292**, a colourless oil which exhibited ir (neat): 3020, 1627, 1255, 871, 779 cm^{-1}; ^1H nmr (400 MHz, C_6D_6) δ: 0.11 (s, 6H, -Si<u>Me</u>$_2$), 0.17 (s, 3H, -Si<u>Me</u>), 0.19 (s, 3H, -Si<u>Me</u>), 1.00 (s, 9H, -Si<u>Bu</u>^{t}), 1.03 (s, 9H, -Si<u>Bu</u>^{t}), 1.73-1.90 (m, 3H, -OCH_2CH_2- and H_A), 2.04-2.18 (m, 3H, H_B, H_D and H_E), 2.64 (m, 1H, H_C), 3.78 (t, 2H, -OCH_2CH_2-, J = 6 Hz), 5.14 (br s, 1H, H_H), 5.33 (dddd, 1H, H_F, J = 10 Hz, J = 3 Hz, J = 3 Hz, J = 1.5 Hz), 6.17 br d, 1H, H_G, J = 10 Hz). *Exact Mass* calcd. for $C_{22}H_{42}O_2Si_2$ (M^+): 394.2723; found: 394.2717. *Anal.* calcd. for $C_{22}H_{42}O_2Si_2$: C 66.94, H 10.72; found: C 67.10, H 10.87.

<u>Preparation of compound **293** and the thermal rearrangement of this compound into the bicyclo[3.2.1]octa-2,6-diene **294**</u>



293

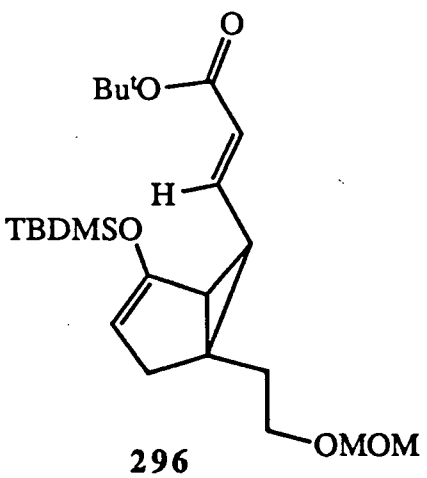


294

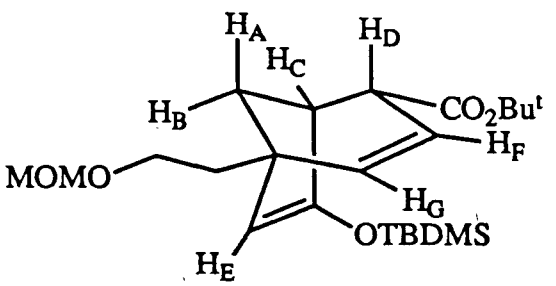
To a cold (-78°C), stirred solution of the ketone **279** (30 mg, 85 μmol) and TBDMSCl (19 mg, 1.5 equiv.) in dry THF (2 mL) (argon atmosphere) was added, quickly, via pasteur pipette, a suspension of KH (approx. 50 mg of a 35% dispersion of KH in mineral oil, 5 equiv.; prewashed with dry THF) in dry THF (approx. 1 mL). The mixture was stirred for 5 min at -78°C and was then allowed to warm to room temperature. The progress of the reaction was monitored by tlc. When all of the ketone had reacted (after 45 min at room temperature) the mixture was cooled to -78°C and saturated aqueous $NaHCO_3$ (2 mL) and Et_2O (5 mL) were added. The vigorously stirred mixture was exposed to air and allowed to warm to room temperature. The phases were separated and the aqueous phase was extracted with Et_2O (2 x 5 mL). The combined organic extracts were washed with brine (5 mL) and were then dried ($MgSO_4$) and concentrated, to give the crude compound **293**. Distillation of this crude oil (170-175°C/0.2 Torr) gave 35 mg (88%) of the compound **294**, a colourless oil which exhibited ir (neat): 1625, 1255, 1112, 869, 779 cm^{-1}; ^1H nmr (400 MHz, C_6D_6) δ: 0.11 (s, 6H, -SiMe$_2$), 0.17 (s, 6H, -SiMe$_2$), 1.00 (s, 9H, -SiBu^t), 1.03 (s, 9H, -SiBu^t), 1.70-1.90 (m, 3H, -OCH$_2$CH$_2$- and H$_A$), 2.11 (ddd, 1H, H$_B$, J = 10 Hz, J = 5 Hz, J = 1.5 Hz), 2.70-2.80 (m, 2H, H$_C$ and H$_D$), 3.25 (s, 3H, -OMe), 3.57-3.72 (m, 2H, -CH$_2$OMOM), 3.76 (t, 2H, -OCH$_2$CH$_2$-, J = 6 Hz), 4.59, 4.66 (d, d, 2H, -OCH$_2$O-, J = 7 Hz), 5.12 (s, 1H, H$_E$), 5.58 (ddd, 1H, H$_F$, J = 10 Hz, J = 2 Hz, J = 2 Hz), 6.24 (br d, 1H, H$_G$, J = 10 Hz). In decoupling experiments, irradiation at δ 6.24 (H$_G$) caused the signal at δ 5.58 (H$_F$) to collapse to a dd (J = 2 Hz, J = 2 Hz), whilst the signal at δ 2.11 (H$_B$) sharpened to a dd (J = 10 Hz, J = 5 Hz); irradiation at δ 5.58 (H$_F$) caused the signal at δ 6.24 (H$_G$) to collapse to a br s; irradiation at δ 3.76 (-OCH$_2$CH$_2$-) caused the signal at 1.70-1.90 (-OCH$_2$CH$_2$- and H$_A$) to simplify to signals at δ 1.76 and δ 1.85 (d, d, 1H each, -OCH$_2$CH$_2$-, J = 14 Hz, J = 14 Hz), plus a signal at 1.81 (d, H$_A$, J = 10 Hz); irradiation at δ 2.70-2.80 (H$_C$ and H$_D$) caused the signal at δ 6.24 (H$_G$) to sharpen to a dd (J = 10 Hz, J = 1.5 Hz) whilst the signal at δ 5.58 (H$_F$) sharpened to a d (J = 10 Hz), and the signal at δ 3.57-3.72 (-CH$_2$O-) collapsed to signals at δ 3.51 (d,

J = 9 Hz) and δ 3.68 (d, J = 9 Hz); irradiation at δ 2.11 ($\underline{H}_B$) caused the signal at δ 6.24 ($\underline{H}_G$) to sharpen to a dd (J = 10 Hz, J = 2 Hz) whilst the signal at δ 1.69-1.89 (-OCH_2CH_2- and $\underline{H}_A$) simplified to a signal at δ 1.69-1.89 (m, -$OCH_2C\underline{H}_2$-) plus a signal at δ 1.81 (s, $\underline{H}_A$). In a COSY experiment (400 MHz, C_6D_6): $\underline{H}_G$ showed correlations into $\underline{H}_D$, and $\underline{H}_F$; $\underline{H}_F$ showed correlations into $\underline{H}_G$, and/or $\underline{H}_C/\underline{H}_D$; $\underline{H}_E$ showed a correlation into $\underline{H}_A$; -$C\underline{H}_2$OMOM showed a correlation into $\underline{H}_D$; $\underline{H}_B$ showed a correlation into $\underline{H}_A$ and $\underline{H}_C$. *Exact Mass* calcd. for $C_{25}H_{48}O_4Si_2$ (M^+): 468.3091; found: 468.3090. *Anal.* calcd. for $C_{25}H_{48}O_4Si_2$: C 64.05, H 10.32; found: C 64.20, H 10.40.

Preparation of compound **296** and the thermal rearrangement of this compound into the bicyclo[3.2.1]octa-2,6-diene **297**



296

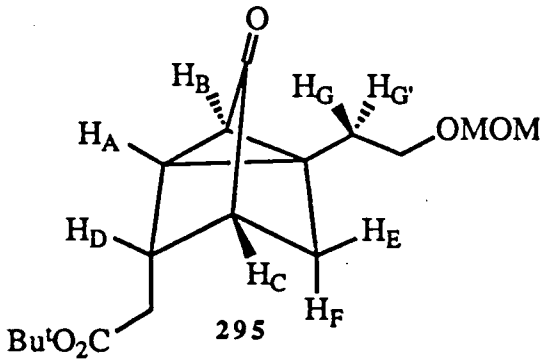


297

To a cold (-78°C), stirred solution of the ketone **280** (9 mg, 29 μmol) in dry CH_2Cl_2 (1.5 mL) (argon atmosphere) was added, successively, dry Et_3N (3 equiv., 13 μL) and TBDMSOTf (1.5 equiv., 11 μL). After the mixture had been stirred for 30 min at -78°C,

saturated aqueous $NaHCO_3$ (1 mL) and Et_2O (3 mL) were added, and the mixture was allowed to warm to room temperature. The phases were separated and the aqueous phase was extracted with Et_2O (2 x 3 mL). The combined organic extracts were washed with brine (2 mL) and were then dried ($MgSO_4$) and concentrated, to give the crude compound **296**. Dry benzene (3 mL) was added to this crude oil, in a base washed round bottom flask, and the solution was warmed to 50°C overnight (argon atmosphere). The solvent was removed and the residual oil was purified by rapid flash chromatography (15:85 Et_2O - petroleum ether; 10 g of silica gel), to give, after removal of traces of solvent under reduced pressure (room temperature/0.5 Torr), 10 mg (82%) of the compound **297**, a colourless oil which exhibited ir (neat): 1733, 1621, 1152, 868, 784 cm^{-1}; ^1H nmr (400 MHz, C_6D_6) δ: 0.20 (s, 3H, -SiMe), 0.22 (s, 3H, -SiMe), 1.03 (s, 9H, -SiBu^t), 1.47 (s, 9H, -CO_2Bu^t), 1.68 (br d, 1H, H_A, J = 10 Hz), 1.65-1.82 (m, 2H, -OCH_2CH_2-), 2.06 (br dd, H_B, J = 10 Hz, J = 5 Hz), 3.13 (m, 2H, H_C and H_D), 3.21 (s, 3H, -OMe), 3.57 (m, 2H, -OCH_2CH_2-), 4.51 (s, 2H, -OCH_2O-), 5.11 (br s, 1H, H_E), 5.68 (ddd, 1H, H_F, J = 10 Hz, J = 2 Hz, J = 2 Hz), 6.15 (br d, 1H, H_G, J = 10 Hz). In a COSY experiment (400 MHz, C_6D_6): H_G showed correlations into H_F and H_D; H_F showed correlations into H_G and H_D/H_C; H_E showed a correlation into H_A; H_B showed correlations into H_A and H_C; H_A showed correlations into H_B and H_E. *Exact Mass* calcd. for $C_{23}H_{40}O_5Si$ (M^+): 424.2600; found: 424.2650. *Anal.* calcd. for $C_{23}H_{40}O_5Si$: C 65.05, H 9.49; found: C 65.32, H 9.63.

Preparation of the compound **295**

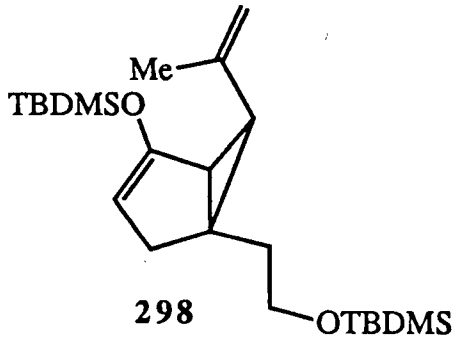


295

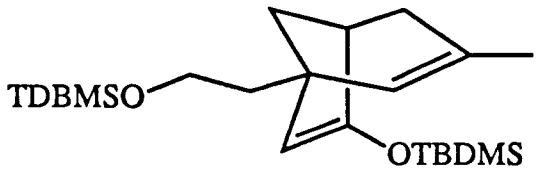
To a cold, (-78°C), stirred solution of the ketone **280** (15 mg, 48 μmol) in dry THF (1 mL) (argon atmosphere) was added a suspension of KH (28 mg of a 35% dispersion of KH in mineral oil, approx. 5 equiv., prewashed with dry THF) in dry THF (0.5 mL), via Pasteur pipette. The mixture was warmed to room temperature and stirred for a further 30 min. Then it was re-cooled to -78°C and saturated aqueous $NaHCO_3$ (1 mL) and Et_2O (3 mL) were added. The vigorously stirred mixture was allowed to warm to room temperature, the phases were separated and the aqueous phase was extracted with Et_2O (2 x 3 mL). The combined organic extracts were washed with brine (3 mL) and were then dried ($MgSO_4$) and concentrated. Flash chromatography of the crude product (1:1 Et_2O - petroleum ether; 15 g of silica gel) gave (after traces of solvent were removed under reduced pressure; room temperature/0.5 Torr) 13 mg (87%) of the compound **295**, a colourless oil which exhibited ir (neat): 1752, 1729, 1151, 1042 cm^{-1}; ^1H nmr (400 MHz, C_6D_6) δ: 1.18 (d, 1H, $\underline{H_B}$, J = 6 Hz), 1.39 (s, 9H, $-CO_2\underline{Bu^t}$), 1.41-1.51 (m, 1H, $-OCH_2C\underline{H}-$), 1.52-1.62 (m, 3H, $OCH_2C\underline{H}-$ and $\underline{H_E}$ and $\underline{H_F}$), 1.67 (br d, 1H, $\underline{H_A}$, J = 6 Hz), 1.84 (br s, 1H, $\underline{H_C}$), 2.0 (m, 2H, $-C\underline{H_2}CO_2Bu^t$), 2.49 (br t, 1H, $\underline{H_D}$, J = 7 Hz), 3.19 (s, 3H, $-O\underline{Me}$), 3.32 (t, 2H, $-OC\underline{H_2}CH_2-$, J = 6 Hz), 4.41, 4.42 (d, d, 2H, $-OC\underline{H_2}O-$, J = 6 Hz, J = 6 Hz). In a COSY experiment (400 MHz, C_6D_6): δ 1.18 ($\underline{H_B}$) showed correlations into δ 1.67 ($\underline{H_A}$)

and δ 1.84 ($\underline{H}_C$); δ 1.67 ($\underline{H}_A$) showed correlations into δ 1.18 ($\underline{H}_B$), δ 1.84 ($\underline{H}_C$) and δ 2.49 ($\underline{H}_D$); δ 1.84 ($\underline{H}_C$) showed correlations into δ 1.67 ($\underline{H}_A$), δ 1.18 ($\underline{H}_B$), δ 2.49 ($\underline{H}_D$) and 1.55-1.65 ($\underline{H}_E/\underline{H}_F$); δ 2.49 ($\underline{H}_D$) showed correlations to δ 2.00 (-$C\underline{H}_2CO_2Bu^t$), δ 1.84 ($\underline{H}_C$) , and δ 1.67 ($\underline{H}_A$); δ 3.32 (-$OC\underline{H}_2CH_2$-) showed correlations to δ 1.41-1.51 and δ 1.52-1.62 (-$OCH_2C\underline{H}_2$-). In a long range COSY experiment (400 MHz, C_6D_6): $\underline{H}_B$ showed correlations into $\underline{H}_E/\underline{H}_F$, $\underline{H}_A$ and $\underline{H}_C$; $\underline{H}_A$ showed correlations into $\underline{H}_B$ $\underline{H}_C$ and $\underline{H}_D$; $\underline{H}_C$ showed correlations into $\underline{H}_D$, $\underline{H}_E/\underline{H}_F$, $\underline{H}_A$ and $\underline{H}_B$; $\underline{H}_D$ showed correlations into -$C\underline{H}_2CO_2Bu^t$, $\underline{H}_C$, $\underline{H}_A$ and $\underline{H}_E/\underline{H}_F$. In nOe difference experiments; irradiation of the signal at δ 1.84 ($\underline{H}_C$) caused signal enhancements at δ 1.58 ($\underline{H}_E$ or $\underline{H}_F$ or both) and at δ 2.49 ($\underline{H}_D$); irradiation of the signal at δ 2.00 (-$C\underline{H}_2CO_2Bu^t$) caused signal enhancements at δ 2.49 ($\underline{H}_D$), δ 1.67 ($\underline{H}_A$), δ 1.84 ($\underline{H}_C$) and δ 1.58 ($\underline{H}_F$); irradiation of the signal at δ 2.49 ($\underline{H}_D$) caused signal enhancement at δ 2.00 (-$C\underline{H}_2CO_2Bu^t$), δ 1.84 ($\underline{H}_C$) and δ 1.67 ($\underline{H}_A$). ^{13}C nmr (50 MHz, C_6D_6) δ: 27.22, 28.03, 30.26, 31.07, 31.52, 36.10, 40.25, 44.89, 54.99, 65.82, 79.98, 96.54, 170.61, 209.00. *Exact Mass* calcd. for $C_{13}H_{18}O_5$ (M^+-C_4H_8): 254.1153; found: 254.1153. Cims (positive ion detection, CH_4): 311 (M^++H).

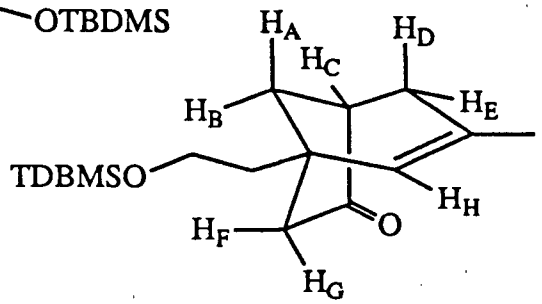
Preparation of compound **298** and the thermal rearrangement of this compound into the bicyclo[3.2.1]octa-2,6-diene **299**. Preparation of the bicyclo[3.2.1]oct-2-en-6-one **300**.



298



299

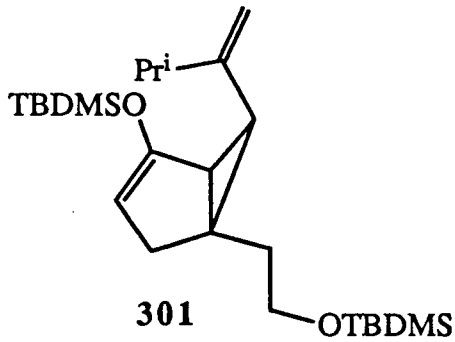


300

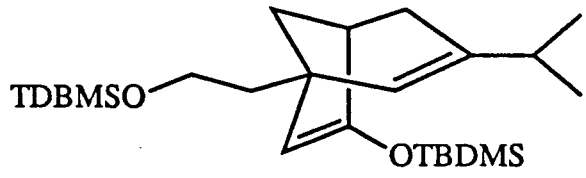
To a cold (-78°C), stirred solution of the mixture of ketones **281** and **282** (10 mg, 34 μmol, 4:1 by glc analysis, respectively) in dry CH_2Cl_2 (1 mL) (argon atmosphere) was added, successively, dry Et_3N (10 mg, 14 μL, 3 equiv.) and TBDMSOTf (13 mg, 12 μL, 1.5 equiv.). After the mixture had been stirred for 20 min at -78°C, saturated aqueous $NaHCO_3$ (1 mL) and Et_2O (3 mL) were added and the mixture was allowed to warm to room temperature. The phases were separated and the aqueous phase was extracted with Et_2O (2 x 3 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Dry benzene (3 mL) was added to the residue in a base washed round bottom flask and the solution was warmed to 50°C overnight (argon atmosphere). Solvent was removed and the residue was dissolved in THF (0.75 mL). Glacial HOAc (0.25 mL) was added to the solution and the mixture was stirred at room temperature for 1.5 h. Water (2 mL) and Et_2O (3 mL) were

added and the vigorously stirred mixture was neutralized by the addition of solid $NaHCO_3$. The phases were separated and the aqueous phase was extracted with Et_2O (3 x 2 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Flash chromatography of the crude product (1:4 Et_2O - petroleum ether; 10 g of silica gel) followed by distillation of the oil thus obtained (130-135°C/0.5 Torr), gave 5.5 mg (55%) of the ketone **300**, a colourless oil which exhibited ir (neat): 1747, 1094, 837, 776 cm^{-1}; ^1H nmr (400 MHz, C_6D_6) δ: 0.07 (s, 6H, -SiMe2), 1.01 (s, 9H, -SiBu^t), 1.41 (s, 3H, -Me), 1.51 (br dd, 1H, H_B, J = 11 Hz, J = 5.5 Hz), 1.53-1.67 (m, 3H, -OCH_2CH_2- and H_A), 1.87 (d, 1H, H_F, J = 17 Hz), 1.97 (br dd, 1H, H_D, J = 17 Hz, J = 5 Hz), 2.05 (br d, 1H, H_E, J = 17 Hz), 2.27 (dd, 1H, H_G, J = 17 Hz, J = 3 Hz), 2.42 (m, 1H, H_C), 3.61 (m, 2H, -OCH_2CH_2-), 5.44 (br s, 1H, H_H). In decoupling experiments, irradiation at δ 2.42 (H_C) caused the signal at δ 1.51 (H_B) to collapse to a br d (J = 11 Hz), whilst the signal at δ 1.97 (H_D) collapsed to a br d (J = 17 Hz); irradiation at δ 3.61 (-OCH_2CH_2-) caused the signal at 1.53-1.67 (-OCH_2CH_2- and H_A) to simplify to a signal at δ 1.65 (dd, H_A, J = 11 Hz, J = 3 Hz) and signals at δ 1.62 (d, J = 13 Hz) and δ 1.56 (d, J = 13 Hz); irradiation at δ 2.27 (H_G) caused the signal at 1.87 (H_F) to collapse to a s; irradiation at δ 1.87 (H_F) caused the signal at δ 2.27 (H_G) to collapse to a br d (J = 3 Hz). *Exact Mass* calcd. for $C_{17}H_{30}O_2Si$ (M^+): 294.2015; found: 294.2024. *Anal.* calcd. for $C_{17}H_{30}O_2Si$: C 69.33, H 10.27; found: C 69.50, H 10.29.

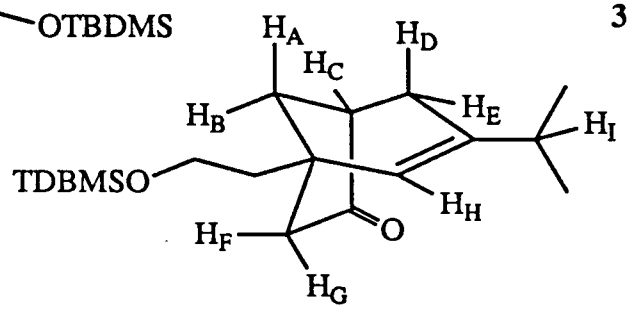
Preparation of compound **301** and the thermal rearrangement of this compound into the bicyclo[3.2.1]octa-2,6-diene **302**. Preparation of the bicyclo[3.2.1]oct-2-en-6-one **303**.



301



302

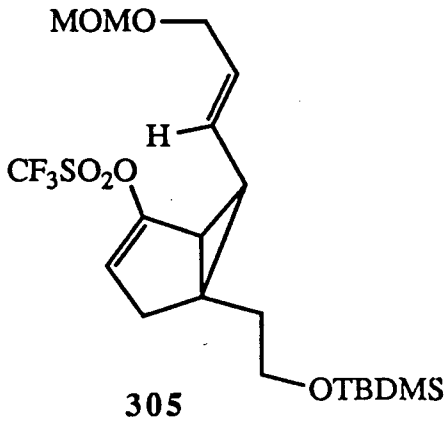


303

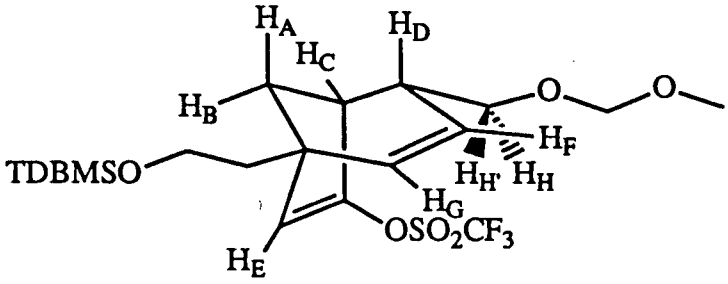
To a cold (-78°C), stirred solution of the mixture of ketones **285** and **286** (17 mg, 53 μmol, 4:1 by glc analysis, respectively) in dry CH_2Cl_2 (2 mL) (argon atmosphere) was added, successively, dry Et_3N (16 mg, 22 μL, 3 equiv.) and TBDMSOTf (21 mg, 18 μL, 1.5 equiv.). After the mixture had been stirred for 20 min at -78°C, saturated aqueous $NaHCO_3$ (1 mL) and Et_2O (3 mL) were added and the mixture was allowed to warm to room temperature. The phases were separated and the aqueous phase was extracted with Et_2O (2 x 3 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Dry benzene (3 mL) was added to the residue in a base washed round bottom flask and the solution was warmed to 50°C overnight (argon atmosphere). The solvent was removed and the residue was dissolved in THF (1 mL). Glacial HOAc (0.3 mL) was added to the solution and the mixture was stirred at room temperature for 1.5 h. Water (2 mL) and Et_2O (3 mL) were

added and the vigorously stirred mixture was neutralized by the addition of solid $NaHCO_3$. The phases were separated and the aqueous phase was extracted with Et_2O (3 x 2 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Flash chromatography of the crude product (1:4 Et_2O - petroleum ether; 10 g of silica gel) followed by distillation of the oil thus obtained (140-150/0.5 Torr), gave 11 mg (65%) of the ketone **303**, a colourless oil which exhibited ir (neat): 1747, 1255, 838, 776 cm^{-1}; ^1H nmr (400 MHz, C_6D_6) δ: 0.10 (s, 6H, -SiMe2), 0.88 (d, 3H, -CHMe, J = 8 Hz), 0.89 (d, 3H, -CHMe, J = 8 Hz), 1.01 (s, 9H, -SiBu^t), 1.54 (br dd, 1H, H_B, J = 11 Hz, J = 5.5 Hz), 1.58-1.68 (m, 3H, -OCH_2CH_2- and H_A), 1.91 (dd, 1H, H_F, J = 17 Hz, J = 1 Hz), 1.96 (m, 1H, H_I), 2.04 (ddd, 1H, H_D, J = 17 Hz, J = 5 Hz, J = 2 Hz), 2.13 (br d, H_E, J = 17 Hz), 2.27 (dd, 1H, H_G, J = 17 Hz, J = 3 Hz), 2.47 (m, 1H, H_C), 3.54 (m, 2H, -OCH_2CH_2-), 5.54 (br s, 1H, H_H). In decoupling experiments, irradiation at δ 5.54 (H_H) caused the signal at δ 2.13 (H_E) to sharpen to a dd (J = 17 Hz, J = 2 Hz), whilst the signal at δ 2.04 (H_D) collapsed to a dd (J = 17 Hz, J = 5 Hz), and the signal at δ 1.54 (H_B) sharpened to a dd (J = 11 Hz, J = 5.5 Hz); irradiation at δ 3.54 (-OCH_2CH_2-) caused the signal at δ 1.58-1.68 (-OCH_2CH_2- and H_A) to simplify to signals at δ 1.60, δ 1.64 (d, d, 1H each, -OCH_2CH_2-, J = 14 Hz, J = 14 Hz) and a signal at δ 1.66 (dd, H_A, J = 11 Hz, J = 3 Hz); irradiation at δ 2.47 (H_C) caused the signal at 1.54 (H_B) to collapse to a br d (J = 11 Hz), whilst the signal at 1.91 (H_F) collapsed to a d (J = 17 Hz), and the signal at δ 2.04 (H_D) collapsed to a dd (J = 17 Hz, J = 2 Hz); irradiation at δ 2.27 (H_G) caused the signal at δ 1.91 (H_F) to collapse to a br s, whilst the signal at δ 1.58-1.68 (-OCH_2CH_2- and H_A) collapsed to signals at δ 1.58-1.68 (m, -OCH_2CH_2-) and δ 1.66 (s, H_A). *Exact Mass* calcd. for $C_{19}H_{34}O_2Si$ (M^+): 322.2328; found: 322.2329. *Anal.* calcd. for $C_{19}H_{34}O_2Si$: C 70.75, H 10.62; found: C 70.76, H 10.80.

Preparation of compound **305** and the thermal rearrangement of this compound into the bicyclo[3.2.1]octa-2,6-diene **306.**



305

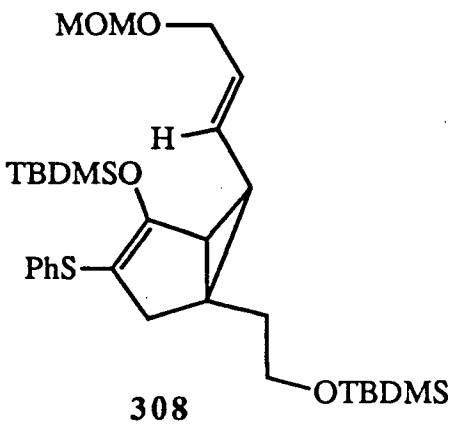


306

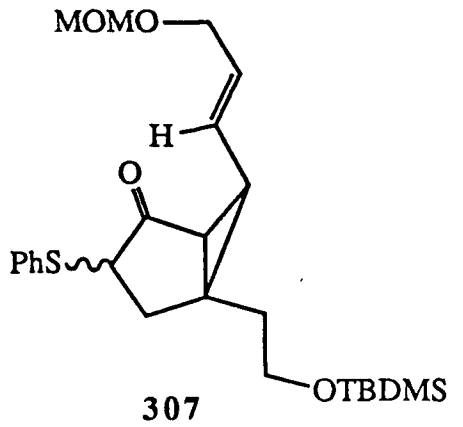
To a cold (-78°C), stirred solution of the ketone **279** (18 mg, 51 μmol) in dry THF (1.5 mL) (argon atmosphere) was added a solution of lithium diisopropylamide (0.3 M, 3 equiv.) in THF. After the mixture had been stirred for 20 min at -78°C and for 30 min at -20°C, solid *N*-phenyltrifluoromethanesulphonimide (66 mg, 4 equiv.) was added and the mixture was stirred for a further 1 h at -20°C. The reaction mixture was passed through a short column of silica gel (in a Pasteur pipette) using Et_2O as eluant. The eluate was concentrated and the crude oil thus obtained was purified by flash chromatography (1:9 Et_2O - petroleum ether; 15 g of silica gel), to give the compound **305**. To this oil, in a base washed round bottom flask was added dry benzene (3 mL). The solution was warmed to 50°C overnight (argon atmosphere). Solvent was removed and the residual oil was purified by flash chromatography (1:9 Et_2O - petroleum ether; 15 g of silica gel) to give (after removal of traces of solvent under reduced pressure; 0.5 Torr/room temperature) 18 mg (73%) of the compound **306**, a colourless oil which exhibited ir (neat): 1645, 1426, 1213, 1104, 778 cm^{-1}; ^1H nmr (400 MHz, C_6D_6) δ: 0.07 (s, 6H, -SiMe2), 0.94 (s, 9H, -SiBu^t), 1.41-1.62 (m, 2H, $-OCH_2CH_2-$), 1.58 (br d, 1H, H_A, J = 10 Hz), 2.07 (ddd, 1H, H_B, J =

10 Hz, J = 5.5 Hz, J = 1.5 Hz), 2.49 (m, 1H, $\underline{H}_D$), 3.12 (ddd, 1H, $\underline{H}_C$, J = 5.5 Hz, J = 5.5 Hz, J = 1.5 Hz), 3.25 (s, 3H, -OMe), 3.25-3.31 (m, 1H, $\underline{H}_H$ or $\underline{H}_{H'}$), 3.45 (dd, 1H, $\underline{H}_H$ or $\underline{H}_{H'}$, J = 10 Hz, J = 6 Hz), 3.52 (m, 2H, -OC$\underline{H}_2$CH$_2$-), 4.55, 4.58 (d, d, 2H, -OCH$_2$O-, J = 6.5 Hz, J = 6.5 Hz), 5.16 (ddd, 1H, $\underline{H}_F$, J = 10 Hz, J = 1.5 Hz, J = 1.5 Hz), 5.81 (br s, 1H, $\underline{H}_E$), 5.89 (ddd, 1H, $\underline{H}_G$, J = 10 Hz, J = 2 Hz, J = 1.5 Hz). In decoupling experiments, irradiation at δ 5.89 ($\underline{H}_G$) caused the signal at δ 5.16 ($\underline{H}_F$) to collapse to a dd (J = 1.5 Hz, J = 1.5 Hz), whilst the signal at δ 2.07 ($\underline{H}_B$) sharpened to a dd (J = 10 Hz, J = 5.5 Hz); irradiation at δ 5.16 ($\underline{H}_F$) caused the signal at δ 5.89 ($\underline{H}_G$) to collapse to a dd (J = 2 Hz, J = 1.5 Hz), whilst the signal at δ 3.12 ($\underline{H}_C$) sharpened to a dd (J = 5.5 Hz, J = 5.5 Hz); irradiation at δ 3.52 (-OC$\underline{H}_2$CH$_2$-) caused the signal at 1.41-1.62 (-OCH$_2$C$\underline{H}_2$-) to simplify to signals at δ 1.45 (d, J = 12 Hz) and δ 1.55 (d, J = 12 Hz); irradiation at δ 2.49 ($\underline{H}_D$) caused the signal at δ 3.25-3.31 ($\underline{H}_H$ or $\underline{H}_{H'}$) to collapse to a d (J = 10 Hz), whilst the signal at δ 3.45 ($\underline{H}_H$ or $\underline{H}_{H'}$) collapsed to a d (J = 10 Hz), the signal at δ 3.12 ($\underline{H}_C$) collapsed to a br d (J = 5.5 Hz), the signal at δ 5.16 ($\underline{H}_F$) sharpened to a dd (J = 10 Hz, J = 1.5 Hz) and the signal at δ 5.89 ($\underline{H}_G$) sharpened to a dd (J = 10 Hz, J = 1.5 Hz); irradiation at δ 2.07 ($\underline{H}_B$) caused the signal at 5.89 ($\underline{H}_G$) to sharpen to a dd (J = 10 Hz, J = 2 Hz), whilst the signal at δ 1.58 ($\underline{H}_A$) collapsed to a s, and the signal at δ 3.12 ($\underline{H}_C$) collapsed to a br d (J = 5.5 Hz); irradiation at δ 3.12 (H_C) caused the signal at δ 2.07 ($\underline{H}_B$) to collapse to a br d (J = 5.5 Hz), whilst the signal at δ 5.14 sharpened to a dd (J = 10 Hz, J = 1.5 Hz). *Exact Mass* calcd. for $C_{16}H_{24}F_3O_6SiS$ (M^+-Bu^t): 429.1015; found: 429.1015 ; cims (positive ion detection, NH_3): 505 (M^++NH_4).

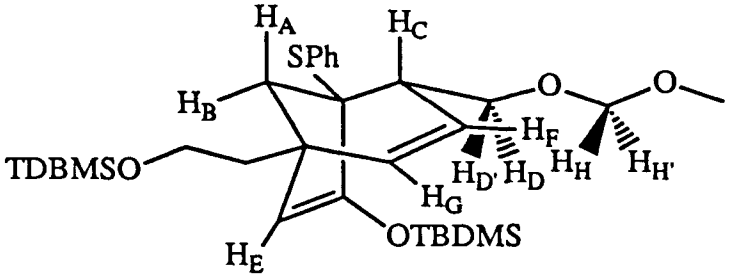
Preparation of compound **308**, via the α-phenylthio ketones **307**, and the thermal rearrangement of this compound into the bicyclo[3.2.1]octa-2,6-diene **309**.



308



307



309

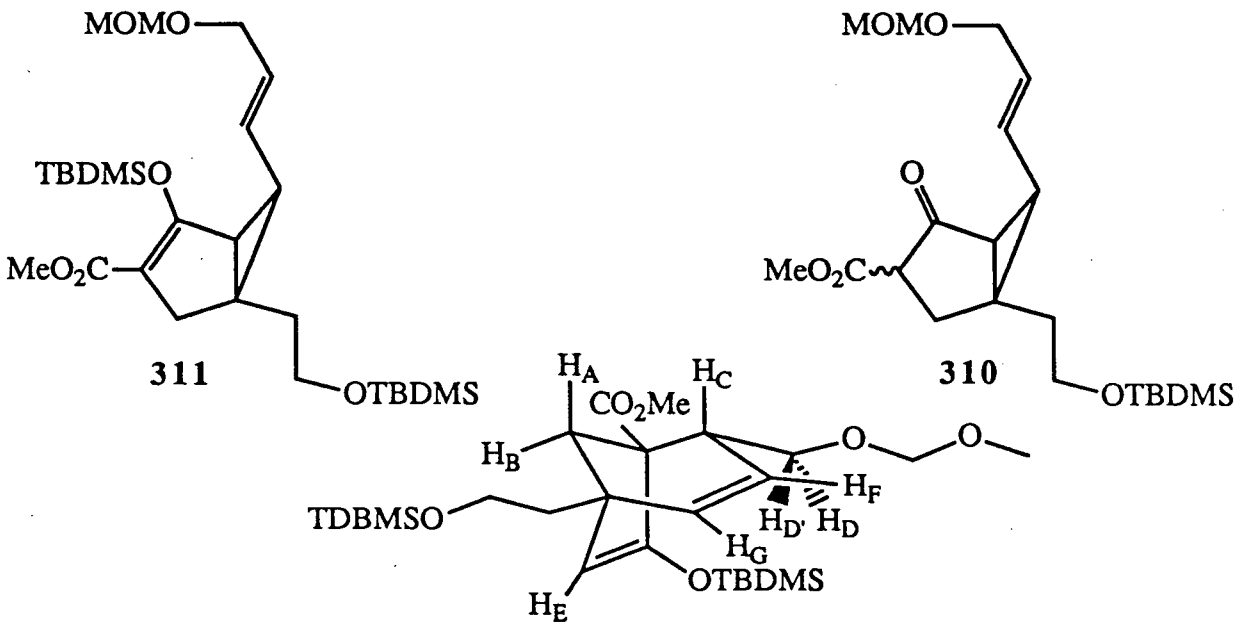
To a cold (-78°C), stirred solution of the ketone **279** (46 mg, 0.13 mmol) in dry THF (3 mL) (argon atmosphere) was added a solution of lithium diisopropylamide (0.3 M, 3 equiv.) in THF. After the mixture had been stirred for 20 min at -78°C and 30 min at -20°C, it was transferred via cannula into a stirred solution of diphenyl disulphide (4.5 equiv., 156 mg) in dry THF (2 mL) at room temperature (argon atmosphere). After the mixture had been stirred for 1.5 h at room temperature, saturated aqueous $NaHCO_3$ (3 mL) and Et_2O (5 mL) were added. The phases were separated and the aqueous phase was extracted with Et_2O (3 x 3 mL). The combined organic extracts were washed with brine (5 mL), dried ($MgSO_4$) and concentrated. Flash chromatography (3:7 Et_2O - petroleum

ether; 25 g of silica gel) of the residual oil afforded 46 mg (77%) of the α-phenylthio ketone **307**, a pale yellow oil, which was used without further purification.

To a cold (-78°C), stirred solution of the reaction product (46 mg, 0.1 mmol) and TBDMSCl (22 mg, 1.5 equiv.) in dry THF (3 mL) (argon atmosphere) was added a suspension of KH (5 equiv., approx. 56 mg of a 35% dispersion of KH in mineral oil, prewashed with dry THF) in dry THF (approx. 1 mL). After the mixture had been stirred at -78°C for 5 min and at room temperature for 45 min it was re-cooled to -78°C and saturated aqueous $NaHCO_3$ (2 mL) and Et_2O (5 mL) were added. The vigorously stirred mixture was allowed to warm to room temperature and the phases were separated. The aqueous phase was extracted with Et_2O (2 x 5 mL) and the combined organic extracts were washed with brine (3 mL), dried ($MgSO_4$)and concentrated, to give the crude compound **308**. To this crude oil (in a base washed round bottom flask) was added dry benzene (4 mL), and the solution (argon atmosphere) was warmed to 60°C overnight. Solvent was removed, and the residue was purified by flash chromatography (7:93 Et_2O - petroleum ether; 20 g of silica gel) to give (after removal of traces of solvent under reduced pressure; 0.5 Torr/room temperature) 33 mg (44% from the ketone **279**) of the compound **309**, a colourless oil which exhibited ir (neat): 3060, 1620, 1254, 840 cm^{-1}; ^1H nmr (400 MHz, C_6D_6) δ: 0.07 (s, 6H, -Si$\underline{Me}_2$), 0.24 (s, 3H, -Si$\underline{Me}$), 0.28 (s, 3H, -Si$\underline{Me}$), 1.0 (s, 9H, -Si$\underline{Bu}^t$), 1.08 (s, 9H, -Si$\underline{Bu}^t$), 1.62-1.78 (m, 2H, -$OCH_2\underline{CH_2}$-), 1.93 (dd, 1H, $\underline{H}_A$, J = 9 Hz, J = 1 Hz), 2.43 (dd, 1H, $\underline{H}_B$, J = 9 Hz, J = 1.5 Hz), 3.04 (m, 1H, $\underline{H}_C$), 3.26 (s, 3H, -O$\underline{Me}$), 3.60-3.70 (m, 3H, -$O\underline{CH_2}CH_2$- and $\underline{H}_D$ or $\underline{H}_{D'}$), 4.62 (d, 1H, $\underline{H}_H$ or $\underline{H}_{H'}$, J = 6 Hz), 4.65-4.72 (m, 2H, $\underline{H}_D$ or $\underline{H}_{D'}$ plus $\underline{H}_H$ or $\underline{H}_{H'}$), 5.13 (d, 1H, $\underline{H}_E$, J = 1 Hz), 5.94 (dd, 1H, $\underline{H}_F$, J = 10 Hz, J = 2.5 Hz), 6.13 (br d, 1H, $\underline{H}_G$, J = 10 Hz), 7.01-7.11 (m, 3H), 7.55 (m, 2H). In decoupling experiments, irradiation at δ 6.13 ($\underline{H}_G$) caused the signal at δ 5.94 ($\underline{H}_F$) to collapse to a d (J = 2.5 Hz), whilst the signal at δ 3.04 ($\underline{H}_C$) sharpened to a ddd (J = 11 Hz, J = 3 Hz, J = 2.5 Hz), and the signal at δ 2.43 ($\underline{H}_B$) sharpened to a d (J = 9 Hz); irradiation at δ 5.94 ($\underline{H}_F$) caused the signal at δ 6.13 ($\underline{H}_G$) to collapse to a br s, whilst the

signal at δ 3.04 ($\underline{H}_C$) sharpened to a ddd (J = 11 Hz, J = 3 Hz, J = 2 Hz); irradiation at δ 5.13 ($\underline{H}_E$) caused the signal at 1.93 ($\underline{H}_A$) to sharpen to a d (J = 9 Hz); irradiation at δ 4.65-4.72 (H_D or $H_{D'}$ plus $\underline{H}_H$ or $\underline{H}_{H'}$) caused the signal at δ 3.04 ($\underline{H}_C$) to sharpen to a ddd (J = 11 Hz, J = 2.5 Hz, J = 2 Hz); irradiation at δ 3.04 ($\underline{H}_C$) caused the signal at δ 6.13 ($\underline{H}_G$) to sharpen to a dd (J = 10 Hz, J = 1.5 Hz), whilst the signal at δ 5.94 ($\underline{H}_F$) sharpened to a d (J = 10 Hz), and the signal at δ 4.65-4.72 (H_D or $\underline{H}_{D'}$ plus H_H or $H_{H'}$) simplified to doublets at δ 4.67 ($\underline{H}_H$ or $\underline{H}_{H'}$, J = 6 Hz) and δ 4.69 ($\underline{H}_D$ or $\underline{H}_{D'}$, J = 9 Hz); irradiation at δ 2.43 ($\underline{H}_B$) caused the signal at δ 6.13 ($\underline{H}_G$) to sharpen to a dd (J = 10 Hz, J = 2 Hz), whilst the signal at 1.93 ($\underline{H}_A$) collapsed to a br s; irradiation of the signal at δ 1.93 ($\underline{H}_A$) caused the signal at δ 2.43 ($\underline{H}_B$) to collapse to a br s. *Exact Mass* calcd. for $C_{31}H_{52}O_4Si_2S$ (M^+): 576.3124; found: 576.3128. *Anal.* calcd. for $C_{31}H_{52}O_4Si_2S$: C 64.53, H 9.08; found: C 64.36, H 9.20.

Preparation of compound **311**, via the β-keto ester **310**, and the thermal rearrangement of this compound into the bicyclo[3.2.1]octa-2,6-diene **312**.



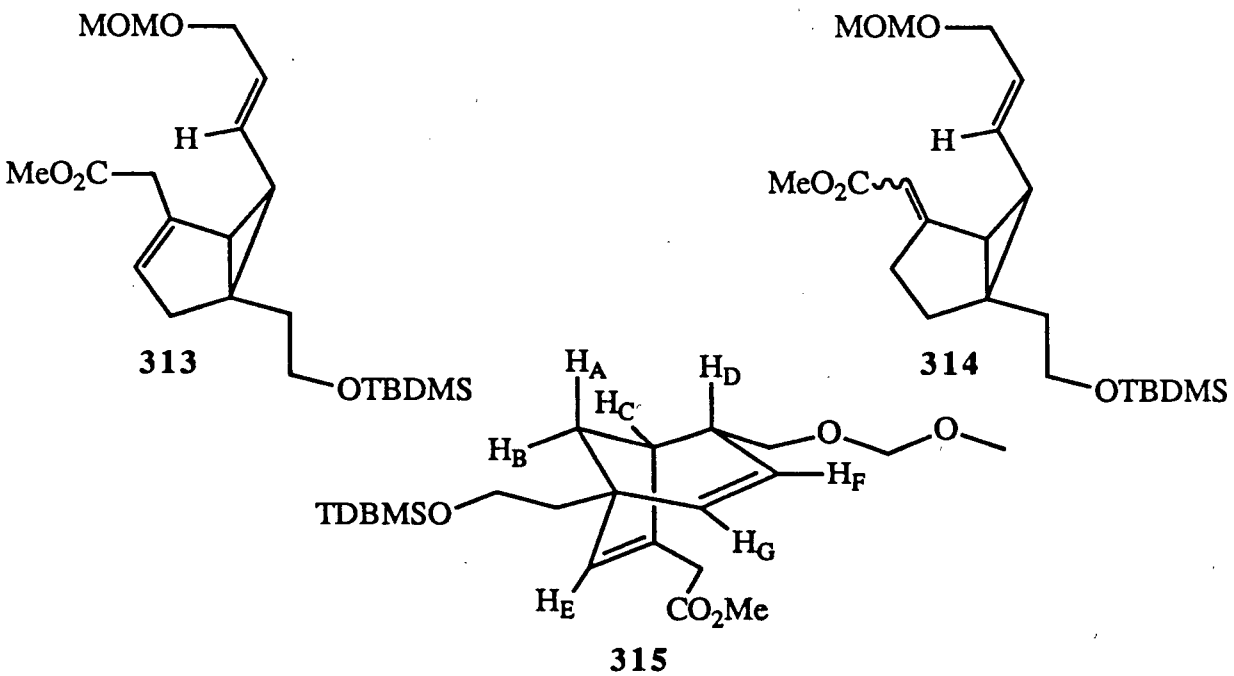
312

To a cold (-78°C), stirred solution of the ketone **279** (21 mg, 59 μmol) in dry THF (1.5 mL) (argon atmosphere) was added a solution of lithium diisopropylamide (0.3 M, 3 equiv.) in THF. After the mixture had been stirred for 20 min at -78°C and for 30 min at -20°C, it was re-cooled to -78°C and HMPA (30 μL, 3 equiv.) and methyl cyanoformate (41 μL, 3 equiv.) were added. After the mixture had been stirred for 15 min at -78°C it was poured into H_2O (5 mL). Diethyl ether (5 mL) was added and the vigorously stirred mixture was allowed to warm to room temperature. The layers were separated and the aqueous layer was extracted with Et_2O (2 x 5 mL). The combined organic extracts were washed with H_2O (3 x 3 mL) and brine (3 mL) and were then dried ($MgSO_4$) and concentrated, to give 30 mg of the crude β-keto ester **310** (after removal of traces of solvent under reduced pressure; room temperature/0.5 Torr). This oil was immediately dissolved in dry THF (2 mL), and

TBDMSCl (17 mg, 1.5 equiv.) was added to the solution. The solution was cooled to -78°C (argon atmosphere) and a suspension of KH (5 equiv. approx. 42 mg of a 35% dispersion of KH in mineral oil, prewashed with dry THF) in dry THF (approx. 0.5 mL) was added. After the mixture had been stirred at -78°C for 5 min and at room temperature for 45 min it was re-cooled to -78°C and saturated aqueous $NaHCO_3$ (2 mL) and Et_2O (5 mL) were added. The vigorously stirred mixture was allowed to warm to room temperature and the phases were separated. The aqueous phase was extracted with Et_2O (2 x 5 mL) and the combined organic extracts were washed with brine (3 mL), dried ($MgSO_4$) and concentrated, to give the crude compound **311**. To this crude oil (in a base washed round bottom flask) was added dry benzene (3 mL), and the solution (argon atmosphere) was warmed to 50°C overnight. Solvent was removed, and the residue was purified by flash chromatography (1:4 Et_2O - petroleum ether; 20 g of silica gel) to give (after removal of traces of solvent at reduced pressure; 0.5 Torr/room temperature) 24 mg (74%) of the compound **312**, a colourless oil which exhibited ir (neat): 1737, 1627, 1253, 841, 780 cm^{-1}; ^1H nmr (400 MHz, C_6D_6) δ: 0.11 (s, 6H, -SiMe$_2$), 0.18 (s, 3H, -SiMe), 0.21 (s, 3H, -SiMe), 0.97 (s, 9H, -SiBu^t), 1.02 (s, 9H, -SiBu^t), 1.68-1.85 (m, 2H, -OCH$_2$CH$_2$-), 1.93 (d, 1H, H_A, J = 9 Hz), 2.50 (br d, 1H, H_B, J = 9 Hz), 3.24 (s, 3H, -OMe), 3.50 (s, 3H, -OMe), 3.50-3.58 (m, 2H, H_C, and H_D or $H_{D'}$), 3.71 (m, 2H, -OCH$_2$CH$_2$-), 4.22 (m, 1H, H_D or $H_{D'}$), 4.61, 4.67 (d, d, 2H, -OCH$_2$O-, J = 6 Hz, J = 6 Hz), 5.08 (s, 1H, H_E), 5.97 (dd, 1H, H_F, J = 10 Hz, J = 2 Hz), 6.18 (br d, 1H, H_G, J = 10 Hz). In decoupling experiments, irradiation at δ 6.18 (H_G) caused the signal at δ 5.97 (H_F) to collapse to a d (J = 2 Hz); irradiation at δ 5.97 (H_F) caused the signal at δ 6.18 (H_G) to collapse to a br s; irradiation at δ 3.71 (-OCH$_2$CH$_2$-) caused the signal at δ 1.68-1.85 (-OCH$_2$CH$_2$-) to simplify to signals at δ 1.72 (d, J = 13 Hz) and δ 1.83 (d, J = 13 Hz); irradiation at δ 3.50-3.58 (H_C plus H_D or $H_{D'}$) caused the signal at δ 5.97 (H_F) to collapse to a d (J = 10 Hz), whilst the signal at δ 4.22 (H_D or $H_{D'}$) collapsed to br s; irradiation at δ 2.50 (H_B) caused the signal at δ 1.93 (H_A) to collapse to a s, whilst the signal at δ 6.18 (H_G) sharpened to a dd (J = 10 Hz, J =

1.5 Hz); irradiation at δ 1.93 ($\underline{H_A}$) caused the signal at δ 2.50 ($\underline{H_B}$) to collapse to a br s. In a COSY experiment (400 MHz, C_6D_6): $\underline{H_G}$ showed correlations into $\underline{H_F}$ and $\underline{H_C}$; $\underline{H_F}$ showed correlations into $\underline{H_G}$ and $\underline{H_C}$; $\underline{H_E}$ showed a correlation into $\underline{H_A}$; $\underline{H_D}/\underline{H_{D'}}$ (δ 4.22) showed a correlation into $\underline{H_D}/\underline{H_{D'}}$ and $\underline{H_C}$ (both at δ 3.50-3.58); $\underline{H_B}$ showed a correlation into $\underline{H_A}$; $\underline{H_A}$ showed correlations into $\underline{H_B}$ and $\underline{H_E}$. *Exact Mass* calcd. for $C_{27}H_{50}O_6Si_2$ (M^+): 526.3146; found: 526.3142. *Anal.* calcd. for $C_{27}H_{50}O_6Si_2$: C 61.55, H 9.57; found: C 61.38, H 9.60.

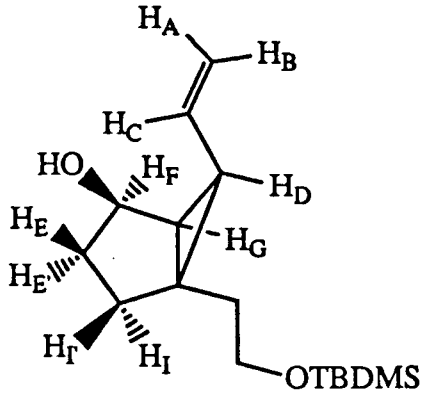
Preparation of compound **313**, via the esters **314**, and the thermal rearrangement of this compound into the bicyclo[3.2.1]octa-2.6-diene **315**



To a cold (0°C), stirred solution of trimethylphosphonoacetate (1.59 mmol, 10 equiv.) in dry THF (3 mL) (argon atmosphere) was added a solution of MeLi (10 equiv.) in Et_2O. After the mixture had been stirred at 0°C for 10 min and at room temperature for 10 min, a solution of the ketone **279** (56 mg, 0.159 mmol, 1 equiv.) in dry THF (2 mL) was added, and the resulting mixture was stirred at room temperature overnight. Water (2 mL) and Et_2O (5 mL) were added and the phases were separated. The aqueous phase was extracted with Et_2O (3 x 5 mL), and the combined organic extracts were washed with H_2O (3 mL), dried ($MgSO_4$) and concentrated. Flash chromatography of the crude reaction product (35:65 Et_2O - petroleum ether; 25 g of silica gel), gave (after removal of traces of solvent under reduced pressure; room temperature/0.5 Torr) 55 mg (85%) of the esters **314** (a 1:1 mixture of E and Z isomers by glc analysis), a colourless oil which was used without further purification. To a cold (-78°C), stirred solution of the reaction product (55 mg, 0.13 mmol) in dry THF (2.5 mL) (argon atmosphere) was added a solution of lithium diisopropylamide (0.3 M, 3.5 equiv.) in THF. After the solution had been stirred at -78°C for 45 min and at 0°C for 10 min it was transferred via cannula into a cold (-78°C) stirred mixture of glacial HOAc (0.5 mL) and THF (0.5 mL). After the resulting mixture had been stirred at -78°C for 10 min it was poured into H_2O (5 ml). Ether (5 mL) was added and then solid $NaHCO_3$ was added to the vigorously stirred mixture until all of the HOAc was neutralized. The layers were separated and the aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organic extracts were washed with H_2O (3 mL), dried ($MgSO_4$) and concentrated, to give the crude compound **313**. Dry benzene (3 mL) was added to this crude oil and the solution thus obtained was warmed to 50°C overnight (argon atmosphere). The solvent was removed and the residue was purified by flash chromatography (1:4 Et_2O - petroleum ether; 25 g of silica gel) to give (after removal of traces of solvent under reduced pressure; 0.5 Torr/room temperature) 38 mg (59% from the ketone **279**) of the compound **315**, a colourless oil which exhibited ir (neat): 3017, 1745, 1256, 1112, 838 cm^{-1}; ^1H nmr (400 MHz, C_6D_6) δ: 0.1 (s, 6H, -Si<u>Me</u>$_2$), 1.03 (s, 9H, -Si<u>Bu</u>^{t}), 1.69-1.82 (m, 2H,

-$OCH_2C\underline{H}_2$-), 1.84 (d, 1H, $\underline{H}_A$, J = 9 Hz), 2.22 (ddd, 1H, $\underline{H}_B$, J = 9 Hz, J = 5 Hz, J = 1.5 Hz), 2.74 (m, 1H, $\underline{H}_D$), 3.08 (m, 3H, $\underline{H}_C$ and -$C\underline{H}_2CO_2Me$), 3.21 (s, 3H, -O$\underline{Me}$), 3.30-3.40 (m, 5H, -O$\underline{Me}$ and -$C\underline{H}_2O$-), 3.71 (t, 2H, -$OC\underline{H}_2CH_2$-, J = 7 Hz), 4.48, 4.50 (d, d, 2H, -$OC\underline{H}_2O$-, J = 7 Hz, J = 7 Hz), 5.24 (ddd, 1H, $\underline{H}_F$, J = 10 Hz, J = 2 Hz, J = 2 Hz), 6.05 (br s, 1H, $\underline{H}_E$), 6.10 (ddd, 1H, $\underline{H}_G$, J = 10 Hz, J = 2.5 Hz, J = 1.5 Hz). In decoupling experiments, irradiation at δ 6.10 ($\underline{H}_G$) caused the signal at δ 5.24 ($\underline{H}_F$) to collapse to a dd (J = 2 Hz, J = 2 Hz), whilst the signal at δ 2.22 ($\underline{H}_B$) sharpened to a dd (J = 9 Hz, J = 5 Hz); irradiation at δ 5.24 ($\underline{H}_F$) caused the signal at δ 6.10 ($\underline{H}_G$) to collapse to a br dd (J = 2.5 Hz, J = 1.5 Hz); irradiation at δ 3.71 (-$OC\underline{H}_2CH_2$-) caused the signal at 1.69-1.82 (-$OCH_2C\underline{H}_2$-) to simplify to signals at δ 1.72 (d, J = 13 Hz) and δ 1.80 (d, J = 13 Hz); irradiation at δ 3.08 (-$C\underline{H}_2CO_2Me$ and $\underline{H}_C$) caused the signal at δ 5.24 ($\underline{H}_F$) to sharpen to a dd (J = 10 Hz, J = 2 Hz), whilst the signal at δ 2.22 ($\underline{H}_B$) collapsed to a dd (J = 9 Hz, J = 1.5 Hz); irradiation at δ 2.74 ($\underline{H}_D$) caused the signal at δ 6.10 ($\underline{H}_G$) to sharpen to a dd (J = 10 Hz, J = 1.5 Hz), whilst the signal at δ 5.24 ($\underline{H}_F$) sharpened to a dd (J = 10 Hz, J = 2 Hz); irradiation at δ 2.22 ($\underline{H}_B$) caused the signal at δ 6.10 ($\underline{H}_G$) to sharpen to a dd (J = 10 Hz, J = 2.5 Hz), whilst the signal at δ 1.84 ($\underline{H}_A$) collapsed to a s; irradiation of the signal at δ 1.84 ($\underline{H}_A$) caused the signal at δ 2.22 ($\underline{H}_B$) to collapse to a dd (J = 5 Hz, J = 1.5 Hz). *Exact Mass* calcd. for $C_{22}H_{38}O_5Si$ (M^+): 410.2489; found: 410.2498. *Anal.* calcd. for $C_{22}H_{38}O_5Si$: C 64.35, H 9.33; found: C 64.57, H 9.46.

Preparation of the alcohol **317**

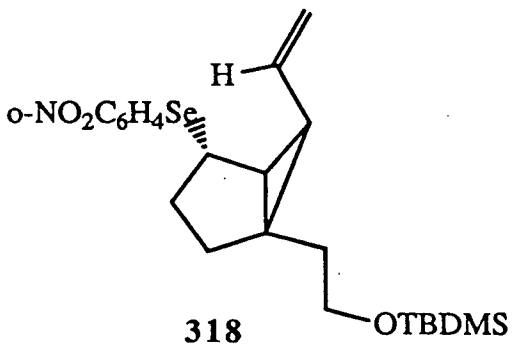


317

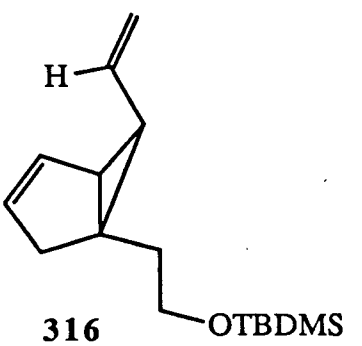
To a cold (-78°C), stirred solution of the ketone **278** (152 mg, 0.5 mmol) in dry THF (3 mL) (argon atmosphere) was added a solution of diisobutylaluminium hydride (1.5 equiv.) in hexane. After the mixture had been stirred at -78°C for 1 h and at 0°C for 20 min, saturated aqueous NH_4Cl (approx. 0.2 mL) was added and the vigorously stirred mixture was exposed to air and was allowed to warm to room temperature. To the white suspension thus obtained was added Et_2O (5 mL) and drying agent ($MgSO_4$). The mixture was suction filtered through a short plug of Florisil® (3 cm x 2 cm) using Et_2O as eluant. The combined eluate was concentrated and the residue was purified by flash chromatography (35:65 Et_2O - petroleum ether; 35 g of silica gel). Distillation (155-165°C/0.5 Torr) of the oil thus obtained gave 142 mg (93%) of the alcohol **317**, a colourless oil which exhibited ir (neat): 3356, 1256, 1099, 836, 776 cm^{-1}; ^{1}H nmr (400 MHz, C_6D_6) δ: 0.08 (s, 6H, -SiMe2), 0.99 (s, 9H, -SiBu^t), 1.16 (br s, 1H, -OH), 1.25-1.40 (m, 3H, -OCH_2CH- and HG and HI or HI'), 1.48 (br dd, 1H, HD, J = 8 Hz, J = 8 Hz), 1.60-1.75 (m, 2H, -OCH_2CH- and HE or HE'), 1.85 (ddd, 1H, HI or HI', J = 9 Hz, J = 8 Hz, J = 1.5 Hz), 2.04 (dddd, 1H, HE or HE', J = 13 Hz, J = 9 Hz, J = 9 Hz, J = 1.5 Hz), 4.56 (m, 1H, HF), 5.12 (ddd, 1H, HA, J = 10 Hz, J = 2 Hz, J = 1 Hz), 5.31 (ddd, 1H, HB, J = 16 Hz, J = 2 Hz, J = 1 Hz),

6.12 (ddd, 1H, J = 16 Hz, J = 10 Hz, J = 8 Hz). On addition of D_2O the signal at δ 1.16 (-O<u>H</u>) disappeared. *Exact Mass* calcd. for $C_{16}H_{30}O_2Si$ (M^+): 282.2015; found: 282.2011.

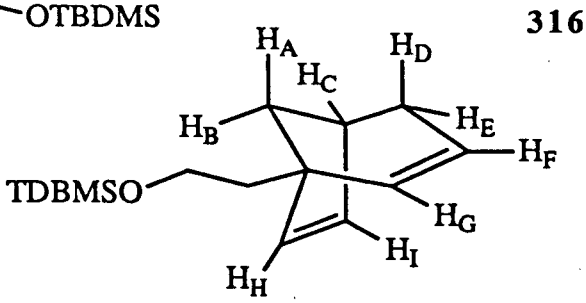
<u>Preparation of compound **316**, via the alcohol **317** and the selenide **318**. The thermal rearrangement of compound **316** to the bicyclo[3.2.1]octa-2,6-diene **320**.</u>



318



316



320

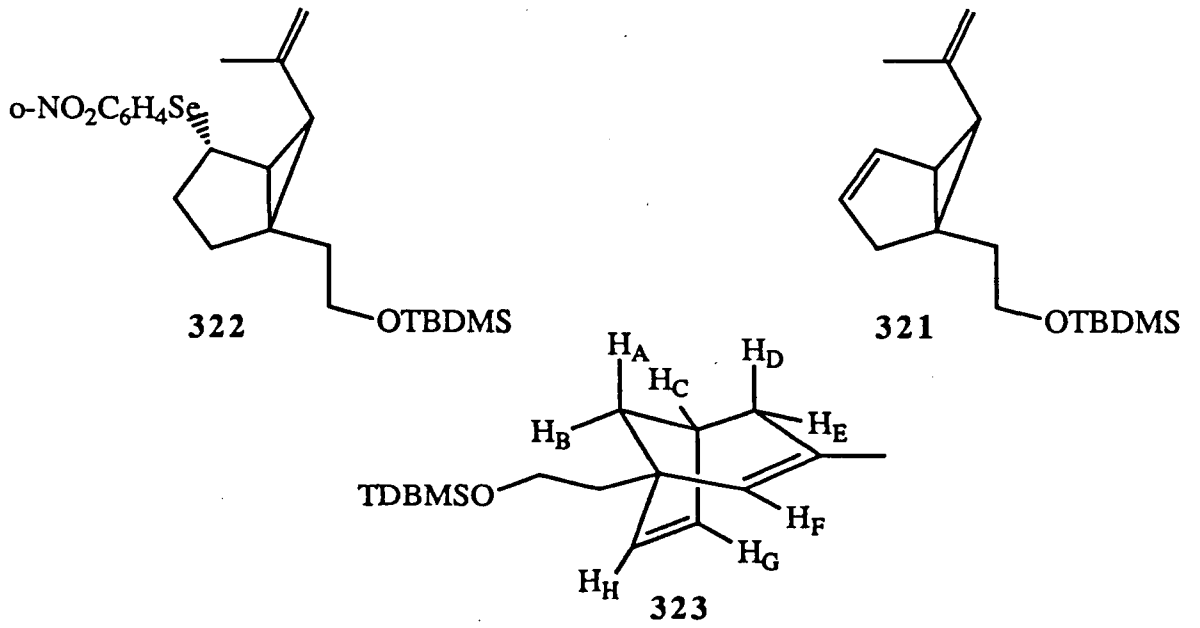
To a stirred solution of the alcohol **317** (98 mg, 0.35 mmol) in dry THF (5 mL) at room temperature (argon atmosphere) was added successively, *o*-nitrophenylselenocyanate (1.3 equiv., 104 mg) and Bu3P (1.3 equiv., 91 mg). After the mixture had been stirred for 20 min at room temperature, the solvent was removed and the residue was purified by flash chromatography (5:95 Et_2O - petroleum ether; 30 g of silica gel), to give 115 mg of the

selenide **318**. This yellow solid was not completely pure, but was carried on to the next step without further purification.

To a stirred solution of the selenide **318** (115 mg) in CH_2Cl_2 (4 mL) at room temperature was added 30% aqueous H_2O_2 (3 mL). The mixture was stirred vigorously for 45 min (the solution became decolourized after approx. 10 min) at room temperature, and then saturated aqueous $NaHCO_3$ (5 mL) and Et_2O (10 mL) were added to the mixture. The phases were separated and the aqueous layer was extracted with Et_2O (3 x 5 mL). The combined organic extracts were washed with brine (3 mL), dried and concentrated. Flash chromatography of the residual oil (3:97 Et_2O - petroleum ether; 20 g of silica gel), followed by distillation of the oil thus obtained (160-170°C/6 Torr) gave 48 mg (52% from the alcohol **317**, 48 % from the ketone **278**) of the compound **320**, a colourless oil which exhibited ir (neat): 3020, 1473, 1255, 1095, 837, 776 cm^{-1}; ^1H nmr (400 MHz, C_6D_6) δ: 0.10 (s, 6H, -Si$\underline{Me}_2$), 1.02 (s, 9H, -Si$\underline{Bu}^t$), 1.65-1.95 (m, 5H, -$OCH_2\underline{CH}_2$- and $\underline{H}_A$, $\underline{H}_B$ and $\underline{H}_E$), 2.17 (dddd, $\underline{H}_D$, J = 18 Hz, J = 5 Hz, J = 3 Hz, J = 2.5 Hz), 2.61 (m, 1H, $\underline{H}_C$), 3.73 (m, 2H, -$OC\underline{H}_2CH_2$-), 5.25 (dddd, $\underline{H}_F$, J = 10 Hz, J = 3 Hz, J = 2.5 Hz, J = 1.5 Hz), 5.61 (dd, 1H, $\underline{H}_I$, J = 6 Hz, J = 3 Hz), 5.98 (m, 1H, $\underline{H}_G$), 6.09 (d, 1H, $\underline{H}_H$, J = 6 Hz). In decoupling experiments, irradiation at δ 6.09 ($\underline{H}_H$) caused the signal at δ 5.61 ($\underline{H}_I$) to collapse to a d (J = 3 Hz); irradiation at δ 5.98 ($\underline{H}_G$) caused the signal at δ 5.25 ($\underline{H}_F$) to collapse to a ddd (J = 3 Hz, J = 2.5 Hz, J = 1.5 Hz), whilst the signal at δ 2.17 ($\underline{H}_D$) sharpened to a ddd (J = 18 Hz, J = 5 Hz, J = 3 Hz); irradiation at δ 5.61 ($\underline{H}_I$) caused the signal at δ 6.09 ($\underline{H}_H$) to collapse to a s, whilst the signal at δ 2.61 ($\underline{H}_C$) simplified to a br dd (J = 5 Hz, J = 5 Hz); irradiation at δ 5.25 ($\underline{H}_F$) caused the signal at δ 5.98 ($\underline{H}_G$) to collapse to a br s, whilst the signal at δ 2.17 ($\underline{H}_D$) sharpened to a ddd (J = 18 Hz, J = 5 Hz, J = 2.5 Hz); irradiation at δ 2.61 ($\underline{H}_C$) caused the signal at δ 5.61 ($\underline{H}_I$) to collapse to a d (J = 6 Hz), whilst the signal at δ 5.25 ($\underline{H}_F$) sharpened to a ddd (J = 10 Hz, J = 3 Hz, J = 2.5 Hz), and the signal at δ 2.17 ($\underline{H}_D$) sharpened to a ddd (J = 18 Hz, J = 3 Hz, J = 2.5 Hz); irradiation at δ 2.17 ($\underline{H}_D$) caused the signal at δ 5.98 ($\underline{H}_G$) to collapse to a br d (J =

10 Hz), whilst the signal at 5.25 ($\underline{H}_F$) sharpened to a ddd (J = 10 Hz, J = 2.5 Hz, J = 1.5 Hz). In a COSY experiment (400 MHz, C_6D_6): $\underline{H}_H$ showed a correlation into $\underline{H}_I$; $\underline{H}_G$ showed correlations into $\underline{H}_F$, $\underline{H}_D$, and $\underline{H}_E$; $\underline{H}_I$ showed correlations into $\underline{H}_H$ and $\underline{H}_C$; $\underline{H}_F$ showed correlations into $\underline{H}_G$, $\underline{H}_D$ and $\underline{H}_E$; $\underline{H}_C$ showed correlations into $\underline{H}_D$, $\underline{H}_E$, $\underline{H}_I$ and $\underline{H}_B$; $\underline{H}_D$ showed correlations into $\underline{H}_F$, $\underline{H}_G$, $\underline{H}_C$ and $\underline{H}_E$; $\underline{H}_B$ showed correlations into $\underline{H}_C$ and $\underline{H}_A$. *Exact Mass* calcd. for $C_{12}H_{19}OSi$ (M^+-Bu^t): 207.1205; found: 207.1204. *Anal.* calcd. for $C_{16}H_{28}OSi$: C 72.66, H 10.67; found: C 72.56, H 10.58.

Preparation of compound **321** via the alcohol **283** and the selenide **322**. The thermal rearrangement of compound **321** into the bicyclo[3.2.1]octa-2,-6-diene **323**.



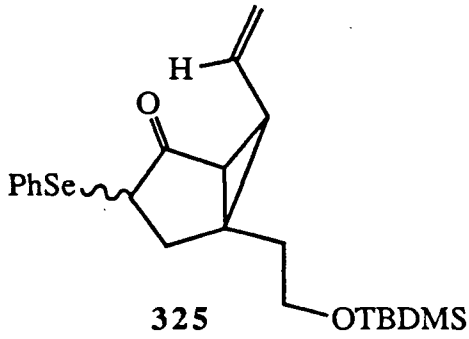
The alcohol **283** was prepared from a mixture of the ketones **281** and **282** as previously described. To a stirred solution of the alcohol **283** (35 mg, 0.12 mmol) in dry

THF (2 mL) at room temperature (argon atmosphere) was added successively, *o*-nitrophenylselenocyanate (1.3 equiv., 35 mg) and Bu_3P (1.3 equiv., 31 mg). After the mixture had been stirred for 20 min at room temperature, the solvent was removed and the residue was purified by flash chromatography (5:95 Et_2O - petroleum ether; 20 g of silica gel), to give 25 mg of the selenide **322**. This yellow solid was not completely pure, but was carried on to the next step without further purification.

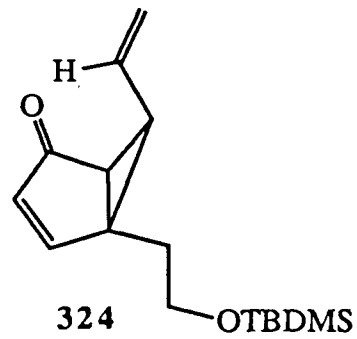
To a stirred solution of the reaction product (25 mg) in CH_2Cl_2 (1 mL) at room temperature was added 30% aqueous H_2O_2 (1 mL). The mixture was stirred vigorously for 45 min (the solution became decolourized after approx. 10 min) at room temperature, and then saturated aqueous $NaHCO_3$ (2 mL) and Et_2O (5 mL) were added to the mixture. The phases were separated and the aqueous layer was extracted with Et_2O (3 x 3 mL). The combined organic extracts were washed with brine (2 mL), dried and concentrated. Flash chromatography of the residual oil (3:97 Et_2O - petroleum ether; 12 g of silica gel), followed by distillation of the oil thus obtained (160-175°C/6 Torr) gave 14.5 mg (44% from the alcohol **283**, 29 % from the mixture of the ketones **281** and **282**) of the compound **323**, a colourless oil which exhibited ir (neat): 3051, 1256, 1093, 837, 775 cm^{-1}; ^1H nmr (400 MHz, C_6D_6) δ: 0.12 (s, 6H, -Si$\underline{Me}_2$), 1.04 (s, 9H, -Si$\underline{Bu}^t$), 1.53 (s, 3H, -$\underline{Me}$), 1.60 (br d, 1H, $\underline{H}_E$, J = 17 Hz), 1.63 (d, 1H, $\underline{H}_A$, J = 9 Hz), 1.82-1.96 (m, 3H, -$OCH_2C\underline{H}_2$- and $\underline{H}_B$), 2.08 (br dd, 1H, $\underline{H}_D$, J = 17 Hz, J = 5 Hz), 2.66 (m, 1H, $\underline{H}_C$), 5.64 (dd, 1H, $\underline{H}_G$, J = 5.5 Hz, J = 2.5 Hz), 5.71 (m, 1H, $\underline{H}_F$), 6.08 (d, 1H, $\underline{H}_H$, J = 5.5 Hz). In decoupling experiments irradiation at δ 6.08 ($\underline{H}_H$) caused the signal at δ 5.64 ($\underline{H}_G$) to collapse to a d (J = 2.5 Hz); irradiation at δ 5.64 ($\underline{H}_G$) caused the signal at δ 6.08 ($\underline{H}_H$) to collapse to a s, whilst the signal at δ 2.66 ($\underline{H}_C$) sharpened to a dd (J = 5.5 Hz, J = 5 Hz); irradiation at δ 3.80 (-$OC\underline{H}_2CH_2$-) caused the signal at δ 1.82-1.96 (-OCH_2CH_2- and $\underline{H}_B$) to simplify to signals at δ 1.85 (d, J = 13 Hz), δ 1.93 (d, J = 13 Hz) and δ 1.88 (dd, $\underline{H}_B$, J = 9 Hz, J = 5 Hz); irradiation at δ 2.66 ($\underline{H}_C$) caused the signal at δ 5.64 ($\underline{H}_G$) to collapse to a d (J = 5.5 Hz), whilst the signal at δ 2.08 ($\underline{H}_D$) collapsed to a br d (J = 17 Hz); irradiation at

δ 2.08 ($\underline{H_D}$) caused the signal at δ 1.60 ($\underline{H_E}$) to collapse to a br s. *Exact Mass* calcd. for $C_{13}H_{21}OSi$ (M^+-Bu^t): 221.1363; found: 221.1352 ; cims (positive ion detection, NH_3): 279 (M^++H).

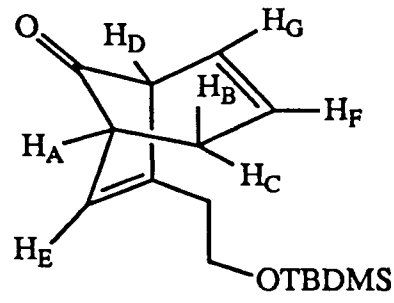
Preparation of compound **324** via the α-phenylselenoketones **325**, and the rearrangement of this compound into the bicyclo[3.2.1]octa-2,6-diene **326**



325



324



326

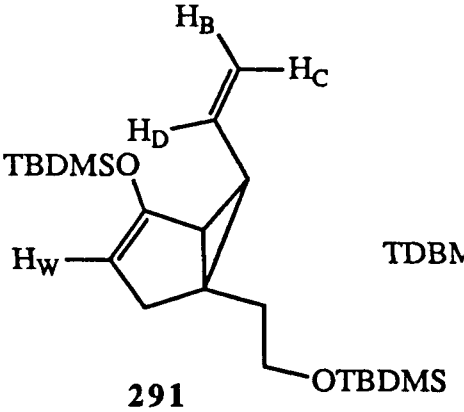
To a cold (-78°C) stirred solution of the ketone **278** (104 mg, 0.37 mmol) in dry THF (3 mL) (argon atmosphere) was added a solution of lithium diisopropylamide (2 equiv., 0.5 M) in THF. After the mixture had been stirred for 30 min at -78°C and 20 min at -20°C, it was re-cooled to -78°C and a solution of PhSeBr (prepared from PhSeSePh (150 mg,

2.6 equiv.) and Br_2 (48 mg, 2.5 equiv., in 2 mL of dry THF) was added, via cannula. After the mixture had been stirred at -78°C for 20 min, saturated aqueous $NaHCO_3$ (3 mL) and Et_2O (5 mL) were added and the vigorously stirred mixture was allowed to warm to room temperature. The phases were separated, the aqueous phase was extracted with Et_2O (2 x 5 mL), and the combined organic extracts were washed with brine (3 mL), dried ($MgSO_4$) and concentrated. Flash chromatography of the residual oil (15:85 Et_2O - petroleum ether; 30 g of silica gel) gave 121 mg (75%) of the selenides **325** (after removal of traces of solvent under reduced pressure; room temperature/0.5 Torr). This yellow oil was carried on to the next step without further purification.

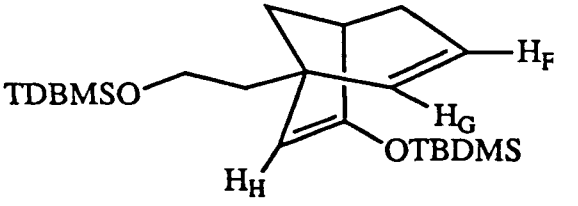
To a stirred solution of the selenides **325** (50 mg, 0.11 mmol) in DME (2 mL) at room temperature, was added solid $NaIO_4$ (3 equiv. 66 mg). A few drops of water were added, and the mixture was stirred at room temperature overnight. Saturated aqueous $NaHCO_3$ (2 mL) and Et_2O (5 mL) were added, the phases were separated and the aqueous phase was extracted with Et_2O (2 x 3 mL). The combined organic extracts were dried ($MgSO_4$) and concentrated. Flash chromatography of the residual oil (35:65 Et_2O - petroleum ether; 25 g of silica gel) followed by distillation of oil thus obtained (120°C/0.2 Torr), gave 26 mg (80%) of the compound **326**, a colourless oil which exhibited ir (neat): 3033, 1770, 1256, 837 cm^{-1}; ^1H nmr (400 MHz, C_6D_6) δ: 0.05 (s, 6H, -Si<u>Me</u>$_2$), 0.99 (s, 9H, -Si<u>Bu</u>^{t}), 1.62 (m, 1H, <u>H</u>$_C$ or <u>H</u>$_B$), 2.03 (td, 2H, -OCH$_2$C<u>H</u>$_2$-, J = 6 Hz, J = 1.5 Hz), 2.27 (m, 1H, <u>H</u>$_B$ or <u>H</u>$_C$), 2.88 (m, 1H, <u>H</u>$_A$), 3.43 (m, 2H, -OC<u>H</u>$_2$CH$_2$-), 4.44 (br d, <u>H</u>$_D$, J = 6.5 Hz), 5.15 (m, 1H, <u>H</u>$_F$), 5.32 (dm, 1H, <u>H</u>$_E$, J = 6.5 Hz), 5.82 (m, 1H, <u>H</u>$_G$). In decoupling experiments, irradiation at δ 2.03 (-OCH$_2$C<u>H</u>$_2$-) caused the signal at δ 5.32 (<u>H</u>$_E$) to sharpen to a dd (J = 6.5 Hz, J = 1.5 Hz), whilst the signal at δ 3.43 (-OC<u>H</u>$_2$CH$_2$-) collapsed to a s; irradiation at δ 2.88 (<u>H</u>$_A$) caused the signal at δ 5.32 (<u>H</u>$_E$) to collapse to a m, whilst the signal at δ 5.15 (<u>H</u>$_F$) sharpened to a dddd (J = 11 Hz, J = 3.5 Hz, J = 3.5 Hz, J =1 Hz); irradiation at δ 3.43 (-OC<u>H</u>$_2$CH$_2$-) caused the signal at δ 2.03 (-OCH$_2$C<u>H</u>$_2$-) to collapse to a d (J = 1.5 Hz); irradiation at δ 4.44 (<u>H</u>$_D$) caused the signal at δ 5.82 (<u>H</u>$_G$) to

sharpen to a ddd (J =11 Hz, J = 2 Hz, J = 2 Hz), whilst the signal at δ 5.15 (H_F) sharpened to a dddd (J = 11 Hz, J = 3.5 Hz, J = 3.5 Hz, J = 1.5 Hz), and the signal at δ 5.32 (H_E) sharpened to a dt (J = 6 5 Hz, J = 1.5 Hz); irradiation at δ 5.32 (H_E) caused the signal at δ 2.03 (-OCH_2CH_2-) to collapse to a t (J = 6.5 Hz); irradiation at δ 5.82 (H_G) caused the signal at δ 4.44 (H_D) to collapse to a br s. *Exact Mass* calcd. for $C_{16}H_{26}O_2Si$ (M^+): 278.1702; found: 278.1698.

General Procedure P. Determination of the rate constants for the Cope rearrangements of the 6-*endo*-(1-alkenyl) bicyclo[3.1.0]hex-2-enes **215** into the corresponding bicyclo[3.2.1]octa-2,6-dienes **216.**



291



292

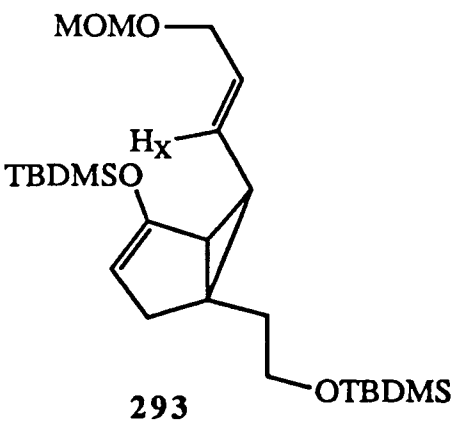
The general procedure which was used to determine the rate of Cope rearrangement of 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hex-2-enes is exemplified by that used to determine the rate of rearrangement of compound **291** into compound **292.** Thus, the ketone **278** (50 mg, 0.18 mmol) was converted to the silyl enol ether **291** as described previously. After extractive workup, the solvent was removed by rotary evaporation at room temperature

(heating was avoided in order to prevent the Cope rearrangement from occurring before beginning the kinetic measurements). All remaining volatile material was removed from the crude reaction product under reduced pressure (room temperature, 0.5 Torr) to give 67 mg of the crude compound **291**. A sample of this oil (15 mg, 38 μmol) was dissolved in enough benzene-d_6 (0.8 mL) to fill a 5 mm nmr tube to 3 cm. The solution was carefully transferred to a dry, base washed 5 mm nmr tube, which was then placed in the probe of the nmr spectrometer (Varian XL-300). A spectrum was recorded (see text). This spectrum represented the situation at t = 0, at which time no Cope rearrangement had occurred. The variable temperature unit was activated and was set at 40°C. This setting actually achieves a temperature of 43°C, as shown by a calibration experiment using ethylene glycol as the standard. The required temperature (43°C) was reached after only a few seconds (as indicated by the digital temperature gauge of the spectrometer). Spectra were then recorded at time intervals (see text), and the relative amounts of **291** compared to the rearrangement product **292** were determined by integration of the signals at δ 5.88 (H_D for **291**) and 6.17 (H_G for **292**). The fraction of **291** remaining after time t (seconds) is listed below in Table 13. A plot of time (s) versus ln{[**291**]/[**291**]+[**292**]} was carried out using "Cricketgraph" software on a Macintosh SE computer. The plot produces a set of points of which the line of best fit (as calculated by the "Cricket Graph" software) has a slope -3.7×10^{-5} s^{-1}.

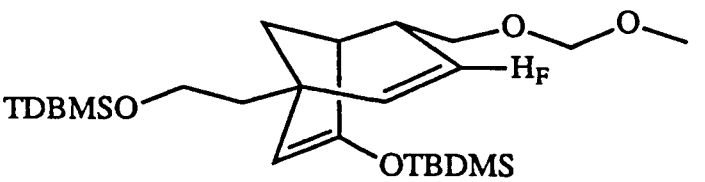
The Cope rearrangements of other 6-*endo*-(1-alkenyl)bicyclo[3.1.0]hex-2-enes were observed in a similar manner. In each case, the ratios of rearranged to unrearranged substrate were determined by integration of well dispersed, diagnostic peaks for these compounds (usually the olefinic peaks). For substrates which undergo rapid Cope rearrangement, the experiment was usually continued until 3 half lives had been observed (after 3 half lives the integration becomes less accurate). For substrates which undergo relatively slow Cope rearrangement, the experiment was usually stopped after two half lives. The probe temperature calibration was performed immediately after each experiment.

Table 13. Kinetic data for the rearrangement of **291** into **292** at 43°C.		
Time, s	[**291**]/[**291**]+[**292**]	ln{[**291**]/[**291**]+[**292**]}
0	1	0
5400	0.83	-0.19
10,800	0.68	-0.38
16,200	0.56	-0.57
18,000	0.53	-0.63
19,800	0.50	-0.69
32,400	0.31	-1.18
36,000	0.27	-1.32
37,800	0.25	-1.39

The rearrangement of compound **293** to compound **294**



293



294

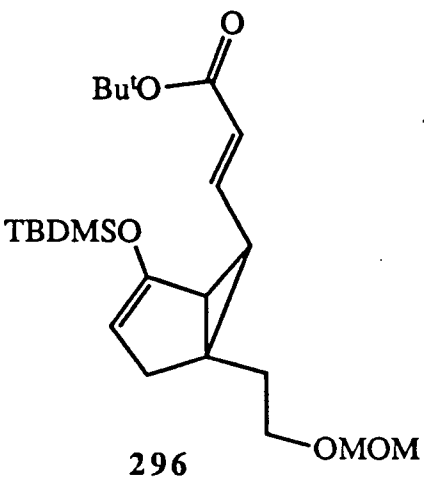
The ketone **279** (10 mg, 28 μmol) was converted into the enol silyl ether **293** as described previously. All volatile material was removed from the crude reaction product under reduced pressure (room temperature, 0.5 Torr), to give 13 mg of the crude compound **293**. This oil (13 mg, 28 mmol) was dissolved in benzene-d_6 (0.8 mL), the solution was carefully transferred to a dry, base washed nmr tube and the rearrangement was carried out as described in general procedure P. The relative amounts of **293** and the rearrangement product **294** which were present after time t seconds were measured by integration of the signals at δ 5.80 ($\underline{H}_X$ **293**) and 5.58 ($\underline{H}_F$ **294**). The fraction of **293** remaining after time t seconds is listed below (Table 15).

A plot of time (s) versus ln{[**293**]/[**293**]+[**294**]} produces a set of points which best fit a straight line (see text) of slope -2.6×10^{-5} s^{-1}.

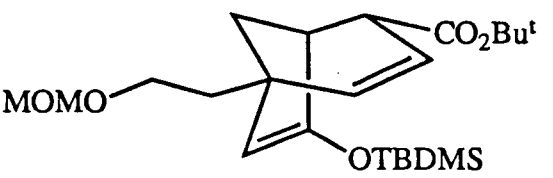
Table 15. Kinetic data for the rearrangement of **293** into **294** at 43°C.

Time, s	[293]/[293]+[294]	ln{[293]/[293]+[294]}
0	1	0
14400	0.67	-0.40
21600	0.54	-0.61
25200	0.52	-0.66
48600	0.28	-1.27

The rearrangement of compound **296** into compound **297**



296



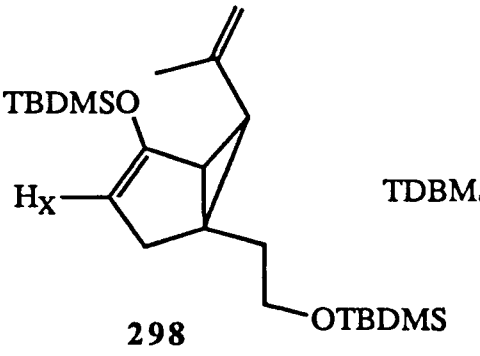
297

The ketone **280** (10 mg, 32 μmol) was converted to the silyl enol ether **296** as described previously. All volatile material was removed from the crude reaction product under reduced pressure (room temperature, 0.5 Torr), to give 12 mg (28 μmol) of the crude compound **296**. This oil was dissolved in benzene-d_6 (0.8 mL), the solution was carefully transferred to a dry, base washed nmr tube and the rearrangement was carried out as described in general procedure P. The relative amounts of **296** and the rearrangement product **297** which were present after time t seconds were measured by integration of the 2-proton signals at δ 3.45 (-OC$\underline{H_2}$CH$_2$-, **296**) and 3.57 (-OC$\underline{H_2}$CH$_2$-, **297**). The fraction of **296** remaining after time t seconds is listed below (Table 16).

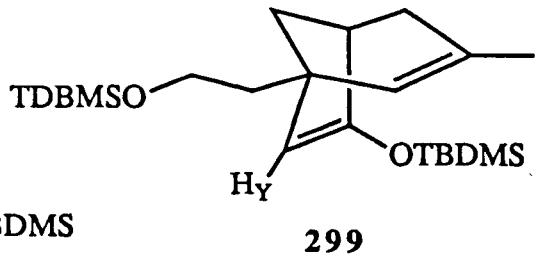
A plot of time (s) versus ln{[**296**]/[**296**]+[**297**]} produces a set of points which best fit a straight line (see text) of slope -2.3×10^{-4} s^{-1}.

Table 16. Kinetic data for the rearrangement of **296** into **297** at 43°C.		
Time, s	[296]/[296]+[297]	ln{[296]/[296]+[297]}
0	0.92	-0.08
1800	0.55	-0.60
2100	0.53	-0.63
2400	0.49	-0.71
4200	0.32	-1.14
4800	0.28	-1.27
7200	0.18	-1.71

The rearrangement of compound **298** into compound **299**



298



299

The *cis* divinylcyclopropane **298** was prepared from a mixture of the ketones **281** and **282** (10 mg, 34 μmol, 4:1 respectively, by glc analysis) as described previously. All volatile material was removed from the crude reaction product under reduced pressure (room

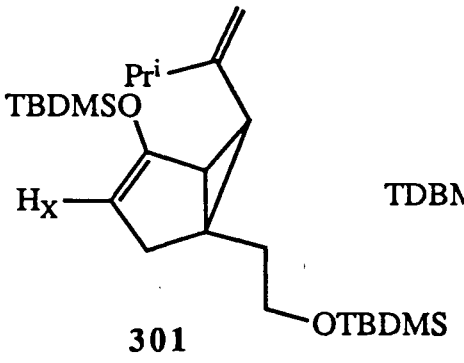
temperature, 0.5 Torr), and the residual oil (12 mg, 29 mmol) was dissolved in benzene-d_6 (0.8 mL). The solution was carefully transferred to a dry, base washed nmr tube and the rearrangement was carried out at 43°C as described in general procedure P. The relative amounts of **298** and the rearrangement product **299** present after time t seconds was measured by integration of the signals at δ 4.32 (H_X **298**) and 5.86 (H_Y **299**). The fraction of **298** remaining after time t seconds is listed below (Table 17).

A plot of time (s) versus ln{[**298**]/[**298**]+[**299**]} produces a set of points which best fit a straight line (see text) of slope -1.1×10^{-4} s^{-1}.

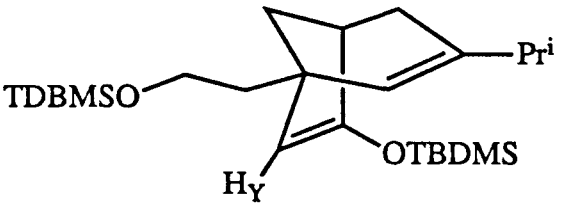
Table 17. Kinetic data for the rearrangement of **298** into **299** at 43°C.

Time, s	[298]/[298]+[299]	ln{[298]/[298]+[299]}
0	1	0
2400	0.72	-0.33
5400	0.58	-0.55
6300	0.51	-0.67
7200	0.46	-0.77
8100	0.42	-0.87
12000	0.27	-1.32
14400	0.20	-1.61

The rearrangement of compound **301** into compound **302**



301



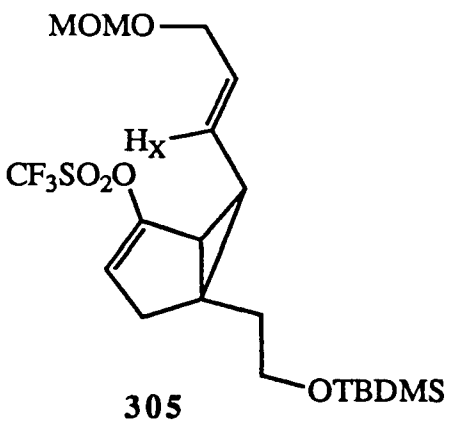
302

The compound **301** was prepared from a mixture of the ketones **285** and **286** (18 mg, 56 μmol, 4:1 respectively, by glc analysis) as described previously. All volatile material was removed from the crude reaction product under reduced pressure (room temperature, 0.5 Torr) to give 22 mg of the crude silyl enol ether **301**. A sample of this oil (16 mg, 37 μmol) was dissolved in benzene-d_6 (0.8 mL). The solution was carefully transferred to a dry, base washed nmr tube and the kinetic measurements were carried out as described in general procedure P. The relative amounts of **301** and the rearrangement product **302** which were present after time t seconds were measured by integration of the signals at δ 4.25 (H_X **301**) and 5.93 (H_Y **302**). The fraction of **301** remaining after time t seconds is listed below (Table 18).

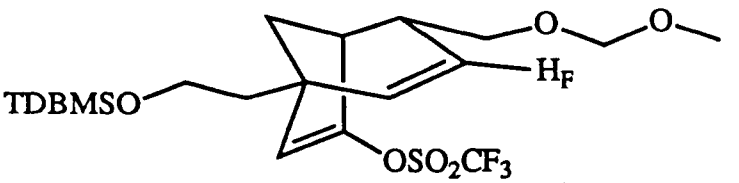
A plot of time (s) versus ln{[**301**]/[**301**]+[**302**]} produces a set of points which best fit a straight line (see text) of slope -4.5×10^{-4} s^{-1}.

Table 18. Kinetic data for the rearrangement of **301** into **302** at 43°C.		
Time, s	[301]/[301]+[302]	ln{[301]/[301]+[302]}
0	0.94	-0.06
600	0.67	-0.40
1200	0.49	-0.71
1500	0.45	-0.80
2400	0.32	-1.14
2700	0.28	-1.28
3000	0.24	-1.44
4500	0.11	-2.17

The rearrangement of compound **305** into the compound **306**



305



306

The ketone **279** (30 mg, 85 μmol) was converted into the enol triflate **305** as described previously. Flash chromatography (1:9 Et_2O - petroleum ether; 25 g of silica gel)

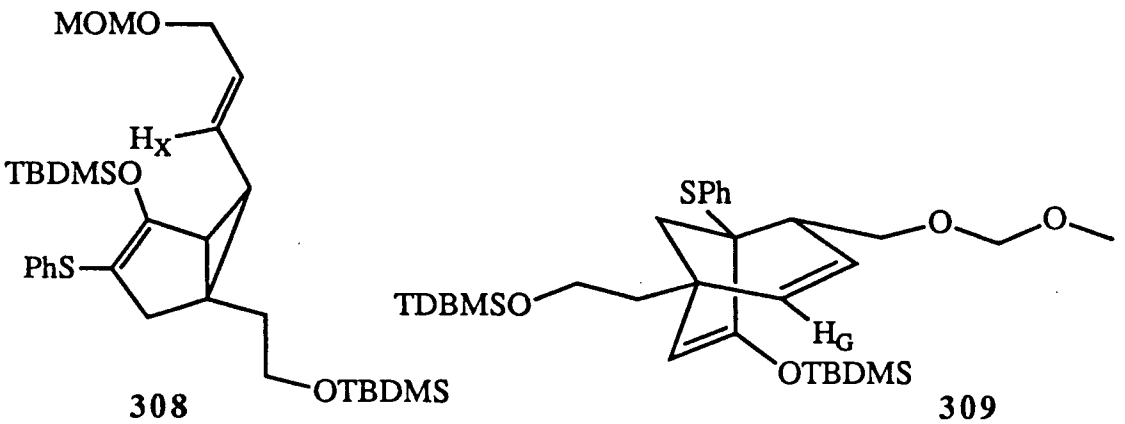
of the crude reaction product gave 30 mg of the compound **305** (after removal of traces of solvent under reduced pressure; room temperature, 0.5 Torr). A sample of this oil (16 mg, 33 mmol) was dissolved in benzene-d_6 (0.8 mL), the solution was carefully transferred to a dry, base washed nmr tube and the rearrangement was carried out as described in general procedure P. The relative amounts of **305** and the rearrangement product **306** which were present after time t seconds were measured by integration of the signals at δ 5.49 ($\underline{H}_X$, **305**) and 5.16 ($\underline{H}_F$, **306**). The fraction of **305** remaining after time t seconds is listed below (Table 19).

A plot of time (s) versus ln{[**305**]/[**305**]+[**306**]} produces a set of points which best fit a straight line (see text) of slope -2.9×10^{-4} s^{-1}.

Table 19. Kinetic data for the rearrangement of **305** into **306** at 43°C.

Time, s	[**305**]/[**305**]+[**306**]	ln{[**305**]/[**305**]+[**306**]}
0	1	0
1200	0.68	-0.39
2400	0.48	-0.73
3000	0.42	-0.88
5100	0.25	-1.38
6000	0.16	-1.85

The rearrangement of compound 308 into compound 309.

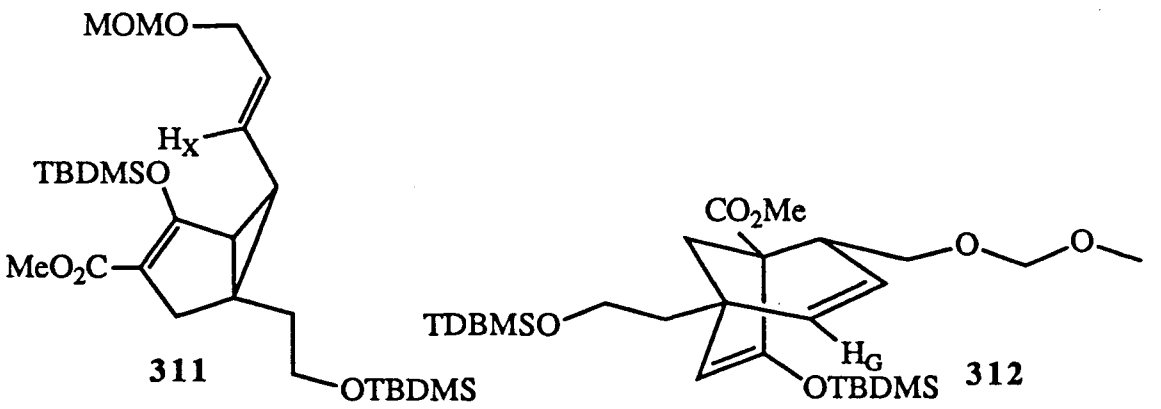


The α-phenylthio ketone **307** (27 mg, 58 μmol) was converted to the silyl enol ether **308** as described previously. All volatile material was removed from the crude reaction product under reduced pressure (room temperature, 0.5 Torr), to give 20 mg (35 μmol) of the crude compound **308**. This oil was dissolved in benzene-d_6 (0.8 mL), the solution was carefully transferred to a dry, base washed nmr tube and the rearrangement was carried out as described in general procedure P. The relative amounts of **308** and the rearrangement product **309** which were present after time t seconds were measured by integration of the signals at δ 5.75 (H_X, **308**) and 6.13 (H_G, **309**). The fraction of **308** remaining after time t seconds is listed below (Table 20).

A plot of time (s) versus ln{[308]/[308]+[309]} produces a set of points which best fit a straight line (see text) of slope -1.5×10^{-5} s^{-1}.

Table 20. Kinetic data for the rearrangement of **308** into **309** at 43°C.		
Time, s	[308]/[308]+[309]	ln{[308]/[308]+[309]}
0	100	0
14400	0.81	-0.21
28800	0.67	-0.40
50400	0.47	-0.75

The rearrangement of compound **311** into compound **312**



The crude β-keto ester **310** (17 mg, 42 μmol) was converted into the silyl enol ether **311** as described previously. All volatile material was removed from the crude reaction product under reduced pressure (room temperature, 0.5 Torr), to give 18 mg (30 μmol) of the crude compound **311**. This oil was dissolved in benzene-d_6 (0.8 mL), the solution was carefully transferred to a dry, base washed nmr tube and the rearrangement was carried out as

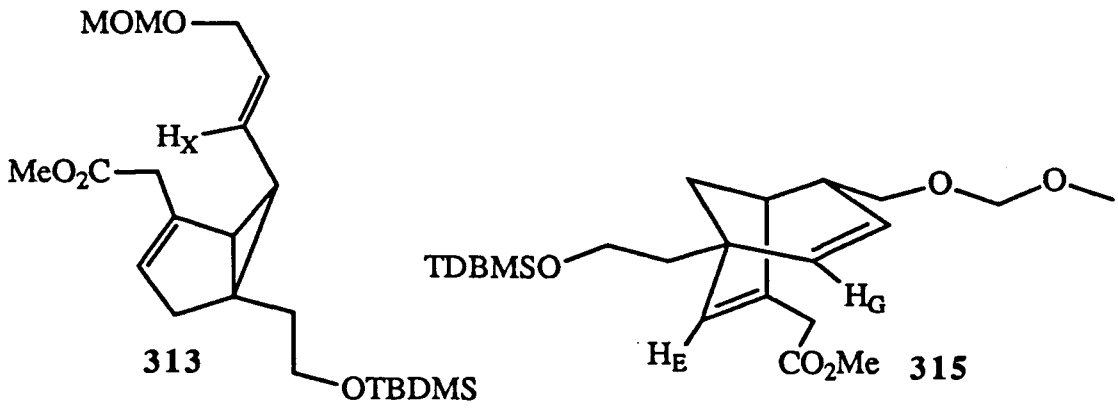
described in general procedure P. The relative amounts of **311** and the rearrangement product **312** which were present after time t seconds were measured by integration of the signals at δ 5.67 (H_X, **311**) and 6.18 (H_G, **312**). The fraction of **311** remaining after time t seconds is listed below (Table 21).

A plot of time (s) versus ln{[**311**]/[**311**]+[**312**]} produces a set of points which best fit a straight line (see text) of slope -6.2×10^{-5} s^{-1}.

Table 21. Kinetic data for the rearrangement of **311** into **312** at 43°C.

Time, s	[311]/[311]+[312]	ln{[311]/[311]+[312]}
0	1	0
11400	0.53	-0.63
12600	0.49	-0.70
22800	0.24	-1.41
24000	0.23	-1.46

The rearrangement of compound **313** into compound **315**



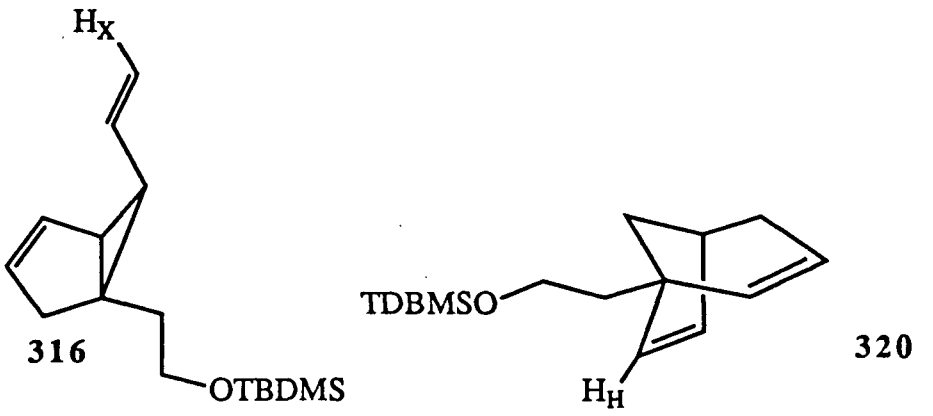
The unsaturated esters **314** (15.5 mg, 38 μmol) were converted into the deconjugated ester **313** as described previously. All volatile material was removed from the crude reaction product under reduced pressure (room temperature, 0.5 Torr), to give 14 mg (34 μmol) of the crude compound **313**. This oil was dissolved in benzene-d_6 (0.8 mL), the solution was carefully transferred to a dry, base washed nmr tube and the rearrangement was carried out as described in general procedure P. The relative amounts of **313** and the rearrangement product **315** which were present after time t seconds were measured by integration of the signals at δ 5.53 ($\underline{H}X$, **313**) and 6.10 ($\underline{H}G$, **315**). The fraction of **313** remaining after time t seconds is listed below (Table 22).

A plot of time (s) versus ln{[**313**]/[**313**]+[**315**]} produces a set of points which best fit a straight line (see text) of slope -1.5×10^{-4} s^{-1}.

Table 22. Kinetic data for the rearrangement of **313** into **315** at 43°C.

Time, s	[313]/[313]+[315]	ln{[313]/[313]+[315]}
0	1	0
1800	0.69	-0.37
3600	0.60	-0.51
3900	0.53	-0.63
8100	0.28	-1.27

The rearrangement of compound **316** into compound **320**

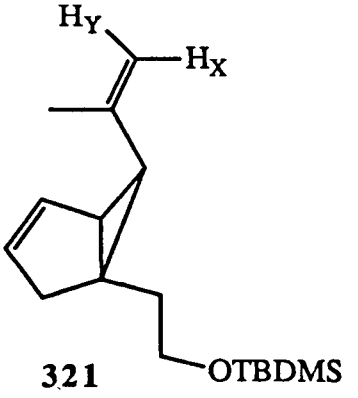


The crude selenide **318** (17 mg, 36 μmol) was converted to the alkene **316** as described previously. Flash chromatography (3:97 Et_2O - petroleum ether; 10 g of silica gel) of the crude reaction product, gave 7 mg (27 μmol) of the alkene **316** [after removal of traces of solvent under reduced pressure (room temperature, 6 Torr)]. This oil was dissolved in benzene-d_6 (0.8 mL), the solution was carefully transferred to a dry, base washed nmr tube and the rearrangement was carried out as described in general procedure P. The relative amounts of **316** and the rearrangement product **320** which were present after time t seconds were measured by integration of the signals at δ 5.33 ($\underline{H}X$, **316**) and 6.09 ($\underline{H}H$, **320**). The fraction of **316** remaining after time t seconds is listed below (Table 23).

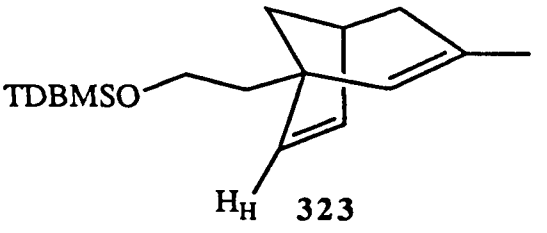
A plot of time (s) versus ln{[**316**]/[**316**]+[**320**]} produces a set of points which best fit a straight line (see text) of slope -9×10^{-5} s^{-1}.

Table 23. Kinetic data for the rearrangement of **316** into **320** at 43°C.		
Time, s	[316]/[316]+[320]	ln{[316]/[316]+[320]}
0	1	0
3600	0.67	-0.40
6000	0.57	-0.56
6600	0.53	-0.62
13200	0.30	-1.21

The rearrangement of compound **321** into compound **323**



321



323

The crude selenide **322** (25 mg, 52 μmol) was converted into the alkene **321** as described previously. Flash chromatography (3:97 Et_2O - petroleum ether; 12 g of silica gel) of the crude reaction product, gave 10 mg (35 μmol) of the alkene **321** [after removal of traces of solvent under reduced pressure (room temperature, 6 Torr)]. This oil was dissolved in benzene-d_6 (0.8 mL), the solution was carefully transferred to a dry, base washed nmr tube and the rearrangement was carried out as described in general procedure P. It was found

that significant rearrangement had occurred during preparation of this substrate. The relative amounts of **321** and the rearrangement product **323** which were present after time t seconds were measured by integration of the signals at δ 5.16 ($\underline{H}_X$, **321**) and 6.08 ($\underline{H}_H$, **323**). The fraction of **321** remaining after time t seconds is listed below (Table 24).

A plot of time (s) versus ln{[**321**]/[**321**]+[**323**]} produces a set of points which best fit a straight line (see text) of slope -6.8×10^{-4} s^{-1}.

Table 24. Kinetic data for the rearrangement of **321** into **323** at 43°C.

Time, s	[**321**]/[**321**]+[**323**]	ln{[**321**]/[**321**]+[**323**]}
0	0.73	-0.31
900	0.37	-0.99
1800	0.21	-1.56
3000	0.10	-2.30
3900	0.05	-3.0

REFERENCES

1. Brown, H. C.; Bhat, N. G. *J. Org. Chem.* **1988**, *53*, 6009.
2. Miyaura, N.; Yamada, K.; Suginome, H.; Suzuki, A. *J. Am. Chem. Soc.* **1985**, *107*, 972.
3. Satoh, M.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1986**, 1329.
4. Alexakis, A.; Duffault, J. M. *Tetrahedron Lett.* **1988**, *29*, 6243.
5. Negishi, E.; Takahashi, T. *Aldrichimica Acta*, **1985**, *18*, 31.
6. Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, *97*, 680.
7. Loots, M. J.; Schwartz, J. *J. Am. Chem. Soc.* **1977**, *99*, 8045.
8. Negishi, E. *Pure & Applied Chem.* **1981**, *53*, 2333.
9. Ireland, R. R.; Wipf, P. *J. Org. Chem.* **1990**, *55*, 1425.
10. Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841.
11. Marfat, A.; McGuirk, P. R.; Helquist, P. *J. Org. Chem.* **1979**, *44*, 3888.
12. Jabri, A.; Alexakis, A.; Normant, J. F. *Tetrahedron Lett.* **1982**, *23*, 1589.
13. Chou, S. P.; Kuo, H.; Wang, C.; Tsai, C.; Sun, C. *J. Org. Chem.* **1989**, *54*, 868.
14. Satoh, Y.; Serizawa, H.; Miyaura, N.; Hara, S.; Suzuki, A. *Tetrahedron Lett.* **1988**, *29*, 1811.
15. Suzuki, A. *Pure & Applied Chem.* **1986**, *58*, 629.
16. Hara, S.; Dojo, H.; Takinami, S.; Suzuki, A. *Tetrahedron Lett.* **1983**, *24*, 731.
17. Chan, T. H.; Fleming, I. *Synthesis* **1979**, 762.
18. Fleming, I.; Newton, T. W.; Roessler, F. *J. Chem. Soc., Perkin Trans. 1* **1981**, 2527.
19. Nozaki, K.; Wakamatsu, K.; Nonaka, T.; Tückmantel, W.; Oshima, K.; Utimoto, K. *Tetrahedron Lett.* **1986**, *27*, 2007.
20. Hayami, H.; Sato, M.; Kanemoto, S.; Morizawa, Y.; Oshima, K.; Nozaki, H. *J. Am. Chem. Soc.* **1983**, *105*, 4491.

21. Okuda, Y.; Wakamatsu, K.; Tückmantel, W.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26*, 4629.

22. M. Pereyre, J. P. Quintard, and A. Rahm, Tin in Organic Synthesis, Butterworth and Co. Ltd., U. K., 1987. (a) Chapter 9, p.149; (b) Chapter 8, p.136.

23. Piers, E.; Skerlj, R. T. *J. Org. Chem.* **1987**, *52*, 4421.

24. Cahiez, G.; Bernard, D.; Normant, J. F. *Synthesis* **1976**, 245.

25. Wang. K. K.; Chu, K.; Lin, Y.; Chen, J. *Tetrahedron* **1989**, *45*, 1105.

26. Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508.

27. Scott, W. J.; Stille, J. K. *J. Am. Chem. Soc.* **1986**, *108*, 3033.

28. Piers, E.; Chong, J. M. *J. Chem. Soc., Chem. Commun.* **1983**, 934.

29. Piers, E.; Chong, J. M. *Can. J. Chem.* **1988**, *66*, 1425

30. Sharma, S.; Oehlschlager, A. C. *Tetrahedron Lett.* **1988**, *29*, 261.

31. Piers, E.; Morton, H. E. *J. Org. Chem.* **1980**, *45*, 4264.

32. Piers, E.; Chong, J. M.; Morton, H. E. *Tetrahedron Lett.* **1981**, 49, 4905.

33. Piers, E.; Chong, J. M.; Morton, H. E. *Tetrahedron* **1989**, *45*, 363.

34. Piers, E.; Llinas-Brunet, M. *J. Org. Chem.* **1989**, *54*, 1484.

35. Piers, E.; Friesen, R. W. *Can. J. Chem.* **1987**, *65*, 1681.

36. This intramolecular cross coupling reaction is based on the intermolecular cross coupling methodology developed by Stille. See reference 27.

37. Piers, E.; Skerlj, R. T. *J. Chem. Soc., Chem. Commun.* **1986**, 626.

38. Mitchell, T. N.; Amamria, A.; Killing, H.; Rutschow, D. *J. Organomet. Chem.* **1986**, *304*, 257.

39. Chenard, B. L.; Van Zyl, C. M. *J. Org. Chem.* **1986**, *51*, 3561.

40. Mitchell, T. N.; WickenKamp, R.; Amamria, A.; Dicke, R.; Schneider, U. *J. Org. Chem.* **1987**, *52*, 4868.

41. Chenard, B. L.; Van Zyl, C. M.; Sanderson, D. R. *Tetrahedron Lett.* **1986**, 27, 2801.

42. Piers, E.; Morton, H. E.; Chong, J. M. *Can. J. Chem.*, **1987**, *65*, 78.

43. Marino, J. P.; Lindermann, R. J. *J. Org. Chem.* **1981**,*46*, 3696.

44. Marino, J. P.; Lindermann, R. J. *J. Org. Chem.* **1983**, *48*, 4621.

45. Klein, J; Levene, R. *J. Chem. Soc., Perkin Trans 2* **1973**, 1971.

46. Lewis, D. E.; Rigby, H. L. *Tetrahedron Lett* **1985**, *26*, 3437.

47. Posner, G. H.; Whitten, C. E.; Sterling, J. J. *J. Am. Chem. Soc.* **1973**, *95*, 7788.

48. Piers, E.; Cheng, K. F.; Nagakura, I. *Can. J. Chem.* **1982**, *60*, 1256.

49. Piers, E.; Chong, J. M. *J. Org. Chem.* **1982**, *47*, 1604.

50. J. M. Chong, Ph. D. Thesis, University of British Columbia, Vancouver, B. C., 1983.

51. Mandeville, W. H.; Whitesides, G. M. *J. Org. Chem.* **1974**, *39*, 400.

52. Gorlier, J. P.; Hamon, L.; Levisalles, J.; Wagnon, J. *J. Chem. Soc., Chem. Commun.* **1973**, 88. See also: (a) Marino, J. P.; Kelly, M. G. *J. Org. Chem.* **1981**, *46*, 4389; (b) Marino, J. P.; Fernandez de la Pradilla, R.; Laborde, E. *J. Org. Chem.* **1987**, *52*, 4898.

53. Bertz, S. H.; Dabbagh, G.; Villacorta, G. M. *J. Am. Chem. Soc.* **1982**, *104*, 5824.

54. Tsuda, T.; Yoshida, T.; Saegusa, T. *J. Org. Chem.* **1988**, *53*, 607.

55. Bertz, S. H.; Dabbagh, G. *J. Org. Chem.* **1984**, *49*, 1119.

56. Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron*, **1984**, *40*, 5005.

57. There has been some doubt as to whether the cyano group is actually bound to copper in these higher order cuprates. See a) Bertz, S. H. *J. Am. Chem. Soc.* **1990**, *112*, 4031. and b) Lipshutz, B. H.; Sharma, S.; Ellsworth, E. L. *J. Am. Chem. Soc.* **1990**, *112*, 4032.

58. Lipshutz, B. H. *Synthesis* **1987**, 325.

59. Lipshutz, B. H.; Koerner, M.; Parker, D. A. *Tetrahedron Lett.* **1987**, *28*, 945.

60. Lipshutz, B. H.; Kozlowski, J. A.; Parker, D. A.; Nguyen, S. L.; McCarthy, K. E. *J. Organomet. Chem.* **1985**, *285*, 437.

61. Gilbertson, S. R.; Challener, C. A.; Bos, M. E.; Wulff, W. D. *Tetrahedron Lett.* **1988**, *29*, 4795.

62. Lipshutz, B. H.; Reuter, D. C.; Ellsworth, E. L. *J. Org. Chem.* **1989**, *54*, 4975.

63. Oehlschlager, A. C.; Hutzinger, M. W.; Aksela, R.; Sharma, S.; Singh, S. M. *Tetrahedron Lett.* **1990**, *31*, 165.

64. Piers, E.; Tillyer, R. D. *J. Org. Chem.* **1988**, *53*, 5366.

65. Marshall, J. A.; Fanta, W. I. *J. Org. Chem.* **1964**, *29*, 2501.

66. Marshall, J. A.; Fanta, W. I.; Roebke, H. *J. Org. Chem.* **1966**, *31*, 1016.

67. Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron Lett.* **1982**, *23*, 3755.

68. Corey, E. J.; Enders, D.; Bock, M. G. *Tetrahedron Lett.* **1976**, 7.

69. Still, W. C. *J. Am. Chem. Soc.* **1977**, *99*, 4836.

70. Pratt, A. J.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1982**, 1115.

71. R. M. Silverstein, G. C. Bassler, and T. C. Morrill, Spectrometric Identification of Crganic Compounds, John Wiley & sons, Inc., Toronto, 1981. (a) p. 237, appendix G; (b) p. 288, appendix A.

72. Occolowitz, J. L. *Tetrahedron Lett.* **1966**, 5921.

73. Still, W. C.; Kahn, M.; Mitra, A. J. *J. Org. Chem.* **1978**, *43*, 2923.

74. D. D. Perrin, W. L. F. Armarego, and D. R. Perrin. "Purification of Laboratory Chemicals", Pergamon Press, Oxford, 1980.

75. Kofron, W. G.; Baclawski, L. M. *J. Org. Chem.* **1976**, *41*, 1879.

76. House, H. O.; Chu, C. Y.; Wilkens, j. M.; Umen, M. J. *J. Org. Chem.* **1975**, *40*, 1460.

77. Wuts, P. G. M. *Synth. Commun.* **1981**, *11*, 139.

78. Rempel, G. A.; Legzdins, P.; Smith, H.; Wilkinson, G. *Inorg. Synth.*, Vol XIII, p. 90.

79. R. F. Heck, Palladium Reagents in Organic Synthesis, Academic Press, Toronto, 1985. p. 2.

80. Collman, J. P.; Hegedus, L. S.; Norton, J. R.; Finke, R. G., Principles and Applications of Organotransition Metal Chemistry, University Science Books, 1987, chap. 14.

81. Gillie, A.; Stille, J. K. *J. Am. Chem. Soc.* **1980**, *102*, 4933.

82. Stang, P. J.; Kowalski, M. H. *J. Am. Chem. Soc.* **1989**, *111*, 3356.

83. Watunabe, H.; Kobayashi, M.; Higuchi, K.; Nagai, Y. *J. Organomet. Chem.* **1980**, *186*, 51.

84. Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190.

85. Auerbach, J.; Weinreb, S. M. *J. Chem. Soc. Chem Commun.*, **1974**, 298.

86. Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, 2647.

87. L. Brandsma, Preparative Acetylenic Chemistry, Elsevier Publishing Company, New York, 1971. (a) p. 69; (b) p. 70-72.

88. Piancatelli, G.; Scettri, A.; D'auria, M. *Synthesis*, **1982**, 245.

89. Corey, E. J.; Schmidt, G. *Tetrahedron Lett.* **1979**, *20*, 399.

90. Marshall, J. A.; Crooks, S. L.; DeHoff, B. S. *J. Org. Chem.* **1988**, *53*, 1616.

91. Narasaka, K.; Morikawa, A.; Saigo, K.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1977**, *50*, 2773.

92. Smissman, E. E.; Makriyannis, A. *J. Org. Chem.* **1973**, *38*, 1652.

93. Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4156.

94. Robins, M. J.; Samano, V.; Johnson, M. D. *J. Org. Chem.* **1990**, *55*, 410.

95. Verkruijsse, H. D.; Heus-Kloos, Y. A.; Brandsma, L. *J. Organomet. Chem.* **1988**, *338*, 289.

96. Piers, E.; Tillyer, R. D. *J. Chem. Soc., Perkin Trans 1* **1989**, 2124.

97. Leusink, A. J.; Budding, H. A.; Marsman, J. W. *J. Organomet. Chem.* **1967**, *9*, 285.

98. R. T. Skerlj, Ph. D. Thesis, University of British Columbia, Vancouver, B. C., (1988).

99. Tsuda, T.; Yoshida, T.; Kawamoto, T.; Saegusa, T. *J. Org. Chem.* **1988**, *53*, 1624.

100. Conia, J. M.; Limasset, J. C. *Bull. Soc. Chim.* . **1967**, 1936.

101. Huet, F.; Pellet, M.; Conia, J. M. *Tetrahedron Lett.* **1977**, 3505.

102. Boutagy, J.; Thomas, R. *Chem. Rev.* **1974**, *74*, 87.

103. Piers, E.; Karunaratne, V. *J. Org. Chem.* **1983**, *48*, 1774.

104. Piers, E.; Yeung, B. W. A. *J. Org. Chem.* **1984**, *49*, 4567.

105. Mil'vitskaya, E. M.; Tarakanova, A. V., Plate, A. F. *Russ. Chem. Rev.* **1976**, *45*, 469.

106. Vogel, E. *Angew. Chem., Int. Ed. Engl.* **1963**, *2*, 1.

107. Wong, H. N. C.; Hon, M-Y.; Tse, C-H.; Yip, Y-C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165.

108. Wender, P. A.; Hillemanne, C. L.; Szymonifka, M. J. *Tetrahedron Lett.* **1980**, *21*, 2205.

109. Pettus Jr, J. A.; Moore, R. E. *J. Am. Chem. Soc.* **1971**, *93*, 3087.

110. Marino, J. P.; Ferro, M. P. *J. Org. Chem.* **1981**, *46*, 1912.

111. Piers, E.; Morton, H. E.; Nagakura, I.; Thies, R. W. *Can. J. Chem.* **1983**, *61*, 1226.

112. Piers, E.; Reudiger, E. H. *Can. J. Chem.* **1983**, *61*, 1239.

113. Baldwin, J. E.; Ullenius, C. *J. Am. Chem. Soc.* **1974**, *96*, 1542.

114. Schneider, M. P.; Rau, A. *J. Am. Chem. Soc.* **1979**, *101*, 4426.

115. Klumpp, G. W. F. K.; Barnick, A. H.; Veekind, A. H., Bickelhaupt, F. *Recl. Trav. Chim. Pays-Bas*, **1969**, *88*, 766.

116. Davies, H. M. L.; Smith, H. D.; Korkor, O. *Tetrahedron Lett.* **1987**, *28*, 1853.

117. Cupas, C.; Watts, W. E.; Schleyer, P. von R. *Tetrahedron Lett.* **1964**, 2503.

118. Piers, E.; Jung, G. L.; Reudiger, E. H. *Can. J. Chem.* **1987**, *65*, 670.

119. Piers, E.; Jung, G. L.; Moss, N. *Tetrahedron Lett.* **1984**, *25*, 3959.

120. Piers, E.; Moss. N. *Tetrahedron Lett.* **1985**, *26*, 2735.

121. Baldwin, J. E.; Gilbert, K. E. *J. Am. Chem. Soc.* **1976**, *98*, 8283.

122. Piers, E.; Jung, G. L. *Can. J. Chem.* **1987**, *65*, 1668.

123. Piers, E.; Jean, M.; Marrs, P. S. *Tetrahedron Lett.* **1987**, *43*, 5075.

124. P. Marrs, Ph. D. Thesis, University of British Columbia, Vancouver, B. C. (1988).

125. Brown, J. M. *J. Chem. Soc., Chem Commun.*,**1965**, 226.

126. Adam, W.; De Lucchi, O.; Scheutzow, D. *J. Org. Chem.* **1981**, *46*, 4130.

127. Davies, H. M. L.; McAfee, M. J.; Oldenburg, C. E. M. *J. Org. Chem.* **1989**, *54*, 930.

128. Hudlicky, T.; Kossyk, F. J.; Dochwat, D. M.; Cantrell, G. L. *J. Org. Chem.* **1981**, *46*, 2911.

129. Tamaru, Y. ; Ochai, H.; Nakamura, T.; Yoshida, Z. *Tetrahedron Lett.* **1986**, *27*, 955.

130. Ethyl 3-iodopropanoate was prepared from commercially available ethyl 3-chloropropanoate via reaction with NaI. See Experimental section for Part 3 of this thesis.

131. R. D. Smith and H. E. Simmons,*Org. Synth.*, Col. Vol. V, Wiley, New York, 1968. p. 855.

132. Hudlicky, T.; Sinai-Zingde, G.; Natchus, M. G.; Ranu, B. C.; Papadopolous, P. *Tetrahedron* **1978**, *43*, 5685.

133. Griffith, W. P.; Ley, S. V. *Aldrichimica Acta*, **1990**, *23*, 13.

134. Doyle, M. P.; Griffin, J. H.; Bagheri, V.; Dorow, R. L. *Organometallics* **1984**, *3*, 53.

135. Doyle, M. P. in "Catalysis of Organic Reactions", Augustine, R. L., Ed.; Marcel Dekker: New York, 1985.

136. Orban, J.; Turner, J. V.; Twitchin, B. *Tetrahedron Lett.* **1984**, *25*, 5099.

137. Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1984**, *25*, 5953.

138. Scott, W. J.; McMurray, J. E. *Acc. Chem. Res.* **1988**, *21*, 47.

139. Trost, B. M.; Salzmann, T. N.; Hiroi, K. *J. Am. Chem. Soc.* **1976**, *98*, 4887.

140. Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425.

141. Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.

142. Sharpless, K. B.; Young, M. W. *J. Org. Chem.* **1976**, *41*, 1486.

143. Reich. H. J.; Renga, J. M.; Reich, I. L. *J. Am. Chem. Soc.* **1975**, *97*. 5434.

144. Clive, D. L. J. *J. Chem Soc., Chem. Commun.* **1973**, 695.

145. The lines of best fit were calculated from the kinetic data using Cricket Graph software on a Macintosh computer.

146. Miller, S. A.; Gadwood, R. C. *J. Org. Chem.* **1988**, *53*, 2214.

147. de Boer, Th. J.; Backer, H. J. *Org Synth.*, Col. Vol. V, Wiley, New York, 1963, p. 250.