Part 1

α-SILYLALLYL CARBANIONS. THEIR SYNTHESIS, REACTIVITY AND APPLICATIONS IN THE SYNTHESIS OF RETINOIDS.

Part 2

SYNTHESIS OF NEW RETINOIC ACID ANALOGS FOR THE TREATMENT OF CANCER.

by

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Synthesis of Retinoic acid and Analogs.

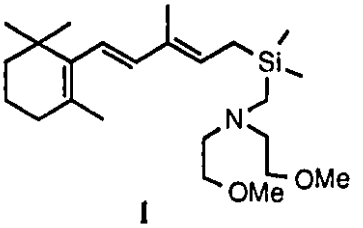
ABSTRACT

The preparation of allylsilanes by silylation of allylsulfones followed by the reductive cleavage of the silylated sulfones, is described. The use of this new methodology in the synthesis of polyenic compounds including *cis* and *trans* retinoic acid was reported.

The preparations and reactions of a series of aminomethyl substituted α-allylsilyl anions with carbonyl electrophiles were studied. The stereoselectivity of these reactions was subject to solvents and temperature effects. For instance, the condensation of these anions with carbonyl electrophiles proceeded to give the corresponding E- homoallylic alcohols in benzene, but the same reactions at a lower temperatures in the presence of dimethoxyethane leads to the formation of the Z- isomers preferentially.

A new method for the preparation of aminomethyl substituted allylsilane **I** via the hydrosilylation of a new allene was described. This allene was prepared using an improved method of elimination of β-hydroxyvinylsilanes.

A number of analogs of retinoic acid were synthesized for their use in the treatment of leukemia. Their syntheses were carried out using the Wittig reaction. Two series of these analogs showed reasonable biological activity in HL-60 and P19 screenings. A third series of compounds was inactive.



I

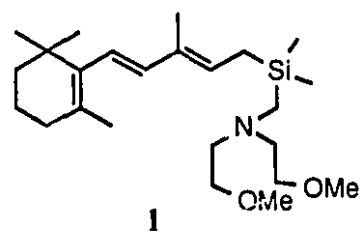
RESUME

Une nouvelle méthode de préparation d'allylsilanes par la silylation d'allylsulfones suivie de la réduction de la sulfone est décrite. L'utilisation des nouveaux allylsilanes dans la synthèse de composés polyinsaturés et des esters de l'acide rétinoique *cis* et *trans* est demontrée.

La préparation d'une série d'anions allyliques α-silyciés portant un groupe chelatant aminomethyl et la réaction de ces anions avec des réactifs carbonylés ont été étudié. La stéréochimie des produits de ces réactions est dépendante des conditions réactionnelles. Par exemple, la condensation de ces anions sur les cétones et aldéhydes dans un solvant comme le toluène mène aux alcools homoallyliques ayant une stéréochimie E, cependant la même réaction éffectuée à plus basse température et en présence de dimethoxyethane mène à la formation de produits ayant une stéréochimie Z.

Une nouvelle méthode pour la préparation de l'allylsilane **1** ayant un groupement chelatant aminomethyle est décrite. Cette méthode est basée sur la reaction d'hydrosilylation d'un nouvel allène qui a lui-même été préparé par une méthode améliorée d'élimination des β-hydroxyvinylsilanes.

La synthèse d'un certain nombre d'analogues de l'acide retinoique a été décrite. Ces composés ont été sélectionnés pour leurs activités biologiques liées à la différentiation cellulaire in-vitro des lignées cellulaires HL-60 et P19. Deux séries de composés ont démontré des activités comparables à l'acide rétinoique, tandis qu'une troisième série de composés s'est révélée inactive.



1

À mes parents, mon frère
et ma compagne Christine.

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CONTRIBUTION TO ORIGINAL KNOWLEDGE.

The use of α-allylsilyl anions has been extended to the synthesis of all-*trans* and of 9-*cis* retinoic acid esters. In the process we have used two different types of methodological approaches to the preparation of allylsilanes and their anions.

A study of the effect of aminomethyl substituents on the addition of allylsilyl anions has been made, and the result permited the preparation of homoallylic alcohol of Z or E stereochemistry depending on the solvent used. These reactions have been rationalized in term of the formation of a seven member ring transition state.

A practical improvement has been developed in the synthesis of allenes via the Chan method which has permitted the preparation of a new allene and of an allylsilane.

Finally, new retinoic acid analogs were prepared as part of a second project. Five of these compounds showed reasonable biological activity ($ED_{50} = 10^{-7}$-10^{-8} M) when submited to HL-60 screenings.

LIST OF ABREVIATIONS.

Ac	acetyl
bp	boiling point
Bu	butyl
CI	chemical ionisation
d	doublet
DEA	diethylamine
DHP	dihydropyrane
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DIPA	diisopropylamine
DMAN	N,N-1-dimethylaminonaphthalene
EI	electron impact
Et	ethyl
gem	geminal
H	hours
HMPA	hexamethylphosphoric triamide
Hz	hertz
IR	infrared
i-Pr	isopropyl
LAH	lithium aluminum hydride
m	multiplet
MCPBA	meta-chloroperbenzoic acid
Me	methyl
min	minute (s)
MHz	megahertz
MM2	molecular mechanics 2
mp	melting point
MS	mass spectrometry
NMR	nuclear magnetic resonance
NOE	nuclear Overhauser enhancement

nPr	n-propyl
Ph	phenyl
PPTS	pyridinium p-toluenesulfonate
ppm	parts per million
ORTEP	Oak Ridge thermal elipsoid plot
q	quartet
RA	retinoic acid
t	triplet

Chapter 3. Synthesis of polyenes.

Chapter 4. Reactivity of the modified silylallyl anions.

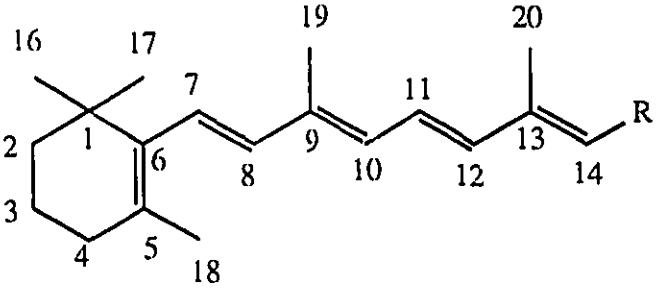
Chapter 5. A new synthesis of (aminomethyl)allylsilanes.

Chapter 6. New retinoic acid analogs.

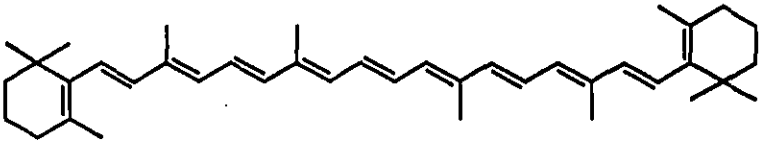
CHAPTER 1
INTRODUCTION.

1.1. Introduction to Retinoids.

The retinoids are a family of naturally occurring compounds containing an extended polyenic chain. They are part of the terpenes family and thus have the isoprene unit repeated in their carbon skeleton forming the general structures **1.1-1.4** shown in Figure 1.1. They are represented by vitamin A (or retinol), retinal, retinoic acid, β-carotene and numerous other natural products routinely reported in the literature.[1] For the IUPAC nomenclature, the numbering of the carbon starts at the carbon substituted by the gem dimethyl group as shown in Figure 1.1.



1.1 retinol (vitamin A) R=CH_2OH
1.2 retinal R=CHO
1.3 retinoic acid R=COOH



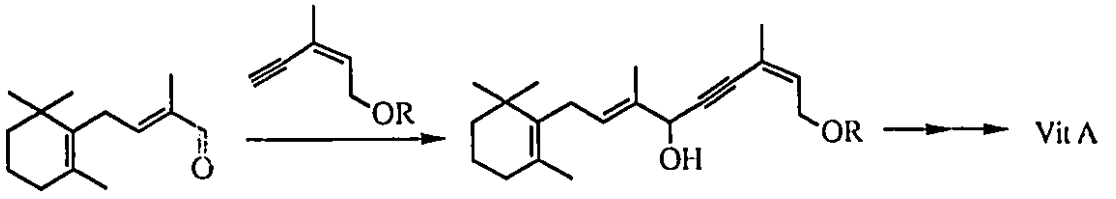
1.4 β-carotene

Figure 1.1

These natural substances demonstrate a wide range of biological effects on cells and organisms. Vitamin A is essential in vision. Its oxidised form, retinal, is bonded to opsin and is responsible for the absorption of the photons of light which catalyzes an enzyme cascade, generating the visual excitation signal.[2] Retinoic acid for its part has been associated with the mechanisms of cellular differentiation[3] as we will see in more details in chapter 6. β-Carotene is one of the numerous biological pigments found in plants where it

is almost always found with chlorophyll.[4] It is used as a source of vitamin A in animals and as an ultraviolet screen.[4] Indeed the usefulness of the members of this family has been recognised for a number of years now. Industrially, massive amounts of these compounds, have been produced for applications as diversed as food coloring[4] to cancer prevention, chemotherapeutic agent[5] and acne suppression.[6]

The use of acetylene chemistry, the Wittig reaction and of allyl sulfones as described in Figure 1.2 are the principal reactions used in the synthesis of retinol in industry. These processes will be discussed in the next chapter.



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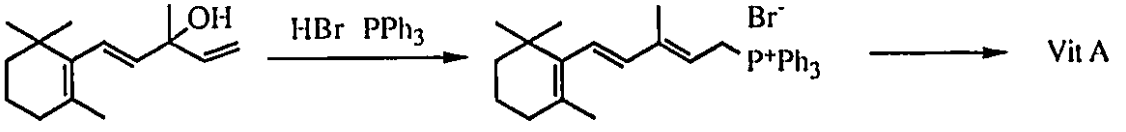
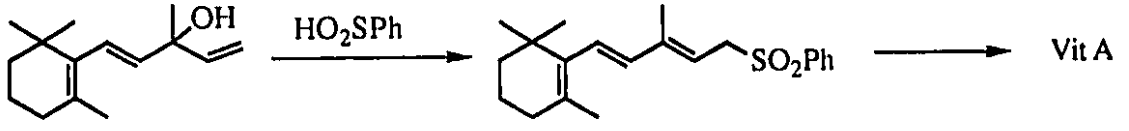


BASF-AG



Rhône Poulenc

Figure 1.2

The diversity of approaches in the industrial processes is limited to the use of β-ionone as the starting material. This is explained by its ease of synthesis and its availability on the market. In fact the manufacturers are able to synthesize β-ionone from very simple starting materials such as acetone and acetylene. The processes used for the synthesis of β-ionone and vitamin A were well described in a recent review.[7]

The search for high yield methodologies, in this field, has spurred the discovery of a number of viable alternative methods that were also used in other applications where the formation of the carbon-carbon double bond was desired, as demonstrated by the discovery and uses of the Julia olefination method.

1.2. Methods for olefin formation and their uses in retinoids synthesis.

The most prominent member of the retinoid family is vitamin A (retinol), it was discovered by Stepp in 1909 and its structure was elucidated by Karrer in 1931. Vitamin A and other retinoids have represented challenging targets for chemists.[8]

The following is intended as a review of the methods for the synthesis of retinoids and more particularily that of vitamin A, retinal, retinoic acid and β-carotene. Emphasis on the references published after 1987 was made since the literature prior to this date has been particularly well covered in other reviews.[9]

Since Wittig discovered the use of phosphonium ylides[10] in the synthesis of olefins, the number of applications for this reaction has grown considerably.[11] But no matter how practical the Wittig reaction is, the demand for better stereo- and regioselectivity has encouraged the development of other types of reactions which complement or replace the Wittig reaction. The synthesis of the retinoids is an ideal field for testing the limitations of these new methodologies, as it will be seen in this chapter.

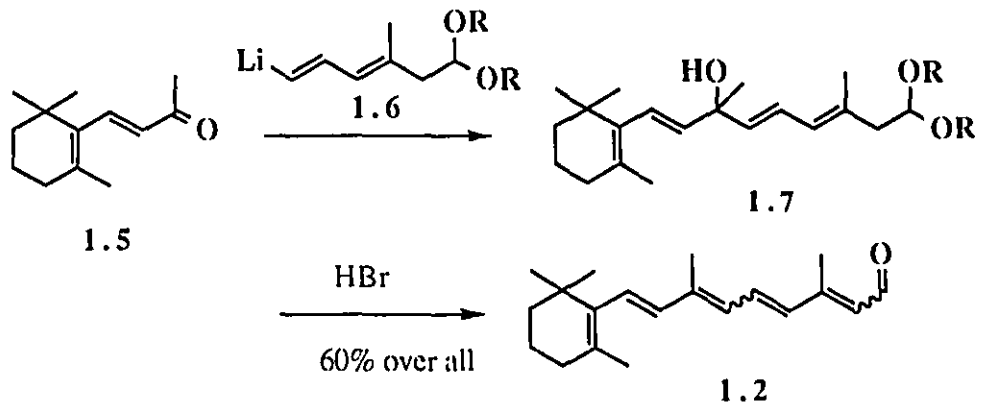
1.2.1 The β-elimination.[12]

According to Carruthers[12a], "one of the most commonly used method for forming carbon-carbon double bonds is the β-elimination reaction" which goes according to Figure 1.3 where X is a leaving group like OH, OCOR, halogen, sulfite, sulfone, N^+R_3, S^+R_2.

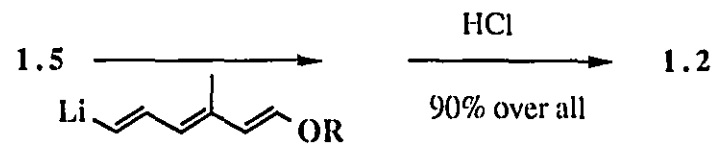
Figure 1.3

These reactions can proceed by the E1 or E2 mechanisms and are often used in synthetic organic chemistry. Their major drawback is their usually poor regio and stereoselectivity. This is why it seems surprising at first hand to see recent literature dealing with the use of this reaction in the synthesis of retinoids. However under

equilibrating conditions, mixtures of retinoic acid stereoisomers invariably equilibrate to the all-*trans* isomer. This explains why these methods can still be useful.



Mixture of isomers 9-cis, 13 cis, all-trans.
Identified by HPLC. Ratio not specified.

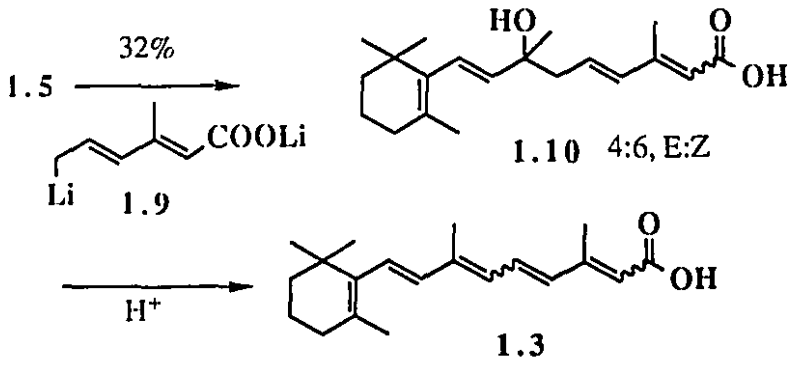


1.8a R=$SiMe_3$
1.8b R=Me

Mixture of isomers 9-cis, 13 cis, all-trans.
Identified by HPLC. Ratio 22%, 10%, 66%.

Scheme 1.1:

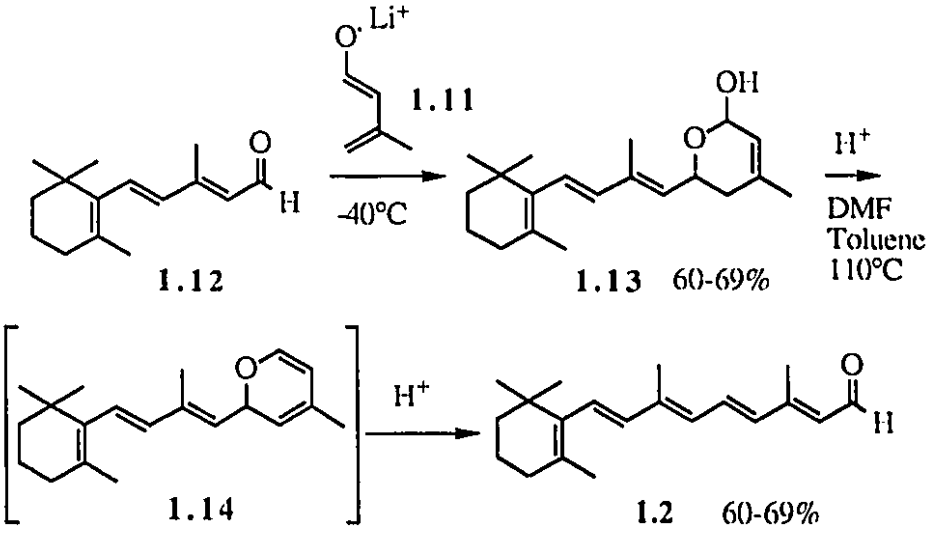
For example, recently L. Duhamel[12b] has shown, using metal halogen exchange, that the intermediate **1.6** could be reacted with β-ionone, giving the corresponding alcohol **1.7** which under acidic conditions, eliminated and was deprotected in one step giving the mixture of retinals **1.2** (3 isomers). Other variations on the same theme (using an enol ether **1.8a** and **1.8b**) were also shown to be workable (second part of Scheme 1.1).[12c,12d] These methods produced many isomers. This evident lack of stereoselection should normally have rendered it useless despite the high yields. However, as mentioned earlier in the case of retinoic acid, the all-*trans* retinal isomer can also be obtained directly from the mixture by equilibration in the presence of iodine. It should be noted that this equilibration is not useful if the desired product is any of the *cis* isomers of the retinoids, such as the 13-*cis* retinoic acid now under several clinical trials.[12c]



Scheme 1.2: Simple synthesis of retinoic acid.

Considering that a complex mixtures of isomers of retinoic acid can undergo isomerization to the all-*trans* retinoic acid isomer, the most concise route to retinoic acid was designed by Mestres *et al.*[12f] which took two readily available cheap starting materials **1.5** and **1.9** and by condensation followed by elimination, were able to get retinoic acid directly, in a reasonable yield (Scheme 1.2). A similar approach had been reported earlier using smaller fragments than **1.9**, but the methodology was mostly used to get some of the *cis* isomers of retinoic acid stereoselectively.[9b]

Another way to build up the retinoid skeleton is by using the aldol condensation reaction. The first examples of the use of this type of reaction were reported by Mukaiyama *et. al.* [12g] who showed that the Lewis acid catalysed condensation of β-ionyldeneacetaldehyde dimethylacetal with 1-trimethylsilyloxy(or ethoxy)-3-methyl-1,3-butadiene provided all-*trans* -retinal **1.2** in 42% yields after elimination and isomerization of the intermediates. A simpler approach based on the same idea was described in a recent report. Duhamel *et. al.* [12h] used the lithium enolate **1.11** with the aldehyde **1.12** to give the tetrahydropyran **1.13**. Acid catalyzed rearrangement of **1.13** is believed to go through the dihydropyran intermediate **1.14** to give the all-*trans* -retinal in good yield (Scheme 1.3).



Scheme 1.3.

1.2.2 The use of allyl sulfone nucleophiles. (the Julia olefination reaction).[13]

Synthesis of olefinic compounds, through the use of sulfone chemistry, is a relatively new field that was studied intensively by Julia *et. al.* [13a,b,c] These researchers have developed three efficient ways of obtaining the formation of a carbon carbon double bond starting from a sulfone (Figure 1.4). The first and most simple avenue is the deprotonation of a sulfone **1.15** followed by its reaction with an alkyl halide giving sulfone **1.16** that can be eliminated to the trans olefin **1.17**.[13a] The other two alternatives consist of the condensation of the sulfone **1.15** nucleophile with an aldehyde followed by acetylation, that can be carried out in situ, giving **1.18**. Reductive elimination of sulfone **1.18** with sodium mercury amalgam produces the olefin **1.17**.[13b] The β-acetoxy-sulfone **1.18** can alternatively be eliminated to the E-vinyl sulfone **1.19** which is then reduced with sodium dithionite to the Z alkene **1.20**.[13c]

Julia and Arnould[13a] investigated different strategies of addition of a sulfone to an allyl halide for the synthesis of retinoic acid, and finally concluded that sulfone **1.21** was the best reagent for this purpose.

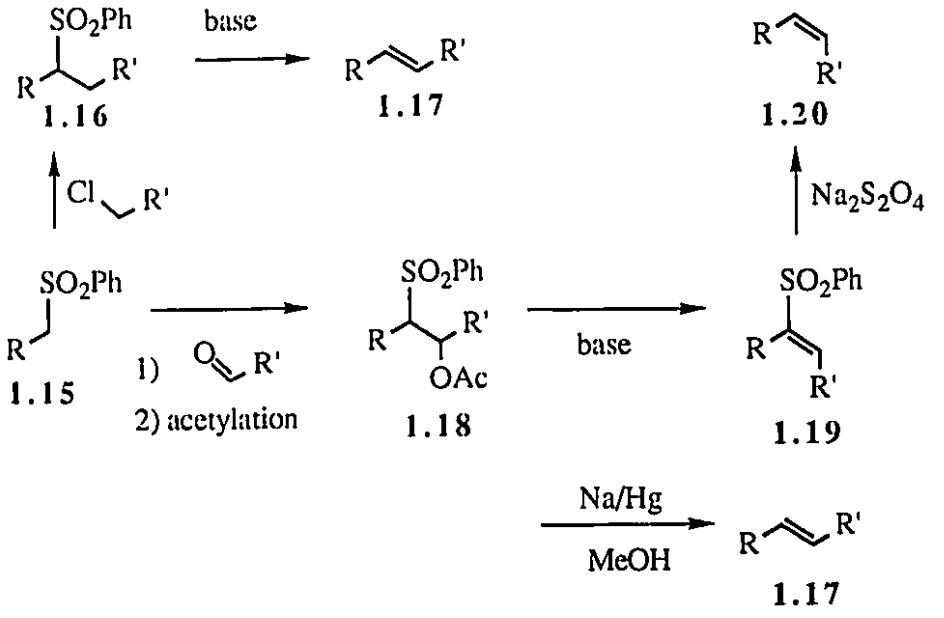
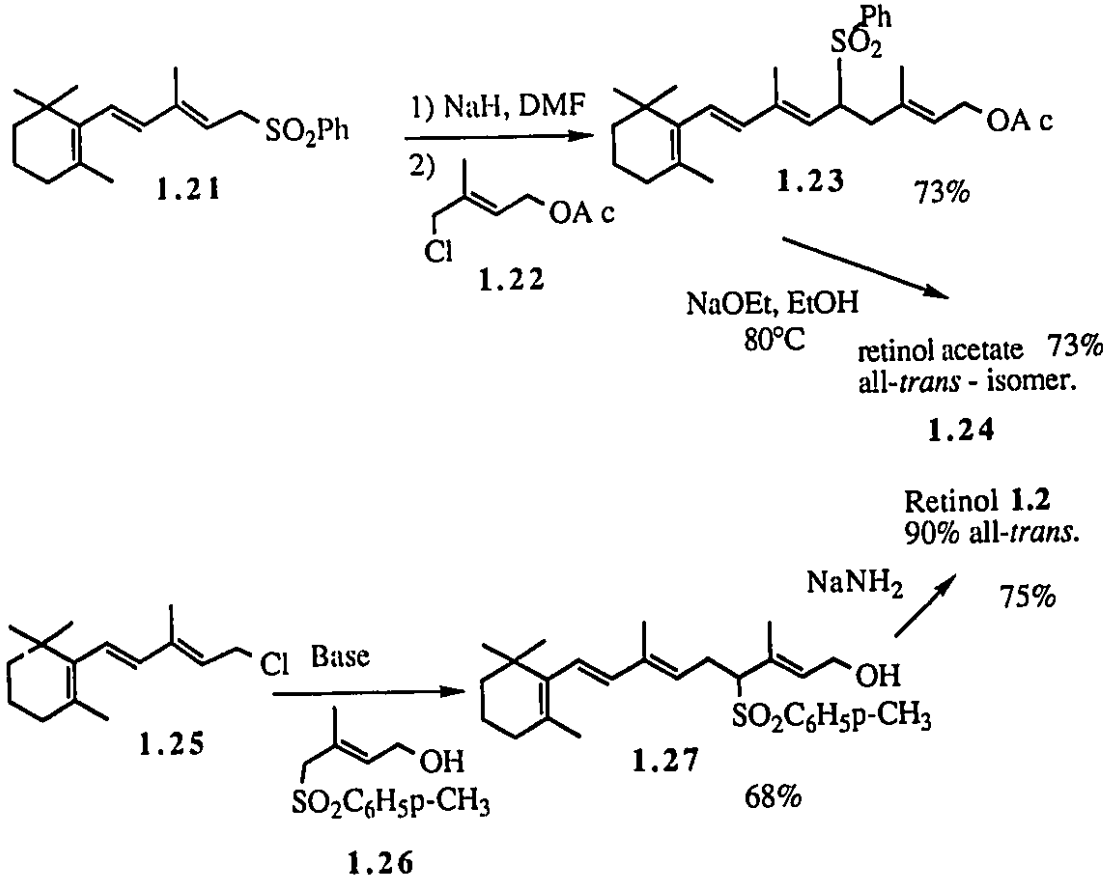
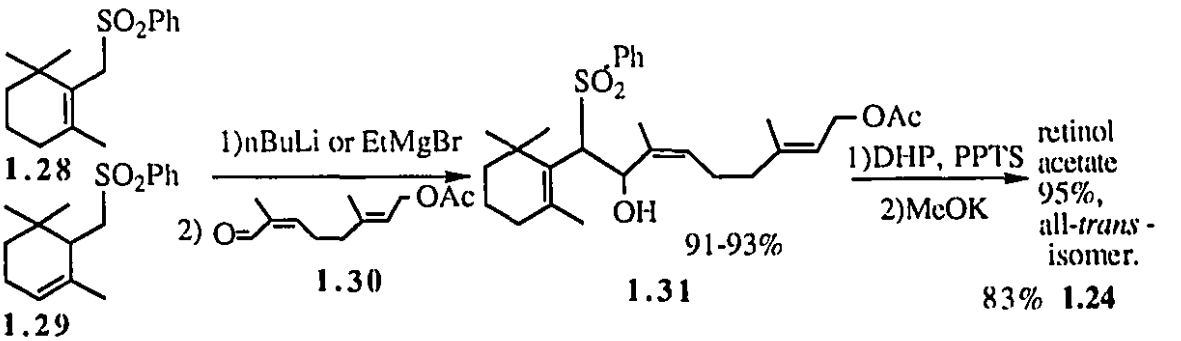


Figure 1.4.



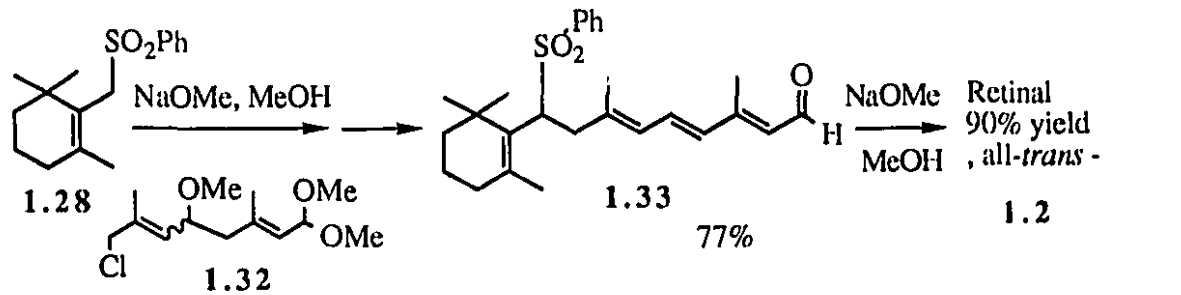
Scheme 1.4.

Later these two strategies were taken-up again, by Marchand [13l] and Olson [13e] which described more direct approaches to the synthesis of vitamin A (Scheme 1.4). Addition of a C15 (15 carbon fragment) sulfone **1.21** to the C5 allyl halide **1.22** fragment provided retinol acetate **1.24** in a respectable yield. This method is now in use in industry (see chapter 1). The alternative approach where the sulfone is attached to the C5 fragment **1.25** which is added to an allyl C15 fragment **1.26** (second part of Scheme 1.4) gives retinol of lower isomeric purity.



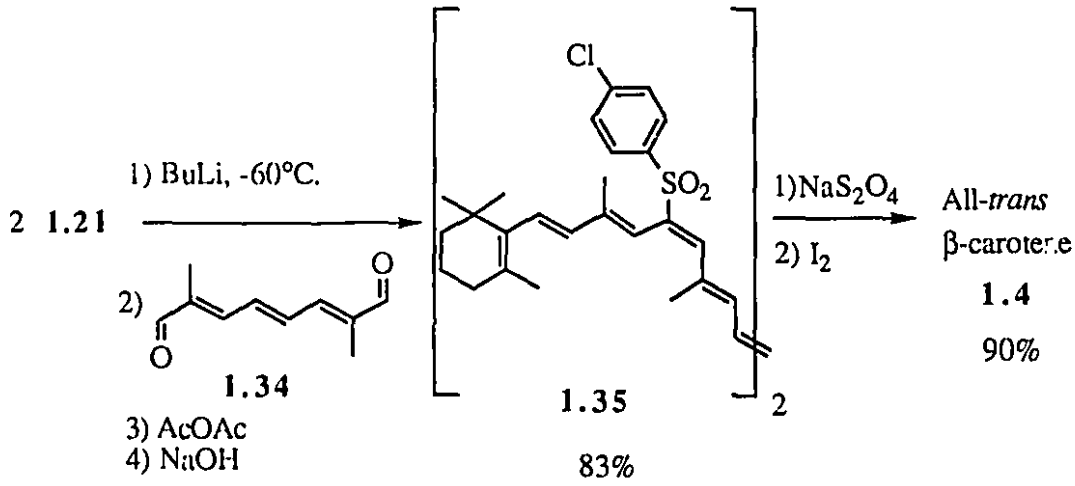
Scheme 1.5.

Cyclogeranylsulfone **1.28** and **1.29** were prepared as a mixture of isomers by Torii and coworkers.[13f] Under the specified reaction conditions, only one of these isomers reacted with the aldehyde **1.30** previously prepared from neryl acetate.[13g] The β-hydroxy-sulfone **1.31** formed in this way can undergo double elimination to the all-*trans* retinol isomer **1.24** (Scheme 1.5).



Scheme 1.6.

More recently, Julia [13h] also used the cyclogeranylphenyl sulfone **1.28** as a synthon for the construction of the retinoid's polyenic structure. The addition of this sulfone **1.28** to the aldehyde **1.32** led to the formation of the aldehyde **1.33** which was eliminated to retinal **1.2** (Scheme 1.6). The synthesis of the starting sulfone was optimized in their laboratories. We recently reported that **1.28** could be separated from **1.29** by recrystallization.[13i]



Scheme 1.7

Bernhard and Mayer[13j] reported the high yield syntheses of β-carotene and other carotenoids by the use of a modified Julia reaction. Condensation of 2 equivalents of the allyl sulfone **1.21** with the dialdehyde **1.34** followed by *in situ* acetylation and elimination gave disulfone **1.35**. This series of reactions eventually gave all-*trans* -β-carotene **1.4** in 90% yield upon treatment of **1.35** with sodium dithionite followed by equilibration (Scheme 1.7). It should be noted that the expected Z stereospecificity (see mechanism at the beginning, Figure 1.4) was not obtained in that instance. The authors presumably got a mixture of isomers, so the synthesis of the *cis* isomers of β-carotene had to be completed using the Wittig reaction.

Other researchers have reported various ways of using sulfones in the synthesis of retinoids.[13k]

1.2.3 The Wittig and Horner-Emmons reactions.[14]

The Wittig reaction was applied in this field even before the elimination reactions and led to the first synthesis of β-carotene.[14a] The Wittig reaction was believed to proceed through a betain intermediate **A** and that this explained the stereospecificity of this reaction. However this assumption has recently been questioned and an asynchronous cycloaddition mechanism, to the corresponding oxaphosphetane **B** , has been proposed instead.[14b] Indeed a stable oxaphosphetane intermediate has been isolated.[14c]

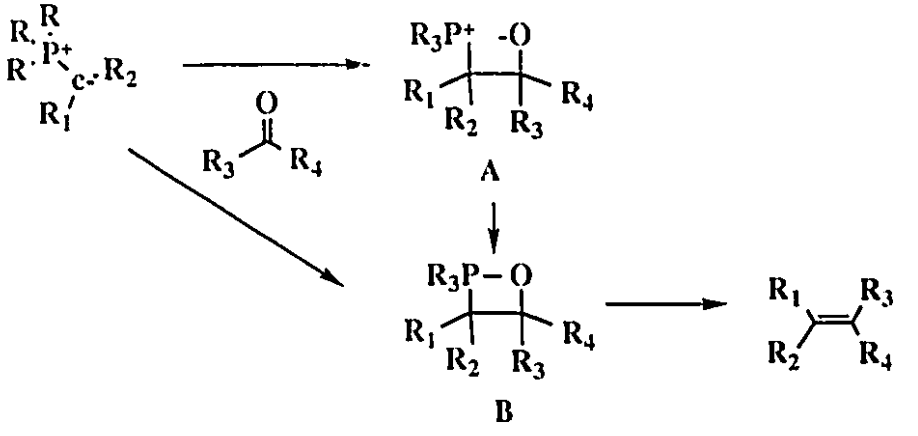
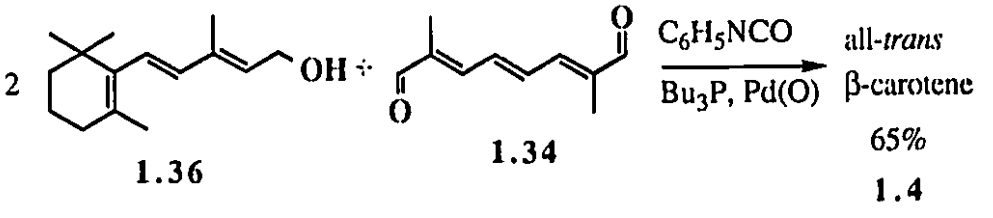


Figure 1.5.

The marked advantage of this reaction is its regiospecificity since the double bond is formed between the phosphorane substituted carbon and the oxygen substituted carbon. Another advantage is that some stereoselectivity can be obtained. However the reactivity can sometimes be a problem if the reagents are hindered. Also the regioselectivity of the first step (the addition to the ketone) can also be a problem when enones or enals are used. Nonetheless as stated earlier, an industrial process was designed for the synthesis of vitamin A using the Wittig reaction as shown in Figure 1.2. Similar processes were used for the synthesis of other retinoids and of β-carotene.[14a] Since these are fairly old and straight forward reactions that have been extensively reviewed we will not review the subject further. That being said, Nakamura *et. al.* have recently published a method of *in situ* generation of a Wittig reagent, from the alcohol **1.36**, similar to the one used in industry and reacted it with 2,5-dimethylhepta-1,2,4,6-triene-1,7-dial **1.34** giving β-carotene **1.4** directly (Scheme 1.8).[14d] Ford *et. al.* have developed some polymer supported Wittig reagents that were used in the synthesis of ethyl retinoate.[14e]

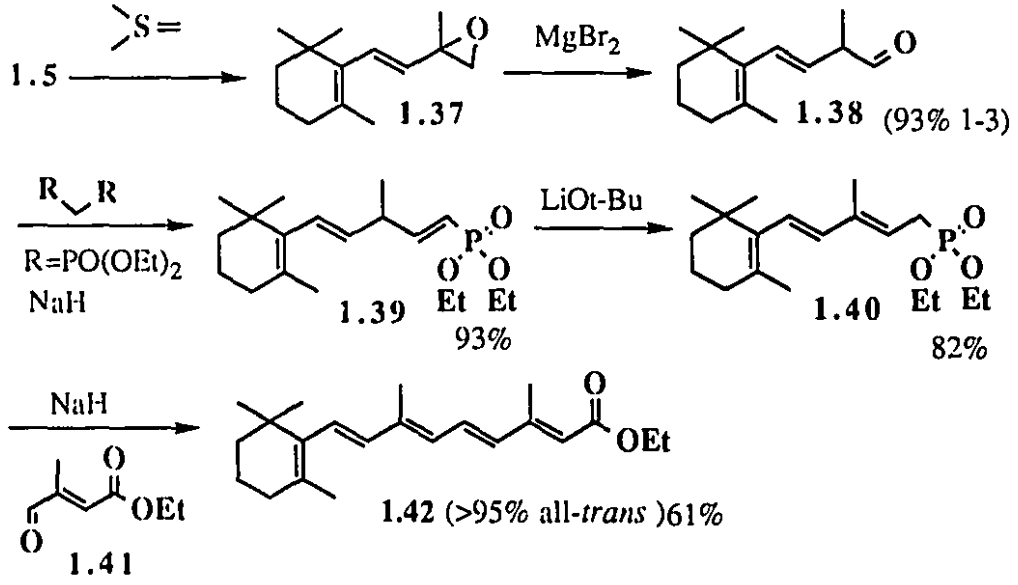


1.36 **1.34** **1.4**

Scheme 1.8:

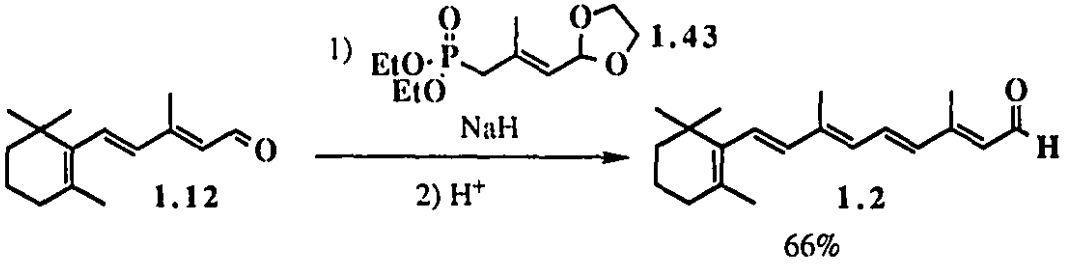
Another reaction based on the use of an phosphorus ylide intermediate is the Wittig-Horner reaction.[14f] Recently this reaction was exploited in the synthesis of retinoids.[14g] The major advancement of this work is the development of a methodology to obtain the

otherwise elusive diethylphosphonate ester **1.40** from β-ionone **1.5** which reacted regio and stereoselectively with aldehyde **1.41** giving the all-*trans* -retinoic acid, ethyl ester **1.42** (Scheme 1.9).



Scheme 1.9:

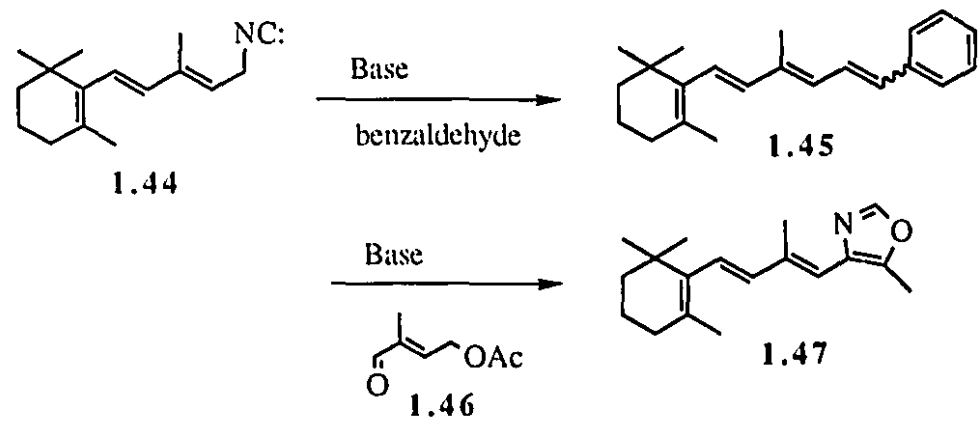
A modified version of this approach where the phosphonate is attached to the other synthon also gave good yields. The phosphonate **1.43** was reacted with the aldehyde **1.12** giving the pure all-*trans* -retinal **1.2** (Scheme 1.10).[14h]



Scheme 1.10:

1.2.4 The isonitrile method.[15]

This method involves the condensation of the isonitrile **1.44** and a carbonyl electrophile. When **1.44** is condensed with benzaldehyde the formation of the carbon-carbon double bond occurs immediately after the addition step giving the aromatic polyene **1.45**.



Scheme 1.11:

When the same reaction was applied to the synthesis of retinol acetate, the oxazole compound **1.47** formed instead of the expected retinol acetate product (Scheme 1.11).

1.2.5 The Mc Murry reaction.[16]

The McMurry reaction consists of the reductive coupling of symmetrical aldehydes and ketones by low valent titanium reagents. The mechanism is believed to take place involving the reduction of the carbonyl compounds to their ketyl radical counterparts which dimerize to a diol intermediate. This diol then undergoes reductive elimination (Figure 1.6) in a stereospecific manner.

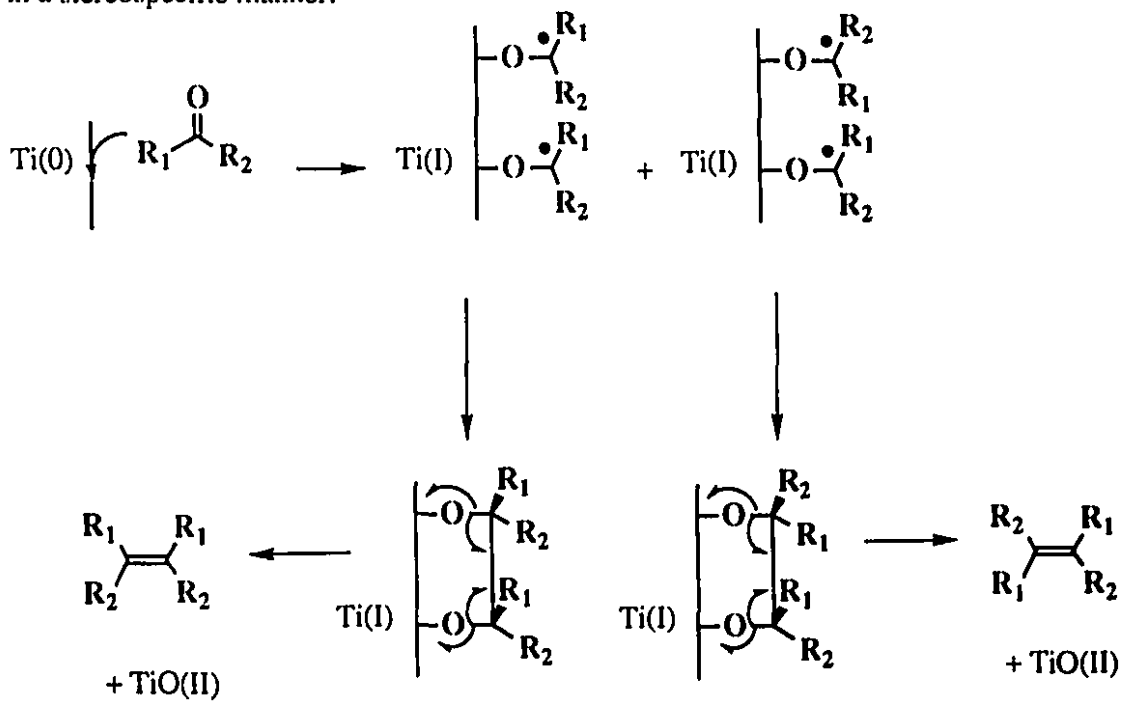
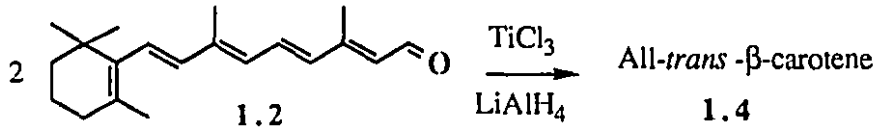


Figure 1.6:



Scheme 1.12:

This very useful reaction has been applied in many instances, as shown in a recent review.[16a] One particular application is in the synthesis of β-carotene which can be synthesized by this method using retinal **1.2** as the starting material (Scheme 1.12).[16b] This method is characterized by high yield and regioselectivity as well as by its simplicity.

1.2.6 The reduction of a propargylic diol to the corresponding allylic diol followed by conjugate reductive elimination with titanium.[17]

Conjugated diol reductive elimination is based on the extension of the principles involved in the second step of the McMurry reaction and is represented in Figure 1.7. The titanium Ti(0) reducing agent cleaves reductively the two hydroxy giving a diene.

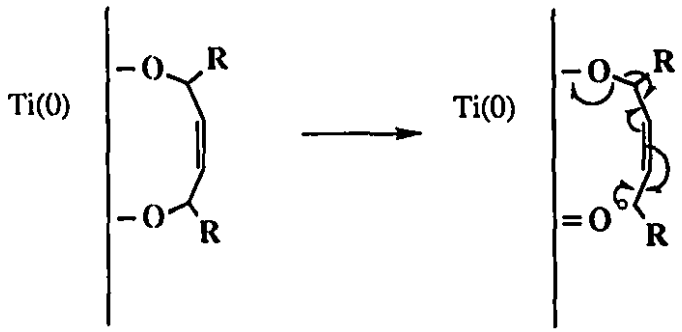
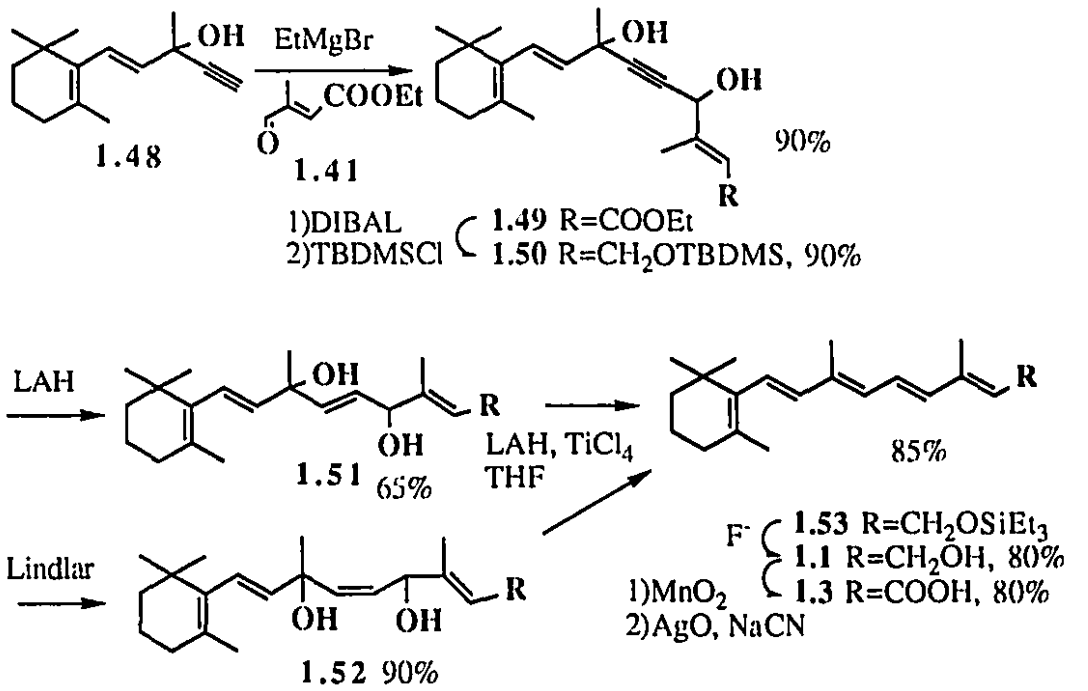


Figure 1.7.

In an application of this reaction, retinol (vitamin A), retinal and retinoic acid were synthesized stereoselectively and only the all-*trans* isomers were formed when a silyl protecting group (**1.50**) was used on the primary alcohol. However, an E:Z mixture was obtained when the acetate group was used. The explanation for this observation is obscure since the starting diol is a mixture of diastereomers and isomerisation of the final product by the titanium reagent cannot be invoked because the 13-*cis* -retinol also obtained via this route was not isomerized to the all-*trans* isomer. Also starting with diols **1.51** and **1.52** in which the central carbon carbon double bond is of either E or Z configuration leads to the formation of the same product **1.53**. The full paper published on this work did not mention any explanations for these observations.[17b]



Scheme 1.13:

Biologically active aromatic analogues of retinoic acid were also synthesised using that methodology showing how general its application can be. It should also be noted that extended conjugated systems can also be reduced in a similar fashon. Therefore conjugated 2,4-dienes-1,6-diols systems have also been reduced ($TiCl_3$, Na/Hg) leading to the formation of all-*trans* trienic systems in very high yields.[17d]

1.2.7 The Stille coupling reaction and related approaches.[18]

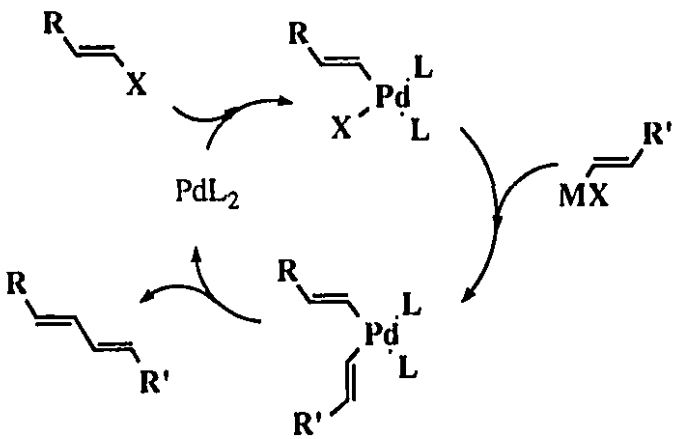
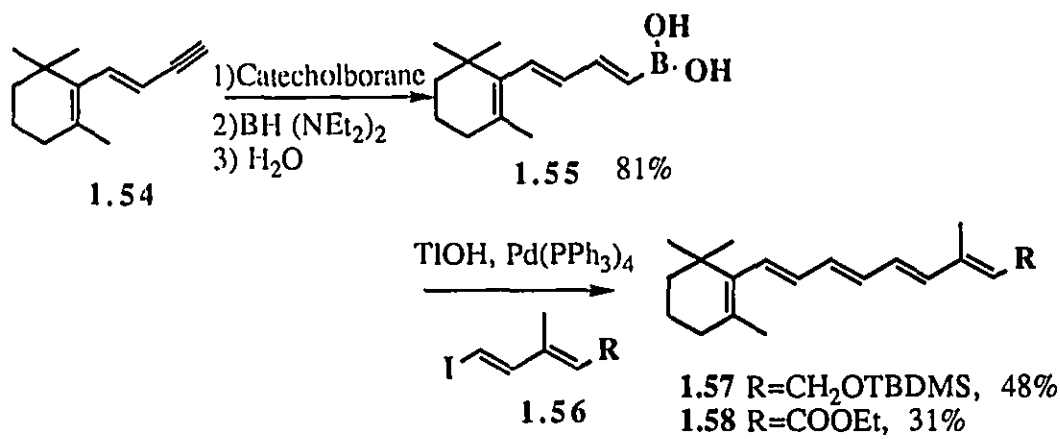


Figure 1.8:

The Stille reaction is a palladium catalyzed coupling of vinyl halides with organometallic compounds (organomagnesium, tin and zinc). The mechanism of this

reaction, as shown in figure 1.8, explains the stereospecificity of this reaction. The stereochemistry of the carbon carbon double bound on the product is dependant on that of the starting material.

As shown recently, the Stille reaction is particularily well suited for the synthesis of long conjugated polyenic compounds.[18a] Application of this approach to the synthesis of retinoic acid and other retinoids has been done with mitigated success at first.[18b] The hydroboration of acetylene **1.54** led to the vinyl borane **1.55** that could be used in the synthesis of demethylated retinoic acid analogue **1.58**. The Stille coupling of **1.55** with the iodide **1.56** went smoothly in the presence of the tetrakis(triphenylphosphine) palladium catalyst (Scheme 1.14).

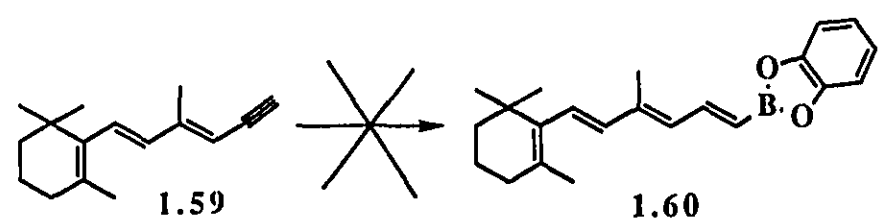


1.54 **1.55** 81%

1.56

1.57 R=CH_2OTBDMS, 48%
1.58 R=COOEt, 31%

Scheme 1.14:

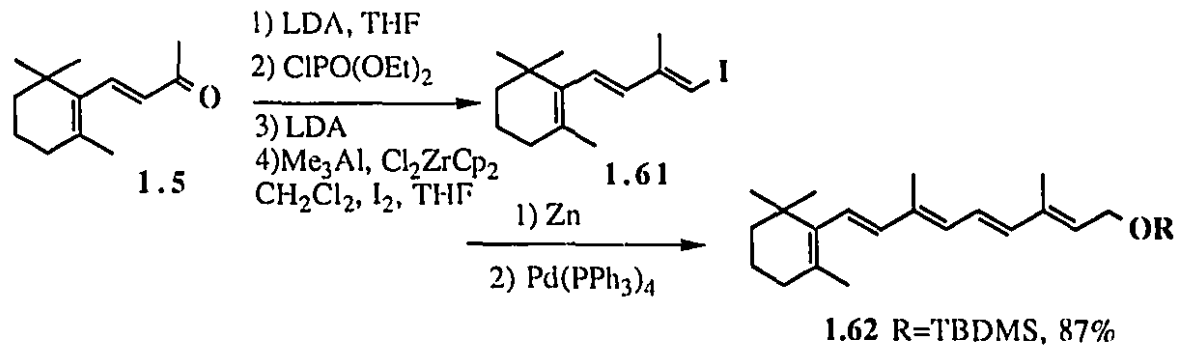


1.59 **1.60**

Scheme 1.15:

However the extension of this strategy to the synthesis of retinoic acid itself has not been successful. The hydroboration of compound **1.59** did not form the desired vinyl borane **1.60** even under catalytic conditions (Scheme 1.15). Despite this difficulty the Stille coupling approach to the synthesis of retinoids was very interesting. The idea was further developed later leading to a high yield synthesis of retinoic acid,[18c] using the iodide

1.61 as a precursor to vinyl metalic species that were in turn used successfully in a Stille coupling strategy for the synthesis of retinoic acid and vitamin A (Scheme 1.16).



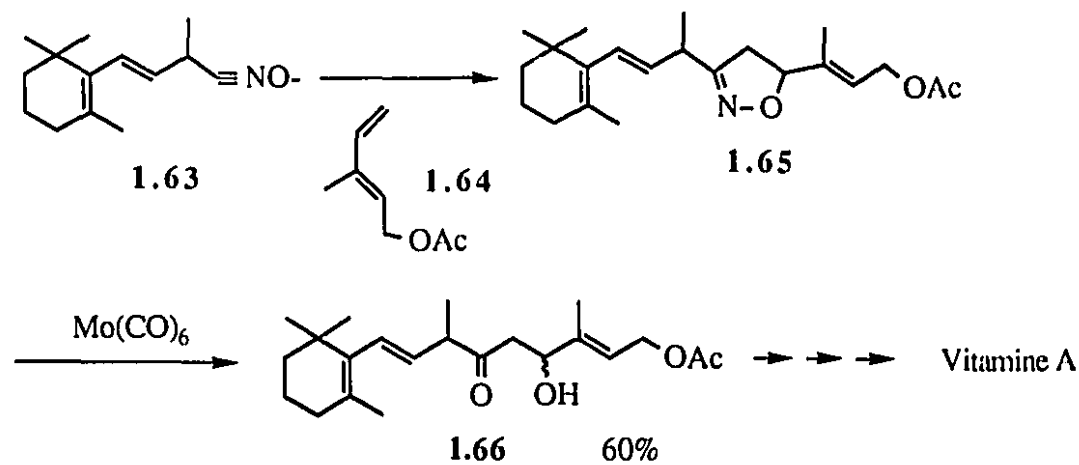
1.5 **1.61**

1.62 R=TBDMS, 87%

Scheme 1.16:

The industrial application of this methodology should theoretically be possible.

1.2.8. 1,3- Dipolar cycloaddition.[19]



1.63 **1.64** **1.65**

1.66 60%

Scheme 1.17:

The 1,3 dipolar cycloaddition of nitrile oxides to dipolarophiles is not a method for carbon-carbon double bond formation. However it was used as a way to couple two vitamin A precursors together in an efficient new way to the synthesis of vitamin A. This justifies the more detailed discussion in this section. It was not included in the elimination section 1.2.1. The use of the acetoxy-2,4-pentadiene **1.64** as dipolarophile was an efficient way of introducing the missing C5 carbon unit to the nitrile oxide **1.63.**[19] The regioselectivity obtained gave the oxazole adduct **1.65** which was reductively cleaved to the corresponding β-hydroxy ketone **1.66** which was in turn converted to vitamin A through a succession of reduction and elimination reactions (Scheme 1.17).

1.2.9 The use of the Peterson olefination reaction in retinoids synthesis.[20]

Silanes are known to undergo nucleophilic attack when subjected to metal alkoxides. This is due to the strong oxygen silicon bond formation. When the alkoxide is present in the same molecule, β to the silicon atom, an intramolecular elimination not different from the Wittig betain intermediate takes place forming the corresponding olefin stereospecifically.[20a] Acidic reaction conditions also lead to the formation of olefin but with the reversed stereospecificity. This silicon assisted elimination reaction is known as the Peterson reaction (Figure 1.9).[20b]

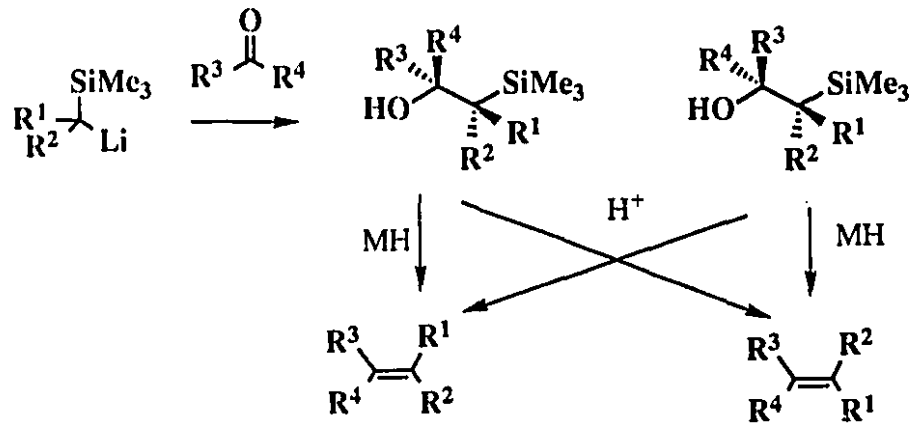


Figure 1.9:

The silyl groups have been used to stabilize carbanions on the α position. The formation of organolithium containing α silyl group is easy and a great number of them are known.[20b] Their addition to carbonyl compounds leads directly to carbon-carbon double bond formation through the Peterson olefination reaction. This olefination reaction starting from carbonyl compounds can even be stereoselective. However no attempts were made of using this reaction in the synthesis of the retinoid natural products . We propose that a stereoselective synthesis of retinoids using the Peterson olefination reaction is possible and that the most direct retrosynthetic scheme involves the use of β-ionone as starting material as represented in Figure 1.10.

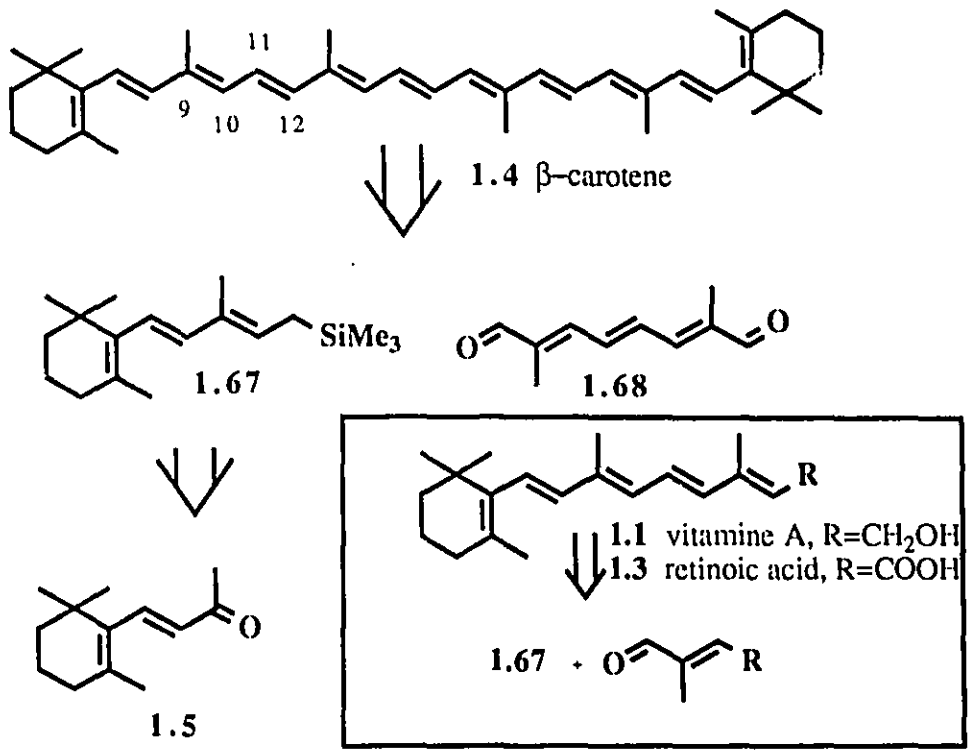


Figure 1.10:

Theoretically this retrosynthesis permits control of the geometry of the carbon carbon double bond between carbon C-11 and C-12 by way of a two step addition and elimination reaction. The objective of this thesis is therefore to investigate the reactivity of triene allylic anion of **1.67** and analogues with carbonyl electrophiles and to establish the approach underlined in Figure 1.10 as a viable way of synthesis of retinoids.

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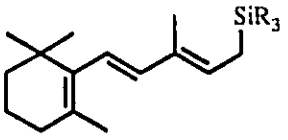
CHAPTER 2.
A NEW SYNTHESIS OF ALLYLSILANES.

2.1 Introduction.



2.1

The goals of the present thesis were stated and put in perspective in the chapter 1. As mentioned in the previous chapter the synthesis of the allylsilane **2.1** is necessary for the present research. Many synthetic methodologies have been reported for the synthesis of allyl silanes.* We tried a few and some of them worked when applied to the synthesis of **2.1**. However in most cases we obtained low yields, associated with the formation of unstable intermediates, and mixtures of *cis* and *trans* products were always obtained. Even if the optimization of the reaction conditions would lead to better yields we were still faced with the problem of having mixtures of isomers **2.1** which did not separate on column chromatography due primarily to the very low polarity of these compounds (the two isomers move close to the solvent front as a single spot on TLC in hexanes). So we have embarked on the development of a novel stereoselective synthesis of **2.1** starting from an easily accessible and stable starting material. We have published a preliminary communication of this work in Tetrahedron Letters 1990, 32, 1149, and it contains the other methodologies tried for the synthesis of **2.1** and the results of these trials. This communication has been integrally included here (except for the format which was changed to fit the thesis. Also an error in table 1 was corrected).

At the end of this section, a table of other substrates used, was included, with a discussion of the important parameters involved in these reactions.

* For a recent review on the subject see reference 7 in the reference section at the end of this chapter.

2.2 Report on the regioselective synthesis of allyl silanes.

A Novel Regioselective Synthesis of Allylsilanes.

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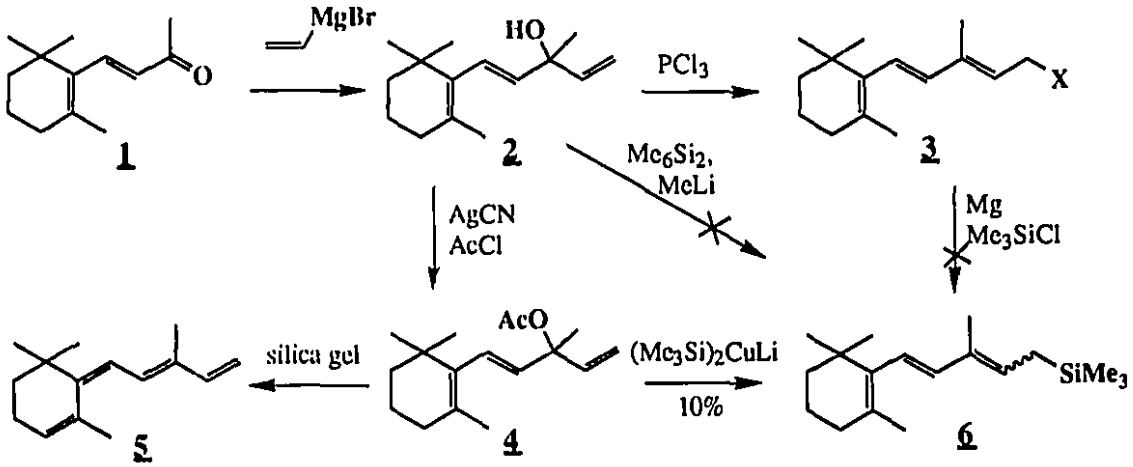
Department of Chemistry, Mc Gill University, Montreal, Quebec, Canada H3A-2K6.

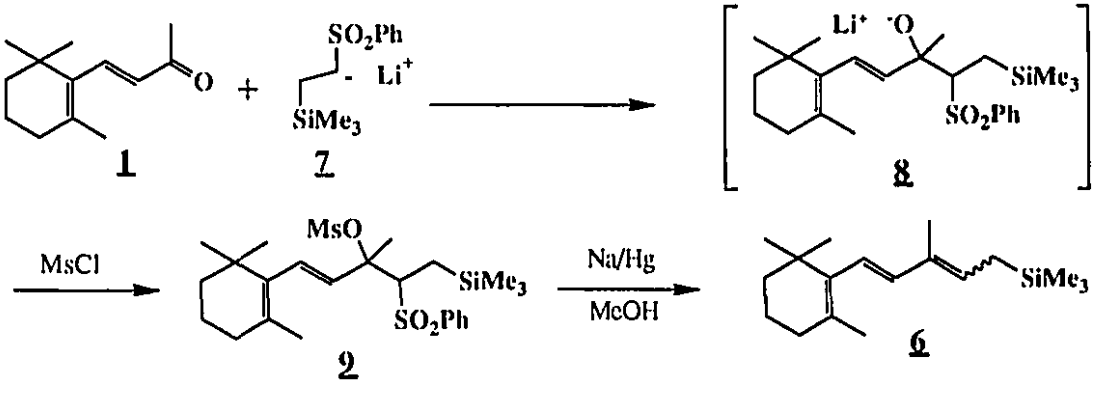
Summary: The anions derived from allyl sulfones were silylated in the α-position. Reductive desulfonylation gave the desired allylsilanes regioselectively.

Allylsilanes have become useful reagents in organic synthesis[1]. A number of methods have been developed for their preparation [2-5]. A major concern in the synthesis of allylsilanes is the control of regiochemistry[6] as well as the stereochemistry of the double bond. As part of our general research in the use of silylallyl anion in organic synthesis[7], we became interested in the synthesis of polyenylsilane **6**. Because of the conjugated polyenic structure and the possible regio- and stereoisomers, the synthesis of **6** is particularily challenging. We attempted a number of the reported general methodologies and none proved to be satisfactory (Scheme 1).



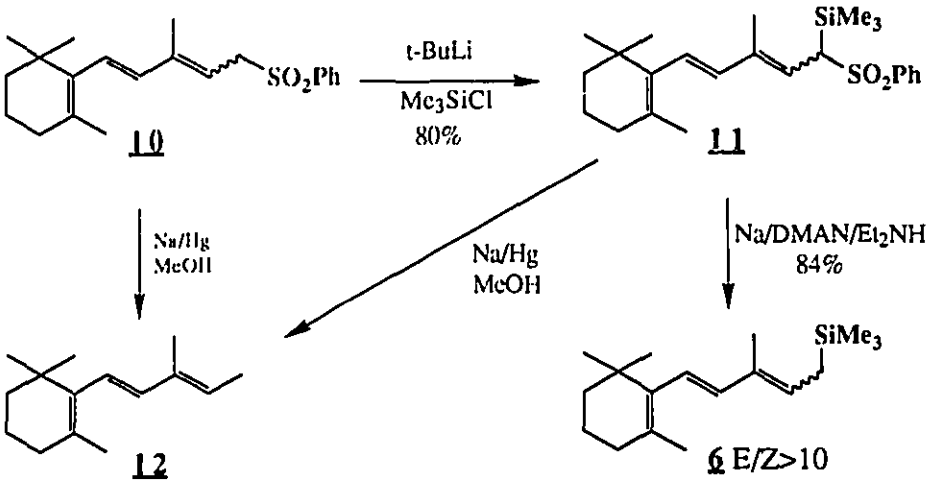
Scheme 1

A common method for the synthesis of allylsilanes is to couple allyl halides with trimethylchlorosilane via the corresponding organometallics. The bromide or chloride **3**, prepared[8] from vinyl-β-ionol **2**, on reaction with Mg and trimethylchlorosilane according to the procedure of Calas et al[3] did not give **6**. Complex mixture of uncharacterisable compounds were obtained. An alternative approach, using the "counterattacking principles" for the silylation of allylic alcohol **2** was equally unsuccessful in our hands. The vinyl alcohol **2**, on treatment with Me_6Si_2/MeLi in THF at 60 °C gave only recovered **2** and none of the desired **6** ; more stringent reaction conditions led to decomposition of starting material. A variation on the same theme is the displacement of an allylic function with silylmetallics. Thus, compound **2** was acetylated[9] with AcBr/AgCN to give the allylic acetate **4**. Treatment of **4** with the silyl cuprate reagent[10] $Li_2Cu(SiMe_3)_2$ did give the desired compound **6**, as a 1:2 E:Z mixture , however only in 10% yield. The low yield may be attributed to the fact that compound **4** was not purified before use, since it was not particularly stable and decomposed on standing or on column chromatography to give the elimination product **5**.[11]



Scheme 2

Alternative approaches to the synthesis of **6** were sought. The organolithium compound **7** , generated from the precursor β-trimethylsilylethylphenyl sulfone[12], reacted with β-ionone to give the adduct **8** which was quenched with methanesulfonyl chloride to give the mesylate **9** in good yield. Reductive elimination[13] of **9** using sodium amalgam gave the desired **6**, again as a mixture of isomers in 2:1 E:Z ratio. The low yield (7 %) was however unsatisfactory (Scheme 2). Nevertheless, the possibility of using sulfone chemistry in the preparation of allylsilanes prompted us to examine the following approach.



Scheme 3

The vinyl-β-ionol **2** was converted to the sulfone **10** folowing a procedure by Julia[13]. Treatment of **10** (1.0 g) with t-BuLi (1.2 eq.) in 50 ml of a 1:1 mixture of THF and ether at -78 °C generated the anion which reacted with trimethylchlorosilane(3 eq) to give the silylated sulfone **11** as brown cristals which could be recrystallized in hexanes , giving 0.96 g (80%) of pale yellow crystals (m.p.:113-114 °C). Sodium amalgam reduction of **11** in methanol gave the desilylated and desulfonylated hydrocarbon **12**. The formation of **12** was attributed to the cleavage of carbon-silicon bond by methoxide ion which was formed under the reduction conditions. Indeed, treatment of **11** with sodium methoxide in methanol gave the starting sulfone **10** in good yield. Sulfone **10** was also reduced under sodium amalgam conditions to give the hydrocarbon **12**. Selective cleavage of the sulfone function was eventually achieved under non-nucleophilic conditions. Sodium/dimethylaminonaphthalene (DMAN) reduction of sulfur containing compounds, developed by Bank[14a]and Ley[14b] succesfully reduced **11** to the desired **6** in 70% yield. The silane **6** was formed as a mixture of E and Z isomers (7:1) with the all-trans compound predominating. The two isomeric compounds were purified by flash column chromatography but could not be separated from each other.

The yield and the selectivity were increased (Scheme 3) by adding diethylamine together with **11** to the Na/ DMAN reducing agent. The radical anion Na/DMAN was not quenched by diisopropylamine or diethylamine under the condition in which the reaction were carried out. Moreover the isomeric ratio in **6** appeared to be dependent on the proton source used to protonate the intermediate allyl anion.

Typical procedure for the reduction of allylsulfonylsilanes: A solution containing 0.100 g of sulfone **11** dissolved in 1.0 ml of anhydrous THF [with 0.5 ml diethyl amine for the improved method] was added under an argon atmosphere at -85°C to a previously prepared solution of Na /DMAN (4 eq.). This solution was prepared by stirring sodium (8 eq.) in 20 ml of THF with DMAN at -10 °C under argon for 3 hours. Immediatelly after addition of the allyl sulfone to this solution at -85°C, 1 ml of distilled water was added and then followed up by the addition of 20 ml of hexanes (at this point the excess sodium was removed from the reaction mixture). The resulting solution was extracted with 20 ml water and twice with 20 ml HCl 10% to remove the DMAN. The organic solvents were evaporated and the residue was purified by flash chromatography using hexanes as eluent affording 0.044 g (70%) [0.056 g (91 %) improved method] of **6** as a clear oil (b.p.= 110 °C at 0.4 mm/Hg.)

To our knowledge, the synthesis of **6** via an allylsulfone represents a completely new way of access to allylsilanes. The regiochemical control is ensured by the sulfonyl group which directs the electrophile to the α-position of the allylic system. We demonstrated the generality of the approach by the synthesis of other allylsilanes and one allylstannane as represented in Table 1.

Acknowledgement: Financial support by NSERC and FCAR is gratefully acknowledged.

1. H. Sakurai, *Pure appl. Chem.*, **1982**, 154, 1; G. Majetich, in Organic Symthesis, Theory and applications, T. Hudlicky, Ed.,Jai Press, Inc., Greenwich, CT.,1989.
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6. Compare, for example, the syntheses of the two regioisomers of geranyltrimethylsilane by two different methods. B.M. Trost, J. Yosilida and M. Lautens, *J.Am.Chem.Soc.*, **1983**, 105, 4494; D. Wang and T.H. Chan, *J. Chem.Soc. Chem. Commun.*, **1984**, 1274.

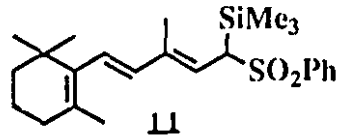
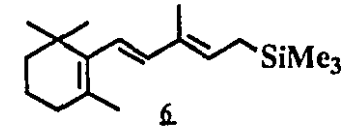
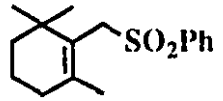
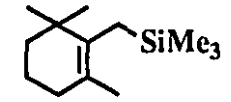
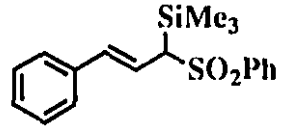
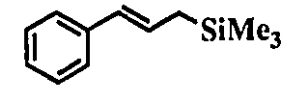
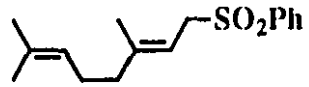
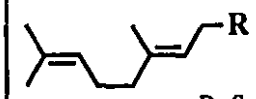
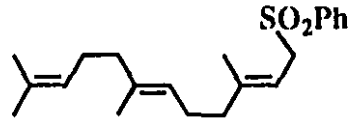
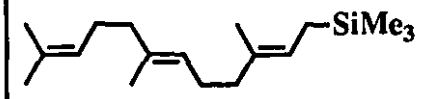
STARTING MATERIAL	METHOD	PRODUCT	YIELD
 11	A	 6	70%[a] 84%[b]
	B		61%[c]
	A		69% 89%[d]
	B	 R=SnMe3	44%
	B	R=SiMe3	68%[e]
	B		66%[e]

Table 1: Method A) as described in text, Method B) the allyl sulfonyl silane was formed in situ and the resulting solution was added to the Na /DMAN as described in the text, a) 7:1 E:Z at C-9, ref.15,16 b) By adding diethylamine as internal anion quencher the yield and selectivity were improved to > 10: 1 E:Z at C-9, c) The corresponding sulfone was recrystallyzed in ethyl acetate from product synthesized using procedure described in reference 17, d) same as in b but selectivity was already good, e) contaminated with 10 % of the corresponding vinylsilane.

7. P.W.K Lau and T.H. Chan, *Tetrahedron Lett.* **1978**, 27, 2383; T.H. Chan and K. Koumaglo, *J. Organomet. Chem.*, **1985**, 285, 109; R.F. Horvath and T.H. Chan, *J.Org.Chem.* **1989**, 54, 317.

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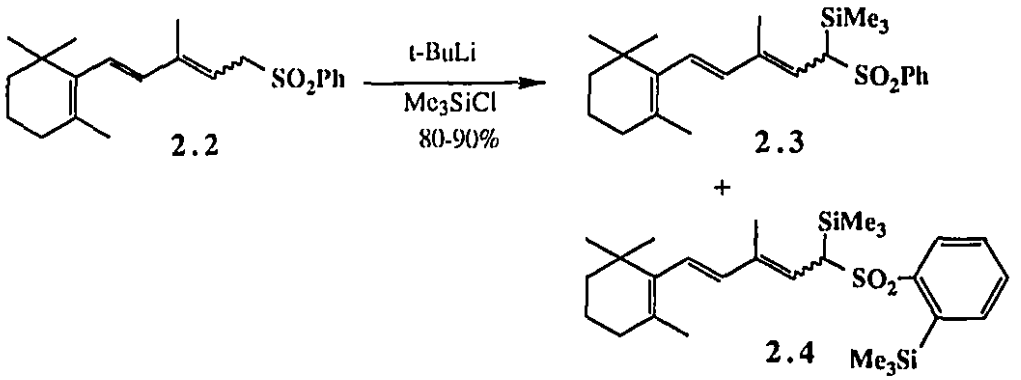
14. a) S. Bank, M. Platz; *Tetrahedron Lett.* **1973**, 23, 2097. b) S.V. Ley, B. Lygo, F. Sternfeld, A. Wonnacott, *Tetrahedron* **1986**, 42, 4333.
15. Spectroscopic data of **6**: ^{1}H NMR($CDCl_3$): 5.93(dd, 16 Hz, 2H), 5.46(t, 9 Hz, 1H), 1.98(m, 2H), 1.71(s, 3H), 1.67(s, 3H), 1.57(d, 9 Hz, 2H), 1.57(m, 2H), 1.43(m, 2H), 0.99(s, 6H), -0.01(s, 9H); ^{13}C NMR($CDCl_3$): 138.3, 138.0, 131.9, 127.9, 127.7, 122.3, 39.6, 34.2, 33.0, 28.9, 21.7, 19.9, 19.4, 12.2, 1.6.
16.Assignment of stereochemistry of **6** was based on comparison with similar compounds in the literature. See G. Englert, *Helv.Chim.Acta* **1975**, 58, 8, 2367; B. D. Sykes, R.Rowan, *J.Am.Chem. Soc.* **1974**, 96, 7000; J.Pugmire, D.M. Grant, D.K. Dalling, S.Berger, R.S. Becker, *J.Am.Chem.Soc.*,**1974**, 96, 7008.
17. S. Torii, K. Uneyama, M. Isihara, *Chemistry Letters*, **1975**, 479.
Spectroscopic data for cyclogeranyltrimethylsilane : ^{1}H NMR($CDCl_3$): 1.9(m, 2H), 1.6(m, 2H), 1.5(s, 3H), 1.4(m, 2H), 0.95(s, 6H), 0.1(s, 9 H). ^{13}C NMR($CDCl_3$): 135.5, 123.1, 39.8, 34.6, 32.6, 28.7, 21.3, 19.6, 17.9, 0.3 .

2.3 Preparation and chemical properties of silylated allylic sulfones.

As stated earlier we decided to use the stable sulfone **2.2** as starting material for the preparation of the desired allylsilane **2.1** (Scheme 2.1). Silylation of this sulfone followed by reductive cleavage of the sulfone group, led to the desired allylsilanes and was the subject of the publication given in section 2.2. During the time this work was being published (section 2.2), we also studied the properties of these silylated sulfone intermediates. The synthesis, and some of the properties of silylated sulfones were reported by other workers.[1,2] The results of our own investigations in this field will be discussed in more detail in this section.

Allyl sulfones could be deprotonated in THF at -78° with *n* -BuLi, *s* -BuLi and *t* -BuLi. We found the use of *t* -BuLi in THF:ether 50:50 at -78°C to be the optimum reaction conditions for the deprotonation of the sulfone **2.2** for use in the silylation reactions as we have reported in section 2.2. The deprotonated sulfone was silylated by the addition of chlorotrimethylsilane at -78° followed by warming the reaction mixture to 0°C for 15 min before adding water. The silylated sulfone **2.3** obtained in this way is very sensitive to

hydrolytic conditions. It is desilylated on silica gel and must be preserved at -20°C for long term storage. Recrystallization in hexanes represents the best method of purification.

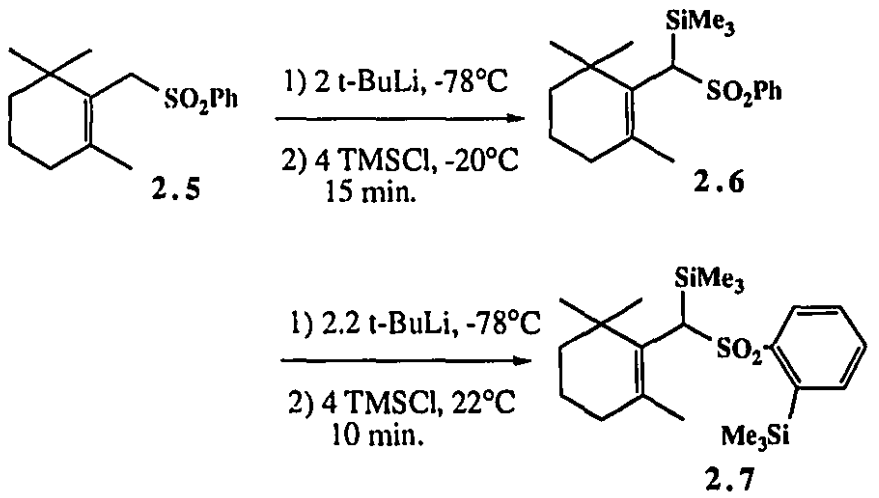


2.2 2.3 2.4

Scheme 2.1:

The formation of some disilylated product was observed when more base was added and when the reaction mixture was allowed to warm up to higher temperatures. The ^1H NMR indicated that the second silylation was taking place on the phenyl group to give structure **2.4**. The second silylation did not occur on the allylic moiety as one would have expected according to the reported results on alkylation reactions.[3] However similar reactions have been observed in the condensation of aldehydes with allylsulfone dianions.[4]

Similar reactions were observed when we silylated the cyclogeranyl sulfone **2.6**. In this case both products **2.6** and **2.7** were stable to flash chromatography and could be purified and separated from each other using 90% hexanes :10% diethyl ether as eluent, permitting the full characterization of the disilylated β-cyclogeranyl sulfone **2.7**.

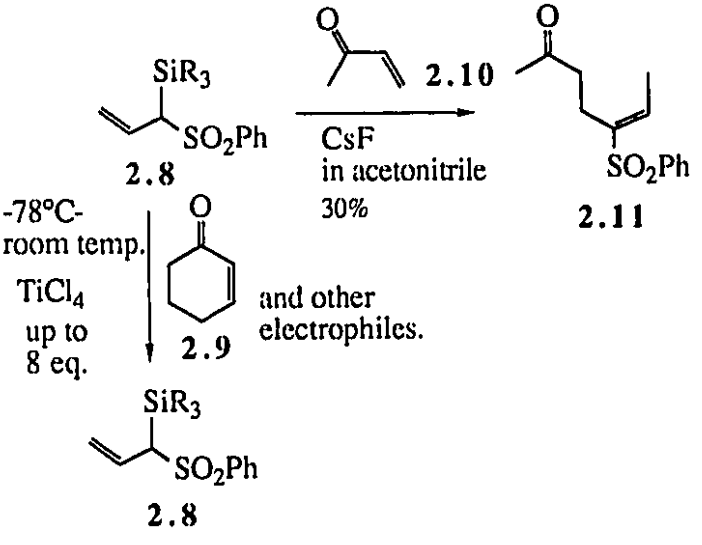


2.5 2.6 2.7

Scheme 2.2:

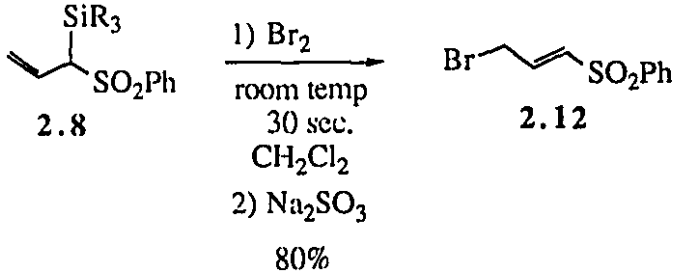
The silylated sulfones and their allylsilane reduction products, synthesized in the course of this thesis are listed in table 2.2 (in the next section). In most instances the yields for the silylation reactions were good. The reduction of the mono and the bis-trimethylsilylated sulfones was carried out with sodium 1-(dimethylamino)naphthalene (NaDMAN) in THF in comparable yields. Table 2.2 shows that better results were obtained when diethylamine (DEA) was added to the silylated sulfones. Also, we were able to use different alkyl groups on the silicon atom without affecting the outcome of the reaction. However when aryl or chloromethyl groups were used, the reduction step did not lead to the formation of the expected allylsilanes. Complex reaction mixtures were obtained.

While investigating the use of these compounds as allylsilane nucleophiles, we found them to be uncharacteristically unreactive. When submitted to Lewis acid catalyzed allylation reaction conditions, they did not react with carbonyl electrophiles. For example silylated sulfone **2.8** was recovered unreacted, even when the allylation reaction was carried out with 8 eq. of $TiCl_4$ and 2-cyclohexene-1-one **2.9** at room temperature for 1 hour. The use of cesium fluoride with methylvinylketone (MVK) **2.10** did however lead to some condensation reaction giving **2.11**, in low yields. The product isolated was obtained via a 1,4 conjugate addition followed by double bond shift. A similar 1,4-conjugate addition product had been made earlier using the lithiated allylsulfone in hexamethylphosphoric triamide (HMPA).[5] One possible explanation for the lack of reactivity of the silylated sulfones, in Lewis acid catalyzed condensation reactions, might be that the Lewis acids forms a complex with the sulfonyl group, thus rendering the carbon-carbon double bond electron deficient, when compared to a normal allylsilanes, and thus less reactive toward electrophiles.



Scheme 2.3:

Despite this observation, α-trimethylsilylated allyl sulfone **2.8** does share most of the chemical properties associated with allyl silanes.[7] As we have seen, when it is activated with cesium fluoride or when it is hydrolysed by weak acids, compound **2.8** does react as it would be expected of allylsilanes in general. Furthermore **2.8** reacted with bromine to give the corresponding *trans* -bromomethylvinylsulfone **2.12** in high yield (*trans* product only).

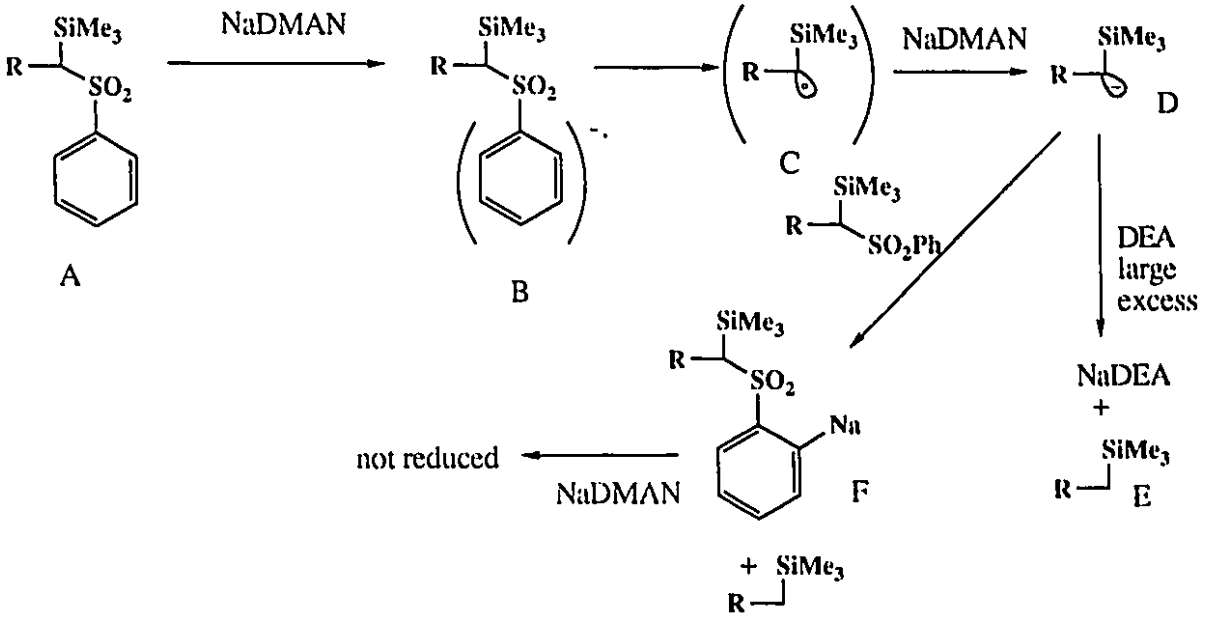


Scheme 2.4:

2.4 Mechanistic consideration of the NaDMAN reduction of the silylated allylsulfones.

In a previous section (section 2.2) we have made the interesting observation that addition of diethylamine to the silylated allylsulfones led to higher selectivities and considerably higher yields in the synthesis of allylsilanes, at least when the reaction was carried out on silylated sulfone **2.3**.

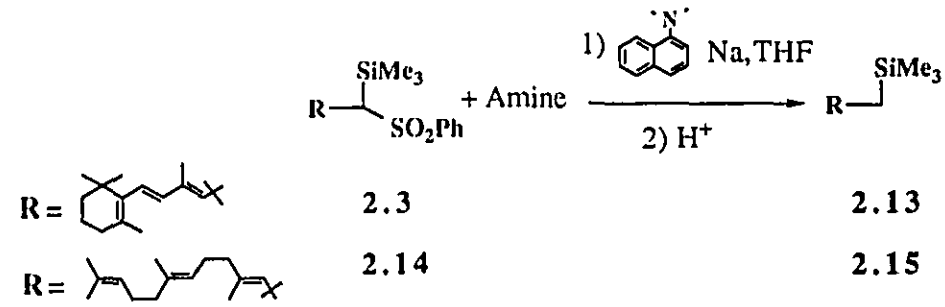
These observations are not easily explainable. However the beneficial effect on the yield of the presence of the diethylamine seems to apply to the reduction of other silylated sulfones as demonstrated in table 2.2. Furthermore the NaDMAN reducing solution in THF does not seem to be affected by the addition of secondary amines; the dark green NaDMAN turned to a light yellow or brown solution when a proton source like water or ethanol, was added. The exchange of sodium from NaDMAN to NaDEA should have changed the color of the solution if it had occured.



Scheme 2.5:

If we assume that the reductive cleavage reaction goes through a process similar to the one outlined in scheme 2.5, then reagent NaDMAN should first transfer an electron to the sulfone to form the radical anion **B**, which undergoes rearrangement to the free radical **C**, which is then further reduced to the anion **D**. The role of the amine could be either to stabilize the free radical **C**, or to be a proton source for quenching the anion **D** as it forms.

We propose that the major cause for the lower yields normally observed in absence of diethylamine, could be due to the free radical **C** polymerization or to interaction between the allylic anion **D** and the starting silylated sulfone **A**. This should take place when the allylic anion product deprotonates the starting material **A** to give the anion **F**, which is less susceptible to reductive cleavage by the NaDMAN. The starting silylated sulfone **2.6** that was isolated after the tentative reduction with NaDMAN of an anion **F** (obtained from the deprotonation of sulfone **2.6**) seems to support this latter theory.



2.3 **2.13**

2.14 **2.15**

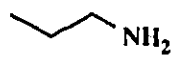
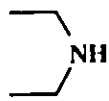
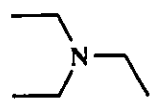
Amine	**2.13** Yield %	**2.15** Yield%
	0	48
	85	95
	68	52
None	70	66

Table 2.1: Effect of an amine additive on the yields of allylsilanes.

To probe the role that diethylamine is playing in this reaction, we tried adding other amines instead of diethylamine (triethylamine and propylamine, see Table 2.1). The use of triethylamine showed no improvement of the observed yields, establishing the importance of the proton in diethylamine and discarding any free radical stabilization effects the amine could have had. However when propylamine was used instead, we obtained even lower yields which appeared to be contradictory to our theory. However we were able to establish that this amine had partially desilylated the starting material prior to its reduction, thus leading to the observed lower yields of allylsilanes.

Having done these experiments, it is possible for us to presume that a small secondary amine present in a very large excess could quench the allyl anion formed, giving a product with a stereochemistry related to that of the starting material and slowing down the deprotonation side reaction. (of course the deprotonation side reaction can be carried out by the NaDEA formed but it can be expected to be slower than the reduction reaction).

We can conclude that the allylsilane **2.13** as well as other allylsilanes and allylstannanes can be prepared with good stereoselectivity and high to moderate yields using the method described here. The investigation of the effects of the diethylamine additive has permitted a better comprehension of the reactions involved in this reductive cleavage. Maybe

these observations will be applicable in other instances, where it could be useful to employ NaDMAN or any other radical anion equivalents in the presence of a proton source. They could also be useful in the development of new dissolving metal reagents to permit the use of amines which do not normally dissolve metals like lithium, sodium or potassium.[8]

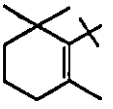
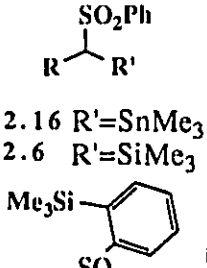
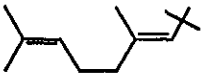
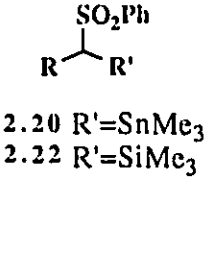
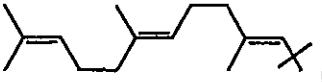
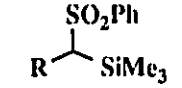
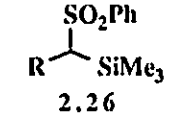
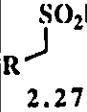
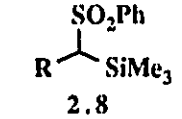
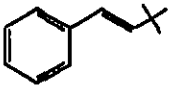
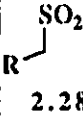
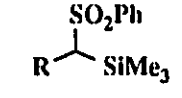
R	S.M.	sulfones	Yields	Reduction	Yields
					
	2.5	2.16 R'=$SnMe_3$ 2.6 R'=$SiMe_3$	- 68%	2.17 R'=$SnMe_3$ 2.18 R'=$SiMe_3$	20%[c] 61%[c] 90%[b]
		2.7	quant.	2.18	80%[b]
					
	2.19	2.20 R'=$SnMe_3$ 2.22 R'=$SiMe_3$	- 96%	2.21 R'=$SnMe_3$ 2.23 R'=$SiMe_3$	44%[c] 68%[c]
			92%		66%[c] 95%[b]
	2.24	2.14		2.15	
			67%	–	
	2.25	2.26			
			64%	–	
	2.27	2.8			
			72%		69%[a] 89%[b]
	2.28	2.29		2.30	

Table 2.2(first part): Preparation of silylated sulfones, allylsilanes and . a) from silylated sulfone, b) from silylated sulfone, addition with DEA. c) from the corresponding sulfone.

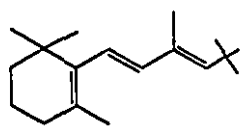
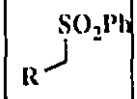
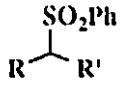
R	S.M.	sulfones	Yields	Reduction	Yields
					
	2.2	2.3 R'=$SiMe_3$	77%	2.1 R'=$SiMe_3$	70%[a], 84%[b]
		2.31 R'=$SiEt_3$	-	2.32 R'=SiEt3	70%[c]
		2.33 R'=$Si(nPr)_3$	-	2.34 R'=$Si(nPr)_3$	50%[c]
		2.35 R'= $SiMe_2iPr$	-	2.36 R'= $SiMe_2iPr$	56%[c]
		2.37 R'= $SiMe_2CH_2Cl$	70%	2.38 R'=$SiMe_2CH_2Cl$	0%

Table 2.2 (second part): Preparation of silyiated sulfones and allylsilanes. a) from silylated sulfone, b) from silylated sulfone, addition with DEA. c) from the corresponding sulfone.

2.5 Experimental.

The starting sulfone **2.2** was prepared from β-ionone according to the method by Julia[9]. The method used for making this sulfone is very well described, however we found the recrystallization of this sulfone to be difficult; by contrast flash chromatography, using a 90:10 mixture of hexanes:ethyl acetate as eluent, gave a product of good isomeric purity.

The starting allyl sulfones **2.25, 2.27** and **2.28** were prepared from the corresponding allyl bromides and the benzenesulfinic acid sodium salt, using the method by Trost[10]. Geranyl bromide was easily prepared from reaction of geraniol with phosphorus tribromide at 0°C in anhydrous ether. (Geranyl bromide is available from Aldrich but the purity of this product was not very good we therefore suggest to prepare geranyl bromide prior to use).

The β-cyclogeranyl sulfone **2.5** was prepared according to the procedure by Torii[12]. Geranyl sulfone was cyclized in a sulfuric acid and acetic acid mixture. This reaction produced the desired cyclogeranyl sulfone contaminated with 20% of α-cyclogeranyl sulfone. We found that the desired sulfone could be purified by recrystallization in ethyl acetate or diethyl ether at low temperature (in a -20°C freezer).

The reagents used in this section were purchased from Aldrich. The solvents tetrahydrofuran (THF), diethyl ether, hexanes and ethyl acetate were purchased from BDH.

THF and diethyl ether were distilled over sodium benzophenone ketyl radical before using them. Hexanes, ethyl acetate, diethylamine, propylamine, and triethylamine were distilled over calcium hydride. Methanol was distilled over magnesium turnings.

The melting points were determined on a Gallenkamp block, and the boiling points are uncorrected. Thin layer chromatography was carried out using commercial, pre-coated plastic-backed silica gel plates (T-6145, 60 Å silica gel with fluorescent indicator) supplied by Sigma co. Flash chromatography was performed on Merk silica gel 60 (230-400 mesh ASTM)

Spectroscopy: All nuclear magnetic resonance spectroscopy were carried out on the following apparatus. The ^{1}H (200 MHz) and ^{13}C (50 MHz) were carried out on the VARIAN Gemini 200 and XL-200. The ^{1}H (270 MHz) and ^{13}C (68 MHz) were carried out on the JEOL-270. The ^{1}H (300 MHz) and ^{13}C (75 MHz) were carried out on the VARIAN XL-300. The chemical shifts are expressed in parts per million (ppm) and the reference is trace of chloroform in $CDCl_3$ giving a signal at 7.24 ppm for ^{1}H and at 77.00 ppm for ^{13}C. The low and high resolution mass spectrometry were done by Dr. O. Mamer at the McGill Biomedical Mass Spectrometry Unit on a HP 5980A or by M. Saadé and J. Finkenbine on a Kratos MS 25RFA spectrometer in the McGill chemistry department. Unless specified the mode of ionisation is the electronic ionisation at 70 eV or chemical ionisation with methane. IR spectra were recorded on an Analet FT, A25-18 or on a BOMEM Michelson Series between NaCl plates (neat liquids or solutions).

The trimethyltin derivative **2.16** and **2.20** were reduced immediately after their preparation. These derivatives were not purified further.

1) Methylvinylketone adduct **2.11**.

Under argon at room temperature, CsF (0.06 g, 0.39 mmol) was added to a solution of trimethylsilylated allylsulfone **2.8** (0.10 g, 0.39 mol) and methyl vinyl ketone (0.03 g, 4.28 mmol) dissolved in 1.0 mL of dry acetonitrile at room temperature. After stirring this solution for 1 hour, 20 mL of ether and 10 mL of distilled water were added. The organic phase was separated and evaporated to give 0.12g of a crude residue. This residue was separated by flash chromatography giving product **2.11**, 0.04g (40%), as an oil.

^{1}H NMR($CDCl_3$, 200MHz) δ 7.83-7.80 (m, 2H), 7.64-7.47 (m, 3H), 7.01 (q, J=7.2 Hz, 1H), 2.68 (dd, J=7.0, 9.5 Hz, 2H), 2.42 (dd, J=7.0, 9.5 Hz, 2H), 2.09 (s, 3H), 2.00 (d, J=7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 207.1, 140.6, 139.4, 138.3, 133.2, 129.2, 128.0, 42.0, 29.8, 20.0, 14.0.

2)*trans* -1-Bromo-3-phenylsulfonyl-2-propene **2.12**.

At room temperature bromine (0.12g, 0.78 mmol) was slowly added to a solution of trimethylsilylated allylsulfone **2.8** (0.20 g, 0.78 mmol) dissolved in 10 ml of dry methylene chloride. After strirring 1 min the excess bromine was quenched with 1mL of a saturated solution of sodium sulfite. Ether (50 mL) was added. The organic phase was separated then washed with distilled water. Evaporation of the solvents gave 0.15g (75%) of compound **2.12** as a clear oil.

^{1}H NMR($CDCl_3$, 200MHz) δ 8.00-7.80 (m, 2H), 7.70-7.30 (m, 3H), 7.04 (dt, J=6.8, 14.8 Hz, 1H), 6.58 (dt, J=1.3, 14.8 Hz, 1H), 4.01 (dd, J=1.4, 6.8 Hz, 2H). ^{13}C NMR ($CDCl_3$, 68 MHz) δ [138.8, 138.7(resolved)], 133.2, 133.1, 128.8, 127.2, 27.9. IR(film) 3053, 1634, 1601, 1447, 1284, 1147, 1085 cm^{-1}. MS (EI) m/z cal'd for $C_9H_9O_2SBr$: 259.9507. Found: 259.9521. 262(6%), 260 (5%), 141 (3%), 125(100%), 77 (33%).

3) The general method used for the preparation of silylated sulfones **2.3**, **2.6**, **2.8**, **2.14**, **2.22**, **2.26**, **2.29**, **2.31**, **2.33**, **2.35**, **2.37** is the same as described in section 2.2 of this chapter and is described in more details in the example below.

3.1) 1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-3-methyl-5-trimethylsilyl-5-benzenesulfonyl-*trans,trans*-penta-1,3-diene **2.3**.

Sulfone **2.2** (1.0 g, 3.0 mmol) was dissolved in 50 mL of a 1:1 mixture of THF and ether. Addition of [t-BuLi 1.7 M in pentane (2.1 mL, 3.6 mmol)] to this solution at -78 °C generated the anion of **2.2**. Trimethylchlorosilane (0.8 mL, 9.0 mmol) was slowly added at -78 °C. The reaction flask was removed from the cold bath and the reaction mixture was stirred 15 min (no more). 10 mL of water was added, the organic phase was separated and then washed with a saturated sodium carbonate solution and brine. Drying over anhydrous

$MgSO_4$ followed by evaporation of the solvents and recrystallization in hexanes gave 0.96 g (77 %) of a pale yellow crystalline powder.

Silylated sulfone **2.3**.

m.p. 113-114 °C

^1H NMR($CDCl_3$, 200MHz) δ 7.75 (m, 2H), 7.57-7.35 (m, 3H), 5.95 (d, J=16.2 Hz, 1H), 5.85 (d, J= 16.2 Hz, 1H), 5.40 (d, 12.1 Hz, 1H), 3.69 (d, 12.1 Hz, 1H), 1.95 (m, 2H), 1.63 (s, 3H), 1.63-1.40 (m, 4H), 1.14 (s, 3H), 0.96 (s, 3H), 0.93 (s, 3H), 0.31 (s, 9H). ^{13}C NMR($CDCl_3$, 50 MHz) δ 140.6, 138.9, 137.3, 136.4, 132.6, 129.3, 128.4, 127.9, 126.7, 119.9, 59.5, 39.4, 34.1, 32.9, 28.8, 28.7, 21.5, 19.2, 11.7, -1.3. IR(film) 3200-2800, 1600, 1447, 1302, 1289, 1250, 1084. MS(CI, NH_3) m/z cal'd for $C_{24}H_{37}SO_2Si$: 417.2284 Found: 417.2283. 434 (M+18, 3%), 417 (18%), 275 (100%).

Bis-silylated sulfone **2.4**:

^1H NMR($CDCl_3$, 200MHz) δ 7.72 (m, 2H), 7.50-7.7.29 (m, 2H) (1 proton less in the aromatic region when compared to **2.3**), 5.95 (d, J=16.2 Hz, 1H), 5.84 (d, J= 16.2 Hz, 1H), 5.41 (d, 1H), 3.73 (d, 1H), 2.00 (m, 2H), 1.65 (s, 3H), 1.65-1.40 (m, 4H), 1.10 (s, 3H), 0.95 (s, 3H), 0.90 (s, 3H), 0.45 (s, 9H), 0.34 (s, 9H).

3.2) Trimethylsilylated β-cyclogeranylsulfone 2.6.

The procedure 3.1 used for the synthesis of sulfone **2.3** was carried out using β-cyclogeranyl phenyl sulfone **2.5** (0.5 g, 1.8 mmol) to give 0.64 g of the crude trimethylsilylated sulfone **2.6** which contained small amount of bis silylated compound **2.7**. The mixture was then separated by flash chromatography using 5 % diethyl ether / 95% hexanes as eluent, providing 0.46 g (68%) of compound **2.6** as a clear oil and 0.10 g (14%) of compound **2.7** as a white powder .

Trimethylsilylated β-cyclogeranylsulfone 2.6:

^1H NMR($CDCl_3$, 200MHz) δ 7.75 (d, J=6.7Hz, 2H), 7.60-7.40 (m, 3H), 3.62 (s, 1H), 2.05 (m, 2H), 1.94 (s, 3H), 1.50-1.20 (m, 4H), 0.75 (s, 3H), 0.32 (s, 9H), 0 (s, 3H). ^{13}C NMR($CDCl_3$, 68MHz) δ 141.8, 136.9, 132.9, 128.7, 128.4, 60.9, 39.9, 35.9, 34.1, 29.4, 26.5, 24.8, 18.8, 1.2; IR (film) 2955-2828, 1600, 1468, 1289, 1249, 1084, 1143, 1102

cm^{-1}; MS(EI) m/z cal'd for $C_{19}H_{30}O_2SSi_2$: 350.1736. Found: 350.1726. 350(7%), 225(8%), 215(38%), 135(54%), 73(100%).

Bis-trimethylsilylated β-cyclogeranyl sulfone **2.7**:

m.p. 113-113.5 °C
^1H NMR($CDCl_3$, 200MHz) δ 7.74 (d, J= 5.8 Hz, 1H), 7.62 (d, J= 5.8Hz, 1H), 7.43 (m, 2H), 3.65 (s, 1H), 2.05 (m, 2H), 2.04 (s, 3H), 1.55-1.45 (m, 1H), 1.30-1.10 (m, 3H), 0.75 (s,3H), 0.44 (s, 9H), 0.40 (s, 9H), -0.27 (s, 3H). ^{13}C NMR($CDCl_3$, 68 MHz) δ 146.4, 140.1, 136.8, 136.2, 131.8, 131.7, 129.0, 128.6, 60.8, 40.1, 36.0, 34.3, 29.5, 25.4, 25.1, 18.9, 1.6, 1.5. IR(nujol) 1600, 1289, 1248, 1146, 1102 cm^{-1}; MS(EI) m/z cal'd for $C_{22}H_{38}O_2SSi_2$: 422.2131. Found: 422.2134. 422(6%), 349(35%), 271(48%), 135(54%), 73(100%).

3.3) Trimethylsilylated allylsulfone 2.8.

The procedure 3.1 was used starting with 1-benzenesulfonylprop-2-ene **2.27** (2.0 g, 11.0 mmol) and [*s* -butyllithium 1.3 M in c-hexane (9.7 mL, 12.7 mmol)] to give 2.6 g of a clear oil. This crude oil was purified by recrystallization in ether (slow evaporation) giving 1.8 g of silylated compound **2.8** as large transparent cubic crystals .

m.p. 79-80.5 °C
^1H NMR($CDCl_3$, 200MHz) δ 7.80 (dm, J=7.9Hz, 2H), 7.60-7.42 (m, 3H), 5.80 (ddd, J=16.8, 10.9, 10.2 Hz, 1H), 5.00 (d, J=10.2 Hz, 1H), 4.70 (d, 16.8 Hz, 1H), 3.39 (d, 10.9 Hz, 1H), 0.32 (s, 9H). ^{13}C NMR($CDCl_3$, 50 MHz) δ 140.4, 132.8, 129.4, 128.5, 127.9, 119.8, 64.4, -1.4. IR(nujol) 1623, 1289, 1248, 1084, 1143, 1102 cm^{-1}, MS(EI) m/z cal'd for $C_{14}H_{22}O_2SSi$: 254.0797 Found: 254.0792. 254 (3%), 237 (3%), 141 (59%), 118 (38%), 117 (43%), 77 (100%), 51 (27%).

3.4) Trimethylsilylated all-*trans* -farnesylsulfone **2.14**.

The procedure 3.1 was carried out using farnesylsulfone **2.24** (1.0 g, 2.9 mmol) and [*t* -butyllithium 1.7 M in pentane (1.9 mL, 3.3 mmol)] to give 3.1 g (92%) of compound **2.14** as a clear oil. This crude oil was about 90% pure but could not be further purified since it desilylated upon column chromatography. It was used as such in the next reaction. The impurity could be a silylated cis isomer present in the starting material.

^{1}H NMR($CDCl_3$, 200 MHz) δ 7.74-7.81 (m, 2H), 7.58-7.39 (m, 3H), 5.21 (d, J=11.8 Hz, 1H), 5.02 (m, 2H), 3.55 (d, J=11.8 Hz, 1H), 2.10-1.85 (m, 8H), 1.67 (s, 3H), 1.58 (s, 3H), 1.55 (s, 3H), 1.04 (s, 3H), 0.28 (s, 9H). ^{13}C NMR($CDCl_3$, 68 MHz) δ 141.4, 140.8, 135.4, 132.5, 131.2, 128.3, 127.8, 124.1, 123.4, 115.0, 58.5, 39.6, 26.6, 26.3, 25.6, 17.6, 15.9, 15.6, -1.4. IR(film) 3086-2856, 1655, 1586, 1304, 1251, 1142, 1085 cm^{-1}. MS(EI) m/z cal'd for $C_{24}H_{38}SO_2Si$: 418.2362 Found: 418.2366, 418 (1%), 353 (2%), 281 (100%), 135 (20%), 73 (55%), 69 (41%).

3.5) Trimethylsilylated geranylsulfone **2.22.**

The procedure 3.1 was carried out using geranylsulfone **2.19** (1.2 g, 4.3 mmol) and [*t* -butyllithium 1.7 M in pentane (2.8 mL, 4.7 mmol)], and gave 1.44 g (96%) of compound **2.22** as a clear oil. This crude oil could be further purified by washing out the hexamethyldisiloxane impurity with hexanes.

^{1}H NMR($CDCl_3$, 200 MHz) δ 7.74 (m, 2H), 7.55-7.36 (m, 3H), 5.16 (d, J=11.8 Hz, 1H), 4.92 (m, 1H), 3.52 (d, J=11.8 Hz, 1H), 1.85 (m, 4H), 1.61 (s, 3H), 1.52 (s, 3H), 1.00 (s, 3H), 0.25 (s, 9H). ^{13}C NMR($CDCl_3$, 68 MHz) δ 141.2, 140.8, 132.5, 131.7, 128.3, 127.8, 123.6, 115.1, 58.5, 39.5, 26.2, 25.6, 17.6, 15.6, -1.5; IR(film) 3086-2856, 1655, 1602, 1447, 1380, 1304, 1251, 1145, 1085 cm^{-1}. MS(EI) M/z cal'd for $C_{19}H_{30}SiSO_2$: 350.1736 Found: 350.1734, 350 (0.7%), 281 (100%), 215 (12%), 199 (9%), 136 (25%), 73 (63%), 69 (27%).

3.6) Trimethylsilyl-3,3-dimethylallyl sulfone **2.26.**

The procedure 3.1 was carried out using 3,3-dimethylallyl sulfone **2.25** (0.50 g, 2.4 mmol) and [*t* -butyllithium 1.7 M in pentane (1.5 mL, 2.5 mmol)] to give 0.52 g of an oily solid. This residue was recrystallized in hexanes to give 0.45 g (67%) of compound **2.26** as white gum.

^{1}H NMR($CDCl_3$, 200MHz) δ 7.75 (d, J=6.9 Hz, 2H), 7.60-7.40 (m, 3H), 5.19 (d, 11.8 Hz, 1H), 3.53 (d, J=11.8 Hz, 1H), 1.60 (s, 3H), 1.0 (s, 3H), 0.29 (s, 9H). ^{13}C NMR($CDCl_3$, 68 MHz) δ . 140.8, 138.1, 132.6, 128.4, 127.9, 115.0, 58.8, 25.6, 17.2, -1.3. IR(film) 3086-2856, 1449, 1379, 1304, 1251, 1144, 1085 cm^{-1}. MS(EI) m/z cal'd

for $C_{14}H_{22}O_2SSi$: 282.1110 Found: 282.1107. 282 (63%), 199 (17%), 166 (34%), 147 (49%), 135 (71%), 125 (28%), 77 (27%), 73 (100%).

3.7) Trimethylsilylcinnamyl sulfone **2.29**.

The procedure 3.1 was carried out using 3,3-dimethylallyl sulfone **2.28** (0.50 g, 1.9 mmol) and [*t* -butyllithium 1.7 M in pentane (1.8 mL, 2.3 mmol)] to give 0.63 g of a yellow solid. This residue was recrystallized in hexanes to give 0.5 g (72 %) of compound **2.29** as white powder.

m.p. 113-115°C
^{1}H NMR($CDCl_3$, 200MHz) δ 7.8 (d, J=7.4Hz, 2H), 7.46 (m, 3H), 7.24 (m, 5H), 6.18 (dd, J=10.4, 15.7 Hz, 1H), 5.99 (d, J=15.7 Hz, 1H), 3.53 (d, J=10.4 Hz, 1H), 0.38 (s, 9H). ^{13}C NMR($CDCl_3$, 68MHz) δ 140.5, 136.4, 134.7, 132.8, 128.6, 128.5, 127.8, 126.2, 120.6, 63.8, -1.19. IR(nujol) 2938-2853, 1463, 1288, 1283, 1141, 1081. MS(EI) m/z cal'd for $C_{18}H_{22}O_2SSi$: 330.1110 Found: 330.1126. 330(41%), 223(19%), 135(41%), 125(37%), 117(100%), 73(85%)

3.8) 1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-3-methyl-5-(chloromethyl)dimethylsilyl-5-benzenesulfonyl-*trans,trans* -penta-1,3-diene **2.37**.

The procedure 3.1 was carried out using sulfone **2.2** (2.0 g, 5.8 mmol) and *t*-butyllithium 1.7 M in pentane (3.6 mL, 6.2 mmol) to give a dark yellow solid. This residue was recrystallized in hexanes to give 1.8 g (69 %) of compound **2.37** as white powder.

m.p. 79-80°C dec.
^{1}H NMR($CDCl_3$, 200MHz) δ 7.76 (d, J=7.2 Hz, 2H), 7.58-7.38 (m, 3H), 5.98 (d, J=16.2, 1H), 5.89 (d, J=16.2, 1H), 5.39 (d, J=12.1 Hz, 1H), 3.91 (d, J=12.1 Hz, 2H), 3.13 (d, J= 13.7 Hz, 1H), 3.01 (d, J= 13.7 Hz, 1H), 1.98 (m, 2H), 1.63 (s, 3H), 1.57 (m, 2H), 1.45 (m, 2H), 1.15 (s, 3H), 0.95 (s, 3H), 0.93 (s, 3H), 0.50 (s, 3H), 0.36 (s, 3H). ^{13}C NMR ($CDCl_3$, 75MHz) δ 140.1, 140.0, 137.2, 136.0, 132.9, 129.5, 128.5, 128.0, 127.5, 118.2, 57.7, 39.4, 34.0, 32.8, 29.6, 28.8, 28.7, 21.5, 19.1, 11.8, -4.5, -4.6. IR(nujol) 1300, 1254, 1209, 1176, 1182. MS(EI) m/z cal'd for $C_{24}H_{35}O_2SSiCl$: 450.1816 Found: 450.1814. 450 (3%), 181 (%), 153 (38%), 69 (24%), 57 (100%).

4) Preparation of allyl silanes:

Method A: the general method for the reductive cleavage of the trimethylsilylated sulfones by their reactions with NaDMAN solution in THF at -78°C are described in section 3.3 of this chapter. Some precisions should be mentioned here, as to how the NaDMAN solution should be prepared. We found Ley's method of dissolution of sodium metal in a DMAN solution in THF at -78° by ultrasound very impractical and much too slow. The formation of the NaDMAN radical anion in THF at higher temperatures is easier; unfortunatelly it also becomes less stable. We obtained the best results by putting sodium metal in a relatively concentrated solution of DMAN in THF (1g/10ml), and pressing the soft metal against the bottom of the flask (with a glass rod) then stirring this reaction mixture under argon at -10 to -20°C for 4-6 h.

Method B: method A was followed with the exception that the silylated sulfone was dissolved in a THF : diethylamine solvent mixture (1 mL of THF: 0.5 mL diethylamine for every 0.1 g of product being reduced) then added to the NaDMAN solution.
Method C: The sulfone reagent was silylated using the method exemplified in 3.1, followed by the reduction of the product of this reaction using method A without prior purification of the silylated sulfone.

4.1) Preparation of 1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-methyl-5-trimethylsilyl-*trans,trans* -penta-1,3-diene **2.1**.

The synthesis of silane **2.1** was described in details in section 3.3.
Method A gave the desired product **2.1** in 70% yield as a 1:7 mixture of isomer the all-trans being the major one.
Method B gave the desired product **2.1** in 87% yield of the all-trans isomer in a >95% isomeric purity.

all-*trans* isomer:[12]
uv: ε=230,000 (ethanol), λ_{max}= 272
^{1}H NMR($CDCl_3$, 200MHz) δ 6.02 (d, J=16.2 Hz, 1H), 5.9 (d, J=16.2 Hz, 1H), 5.49 (t, J=8.2 Hz, 1H), 1.98 (m, 2H), 1.71 (s, 3H), 1.67 (s, 3H), 1.65-1.40 (m, 4H), 1.57 (d, J=8.2 Hz, 2H), 1.02 (s, 6H), 0.04 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.3, 138.0, 131.9, 127.9, 127.8, 122.3, 39.7, 34.2, 33.0, 28.9, 21.7, 19.9, 19.4, 12.2, -1.6. IR

(film) 2919, 1628, 1456, 1145, 1011 cm^{-1}. MS (EI) m/z cal'd for $C_{18}H_{32}Si$: 276.2272 Found: 276.2273. 276 (35%), 261 (14%), 220 (3%), 219 (3%), 119 (28%), 73 (100%).

9-cis isomer:[12] (These values are from a sample synthesized by a method with low selectivity to obtain the spectroscopic values for the 9-*cis* isomer. The NMRs were obtained from a mixture and the mass spectra was obtained from a GCMS).
^1H NMR($CDCl_3$, 200MHz) δ 6.31 (d, J=16.2 Hz, 1H), 6.00 (d, J=16.2 Hz, 1H), 5.34 (t, J=8.2 Hz, 1H), 1.97 (d, J= 8.2 Hz, 2H), 1.67 (s, 3H), 1.59 (s, 3H), 1.57 (d, 2H), 1.57 (m, 2H), 1.43 (m, 2H), 0.99 (s, 6H), -0.04 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.5, 130.0, 128.1, 127.9, 125.8, 125.6, 39.5, 34.1, 32.9, 28.8, 21.8, 20.7, 19.35, -1.72. MS (EI) m/z 276 (66%), 261 (30%), 119 (30%), 73 (100%).

4.2) Farnesyltrimethylsilane **2.15.**

Method B on the trimethylsilylated sulfone **2.14** (0.10 g, 2.4 mmol) gave 0.07 g of product **2.15** (95%) the all-trans isomer in a >90% isomeric purity.
Method C on the trimethylsilylated sulfone **2.14** (0.100 g, 2.4 mmol) gave 0.053 g (66%) of the desired silane product **2.15** with good isomeric purity (7:1).

^1H NMR($CDCl_3$, 200MHz) δ 5.22 (t, J=8.6 Hz, 1H), 5.22-5.05 (m, 2H), 2.15-1.91 (m, 8H), 1.69 (s, 3H), 1.61 (s, 6H), 1.56 (s, 3H), 1.40 (d, J=8.6 Hz, 1H), -0.04 (s, 9H). ^{13}C NMR ($CDCl_3$, 68 MHz) δ 134.7, 132.3, 131.2, 124.4, 124.4, 120.2, 40.0, 39.8, 26.8, 25.7, 18.6, 17.7, 16.0, 15.8, -1.7. IR(film) 2958-2858, 1601, 1448, 1247, 856 cm^{-1}. MS (EI) m/z cal'd for $C_{14}H_{22}O_2SSi$: 278.2430 Found: 278.2437. 278 (6%), 237 (3%), 141 (38%), 73 (100%), 69 (14%).

4.3) Cyclogeranyltrimethylsilane **2.18.**

Method B on trimethylsilylated sulfone **2.6** (1.2 g, 4.9 mmol) gave 0.7g (95%) of the desired silane product **2.18.**
Method B on the bis trimethylsilylated sulfone **2.7** (0.11 g, 2.6 mmol) gave 0.043g (80%) of the desired silane product **2.18.**
Method C on sulfone **2.5** (0.05g, 0.18 mmol) gave 0.023 g (61%) of the desired silane **2.18.**

^{1}H NMR($CDCl_3$, 200MHz) δ 1.94 (m, 2H), 1.93 (m, 2H), 1.51 (s, 3H), 1.66-1.39 (m, 6H), 0.96 (s, 6H), 0.05 (s, 9H); ^{13}C NMR($CDCl_3$, 50 MHz) δ 134.8, 122.5, 40.2, 35.1, 33.1, 29.3, 22.0, 20.3, 18.6, -1.2. IR 2937-2828, 1601, 1468, 1248, 1167 cm^{-1}. MS (EI) m/z cal'd for $C_{13}H_{26}Si$: 210.1804, found: 210.1792.

4.4) Geranyltrimethylsilane **2.23**.

Method A on trimethylsilylated sulfone **2.19** (0.10 g, 0.34 mmol) gave 0.05 g (68%) of the desired silane product **2.23** with good isomeric purity (7:1).

^{1}H NMR($CDCl_3$, 200 MHz) δ 5.18 (t, J= 8.5Hz, 1H), 5.11 (m, 1H), 2.05 (m, 4H), 1.68 (s, 3H), 1.62 (s, 3H), 1.56 (s, 3H), 1.40 (d, J= 8.5 Hz, 2H), -0.01 (s, 9H); ^{13}C NMR($CDCl_3$, 68 MHz) δ 132.2, 131.1, 124.6, 120.3, 40.0, 26.9, 25.7, 18.6, 17.7, 15.7, -1.8. MS (CI, NH_3) m/z cal'd for $C_{13}H_{27}Si$: 211.1882, found: 211.1883. M+18 228(26%), M+1 211 (100%), 195 (97%), 137 (49%).[14]

4.5) Cinnamyltrimethylsilane **2.30**.

Method A on trimethylsilylated sulfone **2.29** (0.1g, 0.3 mmol) gave 0.036 g (69%) of the desired silane product **2.30**.
Method B on trimethylsilylated sulfone **2.29** (0.1g, 0.3 mmol) gave 0.047 g (89%) of the desired silane product **2.30**.

^{1}H NMR($CDCl_3$) δ 7.36-7.1(m, 5H), 6.25 (m, ABX, 2H), 1.66 (m, 2H), 0.3 (s, 9H).[15]

4.6) Preparation of 1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-methyl-5-triethylsilyl-*trans,trans*-penta-1,3-diene **2.32**.

Method C on sulfone **2.2** (1.00 g, 2.9 mmol), using chlorotriethylsilane, gave 0.64 g (70%) of the desired silane product **2.32**. The pure E (>90%) isomer was isolated by flash chromatography using hexanes as eluent.

^{1}H NMR($CDCl_3$, 200MHz) δ 6.00 (d, J=16.1 Hz, 1H), 5.86 (d, J=16.1 Hz, 1H), 5.48 (t, J=8.5 Hz, 1H), 1.99 (m, 2H), 1.74 (s, 3H), 1.68 (s, 3H), 1.65-1.40 (m, 4H), 1.61 (d, J= 8.5 Hz, 2H), 1.01 (s, 6H), 0.94 (t, J=5.1 Hz, 9H), 0.54 (q, J=5.1 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.5, 138.1, 131.6, 128.0, 127.9, 122.2, 39.6, 34.2, 33.0, 28.9,

21.7, 19.4, 14.8, 12.1, 7.4, 3.4. IR (film) 2919, 1628, 1456, 1145, 1011 cm^{-1}. MS (EI) m/z cal'd for $C_{21}H_{38}Si$: 318.2743 Found: 318.2761. 318 (34%), 303 (1%), 289 (1%), 115 (100%), 87 (64%), 59 (15%).

4.7) Preparation of 1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-methyl-5-tri(*n* -propyl)silyl-*trans,trans* -penta-1,3-diene **2.34**.

Method C on sulfone **2.2** (1.00 g, 2.9 mmol), using chlorotri(*n* -propyl)silane, gave 0.51 g (50%) of the desired silane product **2.34**. The E isomer was obtained.

^1H NMR($CDCl_3$, 200MHz) δ 6.00 (d, J=15.9 Hz, 1H), 5.85 (d, J=15.9 Hz, 1H), 5.47 (t, J=8.6 Hz, 1H), 1.99 (m, 2H), 1.73 (s, 3H), 1.69 (s, 3H), 1.65-1.20 (m, 10H), 1.61 (d, J= 8.6 Hz, 2H), 1.01 (s, 6H), 0.94 (m, 9H), 0.51 (m, 6H).

4.8) Preparation of 1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-methyl-5-dimethyl(*i* -propyl)silyl-*trans,trans* -penta-1,3-diene **2.36**.

Method C on silylated sulfone **2.2** (1.00 g, 2.9 mmol), using chlorodimethyl(*i* -propyl)silane, gave 0.49 g (56%) of the desired silane product **2.36**. A 2:1 E:Z isomeric mixture was isolated.

(E+Z) ^1H NMR($CDCl_3$, 200MHz) δ 6.36 ((Z) d, J=16.1 Hz, 1/3 H), 6.00 ((Z+E)2d, J=16.1 Hz, 1H), 5.85 ((E)d, J=16.1 Hz, 2/3 H), 5.48 ((E)t, J=8.6 Hz, 2/3 H), 5.36 ((Z)t, J=9.1 Hz, 1/3 H), 2.02 ((E+Z), m, 2H), 2.00 ((Z), s, 1H), 1.74 ((E) s, 2H), 1.70 ((E+Z) s, 3H), 1.65-1.40 ((E+Z), m, 5H), 1.61 ((E+Z), d, J= 8.6 Hz, 2H), 1.02 ((E+Z) s, 6H), 0.98-0.93 ((E+Z) m, 6H), -0.05 ((E)s, 4H), -0.07 ((Z), s, 2H). (E+Z) ^{13}C NMR ($CDCl_3$, 75MHz) δ 138.5, 138.4, 138.0, 131.8, 130.4, 129.9, 128.1, 127.9, 127.8, 125.8, 125.7, 122.2, 39.7, 39.6, 34.2, 34.1, 33.0, 32.9, 28.9, 21.8, 21.7, 20.7, 19.4, 17.5, 16.8, 15.7, 13.4, 13.3, 12.2, -5.4, -5.5. IR (film) 2936, 1628, 1457, 1146, 1063 cm^{-1}. MS (EI) m/z cal'd for $C_{20}H_{36}Si$: 304.2586 Found: 304.2580. 304 (55%), 289 (4%), 275 (3%), 261 (6%), 101 (100%), 73 (80%), 59 (30%).

5) Allyltrimethylstannanes.

The allyltrimethylstannanes were prepared using method C developed for making the allyl silanes. The intermediate stannylated sulfones **2.16** and **2.20** were not isolated or

characterized. The stannylated sulfones were prepared by the deprotonation of the corresponding sulfones (in ether or THF at -78°C) followed by the addition of 1 equivalent of chlorotrimethyltin.

5.1) β-Cyclogeranyltrimethylstannane **2.17**.

The β-cyclogeranyl sulfone **2.16** (1.30 g, 4.68 mmol), was dissolved in 50 mL of THF:ether (50:50). At -78°C under argon, 4.48 mL of t-BuLi (1.7 M in heptane) was added and the reaction mixture was stirred for an additional hour. Chlorotrimethyltin (2.80 g, 7.6 mmol) was added. The reaction mixture was warmed up to room temperature and left stirring for 50 min. This reaction mixture was worked up by washing with brine followed by separation of the organic phase. Vacuum evaporation of the solvents gave a clear residue, which was dissolved in 10 mL of anhydrous THF and transfered to a 100 mL THF solution, containing 4 eq. NaDMAN at -78°C, previously prepared according to the method described in experiment 4. The reaction mixture was then transfered (via a syringe) back to an Erlenmeyer containing 50 mL of a cold sat. ammonium chloride solution. (care must be taken not to take any excess sodium with the syringe. Use of a small diameter needle is suggested). The reaction was worked out by extracting the product with hexanes and washing with brine. The solvents were evaporated and the product was isolated by flash chromatography using hexanes as eluent leaving 0.7 g of a clear oil, compound **2.17**, contaminated with a volatile side product. Warming this liquid under a high vacuum (or Kugelrohr at 100°C) gave 0.26 g (20%) of the desired stannane **2.17**.

^{1}H NMR($CDCl_3$, 200 MHz) δ 1.95 (m, 2H), 1.65 (s, 3H), 1.64-1.38 (m, 6H), 1.45 (s, 3H), 0.96 (s, 6H), 0.06 (s, 9H); ^{13}C NMR($CDCl_3$, 50 MHz) δ 136.5, 121.5, 39.7, 34.6, 32.5, 28.5, 20.4, 19.7, 14.2, 14.2, -8.6. IR(film) 2966-2825, 1469, 1434, 1115 MS(EI) m/z cal'd for $C_{13}H_{26}Sn$: 302.1056, found: 302.1054. 302 (9%), 165 (100%), 137 (21%), 95 (14%).

5.2) Geranyltrimethylstannane **2.21**.

The geranyl sulfone **2.20** (0.5 g, 1.8 mmol), was dissolved in 1mL of THF. At -78°C under argon, 1.2 mL of t-BuLi (1.7 M in heptane) was added and the reaction mixture was stirred for an additional 30 min. Chlorotrimethyltin (0.43 g, 2.16 mol) dissolved in 1 mL of dry ether was added. The reaction mixture was warmed up to room temperature and left stirring for 24 hours. This reaction mixture was transfered via a syringe to a 10 mL THF

solution containing 2 eq. NaDMAN in solution at -78°C previously prepared according to the method described in experiment 4. The reaction mixture was then transfered (via a syringe) back to an Erlenmeyer containing 10 mL of cold sat. ammonium chloride solution. (care must be taken not to take any excess sodium with the syringe. Use of a small diameter needle is suggested). The reaction was worked out by extracting the product with hexanes and washing with brine. The solvents were evaporated and the product was isolated by flash chromatography using hexanes as eluent leaving 0.2g (44%) of a clear oil.

^{1}H NMR($CDCl_3$, 200 MHz) δ 5.33 (t, J=9.1Hz, 1H), 5.10 (m, 1H), 2.03 (m,4H), 1.68 (m, 5H), 1.61 (s, 3H), 1.56 (s, 3H), 0.08 (s, 9H); ^{13}C NMR($CDCl_3$, 50 MHz) δ 130.5, 129.2, 124.0, 121.8, 40.2, 27.7, 26.4, 18.4, 16.3, 13.3, -8.9. IR(film) 2966-2825, 1653, 1453, 1378 MS(EI) m/z cal'd for $C_{13}H_{26}Sn$: 302.1056, found: 302.1049.

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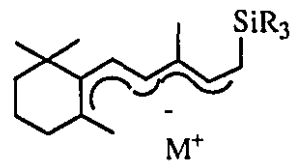
CHAPTER 3
SYNTHESIS OF POLYENES.

3.1. Introduction.



3.1

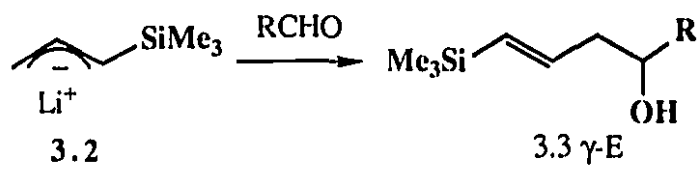
Figure 3.1.

Before we describe the results from the condensation of anions of allylsilanes **3.1** with carbonyl electrophiles, we must give a perspective on what has been done in the field of α-trimethylsilylallyl carbanions and their condensations with ketones and aldehydes.

3.1.1 Allylsilyl carbanions additions to ketones and aldehydes.[1,2]

The reactivity and regioselectivity of the reactions of simple α–silylallyl anions with electrophiles are very well represented by the reactivity of trimethylsilylallyllithium which has been studied extensively and represent the best example for the discussion of this family of reagents.

Trimethylsilylallyllithium **3.2** adds to most aldehydes and ketones to give the γ-E vinylsilanes **3.3** (Scheme 3.1) with no or very small amounts of α-condensation products or of it's Peterson elimination product.[2] The γ-E selectivity is probably best explained by NMR studies carried out in solution which showed that trimethylsilylallyllithium exists exclusively in the exo conformation.[3]

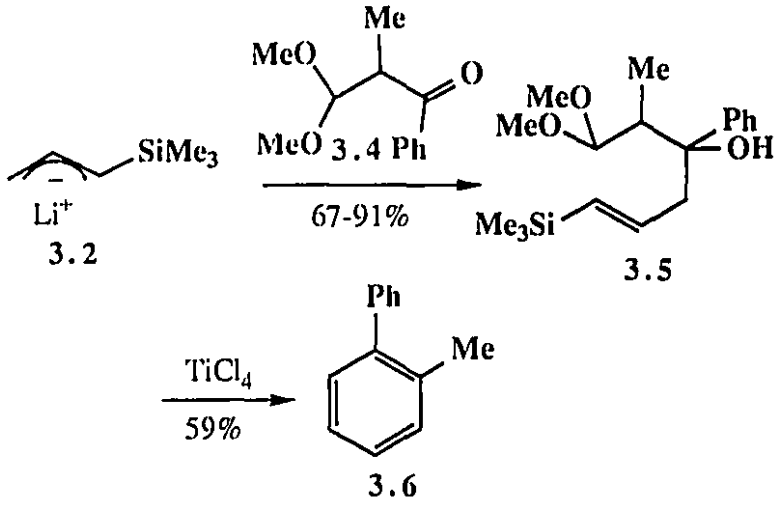


3.2 **3.3 γ-E**

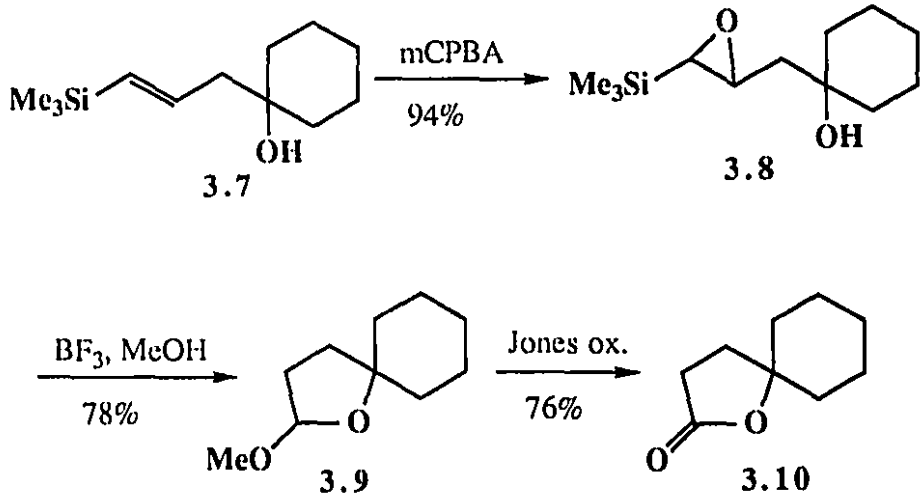
Scheme 3.1.

These γ condensation products are useful in organic synthesis. For example the vinylsilane portion of the addition product **3.5** can be used as an internal nucleophile in cyclisation reactions, as demonstrated in the synthesis of substituted aromatic compounds

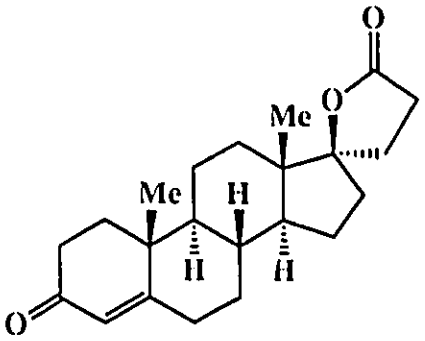
(Scheme 3.2).[4] They can also be used as lactone precursors (Scheme 3.3) as demonstrated in the synthesis of steroidal 17-spiro-γ-lactone **3.11**.[2]



Scheme 3.2.



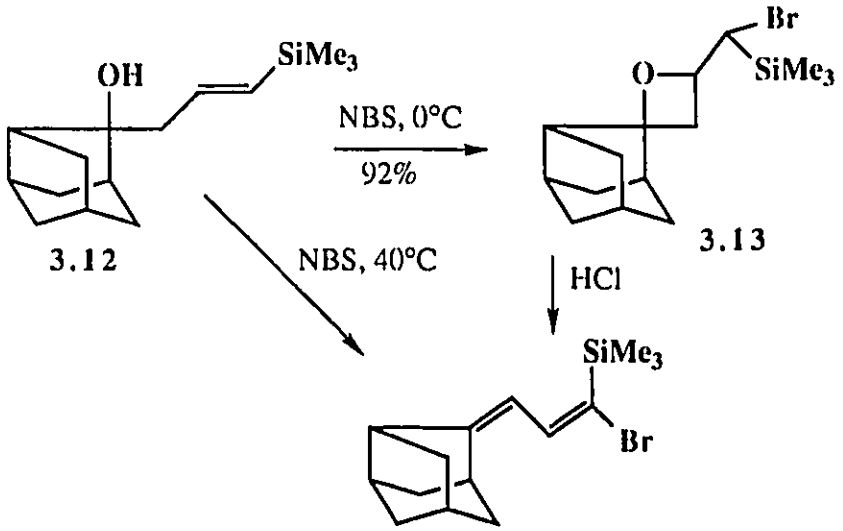
Scheme 3.3.



3.11

Figure 3.2.

The reactivity of the double bond in these hydroxyvinylsilane products (**3.12**) is modulated by the trimethylsilyl group. Their reactions with N-bromosuccinimide led to the formation of a β-bromooxetane **3.13** at 0°C or of a diene product when reacted at 40°C. The formation of the expected tetrahydrofuran product has not been observed (scheme 3.4).[2]

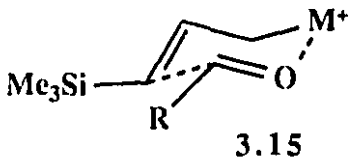


Scheme 3.4.

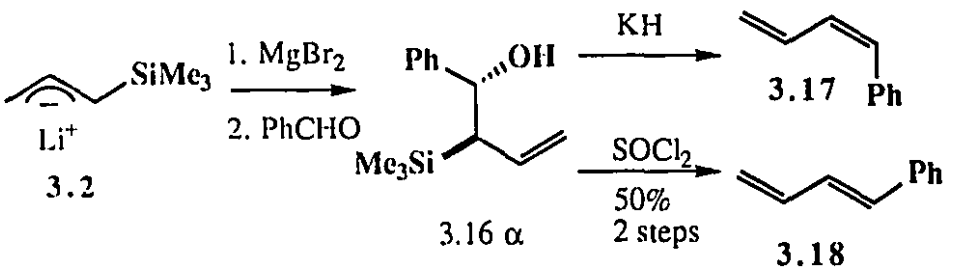
3.1.2 Use of α-silylallyl anions in the synthesis of dienes.

As mentioned above, the reactions of ketones or aldehydes with trimethylsilylallyllithium led to the formation of the γ-condensation products almost

exclusively. This regioselectivity can be modified by the use of different metal counter ions. Thus α-condensation products can be obtained selectively if magnesium bromide or other Lewis acids are added to the reaction media. The resulting alcohols are also diastereomerically enhanced. These observations are explained by the formation of a six-membered ring transition state **3.15** where the metal ion M^+ coordinates with the carbonyl oxygen.



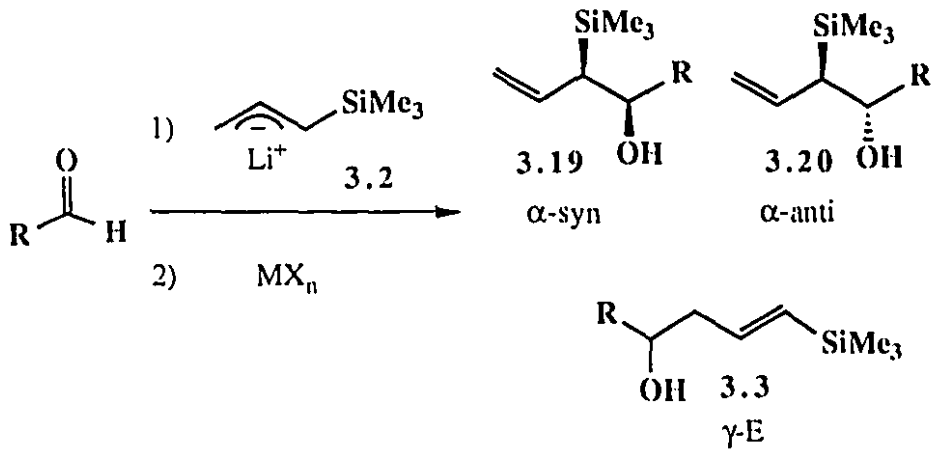
3.15



3.2 3.16 α **3.17** **3.18**

Scheme 3.5.

A list of other reagents that can be added to modify the normal regio- and stereoselectivity of the trimethylsilylallyllithium addition reaction is given in Table 3.1. The alcohols thus obtained are useful since they can be used in generating dienes stereospecifically via the Peterson olefination reaction (Scheme 3.5).[5a]

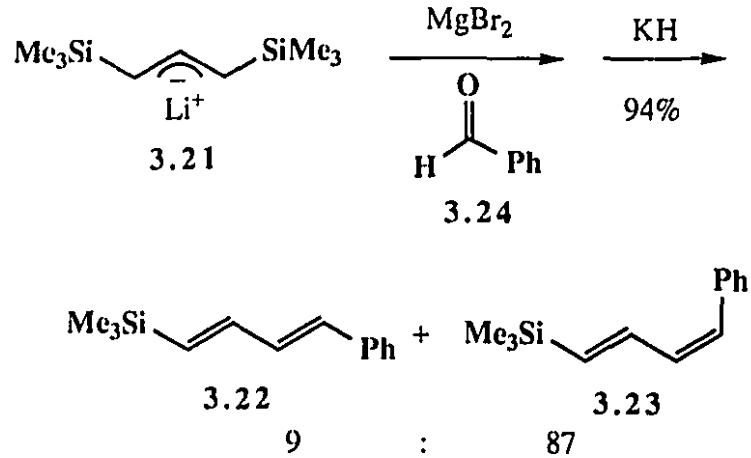


MX	E^+=RCHO	Relative amount of 3.19	3.20	3.3	Combined Yield	Ref.
$ZnEt_2$	Benzaldehyde	100*			74%	5c
BR_2Cl	isobutyraldehyde		100		60%	5d
CuCN	Cinnamaldehyde			100	75%	2c
$AlEt_3$	Benzaldehyde	37	43	2	51%	5d,e
$AlEt_2Cl$		4	88	2	66%	
$SnBu_3$ $+BF_3$	''	100*			77%	5d
$TiCp_2Cl$	''		100*		95%	5f
$Ti(Oi\text{-}Pr)_4$	''		>99	<1	80-83%	5g

TABLE 3.1: Influence of metal salts on the regio- and stereochemistry of the additions to carbonyl electrophiles. * The ratios were inferred from the stereochemistry of the dienes obtained after Peterson eliminations of the α-condensation products.

That same logical approach was used to obtain E-4- or Z-4-(aryl or alkyl), E-1-(trimethylsilyl)buta-1,3-butadienes from the deprotonation of bis-1,3-(trimethylsilyl)propene

3.21, an γ-trimethylsilylated equivalent of trimethylsilylallyllithium, and it's reaction with aldehydes 3.24 (Scheme 3.6).[5b]



Scheme 3.6.

3.1.3 polyene anions.[6]

This chapter is concerned with the reactivity of the polyenic anion **3.1** (Figure 3.1) towards the condensation with aldehydes, ketones, enals and enones. The discussion will be focused on evaluating usefulness of **3.1** in the synthesis of polyenic natural products like the retinoids. The chemistry of polyenic allylsilanes anions has been the subject of only a few extensive studies and they dealt mainly with lithium salts of the mono and polysilylated 2,4-pentadiene compounds **3.25** to **3.27**.[6a]

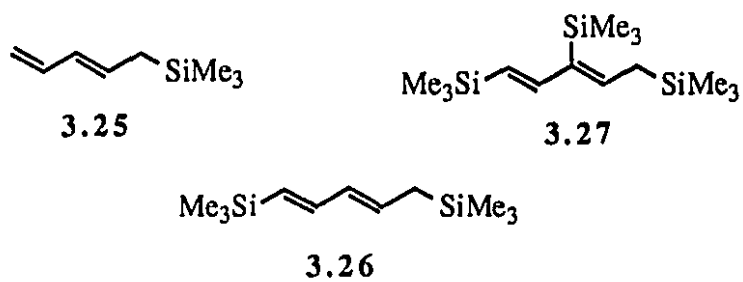


Figure 3.2.

The anion of pentadienylsilane **3.25** is prepared by deprotonation with *n*-BuLi in THF. Silylation of the resulting anion with chlorotrimethylsilane occurs at the ε-position, giving compound **3.26** which can in turn be deprotonated and silylated to give the trisilylated compound **3.27** (Figure 3.2). Studies of the lithium derivative of **3.25** were originally carried out by Oppolzer.[6b] He observed that this derivative

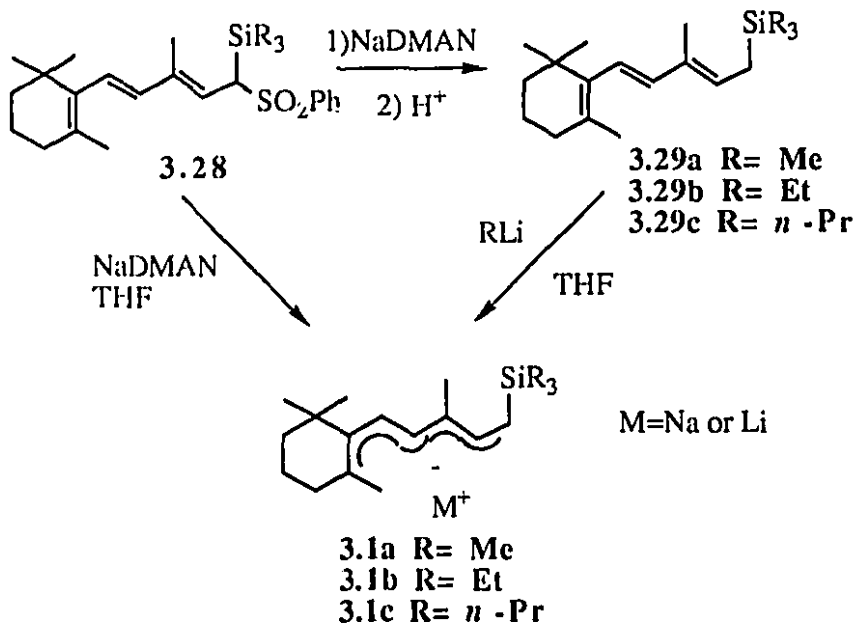
underwent condensation reactions with ketones and aldehydes at the ε position mostly, with the exception of cyclohexanone.

As outlined in section 3.1.2, the addition of metallic salts on α-trimethylsilylallyl anions can have major effects on the regioselectivity of carbonyl addition. The pentadienylic system showed the same effects but gave different products of reaction. For example addition of magnesium bromide to a THF solution of the corresponding anion of silane **3.25** gave γ instead of ε condensation products, upon reactions with ketones and aldehydes, but no α-condensations were observed. This is also true for the other metallic salts.[4c] The observation that the anion of **3.25** generally adds 1,4- to enal and enones will be problematic if **3.1** has a similar regioselectivity.

We were originally very interested by the report[6c] showing the reactivity of the anion of **3.27** toward carbonyl electrophiles because of the similarity of the substitution between the allylic system of diene **3.27** and that of the allylsilane **3.1**, and because the observed regioselectivity agreed with what we wanted to do (complete α regioselectivity with formation of polyenic compounds).

3.2 Methods for the formation of 3.1 and its reaction with carbonyl electrophiles.

We have seen in chapter 2 that the carbon-sulfur bond, in silylated allylsulfones, could be reductively cleaved giving the intermediate silyallyl anions. These anions gave the corresponding allylsilanes with good regio- and stereoselectivity in the presence of DEA. These studies were carried out with two purposes in mind. The first is to synthesize the starting material allylsilanes **3.29a-c** of reasonable isomeric purity. The second is the development of a method giving direct access to the desired allylic anions **3.1a-c**. For example, instead of making the anion **3.1a** from the silylsulfone **3.28** then quenching it with water, we were able to react it with carbonyl electrophiles. Alternatively we can deprotonate the corresponding allylsilanes **3.29a-c** with an alkyllithium then react the anions **3.1a-c** with the desired carbonyl electrophiles. This strategy gave us two possible ways of forming and studying the allyl anions **3.1a-c.**



Scheme 3.7: Preparation of anion **3.1**.

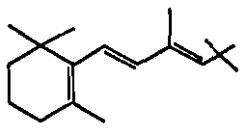
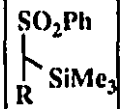
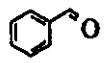
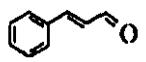
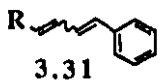
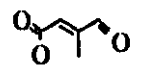
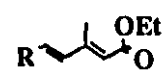
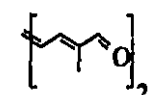
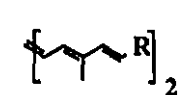
R	S.M.	Electrophiles	Products	Yields
	 3.28		 3.30	10%
			 3.31	2%
		 Et 3.32	 3.33	1%
		 3.34	 3.35	-

Table 3.2: Results obtained from the condensation of aldehydes with anion **3.1a**, prepared in situ via the reductive cleavage of silylated sulfone **3.28**.

The addition of aldehydes (except for dialdehyde **3.34**) to the intermediate allyl anion **3.1a**, which was formed via the reductive cleavage of silylated allysulfone **3.28**, gave the desired condensation products but only in low yields (Table 3.2). For example

following the addition of benzaldehyde, we were able to demonstrate that the 1,2-addition did in fact occur and led to the formation of polyene **3.30** after *in situ* Peterson elimination. Also we were able to demonstrate the use of anion **3.1a** in the synthesis of all-*trans* -retinoic acid ethyl ester, however the yield was quite low (1%).

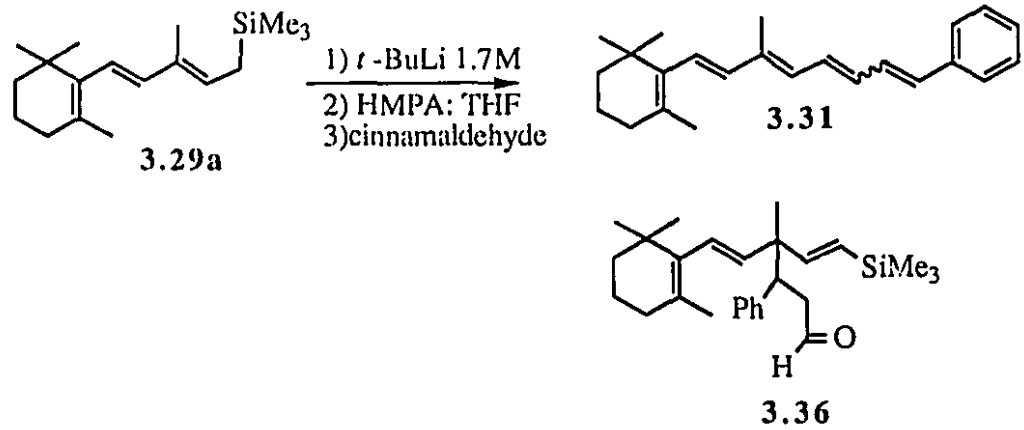
These results demonstrated that the regioselectivity observed in the case of anion **3.1a** is very different from that of the more simple allylsilylanions described in the first part of this chapter and that of pentadienyl silane **3.25**. On the other hand, it is similar to the regioselectivity of addition of carbonyl electrophiles to pentadienyl silane **3.27**.

In addition to the desired products we isolated very large amounts of the allylsilane **3.29a** (up to 50% yield), indicating that most of the anion **3.1a** was protonated before it could react with the electrophiles. This problem was expected based on the mechanistic discussion given in chapter 2 and the results obtained here are in line with the explanations given in that chapter. Another problem associated with the use of anions **3.1a**, prepared *in situ*, is the reduction and coupling of the carbonyl reagents. These side reactions are caused by the excess of NaDMAN in solution. The presence of these side products also make the separation of the products more difficult.

In trying to alleviate these problems and at the same time speeding up the exploration of different reaction conditions, we decided to look at the deprotonation of the corresponding allylsilanes **3.29a-c** with alkyllithiums under different reaction conditions. We were able to deprotonate silanes **3.29a-c** to the respective anions **3.1a-c** using *t* -BuLi in THF:HMPA for 24 hours at -78°C or *s* -BuLi in THF for 24 hours at -20°C. However the deprotonation did not occur when *n* -BuLi was used in THF or when the deprotonations were carried out in less polar solvents (like ether or toluene).

The anion **3.1a** formed with *s*-BuLi in THF reacted with benzaldehyde to give a complex mixture of products with only 20% of the desired compound **3.30**. However when benzaldehyde was added to the same anion, prepared using *t* -BuLi in THF:HMPA, we isolated the polyenic compound **3.30** in 53% yield instead (Table 3.4). This interesting result seemed to have been influenced by the presence of HMPA since the deprotonation of **3.29a** with *s* -BuLi in THF:HMPA and reaction of the resulting anion **3.1a** with benzaldehyde gave similar results. After optimization, we found the best conditions for the deprotonation of **3.29** to be the following.

Dissolution of 0.1 g of silanes **3.29a-c** in 1.0 ml of dry THF with 0.1 ml of HMPA and addition of 2 eq. of *t* -butyllithium followed by stirring at -78°C for 24 hours.



Scheme 3.8.

The reaction of cinnamaldehyde or aldehyde **3.32** with the anion **3.1a** obtained in this way gave surprisingly low yields of the desired products **3.31** and **3.33** (in the order of 3 %, Table 3.3). The major reaction pathway seems to be the 1,4- conjugate addition. When reacted with cinnamaldehyde the anion **3.1a** gave a 50:50 mixture of diastereomeric products **3.36** (Scheme 3.8) up to 60 % yield (when the reaction was carried out in the presence of chlorotrimethylsilane). Although we were not able to isolate the same product from the reaction of **3.1** with aldehyde **3.32** we suspect the same type of reactions to be responsible for the low yields of retinoic acid ester **3.33**.

Studies on the effect of temperature on the addition reactions gave puzzling results. As demonstrated in table 3 the condensation on cinnamaldehyde carried out in the -78 to -20°C temperature range gave the same low yields of polyene **3.31**, but warming the anion to 0°C followed by the addition of the cinnamaldehyde gave a 10% yield of the desired polyene **3.31** and additions at higher temperatures (20 and 50°C) gave **3.31** in 7% yield. The yield of the 1,4- conjugate addition **3.36** peaked at -40°C (table 3.3). We also noticed that better results were obtained when the anion **3.1a** was added to the electrophile maintained at 0°C.

	Addition products.	
°C	3.31, %	3.36, %
-60	3	34
-40	3	57
-20	3	53
0	10	40
20	7	30
50	6	42

Table 3.3: Effect of temperature on the regioselectivity of the addition of anion **3.1** on cinnamaldehyde (see Scheme 3.8).

It is difficult to draw firm conclusions on these observations since they represent a small difference in yields and since the purification of these compounds was not always easy. However the trend maintained itself even with different electrophiles and nucleophiles and in most of these cases the products isolated from a reaction giving 3% were almost always of lower purity then the ones from the reactions where we isolated a 10% yield of material.

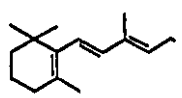
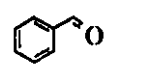
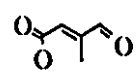
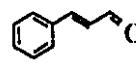
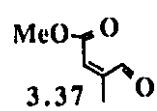
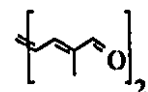
Allyl silanes	Electrophiles	A %	B %	product
 3.29a R=$SiMe_3$ 3.29b R=$SiEt_3$ 3.29c R=$Si(nPr)_3$		53 66 48	50	3.30
3.29a R=$SiMe_3$ 3.29b R=$SiEt_3$ 3.29c R=$Si(nPr)_3$	 3.32	4 5 3	8 9 11	3.33
3.29a R=$SiMe_3$		3	10	3.31
3.29a R=$SiMe_3$	 3.37	2	2	13-*cis* retinoic ester. 3.38
3.29a R=$SiMe_3$	 3.34	0	0	3.35

Table 3.4: Additions of **3.1** to various electrophiles A) at -78 °C, B) at 0°C.

We tried changing the steric bulk around the silicon atom (Table 3.4) by using the trimethyl, triethyl and tri(n-propyl)silyl groups. Interestingly, the yields were not greatly affected by the increase in size of the alkyl groups on the silicon atom. We had expected the yields to go down based on the results from the regioselectivity of the alkylation reaction which showed an increased in γ-alkylation at the expense of α-alkylation when the steric bulk around the silicon is enlarged.[7] We actually observed a slight increase in the yield when using the triethyl and tripropylsilyl derivatives **3.29b** and **3.29c** when the reactions were carried out at 0°C (condition B, Table 3.4).

The addition of benzaldehyde to anion **3.1a** at low temperature, gave a dark blue colored solution at first. This solution rapidly discolored as the benzaldehyde reacted with anion **3.1a**. The color observed did not fade when less than one equivalent of the benzaldehyde was added. Presumably this phenomenon indicates a charge transfer complex between the anion **3.1a** and the polyene **3.31** being formed. When we subjected β-carotene to the anion **3.1a** to see if it was stable to the reaction conditions, we noticed that it deteriorated with time and that we isolated a very small fraction (<5%) of the original material after leaving β-carotene with **3.1a** for 5 min. at room temperature. This means that the polyenes products are probably unstable to anions **3.1a-c**.

Since it appeared to us that a major problem associated with the use of **3.1a** was its tendency to give 1,4-conjugated additions (presumably this was due to the stabilization of the negative charge by the conjugated system, which makes anions **3.1a-c** soft nucleophiles) with enones and enals we decided to try adding cerium chloride to the anion. This did not improve the yields when we tried it on benzaldehyde and on the aldehyde **3.32**. However when the cerium chloride was stirred in THF with the aldehyde **3.32** and that the anion **3.1a** was subsequently added to the suspension at 0°C we obtained a 13% yield of the desired ethyl retinoate ester (based on recovery of starting material).[8]

Use of metallic salts $Ti(OiPr)_4$, $ZnEt_2$, $MgBr_2$ yielded complex mixtures of products. None of which gave any elimination products upon treatment with KH in THF.

The other major problem associated with the use of anions **3.1a-c** are their basicity. For example reaction of **3.1a** with deuterated acetone yielded only the deuteroallylsilane corresponding to **3.29a**. No acetone addition products were isolated from this reaction. Also the deprotonation of the allylsilanes is very slow and can only be carried out in polar solvents like THF and HMPA. There is no deprotonation in diethyl ether or toluene. This restricted the range of solvents we could use and therefore reduced the number of possible experimental factors we were able to change for the optimization of this reaction.

Another problem was the ease with which the Peterson reaction went once the 1,2-product formed. We tried unsuccessfully to quench the 1,2- adduct at low temperature with chlorotrimethylsilane. This represent a major problem because it prevents us from using the silicon methodological possibilities to their fullest (mentioned in the first chapter). That is, in our case, we cannot predict or control the geometry of the double bond formed.

3.3 Experimental.

The equipment and reagents used in this section were the same as the ones described in chapter 2. The allylsilanes **3.29a-c** were prepared following the procedure described in chapter 2. Benzaldehyde and cinnamaldehyde were distilled prior to their use. HMPA was dried and distilled over CaH_2. The dialdehyde **3.34** was provided by Hoffmann-LaRoche.

1) The standard procedure for the formation of the anion **3.1a-c** by reductive desulfonylation of **3.28** and its reactions with electrophiles is described here.

Preparation of **3.1a** was achieved through reductive desulfonylation with NaDMAN:

The silylated sulfone **3.28** was slowly added to a NaDMAN solution in THF maintained at -78°C prepared as described in chapter 2. After stirring the reaction mixture 15 min. 2 equivalents of the electrophile was added and the the reaction mixture was warmed up to room temperature and then worked up by transfering the organic solution (via a syringe or pipette to exclude sodium metal) to an Erlenmeyer containing a sat. solution of ammonium chloride. The procedure described in 1.1 represents a typical procedure for these reactions.

1.1) All-*trans* -1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-methyl-6-phenyl-hexa-1,3,5-triene **3.30**.

The anion **3.1a** was prepared by adding the silylated sulfone **3.28** (0.100 g, 0.24 mmol), dissolved in 1 mL of dry THF, to a NADMAN (1.2 mmol, 0.210 g of DMAN, with 0.100 g of sodium metal) solution in 10 ml THF at -78°C, and stirring at this temperature for 5 min. The electrophile , benzaldehyde (0.200 g, 2 mmol), was then added to the reaction mixture which was then brought to room temperature. The reaction mixture was transfered (via a syringe or a pipette, to avoid taking any sodium metal with it) to an Erlenmeyer flask containing 10 mL of a sat. NH_4Cl solution in water. This reaction mixture was worked up by adding 50 mL of hexanes. The organic phase was washed with distilled water and brine. Evaporation of the solvents followed by flash chromatography (c-hexane as eluent) led to the isolation of 0.010 g (10%) of the polyene **3.30** contaminated with some of the 11-cis isomer.

Further separation gave clean samples for spectroscopy. all-trans 0.007g, 11-cis 0.001g.

The all-*trans* isomer **3.30a**.

^{1}H NMR($CDCl_3$, 200 MHz) δ 7.50-7.20 (m , 5H), 7.17 (dd, J= 12.0 Hz, 15.5 Hz 1H), 6.56 (d, J= 15.5 Hz, 1H), 6.17 (AB, J=16.3 Hz, 2H), 6.17 (d, J= 12.0 Hz, 1H), 2.04 (m, 2H), 2.03 (s, 3H), 1.74 (s, 3H), 1.70-1.45 (m, 4H), 1.05 (s, 6H) ; ^{13}C NMR($CDCl_3$, 50 MHz) δ 137.2, 137.1, 136.9, 135.8, 131.2, 129.4, 128.7, 128.0, 126.6, 126.4, 125.7, 125.0, 40.0, 34.8, 33.6, 29.5, 22.4, 20.0, 13.6. IR(film) 3027-2823, 1652, 1447, 1360, 965, 746, 690. MS(EI) m/z cal'd for $C_{22}H_{28}$: 292.2191, found: 292.2206. 292 (100%), 277 (28%), 221 (14%), 207 (20%).

The 5-*cis* isomer **3.30b**.

^{1}H NMR($CDCl_3$, 200 MHz) δ 7.38-7.18 (m , 5H), 6.57 (ABX, J=9.0, 10.0 Hz, 2H), 6.45 (ABX, J= 9.0, 10.1 Hz, 1H), 6.21 (d, J= 16.2 Hz, 1H), 2.01 (m+s, 5H), 1.70 (s, 3H), 1.70-1.45 (m, 4H), 1.02 (s, 6H) ; ^{13}C NMR($CDCl_3$, 50 MHz) δ 138.3, 137.8, 129.4, 129.2, 129.1, 129.0, 128.2, 127.3, 126.8, 124.7, 126.4, 125.8, 39.6, 34.3, 33.0, 29.0, 21.8, 19.3, 12.5.

1.2) All-*trans* -1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-methyl-6-phenyl-octa-1,3,5,7-tetraene **3.31**.

The anion **3.1a** (1.20 mmol in 20 mL THF) was prepared from sulfone **3.28** (0.500 g, 1.20 mmol) reduced with 4 eq. of NaDMAN as described in the procedure 1.1 and reacted with cinnamaldehyde (0.640 g, 4.80 mmol) at -78°C. Work up and flash chromatography using hexanes as eluent gave 0.007 g (2%) of polyene **3.31** (0.006 g all-trans + 0.001 g of the 5-cis isomer).

^{1}H NMR($CDCl_3$, 200 MHz) δ 7.48-7.12 (m , 5H), 6.92 (dd, J= 10.8, 15.5 Hz, 1H), 6.73 (dd, J= 11.5, 14.6 Hz, 1H), 6.55 (d, J= 10.8, 15.4 Hz, 1H), 6.20 (d, J= 15.8 Hz, 1H), 6.35 (d, J=15.8 Hz, 1H), 6.30 (d, J= 11.5 Hz, 1H), 2.01 (m, 2H), 2.01 (s, 3H), 1.74 (s, 3H), 1.70-1.42 (m, 4H), 1.05 (s, 6H) ; ^{13}C NMR($CDCl_3$, 50 MHz) δ 137.9, 137.6, 136.6, 132.7, 131.7, 130.1, 130.0, 129.7, 129.5, 128.6, 127.3, 127.3, 126.3, 39.63, 34.26, 33.1, 29.0, 21.8, 19.3, 12.7. IR(film) 3027-2823, 1652, 1447, 1360, 965, 746, 690. MS(EI) m/z cal'd for $C_{22}H_{28}$: 318.2347, found: 318.2342. 318 (6%), 289 (7%), 275 (27%), 123 (100%), 77 (68%).

1.3) All-*trans* -retinoic acid, ethyl ester **3.33**.

The anion **3.1a** (0.12 mmol in 20 mL of dry THF) was prepared as described in procedure 1.1 and reacted with aldehyde **3.33**[9] (0.700 g, 4.80 mmol) at -78°C. Work up and flash chromatography using hexanes as eluent gave 0.004 g (1%) of the retinoic acid, ethyl ester **3.33**.

^{1}H NMR($CDCl_3$, 200 MHz) δ 6.98 (dd, J=15.1, 11.3 Hz, 1H), 6.31-6.05 (m, 4H), 5.75 (s, 1H), 4.15 (q, J= 7.0 Hz, 2H), 2.33 (s, 3H), 1.98 (s, 3H), 1.98 (m, 2H), 1.69 (s, 3H), 1.60 (m, 2H), 1.45 (m, 2H), 1.26 (t, J= 7.0 Hz, 3H), 1.0: (s, 6H). (same as lit.[10] with shift -0.03 ppm for every proton). The signals other than the ethyl protons were compared and matched with those of a commercial sample of all-*trans* -retinoic acid and so did the relative intensities of the signals. ^{13}C NMR($CDCl_3$, 50 MHz) δ 167.4, 152.9, 139.7, 137.8, 137.4, 135.3, 131.1, 130.1, 129.6, 128.8, 118.7, 59.6, 39.5, 34.1, 32.9, 28.8, 21.6, 19.0, 14.2, 13.6, 12.7.[10]

2) The standard procedures (A and B) for the formation of **3.1a-c** by deprotonation of the corresponding allylsilanes and their reaction with electrophiles is described here.

Methode A:

Preparation of the lithium salts **3.1a-c** was achieved by the deprotonation of the corresponding allylsilanes **3.29a-c** with 2 equivalents of *t* -butyllithium (1.7 M in pentane), in dry THF:HMPA (10:1) solvent mixtures at -78°C for 24 hours. Deprotonation carried out for longer periods of time could not be kept under argon using the argon lines. Instead the reaction flask was flushed with argon using a needle and septum then sealed by putting an inverted septum over the first one. By using this setup it was possible to keep the organolithium **3.1a-c** at -78°C for up to a week. The electrophile was added to this reaction mixture at -78°C and stirred 5 min. at this temperature before workup.

Method **B**:

The anions **3.1a-c** were prepared according to procedure **A**. The solutions thus obtained were added to the electrophiles dissolved in dry THF maintained at 0°C. The reaction was followed by workup of the reaction mixture.

The procedure described in 2.1 was the typical procedure **B** used in the following experiments.

2.1) All-*trans* -1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-methyl-6-phenyl-hexa-1,3,5-triene **3.30**.

t -Butyllithium [1.7 M in pentane (0.42 mL, 0.72 mmol)] was added to allylsilane **3.29a** (0.100 g, 0.36 mmol) dissolved in 1.0 mL THF with 0.1 mL of HMPA. The solution was stirred for 24 hours at -78°C. The resulting anion **3.1a** was transfered to a solution containing cinnamaldehyde (0.080 g, 0.76 mmol) dissolved in 10 mL of THF and maintained at 0°C. Hexanes (10 mL) and conc. NH_4Cl (10 mL) were added to the reaction mixture and the organic layer was separated, washed with distilled water, brine and dried over $MgSO_4$. The solvents were evaporated and flash chromatography using hexanes as eluent gave 0.056 g (53%) of the all-trans polyene **3.30**.

Starting from allylsilane **3.29b**:

Using **3.29b** (0.05 g, 0.16 mmol) following method **B**, 0.03 g (66%) of the polyene **3.30** was isolated.

Starting from allylsilane **3.29c**:

Using **3.29c** (0.05 g, 0.14 mmol) following method **B**, 0.02 g (49%) of the polyene **3.30** was isolated.

Spectroscopic data for **3.30** was given in 1.1. (p. 63)

2.2) All-*trans* -1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-methyl-6-phenyl-octa-1,3,5,7-tetraene **3.31**. + 1,4-adduct 1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-methyl-3-(vinyl-2-trimethylsilyl)-4-phenyl-hex-1-ene-6-al **3.36**. (Mixture of 2 diastereomers 50:50).

The anion **3.1a** (0.18 mmol) was prepared as described in procedure 2.1 and reacted with cinnamaldehyde (0.050 g, 0.36 mmol) at 0°C. Work up and flash chromatography using hexanes as the eluent gave 0.006 g (10%) of the polyene **3.31**. Further elution with a 5:95 mixture EtOAc: hexanes gave 0.033 g (45%) of 1,4-addition products as a 1:1 mixture of diastereomers.

The spectroscopic data for compound **3.31** was given in 1.2. (p.64)

1,4-adduct: 1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-methyl-3-(vinyl-2-trimethylsilyl)-4-phenyl-hex-1-ene-6-al **3.36**. (Mixture of 2 diastereomers 50:50).

^{1}H NMR($CDCl_3$, 200 MHz) δ 9.55 (s, 1H), 7.30-7.20 (m , 5H), 6.09 (d, J= 19.1 Hz, 1/2 H), 6.01 (d, J= 19.1 Hz, 1/2 H), 6.74 (d, J= 15.8 Hz, 1H), 5.57 (d, J= 19.1 Hz, 1H), 5.41 (d, J=15.8 Hz, 1H), 3.29 (m, 1H), 2.85 (m, 2H), 2.00 (m, 2H), 1.64 (m, 5H), 1.50-1.42 (m, 2H), 1.1-1.08 (s, 9H), 0.12 (s, 4 1/2 H), 0.02 (s, 4 1/2 H); ^{13}C NMR ($CDCl_3$, 50 MHz) of the mixture δ 200.6, 200.5, 151.2, 149.5, 139.3, 139.2, 138.1, 137.7, 136.9, 12[illegible]0, 128.6, 128.2, 127.4, 127.1, 126.9, 126.5, 126.4, 126.2, 49.5, 49.1, 48.1, 48.0, 46.0, 45.6, 39.8, 39.7, 34.7, 34.6, 33.2, 33.1, 29.4, 29.3, 22.6, 22.2, 22.1, 21.7, 20.0, –0.2, –0.26. IR(film) 3027-2826, 1727, 1603,

1454, 1248, 868, 839. MS(EI) m/z cal'd for $C_{18}H_{31}$(M-cinnamyl unit); 275.2195, found: 275.2203. MS(CI) 409 (3%), 291 (3%), 275 (100%), 201 (7%).

2.3) All-*trans* -retinoic acid, ethyl ester **3.33**.

Starting from allylsilane **3.29a**:

The anion **3.1a** (0.36 mmol) was prepared as described in procedure 2.1 and reacted with aldehyde **3.32**[9] (0.100 g, 0.72 mmol) at 0°C. Work up and flash chromatography using hexanes as the eluent gave 0.010 g (8 %) of all-*trans* -retinoic acid, ethyl ester **3.33**.

Starting from allylsilane **3.29b**:

Using **3.29b** (0.050 g, 0.16 mmol) following method **B**, 0.005 g (10 %) of product **3.33** was isolated.

Starting from allylsilane **3.29c**:

Using **3.29c** (0.050 g, 0.14 mmol) following method **B**, 0.005 g (11 %) of product **3.33** was isolated.

Spectroscopic data for **3.33** was given in 1.3. (p. 64)

2.4) 13-*cis* -Retinoic acid methyl ester **3.38**.

The anion **3.1a** (0.18 mmol) was prepared as described in procedure 2.1 and reacted with aldehyde **3.37**[9] (0.100 g, 0.78 mmol) at 0°C. Work up and flash chromatography using hexanes as the eluent gave 0.001 g (2%) of 13-*cis* -retinoic acid methyl ester **3.38**, 85% pure by NMR.

^{1}H NMR($CDCl_3$, 200 MHz) δ 7.76* (d, J= 11.2, 15.4 Hz, 1H), 6.22 (m, 2H), 5.63 (s, 1H), 3.69 (s, 3H), 2.06 (s, 3H), 1.98 (s, 3H), 1.98 (m, 2H), 1.70 (s, 3H), 1.52-1.40 (m, 4H), 1.02 (s, 6H).[10]

* This signal is characteristic of the 13-*cis* isomer of retinoic acid methyl ester.

3.4. References.

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CHAPTER 4.
REACTIVITY OF THE MODIFIED SILYLALLYL ANIONS.

4.1 Introduction.

The introduction of a chelating group on the silicon atom of α-silylallyl anions has been shown to modify the reactivity of these anions to a great extent. Previous studies by Horvath and Chan* have shown the regioselectivity of the alkylation reaction to be strongly influenced by the presence of chelating groups. Indeed, even good diastereoselection could be obtained at the α- prochiral centre on the allyl group, when the chelating group was the chiral methoxymethylpyrrolidine derived from proline.

Very little was known about the reaction of these anions with ketone and aldehyde electrophiles. Since much could be gained, with respect to the subject discussed in chapter 3, by the study of such condensations, we decided to investigate this field. In particular we were looking for ways to modify the γ- regioselection normally observed for allylsilanes.

In the following chapter we will give the results of a model study that was carried out on aminomethyldimethylallylsilanes in order to determine the effects of such amino groups on the reactivity of allylsilanes anions towards ketones and aldehydes.

After treating a number of aminomethylallylsilanes under different reaction conditions with ketones and aldehydes, we were unable to find conditions leading to α-regioselection. However we did observe an interesting Z-stereoselection for the γ-addition reactions. The results of these studies have been dealt with, in section 4.2 which is a reformatted version of a communication published in Tetrahedron Letters in 1992 (p. 7997). Section 4.3 deals with the influence which the chelating group has on a pentadienyl system.

* See references 2,4,5 in section 4.2.

4.2 Stereoselectivity and regioselectivity of the addition of silylallylanions to carbonyl electrophiles.

STEREOSELECTIVE REACTIONS OF α-SILYLALLYL ANIONS WITH CARBONYL COMPOUNDS.

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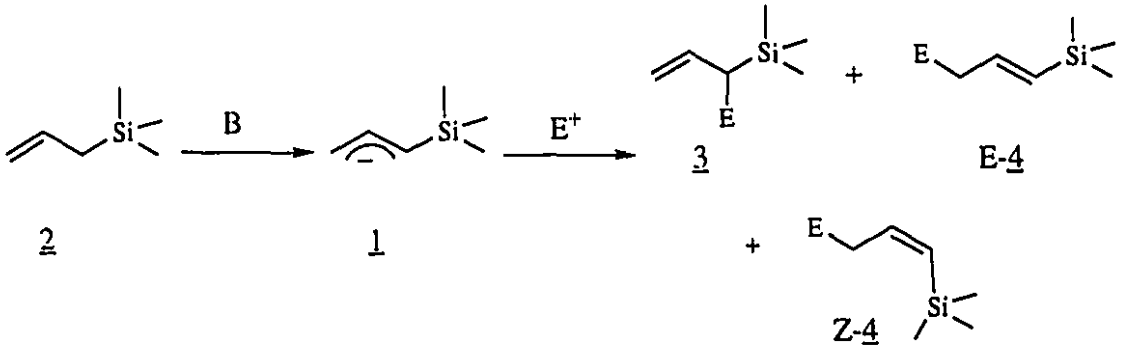
Abstracts: α-silylallyl anions of the type **6** react with carbonyl compounds at the γ-position , and stereoselectively to give the E- or Z-isomer depending on the reaction conditions. Solvent and reaction temperature play a critical role in the controle of stereoselectivity.

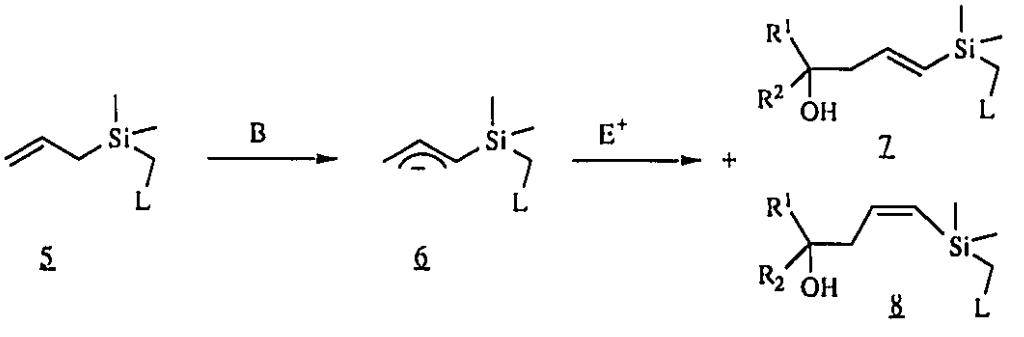
α-Silylallyl anions (**1**), first generated by Corriu *et. al* in the early 70's from the precursor allyl silanes **2**,[1] have been used extensively as synthetic intermediates.[2] In the reactions of **1** with various electrophiles E^+, either the α-(**3**) or the γ-E-(**4**) regioisomeric products could be obtained (Scheme 1). Efforts to control the regioselection of these reactions have been reasonably successful.[3]



Scheme 1

In the case of γ-product, the double bond can assume either the E- or the Z-stereochemistry (E-4 or Z-4). In nearly all the reactions examined so far, and independent of the nature of the electrophiles, the γ-products have inevitably the E- stereochemistry. The high stereoselectivity is ascribed to the structure of the silylallyl anion **1** which seems to adopt exclusively the exo-conformation as evident from recent NMR studies.[4] Since the E-vinylsilane **4** can be converted to the corresponding Z-vinyl iodide with complete inversion of stereochemistry [2c,5], the overall sequence of reactions has been used advantageously as a highly stereoselective synthesis of Z-alkenes.[2c] It would be desirable to be able to prepare selectively the Z-vinylsilane **4** as well and to explore its synthetic potentials [6]. Recently in our study of the reaction of silylallyl anions of the type **6** where the silyl moiety contained a group L capable of internal chelation, [2d,e] we observed a small but significant amount of γ-Z product.

Thus, when **6a** (L=bis-methoxyethylamino), generated from **5a** with s-BuLi in THF at -60° for 12 h, was allowed to react with a number of carbonyl compounds, the reactions took place at the γ-position giving the two geometrical isomers **7a** and **8a** in nearly equal proportions and the selectiveties did not seemed to be affected by the nature of the carbonyl electrophiles (Scheme 2, Table 1). Using acetone as the common electrophile, it was possible to probe the effect of temperature on the stereoselectivity and, by keeping the reaction temperature constant at -60°, the effect of the solvent was also studied (Table 2).



Scheme 2

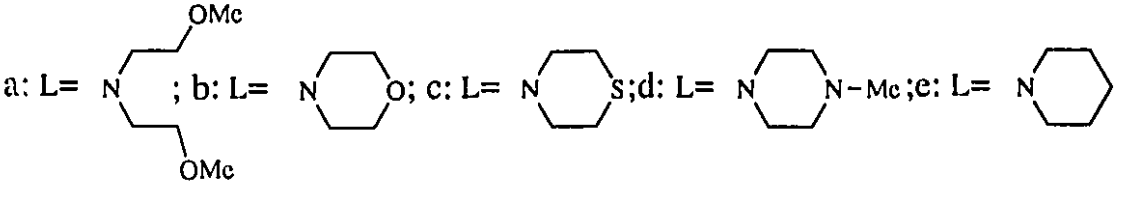


Table 1 Reactions of 6a with Various Carbonyl Compounds

		Reaction Condition[a]				
Entry	Solvent	Temp.[b]	Time[c]	Electrophile	E:Z,7a:8a[d]	Yield[e]
1	THF	-60°	0.5h	Acetone	1.2:1	75%
2	THF	-60°	0.5h	Benzaldehyde	1.2:1	60%
3	THF	-60°	0.5h	Cinnamaldehyde	1.2:1	66%
4	THF	-60°	0.5h	β-ionone	1.2:1	56%
5	THF	-60	0.5h	Cyclohex-2-enone	1.2:1	64%

(a) The carbanion was generated by treating the allylsilane **5a** with s-BuLi in THF at -60° for 12h. (b) The temperature of the reaction of the carbanion with the electrophile. (c) Reaction time of the carbanion with the electrophile. (d) Determined by proton NMR on the crude material. (e) Combined yield of **7a** and **8a** after purification by flash chromatography.

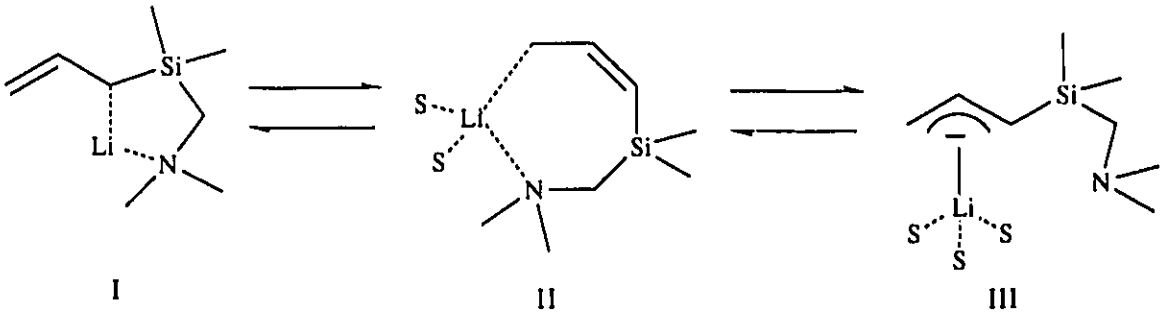
Table 2 Reaction of 6a with Acetone as Electrophile

	Reaction condition[a]			
Entry	Solvent	Temp.[b]	E:Z, 7a:8a[c]	Yield[d]
1	THF	-60°	1.2:1	75%[e]
2	THF-TMEDA	-60°	1:1	91%
3	THF-HMPA	-60°	2:1	89%
4	DME	-60°	5:1	82%
5	ETHER	-60°	7:1	74%
6	TOLUENE	-60°	>10:1	82%
7	THF	-30°	1.5:1	92%
8	THF	-80°	1:1.3	90%
9	THF	-100°	1:2	90%

(a)The deprotonation was carried out with **5a**, s-BuLi and the specified solvent at -25° for 12h. (b)The temperature of reaction of the carbanion with acetone. Reaction time was 15 min in all cases. (c)The ratio was determined by integration of respective signals on proton NMR of the crude products. (d)Crude yield.

These results suggest that silylallyl anions of this class can exist as the following exo-(I), endo-(II) and the open form (III) species. In solvents of high coordinating ability, the

open form (III) is probably responsible for the formation of the E-vinylsilanes on reaction with the electrophiles. This is in agreement with the observation in
table 2, as the solvent is changed from THF to THF-HMPA the ratio of E/Z increased (entries 1 and 3). In solvents of lower coordinating ability (e.g. ether and toluene, table 2), the exo-(I) structure can lead to a high E/Z ratio as well. The endo-(II) responsible for the formation of the Z products seems to be predominant only in specific complexation systems and solvents (table 2 and 4). The temperature effect observed in table 2 (entries 1,7-9) could be due to the change in relative reactivity between the species (I), (II) and (III) or to a change in relative concentration of these species when the temperature is changed. Further studies by such physical methods as low temperature ^{1}H and ^{13}C NMR spectroscopy are needed to determine the structures and the relative concentrations of the reacting species in solution.



I II III

Scheme 3

After considerable experimentation with a number of different amino derivatives, we found that the morpholino compound **6b** reacted with carbonyl compounds to give selectively either the E- or the Z-isomers depending on the specific reaction conditions (A or B) with even better specificity then with allylsilane **6a**, making the reaction synthetically useful. In method A, the silane **5b** (0.10g, 0.5 mmol) was dissolved in toluene (3.0 mL) and s-BuLi (1.3M in c-hexane, 1.5 eq) was added at -20°C under an argon atmosphere. After stirring for 24 h at this temperature, the carbonyl compound (1.5 eq) was added to the mixture at -78°C. After 15 mins., ether (20 mL) and conc. ammonium chloride solution (1.0 mL) were added. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to give predominantly the products with the E stereochemistry. In method B, the silane **5b** was deprotonated in toluene as before. After stirring for 24 h, dimethoxyethane (0.5 mL) was added and the mixture was stirred an additional 30 mins at -25°C. The carbonyl compound (1.5 eq.) was added slowly to the solution at -90 °C.[7] After 15 mins stirring at this temperature, hexane (20 mL) and conc. ammonium chloride solution (2 mL) were added. The organic layer was washed with brine, dried ($MgSO_4$) and evaporated to give the products with predominantly the Z-isomers.

Separation and purification of the stereoisomers were achieved with flash chromatography using 20 % ethyl acetate in hexanes as eluent.

The critical element in the amino structure required for reversal of stereoselectivity under the two reaction conditions A and B appears to be the presence of the piperidine ring and not the heteroatom in the 4' position. Thus, in the reactions of the silylallyl anions **6b-e** with acetone under the same reaction conditions, the stereoselectivity was more or less the same (Table 3).

The profound differences between the selectivities of the reactions of the allylsilanes anions **6b-e** and the anion **6a** in the presence of DME can be explained by the complexation of the lithium with DME in the case **6b-e** as shown in structure (II) but not in the case of **6a** where the lithium cation is tightly complexed by the bis-methoxyethylamino moiety and where structure (I) should predominate (Scheme 3).

Since Z-vinylsilanes have recently found applications in total synthesis, where they were used in preference to the E-isomers[6], the present method offers a short viable route to this type of synthetic intermediate.

Table 3 Reaction of anion 6b-e with Various Electrophiles Under Reaction Conditions A and B.

Entry	anion	Electrophiles	Condition[a]	E:Z,7:8[b]	Yield[c]
1	6b	Acetaldehyde	A	>10:1	66% (33%)
			B	1:6	92% (63%)
2	6b	Acetone	A	>10:1	95% (60%)
			B	1:6	90% (75%)
3	6b	Benzaldehyde	A	>10:1	95% (82%)
			B	1:7	83% (72%)
4	6b	Cinnamaldehyde	A	>10:1	90% (72%)
			B	1:5	97% (65%)
5	6b	2-Cyclohexen-1-one	A	>10:1	93% (85%)
			B	1:6	89% (61%)
6	6b	β-ionone	A	>10:1	83% (52%)
			B	1:8	74% (56%)
7	6c	Acetone	A	>10:1	80% (47%)
			B	1:6	94% (63%)
8	6d	Acetone	A	>4:1	55%
			B	1:7	68%
9	6e	Acetone	A	>10:1	85%
			B	1:7	76%

a)For reaction condition A and B, see text. b)The ratio is determined by integration of the vinylic and methylic proton signals on the NMR of the crudes. c)Yields of crude material after work up and evaporation under vaccuum. The crudes listed in entries 1-6 and 8 contained 10 to 15% of starting material, the ones listed in entries 7-9 contained up to 30% starting material. The combined yields of the pure products after flash chromatography are given in parenthesis.

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4.3 Experimental. (this section was not included in the original communication):

The spectroscopic data were acquired using the equipment and services described in the experimental section of chapter 2.

The starting material allyl(chloromethyl)dimethylsilane, amines, ketones and aldehydes used in this project were all purchased from Aldrich. The amines were distilled over calcium hydride prior to their use. Toluene was distilled over calcium hydride and stored over sodium metal. Tetrahydrofuran (THF) and diethyl ether were dried and distilled over sodium/benzophenone ketyl radical, dimethoxyethane (DME) was dried and distilled over calcium hydride then lithium aluminum hydride. Tetramethylethylenediamine (TMEDA) was dried and distilled over calium hydride. The deprotonation of aminosilanes **5b-5e** required long periods of time at low temperature. Inert atmosphere provided by the argon line was not appropriate since we were not able to obtain significant deprotonation. Static argon atmosphere provided by prior flushing of the reaction flask with argon and use of two septum as shown in scheme 4 gave much better results.

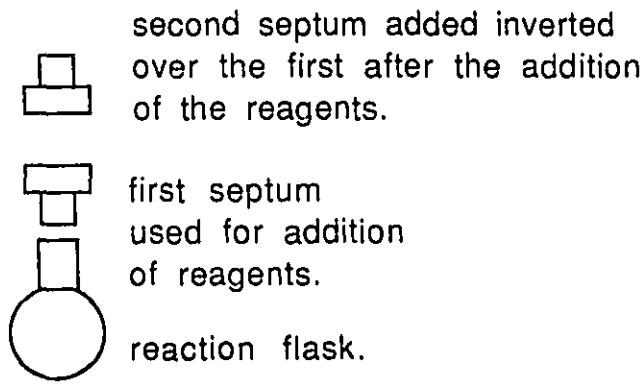


Figure 4: Experiment setup.

1) NN'-[Bis-(methoxyethylene)aminomethyl]dimethylsilyl-1-prop-2-ene **5a** was prepared in good yield following the procedure described by Horvath (ref. 2d from the communication section 4.2 p.77.)

2) General procedure used for the deprotonation and condensation of amine **5a** to aldehydes and ketones listed in table 1, entries 1 to 5:

2.1) Reaction with acetone.

In THF at -60 °C under argon 1.5 eq. of sec-butyllithium (1.3M in c-hexane) was added to the amine **5a** (0.100 g, 0.408 mmol) dissolved in 2.0 mL of anhydrous THF. After 2 hours of stirring, the anion was quenched with 1.5 eq. of acetone. After 5 min. at this temperature, 1 mL of saturated ammonium chloride solution was added. The organic layer was separated and washed with 2x10.0 mL of distilled water and the organic layer dried over anhydrous magnesium sulfate. The solvent was evaporated leaving 1.10 g of a clear oil containing a mixture of 1.3 : 1, trans : cis isomeric products. The two isomers could be separated on column using 40 % ethyl acetate : 60 % hexanes as the eluant, to give a total of 0.090 g (75%) of isolated material.

1)^{1}H NMR (200 MHz, $CDCl_3$) δ **7a (E isomer):** δ 6.2 (dt, J=18,6, 7.0 Hz, 1H), 5.8 (d, J=18.6 Hz, 1H), 3.5 (t, J=6.2 Hz, 4H), 3.3 (s, 6H), 2.75 (t, J=6.2 Hz, 4H), 2.3 (d, J=7.0 Hz, 2H), 2.2 (s, 2H), 1.2 (s, 6H), 0.1 (s, 6H), **8a (Z isomer):** δ 6.5 (dt, J=14.0, 7.7 Hz, 1H), 5.6 (d, J=14.0 Hz, 1H), 3.5 (t, J=6.1 Hz, 4H), 3.3 (s, 6H), 2.7 (t, J=6.1 Hz, 4H), 2.3 (d, J=7.7 Hz, 2H), 2.22 (s, 2H), 1.2 (s, 6H), 0.2 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) **7a :** δ 144.08, 132.61, 70.36, 70.31, 58.80, 56.78, 51.24, 46.38, 29.25, -2.84, **8a :** δ 145.75, 129.56, 70.10, 69.70, 58.76, 56.53, 47.67, 47.43, 29.59, -0.7; IR (film) **7a=8a:** 3414, 2901, 1610, 1457, 1369, 1249, 1197, 1118 cm^{-1}; MS (EI) m/z **7a, 8a:** MI=303 (E=3%(Z=0.5%)), 288 (E=4%(Z=3.3%), 272 (E=1%(Z=0%), 258 (E=72%(Z=3%)), 146 (E=Z=100%), 139 (E=11%(Z=75%)), 114 (E=20%(Z=9%)), 59 (E=42%(Z=32%)).

2.2) Reaction with benzaldehyde:

The amine **5a** (0.100 g, 0.408 mmol) was reacted with benzaldehyde in the manner described previously, to give 0.204 g of a 1.3:1 E:Z mixture of isomers. This mixture was separated by flash chromatography using 10 % ethyl acetate in hexanes as eluant. After elution of the Z isomer the E was washed out of the column using ethyl acetate, giving a total of 0.085g of purified material (60 % yield).

^{1}H NMR (200 MHz, $CDCl_3$) **E isomer:** δ 7.4-7.2 (m, 5H), 6.15 (m, 1H), 5.83 (d, J=18.4 Hz, 1H), 4.74 (dd, J=4.0, 8.8 Hz, 1H), 3.44 (m, 4H), 3.33 (s, 6H), 2.65 (m, 4H), 2.58 (m, 2H), 2.10 (m, 2H), 0.11 (s, 3H), 0.09 (s, 3H), **Z isomer:** δ 7.4-7.2 (m, 5H), 6.40 (ddd, J=6.7, 8.3, 14.0 Hz, 1H), 5.64 (d, J=14.0 Hz, 1H), 4.80 (dd, J=7.6, 4.4 Hz, 1H), 3.50 (m, 4H), 3.30 (s, 6H), 2.72 (m, 4H), 2.58 (m, 2H), 2.24 (s, 2H), 0.17 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) **E isomer:** δ 144.4, 144.1, 133.3, 128.5, 127.5, 125.8, 72.8, 70.9, 58.8,

57.0, 47.1, 46.4, -3.2, -3.3, **Z isomer:** δ 146.2, 144.9, 129.5, 128.3, 127.1, 125.8, 72.3, 70.2, 58.7, 56.5, 47.2, 44.0, -0.9, -1.0; IR (film) **E isomer:** 3385, 3090, 2891, 1663, 1613, 1451, 1197, 1081, 836, 701, **Z isomer:** 3400, 3090, 2893, 1606, 1451, 1196, 1112, 838, 757 cm^{-1}; MS (EI) m/z MI=351 (E=2% (Z=0%)), 336 (E=1% (Z=0.5%)), 320 (E=1% (Z= 0.5%)), 306 (E=81% (Z=4%)), 290 (E=13% (Z=6%)), 146 (E=Z=100%), 130 (E=16% (Z=45%)), 107 (E= 38% (Z=0%)).

2.3) Reaction with cinnamaldehyde:

The amine **5a** (0.100 g, 0.408 mmol) was reacted with cinnamaldehyde in the manner described above, and 0.139 g of a 1.2:1 E:Z mixture of isomers was separated by flash chromatography using 10 % ethyl acetate in hexanes as eluant. After elution of the Z isomer, the E was washed out from the column with ethyl acetate giving a total of 0.100 g of purified material (66% yield).

^1H NMR (200 MHz, $CDCl_3$) **7a (E isomer):** δ 7.43-7.18 (m, 5H), 6.60 (d, J=15.9 Hz, 2H), 6.23 (dd, J=6.1, 15.9 Hz, 1H), 6.14 (ddd, J=6.0, 7.0, 18.6 Hz, 1H), 5.65 (d, J=18.6 Hz, 1H), 4.36 (m, 1H), 3.43 (t, J= 6.2 Hz, 4H), 3.32 (s, 6H), 2.65 (t, J=6.2 Hz, 4H), 2.60-2.30 (m, 2H), 2.11 (s, 2H), 0.12 (s, 3H), 0.10 (s, 3H), **8a (Z isomer):** δ 7.43-7.18 (m, 5H), 6.64 (d, J=15.9 Hz, 1H), 6.46 (ddd, J=6.9, 8.3, 13.9 Hz, 1H), 6.27 (dd, J=5.6, 15.9 Hz, 1H), 5.65 (d, J= 13.9Hz, 1H), 4.38 (m, 1H), 3.50 (t, J=6.1 Hz, 4H), 3.30 (s, 6H), 2.68 (t, J=6.1 Hz, 4H), 2.60-2.30 (m, 2H), 2.22 (s, 2H), 0.17 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) **7a :** δ 143.6, 137.0, 133.4, 132.0, 130.0, 128.7, 127.6, 126.5, 71.3, 70.8, 58.8, 57.0, 46.4, 45.1, -3.1, -3.2, **8a:** δ 146.2, 137.1, 132.8, 129.4, 128.6, 127.4, 126.5, 70.7, 70.2, 58.7, 56.6, 47.2, 42.3, -0.8, -0.9; IR (film) **7a=8a**, 3389, 2893, 1654(E), 1605(E), 1450, 1250, 1196, 1113, 967, 839, 744, 694 cm^{-1}; MS (EI) m/z **isomer 7a and 8a,** MI=377 (E=0.1% (Z=2%)), 362 (E=0% (Z=0.7%)), 346 (E=0% (Z=0.9%)), 332 (E=0% (Z=65%)), 256 (E=29% (Z=0.5%)), 230 (E=58% (Z=2%)), 156 (E=52% (Z=3%)), 146 (E=100% (Z=100%)), 133 (E=18% (Z=49%)).

2.4) Reaction with 2-cyclohexene-1-one.

The amine **5a** (0.100 g, 0.408 mmol) was reacted with 2-cyclohexen-1-one in the manner described previously. After work up and evaporation of the solvent, 0.148 g of a crude 1.2:1 E:Z isomeric mixture was separated by flash column chromatography using 10% ethyl acetate

in hexanes as eluant. After the elution of most of the Z isomer, the E was washed out with ethyl acetate giving a total of 0.092g of purified material (64% yield).

^{1}H NMR (200 MHz, $CDCl_3$) **7a (E isomer):** δ 6.14 (dt, J=6.8, 18.6 Hz, 1H), 5.78 (m, 2H), 5.76 (d, J=18.6 Hz, 1H), 5.58 (dm, J=10.1 Hz, 1H), 3.41 (t, J=6.1 Hz, 4H), 3.30 (s, 6H), 2.63 (t, J=6.1 Hz, 4H), 2.33 (d, J= 6.8Hz, 2H), 2.09 (s, 2H), 1.95 (m, 2H), 1.64 (m, 4H), 0.09 (s, 6H), **8a (Z isomer):** δ 6.51 (dt, J=7.8, 14.0 Hz, 1H), 5.78 (ddd, J=2.9, 3.8, 10.0 Hz, 1H), 5.64 (dt, J=1.3, 14.0 Hz, 1H), 5.62 (dm, J=10 Hz, 1H), 3.469 (t, J=6.2 Hz, 4H), 3.30 (s, 6H), 2.67 (t, J=6.2 Hz, 4H), 2.38 (m, 2H), 2.20 (s, 2H), 2.00 (m, 2H), 1.70 (m, 4H), 0.159 (s, 3H), 0.156 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) **7a :** δ 142.9, 133.7, 132.3, 129.8, 71.0, 69.2, 58.8, 57.1, 49.8, 46.6, 37.7, 25.2, 19.0, -1.9, **8a:** δ 145.0, 132.9, 130.0, 129.6, 70.4, 68.8, 58.7, 58.6, 47.3, 46.3, 36.0, 25.0, 19.0, -1.1; IR (film) **7a** : 3403, 2913, 1613, 1458, 1250, 1112, 841, **8a:** 3423, 2937, 1610, 1448, 1248, 1110, 840 cm^{-1}; MS (E.I.) m/z **isomer 7a and 8a** MI=341 (E=2.2% (Z=0.1%)), 323 (E=1% (Z=0.1%)), 296 (E=56% (Z=3%)), 278 (E=16% (Z=3%)), 200 (E=15% (Z= 5.2%)), 146 (E= 100% (Z=78%)), 97 (E= 86% (Z=40%)).

2.5) Reaction with β-ionone:

The amine **5a** (0.100 g, 0.408 mmol) was reacted with β-ionone in the manner described previously. After work up and evaporation of the solvent, 0.180 g of crude containing a 1.2:1 E:Z isomeric mixture was separated by flash column chromatography using 10% ethyl acetate 90% hexanes as eluant. A total of 0.050 g of isolated products was obtained (56% yield).

^{1}H NMR (200 MHz, $CDCl_3$) **7a (E isomer):** δ 6.10 (ddd, J=6.1, 7.6, 18.5 Hz, 1H), 6.02 (dm, J=16.1 Hz, 1H), 5.78 (dt, J=1.4, 18.5 Hz, 1H), 5.46 (d, J= 16.1 Hz), 3.42 (t, J=6.2 Hz, 4H), 3.31 (s, 6H), 2.63 (t, J=6.2 Hz, 4H), 2.41 (m, 2H), 2.09 (s, 2H), 1.95 (m, 2H), 1.64 (s, 3H), 1.6 (m, 2H), 1.45 (m, 2H), 1.30 (s, 3H), 0.96 (s, 6H), 0.09 (s, 3H), 0.08 (s, 3H), **8a (Z isomer):** δ 6.43 (dt, J=7.7 Hz, 14.0 Hz, 1H), 6.03 (d, J= 16.0 Hz, 1H), 5.62 (d, J=14.0 Hz, 1H), 5.46 (d, J=16.0 Hz, 1H), 3.46 (t, J=6.2 Hz, 4H), 3.28 (s, 6H), 2.65 (m, 4H), 2.40 (d, J= 7.7 Hz, 2H), 2.20 (s, 1H), 2.18 (s, 1H), 1.93 (m, 2H), 1.63 (s, 3H), 1.56 (m, 2H), 1.42 (m, 2H), 1.30 (s, 3H), 0.95 (s, 6H), 0.15 (s, 3H), 0.14 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) **7a:** δ 145.4, 140.5, 137.1, 129.8, 127.7, 124.8, 71.9, 70.3, 58.6, 56.5, 47.3, 46.8, 39.3, 33.9, 32.6, 28.8, 28.7, 21.4, 19.2, -0.7, -0.8, **8a:** δ 143.4, 140.3,

137.1, 133.8, 127.9, 125.1, 72.5, 70.7, 58.8, 57.0, 50.5, 46.5, 39.3, 34.0, 32.6, 28.7, 28.4, 21.4, 19.2, -2.9, -3.0; IR (film) **7a=8a**, 3426, 2900, 1606 (Z) 1613 (E), 1453, 1365, 1251, 1197, 1114, 974, 837 cm^{-1}; MS (EI) m/z **isomer 7a and 8a:** calc'd for $C_{15}H_{45}NO_2Si$: 419.3220, found 419.3219; MI=437 (E=1% (Z=0%)), 419 (E=2% (Z<1%)), 392 (E=26% (Z=0%)), 374 (E=35% (Z= 10%)), 290 (E=5% (Z= 17%)), 275 (E=2.1% (Z=13%)), 193 (E=75% (Z=14%)), 177 (E= 21% (Z=22%)), 146 (E= 100% (Z=100%)), 59 (E=47% (Z= 36%)).

3) Allyl(morpholino-N-methyl)dimethylsilane **5b.**

Allylsilane **5b** was prepared by slight modification of the general method described by Horvath[6]: Under argon, allyl(chloromethyl)dimethylsilane (3.0 g, 12 mmol) was heated neat with freshly distilled morpholine (4 eq.) at 129°C for 6 hours. During the reaction a white precipitate (hydrochloride of the amine) was formed. The reaction mixture in 20 mL of ether was washed twice with 20 mL of distilled water and once with 10 mL of concentrated sodium carbonate solution. The organic layer was dried over anhydrous magesium sulfate and then the solvent was evaporated. Kugelrohr vacuum distillation led to the isolation of 3.0 g (76 % yield) of a clear liquid.

B.p. 60°/0.05 mm Hg; ^1H NMR (200 MHz, $CDCl_3$) δ 5.8 (m, 1H), 4.85 (m, 2H), 3.64 (m, 4H), 2.35 (m, 4H), 1.93 (s, 2H), 1.54 (d, J=8.1 Hz, 2H), 0.03 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 134.5, 113.0, 66.9, 57.2, 49.3, 23.0, -3.4; IR (film) 3075, 2860, 1629, 1249, 1069, 1035 cm^{-1}.

4) Allyl(thiomorpholino-N-methyl)dimethylsilane **5c.**

Allylchloromethyldimethylsilane (3.0 g, 20 mmol) was reacted with thiomorpholine (4.2 g, 40 mmol) at 100°C for 48 hours in the manner described in **3**. Work up and evaporation of the solvents, followed by Kugelrohr distillation (80-90 °C, 0.05 mm/Hg) led to the isolation of 3.5 g (81 % yield) of a clear liquid.

^1H NMR (200 MHz, $CDCl_3$) δ 5.88-5.64 (m, 1H), 4.90-4.76 (m, 2H), 2.61 (s, 8H), 1.91 (s, 2H), 1.53 (d, J=8.1 Hz, 2H), 0.03 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 134.0, 112.6, 58.6, 50.1, 28.7, 23.8, -2.3; IR (film) 3075, 2860, 1629, 1249, 1069, 1035 cm^{-1}.

5) Allyl-N,N-(methylpiperazinomethyl)dimethylsilane **5d.**

Allylchloromethyldimethylsilane (2.0 g, 14 mmol) was reacted with N-methylpiperazine (2.7 g, 28 mmol) at 110°C for 6 hours in the manner described in **3.** Work up and evaporation of the solvents, followed by Kugelrohr distillation (100 °C, 0.05 mm/Hg) led to the isolation of 2.4 g (82 % yield) of a clear liquid.

^{1}H NMR (200 MHz, $CDCl_3$) δ 5.85 (m, 1H), 4.82 (m, 2H), 2.40 (m, 10H), 2.23 (s, 3H), 1.93 (s, 2H), 1.90 (s, 2H) 1.53 (dt, J=1.1, 8.0 Hz, 2H), 0.03 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 134.5, 112.8, 56.5, 48.4, 45.6, 22.7, -3.8.

6) Allyl-N-(piperidinomethyl)dimethylsilane **5e.**

Allylchloromethyldimethylsilane (2.0 g, 14 mmol) was reacted with piperidine (2.3 g, 28 mmol) at 130°C for 10 hours in the manner described in **3.** Work up and evaporation of the solvents, followed by Kugelrohr distillation (80-90°C, 0.05 mm/Hg) led to the isolation of 2.6 g (97 % yield) of a clear liquid.

^{1}H NMR (200 MHz, $CDCl_3$) δ 5.90-5.65 (m, 1H), 4.90-4.76 (m, 2H), 2.4-2.2 (s, 4H), 1.88 (s, 2H), 1.6-1.45 (m, 6H), 1.45-1.3 (m, 2H), 0.05 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 135.0, 112.8, 58.5, 49.9, 26.3, 23.8, 23.4, -3.2; IR (film) 3075-2736, 1630, 1251, 1292, 1053 cm^{-1}.

7) General method for the synthesis of homoallylic alcohols (table 2) with E double bond geometry.

7.1) 5-[(Morpholino-N-methyl) dimethylsilyl]-2-methyl-pent-4E-ene-2-ol.
Entry 2, table 3:

The allyl(morpholino-N-methyl)dimethylsilane **5b** (0.100 g, 0.5 mmol) dissolved in 3.0 mL of toluene was deprotonated by adding 1.5 eq. of sec-butyllithium (1.3 M) in c-hexane at -20 °C under an argon atmosphere. After stirring 12 hours at this temperature, acetone (0.05 g, 1.5 eq.) was added to the solution at -80 °C. 20 mL of ethyl ether and a few mLs of concentrated ammonium chloride solution were then added. The organic layer was washed with 10 mL of brine, dried over anhydrous magnesium sulfate, and the solvents were then evaporated giving 0.120 g of a clear oil which contained trace amounts of the Z isomer. The E isomer was

purified by flash chromatography with 20% ethyl acetate in hexanes to elute the Z isomer, then neat ethyl acetate was used to elute 0.080 g of the E isomer as a clear oil.

Rf= 0.1 (tailing) (30% ethyl acetate in hexanes); ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.12 (dt, J=18.7, 7.0 Hz, 1H), 5.73 (d, J=18.4 Hz, 1H), 3.64 (m, 4H), 2.36 (m, 4H), 2.75 (d, J=7.0 Hz, 2H), 1.93 (s, 2H), 1.19 (s, 6H), 0.11 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.7, 133.2, 70.3, 66.9, 57.2, 56.9, 50.5, 29.1, -2.7; IR (film) 3358, 2899, 1610, 1446, 1371, 1249, 1118, 866, 834 cm^{-1}; MS (E.I.) m/z 257 M.I, 242, 198, 184, 158, 100, 59, 56, (C.I.) (M.I.+1=258 (100%)), 240 (48%).

7.2) 5-[(Morpholino-N-methyl) dimethylsilyl]-pent-4E-ene-2-ol. **Entry 1, table 3:**

The amine **5b** (0.100 g, 0.5 mmol) was reacted with acetaldehyde using the procedure described in section **7.1**. After work up and evaporation of the solvent, 0.081 g of crude containing >10:1 E:Z isomeric mixture was separated by flash column chromatography using 20% ethyl acetate 80% hexanes as eluant. After elution of the Z isomer, the E was washed out from the column with ethyl acetate giving a total of 0.044 g of purified material (33% yield).

^{1}H NMR (200 MHz, $CDCl_3$) δ 6.85 (ddd, J=6.2, 7.3, 18.6 Hz, 1H), 5.77 (dt, J=18.6, 1.2 Hz, 1H), 3.84 (m, 1H), 3.66 (m, 4H), 2.37 (m, 4H), 2.25 (m, 2H), 1.94 (s, 2H), 1.19 (d, J=6.2 Hz, 3H), 0.13 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.4, 132.5, 66.9, 66.5, 57.2, 50.5, 46.6, 22.6, -3.0; IR (film) 3404, 2947, 1618, 1458, 1248, 1116, 845 cm^{-1}; MS (E.I.) m/z MI=243 (1%), 228 (0.7%), 198 (0.8%), 158 (1.1%), 100 (100 %), 56 (11%), 45 (9%).

7.3) 4-[(Morpholino-N-methyl) dimethylsilyl]-1-phenyl-but-3E-ene-1-ol.
Entry 3, table 3:

The amine **5b** (0.100 g, 0.5 mmol) was reacted with benzaldehyde using the procedure described in section **7.1**. After work up and evaporation of the solvent, 0.212 g of crude containing >10:1 E:Z isomeric mixture was separated by flash column chromatography using 20% ethyl acetate 80% hexanes as eluant. After elution of the Z isomer, the E was washed out from the column with ethyl acetate giving a total of 0.125 g of purified material (82% yield).

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.4-7.2 (m, 5H), 6.10 (ddd, J=6.0, 7.1, 18.7 Hz, 1H), 5.80 (d, J=18.7 Hz, 1H), 4.74 (dd, J=5.2, 7.8 Hz, 1H), 3.65 (m, 4H), 2.58 (m, 2H), 2.35 (m,

4H), 1.93 (s, 2H), 0.096 (s, 3H), 0.088 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 144.2, 144.0, 132.8, 128.4, 127.5, 125.9, 72.9, 66.9, 57.1, 50.4, 46.7, -3.0; MS (EI) m/z MI=305 (0.6%), 290 (0.3%), 248 (0.5%), 230 (0.3%), 205 (0.4%), 158 (2.3%), 144 (2.3%), 107 (6.8%), 100 (100%).

7.4) 4-[(Morpholino-N-methyl) dimethylsilyl]-1-phenyl-hexa-1E, 5E-diene-3-ol.

Entry 4, table 3:

The amine **5b** (0.100 g, 0.5 mmol) was reacted with cinnamaldehyde using the procedure described in section **7.1**. After work up and evaporation of the solvent, 0.311 g of crude containing >10:1 E:Z isomeric mixture was separated by flash column chromatography using 20% ethyl acetate 80% hexanes as eluent. After elution of the Z isomer, the E isomer was washed out from the column with ethyl acetate giving a total of 0.120 g of purified material (72% yield).

^1H NMR (200 MHz, $CDCl_3$) δ 7.34-7.15 (m, 5H), 6.57 (dd, J=1.1, 16.0 Hz, 1H), 6.25 (d, J=6.2 Hz, 1H), 6.17 (d, J=6.2 Hz, 1H), 6.11 (dt, J=6.8, 18.7 Hz, 1H), 5.80 (dt, J=1.1, 18.7 Hz, 1H), 4.33 (m, 1H), 3.63 (m, 4H), 2.45 (m, 2H), 2.36 (m, 4H), 1.93 (s, 2H), 0.1 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.7, 136.8, 132.8, 132.0, 130.1, 128.6, 127.7, 126.5, 71.3, 66.8, 57.1, 50.5, 44.9, -2.9; IR (film) 3384, 3025, 2897, 1613, 1449, 1290, 1248, 1115, 982, 845 cm-1; MS (EI) m/z MI=331 (1%), 274 (0.5%), 256 (0.1%), 198 (1.6 %), 133 (9.7%), 100 (100%).

7.5) 1-{1-[(Morpholino-N-methyl) dimethylsilyl]-prop-1E-ene-3-yl}-cyclohex-2-ene-1-ol.

Entry 5, table 3:

The amine **5b** (0.100 g, 0.5 mmol) was reacted with 2-cyclohexene-1-one using the procedure described in section **7.1**. After work up and evaporation of the solvent, 0.203 g of crude containing >10:1 E:Z isomeric mixture was separated by flash column chromatography using 20% ethyl acetate 80% hexanes as eluant. After elution of the Z isomer, the E isomer was washed out from the column with ethyl acetate giving a total of 0.128 g of purified material (85% yield).

^1H NMR (200 MHz, $CDCL_3$) δ 6.13 (dt, J=6.9, 18.6 Hz, 1H), 5.78 (ddd, J=2.7, 4.1, 11.5 Hz, 1H), 5.74 (dt, J=1.2, 18.6 Hz, 1H), 5.57 (dm, J=11.5 Hz, 1H), 3.64 (m, 4H), 2.36 (m, 4H), 2.33 (d, J=6.9 Hz, 1H), 2.34 (d, J=6.9 Hz, 1H), 2.00 (m, 2H), 1.93 (s, 2H), 1.63 (m,

4H), 0.10 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.2, 133.4, 132.4, 130.1, 69.2, 67.0, 57.2, 50.5, 49.6, 35.6, 25.0, 18.7, -2.9; IR (film) 3417, 2903, 1605, 1439, 1249, 1116, 1071, 1008 cm-1; MS (E.I.) m/z MI=295 (2.5%), 280 (0.6 %), 198 (4.8%), 158 (3.4%), 100 (100 %), 97 (20%).

7.6) 6-[(Morpholino-N-methyl) dimethylsilyl]-1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-methyl-hexa-1E, 5E-diene-3-ol. **Entry 6, table 3:**

The amine **5b** (0.100 g, 0.5 mmol) was reacted with β-ionone using the procedure described in section **7.1**. After work up and evaporation of the solvent, 0.238 g of crude containing >10:1 E:Z isomeric mixture was separated by flash column chromatography using 20% ethyl acetate 80% hexanes as eluant. After elution of the Z isomer, the E isomer was washed out from the column with ethyl acetate giving a total of 0.102 g of purified material (52% yield).

^1H NMR (200 MHz, $CDCl_3$) δ 6.08 (ddd, J=6.1, 6.9, 18.6 Hz, 1H), 5.99 (d, J=16.1 Hz, 1H), 5.75 (dq, J=1.1, 18.6 Hz, 1H), 16.1 (d, J=16.1 Hz, 1H), 3.63 (m, 4H), 2.45 (ddd, J=1.2, 6.1, 13.3 Hz, 1H), 2.25-2.38 (m, 5H), 1.95 (m, 2H), 1.90 (s, 2H), 1.62 (s, 3H), 1.55 (m, 2H), 1.41 (m, 2H), 1.28 (s, 3H), 0.94 (s, 6H), 0.73 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.6, 140.4, 137.2, 133.7, 129.1, 125.3, 72.4, 67.0, 57.2, 50.5, 50.3, 39.1, 33.8, 32.4, 28.62, 28.57, 28.2, 21.2, 19.0, -2.9, -3.0; IR (film) 3420, 2896, 1615, 1451, 1367, 1289, 1249, 1118, 838 cm-1; MS (E.I.) m/z calc'd for $C_{23}H_{41}O_2NSi$: M-18=391.2907, found 391.2908; 391 (0.1%), 373 (0.1%), 198 (4%), 193 (12 %), 177 (4.5%), 158 (5%), 100 (100%).

7.7) 5-[(Thiomorpholino-N-methyl) dimethylsilyl]-2-methyl-pent-4E-ene-2-ol.
Entry 7 table 3:

The amine **5c** (0.100 g, 0.47 mmol) was deprotonated with s-butyllithium at 0°C for 12 hours then reacted with acetone using the procedure described in section **7.1**, After work up and evaporation of the solvent, 0.103 g of crude containing >10:1 E:Z isomeric mixture was separated by flash column chromatography using 20% ethyl acetate 80% hexanes as eluant. After elution of the Z isomer, the E isomer was washed out from the column with ethyl acetate giving a total of 0.06 g of pure E allyl alcohol (47% yield).

^1H NMR (200 MHz, $CDCl_3$) δ 6.11 (dt, J=18.6, 7.0 Hz, 1H), 5.72 (d, J=18.6 Hz, 1H), 2.6 (s, 8H), 2.26 (d, J=7.0 Hz, 2H), 1.93 (s, 2H), 1.18 (s, 6H), 0.08 (s, 6H); ^{13}C NMR (68

MHz, $CDCl_3$) δ 143.6, 133.4, 70.3, 58.3, 51.2, 50.9, 29.2, 28.0, -2.7; IR (film) 3389, 2941-2794, 1615, 1417, 1248, 1122 cm^{-1}; MS (C.I.) m/z 274 (100%) M+1, 256 (23%), 174 (48%), 117 (43%).

7.8) 5-[(N-methylpiperazino-N-methyl) dimethylsilyl]-2-methyl-pent-4E-ene-2-ol. **Entry 8 table 3:**

The amine **5d** (0.100 g, 0.51 mmol) was reacted with acetone using the procedure described in section **7.1.** After work up and evaporation of the solvent, 0.07 g of a crude 4:1 E:Z mixture of alcohols was isolated (55% yield). This product was not purified further.

Major isomer:
^1H NMR (200 MHz, $CDCl_3$) δ 6.15 (dt, J=18.5, 7.1 Hz, 1H), 5.75 (d, J=18.5 Hz, 1H), 2.45 (m, 8H), 2.26 (s, 3H), 2.26 (d, J=7.1Hz, 2H), 1.95 (s, 2H), 1.18 (s, 6H), 1.1 (s, 6H).

7.9) 5-[(Piperidino-N-methyl) dimethylsilyl]-2-methyl-pent-4E-ene-2-ol.
Entry 9 table 3:

The amine **5e** (0.100 g, 0.51 mmol) was reacted with acetone using the procedure described in section **7.1.** After work up and evaporation of the solvent, 0.11 g of pure E alcohol was isolated (85% yield).

^1H NMR (200 MHz, $CDCl_3$) δ 6.12 (dt, J=18.7, 7.0 Hz, 1H), 5.73 (d, J=18.7 Hz, 1H), 2.30 (m, 4H), 2.30 (d, J=7.0 Hz, 2H), 1.89 (s, 2H), 1.5 (m, 4H), 1.3 (m, 2H), 1.18 (s, 6H), 0.09 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 143.2, 133.7, 70.2, 58.4, 51.1, 51, 29.1, 26.1, 23.7, -2.6; IR (film) 3355, 2927-2763, 1615, 1414, 1252, 1118 cm^{-1}; MS (E.I.) m/z 255 (1%), 196 (3%), 98 (100%).

8) General method for the synthesis of homoallylalcohol with Z double bond geometry.

8.1) 5-[(Morpholino-N-methyl) dimethylsilyl]-2-methyl-pent-4Z-ene-2-ol.
Entry 2, table 3:

The allyl(morpholino-N-methyl)dimethylsilane **5b** (0.100 g, 0.5 mmol) dissolved in 3.0 mL of toluene was deprotonated by adding 1.5 eq. of sec-butyllithium (1.3 M in c-hexane) at -25 °C under an argon atmosphere. After stirring 12h at this temperature, 0.5 mL of dry dimethoxyethane was added. The solution was stirred an additional 30 minutes at this temperature and 0.100 g (2.5 eq.) of acetone was then added at -90°C (liquid nitrogen ether bath). After 15 minutes stirring at this temperature, hexanes (20 mL) and concentrated ammonium chloride solution (2.0 mL) were added. The water layer was discarded and the organic layer was washed with 10 mL of brine, dried with anhydrous magnesium sulfate and the solvent evaporated giving 0.130 g of a clear oil which contained E and Z isomers in a 1:6 proportion. The Z isomer was purified by flash chromatography with 20% ethyl acetate in hexanes as eluent giving 0.800 g of a clear oil.

^{1}H NMR (200 MHz, $CDCl_3$) δ 6.52 (dt, J=13.9, 7.9 Hz, 1H), 5.58 (d, J=13.9 Hz, 1H), 3.66 (m, 4H), 2.4 (m, 4H), 2.3 (d, J=7.9 Hz, 2H), 2.0 (s, 2H), 1.23 (s, 6H), 0.13 (s, 6H); ^{13}C NMR (67.80 MHz, $CDCl_3$) δ 146.4, 128.5, 68.9, 66.4, 57.1, 51.9, 48.2, 30.0, -0.5; IR (film) 3405, 2961, 1606, 1450, 1370, 1290, 1249, 1119, 840 cm^{-1}; MS (C.I. methane) m/z MI+1=258 (100%), 240 (22%), 158 (33%), 139 (19%).

8.2) 5-[(Morpholino-N-methyl) dimethylsilyl]-pent-4Z-ene-2-ol. **Entry 1, table 3:**

The amine **5b** (0.100 g, 0.5 mmol) was reacted with acetaldehyde using the procedure described in section **8.1**. After work up and evaporation of the solvent, 0.1163 g of crude containing a 1:6 E:Z isomeric mixture was separated by flash column chromatography using 20% ethyl acetate 80% hexanes as eluent. After elution of the Z isomer, the E isomer was washed out from the column with ethyl acetate giving a total of 0.075 g of isolated products (63% yield).

^{1}H NMR (200 MHz, $CDCl_3$) δ 6.44 (ddd, J=6.2, 9.6, 14.0 Hz, 1H), 5.59 (d, J=14.0 Hz, 1H), 3.86 (m, 1H), 3.68 (m, 4H), 2.42 (m, 5H), 2.20 (m, 1H), 1.94 (d, J= 14.5 Hz, 1H), 1.22 (d, J=14.5 Hz, 3H), 0.17 (s, 3H), 0.15 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 147.5, 128.2, 66.3, 65.8, 56.9, 51.4, 44.1, 23.9, -0.5, -1.0; IR (film) 3393, 2950, 1607, 1458, 1249, 1117, 840 cm^{-1}; MS (EI) m/z MI=243 (0.1%), 228 (0.9%), 198 (0.8%), 158 (0.2%), 100 (100 %), 56 (21%), 45 (15%).

8.3) 4-[(Morpholino-N-methyl) dimethylsilyl]-1-phenyl-but-3Z-ene-1-ol.
Entry 3, table 3:

The amine **5b** (0.100 g, 0.5 mmol) was reacted with benzaldehyde using the procedure described in section **8.1**. After work up and evaporation of the solvent, 0.2154 g of crude containing a 1:6 E:Z isomeric mixture was separated by flash column chromatography using 40% ethyl acetate 60% hexanes as eluant. After elution of the Z isomer, the E isomer was washed out from the column with ethyl acetate giving a total of 0.110 g of isolated products (72% yield).

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.4-7.2 (m, 5H), 6.47 (ddd, J=5.7, 9.7, 13.7 Hz, 1H), 5.61 (d, J=13.7 Hz, 1H), 4.81 (dd, J=3.5, 9.2 Hz, 1H), 3.72 (m, 4H), 2.70 (dddd, J=1.6, 3.5, 4.6, 14.1 Hz, 1H), 2.47 (m, 5H), 2.22 (d, J=14.3 Hz, 1H), 1.94 (d, J=14.3 Hz, 1H), 0.18 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 147.5, 145.8, 128.4, 128.3, 127.0, 125.4, 71.8, 66.3, 57.0, 51.3, 45.2, -0.3, -1.1; IR (film) 3401, 2918, 1607, 1450, 1249, 1116, 843, 760, 700 cm^{-1}; MS (E.I.) m/z MI=305 (<0.1%), 290 (0.2%), 248 (0.1%), 205 (4.1%), 158 (2.9%), 107 (17.6%), 100 (100%); C.I. M+1=306 (100%), 288 (60%), 158 (19%).

8.4) 4-[(Morpholino-N-methyl) dimethylsilyl]-1-phenyl-hexa-1E,5Z-diene-3-ol.
Entry 4, table 3:

The amine **5b** (0.100 g, 0.5 mmol) was reacted with cinnamaldehyde using the procedure described in section **8.1**. After work up and evaporation of the solvent, 0.3127 g of crude containing a 1:5 E:Z isomeric mixture was separated by flash column chromatography using 20% ethyl acetate 80% hexanes as eluant. After elution of the Z isomer, the E isomer was washed out from the column with ethyl acetate giving a total of 0.108 g of isolated products (65% yield).

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.4-7.15 (m, 5H), 6.64 (dd, J=1.6, 15.9 Hz, 1H), 6.51 (ddd, J=6.1, 9.5, 13.6 Hz, 1H), 6.27 (dd, J=5.1, 15.8 Hz, 1H), 4.41 (m, 1H), 3.72 (m, 4H), 2.61 (dddd, J=1.3, 3.7, 6.0, 13.9 Hz, 1H), 2.44 (m, 4H), 2.30 (m, 1H), 2.16 (d, J=14.3 Hz, 1H), 1.94 (d, J=14.3 Hz, 1H), 0.18 (s, 3H), 0.13 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 147.0, 137.1, 133.4, 128.8, 128.6, 128.4, 127.4, 126.5, 70.0, 66.2, 56.9, 51.4, 43.0, -0.4,

-1.0; IR (film) 3395, 3025, 2919, 1605, 1449, 1292, 1250, 1115, 967, 845 cm-1; MS (C.I.) m/z M+1=332 (83%), 314 (15%), 158 (100%).

8.5) 1-{1-[(Morpholino-N-methyl) dimethylsilyl]-prop-1Z-ene-3-yl}-cyclohex-2-ene-1-ol. **Entry 5, table 3:**

The amine **5b** (0.100 g, 0.5 mmol) was reacted with cyclohexene-2-one using the procedure described in section 8.1. After work up and evaporation of the solvent, 0.228 g of crude containing a 1:5.5 E:Z isomeric mixture was separated by flash column chromatography using 20% ethyl acetate 80% hexanes as eluant. After elution of the Z isomer, the E isomer was washed out from the column with ethyl acetate giving a total of 0.096 g of isolated products (61% yield).

^{1}H NMR (200 MHz, $CDCl_3$) δ 6.54 (dt, J=7.8, 13.8 Hz, 1H), 6.76 (dt, J=3.4, 18.25 Hz, 1H), 5.64 (m, 1H), 5.61 (d, J=13.8 Hz, 1H), 3.67 (m, 4H), 2.41 (m, 4H), 2.37 (ddd, J=1.2, 2.8, 8.0 Hz, 2H), 2.03 (s, 2H), 2.2-1.6 (m, 6H), 0.18 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 145.9, 133.3, 129.0, 128.8, 68.4, 66.2, 57.0, 51.6, 46.8, 36.6, 25.1, 19.2, -0.7; IR (film) 3649, 3420, 2923, 1604, 1449, 1248, 1116, 840 cm-1; MS (E.I.) m/z MI=295, 277, 195, 167, 158, 100, 97.

8.6) 6-[(Morpholino-N-methyl) dimethylsilyl]-1-(2,6,6-trimethyl-1-cyclohexen-1-yl)-3-methyl-hexa-1E,5Z-diene-3-ol. **Entry 6 table 3.**

The amine **5b** (0.100 g, 0.5 mmol) was reacted with β-ionone using the procedure described in section **8.1.** After work up and evaporation of the solvent, 0.281 g of crude containing a 1:4 E:Z isomeric mixture was separated by flash column chromatography using 10% ethyl acetate 90% hexanes as eluant. After elution of the Z isomer, the E isomer was washed out from the column with ethyl acetate giving a total of 0.120 g of isolated products (56% yield).

^{1}H NMR (200 MHz, $CDCl_3$) δ 6.53 (dt, J=7.9, 13.8 Hz, 1H), 6.05 (d, J=13.7 Hz, 1H), 6.01 (d, J=13.7 Hz, 1H), 5.50 (d, J=16.0 Hz, 1H), 3.69 (m, 4H), 2.41 (m, 6H), 2.03 (d, J=2.7 Hz, 2H), 1.95 (m, 2H), 1.66 (s, 3H), 1.58 (m, 2H), 1.44 (m, 2H), 1.32 (s, 3H), 0.98 (s, 3H), 0.97 (s, 3H), 0.16 (s, 3H), 0.12 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 146.6, 141.8, 137.3, 128.4, 127.8, 124.2, 71.4, 66.3, 56.9, 51.6, 47.3, 39.2, 33.8, 32.5, 28.6, 28.5, 21.2, 19.1, -0.6, -0.8; IR (film) 3342, 2752, 2752, 1606, 1451, 1251, 1206, 1118, 838, 793 cm-1; MS (E.I.) m/z calc'd for $C_{23}H_{41}O_2NSi$: M-18=391.2907, found 391.2908; 391

(0.1%), 373 (0.1%), 291 (2.9%), 177 (4.7%), 175(6.3%), 158 (4.7%), 100 (100%), 75 (39%).

8.7) 5-[(Thiomorpholino-N-methyl) dimethylsilyl]-2-methyl-pent-4Z-ene-2-ol.
Entry 7 table 3:

The allyl(thiomorpholino-N-methyl)dimethylsilane **5c** (0.100 g, 0.47 mmol) was reacted with acetone using the procedure described in section **8.1**, with the exception that the deprotonation was carried out at 0°C during 12 hours. After work up and evaporation of the solvent, 0.12 g of crude containing a 1:6 E:Z isomeric mixture was separated by flash column chromatography using 20% ethyl acetate 80% hexanes as eluant. After elution of the Z isomer, the E was washed out from the column with ethyl acetate giving a total of 0.080 g of isolated products (63% yield).

^{1}H NMR (200 MHz, $CDCl_3$) δ 6.55 (dt, J=13.7, 8.0 Hz, 1H), 5.6 (d, J=13.7 Hz, 1H), 4.70 (s, 1H), 2.65 (s, 8H), 2.3 (d, J= 8.0 Hz, 2H), 2.1 (s, 2H), 1.24 (s, 6H), 0.14 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 146.5, 128.3, 68.9, 58.2, 52.3, 48.1, 30.0, 27.2, -0.4; IR (film) 3450, 3125, 2944-2800, 1606, 1452, 1375, 1250, 1126 cm^{-1}; MS (C.I.) m/z 274 (10%) M+1, 256 (47%), 174 (24%), 116 (95%).

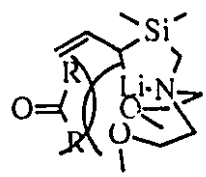
8.8) 5-[(N-Methylpiperazino-N-methyl) dimethylsilyl]-2-methyl-pent-4Z-ene-2-ol.
Entry 8 table 3:

The allyl(N,N-methylpiperazinomethyl)dimethylsilane **5d** (0.100 g, 0.47 mmol) was reacted with acetone using the procedure described in section **8.7**. After work up and evaporation of the solvent we obtained 0.080 g of crude containing a 1:7 E:Z isomeric mixture. The products were not separated and only the proton spectra of the major product is given.
^{1}H NMR (200 MHz, $CDCl_3$) δ 6.55 (dt, J=13.7, 8.0 Hz, 1H), 5.6 (d, J=13.7 Hz, 1H), 2.48 (s, 8H), 2.32 (d, J= 8.0 Hz, 2H), 2.29 (s, 3H), 2.05 (s, 2H), 1.23 (s, 6H), 0.14 (s, 6H); IR (film) 340, 3100, 2944-2700, 1606, 1456, 1371, 1251, 1150 cm^{-1}; MS (C.I.) m/z 271 (96%) M+1, 253 (43%), 171 (45%), 114 (100%).

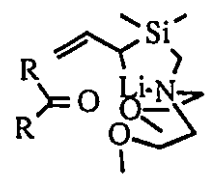
8.9) 5-[(Piperidinomethyl-N-methyl) dimethylsilyl]-2-methyl-pent-4Z-ene-2-ol.
Entry 9 table 3:

The allyl(piperidino-N-methyl)dimethylsilane **5e** (0.100 g, 0.51 mmol) was reacted with acetone using the procedure described in section **8.7**. After work up and evaporation of the solvent, 0.100 g of crude containing a 1:7 E:Z isomeric mixture was separated by flash column chromatography using 20% ethyl acetate 80% hexanes as eluant. Elution of the Z isomer gave a total of 0.030 g of a yellow oil (23% yield). No E isomer was isolated.
^{1}H NMR (200 MHz, $CDCl_3$) δ 6.56 (dt, J=13.7, 8.0 Hz, 1H), 5.59 (d, J=13.7 Hz, 1H), 2.35 (d, J=8.0 Hz, 2H), 2.35 (m, 4H), 2.01 (s, 2H), 1.56 (m, 4H), 1.35 (m, 2H), 1.24 (s, 6H), 0.11 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 146.6, 128.2, 68.5, 58.2, 52.5, 48.2, 30.1, 25.2, 23.4, -0.3; IR (film) 3450, 3125, 2942-2742, 1607, 1453, 1372, 1252, 1122 cm^{-1}; MS (C.I.) m/z 256 (100%) M+1, 238 (63%), 156 (69%), 139 (61%).

4.4 Synthesis and reactivity of pentadienylsilanes.



A

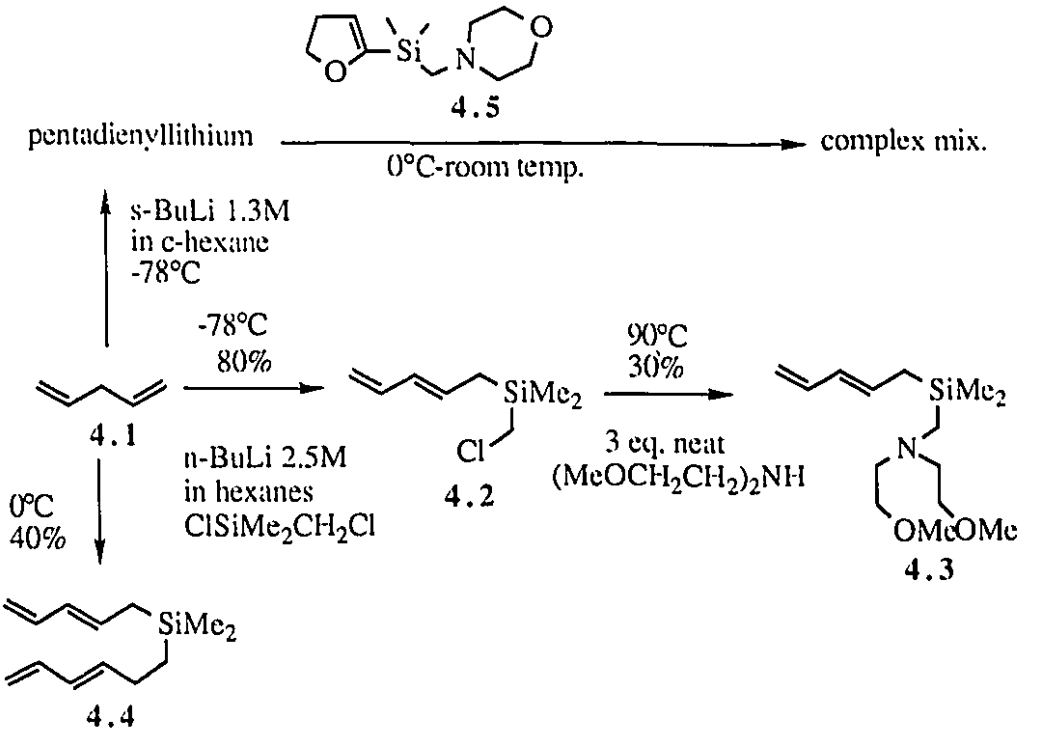


B

Figure 4.1.

We have reported in section 4.2, the dramatic effects caused by the presence of a complexing group, on the stereoselectivity of α-lithioallylsilanes additions to carbonyl electrophiles.[1] However such complexing groups remained ineffective in controlling regioselectivity, because the characteristic γ- selectivity of the addition of α-lithioallylsilanes to ketones and aldehydes was still being observed. Presumably the regioselectivity of the reaction is due to the steric hindrance observed by the electrophile approaching the nucleophilic allyl anion α to the silicon as drawn in **A** (Figure 4.1) We can see in **B** that attack in the opposite orientation is not subject to the same steric crowding. The question that remains to be answered is: can a complexing group have any effect on the regioselectivity of carbonyl addition? For example could we direct the attack γ on a conjugated system where an ε attack is normally favored due to relatively weak steric interactions ?[2]

We decided to answer these questions using the pentadienyl system as a model. Similar models has already been studied by Oppolzer[3] and Nakamura.[4] These made the interpretation of our results easier.

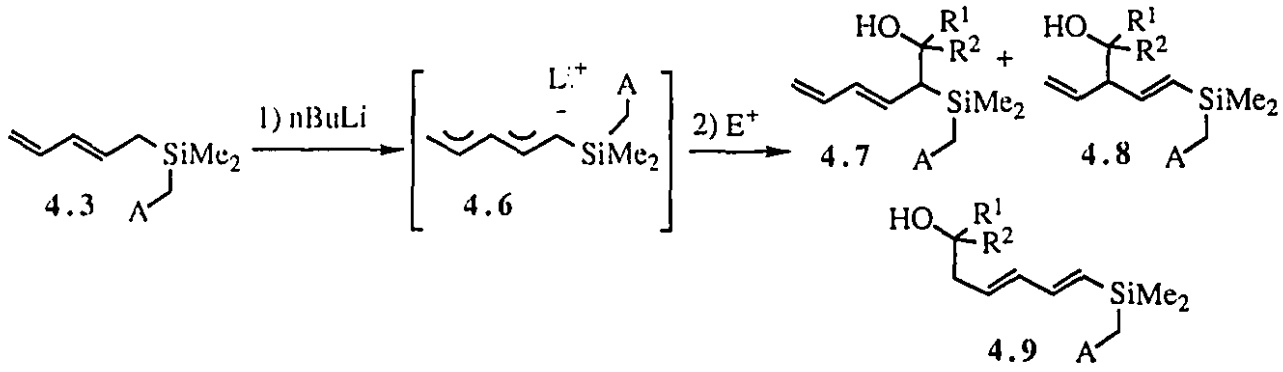


Scheme 4.1: Synthesis of aminomethyldimethylpentadienylsilane **4.3**.[4,5]

Pentadienylsilane **4.2** was prepared by deprotonation of 1,4-pentadiene **4.1** and reaction with chloro(chloromethyl)dimethylsilane. When the reaction was carried out at 0°C the petadienyllithium, substituted both chlorine atoms of the electrophile to form the tetraene **4.4** in 40% yield after distillation. The desired 2,4-pentadienyl(chloromethyl)dimethylsilane **4.2** was synthesized in 80%* yield by the addition of the anion to the electrophile at -78°C. This product was reacted with 3 eq. of the bis(methoxymethylene)amine at 90°C for 24 hours to give the amine **4.3** in 30 % yield after purification by flash chromatography. Attempts at forming the amine **4.3** directly by substitution of the dihydrofuranyl group on compound **4.5** (see next chapter) gave a complex mixture of products (Scheme 4.1).

The results of our studies on the reactivity of a pentadienylsilyllithium reagent bearing a complexing group, seems to support the idea that at least some γ control can be obtained with these reagents. We have reacted the anion **4.6** derived from pentadienylsilane **4.3** with acetone, benzaldehyde, cinnamaldehyde and benzophenone (Table 4.1).

*The side reaction product **4.4** could never be completely eliminated.



entry	electrophile	4.7	4.8	4.9	crude yield
a	acetone	-	100	-	93%
b	benzaldehyde	-	75	25	93%
d	benzophenone	-	-	100	100%

Table 4.1: Addition to aldehyde and ketones.

The aminomethylpentadienylsilane **4.3** was deprotonated at -78 °C in THF and then reacted with carbonyl electrophiles in order to determine the influence of the chelating group on the regioselectivity of the addition. The results given in table 1, seem to indicate a predominance of γ addition product being formed, with the exception of benzophenone which reacted in the ε position. These results, when compared to Oppolzer's indicate a net change in selectivity; Oppolzer reported a net preference for the ε addition product when the chelating group is absent (for benzaldehyde a ratio of 4/1 in preference of the ε addition product like **4.9** was observed).[3] This supports the hypothesis outlined at the beginning of the chapter that the amine complexes the lithium cation and can influence the regioselectivity of the reaction at least to some extent.

Concerning the use of the aminomethylpentadienylsilanes and other aminomethylallylsilanes in the synthesis of polyenic compounds the major difficulty we are facing using this type of approach is that no α addition product was ever isolated from these reactions as was the case in the examples reported by Oppolzer.

The formation of the allyl anions is, on the other hand, much easier when the chelating group is present. Also the deprotonation in solvents such as toluene or ether is possible.

Concerning the α-selectivity, Perhaps the presence of an amino group on synthons like the ones described in chapter 3 would give some more α selectivity. Considering the results outlined here and the easier deprotonation of such systems, we decided to go forward with the synthesis of a retinoic acid synthon having an aminomethylsilyl chelating group attached to it (see chapter 5).

4.5 Experimental.

See section 4.2 for general comments on experimental. 1,4-Pentadiene was purchased from Aldrich.

1) Pentadienylchloromethyldimethylsilane **4.2.**

1,4-Pentadiene (1.77 g, 26 mmol) was deprotonated by the addition of n-BuLi (2.5M (1.2 eq.) in hexanes) in 150 mL of freshly distilled THF at -78°C. The reaction mixture was warmed up to 0°C and left stirring for 2 hours then the temperature was brought down to -80°C and this solution was slowly transferred to a flask containing chloro(chloromethyl)dimethylsilane (3.7 g, 26 mmol) at -78°C . The reaction mixture was warmed up to room temperature, filtered and the solvents were evaporated leaving 4.0 g of crude pentadienyl(chloromethyl)dimethylsilane (80% yield). The proton NMR showed the product to be around 70% pure. This compound was used in the next step without further purification as a mixture of 9:1, E:Z isomers.

^{1}H NMR (200 MHz, $CDCl_3$) δ 6.29 (dt, J=10.2, 16.9 Hz, 1H), 5.97 (dd, J=10.2, 14.9 Hz, 1H), 5.69 (dt, J= 8.3, 14.9 Hz, 1H), 5.0-4.86 (m, 2H), 2.78 (s, 2H), 1.67 (d, J=8.3 Hz, 2H), 0.14 (s, 6H); IR (film) 3083-2925, 1642, 1601, 1253, 1002 cm^{-1}. MS (EI) m/z 176 (4%), 174 (12%), 107 (58%), 93 (37%), 81 (38%), 79 (100%).

2) 2,4-Pentadienyl-N-[bis(methoxyethyl)aminomethyl] dimethylsilane **4.3.**

Under argon, 2,4-pentadienyl(chloromethyl)dimethylsilane (1.0 g , 5.6 mmol) prepared above was heated neat with freshly distilled N,N-[bis(methoxyethyl)amine] (1.53 g, 11.2 mmol) at 110°C for 2 hours. During the reaction a brown oil deposited at the bottom (hydrochloride of the amine). The reaction mixture in 20 mL of ether was washed twice with

20 mL of distilled water and once with 10 mL concentrated sodium carbonate solution. The organic layer was dried over anhydrous magesium sulfate and the solvent evaporated. Flash chromatography using a 20:80 % ethyl acetate / hexanes mixture gave 0.45 g (30% yield) of a dark oil. Longer reaction times and lower reaction temperatures did not give better results. Purification by Kugelrohr vacuum distillation only led to decomposition of the product. This product consisted of a 6:1 E: Z mixture of isomers.

The predominant E isomer:
^{1}H NMR (200 MHz, $CDCl_3$) δ 6.22 (dt, J=10.1, 16.9 Hz, 1H), 5.92 (dd, J=10.1, 14.9 Hz, 1H), 5.69 (dt, J= 8, 14.9 Hz, 1H), 4.90 (d, J= 16.9 Hz, 1H), 4.87 (d, J=10.1 Hz, 1H), 3.43 (t, J=16.2 Hz, 4H), 3.31 (s, 6H), 2.63 (t, J=16.2 Hz, 4H), 2.07 (s, 2H), 1.58 (d, J=8 Hz, 2H), 0.05 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 137.4, 131.7, 130.0, 112.7, 70.9, 58.7, 57.1, 45.5, 21.8, -2.3; IR (film) 3002-2811, 1642, 1601, 1251, 1122 cm^{-1}. MS (EI) m/z 271 (6%), 226 (100%), 216 (42%), 204 (48%), 146 (89%).

3) 2,4-Pentadienyl-3,5-hexadienyldimethylsilane **4.4**. The compound was isolated as a side product in most of the reactions carried out using the procedure 1 but became the major product at higher reaction temperatures .

1,4-Pentadiene (1.0 g, 15 mmol) was deprotonated by the addition of n-BuLi [2.5M (1.2 eq.) in hexanes] in 10 mL of freshly distiled THF at -78°C. The reaction mixture was warmed up to 0°C and left stirring for 3 hours then chloro(chloromethyl)dimethylsilane (2.1 g, 15 mmol) was added to this solution . The reaction mixture was warmed up to room temperature, filtered and the solvents were evaporated leaving 1.2 g (40%) of crude pentadienyl adduct **4.4**.

^{1}H NMR (200 MHz, $CDCl_3$) δ 6.41-6.19 (m, 2H), 6.12-5.60 (m, 4H), 5.14-4.80 (m, 4H), 2.10 (m, 2H), 1.54 (d, J=8Hz, 2H), 0.64 (m, 2H), -0.8 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 137.7, 137.5, 137.2, 131.8, 129.9, 129.7, 114.7, 112.8, 26.6, 22.1, 14.3, -3.6; MS (EI) m/z 206 (5%), 139 (100%), 111 (84%), 73(41%), 59 (88%).

4) General reactions of the anion of **4.3** with carbonyl compounds. The pentadienyl silane **4.3** was deprotonated with s-BuLi (1.3 M in c-hexane) or with n-BuLi (2.5 M in hexanes) at a temperature of -60°C during 4 hours and the resulting anion was reacted with acetone, benzaldehyde, cinnamaldehyde and benzophenone. The results are given in table 1.

4.1) Table 1 entry a: Reaction of silane **4.3** with acetone represents an example of the general procedure used for these reactions.

s-Butyllithium [1.3 M (0.31 mL, 1.2 eq.)] in c-hexane was added to the silane **4.3** (0.05 g, 0.2 mmol), dissolved in 5.0 mL of anhydrous THF at -60°C. This reaction mixture was left stirring for 4 hours. Acetone (0.01g, 1.2 eq.) was then slowly added to this solution at -78°C and left to react for 20 min. The reaction mixture was then warmed up to room temperature and 10 mL of hexanes were added with 1 mL of saturated ammonium chloride solution. The organic phase was separated, washed with 10 mL of water, dried over anhydrous magnesium sulfate and the solvents were evaporated leaving 0.057 g (83%) of a crude yellow oil which contained only the γ-addition product as evaluated by proton NMR.

^{1}H NMR (200 MHz, $CDCl_3$) δ 6.18 (dd, J=18.6, 7.8 Hz, 1H), 5.82 (m, 1H), 5.77 (d, J= 18.6 Hz, 1H), 5.2-5.03 (m, 2H), 3.42 (t, J= 6.2Hz, 4H), 3.31 (s, 6H), 2.70 (m+t, J=6.2 Hz, 5H), 1.17 (s, 6H), 0.12 (s, 3H), 0.10 (s,3H). IR 3438, 2903, 1609, 1248, 1118. MS (EI) m/z 329 (2%), 285 (53%), 226 (18%), 204 (6%), 146 (100%).

4.2) Table 1 entry b: Reaction of silane **4.3** with benzaldehyde:

The silane **3** (0.11 g, 0.4 mmol) dissolved in 5.0 mL of anhydrous THF was reacted with benzaldehyde using the procedure described in section 4.1. Work up and evaporation of the solvents gave 0.14 g (93%) of a yellow oil containing a 4/1 mixture of **4.8b** (mixture of diastereomers) with some ε-addition product **4.9b**. The products were identified by proton NMR spectroscopy using the chemical shifts of the olefinic region reported by Oppolzer.[3]

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.4-7.2 (m, 5H), 6.52 (dd, J=18.4, 10.0 Hz, ε products 1/4 H), 6.12 (dd, J= 18.7, 7.6 Hz, γ products 3/4 H), 5.50-5.90 (m, 2H), 5.18 (m, 1/2 H), 4.98 (m, 11/2 H), 4.63 (d, J= 7.4 Hz), 4.55 (d, J=7.4Hz), 3.43 (t, J= 6.2Hz, 4H), 3.31 (s, 6H), 2.70 (m, 1H), 2.70 (t, J=6.2Hz, 4H), 2.14 (s, 1 1/2 H), 2.02 (s, 1/2 H), 0.15 (m, 4 1/2 H), 0.50 (s, 1 1/4 H), 0.02 (s, 1 1/4 H).

4.3) Table 1 entry d: Reaction of silane **4.3** with benzophenone:

The silane **3** (0.1 g, 0.4 mmol) dissolved in 5.0 mL of anhydrous THF was reacted with benzophenone using the procedure described in section 4.1. Work up and evaporation of the solvents gave 0.18 g (100%) of a yellow oil containing the addition product **4.8d** plus some unreacted benzophenone.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.9-7.1 (m, 10H), 6.45 (dd, J=18.1, 9.9 Hz, 1H), 6.25 (dd, J=10.1, 14.9 Hz, 1H), 5.80 (d, J= 18.1 Hz, 1H), 5.57 (dt, J=7.4, 14.9Hz, 1H), 3.43 (t, J= 6.1 Hz, 4H), 3.30 (d, J= 7.4 Hz, 2H), 2.65 (t, J= 6.1Hz, 4H), 2.12 (s, 2H), 0.11 (s,6H). IR 3415, 3058-2896, 1640, 1448, 1248, 1114. MS (EI) m/z 453 (1%), 408 (33%), 226 (29%), 204 (10%), 183 (68%), 146 (100%), 105 (100%), 77 (55%).

4.6 References.

1. Other groups have also used the complexing moiety with an organosilicon tether.

H. Imanieh, P. Quayle, M. Voaden *Tetrahedron Lett.* **1992**, 33, 543. K. Marumo, S. Inoue, Y. Sato, H. Kato *J. Chem. Soc. Perkin Trans. 1.* **1991**, 2276. K. Tamao, E. Nakajo, Y. Ito *Tetrahedron* **1988**, 44, 3997. and references cited there in.

2. See the short review in chapter 3.

3. W. Oppolzer, S.C. Burford, F. Marazza *Helv. Chim. Act.* **1980**, 63, 555.

4. H. Yasuda, T. Nishi, S. Miyanaga, A. Nakamura *Organometallics*, **1985**, 4, 359.

5. For the synthesis and ^{1}H NMR of pentadienyltrimethysilane see:

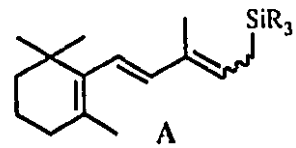
D. Seyferth, J. Pornet *J. Org. Chem.* **1980**, 45, 1722.

6. For the preparation of pentadienyllithium see:

R. B. Bates, D.W. Gosselink, J.A. Kaczynski *Tetrahedron Lett.* **1967**, 199.

CHAPTER 5.
A NEW SYNTHESIS OF (AMINOMETHYL)ALLYLSILANES.

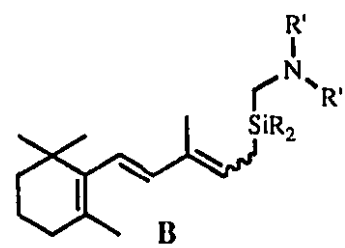
5.1 Introduction.



A

In chapter 1-4 we described the synthesis and reactivity of the anions of allylsilanes. We have shown that although possible, the synthesis of retinoic acid through the use of **A** was not very efficient. Use of additives like cerium and magnesium salts did not help greatly.

In the previous chapter, we concluded that the synthesis of an aminomethylsilane of type **B** may not disfavor the 1,4- conjugate addition product and that the complexing amino functionality may not improve the α-regioselectivity. However we decided to go ahead with the synthesis of **B** because of the challenge, and also because we believed that these reagents should deprotonate more easily, giving us access to a wider range of possible reaction conditions (non-polar solvents). Also, the development of new intermediates necessary for the synthesis of **B** might turn out to be more useful in the synthesis of retinoids than **B** itself. We now report the synthesis of **B** and some interesting methodologies that were developed to this aim.



B

The first part of this chapter is an article co-authored by Chan, Nwe and myself, and deals with the use and the synthesis of aryl(aminomethyl)dimethylsilanes. This article has been accepted for publication in Organometallics (1993). Please note that for the purpose of the demonstration of the usefulness of the method, the entire paper has been reproduced here. Dr. Nwe used the methodology described in the first part of the paper to prepare an (aminomethyl)dimethylpropargylsilane. The second part of this chapter is in the form of a

communication to Tetrahedron Letters and deals with the synthesis of allenes, prepared by the Peterson elimination, of β-hydroxyvinyltrimethylsilanes, under basic conditions. The format of these two articles has been changed to fit the thesis, however the numbering of the compounds has not been changed and is not related to numbering for the rest of the thesis.

The third part of this chapter deals with the tentative studies for the development of new aminomethyl substituted silyl nucleophiles. The fourth deals with the successful use of allene for the synthesis of allyl(aminomethyl)silane **B** via hydrosilylation.

5.2 New aryl(aminomethyl)dimethylsilanes.

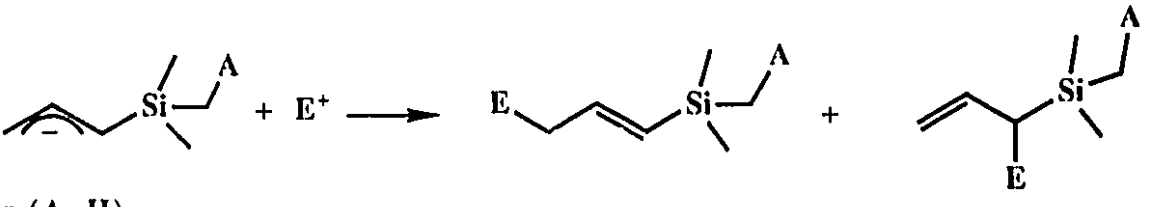
Synthesis of (Aminomethyl)silanes with the Use of an Easily Cleavable Carbon-Silicon Bond.

*D. Labrecque, K. T. Nwe and T. H. Chan**
Department of Chemistry, McGill University, Montreal, Quebec, Canada H3A-2K6

A number of (chloromethyl)dimethylsilanes **8a-c** bearing a heterocyclic substituent $(ClCH_2)(CH_3)_2Si(C_4H_nX)$ (**a**, n = 3, X = O; **b**, n = 3, X = S; **c**, n = 5, X = O) were synthesized and aminated with morpholine to give (aminomethyl)silanes **9a-c** $(C_5H_{10}NO)(CH_3)_2Si(C_4H_nX)$ (**a**, n = 3, X = O; **b**, n = 3, X = S; **c**, n = 5, X = O). They were screened for their capacity to undergo nucleophilic substitution reactions using lithium aluminum hydride. The heterocyclic substituent on silane **9c** was easily replaced with hydride, alkyls, and the trimethylsilyl group. This series of reactions was successfully applied to the synthesis of the pentamethyldisilane **14** $(C_5H_{10}NO)(CH_3)_5Si_2$ and the acetylene (aminomethyl)silane **21** $(C_{13}H_{19}NSi)$ not readily available in pure form by other means.

Introduction

While much of the current interest in the use of organosilicon chemistry for organic synthesis[1] has been focused on silicon compounds bearing simple alkyl or aryl groups, there has been increasing recognition that organosilicon compounds with proximate functional groups may modulate the reactivity patterns.[2] Comparison between a methyl substituted and an α-aminomethyl substituted organosilicon compound is particularly illustrative. It has been well established[3] that the (trimethylsilyl)allyl anion (**1a**, A = H) reacts with an electrophile regioselectively at the γ-position to give the product **2**-γ with ***E*** stereochemistry at the double bond (Scheme 1).



1a (A=H)
1b (A=NR_2)

2-γ

2-α

Scheme 1.

On the other hand, various [(α-aminomethyl)dimethylsilyl]allyl anions (**1b**, A = NR_2) can react with electrophiles giving different regioselectivity[4] and stereochemistry at the double bond.[5] In cases where the amino moiety is chiral, asymmetric synthesis using chiral (α-aminomethyl)organosilicon compounds can be achieved, very often with high stereoselectivity.[6] Another difference is that the carbon-silicon bond of compounds in which the silicon bears an α-aminomethyl group can be cleaved readily by oxidation,[7] first to the corresponding silanol and eventually to the carbinol.[8] A similarly methyl substituted organosilicon compound is likely inert under the same oxidation conditions. This ready oxidation of (α-aminomethyl)silanes may well account for their bioactivity as monoamine oxidase inhibitors.[9]

(α-Aminomethyl)silanes **4** are usually synthesized by nucleophilic displacement of the corresponding (α-chloromethyl)silanes **3** with amines (Scheme 2).[4,10] This approach is quite adequate except in the cases where the precursor is not readily available or when the group R is reactive toward amines and/or amine hydrochloride salts.

Because of our interest in this area, we have examined an alternate approach to the synthesis of (α-aminomethyl)silanes which involved the preparation of (chloromethyl)silane **5**, from chloro(chloromethyl)dimethylsilane, containing a leaving group Y. This group was chosen for its inertness toward amines so that the displacement of the chlorine can take place to give **6**. Finally, the group Y itself is displaced by a nucleophile R to give **4** (Scheme 2). Even though the synthesis is somewhat round about, it does provide the desired (α-aminomethyl)silanes in good overall yield, and permit the synthesis of compounds with a reactive R group.

Results and Discussion

The group Y examined included 2-furyl, 2-thienyl, and 4,5-dihydro-2-furyl.[11] Thus, compounds **8a-c** were prepared by the reactions of **7** with the appropriate organolithium reagents.[12] In all cases, they were found to react with amines to give the corresponding **9a-c** in good yields. Morpholine was chosen as the representative amine, but other amines can be used as well. Nucleophilic displacement of the Y group depends on the nature of Y as well as that of the nucleophile.

Scheme II

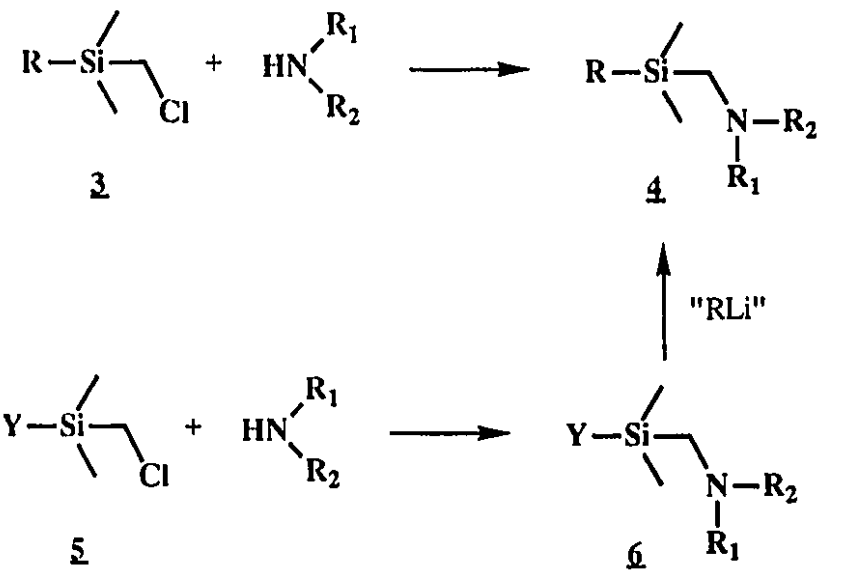
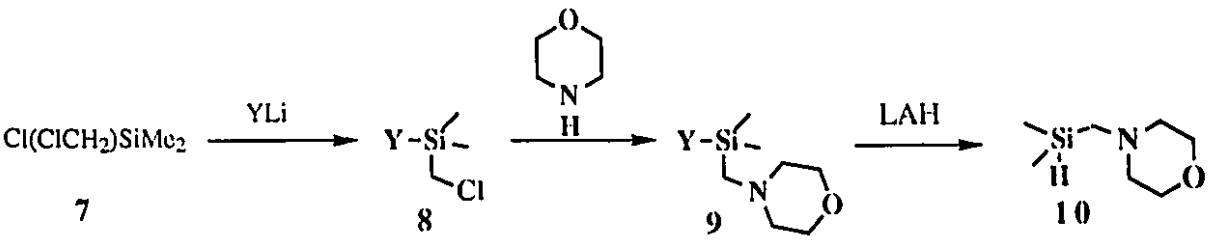
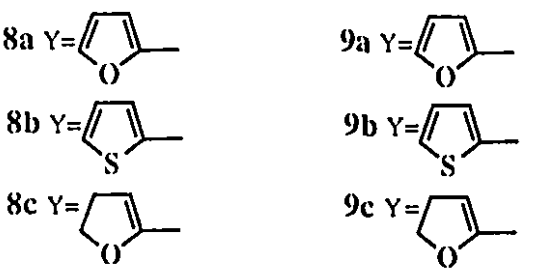


Table 1: Yields (%), for the formation of silane 10 and intermediates, based on silanes starting material.

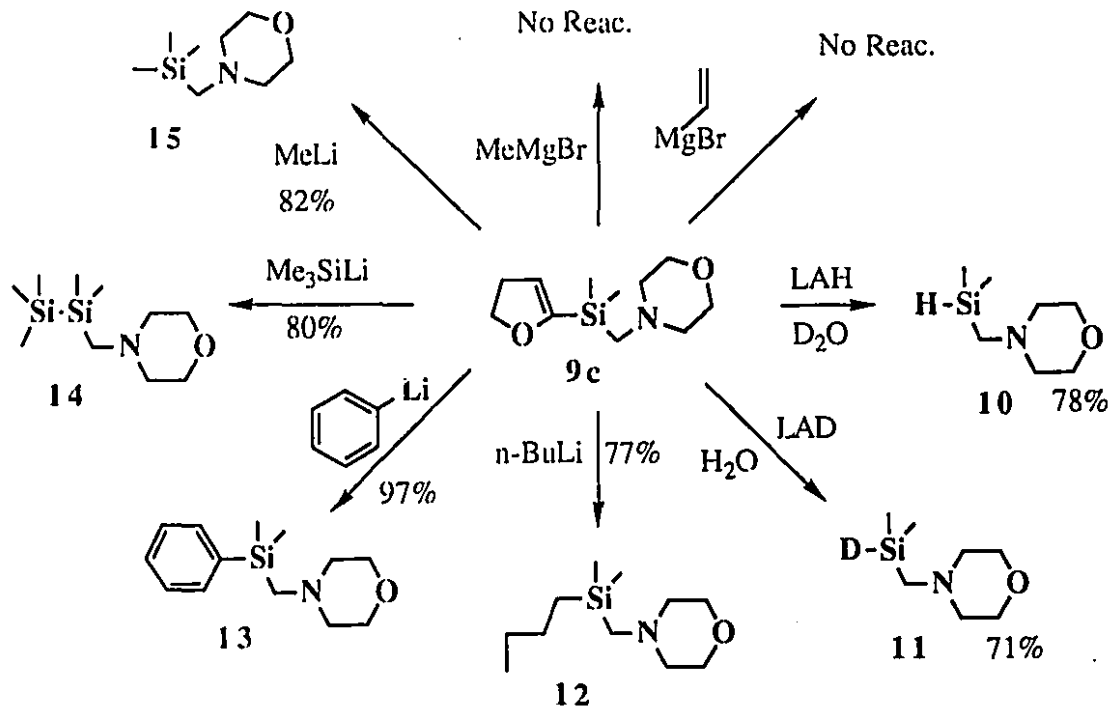




R	8	9	10
2-furyl (a)	87[a]	85[a]	23[a]
2-thienyl (b)	83[a]	84[a]	68[b], 42[a]
4,5-dihydro-2-furyl (c)	89[a]	94[a]	73[c]

[a] The products were purified by Kugelrohr distillation under vacuum.
[b] Crude product, [c] The product was pure as shown by ^{1}H NMR.

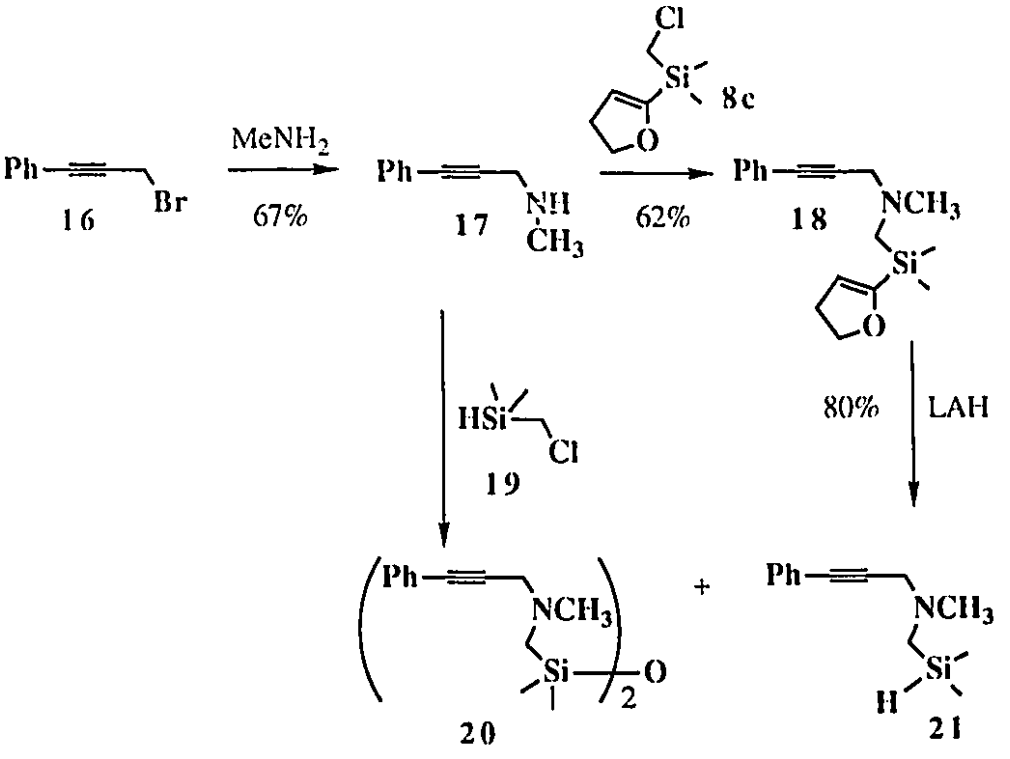
Scheme III



Using lithium aluminum hydride as the common nucleophile, it was possible to evaluate the effectiveness of different Y groups for the synthesis of (aminomethyl)silanes **10**. The results are compared in Table 1. Conversion of **9a** to **10** required heating of the reagents in THF in a sealed tube at 150 °C, and the yield was relatively low (23%). Reductions of **9b** and **9c** to **10** could be carried out under milder reaction temperatures, and with better yields. The 4,5-dihydro-2-furyl group seemed to be the best leaving group of the three, requiring the mildest reaction conditions, and giving the best overall yield from **7** to **10**. Use of lithium aluminum deuteride gave the corresponding deuteriosilane **11**. Other nucleophiles can be used as well (Scheme 3). For example, organolithiums were found to be very effective in displacing the heterocyclic substituent on compound **9c** giving a variety of (aminomethyl)silanes **12-15**. On the other hand, Grignard reagents were found not to displace the 4,5-dihydro-2-furyl group (Scheme 3).

Equally effective is the displacement of the 4,5-dihydro-2-furyl group of **9c** using (trimethylsilyl)lithium as the nucleophile. Compound **14** was obtained in good yield. This illustrates one of the advantages of the present synthetic approach. The alternative approach (Scheme 2) was less versatile and less convenient since (chloromethyl)pentamethyldisilane was not readily available.[13]

Scheme IV



The usefulness of the present synthetic approach was also demonstrated by the synthesis of compound **21**, needed for another project. Direct reaction of (chloromethyl)dimethylsilane **19** with the amine **17** gave a mixture of products including the desired compound **21** and the disiloxane **20**. Because of the sensitivity of **21** to air oxidation, it was difficult to perform chromatography to obtain pure **21**. Similarly, displacement of (chloromethyl)dimethylethoxysilane with amine **17** gave the disiloxane **20** as well. On the other hand, reaction of the amine **17** with **8c** gave the compound **18** in 62% yield. Reduction of **18** with lithium aluminum hydride in THF gave the silane **21** in 80% yield (Scheme 4). Since **21** was the only compound obtained, purification by chromatography was not necessary.

Conclusion

A number of α-aminosilanes have been synthesized by the use of amphiphilic group Y via Scheme 2. This approach can be used for the syntheses of reactive hydrosilanes.

Experimental Section

Diethyl ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl. Hexanes and ethyl acetate were distilled from calcium hydride. NMR spectra were recorded on a Varian Gemini 200 or Varian XL-200 (^{1}H at 200 MHz, ^{13}C at 50 MHz) or Varian XL-300 (^{1}H at 300 MHz, ^{13}C at 75 MHz) or a JEOL-270 (^{1}H at 270 MHz, ^{13}C at 68 MHz). ^{1}H and ^{13}C NMR spectra were referenced internally using the residual solvent resonances relative to tetramethylsilane (δ 0 ppm). Low and high resolution electron impact mass spectra were recorded on a Kratos MS 25RFA spectrometer operating at 70 eV. IR spectra were recorded on a Analet FT, A25-18 or on a BOMEM Michelson Series between NaCl plates (neat liquids or solutions).

(1) (Chloromethyl)dimethyl(2-furyl)silane (8a).

Under argon, 2-furyllithium (0.0136 mol, solution in 20 mL of ether:TMEDA)[11] was transferred at -78 °C to a solution containing (chloromethyl)dimethylchlorosilan (1.5 g, 0.011 mol) in anhydrous ether. The solution was slowly warmed to room temperature, and 20 mL of water was added. The reaction mixture was extracted using 20 mL of hexanes. The organic layer was dried over anhydrous $MgSO_4$ and the solvents were evaporated under reduced pressure. Kugelrohr vacuum distillation (60-70 °C, 0.05mmHg) gave 1.6 g (87%) of a clear liquid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (dd, J=1.7, 0.5 Hz, 1H), 6.75 (dd, J=3.3, 0.5 Hz, 1H), 6.42 (dd, J=3.3,1.7 Hz, 1H), 2.96 (s, 2H), 0.42 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 147.2, 121.3, 108.5, 29.4, -5.0. IR (film) 3115, 2963, 1550, 1395, 1254, 1110, 749-600 cm^{-1}. Exact mass calcd for $C_7H_{11}OSiCl$: 174.0268. Found: 174.0270. MS (EI) m/z 176 (4%), 174 (12%), 125 (100%).

(2) (Chloromethyl)dimethyl(2-thienyl)silane (8b).

Under argon, 2-thienyllithium (31 mL, 1.0 M in THF) was added to 40 mL of anhydrous THF containing chloro(chloromethyl)dimethylsilane (4.0 g, 0.028 mol) maintained at -78 °C. The reaction mixture was then slowly warmed to room temperature. The reaction mixture was extracted using 20 mL of hexanes. The organic layer was dried

over anhydrous $MgSO_4$, and the solvents evaporated under reduced pressure. Kugelrohr vacuum distillation (80-85 °C, 0.05 mmHg) gave 4.4 g (83%) of a clear liquid.

^1H NMR (200 MHz, $CDCl_3$) δ 7.66 (d, J=4.6 Hz, 1H), 7.36 (d, J=3.4 Hz, 1H), 7.23 (dd, J=3.4, 4.6 Hz, 1H), 2.96 (s, 2H), 0.48 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 135.3, 131.4, 128.3, 30.6, -3.4. IR (film) 3103, 2960-25, 1684, 1497, 1402, 1254, 1215, 995, 823 cm^{-1}. Exact mass calcd for $C_7H_{11}SSiCl$: 190.0039. Found: 190.0036. MS (E.I.) m/z 192 (5%), 190 (11%), 141 (100%), 83 (2%), 97(10%).

(3) (Chloromethyl)(4,5-dihydro-2-furyl)dimethylsilane (8c).

(4,5-Dihydro-2-furyl)lithium (0.035 mol in 20 mL of ether:TMEDA) was obtained by adding, at -78 °C, tert-butyllithium (1.7 M in pentane, 22 mL, 0.038 mol) to a solution containing 20 mL of anhydrous ether, 4 mL of TMEDA (distilled over CaH_2), and 4,5-dihydrofuran (5 mL, 0.07 mol). This solution was warmed to room temperature and stirred for 20 min.

The temperature of the (dihydrofuryl)lithium solution was lowered to -78 °C and chloro(chloromethyl)dimethylsilane (5.0 g, 0.035 mol) was then slowly added to it. The reaction mixture was warmed to room temperature, and 20 mL of water was added. The reaction mixture was extracted using 20 mL of hexanes, and the organic layer was dried over anhydrous $MgSO_4$. The solvents were evaporated under reduced pressure and Kugelrohr vacuum distillation of the residue (62-65 °C, 0.05 mmHg) gave 5.5 g (89%) of a clear liquid.

^1H NMR (200 MHz, $CDCl_3$) δ 5.30 (t, J=2.7 Hz, 1H), 4.26 (t, J=9.5 Hz, 2H), 2.87 (s, 2H), 2.59 (dt, J=2.5, 9.5 Hz, 2H), 0.26 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.6, 113.2, 70.3, 30.6, 28.91, -5.5. IR (film) 2964-2866, 1596, 1394, 1252, 1096, 927, 815 cm^{-1}. Exact mass calcd for $C_7H_{13}OSiCl$: 176.0424. Found: 176.0419. MS (EI) m/z 178 (10%), 176 (28%), 127 (48%), 107 (14%), 97 (100%).

(4)N-[(Dimethyl(2-furyl)silyl)methyl]morpholine (9a).

(Chloromethyl)dimethyl(2-furyl)silane **(8a)** (1.0 g, 5.7 mmol) was heated with morpholine (1.25 g, 14.36 mmol) neat at 80 °C for 24 h. During this time a precipitate formed, indicating that the reaction went to completion. The reaction mixture was extracted with ether and water. The ether layer was dried with $MgSO_4$, then evaporated. The residue

was distilled on Kugelrohr under reduced pressure (80-90 °C, 0.05 mmHg), giving 1.1 g (85%) of a clear liquid.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.65 (dd, J=0.6, 1.7 Hz, 1H), 6.68 (dd, J=0.6, 3.2 Hz, 1H), 6.38 (dd, J=1.7, 3.2 Hz, 1H), 3.62 (m, 4H), 2.36 (m, 4H), 2.13 (s, 2H), 0.32 (s, 6H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 158.5, 146.8, 120.4, 109.5, 67.1, 57.2, 49.5, -3.3. IR (film) 3112, 2958-2853, 1545, 1362, 1250, 1117 cm^{-1}. Exact mass calcd for $C_{11}H_{19}O_2NSi$ calcd 225.1185. Found: 225.1186. MS (EI) m/z, 225 (12%), 210 (1%), 139 (1%), 125 (11%), 100 (100%).

(5) N-[(Dimethyl(2-thienylsilyl)methyl)]morpholine (9b).

(Chloromethyl)dimethyl(2-thienyl)silane (**8b**) (2.0 g, 11 mmol) was heated with morpholine (2.3 g, 26 mmol) in the same manner as described for **9a** and distilled on Kugelrohr under reduced pressure (90 °C, 0.05 mmHg), giving 2.1 g (84%) of a clear liquid.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (dd, J=0.8, 4.7 Hz, 1H), 7.33 (dd, J=0.8, 2.3 Hz, 1H), 7.20 (dd, J=3.3, 4.7 Hz, 1H), 3.67 (m, 4H), 2.40 (m, 4H), 2.17 (s, 2H), 0.40 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9, 134.5, 130.8, 128.1, 67.1, 57.3, 50.6, -1.5. IR (film) 3103, 2956-2793, 1407, 1250, 1118, 1008 cm^{-1}. Exact mass calcd for $C_{11}H_{19}NOSSi$: 241.0957. Found:241.0961. MS (EI) m/z 241 (11%), 226 (1%), 198 (1%), 184 (3%), 144 (2%), 141 (12%), 100 (100%).

(6) N-[(Dimethyl(4,5-dihydro-2-furyl)silyl)methyl]morpholine (9c).

The (chloromethyl)dimethyl(4,5-dihydro-2-furyl)silane (**8c**) (1.0 g, 5.7 mmol) was reacted with morpholine (1.4 g, 16.1 mmol) neat at room temperature for 48 h, during which time a white precipitate formed. The reaction mixture was extracted with ether and water. The ether layer was dried with $MgSO_4$, and then evaporated, and the residue was distilled (Kugelrohr) under reduced pressure (88-90 °C, at 0.05 mmHg), giving 1.2 g (94%) of a clear liquid.

^{1}H NMR (200 MHz, $CDCl_3$) δ 5.25 (t, J=2.5 Hz, 1H), 4.25 (t, J=9.5 Hz, 2H), 3.65 (m, 4H), 2.57 (td, J=9.5, 2.5 Hz, 2H), 2.39 (m, 4H), 2.03 (s, 2H), 0.18 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 160.8, 111.8, 70.1, 66.8, 56.9, 48.7, 30.5, -4.0. IR (film) 2956-

2690, 1594, 1450, 1250, 1118, 1093, 928 cm^{-1}. Exact mass calcd for $C_{11}H_{21}O_2NSi$: 227.1342. Found: 227.1341. MS (EI) m/z 227 (11%), 141 (6%), 100 (100%).

(7) N-[(Dimethylsilyl)methyl]morpholine (10).

(a) From Product 9a.

N-[(Dimethyl(2-furyl)silyl)methyl]morpholine (**9a**) (1.9 g, 8.4 mmol) was dissolved in 2.0 mL of THF, lithium aluminum hydride (0.32 g, 8.4 mmol) was added, and THF was evaporated; next, the reaction mixture was heated at 150 °C in a sealed tube with stirring for 48 h. The reaction mixture was then added to 1 mL saturated NH_4Cl with ice and worked up. Evaporation and Kugelrohr distillation (40 °C, 0.05 mmHg) gave 0.3g (23%) of a clear liquid.

(b) From Product 9b.

N-[(Dimethyl(2-thienylsilyl)methyl]morpholine (**9b**) (0.48 g, 2.0 mmol) was dissolved in 10.0 mL of THF, a solution of lithium aluminum hydride (1 M in THF, 1.0 mL, 1.0 mmol) was added, and the reaction mixture was heated at 60 °C with stirring in a sealed tube for 10 h. The reaction mixture was then added to saturated NH_4Cl with ice; workup and evaporation gave 0.21 g (68%) of a crude yellow liquid which upon Kugelrohr distillation (40 °C, 0.05 mmHg) gave 0.13 g (42%) of pure **10**.

(c) From Product 9c.

N-[(Dimethyl(4,5-dihydro-2-furyl)silyl)methyl]morpholine (**9c**) (0.1g, 0.44 mmol) was dissolved in 2.0 mL of THF and lithium aluminium hydride (1M in THF, 0.22 mL, 0.2 mmol) was added and the reaction mixture was left stirring at room temperature for 6 h. The reaction mixture was then added to 1 mL of saturated NH_4Cl with ice, workup and evaporation of the solvents gave the silane **10**, 0.051 g (73%), as a pure clear liquid.

^1H NMR (200 MHz, $CDCl_3$) δ 3.99 (n, J=3.6 Hz, 1H), 3.69 (m, 4H), 2.43 (m, 4H), 2.00 (d, J=3.6 Hz, 2H), 0.12 (d, J=3.6 Hz, 6H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 67.1, 57.1, 49.1, -4.7. IR (film) 2957-2793, 2119, 1449, 1288, 1250, 1119, 890 cm^{-1}. Exact mass calcd for $C_7H_{17}ONSi$: 159.1079 Found: 159.1099. MS (EI) m/z, 159 (10%), 144 (3%), 100 (100%), 86 (4%).

(8) N-[(Deuteriodimethyl)silyl)methyl)morpholine 11.

N-[(Dimethyl(4,5-dihydro-2-furyl)silyl)methyl]morpholine (**9c**) (0.1g, 0.44 mmol), was reacted with lithium aluminum deuteride. Workup and evaporation of the solvents gave 0.05 g (71%) of the silane **11**.

^{1}H NMR (200 MHz, $CDCl_3$) δ 3.67 (m, 4H), 2.40 (m, 4H), 1.9 (s, J=3.6 Hz, 2H), 0.10 (s, J=3.6 Hz, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 67.0, 57.0, 49.0, -4.8.

(9) General Procedure for the Reaction of Organolithium with N-[(dimethyl(4,5-dihydro-2-furyl)silyl)methyl]morpholine (9c).

Under argon, N-[(dimethyl(4,5-dihydro-2-furyl)silyl)methyl]morpholine (**9c**) was dissolved in 1 mL of anhydrous THF or ether. The organolithium in solution was transferred to the flask containing **9c** at 0 °C and the reaction mixture was then warmed to room temperature and left stirring for 6 h, before water was added and the organic layer worked up.

(a) N-[(*n*-Butyldimethylsilyl)methyl]morpholine (12).

A solution of *n* -butyllithium (2.5 M in hexanes, 0.36 mL, 0.88 mmol) was reacted with **9c** (0.1 g, 0.44 mmol) in THF in the manner described above to give 0.08 g (84%) of pure product, upon workup and evaporation of the solvents.

^{1}H NMR (200 MHz, $CDCl_3$) δ 3.64 (m, 4H), 2.85 (s, 2H), 2.35 (m, 4H), 1.25 (m, 4H), 0.85 (m, 3H), 0.5 (m, 2H), 0 (s,6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 67.0, 57.3, 50.0, 26.5, 25.9, 15.1, 13.7, -3.0. IR (film) 2962-2735, 1451, 1282, 1248, 1120 cm^{-1}. Exact mass calcd for $C_{11}H_{25}ONSi$ 215.1705. Found: 215.1707. MS (E.I.) m/z 215 (7%), 158 (20%), 100 (100%).

(b) N-[(Dimethylphenylsilyl)methyl]morpholine (13).

A solution of phenyllithium (1.8 M in cyclohexane ether solution, 0.88 mL, 0.88mmol) was reacted with **9c** (0.1 g, 0.44 mmol) in THF in the manner described previously to give 0.18 g of a crude mixture, upon workup and evaporation of the solvents.

This yellow oil was purified by flash chromatography by first eluting the biphenyl side product with hexanes and then eluting out of the column the desired product using ether as eluent. A quantity of 0.10 g of **13** (97%) was obtained as a clear oil.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.55 (m, 2H), 7.35 (m, 3H), 3.65 (m, 4H), 2.35 (m, 4H), 2.15 (s, 2H), 0.45 (s,6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 67.0, 57.3, 50.0, 26.5, 25.9, 15.1, 13.7, -3.0. IR (film) 2968-2736, 1591, 1450, 1282, 1249, 1117 cm^{-1}. Exact mass calcd for $C_{13}H_{22}ONSi$: 235.1392. Found: 235.1396. MS (EI) m/z 235 (6%), 135 (11%), 100 (100%).

(c) N-[(Pentamethyldisilyl)methyl]morpholine (14).

A solution of (trimethylsilyl)lithium (1.78 mmol in HMPA) prepared by an established method,[14] was reacted with **9c** (0.2 g, 0.88 mmol) in the manner described previously. The reaction mixture was worked up with a saturated ammonium chloride solution and then water and brine. The organic phase was separated. The solvents were evaporated, giving 2.9 g of impure clear oil which was distilled under vacuum (Kugelrohr, 110-120 °C, 0.05 mmHg) and then purified by flash chromatography using an hexanes:ether (85:15) eluent mixture to give 0.16 g (80%) of disilane **14**.

^{1}H NMR (200 MHz, $CDCl_3$) δ 3.65 (m, 4H), 2.35 (m, 4H), 1.95 (s, 2H), 0.05 (s,6H), 0.01 (s,9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 67.2, 57.3, 50.0, -2.1, -3.7. IR (film) 2954-2734, 1451, 1295, 1246, 1120 cm^{-1}. Exact mass calcd for $C_{10}H_{25}ONSi_2$: 231.1475. Found: 231.1487. MS (EI) m/z 231 (3%), 216 (6%), 158 (57%), 100 (100%), 73 (16%).

(d) N-[(Trimethylsilyl)methyl]morpholine (15).

A solution of methyllithium (1.4 M in hexanes, 0.37 mL, 0.53 mmol) was reacted with **9c** (0.1 g, 0.44 mmol) in ether in the manner described previously to give 0.062 g (82%) of pure **15** upon workup and evaporation of the solvents.

^{1}H NMR (200 MHz, $CDCl_3$) δ 3.65 (m, 4H), 2.35 (m, 4H), 1.87 (s, 2H), 0.03 (s, 9H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 67.1, 57.3, 51.2, -1.3. IR (film) 2957-2736, 1451, 1296, 1248, 1120 cm^{-1}. Exact mass calcd for $C_8H_{19}ONSi$: 173.1236. Found: 173.1237. MS (E.I.) m/z 173 (14%), 158 (9%), 116(8%), 100 (100%), 73 (21%).

(10) Phenylpropargyl bromide (16).

To a solution of phenylpropargyl alcohol (1.30 g, 0.01 mol) in 20 mL of anhydrous ether and 0.08 mL of pyridine at 0 °C was added dropwise a solution of PBr_3 (0.78 mL, 0.08 mol) in 10 mL of ether. After the addition, the reaction mixture was refluxed at 45 °C for 3 h. It was then cooled and poured into 30 mL of water and the organic layer was separated. The aqueous layer was extracted with ether, and the combined ether layer was washed with 10% $NaHCO_3$ solution andwater and dried ($MgSO_4$). Removal of the solvent gave a quantitative yield of **16**. Reported yield = 70 %.[15]

^{1}H NMR ($CDCl_3$) δ 7.20-7.50 (m,5H), 4,16 (s,1H); ^{13}C NMR ($CDCl_3$) δ 131.83, 128.83, 128.29, 122.09, 86.68, 84.19, 15.28. IR (film) 3050, 2220, 1598, 1489, 1203, 754, 669, 591 cm^{-1}.

(11) N-Methyl-N-(phenylpropargyl)amine (17).

To a methylamine (33% solution in EtOH, 12 mL, 0.08 mol) at 0 °C was added dropwise a solution (2.0 g, 0.01 mol) of **16** in 5 mL of absolute EtOH, and the reaction mixture was stirred at room temperature for 1 h, after the addition. The solvent was evaporated from the reaction mixture, extracted with ether, and washed with water. Ether was removed to give a crude mixture of di and monopropargylated amine in a 1:4 ratio. Kugelrohr distillation of the mixture afforded 1.0 g (67% yield) of **17**, 80-90°C, 0.05 mmHg. Some of the product seemed to polymerize on distillation.

^{1}H NMR ($CDCl_3$) δ 7.20-7.50 (m,5H), 3.61 (s,2H), 2.54 (s,3H), 1.48 (s,1H). ^{13}C NMR ($CDCl_3$) δ 131.40, 128.03, 127.78, 123.01, 87.22, 83.40, 40.52, 35.09. IR (film) 3300, 2793-2970, 1598, 1489, 1328, 1107, 756, 691 cm^{-1}. Exact mass calcd for $C_{10}H_{11}N$: 145.0891. Found: 145.0888. MS (EI) m/z 145 (27%), 144 (100%), 115 (46%), 68 (11%).

(12) Reaction of 17 with Different Silanes.

(a) With Ethoxy(chloromethyl)dimethylsilane.

A mixture of **17** (0.29 g, 2 mmol) and ethoxy(chloromethyl)dimethylsilane (0.15 g, 1 mmol) was kept in a sealed tube at room temperature for 6 h. Ether was added, the

insoluble solid was filtered out, and the solvent was removed. ^{1}H NMR of the reaction mixture showed the formation of disiloxane **20**.

(b) With (Chloromethyl)dimethylsilane.

A mixture of **17** (0.29 g, 2 mmol) and (chloromethyl)dimethylsilane (0.1 g, 1 mmol) was kept in a sealed tube at room temperature for 6 h. Ether was added, the insoluble solid was filtered out, and the solvent was removed. ^{1}H NMR of the crude mixture showed that **21** and disiloxane **20** were formed in a 1:1 ratio.

(c) With (chloromethyl)(4,5-dihydro-2-furyl)dimethylsilane.

A mixture of **17** (0.29 g, 2 mmol) and (dihydrofuryl)(chloromethyl)dimethylsilane (**8c**) (0.26 g, 1.5 mmol) was heated at 40 °C in a sealed tube for 2 days. Ether was added, the insoluble solid was filtered out and the solvent was removed. Separation of the crude mixture by column chromatography (10% EtOAc + 3% NEt_3 in hexanes) gave 0.176 g (62%) of **18**. Some of the product seemed to decompose on the column.

^{1}H NMR ($CDCl_3$) δ 7.20-7.50 (m,5H), 5.30 (t,J=2.5 Hz,1H), 4.26 (t,J=9.5 Hz, 2H), 3.53 (s,2H), 2.58 (dt, J=2.5,9.5 Hz,2H), 2.37 (s,3H), 2.20 (s,2H), 0.23 (s,6H). ^{13}C NMR ($CDCl_3$) δ 160.73, 131.70, 128.20, 127.91, 123.35, 112.42, 85.66, 84.65, 70.44, 50.25, 46.06, 45.54, 30.73, -3.94. IR ($CHCl_3$) 3000-2782, 1596, 1445, 1325, 1253, 1092, 925 cm^{-1}. Exact mass calcd for $C_{17}H_{23}SiNO$: 285.1549. Found: 285.1553. MS (EI) m/z 285 (4%, M^+), 170 (18%), 158 (51%), 115 (100%).

(13) N-(Dimethylsilylmethyl)-N-methyl-N-phenylpropargylamine 21.

To a solution of **18** (0.028 g, 0.1 mmol) in 1 mL of dried THF was added a solution of LAH (0.008 g, 0.2 mmol) in 1 mL of THF, under argon, and the reaction mixture was stirred at room temperature overnight. Then it was poured onto 1 mL of saturated NH_4Cl solution containing some ice and extracted with ether. The organic layer was dried ($MgSO_4$) and the solvent removed to give 0.017 g (80%) of the silane **21.** The product is very sensitive to air and moisture and is easily converted to the disiloxane.

^{1}H NMR ($CDCl_3$) δ 7.20-7.50 (m, 5H), 3.99 (n, J=3.6 Hz,1H), 3.53 (s,2H), 2.39 (s,3H), 2.14 (d, J=3.6 Hz,2H), 0.14 (d, J=3.6 Hz,6H). ^{13}C NMR ($CDCl_3$) δ 131.64, 128.25,

128.16, 127.88, 123.27, 85.55, 84.55, 50.09, 45.99, 45.18, -4.85. IR($CHCl_3$) 2963, 2779, 2122, 1489, 1254, 1222, 908 cm^{-1}. Exact mass calcd for $C_{13}H_{19}SiN$: 217.1286. Found: 217.1284. MS (CI) m/z 218 (33%, MH^+), 202 (5%), 158 (70%), 115 (100%).

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Supplementary Material Available: Figures of 1H and 13C NMR spectra of new compounds (32 pages). Ordering information is given on any current masthead page.

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5.3 Synthesis of allenes via elimination of β-hydroxyvinylsilanes.

SYNTHESIS OF ALLENES FROM β-HYDROXYVINYLSILANES REVISITED.

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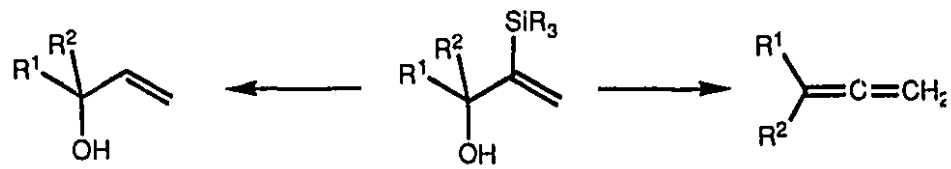
A number of years ago, we reported that allenes **1** could not be obtained by the direct elimination of β-hydroxyvinylsilanes **2**.[1] When **2** was treated with fluoride ion, a protodesilylation (scheme 1) occured to give the desilylated alcohols **3**.[2] This fluoride ion promoted protodesilylation reaction has been confirmed and applied in numerous occasions by others.[3] The reaction is particularly usefull in the addition of α-silylvinyl anion to chiral aldehydes to give good stereoselectivity in the resultant β-hydroxyvinylsilanes. The silylvinyl moiety thus served as a bulky vinyl equivalent since the silyl group can be removed readily.[4] Similarly, when **2** was treated with potassium hydride in HMPA the protodesilylation reaction also occured.[5] These reaction conditions are usually used for Peterson elimination.[6]

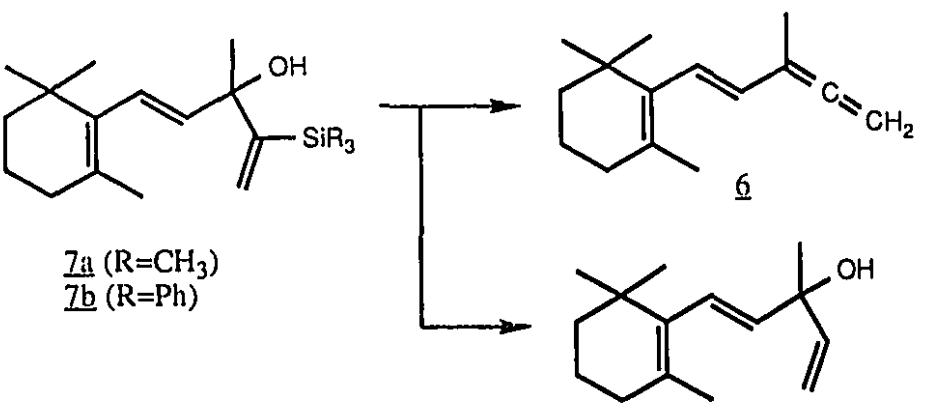


3 **2** **1**

Scheme 1:

Since the oxyanion **4** was likely to be formed first, the desilylation was believed to take place via an homo Brook rearrangement [7] to give the vinyl anion **5** (scheme 3). In order for the allene synthesis to take place, the hydroxy moiety must first be converted to a good leaving group (e.g. chloride), followed by fluoride ion promoted β elimination.[1]

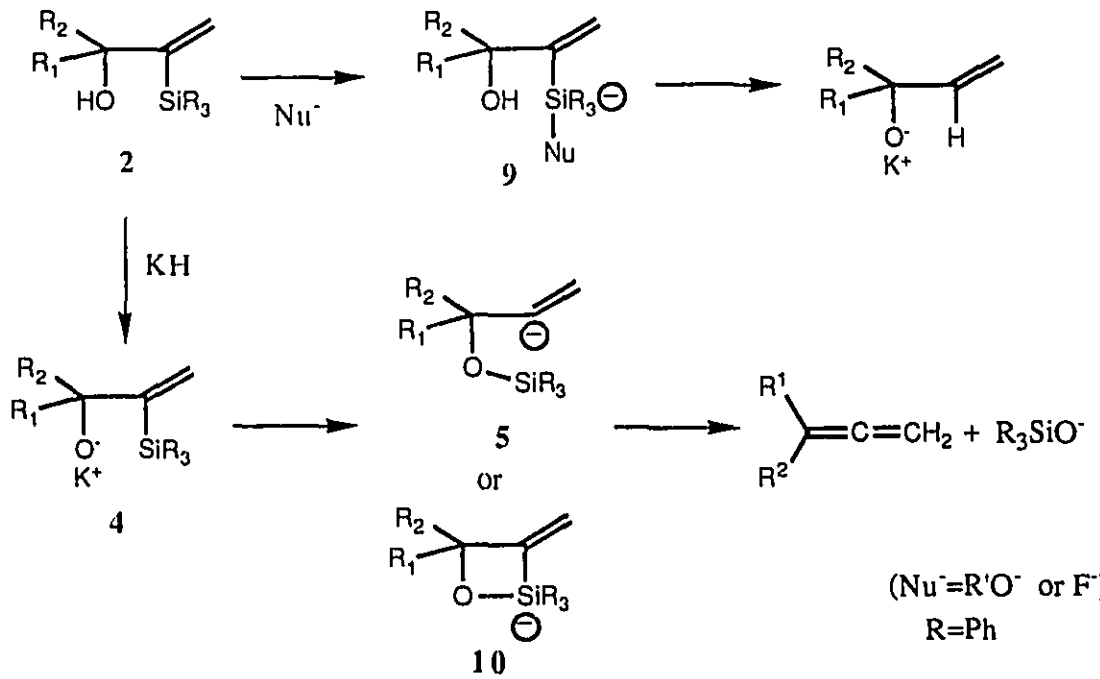
Recently, because of our research in a related project,[8] we were interested in the synthesis of the allene **6**. The β-hydroxyvinylsilanes **7a-b** were prepared in good yields from the reaction of β-ionone with the appropriate trimethylsilyl- or triphenylsilyl-vinyllithium. Attempts to convert **7a** and **7b** to the corresponding chlorides with $SOCl_2$ or similar reagents gave inevitably decomposition. In an attempt to make the methyl ether of **7b**, compound **7b** was treated with KH in THF and methyliodide. The protodesililylated compound **8** was obtained as the major product, a result which was not surprising. However, a very small quantity of the desired allene **6** was also obtained (scheme 3). After numerous experimentations, the following optimal conditions were found for the synthesis of allene **6** directly from the β-hydroxyvinylsilane **7b**. A solution of **7b** (1.0 g) in freshly distilled THF was added slowly (dropwise, over 1/2 to 1h) to a stirred refluxing THF suspension of freshly hexanes-washed KH (2-6 eq., 30 % in oil). After the addition, the reaction was refluxed for no more than 10 min., since the resulting allene **6** was susceptible to isomerisation by KH (this side reaction was noticed when the THF solution turned dark blue). The excess KH was destroyed by adding ethanol to the cold reaction mixture. The mixture was extracted with hexanes or pentanes and washed with water. The dried organic solvents were evaporated[9] and the residue purified by flash chromatography using hexanes or pentane as eluent to give **6** in 70 to 75% yield.



Scheme 2:

Several features of the reaction were of particular interest. The reaction seemed to be very sensitive to potassium alkoxide and hydroxide. This accounted for the need of freshly distilled anhydrous solvents and fresh KH. Excess of KH also facilitated the reaction. This accounted for the need of slow addition of **7b** to a refluxing suspension of excess KH in THF. However large excesses also facilitated the isomerisation of the allene when working in large scales (often a compromise was used after trial and error). In addition exposure of **7a** to identical reaction conditions lead to the formation of allene **6** but in lower yields.

The synthesis of allenes by the elimination of β-hydroxyvinyltriphenylsilanes appeared to be general. A number of examples are presented in table 1. The yields varied from modest to excellent. However, in the case of the simple aromatic allene **14** some isomerisation occured and for the isolated product phenylallene (Table 1, entry 2) we observed complete isomerization (only the acetylene **12** was isolated).



scheme 3:

The divergences of allene formation and protodesilylation under different reaction conditions suggest that the two reactions follow different mechanistic pathways. In view of the sensivity of the protodesilylation to the presence of alkoxides (or fluoride, as we had previously demonstrated), it seems reasonable to suggest that the protodesilylation reaction is more likely to be initiated by the attack of an external nucleophile to the silicon of the vinylsilane moiety, either by a direct displacement, or more likely via an hypervalent silicon intermediate **9**, followed by protonation (scheme 3). The silaoxethane intermediate **10** or **5**, on the other hand, leads to the Peterson elimination product. The lack of allene formation can be due to the ease of formation of **9** or the reluctance of **10** or **5** to eliminate.

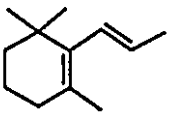
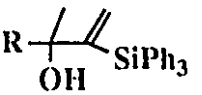
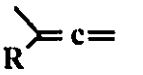
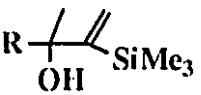
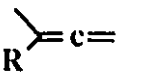
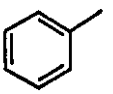
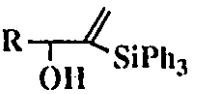
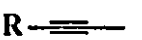
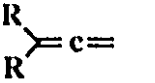
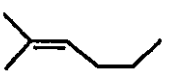
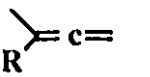
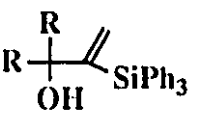
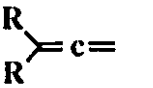
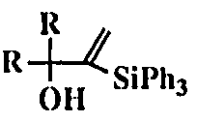
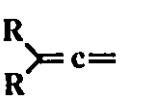
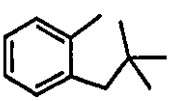
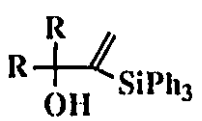
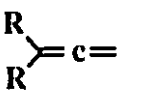
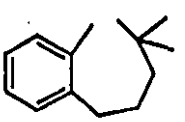
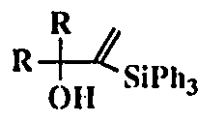
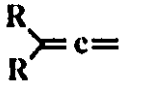
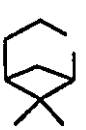
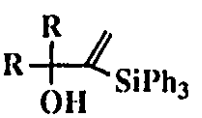
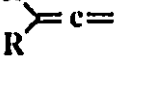
Entry	R=	β-hydroxysilanes	Yields	Product	Yields
1		 7a	88%	 6	75%
2		 7b	60%	 6	50%
3		 11	83%[1]	 12	93%[2]
4		 13	89%[1]	 14	42%[1]
5		 15	75%[1]	 16	39%[1]
6		 17	65%	 18	91%
7		 19	78%	 20	69%
8		 21	78%	 22	75%
9		 23	54%	 24	85%
10		 25	86%	 26	33%

Table 1: Preparation of allenes under basic conditions. 1) See ref. 1 for spectra. 2) The 1H NMR matched exactly with that of a sample purchased from Aldrich.

Acknowledgement. We thank the NSERC and FCAR for the financial support of this research and M. Nadim Saade for the mass spectral analyses.

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2. Chan, T.H.; Mychajlowskij, W. *Tetrahedron Letters* **1974**, 3479.

3. Burke, S.D.; Piscopio, A.D.; Marron, B.E.; Matulenko, M.A.; Pan, G. *Tetrahedron Letters* **1991**, 32, 857.

4. For other applications see: Suzuki, K.; Miyazawa, M.; Shimazaki, M.; Tsuchiashi, G. *Tetrahedron Letters* **1986**, 27, 6237. and references cited there in

5. Wilson, S.R.; Georgiadis, G.M. *J. Org. Chem.* **1983**, 48, 4143. Sato, F.; Tanaka, Y.; Sato, M. *J.Chem. Soc.C.C.* **1983**, 165.

6. Peterson, D.J. *J. Org. Chem.* **1968**, 33, 780; T.H. Chan *Acc. Chem. Res.* **1977**, 10, 442.

7. Brook, A. *Acc. Chem. Res.* **1974**, 7, 77.

8. Chan, T.H.; Labrecque, D.L. *Tetrahedron Letters* **1991**, 32, 1149.

9. In some cases the allenes formed after the reactions are very volatile accounting at least in part for the low yields of some of the entries in table 1. In these instances, evaporation on the rotary-evaporator should be carried out at low temperature (10-20 °C) for short periods of time. Except for example **7b**, most of the elimination reactions were carried-out on a 100 to 200 mg scale (15-30 min. addition time).

10. Kawashima, T.; Iwama, N.; Okazki, R. *J. Am. Chem. Soc.*, **1992**, 114, 7598.

11. T. Sasaki; S. Eguchi; Y. Hirako. *Tetrahedron Letters*. **1976**, 541.

12.Spectral data for the silyl alcohols **7a-b**, **17**, **19**, **21**, **23**, **25**.

Silane **7a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.03 (d, 16.1 Hz, 1H), 5.68 (d, J=2.0 Hz, 1H), 5.57 (d, J=16.1 Hz 1H), 5.43 (d, J=2.0 Hz, 1H), 1.97 (m, 2H), 1.66 (s, 3H), 1.60 (m, 2H) 1.54 (s, 1H), 1.47 (s+m, 5H), 0.98 (s, 6H), 0.17 (s, 9H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 159.1, 140.8, 136.9, 128.4, 124.6, 123.8, 78.1, 39.5, 34.2, 32.8, 30.0, 28.8, 21.4, 19.3, 0.6. IR (film) 3450, 3069-2866, 1590, 1428, 1107 cm^{-1}; MS (E.I.) m/z calc'd for $C_{33}H_{36}Si$:460.2586. Found:460.2581 MS (E.I.) m/e 460(6%), 287(8%), 259(100%), 181(17%), 105(12%), 77(3%).

Silane **7b**: ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.70 (m, 6H), 7.2-7.6 (m, 9H), 6.10 (s, 1H), 6.05 (d, J=16 Hz, 1H), 7.85 (d, J=16Hz, 1H), 5.64 (s, 1H), 2.00 (m, 2H), 1.72 (s, 1H), 1.65 (s+m, 5H), 1.49 (s+m, 5H), 0.99 (s, 6H) ; ^{13}C NMR (68 MHz, $CDCl_3$) δ 155.2, 140.7, 136.8, 136.5, 135.1, 131.1, 129.2, 128.2, 127.7, 124.8, 78.1, 39.4, 34.1, 32.7, 31.0, 28.7, 28.7, 21.3, 19.2.

Silane **17**:m.p. 173.5-174°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.7-7.5 (m, 6H), 7.45-7.25 (m, 9H), 6.32 (s, 1H), 5.76 (s, 1H), 2.2-1.3 (m, 14 H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 151.7, 136.6, 135.6, 130.9, 127.7, 78.7, 37.9, 36.1, 34.9, 32.9, 27.4, 26.6. IR (KBr) 3534, 3070, 2934-2849, 1589, 1424, 1103 cm^{-1}. MS (EI) m/z mass calc'd for $C_{30}H_{32}OSi$:436.2222. Found:436.2212 436(1%), 418(2%), 359(64%), 259(26%), 199(100%), 181(14%), 160 (16%).

Silane **19**:m.p.,140.0-141.0°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.8-7.6 (m, 6H), 7.6-7.3 (m, 9H), 6.42 (d, J=1Hz, 1H), 5.80 (d, J=1 Hz, 1H), 2.1-1.2 (m, 14 H), 1.32 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 152.3, 136.6, 135.7, 130.9, 129.3, 127.6, 35.8, 29.8, 27.4, 21.0, 20.3. IR (KBr) 3536-3518, 3064-2863, 1589, 1424, 1100 cm^{-1}; MS (C.I., NH_3) m/z calc'd for $C_{29}H_{32}OSi$: 424.2222. Found: 424.2221. 424(5%), 407(77%), 347(58%), 286(24%), 269(45%), 259(46%), 199(100%).

Silane **21**:m.p. 123-124°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.8-7.6 (m, 6H), 7.5-7.3 (m, 9H), 7.3-7.1 (m, 4H), 5.68 (d, J=1.2 Hz, 1H), 5.25 (d, J=1.2Hz, 1H), 2.75 (d, J=15.7Hz, 1H), 2.60 (d, J=15.7Hz, 1H), 2.06 (s, 1H), 0.88 (s, 3H), 0.81 (s, 3H) ; ^{13}C NMR (50 MHz, $CDCl_3$) δ 152.0, 149.4, 141.9, 136.9, 135.6, 133.1, 129.1, 127.8, 127.5, 127.0, 124.6, 123.9, 91.7, 48.7, 45.3, 24.7, 24.2. MS (EI) m/z mass calc'd for $C_{31}H_{30}OSi$:446.20658. Found:446.20630. 446(2%), 368(100%), 353(78%), 259(94%), 199(82%), 181(26%).

Silane **23**:m.p. 115.5-117°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.53-7.45 (m, 7H), 7.4-7.2 (m, 9H), 7.03 (s, 1H), 7.02 (s, J=1 Hz, 1H), 6.86 (m, 1H), 6.49 (s, 1H), 6.05 (s, 1H), 3.2 (m, 1H), 2.8 (m, 1H), 2.25 (s, 1H), 2.2-1.9 (m, 1H), 1.8-1.6 (m, 3H), 1.04 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 153.2, 142.0, 141.9, 136.6, 135.8, 132.9, 130.6, 129.1, 128.9, 127.4, 127.1, 125.0, 87.2, 43.4, 40.3, 36.1, 27.9, 25.7, 25.0. IR (KBr) 3563, 3068-2851, 1589, 1428, 1107, 1067, 914-975, 702 cm^{-1}. MS (EI) m/z mass calc'd for $C_{33}H_{34}OSi$:474.23788. Found:474.23540 474(1%), 445(3%), 396(13%), 313(15%), 259(52%), 199(100%).

Silane **25**:m.p. 98.5-99°C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.7-7.45 (m, 6H), 7.4-7.2 (m, 9H), 5.94 (d, 1.2Hz, 1H), 5.46 (d, 1.2Hz, 1H), 2.25 (m, 1H), 2.10 (m, 1H), 1.9-1.4 (m, 8H), 1.12 (s, 1H), 1.15 (s, 3H), 1.0 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 155, 136.6, 135.5, 129.22, 127.6, 126.9, 82.0, 51.4, 39.4, 38.2, 31.5, 28.3, 27.8, 25.0, 23.7. IR

(KBr) 3582, 3150-2865, 1588, 1426, 1105 cm^{-1}. MS (EI) m/z mass calc'd for $C_{29}H_{32}OSi$:424.22223. Found:424.22250 406(6.1%), 347(60%), 259(69%), 199(100%), 181(26%).

13. Spectroscopic data for the allenes **6**, **18**, **20**, **22**, **24**, **26**.
Allene **6**: ^1H NMR (200 MHz, $CDCl_3$) δ 5.93 (s, 2H), 4.78 (q, J=2.9Hz, 2H), 1.98 (m, 2H), 1.84 (t, J=2.9 Hz, 3H), 1.68 (s, 3H), 1.63-1.45 (s, 2H), 1.44-1.40 (m, 2H), 1.00 (s, 6H) ; ^{13}C NMR (68 MHz, $CDCl_3$) δ 211.7, 137.5, 130.7, 128.9, 126.1, 99.8, 74.2, 39.5, 34.2, 32.9, 28.9, 21.6, 19.3, 15.1 ; IR (film) 2962-2864, 1938 cm^{-1}; MS (EI) m/z calc'd for $C_{15}H_{22}$: 202.1721. Found: 202.1723. 204(21%), 202(38%), 187(23%), 159(27%), 145(37%), 133(100%), 119(74%).

Allene **18**: ^{13}C NMR (68 MHz, $CDCl_3$) δ 199.6, 108.6, 73.2, 38.5, 37.1, 34.6, 28.0. ^{13}C NMR (68 MHz, $CDCl_3$) δ 199.6, 108.6, 73.2, 38.5, 37.1, 34.6, 28.0. IR (film) 2914, 2849, 1964, 1446. Exact mass calc'd for $C_{12}H_{11}$:160.1252. Found:160.1255. MS (EI) m/e 160(100%), 150(41%), 117(55%), 105(27%), 91(52%), 79(45%).

Allene **20**: ^1H NMR (200 MHz, $CDCl_3$) δ 4.54 (m, 2H), 2.44 (m, 2H), 2.1-1.7 (m, 10H), 1.55 (m, 2H) ; ^{13}C NMR (68 MHz, $CDCl_3$) δ 199.6, 106.8, 72.8, 34.6, 32.5, 21.5; IR (film) 1963 cm^{-1}; IR (film) 2981-2847, 1963, 1446, 839 cm^{-1}; MS (EI) m/z calc'd for $C_{11}H_{16}$: 148.1252. Found: 188.1254. 148(31%), 133(20%), 119(19%), 105(50%), 91(100%), 79(74%).

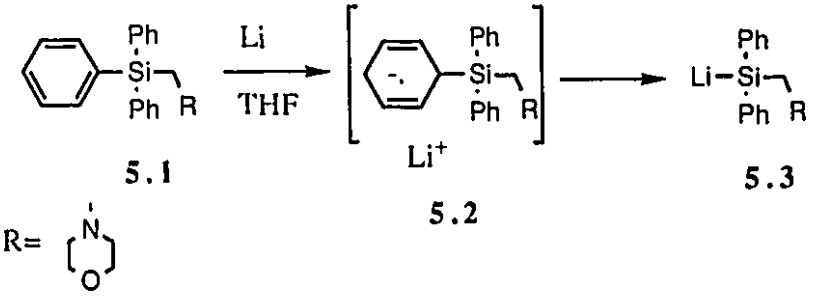
Allene **22**: ^1H NMR (200 MHz, $CDCl_3$) δ 7.3-7.15 (m, 4H), 5.22 (s, 2H), 2.90 (s, 2H), 1.29 (s, 3H), 1.28 (s, 3H) ; ^{13}C NMR (50 MHz, $CDCl_3$) δ 211.7, 137.5, 130.7, 128.9, 126.1, 99.8, 74.2, 39.5, 34.2, 32.9, 28.9, 21.6, 19.3, 15.1 ; IR (film) 3068-3019, 2960-2844, 1946, 1582, 1461, 853, 763, 721 cm^{-1}. MS (EI) m/z calc'd for $C_{13}H_{14}$: 170.1095. Found: 170.1088. 170(51%), 155(5%), 141(11%), 128(33%), 115(15%).

Allene **24**: ^1H NMR (200 MHz, $CDCl_3$) δ 7.2-7.1 (m, 4H), 4.86 (s, 2H), 2.79 (m, 2H), 1.84-1.72 (m, 2H), 1.70-1.62 (m, 2H), 1.08 (s, 6H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 206.1, 140.3, 138.2, 129.4, 128.5, 127.1, 126.0, 114.9, 75.2, 43.7, 35.1, 34.2, 28.7, 23.9 ; IR (film) 3062, 2962-2842, 1947, 1589, 1485, 841, 756 cm^{-1}; MS (EI) m/z calc'd for $C_{15}H_{18}$: 198.1408. Found: 198.1406. 198(63%), 183(60%), 169(17%), 155(100%), 141(99%), 128(82%), 115(60%).

Allene 26: ^{1}H NMR (260 MHz, $CDCl_3$) δ 4.56 (dd, 2.6, 5.3 Hz, 2H), 2.49-2.65 (m, 1H), 2.44 (t, 5.3Hz, 1H), 2.39-2.29 (m, 1H), 2.29-2.14 (m, 1H), 2.05-1.85 (m, 3H), 1.48 (d, 9.9Hz, 1H), 1.22 (s, 3H), 0.82 (s, 3H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 203.5, 103.5, 73.8, 47.6, 40.9, 40.1, 26.8, 26.0, 23.5, 21.9, 19.4. IR (KBr) 3261-2867, 1958, 1458 cm^{-1}; MS (EI) m/z calc'd for $C_{11}H_{16}$: 148.1252. Found: 148.1260. 148(4%), 133(64%), 105(100%), 91(55%), 79(35%), 77(18%).

5.4 Development of new silyl nucleophiles.

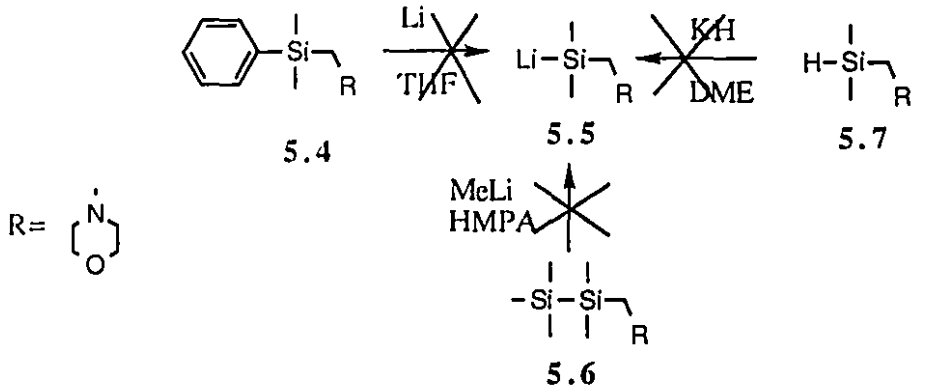
The development of silicon nucleophiles by Fleming[1] and other researchers[2] has led to the discovery of many new applications of organosilicon compounds in organic chemistry. Recently Tamao[3] has reported the use of the first silyllithium reagents substituted with heteroatoms (amines) starting from the corresponding chlorosilanes. We have been able to prepare aminomethyldiphenylsilyllithium via an alternative route. Reductive cleavage of the corresponding aminomethyltriphenylsilane **5.1** with lithium metal in THF[4] at room temperature for 6 hours led to the formation of the silyllithium **5.3** as a dark brown solution.



5.1 **5.2** **5.3**

Scheme 5.1.

The presence of the remaining phenyl groups on the silicon atom is essential for the reductive cleavage reaction to occur. This was demonstrated by reacting the phenyldimethylsilane **5.4** with lithium, sodium or potassium. No silyllithium **5.5** was formed under the reaction conditions used for the formation of **5.3**. We obtained only a complex mixture of products when the resulting reagents were hydrolyzed or reacted with allyl bromide.

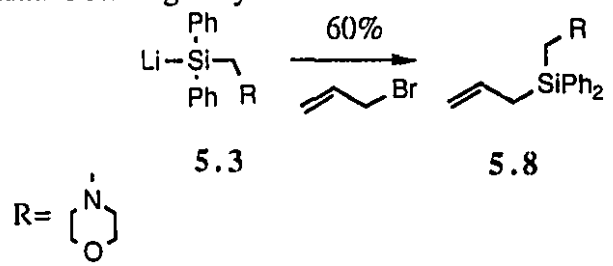


5.4 5.5 5.7

5.6

Scheme 5.2.

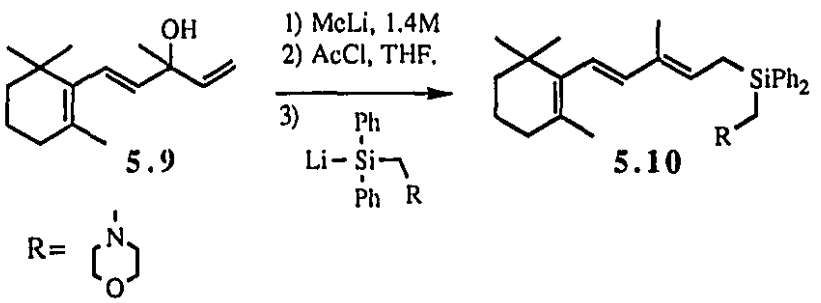
Use of the disilane **5.6** under Still's conditions[1b] or the silane **5.7** under Corriu's reaction conditions[5] did not yield the desired anion **5.5**. The synthesis of **5.6** and **5.7** is given in section 5.2. We were able to use silyllithium **5.3** and react it with allyl bromide to give the aminomethylsilane **5.8** in good yield.



5.3 5.8

Scheme 5.3.

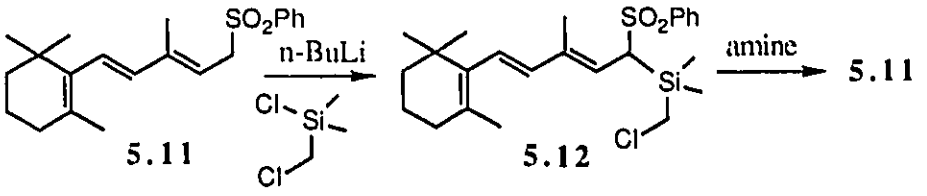
However when we tried to react the silyllithium **5.3** with the acetate **5.9** we were unable to isolate the expected allylsilane **5.10**. The use of copper cyanide did not give better results.



5.9 5.10

Scheme 4:

It should be mentioned that we had first tried the silylsulfone approach developed in chapter 3 (Scheme 5.5); unfortunately the amination of silylsulfone **5.12** only led to the formation of the desilylated starting material **5.11**.



Scheme 5.5.

5.5 Synthesis of allyl(aminomethyl)dimethylsilane via the hydrosilylation reaction.

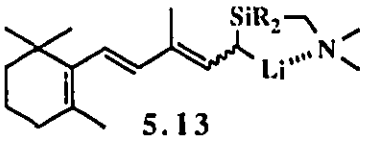
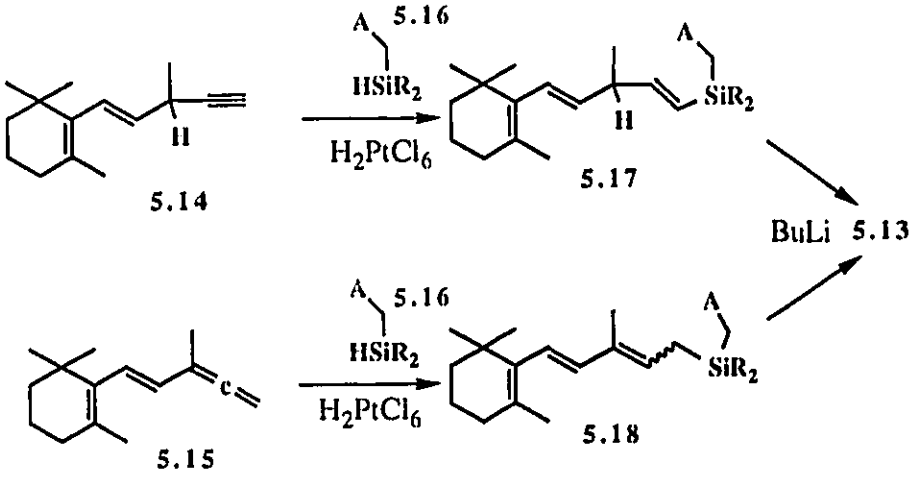


Figure 5.1.

As stated in section 5.1 the synthesis of allylsilanes having a chelating group attached to the silicon atom was of interest to this research. More precisely we wanted to prepare the lithium species **5.13** to see if it could be used as nucleophile in the synthesis of polyene compounds like retinoic acid and β-carotene. Following a series of unsuccessful attempts at the synthesis of the allylsilane **5.18** precursor of **5.13** (section 5.2), a new approach based on the hydrosilylation reaction (Scheme 5.6) was tried out.



A=Bis(methoxymethylene)amine.

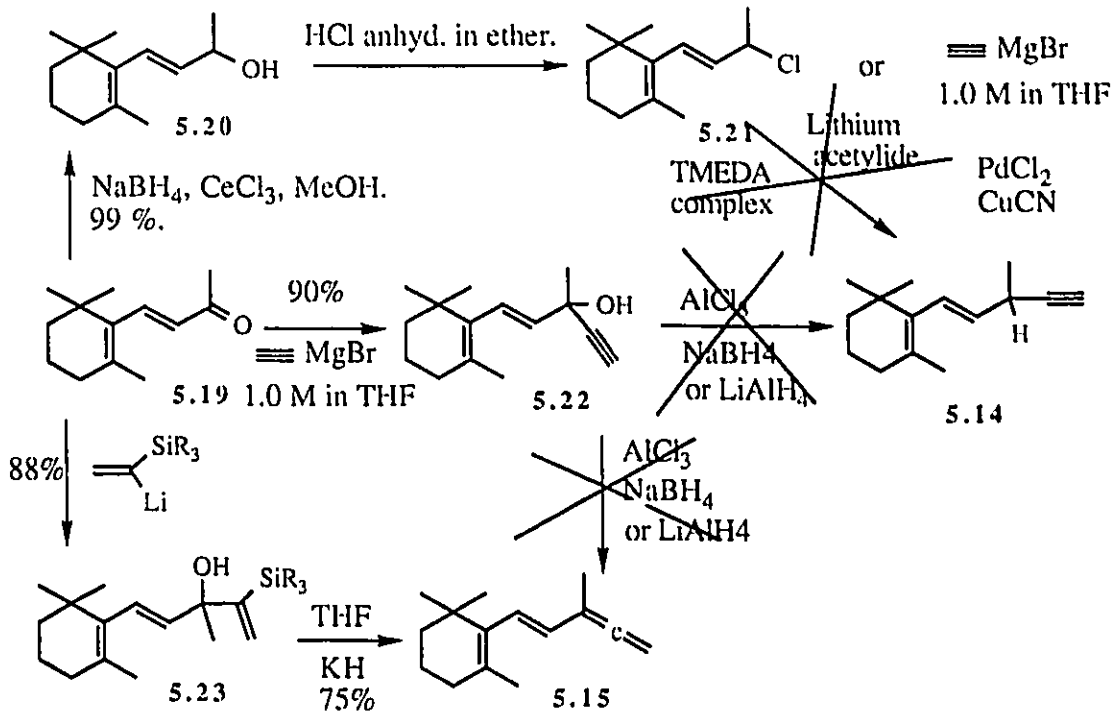
Scheme 5.6.

The first alternative involved the catalyzed hydrosilylation of terminal acetylene **5.14** to the vinylsilane **5.17**. This type of reaction has been shown to give *trans* vinylsilanes with good regioselectivities.[5] Only a few catalysts are known to give *cis* vinysilanes.[6] Silanes like **5.16** or chloromethyldimethylsilane have been shown to be stable in the presence of hexachloroplatinic acid. Unlike palladium catalysts which rearrange α-substituted silanes very rapidly.[8]

Lukevics *et al.*[9] have used silanes substituted with an amino group in screenings of catalysts for the regioselective hydrosilylation of terminal acetylenes. Hexachloroplatinic acid like other platinum based catalysts, have been shown to give good yields and regioselectivities in these trials.

Alternatively allenes like **5.15** could be used to see if the hydrosilylation reaction (catalyzed by hexachloroplatinic acid) would lead to the formation of allyl silane **5.18**. Both vinylsilane **5.17** and allylsilane **5.18** could be used for the generation of **5.13**.

The problem at this point was the synthesis of the starting material acetylene **5.14** or allene **5.15**. Starting from β-ionone, we had access to the alcohol **5.20** through reduction with sodium borohydride cerium chloride under the Luche reaction conditions.[10] Halogenation of the alcohol **5.20** with anhydrous hydrochloric acid in ether gave the allyl chloride **5.21**. Reacting this halide with lithium acetylide/TMEDA complex under a variety of reaction conditions (neat, in DMSO, CuCN, $PdCl_2$) or with the corresponding Grignard never produced any acetylene **5.14**. Reaction of β-ionone with magnesium bromide acetylide gave the acetylene **5.22**. Under reductive reaction conditions (LAH and $AlCl_3$)[11] **5.22** did not give the acetylene **5.14** or the allene **5.15**. Finally reaction of β-ionone with lithio-α-trimethylvinylsilane gave alcohol **5.23** in good yield (88%) under the general reaction conditions by Chan and Michajlowskij.[12] The alcohol **5.23** did not eliminate to the allene **5.15** under the the general reactions conditions specified by Chan and Michajlowskij. Compound **5.23** was unstable under halogenation reaction conditions and gave complex mixtures of products, something the authors had already observed when this methodology was applied to alcohols having labile β-hydrogen atoms.[12] When **5.23** was reacted with KH under the reaction conditions described in section 5.4 of this chapter we obtained the desired allene product **5.15** in good yield (75-78 %).

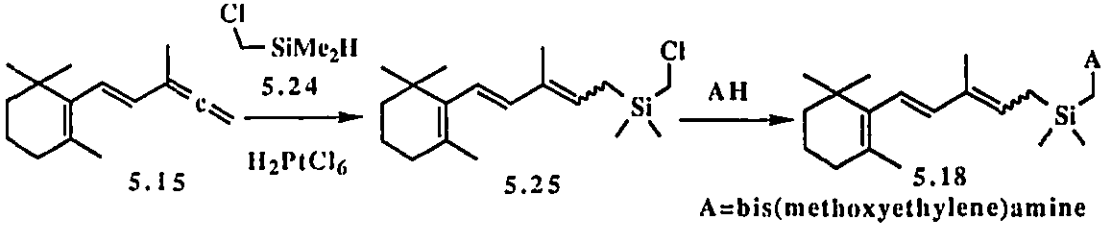


Scheme 5.7.

The hydrosilylation of allenes has only one literature precedent. The paper in question contains little experimental details, but indicated that the reaction was possible.[13] Nevertheless our first trials at the hydrosilylation of the allene **5.15** with neat aminosilane **5.16** prepared in section 5.2 were unsuccessful when used with hexachloroplatinic acid catalyst. Furthermore, hydrosilylation of 1-heptyne under the same reaction conditions did not yield any of the corresponding vinylsilane either. Trials of different catalysts and reaction conditions using 1-heptyne as model showed that solvents like dichloromethane or dichloroethane, which are able to dissolve amine hydrochlorides, were essential to this reaction. Also the reaction gave the best results when hexachloroplatinic acid was dried under vacuum at 100°C. Unfortunately these new reaction conditions have yet to be tried on allene **5.15**.

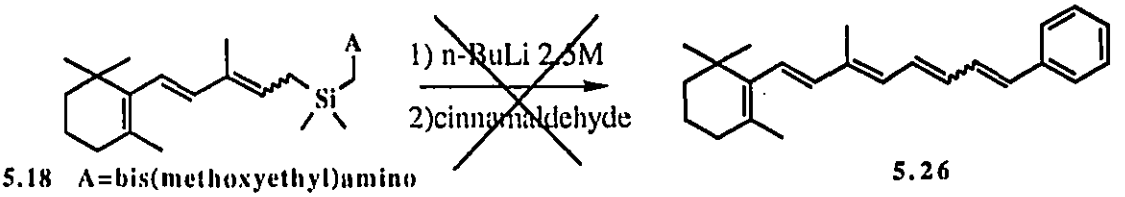
The aminomethylallylsilane **5.18** was eventually prepared via hydrosilylation of allene **5.15** with dry hexachloroplatinic acid as catalyst in neat (chloromethyl)dimethylsilane **5.24** to give 1:1 cis:trans mixture of allylsilane **5.25** (Scheme 5.8). The allyl(chloromethyl)dimethylsilane **5.25** was then heated (110°C) in the presence of 3

equivalents of the desired anhydrous amine for 48 hours and flash chromatography gave compound **5.18**.



Scheme 5.8.

Results from preliminary trials (Scheme 5.9) have revealed that allylsilanes **5.18** was indeed easier to deprotonate than previous allylsilanes not bearing the amino **A** complexing group. However, condensation of the corresponding anion with cinnamaldehyde did not lead to any formation of polyene **5.26**. Further studies on the reaction conditions will be required to establish if allylsilane **5.18** can be used in the synthesis of retinoids.



Scheme 5.9.

5.6 Experimental.

The synthesis or spectral characteristics of compounds **5.9, 5.11, 5.12** have been reported or referenced to in chapter 2. Compounds **5.4, 5.6, 5.7,** have been prepared in section 5.2 of this chapter. Preparation of compound **5.22** has been reported in the litterature.[14] We reported the preparation of allene **5.15** in section 5.3 of this chapter. (Chloromethyl)dimethylsilane was purchased from Petrarch. The drying procedures, spectroscopic instruments and services used are the same ones that were described in chapter 2.

1) N-(Morpholinomethyl)triphenylsilane **5.1**.

N-(Morpholinomethyl)triphenylsilane was prepared in two steps. A solution of phenyllithium [1.8 M in cyclohexane-ether (47.1 ml, 0.084 mol)] was slowly added to (chloromethyl)trichlorosilane (5.0 g, 2.7 mmol) dissolved in 100 mL of THF maintained at -78°C. The reaction mixture was warmed to room temperature and stirred 24 hours. 50 mL of hexanes and 10 mL of water were added to the reaction mixture. The organic layer was separated, washed with distilled water and brine. After drying over $MgSO_4$, the solvent was evaporated leaving a yellow oil. Kugelrohr distillation (170-180°C / 0.5 mmHg) gave 4.1 g (50%) of a white solid (chloromethyl)triphenylsilane. An analitical sample was obtained by recrystallization in a 3:1 hexanes:ether solvant mixture giving transparent cubic crystals.

m.p. 109-110 °C.
^{1}H NMR (200 MHz, $CDCl_3$) δ 7.70-7.60 (m, 6H), 7.62-7.39 (m, 9H), 3.58 (s, 1H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 135.8, 132.3, 130.2, 128.0, 27.7. IR ($CHCl_3$) 3137-2700, 1590, 1429, 1191, 912. MS (EI) m/z calc'd for $C_{19}H_{17}SiCl$: 308.0788. Found: 308.0779. MS (CI, NH_3) m/z 326 (5%), 276 (55%), 259 (100%), 181(17%).

(Chloromethyl)triphenylsilane (1.0 g, 3.2 mmol) was dissolved neat in 3.0 eq. of morpholine (0.9 g, 10 mmol). The reaction mixture was heated at 140°C for 36 hours in a sealed tube. The brown reaction mixture was extracted with 50 mL of ether and 30 mL of distilled water. The organic layer was washed 3x with distilled water then brine. Evaporation of the solvent gave 0.9 g (78%) of a yellow solid compound silane **5.1**. A pure sample was provided by recrystallization in ether (evaporation) as a white powder.

m.p. 97-100°C
^{1}H NMR (200 MHz, $CDCl_3$) δ 7.65-7.57 (m, 6H), 7.50-7.30 (m, 9H), 3.66 (m, 4H), 2.74 (m, 2H), 2.42-2.32 (m, 4H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 135.8, 134.8, 129.6, 127.8, 67.2, 57.5, 48.3. IR ($CHCl_3$) 3137-2700, 1600, 1426, 1290, 1112. MS (EI) m/z calc'd for $C_{11}H_{16}$: 359.1705. Found: 359.1721. 359 (16%), 259 (21%), 100 (100%).

2) Allyl-N-(morpholinomethyl)diphenylsilane **5.8**.

N-(Morpholinomethyl)triphenylsilane (0.050 g, 0.15 mmol) was dissolved in 2 mL of dry THF. Lithium metal (0.050 g, 7 mmol) was added and pressed against the walls of

the flask to expose a fresh surface. After flushing with argon, the reaction flask was sealed using a septum and the mixture was left to react during 24 hours, during that time the reaction mixture turned brown. Allyl bromide (0.1 mL, 0.55 mmol) was added neat to this solution at 0°C. The liquid reaction mixture was then transfered into a Erlenmeyer containing ether and a solution of conc. NH_4Cl in water. The organic phase was washed with distilled water, dried over $MgSO_4$ and the solvent was evaporated leaving a yellow oil. Flash chromatography of this residue using a 70:30, hexanes: ethyl acetate as eluent mixture provided 0.027 g (60%) of a yellow oil, allyl silane **5.8**. (85% pure)

rf=0.54 (70:30 hexanes:EtOAc)
^{1}H NMR (200 MHz, $CDCl_3$) δ 7.65-7.25 (m, 15 H), 5.95 (m, 1H), 4.95 (m, 2H), 3.62 (m, 4H), 2.52 (s, 2H), 2.34 (m, 4H), 2.19 (d, J= 16.1 Hz, 2H).

3) β-Ionol **5.20**.

Reduction of β-ionone with $NaBH_4$ in methanol gave β-Ionol contaminated with 1,4-reduced product (20%). This side reaction was completely suppressed by the addition of cerium chloride hydrate to the $NaBH_4$ in methanol. $NaBH_4$ (0.2 g, 5.5 mmol) with cerium chloride hydrate (2.1 g, 5.5 mmol) were dissolved in 50 mL of dry methanol, β-ionone (1.0 g, 5.5 mmol) in 5.0 mL of dry methanol was then added to this solution. After stirring for 10 min., the methanol was evaporated and the residue was extracted with ether and distilled water. After separation, the organic phase was dried over $MgSO_4$ and the solvent was evaporated leaving 1.0 g (99%) of pure β-ionol which did not need further purification.

^{1}H NMR (200 MHz, $CDCl_3$) δ 6.04 (d, J=16.0 Hz, 1H), 5.48 (dd, J=6.7, 16.0 Hz, 1H), 4.35 (quint, J= 6.4 Hz, 1H), 1.96 (m, 2H), 1.65 (m, 5H), 1.63-1.38 (m, 4H), 1.30 (d, J= 6.4 Hz, 3H), 0.97 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6, 136.6, 128.8, 127.5, 69.5, 39.4, 33.9, 32.7, 28.7, 23.6, 21.3, 19.2.

4) β-Ionyl chloride **5.21**.

β-Ionol (0.10 g, 0.5 mmol) was dissolved in 1 mL of dry ether and anhydrous HCl 1M in ether (10 mL, 10 mmol) was then added to this solution at 0°C. This reaction mixture was stirred at this temperature for 3 hours. The solvent was then evaporated under vacuum between 10-20°C, giving 0.11 g (100%) of the crude chloride **5.21** which was used without purification.

^{1}H NMR (200 MHz, $CDCl_3$) δ 6.10 (d, J=14.5 Hz, 1H), 5.48 (dd, J=6.5, 14.5 Hz, 1H), 4.61 (quint, J= 6.5 Hz, 1H), 1.98 (m, 2H), 1.67 (s, 3H), 1.65 (d, J= 6.5 Hz, 3H), 1.60 (m, 2H), 1.45 (m, 2H), 0.97 (s, 3H), 0.95 (s, 3H).

5)1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-3-methyl-5-(chloromethyl)dimethylsilyl-penta-1,3-diene **5.25**.

The allene **5.15** (0.17 g, 0.8 mmol) was dissolved in chloromethyldimethylsilane (0.5 mL, 4 mmol) and dry hexachloroplatinic acid (dried over vacuum 100°C, 0.0002g, 4 x 10^{-6} mol) was added. The reaction was refluxed for 1 min. at which point the reaction mixture turned brown. 0.1 mL of morpholine was added and the excess (chloromethyl)dimethylsilane was immediately evaporated over the vacuum pump. The residue was separated on silica gel column using hexanes as the eluent. We isolated 0.22 g (77%) of a 1:1 mixture of isomers of allylsilanes **5.25** with 0.03 g of an unknown nonpolar compound.(may be a reduction product).

^{1}H NMR($CDCl_3$, 200 MHz) δ **Cis isomer**: 6.34 (d, J=16.1 Hz, 1 H), 6.41 (d, J=16.1 Hz, 1 H), 5.34 (t, J=9.0 Hz, 1 H), 2.79 (s, 2H), 1.88 (s, 3H), 1.71 (s, 3H), 1.49 (m, 2H), 1.03 (s, 6H), 0.13 (s, 3H). **Trans isomer**: 6.60 (d, J=15.5 Hz, 1 H), 5.72 (d, J=15.5 Hz, 1 H), 5.45 (t, J=9.2 Hz, 1 H), 2.80 (s, 2H), 2.01 (m, 2H), 1.76 (s, 3H), 1.73 (s, 3H), 1.65 (m, 2H), 1.95 (m, 2H), 1.03 (s, 6H), 0.15 (s, 3H). ^{13}C NMR($CDCl_3$, 50MHz) δ 137.2, 137.1, 132.4, 130.5, 129.4, 127.7, 127.6, 126.1, 126.0, 125.1, 123.0, 122.5, 40.0, 39.9, 34.7, 34.6, 33.5, 33.4, 30.5, 29.5, 29.4, 22.4, 22.3, 21.3, 20.0, 17.3, 16.4, 13.0, -3.6, -3.8. MS(EI) m/z cal'd for $C_{18}H_{31}SiCl$: 310.1883, found: 310.1886. 310 (50%), 295 (9%), 133 (53%), 119 (100%), 107 (58%), 79 (66%).

6)1-(2,6,6-Trimethyl-1-cyclohexen-1-yl)-3-methyl-5-[N-bis(methoxymethylene)aminomethyl]dimethylsilyl-penta-1,3-diene **5.18**.

The allylsilane **5.25** (0.17 g, 0.6 mmol) was added neat to dry bis(methoxymethylene)amine (1 mL, 7.5 mmol). This mixture was heated to 110°C and stirred at this temperature for 48 hours. 20 mL of ether with 10 mL of distilled water were added to the reaction mixture. After separation, the organic phase was washed twice with distilled water and once with brine, then dried over $MgSO_4$. The solvent was evaporated

leaving 0.18 g of residue. Separation by flash chromatography using a 8:2 hexanes:ethyl acetate as eluent, gave 0.07 g (32 %) of compound **5.18**, a yellow oil.

^{1}H NMR($CDCl_3$, 200 MHz) δ **Cis isomer** 6.32 (d, J= 16.1 Hz, 1H), 6.02 (d, J=16.1 Hz, 1H), 5.36 (t, J= 8.9 Hz, 1H), 3.44 (t, J= 6.2 Hz, 4H), 3.33 (s, 6H), 2.65 (t, J=6.2, 4H), 2.08 (s, 2H), 1.95 (m, 2H), 1.73 (s, 3H), 1.60 (s, 3H), 1.55 (m, 2H), 1.42 (m, 2H), 1.01 (s, 6H), 0.05 (s, 3H). **Trans isomer** 6.02 (d, J= 16.1 Hz, 1H), 5.87 (d, J=16.1 Hz, 1H), 5.48 (t, J=8.8 Hz, 1H), 3.44 (t, J= 6.2 Hz, 4H), 3.33 (s, 6H), 2.65 (t, J=6.2, 4H), 2.10 (s, 2H), 1.95 (m, 2H), 1.69 (s, 3H), 1.67 (s, 3H), 1.60 (s, 3H), 1.55 (m, 2H), 1.42 (m, 2H), 1.01 (s, 6H), 0.07 (s, 3H). MS(EI) m/z cal'd for $C_{24}H_{45}SiNO_2$: 407.3219, found: 407.3224. 407 (2%), 392 (1%), 362 (11%), 204 (100%), 146 (22%), 59 (17%).

5.7 References.

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CHAPTER 6.
NEW RETINOIC ACID ANALOGS

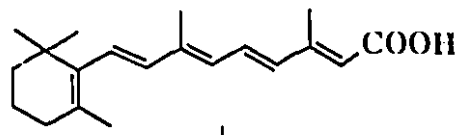
6.1. Introduction.

The present chapter deals with the synthesis and biological activities of new aromatic retinoic acid analogs. The present research was carried out as part of a cooperative project between the department of oncology and the department of chemistry at McGill University. The biological activity determination of the analogs was carried out by Dr. A. Haggarty on the P19 cell line and by Mr. S. Damian on the HL-60 cell line. Tables 3 and 4 of the next section resulted from their biological evaluations. X-ray crystallography and resolution of the crystalline structures, given in this section, were done by Dr. R. Hynes.

6.2. Some aromatic analogs of retinoic acid.

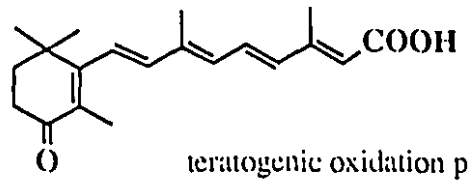
Retinoic acid has been shown to be involved in morphogenesis during the development of the embryo (chick and other mammals)[1]. It was also shown useful in the treatment of leukemia, skin, head and neck cancers[2,3]. Retinoic acid influences cancer cell (promyelocytes in the case of HL-60) into stopping their proliferation and to mature to a more advanced developmental stage in their differentiation process [3]. Thus a retinoic acid therapy offers the possibility of cancer treatment at the cellular level.

Retinoic acid and it's analogs have a wide range of effects on cellular processes, which they modulate through the activation of two different classes of nuclear receptors proteins, the retinoic acid receptors (RARs) and the retinoid X receptors (RXRs). These two types of receptors are then divided in three subtypes named α, β, γ. All these receptors belongs to the steroid/thyroid hormone receptor superfamily. The RXR and RAR receptors bind differently to retinoic acid isomers and they activate different sets of genes. Thus development of new retinoids with higher selectivity for one of these receptor's might result in fewer side effects in therapeutic applications.[4a]



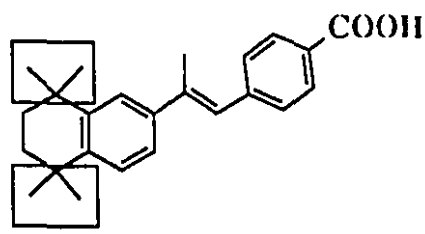
A

liver oxidation



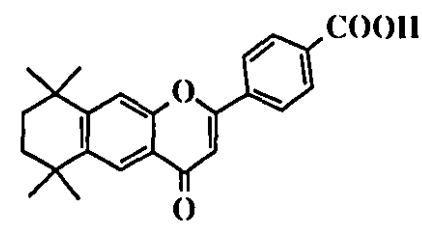
B

teratogenic oxidation product.[6]



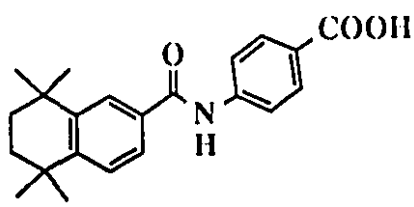
C

☐ Oxidation sites blocked by the gem dimethyl groups.[8]



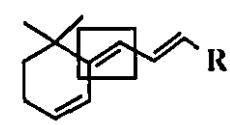
E

27 times more active than RA.[9]



D

Same characteristics towards oxidation as C but D has the possibility to be cleaved at the amide bond for easy elimination by the body.[9]



☐ F

No study on activities of retro-retinoids general structure F, except one report of activity of a diol.[10] Studies on ring size effect limited to five member ring analogs and few studies on steric requirement of lower portion of molecule in the receptor. $R=(X)_nCOOH$

Figure 6.1: Some examples of new active retinoic acid analogs compared to the retroretinoid structure F.

Keeping in mind the numerous discoveries mentioned earlier it is important to underline that this field is in development and that there are serious drawbacks to the use of

retinoic acid in clinic. Recent advances at the chemistry level to make the retinoic acid derivatives more active, less toxic and more easily eliminated by the patient are impressive [5,6]. Some examples of new active retinoic acid analogs are given in Figure 6.1.

The present study was initiated to find new structures with the hope of gaining informations at the receptor level and possibly discriminating between cellular receptors. [5]

Recently, researchers have started to look at the conformational effects on the retinoid receptor selectivity.[4a,b,c] Following the same general idea, we decided to build retinoic acid analogs having different conformational possibilities when compared to retinoic acid. For example, rotation about any of the carbon-carbon single bond along the unsaturated side chain of retinoic acid will lead to conformers with the carboxylic group pointing upward; the only way to get this group pointing downward is to isomerize one of the carbon-carbon double bonds. (Figure 6.2).

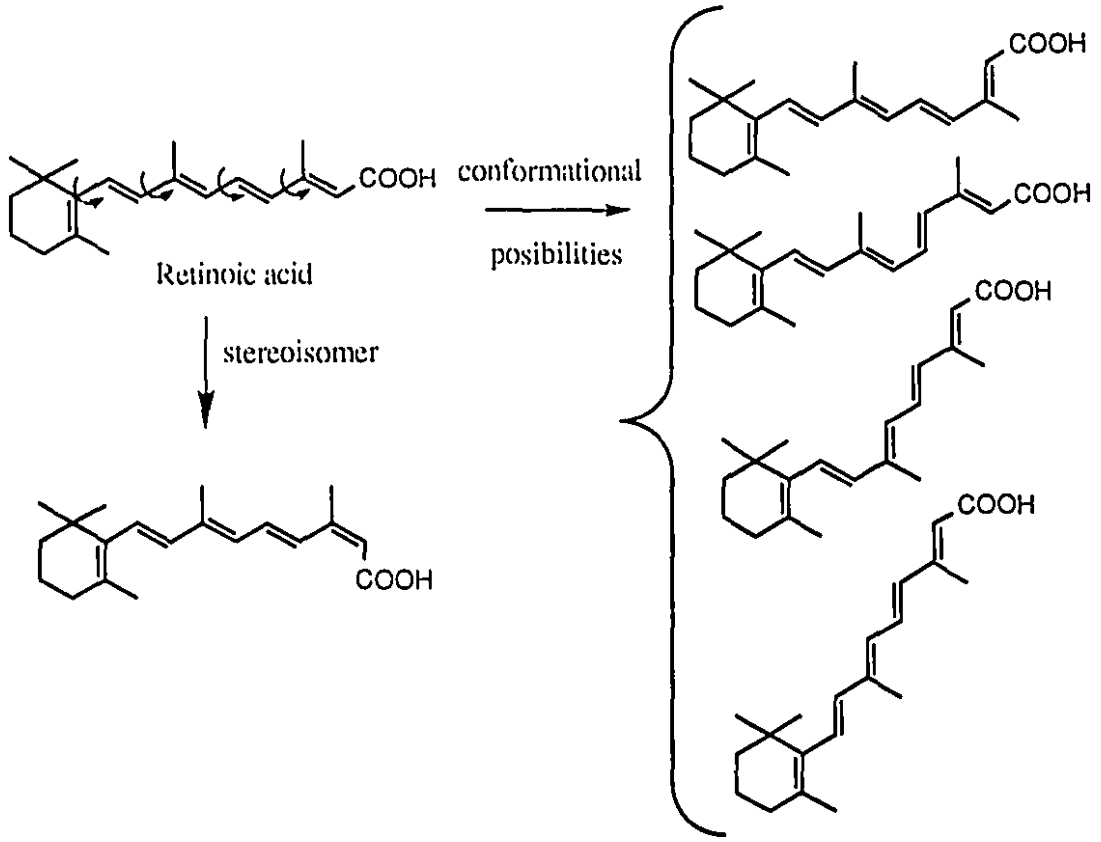


Figure 6.2: Some of the conformers of retinoic acid.

Choosing a retro-retinoid type of structure on which to base our analog series gave us access to the complementary conformational possibilities at C9. This type of analog could be superimposed on the all-*trans* -retinoic acid structure and on the 9-*cis* -retinoic acid structure (if the substitution is correct), and by changing the substituents it can also be superimposed on the 11-*cis* -retinoic acid structure.(Figure 6.3).

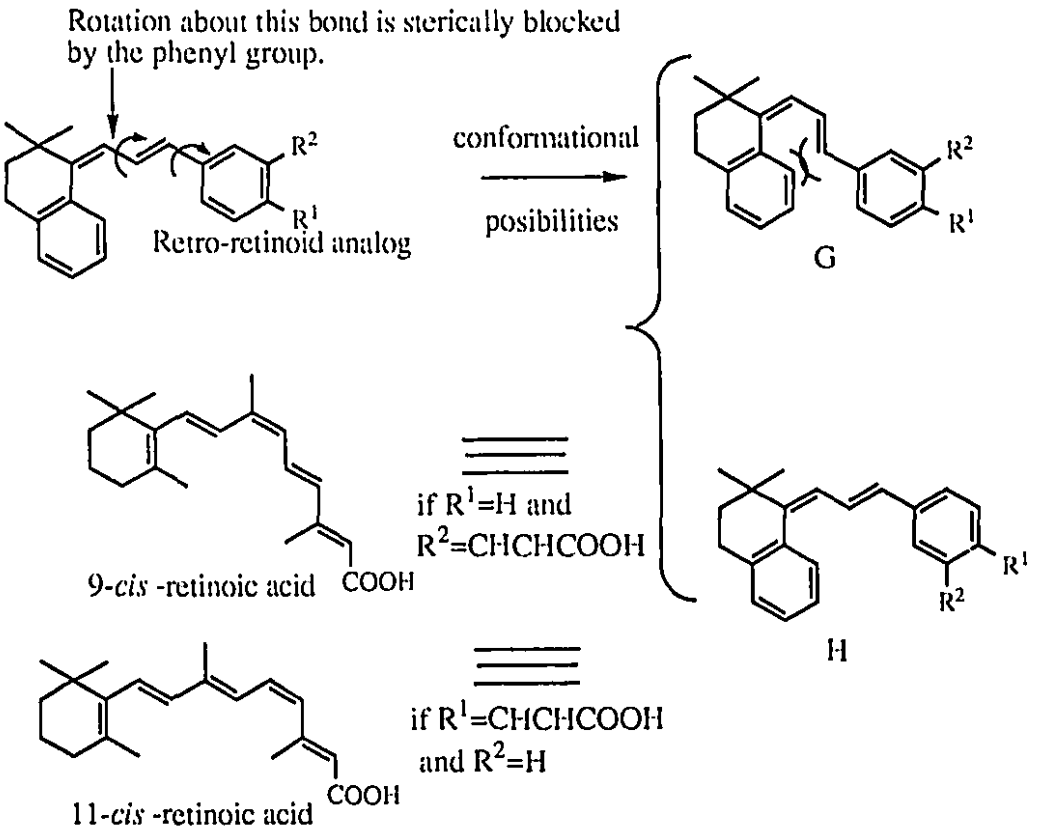
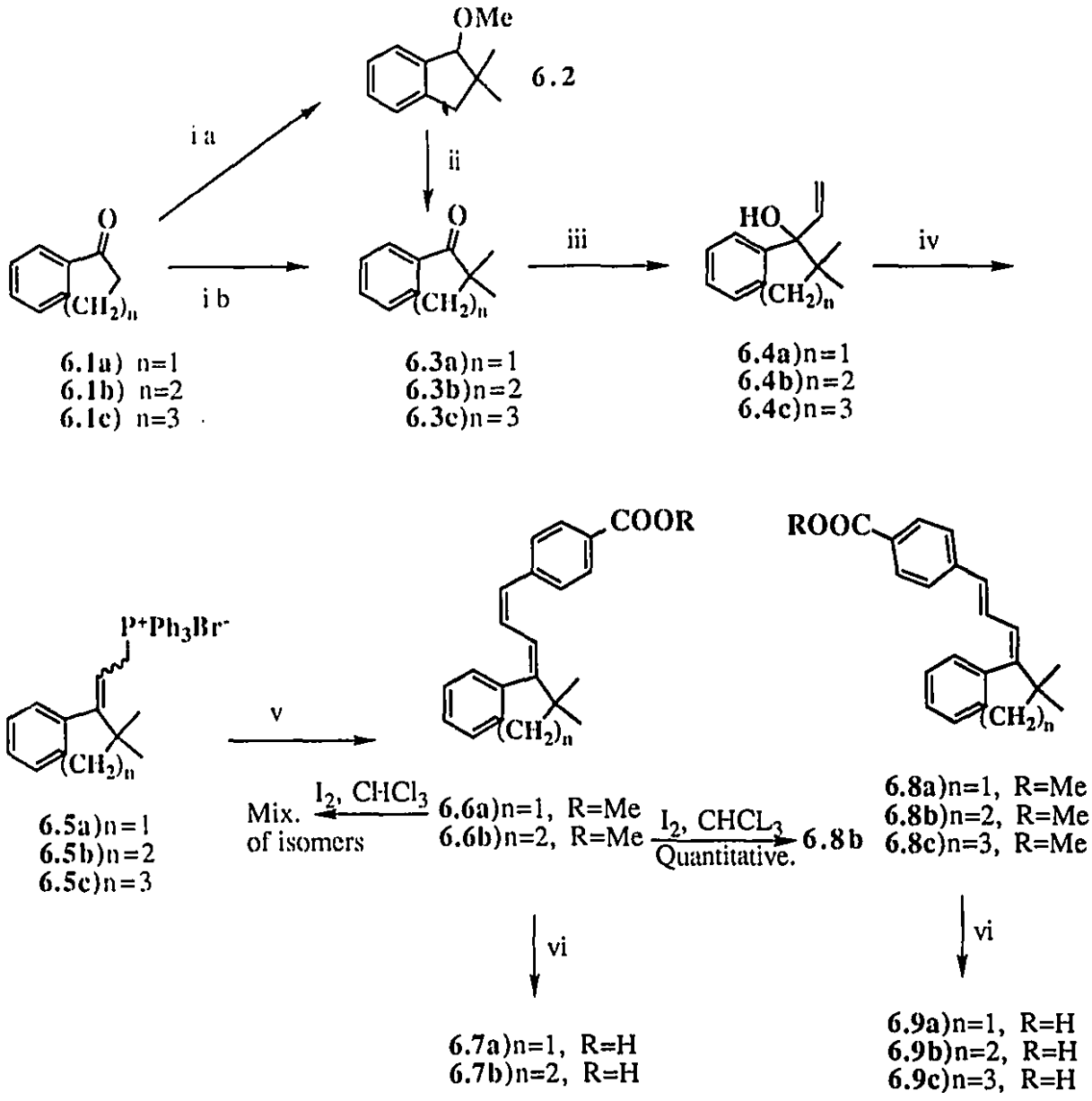


Figure 6.3: two conformational possibilities of the retro analogs and comparison with the retinoic acid isomers.

First the synthesis of the shorter analogs (among the retro structures given in Fig. 6.3) was tried to see if any of them would be an active differentiating agent of the HL-60 cell line. We also studied the effect of modifying the ring size of the alicyclic portion on these molecules.



Scheme 6.1 : Synthesis of retinoids with a 5-7 membered ring.

i) a) >2 eq. KH, b) only 2 eq. KH:DME then MeI, ii) $Ce(NO_3)_2(NH_3)_2$, $KBrO_3$, acetonitrile:water, reflux. iii) Vinylmagnesium bromide 1.0M THF room temp. iv) $P(Ph)_3HBr$, Methanol, room temp. 24H. v) Mixture **6.5** dissolved in THF, -78°C *s* -BuLi 1.3M in c-hexane, methyl 4-formylbenzoate. vi) The ester was dissolved in methanol, conc. NaOH, room temp. 24H; conc. HCl.

The acids **6.7a,b** and **6.9a-c** were synthesized using the route described in Scheme 6.1. The starting aromatic ketones **6.1a-c** were dimethylated using potassium hydride in dry dimethoxyethane. Quenching the enolates with methyl iodide gave the gem dimethylated ketones **6.3b-c** and the ether **6.2**, in the case of the alkylation of indanone. This intermediate **6.2** gave the desired ketone **6.3a** upon oxidation with ceric ammonium nitrate in the presence of potassium perbromate. The ketones **6.3a-c** gave the corresponding vinyl alcohols **6.4a-c** upon reaction with 2 eq. of vinylmagnesium bromide (1.0 M in THF) at room temperature. Reaction of these vinyl alcohols with triphenylphosphonium hydrogen bromide in methanol at room temperature for 48 hours gave the corresponding phosphonium salts **6.5a-b**.[7] These mixtures were reacted without prior purification with *s* -butyllithium 1.3M in c-hexane and then with methyl 4-formylbenzoate at -78° for 30 min. The isolated esters **6.6a-c** and **6.8a-c** were hydrolysed in methanol with sodium hydroxide (some isomerization may occur) or preferably in dioxane:water with lithium hydroxide to give the corresponding acids **6.7a-c** and **6.9a-c**.

The synthesis and condensation of the Wittig reagents **6.5a-c** with aldehydes can yield four isomeric dienes having the Z,E; Z,Z; E,Z and E,E configurations (Figure 6.4).

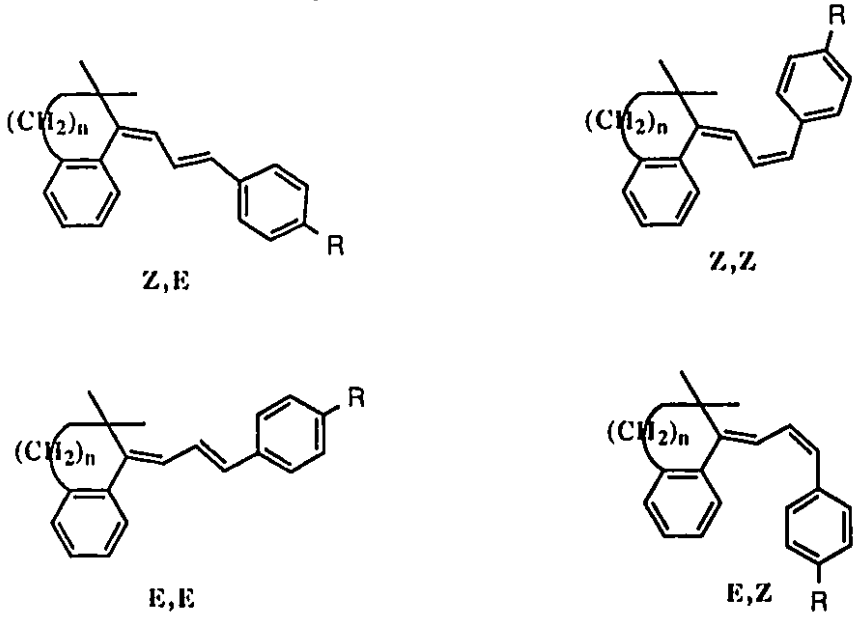
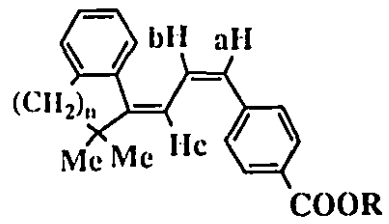


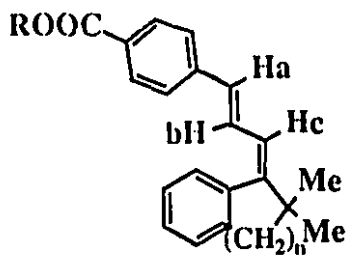
Figure 6.4: Possible isomers formed after reaction of methyl 4-formylbenzoate with Wittig reagents **6.5a-c**.

Determination of double bond configuration.



Series	(Hz) $J_{a,b}$	(Hz) $J_{b,c}$	Spin System	NOE Me-H_c	Other
6a	11.4	11.4	ABX	-	X-Ray
6b	10.6	10.6	ABX second order.	10%*	-

Table 6.1: Structural characterization of the new retinoids.
*inconclusive.



Series	(Hz) $J_{a,b}$	(Hz) $J_{b,c}$	Spin System	NOE Me-H_c	Other
8a	15.2	11.2	ABX	13.7%	-
9b	15.3	10.8	ABX	5%	X-Ray
9c	15.3	10.8	ABC	9%	-

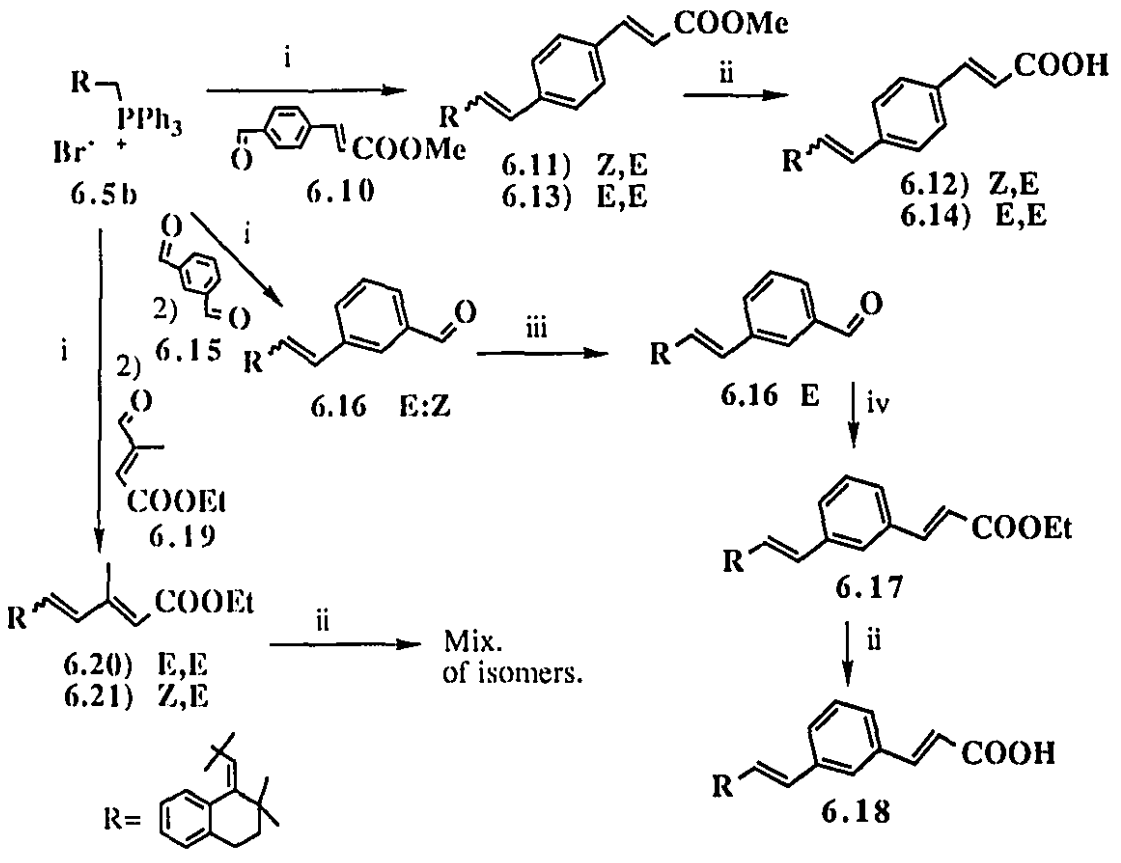
Table 6.2: Structural characterization of the new retinoids.

The identification of the products obtained was made possible by ^{13}C, ^{1}H NMR spectroscopy and X-ray crystallography. The determination of the configuration of the disubstituted double bond was made by measuring the coupling constants between the protons a and b (see Tables 6.1 and 6.2). The determination of the configuration of the other double bond was determined using the nuclear Overhauser effect between the gem dimethyl protons and the nearest vinyl proton c . The results were confirmed by X-ray crystallography when possible. The values from these experiments are tabulated in Tables 6.1 and 6.2.

All the configurations of structures **6.6a** to **6.9c** were confirmed in this way except for compounds **6.6b** and **6.7b** where the protons b and c are overlapped in their ^{1}H NMR, thus making their structure determination impossible by NOE. The proposed Z,Z diene structure was based on the coupling constants of protons a and b and the comparison of their ^{13}C NMR spectra (the gem-dimethyl substituted quaternary carbons have almost identical chemical shifts at 36.7 and 36.3 ppm).

Keeping the same bicyclic system (series b), we synthesized the retinoic acid analogs **6.12, 6.14** and **6.18** having an extended side chain approximating the 9- or 11- *cis* and all-*trans* retinoic acid isomers(Scheme 6.2.2).

The Wittig reagent **6.5b** underwent condensation reaction with the carboxyaldehydes **6.10, 6.15** and **6.19**, which eventually yielded compounds **6.12, 6.14, 6.18, 6.20, 6.21** through the reactions described in Scheme 6.2. The structure of these compounds were confirmed by ^{1}H and ^{13}C spectroscopy and by comparison with the spectral data obtained for the compounds of the **6.8** and **6.9b** series. These compounds were tested along with the compounds synthesized earlier. The results from the exposure of HL-60 and P19 culture cells to these retinoids are given in Tables 6.3 and 6.4.



Scheme 6.2: Synthesis of analogs with modified side chains. i) Compound **6.5** was dissolved in THF and *s* -BuLi (1.3M in c-hexane) was added at -78°C, stirred 6 hours, aldehyde. ii) The ester was dissolved in methanol, 5 drops of conc. NaOH solution were added, room temp. 24 hours; Conc. HCl. iii) I_2, $CHCl_3$. iv) $KCH[PO(OC_2H_5)_2]COOC_2H_5$, THF room temp. 30 min.

Retinoids	% Diff. at 1μM	$ED_{50}(10^{-9}$ M).
All-*trans* -Retinoic acid	91	3
6a	84	50
7a	85	40
8a	96	11
9a	91	13
6b	i	i
7b	i	i
8b	i	i
9b	45	>1000
8c	22	>1000
9c	95	10
12	28	>1000
14	27	>1000
18	i	i
20	i	i
21	i	i

Table 6.3: results from the differentiation of HL-60.

i) The differentiation observed at 1 μM was not significant or was absent.

Retinoids	% aggregates with neurites at 1μM.
All-*trans* -Retinoic acid	82
7a	72
8a	70
9a	75
9b	50
9c	84
14	75
18	45

Table 6.4 : results from the differentiation of the P19 cells.

In the case of HL-60 (human promyelocytic white cells) the response to the retinoic acid analogs was measured by counting the cell that are colored blue by the nitroblue tetrazolium (NBT) dye and calculating the ratio of colored to non colored cells.[11] The P19 (mouse embryonal carcinoma cells) are differentiated to neurons in the presence of retinoic acid, thus a ratio of cell having neurites to cell without neurites can be used to estimate the potency of an analog.[12] The cells were exposed to the retinoids analogs for 4 days (HL-60) and for 6-8 days (P19) before estimating the extent of differentiation. The retinoids analogs were tested along with retinoic acid which was used as a positive control. The results reported in table 3 and 4 show the respective activities of the most active retinoic acid analogs at 1 μM concentration and lower concentrations were used to calculate the ED_{50}.

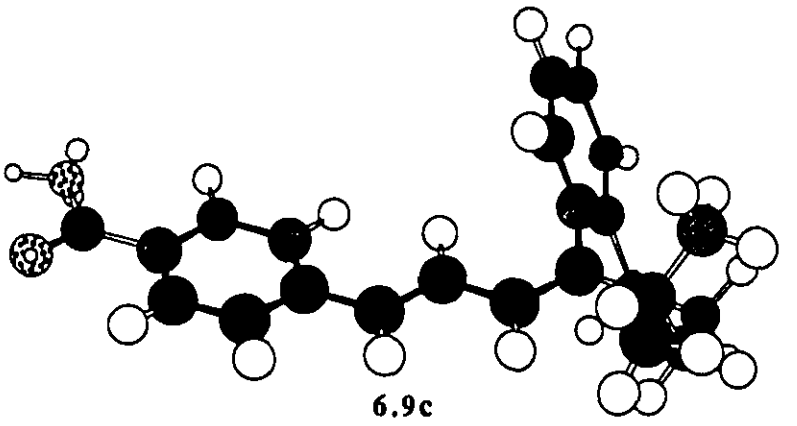
The results from Tables 6.3 and 6.4 show that modifying the ring size at the lipophilic end of the retinoic acid analogs has an important effect on the potency of these compounds. We can see that the seven membered ring compound **6.9c** and the five membered ring compounds **6.7-6.9a,** all showed activities approaching that of retinoic acid. However the six membered ring analog **6.6-6.8** series **b** all showed low to no activity in the HL-60 screenings. Some rationalization could be found for a higher activity of the five membered ring analogs, when compared to the six membered series. The five membered ring system is more planar and more rigid than the six membered analogs (Figure 6.5). Better biological activity could be related to an increased in planarity or conformational rigidity of the five membered ring retinoic acid analogs (see Figure 6.1). However this rationalization falls short with the seven member ring analogs which cannot be planar due to ring strain and should exhibit more conformational flexibility than the five and six member ring analogs.

These conflicting results might be better explained by the presence of other different retinoic acid receptors with different steric requirements in their binding sites. Perhaps compounds **6.9a** and **6.9c** bind to different receptors having similar macroscopic effects on the cell lines.

Some molecular modeling has been done on the compounds **6.9a-c** to better visualize the difference between these compounds in three dimensions (Figure 6.5). The MM2 calculated conformations are probably not too far from reality since the calculated structure of **6.9b** is close to its X-ray structure shown in Figure 6.6. Some dihedral angles have been outlined to give an indication to what extent these structures compare to each other. It can easily be seen that structure **6.9b** is conformationally a middle ground between

structure **6.9a** and **6.9c**. It is difficult to see why a receptor capable of binding well to the two extremes, **6.9a** and **6.9c**, could not bind equally well to **6.9b**.

Changes in side chain do not seem to modify greatly the activity of the six membered ring analogs at least when their biological activity are compared on the HL-60 cell line, as shown in Table 6.3. However when the biological activity of the six membered analogs are compared on the P19 cells, a trend is observed. Compound **6.14** seems to be significantly more active than compound **6.18** for example. The derivatives **6.20** and **6.21** were shown to be completely inactive. Interestingly, results have recently been reported which showed that the use of this particular type of side chain often gave analogs which are less active, when compared to the benzoic type of side chain.[13] The different results obtained from HL-60 and P19 screenings could indicate the presence of an additional retinoic acid receptors (compound **6.14** has a structure more related to that of 11-*cis* retinoic acid than to all-*trans* retinoic acid). As mentioned at the begining of the chapter the receptors for the all-*trans* and for 9-*cis* retinoic acids have been found. However receptors for the 11-*cis* and other retinoic acid isomers are still waiting to be discovered. We must keep in mind however that these discrepencies between the results from different cell lines could be due in large part to the differences in the evaluation process for HL-60 and P19.

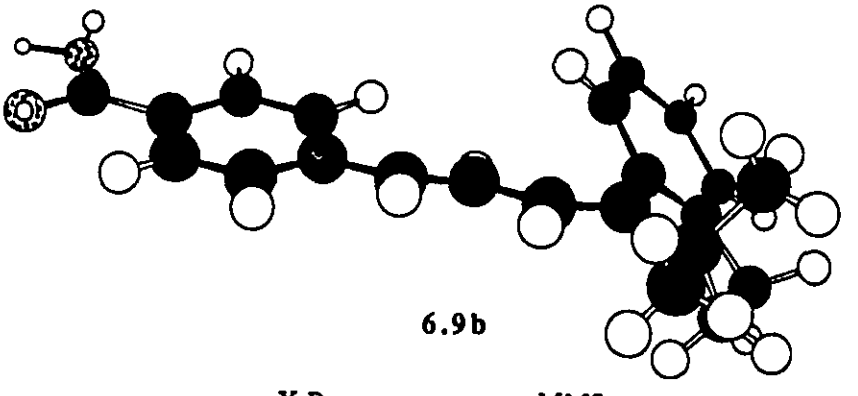


n=3

6.9c

MM2

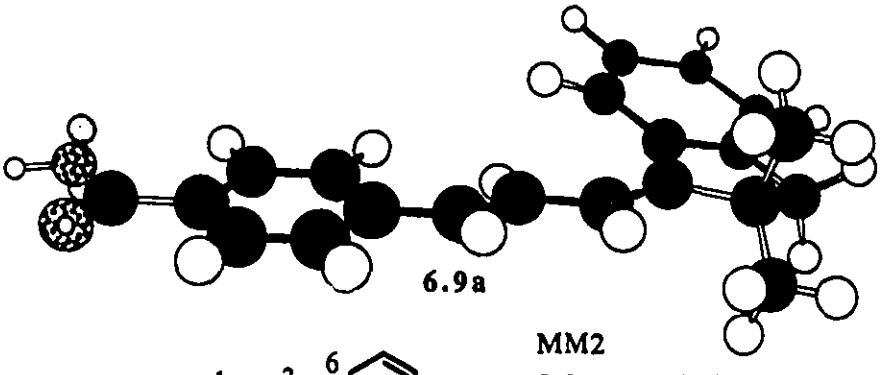
1,2-3,4= -176°
3,4-5,6=72°



n=2

6.9b

X-Ray	MM2
1,2-3,4=172.9°	1,2-3,4= -177.9°
3,4-5,6=43.6°	3,4-5,6=41.4°



n=1

6.9a

MM2

1,2-3,4= -174.9°
3,4-5,6= 17°

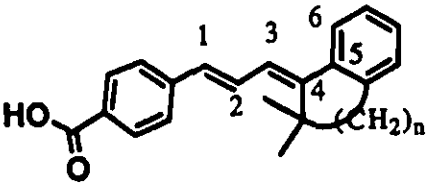


Figure 6.5: MM2 Conformational analysis of the analogs **6.9 a-c**

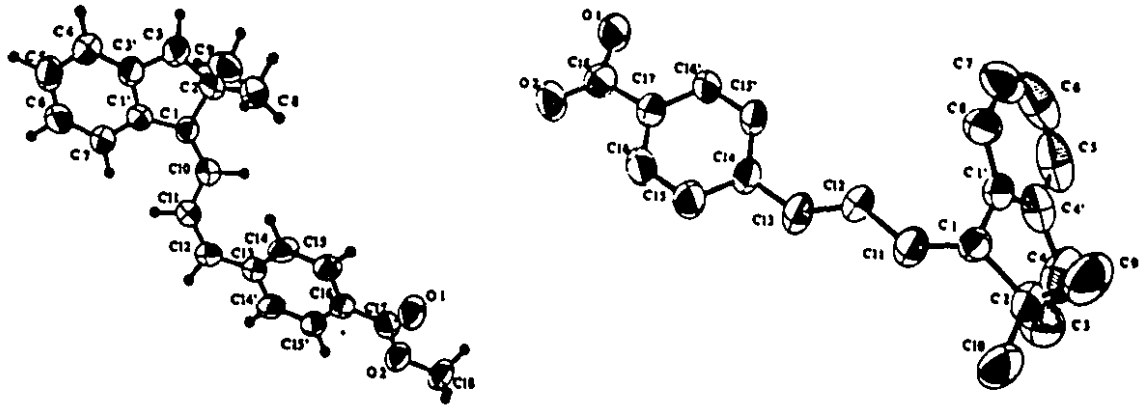


Figure 6.6: X-ray structures obtained for compounds **6.6a** and **6.9b**.

In conclusion, we have synthesized a number of analogs of retinoic acid in which small modifications on the backbone of the molecule lead to large differences in activity. The explanation for such differences should become clearer as biological studies on the receptor selectivity are undertaken. Further studies should be done in five and seven membered ring series. The synthesis of new E,E- analogs would be of interest, since the orientation of the carboxylic group in such derivatives would be different when compared to the Z,E analogs discussed in this work. The carboxylic group in the EE isomer should be closer in space to that of the more active retinoic acid analog C (Figure 6.7) reported in the literature and also shown in another conformation in Figure 6.1.

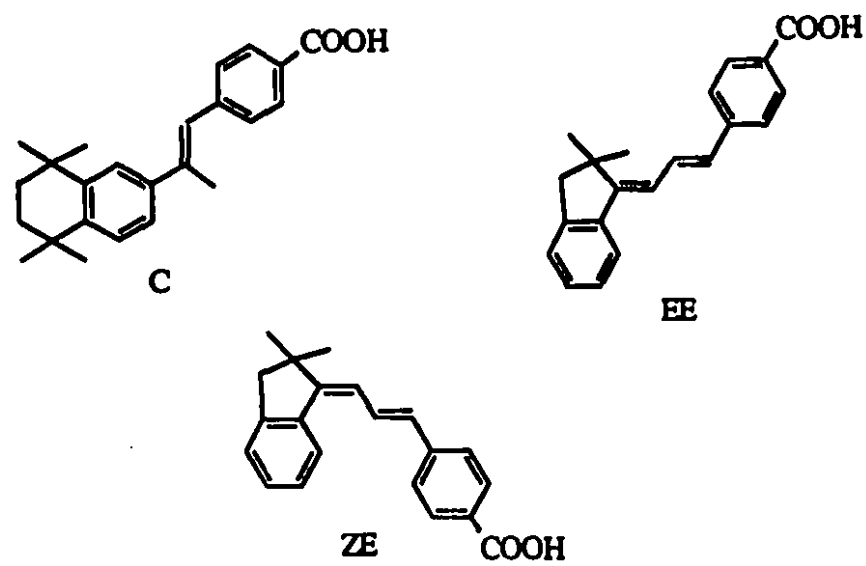


Figure 6.7: Possible direction for future investigation in this field.

6.3. Experimental.

The starting material reagents were purchased from Aldrich. The dimethoxyethane (DME) used in the alkylation step was purchased from Aldrich or BDH and was freshly distilled from lithium aluminium hydride (LAH) prior to its use (Warning!!! Very wet DME will sometime ignite if too much lithium aluminium hydride is added at once. These accidents can be avoided by adding CaH_2 first and leaving it to react for an hour before adding the LAH). The tetrahydrofuran (THF) solvent was dried over the sodium/benzophenone ketyl radical and distilled before use. The 60% potassium hydride suspension was obtained by allowing the 33% potassium hydride suspension sold by Aldrich to separate and discarding the top oily fraction. The triphenylphosphine hydrogen bromide provided by Aldrich was found to contain excess of hydrogen bromide (yellow color); this was found in turn to affect adversely the reactions in which it was used. To improve our yields we added 0.1g of triphenylphosphine to every 5 g of triphenylphosphine hydrogen bromide used in solution.

1) 1-Methoxy-2,2-dimethylindane **6.2.**

22.7 g (excess) of a potassium hydride (KH) 30% suspension in oil was washed 3 times with hexanes, and 250 mL of dry dimethoxyethane were added. The 1-indanone (10 g, 75.8 mmol) dissolved in 20 mL of dimethoxyethane was slowly added under argon to the KH suspension with evolution of hydrogen. At this point, the solution was dark. After 5 minutes of stirring, methyl iodide (32 g, 227.4 mmol) was slowly added until the reaction mixture turned white. The excess potassium hydride was quenched with ethanol and the reaction mixture poured into a beaker containing 100 mL of ice, 100 mL of saturated ammonium chloride solution and 60 mL of hexanes. After separation, the organic phase was dried over anhydrous $MgSO_4$ and the solvent evaporated. This resulted in the isolation of 11.5 g of a crude yellow oil which distilled (Kugelrohr) between 85-90° C (at 0.3 mm/Hg) yielding 9.5 g (71%) of a clear oil which was used without further purification in the next reaction.

^1H NMR (200 MHz, $CDCl_3$) δ 7.2-7.4 (m, 4H), 4.21 (s, 1H), 3.53 (s, 1H), 2.88 (d, J=15.3 Hz, 1H), 2.62 (d, J=15.3 Hz, 1H), 1.18 (s, 3H), 1.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.3, 128.0, 127.5, 127.2, 127.1, 92.0, 58.0, 46.0, 44.5, 28.0, 22.0; MS (E.I.) m/z calc'd for $C_{12}H_{16}O$: MI=176.1201, found 176.1228 ; MI=176 (55%), 161 (13%), 145 (49%), 129 (100%)

2) 2,2-Dimethyl-1-indanone **6.3a.**

A) 1-methoxy-2-dimethylindane **6.2** (27 g, 15 mmol) was dissolved at room temperature in a solution containing 210 mL of distilled water, 90 mL acetonitrile, ceric ammonium nitrate (8.22 g, 15 mmol) and potassium chlorate (8.55 g, 50 mmol). The reaction was refluxed with stirring during 6 hours. After cooling the reaction mixture to room temperature, 60 mL of hexanes were added, the organic phase separated and washed with 50 mL of water. The organic phase was dried over anhydrous $MgSO_4$ and the solvents evaporated. The yellow oil residue was distilled under water pump vacuum (108-110 °C) giving 22 g (90%) of a clear oil that crystallized on standing.

B) 2-dimethyl-1-indanone was obtained directly from 1-indanone when the procedure described for the synthesis of **6.2** was followed using only 2 equivalents of KH and 2 equivalents of iodomethane. This procedure gave the desired 2-dimethyl-1-indanone directly in 98% yield which distilled at 80-90°C (Kugelrohr 0.05 mm/Hg).

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.72 (d, J=7.6 Hz, 1H), 7.55 (m, 1H), 7.43-7.28 (m, 2H), 2.96 (s, 2H), 1.20 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.8, 151.8, 135.0, 134.5,127.1, 126.3, 124.0, 45.0, 42.5, 24.9; IR (film) 3036-2846, 1702, 1470, 1435, 1292, 993, 801, 745 cm^{-1}; MS (E.I.) m/z calc'd for $C_{11}H_{12}O$: MI=160.0888, found 160.0891; 160 (58%), 145 (100%), 131 (8%), 117 (20%).

3) 1-Vinyl-2,2-dimethyl-1-indanol **6.4a.**

The 2-dimethyl-1-indanone **6.3a** (3 g, 18.7 mmol) was slowly added to a solution containing 30 mL of dry THF and 40 mL of a 1M vinyl magnesium bromide in THF (40.0 mmol) at room temperature. This mixture was stirred for an additional 30 min., then poured into a 500 mL beaker containing 50 mL of ice with 50 mL saturated ammonium chloride solution. The resulting mixture was extracted with 50 mL of hexanes, the organic layer washed with distilled water, dried over anhydrous $MgSO_4$ and the solvent evaporated under reduced pressure, leaving 3.2 g (91%) of a clear yellow oil which was used in the next step without further purification. However compound **6.4a** can be purified by Kugelrohr distillation at 95-105°C (0.1 mm/Hg)

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.1-7.3 (m, 4H), 6.20 (dd, J=17.2, 10.6Hz, 1H), 5.28 (dd, J=17.2, 1.7Hz, 1H), 5.24 (dd, J=10.6, 1.7Hz, 1H), 2.90 (d, J=15.3Hz, 1H), 2.63 (d, J=15.3Hz, 1H), 1.61(s, 1H), 1.09 (s,3H), 0.99 (s, 3H). ^{13}C NMR (68 MHz,$CDCl_3$) δ 146.5, 142.4, 139.2, 128.1, 126.5, 125.0, 123.8, 114.3, 86.1, 48.0, 45.1, 24.6, 22.0. I.R. (neat) 3589-3300, 2963-2844, 1637, 1606, 1473, 1409, 1001, 979, 962, 918, 764, 727 cm^{-1}; MS (E.I.) m/z calc'd for $C_{13}H_{16}O$: MI=188.1201, found 188.1201; 188 (9%), 173 (100%), 170 (7%), 155 (23%), 145 (81%), 129 (24%), 91 (17%).

4) (1-EZ)[2-(2',2'-Dimethylindan-1'-ylidene)ethyl] triphenylphosphonium bromide **6.5a.**

The 1-vinyl-2-dimethyl-1-indanol **6.4a** (1.8 g, 9.6 mmol) was added to triphenylphosphine hydrobromide (3.3 g, 9.6 mmol) and dissolved in 20 mL of dry methanol (distilled over magnesium). This solution was left stirring for 24 hours at room temperature. The methanol was evaporated under reduced pressure and the resulting solid pulverized under 20 mL of acetone or THF. The solvent was decanted and the resulting powder dried overnight under vacuum, yielding 4.5 g (88%) of a crude mixture that was used without further purification in the next step.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.9-7.5 (m), 7.3-6.9 (m), 5.70 (dd, J=16.7, 8.2 Hz), 5.5-5.0 (m), 4.90 (dd, 15.2, 8.1Hz), 2.71 (s), 2.59 (s), 1.06 (s), 1.00 (s).

5) 4-(1'Z,2E) and 8a) 4-(1'Z,2Z)[3-(2',2'-Dimethylindan-1'-ylidene)-2-propenyl]benzoic acid, methyl esters **6.6a** and **6.8a.**

The phosphonium salt **6.5a** (1 g, 1.9 mmol) was added to 60 mL of dry THF and the resulting suspension stirred under argon at -78° C. s-Butyllithium (6.4 mL, 7.6 mmol) was slowly added and the solution warmed to -60° C and stirred for 6 hours at this temperature. The reaction mixture turned to a dark homogeneous red. Methyl 4-formylbenzoate (1.24 g, 7.6 mmol) dissolved in tetrahydrofuran, was added and the reaction mixture was warmed to room temperature and stirred an additional 30 min. 20 mL of hexanes and 20 mL of concentrated ammonium chloride were then added. After separation, the organic phase was washed with distilled water, dried over anhydrous $MgSO_4$ and the solvents evaporated. The resulting oil was heated with 25 mL of hexanes and left to cool to room temperature, during which time the triphenylphosphate precipitated out of the solution. The liquid was decanted from the solid and the hexanes evaporated, giving 0.2 g of a cis-trans mixture of product with a third unidentified product which were separated on a column using hexanes as eluent. The separation gave 0.032 g of F1, 0.025 g of F2 and 0.120 g of F3 for a total of 28% yield of conversion.

F1, **6.6a**) Recrystallized from hot hexanes m.p.=104-104.5°C,(yellow needles)
^{1}H NMR (200 MHz, $CDCl_3$) δ 8.04 (d, J=8.4 Hz, 2H), 7.76 (m, 1H), 7.49 (d, J=8.4 Hz, 2H), 7.3-7.22 (m, 3H), 7.09 (dd, J= 11.4, 11.4 Hz, 1H), 6.53 (d, J=11.4 Hz, 1H), 6.49 (dd, J=11.4, 1.3 Hz, 1H), 3.93 (s,3H), 2.85 (s, 2H), 1.23 (s, 6H) ; ^{13}C NMR (68 MHz, $CDCl_3$) δ 167.0, 155.5, 145.1, 142.4, 139.5, 129.5, 129.1, 128.9, 128.4, 128.37, 128.2, 126.5, 125.7, 125.5, 116.9, 52.1, 46.9, 44.3, 28.9; IR (film)3200-2846, 1722, 1628, 1603, 1434, 1278, 1179, 1108, 965, 774 cm^{-1} ; MS (E.I.) m/z calc'd for $C_{22}H_{22}O_2$: MI=318.1620, found 318.1614 ; 318(100%), 303 (33%), 287 (5%), 275 (12%), 143 (10%), 169 (12%).

F2, **6.8a**) Recrystallized from hot hexanes m.p.=120.5-121°C, (yelow plates)
^{1}H NMR (200 MHz, $CDCl_3$) δ 8.00 (d, J=8.3 Hz, 2H), 7.78 (m, 1H), 7.79 (dd, J=15.2, 11.4 Hz, 1H), 7.5 (d, J=8.3 Hz, 2H), 7.34-7.22(m, 3H), 6.66 (d, J=15.3 Hz, 1H), 6.49 (d, J=11.4 Hz, 1H), 3.91 (s,3H), 2.85 (s, 2H), 1.25 (s, 6H) ; ^{13}C NMR (68 MHz, $CDCl_3$) δ 166.9, 154.5, 145.2, 142.4, 139.7, 131.2, 130.0, 128.4, 128.3, 128.2, 126.7, 126.1,

125.6, 125.4, 120.6, 52.0, 46.9, 44.6, 28.9; IR (film) 3200-2846, 1718, 1601, 1603, 1435, 1278, 1178, 1108, 965, 768 cm^{-1} ; MS (E.I.) m/z calc'd for $C_{22}H_{22}O_2$: MI=318.1620, found 318.1617 ; 318(100%), 303 (32%), 287 (5%), 275 (12%), 143 (10%), 169 (11%).

6) 4-(1'Z,2Z)[3-(2',2'-Dimethylindan-1'-ylidene)-2-propenyl]benzoic acid **6.7a.**

The ester **6.6a** (22.6 mg, 0.07 mmol) in 20 mL of methanol was hydrolysed following the addition of 0.5 mL of a saturated sodium hydroxide solution in water and heating to reflux for 5 min. The reaction mixture was then left overnight to react at room temperature. The methanol was evaporated under vacuum, 20 mL of distilled water were added to dissolve the residue and 2 mL of HCl were added. The acid **7a** precipitated out of the solution and was extracted twice with 20 mL of ether. The combined organic phases were dried over $MgSO_4$ and evaporated under vacuum leaving 20.0 mg of a yellow powder which was recrystallized in methanol, yielding 15 mg of pale yellow plates (70%).

Recrystallized from methanol m.p.=190-192°C,
^1H NMR (200 MHz, $CDCl_3$) δ 8.15 (d, J=8.4 Hz, 2H), 7.79 (m, 1H), 7.55 (d, J=8.4 Hz, 2H), 7.31-7.2 (m, 3H), 7.14 (dd, J= 11.4, 11.3, 1H), 6.56 (d, J=11.4, 1H), 6.52 (d, J=11.3, 1H), 2.88 (s, 2H), 1.26 (s, 6H); IR (KBr) 3400-2450, 1686, 1601, 1420, 1288 cm^{-1}; MS (E.I.) m/z calc'd for $C_{21}H_{20}O_2$: MI=304.1463, found 304.1462 ; 304(100%), 289 (39%), 261 (14%), 169 (14%), 167 (21%), 129 (16%).

7) 4-(1'Z,2E)[3-(2',2'-Dimethylindan-1'-ylidene)-2-propenyl]benzoic acid **6.9a.**

The ester **6.8a** (36 mg, 0.11 mmol) dissolved in 30 mL of methanol was hydrolysed by the addition of 1mL of a saturated sodium hydroxide solution in water. The reaction mixture was refluxed for 5 min. and left overnight to react at room temperature. The methanol was evaporated under vacuum and 20 mL of distilled water was added to dissolve the residue and 2 mL of concentrated hydrochloric acid were added. The acid **6.9a** precipitated out of the solution and was extracted twice with 20 mL of ether. The combined organic phases were dried and evaporated under vacuum leaving 32 mg of a yellow powder which was recrystallized in methanol yielding 26 mg of yellow needles (76%).
(warning: When the sodium hydroxide was introduced as a solid, instead of dissolved in water, we observed some isomerization of the product. Use of lithium hydroxide might be preferable).

Recrystallized from methanol, m.p.=200 °C,
^{1}H NMR (200 MHz, $CDCl_3$) δ 8.07 (d, J=8.3Hz, 2H), 7.78 (m, 1H), 7.78 (dd, 15.5, 11.2 Hz, 1H), 7.52 (d, J=8.3 Hz, 2H), 7.34-7.22 (m, 3H), 6.67 (d, J= 15.5, 1H), 6.24 (d, J=11.2, 1H), 2.85 (s, 2H), 1.25 (s, 6H); IR (KBr) 3400-2800, 1688, 1651, 1601, 1540, 1419, 1235 cm^{-1}; MS (E.I.) m/z calc'd for $C_{21}H_{20}O_2$: MI=304.1463, found 304.1461 ; 304(100%), 289 (37%), 261 (14%), 169 (13%), 167 (21%), 129 (40%).

8) 2,2-Dimethyl-1-tetralone **6.3b.**[14]

A 60% KH suspension in oil (11.7g, 138 mmol) was washed 3 times with 20 mL of hexanes, then 150 mL of dry dimethoxyethane was added. 1-Tetralone (10 g, 69 mmol) , was slowly added over argon to the KH suspension in DME giving rise to hydrogen. At this point, the solution turned darker. After stirring 5 minutes, Iodomethane (19 g, 138 mmol) was slowly added. The excess potassium hydride was quenched with ethanol and the reaction mixture poured into a beaker containing 250 mL of distilled water and 100 mL of hexanes. After separation and a wash with brine, the organic phase was dried with anhydrous $MgSO_4$ and the solvent evaporated, yielding 11 g of a crude yellow oil (92%) which was used in the next reaction without further purification. Vacuum distillation (Kugelrohr 80-90°C, 0.05 mm/Hg) provided an analytical sample.

^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (dd, J=1.5, 7.9 Hz, 1H), 7.44 (dt, J= 1.5, 7.5 Hz, 1H), 7.28 (t, J=7.3 Hz, 1H), 7.21 (d, J=7.8 Hz, 1H), 2.98 (t, J= 6.4 Hz, 2H), 1.98 (t, J=6.4 Hz, 2H), 1.21 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.8, 143.3, 132.9, 131.4, 128.6, 127.9, 126.5, 41.5, 36.5, 25.6, 24.3; IR (film) 2938, 1684, 1601, 1309, 1221, 968, 741 cm^{-1}; MS (E.I.) m/z 174 (55%), 159 (25%), 131 (26%), 118 (100%), 90 (31%).

9) 1,2,3,4-Tetrahydro-1-hydroxy-1-vinyl-2,2-dimethylnaphtalene **6.4b.**

The 6-dimethyl-5-tetralone **6.3b** (1.7 g, 10 mmol) was slowly added, at 0°C, to a solution of vinylmagnesium bromide (20 mL, 1M, 20 mmol) dissolved in 30 mL of THF. The reaction mixture was warmed up to room temperature and left stirring for an additional 30 min. The reaction mixture was then slowly added to a 200 mL of ice and saturated ammonium chloride solution (50/50) mixture. After work up, drying and evaporation of the solvents, we isolated 2 g (100%) of a yellow oil that was used in the next reaction without further purification.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.40 (m, 1H), 7.2-7.0 (m, 3H), 6.08 (m, J=17.1, 10.7Hz, 1H), 5.27 (dd, J=17.1, 1.8Hz, 1H), 5.24 (dd, J=10.7, 1.8Hz, 1H), 2.84 (t, J=6.8 Hz, 2H), 1.85 (dt, J=13.6, 6.8 Hz, 1H), 1.67 (dt, J=13.6, 6.8 Hz, 1H), 0.99 (s, 3H), 0.96 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 141.6, 140.3, 135.7, 128.6, 128.0, 127.0, 126.0, 114.2, 78.0, 36.3, 32.7, 25.8, 23.7, 22.8. IR(film) 3600-3300, 3059-2871, 1636, 1487, 1453, 994, 924 cm^{-1}.

10) (1'E,Z)[2-(2',3',4'-Trihydro-2',2'-dimethylnapht-1'-ylidene)ethyl] triphenylphosphonium bromide **6.5b.**

The 1,2,3,4-tetrahydro-1-hydroxy-1-vinyl-2-dimethylnaphtalene **6.4b** (2 g, 9.9 mmol) was reacted with triphenyl phosphinehydrobromide (3.4 g, 9.9 mmol) using the procedure described in the synthesis of the phosphonium **6.5a.** After evaporation of the methanol, 3.6 g of crude phosphonium salt was isolated as a yellow solid which was triturated in THF, filtered and used in the next step after drying 24 hours under vaccuum .

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.8-7.5 (m, 15 H), 7.45 (m, 1H), 7.15 (m, 2H), 7.05 (m, 1H), 5.25 (t, 1H), 4.98 (dd, 2H), 2.49 (t, 2H), 1.31 (t, 2H), 0.85 (s, 6H).

11) 4-(1'Z,2E) and 8b)4-(1'Z,2Z)[3-(2',3',4'-Trihydro-2',2'-dimethylnapht-1'-ylidene)-2-propenyl]benzoic acid, methyl ester **6.6b.**

The phosphonium salt **6.5b** (1.8 g, 3.4 mmol) was reacted with methyl 4-formylbenzoate (0.6 g, 3.4 mmol) in 75 mL of anhydrous THF, using the procedure described for the synthesis of **6.6a** and **6.8a.** Following the reaction and separation of the triphenylphosphine oxide in hexanes, the solvents were evaporated and the residue was separated by flash chromatography using 95% hexanes: 5% ethyl acetate as eluent, yielding two fractions (F1; rf=0.5, F2; rf=0.44, 95:5 hexanes:ethyl acetate) F1=0.15 g , F2=0.38g (53% conversion). F1 was recrystallized in hexanes to give **6.6b** as a white powder (m.p. 86-86.5°C).

F1 Compound **6.6b**:
^{1}H NMR (200 MHz, $CDCl_3$) δ 8.06 (d, J=8.4 Hz, 2H), 7.56-7.46 (d+m, J=8.4Hz, 3H), 7.30-7.20 (m, 3H), 6.67 (m, complex ABX (5 lines), J=10.6 Hz, 2H), 6.46 (m, ABX (6 lines), 10.6 Hz, 1H), 3.95 (s, 3H), 2.84 (t, J= 6.7Hz, 2H), 1.70 (t, J= 6.7Hz, 2H), 1.17 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 165.8, 149.8, 141.8, 137.26, 134.0, 130.5,

130.0, 128.8, 128.1, 127.5, 127.4, 127.0, 124.2, 117.8, 52.3, 38.7, 36.7, 28.5, 27.3; IR (nujol) 1721, 1600, 1459, 1274, 1106 cm^{-1}

F2 Compound **6.8b** was isolated as a yellow oil which was impure. We had to hydrolyse the ester then recrystallize to purify it. See **6.9b**.
^1H NMR (200 MHz, $CDCl_3$) δ 7.99 (d, J=8.5 Hz, 2H), 7.43 (d+m, J=8.5Hz, 3H), 7.42 (dd, J=15.3, 10.8 Hz, 1H), 7.30-7.12 (m, 3H) 6.70 (d, J=15.3, 10.8 Hz, 1H), 6.43 (d, 10.8 Hz, 1H), 3.92 (s, 3H), 2.87 (t, J= 6.7Hz, 2H), 1.76 (t, J= 6.7Hz, 2H), 1.23 (s, 6H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 166.7, 149.8, 142.4, 138.6, 135.1, 131.0, 130.0, 128.2, 128.1, 127.5, 127.4, 125.8, 125.0, 121.7, 51.8, 38.3, 36.3, 27.8, 26.6; IR (film) 3052-2873, 1726, 1601, 1434, 1274, 1107, 765 cm^{-1}

12) 4-(1'Z,2Z)[3-(2',3',4'-Trihydro-2',2'-dimethylnapht-1'-ylidene)-2-propenyl]benzoic acid **6.7b.**

The ester **6.6b** (0.14g, 0.5 mmol) in 1 mL of dioxane was hydrolysed by the addition of 0.1 mL of a saturated NaOH solution in distilled water. The reaction mixture was left stirring for 12 hours before adding 0.5 mL of conc. HCl and extracting the acid **6.7b** with 20 mL of ether. Work-up and evaporation of the solvents gave 0.13 g of residue which, after crystallization in pentane gave 0.1 g (77%) of the pure acid **6.7b** as a white powder.

mp=154-155°C
^1H NMR (200 MHz, $CDCl_3$) δ 8.16 (d, J=8.2Hz, 2H), 7.56 (d, J=8.2Hz, 2H), 7.50 (m, 1H), 7.30-7.15 (m, 3H), 6.72 (m, complex ABX (5 lines), J=9.5 Hz, 2H), 6.50 (m, ABX (6 lines) J= 9.5 Hz, 1H), 2.86 (t, J= 6.8 Hz, 2H), 1.72 (t, J=6.6 Hz, 2H), 1.19 (s, 6H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 171.4, 151.1, 143.5, 138.6, 134.7, 131.6, 130.8, 130.2, 128.8, 128.2, 128.0, 127.8, 127.2, 124.9, 118.3, 121.7, 38.3, 36.4, 28.0, 26.8. MS (E.I.) m/z 318 (32%), 303 (23%), 262 (100%).

13) 4-(1'Z,2E)[3-(2',3',4'-Trihydro-2',2'-dimethylnapht-1'-ylidene)-2-propenyl]benzoic acid **6.9b.**

The ester **6.8b** (0.15 g, 0.45 mmol) in 0.3 mL of dioxane was hydrolysed by adding 0.6 mL of a solution of 0.38 g LiOH in 1 mL of distilled water. This reaction mixture was stirred for 24 hours then 5 mL of conc. HCl were added. The solution was extracted with ether, the organic phase was separated then dried over anhydrous $MgSO_4$ and the solvents

were evaporated leaving a light yellow oil. A wash with hexanes provided 0.14 g (94%) of pure acid **6.9b** obtained as a yellow powder.

m.p. 199-199.5°C.
^{1}H NMR (200 MHz, $CDCl_3$) δ 8.03 (d, J=8.4 Hz, 2H), 7.5-7.25 (m, 7H), 6.69 (d, J=15.3 Hz, 1H), 6.40 (d, J=11.0 Hz, 1H), 2.84 (t, J= 6.7 Hz, 2H), 1.73 (t, J= 6.8 Hz, 2H), 1.19 (s, 6H); ^{13}C NMR (68 MHz, $CDCl_3$) δ 171.9, 150.4, 143.5, 138.9, 135.2, 130.9, 130.6, 130.4, 128.3, 127.7, 127.3, 126.1, 125.1, 121.7, 38.4, 36.4, 27.9, 26.8; MS (E.I.) m/z calc'd for $C_{22}H_{22}O_2$: MI=318.1619, found 318.1612 ; 318 (37%), 303 (24%), 274 (21%), 262 (100%).

14) 7,7-Dimethyl-2,3-benzocycloheptan-1-one **6.3c.**

A 60 % suspension of potassium hydride in oil (4.1 g, 62 mmol) was washed 3 times with 20 mL of hexanes and 150 mL of dry dimethoxyethane were added. 1-Benzosuberone (5 g, 31 mmol) was slowly added under argon to this KH suspension giving rise to hydrogen formation. At this point, the solution was of an almond color. After 5 minutes, methyl iodide (8.7 g, 31 mmol) was slowly added. The excess potassium hydride was quenched with ethanol and the reaction mixture poured into a beaker containing 100 mL of ice, 50 mL of saturated ammonium chloride solution and 60 mL of hexanes. After separation, the organic phase was dried over anhydrous $MgSO_4$ and the solvent evaporated. A crude yellow oil was obtained and distilled (Kugelrohr 100-110°C, 0.3 mm/Hg), yielding 5.6 g (95%) of a clear oil which was used without further purification in the next reaction.

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.18 (m, 3H), 7.09 (d, J= 7 Hz, 1H), 2.74 (t, J=6.7 Hz, 2H), 1.88 (tdd, J=6.7, 7.0, 5.7 Hz, 2H), 1.64 (dd, J= 7.0, 5.7Hz, 1H), 1.16 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 214.8, 141.2, 137.1, 130.5, 128.3, 126.8, 126.3, 45.8, 37.4, 32.8, 25.5, 23.0; MS (E.I.) m/z calc'd for $C_{13}H_{16}O$: MI=188.1201, found 188.1212 ; 188 (40%), 173 (11%), 145 (49%), 129 (100%)

15)1-Vinyl-7,7-dimethyl-2,3-benzocycloheptan-1-ol **6.4c.**

The 7-dimethyl-2,3-benzocycloheptan-1-one **6.3c** (4.0 g, 21 mmol) was reacted with vinylmagnesium bromide 1M in THF (42.6 mL, 42 mmol) using the procedure described for **6.4a**. The alcohol **6.4c** was isolated in 80% yield as a yellow oil that was used without further purification in the next step.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.70 (d, J=7.6Hz, 1H), 7.3-7.0 (m, 3H), 6.69 (dd, J=17.1, 10.7Hz, 1H), 5.20 (dd, J=10.7, 1.3Hz, 1H), 5.10 (dd, J=17.2, 1.3 Hz, 1H), 3.1-2.7(m, 2H), 1.8-1.6 (m, 4H), 1.88 (s,1H), 1.07 (s, 3H), 0.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 141.4, 130.3, 127.0, 126.8, 125.8, 114.9, 81.6, 41.6, 39.0, 36.9, 26.1, 24.4.

16) [2-(7',7'-Dimethyl-2',3'-benzocycloheptan-1'-ylidene)ethyl] triphenylphosphonium bromide, cis-trans mixture **6.5c.**

The 5-vinyl-6-dimethyl-5-benzocycloheptanol **6.4c** (2 g, 9.3 mmol) was reacted with triphenylphosphine hydrobromide (2.54 g, 8 mmol) using the procedure described in the synthesis of the phosphonium salt **6.5a**. After evaporation of the methanol, 4.5 g of crude phosphonium salt was isolated as a yellow solid and used in the next step after drying 24 hours under vaccuum.

17) 4-(1'Z,2E)[3-(7',7'-Dimethyl-2',3'-benzocycloheptan-1'-ylidene)-2-propenyl]benzoic acid, methyl ester **6.8c.**

The phosphonium salt **6.5c** (1g, 1.9 mmol) was deprotonated with sec-butyllithium 1.3 M in c-hexane (1.4 mL, 3.16 mmol) then reacted with methyl 4-formylbenzoate (0.6 g, 3.9 mmol) using the procedure described for the synthesis of **6.6a** and **6.8a.** Following the reaction and separation of the triphenylphosphine oxide in hexanes, the solvents were evaporated and a crystalline material was separated and recrystallized from hot hexanes, yielding 0.15 g (23.8%) of a white powder.

Recrystallized from hot methanol, m.p.=119.5-120°C,
^{1}H NMR (200 MHz, $CDCl_3$) δ 7.85 (d, J=8.4 Hz, 2H), 7.3-7.1 (m, 5H), 7.2 (m, 1H), 6.70 (dd, J=15.2, 10.1 Hz, 1H), 6.56 (d, 15.2 Hz, 1H), 2.47 (d, 10.1Hz, 1H), 3.89 (s, 3H), 2.5-2.8 (m, 2H), 1.8 (m, 1H), 1.7, 1.4 (m, 3H), 1.34 (s, 3H), 0.89 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.9, 156.0, 142.4, 140.1, 139.8, 130.2, 130.1, 129.8, 129.8, 128.3, 128.2, 127.4, 126.0, 125.5, 124.1, 51.9, 43.8, 37.3, 34.0, 28.7, 28.5, 23.7; IR (film) 2949-2846, 1720, 1602, 1435, 1309, 1278, 1177, 1109, 965, 763 cm^{-1} ; MS (E.I.) m/z calc'd for $C_{24}H_{26}O_2$: MI=346.1933, found 346.1937 ; 346 (100%), 331 (33%), 303 (71%), 197 (36%).

18) 4-(1'Z,2E)[3-(7',7'-Dimethyl-2',3'-benzocycloheptan-1'-ylidene)-2-propenyl]benzoic acid **6.9c**.

6.8c (0.056 g, 0.16 mmol) in 20 mL of methanol was hydrolysed using the procedure described for the synthesis of **6.9a**. After recrystallisation in methanol, 40 mg (80%) of the pure acid **6.9c** were obtained as a white powder.

Recrystallized from methanol, m.p.=200°C,
^{1}H NMR (200 MHz, $CDCl_3$) δ 7.93 (d, J=8.2 Hz, 2H), 7.25 (d, J=8.2 Hz, 2H), 7.25-7.1 (m, 3H), 7.02-6.96 (m, 1H), 6.7 (dd, J= 15.5, 10.6 Hz, 1H), 6.54 (d, J=15.5 Hz, 1H), 6.45 (d, J=10.6 Hz, 1H), 2.8-2.5 (m, 2H), 1.9-1.4 (m, 4H), 1.32 (s, 3H), 0.86 (s, 3H); C NMR (68 MHz, $CDCl_3$) δ 171.6, 156.4, 143.3, 140.1, 139.8, 130.6, 130.5, 130.0, 129.7, 128.3, 127.4, 127.2, 126.0, 125.5, 124.1, 37.3, 34.0, 28.7, 28.5, 23.7; MS (E.I.) m/z calc'd for $C_{23}H_{24}O_2$: MI=332.1776, found 332.1768 ; 332 (100%), 317 (32%), 289 (82%), 197 (35%).

19) Methyl 4-formylcinnamate **6.10.** (trans isomer)

The esterification of 4-formylcinnamic acid (1 g, 5.7 mmol) was carried out in 25 mL of THF (some solid did not dissolve). Thionyl chloride (2 g, 17.1 mmol) was added and the reaction mixture was refluxed and stirred for 5 min. during which time the solid dissolved. The reaction was stirred an additional 2 hours at room temperature. The THF and excess of thionyl chloride were evaporated and dry methanol (10 mL) was added to the residue and left to react at room temperature for 2 hours after which time the methanol was evaporated leaving 1.2 g of a yellow crystal containing a 1:2 mixture of cis and trans isomers. This crude product was dissolved in 20 mL of dry ether and dry HCl was bubbled in, during 5 min. The solvent was then evaporated leaving a yellow solid containing only the trans isomer with some impurities which were eliminated by a basic wash with ether and a sodium hydroxide solution. Evaporation of the ether left 0.9g (83%) of a white solid of sufficient purity to be used directly in the next step.

^{1}H NMR (200 MHz, $CDCl_3$) δ 10.00 (s, 1H), 7.88 (d, J= 8.2 Hz, 1H), 7.70 (d, J= 16.1 Hz, 1H), 7.65 (d, J= 8.2 Hz, 1H), 6.53 (d, J=16.1 Hz, 1H), 3.8 (s, 3H).

20) 4-(1'Z,2Z,E), and 4-(1'Z,2E,E)[3-(2',3',4'-Trihydro-2',2'-dimethylnapht-1'-ylidene)-2-propenyl]cinnamic acid, methyl ester **6.11** and **6.13.** Isomeric mixture.

The phosphonium salt **6.5b** (1.0 g, 2.0 mmol) was reacted with methyl 4-formylcinnamate **6.10** (0.6 g, 3.4 mmol) in 75 mL of dry THF, using the procedure described for the synthesis of **6.6a** and **6.8a**. Following the reaction and separation of the triphenylphosphine oxide in hexanes, the solvents were evaporated and the residue was separated by flash chromatography using 80% hexanes: 20% ethyl acetate as eluent, yielding two fractions F1=0.28 g and F2=0.1g (64% conversion). The fractions were not purified further. They were used as such in the esterification reactions.

Compound **6.11** (**1'Z,2Z,E**) F2: rf=0.61 (10% ethyl acetate:hexanes), was impure and was used as is in the next reaction.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.8-7.1 (m, 10H), 6.75 (m, 2H), 6.45 (m, 2H), 3.81 (s, 3H), 2.83 (t, 2H), 1.72 (t, 2H), 1.18 (s, 6H). MS (E.I.) m/z 358 (59%), 343 (27%), 302 (100%).

Compound **6.13** (**1'Z,2E,E**) F1: rf=0.68 (10:90, ethyl acetate:hexanes).

^{1}H NMR (200 MHz, $CDCl_3$)δ 7.80-7.10 (m, 10H), 6.65 (d, 1H), 6.40 (m, 2H), 3.80 (s,3H), 2.83 (t, 2H), 1.73 (t, 2H), 1.20 (s, 6H). MS (E.I.) m/z 358 (63%), 343 (28%), 302 (100%).

21) 4-(1'Z,2Z,E)[3-(2',3',4'-Trihydro-2',2'-dimethylnapht-1'-ylidene)-2-propenyl]-4-cinnamic acid **6.12.**

The saponification was carried out by dissolving ester **6.11** (0.1g, 0.3 mmol) in 1 mL of dioxane, followed by the addition of 0.1 mL of a saturated LiOH solution in distilled water. The reaction mixture was heated to reflux then left stirring at room temperature for 24 hours before adding a few drops of conc. HCl (until pH=1) and extracting the acid **6.12** with 20 mL of ether. Work-up and evaporation of the solvents gave 0.11 g of a yellow solid. This solid was purified by flash chromatography by flushing out the impurities with a mixture of 20:80 ethyl acetate:hexanes, then the desired product was flushed out with ethyl ether to give 0.08g (96%) of a yellow solid.

^{1}H NMR (200 MHz, $CDCl_3$) δ 7.82 (d, J=16 Hz, 1H), 7.58 (d, J=8.3 Hz, 2H), 7.48 (d+m, J=8.3, 3H), 7.21 (m, 3H), 6.7 (m, 2 H), 6.48 (d, J=16 Hz, 1H), 6.42 (m, 1H),

2.84 (t, J=6.7 Hz, 2H), 1.70 (t, J=6.7Hz, 2H), 1.17 (s, 6H); C NMR (68 MHz, $CDCl_3$) δ 172.5, 150.5, 146.7, 140.7, 138.5, 134.8, 130.8, 130.7, 129.4, 128.4, 128.2, 128.1, 127.6, 124.9, 118.6, 116.7, 38.3, 36.3, 28.0, 26.8; MS (E.I.) m/z calc'd for $C_{24}H_{24}O_2$: MI=344.1776, found 344.1726 ; 344 (55%), 329 (26%), 288 (100%).

22) 4-(1'Z,2E,E)[3-(2',3',4'-Trihydro-2',2'-dimethylnapht-1-ylidene)-2-propenyl]cinnamic acid **6.14.**

The saponification was carried out by dissolving the ester **6.13** (0.28 g, 8.3 mmol) in 5 mL of dioxane, then adding a solution of 0.38 g LiOH in 1 mL of distilled water. This reaction mixture was heated to reflux and stirred 24 hours at room temperature, then conc. HCl was added slowly until the reaction became cloudy or the reaction mixture reached a pH of 1. This solution was extracted with ether, the organic phase was dried over anhydrous $MgSO_4$, the solvents were evaporated leaving 0.26 g of a yellow solid. A wash with a hexanes/diethyl ether mixture provided 0.18 g (67%) of pure acid **6.14** obtained as a yellow powder.

^1H NMR (200 MHz, $CDCl_3$) δ 7.76 (d, J=16 Hz, 1H), 7.49 (d, J= 4 Hz, 2H), 7.38 (d, J=16.6 Hz, 2H), 7.38-7.19 (m, 4H), 6.67 (d, J= 16 Hz, 1H), 6.42 (d, J= 15.4 Hz, 1H), 6.39 (d, J= 10.8 Hz, 1H), 2.85 (t, J=6.6 Hz, 2H), 1.73 (t, J=6.6 Hz, 2H), 1.19 (s, 6H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 172.4, 149.6, 146.6, 140.7, 138.8, 135.3, 132.6, 131.2, 130.4, 129.7, 128.8, 128.3, 127.6, 126.7, 127.6, 125.1, 121.9, 116.3, 38.5, 36.4, 27.9, 26.8 ; MS (E.I.) m/z calc'd for $C_{24}H_{24}O_2$: MI=344.1776, found 344.1750 ; 344 (57%), 329 (26%), 288 (100%).

23) 3-(1'Z,2E)[3-(2',3',4'-Trihydro-2',2'-dimethylnapht-1'-ylidene)-2-propenyl]benzaldehyde **6.16 E:Z.**

The phosphonium salt **6.5b** (1.0 g, 2.0 mmol) was reacted with 3-formylbenzaldehyde **6.15** (0.5 g, 3.9 mmol) in 60 mL of anhydrous THF, according to the procedure described for the synthesis of **6.6a** and **6.8a.** Following the reaction and separation of the triphenylphosphine oxide in hexanes, the solvents were evaporated giving 0.37 g of a yellow oil, amixture of compound **15** and **16**, which were separated by flash chromatography using 90% hexanes: 10% ethyl acetate eluent, yielding two fractions (F1; rf=0.56, F2; rf=0.52, 90:10 hexanes:ethyl acetate) F1=0.086 g, F2=0.191g (48% conversion).

Isomer **6.16 (1'Z, 2Z)**. This product was converted quantitatively to compound **6.16 (2E)**when equilibrated with I_2 in dichloromethane or chloroform.

^{1}H NMR (200 MHz, $CDCl_3$)δ 10.04 (s, 1H), 7.95 (s, 1H), 7.76 (d, J=7.5Hz, 1H), 7.64 (d, J=7.5Hz, 1H), 7.45 (d, J=7.5Hz, 1H), 7.40-7.32 (m, 2H), 7.26-7.14 (m, 3H), 6.69 (d, J=15.5Hz, 1H), 6.39 (d, J=10.8 Hz, 1H), 2.84 (t, J=6.6Hz, 2H), 1.73 (t, J=6.6Hz, 2H), 1.20 (s, 6H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 192.3, 149.4, 138.9, 138.7, 136.7, 135.1, 131.7, 130.5, 130.3, 129.4, 129.1, 127.9, 127.5, 127.4, 125.1, 121.6, 38.4, 36.3, 27.8, 26.7. IR 3052-2848, 2724, 1699, 1597, 1480, 1260, 1154, 970 cm^{-1}.

Compound **6.16 (1'Z, 2E)**, was impure and was used as is in the next reaction.

^{1}H NMR (200 MHz, $CDCl_3$)δ 10.04 (s, 1H), 7.81 (s, 1H), 7.68 (d, J=7.5Hz, 1H), 7.68 (d, J=7.5Hz, 1H) 7.55 (d, J=7.5Hz, 1H), 7.47 (m, 1H), 7.26 (m, 3H), 6.65 (m, complex ABX, 2H), 6.45 (d, J=9.6 Hz, 1H), 2.93 (t, J=6.5Hz, 2H), 1.70 (t, J=6.5Hz, 2H), 1.16 (s, 6H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 192.3, 150.5, 138.8, 138.5, 136.4, 134.7, 130.6, 130.2, 128.9, 128.2, 127.8, 127.7, 127.5, 124.9, 118.0, 38.2, 36.3, 28.0, 26.8. IR 3052-2848, 2724, 1699, 1597, 1480, 1260, 1154, 970 cm^{-1}. MS (E.I.) m/z calc'd for $C_{22}H_{22}O$: MI=302.1671, found 302.1669 ; 302 (36%), 287 (16%), 252 (21%), 246(55%), 223(87%), 89(59%), 77(100%).

24) 3-(1'Z,2E,E)[3-(2',3',4'-Trihydro-2',2'-dimethylnapht-1-ylidene)-2-propenyl]cinnamic acid, ethyl ester **6.17.**

A 100 mL, 10 M stock solution of potassium triethylphosphonoacetate was prepared by adding slowly, triethyl phosphonoacetate (2g, 8.9 mmol) to a 100 mL suspension of KH in dry THF (0.35g, 8.8 mmol, KH was washed 3x with dry hexanes, from a 33% suspension in oil) . At room temperature 0.27 mL (0.27 mol) of this solution was added to compound **6.16** (0.27g, 0.9 mmol) dissolved in 10 mL of dry THF. This reaction mixture was left stirring at room temperature for another 5 min. and 20 mL of hexanes were then added with 10 mL of sat. ammonium chloride. The organic phase was separated, washed with water and brine, and then dried with anhydrous $MgSO_4$. The solvents were evaporated and the residue purified by flash chromatography using 5% ethyl acetate: 95% hexanes as eluent. 0.20 g of **6.17** was isolated as a gum.

^{1}H NMR (200 MHz, $CDCl_3$)δ 7.63 (d, J=15.9Hz, 1H), 7.45-7.10 (m, 8H), 6.63 (d, J=15.4Hz, 1H), 6.38 (d, J=16.0 Hz, 1H) 6.36 (d, J=9.8Hz, 1H), 4.25 (d, J=7.1 Hz, 2H), 2.83 (t, J=6.6Hz, 2H), 1.71 (t, J=6.6Hz, 2H), 1.33 (t, J=7.1Hz, 3H), 1.17 (s, 6H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 167.1, 149.3, 144.2, 140.1, 138.8, 135.3, 133.0, 131.3, 130.4, 129.3, 128.4, 128.3, 127.5, 126.6, 125.0, 122.0, 117.3, 64.4, 38.5, 36.4, 27.9, 26.8, 14.3. IR 3200-2800, 1707, 1633, 1596, 1509, 1364, 1260, 1176 cm^{-1}. MS (E.I.) m/z calc'd for $C_{26}H_{28}O_2$: MI=372.2089, found: 372.2093 ; 372 (65%), 257 (27%), 316 (100%).

25) 3-(1'Z,2E,E)[3-(2',3',4'-Trihydro-2',2'-dimethylnapht-1'-ylidene)-2-propenyl]cinnamic acid **6.18.**

The saponification was carried out by dissolving the ester **6.17** (0.22 g, 0.59 mmol) in 5 mL of dioxane (instead of methanol), followed by the addition of an excess of NaOH ((0.2 g in 1 mL) as described in the synthesis of **6.7a.** After recrystallisation in methanol, 20 mg (99 %) of the pure acid **6.18** were obtained as a yelow powder.

^{1}H NMR (200 MHz, $CDCl_3$)δ 7.74 (d, J=16Hz, 1H), 7.46 (d, J=8.6Hz, 2H), 7.40-7.10 (m, 7H), 6.64 (d, J=15.4 Hz, 1H) 6.42 (d, J=8.0Hz, 1H), 6.40 (d, J=16 Hz, 1H), 6.37 (d, J=10.6Hz, 1H), 2.83 (t, J=6.6Hz, 2H), 1.71 (t, J=6.6Hz, 3H), 1.17 (s, 6H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 172.2, 149.6, 146.7, 140.7, 138.8, 135.3, 132.6, 131.2, 130.4, 129.7, 128.8, 128.3, 127.6, 126.7, 125.1, 121.9, 116.2, 38.5, 36.4, 27.9, 26.8. IR 3069-2850, 1690, 1676, 1621, 1592, 1424, 1303 cm^{-1}. MS (E.I.) m/z calc'd for $C_{24}H_{24}O_2$: MI=344.1776, found: 344.1783 ; 344 (55%), 329 (27%), 300 (10%), 288 (100%).

26) (1'Z,2Z,4E) and (1'Z,2Z,4E)-5-(2',3',4'-Trihydro-2-dimethylnapht-1-ylidene)-4-methyl-2,4-pentadienoic acid, ethyl ester **6.20** and **6.21.** Isomeric mixture.

The phosphonium salt **6.5b** (1.0 g, 2.0 mmol) was reacted with (E) ethyl 3-formylcrotonate[15] **6.19** (0.53 g, 3.9 mmol) in 70 mL of anhydrous THF, using the procedure described for the synthesis of **6.6a** and **6.8a.** Following the reaction and work-up, the solvents were evaporated to give 0.9 g of a yellow oil which was separated by flash chromatography using 95% hexanes: 5% ethyl acetate as eluent, yielding two fractions (F1;

rf=0.62, F2; rf=0.57, 95:5 hexanes:ethyl acetate) F1=0.0.081g, F2=0.135g (37% conversion).

F1:Compound **6.20 (1'Z,2Z,4E)**

^{1}H NMR (200 MHz, $CDCl_3$)δ 7.35-7.8 (m, 1H), 7.24-7.08 (m, 3H), 6.64 (d, J=11.0 Hz, 1H), 6.51 (dd, J=11.0, 11.1 Hz, 1H), 5.92 (s+t, J=1.3Hz, 2H), 5.88 (d, J=11.1Hz, 1H), 4.18 (q, J=7.1Hz, 2H), 2.80 (t, J=6.6 Hz, 2H), 2.38 (d, J=1.3Hz, 3H), 1.68 (t, J=6.6Hz, 2H), 1.29 (t, J=7.1 Hz, 3H), 1.15 (s, 6H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 167.1, 153.3, 150.7, 138.7, 134.5, 132.2, 131.5, 130.8, 128.1, 127.7, 124.8, 118.8, 59.6, 38.3, 36.4, 27.9, 26.7, 19.3, 14.4. MS (E.I.) m/z 310 (51%), 208 (45%), 181 (100%).

F2: Compound **6.21 (1'Z,2E,4E)**.

^{1}H NMR (200 MHz, $CDCl_3$)δ 7.34-7.10 (m, 4H), 7.10 (dd, J=11.0, 15.2Hz, 1H), 6.36 (d, J=15.2Hz, 1H), 6.28 (d, J=11.0Hz, 1H), 5.76 (s, 1H), 4.16 (q, J=7.2Hz, 2H), 2.80 (t, J=6.6 Hz, 2H), 2.25 (d, J=1Hz, 3H), 1.69 (t, J=6.6Hz, 2H), 1.28 (t, J=7.2 Hz, 3H), 1.15 (s, 6H). ^{13}C NMR (68 MHz, $CDCl_3$) δ 167.2, 153.0, 151.2, 138.8, 135.5, 135.0, 133.6, 130.2, 128.3, 127.8, 125.0, 121.6, 118.2, 59.6, 38.3, 36.4, 27.9, 26.7, 19.3, 14.4. MS (E.I.) m/z 310 (51%), 208 (45%), 181 (49%), 158 (100%).

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CHAPTER 7.

CONCLUSION.

A new method for the regioselective synthesis of allylsilanes was developed. Reductive desulfonylation of silylated allylsulfones, with the NaDMAN reagent, gave the corresponding allylsilanes in good yields. Improvement of this method using diethylamine as solvent for the silylated sulfones substrates, gave allylsilanes with better yields and stereoselectivity. The mechanistic considerations for this reaction were discussed in chapter 2. The reactivity of silylated sulfones was also discussed in chapter 2. The silylated allylsulfones chemistry is similar to that of allylsilanes in general except under Lewis acid catalyzed allylations reaction conditions, where the silylated allylsulfones were showed to be inert even at room temperature.

The reductive desulfonylation reaction was used to generate an allylsilane anion which was in turn reacted *in situ* with aldehydes to give polyene products. Some of the allylsilanes synthesized in chapter 2 were deprotonated and reacted with carbonyl electrophiles. These reactions permitted the synthesis of *cis* and *trans* retinoic acid esters. The main inconveniences in using this type of approach are the strong basicity of the intermediate allylsilane anions and the 1,4-conjugate addition reaction which seemed to be predominant in the reaction of these anions with enals.

Exploration of the reactivity of α-lithioallylsilanes having an aminomethyl group attached to the silicon atom did not lead to the development of a new method for α-condensation of carbonyl electrophiles. Instead, a new solvent sensitive method for the preparation of *cis* and *trans* vinylsilanes was discovered. The use of dimethoxyethane in benzene led to the formation of the *cis* vinylsilanes; toluene as solvent gave the *trans* isomers. These observations were tentatively explained invoking the formation of a seven membered ring intermediate. The solvent effect remains puzzling.

The exploration into new ways of making and breaking the carbon silicon bond has lead to investigations into two interesting research subjects: The substitution of an aryl group on a silicon atom and the hydrosilylation of an allene to give the corresponding *cis* and *trans* allylsilanes isomers. These studies permitted the preparation of a number of fragile (aminomethyl)silanes.

The second part of this thesis dealt with the synthesis and biological evaluation of a number of new retinoic acid analogs for the treatment of cancer. These compounds were synthesized from very simple starting materials; indanone, tetralone and benzosuberone. The results from the structure-activity relationship demonstrated the definite effect the ring size has on the anticancer activity of these compounds. A discussion of the results was given in chapter 6.

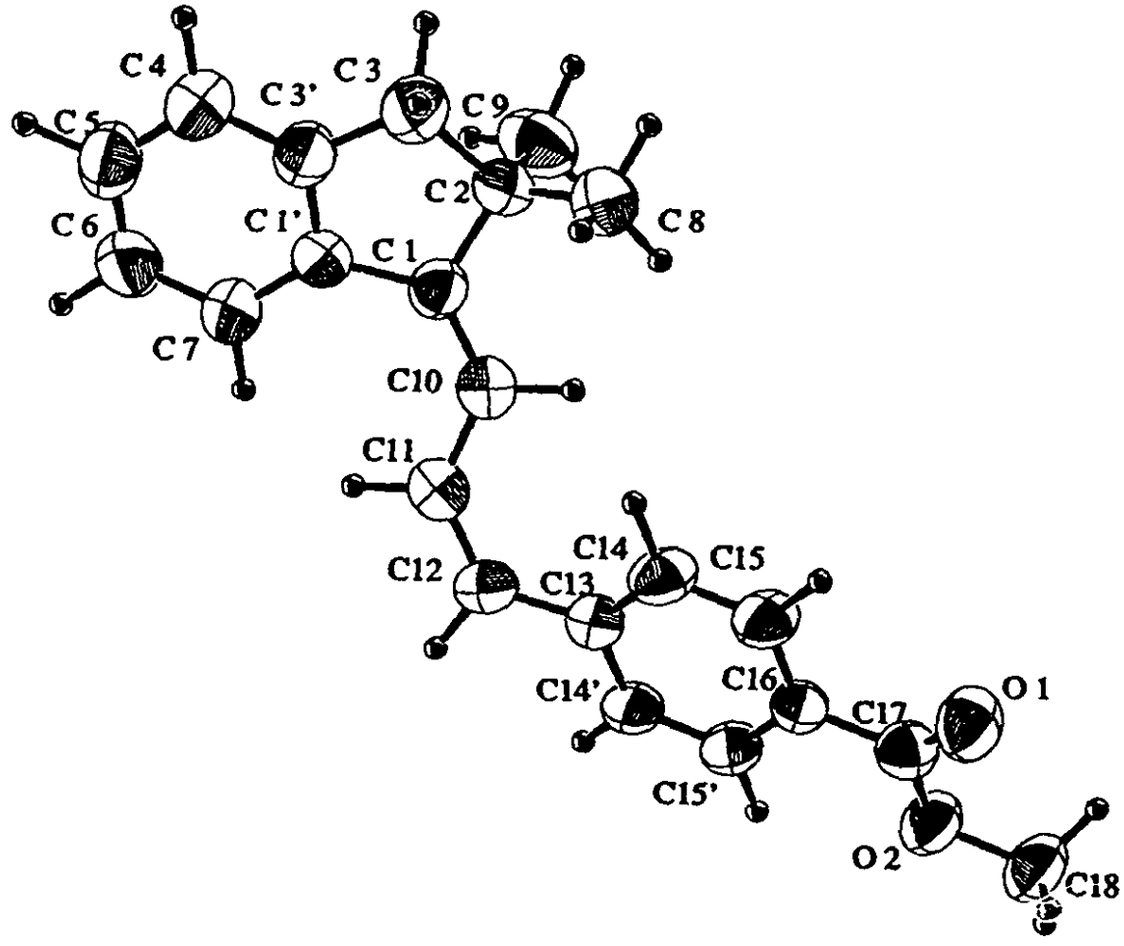
Appendix 1

X-ray Structure Report

for

Compound **6a** (chapter 6)*

* I would like to thank Dr. R. Hynes of the McGill X-ray Facility for this work.


C4
C3'
C3
C5
C9
C2
C6
C1'
C1
C8
C7
C10
C11
C12
C14
C15
C13
C16
C14'
O1
C17
C15'
O2
C18

DENIS2 - DENIS/CHAN - NOV 17/92

Space Group and Cell Dimensions Triclinic, P -1
a 6.1553(11) b 9.6474(16) c 15.044(4)
alpha 92.961(17) beta 92.706(18) gamma 100.191(14)
Volume 876.6(3)A**3

Empirical formula : C22 H22 O2

Cell dimensions were obtained from 25 reflections with 2Theta angle in the range 37.00 - 43.00 degrees.

Crystal dimensions : 0.50 X 0.40 X 0.25 mm

FW = 318.41 Z = 2 F(000) = 340.12

Dcalc 1.206Mg.m-3, mu 0.07mm-1, lambda 0.70930A, 2Theta(max) 45.0

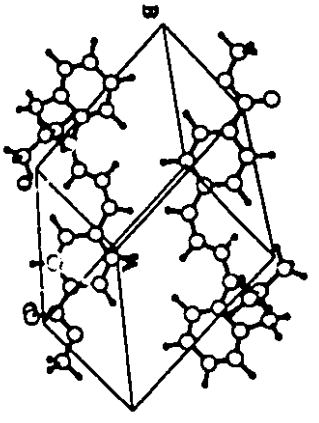
The intensity data were collected on a Rigaku diffractometer, controlled by TEXRAY software, using the theta/2theta scan mode.
The h,k,l ranges used during structure solution and refinement are :--
Hmin,max -6 6; Kmin,max 0 10; Lmin,max -16 16
No. of reflections measured 2576
No. of unique reflections 2317
No. of reflections with Inet > 2.5sigma(Inet) 1740
No correction was made for absorption

The last least squares cycle was calculated with
46 atoms, 305 parameters and 1742 out of 2319 reflections.
Weights based on counting-statistics were used.
The weight modifier K in KFo**2 is 0.000100

The residuals are as follows :--
For significant reflections, RF 0.039, Rw 0.042 GoF 2.05
For all reflections, RF 0.058, Rw 0.043.
where RF = Sum(Fo-Fc)/Sum(Fo),
Rw = Sqrt[Sum(w(Fo-Fc)**2)/Sum(wFo**2)] and
GoF = Sqrt[Sum(w(Fo-Fc)**2)/(No. of reflns - No. of params.)]
The maximum shift/sigma ratio was 0.046.

In the last D-map, the deepest hole was -0.130e/A**3,
and the highest peak 0.130e/A**3.

Standard intensities, monitored throughout the course of collection, showed no decay. (average variation 0.3%) Merging R was 0.7% for 259 pairs of symmetry-related reflections. Structure was solved by direct methods; hydrogens were located in a difference map and refined isotropically. All non-hydrogens were refined anisotropically. All computing for solution and refinement done using the NRCVAX system of crystallographic software.



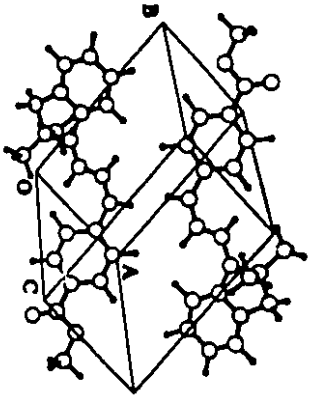


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Table 2. Atomic Parameters x,y,z and Beq
E.S.Ds. refer to the last digit printed.

	x	y	z	Beq
O 1	0.5459(3)	0.35388(17)	0.59349(12)	6.45(10)
O 2	0.1949(3)	0.24586(16)	0.56819(11)	5.65(9)
C 1	1.0662(4)	-0.30571(23)	0.83040(14)	4.52(11)
C 1'	1.1453(4)	-0.44010(23)	0.82770(14)	4.50(11)
C 2	1.2091(4)	-0.20794(24)	0.90168(15)	4.96(11)
C 3	1.4220(5)	-0.2707 (3)	0.90800(23)	5.94(15)
C 3'	1.3536(4)	-0.42071(25)	0.87301(15)	4.94(12)
C 4	1.4690(5)	-0.5293 (3)	0.87862(19)	6.01(15)
C 5	1.3784(5)	-0.6607 (3)	0.84006(19)	6.40(17)
C 6	1.1693(6)	-0.6827 (3)	0.79740(19)	6.44(16)
C 7	1.0537(5)	-0.5736 (3)	0.79090(17)	5.66(14)
C 8	1.2556(7)	-0.0546 (3)	0.8799 (3)	7.27(19)
C 9	1.0960(6)	-0.2267 (4)	0.99021(21)	7.35(20)
C10	0.9057(4)	-0.2628 (3)	0.77996(16)	4.88(12)
C11	0.7594(4)	-0.3423 (3)	0.71142(16)	5.33(13)
C12	0.6110(4)	-0.2968 (3)	0.65763(17)	5.30(13)
C13	0.5625(4)	-0.15560(23)	0.64647(14)	4.41(11)
C14	0.7153(4)	-0.0312 (3)	0.66129(17)	5.11(13)
C14'	0.3525(4)	-0.1427 (3)	0.61306(16)	5.02(12)
C15	0.6631(4)	0.0963 (3)	0.64402(16)	5.12(12)
C15'	0.3001(4)	-0.0141 (3)	0.59594(16)	4.84(13)
C16	0.4535(4)	0.10786(22)	0.61113(14)	4.22(10)
C17	0.4094(4)	0.2483 (3)	0.59053(15)	4.81(12)
C18	0.1359(6)	0.3801 (3)	0.5497 (3)	6.43(18)
H 3A	1.502 (4)	-0.2597 (23)	0.9713 (17)	7.2 (7)
H 3B	1.533 (4)	-0.217 (3)	0.8708 (17)	8.6 (8)
H 4	1.624 (4)	-0.511 (3)	0.9108 (17)	8.6 (8)
H 5	1.464 (4)	-0.742 (3)	0.8424 (16)	8.0 (7)
H 6	1.101 (4)	-0.775 (3)	0.7716 (16)	7.6 (7)
H 7	0.896 (4)	-0.5954 (22)	0.7602 (15)	6.1 (6)
H 8A	1.354 (5)	-0.045 (3)	0.8208 (22)	11.5 (11)
H 8B	1.104 (5)	-0.019 (3)	0.8856 (17)	8.9 (8)
H 8C	1.365 (5)	-0.006 (3)	0.9294 (19)	9.1 (8)
H 9A	0.965 (4)	-0.188 (3)	0.9862 (17)	7.9 (8)
H 9B	1.195 (4)	-0.164 (3)	1.0409 (19)	8.4 (7)
H 9C	1.072 (5)	-0.345 (4)	1.0094 (22)	13.4 (11)
H10	0.884 (3)	-0.1616 (21)	0.7914 (13)	4.9 (5)
H11	0.772 (4)	-0.4485 (24)	0.7063 (14)	6.4 (6)
H12	0.514 (4)	-0.3703 (24)	0.6202 (15)	6.3 (6)
H14	0.857 (4)	-0.0379 (21)	0.6794 (14)	5.3 (6)
H14'	0.250 (3)	-0.2236 (22)	0.6044 (13)	4.8 (5)
H15	0.759 (4)	0.1803 (22)	0.6518 (14)	5.4 (6)
H15'	0.168 (3)	-0.0064 (20)	0.5715 (14)	4.8 (5)
H18A	0.213 (5)	0.417 (3)	0.4985 (20)	9.5 (9)
H18B	-0.017 (5)	0.360 (3)	0.5391 (20)	9.5 (10)
H18C	0.182 (5)	0.448 (3)	0.5981 (20)	9.5 (10)

Beq is the mean of the principal axes of the thermal ellipsoid for atoms refined anisotropically. For hydrogens, Beq = Biso.

Table 3. Bond Distances in Angstroms

O(1)-C(17)	1.198(3)	C(9)-H(9A)	0.95(3)
O(2)-C(17)	1.343(3)	C(9)-H(9B)	1.05(3)
O(2)-C(18)	1.442(3)	C(9)-H(9C)	1.18(4)
C(1)-C(1')	1.463(3)	C(10)-C(11)	1.432(3)
C(1)-C(2)	1.525(3)	C(10)-H(10)	1.015(20)
C(1)-C(10)	1.353(3)	C(11)-C(12)	1.338(4)
C(1')-C(3')	1.401(3)	C(11)-H(11)	1.041(23)
C(1')-C(7)	1.387(3)	C(12)-C(13)	1.461(3)
C(2)-C(3)	1.539(4)	C(12)-H(12)	0.977(24)
C(2)-C(8)	1.513(4)	C(13)-C(14)	1.388(3)
C(2)-C(9)	1.536(4)	C(13)-C(14')	1.393(3)
C(3)-C(3')	1.495(4)	C(14)-C(15)	1.360(4)
C(3)-H(3A)	1.04(3)	C(14)-H(14)	0.913(22)
C(3)-H(3B)	0.99(3)	C(14')-C(15')	1.370(4)
C(3')-C(4)	1.370(4)	C(14')-H(14')	0.912(21)
C(4)-C(5)	1.377(4)	C(15)-C(16)	1.385(3)
C(4)-H(4)	1.03(3)	C(15)-H(15)	0.914(22)
C(5)-C(6)	1.388(5)	C(15')-C(16)	1.373(3)
C(5)-H(5)	1.02(3)	C(15')-H(15')	0.893(21)
C(6)-C(7)	1.375(4)	C(16)-C(17)	1.473(3)
C(6)-H(6)	0.97(3)	C(18)-H(18A)	0.99(3)
C(7)-H(7)	1.035(24)	C(18)-H(18B)	0.93(3)
C(8)-H(8A)	1.10(3)	C(18)-H(18C)	0.95(3)
C(8)-H(8B)	1.05(3)	H(18A)-H(18C)	1.55(4)
C(8)-H(8C)	1.02(3)		

Table 4. Bond Angles in Degrees

C(17)-O(2)-C(18)	115.79(22)	C(2)-C(9)-H(9C)	111.0(16)
C(1')-C(1)-C(2)	107.38(19)	H(9A)-C(9)-H(9B)	104.6(21)
C(1')-C(1)-C(10)	130.47(21)	H(9A)-C(9)-H(9C)	115.3(23)
C(2)-C(1)-C(10)	122.08(20)	H(9B)-C(9)-H(9C)	108.4(21)
C(1)-C(1')-C(3')	108.94(20)	C(1)-C(10)-C(11)	128.20(23)
C(1)-C(1')-C(7)	132.52(23)	C(1)-C(10)-H(10)	117.0(11)
C(3')-C(1')-C(7)	118.53(22)	C(11)-C(10)-H(10)	114.8(11)
C(1)-C(2)-C(3)	102.75(19)	C(10)-C(11)-C(12)	127.95(24)
C(1)-C(2)-C(8)	114.34(21)	C(10)-C(11)-H(11)	113.1(12)
C(1)-C(2)-C(9)	107.76(22)	C(12)-C(11)-H(11)	118.9(12)
C(3)-C(2)-C(8)	111.75(25)	C(11)-C(12)-C(13)	131.35(24)
C(3)-C(2)-C(9)	108.39(24)	C(11)-C(12)-H(12)	115.2(13)
C(8)-C(2)-C(9)	111.4(3)	C(13)-C(12)-H(12)	113.4(13)
C(2)-C(3)-C(3')	104.86(21)	C(12)-C(13)-C(14)	124.83(22)
C(2)-C(3)-H(3A)	114.5(13)	C(12)-C(13)-C(14')	118.68(22)
C(2)-C(3)-H(3B)	109.1(15)	C(14)-C(13)-C(14')	116.36(21)
C(3')-C(3)-H(3A)	113.6(12)	C(13)-C(14)-C(15)	121.87(23)
C(3')-C(3)-H(3B)	111.5(15)	C(13)-C(14)-H(14)	117.8(13)
H(3A)-C(3)-H(3B)	103.4(20)	C(15)-C(14)-H(14)	120.2(13)
C(1')-C(3')-C(3)	110.27(21)	C(13)-C(14')-C(15')	121.68(23)
C(1')-C(3')-C(4)	121.21(23)	C(13)-C(14')-H(14')	117.1(12)
C(3)-C(3')-C(4)	128.48(25)	C(15')-C(14')-H(14')	121.2(12)
C(3')-C(4)-C(5)	119.7(3)	C(14)-C(15)-C(16)	121.26(24)
C(3')-C(4)-H(4)	119.3(14)	C(14)-C(15)-H(15)	124.6(13)
C(5)-C(4)-H(4)	121.0(14)	C(16)-C(15)-H(15)	114.1(13)
C(4)-C(5)-C(6)	119.8(3)	C(14')-C(15')-C(16)	121.12(23)
C(4)-C(5)-H(5)	120.6(14)	C(14')-C(15')-H(15')	121.6(13)
C(6)-C(5)-H(5)	119.6(14)	C(16)-C(15')-H(15')	117.2(13)
C(5)-C(6)-C(7)	120.7(3)	C(15)-C(16)-C(15')	117.72(22)
C(5)-C(6)-H(6)	121.0(15)	C(15)-C(16)-C(17)	118.73(21)
C(7)-C(6)-H(6)	118.3(15)	C(15')-C(16)-C(17)	123.50(21)
C(1')-C(7)-C(6)	120.0(3)	O(1)-C(17)-O(2)	122.84(21)
C(1')-C(7)-H(7)	121.8(12)	O(1)-C(17)-C(16)	125.01(22)
C(6)-C(7)-H(7)	118.2(12)	O(2)-C(17)-C(16)	112.15(21)
C(2)-C(8)-H(8A)	108.8(16)	O(2)-C(18)-H(18A)	108.4(16)
C(2)-C(8)-H(8B)	105.5(14)	O(2)-C(18)-H(18B)	104.4(18)
C(2)-C(8)-H(8C)	105.0(15)	O(2)-C(18)-H(18C)	111.3(17)
H(8A)-C(8)-H(8B)	124.3(22)	H(18A)-C(18)-H(18B)	114.3(25)
H(8A)-C(8)-H(8C)	102.9(23)	H(18A)-C(18)-H(18C)	105.7(24)
H(8B)-C(8)-H(8C)	108.9(20)	H(18B)-C(18)-H(18C)	112.7(25)
C(2)-C(9)-H(9A)	108.3(16)	C(18)-H(18A)-H(18C)	36.3(15)
C(2)-C(9)-H(9B)	109.1(14)	C(18)-H(18C)-H(18A)	38.0(16)

Table S-2. Anisotropic u(i,j) values *100.
E.S.Ds. refer to the last digit printed

	u11	u22	u33	u12	u13	u23
O 1	6.82(12)	5.86(11)	11.52(15)	0.52(10)	-0.66(11)	0.82(10)
O 2	5.94(11)	6.43(11)	9.28(13)	1.92(9)	-1.11(9)	0.75(9)
C 1	5.85(15)	6.14(15)	5.40(14)	1.66(12)	0.33(12)	0.38(11)
C 1'	6.58(16)	5.53(14)	5.04(14)	1.34(12)	0.48(12)	-0.10(11)
C 2	6.14(16)	6.36(16)	6.30(16)	1.55(12)	-0.74(13)	-0.67(12)
C 3	6.30(19)	7.05(18)	9.11(22)	1.52(15)	-0.87(17)	-0.46(16)
C 3'	6.37(16)	6.41(16)	6.25(15)	1.90(13)	0.23(13)	0.50(12)
C 4	7.66(21)	7.35(19)	8.33(19)	2.70(16)	0.16(16)	0.70(15)
C 5	10.18(25)	7.05(20)	8.04(20)	3.98(19)	0.79(18)	0.89(15)
C 6	11.0 (3)	6.11(18)	7.50(19)	2.42(18)	-0.93(18)	-0.29(15)
C 7	8.48(21)	6.22(17)	7.01(18)	2.21(16)	-0.67(16)	0.10(13)
C 8	9.7 (3)	6.31(19)	11.1 (3)	1.43(18)	-2.65(24)	-0.97(18)
C 9	8.43(24)	12.6 (3)	6.88(20)	2.66(23)	0.06(18)	-2.00(20)
C10	6.45(17)	5.72(15)	6.40(15)	1.45(13)	0.04(13)	-0.21(12)
C11	7.54(18)	6.17(17)	6.62(16)	1.89(14)	-0.77(14)	-0.09(13)
C12	6.97(18)	6.11(16)	6.87(17)	1.28(14)	-1.33(14)	-0.18(14)
C13	5.43(15)	5.77(15)	5.46(14)	1.05(12)	-0.63(12)	0.09(11)
C14	4.48(16)	6.99(18)	7.81(18)	0.81(14)	-0.96(14)	1.22(13)
C14'	5.54(16)	5.55(16)	7.42(17)	0.14(14)	-1.42(13)	-0.17(13)
C15	5.28(16)	5.78(17)	7.93(18)	0.02(14)	-1.12(14)	0.91(13)
C15'	4.69(16)	6.70(17)	6.93(17)	1.33(14)	-1.22(13)	0.11(13)
C16	4.82(14)	5.41(14)	5.60(14)	0.61(12)	-0.39(11)	-0.04(11)
C17	6.00(17)	6.10(16)	6.19(16)	1.34(14)	-0.14(13)	0.06(12)
C18	7.62(24)	7.15(20)	10.2 (3)	2.82(18)	-0.63(21)	1.48(19)

Anisotropic Temperature Factors are of the form
Temp=-2*Pi*Pi*(h*h*u11*astar*astar+---+2*h*k*u12*astar*bstar+---)

Table S-3. Torsion Angles in Degrees

C18	O 2	C17	O 1	-1.4(	2)	C18	O 2	C17	C16	178.1(	3)
C 2	C 1	C 1′	C 3′	-15.1(	1)	C 2	C 1	C 1′	C 7	164.4(	3)
C10	C 1	C 1′	C 3′	162.1(	3)	C10	C 1	C 1′	C 7	-18.4(	1)
C 1′	C 1	C 2	C 3	23.2(	1)	C 1′	C 1	C 2	C 8	144.5(	3)
C 1′	C 1	C 2	C 9	-91.2(	2)	C10	C 1	C 2	C 3	-154.3(	3)
C10	C 1	C 2	C 8	-33.0(	2)	C10	C 1	C 2	C 9	91.4(	2)
C 1′	C 1	C10	C11	3.4(	1)	C 2	C 1	C10	C11	-179.7(	3)
C 1	C 1′	C 3′	C 3	0.0(	1)	C 1	C 1′	C 3′	C 4	-178.2(	3)
C 7	C 1′	C 3′	C 3	-179.6(	3)	C 7	C 1′	C 3′	C 4	2.2(	2)
C 1	C 1′	C 7	C 6	179.0(	3)	C 3′	C 1′	C 7	C 6	-1.6(	1)
C 1	C 2	C 3	C 3′	-22.6(	1)	C 8	C 2	C 3	C 3′	-145.6(	3)
C 9	C 2	C 3	C 3′	91.3(	2)	C 2	C 3	C 3′	C 1′	14.8(	1)
C 2	C 3	C 3′	C 4	-167.2(	3)	C 1′	C 3′	C 4	C 5	-0.8(	1)
C 3	C 3′	C 4	C 5	-178.6(	3)	C 3′	C 4	C 5	C 6	-1.3(	1)
C 4	C 5	C 6	C 7	1.9(	2)	C 5	C 6	C 7	C 1′	-0.4(	1)
C 1	C10	C11	C12	-175.1(	3)	C10	C11	C12	C13	5.2(	1)
C11	C12	C13	C14	28.9(	2)	C11	C12	C13	C14′	-155.5(	3)
C12	C13	C14	C15	175.6(	3)	C14′	C13	C14	C15	-0.1(	1)
C12	C13	C14′	C15′	-176.0(	3)	C14	C13	C14′	C15′	-0.1(	1)
C13	C14	C15	C16	0.4(	1)	C13	C14′	C15′	C16	0.0(	1)
C14	C15	C16	C15′	-0.4(	1)	C14	C15	C16	C17	-177.7(	3)
C14′	C15′	C16	C15	0.2(	1)	C14′	C15′	C16	C17	177.4(	3)
C15	C16	C17	O 1	6.0(	1)	C15	C16	C17	O 2	-173.5(	3)
C15′	C16	C17	O 1	-171.1(	3)	C15′	C16	C17	O 2	9.4(	1)

Table S-4. Distances(A) to the Least-Squares Planes

Plane no. 1

Equation of the plane :- 2.634(7)X - 2.019(12)Y + 13.412(9)Z = 8.984(16)

Distances(A) to the plane from the atoms in the plane.

C 1′	-0.011(3)	C 3′	0.009(3)
C 4	0.000(4)	C 5	-0.013(4)
C 6	0.010(4)	C 7	0.007(4)

Chi squared for this plane 41.040

Distances(A) to the plane from the atoms out of the plane.

C 1	-0.037(4)	C 2	0.345(5)
C 3	-0.004(5)		

Plane no. 2

Equation of the plane :- 2.193(6)X + 1.003(10)Y + 14.216(5)Z = 7.800(6)

Distances(A) to the plane from the atoms in the plane.

C13	0.001(3)	C14	0.001(3)
C14′	-0.001(3)	C15	-0.002(3)
C15′	0.000(3)	C16	0.001(3)

Chi squared for this plane 0.978

Distances(A) to the plane from the atoms out of the plane.

O 1	-0.205(4)	O 2	0.097(4)
C17	-0.054(4)	C18	0.098(6)

Dihedral angle between planes A and B

A	B	Angle(deg)
1	2	20.01(9)

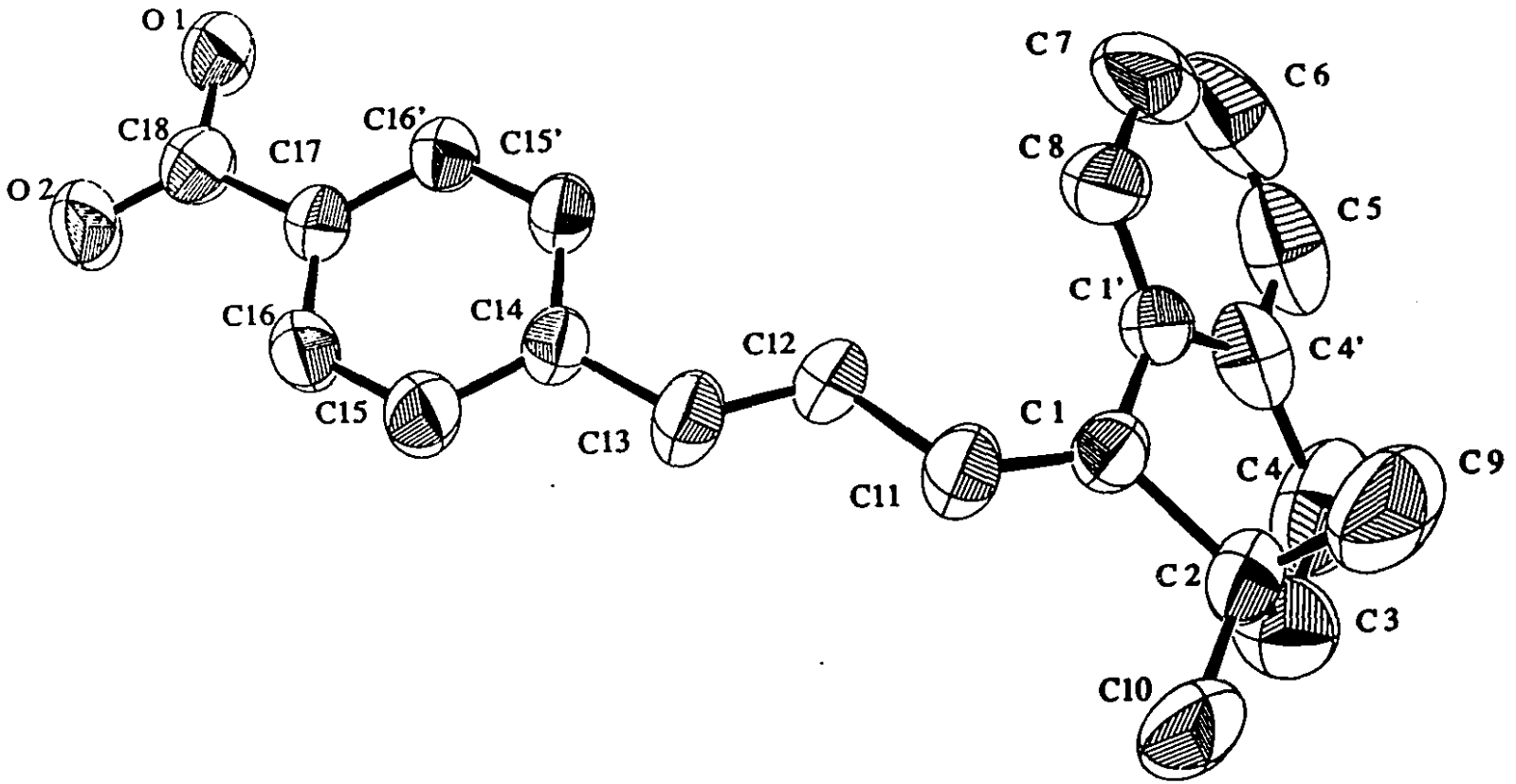
Appendix 2

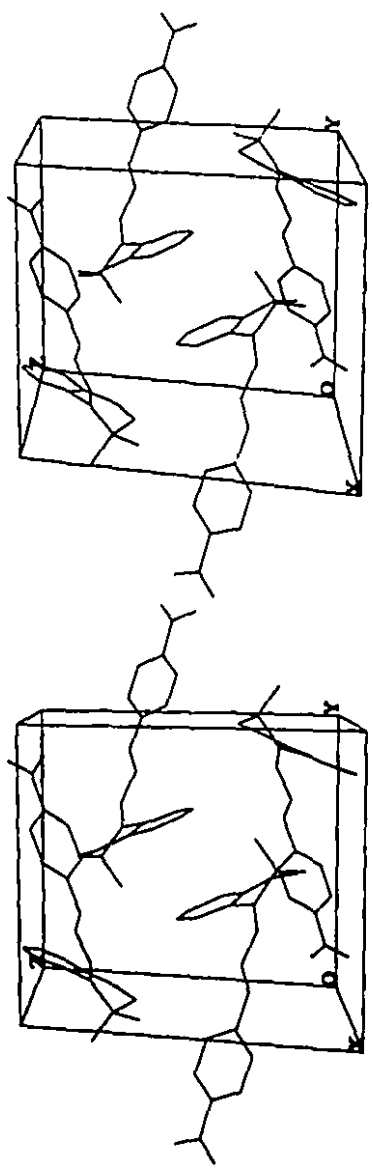
X-ray Structure Report

for

Compound **9b** (chapter 6)*

* I would like to thank Dr. R. Hynes of the McGill X-ray Facility for this work.


O 1
C18
O 2
C17
C16'
C15'
C16
C14
C15
C13
C12
C11
C7
C6
C8
C5
C 1'
C4'
C 1
C4
C9
C2
C3
C10



DENIS1 - DENIS/CHAN - AUG 10/92

Space Group and Cell Dimensions Monoclinic, P 21/c
a 12.5797(23) b 11.3738(18) c 13.491(4)
beta 109.078(16)
Volume 1824.3(6)A**3

Empirical formula : C22 H22 O2

Cell dimensions were obtained from 25 reflections with 2Theta angle in the range 30.00 - 35.00 degrees.

Crystal dimensions : 0.50 X 0.35 X 0.20 mm

FW = 318.41 Z = 4 F(000) = 680.24

Dcalc 1.159Mg.m-3, mu 0.07mm-1, lambda 0.70930A, 2Theta(max) 44.9

The intensity data were collected on a Rigaku diffractometer, controlled by TEXRAY software, using the theta/2theta scan mode.
The h,k,l ranges used during structure solution and refinement are :--
Hmin,max -13 12; Kmin,max 0 12; Lmin,max 0 14

No. of reflections measured	2515
No. of unique reflections	2391
No. of reflections with Inet > 2.5sigma(Inet)	1339

No correction was made for absorption

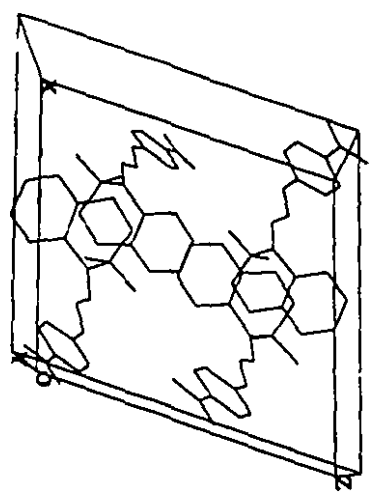
The last least squares cycle was calculated with
49 atoms, 217 parameters and 1339 out of 2391 reflections.
Weights based on counting-statistics were used.
The weight modifier K in KFo**2 is 0.000050

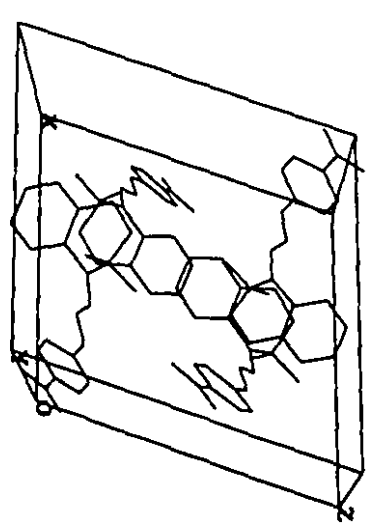
The residuals are as follows :--
For significant reflections, RF 0.057, Rw 0.052 GoF 2.13
For all reflections, RF 0.117, Rw 0.054.
where RF = Sum(Fo-Fc)/Sum(Fo),
Rw = Sqrt[Sum(w(Fo-Fc)**2)/Sum(wFo**2)] and
GoF = Sqrt[Sum(w(Fo-Fc)**2)/(No. of reflns - No. of params.)]
The maximum shift/sigma ratio was 0.048.

In the last D-map, the deepest hole was -0.220e/A**3,
and the highest peak 0.220e/A**3.

Secondary ext. coeff. = 0.375419 sigma = 0.084696

Standard intensities did not change over the course of collection.
Merging R was 1.0% for 124 pairs of symmetry related reflections.
Structure was solved by direct methods and refined by full-matrix least-squares. Hydrogens were included in calculated positions. Non-hydrogens were refined anisotropically, except for C(3), which is disordered over two positions with occupancies of 0.75 C(3), and 0.25 C(3a). All computing done with NRCVAX system of crystallographic programs.





The following references are relevant to the NRCVAX System.

1. Full System Reference :
   NRCVAX, Gabe, E.J., Le Page, Y., Charland, J.-P., Lee, F.l. and White, P.S. (1989) J. Appl. Cryst., 22, 384-387.

2. Scattering Factors from Int. Tab. Vol. 4 :
   International Tables for X-ray Crystallography, Vol. IV, (1974) Kynoch Press, Birmingham, England.

3. ORTEP Plotting :
   Johnson, C.K., (1976) ORTEP - A Fortran Thermal Ellipsoid Plot Program, Tehnical Report ORNL-5138, Oak Ridge, Tennessee.

4. Extinction Treatment :
   Larson, A.C., (1970) p.293, Crystallographic Computing, Munksgaard, Copenhagen.

Table . Distances(A) to the least-squares planes.

Plane no. 1

Equation of the plane : 8.431(14)X - 3.948(5)Y + 5.408(19)Z = 5.241(20)

Distances(A) to the plane from the atoms in the plane.

O 1	0.037(5)	O 2	0.056(5)
C11	0.103(6)	C12	0.112(5)
C13	-0.099(5)	C14	-0.071(5)
C15	-0.026(6)	C15′	-0.097(5)
C16	0.004(6)	C16′	-0.061(5)
C17	-0.017(5)	C18	0.026(6)

Chi squared for this plane 1998.046

Plane no. 2

Equation of the plane : 8.730(20)X - 3.684(22)Y + 5.14(3)Z = 5.03(3)

Distances(A) to the plane from the atoms in the plane.

C14	0.003(6)	C15	-0.001(7)
C15′	-0.004(6)	C16	0.000(7)
C16′	0.003(6)	C17	-0.001(6)

Chi squared for this plane 1.125

Distances(A) to the plane from the atoms out of the plane.

O 1	0.042(9)	O 2	-0.005(9)
C 1	0.652(14)	C11	0.278(12)
C12	0.262(9)	C13	0.005(8)
C18	0.009(8)		

Plane no. 3

Equation of the plane :- 0.54(4)X + 10.595(13)Y - 4.41(4)Z = 4.12(5)

Distances(A) to the plane from the atoms in the plane.

C 1′	-0.023(7)	C 4′	0.024(8)
C 5	-0.005(11)	C 6	-0.037(14)
C 7	0.013(12)	C 8	0.014(8)

Chi squared for this plane 30.365

Distances(A) to the plane from the atoms out of the plane.

C 1	-0.080(10)	C 2	0.764(13)
C 3	0.179(15)	C 4	0.141(12)
C11	-0.871(13)		

Dihedral angle between planes A and B

A	B	Angle(deg)
1	2	2.04(14)
1	3	126.09(18)
2	3	124.32(21)

Table 2. Atomic Parameters x,y,z and Beq
E.S.Ds. refer to the last digit printed.

	x	y	z	Beq
O 1	0.0657(3)	0.1251(3)	0.9648(3)	6.49(22)
O 2	-0.0209(3)	0.0982(3)	1.0837(3)	7.04(23)
C 1	0.3213(4)	0.8994(4)	1.2046(3)	4.14(24)
C 1′	0.3920(5)	0.8799(4)	1.1364(4)	4.5 (3)
C 2	0.3535(5)	1.0097(4)	1.2743(4)	5.4 (3)
C 3	0.4751(7)	0.9886(7)	1.3414(6)	6.94(19)
C 3A	0.4743(23)	1.0553(23)	1.2874(19)	7.3 (6)
C 4	0.5521(5)	0.9648(6)	1.2832(6)	8.8 (4)
C 4′	0.5054(5)	0.9070(5)	1.1769(5)	5.9 (3)
C 5	0.5729(6)	0.8822(6)	1.1156(7)	8.6 (5)
C 6	0.5296(9)	0.8359(7)	1.0169(8)	10.5 (8)
C 7	0.4158(8)	0.8170(6)	0.9743(6)	8.8 (5)
C 8	0.3464(5)	0.8385(4)	1.0342(4)	6.0 (3)
C 9	0.3304(7)	1.1173(5)	1.2072(5)	10.5 (5)
C10	0.2949(7)	1.0193(6)	1.3544(5)	12.1 (6)
C11	0.2423(4)	0.8237(4)	1.2118(4)	4.9 (3)
C12	0.2193(4)	0.7079(4)	1.1646(3)	4.38(25)
C13	0.1466(4)	0.6345(4)	1.1855(4)	5.0 (3)
C14	0.1188(4)	0.5141(4)	1.1460(3)	4.02(24)
C15	0.0605(4)	0.4421(4)	1.1927(4)	5.9 (3)
C15′	0.1482(4)	0.4695(4)	1.0627(3)	4.3 (3)
C16	0.0328(5)	0.3282(4)	1.1582(4)	5.9 (3)
C16′	0.1214(4)	0.3556(4)	1.0281(3)	4.3 (3)
C17	0.0628(4)	0.2843(4)	1.0755(4)	4.3 (3)
C18	0.0323(5)	0.1614(4)	1.0413(4)	5.2 (3)

Beq is the mean of the principal axes of the thermal elipsoid for atoms refined anisotropically. For C(3), C(3a) Beq = Biso.

Table 3. Bond Distances(A) and Angles(Degrees)

O(1)-C(18)	1.301(6)	C(4')-C(5)	1.394(9)
O(2)-C(18)	1.243(6)	C(5)-C(6)	1.368(14)
C(1)-C(1')	1.490(7)	C(6)-C(7)	1.375(15)
C(1)-C(2)	1.540(6)	C(7)-C(8)	1.391(10)
C(1)-C(11)	1.343(7)	C(11)-C(12)	1.449(6)
C(1')-C(4')	1.386(8)	C(12)-C(13)	1.334(7)
C(1')-C(8)	1.391(7)	C(13)-C(14)	1.470(6)
C(2)-C(3)	1.520(11)	C(14)-C(15)	1.381(7)
C(2)-C(3A)	1.56(3)	C(14)-C(15')	1.389(6)
C(2)-C(9)	1.493(8)	C(15)-C(16)	1.383(7)
C(2)-C(10)	1.498(8)	C(15')-C(16')	1.381(6)
C(3)-C(4)	1.457(11)	C(16)-C(17)	1.382(7)
C(3A)-C(4)	1.43(3)	C(16')-C(17)	1.386(6)
C(4)-C(4')	1.511(10)	C(17)-C(18)	1.483(6)

C(1')-C(1)-C(2)	114.0(4)	C(3A)-C(4)-C(4')	106.9(11)
C(1')-C(1)-C(11)	123.6(4)	C(1')-C(4')-C(4)	120.1(5)
C(2)-C(1)-C(11)	122.1(4)	C(1')-C(4')-C(5)	118.0(6)
C(1)-C(1')-C(4')	117.9(4)	C(4)-C(4')-C(5)	121.9(6)
C(1)-C(1')-C(8)	121.8(5)	C(4')-C(5)-C(6)	122.0(7)
C(4')-C(1')-C(8)	120.2(5)	C(5)-C(6)-C(7)	119.7(7)
C(1)-C(2)-C(3)	104.4(5)	C(6)-C(7)-C(8)	119.7(7)
C(1)-C(2)-C(3A)	113.1(10)	C(1')-C(8)-C(7)	120.1(6)
C(1)-C(2)-C(9)	109.7(4)	C(1)-C(11)-C(12)	126.7(4)
C(1)-C(2)-C(10)	114.0(4)	C(11)-C(12)-C(13)	121.9(4)
C(3)-C(2)-C(9)	116.7(5)	C(12)-C(13)-C(14)	127.3(4)
C(3)-C(2)-C(10)	102.6(5)	C(13)-C(14)-C(15)	119.1(4)
C(3A)-C(2)-C(9)	77.6(11)	C(13)-C(14)-C(15')	122.5(4)
C(3A)-C(2)-C(10)	125.8(10)	C(15)-C(14)-C(15')	118.3(4)
C(9)-C(2)-C(10)	109.5(5)	C(14)-C(15)-C(16)	121.0(4)
C(2)-C(3)-C(4)	115.2(6)	C(14)-C(15')-C(16')	121.1(4)
C(2)-C(3A)-C(4)	114.1(17)	C(15)-C(16)-C(17)	120.3(4)
C(3)-C(4)-C(4')	118.1(5)	C(15')-C(16')-C(17)	120.0(4)
		C(16)-C(17)-C(16')	119.2(4)
		C(16)-C(17)-C(18)	118.7(4)
		C(16')-C(17)-C(18)	122.0(4)
		O(1)-C(18)-O(2)	123.0(4)
		O(1)-C(18)-C(17)	115.3(4)
		O(2)-C(18)-C(17)	121.7(4)

Table S-2. Calculated Hydrogen Atoms Parameters

	x	y	z	Biso
HO1	0.039	0.034	0.946	7.5
H 3A	0.479	0.915	1.394	7.8
H 3B	0.506	1.062	1.394	7.8
H 3AA	0.504	1.085	1.370	7.7
H 3AB	0.473	1.129	1.240	7.7
H 4A	0.596	1.042	1.270	8.7
H 4B	0.615	0.905	1.330	8.7
H 5	0.662	0.899	1.145	10.1
H 6	0.586	0.815	0.973	13.2
H 7	0.385	0.786	0.895	10.4
H 8	0.257	0.825	1.002	6.8
H 9A	0.381	1.116	1.156	10.9
H 9B	0.244	1.124	1.158	10.9
H 9C	0.354	1.196	1.254	10.9
H10A	0.205	1.018	1.318	14.5
H10B	0.319	0.945	1.407	14.5
H10C	0.321	1.098	1.401	14.5
H11	0.191	0.852	1.257	5.9
H12	0.264	0.679	1.112	5.1
H13	0.105	0.668	1.238	6.1
H15	0.034	0.476	1.256	7.3
H15'	0.194	0.525	1.024	5.0
H16	-0.012	0.272	1.196	7.2
H16'	0.147	0.321	0.963	5.1

Hydrogen positions calculated assuming C/O-H distance of 1.08A.
Biso(H) is from Uiso(H) = 0.01 + Ueq of the attached atom.

Table S-3. Anisotropic u(i,j) values *100.
E.S.Ds. refer to the last digit printed

	u11	u22	u33	u12	u13	u23
O 1	12.0(3)	5.16(22)	9.0(3)	-2.81(22)	5.56(24)	-2.13(20)
O 2	13.2(3)	5.69(23)	10.1(3)	-3.88(24)	6.9 (3)	-1.75(20)
C 1	5.7(3)	4.6 (3)	4.9(3)	-0.5 (3)	1.0 (3)	-0.34(24)
C 1'	7.2(4)	4.1 (3)	5.7(3)	-0.3 (3)	2.1 (3)	0.3 (3)
C 2	8.5(4)	4.5 (3)	7.8(4)	-1.5 (3)	3.2 (3)	-1.4 (3)
C 4	7.0(5)	9.3 (5)	13.8(6)	-1.8 (4)	-1.3 (4)	-1.0 (5)
C 4'	6.5(4)	6.0 (4)	10.8(5)	0.3 (3)	4.0 (4)	2.0 (3)
C 5	10.2(6)	7.0 (5)	18.0(7)	1.4 (4)	8.2 (6)	3.7 (5)
C 6	20.5(11)	7.4 (6)	18.0(10)	3.9 (7)	14.6 (11)	4.3 (6)
C 7	20.8(9)	6.1 (4)	9.1(5)	1.6 (6)	8.5 (7)	0.8 (4)
C 8	11.6(5)	5.4 (3)	6.1(4)	-0.2 (3)	3.3 (4)	-0.1 (3)
C 9	22.3(9)	5.1 (4)	10.7(5)	0.0 (5)	2.6 (5)	-1.2 (4)
C10	24.3(9)	11.8 (6)	16.2(6)	-9.2 (6)	15.3 (7)	-9.5 (5)
C11	5.9(4)	5.3 (3)	8.1(4)	-1.2 (3)	3.0 (3)	-1.8 (3)
C12	5.5(3)	4.6 (3)	6.2(3)	-0.8 (3)	1.4 (3)	-1.1 (3)
C13	5.9(3)	5.0 (3)	8.9(4)	-1.3 (3)	3.4 (3)	-2.1 (3)
C14	4.5(3)	4.7 (3)	6.1(3)	-0.8 (3)	1.8 (3)	-0.7 (3)
C15	9.6(5)	6.0 (4)	8.7(4)	-2.2 (3)	5.5 (4)	-2.4 (3)
C15'	5.7(3)	4.5 (3)	6.3(3)	-1.2 (3)	1.8 (3)	-0.3 (3)
C16	10.0(5)	5.9 (4)	8.2(4)	-2.6 (3)	5.4 (3)	-1.2 (3)
C16'	6.2(3)	4.8 (3)	5.6(3)	-0.8 (3)	2.4 (3)	-0.37(24)
C17	6.0(3)	4.5 (3)	5.9(3)	-1.0 (3)	1.9 (3)	-0.4 (3)
C18	8.1(4)	5.1 (4)	6.7(4)	-0.9 (3)	2.9 (3)	-1.0 (3)

Anisotropic Temperature Factors are of the form
Temp=-2*Pi*Pi*(h*h*u11*astar*astar+---+2*h*k*u12*astar*bstar+---)

Table S-4. Torsion Angles in Degrees

C 2	C 1	C 1′	C 4′	37.0(3)	C 2	C 1	C 1′	C 8	-141.5(5)
C11	C 1	C 1′	C 4′	-137.9(5)	C11	C 1	C 1′	C 8	43.6(3)
C 1′	C 1	C 2	C 3	-59.9(4)	C 1′	C 1	C 2	C 3A	-18.7(9)
C 1′	C 1	C 2	C 9	65.8(4)	C 1′	C 1	C 2	C10	-171.0(6)
C11	C 1	C 2	C 3	115.2(5)	C11	C 1	C 2	C 3A	156.3(10)
C11	C 1	C 2	C 9	-119.2(5)	C11	C 1	C 2	C10	4.0(3)
C 1′	C 1	C11	C12	6.4(2)	C 2	C 1	C11	C12	-168.1(5)
C 1	C 1′	C 4′	C 4	-5.4(3)	C 1	C 1′	C 4′	C 5	176.2(6)
C 8	C 1′	C 4′	C 4	173.1(6)	C 8	C 1′	C 4′	C 5	-5.3(3)
C 1	C 1′	C 8	C 7	-177.5(6)	C 4′	C 1′	C 8	C 7	4.1(4)
C 3	C 4	C 4′	C 1′	1.0(4)	C 1	C 2	C 3	C 4	55.4(4)
C 3A	C 4	C 4′	C 1′	-43.7(10)	C 9	C 2	C 3	C 4	-65.7(5)
C 1′	C 4′	C 5	C 6	2.0(4)	C10	C 2	C 3	C 4	174.6(8)
C 4′	C 5	C 6	C 7	2.6(4)	C 1	C 2	C 3A	C 4	-30.7(6)
C 6	C 7	C 8	C 1′	0.6(4)	C 9	C 2	C 3A	C 4	-137.1(18)
C11	C12	C13	C14	-177.8(5)	C10	C 2	C 3A	C 4	117.7(16)
C12	C13	C14	C15′	-14.3(2)	C 2	C 3	C 4	C 4′	-28.6(3)
C15′	C14	C15	C16	0.6(3)	C 2	C 3A	C 4	C 4′	60.3(10)
C15	C14	C15′	C16′	-0.9(3)	C 3	C 4	C 4′	C 5	179.3(7)
C14	C15′	C16′	C17	0.9(2)	C 3A	C 4	C 4′	C 5	134.6(11)
C15	C16	C17	C18	179.6(6)	C 4	C 4′	C 5	C 6	-176.3(8)
C15′	C16′	C17	C18	-179.9(5)	C 5	C 6	C 7	C 8	-3.9(3)
C16	C17	C18	O 2	1.3(2)	C 1	C11	C12	C13	172.9(6)
C16′	C17	C18	O 2	-179.5(6)	C12	C13	C14	C15	166.2(5)
					C13	C14	C15	C16	-179.8(5)
					C13	C14	C15′	C16′	179.6(5)
					C14	C15	C16	C17	-0.3(2)
					C15	C16	C17	C16′	0.3(3)
					C15′	C16′	C17	C16	-0.6(3)
					C16	C17	C18	O 1	-178.3(6)
					C16′	C17	C18	O 1	0.9(2)