DIVERSITY ORIENTED SYNTHETIC STRATEGIES FOR FUNCTIONALIZED ORGANO-SILICON COMPOUNDS AND THEIR APPLICATIONS

By

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DECLARATION

I, hereby declare that the investigation presented in the thesis has been carried out by me. The work is original and has not been submitted earlier as a whole or in part for a degree/diploma at this or any other Institution/University.

Pintu Kumar Kundu

Dedicated to…..

My Beloved Parents and Brother

“Fill the brain, therefore, with high thoughts, highest ideals, place them day and night before you, and out of that will come great work. Talk not about impurity, but say that we are pure.”

– Swami Vivekananda

“এক হাতে কর্ম কর, আর এক হাতে ঈশ্বরকে ধরে থাক।”

– শ্রীরামকৃষ্ণ

"I am among those who think that science has great beauty. A scientist in his laboratory is not only a technician: he is also a child placed before natural phenomena which impress him like a fairy tale."

– Marie Curie

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…. Pintu K. Kundu

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SYNOPSIS

SYNOPSIS OF THE THESIS TO BE SUBMITTED TO THE HOMI BHABHA NATIONAL INSTITUTE FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY

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Diversity Oriented Synthetic Strategies for Functionalized Organo-Silicon Compounds and Their Applications

This thesis describes the use of different properties of silicon for the development of diverse organic reactions and methods to provide functionalized organic molecules with desired levels of regio-, stereo-, and chemo-selectivities. The content of the thesis have been divided into five chapters.

CHAPTER 1

An Introduction to Diversity Oriented Synthesis and Organosilicon Chemistry

The importance of stereo chemically pure compounds arises owing to the central role played by them during enantiomer recognition in biological activities.[1] There are many examples of pharmaceutical drugs, agrochemicals and other chemical compounds where the desired biological property is related to the absolute configuration. Nevertheless, the following question remains unanswered: Are the regions of chemistry space defined by natural products and known drugs, which have been so intensely scrutinized to date, the best or most fertile regions for discovering small-molecules that modulate macromolecular function in useful ways? Given the extraordinary potential for such small molecules to promote the understanding and betterment of human health, it is urgent that organic chemists begin to answer this basic question. Diversity-oriented synthesis[2] (DOS), the most diverse approach aims to meet the above mentioned challenges. Diversity-oriented synthesis prefers to yield collection of products having many distinct molecular skeletons with controlled variation of stereochemistry in a small number of steps. The most challenging facet of DOS, and of critical importance to its success, is the ability to incorporate skeletal diversity into a compound collection, *i.e.* the efficient generation of

multiple molecular scaffolds from the same starting material. This 'skeletal diversity oriented synthetic strategy' is the most effective way of increasing structural diversity.

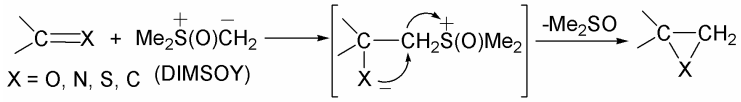
The unique properties of silicon[3] have led to its wide utilization in organic chemistry ranging from protecting functional groups, forming temporary tether and masking hydroxyl group, to highly controlled and selective organic reactions. The stabilization of either an electron deficient centre such as a carbocation at the β-position (β-effect) or a carbanion at the α-position (α-effect) with respect to a silicon group is the central theme of organosilicon chemistry, applied to organic synthesis. The regio- and stereo-selectivity of electrophilic substitution reactions of allyl-, vinyl- and aryl-silanes have been shown to be controlled by the β-effect. This stabilizing effect also plays an important role in directing the regioselectivity in various organic reactions. Silicon groups are also known to impart strong stereoelectronic effects involving reactions of functional groups in the vicinity of it thus control the stereochemical outcome of reactions of electrophiles and nucleophiles with the functional groups. Besides, silicon has unique affinity for fluorine and oxygen, which makes the silicon chemistry highly selective as exemplified in Brook rearrangement and cross-coupling reactions. These special properties of silicon groups are expected to play important role in DOS based synthesis.

CHAPTER 2

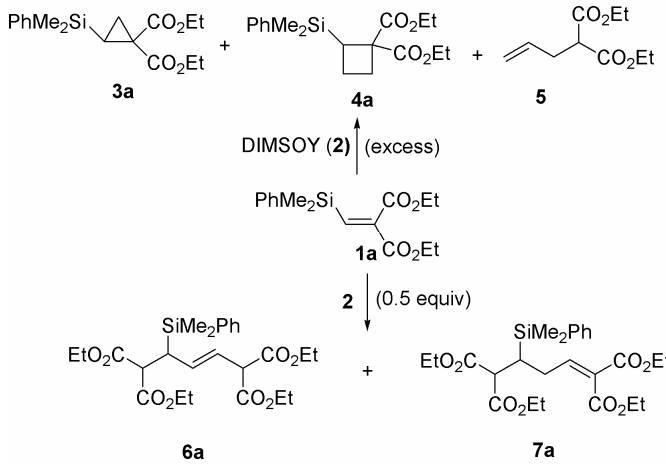
Silicon Assisted Diversified Reaction of Silylmethylene Malonates with Dimethylsulfoxonium Methylide

Sulfoxonium ylides are a class of sulfur-based ylides,[4] particularly, dimethylsulfoxonium methylide (DIMSOY) has been proved to be a versatile nucleophilic agent capable of reacting with a wide variety of different systems. They are known to transfer a methylene

group to certain electrophilic unsaturated linkages, including C=O, C=N, C=S and activated C=C bonds (Scheme 1).



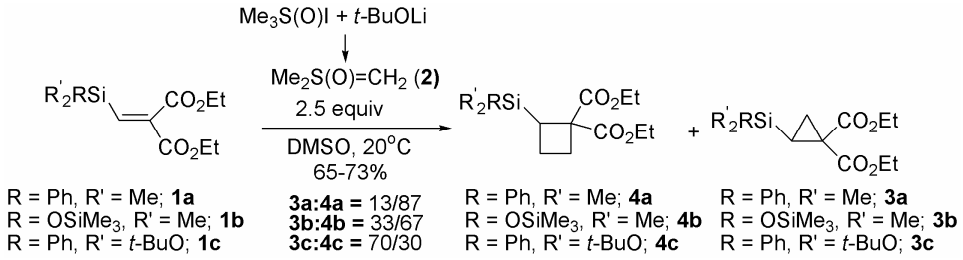
Scheme 1



Scheme 2

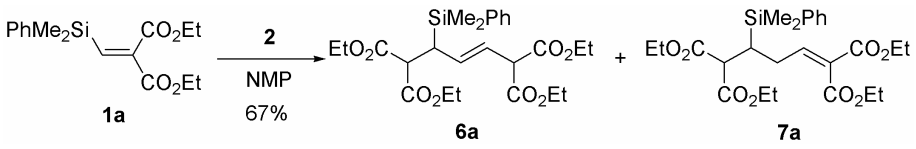
This chapter describes our successful approaches towards 'reagent-based' skeletal diversity oriented synthesis (Scheme 2) by using silylmethylene malonate **1a** as common substrate and varying DIMSOY (**2**) quantity and/or different reaction conditions.[5] When excess DIMSOY **2**, generated from the reaction of trimethylsulfoxonium iodide and sodium hydride in dimethyl sulfoxide (DMSO) was reacted with the silylmethylene malonate **1a** at room temperature, the expected cyclopropane **3a** was formed albeit in moderate yield, associated with two unusual products viz. cyclobutane **4a** and the allylated malonate **5**. However, when stoichiometric quantity of the ylide **2** was used, besides cyclopropane **3a**, a pair of new products, an allylsilane **6a** and its regioisomeric homoallylsilane **7a** were formed. The diversified products formed under different conditions therefore challenged us to formulate conditions for individual products. We,

therefore, first aimed to establish the optimized conditions for the preparation of the silicon functionalized cyclobutane derivative **4a**. To this end, we carried out the reactions of **1a** with DIMSOY which has been generated from trimethylsulfoxonium iodide under different conditions. The best condition was to use 2.5 equivalents each of LiOBu-*t* and trimethylsulfoxonium iodide with respect to malonate **1a** in DMSO at 20 ºC, which gave cyclobutane **4a** and cyclopropane **3a** (**3a**:**4a** = 13/87) in 71% isolated yield (Scheme 3). To survey the generality of this synthetic strategy, two more silylmethylene malonates **1b,c** were prepared and reacted with DIMSOY under the optimized conditions and the results were mentioned in Scheme 3.



Scheme 3

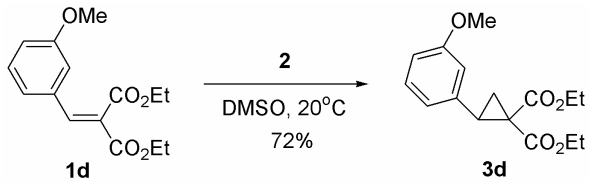
Next, we turned our attention towards the preparation of the functionalized allylsilane **6a** and homoallylsilane **7a**. A large number of reaction conditions were studied to optimize the formation of **6a** and/or **7a**. The best result was obtained by carrying out the reaction with 0.5 equivalents of ylide **2** in DMF or NMP at 5 ^{o}C (Scheme 4).



Scheme 4

To find the role played by the silicon group in these reactions, the arylidene malonate **1d** was reacted with varying amounts of DIMSOY **2** and in all the cases, no trace of cyclobutane or the dimerization products was observed. The cyclopropane **3d** was the

sole product associated with the unreacted starting material in cases where substoichiometric quantity of ylide **2** was used (Scheme 5). Thus, the diversity in the above reactions was found to arise due to the presence of silyl group at the β-positions of the malonate.



Scheme 5

CHAPTER 3

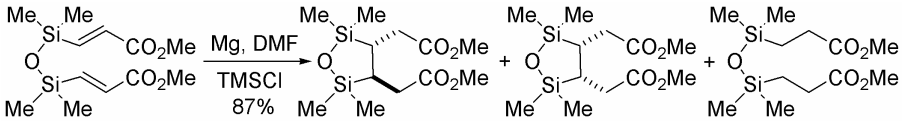
Magnesium-Mediated Intramolecular Reductive Coupling: A Stereoselective Synthesis of C_2-Symmetric 3,4-Bis-Silyl- Substituted Adipic Acid Derivatives

One of the most important DOS protocol, the skeletal diversity can be achieved by two ways. The first one involves the use of different reagents and a common starting material ('reagent-based approach') and we have shown our successful contribution in this area in Chapter 2. Alternate approach is called 'substrate-based approach', which uses different starting materials, containing suitably pre-encoded skeletal information and subjected to a common set of conditions leading to different skeletal outcomes. This chapter and the following one will be dedicated to 'substrate-based DOS approaches'.

Molecules containing stereochemically defined two (or more) silicon-bearing centres and terminal functionalities are useful intermediates in organic synthesis. Highly stereoselective syntheses of the *meso* diastereoisomer of 3,4-bis-silylated adipates have been reported.[6] In order to show the enormous utility, these intermediates have been applied for the synthesis of many natural products such as (±)-2-deoxyribonolactone, (±)-arabonolactone and both the enantiomers of nonactic acid as well as nonactin. The C_2-

symmetric racemic diastereoisomer of 3,4-bis-silylated adipate is also expected to be a starting point for the syntheses of complex molecules. But, there is no method available for making them both in racemic or enantiomerically pure form.

We, therefore, decided to resolve our problem of making C_2-symmetric racemic diastereoisomer by a five-membered ring formation by intramolecular reductive cyclization of symmetrical disiloxane tethered bis-acrylates **8**. A large number of reaction conditions were studied to optimize the reductive cyclization of **8**. In the presence of trimethylsilyl chloride (TMSCl, 12 equiv) as an additive, the Mg (12 equiv) metal-promoted intramolecular reductive cyclization of the disiloxane **8** in DMF (30 mmolar) at 0 °C was found to generate a mixture of diastereoisomeric cyclic products, *cis*-**9** and *trans*-**9**, associated with the double bond reduced product **10** (Scheme 6) *(cis*-**9**:*trans*-**9**:**10 =** 42:42:16) in 87% isolated combined yield.

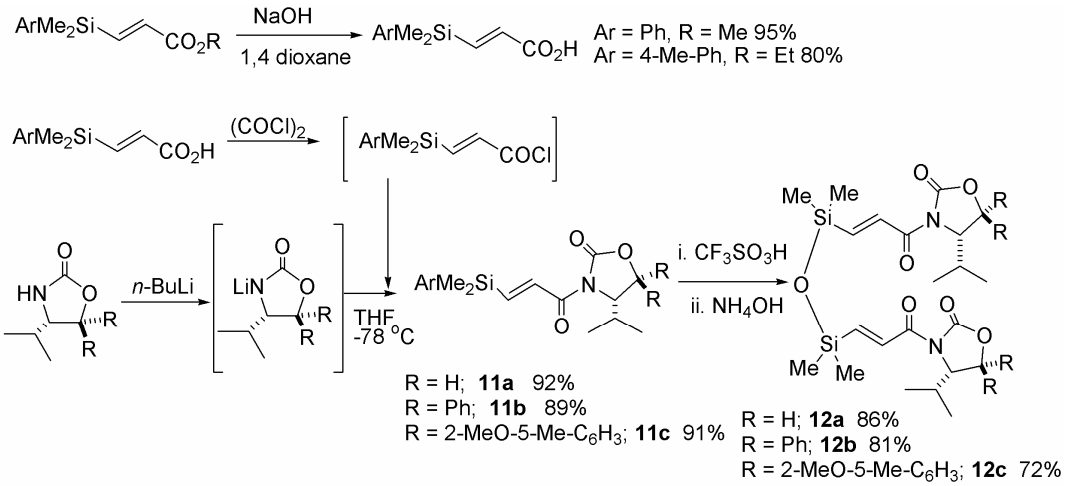


8 *trans*-**9** *cis*-**9** **10**

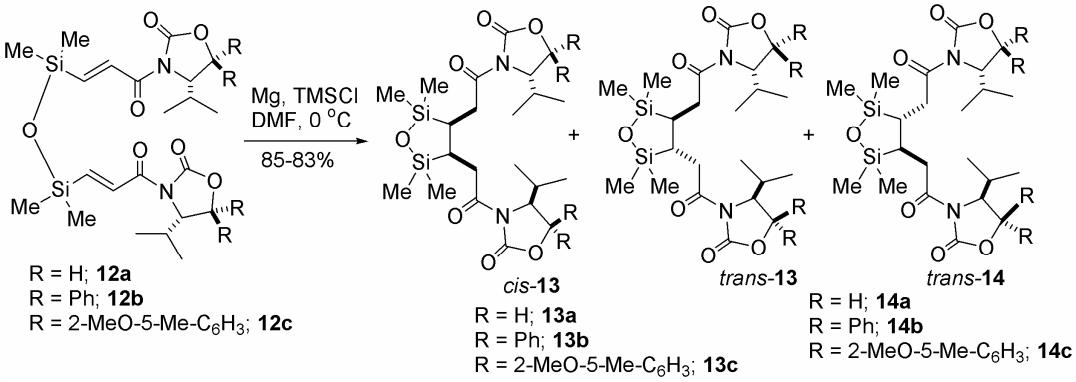
Scheme 6

Our next attempt was to improve the relative stereochemistry (*trans/cis*) as well as to control the absolute configuration during the cyclization to obtain the *trans*-isomer(s) in pure and enantiomeric form. It was envisaged that instead of an ester, the Mg/TMSCl-mediated coupling of the corresponding amide, possessing a suitable chiral amine, might be useful for this purpose. In view of all of this, we prepared the (*S*)-valine derived oxazolidin-2-one[7] derivatives of β-silylacrylic acid **11a, 11b** and **11c** as shown in Scheme 7. Reaction of these amides with TfOH in dichloromethane, followed by quenching with ammonium hydroxide, produced the disiloxane **12a, 12b** and **12c**, respectively, in very

good yield. Next, we subjected the disiloxane **12a** to the optimized reductive cyclization conditions, described for disiloxane **8**, using Mg/TMSCl in DMF at 0 °C which led to complete consumption of the starting material. Interestingly, the crude reaction product showed the formation of a mixture of diastereoisomeric cyclic products, *cis*-**13a** and two *trans*-products (*trans*-**13a**:*trans*-**14a** = 60/40) with a strong preference for the desired *trans* isomers (*trans*:*cis* = 85/15) (Scheme 8). The isolated yield of the cyclic products was also very high (85%), and the *trans*-isomers could be easily separated from the *cis*-**13a** by crystallisation. Notably, even the two diastereoisomeric *trans*-**13a** and *trans*-**14a** could be individually isolated by fractional crystallisation with nearly quantitative recovery.[8] Reductive cyclization of disiloxane **12b** and **12c** under the conditions described for amide **12a**, also resulted in the formation of a mixture of diastereoisomeric cyclic products, *cis*-**13b,c** *trans*-**13b,c** and *trans*-**14b,c** (*trans*:*cis* = 88/12, *trans*-**13b**:*trans*-**14b** = 45/55, *trans*-**13c**:*trans*-**14c** = 45/55).

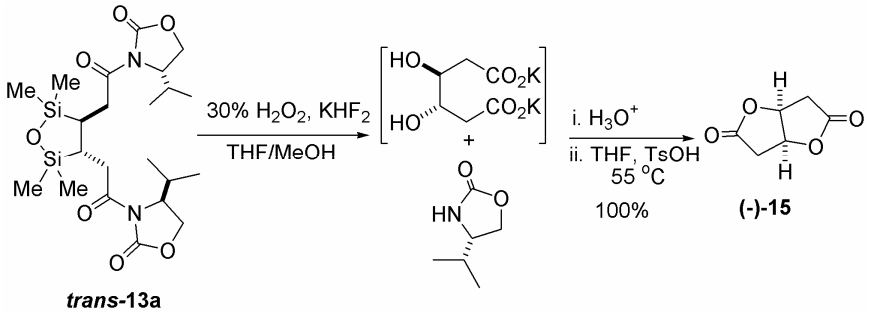


Scheme 7



Scheme 8

To establish the absolute stereochemistry of the individual *trans* diastereoisomers *viz*. *trans*-**13a** and *trans*-**14a**, each of these was converted to known bilactone **15**. For this, *trans*-**13a** was subjected to Fleming–Tamao[9] oxidation using KHF_2-H_2O_2 in 1/1 THF-MeOH at 60 °C (Scheme 9). Besides conversion of the silyloxy group to a hydroxyl group, the oxazolidinone group was also removed under these conditions to give the intermediate dipotassium salt. At this stage, a simple extraction of the reaction mixture with ethyl acetate gave back the oxazolidinone (90%) and acidification of the residue gave (–)-2,6-dioxabicyclo[3.3.0]octane-3,7-dione, (–)-**15**. The (3*S*,4*S*)-configuration of the silicon-bearing asymmetric centre in *trans*-**13a** was confirmed from the specific rotation data of (–)-**15.**[10] Similarly, the minor *trans*-**14a** gave (+)-2,6-dioxabicyclo[3.3.0]octane-3,7-dione (+)-**15** as confirmed from the specific rotation data of (+)-**15**, thus confirming its (3*R*,4*R*)-configuration.



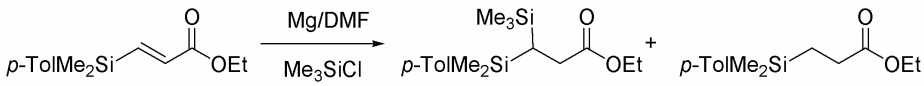
Scheme 9

CHAPTER 4

Magnesium-Induced Regiospecific *C*-Silylation of Suitably Substituted Enoates and Dienoates

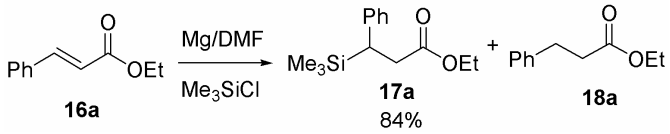
With the invention of a reaction in which a silicon group can be converted to a hydroxyl group with retention of configuration, has opened up a new area of organic synthesis. A silicon group possesses very different properties compared to a hydroxyl group or any protected form of a hydroxyl group. Thus, carbonyl compounds having a silyl group at β-position are popular targets because of their versatile nature and also excellent surrogate for the acetate aldol reaction. The available methods of preparation of β-silyl carbonyl compounds include hydrosilylation and silylmetalation of unsaturated carbonyl compounds and methods based on the use of various transition metal catalysts. Amongst these, silylmetalation of unsaturated carbonyl compounds using dimethyl(phenyl)silyl lithium ($Me_2PhSiLi$)[11] as a source reagent is widely used.

Reductive coupling using Mg/TMSCl/DMF system on silicon-tethered diacrylic esters or amides was shown to prefer for intramolecular reductive coupling of the two acrylic units leading to 3,4-bis-silyl substituted adipic acid derivatives with very high selectivity with no *C*-silylation at the β-position (Chapter 3, Scheme 6, 8). We, therefore, became curious to know the outcome of the above reductive dimerization protocol, using Mg/TMSCl/DMF system on β-dimethyl(aryl)silylacrylates. Which pathway it would follow, reduction, *C*-silylation or dimerization? When β-dimethyl(4-methylphenyl)silylacrylate was subjected under our optimized conditions, it was gratified to note that the crude reaction product showed the formation of Ethyl 3-dimethyl(4-methylphenyl)silyl-3-trimethylsilylpropionate associated with a small amount of double bond reduced product (Scheme 10).



Scheme 10

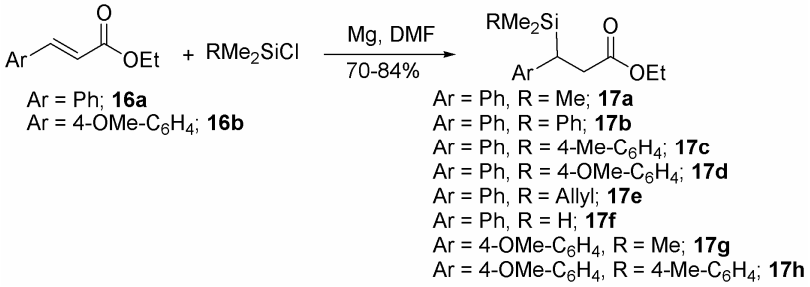
Prior to work with β-dimethyl(aryl)silylacrylates, we decided to find out suitable conditions for the reductive silylation of ethyl cinnamate. The optimized condition for *C*-silylation at the β-position was to add the ethyl cinnamate to a mixture of 6 equiv. of TMSCl, 12 equiv. of Mg in DMF (0.2 M) at 30 ºC for 0.5 h (Scheme 11). Under these conditions the *C*-silylated product **17a** was isolated in 84% yield with the double bond reduction product **18a** found to be negligible (~5%). The double bond reduction product **18a** was also easily separated from *C*-silylated product **17a** by column chromatography.



Scheme 11

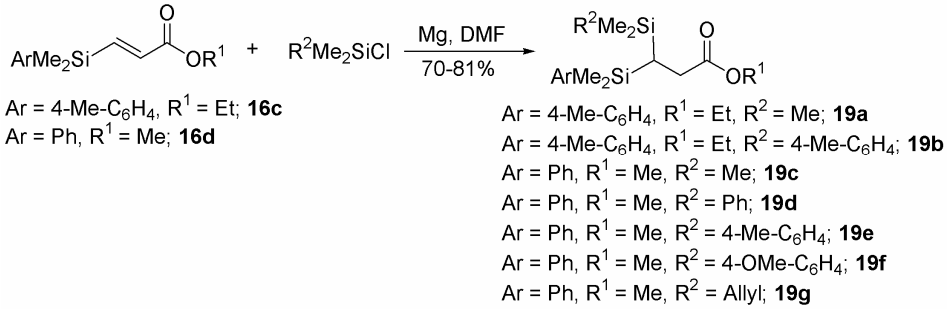
To convert a silyl group to a hydroxyl group, it is mandatory that the silicon has a heteroatomic substitution or an allyl/alkene/aryl group on it. Aryl substituted silyl groups are generally introduced on an organic structure *via* silyl lithium reagents. Unfortunately, when the aryl groups are electron rich, dimethyl(aryl)silyl lithiums could not be made from the corresponding silyl chlorides.[12] So the popularity of Me_2PhSi group remained because of the easy preparation of $Me_2PhSiLi$ from the commercially available silyl chloride and facile conjugate additions of mono- and bis-silylcuprate reagents derived from it to unsaturated carbonyl compounds. To generalize the Mg/TMSCl/DMF system for efficient reductive *C*-silylation at the β-position of ethyl cinnamates, reductive silylation with $PhMe_2SiCl$ and silyl chlorides which do not form the corresponding silyl lithium easily such as *p*-$TolMe_2SiCl$, *p*-$AnsMe_2SiCl$ and $AllMe_2SiCl$ were pursued. The results of

reductive silylation under the optimized conditions are presented in Scheme 12. In all cases the β-silylated product was obtained in very good yield and purity.[13]



Scheme 12

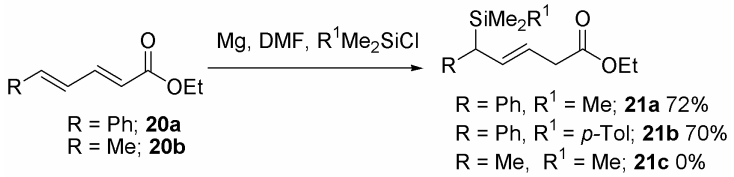
We next turned our attention to know the fate of β-silyl acrylates under these optimized reductive silylation conditions using Mg/chlorosilane/DMF system at 30 °C. Treatment of β-dimethyl(4-methylphenyl)silyl acrylate **16c** under our optimized reductive silylation conditions with TMSCl produced the corresponding silylated product **19a** in good yield (Scheme 13). A similar clean reaction took place for **16c** and **16d** when TMSCl was replaced by various silyl chlorides as presented in Scheme 13. The desired β,β-disilylated products **19a**-**19g** were formed in moderate to good yield.



Scheme 13

The reductive silylation on dienic esters could be interesting because these substrates can react in different modes to produce regio-isomeric β or δ *C*-silylated products. When the dienic ester **20a** was treated under the optimized reductive silylation conditions using TMSCl, the allyl silane **21a** was formed (Scheme 14) without a trace of

the other regioisomer. Moreover, the allylsilane was also formed with high stereoselectivity where (*E*)-isomer was found to be the major product. While changing the silyl chloride from TMSCl to *p*-TolMe$_2$SiCl, the corresponding allyl silane **21b** was formed in good yield and also with high stereoselectivity for the (*E*)-isomer. Interestingly, alkyl substituted dienoate **20b** under the same conditions did not provide the desired allyl silane **21c**.



Scheme 14

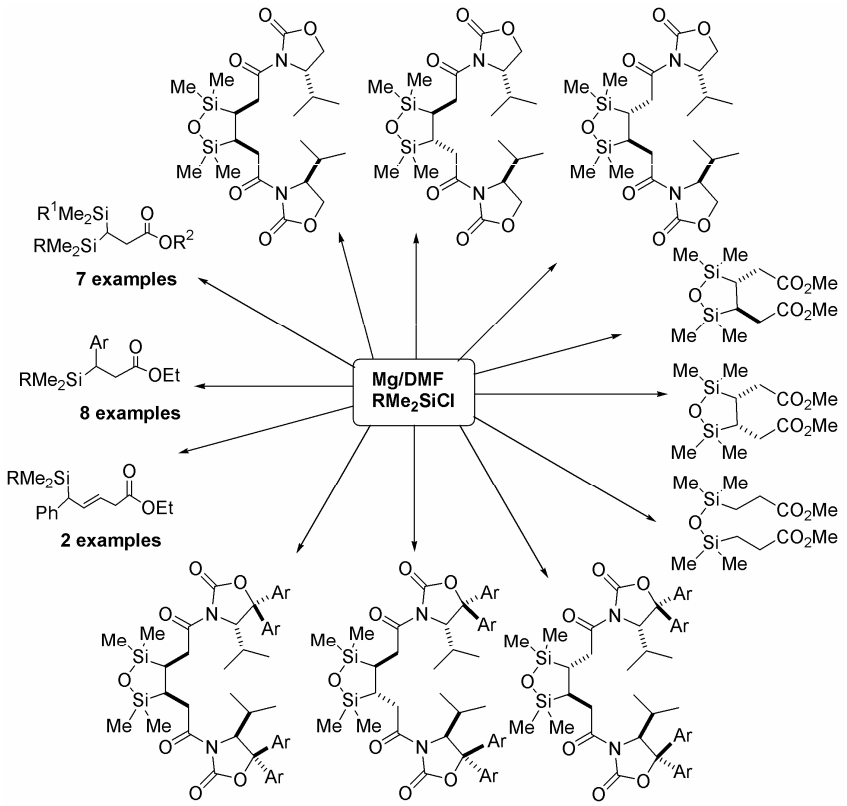


Figure 1

In conclusion, we have described our 'substrate-based DOS-approach', which uses a common set of reducing system, Mg/silyl chloride/DMF and reacts with different α,β-

unsaturated carbonyl compounds leading to highly functionalized skeletally and/or stereochemically diverse products. Two main types of reactions such as reductive cyclization leading to cyclic diester and reductive β-C-silylation leading to β-silyl carbonyl compound have been found to take place as summarized in Fig. 1.

CHAPTER 5

Asymmetric Syntheses of D-Fagomine Isomers from C_2-Symmetric 3,4-Bis-Silyl-Substituted Adipic Acid Derivatives

Polyhydroxylated piperidines (azasugars) have got increasing synthetic interest due to their remarkable biological activity as glycosidase inhibitors.[14] Since glycosidases are involved in numerous biological processes, azasugars are potential therapeutic agents for the treatment of a wide range of diseases, including diabetes, cancer, AIDS, viral infections and many more.[15] These important biological properties have led to many synthetic approaches towards naturally occurring azasugars and their analogs. 1,2-Dideoxy-azasugars such as D-fagomine **22** and its stereoisomers **23, 24** (Fig. 2) are known to have glycosidase inhibition activities. Fagomine itself has strong inhibitory activity towards mammalian α-glucosidase, β-galactosidase and also found to have a potent antihyperglycemic effect in streptozocin-induced diabetic mice and a potentiation of glucose-induced insulin secretion.

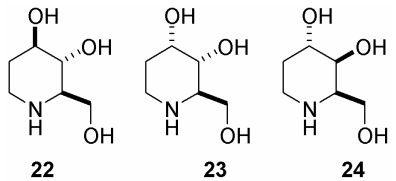
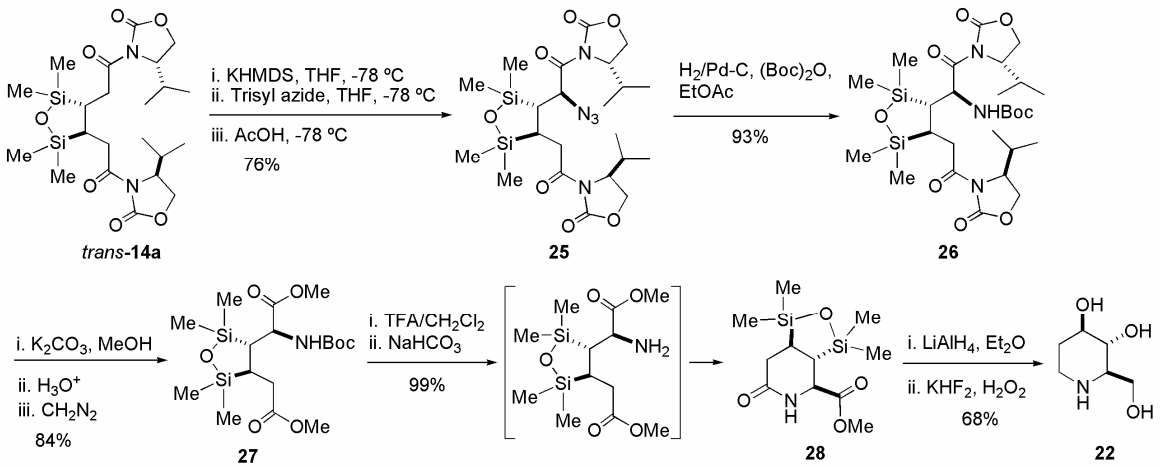


Figure 2

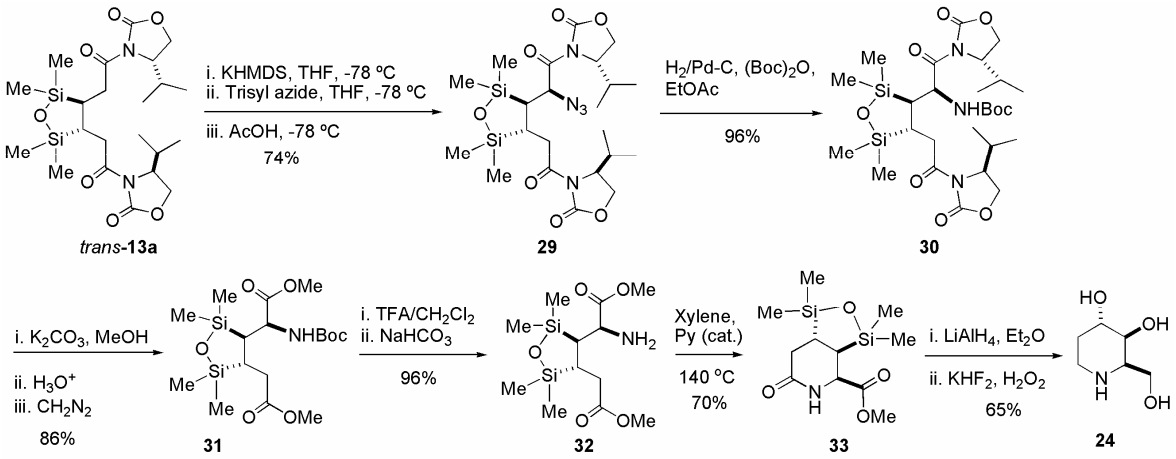
Our research group is involved in the synthesis[16] of hydroxylated piperidine/ pyrrolidine involving organosilicon chemistry. This chapter describes[17] our successful

attempt towards the synthesis of D-fagomine **22** (Scheme 15) and D-3,4-di-epi-fagomine 2**4** (Scheme 16) from C_2-symmetric 3,4-bis-silyl substituted adipic acid derivatives *trans*-**14a** and *trans*-**13a** respectively. For the synthesis of D-fagomine **22**, *trans*-**14a** was chosen as the starting material because the configurations of the Si-bearing centers matches with the configurations required for OH substituents at 3 and 4 positions. The introduction of the azido group at the α-position of the carboxamide in *trans*-**14a** was carried out by using KHMDS and trisyl azide. The azide **25** was formed as a single diastereoisomer and the stereochemical outcome was controlled by the valine derived oxazolidin-2-one auxiliary. Reduction of the azide and in-situ protection of the intermediate amine was achieved with added $(Boc)_2O$ in H_2/Pd-C system in excellent yield. The oxazolidin-2-one groups from **26** were removed by treatment with K_2CO_3 in MeOH resulting in a mixture of dimethyl ester and dicarboxylic acid which on treatment with diazomethane yielded dimethyl ester derivative **27**. The Boc-protection in **27** was removed by treatment with trifluoroacetic acid and the resulting trifluoroacetate salt was basified with $NaHCO_3$ to give the intermediate amine which spontaneously underwent cyclization to lactam **28**. A $LiAlH_4$ reduction followed by Fleming-Tamao oxidation of the lactam **28** using potassium bifluoride and hydrogen peroxide then yielded D-fagomine **22.**



Scheme 15

Synthesis of 3,4-di-epi-fagomine **24** has also been achieved from *trans*-**13a** in an analogous way as shown for D-fagomine **22**. In this case, the lactamization of the amine **32** to lactam **33** was found to be difficult requiring high temperature and prolonged reaction time (Scheme 16). This is due to the fact that cyclization to take place, amine **32** has to adopt a conformation wherein the silyl groups have to be disposed axially. This makes the system energetically unfavorable requiring very high temperature for the lactamization.



Scheme 16

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ABBREVIATIONS

TOS	:Target Oriented Synthesis
DOS	:Diversity Oriented Synthesis
DIMSOY	:Dimethylsulfoxonium methylide
DIMSY	:Dimethylsulfonium methylide
THF	:Tetrahydrofuran
DMSO	:Dimethylsulfoxide
DMF	:*N*, *N*-Dimethylformamide
NMP	:*N*-Methyl-2-pyrrolidone
EtOAc	:Ethyl acetate
TfOH	:Trifluoromethanesulfonic Acid
TFA	:Trifluoroacetic Acid
EtOH	:Ethyl alcohol
MeOH	:Methyl alcohol
HMPA	:Hexamethylphosphoramide
KHMDS	:Potassium hexamethyldisilazide
LHMDS	:Lithium hexamethyldisilazide
DMPU	:1,3-Dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
LDA	:Lithium diisopropylamide
TMSCl	:Trimethylsilyl chloride
DMAP	:Dimethylaminopyridine
TBAT	:Tetrabutylammonium triphenyldifluorosilicate
GC	:Gas Chromatography
NMR	:Nuclear Magnetic Resonance
IR	:Infrared spectra
HRMS	:High Resolution Mass Spectrometry
TLC	:Thin-Layer Chromatography
bp.	:Boiling Point
mp.	:Melting Point

CHAPTER 1

An Introduction to Diversity Oriented Synthesis and Organosilicon Chemistry

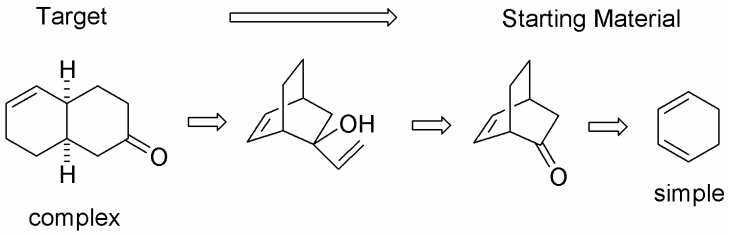
1.1 Introduction to diversity oriented synthetic strategy

Small-molecules can exert powerful effects on the functions of macromolecules that comprise living systems. This remarkable ability makes them useful, both as research tools for understanding life processes and as pharmacological agents for promoting and restoring health. Synthetic organic chemists aim to gain access to these compounds using three general approaches. The first approach is target-oriented synthesis[1,2] (TOS) which relies primarily on nature to discover small-molecules with useful, macromolecule-perturbing properties. Natural compounds can be isolated from extract mixtures, and then structurally characterized by using a variety of spectroscopic techniques. Once such a structure has been identified, it can become a target for chemical synthesis. The aim of the synthesis effort in TOS is to access a precise region of chemical space,[3] which is often defined by a complex natural product known to have a useful function. The second approach uses either medicinal chemistry or combinatorial chemistry[4,5] and aims to explore a dense region of chemistry space in proximity to a precise region known to have useful properties. The source of the starting or lead compounds can vary and may include a natural product, a known drug, or a rationally designed structure developed from a mechanistic hypothesis and/or a crystal structure of a macromolecule of interest. Nevertheless, the following question remains unanswered: Are the regions of chemistry space defined by natural products and known drugs, which have been so intensely scrutinized to date, the best or most fertile regions for discovering small-molecules that modulate macromolecular function in useful ways? Given the extraordinary potential for such small molecules to promote the understanding and betterment of human health, it is urgent that organic chemists begin to answer this basic question. The third and most diverse approach is diversity oriented synthesis[6-8] (DOS) which aims to meet the above mentioned challenges.

DOS prefers to yield collection of products having many distinct molecular skeletons with controlled variation of stereochemistry in a small number (between three and five) of steps. Such collections are the key to chemical genetics, where small molecules are used to explore biology and medicine systematically.

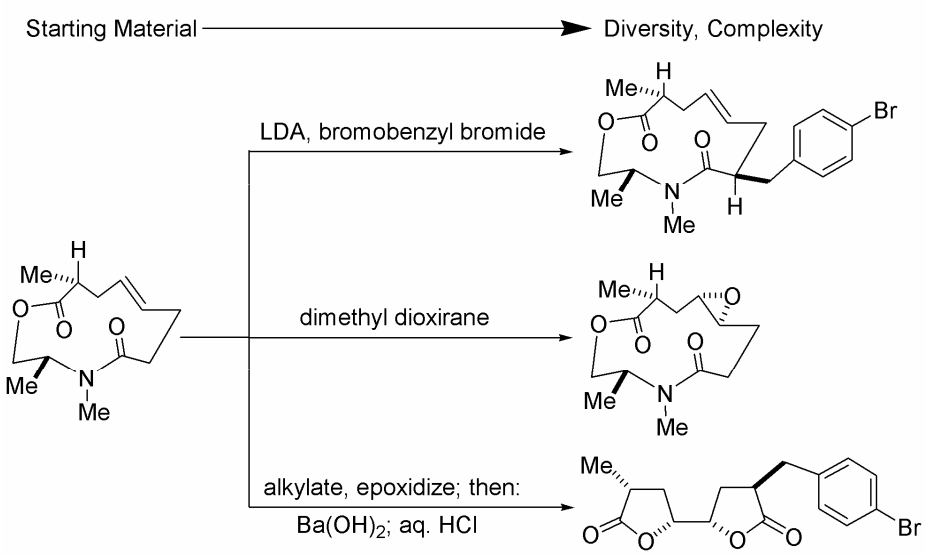
1.1.1 TOS *vs* DOS

Target-oriented synthesis has a long history in organic chemistry. In universities, the targets are often natural products, whereas in pharmaceutical companies, the targets are drugs or libraries of drug candidates. Beginning in the mid-1960s, a systematic method to plan syntheses of target molecules, named retrosynthetic analysis, was devised.[9] This problem-solving technique involves the recognition of key structural elements in reaction products, rather than reaction substrates, that code for synthetic transformations. Repetitive application of this process allows a synthetic chemist to start with a structurally complex target and find a structurally simple compound that can be used to start a synthesis. In the example given in Scheme 1.1, the target is a *cis*-fused bicyclic ring containing olefin and ketone functionalities. This target can be synthesized with the oxy-Cope rearrangement reaction. The oxy-Cope substrate could be obtained from a logical precursor substrate, a bridged bicyclic ring containing ketone functionality. The bridged bicyclic ketone in turn is seen to be the product of a Diels-Alder reaction of cyclohexadiene and ketene.[10]



Scheme 1.1

In contrast to TOS, DOS is not aimed at one particular target. They are instead aimed at a collection of many compounds having structural complexity and diversity. An ambitious goal of DOS is to design a synthetic pathway leading to a collection of compounds with a large number of different scaffolds. Early work by Armstrong[11] and Bartlett[12] laid the groundwork for DOS of natural product-like libraries. Subsequently, Schreiber and co-workers[13,14] synthesized and screened a library of over 2 million complex polycyclic compounds. This type of diversity requires the development of synthetic pathways having branch points, where a splitting step is followed by the addition of reagents to different reaction vessels that cause the common substrate to be transformed into products having different atomic skeletons. In the pathway illustrated in Scheme 1.2, a 12-membered ring scaffold is converted into three different scaffolds, including one containing two linked five-membered rings.[15] These products can be pooled and split and the resulting collection of differing scaffolds subjected to a new set of reagents. If their different scaffolds render such a process problematic, one may avoid the pooling step and continue with additional splitting steps using reaction vessels having single scaffolds.



Scheme 1.2

1.1.2 Different approaches of DOS

A successful DOS algorithm must address three principle types of diversity: substitutional (appendage) diversity, stereochemical diversity and skeletal diversity.[3,16,17] Thus, the products of a DOS should not only be diverse in the appendages they display but also in the three-dimensional orientations of these appendages. The first of these can be achieved by combinatorial variation of building blocks; the second by use of stereocontrolled reactions. The most challenging facet of DOS, and of critical importance to its success, is the ability to incorporate skeletal diversity into a compound collection, *i.e.* the efficient generation of multiple molecular scaffolds from the same starting material.[17] This 'skeletal diversity oriented synthetic strategy' is the most effective way of increasing structural diversity.[18] Schreiber[16,19] in much of his pioneering work described how to create diverse libraries from simple starting materials. Skeletal diversity can be achieved principally in two ways namely *via* 'reagent-based approach' and 'substrate-based approach'. The first involves the use of different reagents and a common starting material. This 'reagent-based approach' is also known as a branching pathway (Fig. 1.1). Alternatively, in the 'substrate-based approach', different starting materials, containing suitably pre-encoded skeletal information, are subjected to a common set of conditions leading to different skeletal outcomes (Fig. 1.2). A review of the literature suggests successful DOS processes utilize these two approaches in a number of ways by either: (1) the use of a *pluripotent functionality*, where the same part of a molecule is subjected to different transformations induced by different reagents; (2) the use of a *densely functionalized molecule*, where different functionalities in the same molecule are transformed by different reagents (*i.e.* pairing different parts of the same densely functionalized molecule); or, (3) the use of a *folding process*, where different structurally

encoding elements, contained in different substrates, are subjected to the same reaction conditions (*i.e.* pairing same parts of different densely functionalized molecules).

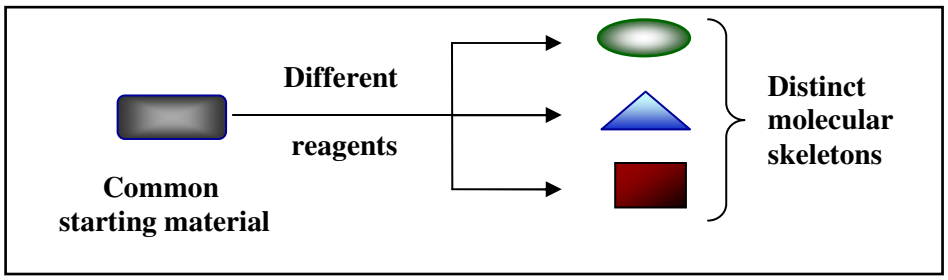


Figure 1.1: Reagent-based approach/branching pathway

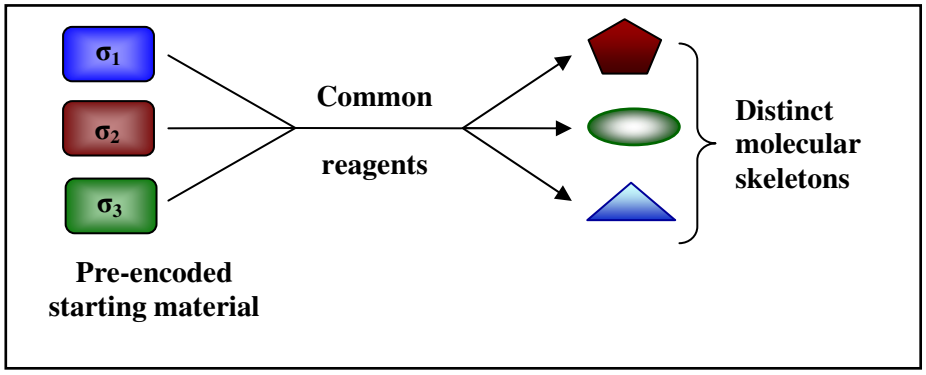


Figure 1.2: Substrate-based approach/folding process

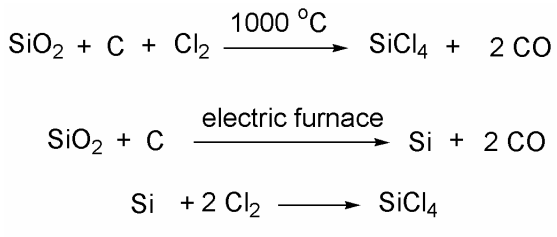
1.2 Introduction to organosilicon chemistry

Organosilicon compounds are known since 1863 when Friedel and Crafts[20] first reported the synthesis of tetraethylsilane from diethylzinc and tetrachlorosilane. In early 20th century, the chemistry of organosilanes has been widely opened after their convenient preparation by F. S. Kipping.[21] The discovery of direct process for the preparation of halogenated organosilane derivatives by the reaction of methyl chloride with the alloy of silicon and copper by E. G. Rochow[22] in the later half of 1940's[23] made a rapid progress of not only silicon industry but also fundamental organosilicon chemistry.[24] Most of the work on organosilanes up to 1960's was based on the use of silanes as protecting groups.[25] Modern development of organosilicon chemistry as applied to organic synthesis really began in late 1960's when Peterson[26] developed the olefination reaction. In early 1970's,

Stork[27] used α-trimethylsilyl methyl vinyl ketone to solve a long standing problem of regiospecific trapping of specific enolate in annulation reactions. At this stage rapid development in organosilicon chemistry had taken place.

1.2.1 Organosilanes

Organosilanes are not naturally occurring. Their origin is from $(SiO_2)_n$ or metal silicates which accounts for c.a. 25% of the earth's crust with a second position in the abundance list of elements. The reactive starting material for all organosilicon compounds is $SiCl_4$ and is easily obtained from $(SiO_2)_n$ as shown in Scheme 1.3.



Scheme 1.3

Silicon belongs to group 14 in 3rd row, right under carbon in the periodic table and electronic configuration of its outer shell is $3s^2 3p^2$ that is isoelectronic with carbon ($2s^2 2p^2$). Therefore, silicon is expected to have a similar character of carbon. However, with the progress of organosilicon chemistry, the points of difference between carbon and silicon have been made clear. For instance, the Si–C bond length is much longer than the analogous C–C bond length (1.89 *versus* 1.54 Å). Relatively long bond is also polarized in the sense $Si^{\delta+}$–$C^{\delta-}$, placing organosilicon compounds in the class of organometallic compounds. Some properties of carbon and silicon are compared in Table 1.1. In addition silicon is also more electropositive than hydrogen with Pauling electronegativities being 1.8 and 2.1 respectively.

Table 1.1: Some properties of carbon and silicon

Properties	Carbon	Silicon
Atomic no.	6	14
Electronic configuration	$1s^2 2s^2 2p^2$	$1s^2 2s^2 2p^6 3s^2 3p^2 3d^0$
Atomic radius	66 pm	106 pm
Pauling electronegativity	2.5	1.8
First I. P.	259 kcal/mol	187.9 kcal/mol
Bond length	C–C 1.54 Å	Si–C 1.89 Å
Bond energy	C–C 79.8 kcal/mol	Si–C 76.0 kcal/mol

Table 1.2: Typical bond lengths and dissociation energies of carbon and silicon

Bond	Length (Å)	Dissociation energy (kJ/mol)
C–C	1.54	334
Si–C	1.89	318
C–O	1.41	340
Si–O	1.63	531
C–Cl	1.78	335
Si–Cl	2.05	471
C–F	1.39	452
Si–F	1.60	808

However, the silicon atom is more accessible to nucleophiles than the equivalent carbon atom. This is due to the fact that the separation between silicon and its substituent is larger than is in the case with carbon. In those cases where carbon forms double or triple bonds, silicon generally forms polymer with single bonds. Moreover, silicon forms very strong covalent bond with oxygen, fluorine and chlorine (Table 1.2). It is to be mentioned here that Si–F bond is one of the strongest single bonds known.

1.2.2 Effect of silicon group on organic reactions

The influence of a silicon group on organic structures and reactions solely depends on its position with respect to the reactive centre.

1.2.2a The *alpha* effect[28]

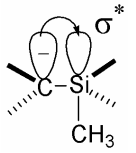
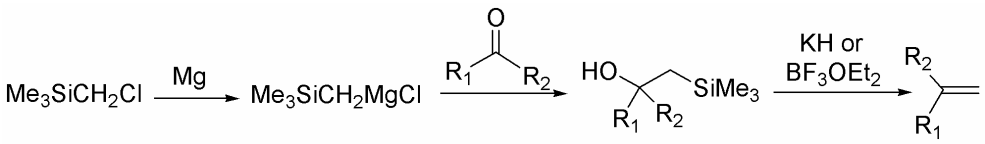


Figure 1.3: α-effect of silicon

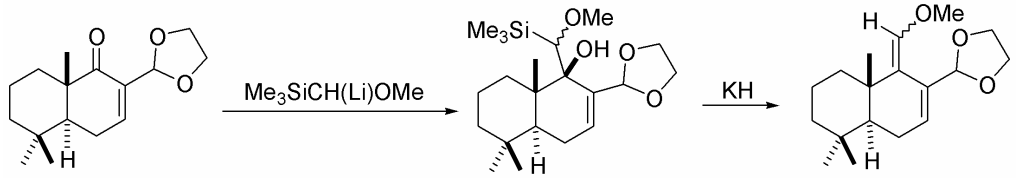
In spite of its electropositive character as compared to carbon and hydrogen, silicon favors the formation of α-carbanions. The most popular reason[29] given for the stabilization of a carbanion adjacent to silyl group is the energy lowering overlap of the filled orbital of the carbanion with large coefficient on carbon with an empty Si *d*-orbital of proper symmetry. Another explanation to this stabilization may be that the empty antibonding σ* orbital of Me–Si bond which will have large coefficient on silicon can overlap well enough with the filled orbital of the carbanion (Fig. 1.3). Other manifestations of the same property include the facts: that silanols are more acidic than water,[30] silyl amines are less basic than simple amines.[31] The first α-metallosilane was prepared by Whitmore and Sommer[32] in 1946 as a Grignard reagent by the reaction of trimethysilylmethyl chloride with magnesium. Subsequently, in 1968, Peterson developed[26] an alkene synthesis method based on the reaction of the Grignard reagent with carbonyl compounds (Scheme 1.4).



Scheme 1.4

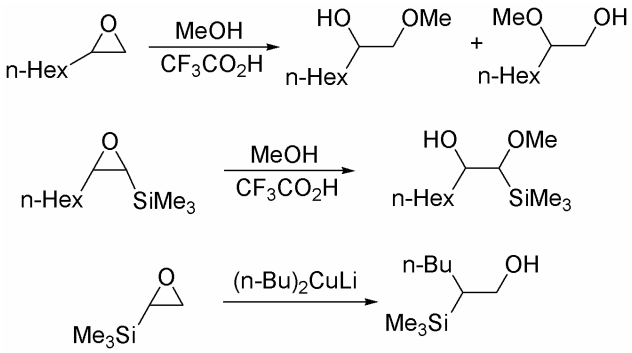
Alpha-silyl carbanions have high nucleophilicity[33] compared with analogous phosphorus or sulfur reagents. Also, α-silyl carbanions are less sterically hindered, presumably

because of longer C–Si bond. These factors have been critically evaluated in the total synthesis of warburganol,[34] an antifeedent sesquiterpene (Scheme 1.5).



Scheme 1.5

Nucleophilic substitution α-to a silicon group is also facilitated because the silicon group can stabilize the transition state of an S_N2 reaction adjacent to it.[29] This argument is supported from the facts discussed for the stabilization of an anion α-to a silicon substituent. This has been exemplified by the regioselective opening of vinylsilane epoxides[35,36] (Scheme 1.6) with different nucleophiles.



Scheme 1.6

1.2.2b The *beta* effect[28]

Because silicon is more electropositive than carbon, the filled σ bonding orbital of C–Si bond have higher co-efficient on carbon than silicon, resulting substantial overlap of these filled orbitals with the empty *p*-orbital of an adjacent carbocation (hyperconjugation). This phenomenon is known as β-effect of silicon and can be represented as in Fig. 1.4.

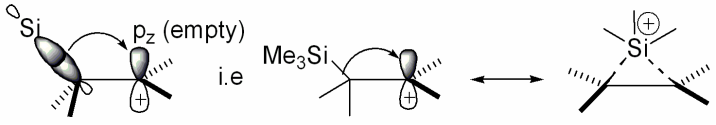
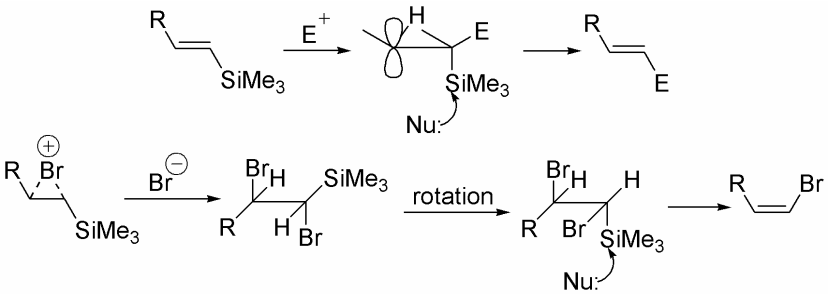


Figure 1.4: β-effect of silicon

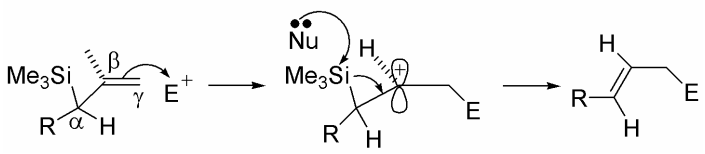
The kinetic magnitude of the effect (at least 10^{12} in solution and higher in gas phase) exceeds almost all other neighboring group effects. Exceptions are silicon's larger congeners germanium and tin, which exhibit even larger kinetic effects.[37] The regio- and stereochemical outcome of the reactions of vinyl- and allyl-silanes with electrophiles are well understood by the β-effect. Most vinyl silanes react with electrophiles with retention of configuration[38] (Scheme 1.7). It is due to the fact that hyperconjugative stabilization of the β-silyl cation restricts rotation about C–C bond (since it requires anti-periplanar geometry) well enough for it to maintain its configuration. When the electrophile is chlorine or bromine, inversion of configuration[39] is observed. The cyclic halonium intermediate opens up stereospecifically *anti* to give a dihalide and elimination then takes places in the usual *anti* stereospecific manner. In either case control of double bond geometry is very good and frequently used in synthesis.



Scheme 1.7

Allylsilanes react with electrophiles in a regio- and stereospecific manner with 1,3-transposition of stereochemical information.[38d] The electrophile always enters to the terminus of the allylsilane leaving behind a carbocation at β-position with respect to silicon. Other things being equal, the electrophile attacks the allylsilane as approximated by the structure (Scheme 1.8) where the hydrogen atom on the stereogenic centre is eclipsing the double bond. The intermediate cation retains its configuration because of the

hyperconjugative overlap of the Si–C bond with the empty *p*-orbital.[40-42] The double bond produced by loss of the silyl group is therefore largely *trans*.



Scheme 1.8

1.2.2c The *gamma* effect[28]

The stabilization of a positive charge by γ-silicon is believed to be the result of a through-space interaction between the back lobe of the C–Si bond and the carbocation *p*-orbital. This is often referred to as homohyperconjugation effect (Figure 1.5).

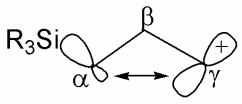


Figure 1.5: γ-effect of silicon

1.2.2d The *delta* effect[28]

The effect of silicon regretfully does not extend beyond γ-position. Rate of ethanolysis of tosylates of *cis*- and *trans*-4-(trimethylsilyl)cyclohexanols are almost identical to those of the *cis*- and *trans*-4-*tert*-butylcyclohexyl tosylates.[43] This is evidently due to the fact that the functional groups are too far away to have an effect on one another.[29]

1.2.3 Role of silicon in organic synthesis

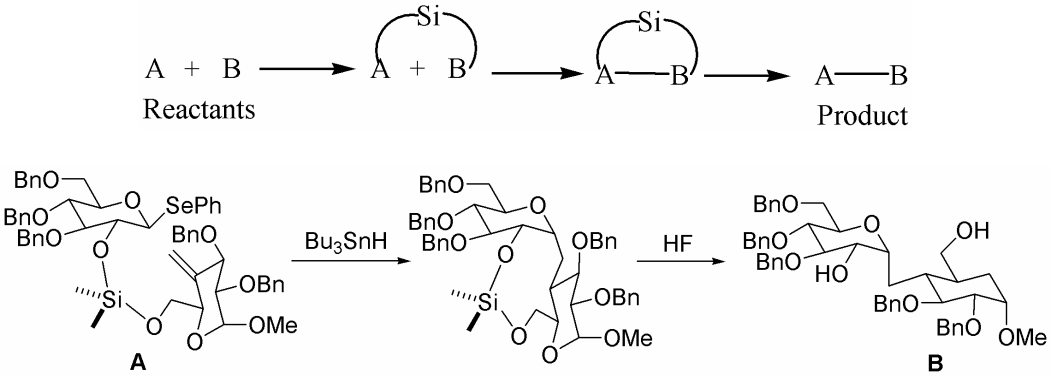
A wide variety of synthetic methods have been developed by using unique properties of silicon. The vast majority of which are based on two major properties of silicon *i.e.* the formation of a strong covalent bond to oxygen or fluorine and α- or β-effect of silicon.

1.2.3a Protecting groups[44]

The protection of alcoholic functionality *via* silyl ethers linkage is one of the most important sets of orthogonal protecting group strategy. Similarly, enols, ketene acetals and carboxylic acids can be protected by suitable silyl-based blocking groups. The same holds for thiols, amines, and heterocycles although, Si–N and Si–S bonds are more labile. Trimethylsilyl protection of a terminal alkynes group is a valuable asset in acetylene chemistry.

1.2.3b Silicon tethers[45]

The most favored and extensively used temporary silicon tethers strategies have been well established to perform intramolecular reactions. In those cases that intermolecular reactions proceed with low yield and stereoselectivity, often intramolecular reaction of the same type provide a higher degree of regio- and stereoselectivity.

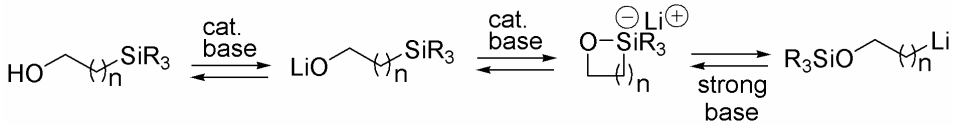


Scheme 1.9

Scheme 1.9 shows a typical strategy comprising introduction of a temporary tether between two individual reactants. An example using a dimethylsilyl acetal as a tether was shown[45c,d] for the synthesis of disaccharide **B** *via* intramolecular radical cyclization. Silaketal **A** was prepared from the suitable protected monosaccharide sub-units and dichlorodimethylsilane. Addition of Bu_3SnH followed by desilylation using aqueous HF leads to the formation of α-C disaccharide **B** as a single diastereoisomer.

1.2.3c Rearrangement reactions[46]

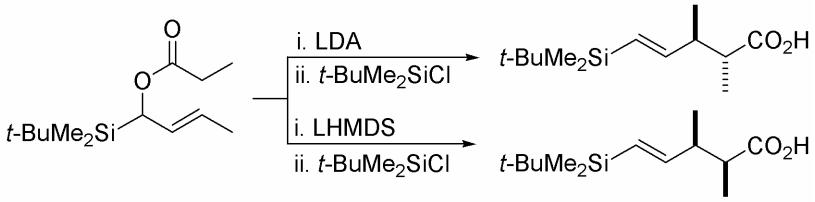
Organosilanes which contain hydroxyl or any other oxygen containing functionality at a particular position, can undergo different types of rearrangement reactions such as [1,2]-, [1,3]-, [1,4]- and [1,5]-silyl shift generally referred as Brook rearrangement (Scheme 1.10). Formation of stronger Si–O bond in the expense of weaker Si–C bond is proved to be the driving force for the above rearrangement reactions.



Scheme 1.10

1.2.4 Silyl group to control chirality[47]

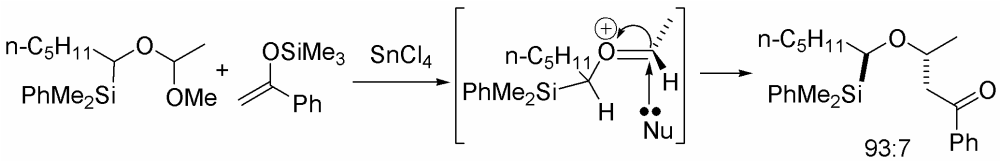
An organosilane group has been a useful functionality to impart chirality into a structure that would otherwise be achiral. Chirality could reside either on the silicon atom or any of the "R" groups attached to the silicon. Due to the presence of a chiral centre in the molecule, the two transition states in a reaction share a diastereomeric relationship and one would be preferred over other on energy grounds. The product from the transition state having lower energy would be the major or exclusive product. For example, the propionate undergoes an Ireland-Claisen[48] rearrangement to give either the 2,3-*trans* acid or 2,3-*cis* acid depending on the geometry of the enolate used (Scheme 1.11).



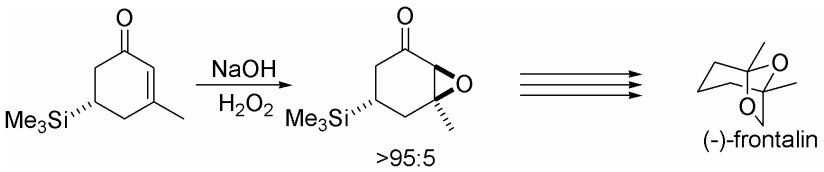
Scheme 1.11

Having served its turn, the silyl group can be removed in the usual way by protodesilylation; so that its net effect is to impart a temporary chirality to the starting

material. In Mukaiyama aldol reaction[49] of acetal with silyl enol ether of acetophenone, the presence of the silyl group makes chiral intermediate and also gives substantial selectivity in favor of the formation of the diastereoisomer as shown in the Scheme 1.12. Silicon group at 5 position in cyclohexenone has also been utilized to control the stereochemistry of epoxidation reaction in the synthesis of (−)-frontalin[50] (Scheme 1.13).



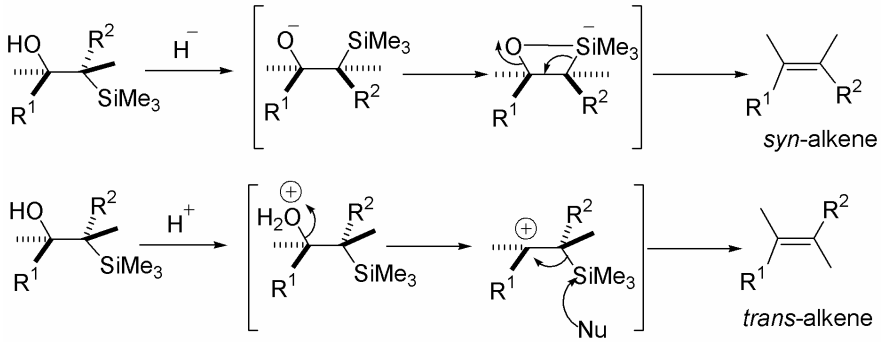
Scheme 1.12



Scheme 1.13

1.2.4a Elimination of β-hydroxy silanes[51]

The organosilicon compounds having β-hydroxy group can undergo 1,2-elimination (Scheme 1.14). The elimination could be directed to a *syn*- or *anti*-fashion by performing the reaction under basic or acidic conditions respectively.



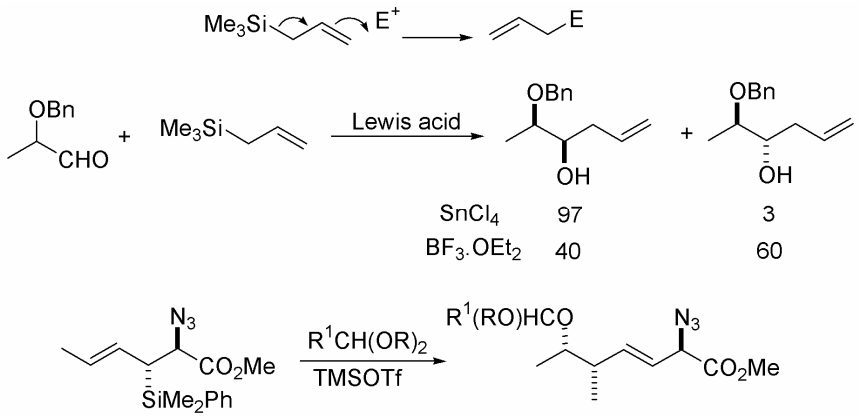
Scheme 1.14

Thus, β-hydroxy silanes with KH afford the *cis*-alkenes stereospecifically *via syn*-elimination of trimethylsilanol. Whereas, acid mediated reaction involve two steps. Initial

ionizations of the C–O bond, oriented anti-periplanar to the silyl moiety, leads to the *trans*-alkene *via* a silyl stabilized carbenium intermediate.

1.2.4b Reactions of allylsilanes

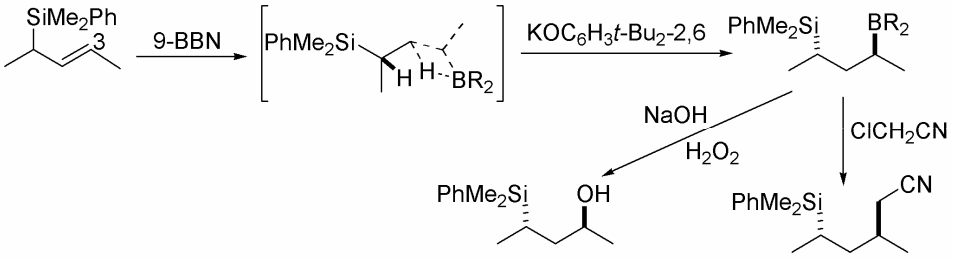
Allylsilanes have proved to be one of the most versatile carbon nucleophiles displaying a high level of stereocontrol in their attack on cationic electrophiles. The outcome largely depends on the electrophile, the allylsilane substituents and its geometry, Lewis acid catalyst and the positioning of the stereogenic centre/s. The stereochemistry of the S_E2' reaction of allylsilane is overall *anti* stereospecific[52-55] (Scheme 1.15).



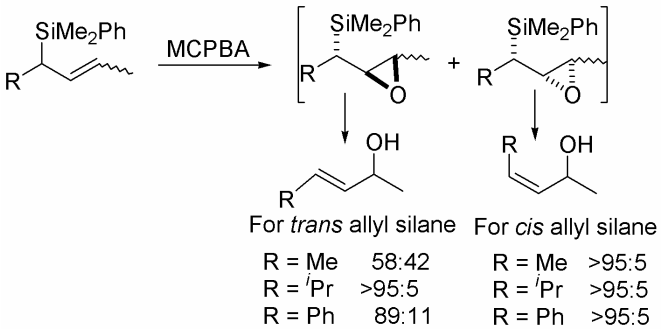
Scheme 1.15

Hydroboration of allylsilanes[56] is only marginally an electrophilic attack, but it is substantially affected by the silyl group. The selectivity for the boron to attach itself to C-3 of the allyl system is higher than for the corresponding alkenes lacking the silyl group, and the stereoselectivity is that expected for *anti* attack. Now with the established boron chemistry, the intermediate boranes can be converted stereospecifically to alcohol functionality or can be used in stereospecific C–C bond formation (Scheme 1.16). Epoxidation of allysilanes[57-59] is highly selective. Allylsilane epoxides are usually unstable to isolation or manipulation, undergoing *anti* stereospecific desilylative elimination directly to the (*E*)- and (*Z*)-alkenes. The former can be prepared with overall high

stereoselectivity, especially when the group R is large and/or the double bond in the starting material is *cis* (Scheme 1.17).



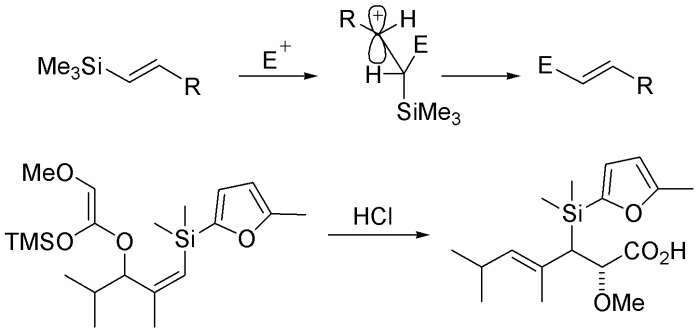
Scheme 1.16



Scheme 1.17

1.2.4c Reactions of vinylsilanes

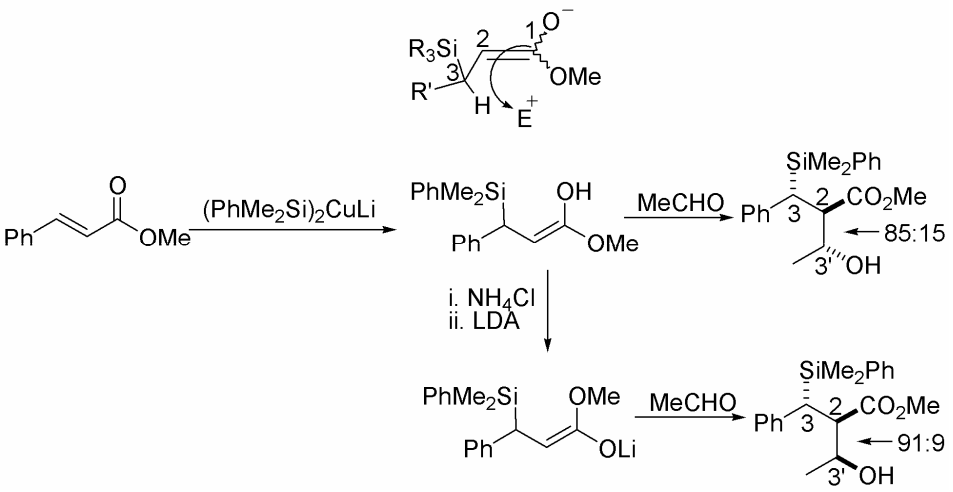
Another important class of organosilanes is vinylsilanes which undergo electrophilic substitution with various electrophiles mostly with retention of configuration controlling the double-bond geometry (Scheme 1.18). However, there are several reactions of vinylsilanes in which the reaction takes place on the double bond and the silyl group remains intact but its presence has stereochemical consequences[60] (Scheme 1.18).



Scheme 1.18

1.2.4d Reactions of β-silyl enolates

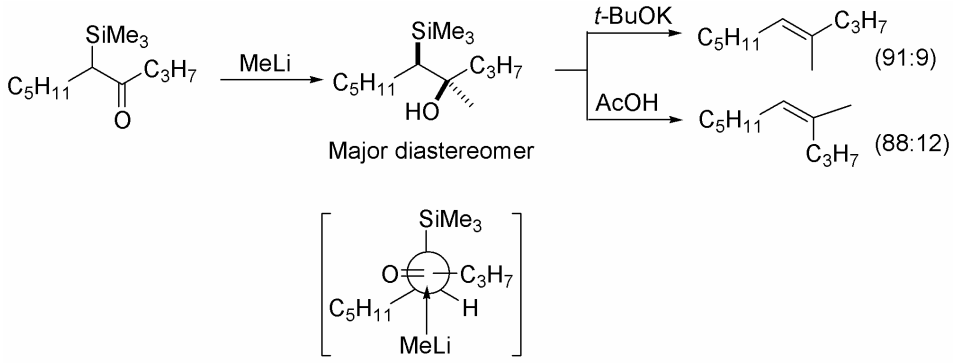
β-Silyl enolates have essentially the same framework as an allylsilane, and hence the same stereochemical imperatives, but due to change of substituents, C-2 becomes the nucleophilic atom. Alkylation and protonation reactions therefore take place with very high *anti* selectivity. β-Silyl enolates also react stereoselectively, and in the same sense, with the triagonal carbon electrophiles e.g., with aldehydes. They react with very high diastereoselectivity, not only with respect to the relationship between C-2 and C-3, but also with the centre C-2 and C-3'[61,62] (Scheme 1.19).



Scheme 1.19

1.2.4e Reactions of α-silyl ketones

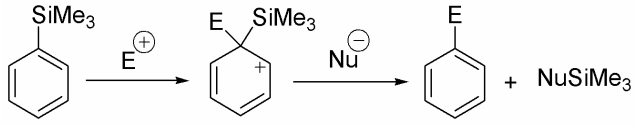
A silyl group in α-silyl ketones controls the diastereoselectivity of nucleophilic attack on the carbonyl group which follows Cram's rule (silyl group is considered as the large group). Both base and acid catalyzed reactions provide stereospecific route to trisubstituted alkenes as shown in Scheme 1.20.[63]



Scheme 1.20

1.2.4f Protodesilylation of arylsilanes

Fleming used Eaborn's protodesilylation principle[64] to introduce an electrophile to the aryl-moiety. In presence of an electrophile, arylsilanes undergo desilylation reaction *via ipso*-substitution which results in the formation of desilylated aryl group through silyl stabilized cationic intermediate (Scheme 1.21) during protodesilylation, the silyl group is converted into a hetero substituted silane.



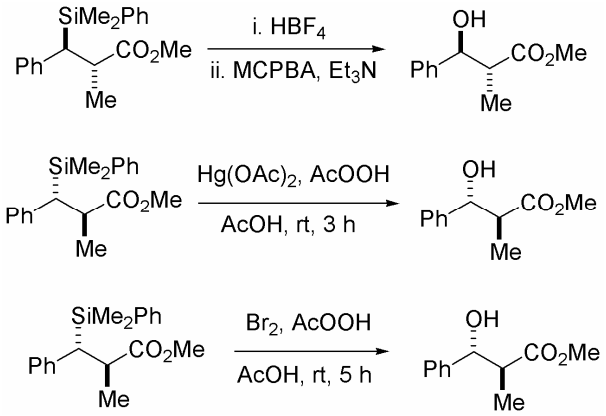
Scheme 1.21

1.2.4g Silicon groups as masked hydroxyl groups

$$[Si] \equiv OH$$

As early as in the early eighties, the conversion of particular silyl moieties into the corresponding alcohol of the carbon-silicon bond has been described by Fleming, Tamao and Kumada.[65,66] The dimethyl(phenyl)silyl group introduced by Fleming served as a masked hydroxy group[67] in total synthesis of many natural products. A (phenyl)dimethylsilyl group attached to carbon can be converted into a hydroxyl group with retention of configuration at the migrating carbon, by any of the three main methods described in Scheme 1.22. The first involves protodesilylation to remove the phenyl ring

from the silicon atom, followed by oxidation of the resulting functionalized silicon atom using peracid or hydrogen peroxide. The second uses mercuric acetate for the same purpose, and can be combined in one pot with the oxidative step using peracetic acid. This method has a variant in which the mercuric ion is combined with palladium (II) acetate, both in less than stoichiometric amounts. The third uses bromine, which can also be used in one pot in conjunction with peracetic acid. In this method, but not in the method based on mercuric acetate, the peracetic acid may be buffered with sodium acetate. The method using bromine as the electrophile for removing the benzene ring has a more agreeable variant in which it is administered in the form of potassium bromide, which is oxidized to bromine by the peracetic acid.

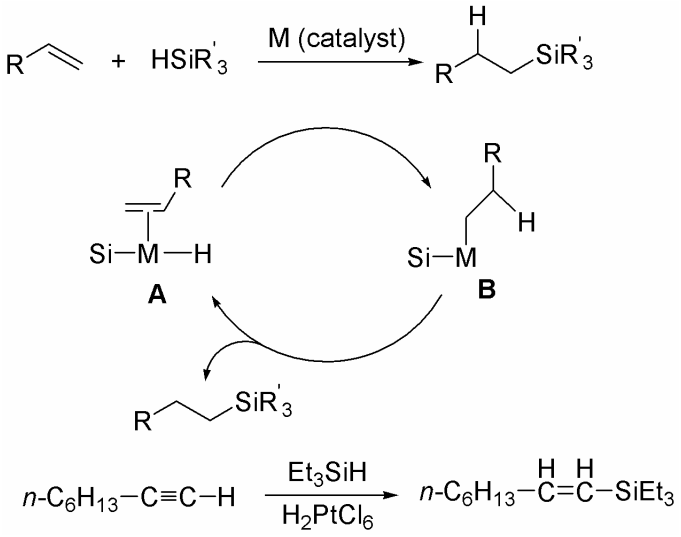


Scheme 1.22

1.2.5 Silylation of organic compounds

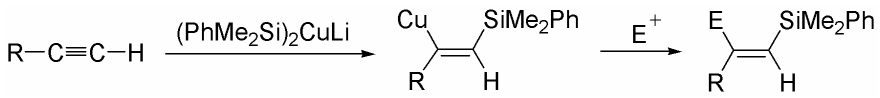
There are many possible ways to introduce a silyl group in carbon framework of organic molecules. The choice of method depends on the type of organosilicon compounds one would like to make. Besides specific methods for a particular class of organosilanes, there are also a few general approaches to prepare organosilicon compounds and are very frequently used in practice. Formation of Si–C bond in alkynes, alkenes, carbonyl compounds etc. are usually done *via* hydrosilylation method.[68] Hydrosilanes, $HSiR_3$, and a

variety of substrates having C=C double bond usually get activated by a transition metal complex, ML_n (L = ligand), especially an electron-rich complex of a late transition metal such as Co(I), Rh(I), Ni(0), Pd(0), or Pt(0) as a pre-catalyst. A catalytic cycle is generally assumed to proceed by the Chalk-Harrod mechanism[68c] (Scheme 1.23). At first, oxidative addition of a hydrosilane gives a hydrido-silyl complex, **A** which then undergoes migratory insertion of the alkene into the M–H bond (*hydrometallation*) to give the alkyl-silyl species, **B**. Reductive elimination of the alkyl and silyl ligands from **B** produced the hydrosilylation product.

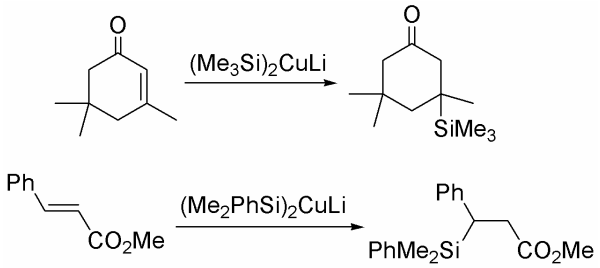


Scheme 1.23

Silyl cuprates easily prepared from silyllithiums and copper halides react with acetylenes[69a] with very high regioselectivity to give functionalized organosilanes (Scheme 1.24). Similarly, silylmagnesium and silylaluminium species add to terminal alkynes[69b] in the presence of transition metal catalysts with high regio and stereoselectivity. Silyl cuprates also undergo clean 1,4-addition[69c] with conjugated carbonyl compounds (Scheme 1.25) providing a method for preparation of large classes of organosilicon compounds.

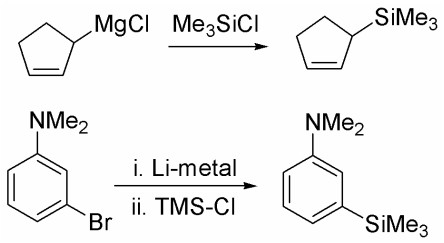


Scheme 1.24



Scheme 1.25

The classical way by replacing a carbon-metal bond[70] with a carbon silicon bond is also very useful to provide a large number of organosilicon products (Scheme 1.26).



Scheme 1.26

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CHAPTER 2

Silicon Assisted Diversified Reaction of Silylmethylene Malonates with Dimethylsulfoxonium Methylide

2.1 Introduction

The term, 'ylide' is obtained from German terms yl (means an open valancy) and id (means anionicity). An ylide can be viewed as a special carbanion, which bears a neighboring heteroatom (sulfur,[71] phosphorus,[72] nitrogen,[73] arsenic,[74] antimony,[75] bismuth,[76] selenium,[77] tellurium,[78] germanium,[79] tin,[80] and iodine[81]) carrying a high degree of positive charge (Fig. 2.1). It can be considered as a special type of zwitter ion where the negatively charged carbon is highly nucleophilic in nature. Sulfur ylides are now a powerful and versatile synthetic tool in the arsenal of organic chemists. Sulfoxonium ylides (Fig. 2.2) are a class of sulfur-based ylides that have been extensively studied after sulfonium ylides in the chemical literature. In particular, dimethylsulfoxonium methylide (Corey's reagent) have been proved to be a versatile nucleophilic agent capable of reacting with a wide variety of different systems.[82]

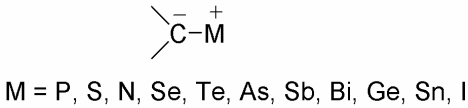


Figure 2.1: General structure of an ylide

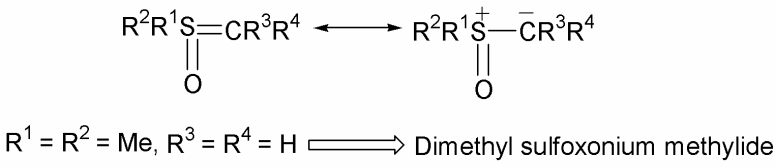
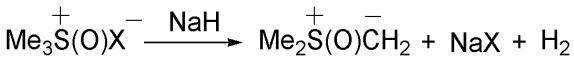


Figure 2.2: General structure of sulfoxonium ylides

In 1962, Corey and Chaykovsky[83] synthesized dimethylsulfoxonium methylide by the reaction of trimethylsulfoxonium chloride or iodide with sodium hydride under inert atmosphere in dry dimethyl sulfoxide (DMSO) (Scheme 2.1). A solution of dimethylsulfoxonium methylide in THF is stable for several months if kept in dry nitrogen or argon atmosphere at 0 ºC. A series of sulfoxonium salts have been used for the synthesis

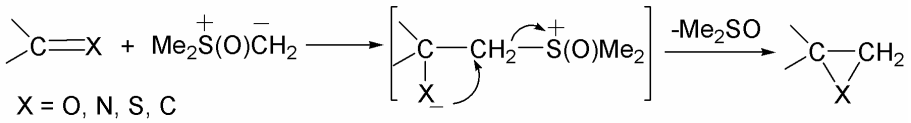
of different types of sulfoxonium ylides such as dialkylsulfoxonium ethylides, dialkylamino(aryl)sulfoxonium methylides, dialkylamino(alkyl)sulfoxonium methylides, dialkylamino(alkyl)sulfoxonium ethylides etc.



Scheme 2.1

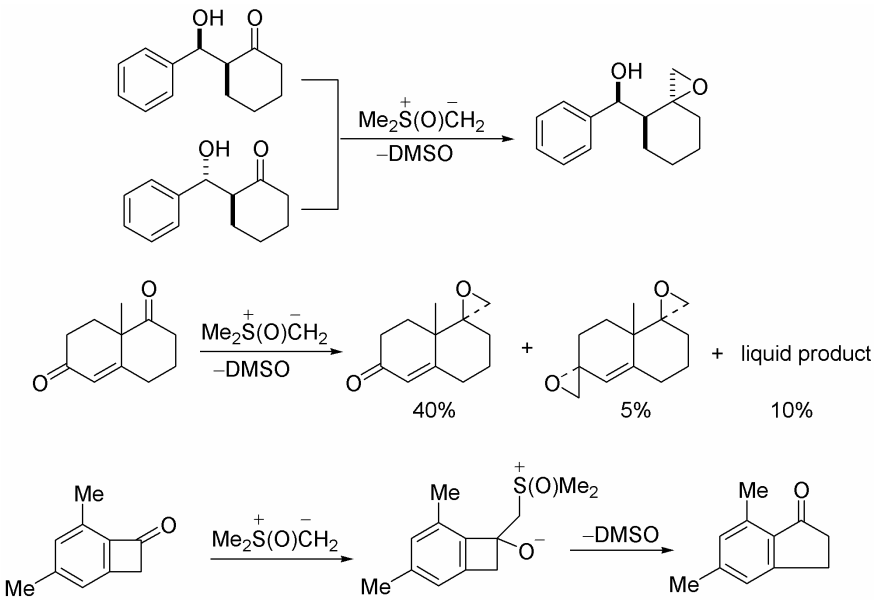
2.1.1 Reactions of DIMSOY with multiple bonds

Both the sulfur ylides, dimethylsulfoxonium methylide (DIMSOY) and dimethylsulfonium methylide (DIMSY) are known to behave as nucleophile and transfer methylene group to certain electrophilic unsaturated linkages, including C=O, C=N, C=S and activated C=C bonds. In these reactions the ylide behaves as a nucleophile in the first step and then subsequent loss of DMSO provides the cyclic products (Scheme 2.2).

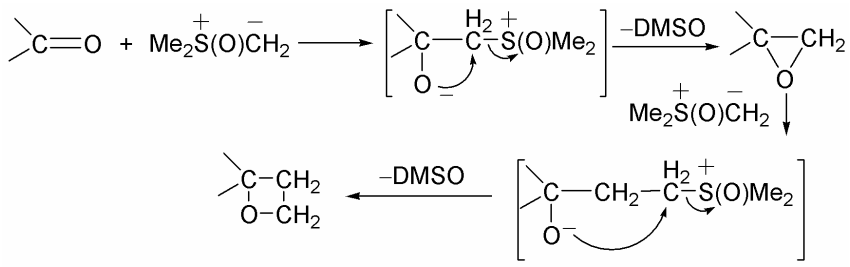


Scheme 2.2

Therefore, DIMSOY reacts with a ketone to produce epoxide. Epoxidation reaction between chiral β-hydroxy ketones and DIMSOY produced only one diastereomeric product (Scheme 2.3).[84] Whereas enedione and DIMSOY gave a mixture of mono- and di-epoxy products along with other products.[85] But 4,6-di-methylbenzocyclobuten-1-one does not lead to an epoxide. Instead, it produces 5,7-dimethylindan-1-one (Scheme 2.3).[86] Reactions of DIMSOY with epoxides lead to ring expansions to give oxetanes *via* the Corey reaction, therefore ketones can be converted to oxetanes by using 2 equivalents of the ylide (Scheme 2.4).

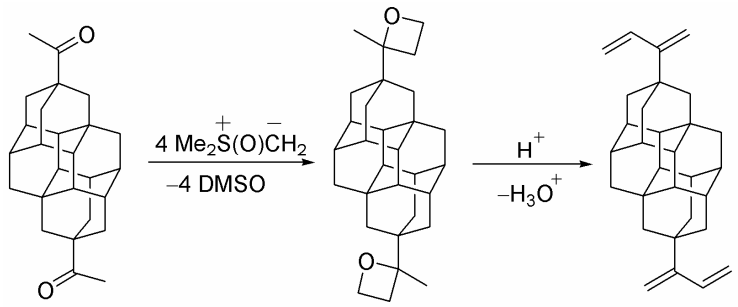


Scheme 2.3



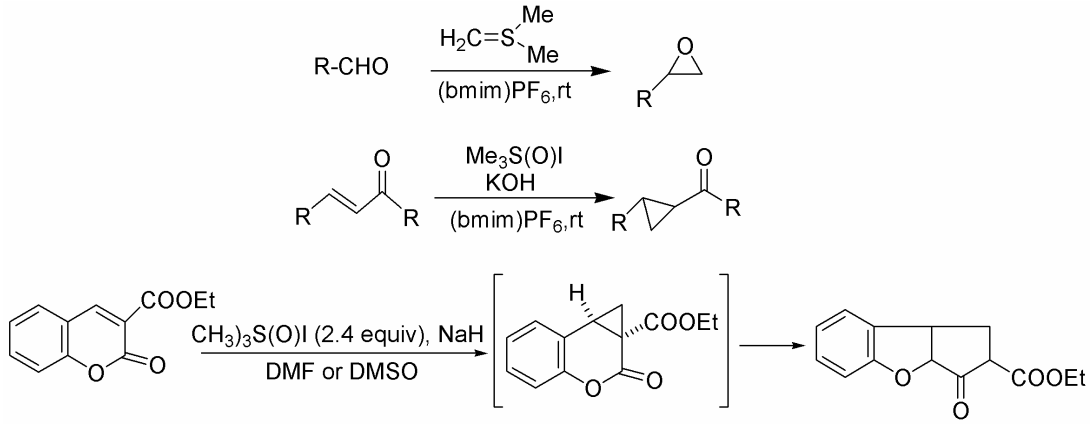
Scheme 2.4

A convenient preparation of terminal diamondoidyl bis-1,3-dienes was achieved[87] by converting bis-acetyl diamondoids to the respective oxetanes using DIMSOY and subsequent acid catalyzed ring opening/dehydration reactions (Scheme 2.5).



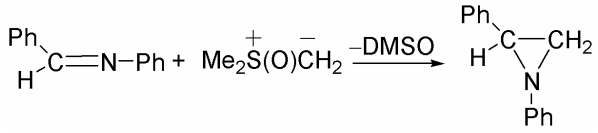
Scheme 2.5

According to Corey and Chaykovsky,[83] the less reactive DIMSOY (stabilized ylide) interacts with the carbonyl function of nonconjugated aldehydes and ketones to form oxiranes. On the other hand, α,β-unsaturated ketones which are Michael acceptor form cyclopropyl ketones. Contrary to DIMSOY, DIMSY reacts with the same substrates to form oxiranes exclusively even with α,β-unsaturated systems. Recently, the use of recyclable ionic liquids like (bmim)PF_6[88] as solvent have been introduced for the Corey-Chaykovsky epoxidation and cyclopropanation reactions (Scheme 2.6). Similarly, 3-ethoxycarbonylcoumarine reacts with 2.4 equiv of the ylide to produce tricyclic product.[89]



Scheme 2.6

Like C=O, C=N also undergoes methylene group insertion reaction to produce azetidines when reacted with DIMSOY (Scheme 2.7) and here also a number of products formed through the participation of other neighboring groups.

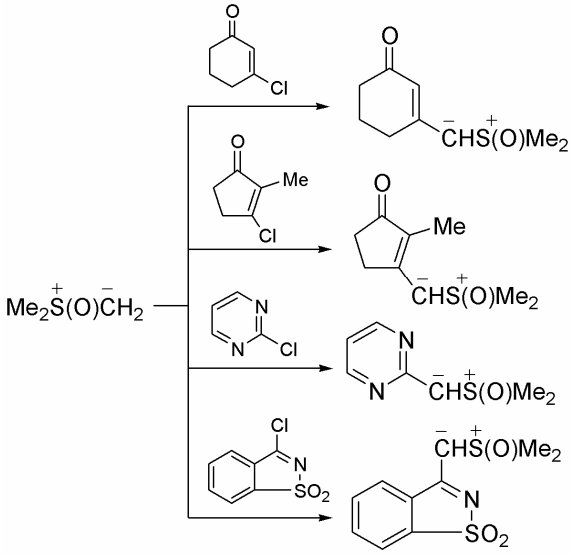


Scheme 2.7

2.1.2 Substitution reactions with DIMSOY[90]

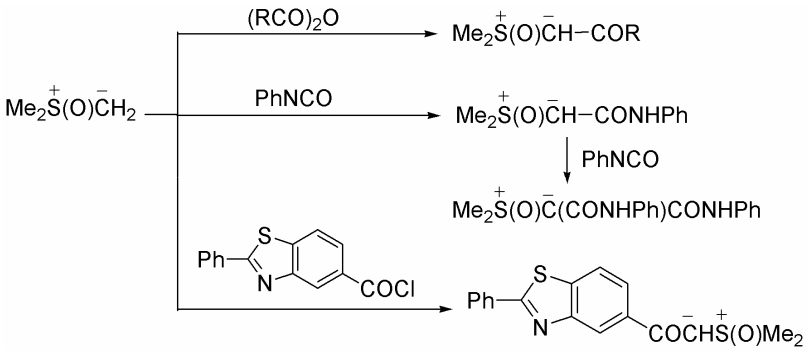
DIMSOY not only reacts with multiple bonds, but also undergoes the substitution reactions with chloro-containing compounds such as 3-chlorocyclohex-2-enone,[90a] 3-

chloro-2-methyl-2-cyclopenten-1-one,[90b] 2-chloropyrimidine[90c] and 3-chlorobenzothiazole 1,1-dioxide.[90c] They result in the formation of new sulfoxonium ylides (Scheme 2.8).

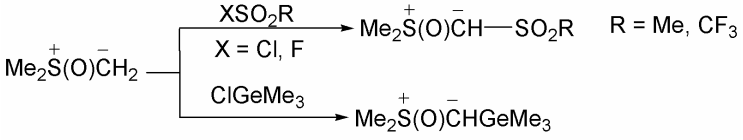


Scheme 2.8

Similarly, substitution reactions with acid anhydrides and phenyl isocyanate, acid chloride provide acyl-substituted ylides (Scheme 2.9).[82] The reaction of the ylide with organoelement acid halides gives the corresponding C-substituted ylides. Such kind of reactions of DIMSOY with methanesulfonyl chloride, tri-fluoromethanesulfonyl fluoride, chloro tri-methylgermane have been presented in Scheme 2.10.[82]



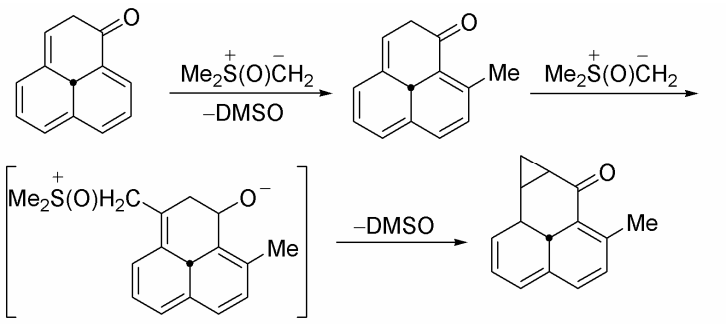
Scheme 2.9



Scheme 2.10

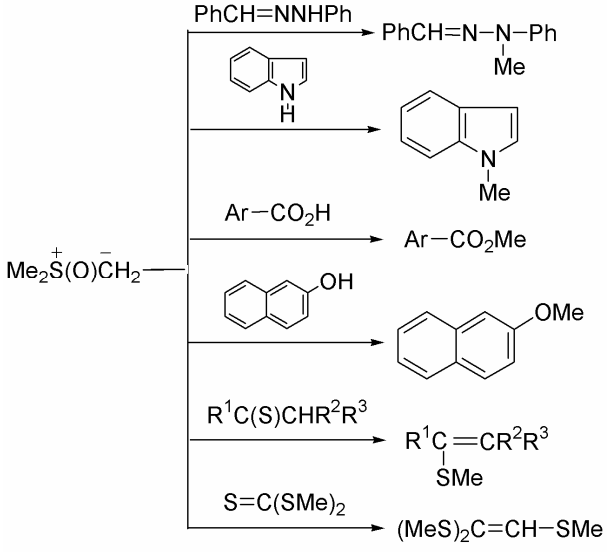
2.1.3 Methylation reactions with DIMSOY

Certain organic compounds also enjoy methylation reactions such as *C*-methylation, *N*-methylation, *O*-methylation and *S*-methylation when treated with DIMSOY. When nitrobenzene and DIMSOY were allowed to react at room temperature, a mixture of products of *o*- and *p*-nitrotoluene was isolated.[91] Similarly, phenalenone upon treatment with excess of the ylide undergoes *C*-methylation and provide 9-methylphenalenone followed by 9-methyl-2,3-homophenalenone (Scheme 2.11).[92]



Scheme 2.11

The deprotonation of N–H group in certain organic compounds was found to be transferred to DIMSOY and generate the trimethylsulfoxonium salt, which then methylates the amide ion resulting into the corresponding *N*-methylation products (Scheme 2.12).

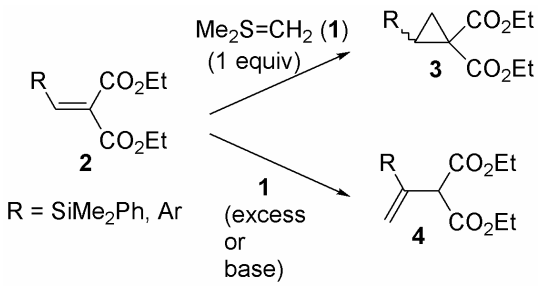


Scheme 2.12

Similarly, weak acids like phenols, carboxylic acids, and oximes undergo *O*-methylation on treatment with the ylide. *S*-Methylated products were also prepared by the reactions of the ylide with *N*-phenyliso-rodanine, certain thioketones and dithiocarboxylic esters (Scheme 2.12).[82]

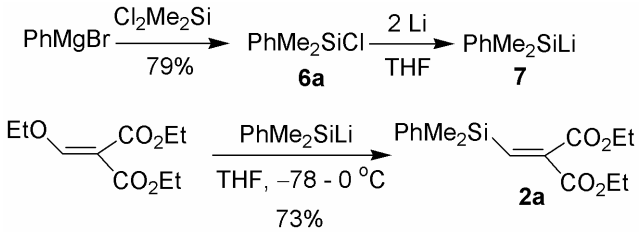
2.2 Present Work

As discussed above, sulfonium and sulfoxonium ylides are extensively used in organic chemistry to achieve the stepwise insertion of a methylene or a substituted methylene across the double bond of a carbonyl, an imine, or an electrophilic olefin to yield an oxirane, an aziridine, or a cyclopropane, respectively. Besides their difference in stability, the outcomes of many reactions with these ylides are similar, although, some notable differences in their reactivity and selectivity are also reported[93]. Recently our group and others have shown that DIMSY (**1**) when used in excess, or in the presence of a base can act as an equivalent of a carbenoid anion and provided interesting product(s) when reacted with various Michael acceptors,[94] activated dienes,[95] carbonyl compounds, imines and epoxides.[96] When DIMSY was reacted with β-silylmethylene or β-arylmethylene malonates **2**, cyclopropane derivatives **3** or olefins **4** were obtained[94] depending upon the quantities of the ylide and base used (Scheme 2.13). We were therefore interested to know if excess DIMSOY (**5**) would react in similar fashion with β-silylmethylene malonate **2a** (R = $SiMe_2Ph$).

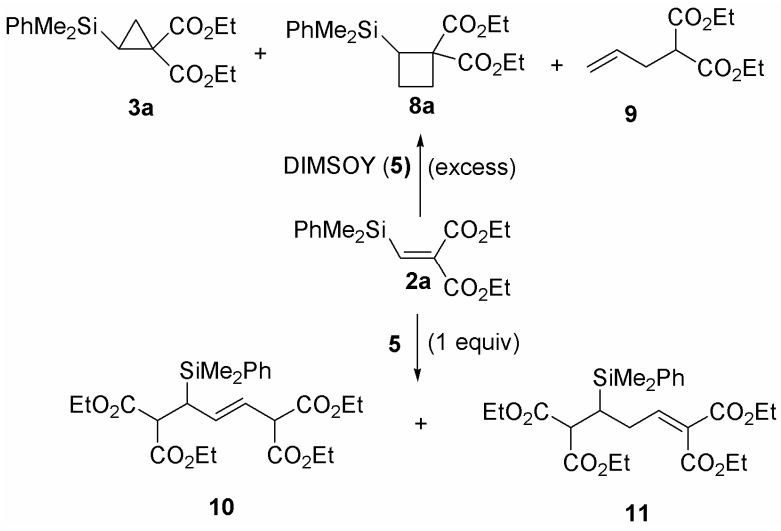


Scheme 2.13

We have prepared **2a** by a conjugate addition-elimination reactions starting from the commercially available diethyl ethoxymethylene malonate (Scheme 2.14). Dimethyl(phenyl)silyl chloride **6a** was obtained by the addition of phenylmagnesium bromide to dichlorodimethylsilane. Dimethyl(phenyl)silyllithium **7** was obtained from the corresponding silyl chloride by reaction with lithium metal and was added to diethyl ethoxymethylene malonate leading to unsaturated diester **2a** in good yield.



Scheme 2.14



Scheme 2.15

Interestingly, when excess DIMSOY, generated from the reaction of trimethylsulfoxonium iodide and sodium hydride in DMSO was reacted with the β-silylmethylene malonate **2a** at room temperature, the expected cyclopropane **3a** was formed albeit in moderate yield, associated with two unusual products *viz.* cyclobutane **8a** and the allylated malonate **9** (Scheme 2.15). However, when stoichiometric quantity of the

ylide **5** was used, besides cyclopropane **3a**, a pair of new products, an allylsilane **10** and its regioisomeric homoallylsilane **11** were formed (Scheme 2.15). The diversified products formed under different conditions therefore challenged us to formulate conditions for individual products. We developed the conditions for two interesting groups of products, cyclobutane and allyl/homoallylsilane with very high selectivity merely by adjusting the stoichiometry of the ylide and reaction conditions.

2.2.1 Preparation of cyclobutane derivatives

Cyclobutanes have been known for more than a century but their use as synthetic intermediates has gained popularity very recently.[97] Their diversity of reactions is the result of the inherent strain associated with the four-membered ring contributing to both angular and torsional effects. Thus, cyclobutanes undergo reactions such as ring opening to acyclic products[98] (23–26 kcal mol^{-1} release of energy), ring enlargement to five- or six-membered ring products[99] (20 and 25 kcal mol^{-1} respectively), and ring contraction to cyclopropanes.[99] The regioselectivity of bond cleavage in cyclobutane is decided by the ring substituents, reagents and conditions.

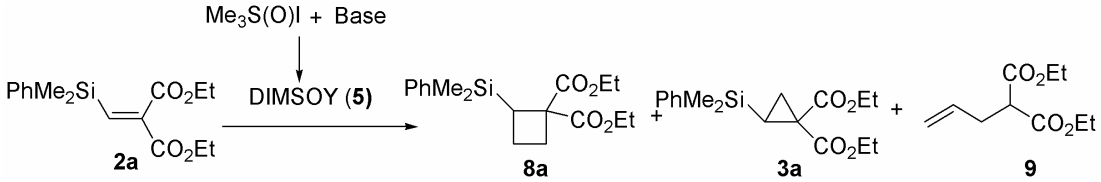
The [2+2] cycloaddition between two alkene moieties represents the most popular method for the construction of cyclobutanes.[97d] However, the above method for the synthesis of cyclobutane derivatives, suffers from the inherent nonselectivity for the thermal process, which is forbidden by orbital symmetry considerations, and thus proceeds *via* intermediates which are sufficiently long lived to undergo stereochemical equilibration. The photochemically induced cycloaddition is allowed by orbital symmetry. However, isolated alkenes possess chromophores which are not accessible to excitation by conventional light sources. On the other hand, conjugated alkenes and enones, which are conveniently excited by conventional UV sources, often undergo intersystem crossing to

the triplet state, producing biradicals which can readily undergo stereochemical equilibration. An additional problem arises when nonsymmetric alkenes with little electronic differentiation are used, giving rise to mixtures of regioisomers.

From the above discussions it is very clear that the synthesis of suitably functionalized cyclobutane derivatives is still challenging. We, therefore, first aimed to establish the optimized conditions for the preparation of the silicon functionalized cyclobutane derivative **8a** (Fig. 2.3). To this end, we carried out the reactions of **2a** with DIMSOY, generated from trimethylsulfoxonium iodide under different conditions (Scheme 2.16) and the results are presented in Table 2.1.

The reaction of **2a** with 2 equivalents of DIMSOY, generated using sodium hydride as base in DMSO at 20 ºC provided the cyclopropane **3a** (Fig. 2.4) associated with a significant amount of cyclobutane **8a** and the allylated malonate **9** (Fig. 2.5) in moderate yield (Table 2.1, entry 1). Further increase in the DIMSOY quantity or changing the temperature did not improve the yield, but led to substantial formation of the undesired byproduct **9** at the expense of the target cyclobutane **8a** (Table 2.1, entries 2 & 3). Changing the base to LiOBu-*t* (generated from *n*-butyl lithium and *tert*-butanol) in DMSO improved the product yield with overwhelming preference for the cyclobutane **8a**. Amongst the solvents studied, DMF showed comparable yields and selectivity. The cation of the base had a dramatic influence on the selectivity of the formation of cyclobutane **8a** over cyclopropane **3a**, and increased in the order Li>Na>K. Hence, the best condition was to use 2.5 equivalents each of LiOBu-*t* and trimethylsulfoxonium iodide with respect to malonate **2a** in DMSO at 20 ºC, which gave cyclobutane **8a** and cyclopropane **3a** (**3a**:**8a** = 13/87) in 71% isolated yield (Table 2.1, entry 5). Increasing the amount of ylide **5** beyond 2.5 equivalents neither enhanced the yield nor selectivity (Table 2.1, entry 6). The effect of

counter ion in the trimethylsulfoxonium salt did not have much impact since the reaction with trimethylsulfoxonium chloride proceeded with similar yield and selectivity (Table 2.1, entry 11).



Scheme 2.16

Table 2.1: Optimization of conditions for the synthesis of cyclobutane 8a

Entry	$Me_3S(O)I$ (equiv)	Base (equiv)	Solvent	**3a:8a:9**[a]	%Yield of **3a+8a**[b]
1	2	NaH (2)	DMSO	24:41:35	34[c]
2	2.5	NaH (2.5)	DMSO	49:2:49	nd[d,e]
3	2.5	NaH (2.5)	DMSO	28:4:68	nd[d,f]
4	2	LiOBu-*t* (2)	DMSO	17:83:0	60
5	2.5	LiOBu-*t* (2.5)	DMSO	13:87:0	71
6	3	LiOBu-*t* (3)	DMSO	12:88:0	69
7	2.5	LiOBu-*t* (2.5)	DMF	13:87:0	69
8	2.5	LiOBu-*t* (2.5)	THF	68:32:0	19
9	2.5	NaOBu-*t* (2.5)	DMSO	43:57:0	61
10	2.5	KOBu-*t* (2.5)	DMSO	59:41:0	60
11	2.5[g]	LiOBu-*t* (2.5)	DMSO	12:88:0	73

[a] Ratios determined by ^{1}H NMR from the crude product; [b] All the reactions (except entries 2 and 3) were performed at 20 ºC; [c] 20% of **9** was also isolated; [d] Yield not determined; [e] Reaction was performed at −10 ºC; [f] Reaction was performed at 50 ºC; [g] $Me_3S(O)Cl$ was used.

To see the generality of this synthetic strategy, we prepared two more silylmethylene malonates **2b**,**c**. The dimethyl(trimethylsilyloxy)silyl substituted methylene malonate **2b** was prepared in 58% yield from **2a** by a selective protiodephenylation of the

(phenyl)dimethylsilyl group with trifluoromethanesulfonic acid in dichloromethane followed by mixed disiloxane formation by adding excess trimethylsilyl chloride to the reaction mixture and then quenching with ammonium hydroxide (Scheme 2.17).

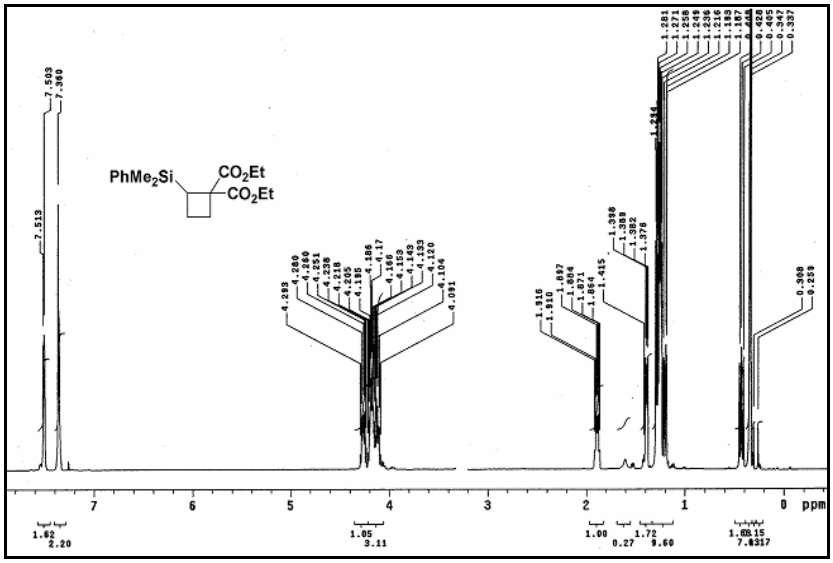


Figure 2.3: ^{1}H NMR of cyclobutane 8a

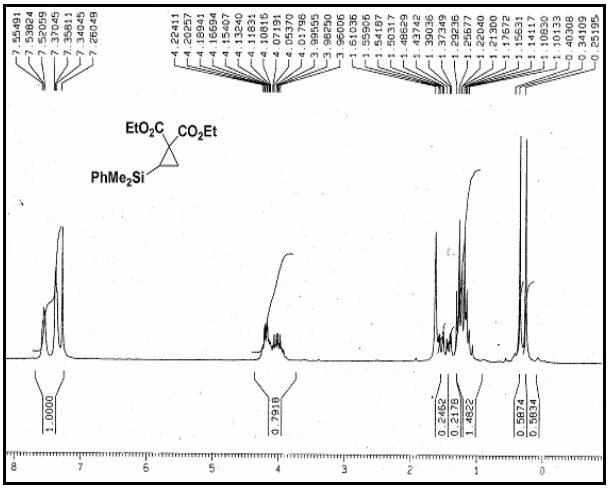


Figure 2.4: ^{1}H NMR of cyclopropane 3a

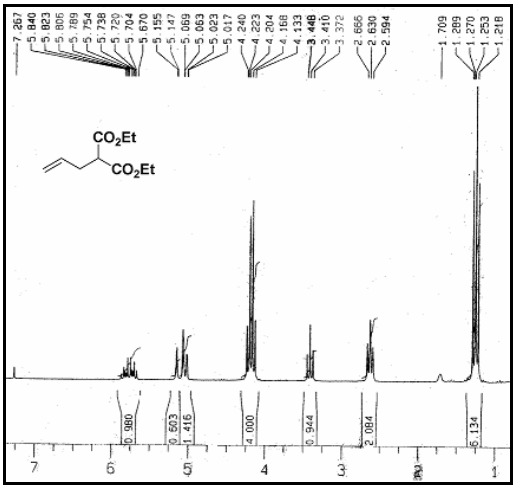
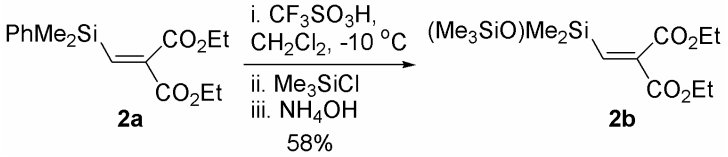


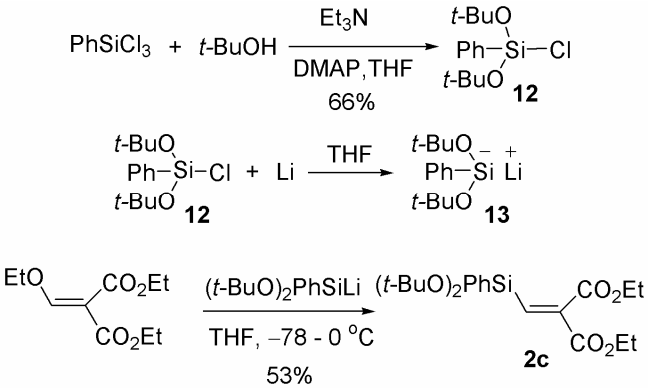
Figure 2.5: ^{1}H NMR of malonate 9

For the preparation of di-*tert*-butyloxy(phenyl)silyl substituted methylene malonate **2c**, we adopted a procedure similar to the preparation of **2a**. Therefore, the known di-*tert*-butyloxy(phenyl)silyl chloride[100] **12** was achieved by the reaction of commercially available phenyltrichlorosilane with *tert*-butyl alcohol in presence of triethylamine and 4-(dimethylamino)pyridine (DMAP). Following the literature procedure,[100] di-*tert*-

butyloxy(phenyl)silyllithium **13** was prepared from the corresponding silyl chloride **12** and reacted with diethyl ethoxymethylene malonate in THF to give **2c** (Scheme 2.18).

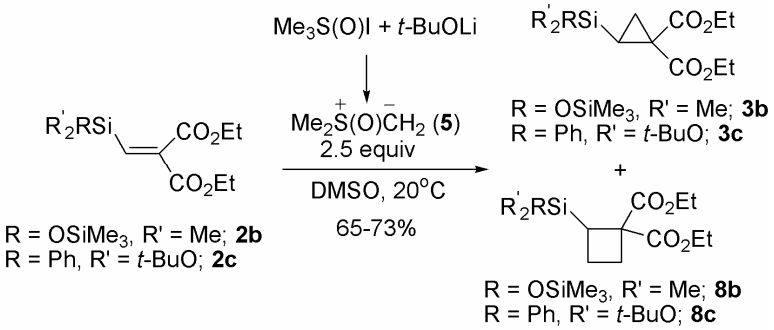


Scheme 2.17



Scheme 2.18

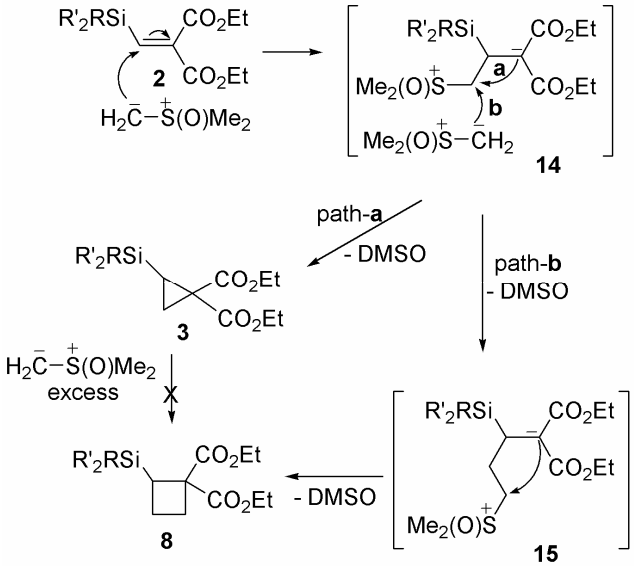
Reaction of silylmethylene malonate **2b** with DIMSOY, generated under the optimized conditions (Table 2.1, entry 5), provided a mixture of cyclopropane **3b** and cyclobutane **8b** in moderate yield and selectivity (**3b**:**8b** = 1/2) (Scheme 2.19). Under these conditions, silylmethylene malonate **2c** also reacted with DIMSOY to give a mixture of cyclopropane **3c** and cyclobutane **8c**. In this case, there was a reversal of selectivity wherein cyclopropane **3c** was formed as the major product (**3c**:**8c** = 7:3). This suggested a crucial role of the silyl substituents on the course of the reaction.



Scheme 2.19

2.2.1a Plausible mechanism for the formation of cyclobutane derivatives

A plausible mechanism for the formation of cyclobutane products from silyl substituted methylene malonates **2** is delineated in Scheme 2.20. The nucleophilic addition of DIMSOY on the β-silylalkylidene malonate **2** produced the intermediate **14** which can give the cyclopropane **3** by loss of DMSO (path-a). Evidently, the cyclobutane **8a**, formed in this reaction was not produced *via* the cyclopropane intermediate. In separate experiments, cyclopropane **3a** was found to be unreactive to the ylide **5** even when treated in large excess. As the silicon group is known to facilitate nucleophilic substitution β-to it, the other favorable pathway (path-b) was the nucleophilic displacement of DMSO on **14** by ylide **5** to give the intermediate **15,** which on intramolecular cyclization provided the cyclobutane **8** with expulsion of DMSO. As the silicon group becomes larger, path-b becomes unfavorable owing to the steric effect. This was clearly manifested in case of **2c** where cyclopropane **3c** was obtained as the major product.

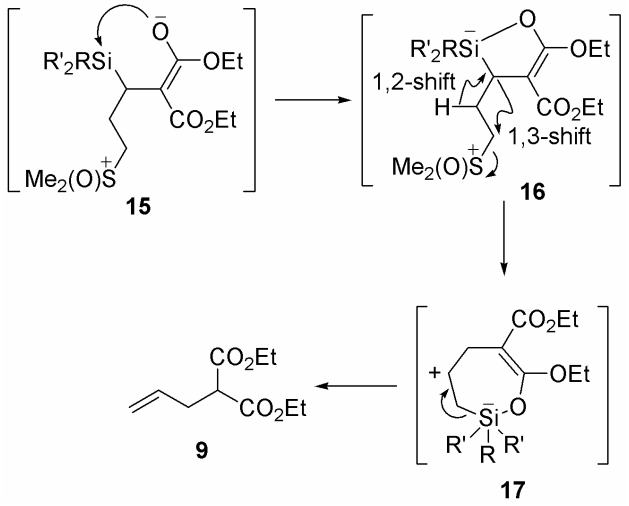


Scheme 2.20

2.2.2 Plausible mechanism for the formation of allylmalonate 9

Although diethyl allylmalonate **9** can be readily prepared from diethyl malonate and allyl bromide, its formation in the reaction of silylmethylene malonates **2** with excess

DIMSOY is somewhat unusual. It is well established that cyclopropylmethyl halides, cyclobutyl halides and homoallyl halides are all in equilibrium in acid solutions and the mixture of products are often formed *via* delocalized cationic intermediate.[101] But, under present circumstances, this situation is unlikely. We believe that the silyl group plays an important role in this reaction also. We propose that the malonate **9** is also formed from the intermediate anion **15** as depicted in Scheme 2.21. The enolate form of **15** probably formed a pentacoordinated silicate[102] species **16** which facilitated a γ-silyl group assisted (neighboring group participation)[103] loss of DMSO to give a primary carbocation that initiated a 1,2-hydride shift induced 1,3-silyl shift to give a β-silicon stabilized cationic intermediate **17**. Loss of silyl group from it then yields **9**.



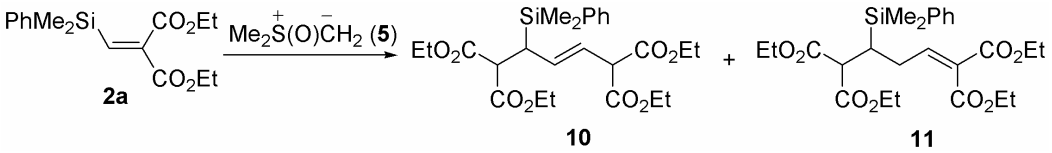
Scheme 2.21

2.2.3 Preparation of allyl and homoallylsilane

Allylsilanes are versatile compounds that are thermally stable and remain unreactive even in the presence of water or oxygen, requiring no special precautions for storage of allylsilanes. It is in part due to this high level of stability that allows high degrees of regioselectivity and stereoselectivity when doing reactions that involve allylsilanes.[104] Along with the synthetic importance of allylsilanes (Chapter 1), some of

these compounds are also incorporated in the reaction schemes of natural products such as prostaglandins,[105a] loganin[105b] etc. Allylsilanes are also known to act as effective allylating agents towards various carbonyl compounds to give homoallyl alcohol derivatives. Due to their enormous synthetic utility, a large number of synthetic procedures of allylsilanes have been reported.[106]

Therefore, we turned our attention towards the preparation of the functionalized allylsilane **10** (Fig. 2.6) and/or homoallylsilane **11** (Fig. 2.7), obtained by the reaction of β-silylmethylene malonate **2a** with the stoichiometric amount of the ylide **5** (Scheme 2.22). The homoallylsilane **11** and the allylsilane **10** are essentially labile olefin regioisomers, and are interconvertible under mild conditions. Their structures suggest that these products are formed from two molecules of malonate **2a**. Therefore, while optimization, the ylide quantity was reduced to half that of the malonate **2a**. A large number of reaction conditions were tried to optimize the formation of **10** and/or **11** as presented in Table 2.2.



Scheme 2.22

Table 2.2: Optimization of conditions for the synthesis of olefins 10 and 11

Entry	Solvent (temp)	%Yield of **10 + 11**[a]	%Yield of **3a**[b]
1	DMSO (5 °C)	55	13
2	DMF (15 °C)	58	11
3	DMF (5 °C)	65	12
4	DMF (0 °C)	51	11
5	NMP (5 °C)	67	11

[a] Refers to combined isolated yield; [b] Product contaminated with 8–10% of **8a**.

The reactions were performed using 0.5 equivalent of DIMSOY generated from 0.5 equivalent of trimethylsulfoxonium iodide and 1.1 equivalent of *t*-BuOLi (with respect to **2a**) at a temperature range of 0–15 °C using different solvents like DMSO, DMF and *N*-methyl pyrrolidone (NMP). The best result was obtained by carrying out the reaction with 0.5 equivalents of ylide **5** in DMF or NMP at 5 °C (Table 2.2; entries 3 and 5).

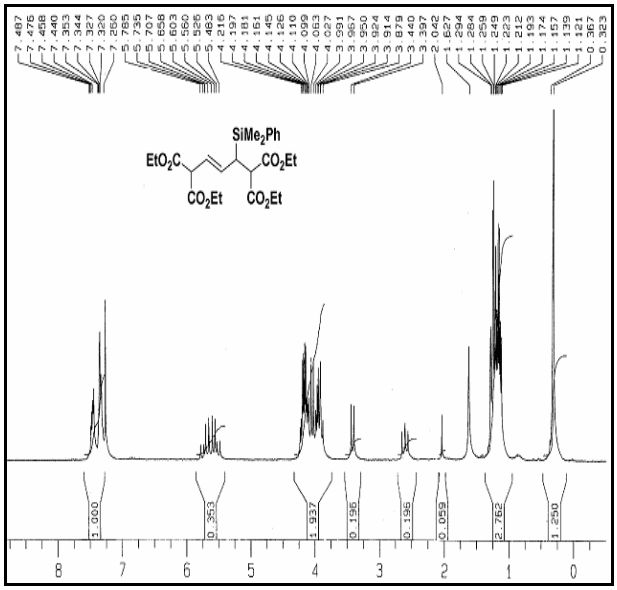


Figure 2.6: ^{1}H NMR of 10

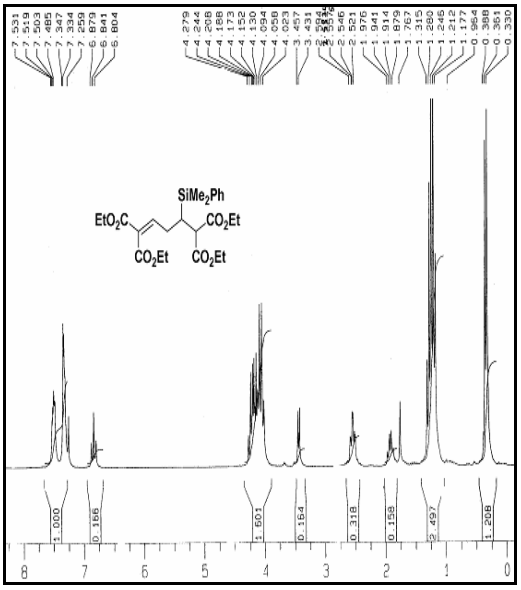
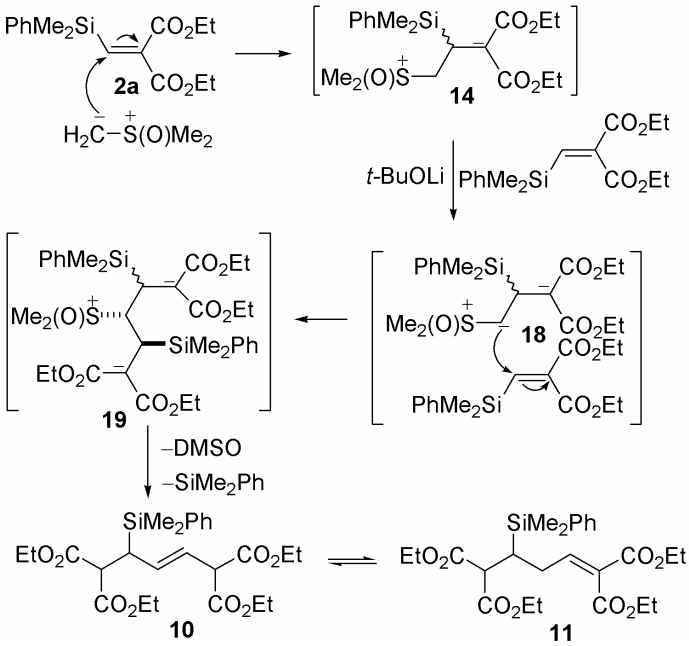


Figure 2.7: ^{1}H NMR of 11

2.2.3a Plausible mechanism for the formation of olefins 10 and 11

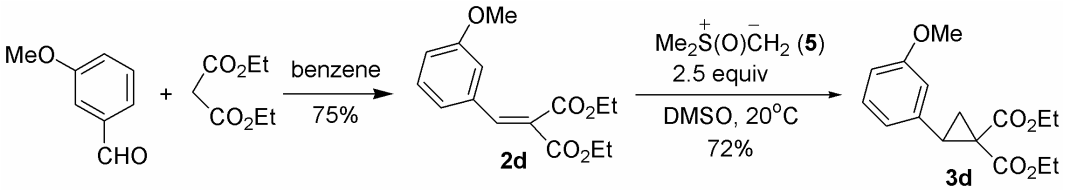
The formation pathway of allylsilane from β-silylalkylidene malonate **2a** under substoichiometric amount of ylide and stoichiometric amount of base is exemplified in Scheme 2.23. The ylide **5** adds to malonate **2a** to give the adduct **14** from which the base abstracts a proton to generate a new ylide **18**. This, in turn, reacts with another molecule of malonate **2a** to give the intermediate **19**. A Peterson type olefination with elimination of $PhMe_2Si$ and $Me_2S(O)^+$ groups afforded the allylsilane **10**. The homoallylsilane **11** is then formed by base induced double bond isomerization of the allylsilane.



Scheme 2.23

2.2.4 Role of silicon group in the diversified reaction of β-silylmethylene malonate and ylide

To find the role played by the silicon group in the above reactions, arylidene malonate **2d**[94] **w**as prepared by refluxing a solution of *m*-anisaldehyde and diethyl malonate in benzene in the presence of piperidinium benzoate. The arylidene malonate **2d** was reacted with varying amounts of DIMSOY, generated from the corresponding iodide and base (Scheme 2.24). In all the cases, no trace of cyclobutane or the dimerization



Scheme 2.24

products was observed. The cyclopropane **3d** was the sole product associated with the unreacted starting material in cases where substoichiometric quantity of ylide **5** was used. These results, unambiguously established the vital role of the silyl group in the malonates

2a-**c** in governing the pathway of the 'reagent-based' skeletal diversity oriented synthesis (Fig 2.8). Where, a common starting substrate is β-silylmethylene malonate and reacts with different reagents and/or different reaction conditions to produce highly functionalized diverse skeletal.

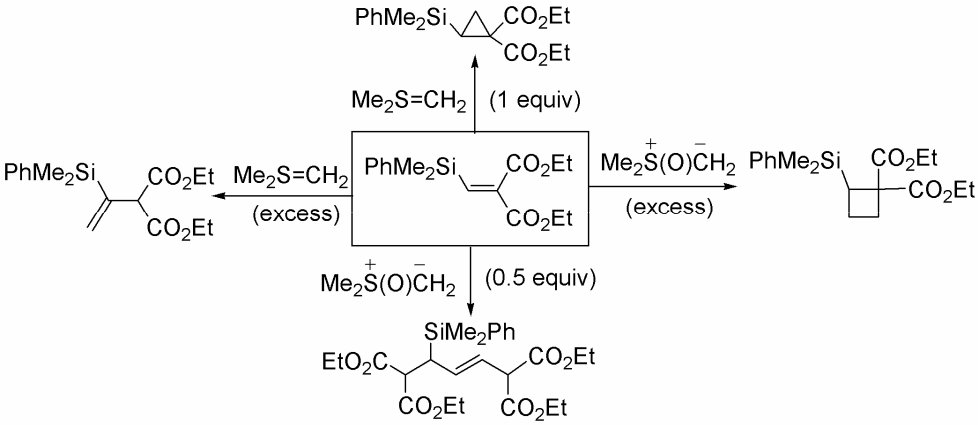


Figure 2.8: Schematic representation of the 'reagent based' DOS approaches

2.3 Conclusion

In conclusion, we have developed for the first time the 'reagent-based' skeletal diversity oriented synthesis of functionalized organosilicon compounds. We have illustrated the reaction of silylmethylene malonates with DIMSOY, which produces diversified products depending upon the stoichiometry of the reactants and reaction conditions. The product(s) formed are unique, and the silicon group plays crucial role either by assisting and/or by participating in the process. The cyclopropanes, cyclobutanes, allyl and homoallyl silanes, produced in this method have synthetic potentials as the chemistry of these classes of molecules are well established. In addition, the present work also exemplified the unique difference in reactivity of DIMSOY and DIMSY with silylmethylene and/or arylmethylene malonates.

2.4 Experimental

All reactions were performed in oven-dried (120 °C) or flame-dried glass apparatus under dry N_2 or argon atmosphere.

Solvent purification and drying

The solvents were dried and distilled from the indicated drying agents: CH_2Cl_2 and $CHCl_3$ from P_2O_5; THF and Et_2O from sodium/benzophenone; Toluene, benzene and hexanes from sodium; *t*-BuOH, DMSO, DMF and NMP from CaH_2 and then stored over 4 Å molecular sieves.

Reagents

Benzaldehyde, *p/m*-anisaldehyde, *p*-chlorobenzaldehyde were freshly distilled, where as *p*-bromobenzaldehyde and *p*-nitrobenzaldehyde were crystallized before use. Diethyl malonate, ethyl cyanoacetate, triethyl phosphonoacetate were distilled under vacuum before use. NaH (55% in oil) was obtained from Aldrich while KH (20% in oil suspension) was obtained from Fluka. *n*-BuLi (1.5 *M* in hexane), $Me_3S(O)I$ and Me_3SI were purchased from Aldrich.

NMR Study

^1H NMR spectra were recorded on a Bruker 200 and 500 MHz spectrometer. ^{13}C NMR spectra were recorded on a Bruker 50 and 125 MHz spectrometer. Spectra were referenced to residual chloroform (δ 7.25 ppm, ^1H; 77.00 ppm, ^{13}C). Chemical shifts are reported in ppm (δ); multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), quint (pentet), m (multiplet) and br (broad). Coupling constants, *J*, are reported in Hertz.

Mass Spectrometry

The mass spectra were recorded on a Shimadzu GC-MS 2010 mass spectrometer (EI 70 eV). High resolution mass spectra were recorded at 60–70 eV with a Waters Micromass Q-TOF spectrometer (ESI, Ar).

IR Study

Infrared spectra (IR) were recorded on a JASCO FT IR spectrophotometer in NaCl cells or in KBr discs. Peaks are reported in cm^{-1}.

Melting Points

Melting points (mp) were determined on a Fischer John's melting point apparatus and are uncorrected.

Gas Chromatography

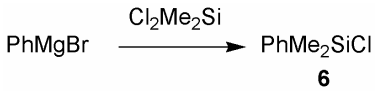
Gas chromatography (GC) studies were carried out using Younglin Acme 6000M Gas Chromatograph fitted with a capillary column (WCOT Fused Silica, CP-SIL-5-CB, 50 m × 0.25 mm/0.39 mm, 0.25 µm; Carrier: helium 1 mL/min).

TLC

Analytical thin-layer chromatography was performed using home made Acme silica gel plates (about 0.5 mm).

Column Chromatography

Column Chromatography was performed using Silica Gel 230–400 mesh (for flash chromatography) obtained from Sisco Research Laboratories Pvt. Ltd.



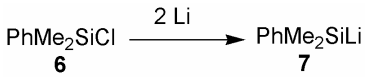
Dimethyl(phenyl)silyl chloride 6

A solution of bromobenzene (52.7 mL, 500 mmol) in ether (500 mL) was added drop wise on magnesium turnings (13.2 g, 550 mmol) with stirring and under gentle reflux. The reaction mixture was stirred with reflux for 2 h. This phenylmagnesium bromide solution was added to dichlorodimethylsilane (97 mL, 800 mmol) with stirring at 0 °C. The reaction mixture was heated under reflux with stirring overnight. The reaction mixture was filtered under vacuum and the filtrate was concentrated on oil bath (bath 60 °C). The residue was distilled to give dimethyl(phenyl)silyl chloride **6** (66.7 g, 79%).(Caution! the

material has frothing nature, therefore, glass wool and bigger size flask has to be used during distillation).

bp. 75–80 ^{o}C/5 mmHg.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.69 (6 H, s, 2 × MeSi), 7.35–7.44 (3 H, m, Ar), 7.61–7.66 (2 H, m, Ar).



Dimethyl(phenyl)silyllithium 7

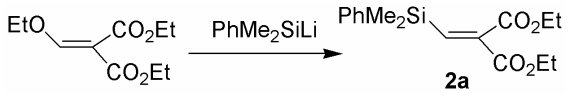
Dimethyl(phenyl)silyl chloride (20 mL) was added to a stirred suspension of lithium metal (2 g, 0.286 gatom) in THF (90 mL) at 0 °C under argon. The reaction mixture was stirred under this condition for 5 h (color of the solution became deep red).

Estimation of the strength of the dimethyl(phenyl)silyllithium solution:

A) 1 mL of the reagent was quenched with water and titrated with standard oxalic acid solution (0.1 *N*) using phenolphthalein indicator which gave total lithium content in solution.

B) 1 mL of the reagent was first quenched with 1,2-dibromoethane (1 mL) in ether (10 mL), stirred under argon for 5 min and then quenched with water and titrated as above which gave lithium content not present as silyllithium.

The difference of the two titer values (A–B) gave the actual silyllithium concentration which was found to be 0.85 *M* in this case.



Ethyl 2-ethoxycarbonyl-3-phenyldimethylsilyl-2-propenoate 2a

Dimethyl(phenyl)silyllithium **7** (0.85 *M* solution in THF) (105 mL, 89 mmol) was added drop wise to a stirred solution of diethyl ethoxymethylene malonate (18 mL, 89 mmol) in

THF (200 mL) at –78 °C over 0.5 h. After the addition was over, the reaction mixture was stirred for 5 min and the cold bath was removed. The reaction mixture was allowed to attain to room temperature (about 25 min) and poured into saturated ammonium chloride solution, extracted with Et_2O (2 × 250 mL). The organic extract was washed with water and with brine, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica using hexane-EtOAc (95:5) to give the diester **2a** (19.9 g, 73%) as colorless oil.

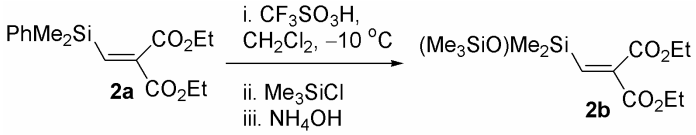
R_f 0.6 (hexane/EtOAc, 95:5).

IR (neat): 1727, 1604, 1236, 1114 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.45 (6 H, s, 2 × SiMe), 1.19 (3 H, t, *J* = 7.1 Hz, *Me*CH_2OCO), 1.29 (3 H, t, *J* = 7.1 Hz, *Me*CH_2OCO), 4.00 (2 H, q, *J* = 7.1 Hz, Me*C*H_2OCO), 4.24 (2 H, q, *J* = 7.1 Hz, Me*C*H_2OCO), 7.31 (1 H, s, C=CHSi), 7.34–7.38 (3 H, m, Ph), 7.50–7.55 (2 H, m, Ph).

^{13}C-NMR (50 MHz, $CDCl_3$): δ –2.8, 13.7, 13.9, 61.0, 61.4, 127.7, 129.3, 133.7, 136.1, 141.6, 147.3, 163.6, 165.9.

MS (ESI) *m/z*: 329 (M+Na, 15%), 307 (M+H, 5), 229 (M–Ph, 100), 128 (82), 173 (41), 155 (37).



Diethyl dimethyl(trimethylsilyloxy)silylmethylene malonate 2b

Trifluoromethanesulfonic acid (4.3 mL, 49 mmol, 5 equiv) was added to a stirred solution of **2a** (3 g, 9.8 mmol) in dry CH_2Cl_2 (15 mL) at –2 °C. After 10 min, chlorotrimethylsilane (12.5 mL, 98 mmol, 10 equiv) was added to the reaction mixture. The reaction mixture was poured into ice-cold saturated NH_4OH solution (100 mL) and extracted with $CHCl_3$. The

organic extract was dried over anhydrous sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography to give **2b** (1.8 g, 58%) as colorless oil.

R_f 0.58 (hexane/EtOAc, 95:5).

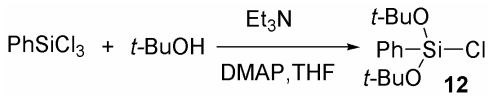
IR (film): 2982, 2958, 2904, 1732, 1370, 1318, 1254, 1198, 1051, 844, 809, 754 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ –0.02 (9 H, s, Me_3SiO), 0.13 (6 H, s, Me_2Si), 1.18 (3 H, t, *J* = 6 Hz, OCH_2CH_3), 1.20 (3 H, t, *J* = 6 Hz, OCH_2CH_3), 4.13 (2 H, q, *J* = 6 Hz, OCH_2CH_3), 4.15 (2 H, q, *J* = 6 Hz, OCH_2CH_3), 6.99 (1 H, s, SiCH=C).

^{13}C-NMR (50 MHz, $CDCl_3$): δ 0.5 (2 C), 1.6 (3 C), 13.7 (2 C), 60.9, 61.1, 140.1, 149.4, 163.8, 165.5.

HRMS (ESI) *m/z*: Found MNa^+ 341.1219, $C_{13}H_{26}O_5Si_2Na$ requires 341.1217.

MS (ESI) *m/z*: 341 (M+Na, 43%), 201(16), 155 (10), 83 (100).



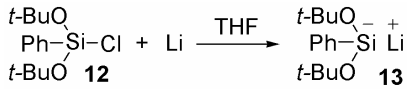
Di-*tert*-butyloxy(phenyl)silyl chloride 12[100a]

A solution of *t*-butyl alcohol (10.4 mL, 110 mmol) in THF (10 mL) was added to a mixture of phenyltrichlorosilane (8 mL, 50 mmol), triethylamine (15.3 mL, 110 mmol) and DMAP (305 mg, 2.5 mmol) in THF (100 mL). The mixture was stirred at room temperature for 6 h. The reaction mixture was diluted with dry hexane (100 mL), filtered with suction to remove the salt. The filtrate was concentrated and the residue was distilled to give the desired product **12** (9.5 g, 66%) as colorless oil.

bp 85–91 ^oC/0.6 mmHg.

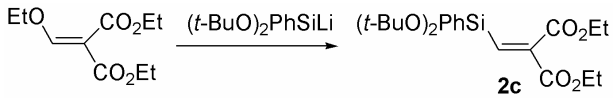
^{1}H-NMR (200 MHz, C_6D_6): δ 1.41 (s, 18 H, 2 × *t*-BuO), 7.20–7.23 (m, 3 H, Ph), 7.96–8.00 (m, 2 H, Ph).

^{13}C-NMR (50 MHz, C_6D_6): δ 31.6 (6 C), 75.8 (2 C), 128.1 (2 C), 130.6, 134.4 (2 C), 135.6.



Di-*tert*-butyloxy(phenyl)silyllithium 13[100b]

Di-*tert*-butyloxy(phenyl)silyl chloride (8.5 g, 29.6 mmol) was added to a stirred suspension of lithium metal (830 mg, 0.118 gatom) in THF (30 mL) at room temperature under argon. After 40 min, the reaction mixture was cooled to 0 °C and stirred for 4 h to get deep red silyllithium solution.



Diethyl di-tert-butyloxy(phenyl)silylmethylene malonate 2c

The deep red di-*tert*-butyloxy(phenyl)silyllithium solution (as prepared above) was slowly cannulated to a stirred solution of diethyl ethoxymethylene malonate (6.5 mL, 32.6 mmol, 1.1 equiv) in THF (30 mL) at –78 °C over 15 min. After the addition was over, the reaction mixture was stirred for 30 min and the cold bath was removed. The reaction mixture was allowed to attain to room temperature (about 25 min) and poured into saturated ammonium chloride solution, extracted with Et_2O. The organic extract was washed with water and with brine, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica using hexane-EtOAc (95:5) to give the diester **2c** (6.6 g, 53%) as colorless oil.

R_f 0.62 (hexane/EtOAc, 95:5).

IR (film): 3070, 2978, 1731, 1615, 1390, 1366, 1331, 1235, 1119, 1046, 899, 870 cm^{-1}.

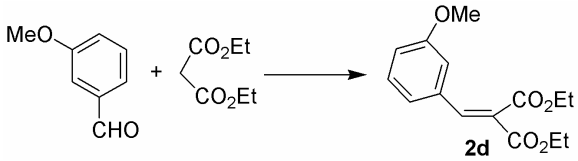
^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.13 (3 H, t, *J* = 7 Hz, $OCH_2\mathit{CH_3}$), 1.29 (3 H, t, *J* = 7 Hz, $OCH_2\mathit{CH_3}$), 1.29 (18 H, s, OBu-*t*), 3.89 (2 H, q, *J* = 6 Hz, $O\mathit{CH_2}CH_3$), 4.23 (2 H, q, *J* = 6

Hz, O*CH*$_2$CH$_3$), 7.12 (1 H, s, SiCH=C), 7.28–7.37 (3 H, m, Ar), 7.62–7.67 (2 H, m, Ar).

^{13}C-NMR (50 MHz, CDCl$_3$): δ 13.4, 13.8, 31.6 (6 C), 60.5, 61.2, 73.9 (2 C), 127.2 (2 C), 129.6, 134.4 (2 C), 135.3, 141.0, 143.5, 163.4, 165.6.

HRMS (ESI) *m/z*: Found MNa$^+$ 445.2026, $C_{22}H_{34}O_6SiNa$ requires 445.2022.

MS (ESI) *m/z*: 445 (M+Na, 17), 349 (23), 265 (100), 219 (47), 147 (23).



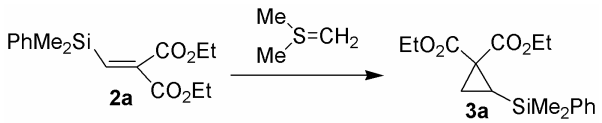
Ethyl 2-ethoxycarbonyl-3-(3-methoxyphenyl)-2-propenoate 2d

A solution of *m*-anisaldehyde (3.7 mL, 30 mmol) and diethyl malonate (5 mL, 33 mmol), piperidinium benzoate (20 mol%) in benzene (80 mL) was heated under reflux fitted with a Dean-Strake apparatus overnight. The reaction mixture was cooled, washed with water and with brine, dried over anhydrous MgSO$_4$ and evaporated. The residue was purified by column chromatography on silica using hexane-EtOAc (95:5) to give the diester **2d** (6.3 g, 75%) as colorless oil.

IR (neat): 2989, 1726, 1629 cm^{-1}.

^{1}H-NMR (200 MHz, CDCl$_3$): δ 1.29 (3 H, m, *Me*CH$_2$OCO), 1.34 (3 H, m, *Me*CH$_2$OCO), 3.79 (3 H, s, OMe), 4.33 (2 H, q, *J* = 7 Hz, Me*CH*$_2$OCO), 4.36 (2 H, q, *J* = 7.2 Hz, Me*CH*$_2$OCO), 6.92–7.05 (2 H, m, Ar), 7.24–7.32 (2 H, m, Ar), 7.70 (1 H, s, C=C*H*Ar).

^{13}C-NMR (50 MHz, CDCl$_3$): δ 13.4, 13.7, 54.7, 61.2 (2 C), 113.9, 116.1, 121.5, 126.2, 129.4, 133.7, 141.4, 159.3, 163.5, 166.1.



Diethyl 2-dimethyl(phenyl)silylcyclopropane-1,1-dicarboxylate 3a

A solution of sodium dimsylate (1 mmol) in DMSO (4 mL) was prepared. The solution

was diluted with THF (1 mL) and cooled to 0 °C. Solid trimethylsulfonium iodide (0.205 g, 1 mmol) was introduced into the flask and the reaction mixture was stirred under same conditions for 15 min. A solution of **2a** (0.306 g, 1 mmol) in dry THF (0.75 mL) was rapidly added to the reaction mixture. It was slowly brought to room temperature (about 1 h) and stirred for 1 h. The reaction mixture was diluted with water and extracted with ether. The organic extract was washed with brine, dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography on silica using hexane-EtOAc (95:5) as eluent to give the cyclopropane **3a** (0.173 g, 55%).

R_f 0.32 (hexane/EtOAc, 95:5).

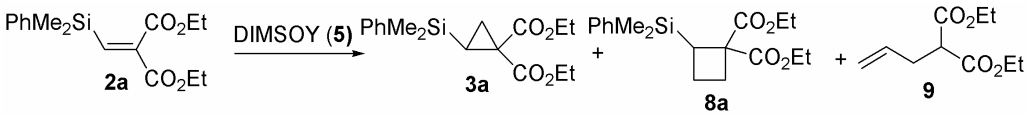
IR (neat): 1731, 1249, 1116 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.25 (3 H, s, SiMe), 0.34 (3 H, s, SiMe), 1.10 (1 H, dd, *J* = 9.5, 11 Hz, SiCH), 1.18 (3 H, t, *J* = 7.1 Hz, *Me*CH_2OCO), 1.26 (3 H, t, *J* = 7 Hz, *Me*CH_2OCO), 1.41 (1 H, dd, *J* = 3.4, 9.5 Hz, C$H_A$$H_B$CHSi), 1.52 (1 H, dd, *J* = 3.4, 11 Hz, $CH_A$$H_B$CHSi), 3.80–4.30 (4 H, m, 2 × MeCH_2OCO), 7.30–7.75 (5 H, m, Ar).

^{13}C-NMR (50 MHz, $CDCl_3$): δ −3.3, −3.2, 13.8, 14.0, 15.4, 18.4, 33.3, 61.2, 61.6, 127.7 (2 C), 129.1, 133.8 (2 C), 137.9, 169.1, 171.0.

MS (EI) *m/z*: 305 (M−Me, 100%), 275 (11), 243 (70), 231 (90), 215 (21), 187 (76), 169 (73), 159 (27), 135 (41), 105 (29).

Anal. Calacd for $C_{17}H_{24}O_4Si$: C, 63.72; H, 7.55. Found: C, 63.36; H, 7.88%.



Reaction of 2a with 2.5 equivalents of 5 using sodium hydride as base

Sodium hydride (96 mg, 50% in oil, 2 mmol, 2 equiv) was made oil free by washing with dry hexane and dry DMSO (2 mL) was added into it. Trimethylsulfoxonium iodide (440

mg, 2 mmol, 2 equiv) was added and the suspension was stirred under argon atmosphere for 30 min. The solution was cooled to 20 °C and a solution of **2a** (306 mg, 1 mmol, 1 equiv) in dry DMSO (1 mL) was added slowly (10 min) to the reaction mixture. The reaction mixture was stirred at room temperature for 30 min and diluted with water (50 mL), extracted with 5% ethyl acetate in hexane (3 × 30 mL). The combined extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica using hexane-EtOAc (97:3) to give the pure cyclopropane **3a**[94b] (42 mg, 13%), cyclobutane **8a** (70 mg, 21%) and malonate **9**[107] (40 mg, 20%).

Data for 8a

R_f 0.45 (hexane/EtOAc, 95:5).

IR (film): 3070, 2981, 2958, 2904, 1724, 1427, 1371, 1251, 1135, 1114, 1025, 836 cm^{-1}.

^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.34 (3 H, s, SiMe), 0.35 (3 H, s, SiMe), 0.43 (1 H, dd, *J* = 11.5, 11.5 Hz, SiCH), 1.20 (1 H, dd, *J* = 3, 11.5 Hz, SiCHC$H_A$$H_B$), 1.25 (3 H, t, *J* = 6.5 Hz, OCH_2CH_3), 1.24–1.27 (1 H, m, C$H_A$$H_B$C), 1.28 (3 H, t, *J* = 6.5 Hz, OCH_2CH_3), 1.39 (1 H, dd, *J* = 3, 7 Hz, CH_AH_BC), 1.86–1.92 (1 H, m, SiCHC$H_A$$H_B$), 4.09–4.29 (4 H, m, 2 × O$CH_2$$CH_3$), 7.36 (3 H, s, Ar), 7.50–7.51 (2 H, m, Ar).

^{13}C-NMR (50 MHz, $CDCl_3$): δ −3.4, −3.3, 13.8, 14.0, 14.8, 22.2, 24.8, 34.6, 60.9 (2 C), 127.6 (2 C), 128.9, 133.3 (2 C), 137.9, 167.9, 170.1.

HRMS (ESI) *m/z*: Found MNa^+ 357.1505, $C_{18}H_{22}O_4SiNa$ requires 357.1498.

MS (ESI) *m/z*: 357 (M+Na, 100%), 243 (6), 201 (16), 135 (10), 111 (6).

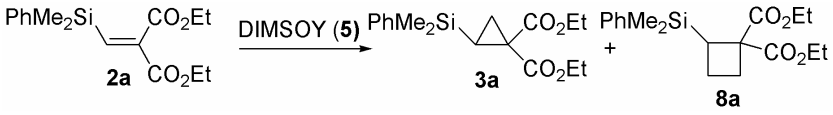
Data for 9

R_f 0.58 (hexane/EtOAc, 95:5).

IR (film): 3082, 2984, 2939, 1733, 1644, 1466, 1370, 1336, 1237, 1178, 1033, 916 cm^{-1}.

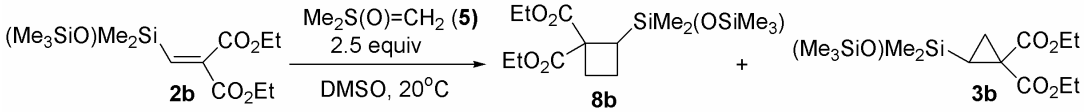
^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.25 (6 H, t, *J* = 7.2 Hz, 2 × OCH_2CH_3), 2.63 (2 H, t, *J* = 7.6 Hz, CH_2=$CHCH_2$), 3.41 (1 H, t, *J* = 7.6 Hz, $CH(CO_2Et)_2$), 4.18 (4 H, q, *J* = 7.2 Hz, 2 × OCH_2CH_3), 5.04 (1 H, d, *J* = 9.6 Hz, C=C$H_A$$H_B$), 5.10 (1 H, d, *J* = 16.8 Hz, C=C$H_A$$H_B$), 5.67–5.84 (1 H, m, H_2C=C*H*).

^{13}C-NMR (50 MHz, $CDCl_3$): δ 13.9 (2 C), 32.7, 51.5, 61.2 (2 C), 117.3, 133.9, 168.7 (2 C).



Reaction of 2a with 2.5 equivalents of 5 using lithium *tert*-butoxide as base

Dry *t*-BuOH (0.26 mL, 2.7 mmol) was added drop wise to *n*-BuLi (1.7 mL, 1.5 *M* solution in hexane, 2.5 mmol) under argon atmosphere. The solvent was removed under vacuum and the residue was dissolved in dry DMSO (2 mL). The solution was cooled to 20 ^oC and solid trimethylsulfoxonium iodide (550 mg, 2.5 mmol) was added into it. After 20 minutes, a solution of **2a** (306 mg, 1 mmol, 1 equiv) in dry DMSO (1 mL) was added slowly (10 min) to the reaction mixture. The reaction mixture was stirred at room temperature for 30 min and diluted with water (50 mL), extracted with 5% ethyl acetate in hexane (3 × 30 mL). The combined extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica using hexane-EtOAc (97:3) to give the pure cyclopropane **3a** (25 mg, 8%) and cyclobutane **8a** (210 mg, 63%).



Reaction of 2b with 2.5 equivalents of 5 using lithium *tert*-butoxide as base

Following the procedure described for the reaction of **2a** with ylide **5**, trimethylsulfoxonium iodide (550 mg, 2.5 mmol), *t*-BuOH (0.26 mL, 2.7 mmol), *n*-BuLi

(1.7 mL, 1.5 *M* solution in hexane, 2.5 mmol) and **2b** (318 mg, 1 mmol, 1 equiv) gave a mixture of cyclopropane **3b** and cyclobutane **8b** (220 mg, 65%; **3b:8b** = 1/2 by ^{1}H-NMR) which could not be separated.

Data for mixture of 3b and 8b

R_f 0.47 (hexane/EtOAc, 95:5).

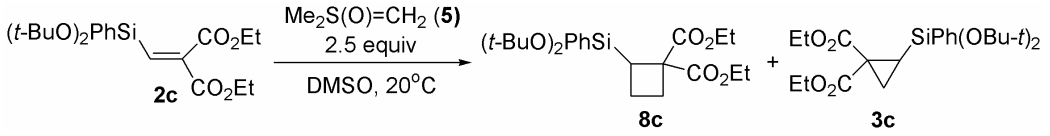
IR (film): 2981, 2958, 2903, 1728, 1371, 1321, 1284, 1254, 1207, 1135, 1057, 843 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): (recognizable peaks for **3b**) δ 0.84 (1 H, dd, J = 9.4, 11.2, Hz, SiCH); (recognizable peaks for **8b**) δ 0.97 (1 H, dd, J = 3.4, 14.4 Hz, SiCHCH_AH$_B$), 1.83–1.98 (1 H, m, SiCHCH$_A$$H_B$).

GC: (column: WCOT Fused Silica, CP-SIL-5-CB, 50m × 0.25 mm/0.39 mm, 0.25 µm; Carrier: helium 1 mL/min; temp: 60 ºC-2 min-10 ºC/min-300 ºC): t_R 7.34 min (**3b**) (35%); t_R 8.61 min (**8b**) (57%).

MS (EI) *m/z*: for 3b; 317 (M–Me, 73%), 287 (20), 243 (100), 199 (34) 169 (80, 157 (35), 147 (27), 133 (40), 95 (14), 73 (23).

MS (EI) *m/z*: for 8b; 346 (M, 1%), 331 (20), 301 (12), 273 (19), 257 (8), 177 (15), 147 (100), 133 (29), 108 (39), 81 (44).



Reaction of 2c with 2.5 equivalents of 5 using lithium *tert*-butoxide as base

Following the procedure described for the reaction of **2a** with ylide **5**, trimethylsulfoxonium iodide (550 mg, 2.5 mmol), *t*-BuOH (0.26 mL, 2.7 mmol), *n*-BuLi (1.7 mL, 1.5 *M* solution in hexane, 2.5 mmol) and **2c** (422 mg, 1 mmol, 1 equiv) gave a mixture of cyclopropane **3c** and cyclobutane **8c** (322 mg, 73%; **3c:8c** = 7/3 by ^{1}H-NMR) which could not be separated.

Data for mixture of 3c and 8c

R_f 0.65 (hexane/EtOAc, 95:5).

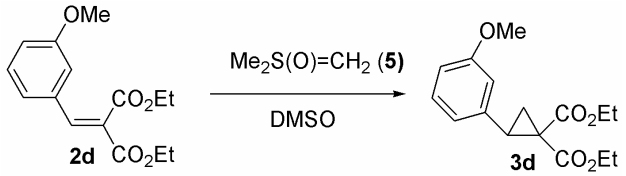
IR (film): 2977, 2933, 1731, 1429, 1366, 1330, 1241, 1194, 1118, 1060, 702 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): (recognizable peaks for **3c**) δ 0.99 (1 H, dd, *J* = 9.6, 10.8 Hz, SiCH), 1.46 (1 H, dd, *J* = 3, 10.8 Hz, SiCHCH_AH$_B$), 1.61 (1 H, dd, *J* = 3, 9.6 Hz, SiCHCH$_A$$H_B$). (recognizable peaks for **8c**) δ 0.44 (1 H, dd, *J* = 11.6, 14.6 Hz, SiCH), 1.96–2.12 (1 H, m, SiCHCH_AH$_B$).

GC: (column: WCOT Fused Silica, CP-SIL-5-CB, 50 m × 0.25 mm/0.39 mm, 0.25 μm; Carrier: helium 1 mL/min; temp: 60 ºC-2 min-10º C/min-300 ºC): t_R 12.91 min (**3c**) (66%); t_R 13.66 min (**8c**) (31%).

MS (EI) *m/z*: for 3c; 363 (M–*t*-BuO, 100%), 360 (71), 335 (11), 307 (13), 279 (23), 247 (11), 233 (39), 219 (24), 189 (18), 173 (14), 161 (12), 140 (12), 139 (88).

MS (EI) *m/z*: for 8c; 450 (M, 2%), 393 (6), 377 (8), 349 (5), 293 (4), 251 (5), 195 (15), 140 (13), 139 (100), 108 (4).



Reaction of 2d with 2.5 equivalents of 5 using lithium *tert*-butoxide as base

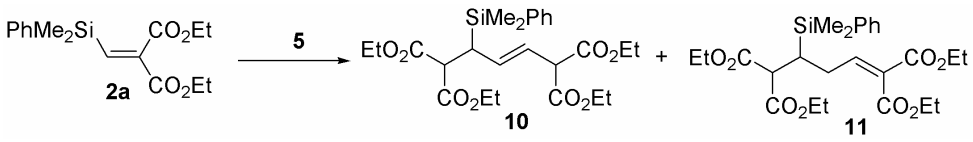
Following the procedure described for the reaction of **2a** with ylide **5**, trimethylsulfoxonium iodide (550 mg, 2.5 mmol), *t*-BuOH (0.26 mL, 2.7 mmol), *n*-BuLi (1.7 mL, 1.5 *M* solution in hexane, 2.5 mmol) and **2d** (278 mg, 1 mmol, 1 equiv) gave diethyl 2-(3-methoxyphenyl) cyclopropane-1, 1-dicarboxylate **3d**[108] (210 mg, 72%).

R_f 0.44 (hexane/EtOAc, 90:10).

IR (film): 2981, 2938, 2837, 1725, 1603, 1585, 1491, 1465, 1371, 1280, 1208, 1131, 1032, 991, 862 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.87 (3 H, t, *J* = 7 Hz, OCH_2CH_3), 1.26 (3 H, t, *J* = 7 Hz, OCH_2CH_3), 1.65 (1 H, dd, *J* = 5.2, 9.4 Hz, CH_AH_B), 2.11 (1 H, dd, *J* = 5.2, 8 Hz, CH_AH_B), 3.16 (1 H, dd, *J* = 8.6, 8.6 Hz, Ar*CH*), 3.74 (3 H, s, ArO*Me*), 3.84 (2 H, q, *J* = 7 Hz, OCH_2CH_3), 4.14–4.29 (2 H, m, OCH_2CH_3), 6.72–6.77 (3 H, m, Ar), 7.10–7.18 (1 H, m, Ar).

^{13}C-NMR (50 MHz, $CDCl_3$): δ 13.6, 14.0, 18.8, 32.0, 37.3, 55.1, 61.0, 61.6, 113.0, 114.0, 120.7, 129.0, 136.2, 159.3, 166.5, 169.7.



Reaction of 2a with 0.5 equivalents of 5 using lithium *tert*-butoxide as base

Dry *t*-BuOH (0.1 mL, 1 mmol) was added drop wise to *n*-BuLi (0.67 mL, 1.5 *M* solution in hexane, 1 mmol) under argon atmosphere. The solvent was removed under vacuum and the residue was dissolved in dry *N*-methyl pyrrolidone (1 mL). The solution was cooled to 20 ^oC and solid trimethylsulfoxonium iodide (110 mg, 0.5 mmol) was added into it. After 20 minutes, this ylide solution was added drop wise to neat **2a** (306 mg, 1 mmol) over 15 min at 5 ^oC under argon atmosphere. The reaction mixture was allowed to attain to room temperature and stirred for 20 min, diluted with water (30 mL) and extracted with 10% ethyl acetate in hexane (3 × 30 mL). The combined extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica using hexane-EtOAc (96:4) to give the pure allylsilane **10** (10 mg, 4%) and homoallylsilane **11** (155 mg, 63%). A small amount of a mixture of cyclopropane **3a** and cyclobutane **8a** (36 mg, 11%) was also isolated.

Data for 10

R_f 0.34 (hexane/EtOAc, 95:5).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.32 (6 H, s, 2 × SiMe), 1.12–1.29 (12 H, m, 4 × OCH_2CH_3), 2.60 (1 H, t, *J* = 9.4 Hz, SiCH), 3.42 (1 H, d, *J* = 8.6 Hz, C*H*($CO_2Et)_2$), 3.88–4.22 (9 H, m, 4 × OCH_2CH_3, C*H*($CO_2Et)_2$), 5.54 (1 H, dd, *J* = 8.6, 15.4 Hz, C*H*=CH), 5.72 (1 H, dd, *J* = 10, 15.4 Hz, CH=C*H*), 7.32–7.49 (5 H, m, Ar).

Data for 11

R_f 0.34 (hexane/EtOAc, 95:5).

IR (film): 3070, 2982, 2938, 2906, 1725, 1644, 1446, 1371, 1254, 1153, 1111, 1028, 836, 817, 777, 737 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.33 (3 H, s, SiMe), 0.36 (3 H, s, SiMe), 1.17–1.32 (12 H, m, 4 × OCH_2CH_3), 1.88–1.98 (1 H, m, SiCH), 2.50–2.60 (2 H, m, C=CHCH_2), 3.43 (1 H, d, *J* = 5.2 Hz, C*H*($CO_2Et)_2$), 4.02–4.28 (8 H, m, 4 × OCH_2CH_3), 6.84 (1 H, t, *J* = 7.6 Hz, C=C*H*), 7.33–7.53 (5 H, m, Ph).

^{13}C-NMR (50 MHz, $CDCl_3$): δ −3.9, −3.4, 13.9 (2 C), 14.0 (2 C), 26.1, 28.3, 52.2, 61.1 (2 C), 61.2 (2 C), 127.7 (2 C), 128.7, 129.2, 134.0 (2 C), 137.3, 149.1, 163.7, 165.0, 169.1, 169.5.

HRMS (ESI) *m/z*: Found MNa^+ 515.2099, $C_{25}H_{36}O_8SiNa$ requires 515.2077.

MS (EI) *m/z*: 515 (M+Na, 93%), 510 (33), 447 (33), 415 (10), 401 (37), 369 (100), 323 (6).

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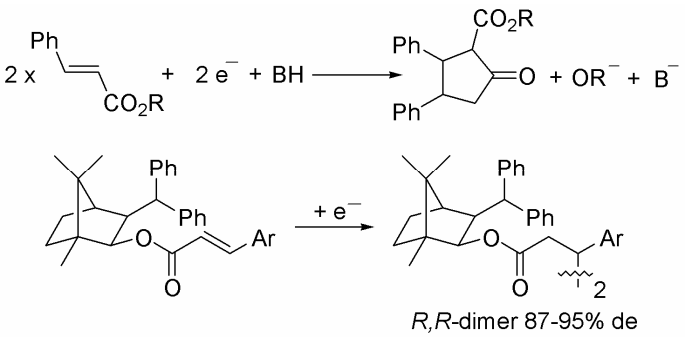
CHAPTER 3

Magnesium-Mediated Intramolecular Reductive Coupling: A Stereoselective Synthesis of C_2-Symmetric 3,4-Bis-Silyl-Substituted Adipic Acid Derivatives

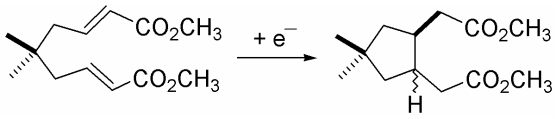
3.1 Introduction

Unsaturated systems attached to electron withdrawing groups undergo reductive coupling reactions in intermolecular or intramolecular fashion by using one-electron transfer reducing agents. Electrochemical method[109] is a chemical free, useful and versatile synthetic methodology for the carbon-carbon bond forming reactions such as electrohydrodimerization (Scheme 3.1).[110a] According to Klemm and co-workers,[110b] electroreduction of α,β-unsaturated esters such as *trans*-cinnamate at constant cathodic potential in anhydrous acetonitrile-tetraethylammonium bromide produce the crystalline hydrodimer, 2,3-diaryl-5-oxocyclopentane-1-carboxylate in good yield. Asymmetric version of the above reaction had also been performed by Kise *et al.*[110c] wherein [(1*R*)-*exo*]-3-*exo*-(diphenylmethyl)borneol has been used as a highly effective chiral auxiliary to product the *R,R*-dimer in good yield and diastereomeric excess (Scheme 3.2). Electroreductive cyclization[111] of a bisenoate tethered by a propyl chain was found to give 1,2-disubstituted cyclopentane system with moderate to high *trans* selectivity depending upon the proton source (Scheme 3.3).[111d]

Scheme 3.1

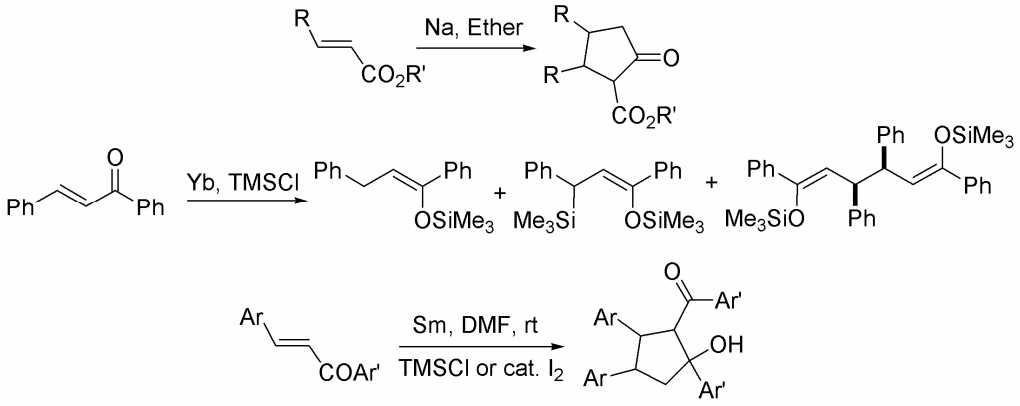


Scheme 3.2



Scheme 3.3

Intermolecular reductive hydrocoupling of α,β-unsaturated carbonyl compounds is also known to be mediated by metals like Na, Yb and Sm (Scheme 3.4). Enoates also undergo 1,4-conjugate addition followed by Dieckmann cyclization when treated with sodium in ether.[112a] Similarly, reductive coupling of *trans*-α,β-unsaturated ketone with Na in hexamethylphosphoric triamide (HMPA) at −78 °C yielded the racemic dimer whereas *cis*-ketone produced a mixture of the racemic dimer and the *meso* dimer.[112b,c] The reaction

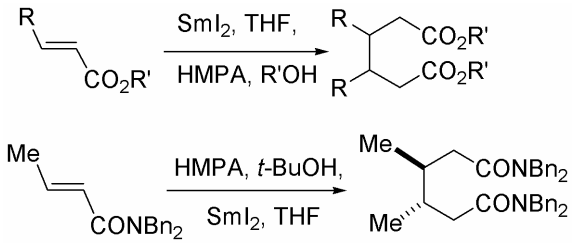


Scheme 3.4

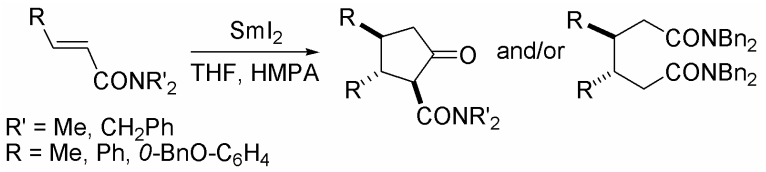
of chalcones with an equimolar amount of Yb metal in the presence of excess trimethylsilyl chloride (TMSCl) produced three-type of products due to reductive dimerization, simple double bond reduction and β-*C*-silylation.[113] On the other hand, chalcones preferred reductive coupling-cyclization when samarium metal[114] was used in presence of TMSCl as an additive or I_2 as catalyst.

Kagan *et al.*[115] had invented divalent lanthanide halides such as SmI_2 and YbI_2 as reducing or coupling agents. Amongst them SmI_2 is frequently used.[116] Inanaga *et al.*[117a] has shown that a verity of α,β-unsaturated esters instantly hydrodimerized with C–C bond formation at β-positions by using SmI_2/THF/HMPA and a proton source. The reaction can

be performed in an intermolecular or intramolecular fashion with racemic diastereomer as the preferred product. Interestingly, the reaction of *N*,*N*-dibenzyl crotonamide, under the same conditions provides the corresponding racemic 3,4-dimethyl-adipiamide as a single diastereoisomer (Scheme 3.5).[117b] Kanemasa[117c] used the SmI_2/THF/HMPA system, for the reduction of *N*,*N*-dimethyl dibenzylamides of (*E*)-α,β-unsaturated acids. The reaction produced the 1,2-*trans*-2,3-*trans* stereoisomers of 2,3-disubstituted 5-oxo-1-cyclopentanecarboxamides *via* highly diasteroselective reductive coupling followed by Dieckmann condensation (Scheme 3.6).

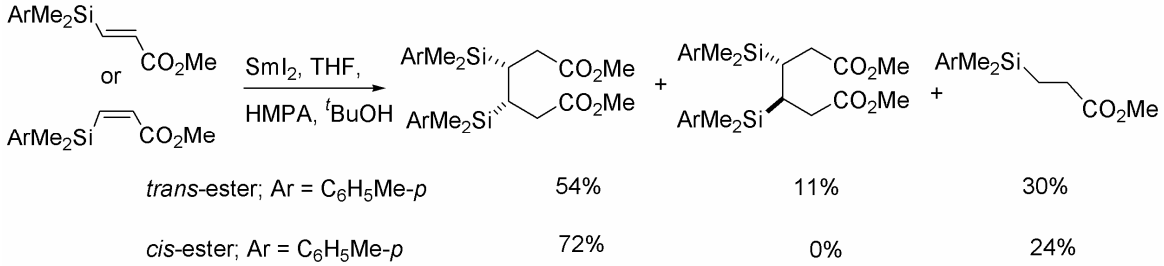


Scheme 3.5



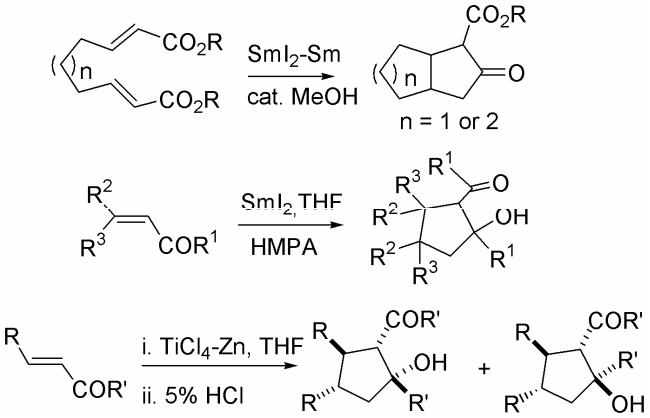
Scheme 3.6

Fleming and Ghosh[118] have reported highly stereoselective syntheses of the *meso* diastereoisomer of 3,4-bis-silylated adipates by a SmI_2-induced hydrodimerization of β-dimethyl(aryl)silylacrylates. The reductive coupling was associated with unavoidable reduction of C=C double bond which was in agreement with Inanaga.[117] However, in contrast to Inanaga, the β-silylated acrylic ester favored the *meso* diastereomers (Scheme 3.7).



Scheme 3.7

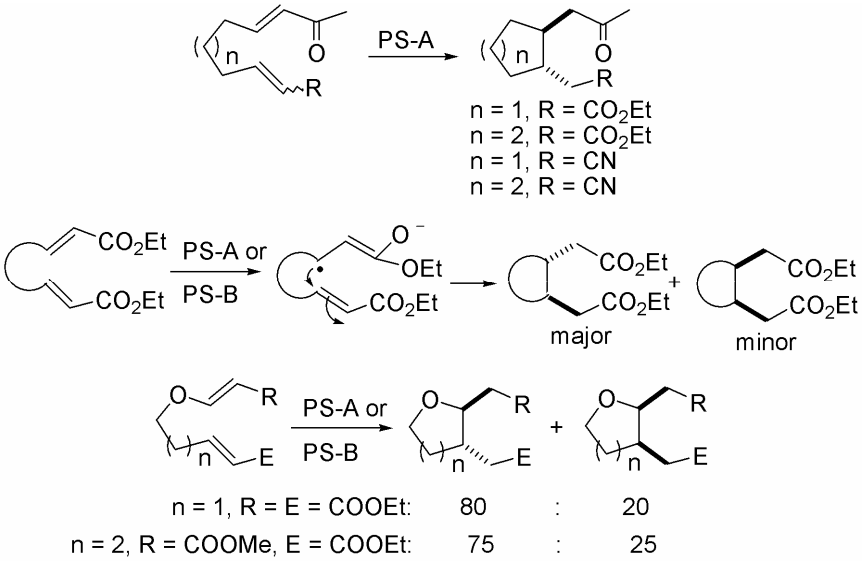
Nagaoka *et al.*[119a] have established SmI_2-induced method for the tandem cyclization of bis-α,β-unsaturated ester to afford bicyclic compounds, bicyclo[4.3.0]octane-8-ones and bicyclo[3.3.0]nonan-3-ones in the presence of catalytic amount of methanol (Scheme 3.8). Like α,β-unsaturated esters, the reaction of α,β-unsaturated ketones with SmI_2 in the absence of alcohol, leads to reductive or cycloreductive stereo controlled coupling reactions.[119b] In all cases, the use of HMPA as a co-promoter increases the yield of the dimer. A similar cycloreductive coupling reaction of α,β-unsaturated ketones take place when a low valent titanium reagent, $TiCl_4$-Zn[120] was used (Scheme 3.8).



Scheme 3.8

Using reagents other than SmI_2, a few recent reports[121-123] have been documented where intramolecular reductive coupling of α,β-unsaturated carbonyl compounds joined by a suitable tether lead to cyclic systems with preferential formation of *trans*

diastereoisomer. Pandey *et al.*[122] have developed two photosystems, called **PS-A** and **PS-B** to harvest visible-light photons that promotes sequential electron transfer process thus initiating photosensitized one electron reductive β-activation of α,β-unsaturated ketones. Photosystem-A i.e. **PS-A** consists of DCA (9,10-dicyanoanthracene) as light harvesting electron acceptor and PPh_3 as sacrificial electron donor, whereas photosystem-B i.e. **PS-B** employed DCA as usual electron acceptor, DMN (1,5-dimethoxynaphthalene) as a primary electron donor and ascorbic acid as a secondary and sacrificial electron donor.

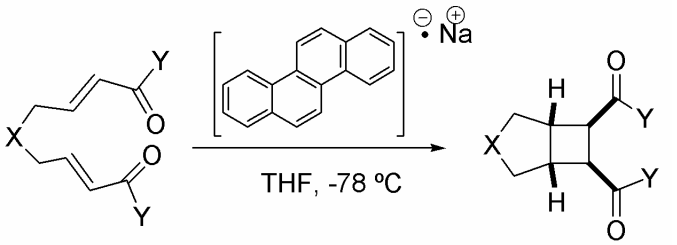


Scheme 3.9

α,β-unsaturated ketones were selected as secondary electron acceptor due to there suitability for testing the concept as upon acceptance of an electron this functionality would activate its β-position as carbon centered radical, which would cyclize to tethered olefin to give 1,2-disubstituted cycloalkane derivatives. The *anti* stereochemistry of the product appeared to be in marked contrast to the general trend of *syn* stereochemistry expected in 5-hexenyl radical cyclization. These cyclizations follow the well established 5- and 6-*exo-trig* radical cyclization rules. They have also developed[122e] a new strategy for

construction of carbo- and oxycycles by intramolecular reductive coupling of α,β-unsaturated esters by using these photosystems (Scheme 3.9).

The first example of anion radical cycloaddition, induced by homogeneous electron transfer from chemical reagents was reported by Krische and co-workers.[121b] The chrysene radical anion-induced intramolecular reductive cyclization of bis(enone) led to a *cis* ring junction preferentially with moderate yield as described in Scheme 3.10.

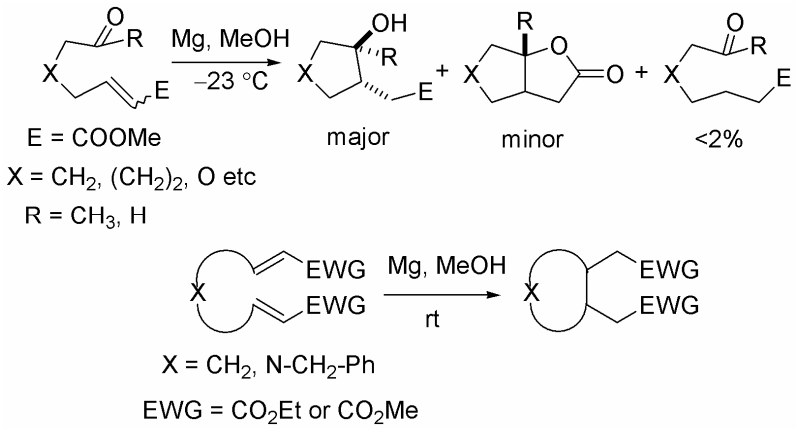


X = CH_2, Y = Ph	31.5%
X = O, Y = Ph	35.0%
X = CH_2, Y= 4-Ph-Ph	60.4%
X = CH_2, Y= 2-naphthyl	61.7%
X = CH_2, Y= 4-Cl-Ph	50.8%
X = CH_2, Y= 3,4-Cl_2-Ph	41.4%

Scheme 3.10

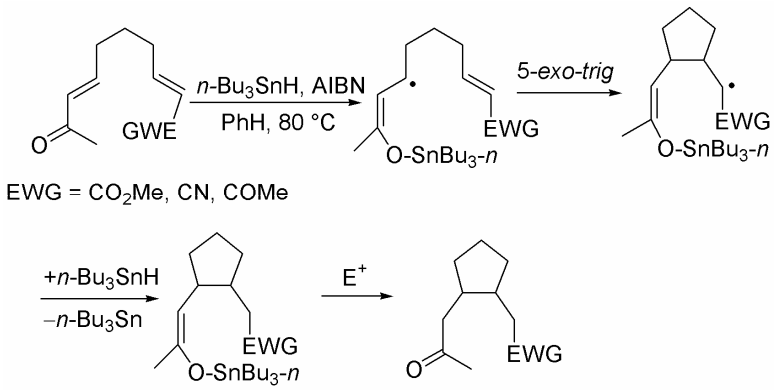
Magnesium in methanol can induce intramolecular reductive cyclization of ketones[121c] tethered to activated olefins. Under the above reaction conditions, olefins such as α,β-unsaturated esters, nitriles, sulfoxides and sulfides tethered to ketones undergo reductive cyclizations to produce mono and bicyclic alcohol products resulting from carbon-carbon bond formation between the β-carbon of the activated olefin and the carbonyl carbon.[121d,e] The reaction was accelerated by the catalytic amount of mercuric chloride, without affecting the stereo selectivity of the reaction. The cyclization reactions of tethered α,β-unsaturated ester and ketone proceeded smoothly under the above conditions producing a mixture of *trans* and *cis* isomers in excellent yield along with some amount of simple double bond reduction products. In all cases, *trans* isomers were predominantly formed and the minor *cis* isomers were lactonized under the reaction

conditions. The diastereoisomer ratio was found to be independent of the substrate geometry (*E* or *Z*) (Scheme 3.11). Chavan and Ethiraj[121f] have also used magnesium in methanol for activated olefins connected by a tether to give cyclic products with 3-, 5- and 6-membered rings, associated with varying quantities of double bond reduction products. The diastereoisomer ratio in the products depended on the substituents at the activated olefins and the tether. In most cases, it varied between 1.1 and 2.8, favoring for the *trans* isomers (Scheme 3.11).



Scheme 3.11

Tributyltin hydride (*n*-Bu_3SnH) has been applied to diverse free radical reactions. The tin hydride induced intramolecular reductive cyclizations of α,β-unsaturated ketones with electron-deficient olefins was studied by Enholm and Kinter.[123] The reaction was initiated by an *O*-stannyl ketyl formed by the addition of a tribytyltin radical to a carbonyl, which has both anionic and radical character. Intramolecular addition of the radical (formed after resonance) to an alkene leads to the cyclized product by a 5-*exo*-*trig* ring closure with high *trans*-selectivity (Scheme 3.12). The minor *cis* isomer underwent second intramolecular cyclization with the tin enolate to produce the corresponding bicyclic products.



Scheme 3.12

3.2 Present Work

As discussed in Chapter 1, diversity-oriented synthesis (DOS) aims to yield skeletally and stereochemically diverse products and so have high potential. Principally, skeletal diversity-oriented synthesis can be achieved in two ways. The first one involves the use of different reagents and a common class of starting materials and we have shown our achievement in this area in Chapter 2. The other approach is called 'substrate-based approach', wherein different starting materials, containing pre-encoded skeletal informations are subjected to a common set of reaction conditions leading to different skeletal diversity. This Chapter deals with a 'substrate-based DOS approaches' for generating diverse skeletal products.

Molecules containing stereochemically defined two (or more) silicon-bearing centres and terminal functionalities are useful intermediates in organic synthesis. A silicon group can effect stereochemical control[47a,b] in a 1,2-related and a 1,3-related fashion. Therefore, molecules with two adjacent silicon-bearing centres can effectively control stereocentres which are 1,4-related & beyond.[47c,d] As shown in Scheme 3.7, highly stereoselective syntheses of the *meso* diastereoisomer of 3,4-bis-silylated adipates have been achieved with great stereo control.[118,124] These intermediates have been applied for

the synthesis of many natural products[118,124] (Fig. 3.1) such as ribonolactone, deoxyribonolactone, both the enantiomers of nonactic acid as well as nonactin.

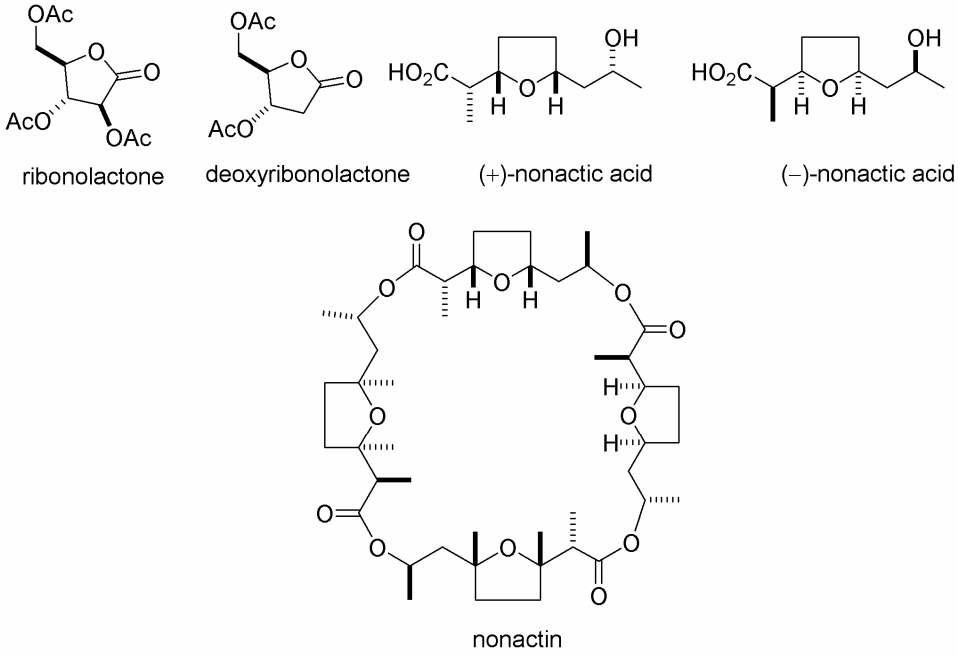


Figure 3.1: Structure of natural products derived from *meso* 3,4-bis-silylated adipate

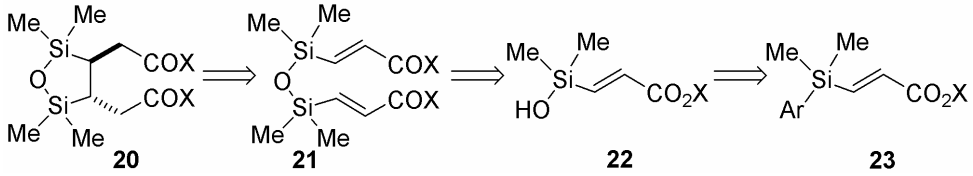
The C_2-symmetric racemic diastereoisomers of 3,4-bis-silylated adipates are also expected to be a starting point for the syntheses of complex molecules. Besides, C_2-symmetric molecules have privileged structures with high potential for the generation of molecular species suitable in asymmetric catalysis. There is no method available for making them both in racemic or enantiomerically pure form. Therefore, our plan was to find out a synthetic procedure for the stereoselective synthesis of chiral C_2-symmetric 3,4-bis-silyl-substituted adipic acid derivatives to show their reactivity and utility.

3.2.1 Syntheses of C_2-symmetric racemic diastereoisomers of 3,4-bis-silyl-substituted adipic acid derivatives

As described in the introduction part of this Chapter, intermolecular reductive hydrocoupling of α,β-unsaturated carbonyl compounds is known to be mediated by metals like Na, Yb and Sm or reducing agents like SmI_2 and $TiCl_4$-Zn. Amongst these, SmI_2,

which is frequently used for this purpose, can induce hydrodimerization of β-aryl/alkyl acrylic acid derivatives to give 3,4-diaryl/alkyl-substituted adipates/adipamides in favor (66–100%) of the C_2-symmetric diastereoisomer. However, the same hydrodimerization of β-silylacrylic acid esters favored the *meso* diastereoisomer (76–100%).

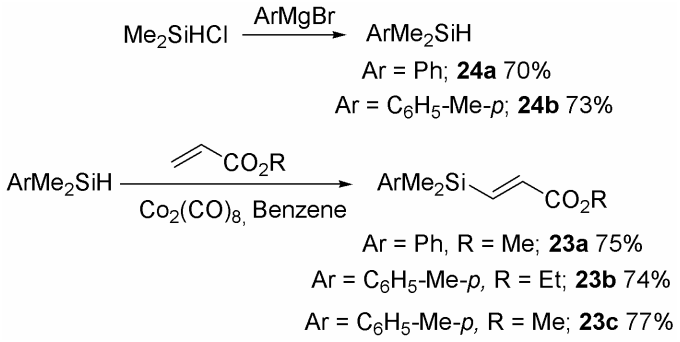
Making a five membered ring with *trans* geometry of the substituents is energetically more favored. We, therefore, decided to resolve our problem of making C_2-symmetric racemic diastereoisomers of 3,4-bis-silyl-substituted adipic acid derivative **20** by a five-membered ring formation (Scheme 3.13) which can be expected to be achieved by intramolecular reductive cyclization of symmetrical disiloxane tethered bis-acrylates **21** (X = OR). One possible way of making disiloxane **21** would be by the dehydrative dimerization of the corresponding silanol **22**. The silanol in turn could be obtained from the corresponding aryldimethyl silyl substituted acrylate **23**.



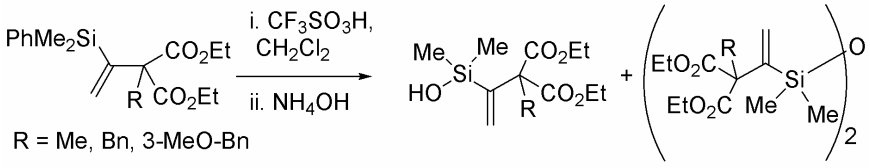
Scheme 3.13

Our first task was, therefore, to make the symmetric disiloxane **21a** (X = OMe), as the syntheses of these types of molecules are not known. For this, the β-silylated α,β-unsaturated ester **23a-c** was synthesized from the readily available chlorodimethylsilane as shown in Scheme 3.14. Addition of phenylmagnesium bromide on chlorodimethylsilane provided dimethyl(phenyl)silane **24a** whereas 4-methylphenylmagnesium bromide with chlorodimethylsilane gave dimethyl(4-methylphenyl)silane **24b.** Dimethyl(phenyl)silane **24a** on reaction with methyl acrylate in the presence dicobalt octacarbonyl as the catalyst provided (*E*)-β-silyl acrylate **23a**. Similarly, dimethyl(4-methylphenyl)silane **24b** with

ethyl and methyl acrylate produced (*E*)-β-silyl acrylates **23b/23c**, respectively. The synthesis of vinylsilanols and vinyldisiloxanes have been achieved (Scheme 3.15)[94c-e] from

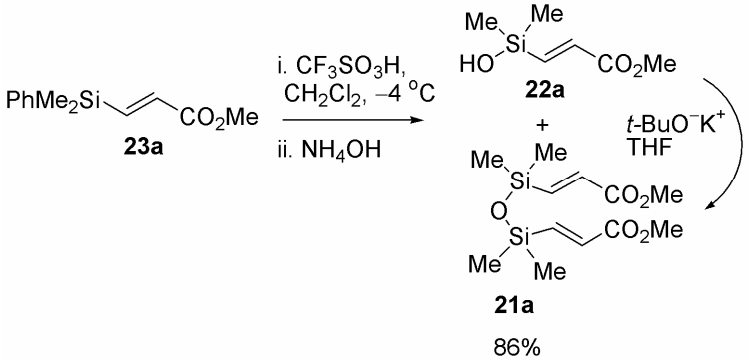


Scheme 3.14



Scheme 3.15

trifluoromethanesulfonic acid (TfOH) or trifluoroacetic acid (TFA). We were pleased to see that silylacrylate **23a** on treatment with TfOH at –4 °C in dichloromethane gave the desired disiloxane **21a** in excellent yield (Scheme 3.16). It is worth mentioning that sometimes the product is contaminated with a small amount of silanol **22a**, which either on standing or treatment with a sub-stoichiometric amount of potassium *t*-butoxide gets converted to the desired disiloxane **21a** (Fig. 3.2).



Scheme 3.16

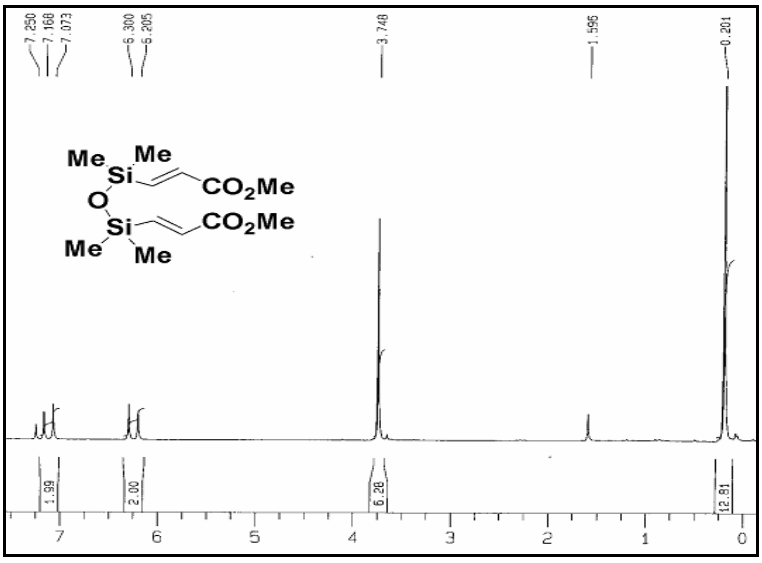
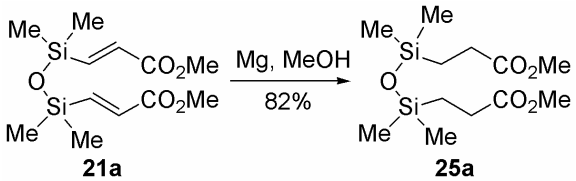


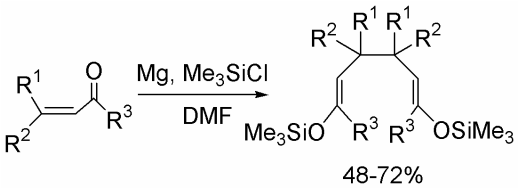
Figure 3.2: ^{1}H NMR of 21a

After successful synthesis of the disiloxane **21a**, our next goal was to find out an appropriate reducing system for the reductive cyclization reaction. The commonly used reducing agent, SmI_2 is reactive, expensive, highly air-sensitive to certain carboxylic acid derivatives like *N*-acyl oxazolidin-2-ones,[125] and requires THF as a co-solvent. Magnesium metal and SmI_2 have similar reduction potentials (Mg: −2.38 V *vs* SCE; SmI_2: −2.05 V *vs* $Ag/AgNO_3$).[126] Magnesium has already been used in reductive reactions involving unsaturated esters as well as in intramolecular reductive cyclizations.[121d-f] When we carried out the reductive cyclization of disiloxane **21a** with Mg metal in dry MeOH following the reported procedure,[121f] only the double bond reduced product **25a** (Scheme 3.17) was isolated. The reaction did not proceed at all in solvents like THF, acetonitrile or DMF even after prolong stirring at room temperature.



Scheme 3.17

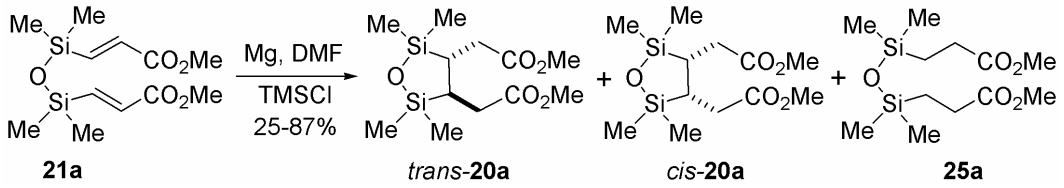
Recently, Nishiguichi *et al.*[127] have shown that in the presence of trimethylsilyl chloride (TMSCl) as an additive, the Mg metal-promoted reductive dimerization of α,β-unsaturated aldehydes and ketones in DMF generate bis-(silyl enol) ethers with very high regioselectivity (Scheme 3.18).



Scheme 3.18

When disiloxane **21a** was subjected to react under the reported conditions,[127] we were pleased to see that the reaction took place with complete consumption of starting material (Scheme 3.19, Table 3.1, entry 1). Analysis of the crude product by ^{1}H NMR spectroscopy revealed the formation of a mixture of diastereoisomeric cyclic products, *cis*-**20a** and *trans*-**20a**, associated with the double bond reduced product **25a** and some unidentified oligomeric materials. We, then modified the procedure by adding the disiloxane **21a** to the mixture of Mg and TMSCl in DMF under various conditions as presented in Table 3.1. Under all these conditions, the formation of the double bond reduction product **25a** (10-24%) could not be avoided. The stereo selectivity of the cyclization was marginal in all these conditions as shown in Table 3.1. Catalytic amount of SmI_2 or SmI_3 and stoichiometric amount of a reducing agent like Mg can induce various types of reactions on carbonyl compounds including pinacol type self couplings[128] or couplings with activated olefins.[129] Being a lanthanide, samarium in trivalent state is known to be a good complexing agent[130] thus can activate the substrate as well as make the transition state compact for a better stereocontrol. Therefore, we were interested to see the effect of SmI_3 in this coupling reactions and a marginal preference for *cis*-**20a** was

observed when SmI_3 (0.2 equiv) was added to the above reagents (Table 3.1, entry 8). The optimized conditions for the cyclization were therefore to use 12 equiv each of Mg and TMSCl in DMF with a 30 mmolar concentration of the unsaturated ester **21a** at 0 °C which gave a mixture of *cis*-**20a**, *trans*-**20a** and reduced diester **25a** in 87% isolated combined yield (Table 3.1, entry 7). Although little selectivity in the cyclization was observed, the formation of the reduction product was substantially reduced (**20a**:**25a** = 84/16) under the optimized conditions.



Scheme 3.19

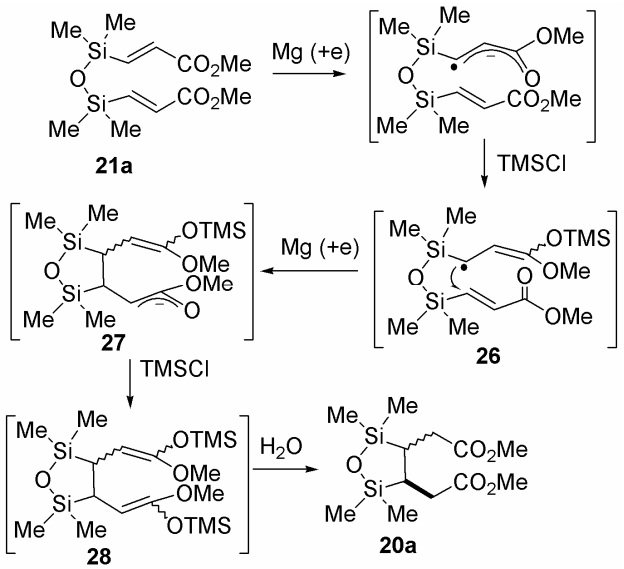
Table 3.1: Reductive cyclization of disiloxane 21a promoted by Mg/TMSCl

Entry	Mg/TMSCl (equiv)	Conc. of **21a** in DMF	Temp (°C)/ addition time	Ratio of products [a] *cis*-**20a**:*trans*-**20a**:**25a**	Yield (%)[b]
1	12/12	100 mM	28/1 min	42:40:18	25
2	12/6	100 mM	0/10 min	43:40:17	70
3	12/12	12 mM	28/3 h	39:40:21	75
4	12/24	15 mM	10/3 h	42:38:20	75
5	24/24	8 mM	28/5 h	46:30:24	80
6	12/12	10 mM	10/1 h	52:30:18	80 [c]
7	12/12	30 mM	0/1.3 h	42:42:16	87
8	12/6	15 mM	28/3 h	63:27:10	85 [d]

[a] ^{1}H NMR spectrum of the crude product; [b] Isolated combined yield of *cis*-**20a**, *trans*-**20a** and **25a**; [c] Reaction performed under sonication; [d] SmI_3 (0.2 equiv) was added as an additive.

3.2.2 Plausible mechanism and role of trimethyl silylchloride in the reductive cyclization reaction

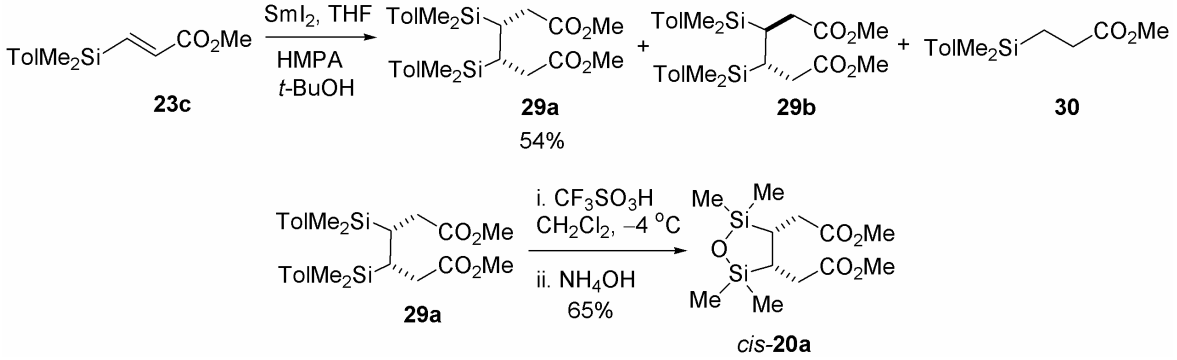
The role of TMSCl in this reaction was manifold. Without it, the reaction did not take place in DMF. The reaction did not proceed at all in solvent like THF and acetonitrile even in the presence of TMSCl. Therefore, the presence of TMSCl accelerated the redox process between Mg and the disiloxane substrate in DMF. Its presence also increases the chemoselectivity of the reaction in favor of the reductive cyclization products over double bond reduction product. This can be explained by the mechanism proposed in Scheme 3.20. The reductive cyclization process was probably accelerated by quenching the radical anion, formed by electron transfer from Mg to the substrate **21a**, with TMSCl to give the radical **26**. This radical underwent intramolecular conjugate addition to the unsaturated ester functionality and finally one more electron addition gave the intermediate anion **27** which was then quenched by TMSCl to give bis silyl ketene acetal **28**. The silyl acetal **28** underwent hydrolysis during aqueous work-up conditions and provided the diester **20a**. By this process, TMSCl also protected the reductive cyclization product from further reactions like Dieckmann condensation or oligomerizations.



Scheme 3.20

3.2.3 Stereochemistry of the products formed in the reductive cyclization reaction

Racemic *trans*-**20a** (Fig. 3.3) is a crystalline solid and easily crystallizes out from a hexane solution of the crude reaction product leaving behind the *cis*-**20a** (Fig. 3.4) and the reduced product **25a** in the solution which was then separated by chromatography. The stereochemistry of the cyclic products was confirmed by converting the known[118] *meso* diester **29a** to the *cis*-**20a** (Scheme 3.21). For that, at first, we have prepared 0.1 *M* SmI_2 solution in THF as described by Inanaga.[117a] As mentioned in the introduction of this Chapter, β-silylated α,β-unsaturated ester **23c** undergoes reductive dimerization when treated with SmI_2/HMPA/*t*-BuOH as the reducing system. The *meso* diester **29a** was formed as the major product along with the racemic diastereomer **29b** (**29a**:**29b** = 82:18) and double bond reduction product **30**. Desire *meso* diester **29a** was purified from the mixture of products with 65% yield. The *meso* diester **29a** was then briefly treated with TfOH in dichloromethane at −4 °C and quenched with ammonium hydroxide to provide *cis*-**20a**. Comparing the ^{1}H NMR (δ SiMe 0.09 and 0.24 for *trans*-**20a,** 0.14 and 0.18 for *cis*-**20a)** the stereochemistry of the crystalline product was confirmed to be the racemic *trans*-**20a**.



Scheme 3.21

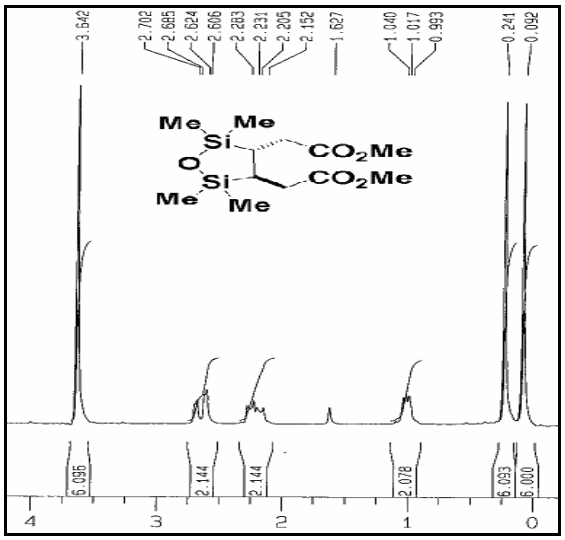


Figure 3.3: ^{1}H NMR of *trans*-20a

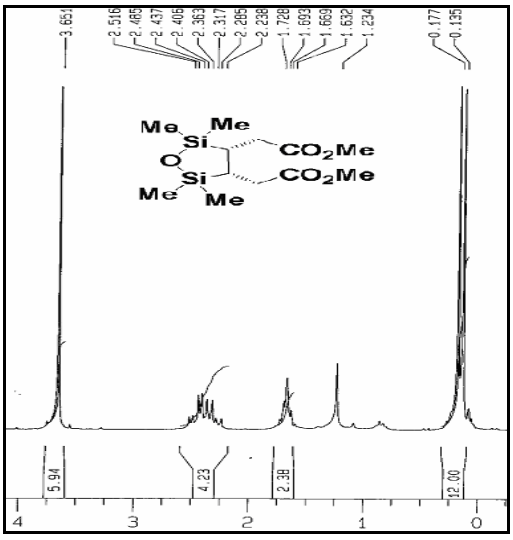
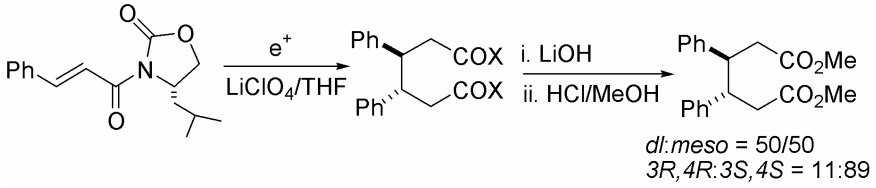


Figure 3.4: ^{1}H NMR of *cis*-20a

3.2.4 Effect of chiral auxiliaries in the reductive coupling

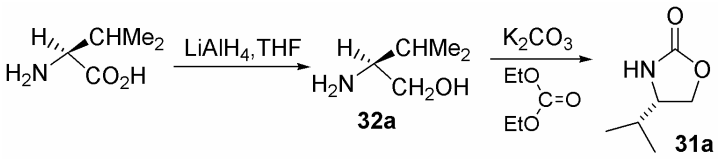
Our next aim was to improve the relative stereochemistry (*trans/cis*) as well as control the absolute configuration during the cyclization to obtain the *trans* isomer(s) in pure and enantiomeric form. It was envisaged that instead of an ester, the Mg/TMSCl-mediated coupling of the corresponding amide, possessing a suitable chiral amine, might be useful for this purpose. Amongst the amides, chiral oxazolidin-2-ones,[131] initially introduced by Evans[132] are widely used as chiral auxiliaries. These oxazolidin-2-ones when attached to carboxylic acids control the diastereoselectivity[132c] of reactions at the position α to the carboxylic acid group. Oxazolidin-2-ones are also known for their strong directing effect[133] on the conjugate addition of nucleophiles to the β-position of unsaturated acid derivatives. Kise *et al.*[134] have shown that reductive hydrocoupling of chiral 3-*trans*-cinnamoyloxazolidin-2-one by electrochemical method (Scheme 3.22), produced diastereoselective products and the selectivity at the β-position changes with the electrolyte used in the reaction. Sibi[133b] has shown that various oxazolidin-2-one derivatives of α,β-unsaturated carboxylic acids can control the stereoselectivity of C–C bond formation at the

β-position in radical reactions. Unlike alkyl amides, the oxazolidin-2-one amide bond is easily hydrolysed to give acids.



Scheme 3.22

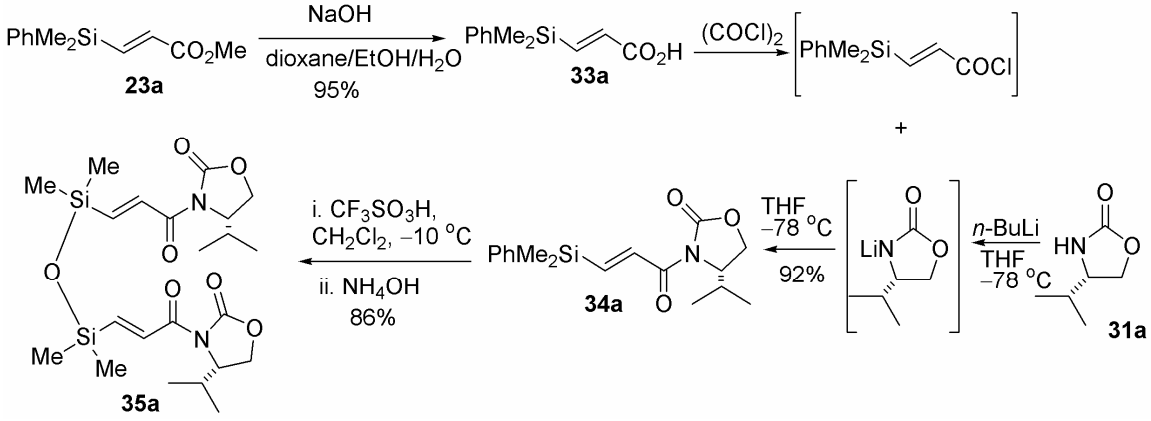
The synthesis of chiral oxazolidin-2-one **31a** is shown in Scheme 3.23. Commercially available (*S*)-valine was reduced with $LiAlH_4$ to give (*S*)-valinol **32a** which on treatment with diethyl carbonate in presence of potassium carbonate under reflux condition produced the desired oxazolidin-2-one **31a**. The next step was to attach this oxazolidin-2-one **31a** to β-silylacrylic acid.



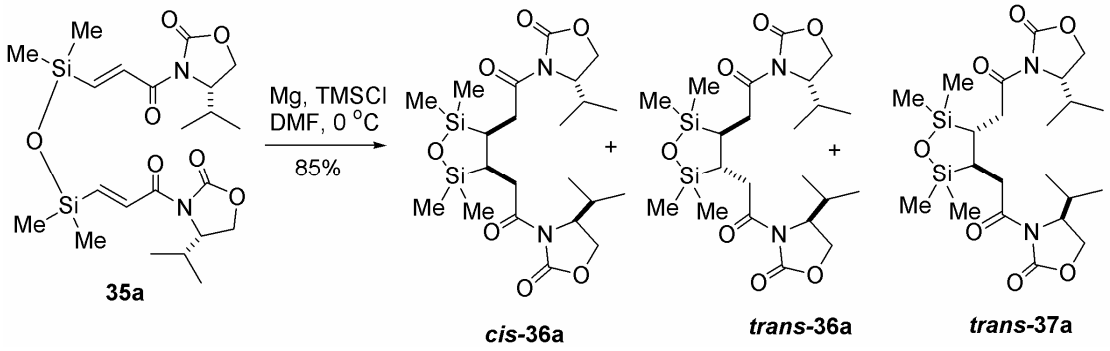
Scheme 3.23

The *trans*-β-silylacrylic ester **23a** was hydrolysed to the acid **33a**, which was then converted to the intermediate acid chloride by reacting with oxalyl chloride and subsequently reacted with the lithium salt of Evans' oxazolidin-2-one **31a** to give the oxazolidin-2-one derivative **34a** in 92% yield (Scheme 3.24). Reaction of amide **34a** with TfOH (3.6 equiv) in dichloromethane at −10 °C, followed by quenching with ammonium hydroxide, produced the disiloxane **35a** in very good yield. We subjected the disiloxane **35a** to the optimized reductive cyclization conditions (Table 3.1, entry 7), described for disiloxane **21a**, using Mg/TMSCl in DMF at 0 °C which led to complete consumption of the starting material. Interestingly, the crude reaction product showed the formation of a mixture of diastereoisomeric cyclic products, *cis*-**36a** and two *trans*-products (*trans*-

36a:*trans*-**37a** = 60/40) with a strong preference for the desired *trans* isomers (*trans*:*cis* = 85/15) (Scheme 3.25, Table 3.2, entry 1).



Scheme 3.24



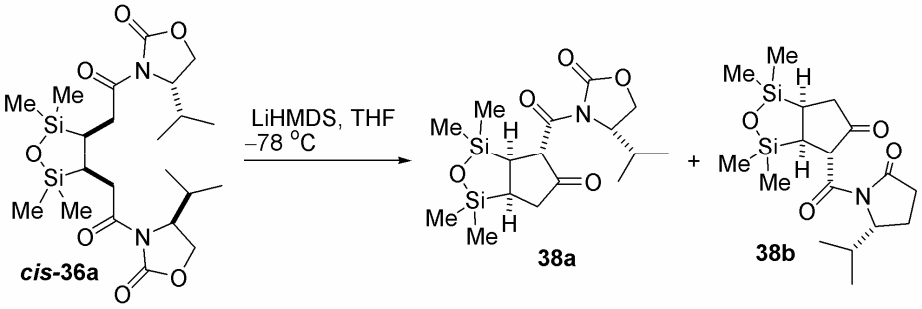
Scheme 3.25

Also, the formation of the double bond reduced product was significantly reduced (not seen in the ^{1}H NMR spectrum of the crude product). The isolated yield of the cyclic products was also very high (85%). To see the effect of SmI_3 in the reductive cyclization, the reaction was also carried out using disiloxane **35a**, TMSCl and SmI_3 (0.2 equiv) as an additive under the above conditions. This reduced the *trans*/*cis* ratio to 67/33, with a marginal change in the selectivity between the *trans* isomers (Table 3.2, entry 2).

3.2.4a Separation of individual diastereoisomers

The individual isomers could not be separated easily by column chromatography because of very close R_f values. We have adopted simple procedures by which the *trans*

isomers are separated from the *cis*-**36a** and then individual *trans* isomers by crystallization (Scheme 3.26 and Fig. 3.5). Initially, the mixture of *cis*-**36a,** *trans*-**36a** and *trans*-**37a** was



Scheme 3.26

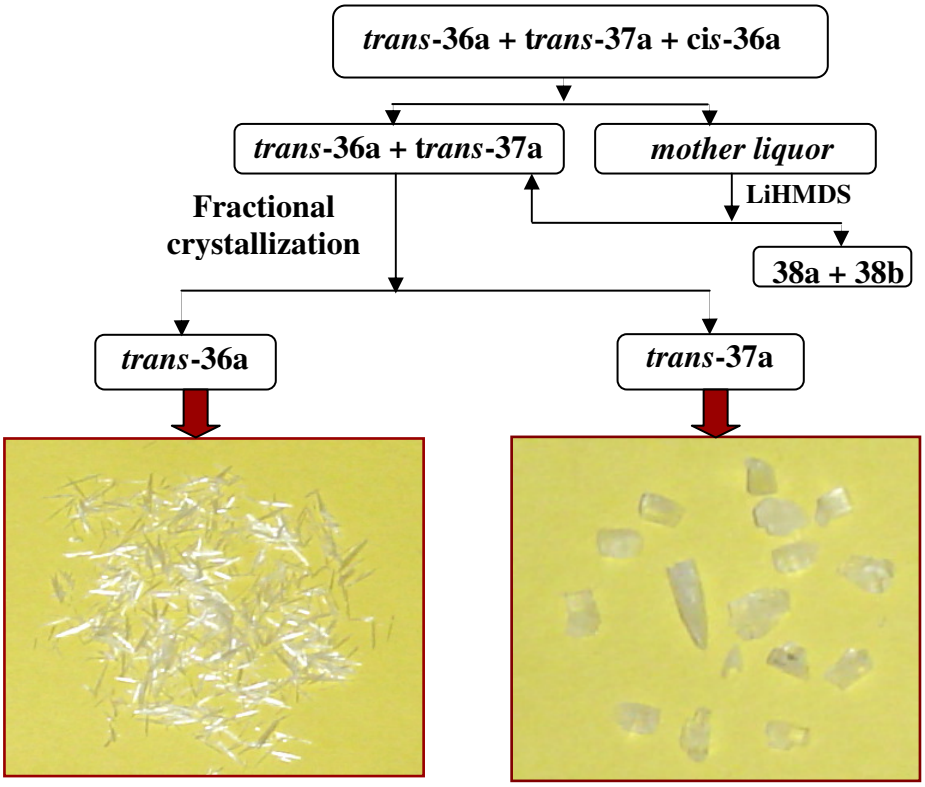


Figure 3.5: Separation of diastereoisomers

dissolved in ethyl acetate and the *trans*-isomers were precipitated out by adding hexane into the solution. After separating the solid mixture of *trans*-**36a** and *trans*-**37a** (55%), the gummy mixture containing all three isomers (30%) was treated with lithium hexamethyldisilyl amide in THF at –78 ºC. Under these conditions, the *cis*-**36a** underwent cyclization to cyclic β-keto esters **38a** and **38b** (Scheme 3.26) while the *trans* isomers

(15%) remained unaffected leading to easy separation by column chromatography. The combined yield of the *trans* isomers thus improved to 70%. Individual *trans* isomers were then separated by fractional crystallization. For this, the mixture of *trans*-**36a** and *trans*-**37a** was crystallized from benzene-hexane to give pure *trans*-**36a** product (38%, Fig. 3.6 and 3.7) as needle shaped crystals, and the remaining mass on crystallization from hexane-ethyl acetate gave *trans*-**37a** (27%, Fig. 3.8 and 3.9) as sugar like crystals.

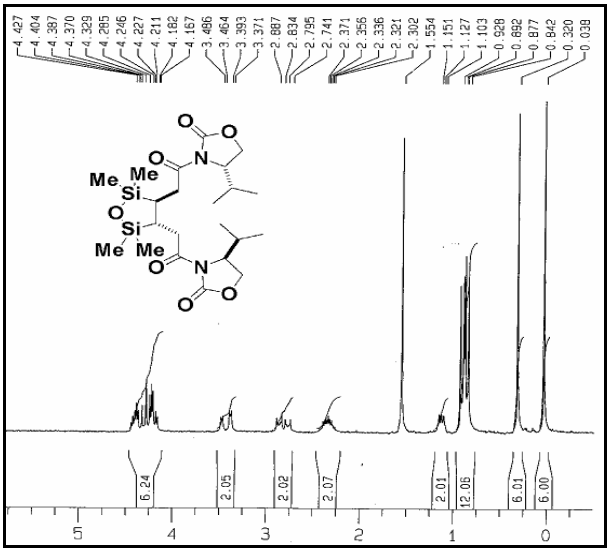


Figure 3.6: ^{1}H NMR of *trans*-36a

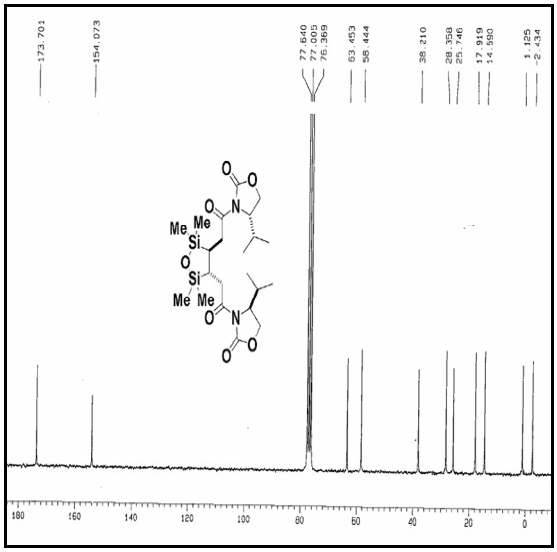


Figure 3.7: ^{13}C NMR of *trans*-36a

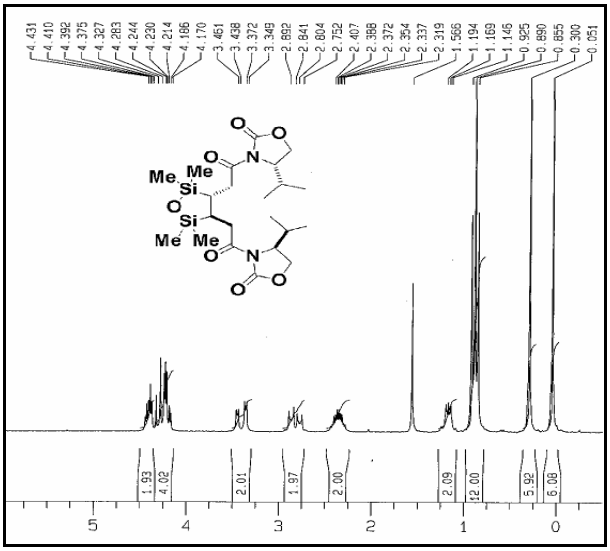


Figure 3.8: ^{1}H NMR of *trans*-37a

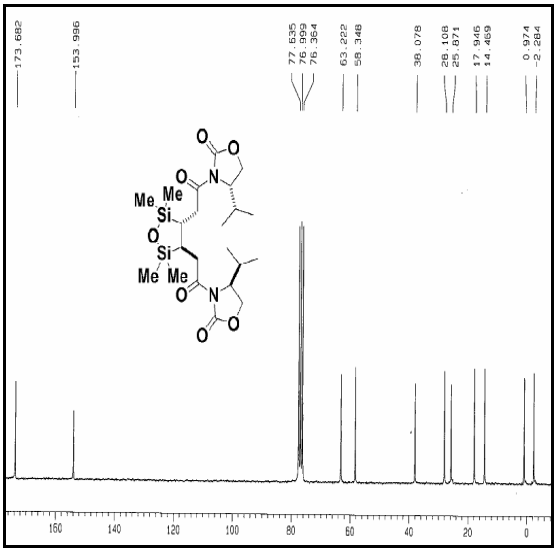
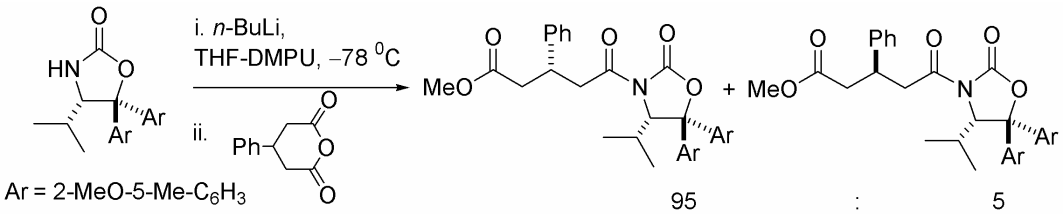


Figure 3.9: ^{13}C NMR of *trans*-37a

3.2.4b Effect of 'SuperQuats' chiral auxiliaries in the reductive coupling

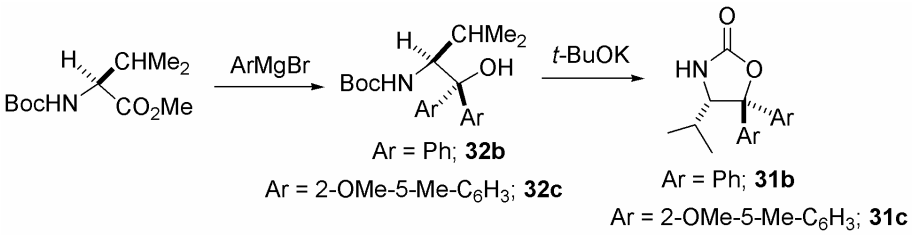
For further improvement of stereoselectivity, we decided to modify the oxazolidin-2-one with various substituents. A number of research groups[135] had independently introduced 5,5-disubstituted oxazolidin-2-ones, called 'SuperQuats', as chiral auxiliaries mainly to obviate the problems *viz*. purification of products by crystallization, and limit endocyclic cleavage during removal, which is known to be problematic with Evans' oxazolidin-2-one **31a**.[132] We were specifically interested to see the effect of 5,5-disubstituted oxazolidin-2-ones on the reductive cyclization because a dramatic improvement of diastereoselectivity (95:5) in anhydride opening (Scheme 3.27)[136] reaction has been observed by our group.



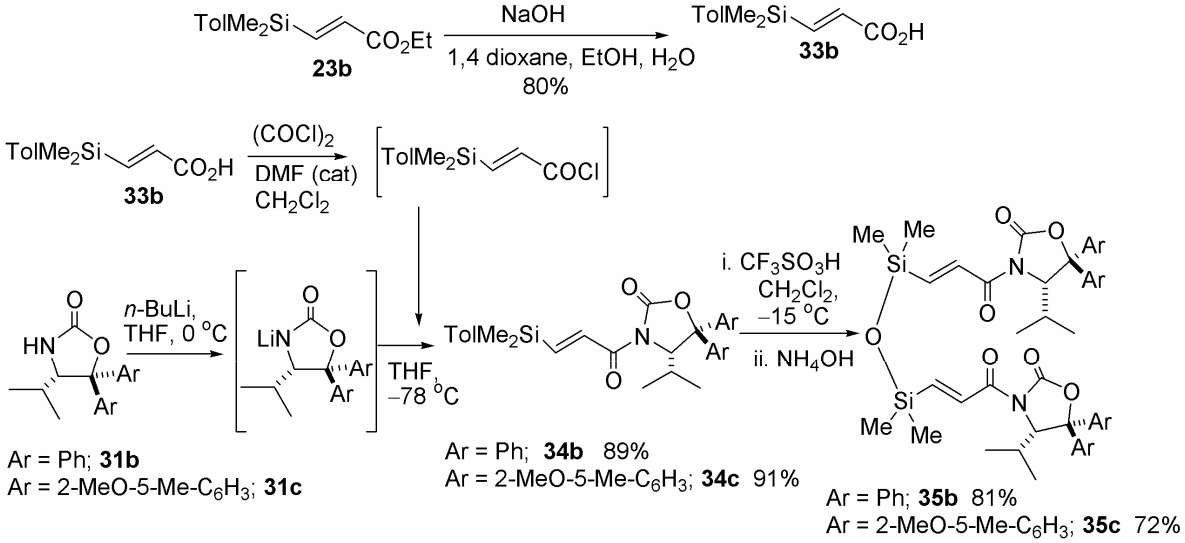
Scheme 3.27

We prepared 4-isopropyl-5,5-diphenyloxazolidin-2-one **31b** and 4-isopropyl-5,5-diaryloxazolidin-2-one **31c** from Boc-protected (*S*)-valine methyl ester following the reported procedures[136,137] (Scheme 3.28). Boc-protected (*S*)-valine methyl ester was reacted with phenylmagnesium bromide to give the corresponding alcohol **32b**, which on treatment with potassium *t*-butoxide produced oxazolidin-2-one **31b**. Similarly, Boc-protected (*S*)-vallin methyl ester with 2-methoxy-4-methylphenylmagnesium bromide gave the Boc-protected amino alcohol **32c**. 5,5-Diaryloxazolidin-2-one **31c** was synthesized from **32c** by treating with potassium *t*-butoxide. The lithium salts of the oxazolidin-2-ones **31b**, **31c** were made in THF using *n*-BuLi at 0 ºC and reacted with the intermediate acid chloride generated from acid **33b** (obtained from the hydrolysis of **23b)** at −78 ºC in THF

to give the amides **34b** and **34c**, respectively. The $TolMe_2Si$ group was chosen in these cases because this group is expected to proteodearylate under milder conditions compared to the $PhMe_2Si$ group. This was essential to prevent degradation of the oxazolidin-2-one moieties in **34b** and **34c**. Unlike amide **34a**, the conversion of the amides **34b** and **34c** to the corresponding disiloxanes **35b** and **35c** was performed with less TfOH (2.5–3 equiv) and at lower temperature (−15 °C) (Scheme 3.29).

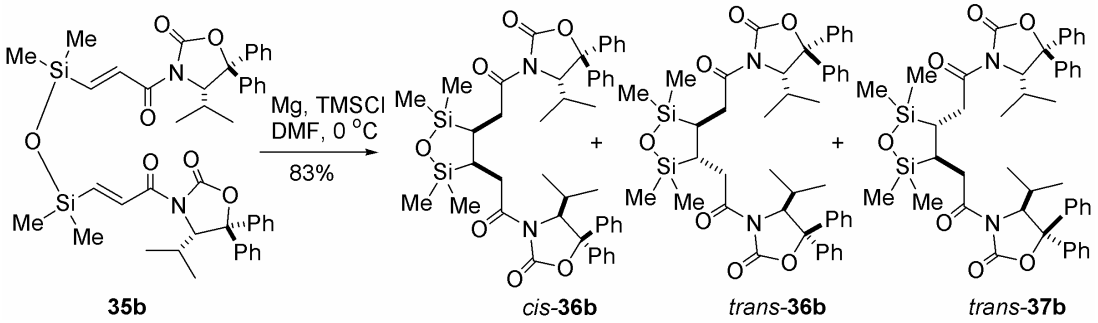


Scheme 3.28



Scheme 3.29

Reductive cyclization of disiloxane **35b** (Scheme 3.30), under the conditions described for amide **35a**, resulted in the formation of a mixture of diastereoisomeric cyclic products, *cis*-**36b** and two diastereoisomeric *trans* products (*trans*-**36b**:*trans*-**37b** = 45/55) with a marginally higher preference for the desired *trans* isomers (*trans*:*cis* = 88/12) (Table 3.2, entry 3).



Scheme 3.30

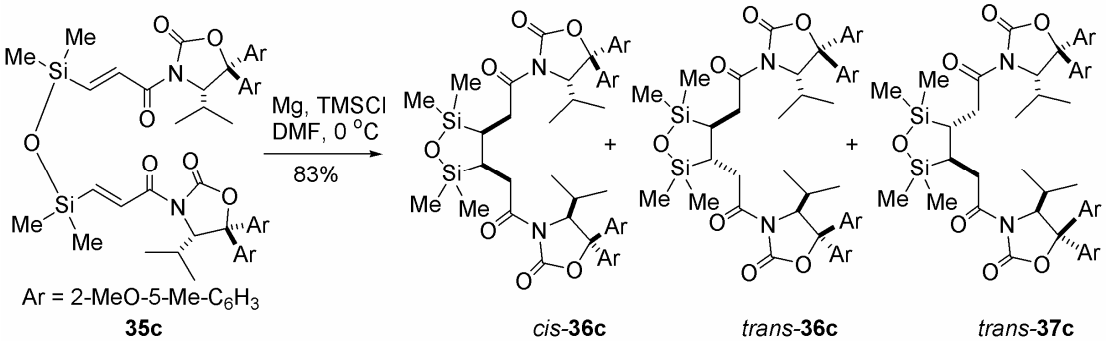
Table 3.2: Mg/TMSCl promoted reductive cyclization of oxazolidin-2-one-attached disiloxanes 35a-35c

Entry	Disiloxane	Cyclized products		
		trans:cis [a]	trans-**36**:trans-**37**	%Yield[b]
1	**35a**	85:15	60:40	85
2	**35a**	67:33	53:47	75[c]
3	**35b**	88:12	45:55	83
4	**35c**	87:13	45:55	83

[a] Obtained from ^{1}H NMR spectrum of the crude product; [b] Combined isolated yield of all isomers; [c] SmI_3 (0.2 equiv) was used as an additive.

Similarly, the disiloxane **35c** also gave a mixture of *cis*-**36c** and two diastereoisomeric *trans* products (*trans*-**36c**:*trans*-**37c** = 45/55) on reductive cyclization with Mg and TMSCl (Scheme 3.31). Fractional crystallization then provided pure *trans*-**37b** (Fig. 3.10) from the mixture of *trans*-**36b,** *trans*-**37b** and *cis*-**36b**, obtained from the reductive cyclization reaction of disiloxane **35b.** But other isomers *viz. cis*-**36b** and *trans*-**36b** could not be separated by crystallization. Similar results were found during crystallization, from the mixture of *trans*-**36c,** *trans*-**37c** and *cis*-**36c** obtained from the reductive cyclization reaction of disiloxane **35c,** where *trans*-**37c** (Fig. 3.11) was separated

easily but other isomers *viz. cis*-**36c** and *trans*-**36c** could not be separated by crystallization or chromatography.



Scheme 3.31

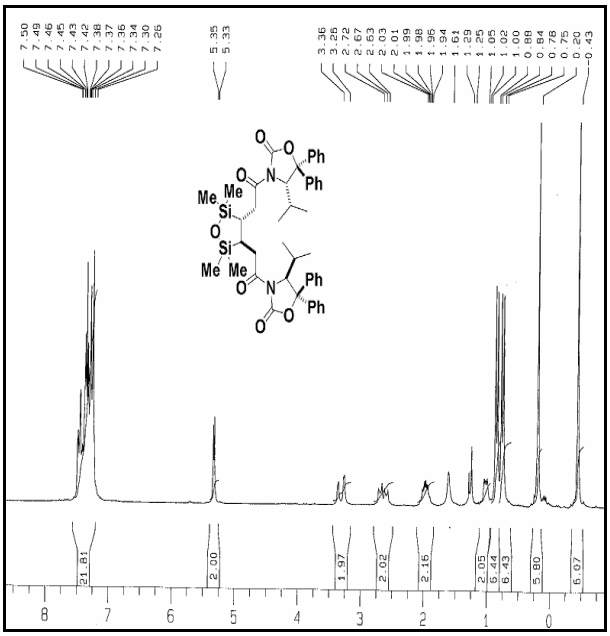


Figure 3.10: ^{1}H NMR of *trans*-37b

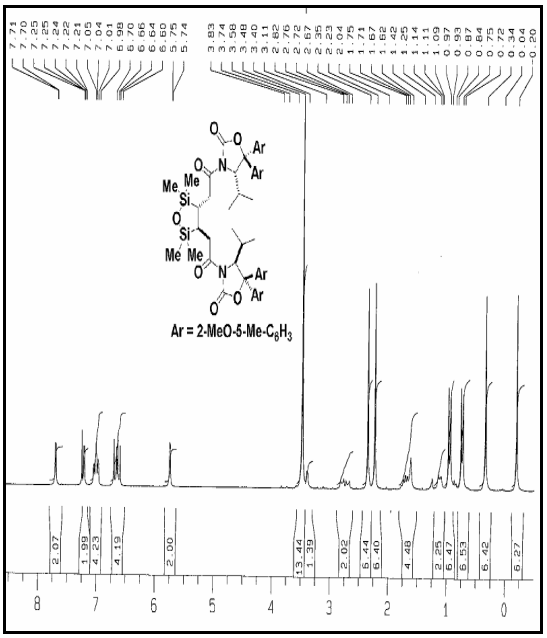
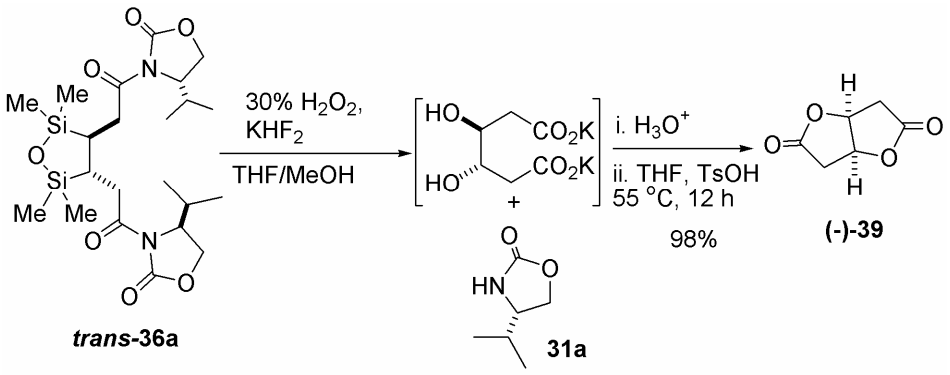


Figure 3.11: ^{1}H NMR of *trans*-37c

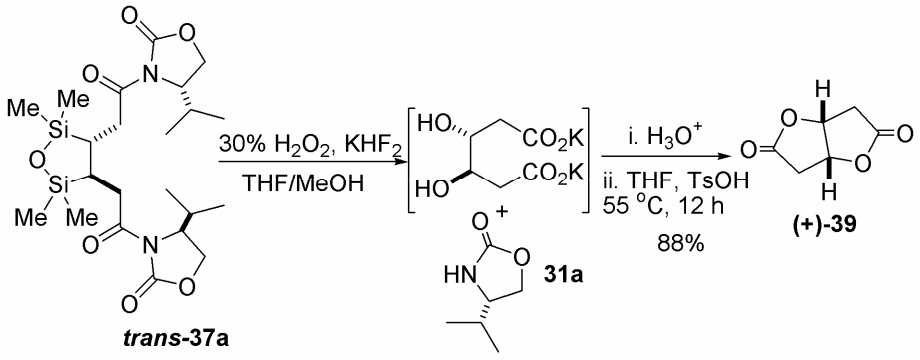
3.2.5 Synthesis of dioxabicyclo[3.3.0]octane-3,7-diones and confirmation of absolute stereochemistry of the individual *trans* isomers

To establish the absolute stereochemistry of the individual *trans* diastereoisomers *viz. trans*-**36a** and *trans*-**37a**, each of them was converted to known bislactone **39**.[138] The *trans*-**36a** was subjected to Fleming–Tamao[65,66] oxidation using KHF_2-H_2O_2 in 1/1 THF-MeOH at 60 °C (Scheme 3.32). Besides conversion of the silyloxy group to a hydroxyl

group, the oxazolidin-2-one group was also removed under these conditions to give the intermediate dipotassium salt. At this stage, a simple extraction of the reaction mixture with ethyl acetate gave back the oxazolidin-2-one **31a** (90%) and acidification of the residue gave the dilactone (−)-**39**. The (3*S*,4*S*)-configuration of the silicon-bearing asymmetric centre in *trans*-**36a** was confirmed from the specific rotation data of (−)-**39** ($[\alpha]_D^{23}$ = −145.3, *c* 0.64, H_2O) (lit.:[139] $[\alpha]_D^{19}$ = +143 ± 2.5, *c* 0.785, H_2O for the antipode). Similarly, the minor *trans*-**37a** under Fleming–Tamao oxidation using KHF_2-H_2O_2 in 1/1 THF-MeOH at 60 °C followed by acidification (Scheme 3.33) gave (+)-2,6-dioxabicyclo[3.3.0]octane-3,7-dione (+)-**39** as confirmed from the specific rotation data of (+)-**39** ($[\alpha]_D^{25}$ = +142.1, *c* 0.38, H_2O) (lit.:[139] $[\alpha]_D^{19}$ = +143 ± 2.5, *c* 0.785, H_2O), thus confirming its (3*R*,4*R*)-configuration.

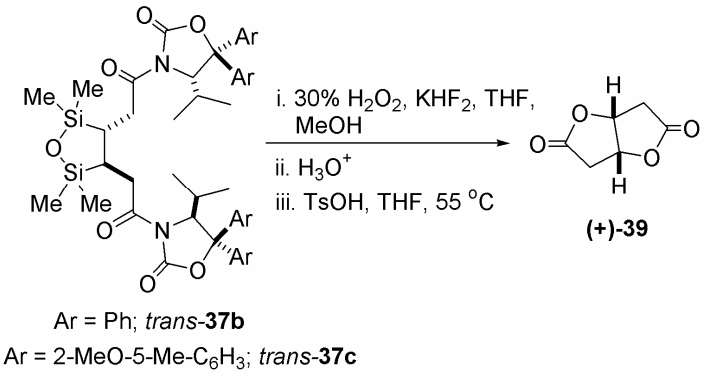


Scheme 3.32



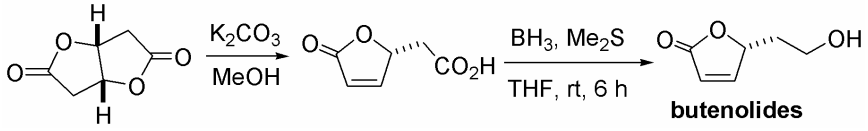
Scheme 3.33

Interestingly, the major *trans* diastereoisomers containing 'SuperQuat' oxazolidin-2-ones, *trans*-**37b** and *trans*-**37c**, after Fleming–Tamao oxidation gave (+)-2,6-dioxabicyclo[3.3.0]octane-3,7-dione (+)-**39** (Scheme 3.34). The marginal difference in stereocontrol behaviour between oxazolidin-2-ones **31a** and **31b** or **31c** is probably due to the steric crowding caused by the 5,5-diaryl groups in **31b** or **31c**.

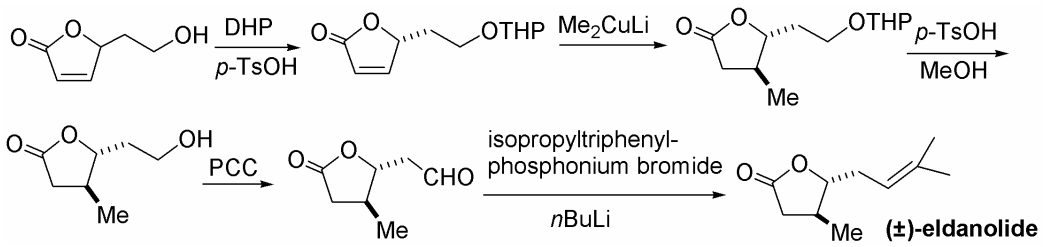


Scheme 3.34

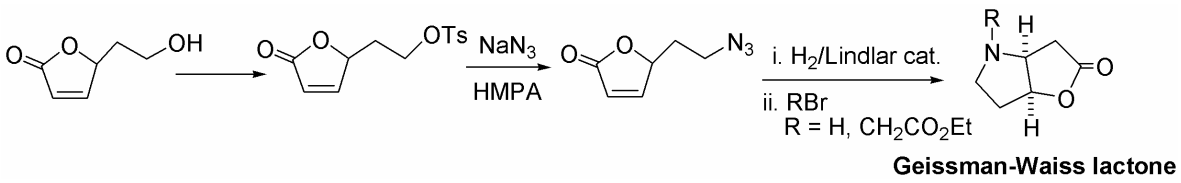
It is important to note that the bis-lactone **39** has been shown to be a useful intermediate in the synthesis of some important biologically active compounds such as butenolides (Scheme 3.35),[138] eldanolide (Scheme 3.36),[140] the Geissman-Waiss lactone (Scheme 3.37),[141] prostaglandin analogues,[142] *trans*-laurediols[143] and 8,9-epoxyeicosatrienoic acid.[144]



Scheme 3.35



Scheme 3.36



Scheme 3.37

3.3 Conclusion

In conclusion, we have successfully developed Mg/TMSCl-mediated intramolecular reductive cyclization of symmetric disiloxanes made from chiral oxazolidin-2-one derivatives of β-silylacrylic acid. C_2-Symmetric *trans*-diastereoisomers were produced with high stereoselectivity but the stereocontrol is marginal amongst the *trans*-diastereoisomers. The *trans* diastereoisomers attached to Evans' oxazolidin-2-ones were easily separated from the *cis* diastereoisomer and individual *trans*-diastereoisomers were also separated by fractional crystallization with ease and high recoveries. The individual isomers of cyclic products containing "SuperQuat" oxazolidin-2-ones are difficult to separate. Efficient and short syntheses of enantiomerically pure enantiomers of 2,6-dioxabicyclo[3.3.0]octane-3,7-dione have been achieved from the bis-silylated adipic acid derivatives by Fleming-Tamao oxidation as the key step. It is also important to note that the bis-lactone **39** has been shown to be a useful intermediate in the synthesis of some important biologically active compounds. However, in spite of the significant utility of the bis-lactone **39**, to our knowledge, only two reports are available for the asymmetric synthesis of the (+)-**39** and none for (−)-**39**.

3.4 Experimental

The general experimental and instrumental descriptions are provided in the experimental section of Chapter 2. Compounds **31a**,[132] **31b**[137] and **31c**[136] were prepared following the published procedures and included in the experimental section. DMF was dried over CaH_2 followed by storage over 4 Å molecular sieves. Mg turnings were purified by washing with dilute hydrochloric acid, water followed by washing with acetone and dried under vacuum. TMSCl was distilled over CaH_2 before use. *n*-BuLi (~1.6 *M* in hexanes) was purchased from Aldrich and its strength was determined by titration prior to use. Trifluoromethanesulfonic acid, KHF_2, H_2O_2 (30%), $KOBu^t$ and oxalyl chloride were used as received from commercial sources.

Dimethyl(phenyl)silane 24a

A solution of bromobenzene (29 mL, 275 mmol) in dry ether (250 mL) was added drop wise to magnesium turnings (7.2 g, 296 mmol) with stirring under argon. The mixture was heated under reflux for additional 1 h and cooled on an ice-water bath. A solution of chlorodimethylsilane (30.6 mL, 275.5 mmol) in dry ether (100 mL) was added to this Grignard solution and the mixture was stirred at room temperature overnight followed by refluxing for 2 h. The reaction was filtered to remove the precipitated magnesium salts and evaporated. The residue was distilled to give dimethyl(phenyl)silane **24a** (26 g, 70%) as colorless liquid.

bp. 68–69 ºC/30 mmHg.

IR (film): 3069, 3019, 2960, 2119, 1427, 1250, 1116, 879, 836, 709 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.35 (6 H, d, *J* = 3.6 Hz, $SiMe_2$), 4.44 (1 H, septet, *J* = 3.6 Hz, SiH), 7.34–7.38 (3 H, m, Ph), 7.53–7.58 (2 H, m, Ph).

^{13}C-NMR (50 MHz, $CDCl_3$): δ −3.8 (2 C), 127.9 (2 C), 129.2, 134.0 (2 C), 137.4.

Dimethyl(4-methylphenyl)silane 24b

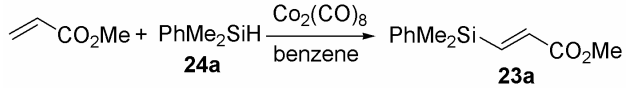
Following the procedure for the preparation of **24a**, 4-methylbromobenzene (34 mL, 275 mmol), chlorodimethylsilane (30.6 mL, 275.5 mmol) gave dimethyl(4-methylphenyl)silane **24b** (30 g, 73%) as a colorless liquid.

bp. 68–69 ºC/30 mmHg.

IR (film): 3066, 3012, 2959, 2921, 2117, 1602, 1422, 1249, 1109, 880, 836, 763 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.42 (6 H, d, *J* = 3.8 Hz, $SiMe_2$), 2.43 (3 H, s, Ph-*Me*), 4.52 (1 H, septet, *J* = 3.6 Hz, SiH), 7.27 (2 H, d, *J* = 7.6 Hz, Ar), 7.53 (2 H, d, *J* = 7.6 Hz, Ar).

^{13}C-NMR (50 MHz, $CDCl_3$): δ –3.7 (2 C), 21.4, 128.7 (2 C), 133.6, 134.0 (2 C), 138.8.



(*E*)-methyl 3-dimethyl(phenyl)silylpropenoate 23a

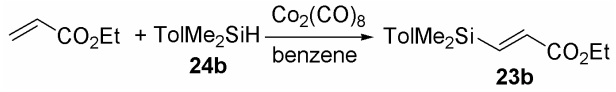
A solution of dimethyl(phenyl)silane (24.1 g, 177 mmol) in dry benzene (35 mL) was added to a stirred solution of methyl acrylate (79.5 mL, 882.8 mmol) and dicobalt octacarbonyl (2.41 g, 7.05 mmol) in dry benzene (150 mL) under argon atmosphere. After 4 h, the solvent and excess methyl acrylate was evaporated under reduced pressure and the residue was purified by column chromatography on silica using hexane-EtOAc (98:2) as eluent to give the acrylate **23a** (29.25 g, 75%) as a colorless liquid.

R_f 0.67 (hexane/EtOAc, 95:5).

IR (film): 3070, 2953, 1730, 1429, 1308, 1251, 1227, 1168, 1116, 997, 841, 701 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.41 (6 H, s, 2 × SiMe), 3.74 (3 H, s, CO_2CH_3), 6.26 (1 H, d, *J* = 18.8 Hz, *CH*=$CHCO_2CH_3$), 7.31–7.40 (3 H, m, Ar), 7.36 (1 H, d, *J* = 18.8 Hz, CH=*CH*CO_2CH_3), 7.47–7.51 (2 H, m, Ar).

^{13}C-NMR (50 MHz, $CDCl_3$): δ −3.4 (2 C), 51.4, 127.8 (2 C), 129.4, 133.63 (2 C), 134.8, 136.1, 147.5, 165.8.



(*E*)-ethyl 3-dimethyl(4-methylphnyl)silylpropenoate 23b

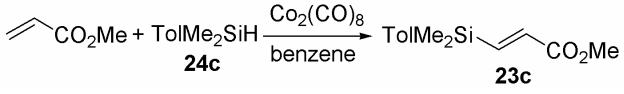
Following the procedure for the preparation of **23a**, dimethyl(4-methylphenyl)silane (30.6 g, 204 mmol), ethyl acrylate (111 mL, 1.02 mol) and dicobalt octacarbonyl (2.8 g, 8.2 mmol) gave (*E*)-ethyl 3-dimethyl(4-methylphenyl)silylpropenoate **23b** (37.5 g, 74%) as a colorless liquid.

R_f 0.66 (hexane/EtOAc, 95:5).

IR (film): 3067, 3014, 2959, 2922, 1700, 1410, 1299, 1254, 1218, 1190, 1107, 997 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.40 (6 H, s, 2 × SiMe), 1.29 (3 H, t, *J* = 7 Hz, $CO_2CH_2CH_3$), 2.35 (3 H, s, Ph-*Me*), 4.20 (2 H, q, *J* = 7 Hz, $CO_2CH_2CH_3$), 6.26 (1 H, d, *J* = 18.8 Hz, *CH*=$CHCO_2Et$), 7.19 (2 H, d, *J* = 7.6 Hz, Ar), 7.35 (1 H, d, *J* = 18.8 Hz, CH=*CH*CO_2CH_3), 7.44 (2 H, d, *J* = 7.6 Hz, Ar).

^{13}C-NMR (50 MHz, $CDCl_3$): δ −3.3 (2 C), 14.0, 21.2, 60.2, 128.6 (2 C), 132.4, 133.7 (2 C), 135.1, 139.2, 147.3, 165.4.



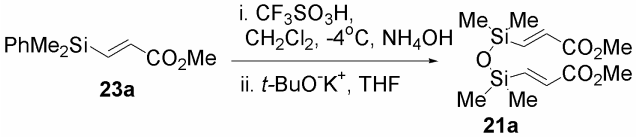
(*E*)-methyl 3-dimethyl(4-methylphnyl)silylpropenoate 23c

Following the procedure for the preparation of **23a**, dimethyl(4-methylphenyl)silane (9 g, 60 mmol), methyl acrylate (27 mL, 300 mmol) and dicobalt octacarbonyl (0.82 g, 2.4 mmol) gave (*E*)-methyl 3-dimethyl(4-methylphenyl)silylpropenoate **23c** (10.8 g, 77%) as a colorless liquid.

R_f 0.42 (hexane/EtOAc, 95:5).

IR (film): 3015, 2959, 2912, 1735, 1410, 1300, 1250, 1218, 1191, 1106, 998 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.39 (6 H, s, 2 × SiMe), 2.34 (3 H, s, Ph-*Me*), 3.73 (3 H, s, OMe), 6.25 (1 H, d, *J* = 18.8 Hz, *CH*=CHCO$_2$Et), 7.18 (2 H, d, *J* = 7.8 Hz, Ar), 7.35 (1 H, d, *J* = 18.8 Hz, CH=*CH*CO$_2$CH$_3$), 7.39 (2 H, d, *J* = 7.8 Hz, Ar).



1,1,3,3-Tetramethyl-1,3-di-[(2-methoxycarbonyl)ethenyl]disiloxane 21a

Trifluoromethanesulfonic acid (4.8 mL, 54.6 mmol, 5.5 equiv) was added to a stirred solution of (*E*)-methyl 3-dimethyl(phenyl)silylpropenoate **23a** (2.2 g, 10 mmol) in dry dichloromethane (70 mL) at –4 ºC. The reaction mixture was stirred for 20 min at that temperature, poured slowly into a stirred ice-cold aqueous ammonia solution (25%, 230 mL) and extracted with chloroform. The organic extract was washed with brine, dried over anhydrous $MgSO_4$ and evaporated. The residue was dissolved in THF (7 mL) and potassium *t*-butoxide (8 mg, 0.07 mmol) was added into it. The reaction mixture was stirred at room temperature overnight, diluted with water and extracted with ethyl acetate. The organic extract was washed with brine, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica using hexane-EtOAc (95:5) as eluent to give the disiloxane **21a** (1.3 g, 86%) as a colorless liquid.

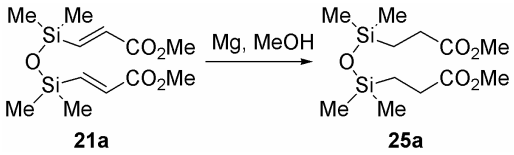
R$_f$ 0.64 (hexane/EtOAc, 90:10).

IR (film): 3033, 2956, 2904, 2844, 1731, 1601, 1436, 1308, 1273, 1257, 1227, 1192, 1170, 1054, 998, 844, 802, 702 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.20 (12 H, s, 4 × SiMe), 3.75 (6 H, s, 2 × CO_2CH_3), 6.25 (2 H, d, *J* = 19 Hz, 2 × CH=*CH*CO$_2$CH$_3$), 7.12 (2 H, d, *J* = 19 Hz, 2 × *CH*=CHCO$_2$CH$_3$).

^{13}C-NMR (50 MHz, $CDCl_3$): δ –0.3 (4 C), 50.9 (2 C), 133.9 (2 C), 146.5 (2 C), 165.3 (2 C).

MS (EI) *m/z*: 287 (M–15, 30%), 233 (18), 179 (100), 163 (60), 149 (68), 133 (53), 119 (24), 73 (18).



1,1,3,3-Tetramethyl-1,3-di-[(2-methoxycarbonyl)ethyl]disiloxane 25a

Magnesium turnings (101 mg, 4.1 mmol) were added to a stirred solution of the diester **21a** (125 mg, 0.41 mmol) in dry methanol (6 mL) at room temperature under an argon atmosphere. After 4 h, the reaction mixture was poured into cold aqueous HCl (0.3 N, 30 mL) and extracted with ethyl acetate. The extract was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was quickly filtered through a plug of silica gel to give the diester **25a** (103 mg, 82%) as colorless oil.

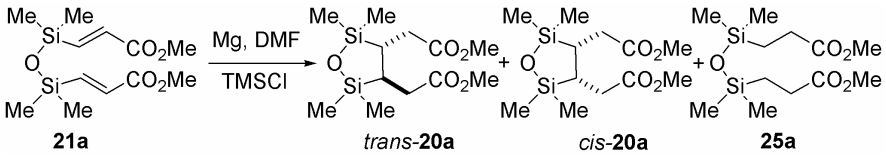
R_f 0.67 (hexane/EtOAc, 90:10).

IR (film): 2954, 2900, 1742, 1437, 1353, 1255, 1212, 1162, 1125, 1051, 843, 793 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.05 (12 H, s, 4 × SiMe), 0.83 (4 H, t, J = 8.4 Hz, 2 × Me_2SiCH_2), 2.27 (4 H, t, J = 8.4 Hz, 2 × CH_2CO_2Me), 3.64 (6 H, s, 2 × CO_2CH_3).

^{13}C-NMR (50 MHz, $CDCl_3$): δ 0.0 (4 C), 13.1 (2 C), 27.9 (2 C), 51.5 (2 C), 175.3 (2 C).

MS (EI) *m/z*: 291 (M–15, 3%), 219 (75), 163 (100), 145 (74), 133 (45), 119 (13). 89 (15), 73 (15).



Reductive cyclization of 21a to give *trans*-20a, *cis*-20a and 25a

Freshly distilled TMSCl (5.2 mL, 41 mmol) was added to a stirred suspension of magnesium turnings (1 g, 41 mmol) in dry DMF (95 mL) at room temperature under an argon atmosphere. After 30 min, the reaction mixture was cooled on an ice-water bath and a solution of disiloxane **21a** (1 g, 3.3 mmol) in dry DMF (15 mL) was added slowly over 1.3 h to the stirred reaction mixture. After the addition was over, the reaction mixture was stirred for 5.5 h and the cold bath was removed. The reaction mixture was allowed to attain to room temperature (about 30 min) and poured into cold saturated sodium bicarbonate solution and then extracted three times with 10% ethyl acetate-hexane. The organic extract was washed with brine, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica using benzene-EtOAc (99:1) as eluent to give the reduction product **25a** (125 mg, 12%) as a colorless liquid, the *trans*-**20a** (380 mg, 38%) as a colorless solid, and the *cis*-**20a** (375 mg, 37%) as a colorless liquid.

Data for *trans*-20a

mp. 99–100 ºC (hexane).

R_f 0.60 (hexane/EtOAc, 90:10).

IR (KBr): 3005, 2985, 2956, 2899, 2856, 1731, 1436, 1421, 1357, 1306, 1250, 1205, 1176, 1145, 1052, 930, 873, 841, 789 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.09 (6 H, s, 2 × SiMe), 0.24 (6 H, s, 2 × SiMe), 0.86–1.10 (2 H, m, 2 × $Me_2Si\mathit{CH}CH_2$), 2.22 (2 H, dd, J = 10.6, 15.8 Hz, 2 × $Me_2SiCHC\mathit{H_A}H_B$), 2.65 (2 H, dd, J = 3.6, 15.8 Hz, 2 × $Me_2SiCHCH_A\mathit{H_B}$), 3.64 (6 H, s, 2 × CO_2CH_3).

^{13}C-NMR (50 MHz, $CDCl_3$): δ −2.5 (2 C), 0.6 (2 C), 27.0 (2 C), 35.4 (2 C), 51.5 (2 C), 174.2 (2 C).

MS (EI) *m/z*: 289 (M−Me, 7%), 245 (10), 231 (56), 179 (10), 163 (100), 149 (23), 133 (92), 119 (23), 73 (46).

Anal. (Found: C, 47.18; H, 8.08. $C_{12}H_{24}O_5Si_2$ requires C, 47.33; H, 7.94%).

Data for *cis*-20a

R_f 0.51 (hexane/EtOAc, 90:10).

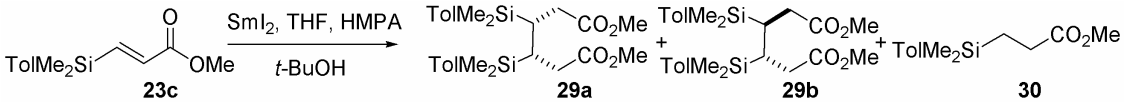
IR (film): 3021, 2954, 2917, 2848, 1738, 1437, 1356, 1254, 1204, 1164, 1114, 924, 847, 794, 758 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.14 (6 H, s, 2 × SiMe), 0.18 (6 H, s, 2 × SiMe), 1.60–1.73 (2 H, m, 2 × $Me_2SiCHCH_2$), 2.30 (2 H, dd, J = 9.4, 15.8 Hz, 2 × $Me_2SiCHCH_AH_B$), 2.46 (2 H, dd, J = 6.2, 15.8 Hz, 2 × $Me_2SiCHCH_AH_B$), 3.65 (6 H, s, 2 × CO_2CH_3).

^{13}C-NMR (50 MHz, $CDCl_3$): δ −1.4 (2 C), 0.2 (2 C), 23.8 (2 C), 31.8 (2 C), 51.7 (2 C), 174.2 (2 C).

MS (EI) *m/z*: 289 (M−15, 9%), 231 (54), 179 (15), 163 (100), 149 (22), 133 (63), 119 (16), 73 (28).

Anal. (Found: C, 47.49; H, 7.95. $C_{12}H_{24}O_5Si_2$ requires C, 47.33; H, 7.94%).



23c **29a** **29b** **30**

(3*SR*,4*SR*)-Dimethyl 3,4-bis-dimethyl(4-methylphenyl)silyl-1,6-hexandioate 29a

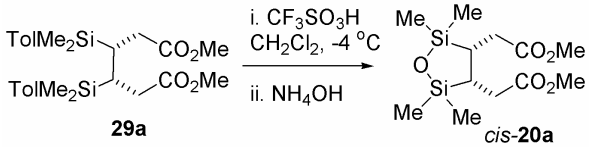
A freshly prepared samarium diiodide[117a] (100 mL, 0.1 *M* in THF) was added to a stirred solution of (*E*)-acrylate **23c** (2.55 g, 10 mmol based on 92% purity), *t*-butyl alcohol (740 mg, 10 mmol) in dry HMPA (20 mL) under nitrogen over 25 min at room temperature. After 1 min, the reaction mixture was quenched with saturated sodium bicarbonate solution and extracted with ether. The extract was washed with water and brine, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica using hexane-EtOAc (85:15) as eluent to give *meso* diester **29a** (1.26 g, 54%), racemic diester **29b** (265 mg, 11%) and the reduction product **30** (703 mg, 30%).

Data for 29a

R_f 0.2 (hexane/EtOAc, 90:10).

IR (film): 1735, 1260, 1204, 1164, 1110, 924, 845, 796 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.21 (6 H, s, 2 × SiMe), 0.26 (6 H, s, 2 × SiMe), 1.84–1.76 (2 H, m, 2 × $Me_2SiCHCH_2$), 2.33 (6 H, s, 2 × 4-*Me*-ph), 2.34 (2 H, dd, *J* = 5.9, 16.4 Hz, 2 × $CH_AH_BCO_2Me$), 2.45 (2 H, dd, *J* = 7.5, 16.4 Hz, 2 × $CH_AH_BCO_2Me$), 3.50 (6 H, s, 2 × CO_2CH_3), 7.14 (4 H, d, *J* = 7.8 Hz, Ar), 7.32 (4 H, d, *J* = 7.8 Hz, Ar).



Protodesilylation of 29a to *cis*-20a

Following the procedure for the preparation of disiloxane **21a**, *meso* diester **29a** (75 mg, 0.16 mmol), CF_3SO_3H (0.08 mL, 0.9 mmol) gave ***cis*-20a** (31.6 mg, 65%).

R_f 0.51 (hexane/EtOAc, 90:10).

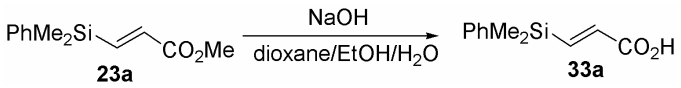
IR (film): 3021, 2954, 2917, 2848, 1738, 1437, 1356, 1254, 1204, 1164, 1114, 924, 847, 794, 758 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.14 (6 H, s, 2 × SiMe), 0.18 (6 H, s, 2 × SiMe), 1.60–1.73 (2 H, m, 2 × $Me_2SiCHCH_2$), 2.30 (2 H, dd, *J* = 9.4, 15.8 Hz, 2 × $Me_2SiCHCH_AH_B$), 2.46 (2 H, dd, *J* = 6.2, 15.8 Hz, 2 × $Me_2SiCHCH_AH_B$), 3.65 (6 H, s, 2 × CO_2CH_3).

^{13}C-NMR (50 MHz, $CDCl_3$): δ −1.4 (2 C), 0.2 (2 C), 23.8 (2 C), 31.8 (2 C), 51.7 (2 C), 174.2 (2 C).

MS (EI) *m/z*: 289 (M−15, 9%), 231 (54), 179 (15), 163 (100), 149 (22), 133 (63), 119 (16), 73 (28).

Anal. (Found: C, 47.49; H, 7.95. $C_{12}H_{24}O_5Si_2$ requires C, 47.33; H, 7.94%).



(*E*)- 3-Dimethyl(phenyl)silylpropenoic acid 33a

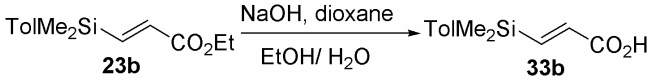
A solution of sodium hydroxide (15 *M*, 30 mL, 450 mmol) in water was added portionwise to a stirred solution of (*E*)-methyl 3-[dimethyl(phenyl)silyl]propenoate **23a** (32.5 g, 147.5 mmol) in 1,4 dioxane (580 mL). Ethanol (20 mL) was added to the reaction mixture to make it homogeneous and stirred overnight. The solvent was removed under reduced pressure, diluted with water (300 mL) and extracted with ether. The aqueous phase was acidified with citric acid (pH ~ 4) and extracted with ethyl acetate. The organic extract was washed with brine, dried over anhydrous $MgSO_4$ and evaporated to give acid **33a** (29 g, 95%) as a thick gum.

IR (film): 3500–2500 (br), 3070, 3022, 2959, 1696, 1594, 1427, 1411, 1300, 1253, 1117, 997, 938, 843, 822, 732, 700 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.44 (6 H, s, 2 × SiMe), 6.28 (1 H, d, *J* = 18.8 Hz, CH=*CH*CO_2H), 7.34–7.54 (6 H, *CH*=CHCO_2H, Ar).

^{13}C-NMR (50 MHz, $CDCl_3$): δ −3.4 (2 C), 128.0 (2 C), 129.5, 133.7 (2 C), 134.5, 135.8, 150.7, 171.0.

MS (EI) *m/z*: 206 (M, 9%), 205 (32), 191 (32), 163 (25), 145 (21), 135 (26), 121 (28), 105 (19), 75 (100), 69 (25).



(*E*)- 3-Dimethyl(4-methylphenyl)silylpropenoic acid 33b

Following the procedure for the preparation of **33a**, (*E*)-ethyl 3-dimethyl(4-methylphenyl)silylpropenoate **23b** (12.5 g, 50.3 mmol) gave acid **33b** (8.9 g, 80%) as a crystalline solid.

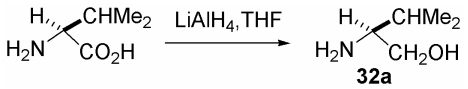
mp. 78–80 ºC (hexane).

IR (KBr): 3500–2500 (broad), 3066, 3011, 2968, 2921, 1697, 1611, 1402, 1298, 1247, 1110, 1001, 935, 838, 795, 777 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.40 (6 H, s, 2 × SiMe), 2.35 (3 H, s, Ar-*Me*), 6.25 (1 H, d, *J* = 18.8 Hz, CH=*CH*CO_2H), 7.19 (2 H, d, *J* = 7.6 Hz, Ar), 7.39 (2 H, d, *J* = 7.6 Hz, Ar), 7.46 (1 H, d, *J* = 18.8 Hz, *CH*=$CHCO_2H$).

^{13}C-NMR (50 MHz, $CDCl_3$): δ −3.3 (2 C), 21.4, 128.9 (2 C), 132.2, 133.8 (2 C), 134.4, 139.5, 151.1, 171.2.

MS (EI) *m/z*: 220 (M, 11%), 219 (14), 205 (51), 177 (28), 159 (25), 149 (22), 135 (25), 91 (22), 75 (100), 69 (24).



32a

(*S*)-2-Amino-3-methylbutan-1-ol 32a[145]

Lithium aluminium hydride (15 g, 394.7 mmol) was charged into an oven dried three necked flask under argon atmosphere followed by addition of dry THF (375 mL). (S)-valine (33 g, 281.7 mmol) was added portion wise over 1 h to the above stirred suspension kept at ice-water bath. After the addition over, the reaction mixture was slowly brought to room temperature. After refluxing for 16 h, the reaction mixture was cooled to 10 ºC and diluted with ether (310 mL). The reaction mixture was then quenched with water (15 mL), aqueous 15% sodium hydroxide (15 mL) and water (45 mL). After stirring, the white precipitate was filtered and washed with ether. The organic filtrate were combined, dried over anhydrous $MgSO_4$ and evaporated. Distillation of the residue under vacuum affords amino alcohol **32a** (21.5 g, 74%) as liquid.

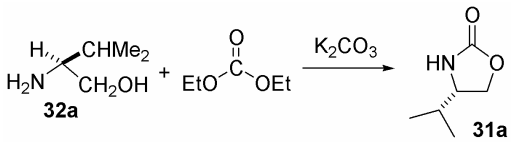
bp. 65 ºC/0.9 mmHg.

$[\alpha]_D^{26}$ +19.4 (*c* 10, $CHCl_3$) (lit.:[145] $[\alpha]_D^{20}$ +14.6, neat).

IR ($CHCl_3$): 3357, 2959, 2874, 1592, 1468, 1369, 1053, 732 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.91 (3 H, d, *J* = 6.8 Hz, CH$Me_A$$Me_B$), 0.93 (3 H, d, *J* = 6.8 Hz, CH$Me_A$$Me_B$), 1.50–1.71 (1 H, m, NCH$CH$$Me_2$), 2.62 (3 H, s, broad, NH_2 & OH), 2.54–2.61 (1 H, m, N$CH$$CHMe_2$), 3.32 (1 H, dd, *J* = 8.8, 10.6 Hz, C$H_A$$H_B$OH), 3.66 (1 H, dd, *J* = 4.0, 10.6 Hz, CH_AH_BOH).

^{13}C-NMR (50 MHz, $CDCl_3$): δ 17.7, 18.6, 30.0, 57.7, 63.5.



(4*S*)-4-isopropyloxazolidin-2-one 31a

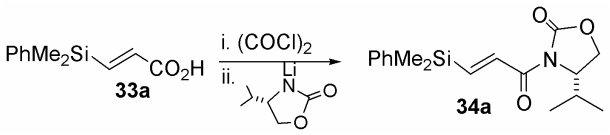
A mixture of **32a** (46.5 g, 450.8 mmol), dry potassium carbonate (6.2 g, 45 mmol), and diethyl carbonate (109.8 mL, 901.5 mmol) was refluxed with stirring for 5 h. The solvent was removed by downward distillation. The residue was diluted with water and extracted with ethyl acetate. The organic extract was washed with brine, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by crystallization to give the oxazolidin-2-one **31a** (43 g, 74%).

$[\alpha]_D^{27}$ +14.8 (*c* 6, $CHCl_3$) (lit.:[132] $[\alpha]_D^{20}$ +14.8, *c* 7, $CHCl_3$).

IR ($CHCl_3$): 3278, 2964, 2877, 1748, 1407, 1393, 1242, 1015, 978 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.89 (3 H, d, *J* = 6.8 Hz, CH$Me_A$$Me_B$), 0.95 (3 H, d, *J* = 6.6 Hz, CH$Me_A$$Me_B$), 1.63–1.82 (1 H, m, C$H$$Me_2$), 3.60 (1 H, dd, *J* = 6.8, 15.4 Hz, $CO_2CH_AH_B$), 4.09 (1 H, dd, *J* = 6.4, 8.8 Hz, $CO_2CH_AH_B$), 4.44 (1 H, t, *J* = 8.8 Hz, NC$H$$CHMe_2$), 6.5 (1 H, s, broad, NH).

^{13}C-NMR (50 MHz, $CDCl_3$): δ 17.4, 17.6, 32.4, 58.1, 68.4, 160.7.



(4*S*)-3-*trans*-(2-Dimethylphenylsilyl)acryloyl-4-isopropyl-2-oxazolidin-2-one 34a

Dry DMF (0.03 mL, 0.38 mmol) was added to a stirred solution of acid **33a** (15 g, 72.7 mmol) in dry dichloromethane (100 mL) and the reaction mixture was cooled in an ice-water bath. Oxalyl chloride (25.4 mL, 291 mmol) was added and the reaction mixture was allowed to attain to room temperature. After 3.5 h, the solvent and volatiles were removed under reduced pressure to give the crude acid chloride which was dissolved in dry THF (68 mL). The acid chloride solution was added into a stirred solution of lithium salt of oxazolidin-2-one at −78 ºC which was prepared from oxazolidin-2-one **31a** (9.4 g, 72.7 mmol) and *n*-BuLi (48.5 mL, 1.5 *M* solution in hexane, 72.7 mmol) in dry THF (136 mL) at −78 ºC. The reaction mixture was stirred under the same conditions for 30 min followed by 15 min in an ice-water bath. A saturated aqueous ammonium chloride solution (600 mL) was added into the reaction mixture and extracted with ether. The extract was washed successively with saturated aqueous sodium bicarbonate and brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure. The residue was purified by column chromatography on silica using hexane-EtOAc (93:7) as eluent to give the pure amide **34a** (21.2 g, 92%) as a colorless solid.

mp. 60 ºC (hexane).

$[\alpha]_D^{25}$ +78.52 (*c* 1.08, EtOH).

R_f 0.53 (hexane/EtOAc, 85:15).

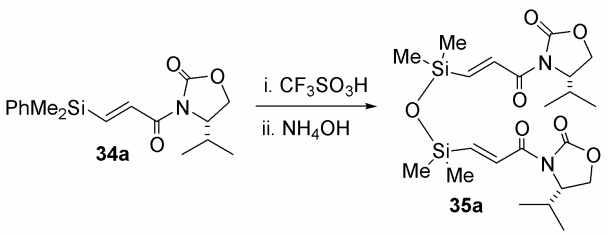
IR ($CHCl_3$): 3070, 3049, 2963, 2876, 1781, 1683, 1592, 1487, 1428, 1364, 1337, 1254, 1207, 1116, 1060, 974, 860, 819, 774 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.45 (6 H, s, 2 × SiMe), 0.88 (3 H, d, *J* = 7.2 Hz, CH*Me*$_A$Me$_B$), 0.92 (3 H, d, *J* = 7.2 Hz, CHMe$_A$*Me*$_B$), 2.33–2.49 (1 H, m, NCH*CH*Me$_2$), 4.18–4.32 (2 H, m, NCO$_2$*CH*$_2$CH), 4.44–4.51 (1 H, m, N*CH*CHMe$_2$), 7.33–7.40 (3 H, m, Ar), 7.50 (1 H, d, *J* = 18.8 Hz, CH=*CH*CON), 7.47–7.60 (2 H, m, Ar), 7.70 (1 H, d, *J* = 18.6 Hz, *CH*=CHCO).

^{13}C-NMR (50 MHz, $CDCl_3$): δ −3.3 (2 C), 14.6, 17.9, 28.3, 58.5, 63.3, 127.9 (2 C), 129.3, 133.7 (2 C), 133.9, 136.4, 148.8, 153.8, 164.2.

MS (EI) *m/z*: 302 (M−15, 43%), 240 (17), 230 (31), 216 (60), 202 (90), 189 (46), 161 (54), 145 (55), 135 (100), 105 (40), 75 (26), 69 (42).

Anal. (Found: C, 64.16; H, 7.58; N, 4.38. $C_{17}H_{23}NO_3Si$ requires C, 64.32; H, 7.30; N, 4.41%).



1,1,3,3-Tetramethyl-1,3-di-{2-[3-(4*S*)-3-carbonyl-4-isopropyl-2-oxazolidin-2-one]ethenyl}disiloxane 35a

Trifluoromethanesulfonic acid (13.8 mL, 157 mmol, 2.5 equiv) was added to a stirred solution of **34a** (20 g, 63 mmol) in dry dichloromethane (400 mL) at –10 ºC. After 1 h, another portion of TfOH (6 mL, 68.3 mmol, 1.1 equiv) was added to the reaction mixture and stirred under the same conditions for 1 h. The reaction mixture was poured slowly into a stirred ice-cold aqueous ammonia solution (25%, 1.4 L) and stirred for 2.5 h. The reaction mixture was extracted with chloroform and the extract was washed with brine, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica using hexane-EtOAc (85:15) as eluent to give the disiloxane **35a** (13.5 g, 86%) as a colorless solid.

mp. 78–88 ºC (hexane-EtOAc).

$[\alpha]_D^{23}$ +93.1 (*c* 1.01, EtOH).

R_f 0.72 (hexane/EtOAc, 70:30).

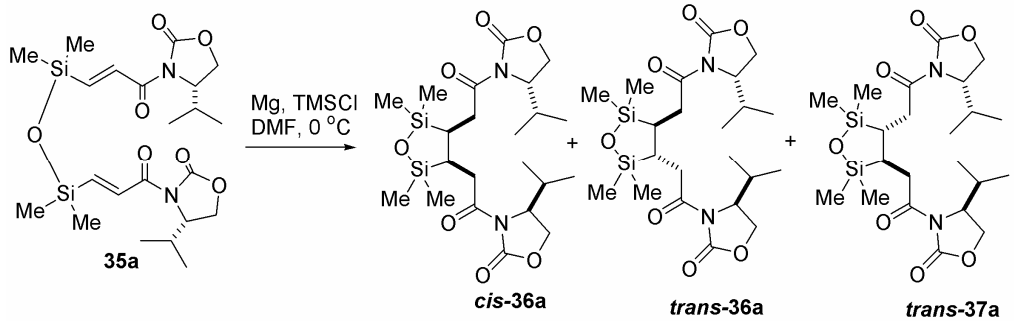
IR ($CHCl_3$): 3020, 2964, 2877, 1781, 1683, 1487, 1388, 1365, 1337, 1256, 1208, 1120, 1098, 1060, 840, 756 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.25 (12 H, s, 4 × SiMe), 0.89 (6 H, d, *J* = 7.8 Hz, 2 × CH*Me*$_A$Me$_B$), 0.93 (6 H, d, *J* = 7.8 Hz, 2 × CHMe$_A$*Me*$_B$), 2.33–2.49 (2 H, m, 2 × NCH*CH*Me$_2$), 4.18–4.34 (4 H, m, 2 × NCO$_2$*CH*$_2$CH), 4.44–4.51 (2 H, m, 2 × NC*H*CHMe$_2$), 7.28 (2 H, d, *J* = 18.6 Hz, 2 × CH=*CH*CON), 7.67 (2 H, d, *J* = 18.6 Hz, 2 × *CH*=CHCON).

^{13}C-NMR (50 MHz, $CDCl_3$): δ 0.3 (2 C), 0.4 (2 C), 14.7 (2 C), 18.0 (2 C), 28.4 (2 C), 58.6 (2 C), 63.4 (2 C), 133.4 (2 C), 148.7 (2 C), 153.9 (2 C), 164.5 (2 C).

MS (EI) *m/z*: 481 (M−15, 19%), 324 (16), 261 (22), 260 (100), 186 (19), 157 (41), 133 (22), 69 (15).

Anal. (Found: C, 53.34; H, 7.62; N, 5.77. $C_{22}H_{36}N_2O_7Si_2$ requires C, 53.20; H, 7.31; N, 5.64%).



Reductive cyclization of 35a to give *trans*-36a, *trans*-37a and *cis*-36a

Following the procedure of intramolecular reductive cyclization of disiloxane **21a**, disiloxane **35a** (7 g, 14.1 mmol), magnesium turnings (4.1 g, 168.8 mmol) and TMSCl (21.4 mL, 168.8 mmol) gave a mixture of *trans*-**36a**, *trans*-**37a** and *cis*-**36a** (6 g, 85%). All

the three individual isomers were separated by fractional crystallization as mentioned earlier. A pure sample of *cis*-**36a** for characterization purposes was obtained by careful column chromatography of the gummy residue containing mixture of all isomers.

Data for (4*S*,4'*S*)-3,3'-(2,2'-((3*S*,4*S*)-2,2,5,5-tetramethyl-1,2,5-oxadisilolane-3,4-diyl)bis(acetyl))bis(4-isopropyloxazolidin-2-one) *trans*-36a

mp. 162–163 ºC (hexane-EtOAc).

$[\alpha]_D^{28}$ −5.3 (*c* 0.87, EtOH).

R_f 0.71 (hexane/EtOAc, 70:30).

IR ($CHCl_3$): 3019, 2966, 1780, 1697, 1388, 1376, 1302, 1252, 1215, 1098, 919, 846, 759 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.04 (6 H, s, 2 × SiMe), 0.32 (6 H, s, 2 × SiMe), 0.87 (6 H, d, *J* = 7.8 Hz, 2 × CH*Me*$_A$Me$_B$), 0.92 (6 H, d, *J* = 7.8 Hz, 2 × CHMe$_A$*Me*$_B$), 1.10–1.51 (2 H, m, 2 × Me$_2$Si*CH*CH$_2$), 2.27–2.43 (2 H, m, 2 × NCH*CH*Me$_2$), 2.81 (2 H, dd, *J* = 10.8, 18.6 Hz, 2 × C*H*$_A$H$_B$CON), 3.43 (2 H, dd, *J* = 4.4, 18.6 Hz, 2 × CH$_A$*H*$_B$CON), 4.17–4.33 (4 H, m, 2 × NCO$_2$*CH*$_2$CH), 4.37–4.44 (2 H, m, 2 × N*CH*CHMe$_2$).

^{13}C-NMR (50 MHz, $CDCl_3$): δ −2.4 (2 C), 1.1 (2 C), 14.6 (2 C), 17.9 (2 C), 25.8 (2 C), 28.4 (2 C), 38.2 (2 C), 58.4 (2 C), 63.5 (2 C), 154.1 (2 C), 173.7 (2 C).

MS (EI) *m/z*: 483 (M−15, 5%), 327 (27), 328 (100), 260 (81), 228 (15), 213 (19), 199 (71), 174 (34), 149 (32), 133 (66), 117 (19), 73 (22), 69 (21).

Anal. (Found: C, 52.95; H, 7.85; N, 5.88. $C_{22}H_{38}N_2O_7Si_2$ requires C, 52.98; H, 7.68; N, 5.62%).

Data for (4*S*,4'*S*)-3,3'-(2,2'-((3*R*,4*R*)-2,2,5,5-tetramethyl-1,2,5-oxadisilolane-3,4-diyl)bis(acetyl))bis(4-isopropyloxazolidin-2-one) *trans*-37a

mp. 141–142 ºC (hexane-EtOAc).

$[\alpha]_D^{27}$ +152.9 (*c* 0.90, EtOH).

R_f 0.71 (hexane/EtOAc, 70:30).

IR ($CHCl_3$): 3019, 2965, 2877, 1779, 1696, 1487, 1388, 1302, 1251, 1210, 1096, 920, 846, 751 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.05 (6 H, s, 2 × SiMe), 0.30 (6 H, s, 2 × SiMe), 0.88 (6 H, d, *J* = 7.8 Hz, 2 × CH*Me*$_A$Me$_B$), 0.92 (6 H, d, *J* = 7.8 Hz, 2 × CHMe$_A$*Me*$_B$), 1.15–1.19 (2 H, m, 2 × Me$_2$Si*CH*CH$_2$), 2.28–2.44 (2 H, m, 2 × NCH*CH*Me$_2$), 2.82 (2 H, dd, *J* = 10.4, 17.8 Hz, 2 × C*H*$_A$H$_B$CON), 3.41 (2 H, dd, *J* = 4.6, 17.8 Hz, 2 × CH$_A$*H*$_B$CON), 4.17–4.33 (4 H, m, 2 × NCO$_2$*CH*$_2$CH), 4.38–4.45 (2 H, m, 2 × N*CH*CHMe$_2$).

^{13}C-NMR (50 MHz, $CDCl_3$): δ −2.3 (2 C), 1.0 (2 C), 14.5 (2 C), 18.0 (2 C), 25.9 (2 C), 28.1 (2 C), 38.1 (2 C), 58.4 (2 C), 63.2 (2 C), 154.0 (2 C), 173.7 (2 C).

MS (EI) *m/z*: 483 (M−15, 5%), 327 (26), 328 (100), 260 (80), 228 (15), 213 (19), 199 (69), 174 (35), 149 (32), 133 (64), 117 (18), 73 (22), 69 (21).

Anal. (Found: C, 52.99; H, 7.74; N, 6.21. $C_{22}H_{38}N_2O_7Si_2$ requires C, 52.98; H, 7.68; N, 5.62%).

Data for (4*S*,4'*S*)-3,3'-(2,2'-((3*R*,4*R*)-2,2,5,5-tetramethyl-1,2,5-oxadisilolane-3,4-diyl)bis(acetyl))bis(4-isopropyloxazolidin-2-one) *cis*-36a

$[\alpha]_D^{31}$ +58.2 (*c* 0.67, EtOH).

R_f 0.71 (hexane/EtOAc, 70:30).

IR ($CHCl_3$): 2963, 2977, 1780, 1698, 1387, 1302, 1252, 1208, 1097, 10120, 919 cm^{-1}.

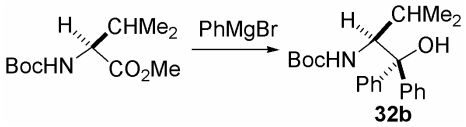
^{1}H-NMR (500 MHz, $CDCl_3$): δ 0.16 (3 H, s, SiMe), 0.17 (3 H, s, SiMe), 0.23 (3 H, s, SiMe), 0.25 (3 H, s, SiMe), 0.88 (6 H, d, *J* = 7 Hz, 2 × CH*Me*$_A$Me$_B$), 0.92 (6 H, d, *J* = 7.8 Hz, 2 × CHMe$_A$*Me*$_B$), 1.69–1.73 (1 H, m, Me$_2$Si*CH*CH$_2$), 1.82–1.86 (1 H, m, Me$_2$Si*CH*CH$_2$), 2.30–2.43 (2 H, m, 2 × NCH*CH*Me$_2$), 2.95 (2 H, dd, *J* = 9, 17.5 Hz, 2 × C*H*$_A$H$_B$CON), 3.15 (1 H, dd, *J* = 6, 17.5 Hz, CH$_A$*H*$_B$CON), 3.22 (1 H, dd, *J* = 7.5, 18 Hz,

CH_AH_BCON), 4.18–4.23 (2 H, m, NCO_2CH_2CH), 4.26–4.34 (2 H, m, NCO_2CH_2CH), 4.39–4.42 (1 H, m, $NCHCHMe_2$), 4.44–4.47 (1 H, m, $NCHCHMe_2$).

^{13}C-NMR (125 MHz, $CDCl_3$): δ−1.3, −1.1, 0.1, 0.5, 14.5, 14.5, 18.0 (2 C), 22.4, 22.9, 28.2, 28.3, 32.9, 33.5, 58.5 (2 C), 63.2, 63.3, 154.1, 154.2, 173.4, 173.6.

HRMS (ESI) *m/z*: Found MH^+ 499.2275, $C_{22}H_{39}N_2O_7Si_2$ requires 499.2290.

MS (EI) *m/z*: 521 (M+Na, 69%), 499 (M+H, 100), 481 (26), 370 (19), 279 (41), 132 (16).



32b

(2*S*)-2-*tert*-butyloxycarbonylamino-1,1-di(phenyl)-3-methylbutanol 32b

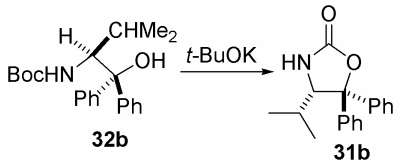
A solution of bromobenzene (11 mL, 105 mmol) in THF (70 mL) was added drop wise to magnesium turnings (2.6 g, 107 mmol) with stirring under argon. The mixture was heated under reflux for additional 1 h and cooled on an ice-water bath. A solution of *N*-(*tert*-butoxycarbonyl)-(*S*)-valine methyl ester (6.9 g, 30 mmol) in dry THF (30 mL) was added slowly in portions to the Grignard solution at 0 ºC. After the addition was over, the reaction mixture was allowed to warm to room temperature and stirring was continued for 15 h. The reaction mixture was slowly poured into an ice-cold saturated NH_4Cl solution and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed followed by crystallization from ethyl acetate-petroleum ether to give (2*S*)-2-*tert*-butyloxycarbonylamino-1,1-di(phenyl)-3-methylbutanol **32b** (8.8 g, 80%).

mp. 188–189 ºC (Lit.:[137] 188.5–189 ºC).

$[\alpha]_D^{22}$ −64 (*c* 1, CH_2Cl_2) [Lit.:[137] $[\alpha]_D^{r.t.}$ −65 (*c* 1, CH_2Cl_2)].

IR ($CHCl_3$): 3446, 2966, 1703, 1498, 1368 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.88 (3 H, d, *J* = 6.8 Hz, CH*Me*$_A$Me$_B$), 0.90 (3 H, d, *J* = 6.9 Hz, CHMe$_A$*Me*$_B$), 1.34 (9 H, s, *t*-BuO), 1.74–1.82 (1 H, m, *CH*Me$_2$), 2.63 (1 H, s, OH), 4.58-4.62 (1 H, m, NC*H*), 5.01 (1 H, d, *J* = 10.2 Hz, NH), 7.13–7.55 (10 H, m, Ph).



32b **31b**

(4S)-5,5-Diphenyl-4-isopropyloxazolidino-2-one 31b[137]

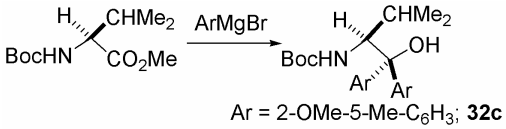
Potassium *tert*-butoxide (3.7 g, 33 mmol) was added to a stirred solution of the alcohol **32b** (9.8 g, 27.5 mmol) in dry THF (180 mL) at 0 ºC. After 2.5 h, the resulting suspension was poured into a 10% aqueous solution of NH_4Cl (200 mL). The white solid were collected and crystallized from methanol to give oxazolidin-2-one **31b** (7 g, 91%).

mp. 253–254 ºC (EtOAc) (Lit.:[137] 253.5–254 ºC).

[α]$_D^{29}$ –243 (*c* 0.6, CH_2Cl_2) [Lit.:[137] [α]$_D^{r.t.}$ –244 (*c* 0.61, CH_2Cl_2)].

IR ($CHCl_3$): 3461, 2968, 1759 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.68 (3 H, d, *J* = 6.6 Hz, CH*Me*$_A$Me$_B$), 0.89 (3 H, d, *J* = 6.8 Hz, CHMe$_A$*Me*$_B$), 1.78–1.91 (1 H, m, *CH*Me$_A$Me$_B$), 4.35 (1 H, d, *J* = 3.6 Hz, NC*H*), 6.34 (1 H, br, NH), 7.24–7.40 (8 H, m, Ph), 7.51–7.56 (2 H, m, Ph).



Ar = 2-OMe-5-Me-C_6H_3; **32c**

(2*S*)-2-*tert*-butyloxycarbonylamino-1,1-di(2-methoxy-5-methylphenyl)-3-methylbutanol 32c

A solution of 2-methoxy-4-methylphenylmagnesium bromide was prepared in the usual way by using 2-bromo-4-methylanisole (30.4 g, 151 mmol), Mg turnings (3.7 g, 154 mmol) and THF (100 mL) under argon atmosphere. A solution of *N*-(*tert*-butoxycarbonyl)-(*S*)-valine methyl ester (10 g, 43.2 mmol) in dry THF (50 mL) was added drop wise to the

Grignard solution at 0 ºC. After the addition was over, the reaction mixture was allowed to warm to room temperature and stirring was continued for 18 h. The reaction mixture was slowly poured into an ice-cold saturated NH_4Cl solution and extracted with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure. The residue was chromatographed followed by crystallization from petroleum ether to give (2*S*)-2-*tert*-butyloxycarbonylamino-1,1-di(2-methoxy-5-methylphenyl)-3-methylbutanol **32c** (14.8 g, 77%).

mp. 112-113 ºC.

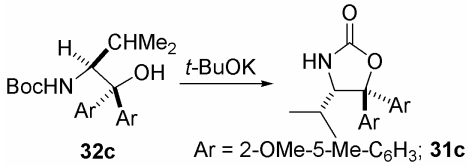
$[\alpha]_D^{22}$ −143 (*c* 1, EtOH).

R_f 0.55 (hexane/EtOAc, 90:10).

IR ($CHCl_3$): 3502, 3454, 1700, 1497 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.84 (6 H, d, *J* = 6.8 Hz, CH*Me*$_2$), 1.40 (9 H, s, *t*-BuO), 1.51–1.67 (1 H, m, *CH*Me$_2$), 2.28 (3 H, s, Ar*Me*), 2.32 (3 H, s, Ar*Me*), 3.47 (3 H, s, ArO*Me*), 3.48 (3 H, s, ArO*Me*), 5.05 (1 H, d, *J* = 10 Hz, NC*H*), 5.05 (1 H, d, *J* = 10.2 Hz, NH), 5.29 (1 H, s, br, OH), 6.60 (1 H, d, *J* = 7.8 Hz, Ar), 6.64 (1 H, d, *J* = 7.8 Hz, Ar), 6.90–6.98 (2 H, m, Ar), 7.52 (1 H, s, Ar), 7.58 (1 H, d, *J* = 2 Hz, Ar).

^{13}C-NMR (50 MHz, $CDCl_3$): δ 17.1, 20.6, 20.8, 22.6, 28.3 (3 C), 29.5, 55.2, 55.3, 55.9, 78.2, 81.6, 111.7, 112.3, 127.4, 127.9, 128.1, 128.8, 129.6, 129.7, 132.5, 133.0, 153.8, 154.8, 156.2.



32c Ar = 2-OMe-5-Me-C_6H_3; **31c**

(4*S*)-5,5-Di(2-methoxy-5-methylphenyl)-4-isopropyloxazolidin-2-one 31c[136]

Potassium *tert*-butoxide (4.2 g, 37.8 mmol) was added to a stirred solution of the alcohol **32c** (14.0 g, 31.5 mmol) in dry THF (205 mL) at 0 ºC. After 2.5 h, the resulting suspension

was poured into a 10% aqueous solution of NH_4Cl (350 mL) and extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was crystallized from ethyl acetate to give oxazolidin-2-one **31c** (10 g, 86%).

mp. 266-269 ºC (Lit.:[136] 266-268 ºC).

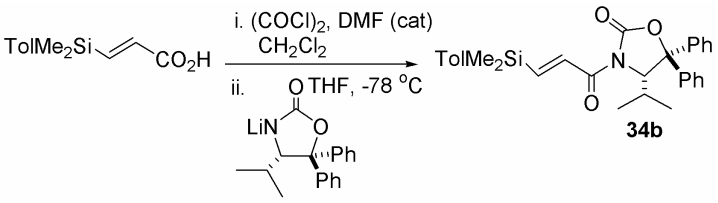
$[\alpha]_D^{25}$ −346 (*c* 0.5, $CHCl_3$) [Lit.:[136] $[\alpha]_D^{24}$ -346.6 (*c* 0.5, $CHCl_3$)].

R_f 0.4 ($CHCl_3$).

IR (KBr)**:** 3359, 1764, 1503 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.66 (3 H, d, *J* = 6.6 Hz, CH*Me*$_A$Me$_B$), 0.92 (3 H, d, *J* = 7.2 Hz, CHMe$_A$*Me*$_B$), 1.51–1.67 (1 H, m, *CH*Me$_A$Me$_B$), 2.27 (3 H, s, Ar*Me*), 2.32 (3 H, s, Ar*Me*), 3.43 (3 H, s, OMe), 3.51 (3 H, s, OMe), 4.76 (1 H, d, *J* = 1.6 Hz, NCH), 6.22 (1 H, br, NH), 6.62 (1 H, d, *J* = 8.2 Hz, Ar), 6.69 (1 H, d, *J* = 8.2 Hz, Ar), 6.97–7.05 (2 H, m, Ar), 7.24 (1 H, s, d, *J* = 1 Hz, Ar), 7.67(1 H, d, *J* = 2 Hz, Ar).

^{13}C-NMR (50 MHz, $CDCl_3$): δ 15.0, 20.6, 20.8, 21.4, 29.2, 55.5, 56.2, 61.6, 88.8, 111.3, 114.0, 127.9, 128.0, 128.7, 128.7, 129.0, 129.1, 129.5, 129.6, 152.9, 156.3, 159.8.



(4*S*)-3-*trans*-(2-Dimethyltolylsilyl)acryloyl-5,5-diphenyl-4-isopropyl-2-oxazolidin-2-one 34b

Following the procedure for the preparation of **34a**, (*E*)-3-[dimethyl(tolyl)silyl]propenoic acid **33b** (1.06 g, 4.8 mmol), oxazolidin-2-one **31b** (1.36 g, 4.8 mmol) and *n*-BuLi (3.2 mL, 1.5 *M* solution in hexane, 4.8 mmol) gave *N*-substituted oxazolidin-2-one **34b** (2.06 g, 89%) as a crystalline solid.

mp. 105–107 ºC (hexane-EtOAc).

$[\alpha]_D^{25}$ −163.95 (*c* 1.03, $CHCl_3$).

R_f 0.62 (hexane/EtOAc, 90:10).

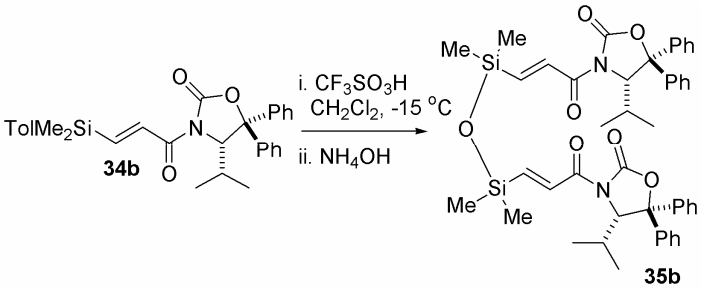
IR ($CHCl_3$): 3065, 3031, 2965, 2878, 1784, 1683, 1602, 1495, 1450, 1394, 1363, 1334, 1250, 1108, 1001, 762 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.39 (3 H, s, SiMe), 0.40 (3 H, s, SiMe), 0.76 (3 H, d, *J* = 6.6 Hz, CH$Me_A$$Me_B$), 0.89 (3 H, d, *J* = 6.8 Hz, CH$Me_A$$Me_B$), 1.91–2.06 (1 H, m, NCH*CH*Me_2), 2.33 (3 H, s, Ar-*Me*), 5.46 (1 H, d, *J* = 3.2 Hz, N*CH*CHMe_2), 7.16–7.66 (16 H, m, 2 × Ph, Ar, CH=CHCON).

^{13}C-NMR (50 MHz, $CDCl_3$): δ −3.2 (2 C), 16.3, 21.4, 21.7, 30.1, 64.4, 89.2, 125.6 (2 C), 125.9 (2 C), 127.9, 128.3 (2 C), 128.5, 128.8 (2 C), 128.8 (2 C), 132.7, 133.2, 133.8 (2 C), 138.2, 139.3, 142.2, 149.8, 152.8, 164.2.

MS (EI) *m/z*: 468 (M−15, 5%), 424 (16), 337 (21), 262 (14), 222 (34), 207 (100), 167 (40), 149 (55), 129 (22), 105 (24), 91 (16).

Anal. (Found: C, 75.02; H, 6.78; N, 2.91. $C_{30}H_{33}NO_3Si$ requires C, 74.50; H, 6.88; N, 2.90%).



1,1,3,3-Tetramethyl-1,3-di-{2-[3-(4*S*)-3-carbonyl-5,5-diphenyl-4-isopropyl-2-oxazolidin-2-one]ethenyl}disiloxane 35b

Following the procedure for the preparation of disiloxane **35a**, oxazolidin-2-one **34b** (1.8 g, 3.7 mmol) and trifluoromethanesulfonic acid (0.98 mL, 11.15 mmol, 3 equiv) at –15 ºC gave the disiloxane **35b** (1.2 g, 81%) as a colorless solid.

mp. 150 ºC (hexane-EtOAc).

$[\alpha]_D^{24}$ −193.2 (*c* 1.03, $CHCl_3$).

R_f 0.52 (hexane/EtOAc, 85:15).

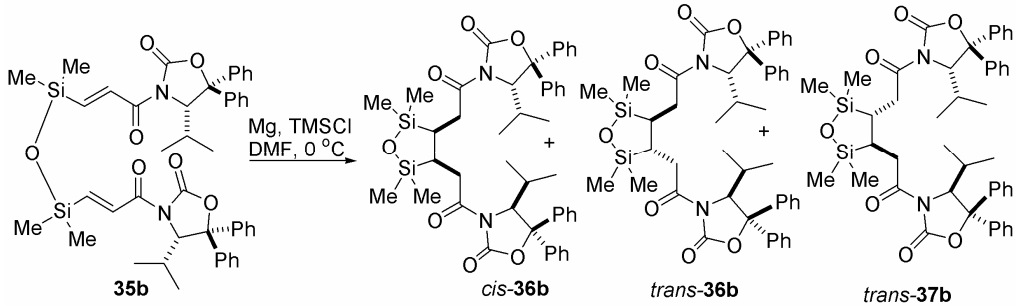
IR ($CHCl_3$): 3024, 2965, 2877, 1782, 1683, 1450, 1364, 1335, 1256, 1213, 1176, 1053, 752 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.18 (6 H, s, 2 × SiMe), 0.19 (6 H, s, 2 × SiMe), 0.77 (6 H, d, *J* = 6.8 Hz, 2 × CH$Me_A$$Me_B$), 0.89 (6 H, d, *J* = 7 Hz, 2 × CHMe$_A$$Me_B$), 1.91–2.06 (2 H, m, 2 × NCH*CH*Me_2), 5.45 (2 H, d, *J* = 3.2 Hz, 2 × N*CH*$CHMe_2$), 7.20–7.62 (24 H, m, 4 × Ph, 2 × CH=CHCON).

^{13}C-NMR (50 MHz, $CDCl_3$): δ 0.2 (4 C), 16.2 (2 C), 21.6 (2 C), 29.9 (2 C), 64.4 (2 C), 89.1 (2 C), 125.4 (4 C), 125.7 (4 C), 127.7 (2 C), 128.1 (4 C), 128.3 (2 C), 128.7 (4 C), 132.7 (2 C), 138.1 (2 C), 142.1 (2 C), 149.2 (2 C), 152.5 (2 C), 164.1 (2 C).

MS (EI) *m/z*: 823 (M+Na, 8%), 801 (M+H, 100).

Anal. (Found: C, 68.83; H, 6.59; N, 3.59. $C_{46}H_{52}N_2O_7Si_2$ requires C, 68.97; H, 6.54; N, 3.50%).



Reductive cyclization of 35b to give *trans*-36b, *trans*-37b and *cis*-36b

Following the procedure of intramolecular reductive cyclization of disiloxane **21a**, disiloxane **35b** (0.945 g, 1.18 mmol), magnesium turnings (0.344 g, 14.2 mmol) and TMSCl (1.8 mL, 14.2 mmol) gave a mixture of *trans*-**36b**, *trans*-**37b** and *cis*-**36b** (0.79 g, 83%). The residue was crystallized from hexane-ethyl acetate to give the major *trans*-**37b**

(0.28 g, 29%). The remaining portion (0.5 g, 54%) consisted of a mixture of all three isomers from which the individual isomers could not be separated by crystallisation or chromatography.

Data for *trans*-37b

mp. 93–95 ºC (hexane-EtOAc).

$[\alpha]_D^{26}$ −98.3 (*c* 0.6, $CHCl_3$).

R_f 0.51 (hexane/EtOAc, 85:15).

IR ($CHCl_3$): 3062, 3029, 2966, 2878, 1783, 1701, 1450, 1369, 1251, 1176, 929, 758 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ −0.43 (6 H, s, 2 × SiMe), 0.20 (6 H, s, 2 × SiMe), 0.77 (6 H, d, *J* = 6 Hz, 2 × CH*Me*$_A$Me$_B$), 0.86 (6 H, d, *J* = 8 Hz, 2 × CHMe$_A$*Me*$_B$), 1.00–1.05 (2 H, m, 2 × Me$_2$Si*CH*CH$_2$), 1.91–2.06 (2 H, m, 2 × NCH*CH*Me$_2$), 2.65 (2 H, dd, *J* = 11, 18.6 Hz, 2 × C*H*$_A$H$_B$CON), 3.32 (2 H, dd, *J* = 3.4, 18.6 Hz, 2 × CH$_A$*H*$_B$CON), 5.34 (2 H, d, *J* = 4 Hz, 2 × N*CH*CHMe$_2$), 7.26–7.50 (20 H, m, 4 × Ph).

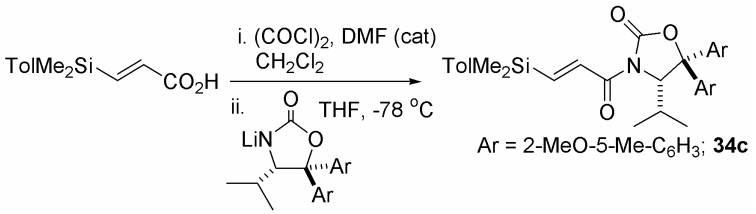
^{13}C-NMR (50 MHz, $CDCl_3$): δ −3.0 (2 C), 1.1 (2 C), 16.5 (2 C), 21.5 (2 C), 25.4 (2 C), 29.8 (2 C), 37.6 (2 C), 64.7 (2 C), 89.5 (2 C), 125.5 (4 C), 125.8 (4 C), 127.9 (2 C), 128.3 (4 C), 128.6 (2 C), 128.9 (4 C), 137.9 (2 C), 142.3 (2 C), 153.1 (2 C), 173.3 (2 C).

HRMS (ESI) *m/z*: Found MH^+ 803.3507, $C_{46}H_{55}N_2O_7Si_2$ requires 803.3542.

MS (EI) *m/z*: 825 (M+Na, 6%), 803 (M+H, 63), 279 (100), 132 (33).

Data for *trans*-36b from the mixture containing about 55% of *trans*-37b

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.03 (6 H, s, 2 × SiMe), 0.20 (6 H, s, 2 × SiMe), 0.72 (6 H, d, *J* = 6 Hz, 2 × CH*Me*$_A$Me$_B$), 0.86 (6 H, d, *J* = 8 Hz, 2 × CHMe$_A$*Me*$_B$), 0.93–1.05 (2 H, m, 2 × Me$_2$Si*CH*CH$_2$), 1.91–2.06 (2 H, m, 2 × NCH*CH*Me$_2$), 2.74 (2 H, dd, *J* = 11, 19.6 Hz, 2 × C*H*$_A$H$_B$CON), 3.17 (2 H, dd, *J* = 3.2, 19.6 Hz, 2 × CH$_A$*H*$_B$CON), 5.32 (2 H, d, *J* = 4 Hz, 2 × N*CH*CHMe$_2$), 7.23–7.50 (20 H, m, 4 × Ph).



(4*S*)-3-*trans*-(2-dimethyltolylsilyl)acryloyl-4-isopropyl-5,5-di(2-methoxy-5-methyl)-2-oxazolidin-2-one 34c

Following the procedure for the preparation of **34a**, (*E*)-3-[dimethyl(4-methylphenyl)silyl]propenoic acid **33b** (1.02 g, 4.6 mmol), oxazolidin-2-one **31c** (1.7 g, 4.6 mmol) and *n*-BuLi (3.1 mL, 1.5 *M* solution in hexane, 4.6 mmol) gave *N*-substituted oxazolidin-2-one **34c** (2.4 g, 91%) as a crystalline solid.

mp. 160–161 ºC (hexane-EtOAc).

$[\alpha]_D^{28}$ −215.8 (*c* 1.05, EtOAc).

R_f 0.69 (hexane/EtOAc, 85:15).

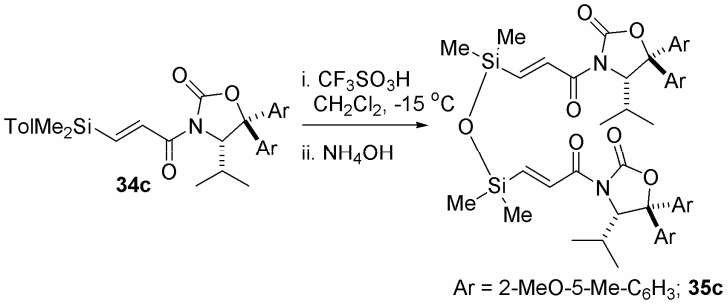
IR ($CHCl_3$): 3072, 3035, 3012, 2999, 2964, 2835, 1772, 1683, 1604, 1504, 1465, 1342, 1250, 1201, 1107, 1034, 910, 821, 730 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.39 (3 H, s, SiMe), 0.40 (3 H, s, SiMe), 0.73 (3 H, d, *J* = 6.8 Hz, CH*Me*$_A$Me$_B$), 0.97 (3 H, d, *J* = 7 Hz, CHMe$_A$*Me*$_B$), 1.67–1.82 (1 H, m, NCH*CH*Me$_2$), 2.23 (3 H, s, Ar-*Me*), 2.34 (3 H, s, Ar-*Me*), 2.36 (3 H, s, Ar-*Me*), 3.48 (3 H, s, O*Me*-Ar), 3.49 (3 H, s, O*Me*-Ar), 5.85 (1 H, d, *J* = 1.8 Hz, N*CH*CHMe$_2$), 6.66 (2 H, dd, *J* = 8.2, 10 Hz, Ar), 6.98–7.10 (2 H, m, Ar), 7.16–7.70 (8 H, m, Ar, CH=CHCON).

^{13}C-NMR (50 MHz, $CDCl_3$): δ −3.1 (2 C), 16.0, 20.7 (2 C), 21.4, 22.6, 30.1, 55.4, 56.0, 62.3, 89.0, 111.0, 113.8, 126.7, 127.6, 128.1, 128.7 (3 C), 128.9, 129.0, 129.1, 130.0 133.0, 133.9 (3 C), 139.2, 148.4, 152.7, 153.3, 156.2, 164.4.

MS (EI) *m/z*: 571(M, 3%), 556 (M−15, 2), 512 (15), 310 (26), 293 (18), 271 (20), 255 (28), 203 (55), 149 (100), 135 (45), 105 (20), 91 (14).

Anal. (Found: C, 71.61; H, 7.38; N, 2.89. $C_{34}H_{41}NO_5Si$ requires C, 71.42; H, 7.23; N, 2.45%).



1,1,3,3-Tetramethyl-1,3-di-{2-[3-(4*S*)-3-carbonyl-5,5-di(2-methoxy-5-methyl)-4-isopropyl-2-oxazolidin-2-one]ethenyl}disiloxane 35c

Following the procedure for the preparation of disiloxane **35a**, oxazolidin-2-one **34c** (1.32 g, 2.3 mmol) and TfOH (0.51 mL, 5.8 mmol, 2.5 equiv) at –15 ºC gave the disiloxane **35c** (0.81 g, 72%) as a colorless solid.

mp. 179–180 ºC (hexane-EtOAc).

$[\alpha]_D^{24}$ –235.8 (*c* 1.02, EtOAc).

R_f 0.65 (hexane/EtOAc, 75:25).

IR ($CHCl_3$): 3019, 2964, 2879, 2836, 1778, 1683, 16011, 1503, 1465, 1343, 1253, 1201, 1033, 760 cm^{-1}.

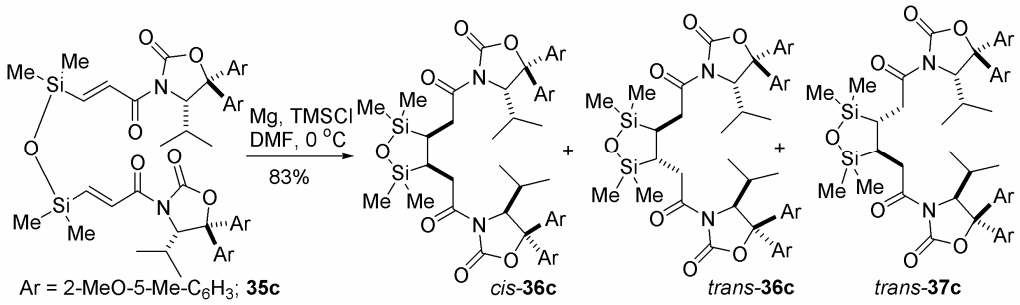
^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.20 (12 H, s, 4 × SiMe), 0.74 (6 H, d, *J* = 6.8 Hz, 2 × CH*Me*$_A$Me$_B$), 0.98 (6 H, d, *J* = 7.2 Hz, 2 × CHMe$_A$*Me*$_B$), 1.69–1.77 (2 H, m, 2 × NCH*CH*Me$_2$), 2.23 (6 H, s, 2 × Ar-*Me*), 2.35 (6 H, s, 2 × Ar-*Me*), 3.49 (12 H, s, 4 × O*Me*-Ar), 5.85 (2 H, d, *J* = 1.8 Hz, 2 × N*CH*CHMe$_2$), 6.65 (4 H, t, *J* = 9.2 Hz, Ar), 6.95–7.10 (4 H, m, Ar), 7.16 (1 H, s, Ar), 7.26 (2 H, d, *J* = 18.6 Hz, 2 × CH=*CH*CON), 7.36 (1 H, s, Ar), 7.61 (2 H, d, *J* = 18.6 Hz, 2 × *CH*=CHCON), 7.69 (1 H, s, Ar), 7.70 (1 H, s, Ar).

^{13}C-NMR (50 MHz, $CDCl_3$): δ 0.1 (4 C), 15.8 (2 C), 20.4 (4 C), 22.4 (2 C), 29.8 (2 C), 55.0 (2 C), 55.5 (2 C), 62.1 (2 C), 88.8 (2 C), 110.8 (2 C), 113.4 (2 C), 126.3 (2 C), 127.4

(2 C), 127.7 (2 C), 128.4 (2 C), 128.6 (2 C), 128.6 (2 C), 128.9 (2 C), 129.8 (2 C), 133.2 (2 C), 148.0 (2 C), 152.4 (2 C), 153.0 (2 C), 155.9 (2 C), 164.2 (2 C).

MS (EI) *m/z*: 999 (M+Na, 19%), 977 (M+H, 15), 500 (100).

Anal. (Found: C, 66.70; H, 7.17; N, 2.92. $C_{54}H_{68}N_2O_{11}Si_2$ requires C, 66.36; H, 7.01; N, 2.87%).



Reductive cyclization of 35c to give *trans*-36c, *trans*-37c and *cis*-36c

Following the procedure of intramolecular reductive cyclization of disiloxane **21a**, disiloxane **35c** (0.695 g, 0.71 mmol), magnesium turnings (0.21 g, 8.64 mmol) and TMSCl (1.1 mL, 8.68 mmol) gave a mixture of *trans*-**36c,** *trans*-**37c** and *cis*-**36c** (0.58 g, 83%). The residue was crystallized from hexane-ethyl acetate to give the major *trans*-**37c** (0.21 g, 30%). The remaining portion (0.37 g, 53%) consisted of a mixture of all three isomers from which the individual isomers could not be separated.

Data for *trans*-37c

mp. 250–252 ºC (hexane-EtOAc).

$[\alpha]_D^{24}$ −135.1 (*c* 0.6, $CHCl_3$).

R_f 0.63 (hexane/EtOAc, 75:25).

IR ($CHCl_3$): 2957, 2926, 2856, 1779, 1695, 1502, 1464, 1372, 1252, 1200, 1032 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ −0.20 (6 H, s, 2 × SiMe), 0.34 (6 H, s, 2 × SiMe), 0.74 (6 H, d, *J* = 6.6 Hz, 2 × CH$Me_A$$Me_B$), 0.95 (6 H, d, *J* = 7.2 Hz, 2 × CH$Me_A$$Me_B$), 1.09–1.14 (2 H, m, 2 × Me_2Si*CH*CH_2), 1.61–1.75 (2 H, m, 2 × NCH*CH*Me_2), 2.23 (6 H, s, 2 × Ar-*Me*),

2.35 (6 H, s, 2 × Ar-*Me*), 2.74 (2 H, dd, *J* = 11.4, 19 Hz, 2 × C$H_A$$H_B$CON), 3.44 (2 H, dd, *J* = 3, 19 Hz, CH$_A$$H_B$CON), 3.48 (12 H, s, 4 × O*Me*-Ar), 5.75 (2 H, d, *J* = 2 Hz, 2 × N*CH*CHMe$_2$), 6.65 (4 H, dd, *J* = 8.2, 12.8 Hz, Ar), 6.96–7.10 (4 H, m, Ar), 7.21 (1 H, s, Ar), 7.22 (1 H, s, Ar), 7.70 (1 H, s, Ar), 7.71 (1 H, s, Ar).

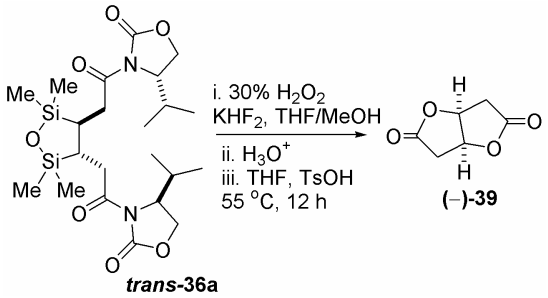
^{13}C-NMR (50 MHz, CDCl$_3$): δ –2.6 (2 C), 1.5 (2 C), 16.0 (2 C), 20.6 (2 C), 20.8 (2 C), 22.4 (2 C), 25.1 (2 C), 29.9 (2 C), 38.1 (2 C), 55.3 (2 C), 56.0 (2 C), 61.7 (2 C), 89.0 (2 C), 111.0 (2 C), 114.1 (2 C), 126.3 (2 C), 126.9 (2 C), 127.9 (2 C), 128.9 (6 C), 129.1 (2 C), 130.1 (2 C), 152.7 (2 C), 153.5 (2 C), 156.4 (2 C), 173.5 (2 C).

HRMS (ESI) *m/z*: Found MH$^+$ 979.4545, $C_{54}H_{71}N_2O_{11}Si_2$ requires 979.4591.

MS (EI) *m/z*: 1001 (M+Na, 11%), 979 (M+H, 100), 318 (14), 279 (45), 132 (7).

Data for *trans*-36c from the mixture containing about 5% of *trans*-37c

^{1}H-NMR (200 MHz, CDCl$_3$): δ 0.07 (6 H, s, 2 × SiMe), 0.37 (6 H, s, 2 × SiMe), 0.69 (6 H, d, *J* = 6.6 Hz, 2 × CH*Me$_A$*Me$_B$), 0.95 (6 H, d, *J* = 7 Hz, 2 × CHMe$_A$*Me$_B$*), 1.09–1.14 (2 H, m, 2 × Me$_2$Si*CH*CH$_2$), 1.61–1.75 (2 H, m, 2 × NCH*CH*Me$_2$), 2.24 (6 H, s, 2 × Ar-*Me*), 2.34 (6 H, s, 2 × Ar-*Me*), 2.93 (2 H, dd, *J* = 11.2, 19 Hz, 2 × C$H_A$$H_B$CON), 3.12 (2 H, dd, *J* = 4, 19 Hz, CH$_A$$H_B$CON), 3.46 (6 H, s, 2 × O*Me*-Ar), 3.48 (6 H, s, 2 × O*Me*-Ar), 5.76 (2 H, d, *J* = 1.5 Hz, 2 × N*CH*CHMe$_2$), 6.64 (4 H, dd, *J* = 8.4, 12 Hz, Ar), 6.96–7.10 (4 H, m, Ar), 7.14 (1 H, s, Ar), 7.15 (1 H, s, Ar), 7.66 (1 H, s, Ar), 7.67 (1 H, s, Ar).



(3*S*,4*S*)-Dihydroxyadipic-γ,γ′-dilactone (–)-39

Hydrogen peroxide (0.6 mL, 30%) was added to a stirred mixture of *trans*-**36a** (0.15 g, 0.3 mmol) and KHF_2 (0.14 g, 1.8 mmol) in THF/MeOH (6 mL, 1:1). After 24 h at 60 ºC, H_2O_2

(0.3 mL) was added to the reaction mixture followed by addition of THF/MeOH (2 mL, 1:1). After 15 h, the solvent was evaporated under reduced pressure. The white residue was triturated with hot EtOAc and filtered. The filtrate on evaporation gave the oxazolidin-2-one (35 mg, 90%). The solid residue was taken up in 0.2 molar methanolic HCl (10 mL) and evaporated. The residue was triturated with ethyl acetate and filtered. The filtrate was evaporated under reduced pressure and the residue was dissolved in THF (2 mL), TsOH (2 mg, 0.01 mmol) was added into it and the mixture was heated at 55 ºC for 12 h. Sodium bicarbonate (3 mg) was added into the reaction mixture, diluted with hot EtOAc, filtered and the filtrate was evaporated to give the lactone (−)-**39** (42 mg, 98%) as a solid.

mp. 122–124 ºC (hexane-EtOAc) (lit.:[139] mp. 122–123 ºC, for the antipode).

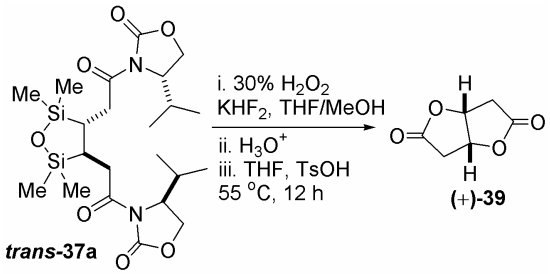
$[\alpha]_D^{23}$ −145.3 (*c* 0.64, H_2O) (lit.:[139] $[\alpha]_D^{19}$ +143 ± 2.5, *c* 0.785, H_2O for the antipode).

R_f 0.57 (hexane/EtOAc, 2:8).

IR ($CHCl_3$): 3023, 2993, 2958, 1783, 1401, 1343, 1309, 1191, 1165, 1051 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.83–3.04 (4 H, m, 2 × CH_2), 5.18–5.24 (2 H, m, 2 × CH).

^{13}C-NMR (50 MHz, $CDCl_3$): δ 35.1 (2 C), 78.3 (2 C), 172.9 (2 C).



(3*R*,4*R*)-Dihydroxyadipic-γ,γ′-dilactone (+)-39

Following the procedure of conversion of *trans*-**36a** to (−)-**39**, disiloxane *trans*-**37a** (0.1 g, 0.2 mmol) and H_2O_2 (0.7 mL, 30%) gave lactone (+)-**39** (25 mg, 88%) as a solid and oxazolidin-2-one **31a** (27 mg, 80%).

mp. 121–123 ºC (hexane-EtOAc) (lit.:[139] mp. 122–123 ºC).

$[\alpha]_D^{25}$ +142.11 (*c* 0.38, H_2O) (lit.:[139] $[\alpha]_D^{19}$ +143 ± 2.5, *c* 0.785, H_2O).

R_f 0.57 (hexane/EtOAc, 20:80).

IR ($CHCl_3$): 3023, 2993, 2958, 1783, 1401, 1343, 1309, 1191, 1165, 1051, 927, 836 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 2.83–3.04 (4 H, m, 2 × CH_2), 5.18–5.24 (2 H, m, 2 × CH).

^{13}C-NMR (50 MHz, $CDCl_3$): δ 35.1 (2 C), 78.3 (2 C), 172.9 (2 C).

This compound was also obtained by Fleming-Tamao oxidation of *trans*-**37b** in 85% yield. Recovery of oxazolidin-2-one **31b** was 75%. This compound was also obtained by Fleming-Tamao oxidation of *trans*-**37c** in 84% yield. Recovery of oxazolidin-2-one **31c** was 70%.

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CHAPTER 4

Magnesium-Induced Regiospecific *C*-Silylation of Suitably Substituted Enoates and Dienoates

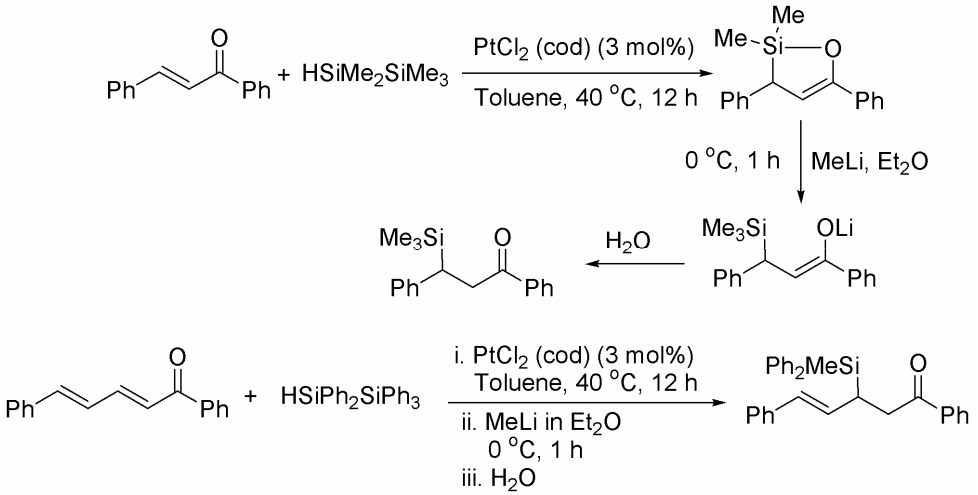
4.1 Introduction

With the invention of a reaction in which a silicon group can be converted to a hydroxyl group with retention of configuration, has opened up a new area of organic synthesis. A silicon group possesses very different properties compared to a hydroxy group or any protected form of a hydroxy group. The neutral silyl group is stable to wide range of reaction conditions and can be carried along a multistep synthesis. Similarly, the protection-deprotection sequence required for hydroxyl functions during total synthesis may sometimes be troublesome. More interestingly, a silicon group has certain properties that are complementary to a hydroxy group with respect to controlling of stereochemical aspects in organic reactions. The electropositive silicon centre and electronegative OH group introduce opposite electronic effects. In contrast to a hydroxy group, a silicon group does not possess a lone pair of electrons and does not coordinate with incoming organometallic reagents, electrophiles or Lewis acids.

Carbonyl compounds having a silyl group at the β-position are popular targets because of their versatile nature[47b] and also excellent surrogate for the acetate aldol[146] reaction. As described in Chapter 1, hydrosilylation is one of the most common pathways that provide β-silyl carbonyl compounds.[147] The reaction of 1,3-diphenyl-2-propenone with pentamethyldisilane proceeded well with $PtCl_2$(cod) (cod = 1,5-cyclooctadiene) to produce oxasilacyclopentene (Scheme 4.1).[147c] The same protocol using 1,5-diphenyl-2,4-diene-pentanone instead of 1,3-diphenyl-2-propenone also gave β-silylated product with good yield.

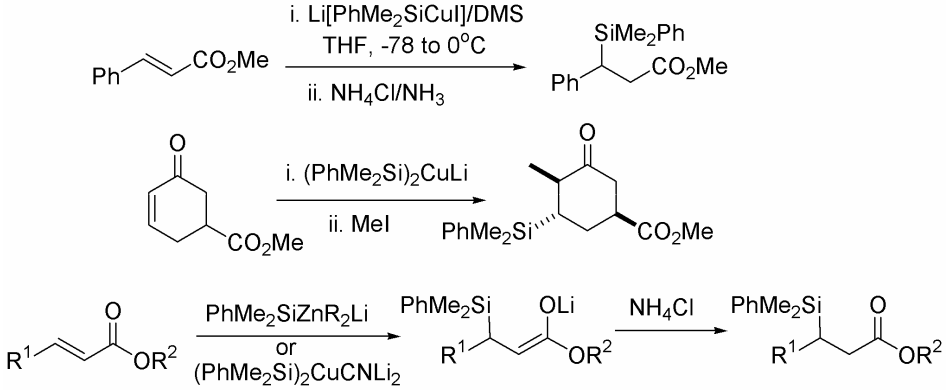
Silylmetalation of unsaturated carbonyl compounds[148] is another most popular and useful methodology for the synthesis of β-silyl carbonyl compounds. The silyl anions

usually have their counter-cations as Li, Na, K, Rb, Cs (Group 1); Mg (Group 2); Cu (Group 11) and Zn, Cd, Hg (Group 12) metals.[149]



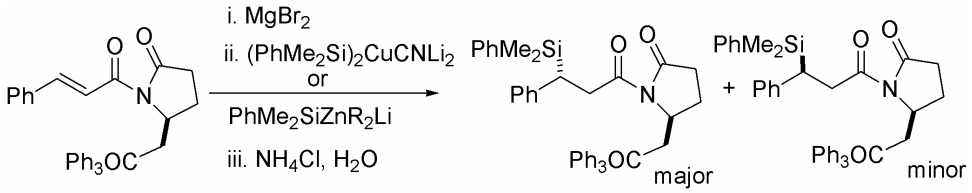
Scheme 4.1

The conjugate silylation of enone can be classified into two types of reactions. One is the stoichiometric conjugate addition of silyl anion to enones, and the other is the transition metal catalyzed reaction of disilane with enones to give γ-siloxyallylsilane. In 1976, Still[150] has shown that the conjugate addition to α,β-unsaturated carbonyl compounds with trimethylsilyllithium in presence of hexamethylphosphoric triamide (HMPA) produced β-silylated product. Two years later, Fleming *et al.*[151] has started reporting their observations in this area. Preparation of dimethyl(phenyl)silyllithium is easier than that of trimethylsilyllithium reagent. In presence of copper(I) iodide, dimethyl(phenyl)silyllithium undergoes conjugate addition to α,β-unsaturated carbonyl compounds to produce the corresponding β-silylated products in high yield (Scheme 4.2).[148a-c,151]

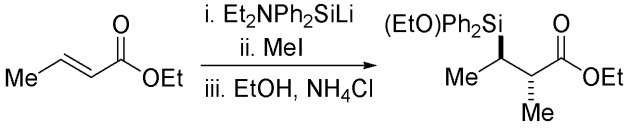


Scheme 4.2

The above conjugate addition has also been done with siliylzincate[148d-f] reagent, formed by the reaction of dimethyl zinc and silyllithium. The yield of the β-silylated product is comparatively higher while using silylzincate reagent than that of the siliylcuprate reagent. The asymmetric version of these reactions using α,β-unsaturated carbonyl compounds attached to chiral auxiliaries gave both the diastereoisomers with moderate to good diastereoselectivity (Scheme 4.3). Tamao and Ito[149e] have prepared three stable amino(phenyl)silyl anions by the standard direct reaction of aminochlorosilanes with lithium metal to produce (diaminosily1)lithium in quantitative yields. (Aminosilyl)lithium thus formed are also useful reagent as it undergoes conjugate addition to α,β-unsaturated ester to produce β-silylated product (Scheme 4.4).

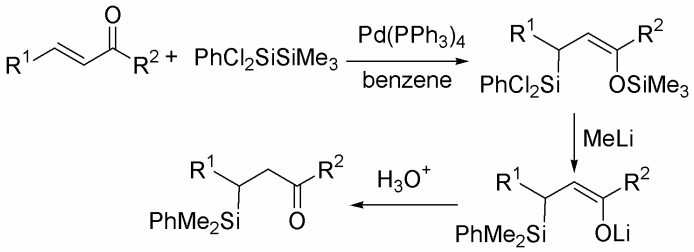


Scheme 4.3



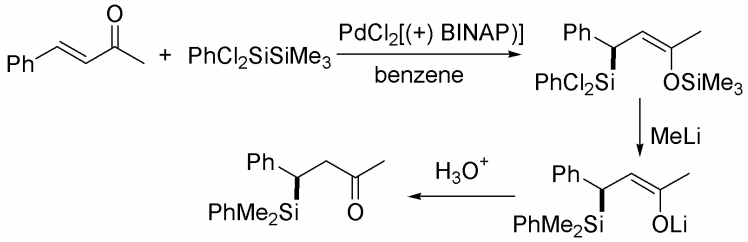
Scheme 4.4

Hayashi *et al.*[149] have given a major contribution to the conjugate silylation of enone by using transition metal catalyzed reaction of disilane. Palladium-catalyzed symmetric/asymmetric 1,4-addition of disilanes were thoroughly studied by them. 1,4-disilylation of α,β-unsaturated ketones was shown to proceed with 1,1-dichloro-1-phenyl-2-trimethyldisilane in the presence of a phosphine-palladium catalyst in benzene. Excess amount of methyllithium reacts with the disilylated product to give β-silyllithium enolate, which on hydrolysis produce β-silyl carbonyl compounds with satisfactory yield (Scheme 4.5).



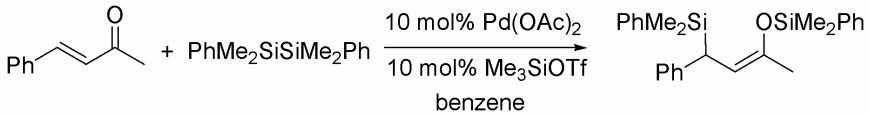
Scheme 4.5

Transition metal catalysts containing chiral ligands can, in principle, make the silylation result with the formation of optically active β-silyl carbonyl compounds. Optically active β-hydroxy carbonyl compounds were synthesized by palladium-catalyzed asymmetric 1,4-disilylation of α,β-unsaturated ketones followed by oxidative cleavage of the carbon-silicon bond. Catalyst, $PdCl_2$[(*R*)-(+)-BINAP] (BINAP = 2,2′-bis(di-phenylphosphino)-1,1′-binapththyl) was found to be the most effective chiral catalyst for enantioselective disilylation reactions (Scheme 4.6).[149a,b]



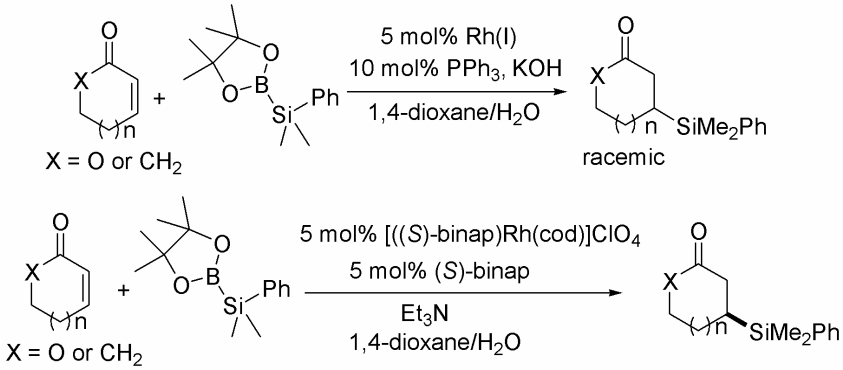
Scheme 4.6

Oxidative addition of disilanes is likely to be a crucial process in the palladium-catalyzed bis-silylation of the unsaturated bond which require the reactive disilanes and heating conditions. Thus, bis-silylation of α,β-unsaturated carbonyl compounds, which does not proceed *via* oxidative addition of disilane was an important issue. It was thought that the silylation of the η^3-siloxyallylpalladium complex with disilane can give the desired product under milder conditions, because the reaction of the η^3-allylpalladium intermediate with disilane has been known to give allylsilanes rather easily. The palladium/Me_3SiOTf-catalyzed addition of disilane to α,β-unsaturated carbonyl compounds was found to proceed smoothly to give the desired β-silylated products (Scheme 4.7)[149d] even under mild reaction conditions.



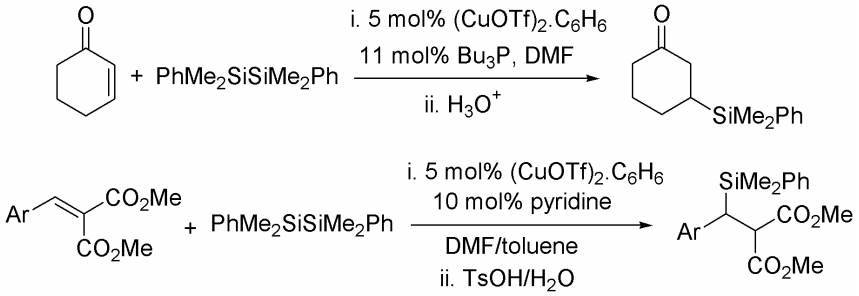
Scheme 4.7

Recently, Oestreich and co-workers[149f] have invented a novel carbon-silicon bond formation reaction by using Si–B linkage instead of Si–Si linkage (disilanes) and reacted with α,β-unsaturated ketones under catalytic conditions. It was shown that racemic as well as asymmetric silyl transfer took place when boron linked silane was treated with various α,β-unsaturated carbonyl compounds catalyzed by Rh(I)-complex (Scheme 4.8).



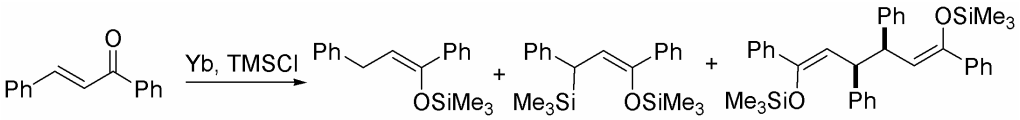
Scheme 4.8

The conjugate silylation reaction of α,β-unsaturated ketones with different disilanes were also seen to be catalyzed by $(CuOTf)_2$.benzene in presence of tributylphosphine to give the corresponding β-silylated product.[149g,h] Whereas, $(CuOTf)_2$.benzene-catalyzed disilylation of alkylidene malonates with disilanes provided higher yield of the β-silyl diesters when pyridine was used as Lewis base instead of phosphine (Scheme 4.9).



Scheme 4.9

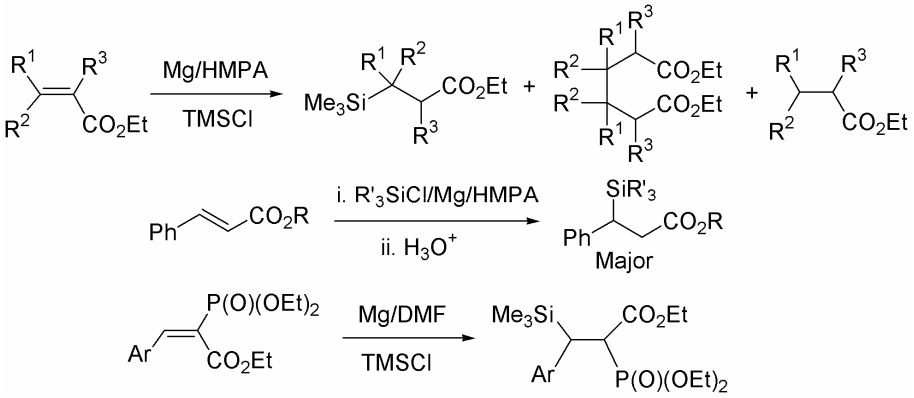
Reductive silylation of α,β-unsaturated carbonyl compounds is another important way of synthesizing β-C-silyl carbonyl compounds. The reducing agent used for the reductive silylation could be metals such as ytterbium,[113] magnesium[152a-c] and lithium.[152d] The outcome of these reactions depended upon the functionalities attached to the double bond, metal and the solvent used in these reactions. Reaction of chalcone with an equimolar amount of Yb in presence of excess TMSCl produced three products such as, reductive dimerization product, simple double bond reduction product and β-*C*-silylated product (Scheme 4.10).



Scheme 4.10

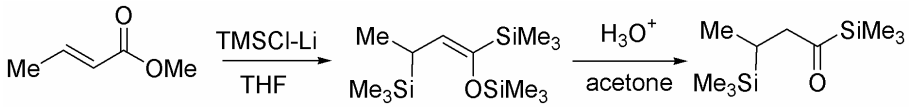
Picard *et al.*[152a,b] have shown that α,β-unsaturated esters in the presence of Mg and TMSCl in HMPA can produce three different types of products viz. C-silylation at the *β*-position with respect to the ester moiety, reductive dimerization and simple saturation of the double bond (Scheme 4.11). The quantum of each product depended on the

functionalities attached to the double bond. The *C*-silylation at the β-position was the main pathway when reacted with cinnamic esters and so the corresponding β-silylated hydrocinnamic ester/acid was formed as the major product (~50% yield).[152b] Similar results were obtained when β-aryl α-phosphorylacrylate derivatives[152c] were subjected under reductive silylation conditions using Mg/TMSCl/DMF system. Whereas, arylidene malonates/aceto acetates/cyanoacetates were not so selective under these conditions and produced in addition to the *C*-silylated product, a significant amount of double bond reduced product.



Scheme 4.11

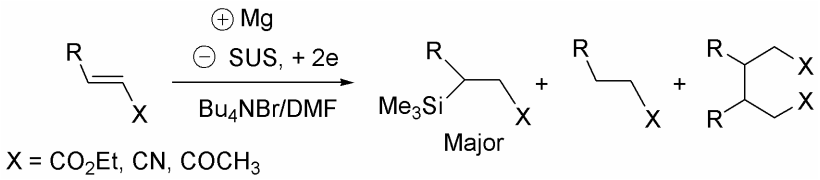
TMSCl/Li/THF system[152d] had also been used for the silylation of unsaturated carbonyl compounds. The β-silylation along with silylation of the ester was found to be the major product when methyl crotonate was treated with Li/TMSCl/THF system (Scheme 4.12).



Scheme 4.12

Electrochemical methods have also been used although rarely to produce silicon-carbon bond at the β-position of the α,β-unsaturated carbonyl compounds. Reductive trimethylsilylation of β-aryl-α,β-unsaturated ketones, esters and nitriles using a sacrificial

Mg anode in an undivided electrochemical cell[152e] mainly produced the β-*C*-silylated products in moderate yields (Scheme 4.13). While α,β-unsaturated aldehydes and ketones under these conditions preferred for reductive dimerization[127] to generate bis-(enol silyl) ethers with very high regioselectivity (Scheme 3.18, Chapter 3).

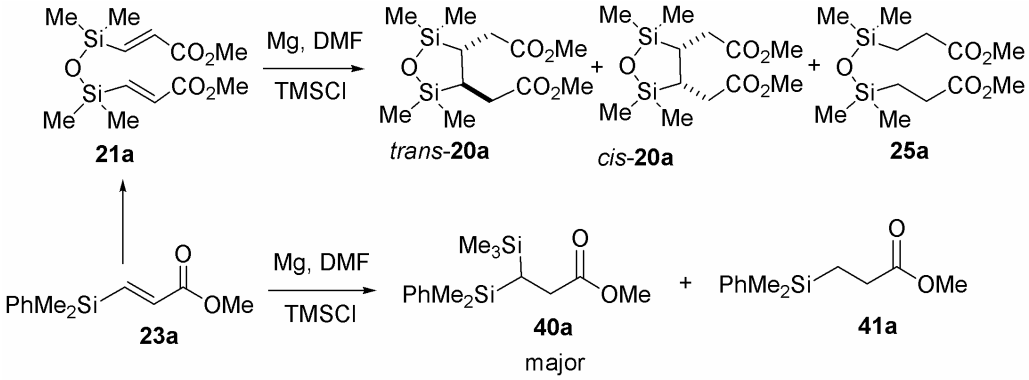


Scheme 4.13

4.2 Present Work

Reductive coupling reactions using Mg/TMSCl/DMF system on silicon-tethered diacrylic esters or amides (Chapter 3) preferred for intramolecular reductive coupling of the two acrylic units leading to 3,4-bis-silyl substituted adipic acid derivatives with very high selectivity without any *C*-silylation at the β-position (Scheme 4.14). We, therefore, became curious to know the outcome of this reductive dimerization protocol on the monomeric esters viz. β-dimethyl(aryl)silylacrylates **23**. Which pathway it would follow, reduction, *C*-silylation or dimerization? When β-dimethyl(phenyl)silylacrylate **23a** was subjected under our reported[153] (as described in Chapter 3) conditions (reactant concentration 0.1 *M* in DMF, 12 equiv each of Mg and TMSCl with respect to silyl acrylate, at 0 °C), it was gratifying to note that the reaction took place with complete consumption of starting material. Surprisingly, the crude reaction product showed the formation of methyl 3-dimethyl(phenyl)silyl-3-trimethylsilylpropionate **40** associated with a small amount of double bond reduced product **41**. Thus, the above observation of β-*C*-silylation reaction prompt us to do an elaborate study of our 'substrate based' diversity oriented synthetic strategy by using Mg/DMF/silyl chloride system as a common reagent

and varying the substrate to produce a diverse skeletons.

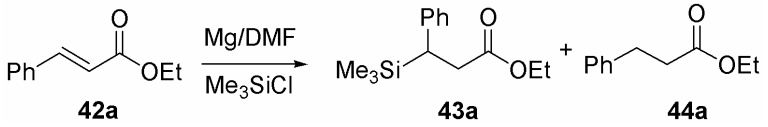


Scheme 4.14

4.2.1 Optimization of the reaction conditions for the synthesis of β-*C*-silylated cinnamates

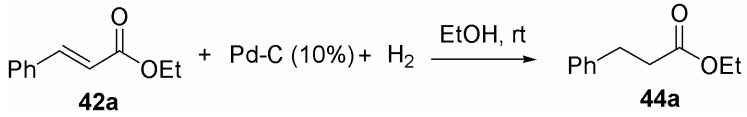
Prior to work with β-dimethyl(aryl)silylacrylates **23**, we decided to find out a suitable conditions for the reductive silylation of ethyl cinnamate as it is known[152b] to react with Mg/TMSCl/HMPA system to produced β-*C*-silylated product along with reductive dimerization and simple double bond reduction product (Scheme 4.11). A trial set of conditions were performed to optimize the process. Therefore, TMSCl (12 equiv) was added to a stirred suspension of Mg (12 equiv) and ethyl cinnamate **42a** (1 equiv, 0.1 *M*) in DMF at 0 °C and stirred for 1.5 h. We were pleased to see that the reaction took place with complete consumption of the starting material (Scheme 4.15). The crude reaction product indeed showed the formation of ethyl β-phenyl β-trimethylsilyl propionate **43a** associated with a small amount of double bond reduced product, ethyl dihydrocinnamate **44a** (**43a**:**44a** = 9/1 as revealed by ^{1}H NMR). An authentic sample of ethyl dihydrocinnamate **44a** was also synthesized form ethyl cinnamate by the palladium-charcoal reduction reaction (Scheme 4.16). No reductive dimerization product could be detected from the crude product. The *C*-silylated product **43a** was also isolated in 76% yield. To improve

upon the yield and selectivity, the procedure was then modified by adding ethyl cinnamate to the mixture of Mg and TMSCl under various conditions as presented in Table 4.1.



42a **43a** **44a**

Scheme 4.15



42a **44a**

Scheme 4.16

Table 4.1: Optimization of conditions for the reductive silylation of ethyl cinnamate[a]

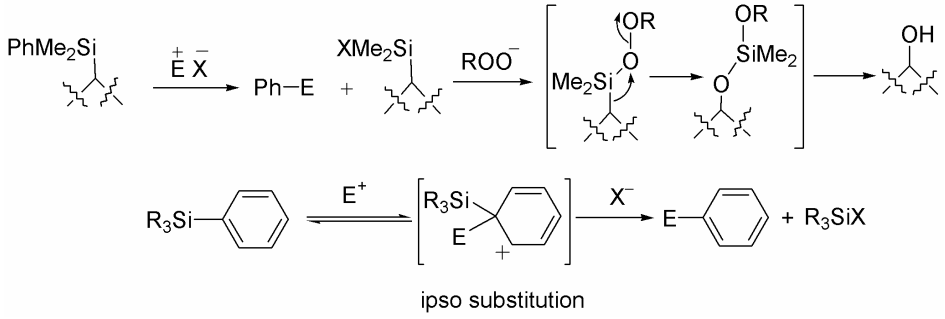
Entry	Me_3SiCl (equiv)	Conc. of **42a** (*M*) in DMF	Temperature (ºC)/ time (h)	**43a:44a**[b]	Yield of **43a** (%)[c]
1	3	0.1	0/1.5	85:15	68
2	6	0.1	0/1.5	91:9	75
3	12	0.1	0/1.5	91:9	76
4	15	0.1	0/1.5	91:9	76
5	20	0.1	0/1.5	91:9	76
6	6	0.2	0/1.5	92:8	77
7	6	0.06	0/1.5	90:10	73
8	6	0.05	0/1.5	89:11	72
9	6	0.1	– 15/1.5	71:19	50
10	6	0.2	30/0.5	95:5	84
11	6	0.2	65/0.15	91:9	79
12	6	0.2	30/0.5	94:6	78[d]
13	6	0.2	30/1	94:6	73[e]
14	6	0.2	30/1.5	93:7	70[f]

[a] Unless stated, 12 equiv of Mg metal was used; [b] Ratio determined by ^1H NMR; [c] Yield of homogeneous material obtained after silica-gel chromatography; [d] 9 equiv of Mg metal was used; [e] 6 equiv of Mg metal was used; [f] 3 equiv of Mg metal was used.

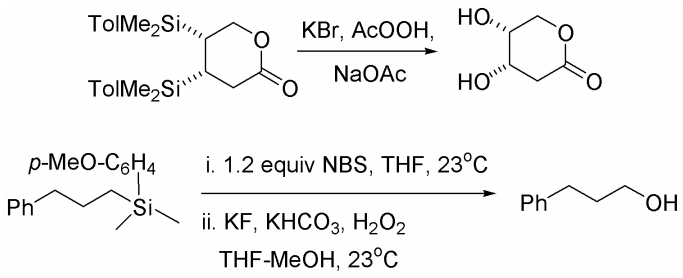
As our study aimed to introduce various silyl groups, optimization of the quantity of silyl chloride was therefore essential. We began our studies with the use of 3 equiv of TMSCl with respect to ethyl cinnamate at 0 ºC (Table 4.1, entry 1). Increasing the proportion of TMSCl from 3 equiv to 6 equiv reduced the formation of the reduction product **44a** and the overall yield was also improved (Table 4.1, entry 2). Further increase in TMSCl quantity did not improve the yield of the silylated product **43a** much (Table 4.1, entries 3–5). Increasing the reactant concentration did not change the selectivity or the yield while reactions under dilute conditions produced more double bond reduction product **44a** (Table 4.1, entries 6–8). When the reaction temperature was lowered, the selectivity of *C*-silylation versus double bond reduction deteriorated (Table 4.1, entry 9) and also the isolated yield of **43a** decreased significantly. Interestingly, carrying out the reaction at room temperature (30 ºC) increased the reaction rate, the yield of product **43a** and the selectivity of the reaction (Table 4.1, entry 10). Further increase in the reaction temperature shortened the reaction time but yield and selectivity dropped marginally (Table 4.1, entry 11). We also varied the quantity of magnesium (9–3 equiv; Table 4.1, entries 12–14) and carried out the silylation reaction of ethyl cinnamate with 6 equiv of TMSCl in each case at room temperature. The β-silylated product **43a** was formed in all cases but required longer reaction time. Although, the ratio of silylation to reduction *i.e.* the formation of **43a/44a** did not change, significant drop in the isolated yield of **43a** was observed. The best condition is therefore to add the ethyl cinnamate to a mixture of 6 equiv of TMSCl, 12 equiv of Mg in DMF (0.2 M) at 30 ºC for 0.5 h (Table 4.1, entry 10). Under these conditions the *C*-silylated product **43a** was isolated in 84% yield with the double bond reduction product **44a** now found to be negligible (~5%). The reduction product **44a** was easily separated from *C*-silylated product **43a** by column chromatography.

4.2.1a *C*-Silylation at the β-position of ethyl cinnamates using different silyl chlorides

Although Me_2PhSi group is equivalent to a hydroxyl group, it is not the most easily oxidizable group. The proposed mechanism (Scheme 4.17)[154] shows that the phenyl group undergoes an *ipso*-substitution by first reacting with an electrophile such as bromine or mercuric acetate. It is therefore expected that electron rich aryl ring would make this ipso-substitution more facile. This has been demonstrated by converting dimethyl(4-methylphenyl)silyl[118,124] and (2-methoxyphenyl)dimethylsilyl groups[155] (Scheme 4.18) to a hydroxyl functionality under milder conditions and better yields.



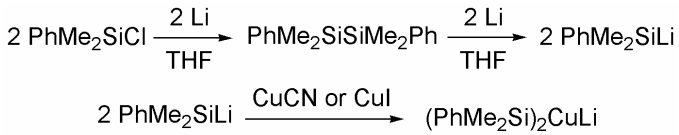
Scheme 4.17



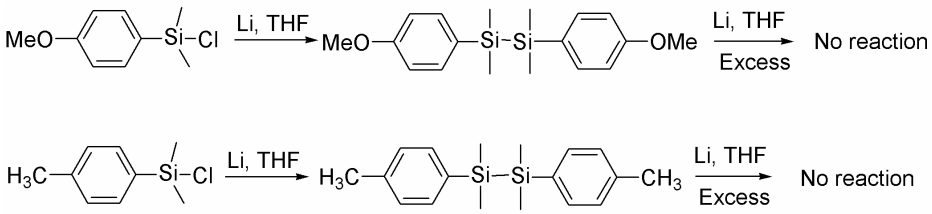
Scheme 4.18

The dimethyl(phenyl)silyl lithium is usually prepared by the reaction of (phenyl)dimethylsilyl chloride and two equivalents of lithium in THF. Reaction of (phenyl)dimethyl silyllithium with equimolar amount of copper(I) cyanide/iodide generates the silylcuprate which then undergoes conjugate silylation to acrylate systems easily (Scheme 4.19). This process is not applicable to a silyl group with an electron-rich

aryl substituent. The major hurdle was the preparation of dimethyl(aryl)silyllithiums from the corresponding dimethyl(aryl)silyl chloride having electron rich aryl groups. Dimethyl(aryl)silyl chloride in Li/THF suspension reacts to form the corresponding disilane with low yield which does not cleave even in presence of excess amount of Li (Scheme 4.20).[156a,b] So the popularity of Me_2PhSi group remained because of the easy preparation of $Me_2PhSiLi$[156c,d] from the commercially available silyl chloride and facile conjugate additions of mono-silylcuprate[156e,f] or bis-silylcuprate[148a-c,151] (Scheme 4.2) reagents derived from it to unsaturated carbonyl compounds.

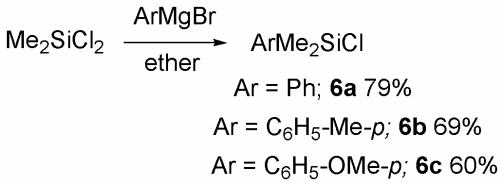


Scheme 4.19



Scheme 4.20

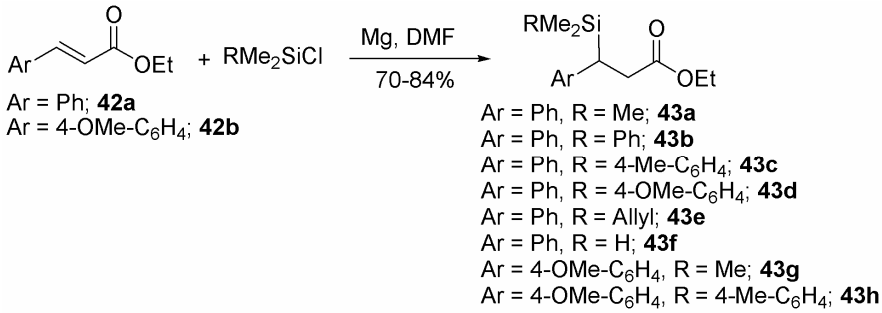
As suitable substituents on silicon, especially electron rich aryl groups make the silyl group as a potent masked hydroxyl group, different (aryl)silyl chlorides **6a-c** were synthesized from dichlorodimethylsilane *via* Grignard reaction (Scheme 4.21).



Scheme 4.21

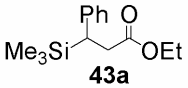
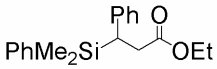
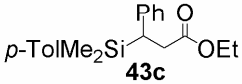
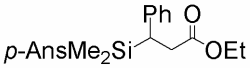
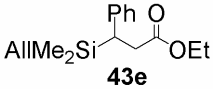
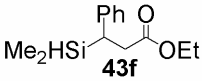
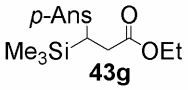
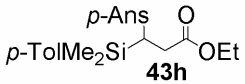
To generalize the Mg/TMSCl/DMF system for efficient reductive *C*-silylation at the β-position of ethyl cinnamates, reductive silylation with $PhMe_2SiCl$ and silyl chlorides which do not form the corresponding silyllithium easily such as *p*-$TolMe_2SiCl$, *p*-

$AnsMe_2SiCl$ and $AllMe_2SiCl$ were pursued. All these silyl groups[118,124,157] are also known to be the surrogate of the hydroxyl group. The results of reductive silylation under the optimized conditions are presented in Scheme 4.22 and Table 4.2.



Scheme 4.22

Table 4.2: Reductive silylation of cinnamates with various silyl chlorides

Entry	Cinnamate	Silyl chloride	Product	Yield (%)[a,b] of **43**
1	**42a**	Me_3SiCl	 **43a**	84
2	**42a**	$PhMe_2SiCl$	 **43b**	75
3	**42a**	*p*-$TolMe_2SiCl$	 **43c**	75
4	**42a**	*p*-$AnsMe_2SiCl$	 **43d**	80
5	**42a**	$AllMe_2SiCl$	 **43e**	89
6	**42a**	Me_2SiHCl	 **43f**	85
7	**42b**	Me_3SiCl	 **43g**	70
8	**42b**	*p*-$TolMe_2SiCl$	 **43h**	71

[a] Reaction time was 30 min in all the reactions; [b] Isolated yield.

In all cases the β-silylated product **43** (Fig. 4.1–4.4) was obtained in very good yield and purity (Table 4.2, entries 1–6). Even, chlorodimethylsilane reacts very cleanly to produce the corresponding β-silylated product **43f** in high yield (Table 4.2, entry 6). Electron donating substituent at the phenyl ring of the substituted ethyl cinnamate did not hinder the reaction (Table 4.2, entries 7, 8).

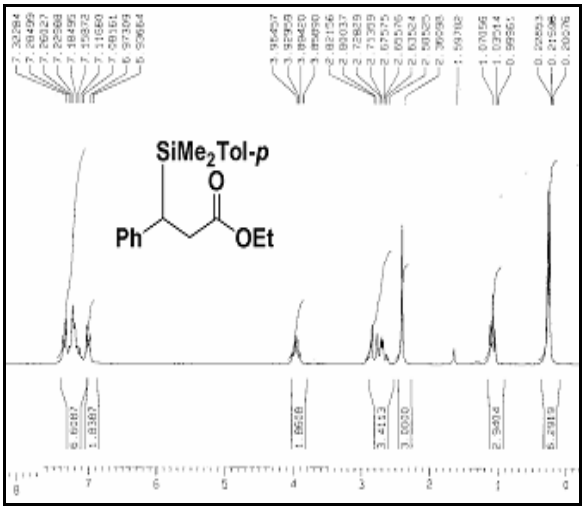


Figure 4.1: ^{1}H NMR of 43c

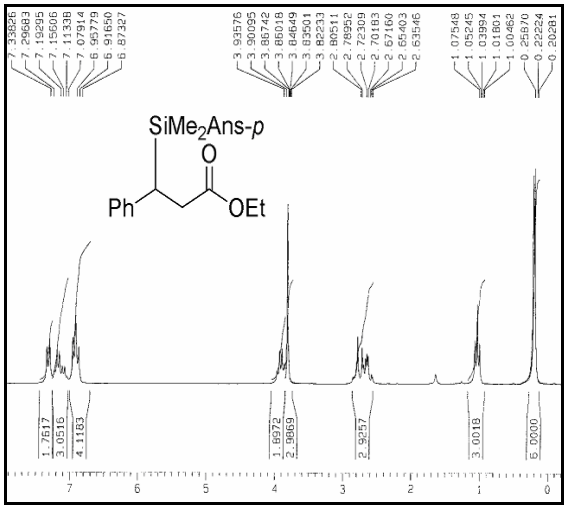


Figure 4.2: ^{1}H NMR of 43d

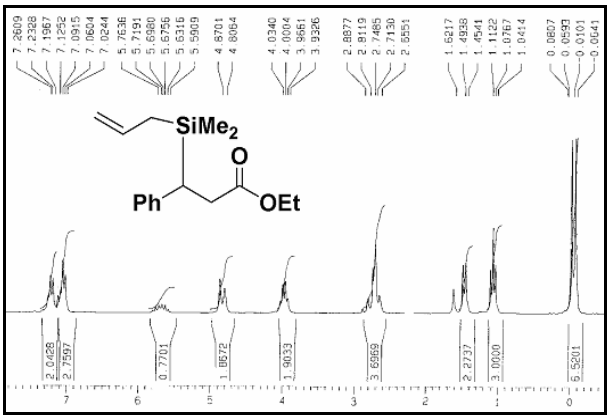


Figure 4.3: ^{1}H NMR of 43e

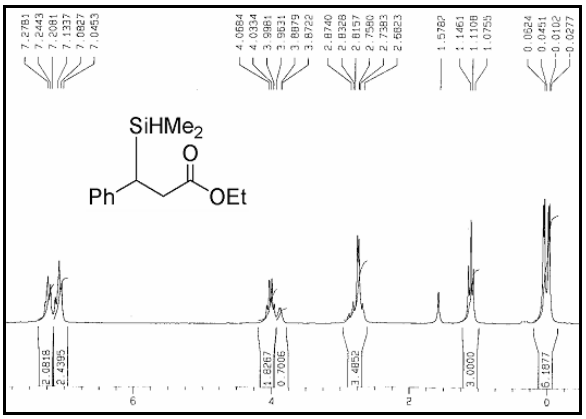
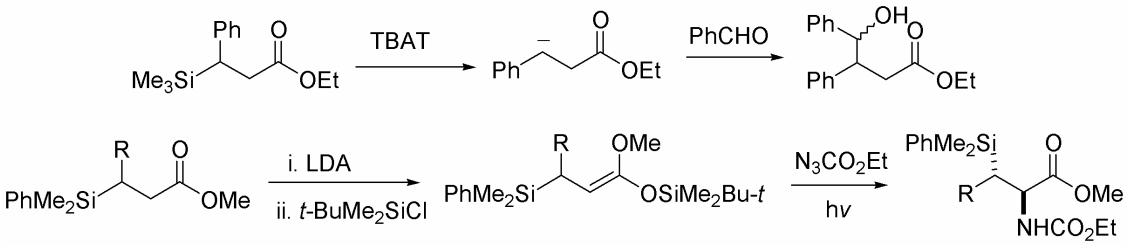


Figure 4.4: ^{1}H NMR of 43f

It is pertinent to mention here that the β-aryl-β-silyl propionate thus formed can be considered as an ester homoenolate. Tetrabutylammonium triphenyldifluorosilicate (TBAT) can cause desilylation to generate aryl and silyl stabilized carbanion which can be trapped with different electrophiles.[158a] As homoenolates are considered equivalent to

umpolung of acrylates, the present methodology is thus amounted to overall umpolung generation while making the silylated compounds from the acrylates as well as their possible uses. The β-silylated silyl ketene acetals with (ethoxycarbonyl)nitrene, generated by photolysis of N_3CO_2Et, produces β-silylated *N*-(ethoxycarbonyl)-α-amino esters. The attack of the electrophile was shown to be *anti* to the silyl group (Scheme 4.23).[158b]

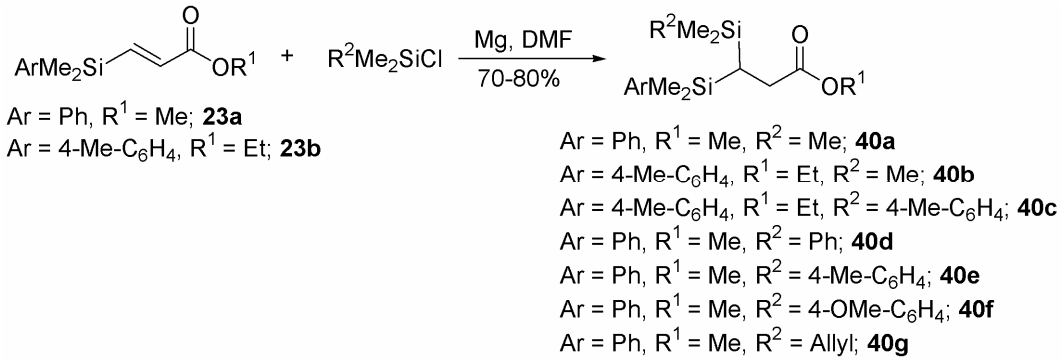


Scheme 4.23

4.2.2 *C*-silylation of β-silyl acrylates to synthesize β,β-disilylated acrylates

We next turned our attention to know the fate of β-silyl acrylates under these optimized reductive silylation conditions using Mg/chlorosilane/DMF system at 30 °C. β-silyl acrylates **23a** and **23b** was prepared following the reported procedures[159] using cobalt carbonyl mediated silylation of ethyl/methyl acrylate as shown in Chapter 3, Scheme 3.14. When β-dimethyl(aryl)silyl acrylate **23a** and **23b** were subjected under the reductive silylation conditions using Mg/silyl chloride/DMF system, the β,β-disilylated products were isolated (Scheme 4.24). Treatment of β-dimethyl(phenyl)silyl acrylate **23a** under our optimized reductive silylation conditions with TMSCl produced the corresponding silylated product **40a** in good yield (Table 4.3, entry 1). β-dimethyl(4-methylphenyl)silyl acrylate ethyl ester **23b** under the above reaction conditions provide **40b** in 81% isolated yield (Table 4.3, entry 2). Although a trace amount (<5%) of reductive dimerization product was formed, no double bond reduction could be seen in the crude reaction product. A similar clean reaction took place for **23b** when TMSCl was replaced by dimethyl(4-

methylphenyl)silyl chloride (Table 4.3, entry 3). The reductive *C*-silylation was then repeated with the silyl acrylate methyl ester **23a** using various silyl chlorides as presented in Table 4.3. The desired β,β-disilylated products (Fig. 4.5-4.8) **40d**–**40g** were formed in moderate to good yield.



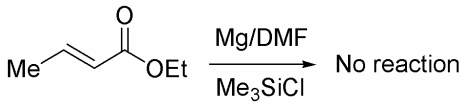
Scheme 4.24

Table 4.3: Reductive silylation of β-silyl substituted acrylates 23[a]

Entry	Acrylate	Silyl chloride	Product	Yield (%)[b]
1	**23a**	Me_3SiCl	Me_3Si, $PhMe_2Si$, OMe **40a**	70
2	**23b**	Me_3SiCl	Me_3Si, *p*-$TolMe_2Si$, OEt **40b**	81
3	**23b**	*p*-$TolMe_2SiCl$	*p*-$TolMe_2Si$, *p*-$TolMe_2Si$, OEt **40c**	79
4	**23a**	$PhMe_2SiCl$	$PhMe_2Si$, $PhMe_2Si$, OMe **40d**	71
5	**23a**	*p*-$TolMe_2SiCl$	$PhMe_2Si$, *p*-$TolMe_2Si$, OMe **40e**	70
6	**23a**	*p*-$AnsMe_2SiCl$	$PhMe_2Si$, *p*-$AnsMe_2Si$, OMe **40f**	70
7	**23a**	$AllMe_2SiCl$	$PhMe_2Si$, $AllMe_2Si$, OMe **40g**	72

[a] 12 equiv of Mg metal and 6 equiv of silyl chloride were used in all experiments and the reaction time was 30-60 min; [b] Yield of homogeneous material obtained after silica-gel chromatography.

Compared to ethyl ester **23b**, methyl ester **23a** produced slightly more amount of the reductive dimerization products (10–15%) as judged from the crude reaction product by ^{1}H NMR affecting the isolated yields of β,β-disilylated products **4d**–**4g** (Table 4.3, entries 1, 4–7). The reactivity of β-dimethyl(aryl)silyl acrylate **23a** and **23b** was slightly less than that of ethyl cinnamate **42.** Also, dimethyl(aryl)silyl chloride took longer reaction time than trimethylsilyl chloride when reacted with β-dimethyl(aryl)silyl acrylates. However, acrylates with a β-alkyl group viz. ethyl crotonate or ethyl 5-phenyl-2-pentenoate under the same conditions did not react (Scheme 4.25). After prolonged stirring at room temperature some unidentified products were formed presumably by cross reaction with the solvent *i.e.* DMF under the reaction conditions.



Scheme 4.25

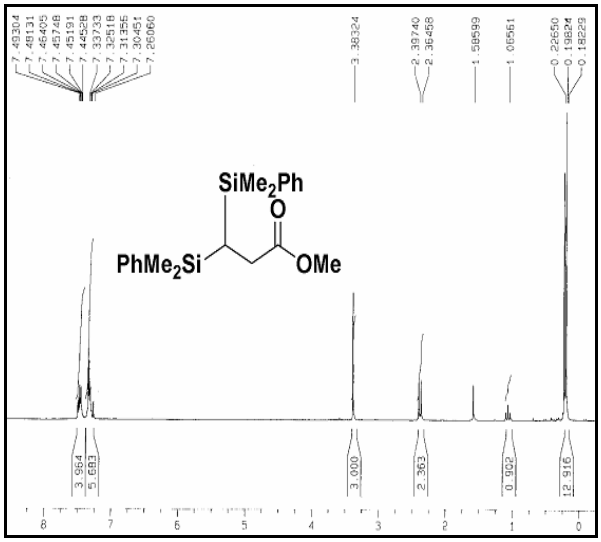


Figure 4.5: ^{1}H NMR of 40d

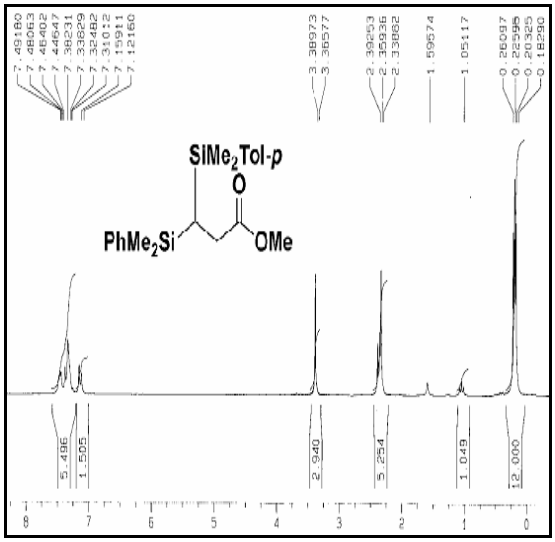


Figure 4.6: ^{1}H NMR of 40e

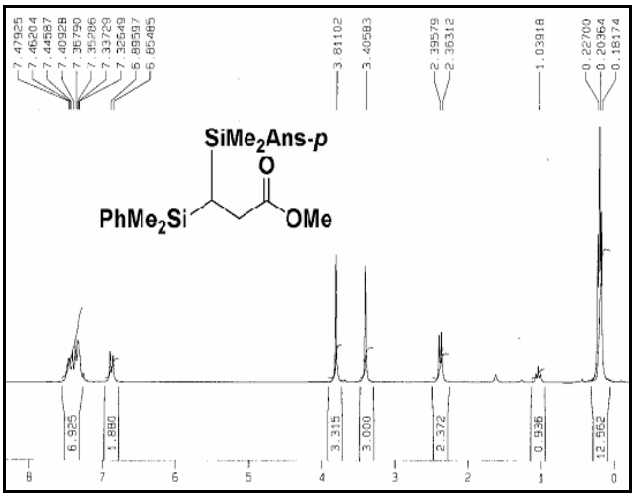


Figure 4.7: ^{1}H NMR of 40f

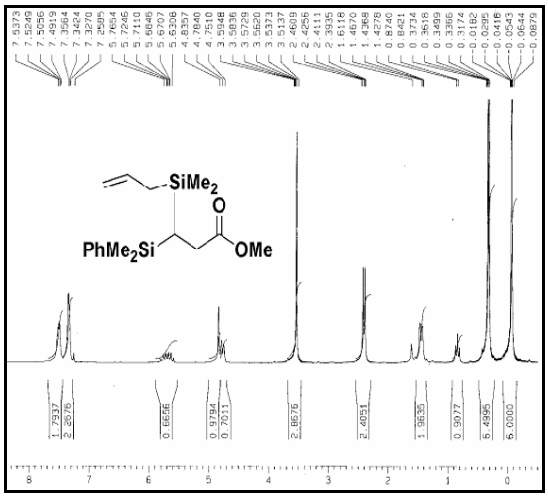
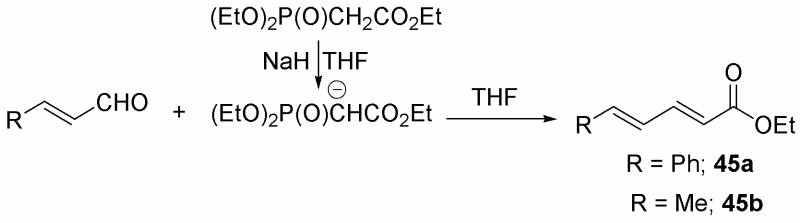


Figure 4.8: ^{1}H NMR of 40g

4.2.3 Reductive silylation of δ-aryl substituted dienoates

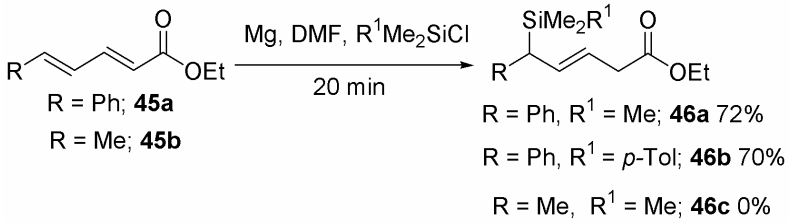
Reductive silylation on dienic esters can produce regio-isomeric *C*-silylated products. Therefore dienic ester **45a** and **45b** were prepared by Horner-Wittig reaction using triethyl phosphonoacetate, sodium hydride and the α,β-unsaturated aldehyde (Scheme 4.26).



Scheme 4.26

When the dienic ester **45a** was treated under the optimized reductive silylation conditions as described for ethyl cinnamate, (Scheme 4.27) using TMSCl, the allyl silane **46a** (Fig. 4.9) was formed without a trace of the other regioisomer. Moreover, the allylsilane was also formed with high stereoselectivity where (*E*)-isomer was found to be the major product (*E*/*Z* = 86/14 by GC) as revealed from the ^{1}H NMR coupling constant values of the olefinic protons (*J* = 16 Hz). While changing the silyl chloride from TMSCl

to *p*-TolMe$_2$SiCl, the corresponding allyl silane **46b** was formed in good yield. Here also (*E*)-isomer of **46b** was contaminated with a small amount of the (*Z*)-isomer (19%).



Scheme 4.27

Interestingly, alkyl substituted dienoate **45b** under the same conditions did not provide the desired allyl silane **46c**. Instead, some unidentified oligomeric products were formed. The allylsilanes are known as useful synthetic intermediates and a number of research groups had paid attention towards the synthesis of functional allysilanes as stated in Chapter 2. The present synthesis of highly functionalized allylsilanes and the additional ester functionality at the terminal of the allysilane would enhance their utility.

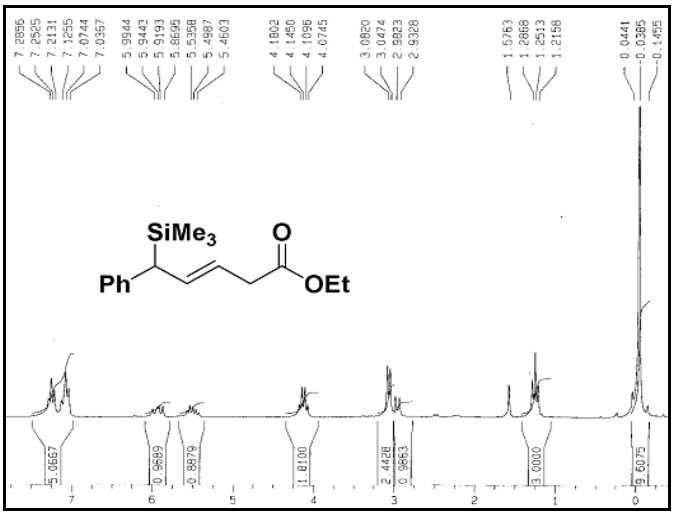
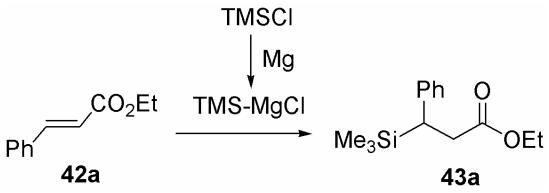


Figure 4.9: ^{1}H NMR of 46a

4.2.4 Investigation on plausible mechanism in the reductive β-*C*-silylation reaction

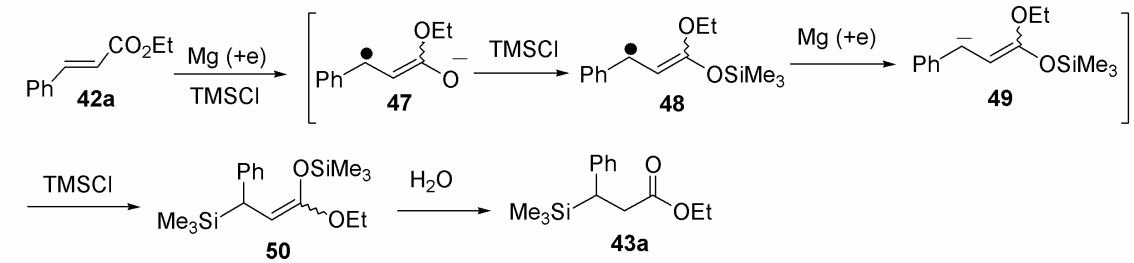
The reductive β-*C*-silylation of cinnamate can occur by two pathways. The silyl chloride can react with magnesium metal to give intermediate silyl Grignard species

which then undergo 1,4-addition to cinnamate **42a** to give the product **43a** (Scheme 4.28). The other possibility is the single electron transfer from Mg metal to the cinnamate, activated by silyl chloride, to generate a benzyl radical which accepts another electron from Mg to give the anion species that is quenched by the silyl chloride to give the β-*C*-silylated product. The former pathway seems to be not operative in the present case. When a mixture of TMSCl and Mg metal in DMF was stirred at room temperature and the supernatant was added to ethyl cinnamate **42a**, no silyl addition product **43a** was observed. No reaction also took place when a DMF solution of ethyl cinnamate was added to the residual Mg metal. But the desired product **43a** was formed when 6 equiv of TMSCl was added to this mixture. Although silyl Grignard reagents are known to be produced from silyl chlorides having aryl substitutions, trialkylsilyl chlorides do not form such species under normal conditions.[160]



Scheme 4.28

The alternate and most plausible mechanism for the reductive *C*-silylation is depicted in Scheme 4.29. Without TMSCl, there was no reaction including the double bond reduction. The role of the silyl chloride was manifold. First, it probably activates the metal by cleaning the oxide/hydroxide/carbonate coating from the surface.



Scheme 4.29

TMSCl is also known to increase the reduction potential value of octanoylimidazole from −2.00 to −1.04 V vs SCE[161a] or acetophenone −2.34 to −1.38 V vs SCE.[161b] It is logically expected that TMSCl would increase the reduction potential value of the cinnamate substrate thus accelerates the single electron transfer from Mg to the substrate. Its presence also increases the chemoselectivity of the reaction in favor of the *C*-silylation products over double bond reduction product or dimerization. The reductive *C*-silylation process was probably accelerated by quenching the radical anion **47**, formed by electron transfer from Mg to the acrylate **42a**, with TMSCl to give the ketene silyl acetal radical **48**. One more electron transfer from Mg to **48** provided the intermediate anion **49** which was then quenched by silyl chloride to give the β-*C*-silylated silyl ketene acetal **50**. The silyl acetal **50** underwent hydrolysis during aqueous work-up conditions and provided the β-silyl propionate **43a**. By this process, TMSCl also protected the reductive silylation product from further reactions like Claisen condensation or oligomerizations. The *C*-silylation took place only with β-aryl/silyl acrylates and not with β-alkyl acrylates. The aryl groups are known to stabilize the carbanion at the benzylic positions and a silicon group is also known to stabilize a carbanion α to it. As the reduction potential of benzyl radical (−1.45 V vs SCE)[161c] and α-silyl radical (−1.51 V vs SCE)[161d] is higher compared to alkyl radicals (−2.0 V vs SCE),[161c] the reductive silylation process was favored with these two classes of substrates.

4.2.5 Our findings in 'substrate-based DOS-approach'

We have described our 'substrate-based DOS-approach', which uses a common set of reducing system, Mg/silyl chloride/DMF and reacts with different α,β-unsaturated carbonyl compounds leading to highly functionalized skeletally and stereochemically

diverse products. Two main types of reactions such as reductive cyclization leading to cyclic diester and reductive β-C-silylation leading to β-silyl carbonyl compound have been found to take place (Fig. 4.10).

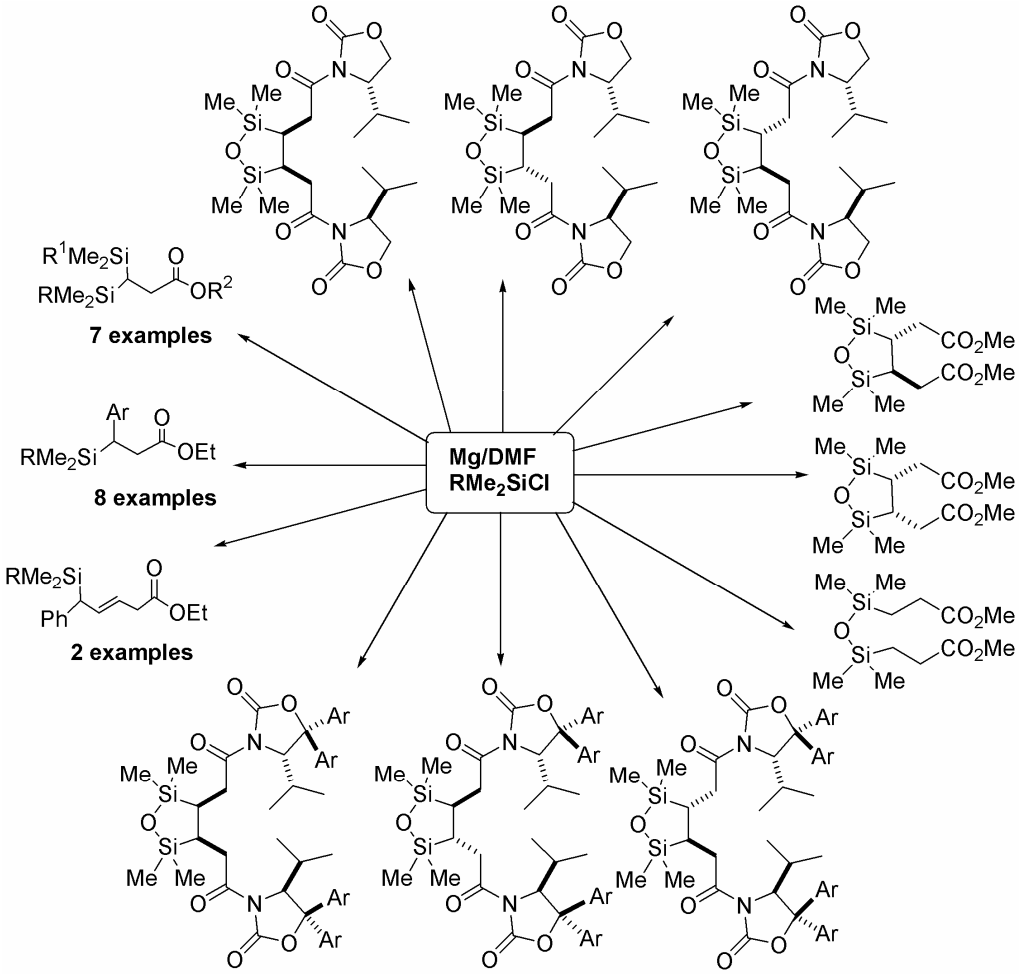


Figure 4.10: Substrate-based DOS-approach

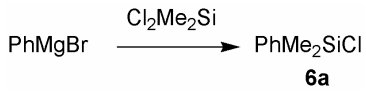
4.3 Conclusion

In conclusion, we have successfully developed a Mg/silyl chloride/DMF system for the reductive *C*-silylation at the β-position of β-aryl and β-silyl substituted enoates with very good yields and purity. The *C*-silylation selectivity was very high over the reductive dimerization or the simple double bond reduction. The reductive silylation conditions are

applicable to δ-aryl substituted dienoates wherein silylation took place at the δ-position leading to the synthesis of allylsilanes as single regioisomer and with very high stereoselectivity. The allylsilanes are known as useful synthetic intermediates and the additional ester functionality at the terminal of the allysilane would enhance their utility. The present methodology of making the silylated compounds from the acrylates is amounted to overall umpolung generation. The *C*-silylations described here is electrophilic. Thus, there is no limitation for the choice of silyl groups, a crucial factor for nucleophilc silylation reactions. Although β-silylation using the silyl chloride like *p*-TolMe_2SiCl, *p*-AnsMe_2SiCl, AllMe_2SiCl etc. are not possible by using the conventional procedure of 1,4 addition using silylcuprate reagents, it is easily done by using Mg/silyl chloride/DMF system.

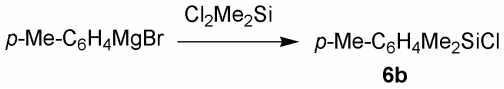
4.4 Experimental

The general experimental and instrumental descriptions are provided in the experimental section of Chapter 2. DMF was dried over CaH_2 followed by storage over 4 Å molecular sieves. Mg turnings were purified by washing with dilute hydrochloric acid, water followed by washing with acetone and dried under vacuum. Ethyl cinnamate, TMSCl was distilled before use. PhMe_2SiCl, *p*-TolMe_2SiCl and *p*-AnsMe_2SiCl were synthesized *via* Grignard reaction where as AllMe_2SiCl and Me_2SiHCl were purchased. Silylated acrylates **23a** and **23b** were prepared following the reported procedure[159] and included in the experimental section of Chapter 3. Dienoates **45a** and **45b** were synthesized by Horner-Wittig reaction.



Dimethyl(phenyl)silyl chloride 6a

Has been given in the experimental section of Chapter 2.

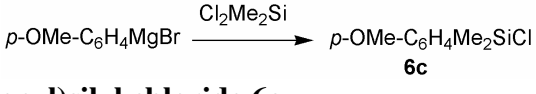


Dimethyl(4-methylphenyl)silyl chloride 6b

A solution of 4-bromotoluene (30.7 mL, 250 mmol) in ether (250 mL) was added drop wise on magnesium turnings (6.7 g, 275 mmol) with stirring and under gentle reflux. The reaction mixture was stirred with reflux for 2 h. (4-methylphenyl)magnesium bromide solution was added to dichlorodimethylsilane (48.2 mL, 400 mmol) in ether (100 mL) with stirring at 0 °C. The reaction mixture was heated under reflux with stirring overnight. The reaction mixture was filtered under vacuum and the filtrate was concentrated on oil bath (bath 60 °C). The residue was distilled to give dimethyl(4-methylphenyl)silyl chloride **6b** (32 g, 69%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.71 (6 H, s, Me_2Si), 2.4 (3 H, s, *Me*ArMe_2SiCl), 7.27 (2 H, d, *J* = 7.7 Hz, Ar), 7.57 (2 H, d, *J* = 7.7 Hz, Ar).

^{13}C-NMR (50 MHz, $CDCl_3$): δ 2.1 (2 C), 21.5, 128.8 (2 C), 132.6, 133.0 (2 C), 140.1.

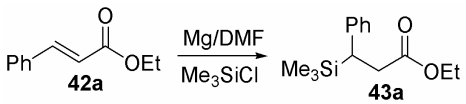


Dimethyl(4-methoxyphenyl)silyl chloride 6c

Following the procedure for the preparation of **6b**, 4-bromoanisol (31.3 mL, 250 mmol), magnesium turnings (6.7 g, 275 mmol) and dichlorodimethylsilane (48.2 mL, 400 mmol) gave dimethyl(4-methoxyphenyl)silyl chloride **6c** (30 g, 60%).

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.67 (6 H, s, Me_2Si), 3.83 (3 H, s, *Me*OArMe_2SiCl), 6.96 (2 H, d, *J* = 8.6 Hz, Ar), 7.57 (2 H, d, *J* = 8.6 Hz, Ar).

^{13}C-NMR (50 MHz, $CDCl_3$): δ 2.0 (2 C), 54.7, 113.7 (2 C), 126.9, 134.6 (2 C), 161.3.



General Procedure: Preparation of (3*RS*)-Ethyl 3-phenyl-3-trimethylsilylpropionate 43a[151e]

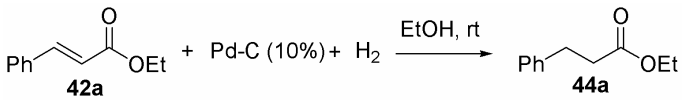
Freshly distilled TMSCl (3.8 mL, 30 mmol) was added to a stirred suspension of magnesium turnings (1.46 g, 60 mmol) in dry DMF (20 mL) at room temperature under an argon atmosphere. After 15 min, a solution of *trans*-ethyl cinnamate **42a** (0.88 g, 5 mmol) in dry DMF (5 mL) was added to the reaction mixture, stirred for 0.5 h and poured into cold saturated sodium bicarbonate solution. The reaction mixture was extracted with 15% ethyl acetate-hexane. The organic extract was washed with brine, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica using hexane-EtOAc (98:2) as eluent to give the product **43a** (1.05 g, 84%) as a colourless liquid.

R_f 0.52 (hexane/EtOAc, 95:5).

IR (film): 3026, 2956, 2899, 1736, 1601, 1495, 1450, 1250, 1163, 1034, 839, 700 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ –0.04 (9 H, s, Me_3Si), 1.08 (3 H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 2.59– 2.81 (3 H, m, Ph*CHCH*$_2$CO), 3.99 (2 H, q, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 7.00–7.11 (3 H, m, Ph), 7.18–7.26 (2 H, m, Ph).

^{13}C-NMR (50 MHz, $CDCl_3$): δ –3.2 (3 C), 14.0, 32.5, 34.8, 60.1, 124.7, 128.0 (2 C), 127.3 (2 C), 142.4, 173.1.



Ethyl dihydrocinnamate 44a

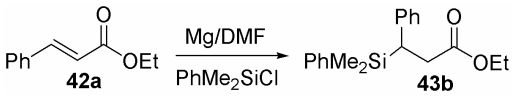
A suspension of ethyl cinnamate (0.35 g, 2 mmol) and catalytic amount of Pd-C (10%) in dry ethanol (10 mL) was stirred under hydrogen atmosphere. After overnight stirring at room temperature, the reaction mixture was filtered through a bed of celite and silica. The filtrate was concentrated under reduced pressure to get the crude product. The residue was purified by column chromatography on silica using hexane-EtOAc (98:2) as eluent to give the product **44a** (0.33 g, 92%) as a colourless liquid.

R_f 0.49 (hexane/EtOAc, 95:5).

IR (film): 3063, 3029, 2981, 2934, 2871, 1734, 1496, 1373, 1180, 1161, 1038, 752, cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.23 (3 H, t, *J* = 7.1 Hz, $CO_2CH_2\mathit{CH_3}$), 2.62 (2 H, t, *J* = 7.9 Hz, $PhCH_2\mathit{CH_2}CO$), 2.96 (2 H, t, *J* = 7.9 Hz, $Ph\mathit{CH_2}CH_2CO$), 4.13 (2 H, q, *J* = 7.1 Hz, $CO_2\mathit{CH_2}CH_3$), 7.20–7.30 (5 H, m, Ph).

^{13}C-NMR (50 MHz, $CDCl_3$): δ 13.8, 30.6, 35.5, 59.9, 125.9, 127.9 (2 C), 128.1 (2 C), 140.2, 172.4.



(3*RS*)-Ethyl 3-dimethyl(phenyl)silyl-3-phenylpropionate 43b[147]

Following the procedure for the preparation of **43a**, *trans*-ethyl cinnamate **42a** (0.88 g, 5 mmol), Mg (1.46 g, 60 mmol), dimethyl(phenyl)silyl chloride **6a** (5 mL, 30 mmol) gave **43b** (1.17 g, 75%) as colorless liquid.

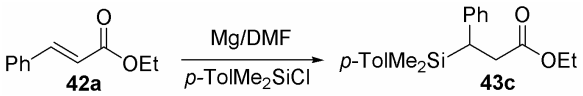
R_f 0.53 (hexane/EtOAc, 95:5).

IR (film): 3069, 3025, 2959, 2901, 1733, 1600, 1494, 1450, 1251, 1167, 1114, 1033, 908, 835, 699 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.21 (3 H, s, $Si\mathit{Me_A}Me_BPh$), 0.25 (3 H, s, $SiMe_A\mathit{Me_B}Ph$), 1.03 (3 H, t, *J* = 7.1 Hz, $CO_2CH_2\mathit{CH_3}$), 2.56–2.88 (3 H, m, $Ph\mathit{CHCH_2}CO$), 3.90 (2 H, q, *J* = 7.1 Hz, $CO_2\mathit{CH_2}CH_3$), 6.92–6.96 (2 H, m, Ph), 7.07–7.26 (4 H, m, Ph), 7.30–7.38 (4

H, m, Ph).

^{13}C-NMR (50 MHz, $CDCl_3$): δ –5.6, –4.3, 13.8, 32.2, 34.8, 60.0, 124.8, 127.4 (2 C), 127.6 (2 C), 127.9 (2 C), 129.1, 134.0 (2 C), 136.3, 141.6, 172.7.



(3*RS*)-Ethyl 3-dimethyl(4-methylphenyl)silyl-3-phenylpropionate 43c

Following the procedure for the preparation of **43a**, *trans*-ethyl cinnamate **42a** (0.88 g, 5 mmol), Mg (1.46 g, 60 mmol), dimethyl(4-methylphenyl)silyl chloride **6b** (5.5 g, 30 mmol) gave **43c** (1.22 g, 75%) as colorless liquid.

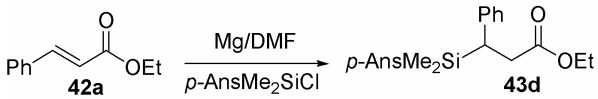
R_f 0.50 (hexane/EtOAc, 95:5).

IR (film): 3062, 3025, 2958, 1735, 1602, 1494, 1450, 1250, 1164, 1106, 1034, 836 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.20 (3 H, s, SiMe_AMe$_B$Ar), 0.23 (3 H, s, SiMe$_A$$Me_B$Ar), 1.04 (3 H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 2.36 (3 H, s, Ar*Me*), 2.50–2.96 (3 H, m, Ph$CHCH_2$CO), 3.91 (2 H, q, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 6.95 (2 H, d, *J* = 7.6 Hz, Ar), 7.06–7.27 (5 H, m, Ph), 7.30 (2 H, d, *J* = 7.6 Hz, Ar).

^{13}C-NMR (50 MHz, $CDCl_3$): δ –5.5, –4.1, 13.9, 21.3, 32.3, 34.8, 60.0, 124.8, 127.5 (2 C), 127.9 (2 C), 128.5 (2 C), 132.7, 134.1 (2 C), 139.0, 141.8, 172.9.

HRMS (ESI) *m/z*: Found M^+ 326.1727, $C_{20}H_{26}O_2Si$ requires M^+ 326.1702.



(3*RS*)-Ethyl 3-dimethyl(4-methoxyphenyl)silyl-3-phenylpropionate 43d

Following the procedure for the preparation of **43a**, *trans*-ethyl cinnamate **42a** (0.88 g, 5 mmol), Mg (1.46 g, 60 mmol), dimethyl(4-methoxyphenyl)silyl chloride **6c** (6 g, 30 mmol) gave **43d** (1.37 g, 80%) as colorless liquid.

R_f 0.36 (hexane/EtOAc, 95:5).

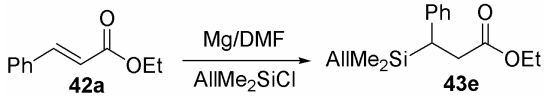
IR (film): 3060, 3023, 2957, 2903, 2837, 1732, 1595, 1504, 1278, 1250, 1183, 1112, 1033, 822 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.20 (3 H, s, SiMe_AMe$_B$Ar), 0.22 (3 H, s, SiMe$_A$$Me_B$Ar), 1.04 (3 H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 2.57–2.86 (3 H, m, Ph$CHCH_2$CO), 3.82 (3 H, s, OMe), 3.95 (2 H, q, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 6.89 (2 H, d, *J* = 8.5 Hz, Ar), 6.90–6.97 (2 H, m, Ph), 6.90–7.20 (3 H, m, Ph), 7.32 (2 H, d, *J* = 8.5 Hz, Ar).

^{13}C-NMR (50 MHz, $CDCl_3$): δ –5.3, –4.0, 13.9, 32.5, 34.9, 54.9, 60.1, 113.4 (2 C), 124.8, 127.1, 127.5 (2 C), 127.9 (2 C), 135.5 (2 C), 141.8, 160.5, 173.0.

HRMS (ESI) *m/z*: Found MNa^+ 365.1542, $C_{20}H_{26}O_3SiNa$ requires 365.1543.

MS (EI) *m/z*: 342 (M, 15%), 327 (M–Me, 4), 297 (5), 207 (5), 195 (14), 165 (100), 135 (13), 122 (8), 104 (11).



42a **43e**

(3*RS*)-Ethyl 3-dimethyl(2-propenyl)silyl-3-phenylpropionate 43e

Following the procedure for the preparation of **43a**, *trans*-ethyl cinnamate **42a** (0.88 g, 5 mmol), Mg (1.46 g, 60 mmol), (allyl)dimethylsilyl chloride (4.5 mL, 30 mmol) gave **43e** (1.23 g, 89%) as colorless liquid.

R_f 0.52 (hexane/EtOAc, 95:5).

IR (film): 3078, 3060, 3026, 2958, 2901, 1736, 1630, 1600, 1370, 1251, 1163, 1035, 897, 838, 701 cm^{-1}.

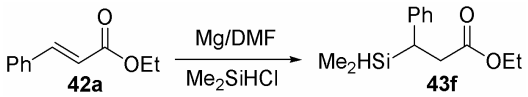
^{1}H-NMR (200 MHz, $CDCl_3$): δ –0.06 (3 H, s, SiMe_AMe$_B$), –0.01 (3 H, s, SiMe$_A$$Me_B$), 1.08 (3 H, t, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 1.47 (2 H, d, *J* = 7.9 Hz, SiCH_2CH=CH_2), 2.66–2.89 (3 H, m, Ph$CHCH_2$CO), 3.98 (2 H, q, *J* = 7.1 Hz, $CO_2CH_2CH_3$), 4.81–4.87 (2 H, m,

$SiCH_2CH=CH_2$), 5.60–5.76 (1 H, m, $SiCH_2CH=CH_2$), 7.02–7.13 (3 H, m, Ph), 7.20–7.26 (2 H, m, Ph).

^{13}C-NMR (50 MHz, $CDCl_3$): δ −5.3 (2 C), 13.9, 21.4, 31.4, 34.8, 60.1, 113.5, 124.8, 127.3 (2 C), 128.1 (2 C), 134.1, 141.9, 172.8.

HRMS (ESI) *m/z*: Found MNa^+ 299.1411, $C_{16}H_{24}O_2SiNa$ requires 299.1444.

MS (EI) *m/z*: 276 (M, 1%), 261 (M−Me, 5), 235 (M−C_3H_5, 100), 207 (27), 171 (9), 147 (9), 99 (60), 75 (66).



(3*RS*)-Ethyl 3-dimethyl(hydro)silyl-3-phenylpropionate 43f

Following the procedure for the preparation of **43a**, *trans*-ethyl cinnamate **42a** (0.88 g, 5 mmol), Mg (1.46 g, 60 mmol), dimethylchlorosilane (3.3 mL, 30 mmol) gave **43f** (1.00 g, 85%) as colorless liquid.

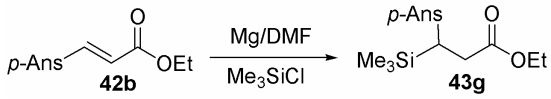
R_f 0.56 (hexane/EtOAc, 95:5).

IR (film): 3061, 3025, 2961, 2903, 2116, 1734, 1601, 1494, 1450, 1371, 1252, 1166, 1034, 908, 881, 758 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ −0.02 (3 H, s, J = 3.5 Hz, $SiMe_AMe_BH$), 0.11 (3 H, s, J = 3.5 Hz, $SiMe_AMe_BH$), 1.11 (3 H, t, J = 7.1 Hz, $CO_2CH_2CH_3$), 2.68–2.89 (3 H, m, $PhCHCH_2CO$), 3.85–3.93 (1 H, m, Me_2SiH), 4.02 (2 H, q, J = 7.1 Hz, $CO_2CH_2CH_3$), 7.04–7.14 (3 H, m, Ph), 7.20–7.28 (2 H, m, Ph).

^{13}C-NMR (50 MHz, $CDCl_3$): δ −6.1, −5.7, 14.0, 30.5, 35.5, 60.2, 125.0, 127.2 (2 C), 128.2 (2 C), 142.1, 172.7.

MS (EI) *m/z*: 236 (M, 11%), 221 (M−Me, 6), 207 (7), 193 (17), 163 (17), 147 (11), 135 (52), 117 (33), 104 (100), 91 (16), 75 (41).



(3*RS*)-Ethyl 3-(4-methoxyphenyl)-3-trimethylsilylpropionate 43g[151e]

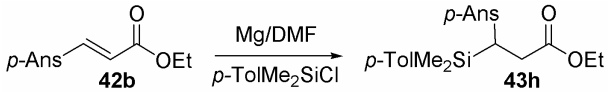
Following the procedure for the preparation of **43a**, (*E*)-ethyl 3-(4-methoxyphenyl)propenoate **42b** (1 g, 5 mmol), Mg (1.46 g, 60 mmol), TMSCl (3.8 mL, 30 mmol) gave **43g** (0.98 g, 70%) as colorless liquid.

R$_f$ 0.58 (hexane/EtOAc, 90:10).

IR (film): 3069, 2955, 2901, 2835, 1733, 1610, 1510, 1249, 1162, 1108, 1038, 841 cm^{-1}.

^{1}H-NMR (200 MHz, CDCl$_3$): δ −0.05 (9 H, s, SiMe$_3$), 1.09 (3 H, t, *J* = 7.1 Hz, $CO_2CH_2\mathit{CH_3}$), 2.50–2.80 (3 H, m, Ar$\mathit{CHCH_2}$CO), 3.76 (3 H, s, OMe), 3.99 (2 H, q, *J* = 7.1 Hz, $CO_2\mathit{CH_2}CH_3$), 6.78 (2 H, d, *J* = 8.5 Hz, Ar), 6.95 (2 H, d, *J* = 8.5 Hz, Ar).

^{13}C-NMR (50 MHz, CDCl$_3$): δ −3.3 (3 C), 13.9, 31.3, 34.9, 54.9, 60.0, 113.3 (2 C), 128.0 (2 C), 134.1, 156.8, 173.0.



(3*RS*)-Ethyl 3-dimethyl(4-methylphenyl)silyl-3-(4-methoxyphenyl)propionate 43h

Following the procedure for the preparation of **43a**, (*E*)-ethyl 3-(4-methoxyphenyl)propenoate **42b** (1 g, 5 mmol), Mg (1.46 g, 60 mmol), dimethyl(4-methylphenyl)silyl chloride **6b** (5.5 g, 30 mmol) gave **43h** (1.27 g, 71%) as colorless liquid.

R$_f$ 0.56 (hexane/EtOAc, 90:10).

IR (film): 3065, 3032, 2956, 2904, 2834, 1734, 1606, 1509, 1442, 1247, 1162, 1107, 1038, 842, 795, 778 cm^{-1}.

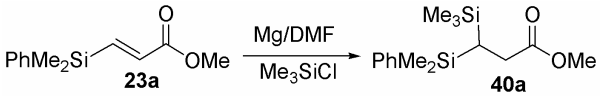
^{1}H-NMR (200 MHz, CDCl$_3$): δ 0.18 (3 H, s, Si$\mathit{Me_A}$Me$_B$), 0.21 (3 H, s, SiMe$_A\mathit{Me_B}$), 1.04 (3 H, t, *J* = 7.1 Hz, $CO_2CH_2\mathit{CH_3}$), 2.35 (3 H, s, Ar*Me*), 2.52–2.79 (3 H, m, Ar$\mathit{CHCH_2}$CO),

3.76 (3 H, s, OMe), 3.91 (2 H, q, J = 7.1 Hz, $CO_2CH_2CH_3$), 6.74 (2 H, d, J = 8.6 Hz, Ar), 6.86 (2 H, d, J = 8.6 Hz, Ar), 7.16 (2 H, d, J = 7.6 Hz, Ar), 7.30 (2 H, d, J = 7.6 Hz, Ar).

^{13}C-NMR (50 MHz, $CDCl_3$): δ −5.5, −4.1, 13.9, 21.3, 31.2, 35.1, 55.0, 60.0, 113.4 (2 C), 128.4 (2 C), 128.5 (2 C), 132.8, 133.60, 134.1 (2 C), 139.0, 157.0, 173.0.

HRMS (ESI) *m/z*: Found MNa^+ 379.1696, $C_{21}H_{28}O_3SiNa$ requires 379.1705.

MS (EI) *m/z*: 356 (M, 6%), 149 (100), 134 (22), 121 (13), 91 (4).



(3*RS*)-Methyl 3-dimethyl(phenyl)silyl-3-trimethylsilylpropionate 40a

Following the procedure for the preparation of **43a**, (*E*)-methyl 3-dimethyl(phenyl)silylpropenoate **23a** (1.1 g, 5 mmol), Mg (1.46 g, 60 mmol), TMSCl (3.8 mL, 30 mmol) gave **40a** (1.03 g, 70%) as a colorless liquid.

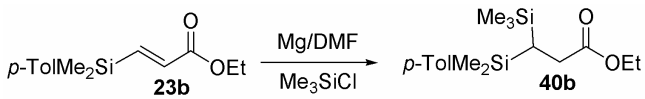
R_f 0.58 (hexane/EtOAc, 95:5).

IR (film): 3069, 2999, 2952, 2898, 1739, 1428, 1348, 1252, 1204, 1050, 1032, 837 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ −0.06 (9 H, s, $SiMe_3$), 0.30 (3 H, s, $Si\mathit{Me}_A Me_B$), 0.32 (3 H, s, $SiMe_A\mathit{Me}_B$), 0.77 (1 H, t, J = 6.5 Hz, $SiCHCH_2CO$), 2.38 (2 H, d, J = 6.5 Hz, $SiCH\mathit{CH}_2CO$), 3.53 (3 H, s, CO_2CH_3), 7.32–7.35 (3 H, m, Ph), 7.47–7.54 (2 H, m, Ph).

^{13}C-NMR (50 MHz, $CDCl_3$): δ −2.6, −1.5, −0.5 (3 C), 8.7, 30.6, 51.4, 127.6 (2 C), 128.8, 133.7 (2 C), 139.0, 174.8.

MS (EI) *m/z*: 294 (M, 2%), 279 (M−Me, 80), 217 (50), 163 (19), 151 (27), 135 (100), 121 (26), 89 (41), 73 (30).



(3*RS*)-Ethyl 3-dimethyl(4-methylphenyl)silyl-3-trimethylsilylpropionate 40b

Following the procedure for the preparation of **43a**, (*E*)-ethyl 3-dimethyl(4-

methylphenyl)silylpropenoate **23b** (1.24 g, 5 mmol), Mg (1.46 g, 60 mmol), TMSCl (3.8 mL, 30 mmol) gave **40b** (1.31 g, 81%) as a colorless liquid.

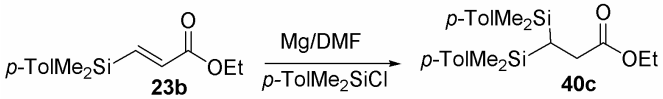
R$_f$ 0.65 (hexane/EtOAc, 95:5).

IR (film): 3067, 2955, 2899, 1736, 1369, 1252, 1199, 1105, 1037, 837, 734 cm^{-1}.

^{1}H-NMR (200 MHz, CDCl$_3$): δ –0.06 (9 H, s, SiMe$_3$), 0.28 (3 H, s, Si*Me*$_A$Me$_B$), 0.30 (3 H, s, SiMe$_A$*Me*$_B$), 0.76 (1 H, t, *J* = 6.4 Hz, Si*CH*CH$_2$CO), 1.19 (3 H, t, *J* = 7.1 Hz, CO$_2$CH$_2$*CH*$_3$), 2.33 (3 H, s, Ar*Me*), 2.37 (2 H, d, *J* = 6.4 Hz, *CH*$_2$CO), 3.92–4.06 (2 H, m, CO$_2$*CH*$_2$CH$_3$), 7.15 (2 H, d, *J* = 7.6 Hz, Ar), 7.41 (2 H, d, *J* = 7.6 Hz, Ar).

^{13}C-NMR (50 MHz, CDCl$_3$): δ –2.4, –1.4, –0.4 (3 C), 8.6, 14.1, 21.4, 30.9, 60.3, 128.4 (2 C), 133.8 (2 C), 135.4, 138.5, 174.6.

MS (EI) *m/z*: 307 (M–Me, 70%), 249 (8), 231 (43), 149 (100), 133 (19), 121 (11), 103 (12), 73 (19).



Ethyl 3,3-bis-dimethyl(4-methylphenyl)silylpropionate 40c

Following the procedure for the preparation of **43a**, (*E*)-ethyl 3-dimethyl(4-methylphenyl)silylpropenoate **23b** (1.24 g, 5 mmol), Mg (1.46 g, 60 mmol), dimethyl(4-methylphenyl)silyl chloride **6b** (5.5 g, 30 mmol) gave **40c** (1.57 g, 79%) as a colorless liquid.

R$_f$ 0.60 (hexane/EtOAc, 95:5).

IR (film): 3066, 3010, 2955, 1734, 1603, 1251, 1104, 1036, 835, 796 cm^{-1}.

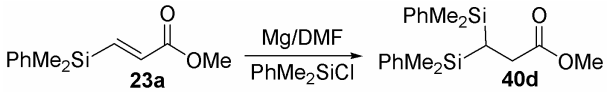
^{1}H-NMR (200 MHz, CDCl$_3$): δ 0.18 (6 H, s, 2 × Si*Me*$_A$Me$_B$), 0.20 (6 H, s, 2 × SiMe$_A$*Me*$_B$), 1.05 (1 H, t, *J* = 6.5 Hz, Si*CH*CH$_2$CO), 1.20 (3 H, t, *J* = 7.2 Hz, CO$_2$CH$_2$*CH*$_3$), 2.33 (6 H, s, 2 × Ar*Me*), 2.34 (2 H, d, *J* = 6.5 Hz, SiCH*CH*$_2$CO), 3.84 (2 H, q, *J* = 7.2 Hz,

$CO_2CH_2CH_3$), 7.13 (4 H, d, J = 7.5 Hz, Ar), 7.36 (4 H, d, J = 7.5 Hz, Ar).

^{13}C-NMR (50 MHz, $CDCl_3$): δ −2.5 (2 C), −1.5 (2 C), 8.1, 13.9, 21.3 (2 C), 31.0, 60.2, 128.4 (4 C), 133.8 (4 C), 135.3 (2 C), 138.5 (2 C), 174.2.

HRMS (ESI) *m/z*: Found MNa^+ 421.1977, $C_{23}H_{34}O_2Si_2Na$ requires 421.1995.

MS (EI) *m/z*: 398 (M, 1%), 383 (M−Me, 45), 308 (17), 307 (54), 249 (11), 207 (14), 149 (100), 133 (26), 121 (16), 103 (11).



Methyl 3,3-bis-dimethyl(phenyl)silylpropionate 40d

Following the procedure for the preparation of **43a**, (*E*)-methyl 3-dimethyl(phenyl)silylpropenoate **23a** (1.1 g, 5 mmol), Mg (1.46 g, 60 mmol), dimethyl(phenyl)silyl chloride **6a** (5 mL, 30 mmol) gave **40d** (1.27 g, 71%) as a colorless liquid.

R_f 0.56 (hexane/EtOAc, 95:5).

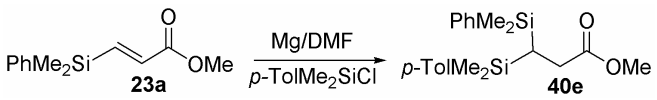
IR (film): 3069, 3049, 2952, 2899, 2843, 1738, 1427, 1349, 1253, 1206, 1112, 1048, 1027, 838, 813, 700 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.20 (6 H, s, 2 × Si$Me_A$$Me_B$), 0.30 (6 H, s, 2 × Si$Me_A$$Me_B$), 1.07 (1 H, t, J = 6.6 Hz, Si$CH$$CH_2CO$), 2.38 (2 H, d, J = 6.6 Hz, SiCHCH_2CO), 3.38 (3 H, s, CO_2CH_3), 7.30–7.34 (6 H, m, Ph), 7.44–7.49 (4 H, m, Ph).

^{13}C-NMR (50 MHz, $CDCl_3$): δ −2.6 (2 C), −1.6 (2 C), 8.3, 30.8, 51.4, 127.6 (4 C), 128.9 (2 C), 133.8 (4 C), 138.9 (2 C), 174.6.

HRMS (ESI) *m/z*: Found MNa^+ 379.1510, $C_{20}H_{28}O_2Si_2Na$ requires 379.1526.

MS (EI) *m/z*: 356 (M, 3%), 341 (M−Me, 59), 279 (60), 231 (15), 221 (34), 193 (13), 151 (23), 135 (100), 121 (22), 107 (11), 89 (14).



(3*RS*)-Methyl 3-dimethyl(4-methylphenyl)silyl-3-dimethyl(phenyl)silylpropionate 40e

Following the procedure for the preparation of **43a**, (*E*)-methyl 3-dimethyl(phenyl)silylpropenoate **23a** (1.1 g, 5 mmol), Mg (1.46 g, 60 mmol), dimethyl(4-methylphenyl)silyl chloride **6b** (5.5 g, 30 mmol) gave **40e** (1.30 g, 70%) as a colorless liquid.

R$_f$ 0.57 (hexane/EtOAc, 95:5).

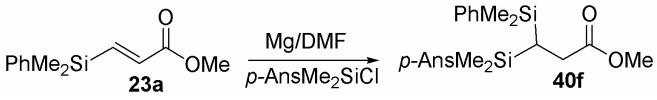
IR (film): 3068, 3011, 2952, 2900, 1739, 1428, 1348, 1252, 1204, 1105, 1032, 831 cm^{-1}.

^{1}H-NMR (200 MHz, CDCl$_3$): δ 0.18 (3 H, s, Si*Me*$_A$Me$_B$), 0.20 (6 H s, , 2 × SiMe$_A$*Me*$_B$), 0.23 (3 H, s, Si*Me*$_A$Me$_B$), 1.05 (1 H, t, *J* = 6.6 Hz, Si*CH*CH$_2$CO), 2.34 (3 H, s, Ar*Me*), 2.38 (2 H, d, *J* = 6.6 Hz, SiCH*CH*$_2$CO), 3.39 (3 H, s, CO$_2$*CH*$_3$), 7.14 (2 H, d, *J* = 7.5 Hz, Ar), 7.28–7.49 (7 H, m, Ar).

^{13}C-NMR (50 MHz, CDCl$_3$): δ −2.6, −2.5, −1.5 (2 C), 8.4, 21.4, 30.8, 51.4, 127.6 (2 C), 128.5 (2 C), 128.8, 133.9 (4 C), 135.2, 138.7, 139.0, 174.7.

HRMS (ESI) *m/z*: Found MNa$^+$ 393.1665, $C_{21}H_{30}O_2Si_2Na$ requires 393.1682.

MS (EI) *m/z*: 370 (M, 1%), 355 (M−Me, 56), 280 (15), 279 (53), 235 (17), 193 (11), 165 (18), 149 (100), 135 (80), 121 (30), 105 (15), 89 (23).



(3*RS*)-Methyl 3-dimethyl(4-methoxyphenyl)silyl-3-dimethyl(phenyl)silylpropionate 40f

Following the procedure for the preparation of **43a**, (*E*)-methyl 3-dimethyl(phenyl)silylpropenoate **23a** (1.1 g, 5 mmol), Mg (1.46 g, 60 mmol), dimethyl(4-methoxyphenyl)silyl chloride **6c** (6 g, 30 mmol) gave **40f** (1.35 g, 70%) as a colorless

liquid.

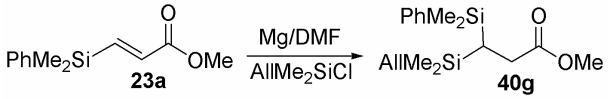
R_f 0.47 (hexane/EtOAc, 95:5).

IR (film): 3068, 3019, 2999, 2952, 2902, 2837, 1738, 1503, 1428, 1278, 1249, 1205, 1183, 1111, 1032, 834, 810 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.18 (3 H, s, SiMe_AMe$_B$), 0.20 (6 H, s, 2 × SiMe$_A$$Me_B$), 0.28 (3 H, s, Si$Me_AMe_B$), 1.04 (1 H, t, *J* = 6.5 Hz, Si*CH*CH_2CO), 2.38 (2 H, d, *J* = 6.5 Hz, SiCH*CH_2*CO), 3.41 (3 H, s, ArO*Me*), 3.81 (3 H, s, CO_2CH_3), 6.88 (2 H, d, *J* = 8.2 Hz, Ar), 7.32–7.48 (7 H, m, Ar).

^{13}C-NMR (50 MHz, $CDCl_3$): δ −2.6, −2.4, −1.6, −1.5, 8.5, 30.8, 51.4, 54.9, 113.3 (2 C), 127.6 (2 C), 128.8, 129.6, 133.8 (2 C), 135.2 (2 C), 139.0, 160.2, 174.7.

MS (EI) *m/z*: 371 (M−Me, 58%), 231(11), 181 (14), 165 (100), 151 (32), 135 (65), 121 (23), 89 (21).



(3*RS*)-methyl 3-dimethyl(2-propenyl)silyl-3-dimethyl(phenyl)silylpropionate 40g

Following the procedure for the preparation of **43a**, (*E*)-methyl 3-dimethyl(phenyl)silylpropenoate **23a** (1.1 g, 5 mmol), Mg (1.46 g, 60 mmol), (allyl)dimethylsilyl chloride (4.5 mL, 30 mmol) gave **40g** (1.15 g, 72%) as a colorless liquid.

R_f 0.57 (hexane/EtOAc, 95:5).

IR (film): 3070, 2952, 2901, 1739, 1630, 1428, 1254, 1204, 1157, 1112, 1028, 814 cm^{-1}.

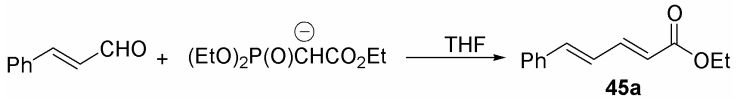
^{1}H-NMR (200 MHz, $CDCl_3$): δ −0.06 (3 H, s, SiMe_AMe$_B$), −0.05 (3 H, s, SiMe_AMe$_B$), 0.32 (3 H, s, SiMe$_A$$Me_B$), 0.34 (3 H, s, SiMe$_A$$Me_B$), 0.84 (1 H, t, *J* = 6.4 Hz, Si*CH*CH_2CO), 1.43–1.48 (2 H, m, Si*CH_2*CH=CH_2), 2.41 (2 H, d, *J* = 6.4 Hz, SiCH*CH_2*CO), 3.51 (3 H, s,

CO_2CH_3), 4.75–4.84 (2 H, m, $SiCH_2CH=CH_2$), 5.59–5.81 (1 H, m, $SiCH_2CH=CH_2$), 7.33–7.36 (3 H, m, Ph), 7.49–7.54 (2 H, m, Ph).

^{13}C-NMR (50 MHz, $CDCl_3$): δ −3.1, −2.5, −2.4, −1.5, 7.5, 23.6, 30.5, 51.5, 113.2, 127.6 (2 C), 128.9, 133.8 (2 C), 134.7, 138.8, 174.7.

HRMS (ESI) *m/z*: Found MNa^+ 343.1526, $C_{17}H_{28}O_2Si_2Na$ requires 343.1526.

MS (EI) *m/z*: 305 (M−Me, 3%), 279 (M−C_3H_5, 94), 231 (23), 163 (41), 151 (25), 135 (100), 121 (31), 89 (62).



45a

(2*E*,4*E*)-Ethyl 5-phenyldienoate 45a

Triethyl phosphonoacetate (4.4 mL, 22 mmol) was added drop wise to a suspension of sodium hydride (0.96 g, 50% in oil, 20 mmol) in THF (4 mL) and stirred under argon atmosphere. After 15 min, freshly distilled cinnamaldehyde (2.5 mL, 20 mmol) was added to the above reaction mixture and stirred for 1.5 h. The reaction mixture was quenched with water, extracted with 5% ethyl acetate in hexane. The combined extract was washed with brine, dried over anhydrous magnesium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on silica using hexane-EtOAc (96:4) to give the pure dienoate **45a** (3.3 g, 82%).

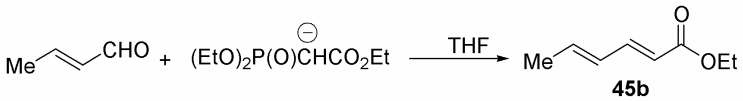
R_f 0.50 (hexane/EtOAc, 95:5).

IR (film): 3060, 3027, 2980, 2936, 1706, 1626, 1367, 1259, 1239, 1134, 1038, 998 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.32 (3 H, t, *J* = 7.0 Hz, $CO_2CH_2CH_3$), 4.23 (2 H, q, *J* = 7.0 Hz, $CO_2CH_2CH_3$), 5.99 (1 H, d, *J* = 15.2 Hz, $CH=CHCO_2Et$), 6.87–7.48 (8 H, m, Ph-CH=CHCH).

^{13}C-NMR (50 MHz, $CDCl_3$): δ 14.0, 59.9, 121.0, 125.8, 126.8 (2 C), 128.4 (2 C), 128.6,

135.6, 139.9, 144.1, 166.5.

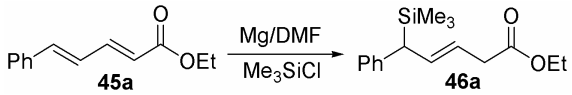


(2*E*,4*E*)-Ethyl 5-methyldienoate 45b

Following the procedure for the preparation of **45a**, triethyl phosphonoacetate (4.4 mL, 22 mmol), sodium hydride (0.96 g, 50% in oil, 20 mmol) and crotonaldehyde (1.65 mL, 20 mmol) gave dienoate **45b** (2.2 g , 78%) as a colorless liquid.

R$_f$ 0.4 (hexane/EtOAc, 95:5).

^{1}H-NMR (200 MHz, CDCl$_3$): δ 1.29 (3 H, t, *J* = 7.1 Hz, $CO_2CH_2\mathit{CH_3}$), 1.85 (3 H, d, *J* = 4.8 Hz, *Me*-CH=CHCH), 4.20 (2 H, q, *J* = 7.1 Hz, $CO_2\mathit{CH_2}CH_3$), 5.76 (1 H, d, *J* = 15.4 Hz, CH=*CH*CO_2Et), 6.06–6.27 (2 H, m, *CH*=*CH*CH). 7.19–7.31 (1 H, m, Me-CH=CH*CH*).



(3*E*,5*RS*)-Ethyl 5-phenyl-5-trimethylsilylpentanoate 46a

Following the procedure for the preparation of **43a**, dienoate **45a** (1 g, 5 mmol), Mg (1.46 g, 60 mmol), TMSCl (3.8 mL, 30 mmol) gave **46a** (0.99 g, 72%) as a colorless liquid contains 14% of (3*Z*,5*RS*)-isomer.

R$_f$ 0.58 (hexane/EtOAc, 95:5).

IR (film): 3061, 3026, 2980, 2957, 2898, 2871, 1737, 1638, 1600, 1495, 1368, 1249, 1159, 1031, 968, 839, 700 cm^{-1}.

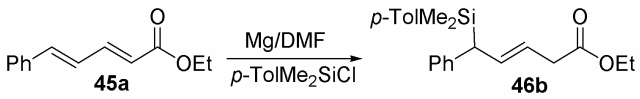
^{1}H-NMR (200 MHz, CDCl$_3$): δ –0.04 (9 H, s, $SiMe_3$), 1.25 (3 H, t, *J* = 7.1 Hz, $CO_2CH_2\mathit{CH_3}$), 2.96 (1 H, d, *J* = 10.0 Hz, *CH*CH=$CHCH_2$), 3.06 (2 H, d, *J* = 6.9 Hz, CHCH=CH$\mathit{CH_2}$), 4.13 (2 H, q, *J* = 7.1 Hz, $CO_2\mathit{CH_2}CH_3$), 5.43–5.57 (1 H, m, SiCHCH=*CH*CH_2), 5.93 (1 H, dd, *J* = 10.0, 15.0 Hz, SiCH*CH*=$CHCH_2$), 7.04–7.29 (5 H, m, Ph).

^{13}C-NMR (50 MHz, $CDCl_3$): δ –3.1 (3 C), 14.1, 38.3, 42.9, 60.4, 120.0, 124.5, 127.0 (2 C), 128.2 (2 C), 133.7, 142.2, 171.9.

GCMS: (column: WCOT Fused Silica, CP-SIL-5-CB, 5 0m × 0.25 mm/0.39 mm, 0.25 µm; Carrier: helium 1 mL/min; temp: 60 ºC-2 min-10º C/min-300 ºC): t_R 16.57 min, **(3*E*,5*RS*)-46a** (86%); t_R 16.79 min, **(3*Z*,5*RS*)-46a** (14%).

MS (EI) *m/z*: for (3*E*,5*RS*)-46a: 276 (M, 11%), 261 (M–Me, 3), 158 (21), 130 (99), 115 (23), 73 (100);

MS (EI) *m/z*: for (3*Z*,5*RS*)-46a: 276 (M, 11%), 261 (M–Me, 3), 158 (10), 130 (67), 115 (19), 73 (100).



(3*E*,5*RS*)-Ethyl 5-dimethyl(4-methylphenyl)silyl-5-phenylpentanoate 46b

Following the procedure for the preparation of **43a**, dienoate **45a** (1 g, 5 mmol), Mg (1.46 g, 60 mmol), dimethyl(4-methylphenyl)silyl chloride **6b** (5.5 g, 30 mmol) gave **46b** (1.23 g, 70%) as a colorless liquid contains 19% of (3*Z*,5*RS*)-isomer.

R_f 0.57 (hexane/EtOAc, 95:5).

IR (film): 3061, 3025, 2979, 2871, 1733, 1659, 1601, 1494, 1369, 1248, 1157, 1106, 1030, 967, 831, 760 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.23 (6 H, s, $SiMe_2$), 1.25 (3 H, t, *J* = 7.1 Hz, $CO_2CH_2\mathit{CH_3}$), 2.35 (3 H, s, Ar*Me*), 3.03 (2 H, d, *J* = 7.1 Hz, SiCHCH=CH$\mathit{CH_2}$), 3.12 (1 H, d, *J* = 9.9 Hz, Si*C*HCH=CHCH_2), 4.13 (2 H, q, *J* = 7.1 Hz, $CO_2\mathit{CH_2}CH_3$), 5.36–5.51 (1 H, m, SiCHCH=*C*HCH_2), 5.85 (1 H, dd, *J* = 9.9, 15.0 Hz, SiCH*C*H=CHCH_2), 6.90 (2 H, d, *J* = 7.3 Hz, Ar), 7.04–7.41 (7 H, m, Ph and Ar).

^{13}C-NMR (50 MHz, $CDCl_3$): δ –4.8, –4.3, 14.1, 21.4, 38.3, 42.7, 60.4, 120.2, 124.6,

127.3 (2 C), 128.0 (2 C), 128.2 (2 C), 132.8, 133.6, 134.3 (2 C), 138.8, 141.6, 171.8.

HRMS (ESI) *m/z*: Found MH^+ 353.1921, $C_{22}H_{29}O_2Si$ requires 353.1937.

GCMS: (column: WCOT Fused Silica, CP-SIL-5-CB, 50m × 0.25mm/0.39mm, 0.25 μm; Carrier: helium 1 mL/min; temp: 60 ºC-2 min-10º C/min-300 ºC): t_R 21.6 min, **(3*E*,5*RS*)-46b** (80%); t_R 21.94 min, **(3*Z*,5*RS*)-46b** (20%).

MS (EI) *m/z*: for (3*E*,5*RS*)-46b: 352 (M, 7%), 149 (100), 130 (28), 121 (11).

MS (EI) *m/z*: for (3*Z*,5*RS*)-46b: 352 (M, 13%), 149 (100), 130 (41), 121 (15).

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CHAPTER 5

Asymmetric Syntheses of D-Fagomine Isomers from C_2-Symmetric 3,4-Bis-Silyl-Substituted Adipic Acid Derivatives

5.1 Introduction

Polyhydroxylated piperidines (azasugars) have gained increasing synthetic interest due to their remarkable biological activity as glycosidase inhibitors.[162] Since glycosidases are involved in numerous biological processes, azasugars are potential therapeutic agents for the treatment of a wide range of diseases, including diabetes, cancer, AIDS, viral infections and many more.[163] These important biological properties have led to many synthetic approaches[164] towards naturally occurring azasugars (Fig. 5.1) and their analogues.

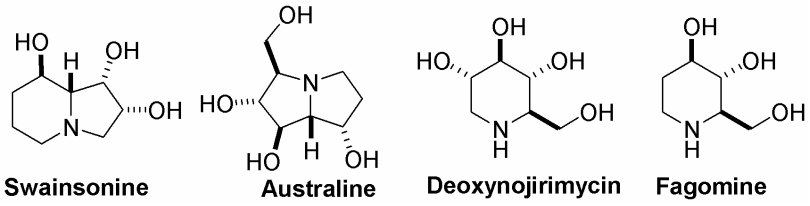


Figure 5.1: Structure of some representative azasugars

1,2-Dideoxy-azasugars such as D-fagomine **51** and its stereoisomers **52, 53** (Fig. 5.2) have been isolated from buckwheat seeds of Japanese buckwheat *Fagopyrum esculentum australe* Moench[165] and also from the seeds of *Castanospermum australe* (Leguminosae).[166] More recently, the isomers of fagomine such as **52** and **53** have been isolated from the leaves and roots of *Xanthocericis zambesiaca*.[167] Fagomine itself has a strong inhibitory activity towards mammalian α-glucosidase, β-galactosidase,[167] and has also been found to have a potent antihyperglycemic effect in streptozocin-induced diabetic mice and a potentiation of glucose-induced insulin secretion.[168]

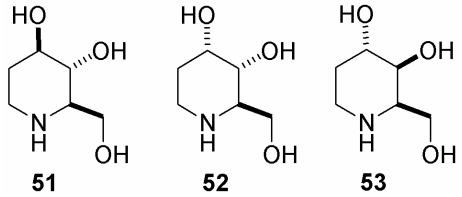
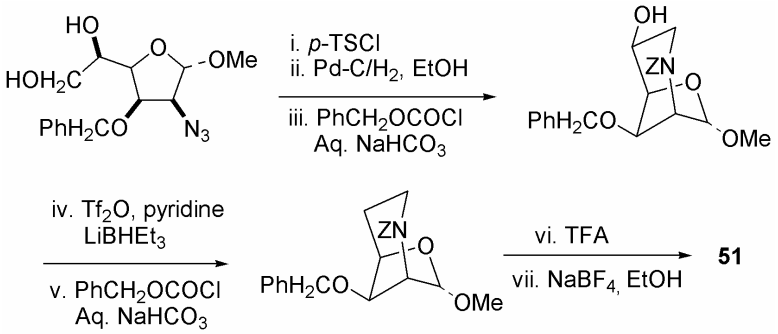


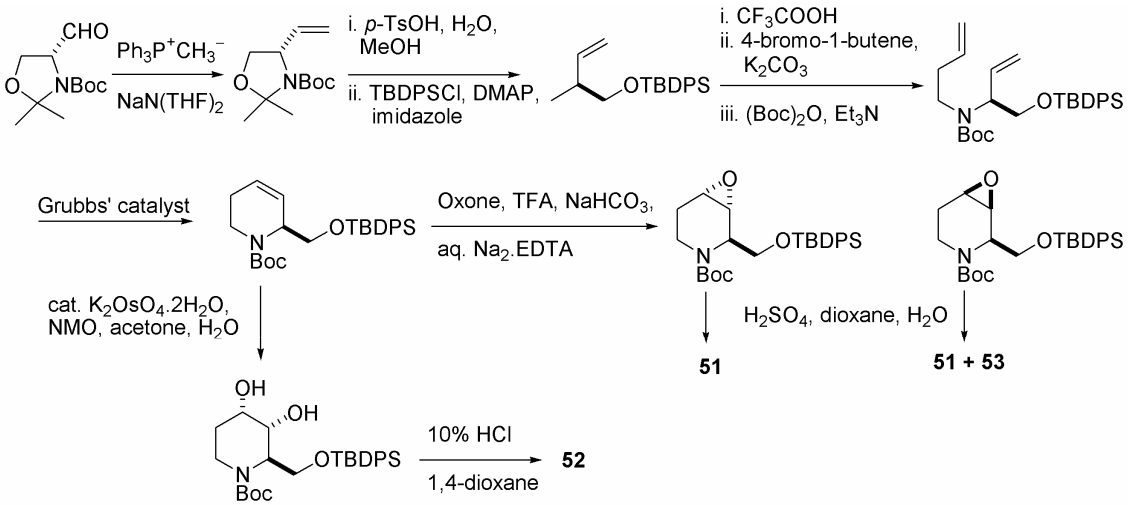
Figure 5.2: Fagomine and its stereoisomers

The first asymmetric synthesis of fagomine **51** was reported[169] in 1985 from methyl 2-azido-3-*O*-benzyl-2-deoxy-α-D-mannofuranoside (Scheme 5.1) which in turn was synthesized form D-glucose. The first enzymatic synthesis of **51** was achieved in 1992 by Effenberger and Null.[170]



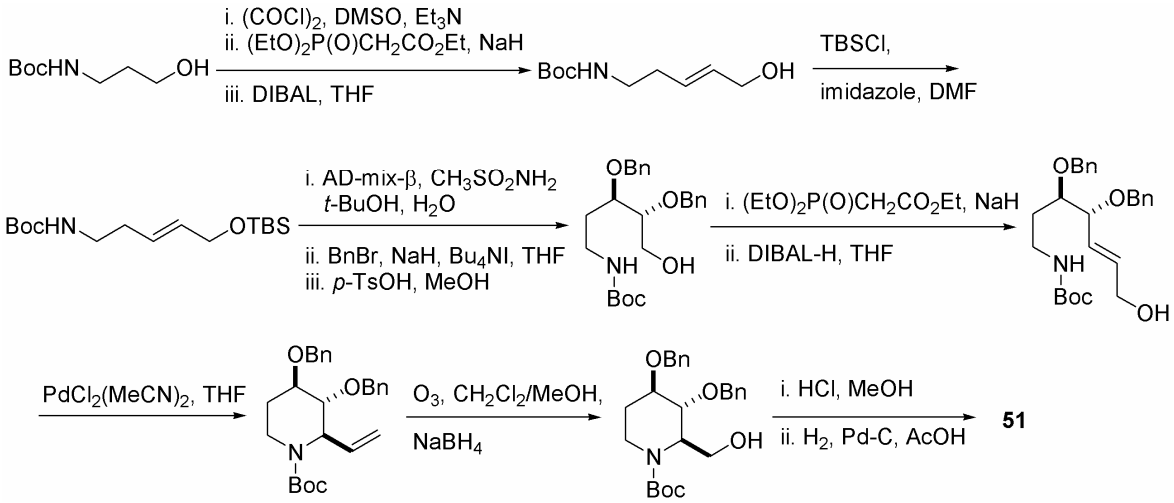
Scheme 5.1

Takahata *et al.*[171] has shown the asymmetric synthesis of all the naturally occurring fagomine isomers **51**–**53**. An intermediate unsaturated piperidine ring was constructed from D-serine-derived Garner aldehyde by catalytic ring-closing metathesis reaction as shown in Scheme 5.2. Stereoselective dihydroxylation of the double bond in piperidine under modified Upjohn[171c] conditions produced 3-*epi*-fagomine **52.** Epoxidation of the double bond followed by stereoselective cleavage of the epoxy ring using super-hydride produced a mixture of fagomine **51** and 3,4-di-*epi*-fagomine **53**.



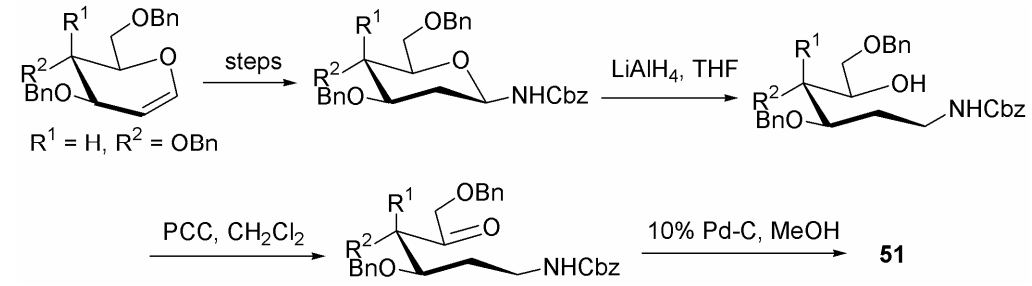
Scheme 5.2

Fagomine **51** have also been synthesized *via* Sharpless asymmetric dihydroxylation and Pd(II)-catalyzed cyclization as the key steps (Scheme 5.3).[172]

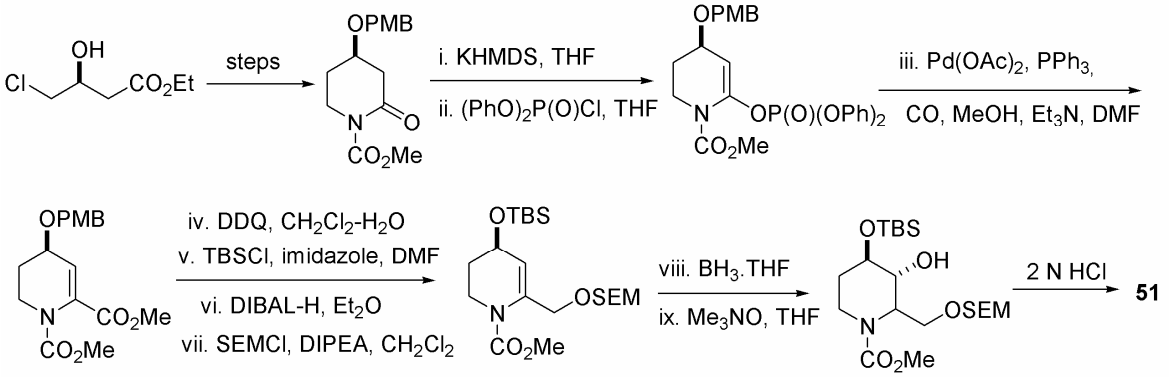


Scheme 5.3

The report by Vankar *et al.*[173] show that introduction of amino functionalities into D-glycals, followed by ring-opening to cleave the C–O bonds, and finally cyclization can afford fagomine isomers (Scheme 5.4). Most recently, Occhiato[174] has shown an efficient synthetic protocol for the synthesis of fagomine isomers. Pd-catalyzed methoxycarbonylation reaction of a lactam-derived vinyl phosphate followed by stereoselective hydroboration-oxidation of the enamine double bond provided fagomine **51** (Scheme 5.5). Chemo-enzymatic approaches using lipase-catalyzed kinetic resolution gave an access to both the enantiomers of fagomine such as D- and L-fagomine.



Scheme 5.4



Scheme 5.5

5.2 Present Work

In Chapter 3, we have shown[153] the asymmetric synthesis of C_2-symmetric 3,4-bis-silyl substituted adipic acid derivatives *trans*-**36a** and *trans*-**37a** (Fig. 5.3). Absolute stereochemistry and application of these *trans*-diastereoisomers were revealed by efficient syntheses of both the enantiomers of 2,6-dioxabicyclo[3.3.0]octane-3,7-dione **39** (Fig. 5.4). Enantiomerically pure (−)-**39** have been synthesized from the *trans*-**36a** using Fleming-Tamao oxidation as the key steps, whereas *trans*-**37a** under the same reaction conditions produced enantiomerically pure (+)-**39**. Diverse functionality of the above mentioned *trans*-diastereoisomers prompted us to explore their further synthetic utility towards the synthesis of biologically active natural products such as azasugar.

As described in the introduction, several syntheses of D-fagomine **51**[169-175] have been reported from carbohydrates, amino acids and other precursors. However, the number of syntheses of fagomine isomers such as **52** and **53** are rare. The only synthesis of the stereoisomeric 3,4-di-*epi*-fagomine **53** has been reported as a mixture of diastereoisomers starting from D-serine-derived Garner aldehyde (Scheme 5.2).[171]

In continuation of our efforts for the silicon-mediated hydroxylated piperidine/pyrrolidine syntheses,[176] we present in this chapter our successful attempt towards the synthesis of D-fagomine **51** and D-3,4-di-*epi*-fagomine **53** from C_2-symmetric 3,4-bis-silyl substituted adipic acid derivatives *via* stereocontrolled azidation and silicon to hydroxyl conversion as the key steps.

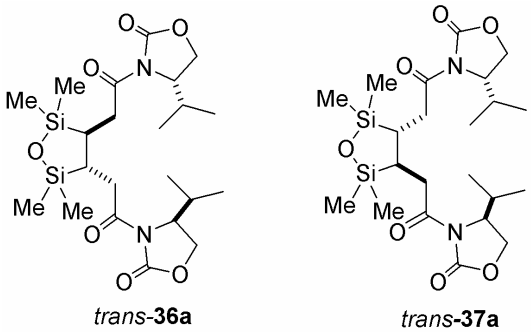


Figure 5.3: Structure of C_2-symmetric diastereoisomers

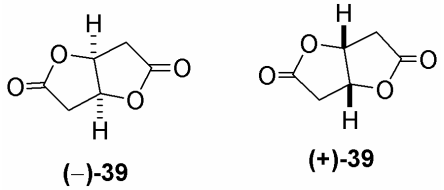
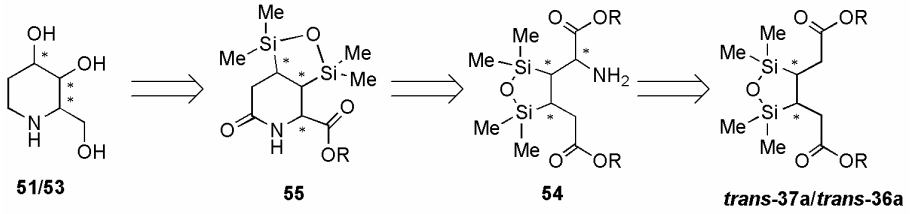


Figure 5.4: Structure of dilactones

5.2.1 Retrosynthetic strategy for fagomine stereoisomers

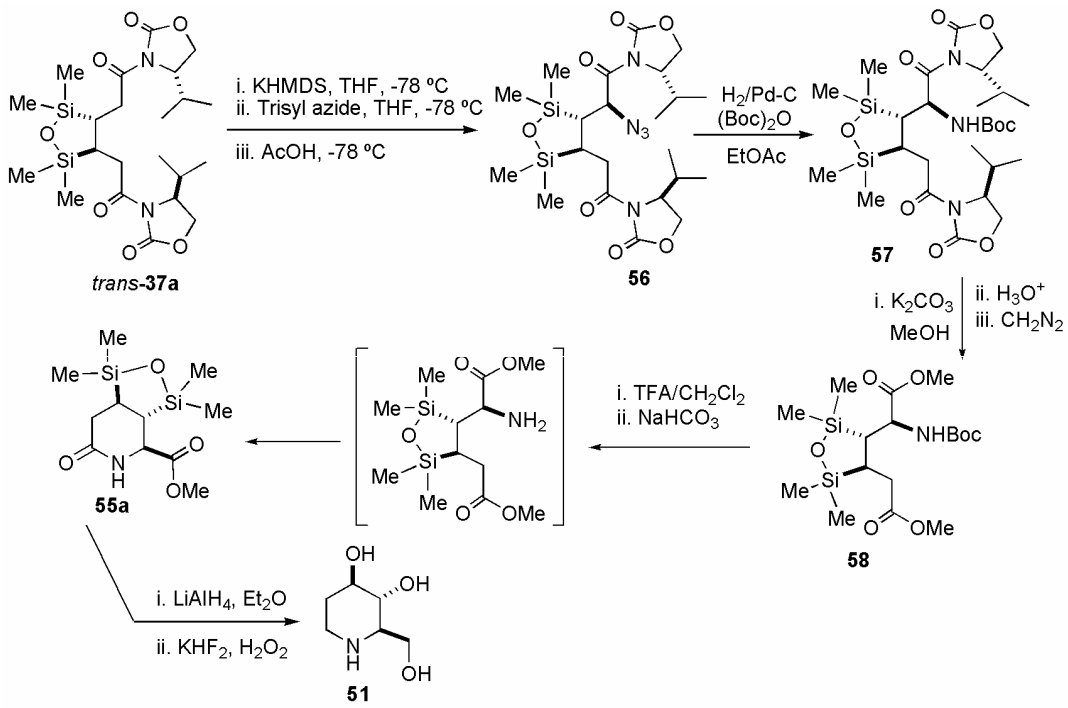
Our proposed general retrosynthetic strategy (Scheme 5.6) for the synthesis of fagomine and its stereoisomers from 3,4-bis-silyl substituted adipic acid derivatives *trans*-**37a** and *trans*-**36a** is based on, (i) stereoselective introduction of an amino functionality at the α-position of one of the derivatized carboxylic acid to give the amine **54**, (ii) intramolecular cyclization to give the lactam **55**, and (iii) reduction of the carbonyl groups and the conversion of the silicon groups to hydroxyl groups with retention of configuration to give 1,2-dideoxy azasugars **51** and **53**.



Scheme 5.6

5.2.2 Synthesis of D-fagomine 51

For the synthesis of D-fagomine **51**, 3,4-bis-silyl substituted adipic acid derivatives *trans*-**37a** was chosen as the starting material because the configurations of the Si-bearing centres matched with the configurations required for OH substituents at 3 and 4 positions. The introduction of an azido group at the α-position of the carboxamide in *trans*-**37a** was carried out following the electrophilic azidation procedure as described by Evans and co-workers,[177] using KHMDS and trisyl azide. Azide **56** (Fig. 5.5 & Fig. 5.6) was formed as a single diastereoisomer in good yield (76%, Scheme 5.7).



Scheme 5.7

The stereochemical outcome of the azidation reactions was controlled by the valine derived oxazolidin-2-one auxiliary[131c] and not by the β-silyl group. The reduction of azide **56** and the in-situ protection of the intermediate amine were achieved by the addition of $(Boc)_2O$ in an H_2/Pd-C system to give urethane **57** in excellent yield. The oxazolidin-2-one groups from **57** were removed by treatment with K_2CO_3 in MeOH, resulting in a mixture of dimethyl ester and dicarboxylic acid which upon treatment with diazomethane yielded dimethyl ester derivative **58**. The Boc-protecting group in **58** was removed by treatment with trifluoroacetic acid and the resulting trifluoroacetate salt was basified with $NaHCO_3$ to give the intermediate amine which spontaneously underwent cyclization to lactam **55a**. A $LiAlH_4$ reduction followed by Fleming-Tamao oxidation[66,154] of the lactam **55a** using potassium bifluoride and hydrogen peroxide yielded D-fagomine **51** (Fig. 5.7 & Fig. 5.8) as confirmed from the ^1H and ^{13}C NMR chemical shift values, and comparing the specific rotation value ($[\alpha]_D^{22}$ = +18.6, *c* 0.43, H_2O; *lit.*[171] $[\alpha]_D^{25}$= +18.0, *c* 0.92, H_2O).

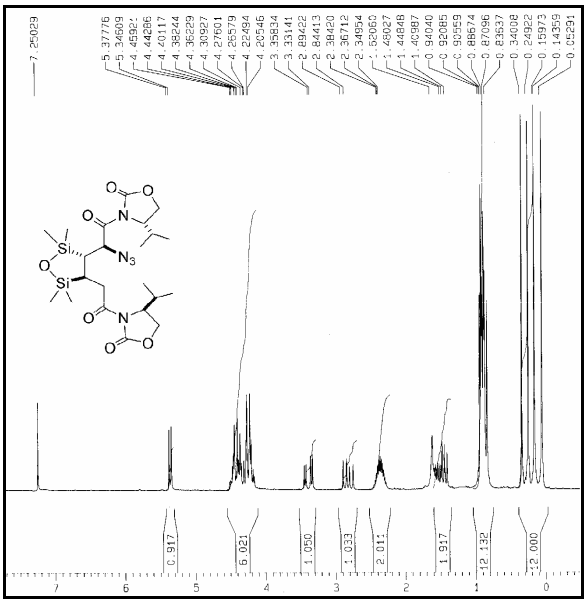


Figure 5.5: ^1H NMR of 56

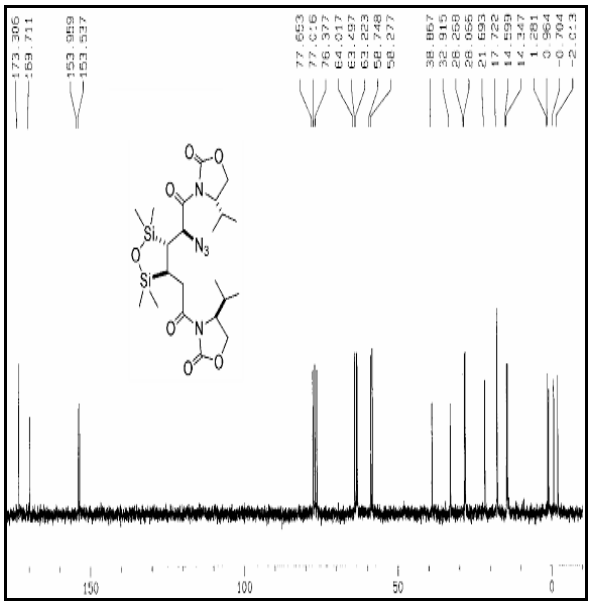


Figure 5.6: ^{13}C NMR of 56

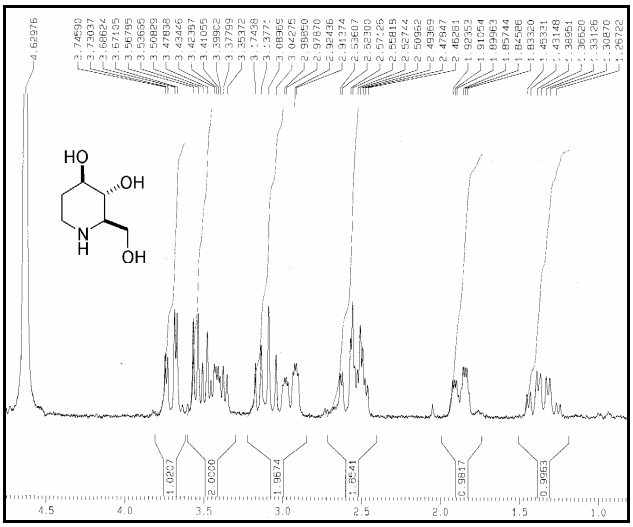


Figure 5.7: ^{1}H NMR of 51

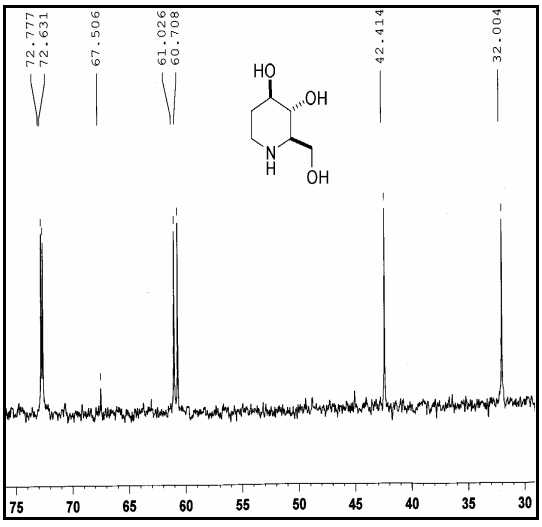
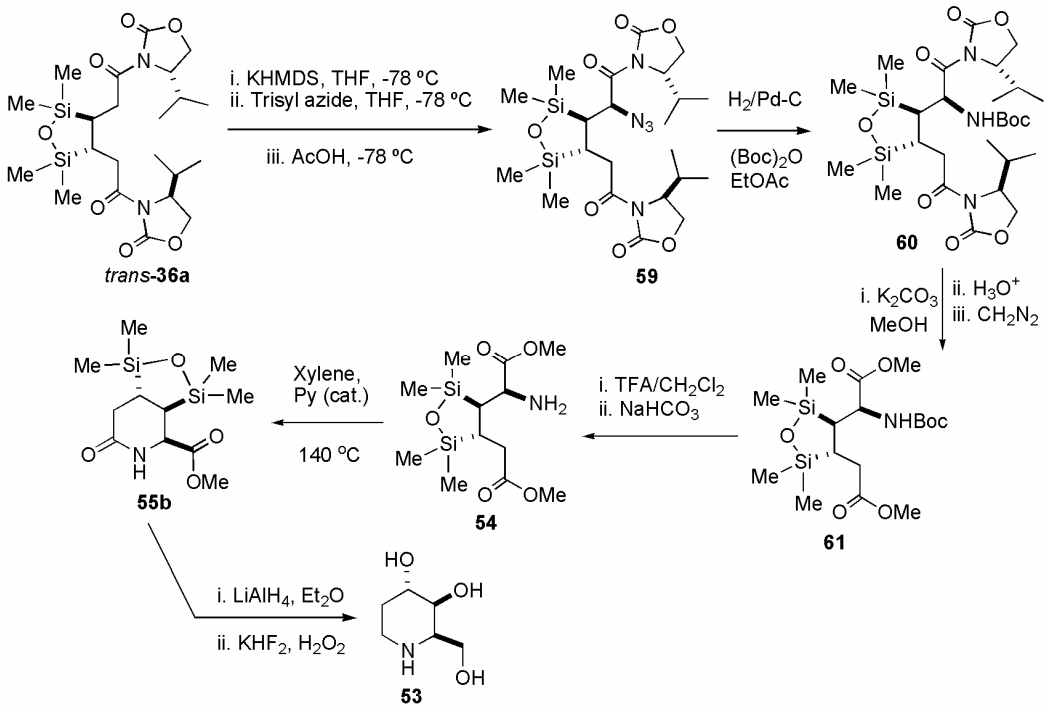


Figure 5.8: ^{13}C NMR of 51

5.2.3 Synthesis of D-3,4-di-*epi*-fagomine 53

The synthesis of 3,4-di-*epi*-fagomine was achieved in an analogous way as shown for D-fagomine **51**. For this purpose, 3,4-bis-silyl substituted adipic acid derivatives ***trans*-36a** was chosen as the starting material because the configurations of the Si-bearing centres matches with the configurations required for OH substituents at 3 and 4 positions.



Scheme 5.8

The stereochemical outcome in the electrophilic azidation in *trans*-**36a** was also controlled by the oxazolidin-2-one auxiliary, thus giving azide **59** as a single diastereoisomer (Scheme 5.8). Similar to the D-fagomine series, the reduction of azide **59** and the in-situ protection of the intermediate amine was achieved by adding $(Boc)_2O$ in an H_2/Pd-C system to give the urethane **60**. The oxazolidin-2-one groups from **60** were removed and converted to dimethyl ester derivative **61**. The Boc-protecting group in **61** was removed by treatment with trifluroacetic acid and the resulting trifluoroacetate salt was basified with $NaHCO_3$ to give the amine **54** (Fig. 5.9 & Fig. 5.10). It is interesting to note that the amine **54** is stable and did not cyclize to lactam **55b**. The cyclization of the amine **54** to lactam **55b** was finally achieved by refluxing a xylene solution of the amine **54**. A $LiAlH_4$ reduction followed by Fleming-Tamao[66,154] oxidation of lactam **55a** using potassium bifluoride and hydrogen peroxide then yielded 3,4-di-*epi*-fagomine **53** (Fig. 5.11 & Fig. 5.12) as confirmed from the ^1H and ^{13}C NMR chemical shift values, and comparing the specific rotation value ($[\alpha]_D^{24}$ = 12.1, *c* 0.33, H_2O; *lit.*[171] $[\alpha]_D^{25}$ = +13.4, *c* 0.32, H_2O).

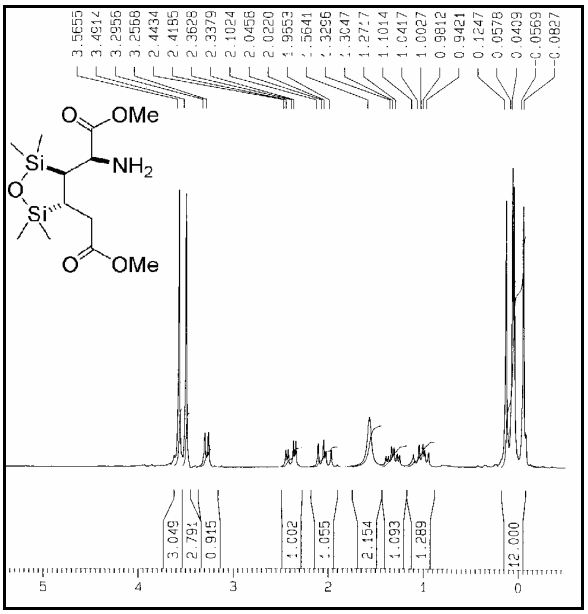


Figure 5.9: ^1H NMR of 54

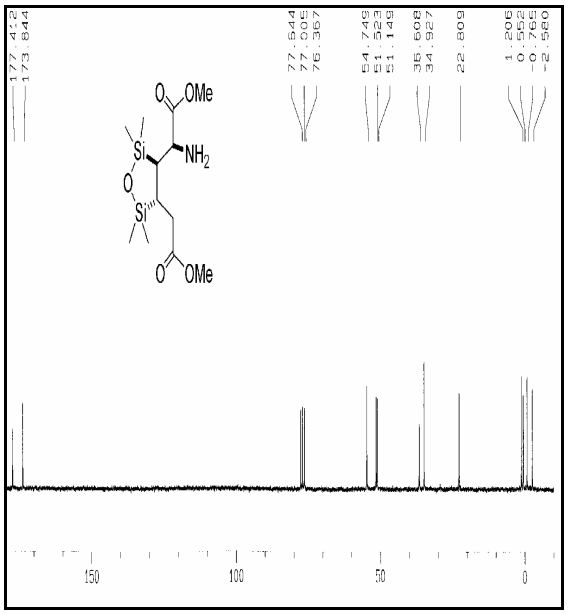


Figure 5.10: ^{13}C NMR of 54

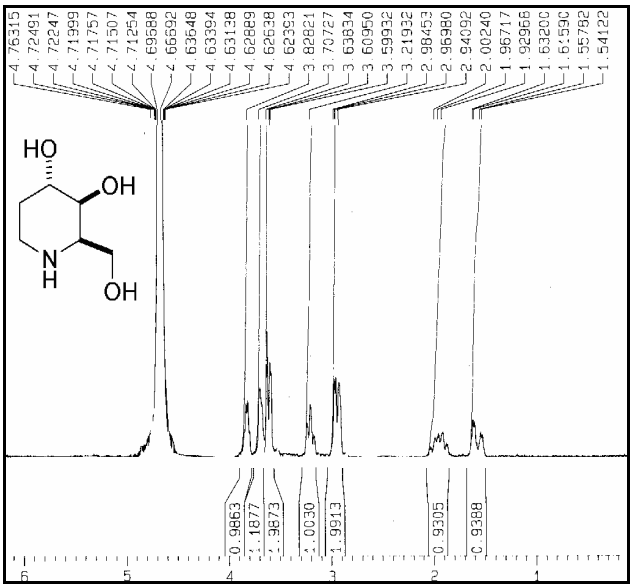


Figure 5.11: ^{1}H NMR of 53

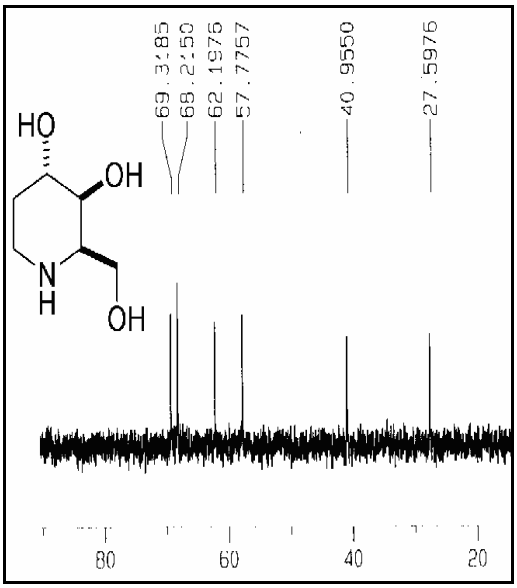
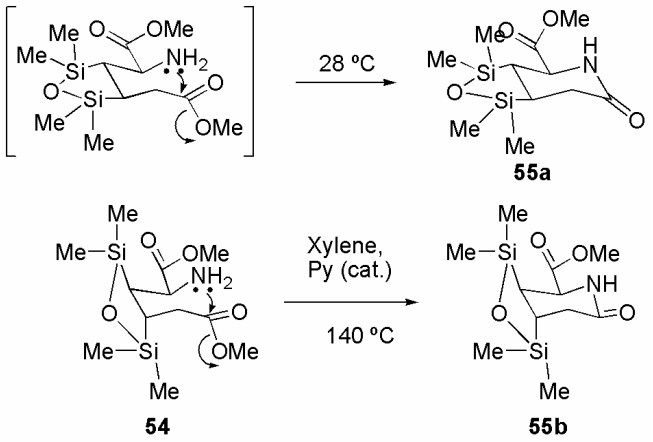


Figure 5.12: ^{13}C NMR of 53

5.2.4 Proposed transition states for amines undergoing cyclization

The lactamization of the intermediate amine derived from **58** was smooth whereas the same for amine **54** to lactam **55b** was very difficult requiring high temperature and prolonged reaction time. The proposed transition states for both the amines undergoing cyclization is shown in Scheme 5.9.



Scheme 5.9

While cyclization to take place, amine **54** has to adopt a conformation wherein the silyl groups have to be disposed axially and methoxycarbonyl group in equatorial position.

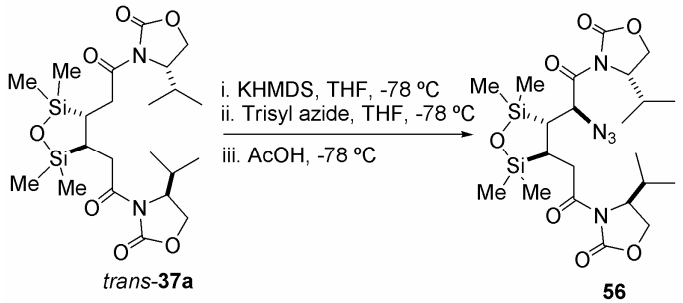
This makes the system energetically unfavorable requiring very high temperature for the lactamization. On the other hand, amine derived from urethane **58**, the silyl groups and methoxycarbonyl group can adopt equatorial positions making the system smooth for lactamization.

5.3 Conclusion

In conclusion, we have successfully achieved the stereocontrolled synthesis of D-fagomine from C_2-symmetric 3,4-bis-silyl substituted adipic acid di-oxazolidin-2-one *trans*-**37a**. The successful synthesis of enantio pure D-3,4-di-*epi*-fagomine was also achieved from C_2-symmetric 3,4-bis-silyl substituted adipic acid derivative *trans*-**36a**. The Evans' oxazolidin-2-one controlled the stereochemical outcome of the azidation that supersedes the directing effects of the silyl substituent.

5.4 Experimental

The general experimental and instrumental descriptions are provided in the experimental section of Chapter 2. KHMDS was freshly prepared where as TFA was distilled before use. THF and diethyl ether were distilled over Na/benzophenone. Lithium aluminium hydride, Pd/C (10%), $(Boc)_2O$, trifluoromethanesulfonic acid, KHF_2 and H_2O_2 (30%) were used as received from commercial sources.



(*S*)-3-((*R*)-2-azido-2-((3*R*,4*R*)-4-(2-((*S*)-4-isopropyl-2-oxooxazolidin-3-yl)-2-oxoethyl)-2,2,5,5-tetramethyl-1,2,5-oxadisilolan-3-yl)acetyl)-4-isopropyloxazolidin-2-one 56

Freshly prepared potassium hexamethyldisilazide (KHMDS) solution (1.3 mL, 1 *M* solution in THF, 1.3 mmol, 1.3 equiv) was added to a stirred solution of *trans*-**37a** (0.5 g, 1 mmol) in dry THF (2.5 mL) at −78 ºC. After 30 min, a solution of trisyl azide (0.4 g, 1.3 mmol) in THF (3 mL) was canulated into the reaction mixture and stirred for 8 min. The reaction mixture was quenched with acetic acid (0.3 mL, 5 mmol) at −78 ºC and slowly raised the temperature to 30 ºC. The reaction mixture was evaporated under reduced pressure and the residue was diluted with brine. The reaction mixture was extracted with chloroform and the combined extract was washed with sodium bicarbonate solution, dried over anhydrous $MgSO_4$ and evaporated. The residue was purified by column chromatography on silica using hexane-EtOAc (85:15) as eluent to give the azide **56** (0.41 g, 76%) as a thick gum.

$[\alpha]_D^{25}$ +89.8 (*c* 1.06, $CHCl_3$).

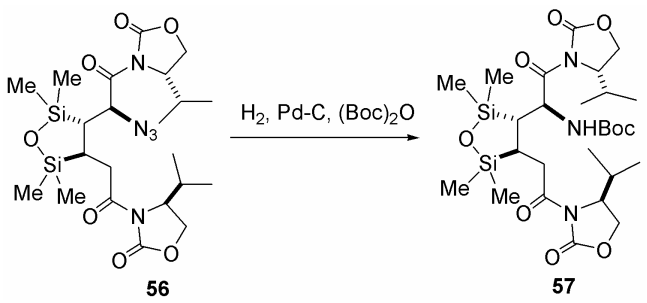
R_f 0.66 (hexane/EtOAc, 75:25).

IR ($CHCl_3$): 3013, 2965, 2878, 2106, 1780, 1698, 1388, 1252, 1207, 1101, 935, 846 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.05 (3 H, s, SiMe), 0.16 (3 H, s, SiMe), 0.25 (3 H, s, SiMe), 0.34 (3 H, s, SiMe), 0.84–0.97 (12 H, m, 2 × $NCO_2CH_2CHCHMe_2$), 1.41–1.59 (2 H, m, 2 × $Me_2SiCHCH_2$), 2.28–2.44 (2 H, m, 2 × $NCHCHMe_2$), 2.82 (1 H, dd, *J* = 10.2, 18.4 Hz, CH_AH_BCON), 3.39 (1 H, dd, *J* = 5.4, 18.4 Hz, CH_AH_BCON), 4.16–4.51 (6 H, m, 2 × NCO_2CH_2CH, 2 × $NCHCHMe_2$), 5.36 (1 H, d, *J* = 6.3 Hz, CHN_3).

^{13}C-NMR (50 MHz, $CDCl_3$): δ −2.0, −0.7, 1.0, 1.3, 14.4, 14.6, 17.7 (2 C), 21.7, 28.1, 28.3, 32.9, 38.9, 58.3, 58.8, 63.2, 63.5, 64.0, 153.5, 154.0, 169.7, 173.3.

Anal. (Found: C, 48.85; H, 6.93; N, 12.81. $C_{22}H_{37}N_5O_7Si_2$ requires C, 48.96; H, 6.91; N, 12.98%).



56 **57**

(*S*)-3-((*R*)-2-((*tert*-butyloxycarbonyl)amino)-2-((3*R*,4*R*)-4-(2-((*S*)-4-isopropyl-2-oxooxazolidin-3-yl)-2-oxoethyl)-2,2,5,5-tetramethyl-1,2,5-oxadisilolan-3-yl)acetyl)-4-isopropyloxazolidin-2-one 57

Catalytic amount of Pd-C (10%) was added to a solution of the azide **56** (0.24 g, 0.44 mmol) and $(Boc)_2O$ (0.3 g, 1.4 mmol) in ethyl acetate (8 mL) and the solution was stirred under hydrogen atmosphere for 24 h at room temperature. The reaction mixture was filtered through a celite pad, and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography on silica using hexane-EtOAc (85:15) as eluent to give the product **57** (0.25 g, 93%) as a colourless solid. mp 147 ºC (from hexane-EtOAc).

$[\alpha]_D^{23}$ +139.89 (*c* 1.07, $CHCl_3$).

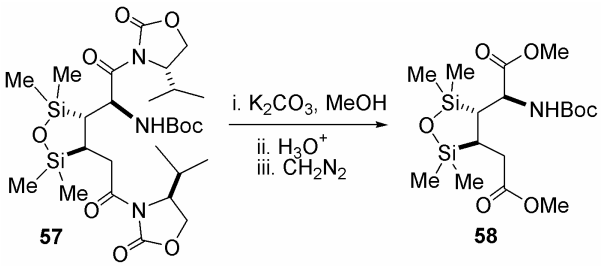
R_f 0.54 (hexane/EtOAc, 75:25).

IR ($CHCl_3$): 3379, 3019, 2966, 2932, 2877, 1780, 1699, 1489, 1253, 1207, 929 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.00 (3 H, s, SiMe), 0.15 (3 H, s, SiMe), 0.30 (3 H, s, SiMe), 0.33 (3 H, s, SiMe), 0.82–0.91 (12 H, m, 2 × $NCO_2CH_2CHCH\mathit{Me_2}$), 1.19–1.52 (2 H, m, 2 × $Me_2SiC\mathit{H}CH_2$), 1.40 (9 H, s, NH*Boc*), 2.29–2.45 (2 H, m, 2 × $NCHC\mathit{H}Me_2$), 2.63 (1 H, dd, *J* = 9.8, 19.0 Hz, $C\mathit{H_A}H_BCON$), 3.20 (1 H, dd, *J* = 4.4, 19.0 Hz, $CH_A\mathit{H_B}CON$), 4.15–4.47 (6 H, m, 2 × $NCO_2C\mathit{H_2}CH$, 2 × $NC\mathit{H}CHMe_2$), 5.36–5.50 (2 H, m, *CHNH*Boc).

^{13}C-NMR (50 MHz, $CDCl_3$): δ –2.2, –0.9, 0.2, 1.0, 14.4, 14.6, 17.8 (2 C), 19.1, 28.2 (5 C), 33.1, 38.6, 52.0, 58.4, 59.1, 63.3, 64.0, 79.8, 153.4, 154.0, 155.3, 173.4, 174.7.

Anal. (Found: C, 52.92; H, 7.73; N, 6.76. $C_{27}H_{47}N_3O_9Si_2$ requires C, 52.83; H, 7.72; N, 6.85%).



(*R*)-Methyl 2-((tert-butyloxycarbonyl)amino)-2-((3*R*,4*R*)-4-(2-methoxy-2-oxoethyl)-2,2,5,5-tetramethyl-1,2,5-oxadisilolan-3-yl)acetate 58

Potassium carbonate (138 mg, 1 mmol) was added to a solution of **57** (0.21 g, 0.34 mmol) in methanol (8 mL) at 30 ºC and stirred for an hour. After removing the solvent under reducing pressure, the residue was dissolved in water, acidified with dilute HCl and extracted with ethyl acetate. The organic extract was evaporated under reduced pressure and the residue was treated with ethereal diazomethane. The reaction mixture was evaporated under reduced pressure and the residue was purified by column

chromatography on silica using hexane-EtOAc (85:10) as eluent to give the product **58** (0.12 g, 84%) as a colourless liquid.

$[\alpha]_D^{25}$ +49.17 (*c* 1.2, $CHCl_3$).

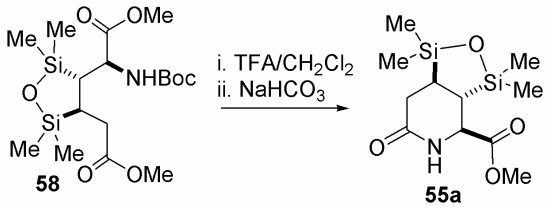
R_f 0.7 (hexane/EtOAc, 75:25).

IR ($CHCl_3$): 3364, 3019, 2955, 2904, 1733, 1715, 1456, 1366, 1254, 1210, 1162, 1055, 933, 847 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.09 (3 H, s, SiMe), 0.11 (3 H, s, SiMe), 0.22 (3 H, s, SiMe), 0.26 (3 H, s, SiMe), 0.87–0.96 (1 H, m, $Me_2SiCHCH_2$), 1.21–1.40 (1 H, m, $Me_2SiCHCH_2$), 1.43 (9 H, s, NH*Boc*), 2.27 (1 H, dd, *J* = 9.7, 16.8 Hz, $CH_AH_BCO_2Me$), 2.77 (1 H, dd, *J* = 5.0, 16.76 Hz, $CH_AH_BCO_2Me$), 3.64 (3 H, s, CO_2Me), 3.71 (3 H, s, CO_2Me), 4.39–4.52 (1 H, m, NHC*H*), 5.29 (1 H, d, *J* = 8.6 Hz, NH).

^{13}C-NMR (50 MHz, $CDCl_3$): δ −2.4, −1.3, 0.6, 0.7, 22.5, 28.3 (3 C), 34.3, 35.6, 51.5, 52.1, 53.2, 79.9, 155.2, 173.3, 174.3.

Anal. (Found: C, 49.08; H, 7.93; N, 2.91. $C_{17}H_{33}NO_7Si_2$ requires C, 48.66; H, 7.93; N, 3.34%).



(3a*R*, 4*R*, 7a*R*)-methyl octahydro-1,1,3,3-tetramethyl-6-oxo-[1,2,5]oxadisilolo[3,4-c]pyridine-4-carboxylate 55a

Freshly distilled TFA (0.3 mL) was added to a stirred solution of **58** (85 mg, 0.2 mmol) in CH_2Cl_2 (0.3 mL) at 30 ºC. After 1 h, the reaction mixture was evaporated and the residue was quenched with aqueous sodium bicarbonate solution. The reaction mixture was extracted with CH_2Cl_2 and the organic extract was washed with brine, dried over

anhydrous $MgSO_4$ and evaporated to give the cyclized product **55a** (57 mg, 99%) as a colourless liquid.

$[\alpha]_D^{25}$ −20.0 (*c* 1.0, $CHCl_3$).

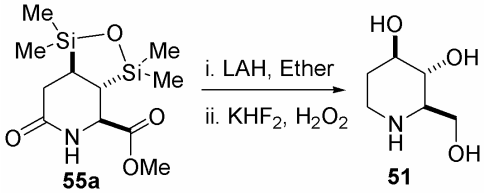
R_f 0.51 ($CHCl_3$/MeOH, 95:5).

IR ($CHCl_3$): 3303, 3008, 2955, 2898, 1740, 1659, 1469, 1352, 1255, 1201, 1133, 1042, 927, 843 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.10 (3 H, s, SiMe), 0.21 (3 H, s, SiMe), 0.25 (3 H, s, SiMe), 0.28 (3 H, s, SiMe), 1.02–1.34 (2 H, m, 2 × $Me_2SiCHCH_2$), 2.17 (1 H, dd, *J* = 12.0, 18.0 Hz, CH_AH_BCON), 2.54 (1 H, dd, *J* = 4.0, 18.0 Hz, CH_AH_BCON), 3.77 (3 H, s, CO_2Me), 4.12 (1 H, d, *J* = 12 Hz, *CH*NH), 6.81 (1 H, s, broad, NH).

^{13}C-NMR (50 MHz, $CDCl_3$): δ −3.1, −2.5, −0.8, −0.1, 25.4, 30.2, 32.7, 52.3, 58.3, 171.9, 171.8.

HRMS (ESI) *m/z*: Found MH^+ 288.1080, $C_{11}H_{22}NO_4Si_2$ requires 288.1087.



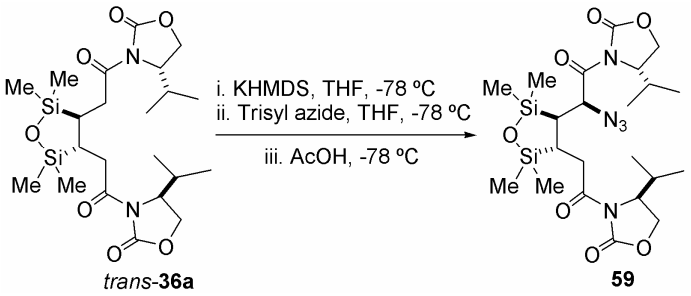
D-Fagomine 51

A solution of LAH (91 mg, 2.4 mmol) in dry ether (10 mL) was cannulated to the lactam **55a** (50 mg, 0.17 mmol) at 0 ºC under argon. The reaction temperature was raised to 30 ºC and heated under reflux for 4 h. After cooling to 0 ºC, the reaction mixture was diluted with ether and quenched with 15% aqueous NaOH solution and water. The reaction mixture was filtered and the residue was washed well with ether. The combined filtrate was concentrated and hydrogen peroxide (0.5 mL, 30%) was added to it followed by the addition of KHF_2 (90 mg, 1.2 mmol) and THF/MeOH (6 mL, 1:1) as the solvent. After 15

h at 60 ºC, the solvent was evaporated under reduced pressure and the white residue was purified by ion-exchange resin to give pure Fagomine **51** (17 mg, 68%) as a white solid. **$[\alpha]_D^{22}$** +18.6 (*c* 0.43, H_2O), [*lit.*:[171] $[\alpha]_D^{25}$ +18.0 (*c* 0.92, H_2O)].

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.35 (1 H, dq, *J* = 4.4, 13 Hz), 1.80–1.95 (1 H, m), 2.46–2.64 (2 H, m), 2.91–3.04 (1 H, m), 3.09 (1 H, t, *J* = 9.4 Hz), 3.35–3.57 (2 H, m), 3.71 (1 H, dd, *J* = 3.1, 12.0 Hz).

^{13}C-NMR (125 MHz, $CDCl_3$): δ 32.0, 42.4, 60.7, 61.0, 72.6, 72.8.



(*S*)-3-((*R*)-2-azido-2-((3*S*,4*S*)-4-(2-((*S*)-4-isopropyl-2-oxooxazolidin-3-yl)-2-oxoethyl)-2,2,5,5-tetramethyl-1,2,5-oxadisilolan-3-yl)acetyl)-4-isopropyloxazolidin-2-one 59

Following the procedure for the preparation of **56**, *trans*-**36a** (2 g, 4 mmol), KHMDS (8 mL, 1 *M* solution in THF, 8 mmol, 2 equiv), trisyl azide (2.4 g, 8 mmol) and acetic acid (1.2 mL, 20 mmol) gave azide **59** (1.6 g, 74%) as a colorless solid. mp 125 ºC (from hexane-EtOAc).

$[\alpha]_D^{28}$ +35.79 (*c* 1.01, MeOH).

R_f 0.65 (hexane/EtOAc, 75:25).

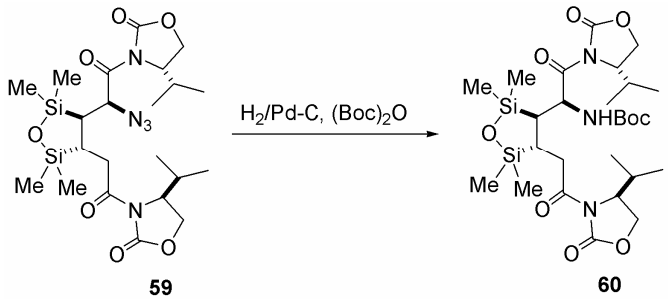
IR ($CHCl_3$): 3019, 2965, 2877, 2105, 1780, 1698, 1387, 1251, 1207, 1102, 934, 844 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.06 (3 H, s, SiMe), 0.24 (3 H, s, SiMe), 0.27 (3 H, s, SiMe), 0.34 (3 H, s, SiMe), 0.82–0.95 (12 H, m, 2 × $NCO_2CH_2CHCH\mathit{Me_2}$), 1.18–1.40 (1 H, m, $Me_2SiC\mathit{H}CH_2$), 1.49–1.59 (1 H, m, $Me_2SiC\mathit{H}CH_2$), 2.23–2.47 (2 H, m, 2 × $NCHC\mathit{H}Me_2$), 2.58 (1 H, dd, *J* = 10.8, 18.0 Hz, $C\mathit{H_A}H_BCON$), 3.48 (1 H, dd, *J* = 5.4, 18.0

Hz, CH_AH_BCON), 4.05–4.59 (6 H, m, 2 × NCO_2CH_2CH, 2 × $NCHCHMe_2$), 5.39 (1 H, d, *J* = 7.6 Hz, CHN_3).

^{13}C-NMR (50 MHz, $CDCl_3$): δ −2.3, −0.9, 0.8, 1.1, 14.4, 14.5, 17.7, 17.8, 23.2, 28.1 (2 C), 33.3, 37.2, 58.2, 58.6, 61.9, 63.3, 63.9, 153.7, 154.0, 170.5, 173.2.

Anal. (Found: C, 49.10; H, 6.96; N, 12.96. $C_{22}H_{37}N_5O_7Si_2$ requires C, 48.96; H, 6.91; N, 12.98%).



59 60

(*S*)-3-((*R*)-2-((*tert*-butyloxycarbonyl)amino)-2-((3*S*,4*S*)-4-(2-((*S*)-4-isopropyl-2-oxooxazolidin-3-yl)-2-oxoethyl)-2,2,5,5-tetramethyl-1,2,5-oxadisilolan-3-yl)acetyl)-4-isopropyloxazolidin-2-one 60

Following the procedure for the preparation of **57**, azide **59** (1.5 g, 2.8 mmol) and $(Boc)_2O$ (1.2 g, 5.5 mmol) gave protected amine **60** (1.65 g, 96%) as a colorless solid. mp 181 ºC (from hexane-EtOAc).

$[\alpha]_D^{28}$ +46.73 (*c* 1.01, $CHCl_3$).

R_f 0.5 (hexane/EtOAc, 75:25).

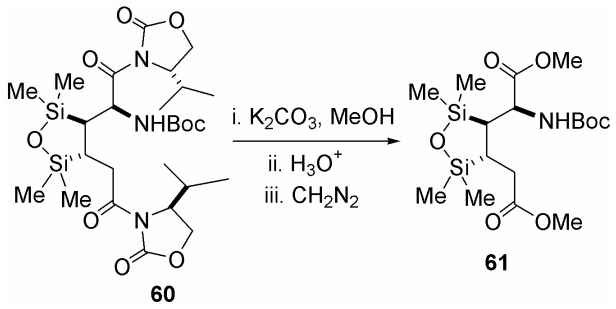
IR ($CHCl_3$): 3453, 3345, 3019, 2967, 2878, 1782, 1697, 1488, 1389, 1251, 1205, 1101, 919, 844 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.02 (3 H, s, SiMe), 0.11 (3 H, s, SiMe), 0.27 (3 H, s, SiMe), 0.35 (3 H, s, SiMe), 0.82–0.91 (12 H, m, 2 × $NCO_2CH_2CHCHMe_2$), 1.24–1.56 (2 H, m, 2 × $Me_2SiCHCH_2$), 1.40 (9 H, s, NH*Boc*), 2.24–2.45 (2 H, m, 2 × $NCHCHMe_2$), 2.78 (1 H, dd, *J* = 10.6, 19.2 Hz, CH_AH_BCON), 3.72 (1 H, dd, *J* = 4.6, 19.2 Hz,

CH_AH_BCON), 4.13–4.37 (6 H, m, 2 × NCO_2CH_2CH, 2 × $NCHCHMe_2$), 4.98 (1 H, s, broad, *NH*), 5.69–5.77 (1 H, m, *CH*NHBoc).

^{13}C-NMR (50 MHz, $CDCl_3$): δ −2.5, −0.2, 0.6, 1.2, 14.4, 14.5, 17.6, 17.7, 21.8, 28.0 (3 C), 28.3 (2 C), 34.8, 36.9, 52.4, 58.2, 58.5, 63.2, 63.5, 79.6, 153.0, 153.7, 155.0, 173.7, 174.7.

Anal. (Found: C, 53.03; H, 7.70; N, 6.86. $C_{27}H_{47}N_3O_9Si_2$ requires C, 52.83; H, 7.72; N, 6.85%).



(*R*)-Methyl 2-((*tert*-butyloxycarbonyl)amino)-2-((3*S*,4*S*)-4-(2-methoxy-2-oxoethyl)-2,2,5,5-tetramethyl-1,2,5-oxadisilolan-3-yl)acetate 61

Following the procedure for the preparation of **58**, the dioxazolidin-2one **60** (1.4 g, 2.3 mmol), K_2CO_3 (1 g, 7.2 mmol), methanol (30 mL) and diazomethane gave the pure product **61** (0.83 g, 86%) as a colorless liquid.

$[\alpha]_D^{28}$ −11.0 (*c* 1.02, $CHCl_3$).

R_f 0.7 (hexane/EtOAc, 75:25).

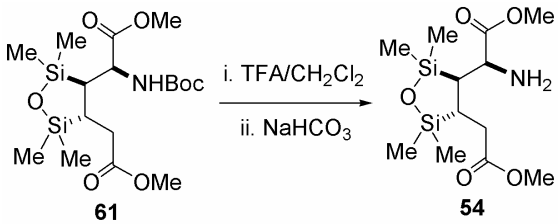
IR ($CHCl_3$): 3517, 3345, 3019, 2954, 2903, 1735, 1718, 1499, 1366, 1253, 1204, 1169, 936, 846 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ 0.10 (3 H, s, SiMe), 0.12 (3 H, s, SiMe),) 0.22 (3 H, s, SiMe), 0.30 (3 H, s, SiMe), 1.19–1.52 (2 H, m, 2 × $Me_2SiCHCH_2$), 1.43 (9 H, s, NH*Boc*), 2.18 (1 H, dd, *J* = 11.2, 16.2 Hz, $CH_AH_BCO_2Me$), 2.90 (1 H, dd, *J* = 3.5, 16.2 Hz,

$CH_AH_BCO_2Me$), 3.64 (3 H, s, CO_2Me), 3.73 (3 H, s, CO_2Me), 4.44–4.59 (1 H, m, NHC*H*), 4.76 (1 H, s, broad, NH).

^{13}C-NMR (50 MHz, $CDCl_3$): δ −2.7, −0.3, 0.3, 0.6, 22.3, 28.0 (3 C), 34.7, 35.1, 51.1, 51.8, 52.4, 79.8, 155.1, 173.8 (2 C).

Anal. (Found: C, 48.76; H, 7.91; N, 3.41. $C_{17}H_{33}NO_7Si_2$ requires C, 48.66; H, 7.93; N, 3.34%).



(*R*)-Methyl 2-(amino)-2-((3*S*,4*S*)-4-(2-methoxy-2-oxoethyl)-2,2,5,5-tetramethyl-1,2,5-oxadisilolan-3-yl)acetate 54

Freshly distilled TFA (2 mL) was added to a stirred solution of urethane **61** (0.5 g, 1.2 mmol) in CH_2Cl_2 (2 mL) at 30 ºC. After 1 h, the solvent was removed under reduced pressure and the residue was diluted with aqueous sodium bicarbonate solution. The mixture was extracted with CH_2Cl_2 and the organic extract was washed with brine, dried over anhydrous $MgSO_4$ and evaporated to give amine **54** (0.37 g, 96%) as a brownish liquid.

$[\alpha]_D^{24}$ −10.4 (*c* 1.04, $CHCl_3$).

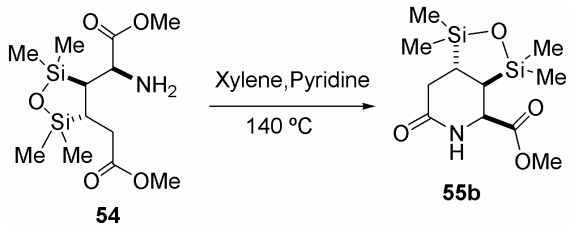
R_f 0.35 (hexane/EtOAc, 75:25).

IR ($CHCl_3$): 3430, 3394, 3302, 3017, 2953, 2903, 2847, 1735, 1437, 1353, 1252, 1202, 1105, 1008, 930, 846 cm^{-1}.

^{1}H-NMR (200 MHz, $CDCl_3$): δ −0.06 (3 H, s, SiMe), 0.04 (3 H, s, SiMe), 0.06 (3 H, s, SiMe), 0.12 (3 H, s, SiMe), 0.94–1.10 (1 H, m, $Me_2SiCHCH_2$), 1.25–1.39 (1 H, m, $Me_2SiCHCH_2$), 1.56 (2 H, s, broad, NH_2), 2.03 (1 H, dd, *J* = 11.4, 16.1 Hz,

C*H*$_A$H$_B$CO$_2$Me), 2.39 (1 H, dd, *J* = 5.0, 19.2 Hz, CH$_A$*H*$_B$CO$_2$Me), 3.28 (1 H, d, *J* = 7.8 Hz, *CH*NH$_2$), 3.49 (3 H, s, CO$_2$Me), 3.57 (3 H, s, CO$_2$Me).

^{13}C-NMR (50 MHz, CDCl$_3$): δ −2.6, −0.8, 0.6, 1.2, 22.8, 34.9, 36.6, 51.2, 51.5, 54.8, 173.8, 177.4.



54 55b

(3a*S*, 4*R*, 7a*S*)-methyl octahydro-1,1,3,3-tetramethyl-6-oxo-[1,2,5]oxadisilolo[3,4-c]pyridine-4-carboxylate 55b

A solution of the amine **54** (0.35 g, 1.1 mmol) and pyridine (0.3 mL) in freshly distilled *p*-xylene (45 mL) was gently refluxed at 145 ºC under argon atmosphere. After 9 h, the reaction mixture was evaporated under reduced pressure and the residue was purified by column chromatography on silica using CHCl$_3$-MeOH (97:3) as eluent to give the product **55b** (0.22 g, 70%) as a colourless liquid.

[α]$_D^{27}$ +80.9 (*c* 0.88, CHCl$_3$).

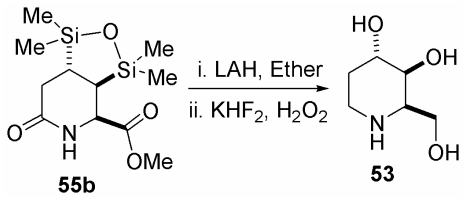
R$_f$ 0.5 (CHCl$_3$/MeOH, 95:5).

IR (CHCl$_3$): 3301, 3009, 2955, 2899, 1741, 1659, 1469, 1353, 1256, 1201, 1132, 1042, 925, 842 cm^{-1}.

^{1}H-NMR (200 MHz, CDCl$_3$): δ 0.00 (3 H, s, SiMe), 0.10 (3 H, s, SiMe), 0.20 (3 H, s, SiMe), 0.30 (3 H, s, SiMe), 1.33–1.43 (1 H, m, Me$_2$SiC*H*CH$_2$), 1.56–1.72 (1 H, m, Me$_2$SiC*H*CH$_2$), 2.16 (1 H, dd, *J* = 12.2, 17.7 Hz, C*H*$_A$H$_B$CON), 2.51 (1 H, dd, *J* = 5.1, 17.7 Hz, CH$_A$*H*$_B$CON), 3.68 (3 H, s, CO$_2$Me), 4.33 (1 H, dd, *J* = 3, 5.9 Hz, *CH*NH), 7.03 (1 H, s, broad, NH).

^{13}C-NMR (50 MHz, $CDCl_3$): δ −3.2, −1.7, −0.4 (2 C), 19.8, 29.2, 32.7, 52.1, 55.5, 171.9, 172.9.

HRMS (ESI) *m/z*: Found MH^+ 288.1094, $C_{11}H_{22}NO_4Si_2$ requires 288.1087.



D-3,4-Di-*epi*-fagomine 53

Following the procedure for the preparation of fagomine **51**, the lactam **55b** (70 mg, 0.24 mmol), lithium aluminium hydride (100 mg, 2.6 mmol), hydrogen peroxide (0.6 mL, 30%) and KHF_2 (0.11 g, 1.4 mmol) gave pure 3,4-di-*epi* fagomine **53** (23 mg, 65%) as a colorless liquid.

$[\alpha]_D^{24}$ +12.1 (*c* 0.33, H_2O) [(*lit.*:[171] $[\alpha]_D^{25}$ +13.4 (*c* 0.32, H_2O)].

^{1}H-NMR (200 MHz, $CDCl_3$): δ 1.51–1.67 (1 H, m), 1.87–2.06 (1 H, m), 2.90–3.02 (2 H, m), 3.16–3.27 (1 H, m), 3.58–3.66 (2 H, m), 3.66–3.74 (1 H, m), 3.79–3.88 (1 H, m).

^{13}C-NMR (50 MHz, $CDCl_3$): δ 27.6, 41.0, 57.8, 62.2, 68.2, 69.3.

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LIST OF PUBLICATIONS

Journal publications

1. **Pintu K. Kundu** and Sunil K. Ghosh*. Silicon-mediated asymmetric synthesis of fagomine and 3,4-di-epi-fagomine. *Tetrahedron: Asymmetry*, **2011**, *22*, 1090-1096.

2. **Pintu K. Kundu** and Sunil K. Ghosh*. Magnesium-induced regiospecific C-silylation of suitably substituted enoates and dienoates. *Tetrahedron*, **2010**, *66*, 8562-8568.

3. **Pintu K. Kundu** and Sunil K. Ghosh*. Magnesium-mediated intramolecular reductive coupling: a stereoselective synthesis of C_2-symmetric 3,4-bis-silyl-substituted adipic acid derivatives. *Org. Biomol. Chem.*, **2009**, *7*, 4611-4621.

4. **Pintu K. Kundu**, Rekha Singh and Sunil K. Ghosh*. Silicon assisted diversified reaction of a β-silylmethylene malonate with dimethylsulfoxonium methylide. *J. Organomet. Chem.*, **2009**, *694*, 382-388.

Bulletin publications

5. **Pintu K. Kundu** and Sunil K. Ghosh. Functionalized organosilicon compounds: synthesis and applications. *Society for Materials Chemistry,* **2011**, accepted.

Symposium and conference publications and presentations

6. **Pintu K. Kundu** and Sunil K. Ghosh. Silicon-mediated asymmetric synthesis of some bio-active molecules. *National Conference on Chirality*, **2011**, The M. S. University of Baroda, Vadodara, India (**Oral Presentation**).

7. **Pintu K. Kundu** and Sunil K. Ghosh. Organo-silicon compounds in diversified organic synthesis. *Chemistry Research Scholars' Meet,* **2011,** IGCAR, Kalpakkam, India (**Oral Presentation).**

8. **Pintu K. Kundu** and Sunil K. Ghosh. Diversity oriented synthetic strategies for functionalized organo-silicon compounds and their applications. *23rd Research Scholars' Meet*, **2011,** N. G. Acharya & D. K. Marathe College, Mumbai, India (**Oral Presentation).**

9. **Pintu K. Kundu** and Sunil K. Ghosh. Diversity oriented synthesis of functionalized small molecules using organo-silicon compounds. *3rd DAE-BRNS International Symposium on Materials Chemistry*, **2010,** BARC, Mumbai, India (**Poster Presentation).**

10. **Pintu K. Kundu** and Sunil K. Ghosh. Regiospecific C-silylation of suitably substituted enoates and stereoselective synthesis of C_2-symmetric 3,4-bis-silyl-substituted adipic acid derivatives by Mg/silyl chloride/system. *5th Mid-Year Chemical Research Society of India Symposium in Chemistry*, **2010,** NIIST, Thiruvananthapuram, India (**Poster Presentation).**

11. **Pintu K. Kundu** and Sunil K. Ghosh. Stereoselective synthesis of C_2-symmetric 3,4-bis-silyl-substituted adipic acid derivatives by a magnesium-mediated reductive coupling. *5th J-NOST Conference for Research Scholars*, **2009,** IIT-Kanpur, Kanpur, India (**Oral Presentation).**

12. **Pintu K. Kundu,** Rekha Singh and Sunil K. Ghosh. Silicon assisted diversified reaction of a β-silylmethylene malonate with dimethylsulfoxonium methylide. *2nd DAE-BRNS International Symposium on Materials Chemistry*, **2008,** BARC, Mumbai, India (**Poster Presentation).**