MICHAEL ADDITION REACTION FOR THE SYNTHESIS OF FUNCTIONALIZED ORGANIC MOLECULES AND THEIR APPLICATIONS

By

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DECLARATION

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Raghunath Chowdhury

“The book one must read to learn chemistry is the book of nature”

— Swami Vivekananda

DEDICATED TO……

MY
TEACHERS

AND

MY
PARENTS

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……..***Raghunath***

CONTENTS

SYNOPSIS

MICHAEL ADDITION REACTION FOR THE SYNTHESIS OF FUNCTIONALIZED ORGANIC MOLECULES AND THEIR APPLICATIONS

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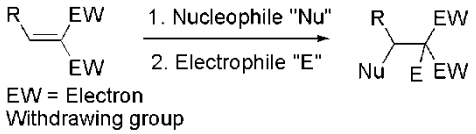
Michael Addition Reaction for the Synthesis of Functionalized Organic Molecules and Their applications

This thesis describes the reagent control and organocatalyzed Michael addition reaction for the synthesis of functionalized organic molecules and their applications for natural and unnatural product synthesis. The content of this thesis has been divided into five chapters.

Chapter 1

Michael Addition Reaction

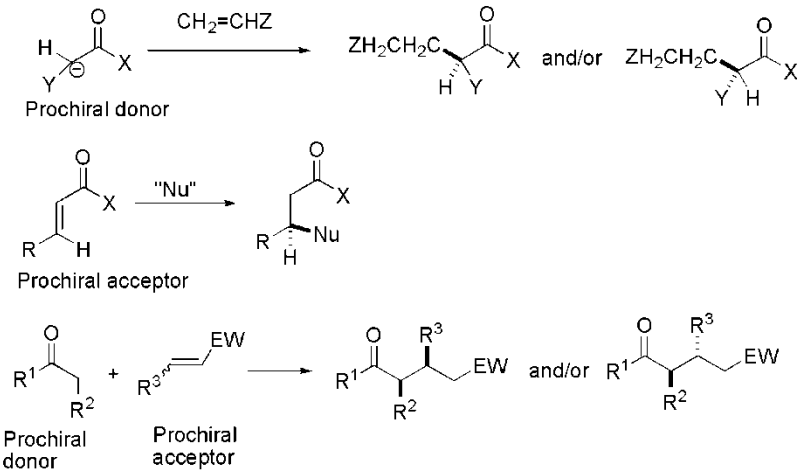
This chapter presents a brief overview of Michael addition[1] reaction in terms of recent developments and usefulness. Michael addition involves the addition of a nucleophiles (also known as donor, which can be carbon or heteroatom based) to an alkene or alkyne attached to electron withdrawing groups (also known as acceptor).[2] This nucleophilic addition is followed by a trapping of the anionic intermediate with an electrophile, which is a proton in the simplest case (Scheme 1).



Scheme 1. General Michael addition reaction**.**

The carbon centered nucleophilic addition may take place enantioselective or non-enantioselective manner. As the demand for the optically active compounds is increasing in recent years, much progress has been made in the asymmetric version of this reaction,

providing the Michael adduct with high enantiomeric purity. The asymmetric Michael reaction could be categorized in three groups: (i) enantioselective addition of prochiral donor to acceptor; (ii) enantioselective addition of a donor to a prochiral acceptor; (iii) enantio- and diastereoselective addition of of prochiral donor to prochiral acceptor (Scheme 2).



Scheme 2. Reactions of prochiral Michael donors and acceptors.

Out of several procedures for the enantiocontrolled synthesis, the use of asymmetric catalysis has been well recognized. It offers the best "atom economy" as the stoichiometric addition or removal of chiral auxaliaries can be avoided. The asymmetric version of Michael reaction can be catalyzed by both organo-catalysts and organometallic compounds. Metal based catalysis has long been the dominant approach but recently organocatalytic methods have growing attention. The advantages of metal based catalysts are due to the properties of the metal because metal can act as Lewis acid or Lewis base. Besides the reactivity, the catalysts can be fine tuned by changing the ligand surroundings the metal. The disadvantages of these catalysts are: (i) most of the metal catalysts are

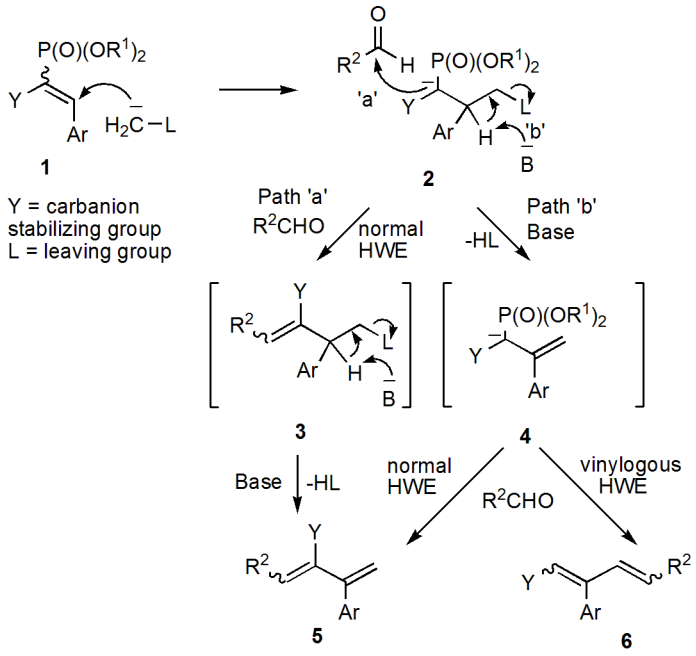
sensitive to air and moisture so metal catalyzed reaction require the exclusion of air and moisture; (ii) in addition, some of the metal catalyst are poisonous and some of them are expensive, which are the real challenges in the preparation of pharmaceutical compounds. On the other hand the organocatalysts are small purely "organic" molecules. They are usually stable in air and moisture and also easy to handle and they can be easily removed from the desired products. They also mimic the role of a metal as a Lewis acid or Lweis base. The acidity or the basicity arises from the type of heteroatom (N, O, S and P) present in the organocatalyst.[3]

Chapter 2

A Domino Michael-HWE-elimination Route for the Synthesis of Functionalised Trisubstituted 1,3–Butadiens

Aryl-substituted conjugated dienes are useful building blocks due to their utilization in numerous transformations such as the Diels-Alder reactions. They also appear as important structural subunits in natural products and have applications in material sciences. A large number of methods are available for their syntheses involving multiple stages of reactions. The direct and efficient preparation of stereo defined substituted and functionalized conjugated dienes is not straightforward and remains an area of current investigation. This chapter describes a domino Michael-HWE-elimination route for the synthesis of functionalised trisubstituted 1,3–butadiens. It involves a one-pot four-component sequential double-olefination reaction of lithium dimsylate, lithium ethoxide, 2-(arylmethylidene)-2-phosphonoacetonitriles and aldehydes leading to the selective construction of trisubstituted 1,3–butadiens.

A multicomponent domino approach to highly and differentially substituted regio- and stereoisomeric 1,3-dienes could be envisaged from simple building blocks viz. an activated vinyl phosphonate, a carbenoid and an aldehyde as shown in (Scheme 3).

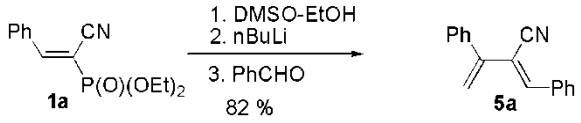


Scheme 3. Proposed pathways for synthesis of isomeric 1,3-dienes.

Carbanion with a leaving group attached to that carbon in combination with a base can be considered as 'carbenoid' equivalent. The addition of a nucleophilic L-H_2C^- carbanion (L is a leaving group) (Scheme 3) to a Michael acceptor containing a phosphonate activating group **1** is expected to lead to the adduct **2.** In the presence of a base and an aldehyde, this adduct could subsequently provide the dienes **5** and / or **6** by two routes via intermediates **3** (Path 'a') and **4** (Path 'b'). In Path 'a', the adduct **2** would first undergo a Horner–Wadsworth–Emmons (HWE) reaction with the added aldehyde followed by a base induced elimination to give **5** only. Path 'b' would follow a reverse sequence of reactions where the base induced elimination would precede to give the intermediate allylic phosphonate ylide **4**. Unlike Path 'a', the mesomeric forms of ylide **4**

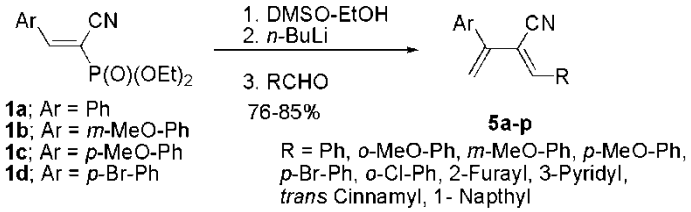
in Path ‘b’ can, in principle, serve as a precursor for diverse products either by enduring a normal HWE reaction (α-attack) or a vinylogous HWE reaction[4] (γ-attack) with the aldehyde to provide **5** or **6**, respectively.

A few 2-(arylmethylidene)-2-phosphonoacetonitriles **1** were prepared in very good yields using diethyl (cyanomethyl)phosphonate and the corresponding aromatic aldehydes by a Knoevenagel type reaction.[5] When 2-(phenylmethylidene)-2-phosphonoacetonitrile **1a** (Scheme 4) was added to the reaction mixture containing 2.5 equiv of *n*-BuLi, 1.5 equiv of each of DMSO and ethanol followed by quenching the reaction with benzaldehyde, it gave the diene **5a** in good yield with excellent regio- and stereoselectivity.



Scheme 4. Reaction of **1a** with Li-dimsylate /LiOEt and PhCHO.

The generality of this sequential double olefination for the synthesis of the tri-substituted 1,3-dienes has been established with a wide range of aldehydes bearing aryl, heteroaryl and alkenyl groups and vinyl phosphonate **1a-d**. In all cases, the desired products were formed in good yield and with excellent regio, and stereoselectivity[6] as showen in Scheme 5**.** The method was also used for the synthesis of 4,4-dideuterated dienes using DMSO-d_6.



Scheme 5. Synthesis of 1,3 dienes.

Chapter 3

Organocatalyzed Enantioselective Michael Addition of Alkyl-Methyl Ketones to a Silylmethylene Malonate

Carbonyl compounds having a silyl group at β-position are popular targets because of their versatile nature and are also excellent surrogate for the acetate aldol reaction. We are concerned for the asymmetric synthesis of intermediates of type **6** or **7** (Figure 1) containing a silicon group positioned at β to both a ketone and an ester functionalities. Earlier efforts from our group used the desymmetrization reaction on 3-silyl-glutaric anhydride followed by selective alkylation of one of the carboxylic acid group to achieve this. Since then we were in search better methodologies for the same.

The Michael addition is one to be the most frequently used reaction because of its efficiency and effectiveness. Significant development has been made in the asymmetric version of this reaction, providing adducts with high enantiomeric purity. Aldehydes and ketones have generally been used as donors after their modifications to more activated species such as enolate or enamines. The major drawbacks for the enolate/enamine use are the addition of extra synthetic step(s) and stoichiometric use of chiral induction reagent. In recent times, organocatalysis route has been developed for the direct addition of ketones or aldehydes to activated olefins, especially to nitroolefins with satisfactory results. However, the addition of the same donors to alkylmethylene malonates is less successful. Some reports[7-9] have been published in this type of addition with arylmethylene malonates but the adducts were formed in moderate to good yields and good to high enantioselectivities, depending upon the substituents present on the ketones and the arylmethylene malonates. Alkylmethylene malonates were not good acceptors for this reaction. Although cyclic

ketones reacted with good diastereo- and enantioselectivities, acyclic ketones gave poor results. Despite some success of these methodologies, reaction with acyclic non-symmetrical ketones, especially the methyl ketones remains very challenging. Besides yield and enantioselectivity, the regioselectivity of the addition is also an important issue. This chapter describes our efforts for the development of an efficient, highly regio and enantioselective organocatalytic conjugate addition of acyclic methyl ketones to the silylmethylene malonate **8** (Figure1) providing β-silyl-δ-keto-diesters **7**.

We first choose acetone as the model ketone to obviate the regioselectivity issue and concentrated our effort to optimize the yield and enantioselectivity of the adduct. For this reaction, we surveyed few natural amino-acid and some pyrrolidine based organocatalysts **9** (Fig. 1) derived from proline. Out of these, the catalysts **9c**, **9d** and **9e** only could promote the reaction, although initially with moderate yield and enantioselectivity.

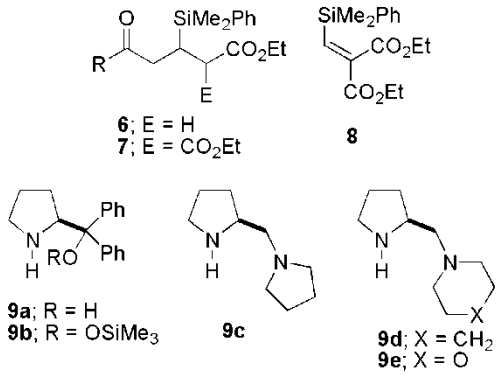
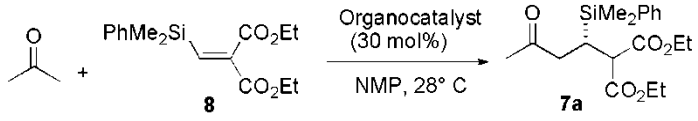


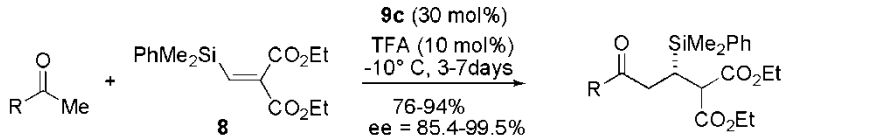
Figure 1. Structure of the catalysts, substrate, and targets.



Scheme 6. Organocatalysed direct addition of acetone to **8**.

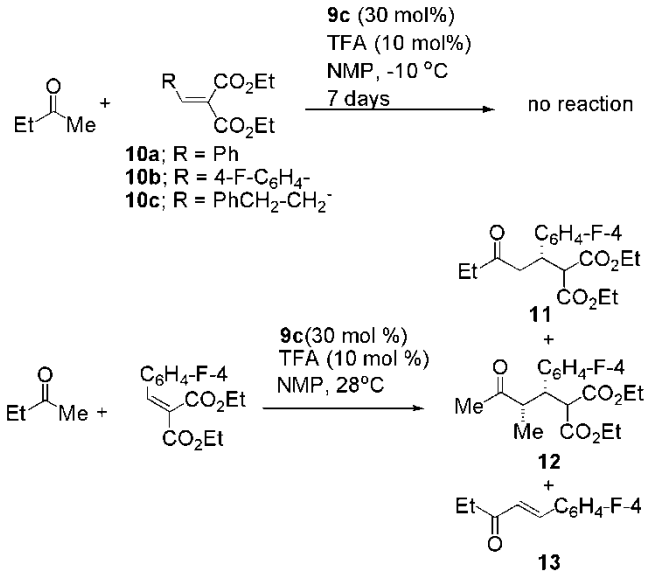
We could establish an optimized condition using catalyst **9c**. The optimized conditions is to use 12 equiv. of acetone with respect to silylmethylene malonate **8** and 30 mol% of catalyst **9c** in combination with 10 mol% of TFA in NMP (0.25 M) at –10 °C for 7 days providing the adduct **7a** in 76% yield and with 90% ee.

With optimal catalyst, additive and reaction conditions established with acetone, we went one step ahead by introducing unsymmetrical alkyl methyl ketones as donors. Unlike acetone, alkyl methyl ketones introduce the problem of regioselectivity. When methyl isopropyl ketone was reacted with silylmethylene malonate **8** under the optimized condtions, we obtained only one regioisomeric product **7b** in very high yield and with excellent enantioselectivity (Scheme 7). Initially it was envisaged that the high regioselectivity might be an outcome of the steric crowding by the isopropyl group. However, this was discounted from the results with several other ketones, lacking any such steric congestion. In all the cases the adducts (**7c-k**) were formed only by the reaction at the methyl terminal of the acetyl group of the ketones.[10] Also, the adducts were obtained in very good yield and enantioselectivity. The reactions required excess amount of the ketone (2-12 equiv.) to get an appreciable rate of the reaction and completion within the time period mentioned. Valuable ketones can be recovered as other by-product formations were not observed.



Scheme 7. Regioselctive addition of alkyl methyl ketones to **8**.

We next attempted to generalize this regio- and enantioselective methyl ketone addition to arylidene and alkylidene malonates. Therefore, the diethyl esters of phenylmethylene, 4-flurophenylmethylene and 2-phenylethylmethylene malonates **10a-c** were reacted with methyl ethyl ketone in the presence of catalyst **9c** under the optimized conditions described for silylmethylene malonate **8** (Scheme 8). No reaction took place with none of these methylene malonates. Even at higher temperature (28 °C), the reaction between diethyl 4-flurophenylmethylene malonate **10b** and methyl ethyl ketone catalyzed by **9c** was very sluggish and regioisomeric product **12** and by-product **13** were formed along with the desired **11**.



Scheme 8. Addition of ethyl methyl ketone to aryl and alkylmethylene malonates.

So, we have developed an organocatalytic asymmetric Michael addition of alkyl methyl ketones to a β-silylmethylene malonate **8** with high regio- and enantioselectivity. This is the first successful attempt to engage unsymmetrical methyl ketone to add via methyl terminal and for the silyl group is the key of success.

Chapter 4

Synthetic Applications of β-Silyl-δ-keto Esters for Natural Products and Their Analogs

Carbonyl compounds having a silyl group at β-position are popular targets because of their versatile nature and are also excellent surrogate for the acetate aldol reaction. We are concerned for the asymmetric synthesis of intermediates of type **6** or **7** (Figure 1) containing a silicon group positioned at β to both a ketone and an ester functionalities because they could be synthons for *privileged* structures containing chiral *N*- and *O*-heterocycles. In the preceding chapter we described the asymmetric synthesis of intermediates of type **7** (Fig 2) containing a silicon group positioned β to both a carbonyl and an ester functionality. This chapter describes the conversion of these diesters to β-silyl-δ-keto esters **6** (Fig. 2) and their uses in natural product and analogs syntheses.

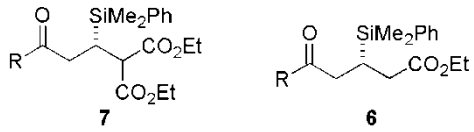
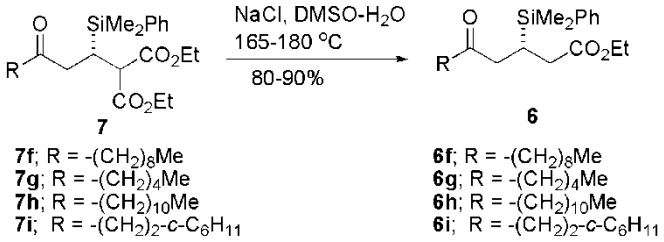


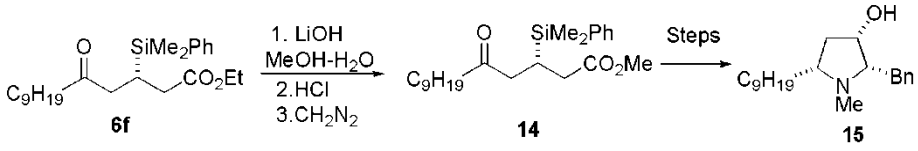
Figure 2. β-silyl-δ-keto esters intermediates.

A few ketodiesters **7f-i** (see, Chapter 3) were subjected to Krapcho deethoxycarbonylation[11] leading to ketoesters **6f-i**, respectively (Scheme 9) in very good yields. The ketoesters can further be parlayed to natural products with well known biological activities. For example, ketoester **6f** (Scheme 10) was hydrolyzed with LiOH followed by esterification with diazomethane gave the keto methyl ester **14**. By comparing the sign and magnitude of the optical rotation value of **14** ($[\alpha]_D^{24}$ = –0.8, *c* 0.8, $CHCl_3$) with the reported value[12] ($[\alpha]_D^{21}$ = –0.8, *c* 0.79, $CHCl_3$), the stereochemistry of the Si-

bearing chiral centre was concluded to be of (*S*) configuration. This also confirmed the absolute stereochemistry of the adduct **6f**. This keto ester **14** can be converted to a pyrrolidine skeleton easily and has already been transformed into (+)-preussin **15**, a hydroxylated pyrrolidine natural product in a few steps.



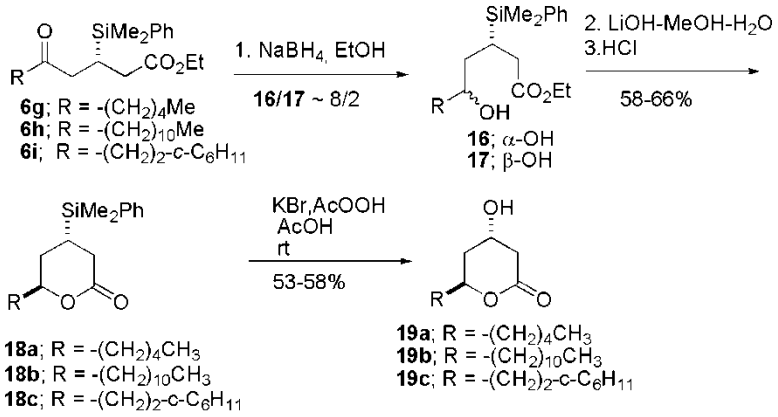
Scheme 9. Synthesis of δ-keto-β-silyl esters.



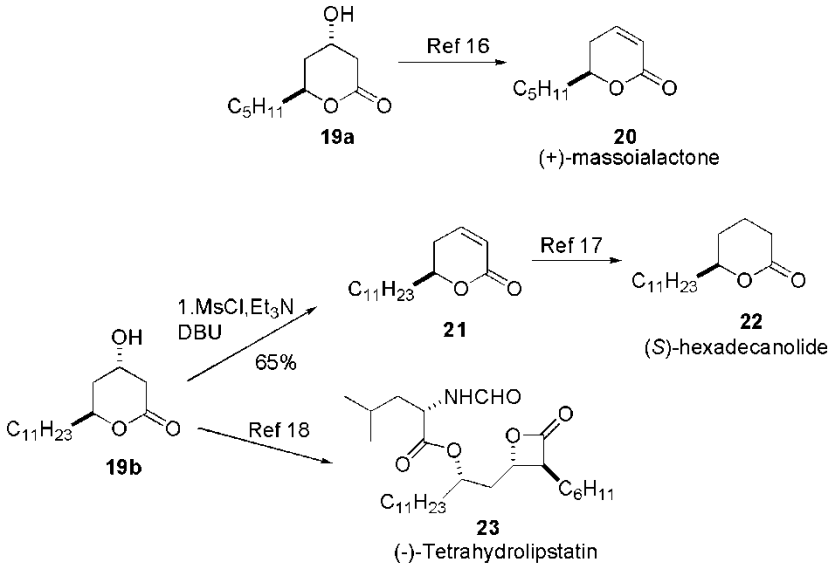
Scheme 10. Synthesis of (+)-preusssin.[12]

The keto-esters **6g-i** were converted to known chiral δ-valerolactones intermediates[13] (Scheme 11) known to be used for the synthesis of natural products having a large spectrum of biological properties including important pharmacological activities. For this, a silicon-directed stereoselective reduction[14] of the ketones **6g-i** with sodium borohydride gave an inseparable mixture of diastereoisomeric alcohols **16a-c** and **17a-c** (**16**/**17** ~ 80:20) in very good yield (Scheme 11). The diastereoisomeric hydroxy ester mixture in each case was then hydrolyzed and the intermediate hydroxy acids underwent a smooth cyclization to give the major δ-lactones **18a-c**. The dimethyl(phenyl)silyl group in **18a-c** was then converted to the hydroxy group following Fleming oxidation[15] using potassium bromide and peracetic acid with retention of configuration leading to hydroxy lactones **19a-c**. Lactone (–)-**19a**[16] is the antipode of the hydroxy lactone that has already

been converted to the natural product, (+)-massoialactone **20** (Scheme 12). The hydroxy valerolactone **19b** was converted to the intermediate unsaturated lactone **21** which has already been converted[17] to (*S*)-hexadecanolide **22**. (–)-Tetrahydrolipstatin **23** has also been prepared from the lactone **19b**[18] (Scheme 12)**.** Lactone **19c**[19] is the antipode of a reported mevinolin analog.



Scheme 11. Synthesis of hydroxy lactones.



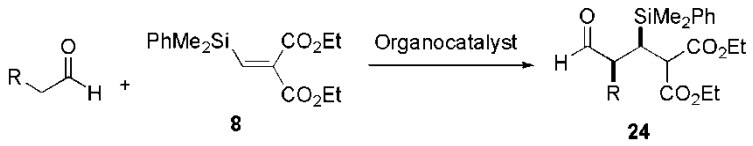
Scheme 12. Synthesis of δ-valerolactone based natural products.

Chapter 5

Organocatalyzed Enantioselective Michael Addition of Unmodified Aldehydes to a Silylmethylene Malonate and Their Applications

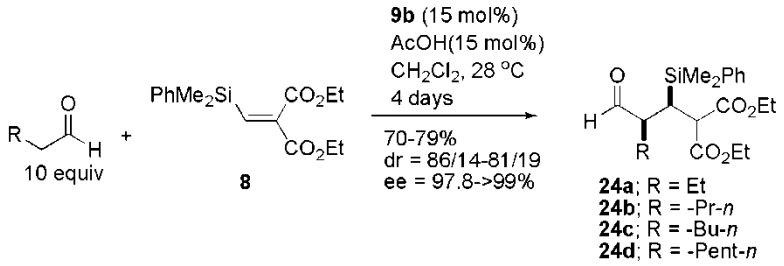
Amongst the asymmetric Michael reactions developed in the field of organocatalysis, direct addition of ketones or aldehydes to activated olefins have been tested with satisfactory results. However, the addition of the same donors[7] to alkylidene malonates is less successful in terms of generality, efficacy and selectivity. Very recently, a number of efforts have been made by others including us (see Chapters 3 and 4) to address those issues in ketone addition to alkylidene malonates. Like ketones, the addition of aldehyde donors to alkylidene malonates is a useful objective. Initial studies on the use of unmodified aldehydes was not successful to this class of Michael acceptors. Only two successful report[20,21] has appeared very recently wherein unmodified aldehydes were engaged to add to alkylidene malonates with very high diastereo and enantioselectivity.

This chapter describes an efficient, highly diastereo- and enantioselective organocatalytic Michael addition of enolizable aldehydes to the β-silylmethylene malonate **8** (Figure 1) leading to β-silylaldehydes **24** (Scheme 13). These adducts can easily be transformed into medium-sized rings leading to skeletal and stereochemical diversity of complex structures, patterned after the hydroxylated pyrrolidine and valerolactones including some natural products and analogs.



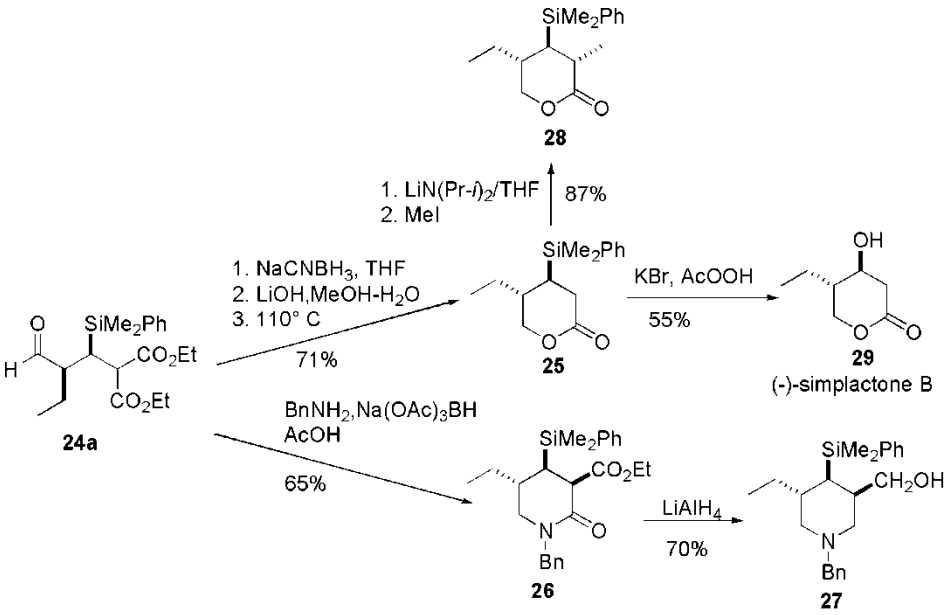
Scheme 13. Organocatalysed direct addition of an aldehyde to **8**.

We first choose butyraldehyde as our model aldehyde for this conjugate reaction and carried out a number of experiments with different catalysts (Fig 1) under various conditions to obtain the best yield, diastereo- and enantioselectivity. The optimized conditions was to use 1 equiv of silylmethylene malonate **8** (Fig 1), 10 equiv of butyraldehyde, a combination of 15 mol% each of **9b** (Fig 1) and acetic acid as the catalyst system and dichloromethane as the solvent (Scheme 14). The reactions require to be left standing at room temperature for 4 days. Thus butyraldehyde with **8** gave the adduct **24a** with a decent yield, good diasteroselectivity and excellent enantiselectivity. *n*-Pentanal *n*-hexanal and *n*-heptanal also reacted smoothly with the silylalkylidene malonate **8** under the optimized conditions to give the desired products in good yield, high diastereoselectivity and excellent enantioselectivity (Scheme 14).



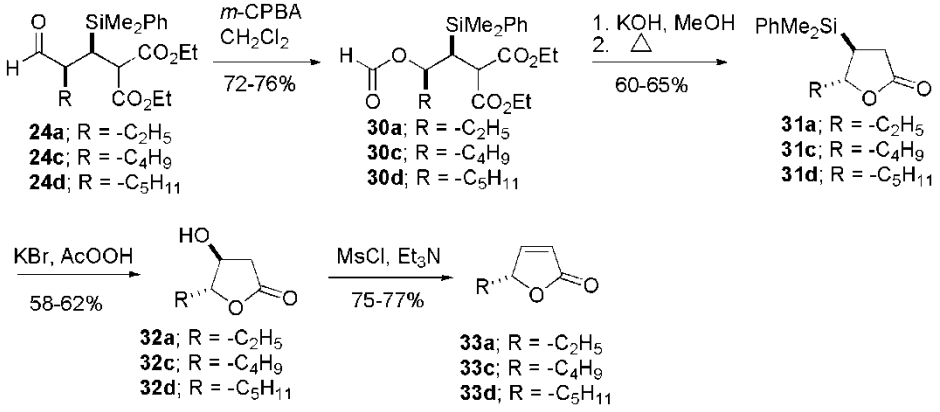
Scheme 14. Addition of unmodified aldehydes to **8**.

The β-silylaldehydes **24** are the building block of chiral lactones and lactams. To exemplify this, the aldehyde **24a** was converted to a six member lactone **25**[22] and a lactum **26**[22] and then to a piperidine skeleton **27**. Lactone **25** was methylated to give lactone **28** (Scheme 15). The lactone **29** was obtained from **25** by converting the silyl group to hydroxy group with retention of configuration. Lactone **29** is the antipode of natural simplactone B.[23]



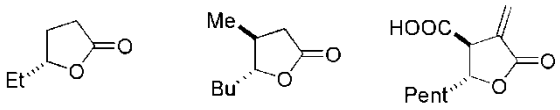
Scheme 15. Synthesis of some chiral *N*- and *O*-heterocycles from the **24a**.[22]

The aldehyde adducts can be converted to their corresponding γ-alkyl butenolides which are known intermediates for many natural products. For this, the adducts **24a**, **24c** and **24d** were subjected to Bayer-Villiger oxidation to give the formates which upon hydrolysis and lactonization gave the butanolides. The hydroxy group was then eliminated via the corresponding mesylates to give the butenolides **33a, 33c** and **33d** as shown in Scheme 16.[24]



Scheme 16. Preparation of enantiopure γ-alkyl butenolides.[24]

These butenolides are the advanced intermediate of many natural products (Scheme 17). Butenolide **33a**[25] has already been converted to the natural product, (+)-γ-caprolactone **34**. (–)-Quercus lactone **35** is known to be made from butenolide **33c**[26] whereas butenolide **33d**[27] is the advanced intermediate of the natural product (+)-methylenolactocine **36**.



Scheme 17. γ-Lactone based natural product accessible from γ-alkyl butenolides.

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ABBREVIATIONS

AcOH:	Acetic Acid
AcOCHO:	Formic Acetic Anhydride
Ac_2O:	Acetic Anhydride
$BnNH_2$:	Benzyl Amine
BOPCl:	Bis(2-oxo-3-oxazolidinyl)phosphinic Chloride
BzOH:	Benzoic Acid
Cbz:	Benzyloxycarbonyl
CSA:	Camphorsulfonic Acid
Cy:	Cyclohexyl
DBU:	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC:	*N*,*N*′Dicyclohexylcarbodiimide
DDQ:	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIPC:	*N*,*N*′Diisopropylcarbodiimide
DIABAL:	Diisobutylaluminum Hydride
DIPEA:	Diisopropylethylamine
DMAP:	4-Dimethylaminopyridine
DMF:	Dimethylformamide
DMSO:	Dimethylsulphoxide
d.r:	Diastereomer Ratio
ee:	Enantiomeric Excess
EtOH:	Ethanol
EtOAc:	Ethyl Acetate

EW:	Electron- Withdrawing Group
g:	Gram
GC:	Gas Chromatography
HF:	Hydrofluoric Acid
HOMO:	Highest Occupied Molecular Orbital
HPLC:	High Performance Liquid Chromatography
HRMS:	High Resolution Mass Spectroscopy
Hz:	Hertz
IBX:	2-Iodoxybenzoic acid
IR:	Infrared
KHMDS:	Potassium bis(trimethylsilyl)amide
LC:	Liquid Crystal
LDA:	Lithium Diisopropylamide
LUMO:	Lowest Unoccupied Molecular Orbital
M:	Molar
m:	*meta*
m-CPBA:	*meta*-Chloroperoxybenzoic Acid
mg:	milligram
mL:	milliliter
mmol:	millimole
MsCl:	Methanesulfonyl Chloride
NaHMDS:	Sodium bis(trimethylsilyl)amide
noe:	Nuclear Overhauser Effect

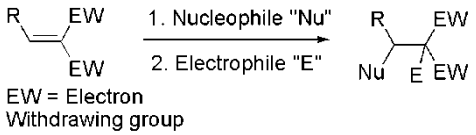
NMO:	*N*-Methylmorpholine-*N*-oxide
NMP:	*N*-Methylpyrrolidone
NMR:	Nuclear Magnetic Resonance
o:	*ortho*
ODCB:	*o*-Dichlorobenzene
Organocatalysis:	Catalysis of a transformation by a wholly organic catalyst
P:	*Para*
ppm:	Parts Per Million
PPTS:	Pyridinium p-Toluene Sulphonate
SOMO:	Singly Occupied Molecular Orbital
TBDMS:	tert-Butyldimethylsilyl Ether
TFA:	Trifluoroacetic Acid
THF:	TetrahydroFuran
TMS:	Trimethylsilyl Ether
TLC:	Thin Layer Chromatography

Chapter 1

Michael Addition Reaction

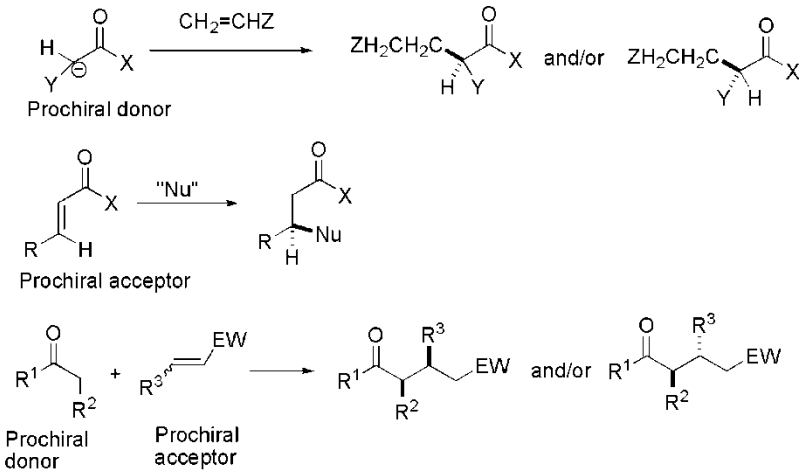
1.1 Introduction

This chapter presents a brief overview of Michael addition[1] reaction in terms of recent developments and usefulness. Michael addition involves the addition of a nucleophile (also known as donor, which can be carbon or heteroatom based) to an alkene or alkyne attached to electron withdrawing groups (also known as acceptor).[2] This nucleophilic addition is followed by a trapping of the anionic intermediate with an electrophile, which is a proton in the simplest case (**Scheme 1.1**).



Scheme 1.1

The carbon centered nucleophilic addition may take place in enantioselective or non-enantioselective manner. As the demand for optically active compounds is increasing in recent years, much progress has been made in the asymmetric version of this reaction, providing the Michael adduct with high enantiomeric purity. The asymmetric Michael reaction could be categorized in three groups: (i) enantioselective addition of prochiral donor to acceptor; (ii) enantioselective addition of a donor to a prochiral acceptor; (iii) enantio- and diastereoselective addition of prochiral donor to prochiral acceptor (**Scheme 1.2**).



Scheme 1.2

Out of several procedures for the enantiocontrolled synthesis, the use of asymmetric catalysis has been well recognized. It offers the best "atom economy" as the stoichiometric addition or removal of chiral auxiliaries can be avoided. Asymmetric catalysis has received considerable attention over the past few decades, and its contribution toward organic synthesis has become increasingly significant. A wide variety of enantioselective chemical transformations are now performed with only catalytic amounts of chiral promoters, providing highly economic access to optically active compounds. Some of these enantioselective transformations can be applied to industrial production. The synergistic functions of the active sites of the catalyst molecules make substrates more reactive in the transition state and control their positions so that the functional groups are proximal to each other. This concept of *multifunctional* catalysis is key to increasing the scope of natural and artificial catalysts. The asymmetric version of Michael reaction can be catalyzed by both organometallic compounds and pure organocatalysts.

1.2 Organometallic compound catalyzed Michael reactions

The development of asymmetric catalysis to date has been accomplished by employing various metal elements on the basis of the type of reaction targeted. The importance of enantioselective metal catalysis has been well recognized by the award of the 2001 Noble Prize in chemistry to Knowles,[3] Noyori,[4] and Sharpless[5] for their pioneering work in this field. The advantages of metal based catalysts are due to the properties of the metal because metal can act as Lewis acid or Lewis base. Besides the reactivity, the catalysts can be fine tuned by changing the ligands surroundings the metals.

Traditionally, Michael reactions are carried out in the presence of strong basic catalysts such as metal alkoxides or hydroxides. Although these base catalyzed reactions often produce good results, these basic catalysts some time generate by-products due to competing side reactions. In order to avoid the strongly basic conditions, several alternatives have been developed. The most promising one is the organometallic compound catalyzed Michael reactions because the organometallics work formally under neutral conditions. The breakthrough in this field was the discovery of hetero-bimetallic alkali-lanthanide-binolate catalysts by Shibasaki et. al.[6] which facilitated highly efficient catalytic asymmetric Michael reactions with excellent enantioselectivities. Heterobimetalic complexes[7] in which metal plays a different role in the enantiodifferentiation process represent a class of asymmetric catalysts for the Michael reactions. The development of heterobimetallic complexes[8,9] (**Fig.1.1**) that contain a lanthanide and alkali metal offer a versatile framework for asymmetric catalysts, because the property of the catalyst can be

tuned dramatically according to the choice of alkali metal and further refined by choosing the proper lanthanide. The development of these catalysts marked the milestone in this area enabling catalytic Michael reaction (**Scheme 1.3**).

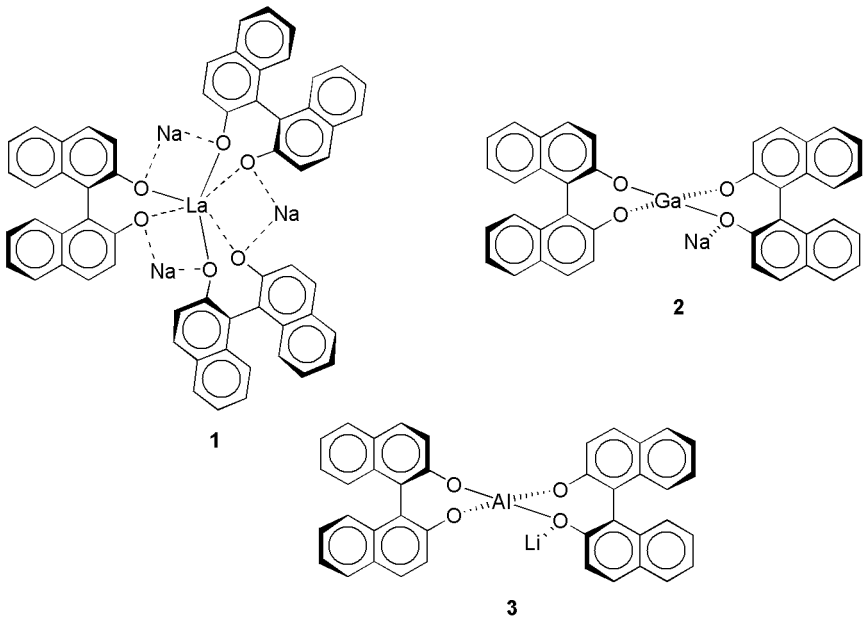
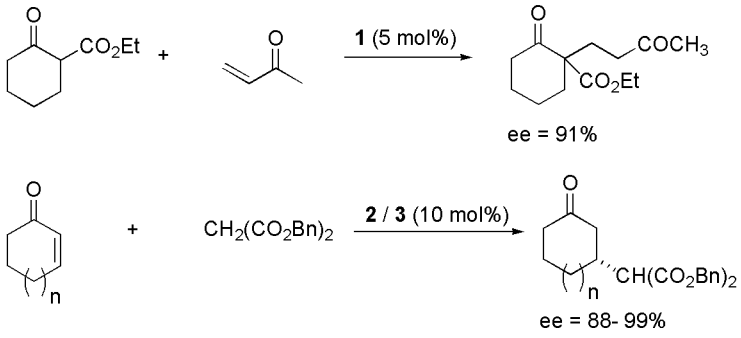


Fig. 1.1 Heterobimetalic catalysts



Scheme 1.3

The transition metal based asymmetric catalyst has long been the dominant approach in asymmetric Michael additions. The first enantioselective example of transition-metal catalysis was reported by Burner and Hammer,[10] who applied $Co(acac)_2$

and a C_2-symmetrical diamine (**Fig 1.2**) as the chiral ligand **4** for the Michael reaction of ketoesters to methyl vinyl ketone. Ikariya et. al.[11] developed chiral Ru-amido complexes **5** (**Fig 1.2**) for the Michael reaction of nitro alkenes to malonate **(Scheme 1.4)**. A new class of chiral bis(dihydrooxazolylphenyl)oxalamides Co complex **6** (**Fig 1.2**) has been developed to catalyze the Michael reaction of malonates to chalcone (**Scheme 1.4**).[12] Others groups have also reported asymmetric Michael reactions using chiral diamines,[13] chiral diphosphanes[14] and chiral salicyimines[15] metal-complexes as catalysts.

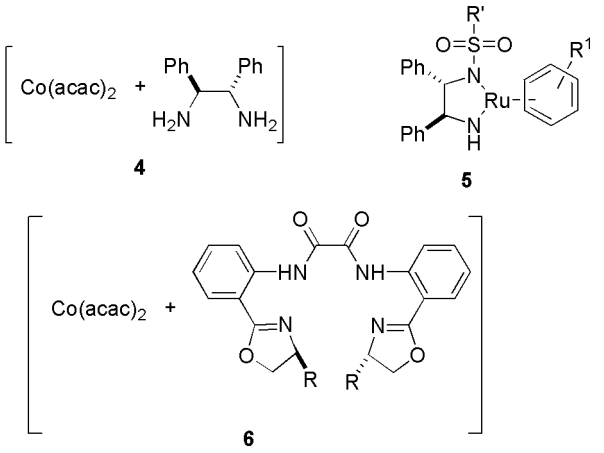
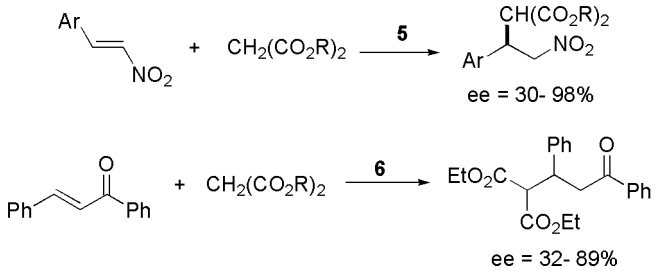


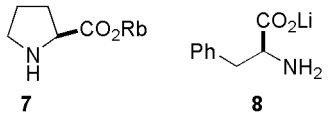
Fig. 1.2 Transition metal based asymmetric catalyst



Scheme 1.4

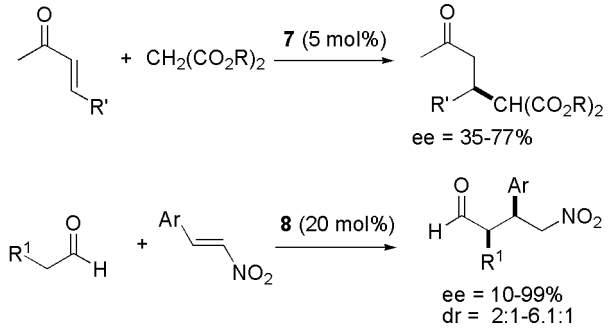
The metal salts of amino acids (**Fig.1.3**) are another class of asymmetric Metal catalysts. The asymmetric induction in these Michael reactions take place through enantioface differentiation of the Michael acceptors. Yamaguchi et al.[16] has reported the

first catalytic Michael addition of simple enones and enals employing readily available rubidium salts of L-proline **7** (**Scheme 1.5**). Michael addition of simple aldehydes to nitro olefins was catalyzed by L-phenylalanine lithium salt **8** [17] (**Scheme 1.5**).



7 **8**

Fig.1.3 The metal salts of amino acids



Scheme 1.5

Although metal based catalysis provided exciting results, it had some limitations. The disadvantages of these catalysts are: (i) most of the metal catalysts are sensitive to air and moisture so metal catalyzed reaction require the exclusion of air and moisture; (ii) in addition, some of the metal catalyst are poisonous and some of them are expensive, which are the real challenges in the preparation of pharmaceutical compounds.

1.3 Organocatalyzed asymmetric Michael reactions

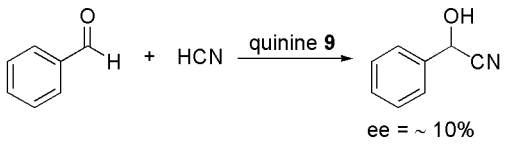
1.3.1 A brief review of organoctalysis

Metal based catalysis had dominance for a long time. But recently organocatalytic methods where the catalyst is made up of only small organic molecule(s), has become a very active area of research in organic synthesis.[18] The use of small organic molecules as catalyst have many benefits compared to the widely used metal catalysts. Organocatalysts are small purely "organic" molecules. They are usually stable in air and moisture, easy to handle and they can mimic the role of a metal as a Lewis acid or Lewis base. The acidity or the basicity arises from the type of heteroatom (N, O, S and P) present in the organocatalyst.[19] These organocatalysts also possess typical characteristics with respect to technical applications: (i) accessibility of both the enantiomers with comparable price, (iii) low molecular weight, (iv) easy separation from the product, and (v) some of the catalysts can be recovered after work up without racemization

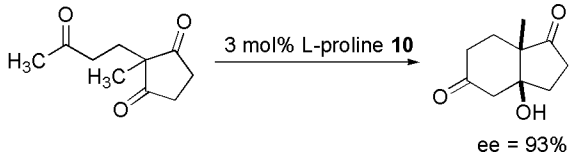
Like the other catalytic system, it has some limitations. For examples, high catalytic loadings, long reaction time and low temperature are essential in many successful transformations. Future development to overcome these limitations as well as to develop new organocatalysts and new organic reactions are desired.

There have been reports for using small organic molecule as asymmetric catalysts for almost a century ago. Two German chemists, Bredig and Fiske, reported the cyanohydrin synthesis with modest enantioselectivity using quinine **9** as a catalyst in 1912 (**Scheme 1.6**).[20] Much later, Pracejus reported an organocatalysed asymmetric ketene methanolysis reaction.[21,22] In 1970, Hajos and Wiechert reported the proline **10** catalyzed

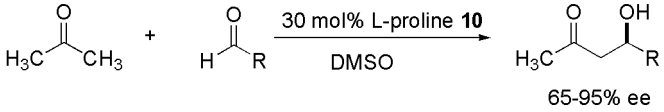
highly enantioselectivite intramolecular aldol reaction of the symmetrical triketone (**Scheme 1.7**).[23,24] This reaction is known as Hajos-Parrish-Eder-Sauer-Wiechert reaction which is widely used in the synthesis of natural products.[25] A major break-through was achieved in 2000 when List and co-workers[26] developed for the first time a proline catalysed intermolecular version of the aldol reaction (**Scheme 1.8**). They reacted acetone with aromatic aldehydes to get β-hydroxy ketones. Since then, the general filed of the asymmetric organocatalysis has unfurled at a breathtaking peace; new catalysts are being designed, new activation mode are being discovered, and new reactions are being discovered and applied for asymmetric synthesis.



Scheme 1.6



Scheme 1.7



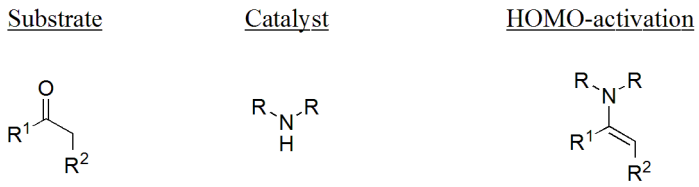
Scheme 1.8

1.3.2 Different activation modes of the organocatalysis

(i) Enamine catalysis:

An enamine can be formed by the condensation of a secondary amine and an aldehyde or a ketone (**Scheme 1.9**). The resulting enamine has a higher HOMO than the

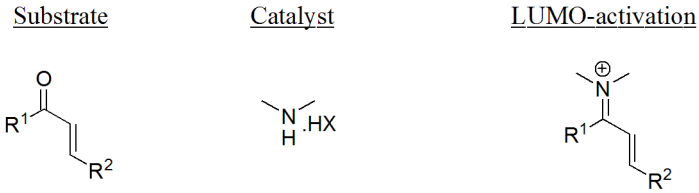
corresponding aldehyde or the ketone, and therefore, is activated towards further transformation. This is analogous to the formation of a nucleophile enol from a carbonyl compound.



Scheme 1.9

(ii) Iminium catalysis:

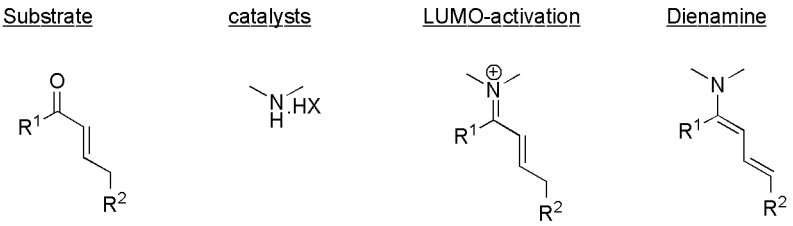
The reversible formation of an iminium ions from the corresponding amine and α,β-unsaturated aldehydes or ketones leads to the lowering the LUMO of the corresponding α,β-unsaturated aldehyde or ketone (**Scheme 1.10**). This activation through LUMO-lowering and reversible iminium ion formation is analogous to the Lewis acid catalyzed reaction involving α,β-unsaturated carbonyl compounds.



Scheme 1.10

(iii) Dienamine catalysis[27]:

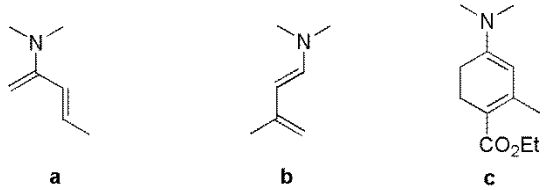
Amine can react with α,β-unsaturated carbonyl compound to generate iminium ions. The deprotonation of this iminium ions leads to the formation of dienamine (**Scheme 1.11**)



Scheme 1.11

Dienamines are classified in three categories as follows (**Scheme 1.12**)

a.Barbas' dienamines (2-amino-1,3-dienes), **b.** Serebryakov dienamines (2-amino-1,3-dienes) and **c.** Push-pull dienamines (Ramachary dienamines).



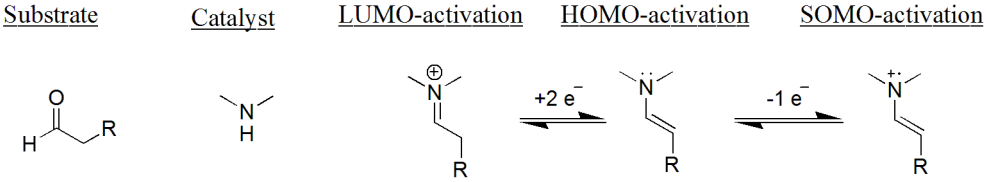
Scheme 1.12

Dienamines differ from simple enamines in three main aspects: i) in an additional nucleophilic site at the δ-position and an electrophilic site at the γ-position for 1-aminobuta-1,3-dienes, ii) three types of reactivity modes (diene reactivity, vinylogous reactivity and enamine reactivity) exist for dienamines both of 1-aminobuta-1,3-dienes and of 2-aminobuta-1,3-dienes, and iii) dienamines can act as electron-rich olefin sources in inverse-electron demand Diels–Alder reactions by increasing the energy of the olefin HOMO.

(iv) SOMO (singly occupied molecular orbital) catalysis[28]:

Amine can react with carbonyl compound to generate iminium ions which rapidly interconvert to an enamine via a redox process (enamine has four π electrons and iminium

has two π electrons). Now one electron oxidation of the transient enamine speices generate a three π electron radical cation with a singly occupied molecular orbital (SOMO) (**Scheme 1.13**) that is activated towards a range of catalytic enantioselective transformations.



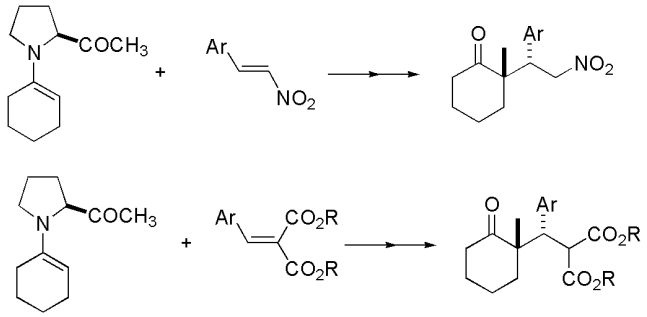
Scheme 1.13

Out of these activation modes, enamine catalysis has developed into a powerful strategy for asymmetric Michael reactions.

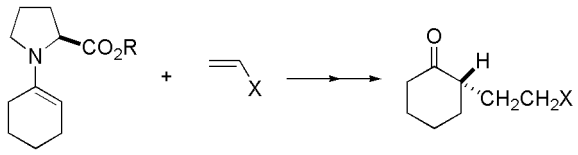
1.3.3 Enamine catalysis in Asymmetric Michael reactions

The use of preformed enamines in the Michael addition reaction has been pioneered by Strok et. al.[29] and ever since several asymmetric and non asymmetric version of this reaction has been reported. For example, asymmetric Michael addition of performed enamines derived from chiral amines to conjugated nitroalkenes and alkylidene malonates have been reported by Seebach et. al.[30,31] as shown in **Scheme 1.14**. Yamada and co-workers reported early examples of the asymmetric Michael addition of (*S*)-proline-derived performed enamines to acrylonitirles, acrylates and methyl vinyl ketones.[32,33] as shown in **Scheme 1.15**. This preformed enamines and enolates of carbonyl compounds are not atom economic. Besides, they required additional reagents and produce unwanted waste. So a more promising and atom economic strategy would involve direct addition of unmodified carbonyl compound to a Michael acceptor. Surprisingly, the catalytic version of this reaction was not explored until recently, when Barbas,[34] List[35,36] and Enders[37]

independently reported the Michael addition of ketones to nitroalkenes using catalytic quantities of chiral secondary amines.

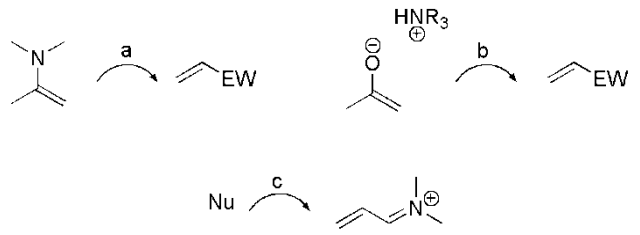


Scheme 1.14

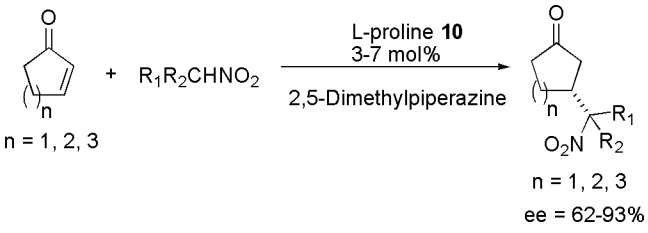


Scheme 1.15

Catalytic enantioselective Michael reaction normally proceed by activation of either the Michael donor or acceptor with the chiral catalyst. Simultaneous activation approach of both the partners has also been investigated. In Michael addition reactions, the Michael donor (mainly the carbonyl compounds) can be catalytically activated either by enamine or enolate formation for the addition to a Michael acceptor (**Scheme 1.16**), paths a, paths b). Complementary, carbonyl derived Michael acceptors can be activated via formation of an iminium species (**Scheme 1.16**, paths c). For example, the Michael addition of active methylene compounds as Michael donor to the α,β-unsaturated carbonyl compounds as Michael acceptor in the presence of amino catalysts (**Scheme 1.17**)[38] follows this principle. In these cases, the α,β-unsaturated carbonyl compounds are most likely activated through iminium ion intermediates.

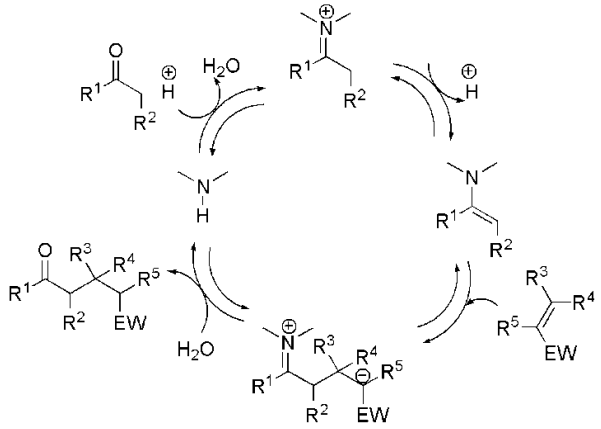


Scheme 1.16



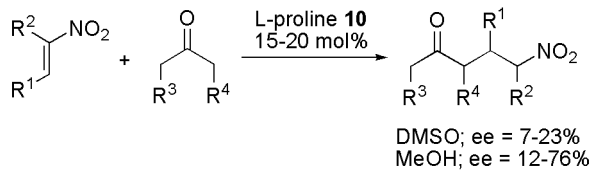
Scheme 1.17

Enamine are formed reversibly from amine and carbonyl compounds and used as intermediates in a catalytical cycle (**Scheme 1.18**). Further reaction with an acceptor leads to the desired Michael adduct. Importantly, hydrolysis with the in situ generated water liberates the product and regenerates the catalyst. This concept of enamine catalysis has also been extended for the highly enantioselective aldol reaction, α-functionalization reactions of ketones, aldehydes, such as aminations,[39] hydroxylations,[40] alkylation,[41] halogenations,[42] oxygenation[43] and an intramolecular Michael reaction.[44]



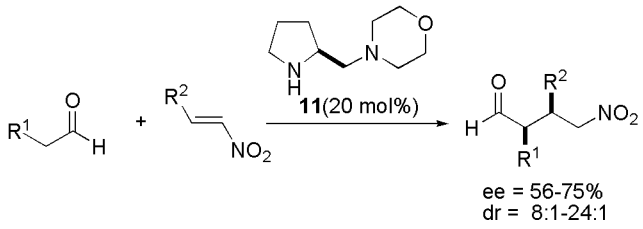
Scheme 1.18

In enamine-catalytic Michael additions, many successes have been realized by applying organocatalysts to highly reactive Michael donor or acceptors. For example, List et. al.[35,36] were the first to report that L-proline **10** catalyzes the addition of several ketones to nitroolefines (**Scheme 1.19**). Both the selectivity and diastereoselectivity were high in DMSO, but the enantiomeric excess did not exceed 23%. A related study of this process by Enders et. al.[37] resulted in high enantiomeric excess up to 76% in methanol as a solvent.



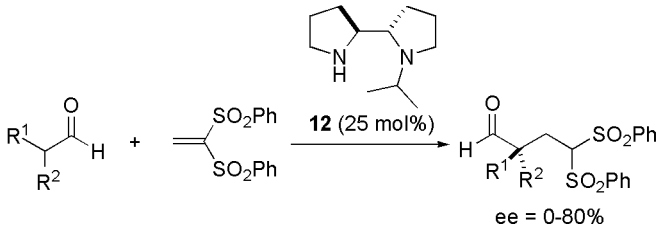
Scheme 1.19

Barbas et. al.[45] first reported the Michael addition of unmodified aldehydes to nitroolefins using the (*S*)-2-(morpholinomethyl)pyrrolidine **11** (**Scheme 1.20**). Later on Alexakis,[46] Hayashi,[47] Palomo[48] independently developed different organocatalysts for the Michael reaction of unmodified aldehydes to nitroolefins.



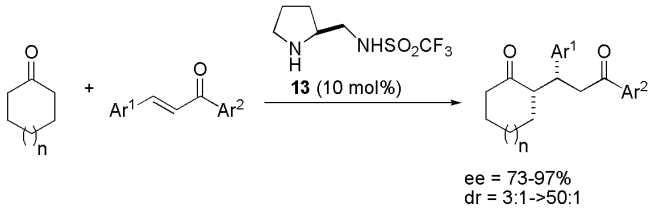
Scheme 1.20

Vinyl sulphones are well known Michael acceptor. The first direct organocatalytical Michael reaction of aldehydes to vinyl sulphones was reported by Alexakis et. al.[49](**Scheme 1.21**).



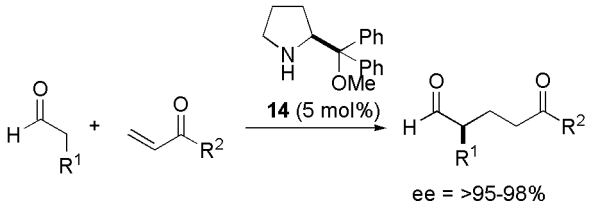
Scheme 1.21

Wang et. al.[50] have developed a highly enantioselective, organocatalytic Michael addition reaction of cyclic ketones with α,β-unsaturated ketones as showen in **Scheme 1.22**. The reaction was catalyzed by (*S*)-pyrrolidinesulphonamide **13** and produced the synthetically useful 1,5-dicarbonyl compounds.



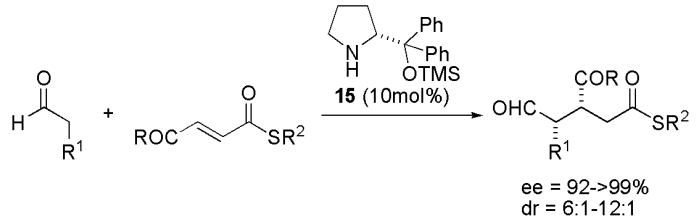
Scheme 1.22

Gellman et. al.[51] reported diphenylprolinol ether **14** as a very efficient catalyst for the Michael addition of aldehydes to methyl vinyl ketones as in **Scheme 1.23**.



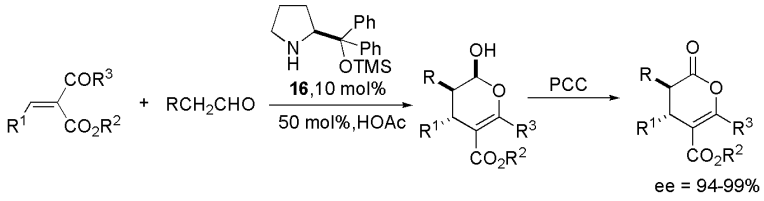
Scheme 1.23

(*R*)-Diphenylprolinol silyl ether **15** catalyszed the Michael addition of aldehydes to γ-substituted α,β-unsaturated thiol esters to deliver the corresponding Michael adducts with excellent selectivity (**Scheme 1.24**).[52] This provides another successful example of enamine catalyzed Michael additions reaction.



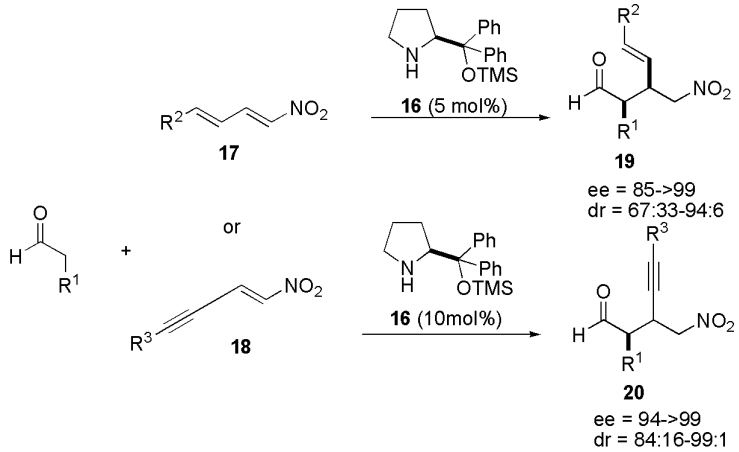
Scheme 1.24

Ma et. al.[53] have developed an enamine catalyzed cascade Michael addition and cyclization of aldehydes and α-keto-α,β-unsaturated esters. This method proceeds smoothly to afford cyclic hemiacetals, which are oxidized subsequently to furnish highly functionalized 3,4,5,6-tetrasubstituted dihydropyrones with excellent enantioselectivities (**Scheme 1.25**).



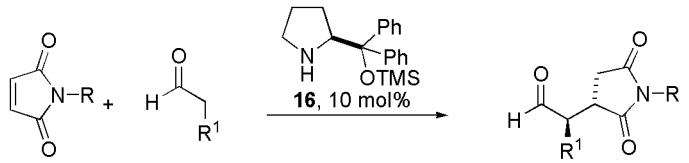
Scheme 1.25

Very recently, Alexakis et. al.[54] have developed an organocatalyzed Michael additions of carbonyl compounds and nitrodienes **17** or nitroenynes **18** (**Scheme 1.26**).



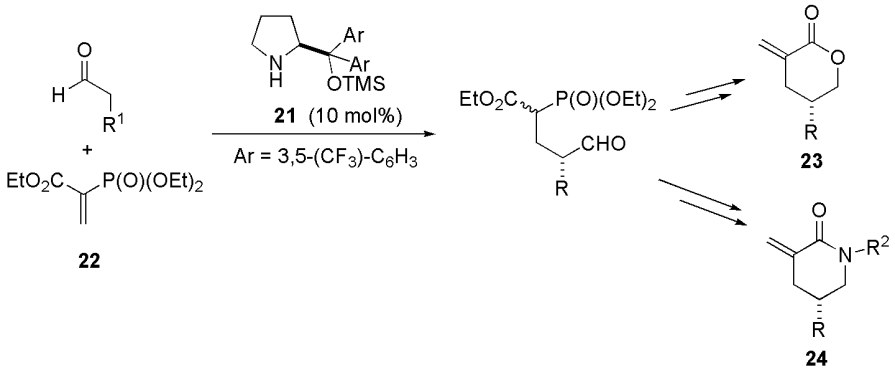
Scheme 1.26

Co´rdova et. al.[55] have developed an organocatalytic Michael addition reaction of unmodified aldehydes to maleimides (**Scheme1.27**). The reaction produces the Michael adducts with excellent enantioselectivity.



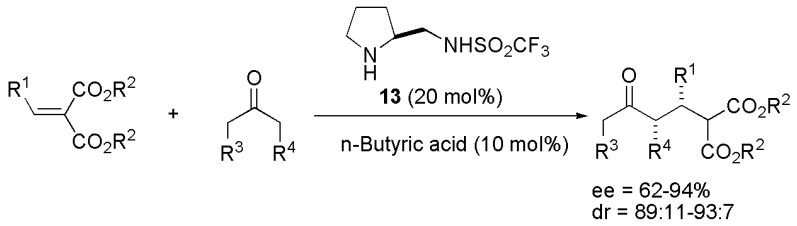
Scheme 1.27

Organocatalyzed Michael addition of unmodified aldehydes to ethyl 2-(diethoxyphosphoryl)acrylate **22** leads to highly enantiomerically enriched adducts. These adducts were transformed to optically active *γ*-substituted α-methylene-*δ*-lactones **23** and *δ*-lactams **24** (**Scheme 1.28**). [56]



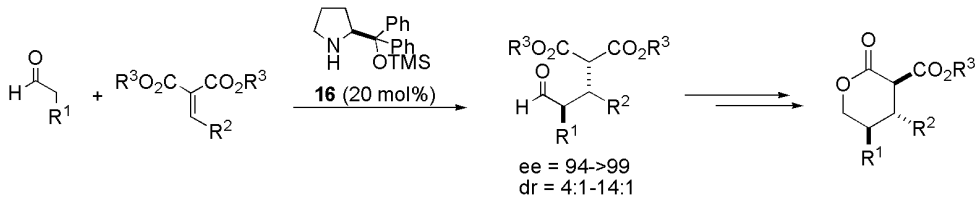
Scheme 1.28

Cao et.al.[57] have developed an organocatalytic asymmetric Michael addition reaction of ketones with alkylidene malonates (**Scheme 1.29**). This reaction was carried out under mild conditions to afford potentially useful 1,3-diester compounds in moderate to good yields with good to high enantio- and diastereoselectivities.



Scheme 1.29

Cordova et.al.[58] have developed an organocatalytic asymmetric Michael addition reaction which employs unmodified aldehydes and alkylidene malonates (**Scheme 1.30**). These reactions provided α-aryl- or α-alkyl-β-formyl-substituted malonates with high enantio- and diastereoselectivity.



Scheme 1.30

Within a few years since its conceptualization in 2000, enamine catalysis has developed into a flourishing field of research and established itself as a powerful methodology for asymmetric synthesis. Essentially all types of ketones and aldehydes have been used as nucleophiles in reactions with a broad range of electrophile classes and an ever increasing number of aminocatalysts.

Chapter 2

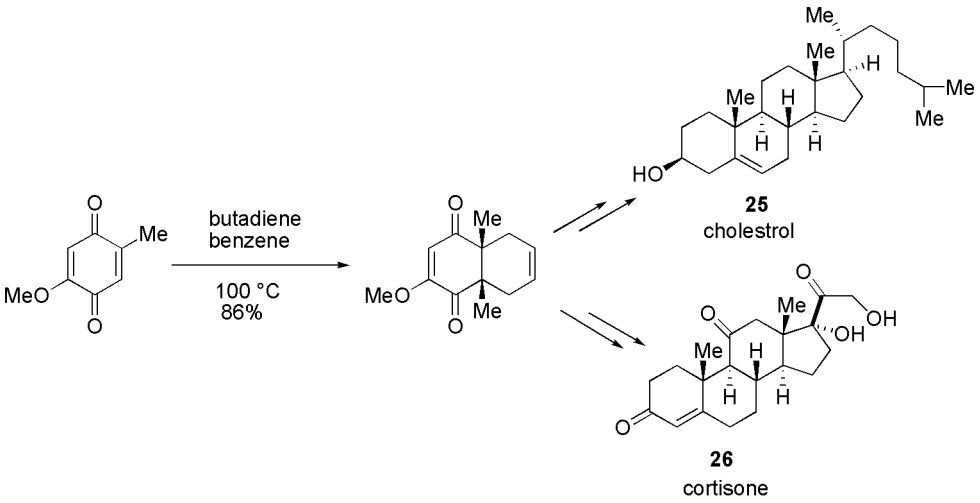
A Domino Michael-Horner-Wadsworth-Emmons Elimination Route for the Synthesis of Functionalized Trisubstituted 1,3–Butadiens

2.1 Introduction

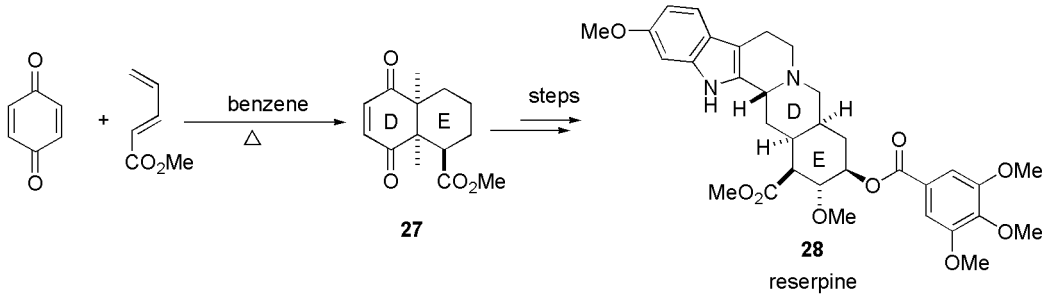
Aryl-substituted conjugated dienes are useful building blocks due to their utilization in numerous transformations including Diels-Alder reactions. They also appear as important structural subunits in natural products and have applications in material sciences. The Diels-Alder reaction has both enabled and shaped the art and science of total synthesis over the last few decades to an extent which, arguably, has yet to be eclipsed by any other transformation in the current synthetic repertoire. With myriad applications of this magnificent pericyclic reaction, often as a crucial element in elegant and programmed cascade sequences facilitating complex molecule construction, the Diels-Alder cycloaddition has afforded numerous and unparalleled solutions to a diverse range of synthetic puzzles provided by nature in the form of natural products.[59] In 1952, Woodward et. al.[60] disclosed their historic routes to the synthesis of steroids such as cholesterol **25** and cortisone **26** where the Diels-Alder reaction of quinone and butadiene is the key step (**Scheme 2.1**).

Again in 1956, Woodward et al.[61] applied the Diels-Alder reaction to form a the critical bicyclic system **27** that would serve as the scaffold for the synthetic of reserpine **28** as shown in **Scheme 2.2.** Moreover, these two examples from Woodward's research group are illustrative of a new school of thought that emerged in the 1950s which involved approaching the synthesis of complex molecules by rational synthetic strategies, and they admirably demonstrated the inherent strength of the Diels-Alder reaction to solve challenging synthetic puzzles which might otherwise have remained hopelessly complex. Another well-celebrated application of the Diels-Alder reaction in the context of natural

products synthesis is found very recently in the total synthesis of taxol **29** (**Scheme 2.3**), in which Nicolaou et al.[62] employed two different [4+2] cycloadditions to construct the target molecule.

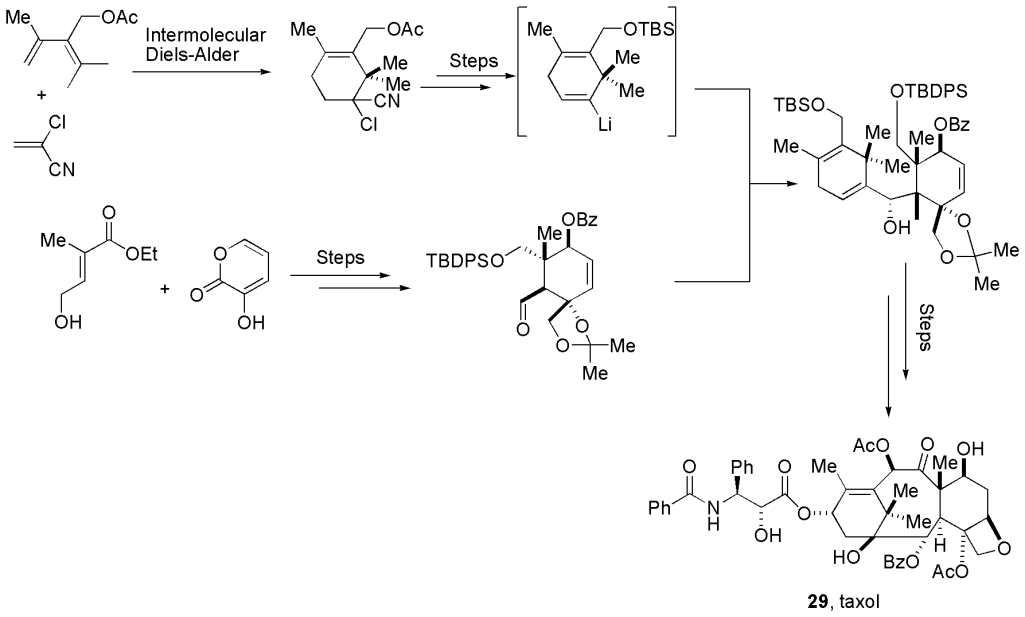


Scheme 2.1



Scheme 2.2

There are numerous reports of the Diels-Alder reaction for the synthesis of natural products. The usefulness of Diels-Alder reaction in synthesis arises from its versatility and from its remarkable stereoselectivity. By varying the nature of the diene and dienophile many different ring structures can be built up.



Scheme 2.3

Besides the participation in famous Diels-Alder reaction for building skeleton of complex molecules, the conjugated dienes are widely used in material sciences. Aryl-substituted conjugated dienes possess special photochemical and photophysical properties[63] and are widely used as advanced materials in nonlinear optics as well as liquid crystals.[64] Butadiene based liquid crystalline material are well known, for example, alkoxy-cyano substituted diphenylbutadiene (**Fig. 2.1**).[65] Diene **30** exhibited the characteristic of a nematic phase while diene **31** possessed a nematic LC phase .

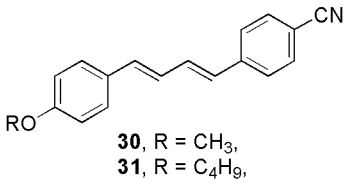
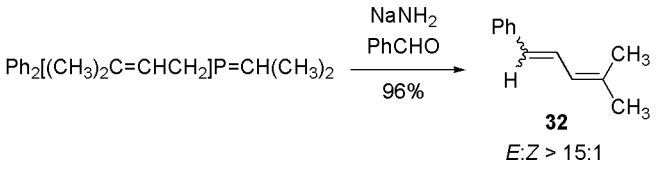
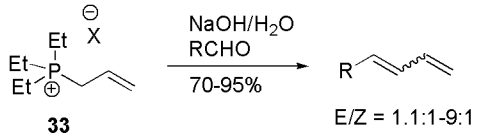


Fig 2.1 Liquid crystalline dienes

A large number of methods are available for the synthesis of 1,3-dienes involving multiple stages of reactions.[66] The direct and efficient preparation of stereo defined substituted and functionalized conjugated dienes is not straightforward and remains an area of current investigation. Among the method available for making double bonds, Wittig reaction is one of the most attractive for the synthesis of dienes. For this modified phosphorous ylides, Ph_3P=CHCH=CHR, are used, but the stereoselctivity is the major problem in this reaction. In 1984, Vedjes and Huang[67] reported that the reaction between the phosphoranes Ph_2R_1P=CHCH=CHR (R_1= Me or CH_2CH=CHR) and the aldehydes provided major product as (*E*)-dienes **32** when the reaction was carried out in salt free conditions as shown in **Scheme 2.4**. On the other hand, very recently, a Wittig reaction of ylides derived from trialkyl-allyl phosphonium salts **33** has been demonstrated for the first time in water using sodium hydroxide as base. Ylide formation occurs exclusively through deprotonation at the allylic position. The resulting ylides were shown to react with a series of aromatic, unsaturated, and enolizable aliphatic aldehydes yielding a structurally diverse range of useful 1,3-dienes as shown in **Scheme 2.5**.[68]

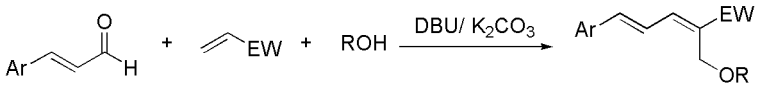


Scheme 2.4



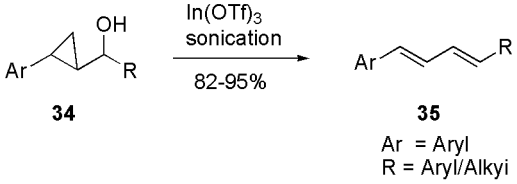
Scheme 2.5

Dienes can also be synthesized by a base catalyzed multi-component domino reaction between α,β-unsaturated carbonyl compounds, aldehydes and alcohols. Base-induced domino sequence strating with oxa-Michael addition of alcohols to α,β-unsaturated acceptors followed by an intermolecular aldol/dehydration steps with aldehydes. The overall oxa-Michael/aldol/dehydration sequence gives the expected dienes as shown in **Scheme 2.6**.[69]



Scheme 2.6

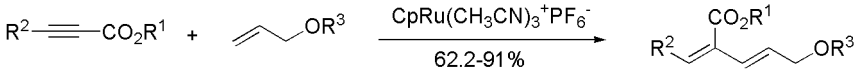
Indium(III) triflate is a well known Lewis acid and it has been applied in variety of useful organic reactions. Ranu et.al.[70] demonstrated that indium triflate is an efficient Lewis acid catalyst for the rearrangement of cyclopropyl carbinol **34** derivatives, leading to the stereoselective synthesis of conjugated butadienes **35** (**Scheme 2.7**). This reaction protocol provided the conjugated *all-trans*-butadiene systems.



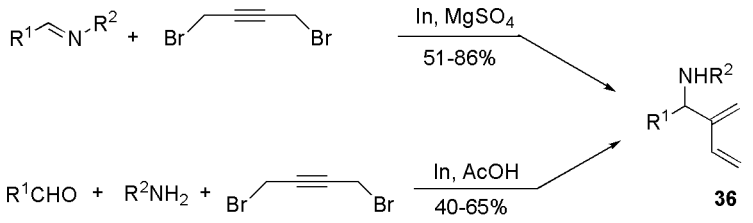
Scheme 2.7

Transition-metal-catalyzed reactions have emerged as powerful and general methods for the synthesis of dienes. The Ru-catalyzed alkene-alkyne cross-metathesis reaction to form 1,3-dienes has been developed very recently as shown in **Scheme 2.8**.[71] A variety of 2-aminomethyl-1,3-dienes **36** were prepared by the reaction of imines with an organoindium reagent generated in situ from indium and 1,3-dibromo-2-butyne (**Scheme**

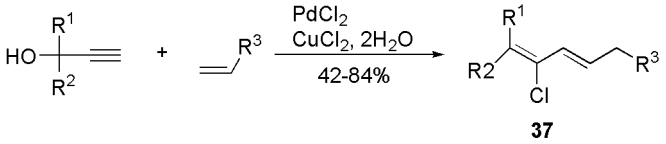
2.9).[72] A Pd-catalyzed intermolecular reaction of alkynols and alkenes was developed for the synthesis of 2-chloro-1,3-dienes **37** (**Scheme 2.10**).[73]



Scheme 2.8



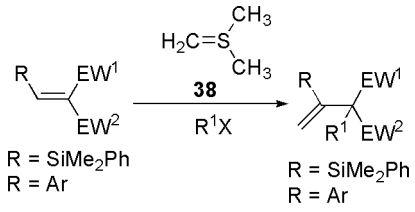
Scheme 2.9



Scheme 2.10

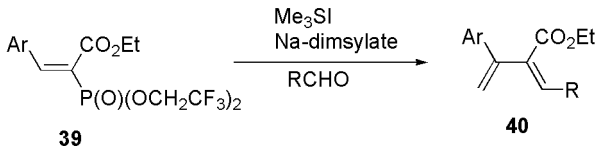
2.2 Present Work

Our group has shown that dimethylsulfonium methylide **38**[74] in combination with a base[75] or excess of itself[76] can act as an equivalent of a carbenoid anion and also demonstrated that this ylide-base combination on reaction with 2-silyl/2-arylidene malonate/arylidene phosphonate/arylidene cyanoacetate derivatives and various alkyl halides leads to 1-substituted alkenylsilanes/styrene derivatives (**Scheme 2.11**).



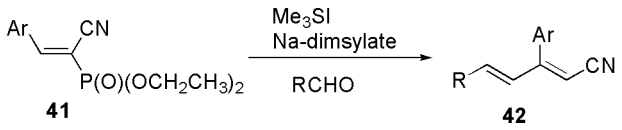
Scheme 2.11

The reaction was also extended to vinyl phosphonate **39** type of Michael acceptors and in this case if the reaction is quenched with aldehydes rather than alkyl halides, it undergoes Horner–Wadsworth-Emmons (HWE) type olefination[77] leading to densely substituted butadienes **40** (**Scheme 2.12**)[78] with high stereoselectivity but with low yields.



Scheme 2.12

When the reaction was carried out with vinyl phosphonate **41** having a cyano substituent and subsequently with an aldehyde leads to a sequential tandem double olefination (**Scheme 2.13**) to provide the dienes **42** with very high regio- and stereoselectivity.[79]

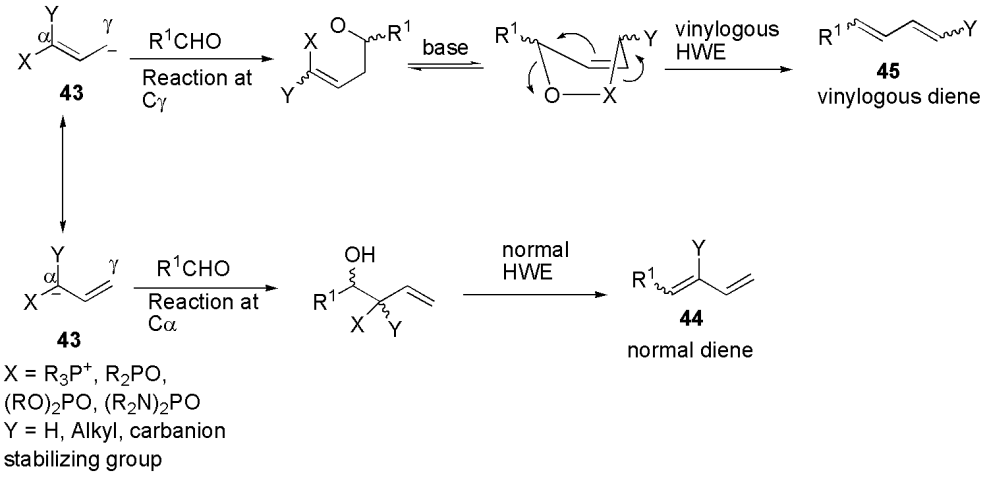


Scheme 2.13

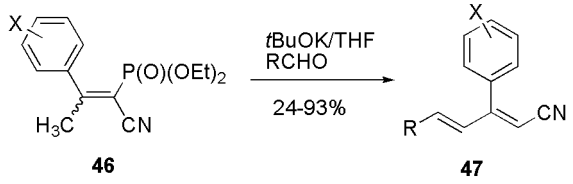
The regioselectivity depended essentially on the activating groups present in the vinyl phosphonates. For example, 2-(arylmethylidene)-2-phosphonoacetate **39a** (Ar = Ph **Scheme 2.12**) favored a normal HWE olefination[78] where as the phosphonoacetonitrile **41a** (Ar =Ph, **Scheme 2.13**) gave diene **42** via vinylogous HWE reaction.[79] This posed a challenge to make both type of dienes from the same starting material.

Allylic phosphorous ylides **43** can react both at α- and γ-position (**Scheme 2.14**) with respect to the electron withdrawing group (Y). When the reaction takes place at

the α-position of the allylic phosphorous ylide **43**,[80] it leads to normal HWE reaction[81] to give normal dienes **44** but when the reaction takes place at the γ-position of the allylic phosphorous ylide, it leads to vinylogous HWE reaction **45**[79,82] to give new kind of diene, different from the normal HWE product. Very recently our group has developed for the first time an unprecedented HWE reaction of aldehydes with cyano substituted vinyl phosphonates **46** for the synthesis of stereochemically pure 1,3 dienes **47** (**Scheme 2.15**).[79] The cyano group played an important role because the reaction did not proceed in the vinylogous fashion with allylic phosphorus ylides containing α-alkoxy/siloxy or even with anion stabilizing carboxyl ester functionality.



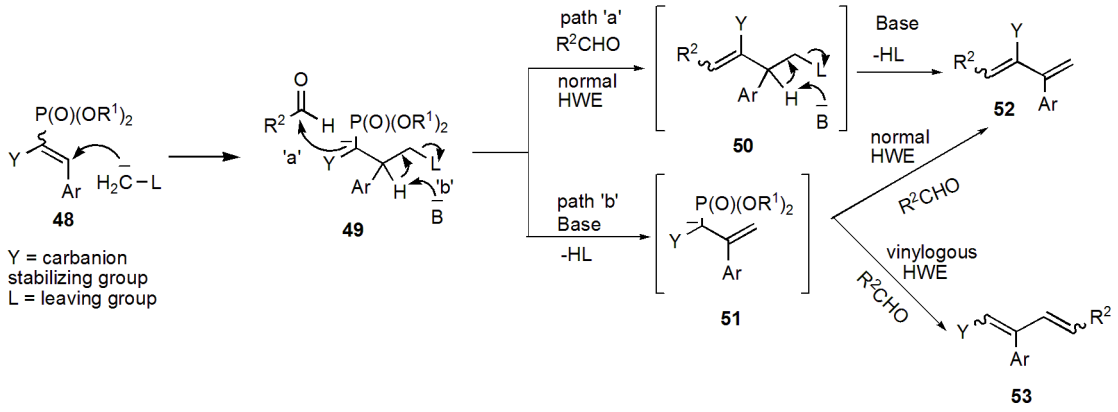
Scheme 2.14



Scheme 2.15

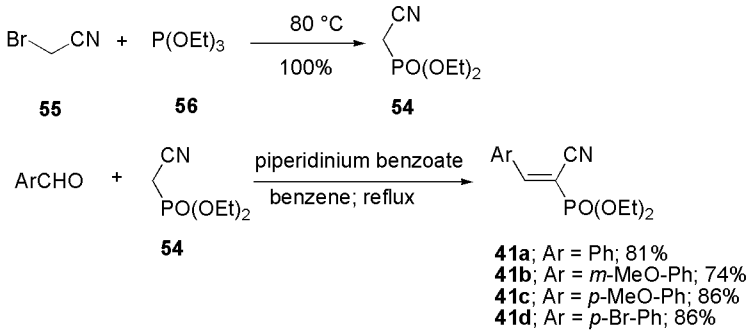
2.2.1 Domino route for the synthesis of highly substituted 1,3-butadienes

A multicomponent domino approach[83] to highly and differentially substituted regio- and stereoisomeric 1,3-dienes could be envisaged from simple building blocks viz. an activated vinyl phosphonate, a carbenoid and an aldehydeas shown in (**Scheme 2.16**). Carbanion with a leaving group attached to that carbon in combination with a base can be considered as 'carbenoid' equivalent. Therefore, the addition of a nucleophilic $L–H_2C^-$ carbanion (L is a leaving group) (**Scheme 2.16**) to a Michael acceptor containing a phosphonate activating group **48** is expected to lead to the adduct **49**. In the presence of a base and an aldehyde, this adduct could subsequently provide the dienes **52** and/or **53** by two routes via intermediates **50** (Path 'a') and **51** (Path 'b'). In path 'a', the adduct **50** would first undergo a HWE reaction with the added aldehyde followed by a base induced elimination to give **52** only. "Path b'' would follow a reverse sequence of reactions where the base induced elimination would precede to give the intermediate allylic phosphonate ylide **51**. Unlike "path a'', the mesomeric forms of ylide **51** in "path b" can, in principle, serve as a precursor for diverse products either by enduring a normal HWE reaction[78,81] (α-attack) or a vinylogous[79,82] HWE reaction (γ-attack) with the aldehyde to provide **52** or **53**, respectively.



Scheme 2.16

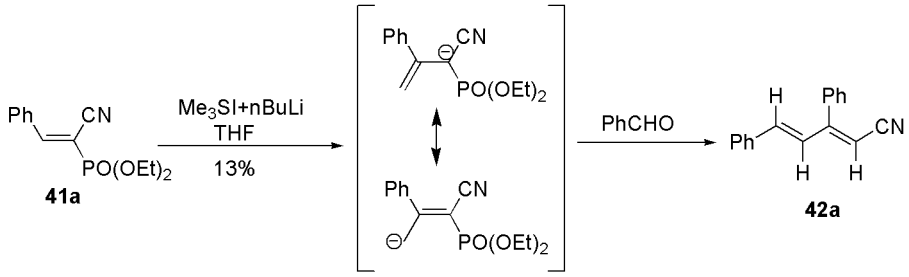
The arylidene cyanophosphonates **41a-d** were prepared from diethyl (cyanomethyl)phosphonate **54** and the corresponding aromatic aldehydes by a Knoevenagel type reaction in which *E*-isomer was formed exclusively.[84] This diethyl (cyanomethyl)phosphonate **54** was prepared from bromoacetonitrile **55** and triethyl orthophosphate **56** by a Arbuzov type reaction as shown in **Scheme 2.17**.



Scheme 2.17

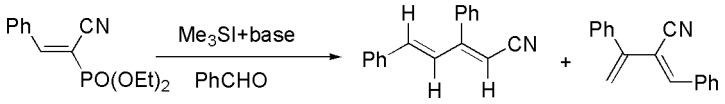
When the vinyl phosphonate **41a** was added to a reaction mixture containing 2.5 equiv. of sodium dimsylate and 1.2 equiv trimethylsulfonium iodide (Me_3SI) and quenched with benzaldehyde, the vinylogous diene **42a** was formed along with a trace amount of normal diene **57a**. As our group had already addressed the synthesis of dienes **42a**[79] from **41a**, our next aim was to switch the regioselectivity of the reaction. We initially planned to

achieve our goal by changing the ylide generation conditions using trimethylsulfonium iodide and different bases/solvents. When the ylide was generated using 3 equiv each of Me_3SI and *n*-BuLi in THF and reacted with **41a** followed by quenching the intermediate with benzaldehyde, diene **42a** was formed. **(Scheme 2.18** and **Table 2.1**, entry 1) with poor yield (ca. 13%) but with excellent regio- and stereoselectivity (**42a:57a** = 97:3).[85] The *E* stereochemistry of the disubstituted double bond in diene **42a** was ascertained from the coupling constant in the ^{1}H NMR (J = 16 Hz) (**Fig. 2.2**) while the *Z* stereochemistry of the trisubstituted double bond was confirmed from nOe interaction between olefinic protons. To improve the yield of the reaction, we screened a few more bases. When Li, Na or K hexamethyldisilazide was used as a base (**Table 2.1**, entry 2-4) for the olefination reactions and THF as a solvent, the desired product was not formed. Even the reaction did not proceed with the base like LDA or *t*-BuOK (**Table 2.1**, entries 5 and 6).



Scheme 2.18

Table 2.1 Screening of bases for the generation of dimethylsulphonium methylide and its use in the double olefination reaction of vinyl phosphonate 41a and benzaldehyde.



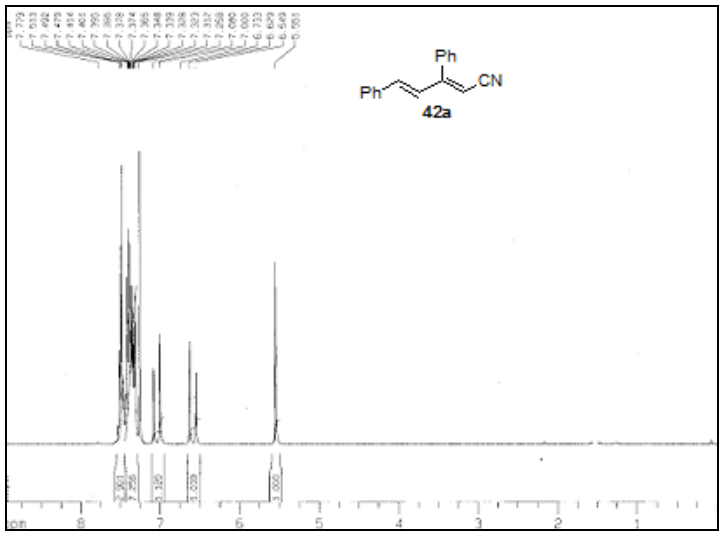
41a **42a** **57a**

Entry	Base	Solvent[a]	Product ratio[b] **42a:57a**	Yield of **42a**[c]
1.	*n*-BuLi	THF	97:3	13%
2.	LiHMDS	THF	------	ND[d]
3.	KHMDS	THF	------	ND [d]
4.	NaHMDS	THF	------	ND[d]
5.	LDA	THF	------	ND [d]
6.	*t*-BuOK	THF	------	ND [d]

[a] Base (3 equiv) was added to Me_3SI suspension in THF at –10 °C. After 15 min, **41a** (1 equiv) was added and the reaction mixture was brought to room temperature. PhCHO (1.2 equiv) was added to the reaction mixture and stirred for 3 h; [b] The ratio was determined from ^{1}H NMR of the crude product; [c] Isolated yield of TLC homogeneous material; [d] The product formation was not detected by ^{1}H NMR and TLC analysis.

From the results presented in **Table 2.1**, it can be concluded that *n*-BuLi is a promising base for ylide generation and this double olefination reaction. We screened a few more ylide generation conditions using *n*-BuLi as a base and we observed an interesting and dramatic change in the regioselectivity of the sequential olefinations when DMSO was used as a co-solvent in the reaction mixture. When the ylide was generated

using 3.0 equiv each of Me_3SI and 3.0 equiv of *n*-BuLi in THF containing 1.5 equiv. of DMSO and subsequent reaction with **41a** and benzaldehyde (1.5 equiv), we were delighted to see the formation of the desired diene **57a** (**Fig. 2.3** and **Fig. 2.4)** albeit in moderate yield (35%) (**Table 2.2**, entry 1).



.

Fig. 2.2 ^{1}H NMR of 42a

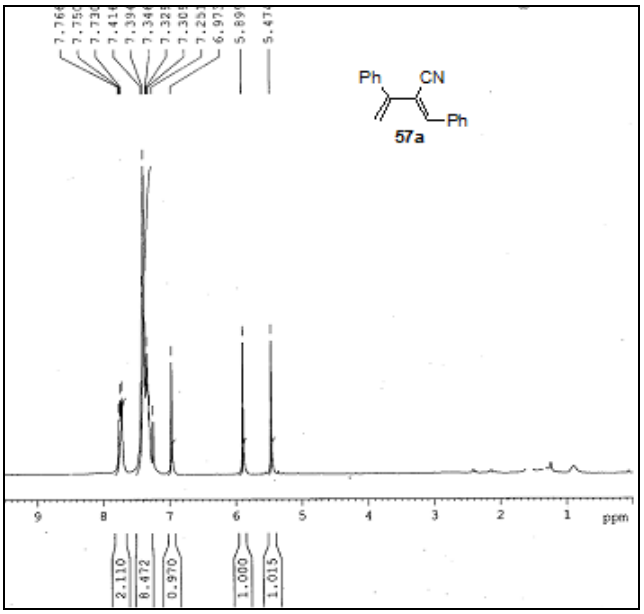


Fig. 2.3 ^{1}H NMR of 57a

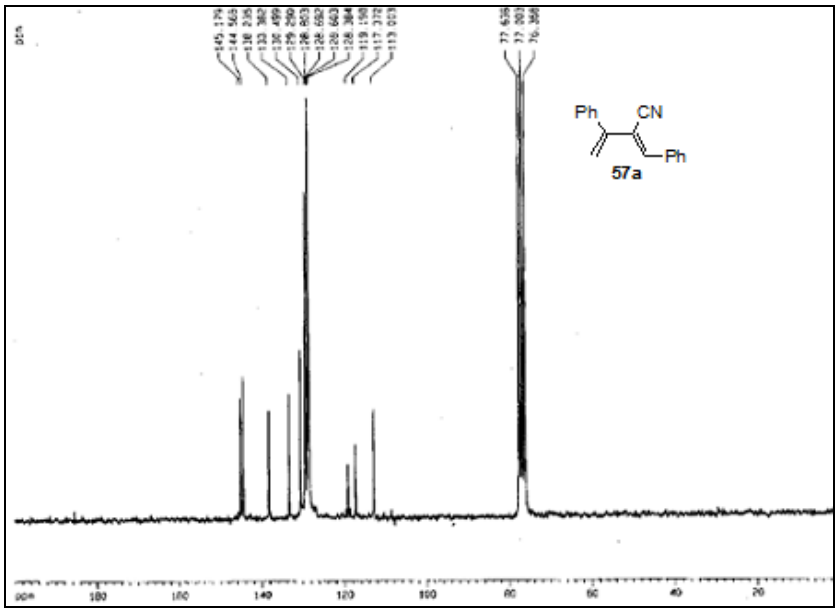
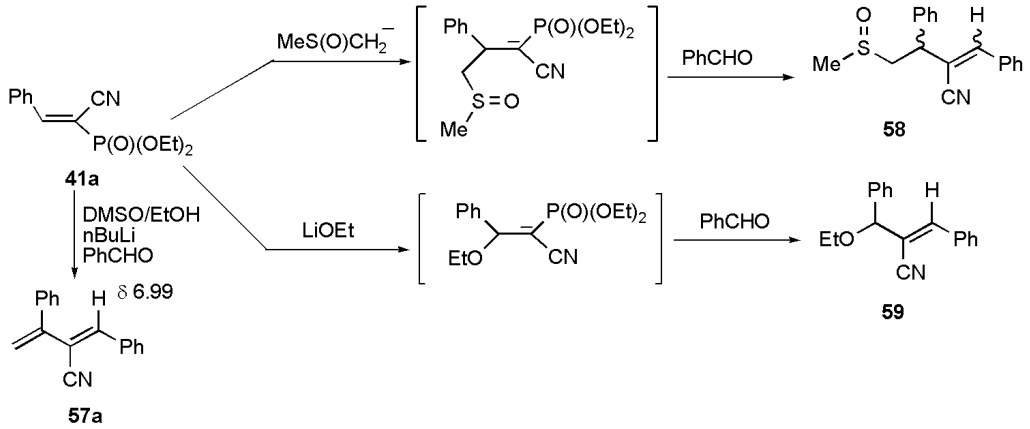


Fig 2.4 ^{13}C NMR of 57a

Our next aim was to improve the yield of the product **57a** and carried out a number of experiments by changing the amount of Me_3SI, *n*-BuLi, DMSO (**Table 2.2**, entries 2 and 3). The yield of the reaction did not improve and it was in the range of 25-35%. The main by- product of the reaction was found to be the sulphoxide **58**[82] (**Scheme 2.19**) which was formed due to Michael addition of lithium dimsylate on **41a** followed by a normal HWE reaction with benzaldehyde. The formation of sulphoxide **58** suggested that the ylide **38** is less nucleophilic than the dimsylate anion.

To prevent the formation of sulphoxide **58**, we next decided to add a proton source like an alcohol into the reaction medium to tap on the concentration of dimsylate anion. Amongst the alcohols we screened (**Table 2.2**, entries 4-7) ethanol was found to be best. A number of reactions were carried out to optimize the quantity of ethanol. It was found that a gradual increase in ethanol quantity initially increased the yield of **57a** with simultaneous decrease in sulphoxide **58** formations. The optimum quantity of ethanol was found to be

1.5 equiv beyond which a side product **59** [85] (**Table 2.2**, entry 9) started forming due to ethoxide addition on **41a** followed by HWE reaction with PhCHO (**Scheme 2.19**). From the above experiments, it was concluded that the ylide **38** was less nucleophilic than both the dimsylate anion and the ethoxide. To know the exact role of lithium dimsylate and lithium ethoxide in this reaction, we carried out this olefination reaction omitting Me_3SI (**Table 2.2**, entry 10, 11). When **41a** was treated with lithium dimsylate, generated using 2.5 equiv each of *n*-BuLi and DMSO followed by addition of 2.5 equiv of benzaldehyde, the olefination took place leading to the formation of **57a**. But the product was associated with significant amount of sulphoxide **58** (**Table 2.2**, entry 10). Finally we achieved a optimized condition (**Table 2.2**, entry 11) by using 1.5 equiv each of DMSO and EtOH, 1.2 equiv of benzaldehyde and 2.5 equiv. of *n*-BuLi with respect to vinyl phophonate **41a** in THF at ambient temperature giving the diene **57a** in 82% yield.[85] The stereoisomeric purity of **57a** was checked by GC and was found to be > 97%. The other regioisomeric diene **42a** was not detected. The above experiments confirmed that the lithium dimsylate–lithium ethoxide combination is equivalent to a carbenoid anion acting as the olefination reagent, and is an excellent surrogate of dimethylsulfonium methylide **38**.



Scheme 2.19

Table 2.2 Optimization of the double olefination of vinyl phosphonate 41a and benzaldehyde.

Entry	*n*BuLi/Me_3SI (equiv.)	Alcohol (ROH)	DMSO/ROH (equiv.)	**57a/42a/58**[a]	Yield of **57a**[%][b]
1.	3/3		1.5/0	70:00:30	35
2.	2.5/3		1.0/0	45:00:55	30
3.	2.5/1.5		1.5/0	40:00:60	25
4.	2.5/1.5	$C_6H_5CH_2OH$	1.5/1.0	77:00:23	47
5.	2.5/1.5	$(CH_3)_2CHCH_2OH$	1.5/1.0	75:00:25	45
6.	2.5/1.5	$(CH_3)_3CCH_2OH$	1.5/1.0	75:00:25	44
7.	2.5/1.5	C_2H_5OH	1.5/1.0	80:00:20	51
8.	2.5/1.5	C_2H_5OH	1.5/1.5	100:00:00	62
9.	2.5/1.5	C_2H_5OH	1.5/2.0	100:00:00	48[c]
10.	2.5/0		2.5/0	65:00:35	53
11.	2.5/0	C_2H_5OH	1.5/1.5	100:00:00	82[d]

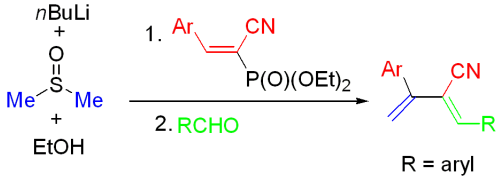
[a]The ratio was found from the crude product by ^1H NMR spectroscopy; [b] Isolated yield of TLC homogeneous material; [c] 26% of **59** was isolated; [d] Conditions provided in the experimental section.

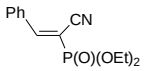
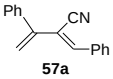
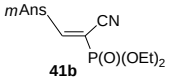
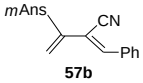
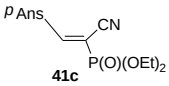
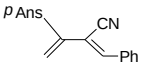
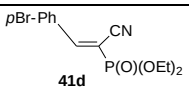
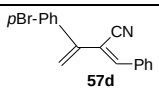
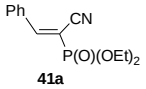
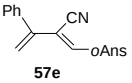
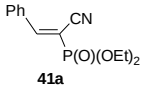
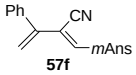
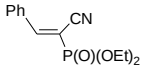
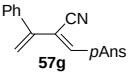
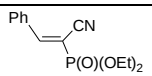
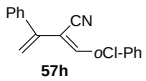
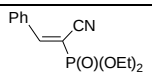
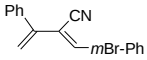
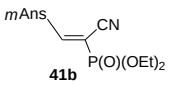
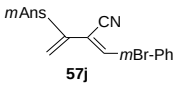
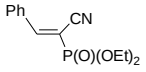
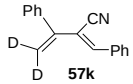
With the optimized conditions in hand, the scope of the sequential olefination reaction was investigated. A wide range of aldehydes bearing aryl, heteroaryl and alkenyl groups were reacted with phosphonates **41a-d**. In all case the desired oleifinic products

were obtained in very good yields, with excellent regio and stereoselectivity. Benzaldehyde reacted with all the four vinyl phosphonate (**41a-d)** and the desired dienes (**Table 2.3**, entry 1-4) were obtained with good yields as well as excellent isomeric purity. In none of the cases, the other regioisomeric product was detected. The purity of these product was confirmed by the GC analysis which was found >94% of the crude as well as the pure dienes. *o*-Anisaldehyde and *m*-anisaldehyde (**Table 2.3**; entries 5,6) also gave the desired products but with slightly erroded stereoselectivity. Importantly, no other regioisomers were detected. Thus, aromatic aldehydes having both the electron withdrawing or donating substitutent work well under the reaction conditions to give the desired dienes in good yield, selectivity and purity. This reaction was also used for the synthesis of 4,4-dideuterrated dienes (**Table 2.3**; entry 11) when the reaction of **41a** with benzaldehyde was carried out in presence of DMSO-d_6.[85]. The selectivity and purity of the diene was found to be very good but the isotopic purity was >91%. The slightly lower isotopic purity (91%) was probably due to H – D exchange from ethanol used in the reaction.

2-Furaldehyde and 1-naphthaldehyde (**Table 2.4**; entries 1, 2 and 4) also gave the desired products with slightly erroded stereoselectivity, but no other regioisomers were detected. When **41a** reacted with *trans*-cinnamaldehyde, the desired normal HWE reaction led to a triene **57p** with excellent yield and purity (**Table 2.4**; entry 5). The formation of the triene was confirmed from ^{1}H and ^{13}C NMR spectra (**Fig. 2.5** and **Fig. 2.6**).

Table 2.3 Stereoselective sequential tandem double olefination of arylidene phosphonoacetonitriles 41a-d with aromatic aldehydes.

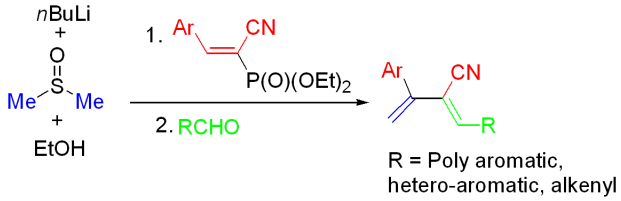


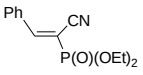
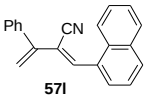
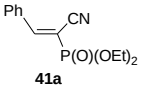
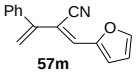
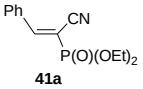
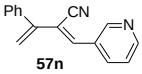
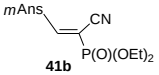
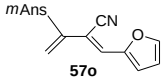
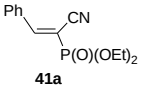
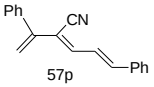
Entry	Substrate	Aldehydes	Product	Yield(%)[a]	Purity (%)[b,c]
1.	 **41a**	Benzaldehyde	 **57a**	82	>97
2.	 **41b**	Benzaldehyde	 **57b**	80	95
3.	 **41c**	Benzaldehyde	 **57c**	84	>94
4.	 **41d**	Benzaldehyde	 **57d**	80	>96
5.	 **41a**	*o*-Anisaldehyde	 **57e**	76	>94
6.	 **41a**	*m*-Anisaldehyde	 **57f**	79	>93
7.	 **41a**	*p*-Anisaldehyde	 **57g**	81	>99.5
8.	 **41a**	*o*-Chlorobenzaldehyde	 **57h**	80	>95
9.	 **41a**	*m*-Bromobenzaldehyde	 **57i**	82	96.7
10.	 **41b**	*m*-Bromobenzaldehyde	 **57j**	85	98.9
11.	 **41a**	Benzaldehyde	 **57k**	82	>91[d]

[a] Isolated yield of TLC homogenous material; [b] Isomeric purity determined by capillary GC/ ^{1}H NMR of the crude product/pure product; [d] isotopic purity.

Heteroaromatic aldehydes like 2-furyl and 3-pyridyl carboxaldehyde react smoothly to give the desired dienes **57m, 57n** and **57o** respectively. In contrast to aromatic and hetero-aromatic aldehydes, the reaction did not proceed with aliphatic aldehydes and ketones

Table 2.4 Stereoselective sequential tandem double olefination of arylidene phosphonoacetonitriles 41a-d with aromatic/ hetero-aromatic/alkenyl aldehydes.



Entry	Substrate	Aldehydes	Product	Yield(%)[a]	Purity (%)[b,c]
1.	 **41a**	1-Napthaldehyde	 **57l**	74	93.0
2.	 **41a**	2-Furaldehyde	 **57m**	82	>97.0
3.	 **41a**	3-Pyridine carboxaldehyde	 **57n**	81	99.0
4.	 **41b**	2-Furaldehyde	 **57o**	76	97.8
5.	 **41a**	*trans*-Cinnamaldehyde	 57p	85	>94.0

[a] Isolated yield of TLC homogenous material; [b] Isomeric purity determined by capillary GC/ ^{1}H NMR of the crude product/pure product; [d] isotopic purity.

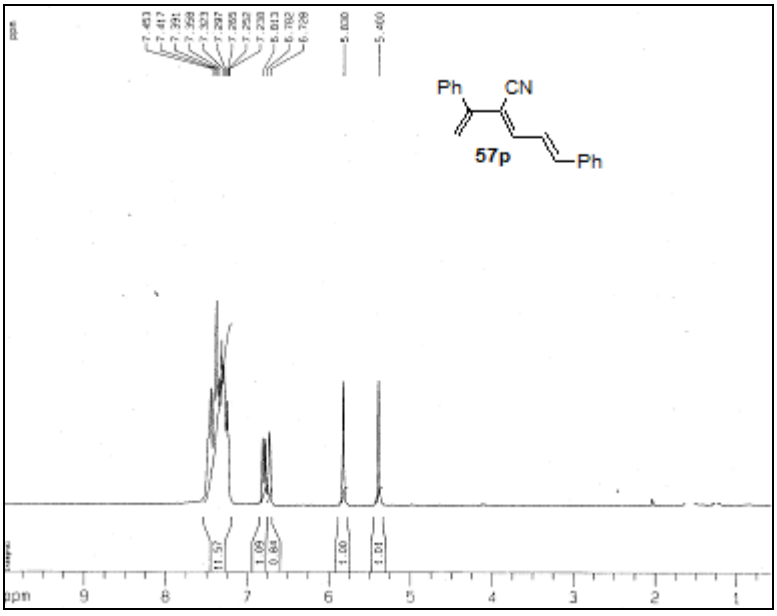


Fig 2.5 ^{1}H NMR of 57p

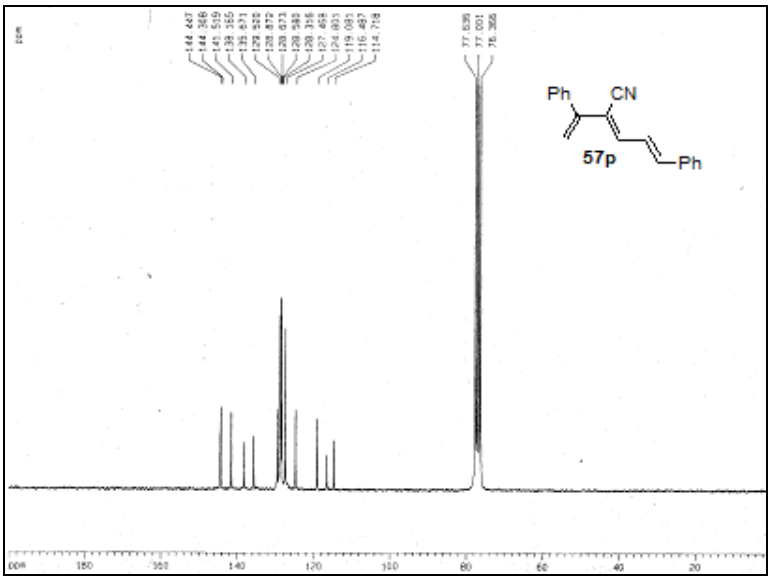
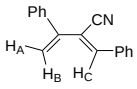
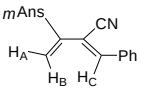
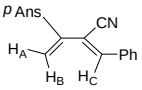
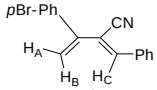
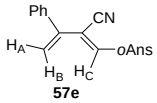
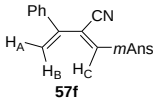
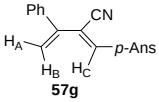
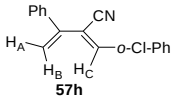
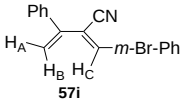
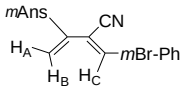
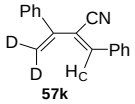


Fig 2.6 ^{13}C NMR of 57p

The (*Z*)-stereochemistry of the tri-substituted double bond in dienes **57a-p** was confirmed from the ^{1}H NMR analysis.[78,86] In general the chemical shift value of this olefinic protons in (*Z*)-double bond is expected to resonant at about δ = 5.7-7.0 ppm while olefinic protons in (*E*)-double bond is expected to resonant further down field at about δ =

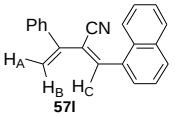
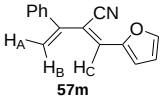
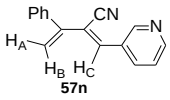
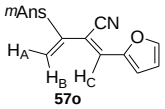
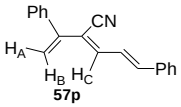
7.0-7.5 ppm. The chemical shift values of the olefinic protons in dienes **57a-p** are given in **Table 2.5** and **Table 2.6**.

Table 2.5 Chemical shifts of Olefinic Protons for 57a-k

Entry	Diene	δ H_A	δ H_B	δ H_C
1.	 **57a**	5.47	5.90	6.97
2.	 **57b**	5.45	5.89	7.00
3.	 **57c**	5.43	5.82	7.01
4.	 **57d**	5.46	5.90	6.93
5.	 **57e**	5.46	5.85	-[a]
6.	 **57f**	5.47	5.90	6.94
7.	 **57g**	5.41	5.83	6.89
8.	 **57h**	5.54	5.95	-[a]
9.	 **57i**	5.51	5.93	6.87
10.	 **57j**	5.51	5.92	6.90
11.	 **57k**	-	-	6.98

[a] signal overlap with the aromatic protons

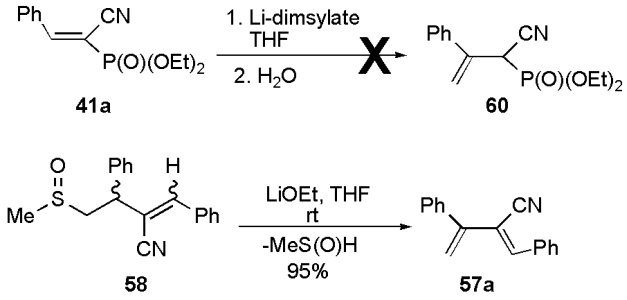
Table 2.6 Chemical shifts of Olefinic Protons for 57l-p

Entry	Diene	δ H_A	δ H_B	δ H_C
1.	 **57l**	5.55	5.97	7.70
2.	 **57m**	5.41	5.87	6.75
3.	 **57n**	5.55	5.96	6.95
4.	 **57o**	5.42	5.85	6.77
5.	 **57p**	5.40	5.83	6.73

2.2.2 Establishment of elementary steps of domino reaction

Each of the elementary steps of the domino reaction was confirmed experimentally.[85] For this, we carried out two reactions as depicted in **Scheme 2.20**. When the reaction of **41a** and lithium dimsylate–lithium ethoxide was carried out without adding PhCHO, no olefination product **60** was isolated (**Scheme 2.20**). However, when **58** was treated with lithium ethoxide (generated in-situ by the reaction of *n*BuLi and EtOH) in THF at room temperature, **57a** was formed in nearly quantitative yield indicating its intermediacy in the reaction (**Scheme 2.20**). Therefore, the domino process follows path 'a' (**Scheme 2.16**) involving first the Michael addition of dimsyl lithium to arylidene phosphonoacetonitrile **41a**, a HWE reaction of the resulting phosphonate ylide with the added aldehyde gave the

intermediate sulphoxide **58** which then underwent lithium ethoxide induced methylsulfenoxy elimination resulting in the formation of diene **57a**.



Scheme 2.20

2.3 Conclusions

We have developed a new regio- and stereoselective one-pot four component sequential double olefination reaction of lithium dimsylate, lithium ethoxide arylidene phosphonoacetonitriles and aldehydes leading to the syntheses of differentially functionalized trisubstituted 1,3-dienes in very good yields and excellent isomeric purity. This is also useful for the synthesis of deuterated dienes. The most imortant feature of this reaction is the excellent stereoselectivity of the trisubstituted double bond. All cases the Z-isomer was formed exclusively. It is found that lithium dimsylate–lithium ethoxide system can be treated as a surrogate of dimethylsulfonium methylide base combination and equivalent to a “carbenoid” anion.

2.4 EXPERIMENTAL SECTION

General Details:

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

Solvent purification: The solvents were dried and distilled from the indicated drying agents: THF from sodium/benzophenone; DMSO from CaH_2 and then stored over Ca metal. Di-isopropylamine was dried from CaH_2. EtOH was dried over Mg and then stored over MS 4Å. All other alcohols were dried from CaH_2 and stored over molecular sieves.

Reagents: Benzaldehyde, *m/p*-anisaldehyde, *o*-chlorobenzaldehyde, *m* bromobenzaldehyde, 2-furaldehyde, 3-pyridyl carboxaldehyde, 1-naphthaldehyde, *trans*-cinnamaldehyde were freshly distilled before use where as *p*-bromobenzaldehyde and *o*-anisaldehyde were crystallised before use. All the aldehydes were obtained either from Aldrich and Spectrochem (India). NaHMDS (2.0 M in tolune), KHMDS (2.0 M in toluene), LiHMDS (2.0 M in tolune), *n*-BuLi (1.6 M in hexanes), *t*-BuOK and bromoacetonitrile were obtained from Aldrich. Trimethylsulfonium iodide and Triethylphosphonate were obtained from Spectrochem (India). Triethylphosphonate was distilled under vacuum before use.

NMR Study: ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 200 MHz spectrometer. Spectra were referenced to residual chloroform (δ 7.26 ppm, ^{1}H; 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: Mass spectra were recorded on a Fissons VG Quatro II mass spectrometer (EI 70 V; CI 30 V). HRMS were recorded in a Waters Micromass Q-TOF Mass Spectrometer.

IR Study: IR spectra were recorded on a Nicolet Impact 410 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.

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.

Diethyl (cyanomethyl)phosphonate 54:

A mixture of bromoacetonitrile **55** (7 mL, 100 mmol) and triethylphosphonate **56** (17.2 mL, 100 mmol) was heated at 80 °C under argon atmosphere for overnight to give the phosphonate **54**. Yield: 17.7 g (100%); ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.34 (6 H, t, *J* = 7.2 Hz, 2 × C*H*$_3$CH$_2$O), 2.86 (2 H, d, *J* = 21 Hz, C*H*$_2$P[O]), 4.20 (2 H, q, *J* = 7.2 Hz, CH$_3$C*H*$_2$O), 4.25 (2 H, q, *J* = 7.2 Hz, CH$_3$C*H*$_2$O).

General Procedure 2.4.I. Preparation of Arylidene Phoshonoacetonitrile 41a-d: Following the reported procedure,[84] a solution of an aromatic aldehyde (12 mmol), diethyl cyanomethylphosphonate **54** (1.6 mL, 10 mmol) and piperidinium benzoate (415 mg, 2 mmol) in benzene (80 mL) was heated under reflux fitted with a Dean-Stark apparatus for 2 d. The reaction mixture was cooled, washed with water and with brine, dried ($MgSO_4$)

and evaporated. The residue was purified by silica-gel chromatography using hexane/ethyl acetate to give the corresponding arylidene phosphonoacetonitrile **41a-d.**

(*E*)-Diethyl 1-cyano-2-phenylethene-2-phosphonate 41a: Prepared from diethyl cyanomethylphosphonate **54** (1.6 mL, 10 mmol) and benzaldehyde (1.22 mL, 12 mmol) according to *General Procedure* **2.4.I.** Yield: 2.15 g (81%); IR (neat): 2985, 2935, 2909, 2212, 1595, 1572, 1449, 1392, 1369, 1260, 1211, 1163, 1015, 973, 831, 787, 762 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.40 (6 H, t, *J* = 7 Hz, 2 × CH_3CH_2O), 4.30- 4.14 (4 H, m, 2 × CH_3CH_2O), 7.58- 7.44 (3 H, m, Ar), 7.97- 7.93 (2 H, m, Ar), 8.00 (1 H, d, *J* = 21.4 Hz, ArC*H*); ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 15.6 (d, *J* = 5.9 Hz), 62.9 (d, *J* = 4.4 Hz), 99.6 (d, *J* = 195 Hz), 114.7 (d, *J* = 10.2 Hz), 128. 6 (2 C), 129.7 (2 C), 131.8 (d, *J* = 17.7 Hz), 132.4, 158.1.

(*E*)-Diethyl 1-cyano-2-(3-methoxyphenylethene)-2-phosphonate 41b: Prepared from diethyl cyanomethylphosphonate **54** (1.6 mL, 10 mmol) and meta-anisaldehyde (1.63 g, 12 mmol) according to *General Procedure* **2.4.I.** Yield: 2.18 g (74%); IR (neat): 3007, 2939, 2910, 2213, 1599, 1576, 1491, 1483, 1465, 1433, 1264, 1216, 1173, 1162, 1023, 978, 754, 684 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.39 (6 H, t, *J* = 7.2 Hz, 2 × CH_3CH_2O), 3.84 (3 H, s, O*Me*), 4.15 (2 H, q, *J* = 7.2 Hz, CH_3CH_2O), 4.23 (2 H, q, *J* = 7.2 Hz, CH_3CH_2O), 7.07 (1 H, d, *J* = 8 Hz, Ar), 7.33-7.54 (3 H, m, Ar), 8.00 (1 H, d, *J* = 21.4 Hz, ArC*H*); ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 16.2 (d, *J* = 6.2 Hz), 55.3, 63.5 (d, *J* = 5.8 Hz), 100.2 (d, *J* = 195 Hz), 114.0, 115.4 (d, *J* = 10.1 Hz), 119.8, 123.4, 130.1, 133.6 (d, *J* = 17.7 Hz), 158.8 (d, *J* = 7 Hz), 159.9.

(*E*)-Diethyl 1-cyano-2-(4-methoxyphenylethene)-2-phosphonate 41c: Prepared from diethyl cyanomethylphosphonate **54** (1.6 mL, 10 mmol) and para-anisaldehyde (1.46 mL, 12 mmol) according to *General Procedure* **2.4.I.** Yield: 2.54 g (86%); IR (neat): 3063, 3016, 2988, 2938, 2908, 2842, 2210, 1588, 1562, 1512, 1427, 1309, 1264, 1180, 1065, 1024, 974, 834, 794, 756 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.36 (6 H, t, *J* = 7 Hz, 2 × *CH*$_3$$CH_2O$), 3.88 (3 H, s, O*Me*), 4.22 (2 H, q, *J* = 7 Hz, CH_3*CH*$_2$O), 4.19 (2 H, q, *J* = 7.1 Hz, CH_3*CH*$_2$O), 6.97 (2 H, d, *J* = 8.8 Hz, Ar), 7.92 (1 H, d, *J* = 23 Hz, ArC*H*), 7.96 (2 H, d, *J* = 8.7 Hz, Ar) ;^{13}C-NMR (50 MHz, $CDCl_3$): δ = 16.2 (d, *J* = 5.8 Hz), 55.5, 63.3 (d, *J* = 5.6 Hz), 95.5 (d, *J* = 198 Hz), 114.6 (2 C), 116.0 (d, *J* = 10.3 Hz), 125.4 (d, *J* = 14 Hz), 132.9 (2 C), 158.2, 163.5.

(*E*)-Diethyl 1-cyano-2-(4-bromophenylethene)-2-phosphonate 41d: Prepared from diethyl cyanomethylphosphonate **54** (1.6 mL, 10 mmol) and 4-bromobenzaldehyde (2.22g, 12 mmol) according to *General Procedure* **2.4.I.** Yield: 2.96 g (86%); IR (neat): 2985, 2933, 2908, 2212, 1586, 1558, 1487, 1443, 1403, 1369, 1262, 1163, 1098, 1022, 975, 824, 783, 751 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.40 (6 H, t, *J* = 7 Hz, 2 × *CH*$_3$$CH_2O$), 4.29-4.09 (4 H, m, 2 × CH_3*CH*$_2$O), 7.62 (2 H, d, *J* = 8.4 Hz, Ar), 7.81 (2 H, d, *J* = 8.6 Hz, Ar), 7.93 (1 H, d, *J* = 21 Hz, ArC*H*);. ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 15.9 (d, *J* = 6 Hz), 63.4 (d, *J* = 5.6 Hz), 100.6 (d, *J* = 196 Hz), 114.8 (d, *J* = 9.9 Hz), 127.5, 130.9 (d, *J* = 18 Hz), 131.4 (2 C), 132.2 (2 C), 156.9 (d, *J* = 7.1 Hz).

(1*Z*, 3*E*)-1-cyano-2,4-diphenyl-1,3-butadiene 42a: *n*BuLi (2.0 mL, 3.2 mmol, 1.6 M hexane solution) was added to Me_3SI (652 mg, 3.2 mmol) suspension in THF (4ml) at -10 ºC. After 15 min, **41a** (265 mg, 1.0 mmol) in THF (2mL) was added and the reaction

mixture was brought to room temperature. PhCHO (0.15 mL, 1.5 mmol) was added to the reaction mixture and stirred for 3 h. The reaction mixture was diluted with water and extracted with ether. The combined extract was washed with brine, dried over magnesium sulfate, filtered and concentrated under *vacuum*. The residue was purified on silica-gel using hexane/ethyl acetate to give the diene **42a** as a white crystalline solid. Yield: 30 mg (13%); M.p. = 57 ºC; IR ($CHCl_3$): 3034, 2209, 1615, 1581, 1561, 1491, 1449, 1375, 1199, 1071, 1005, 966, 803, 779, 753, 705, 690 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 5.55 (1 H, s, C*H*CN), 6.59 (1 H, d, *J* = 16 Hz, CH=C*H*-Ph), 7.04 (1 H, d, *J* = 16 Hz, C*H*=CH-Ph), 7.31-7.52 (10 H, m, 2 × Ph); ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 97.4, 117.7, 127.3 (2 C), 128.1, 128.6 (2 C), 128.7 (2 C), 128.8 (2 C), 129.3 (2 C), 135.0, 135.4, 139.8, 160.7; ESI MS: *m*/*z* (%) = 232 (2) (M^+ + 1), 124 (100); GC: (260 ºC isothermal) t_R = 9.025 min (100%); ESI-HRMS: Found: M^+ + H, 232.1122. $C_{17}H_{14}N$ requires M^+ + H 232.1126; Anal. Calcd for $C_{17}H_{13}N$: C 88.28, H 5.67, N 6.06 %; found C 88.04, H 5.74, N 5.92 %.

General Procedure 2.4.II. Preparation of 1,3-Dienes 57a-p: *n*BuLi (1.6 mL, 2.5 mmol, 1.6 M hexane solution) was added to a stirred solution of DMSO (0.11 mL, 1.5 mmol) and EtOH (0.09 mL, 1.5 mmol) in THF (4 mL) at 0 ^{o}C. After 2 min, arylidene phosphonoacetonitrile **41a-d** (1.0 mmol) in THF (2 mL) was added to the reaction mixture followed by the addition of the aldehyde (1.2 mmol). The reaction mixture was brought to room temperature and stirred for 3–12 h. The reaction mixture was diluted with water and extracted with ether. The combined extract was washed with brine, dried over magnesium sulfate, filtered and concentrated under *vacuum*. The residue was purified on silica-gel using hexane/ethyl acetate to give the corresponding diene **57a-p**.

(1*Z*)-2-Cyano-1,3-diphenyl-1,3-butadiene 57a: Prepared from **41a** (265 mg, 1 mmol) and benzaldehyde (0.125 mL, 1.2 mmol) according to *General Procedure* **2.4.II.** Yield: 190 mg (82%); M.p. = 51–52 ºC; IR ($CHCl_3$): 3054, 2211, 1607, 1570, 1493, 1445, 1209, 1100, 1072, 1029, 936, 908, 754, 682 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 5.49 (1 H, s, C=CH_AH$_B$), 5.92 (1 H, s, C=CH$_A$$H_B$), 6.99 (1 H, s, PhC*H*=C), 7.30-7.43 (8 H, m, Ar), 7.73-7.78 (2 H, m, Ar) ; ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 113.0, 117.4, 119.2, 128.4, 128.6 (2 C), 128.7 (2 C), 128.8 (2 C), 129.3 (2 C), 130.5, 133.4, 138.2, 144.6, 145.2; ESI MS: *m*/*z* (%) = 232 (60) (M^+ + 1), 148 (100); GC: (260 ºC isothermal) t_R = 7.642 min (100%). Anal. Calcd for $C_{17}H_{13}N$: C 88.28, H 5.67, N 6.06 %; found C 88.11, H 5.82, N 5.80 %.

(1*Z*)-2-Cyano-3-(3-methoxyphenyl)-1-phenyl-1,3-butadiene 57b: Prepared from **41b** (295 mg, 1 mmol) and benzaldehyde (0.125 mL, 1.2 mmol) according to *General Procedure* **2.4.II.** Yield: 209 mg (80%); IR (neat): 3062, 3020, 2958, 2938, 2834, 2218, 1597, 1577, 1448, 1321, 1286, 1239, 1044, 754, 690 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.83 (3 H, s, OMe), 5.47 (1 H, s, C=CH_AH$_B$), 5.89 (1 H, s, C=CH$_A$$H_B$), 6.85-6.97 (3 H, m, Ar), 7.00 (1 H, s, ArC*H*=C), 7.25-7.41 (4 H, m, Ph, Ar), 7.73-7.77 (2 H, m, Ar); ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 55.3, 112.8, 113.8, 114.4, 117.4, 119.1, 121.1, 128.8 (2 C), 129.3 (2 C), 129.6, 130.5, 133.4, 139.6, 144.6, 145.0, 159; ESI MS: *m*/*z* (%) = 262 (100) (M^+ + H), 184 (31); GC: (200 ºC–10 ºC/min–260 ºC–5 ºC/min–300 ºC) t_R = 12.43 min (100%); ESI-HRMS: Found: M^+ + H, 262.1224. $C_{18}H_{16}NO$ requires M^+ + H, 262.1232.

(1*Z*)-2-Cyano-1-phenyl-3-(4-methoxyphenyl)-1,3-butadiene 57c: Prepared from **41c** (295 mg, 1 mmol) and benzaldehyde (0.125 mL, 1.2 mmol) according to *General Procedure* **2.4.II.** Yield: 219 mg (84%); IR (neat): 3018, 2960, 2935, 2838, 2217, 1608,

1509, 1451, 1290, 1250, 1215, 1179, 1029, 837, 754 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.84 (3 H, s, OMe), 5.42 (1 H, s, C=C$H_A$$H_B$), 5.82 (1 H, s, C=C$H_A$$H_B$), 6.92 (2 H, d, *J* = 8.2 Hz, Ar), 7.00 (1 H, s, ArC*H*=C), 7.20-7.27 (2 H, m, Ph), 7.37-7.41 (3 H, m, Ph), 7.74 (2 H, d , *J* = 8.2 Hz, Ar); ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 55.3, 113.2, 114.0 (3 C), 117.5, 118.3, 128.8 (2 C), 129.3 (2 C), 129.8 (2 C), 130.4, 133.5, 144.5, 144.8, 159.7; EI MS: *m*/*z* (%) = 262 (35) (M^+ + H), 261 (67) (M^+), 246 (29), 230 (38), 218 (34), 217 (66), 190 (30), 140 (36), 127 (41), 121 (50), 108 (60), 89 (69), 77 (100), 63 (78); GC: (200 ºC–10 ºC/min–260 ºC–5 ºC/min–300 ºC) t_R = 12.80 min (100 %); ESI-HRMS: Found: M^+ + H, 262.1233. $C_{18}H_{16}NO$ requires M^+ + H, 262.1232.

(1*Z*)-2-Cyano-3-(4-bromophenyl)-1-phenyl-1,3-butadiene 57d: Prepared from **41d** (344 mg, 1 mmol) and benzaldehyde (0.125 mL, 1.2 mmol) according to *General Procedure* **2.4.II.** Yield: 248 mg (80%); IR (neat): 3062, 3029, 2217, 1588, 1571, 1485, 1447, 1392, 1210, 1068, 1010, 832 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 5.46 (1 H, s, C=C$H_A$$H_B$), 5.90 (1 H, s, C=C$H_A$$H_B$), 6.93 (1 H, s, PhC*H*=C), 7.21 (2 H, d, *J* = 8.4 Hz, Ar), 7.37-7.43 (3 H, m, Ph), 7.55 (2 H, d, *J* = 8.4 Hz, Ar), 7.64-7.77 (2 H, m, Ph); ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 112.6, 117.2, 119.5, 122.6, 128.9 (2 C), 129.4 (2 C), 130.3 (2 C), 130.7, 131.9 (2 C), 133.2, 137.2, 144.2, 144.7; ESI MS: *m*/*z* (%) = 312 (51) ($C_{17}H_{13}N^{81}Br$, M^+ + H), 310 (58) ($C_{17}H_{13}N^{79}Br$, M^+ + H), 231(100); GC: (200 ºC–10 ºC/min–260 ºC–5 ºC/min–300 ºC) t_R = 13.31 min (100 %); ESI-HRMS: Found: M^+ + H, 310.0237. $C_{17}H_{13}N^{79}Br$ requires M^+ + H, 310.0231.

(1*Z*)-2-Cyano-1-(2-methoxyphenyl)-3-phenyl-1,3-butadiene 57e: Prepared from **41a** (265 mg, 1 mmol) and *o*-anisaldehyde (163 mg, 1.2 mmol) according to *General*

Procedure **2.4.II.** Yield: 198 mg (76%). M.p. = 81–82 ºC; IR ($CHCl_3$ film): 3019, 2219, 1599, 1491, 1466, 1437, 1251, 1179, 1027, 908 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.75 (3 H, s, OMe), 5.46 (1 H, s, C=CH_AH$_B$), 5.85 (1 H, s, C=CH$_A$$H_B$), 6.86 (1 H, d, *J* = 8.4 Hz, Ar), 7.03 (1 H, t, *J* = 7.4 Hz, Ar), 7.30-7.43 (7 H, m, Ph, Ar and ArC*H*=C), 8.06 (1 H, d, *J* = 7.4 Hz, Ar); ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 55.5, 110.6, 113.1, 117.6, 118.5, 120.7, 122.8, 128.3, 128.4 (2 C), 128.6 (3 C), 131.8, 138.4, 140.3, 145.4, 157.7; EI MS: *m*/*z* (%) = 262 (44) (M^+ + H), 261 (100) (M^+), 246 (32), 230 (92), 219 (30), 218 (29), 202 (21), 184 (68), 169 (23), 108 (29), 91 (63), 77 (90), 63 (23); GC: (200 ºC–10 ºC/min–260 ºC–5 ºC/min–300 ºC) t_R = 11.97 min (1.5 %), t_R = 12.21 min (98.5%); ESI-HRMS: Found: M^+ + H, 262.1237. $C_{18}H_{16}NO$ requires M^+ + H, 262.1232.

(1*Z*)-2-Cyano-1-(3-methoxyphenyl)-3-phenyl-1,3-butadiene 57f: Prepared from **41a** (265 mg, 1 mmol) and *m*-anisaldehyde (0.146 mL, 1.2 mmol) according to *General Procedure* **2.4.II.** Yield: 206 mg (79%); IR (neat): 2935, 2220, 1600, 1491, 1040, 928 cm^{-1}. ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.83 (3 H, s, OMe), 5.47 (1 H, s, C=CH_AH$_B$), 5.90 (1 H, s, C=CH$_A$$H_B$), 6.94 (1 H, s, ArC*H*=C), 6.92-6.96 (1 H, m, Ar), 7.25-7.42 (8 H, m, Ar); ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 55.4, 113.2, 113.5, 117.1, 117.4, 119.3, 122.2, 128.4, 128.6 (2 C), 128.7 (2 C), 129.8, 134.7, 138.3, 144.5, 145.2, 159.8; EI MS: *m*/*z* (%) = 230 (100%) (M^+- OMe), 216 (22), 203 (27), 190 (16), 178 (16), 153 (56), 115 (32), 101 (24), 91 (67), 77 (56), 63 (15); GC: (200 ºC–10 ºC/min–260 ºC–5 ºC/min–300 ºC) t_R = 12.46 min (100%); Anal. Calcd for $C_{18}H_{15}NO$: C 82.73, H 5.79, N 5.36 %; found C 82.34, H 5.83, N 5.20 %.

(1*Z*)-2-Cyano-3-(4-methoxyphenyl)-3-phenyl-1,3-butadiene 57g: Prepared from **41a** (265 mg, 1 mmol) and *p*-anisaldehyde (0.146 mL, 1.2 mmol) according to *General Procedure* **2.4.II.** Yield: 212 mg (81%); IR (neat): 3019, 2935, 2838, 2215, 1602, 1511, 1308, 1260, 1279, 1031, 904, 832, 764 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.84 (3 H, s, OMe), 5.41 (1 H, s, C=C$H_A$$H_B$), 5.83 (1 H, s, C=C$H_A$$H_B$), 6.89 (1 H, s, ArC*H*=C), 6.90 (2 H, d, *J* = 8.8 Hz, Ar), 7.28-7.43 (5 H, m, Ph), 7.73 (2 H, d, *J* = 8.8 Hz, Ar); ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 55.4, 110.1, 114.2 (2 C), 117.9, 118.0, 126.1, 128.3, 128.5 (2 C), 128.7 (2 C), 131.2 (2 C), 138.5, 144.1, 145.4, 161.4; ESI MS: *m*/*z* (%) = 262 (18) (M^++1), 261 (100) (M^+), 260 (52) (M^+-1), 245 (17), 230 (55), 217 (25), 184 (46), 169 (17), 91 (36), 77 (28); GC: (200 ºC–10 ºC/min–260 ºC–5 ºC/min–300 ºC) t_R = 13.29 min (100%); Anal. Calcd for $C_{18}H_{15}NO$: C 82.73, H 5.79, N 5.36 %; found found C 82.41, H 5.86, N 5.23 %.

(1*Z*)-2-Cyano-1-(2-chlorophenyl)-3-phenyl-1,3-butadiene 57h: Prepared from **41a** (265 mg, 1 mmol) and *o*-chlorobenzaldehyde (0.135 mL, 1.2 mmol) according to *General Procedure* **2.4.II.** Yield: 212 mg (80%); M.p. = 62–63 ºC; IR ($CHCl_3$ film): 3058, 3027, 2925, 2222, 1612, 1588, 1574, 1493, 1466, 1441, 1053, 1036, 906, 762, 752 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 5.54 (1 H, s, C=C$H_A$$H_B$), 5.95 (1 H, s, C=C$H_A$$H_B$), 7.30-7.46 (9 H, m, Ph, Ar and ArC*H*=C), 8.00-8.05 (1 H, m, Ar); ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 116.1, 116.6, 120.1, 127.1, 128.5 (2 C), 128.6 (4 C), 129.4, 129.7, 131.2, 134.7, 137.8, 141.4, 144.9; ESI MS: *m*/*z* (%) = 288 (12) (M^+ + Na), 266 (100) (M^+ + H), 154 (7); GC: (200 ºC–10 ºC/min–260 ºC–5 ºC/min–300 ºC) t_R = 11.72 min (100 %); ESI-HRMS: Found: M^+ + H, 266.0740. $C_{17}H_{13}ClN$ requires M^+ + H, 266.0737.

(1*Z*)-2-Cyano-1-(3-bromophenyl)-3-phenyl-1,3-butadiene 57i: Prepared from **41a** (265 mg, 1 mmol) and *m*-bromobenzaldehyde (0.144 mL, 1.2 mmol) according to *General Procedure* **2.4.II.** Yield: 254 mg (82%); IR (neat): 3019, 2935, 2221, 1593, 1569, 1493, 1474, 1444, 1426, 1075, 914 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 5.50 (1 H, s, C=C$H_A$$H_B$), 5.93 (1 H, s, C=C$H_A$$H_B$), 6.87 (1 H, s, ArC*H*=C), 7.27-7.43 (6 H, m, Ph and Ar), 7.51 (1 H, d, *J* = 8 Hz, Ar), 7.73 (1 H, s, Ar), 7.79 (1 H, d, *J* = 8 Hz, Ar); ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 114.7, 116.8, 120.1, 122.8, 127.2, 128.6, 128.7 (4 C), 130.3, 132.4, 133.3, 135.4, 137.9, 142.6, 144.9; ESI MS: *m*/*z* (%) = 311 (6) ($C_{17}H_{12}{}^{81}BrN^{+}$), 309 (6) ($C_{17}H_{12}{}^{79}BrN^{+}$), 230 (100), 202 (13), 101 (19), 77 (26); GC: (200 ºC–10 ºC/min–260 ºC–5 ºC/min–300 ºC) t_R = 13.08 min (100%); Anal. Calcd for $C_{17}H_{12}BrN$: C 65.83, H 3.90, N 4.52 %; found C 65.59, H 4.01, N 4.38 %.

(1*Z*)-2-Cyano-1-(3-bromophenyl)-3-(3-methoxyphenyl)-1,3-butadiene 57j: Prepared from **41b** (295 mg, 1 mmol) and *m*-bromobenzaldehyde (0.144 mL, 1.2 mmol) according to *General Procedure* **2.4.II.** Yield: 289 mg (85%); IR (neat): 3019, 2962, 2836, 2220, 1596, 1576, 1486, 1474, 1427, 1321, 1287, 1215, 1042 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.83 (3 H, s, OMe), 5.51 (1 H, s, C=C$H_A$$H_B$), 5.91 (1 H, s, C=C$H_A$$H_B$), 6.82-6.96 (3 H, m, Ar), 6.90 (1 H, s, ArC*H*=C), 7.26 (1 H, d, *J* = 8 Hz, Ar), 7.35 (1 H, d, *J* = 8 Hz, Ar), 7.51 (1 H, d, *J* = 8 Hz, Ar), 7.74 (1 H, s, Ar), 7.79 (1 H, d, *J* = 8 Hz, Ar); ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 55.3, 112.0, 113.9, 114.5, 116.8, 120.0, 121.1, 122.8, 127.3, 129.8, 130.4, 132.4, 133.3, 135.4, 139.3, 142.7, 144.8, 159.8; EI MS: *m*/*z* (%) = 341 (23) ($C_{18}H_{14}{}^{81}BrNO^{+}$), 339 (23) ($C_{18}H_{14}{}^{79}BrNO^{+}$), 260 (100), 245 (43), 217 (45); GC: (200 ºC–

10 ºC/min–260 ºC–5 ºC/min–300 ºC) t_R = 15.14 min (100 %); ESI-HRMS: Found: M^+ + H, 340.0334. $C_{18}H_{15}NO^{79}Br$ requires M^+ + H, 340.0337.

(1*Z*)-2-Cyano-1,3-diphenyl-1,3-butadiene 57k: *n*BuLi (1.6 mL, 2.5 mmol, 1.6 M hexane solution) was added to a stirred solution of DMSO-d_6 (0.106 mL, 1.5 mmol) and EtOH (0.09 mL, 1.5 mmol) in THF (4 mL) at 0 ^oC. After 2 min, arylidene phosphonoacetonitrile **41a** (1.0 mmol) in THF (2 mL) was added to the reaction mixture followed by the addition of the benzaldehyde (0.125 mL; 1.2 mmol). The reaction mixture was brought to room temperature and stirred for 3 h. The reaction mixture was diluted with water and extracted with ether. The combined extract was washed with brine, dried over magnesium sulfate, filtered and concentrated under *vacuum*. The residue was purified on silica-gel using hexane/ethyl acetate to give the diene **57k**. Yield: 191 mg (82%); M.p. = 49–51 ºC; IR (neat): 3019, 2219, 1598, 1572, 1491, 1445, 1215 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 6.99 (1 H, s, PhC*H*=C), 7.30-7.43 (8 H, m, Ar), 7.73-7.78 (2 H, m, Ar); ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 112.9, 117.4, 118.1-119.4 (m), 128.4, 128.6 (2 C), 128.7 (2 C), 128.8 (2 C), 129.3 (2 C), 130.5, 133.4, 138.2, 144.6, 145.0; EI MS: *m*/*z* (%) = 233 (90) (M^+), 232 (100), 231 (45), 217 (15), 204 (22), 155 (42), 129 (17), 116 (24), 92 (32), 77 (24), 63 (8).

(1*Z*)-2-Cyano-1-(1-naphthyl)-3-phenyl-1,3-butadiene 57l: Prepared from **41a** (265 mg, 1 mmol) and 1-napthaldehyde (0.162 mL, 1.2 mmol) according to *General Procedure* **2.4.II.** Yield: 208 mg (74%); M.p. = 81–82 ºC; IR ($CHCl_3$ film): 3062, 3019, 2223, 1598, 1575, 1509, 1495, 1444, 1051, 1027, 912 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 5.55 (1 H, s, C=C$H_A$$H_B$), 5.97 (1 H, s, C=C$H_A$$H_B$), 7.46-7.64 (9 H, m, Ph and Ar), 7.70 (1 H, s, =C*H*Np), 7.88 (2 H, t, *J* = 7.4 Hz, Ar), 8.05 (d, *J* = 7.4 Hz, 1 H, Ar); ^{13}C-NMR (50 MHz,

$CDCl_3$): δ = 116.5, 117.1, 119.7, 123.2, 125.5, 126.3, 126.9, 127.0, 128.5, 128.7 (2 C), 128.8 (2 C), 128.9, 130.7, 130.8, 131.4, 133.4, 138.3, 143.0, 145.0; ESI MS: *m*/*z* (%) = 282 (100) (M^+ + H); ESI-HRMS: Found: M^+ + H, 282.1276. $C_{21}H_{16}N$ requires M^+ + H, 282.1283.

(1*Z*)-2-Cyano-1-(2-fuyrl)-3-phenyl-1,3-butadiene 57m: Prepared from **41a** (265 mg, 1 mmol) and 2-Furaldehyde (0.1 mL, 1.2 mmol) according to *General Procedure* **2.4.II.** Yield: 181 mg (82%); IR (neat): 3140, 3056, 2929, 2218, 1592, 1493, 1469, 1444, 1151, 1088, 1025, 899, 886, 782, 754 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 5.41 (1 H, s, C=C$H_A$$H_B$), 5.87 (1 H, s, C=C$H_A$$H_B$), 6.51 (1 H, d, *J* = 1.6 Hz, Fur), 6.75 (1 H, s, ArC*H*=C), 7.07 (1 H, d, *J* = 3.4 Hz, Fur), 7.26-7.33 (2 H, m, Ar), 7.35-7.43 (3 H, m, Ar), 7.54 (1 H, s, Fur); ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 109.2, 112.8, 115.6, 117.2, 118.9, 128.4, 128.6 (2 C), 128.7 (2 C), 130.4, 138.0, 144.6, 145.0, 149.8; EI MS: *m*/*z* (%) = 222 (13) (M^++ H), 221 (62) (M^+), 192 (42), 165 (100), 140 (28), 139 (29), 115 (30), 89 (35), 77 (87), 63 (65); GC: (200 ºC–10 ºC/min–260 ºC–5 ºC/min–300 ºC) t_R = 9.48 min (98.3 %), t_R = 10.16 min (1.7 %); ESI-HRMS: Found: M^+ + H, 222.0916. $C_{15}H_{12}NO$ requires M^+ + H, 222.0919.

(1*Z*)-2-Cyano-3-phenyl-1-(3-pyridyl)-1,3-butadiene 57n: Prepared from **41a** (265 mg, 1 mmol) and 3-pyridine-carboxaldehyde (0.113 mL, 1.2 mmol) according to *General Procedure* **2.4.II.** Yield: 188 mg (81%); IR ($CHCl_3$ film): 3019, 2222, 1582, 1493, 1481, 1412, 1215, 1024, 913 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 5.54 (1 H, s, C=C$H_A$$H_B$), 5.96 (1 H, s, C=C$H_A$$H_B$), 6.95 (1 H, s, PyC*H*=C), 7.27-7.33 (2 H, m, Ph), 7.38-7.49 (4 H, m, Ph and Py), 8.44 (1 H, d, *J* = 8 Hz, Py), 8.60 (1 H, d, *J* = 8 Hz, Py), 8.62 (1 H, s, Py);

^{13}C-NMR (50 MHz, $CDCl_3$): δ = 115.8, 116.8, 120.5, 123.7, 128.7 (3 C), 128.8 (2 C), 129.6, 135.0, 137.7, 140.3, 144.8, 150.7, 151.0; ESI MS: *m*/*z* (%) = 233 (100) (M^+ + H); GC: (200 ºC–10 ºC/min–260 ºC–5 ºC/min–300 ºC) t_R = 10.92 min (99 %); ESI-HRMS: Found: M^+ + H, 233.1084. $C_{15}H_{12}NO$ requires M^+ + H, 233.1079.

(1*Z*)-2-Cyano-1-(2-fuyrl)-3-(3-methoxyphenyl)-1,3-butadiene 57o: Prepared from **41b** (295 mg, 1 mmol) and 2-Furaldehyde (0.1 mL, 1.2 mmol) according to *General Procedure* **2.4.II.** Yield: 191 mg (76%); IR ($CHCl_3$ film): 3018, 2219, 1596, 1578, 1467, 1428, 1233, 1042, 903 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 3.82 (3 H, s, OMe), 5.41 (1 H, s, C=CH_AH$_B$), 5.85 (1 H, s, C=CH$_A$$H_B$), 6.51-6.53 (1 H, m, Fur), 6.77 (1 H, s, ArC*H*=C), 6.79-6.95 (3 H, m, Ar and Fur), 7.07 (1 H, d, *J* = 3.2 Hz, Fur), 7.31 (1 H, t, *J* = 8 Hz, Ar), 7.54 (1 H, s, Ar); ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 55.3, 109.0, 112.8, 113.8, 114.4, 115.6, 117.1, 118.8, 121.1, 129.7, 130.5, 139.4, 144.5, 145.0, 149.8, 159.7; EI MS: *m*/*z* (%) = 252 (17) (M^+ + H), 251 (100) (M^+), 222 (47), 207 (21), 195 (51), 190 (36), 180 (24), 165 (28), 152 (33), 140 (15), 127 (16), 89 (21), 77 (18), 63 (27); GC: (200 ºC–10 ºC/min–260 ºC–5 ºC/min–300 ºC) t_R = 10.99 min (100 %); ESI-HRMS: Found: M^+ + H, 252.1032. $C_{16}H_{14}NO_2$ requires M^+ + H, 252.1025.

(1*E*,2*Z*)-4-Cyano-1,5-diphenyl-1,3,5-hexatriene 57p: Prepared from **41a** (265 mg, 1 mmol) and *trans*-cinnamaldehyde (0.152 mL, 1.2 mmol) according to *General Procedure* **2.4.II.** Yield: 219 mg (85%); M.p. = 93 ºC; IR (neat): 3019, 2222, 1603, 1577, 1495, 1447, 1215 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 5.40 (1 H, s, C=CH_AH$_B$), 5.83 (1 H, s, C=CH$_A$$H_B$), 6.76 (1 H, d, *J* = 10.8 Hz, CH=CCN), 6.77 (1 H, d, *J* = 16.4 Hz, PhC*H*=CH), 7.23-7.45 (11 H, m, 2 × Ph, C=CH); ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 114.7, 116.5, 119.1,

124.8, 127.5 (2 C), 128.3, 128.6 (2 C), 128.7 (2 C), 128.9 (2 C), 129.5, 135.7, 138.2, 141.5, 144.3, 144.5; ESI MS: *m*/*z* (%) = 258 (100) (M^+ + H); ESI-HRMS: Found: M^+ + H, 258.1283. $C_{19}H_{16}N$ requires M^+ + H, 258.1283.

2-[2-(Methylsulfinyl)-1-phenylethyl]-3-phenylacrylonitrile 58 (mixture of diastereoisomers): *n*BuLi (1.6 mL, 2.5 mmol, 1.6 M hexane solution) was added to Me_3SI (306 mg, 1.5 mmol) suspension in THF (4 mL)-DMSO (0.11 mL, 1.5 mmol) at -10 ºC. After 15 min, arylidene phosphonoacetonitrile **41a** (265 mg, 1.0 mmol) in THF (2 mL) was added to the reaction mixture followed by the addition of the benzaldehyde (0.125 mL, 1.2 mmol). The reaction mixture was brought to room temperature and stirred for 3h. The reaction mixture was diluted with water and extracted with ether. The combined extract was washed with brine, dried over magnesium sulfate, filtered and concentrated under *vacuum*. The residue was purified on silica-gel using hexane/ethyl acetate to give the corresponding diene **57a** as well as **58**. Yield of **58**: 118 mg (40%); IR (film): 3063, 3016, 2210, 1615, 1494, 1452, 1408, 1215, 1049, 966, 931, 889, 700, 666 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): (non-polar isomer) δ = 2.69 (3 H, s, CH_3S), 3.18 (1 H, dd, *J* = 12.6 and 2.6 Hz, CH_AH$_B$S), 3.47(1 H, dd, *J* = 12.6 and 12.6 Hz, CH$_A$$H_B$S), 4.36 (1 H, dd, *J* = 12.6 and 2.6 Hz, C*H*CH$_2$S), 7.33 (1 H, s, ArC*H*), 7.37-7.40 (8 H, m, Ar), 7.72-7.78 (2 H, m, Ar); ^{1}H-NMR (200 MHz, $CDCl_3$): (polar isomer) δ = 2.63 (3 H, s, CH_3S), 3.12-3.52 (2 H, m, CH_2S), 4.32 (1 H, dd, *J* = 5.0 and 10.4 Hz, C*H*CH$_2$S), 7.17 (1 H, s, ArC*H*), 7.35-7.41 (8 H, m, Ar), 7.70-7.76 (2 H, m, Ar); ^{13}C-NMR (50 MHz, $CDCl_3$):(mixture of isomers) δ = 39.3, 45.5, 58.2, 58.8, 111.3, 112.9, 117.3, 117.7, 127.2, 127.8, 128.2, 128.4, 128.9, 129.1, 129.2, 129.3, 130.7, 130.8, 132.9, 137.9, 139.1, 144.8, 146.2.

(3*R,S*) (1*E*)-2-Cyano-1,3-diphenyl-3-ethoxy-1-propene 59: *n*BuLi (1.6 mL, 2.5 mmol, 1.6 M hexane solution) was added to Me_3SI (306 mg, 1.5 mmol) suspension in THF (4 mL)-DMSO (0.11 mL, 1.5 mmol)-EtOH (0.118 mL, 2 mmol) at -10 ºC. After 15 min, arylidene phosphonoacetonitrile **41a** (265 mg, 1.0 mmol) in THF (2 mL) was added to the reaction mixture followed by the addition of the benzaldehyde (0.125 mL, 1.2 mmol) mixture and stirred for 3 h. The reaction mixture was diluted with water and extracted with ether. The combined extract was washed with brine, dried over magnesium sulfate, filtered and concentrated under *vacuum*. The residue was purified on silica-gel using hexane/ethyl acetate to give the diene **57a** as well as **59**.

Yield of **59**: 68 mg (26%); IR ($CHCl_3$ film): 3019, 2975, 2836, 2216, 1600, 1561, 1488, 1268, 1098, 760 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.30 (3 H, t, *J* = 7 Hz, CH_3CH_2O), 3.43-3.74 (2 H, m, $CH_3CH_AH_BO$), 5.01 (1 H, s, PhC*H*O), 7.22 (1 H, s, ArC*H*), 7.27-7.48 (8 H, m, Ar), 7.72-7.79 (2 H, m, Ar); ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 15.2, 65.0, 82.7, 113.6, 126.9 (2 C), 128.5, 128.7 (2 C), 128.8 (2 C), 129.1 (2 C), 133.1, 138.6, 143.0; EI MS: *m*/*z* (%) = 264 (80) (M^++ H), 235 (82), 217 (98), 206 (50), 190 (97), 179 (92), 158 (55), 140 (98), 136 (93), 128 (100), 106 (99), 102 (100), 91 (48), 78 (98).

Chapter 3

Organocatalyzed Enantioselective Michael Addition of Alkyl-Methyl Ketones to a Silylmethylene Malonate

3.1 Introduction

The unique properties of silicon[87] have led to its wide utilization in organic chemistry ranging from protecting functional groups[88] to temporary tether[89] in general and as masked hydroxyl group,[90] to highly controlled and selective organic reactions[87,91] in particular. Carbonyl compounds having a silyl group at β-position are popular targets because of their versatile nature[92] and are also excellent surrogate for the acetate aldol[93] reaction. We are concerned for the asymmetric synthesis of intermediates of type **61** or **62** (**Fig. 3.1**) containing a silicon group positioned at β to both a ketone and an ester functionalities because they could be synthons[94] for *privileged* structures containing chiral *N*- and *O*-heterocycles (**Fig. 3.2**).

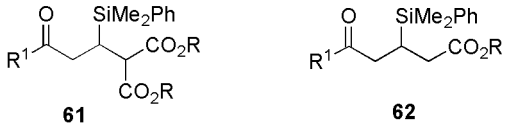


Fig 3.1 β-Silyl-δ-keto esters intermediates

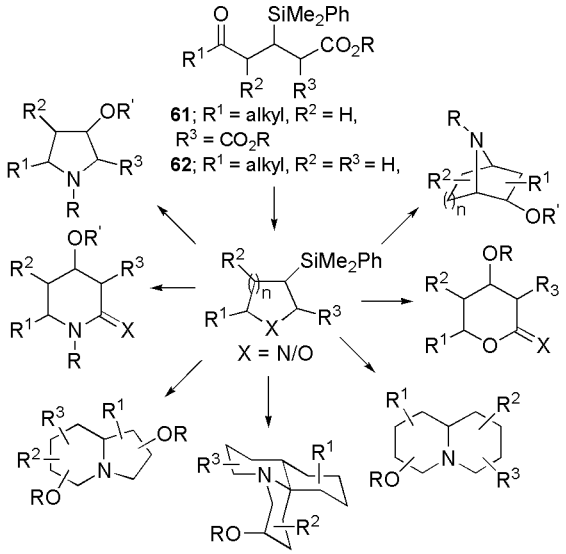
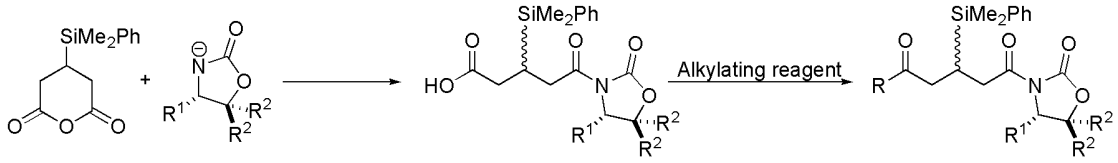


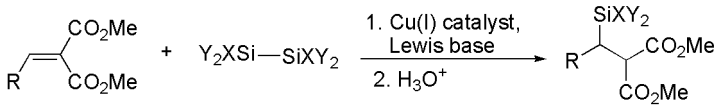
Fig. 3.2 Diverse skeletal types predicted from silylated compounds 61 and 62

Synthesis of β-silyl-δ-keto esters **61** has been achieved by our research group[95,96] following asymmetric desymmetrization of 3-[dimethyl(phenyl)silyl]glutaric anhydride with chiral oxazolidin-2-ones followed by selective alkylation of one of the carboxyl functionalities (**Scheme 3.1**). Although high selectivity[96] was achieved in the desymmetrization process, it required specially designed *SuperQuat*[97] oxazolidin-2-ones.



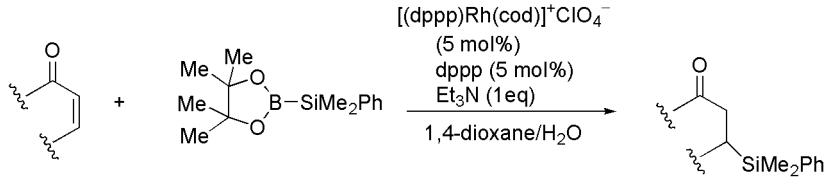
Scheme 3.1

The desymmetrization of anhydrides with a limited type of carbon nucleophiles[98] has been reported recently to produce keto esters. But these protocols involved operational complexity, and also the use of complex organometallic reagents, transition metal catalysts and chiral ligands. Also, a limited number of organometallic reagents containing ethyl and aryl groups were commonly used. Enantio/diastereo-selective conjugate silylation[99] of an unsaturated carbonyl compound is an important tool, and the reaction is usually achieved by the use of silyl nucleophiles such as silyl copper[100] or silyl zinc[101] reagents. Transition metal-catalyzed reactions of disilanes[102] and α,β-unsaturated carbonyl compounds resulted silylated products equiv to 1,4-silicon addition. Recently, Cu(I)[103] salts also produce conjugate silicon addition products with α,β-unsaturated carbonyl compounds or arylidene malonates. Scheidt et.al.[103b] reported the copper(I)-catalyzed disilyation of alkylidene malonates with disilanes in the presence of Lewis bases to yield functionalized β-silyl diesters (**Scheme 3.2**).



Scheme 3.2

Enantioselective conjugate silyl transfer to acyclic and cyclic α,β-unsaturated carbonyl acceptors has been reported under Rh(I)-catalysis using silicon reagents with a Si-B linkage leading to β-silyl carbonyl compounds (**Scheme 3.3**).[104]

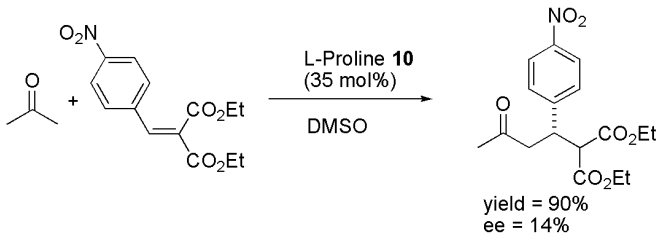


Scheme 3.3

However, the most suited chemical transformation that avoids additional reagents and waste production would be an atom economic regio-, stereo- and enantioselective Michael addition of an alkyl methyl ketone to a silylmethylene malonate.

The Michael addition is one of the most frequently used reaction because of its efficiency and effectiveness. Significant development has been made in the asymmetric version of this reaction, providing adducts with high enantiomeric purity as discussed in **Chapter 1**. Aldehydes and ketones have generally been used as donors after their modifications to more activated species such as enolate or enamines.[27-30] The major drawbacks for the enolate/enamine use are the addition of extra synthetic step(s) and stoichiometric use of chiral induction reagent. In recent times, organocatalysis[17] route has been developed for the direct addition of ketones or aldehydes to activated olefins, especially to nitroolefins with satisfactory results. However, the addition of the same donors[22] to alkylmethylene malonates is less successful.

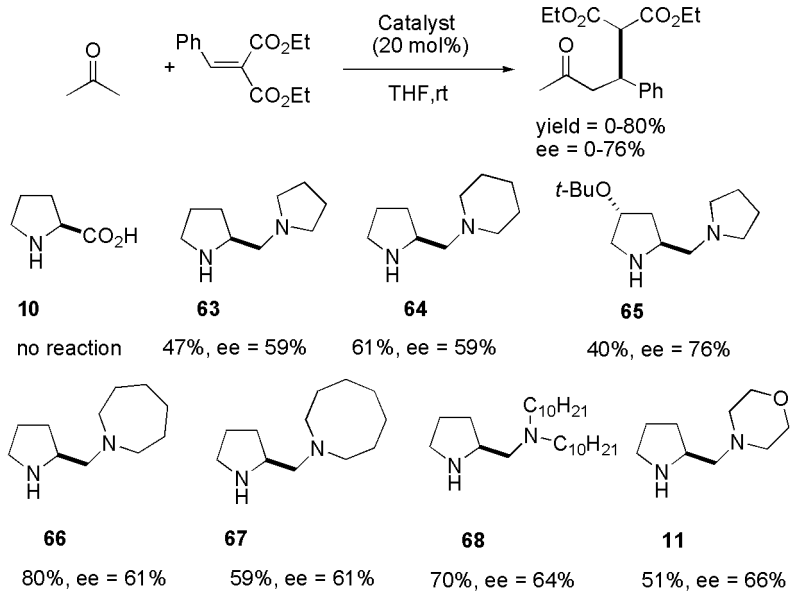
Like the Michael addition of carbonyl compounds to nitroolefin, the addition of same donors to alkylidene malonates is also a useful objective. The development of catalytic asymmetric variants of this process would provide access to optically enriched 1,5-dicarbonyl synthons. List and co-workers[32,33] treated a mixture of acetone and proline **10** (35 mol%) in DMSO with diethyl 4-nitrobenzylidene malonate. While the expected Michael adduct was formed, the enantioselectivity remained unsatisfactory (**Scheme 3.4**).



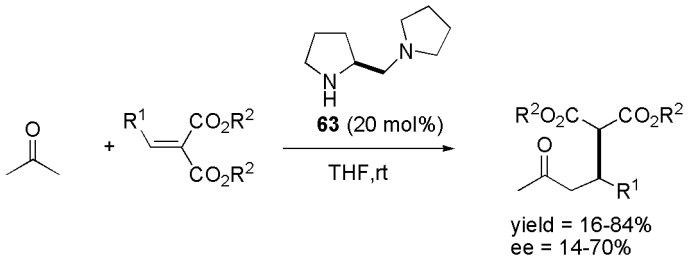
Scheme 3.4

Barbas III and co-workers[105] demonstrated that acetone can add to various arylmethylene and alkylmethylene malonates via organocatalysis with moderate yields and enantioselectivities. They investigated the Michael addition of acetone to highly activated diethyl benzalmalonate in DMSO as a model transformation. Since the desired Michael adducts were obtained in racemic form, a variety of chiral amines were screened as catalysts for the reaction. The best results were obtained using 20 mol% (*S*)-1-(2-pyrrolidinylmethyl)pyrrolidine **63** in THF at room temperature (**Scheme 3.5**). Although higher enantioselectivities were observed at lower temperatures, yields were poor (–25 °C, 5%, 72% ee). A variety of aromatic and aliphatic alkylidene malonates were evaluated as Michael acceptors, using acetone as donor (**Scheme 3.6**). Generally, the products were obtained in moderate yields (16-84%) and moderate enantioselectivities (up to 70% ee). In

contrast, the aliphatic alkylidene malonates furnished the Michael adducts in low yields (up to 27%) and low enantioselectivities (up to 24% ee).



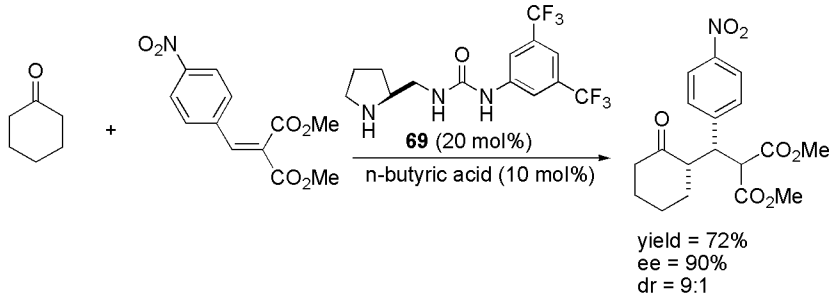
Scheme 3.5



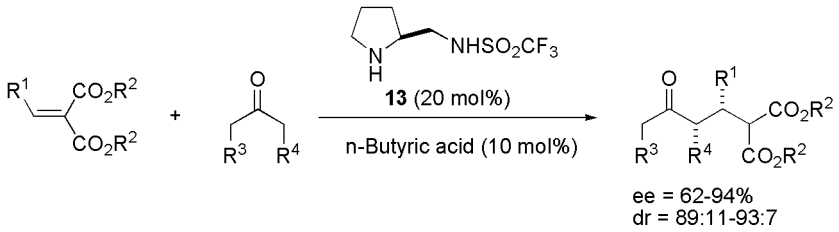
Scheme 3.6

Cao et.al.[54] recently designed and synthesized pyrrolidine-urea based bifunctional organocatalysts **69** which catalyzed the Michael addition of cyclohexanone with dimethyl 2-(4-nitrobenzylidene) malonate to afford the desired product in good yield (72%) and good selectivity (**Scheme 3.7**). When the above reaction was carried out in the presence of pyrrolidine trifluoromethanesulfonamide **13** in combination of 10 mol% of *n*-butyric acid, the product was isolated in nearly quantitative yield with high diastereoselectivity (93/7)

and high enantioselectivity (90%) (**Scheme 3.8**). A variety of ketones and alkylidene malonates with different structures were tested to investigate the generality of the reaction. Various alkylidene malonates reacted smoothly with cyclohexanone in moderate to good yields with high enantioselectivities but acyclic ketones were not suitable for this reaction.

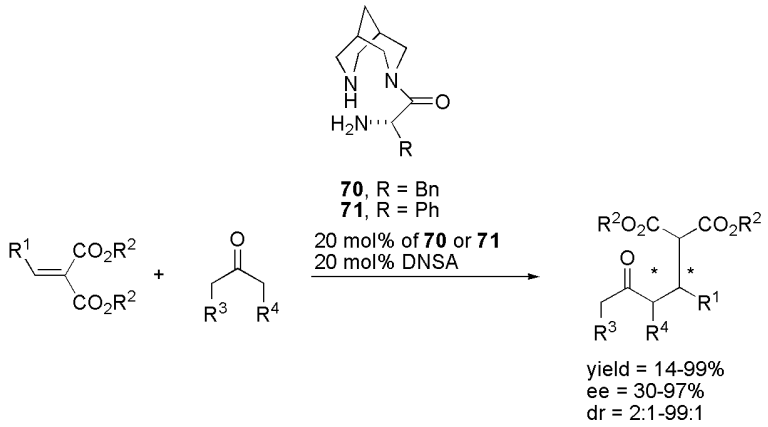


Scheme 3.7



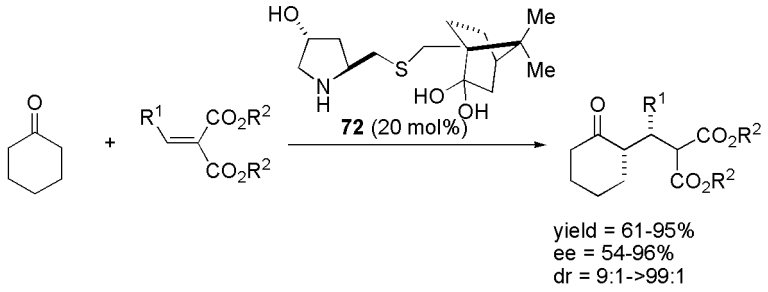
Scheme 3.8

Feng et. al.[106] reported bispidine-based primary-secondary diamine catalysts **70** and **71**, which were successfully applied to the asymmetric Michael addition of aliphatic ketones to alkylidene malonates (**Scheme 3.9**). A varity of ketones and alkylidene malonates with different substituent were tested to investigate the generality of the reaction and in all the cases the corresponding products were obtained in moderate to high yields. The products were formed with high diastereoselectivities (up to 99:1) and excellent enantioselectivity (up to 97%).



Scheme 3.9

Very recently, various pyrrolidinyl–camphor-based organocatalysts were designed and synthesized.[107] Out of these, the catalyst **72** was most promising one for the Michael addition of ketones to alkylidene malonates (**Scheme 3.10**).Various cyclic and acyclic ketones were subjected to the optimal reaction conditions to give the desired Michael adducts with good to high chemical yields and with high diastereoselectivities (upto 99:1) and excellent enantioselectivity (upto 96%).

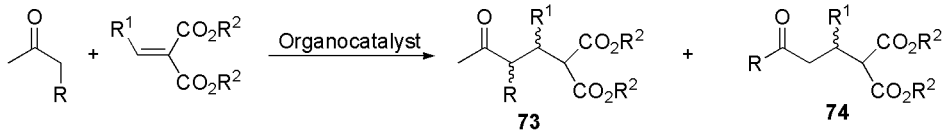


Scheme 3.10

3.2 Present work

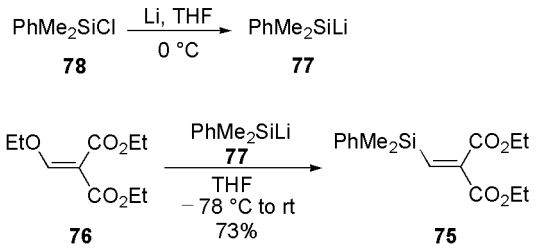
Efforts have been made to engage alkylidene malonates and ketones to undergo Michael addition reactions with various organocatalysts as described in the introduction part.[32,33,54,105-107] The reactivity and regioselectivity issues were not addressed in case of

unsymmetrical ketones. The Michael addition of unsymmetrical ketones to alkylidene malonates can lead to the both the regioisomers (branched adduct **73** and linear adduct **74**) as shown in **Scheme 3.11**. The favorable formation of the corresponding regioisomer is due to the difference of acidity between α and α′ hydrogen's of the carbonyl compounds. As we aim to make silylated keto-esters wherein the silicon is placed at β-position with respect to both functional groups, we decided to address the regioselectivity issues of the Michael addition of unsymmetrical ketones, especially methyl ketones with the silylmethylene malonate **75**.



Scheme 3.11

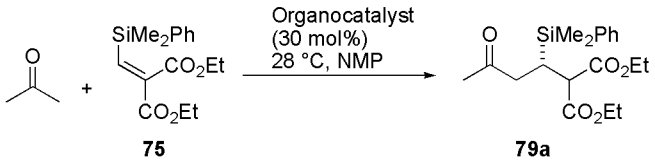
The silylmethylene malonate **75** was prepared[108] by a conjugate addition-elimination starting from the commercially available diethyl ethoxymethylene malonate **76**. Dimethyl(phenyl)silyllithium[109] **77** in turn was prepared from dimethyl(phenyl)silylchloride **78** and lithium. When this dimethyl(phenyl)silyllithium **77** was added to diethyl ethoxymethylene malonate **76**, the desired silylmethylene malonate **75** was obtained as a result of silyl addition followed by alkoxide elimination (**Scheme 3.12**).



Scheme 3.12

3.2.1 Addition of acetone to silylmethylene malonate 75

In our orientation studies, we first choose acetone as the model ketone to be added to silylmethylene malonate **75**. The choice of acetone was made to obviate the regioselectivity issue and concentrated our effort to optimize the yield and enantioselectivity of the addition product **79a** (**Scheme 3.13**).



75 **79a**

Scheme 3.13

The Michael addition of acetone to silylmethylene malonate **75** using catalytic amount of racemic amino acids for the synthesis of silylated ketodiester (±)-**79a** has already been demonstrated[108] by our group to develop silicon based linkers for solid-phase organic synthesis.[110]Amongst the amino acids tested for this purpose, proline **10** and tryptophan **80** (**Fig. 3.3**) gave excellent result in terms of the yield. Unfortunately, asymmetric version of this addition reaction with these chiral amino acids (30 mol%) using 12 equiv of acetone in *N*-methylpyrrolidone (NMP) at room temperature resulted in very poor enantioselectivity (<5% ee) (**Table 3.1**, entries 1 and 2). Amongst the other chiral amino acids we tried, (*S*)-arginine **81** gave **79a** in moderate yield (42%) with 12% ee (**Table 3.1**, entry 3). Reaction with simple pyrrolidines derived from proline viz. diphenylprolinol **82** and its silyl ether **16** (**Fig. 3.3**) were not effective for this addition (**Table 3.1**, entries 4 and 5). Pyrrolidine based diamines derived from natural proline have been used as organocatalysts for many reactions including aldol[111] Michael addition[105,112] and Mannich reactions.[113] We next focused our attention for the use of these group of

catalysts as they can be easily made from Cbz-proline **83** and also, Barbes III has used such catalysts in his seminal work on asymmetric addition of acetone to arylidene malonates.[105] We prepared[114] three such catalysts, *N*-(2-pyrrolidinylmethyl)pyrrolidine **63**, *N*-(2-pyrrolidinylmethyl)piperidine **64** and (*S*)-2-(Morpholinomethyl)pyrrolidine **11** (**Fig. 3.3**) as shown in **Scheme 3.14**, to examine their ability for the Michael addition of acetone to silylmethylene malonate **75**. These catalysts were synthesized from (*S*)-*N*-(benzyloxycarbonyl) proline **83**. (*S*)-*N*-(Benzyloxycarbonyl) proline **83** was coupled with corresponding amines using diisopropylcabodiimide in dichloromethane to afford the respective amides **84a-c**. Hydrogenolysis of **84a-c** under hydrogen atmosphere in the presence of catalytic amount of 5% Pd-C in methanol gave the *N*,*N*-disubstituted (*S*)-prolinamides which were then reduced with lithium aluminum hydride ($LiAlH_4$) to give the chiral diamine **63**, **64**, **11**.[114] When pyrrolidine **63** was used under the reported[105] conditions using THF as the solvent, the addition of acetone to silylmethylene malonate **75** was very slow and the desired addition product **79a** was formed in poor yield as well as with moderate enantioselectivity (**Table 3.1**, entry 6). The catalytic ability of pyrrolidine **63** was increased substantially with slight erosion of enantioselectivity by changing the solvent to NMP (**Table 3.1**, entry 7).[115] Similarly, pyrrolidine **64** (30 mol%) also showed moderate yield and selectivity in NMP (**Table 3.1**,entry 8).

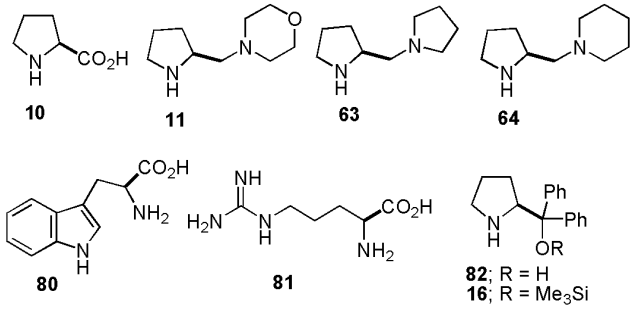
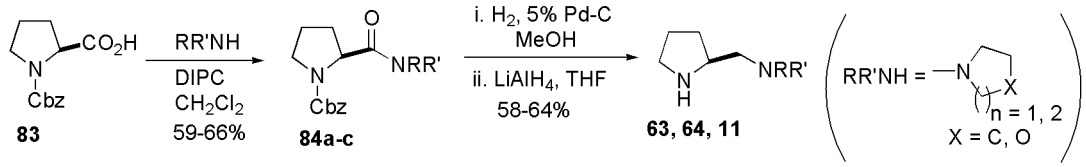
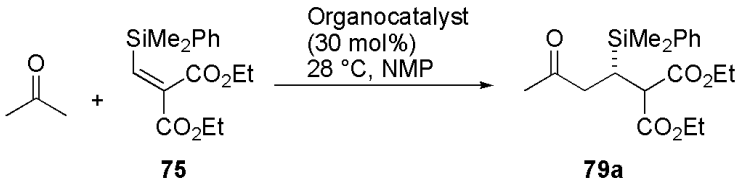


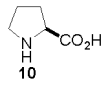
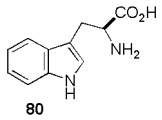
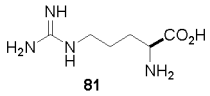
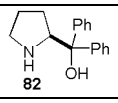
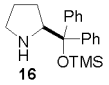
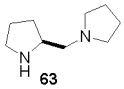
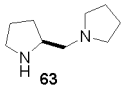
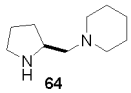
Fig. 3.3. Structure of the organocatalysts



Scheme 3.14

Table 3.1 Screening of catalysts for direct acetone addition on silylmethylene malonate 75



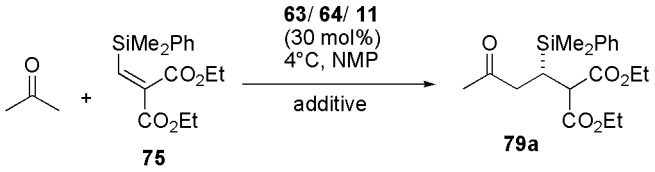
Entry	Catalyst	temp (ºC)/time	Yield (%)[a] of **79a**	ee (%)[b] of **79a**
1.	 10	28/1 d	75	<5
2.	 80	28/1 d	56	<5
3.	 81	28/5 d	42[c]	12
4.	 82	28/7 d	trace	ND[d]
5.	 16	28/7 d	trace	ND[d]
6.	 63	28/6 d	10[e]	66
7.	 63	28/3.5 d	61	55
8.	 64	28/3.5 d	40[c]	55

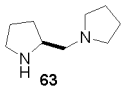
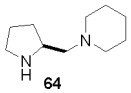
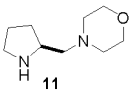
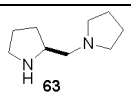
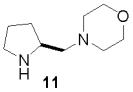
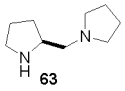
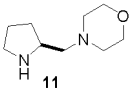
[a]Yield of chromatographically homogeneous product.[b]Determined by HPLC.[c] Incomplete reaction. [d] ND = not determined. [e] Reaction was performed in THF.

We next planned to introduce different additives in association with catalysts **63**, **64** and **11** to improve the yield and the enantioselectivity of adduct **79a**. Many research groups have used varying amount of Bronsted acids as additives to accelerate the amine-catalyzed Michael addition of aldehydes and ketones to nitroolefins[112,116] resulting in good yields and stereoselectivities. Barbas III[105] has suggested that these reactions proceed through enamine intermediates[27,28] of the carbonyl donors. It is well known that enamine formation between an amine and a carbonyl compound is facilitated by acids. Hine[117] in his seminal work has shown that the process was 15 times faster with the protonated primary amines than the free base. Therefore, the Michael addition of acetone with silylmethylene malonate **75** was next examined with the pyrrolidine catalysts **63**, **64** and **11** in the presence of organic acids such as AcOH and *p*-nitrobenzoic acid, (+)-camphor sulfonic acid in NMP.[115]

The addition of 10 mol% of AcOH in combination with 30 mol% of catalysts **63** or **64** or **11** at 4 °C provided the desired product **79a** in good yield (65-72%) (**Table 3.2**, entries 1-3) with a significant improvement of enantioselectivity (ee = 84-88.7 %). Similarly, the combination of *p*-nitrobenzoic acid (PNBA) with 30 mol% of catalyst **63** or **11** at 4 °C provided the desired product **79a** with comparable yield (**Table 3.2**, entries 4 and 5) and selectivity.[115] Next, we wanted to see the effect of chiral additives and for this we carried out two reactions using the catalysts **63** and **11** in combination with 10 mol% of (+)-camphorsulfonic acid (CSA). In both the cases the yield (**Table 3.2**, entries 6, 7) and enantioselectivity were comparable to the non-chiral additives. Therefore, the chiral additives have no influence in the course of the reaction.

Table 3.2 Optimization of direct acetone addition on silylmethylene malonate 75 using additives at 4 °C



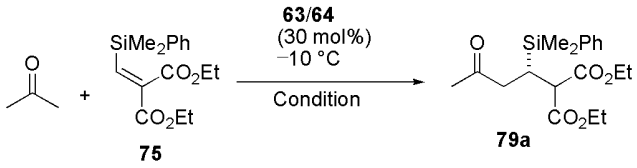
Entry	Catalyst (30 mol%)	Additive (10 mol%)	Solvent/temp (°C)/time (days)	ee (%)[a] (yield %)[b] of **79a**
1.	 63	AcOH	NMP/4/5	84.0 (72)
2.	 64	AcOH	NMP/4/5	86.0 (70)
3.	 11	AcOH	NMP/4/5	88.7 (65)
4.	 63	PNBA	NMP/4/5	80.0 (79)
5.	 11	PNBA	NMP/4/5	78.6 (72)
6.	 63	(+) CSA	NMP/4/7	82.0 (71)
7.	 11	(+) CSA	NMP/4/7	79.0 (79)

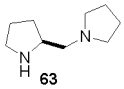
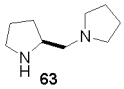
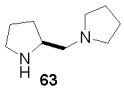
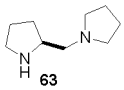
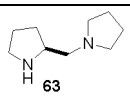
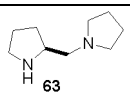
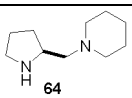
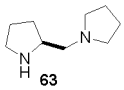
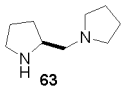
[a] Determined by HPLC; [b] Yield of chromatographically homogeneous product.

Next, the temperature of the reaction was lowered to see its effect on the selectivity. Therefore, the reactions using catalyst **63** and with or without 10 mol% AcOH were carried out at –10 °C for 7 days. Although this improved the enantioselectivity, the conversion was abysmally poor (**Table 3.3**, entries 1 and 2). Interestingly, trifluoroacetic acid (TFA) appeared to be a better additive and using 10 mol% of it with 30 mol% of catalyst **63** at –

10 °C for 7 days gave a decent yield of the product **79a** with excellent enantioselectivity (**Table 3.3**, entry 3).

Table 3.3 Optimization of direct acetone addition on silylmethylene malonate 75 using additives at –10 °C



Entry	Catalyst (30 mol%)	Additive (mol%)	Solvent/temp (°C)/time (days)	ee (%)[a] and (yield %)[b] of **79a**
1.	 63	Nil	NMP/–10/7	80 (<5)[c]
2.	 63	AcOH (10 mol%)	NMP/–10/7	80 (<5)[c]
3.	 63	TFA (10 mol%)	NMP/–10/7	90 (76)
4.	 63	TFA (5 mol%)	NMP/–10/7	88 (56)
5.	 63	TFA (15 mol%)	NMP/–10/7	88 (57)
6.	 63	TFA (30 mol%)	NMP/–10/7	90 (44)[c]
7.	 64	TFA (10 mol%)	NMP/–10/10	84 (44)[c]
8.	 63	TFA (10 mol%)	DMF/–10/7	84 (78)
9.	 63	TFA (10 mol%)	Tol/–10/7	82 (88)

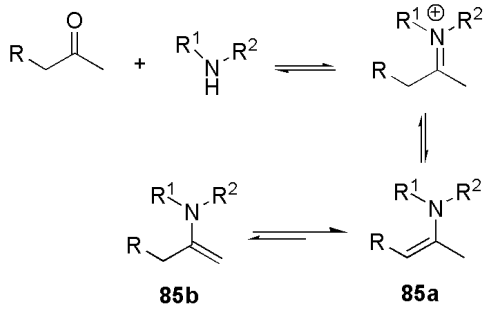
[a]Determined by HPLC. [b]Yield of chromatographically homogeneous product.[c] Incomplete reaction.

Additional experiments with varying amounts of TFA (5-30%) (**Table 3.3**, entries 4-6) were carried out and all the cases yields dropped except for 10 mol% TFA, but the enantioselectivity was almost same in all cases. Therefore, 10 mol% of TFA was found to be the optimum for the reaction. We also wanted to see the effect of solvents on the enantioselectivity and examined the reaction in DMF and toluene. Although the yield was comparable in these solvents, the enantioselectivity was dropped (**Table 3.3**, entries 8 and 9). The other catalyst **64** turned out to be poor, as revealed from the results in **Table 3.3**, entry 7. Therefore, the optimized condition is to use 12 equiv of acetone with respect to silylmethylene malonate **75** and 30 mol% of catalyst **63** in combination with 10 mol% of TFA in NMP (0.25 M) at –10 °C for 7 days providing the adduct **79a** in 76% yield and with 90% ee (**Table 3.3**, entry 3).[115]

3.2.2 Regioselective addition of alkyl methyl ketones to silylmethylene malonate 75

With optimal catalyst, additive and reaction conditions established with acetone, we went one step ahead by introducing unsymmetrical alkyl methyl ketones as donors. Unlike acetone, alkyl methyl ketones introduce the problem of regioselectivity. These reactions are known to proceed through enamine intermediate[27,28,105] of the carbonyl donors. It is well established[112] that in the presence of acid, the prototropy of the reactive enamine is more favorable and the equilibration between the more and the less substituted enamines **85a** and **85b** (**Scheme 3.15**) could occur. This leads to the formation of the more stable substituted enamine **195a** on thermodynamic grounds. But the regiocontrol of the reaction is often governed by Curtin-Hammett kinetics. Therefore, the balance between Curtin-Hammett kinetics and acidity decides the regioselectivity. Many research groups have

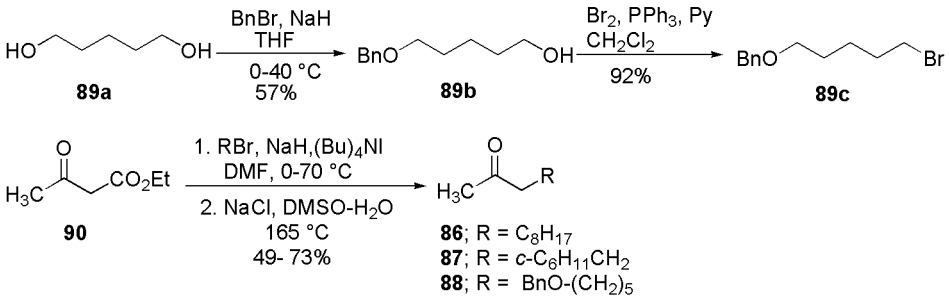
addressed the issue of regioselectivity during aldol[118] and Michael[119] addition involving unsymmetrical ketone donors, by tuning the acidity of α and α' protons with suitable functional groups. When methyl isopropyl ketone was reacted with silylmethylene malonate **75** under the optimized conditions as described in **Table 3.3**, we obtained only one regioisomeric product **79b**, as revealed by ^{1}H NMR spectrum of the crude reaction product in very high yield and with excellent enantioselectivity (**Fig 3.5**). Similar result was obtained in case of methyl isobutyl ketone. Initially it was envisaged that the high regioselectivity might be an outcome of the steric crowding by the isopropyl group and isobutyl groups. However, this was discounted from the results with several other ketones, lacking any such steric congestion. In all the cases, (**Table 3.4**) the adducts **79b-k** were formed only by the reaction at the methyl terminal of the acetyl group of the ketones. Also, the adducts were obtained in very good yield and enantioselectivity.[115, 120]



Scheme 3.15

When the reactions were carried out with methyl isopropyl ketone, methyl isobutyl ketone and 2-heptanone with silylmethylene malonate **75**, the corresponding products were obtained in very high yield (82-94%) (**Table 3.4** entry 2,3 and 7) and with excellent enantioselectivity (96.7-99.6%). The products from others ketones shows slightly eroded stereoselectivity. 2-Undecanone **86**, 4-cyclohexyl-2-butanone **87** and 8-benzyloxy-2-

octanone **88** were synthesized as shown in **Scheme 3.16**. When 2-decanone was reacted with silylmethylene malonate **75** at –10 °C, the conversion of the reaction was poor. But when the reaction was carried out at 4 °C the product was obtained in very high yield (**Table 3.4** entry 8) and good enantioselectivity.[120] The reactions required excess amount of the ketone (2-12 equiv) to get an appreciable rate of the reaction and completion within the time period mentioned. Valuable ketones can be recovered as other by-product formations were not observed.



Scheme 3.16

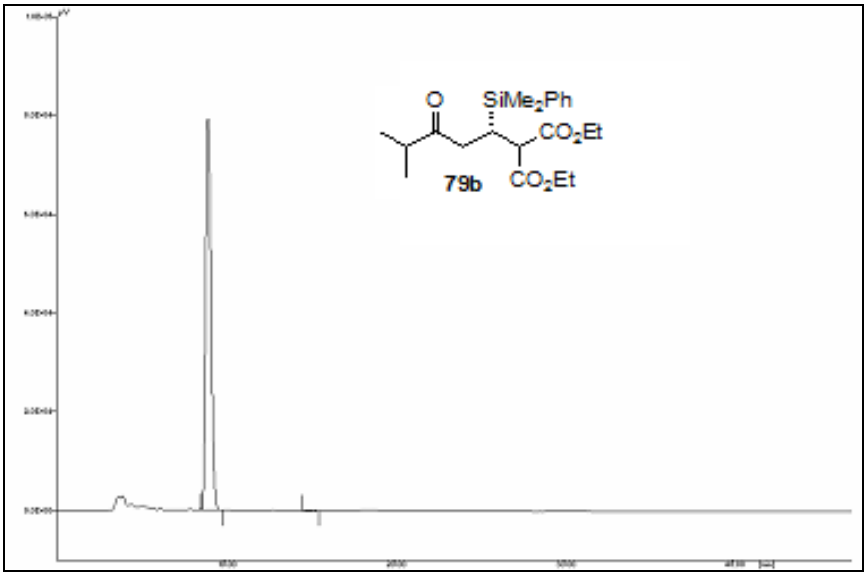
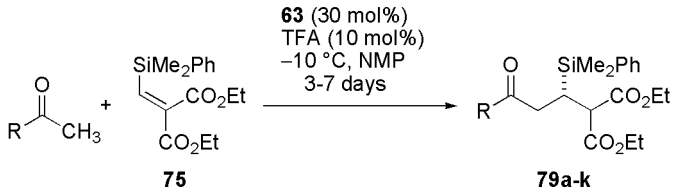
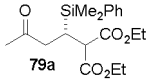
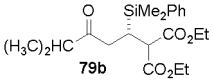
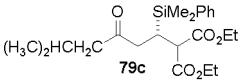
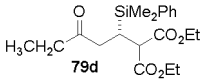
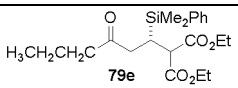
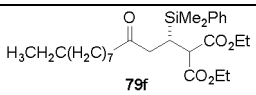
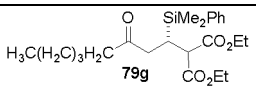
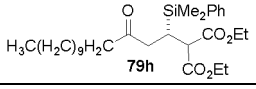
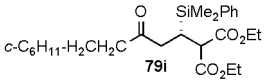
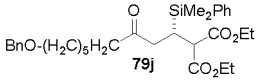
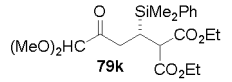


Fig 3.4. HPLC profile of compound 79b

Table 3.4 Regioselective direct addition of alkyl methyl ketones to silylmethylene malonate 75

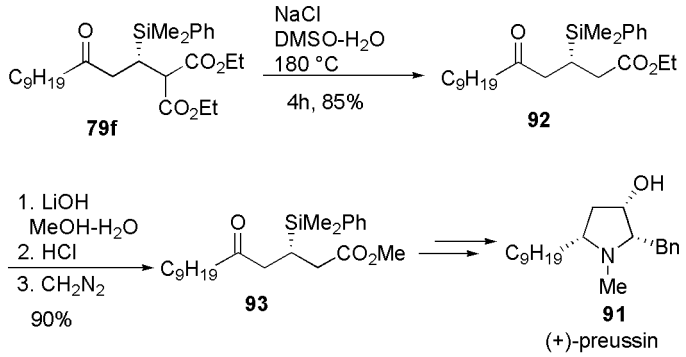


Entry	Ketone (equiv)	Time (days)	Product	ee (%)[a] and (% yield)[b]
1.	CH_3COCH_3 (12)	7	 79a	90.0 (76)
2.	$CH_3COCH(CH_3)_2$ (12)	7	 79b	99.5 (82)
3.	$CH_3COCH_2CH(CH_3)_2$ (5)	6	 79c	96.7 (82)
4.	$CH_3COCH_2CH_3$ (12)	7	 79d	92.8 (81)
5.	$CH_3CO(CH_2)_2CH_3$ (12)	7	 79e	91.8 (85)
6.	$CH_3CO(CH_2)_8CH_3$ (5)	3	 79f	91.1 (88)
7.	$CH_3CO(CH_2)_4CH_3$ (5)	3	 79g	99.6 (94)
8.	$CH_3CO(CH_2)_{10}CH_3$ (6)	6	 79h	87 (80)[c]
9.	$CH_3CO(CH_2)_2$-*c*-C_6H_{11} (5)	5	 79i	90.5 (76)
10	$CH_3CO(CH_2)_6$-OBn (2)	6	 79j	91.3 (92)
11.	$CH_3COCH(OCH_3)_2$ (6)	7	 79k	85.4 (78)

[a]Yield of chromatographically homogeneous product. [b]Determined by HPLC. [c]Reaction performed at 4 °C.

3.2.3 Determination of sense of asymmetric induction in methyl ketone addition to 75

To determine the stereochemistry of the carbon atom bearing the silicon group in the Michael addition products, one of the product was converted to a advanced precursor of known natural product (+)-preussin **91**. For this, the diester **79f** was subjected to Krapcho deethoxycarbonylation[121] to give the monoester **92**, which on hydrolysis followed by esterification with diazomethane gave the methyl ester **93** (**Scheme 3.17**). By comparing the sign and magnitude of the optical rotation value of **93** ($[\alpha]_D^{24}$ = –0.8, *c* 0.8, $CHCl_3$) with the reported[122] value ($[\alpha]_D^{21}$ = –0.8, *c* 0.79, $CHCl_3$), the stereochemistry of the Si-bearing chiral centre was concluded to be of (*S*) configuration. This also confirmed the absolute stereochemistry of the adduct **79f**.



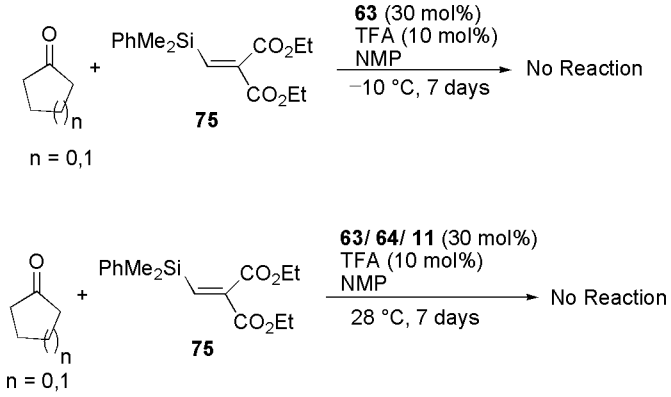
Scheme 3.17

The absolute configuration of other products **79a-e** and **79j,k** were tentatively assigned in analogy with **79f**. The absolute configurations of other products **79g-i** were assigned by converting them into known chiral valerolactones intermediates which will be discussed in the next chapter.

3.2.4 Addition of cyclic ketones to silylmethylene malonate 75

After successful employment of alkyl methyl ketones for the Michael addition reaction to β-silylmethylene malonate **75**, our next aim was to engage cyclic ketones for the same. The addition of cyclic ketone donors to alkylidene malonates is a useful objective because the product derived from this would produces two close by stereogenic centers in one short which can then be used to generate a third or fourth one by stereochemical induction in close vicinity.

Cyclohexanone and cyclopentanone were reacted with silylmethylene malonate **75** in the presence of catalyst **63** under the optimized conditions described for silylmethylene malonate **75**. No reaction took place with none of these ketones (**Scheme 3.18**), even when the reaction were carried out at higher temperature (28 °C) and with other catalysts such as **63** and **11** (**Scheme 3.18**).

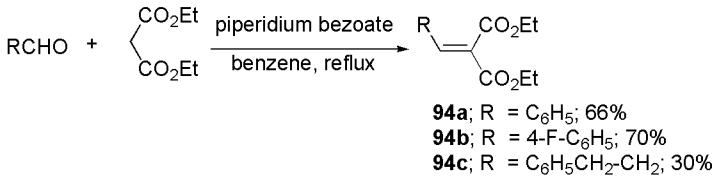


Scheme 3.18

3.2.5 Addition of alkyl methyl ketones to other alkylidene malonates

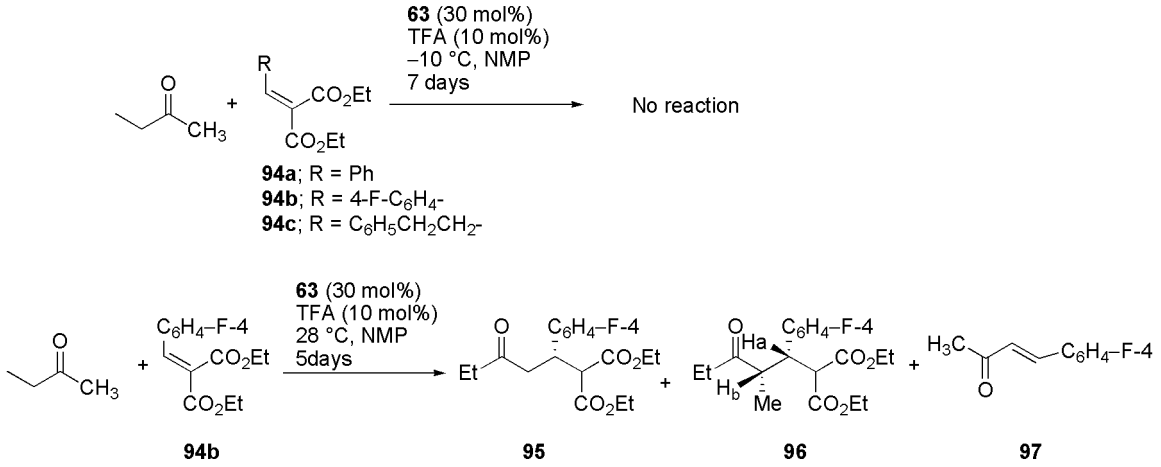
We next attempted to generalize this regio- and enantioselective methyl ketone addition to arylidene and alkylidene malonates. The arylidene and alkylidene malonates

94a-c were prepared from diethyl malonate and the corresponding aldehydes by a Knoevenagel type reaction (**Scheme 3.19**).



Scheme 3.19

The diethyl esters of phenylmethylene, 4-fluorophenylmethylene and 2-phenylethylmethylene malonates **94a-c** were reacted with methyl ethyl ketone in the presence of catalyst **63** under the optimized conditions described for silylmethylene malonate **75**.[115] No reaction took place with any of these methylene malonates. Even at higher temperature (28 °C), the reaction between diethyl 4-fluorophenylmethylene malonate **79b** and methyl ethyl ketone catalyzed by **63** and TFA in NMP was very sluggish. The reaction was incomplete even after 5 days. Moreover, it produced a 3:2 regioisomeric mixture of adducts **95** and **96** in 18% and with the acetyl terminal adduct as the major one (**Scheme 3.20**). The internal adduct **96** also appeared to be the *syn*-diasteroisomer[105b] as judged by ^{1}H NMR spectroscopy (J_{HaHb} = 7 Hz). Besides, a substantial amount (32%) of an unsaturated ketone **97** was also produced. The source of this ketone **97** could be the retro Knoevenagel of 4-fluorophenylmethylene malonate **94b** producing 4-fluorobenzaldehyde followed by its organocatalyzed aldol-dehydration[105b,123] with methyl ethyl ketone. This study clearly indicated that the silyl substitution is crucial for the reactivity of the silylmethylene malonate **75** as well as regioselectivity of the addition.



Scheme 3.20

3.2.6 Proposed Mechanism of alkyl methyl ketones addition to silylmethylene malonate 75

Considering that the reaction goes via enamine mechanism the stereochemical outcome for the formation of **79a-k** can be explained by a transition state assembly[54] depicted in **Fig. 3.5**. The silylmethylene malonate **75** approaches the enamine from the less hindered *Si* face. The hydrogen bonding interaction of tertiary nitrogen, one of the carbonyl group of silylmethylene malonate and TFA activated the substrates by bringing them to proximity, explaining well that a catalytic amount of TFA can speed up the reaction.

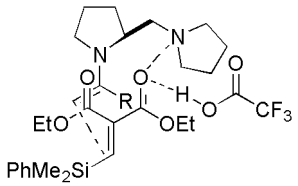


Fig. 3.5. Potential transition state

3.3 Conclusions

In conclusion, we have developed an organocatalytic asymmetric Michael addition of alkyl methyl ketones to a silylmethylene malonate with high regio- and enantioselectivity. The cyclic ketones were not good candidate for this reaction and the arylidene and alkylidene malonates were inactive for this reaction in our optimized conditions. This is the first successful attempt to engage unsymmetrical methyl ketones to add via terminal carbon in such reactions, where the silyl group is the key to this success.

3.4 EXPERIMENTAL SECTION

General Details: As described in **Chapter-2**.

Reagents:

HPLC grade acetone, NMP, DMF, toluene, THF, methanol were used as received. Pentane-1,5-diol, isopropyl methyl ketone, ethyl methyl ketone, methyl propyl ketone, isobutyl methyl ketone, 2-heptanone, 2-Tridecanone, pyruvaldehyde dimethyl acetal, (Bromomethyl)-cyclohexyl, benzyl and octyl bromides are commercially available, and distilled prior to use. Undecanone **86**, 4-cyclohexyl-2-butanone **87** and 8-Benzyloxy-2-octanone **88** were synthesized. Silylmethylene malonate **75** was prepared following a procedure reported from our laboratotary.[108] Diphenylprolinol **82** was purchased from Aldrich and its TMS-ether **16** was prepared according to the literature[124] procedure. All the amino acids were purchased from Merck. The catalyst **63, 64** and **11** were prepared following the literature procedures.[114]

HPLC: Enantiomeric excess (ee) determinations were carried out by HPLC using a JASCO (JASCO PU-2080) instrument fitted with a Daicel chiralpak AD-H column and UV-2075 detector with λ fixed at 254 nm.

Optical rotation: Optical rotations were measured in a JASCO DIP polarimeter.

3.4.1. Preparation of substrate 75, methyl ketones and catalysts

Ethyl 2-ethoxycarbonyl-3-Phenyldimethylsilyl-2-propenoate 75

Following the literature[108] procedure, dimethyl(phenyl)silyllithium **77** (0.85 *M* solution in THF, prepared using dimethylphenylsilyl chloride **78** and lithium) (105 mL, 89 mmol) was added drop wise to a stirred solution of diethyl ethoxymethylene malonate **76** (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 **75**.

Yield: 19.9 g (73%); IR (neat): 1727, 1604, 1236, 1114 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 0.45 (6 H, s, 2 × SiC*H*$_3$), 1.19 (3 H, t, *J* =7.1 Hz, C*H*$_3$CH$_2$OCO), 1.29 (3 H, t, *J* =7.1 Hz, C*H*$_3$CH$_2$OCO), 4.00 (2 H, q, *J* = 7.1 Hz, CH$_3$C*H*$_2$OCO), 4.24 (2 H, q, *J* = 7.1 Hz, CH$_3$C*H*$_2$OCO), 7.31 (1 H, s, C=C*H*Si), 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 (2 C), 13.7, 13.8, 61.0, 61.4, 127.7 (2 C), 129.3, 133.7 (2 C), 136.14, 141.5, 147.3, 163.5, 165.8; MS (ESI) *m/z*: 329 (M^+ + Na, 15), 307 (M^+ + H, 5), 229 (M - Ph, 100), 128 (82), 173 (41), 155 (37).

2-Undecanone 86

A solution of freshly distilled ethyl acetoacetate **90** (10.93 mL, 86 mmol) in DMF (50 mL) was slowly added to a oil free suspension of NaH (3.2 g, 66 mmol, 50% in oil) in DMF (30 mL) at 0 °C. After the addition was over, the reaction mixture was brought to room temperature and a solution of the octyl bromide (11.4 mL, 66 mmol) in DMF (50 mL) was added drop-wise into it followed by the addition of Bu_4NI (2.43 g, 0.66 mmol). The reaction mixture was stirred at 70 °C for overnight, diluted with water (400 mL) and extracted with Et_2O (3 × 100 mL). The combined extract was washed with brine, dried

over Na_2SO_4 and evaporated under reduced pressure to give crude ethyl (2*RS*)-2-acetylnonanoate (12 g, 75%). A stirred solution of this keto ester, sodium chloride (2 g, 34 mmol) and water (10 mL) in DMSO (300 mL) was heated at 165 °C under nitrogen for 6 h. The reaction mixture was diluted with water (1.5 L) and extracted with ether. The organic extract was washed with water and with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was distilled under reduced pressure (63 ˚C/0.22 Torr) to give pure 2-undecanone.

Yield: 6.0 g (71%); IR (neat): 2925, 2855, 1718, 1465, 1358, 1161 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 0.87 (3 H, t, *J* = 6.8 Hz, -CH_2CH_3), 1.25 (14 H, bs, $[CH_2]_7CH_3$), 2.12 (3 H, s, $COCH_3$), 2.41 (2 H, t, *J* = 7.4 Hz, $COCH_2$); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0, 22.6, 23.8, 29.1, 29.2, 29.4 (2 C), 29.7, 31.8, 43.7, 209.2.

4-cyclohexyl-2-butanone 87

A solution of freshly distilled ethyl acetoacetate **90** (8.4 mL, 66 mmol) in DMF (30 mL) was slowly added to a oil free suspension of NaH (2.8 g, 60 mmol, 50% in oil) in DMF (20 mL) at 0 °C. After the addition was over, the reaction mixture was brought to room temperature and a solution of the (Bromomethyl)-cyclohexyl (8.4 mL, 60 mmol) in DMF (45 mL) was added drop-wise into it followed by the addition of Bu_4NI (2.2 g, 0.6 mmol). The reaction mixture was stirred at 70 °C for overnight, diluted with water (400 mL) and extracted with Et_2O (3 × 100 mL). The combined extract was washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure to give crude ethyl (2*RS*)-2-acetyl-3-cyclohexylpropionate (10.8 g, 80%). A stirred solution of this keto ester, sodium chloride (2 g, 34 mmol) and water (10 mL) in DMSO (250 mL) was heated at 165 °C under

nitrogen for 6 h. The reaction mixture was diluted with water (1.5 L) and extracted with ether. The organic extract was washed with water and with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was distilled under reduced pressure (82 ˚C/0.27 Torr) to give pure 4-cyclohexyl-2-butanone.

Yield: 4.53 g (49%); IR (neat): 2923, 2851, 1718, 1448, 1355, 1091, 735 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 0.82-0.93 (2 H, m, c-C_6H_{11}), 1.12-1.27 (4 H, m, c-C_6H_{11}); 1.39-1.46 (2 H, m, c-C_6H_{11}), 1.50-1.69 (5 H, m, c-$C_6H_{11,}$ *c*-$C_6H_{11}C\mathit{H}_2CH_2CO$), 2.12 (3 H, s, $COCH_3$), 2.41 (2 H, t, *J* = 7.7 Hz, *c*-$C_6H_{11}C\mathit{H}_2C\mathit{H}_2CO$); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.0 (2 C), 26.4, 29.5, 31.0, 33.0 (2 C), 37.0, 41.2, 208.9.

8-Benzyloxy-2-octanone 88

A solution of pentane-1,5-diol **89a** (10.4 g, 100 mmol) in THF (130 mL) was added slowly to a suspension of oil free NaH (4.8 g, 100 mmol, 50% in oil) in THF (50 mL) at 60 °C. After the addition was over, the reaction mixture was stirred for 2 h. The reaction mixture was cooled to room temperature and a solution of benzyl bromide (11.9 mL, 100 mmol) in THF (100 mL) was added to it. After 20 h at 40 °C, the reaction mixture was cooled to room temperature. The reaction mixture was diluted with water and extracted with EtOAc. The extract was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography (SiO_2, hexane/EtOAc: 6/4) to give 5-benzyloxypentane-1-ol **89b**. Yield: 11.0 g (57%); IR (neat): 3550-3100 (br), 3029, 2936, 2860, 1454, 1363, 1096, 733 cm^{-1}.^1H NMR (200 MHz, $CDCl_3$): δ = 1.39-1.68 (7 H, m, [$C\mathit{H}_2$]$_3CH_2OBn$ and OH), 3.48 (2 H, t, *J* = 6.4 Hz, $C\mathit{H}_2$-OBn), 3.64 (2 H, t, *J* = 6.2 Hz, $C\mathit{H}_2$-OH), 4.49 (2 H, s, $OC\mathit{H}_2Ph$), 7.26-7.35 (5 H, m, Ar); ^{13}C NMR (50 MHz, $CDCl_3$): δ =

22.1, 29.0, 32.0, 61.8, 70.0, 72.5, 127.2, 127.3 (2 C), 128.0 (2 C), 138.0. A solution of bromine (2.0 mL, 39 mmol) in CH_2Cl_2 (30 mL) was added to a stirred solution of triphenylphosphine (10.3 g, 39.4 mmol) in CH_2Cl_2 (40 mL) at 0 °C. After the bromine color disappeared, a solution of 5-benzyloxypentane-1-ol (7.6 g, 39 mmol) and pyridine (3.15 mL, 39 mmol) in CH_2Cl_2 (50 mL) was added to it. The reaction mixture was allowed to attain to room temperature and stirred for 2 h. The reaction mixture was concentrated under reduced pressure and the residue was wash triturated with hexane (5 × 50 mL) and decanted. The combined organic phase was evaporated under reduced pressure and the residue was purified by column chromatography on silica gel to give 5-benzyloxypentyl bromide **89c**. Yield: 9.2 g (92%); IR (neat): 3028, 2937, 2857, 1454, 1362, 1103, 733, 697 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.49-1.60 (6 H, m, $[CH_2]_3CH_2Br$), 3.34-3.47 (4 H, m, -CH_2Br and CH_2OBn), 4.46 (2 H, s, OCH_2Ph), 7.27-7.33 (5 H, m, Ar); ^{13}C NMR (50 MHz, $CDCl_3$): δ 24.9, 28.9, 32.5, 33.7, 69.9, 72.9, 127.5, 127.6 (2 C), 128.4 (2 C), 138.5. A solution of freshly distilled ethyl acetoacetate **90** (5.49 mL, 43 mmol) in DMF (30 mL) was slowly added to a oil free suspension of NaH (1.72 g, 36 mmol, 50% in oil) in DMF (20 mL) at 0 °C. After the addition was over, the reaction mixture was brought to room temperature and a solution of the 5-benzyloxypentyl bromide **89c** (9.2 g, 36 mmol) in DMF (50 mL) was added drop-wise into it followed by the addition of Bu_4NI (1.32 g, 3.6 mmol). The reaction mixture was stirred at 70 °C for overnight, diluted with water (300 mL) and extracted with Et_2O (3 × 100 mL). The combined extract was washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure to give crude ethyl (2*RS*)-2-acetyl-7-benzyloxyheptanoate (7.2 g, 65%). A stirred solution of this keto ester, sodium chloride (2 g, 34mmol) and water (10 mL) in DMSO (300 mL) was heated at 165 °C under

nitrogen for 6 h. The reaction mixture was diluted with water (1.5 L) and extracted with ether. The organic extract was washed with water and with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, hexane/EtOAc: 95/5) to give 8-benzyloxy-2-octanone **88**.

Yield: 4.0 g (73%); IR (neat): 2933, 2857, 1715, 1455, 1362, 1099, 735 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 1.22-1.67 (8 H, m, $COCH_2[CH_2]_4$), 2.12 (3 H, s, $COCH_{3)}$, 2.40 (2 H, t, J = 7.4 Hz, CH_3COCH_2), 3.45 (2 H, t, J = 6.4 Hz, CH_2OCH_2Ph), 4.49 (2 H, s, OCH_2Ph), 7.26-7.34 (5 H, m, Ar); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 23.5, 25.8, 28.7, 29.4, 29.6, 43.4, 70.0, 72.6, 127.2, 127.3 (2 C), 128.0 (2 C), 138.4, 208.8; EI-MS: *m*/*z* 128 (M^+ - OCH_2Ph, 18%), 107 (27), 91 (100), 77 (26).

(*S*)-1-[*N*-(Benzyloxycarbonyl)proly]pyrrolidine 84a

Following the literature[114] procedure, a solution of diisopropylcarbodimide (6.9 mL, 44.4 mmol) in CH_2Cl_2 (20 mL) was added to a stirred solution of (*S*)-*N*-(benzyloxycarbonyl)proline **83** (11 g, 44.4 mmol) in dichloromethane (20 mL) at 0 °C under N_2 atmosphere. After 30 min, a solution of pyrrolidine (3.7 mL, 44.4 mmol) in CH_2Cl_2 (20 mL) was added drop-wise to the reaction mixture. After 12 h at room temperature, the reaction mixture was filtered and the filtrate was washed successively with dil. HCl, saturated $NaHCO_3$ solution, water and with brine. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was crystallized to give pure (*S*)-1-[*N*-(benzyloxycarbonyl)proly]pyrrolidine **84a**.

Yield: 8.0 g (59%); M.p : 132-134 °C (ethyl acetate); lit.[114] 130-132 °C (ethyl acetate); IR ($CHCl_3$): 3018, 2976, 1700, 1644, 1421, 1357, 756 cm^{-1}; ^1H-NMR (200 MHz, $CDCl_3$): δ

= 1.58-2.22 (8H, m, 4 × CH_2), 3.27-3.78 (6 H, m, 3 × NCH_2), 4.36-4.54 (1 H, m, NC*H*), 4.94-5.21 (2 H, m, OCOCH_2Ph), 7.29-7.34 (5 H, m, Ph); $[\alpha]_D^{25}$ = –13.0 (*c* = 1.6, MeOH); lit.[111] $[\alpha]_D^{22}$ = –14.1 (*c* = 1.61, MeOH).

(*S*)-2-(1-Pyrrolidinylmethyl)pyrrolidine 63

Following the literature[114] procedure, a solution of (*S*)-1-[*N*-(benzyloxycarbonyl)proly]pyrrolidine **84a** (3.5 g, 11.6 mmol) in MeOH (16 mL) was stirred over 5% Pd on charcoal (222 mg) under a hydrogen atmosphere at room temperature overnight. The catalyst was filtered through a pad of celite and the filtrate was under reduced pressure to give the crude amide as viscous oil (1.89 g, 97%). A solution of this amide in THF (15 ml) was added slowly to a suspension of $LiAlH_4$ (1.5 g, 40 mmol) in THF (15 mL) at 0 °C under N_2 atmosphere. After heating the mixture under reflux for 20 h, the reaction mixture was cooled on an ice-water bath and a saturated solution of Na_2SO_4 (2 mL) was added into it. The reaction mixture was filtered through a celite pad and the filtrate was concentrated under reduced pressure. The residue was distilled (110 °C/ 5.5 Torr) to give the **63** as a colorless oil.

Yield: 1.1 g (64%); IR ($CHCl_3$): 3294 (br), 2960, 2872, 2785, 1459, 1406, 1352, 1292, 1146, 881 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.43-2.10 (8H, m, *N*[CH_2]$_4$), 2.10-3.40 (9 H, m, *N*[CH_2]$_3$), 3.74 (1 H, bs, N*H*); ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 23.4 (2 C), 24.9, 29.9, 45.9, 54.5 (2 C), 57.3, 61.8; $[\alpha]_D^{20}$ = +8.5 (*c* = 2.4, EtOH); lit.[114] $[\alpha]_D^{26}$ = +7.0 (*c* = 2.38, EtOH);

(*S*)-1-[*N*-(Benzyloxycarbonyl)proly]piperidine 84b

Following the literature[114] procedure, a solution of diisopropylcarbodimide (6.9 mL, 44.4 mmol) in CH_2Cl_2 (20 mL) was added to a solution of (*S*)-*N*-(Benzyloxycarbonyl)proline **83** (11 g, 44.4 mmol) in dichloromethane (20 mL) at 0 °C under N_2 atmosphere. After stirring for 30 min, a solution of piperidine (4.4 mL, 44.4 mmol) in CH_2Cl_2 (20 mL) was added drop-wise to the reaction mixture and stirred overnight at room temperature. The reaction mixture was filtered and the filtrate was washed successively with dil. HCl, saturated $NaHCO_3$ solution, water and with brine. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was crystallized in ethyl acetate to give pure (*S*)-1-[*N*-(benzyloxycarbonyl)proly]piperidine **84b** (8.3 g, 59%).

Yield: 8.0 g (59%); M.p: 92-93 °C (ethyl acetate); lit.[111] 90-91 °C (ethyl acetate); IR ($CHCl_3$): 3019, 2975, 1697, 1646, 1420, 1361, 758 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.13-2.18 (10 H, m, $N[CH_2]_5$), 3.28-3.79 (6 H, m, $N[CH_2]_3$), 4.58-4.74 (1 H, m, *N*C*H*), 5.01-5.23 (2 H, m, OCOCH_2Ph), 7.29-7.34 (5 H, m, Ar); $[\alpha]_D^{24}$ = –14.0 (*c* = 2.0, EtOH); lit.[114] $[\alpha]_D^{29}$ = –14.3 (*c* = 2.0, EtOH).

(*S*)-2-(1-Piperidinomethyl)pyrrolidine 64

Following the literature[114] procedure, a solution of (*S*)-1-[*N*-(benzyloxycarbonyl)proly]piperidine **84b** (3.7 g, 11.6 mmol) in MeOH (16 mL) was stirred over 5% Pd on charcoal (222 mg) under a hydrogen atmosphere at room temperature overnight. The catalyst was filtered through a pad of celite and the filtrate was under reduced pressure to give the crude amide as viscous oil (2 g, 96%). A solution of this amide in THF (15 ml) was added slowly to a suspension of $LiAlH_4$ (1.5 g, 40 mmol) in

THF (15 mL) at 0 °C under N_2 atmosphere. After heating the mixture under reflux for 20 h, the reaction mixture was cooled on an ice-water bath and a saturated solution of Na_2SO_4 (2 mL) was added into it. The reaction mixture was filtered through a celite pad and the filtrate was concentrated under reduced pressure. The residue was distilled (120 °C/5.5 Torr) to give **64**.

Yield: 1.12 g (61%); IR ($CHCl_3$): 3294 (br), 2957, 2855, 2807, 1455, 1398, 1295, 1141, 865 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.26-2.0 (10 H, m, *N*[C*H*$_2$]$_5$), 2.24-2.55 (6 H, m, *N*[C*H*$_2$]$_3$), 2.83-3.99 (3 H, m, -*N*CHCH$_2$*N*-), 3.44 (1 H, bs, N*H*); $[\alpha]_D^{30}$ = +18.6 (*c* = 9.85, EtOH); lit.[114] $[\alpha]_D^{26}$ = +16 (*c* = 2.0, EtOH).

(*S*)-1-[*N*-(Benzyloxycarbonyl)proly]morpholine 84c

Following the literature[114] procedure, a solution of diisopropylcarbodimide (6.9 mL, 44.4 mmol) in CH_2Cl_2 (20 mL) was added to a stirred solution of (*S*)-*N*-(benzyloxycarbonyl)proline **83** (11 g, 44.4 mmol) in dichloromethane (20 mL) at 0 °C under N_2 atmosphere. After 30 min, a solution of morpholine (3.9 mL, 44.4 mmol) in CH_2Cl_2 (20 mL) was added drop-wise to the reaction mixture. After 12 h at room temperature, the reaction mixture was filtered and the filtrate was washed successively with dil. HCl, saturated $NaHCO_3$ solution, water and with brine. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was crystallized to give pure (*S*)-1-[*N*-(benzyloxycarbonyl)proly]pyrrolidine **84c** (9.3 g, 66%).

Yield: 9.3 g (66%); M.p: 142-143 °C (ethyl acetate); lit.[114] 141-142 °C (ethyl acetate); IR ($CHCl_3$): 3019, 2975, 1697, 1646, 1420, 1361, 758 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.6-2.16 (4 H, m, *N*[C*H*$_2$]$_2$), 3.35-3.79 (10 H, m, *N*[C*H*$_2$]$_4$O, NC*H*$_2$), 4.4-4.74 (1 H, m,

NCH), 5.0-5.23 (2 H, m, OCOCH_2Ph), 7.29-7.34 (5 H, m, Ar); $[\alpha]_D^{27}$ = –17.9 (*c* = 2.0, EtOH); lit.[114] $[\alpha]_D^{28}$ = –16.5 (*c* = 2.0, EtOH).

(*S*)-2-(Morpholinomethyl)pyrrolidine 11

Following the literature[114] procedure, a solution of (*S*)-1-[*N*-(benzyloxycarbonyl)morpholine **84c** (1.9 g, 6 mmol) in MeOH (8 mL) was stirred over 5% Pd on charcoal (112 mg) under a hydrogen atmosphere at room temperature overnight. The catalyst was filtered through a pad of celite and the filtrate was under reduced pressure to give the crude amide as viscous oil (1.0 g, 91%). A solution of this amide in THF (10 ml) was added slowly to a suspension of $LiAlH_4$ (722 mg, 19 mmol) in THF (7 mL) at 0 °C under N_2 atmosphere. After heating the mixture under reflux for 20 h, the reaction mixture was cooled on an ice-water bath and a saturated solution of Na_2SO_4 (1 mL) was added into it. The reaction mixture was filtered through a celite pad and the filtrate was concentrated under reduced pressure. The residue was distilled (120 °C/1.2 Torr) to give **11**.

Yield: 591 mg (58%); IR ($CHCl_3$): 3330 (br), 2957, 2855, 2807, 1455, 1398, 1295, 1141, 865 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.4-2.4 (4 H, m, *N*[CH_2]$_2$), 2.34-2.62 (6 H, m, *N*[CH_2]$_2$O, NCH_2), 3.0-3.2 (4 H, m, -*NCHCH*$_2$*N*-, 1 H, bs, N*H*), 3.66-4.17 (4 H, m, *N*[CH_2]$_2$O); ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 24.8, 29.7, 45.8, 53.9 (2 C), 54.8, 63.8, 66.9 (2 C); $[\alpha]_D^{30}$ = +17.6 (*c* = 9.98, EtOH); lit.[114] $[\alpha]_D^{25}$ = +15.0 (*c* = 1.3, EtOH).

(S)-(-)-α,α-Diphenyl-2-pyrroldinyl methyl TMS ether 16

Following the literature[123] procedure, TMSOTf (0.992 mL, 5.1 mmol) was added to a stirred solution of diphenylprolinol **82**(1 g, 3.95 mmol) and Et_3N (0.71 mL) in CH_2Cl_2 (20 mL) at 0 ° C. The reaction mixture was stirred at room temperature for 17 h and quenched

with water (10 mL). The aqueous layer was extracted with CH_2Cl_2. The combined organic extracts were stirred with $NaHCO_3$ for 15 min, dried over anhydrous Na_2SO_4 and concentrated under vacuum after filtration. Purification with silica gel column chromatography (EtOAc/hexane, 15:85-25:75) furnished **16** as a thick oil.

Yield: 1.3 g (99%); ^{1}H NMR (CDCl3, 200 MHz): δ = 0.03 (9 H, s), 1.53–1.71 (4 H, m), 2.81–2,93 (2 H, m), 4.09 (1 H, t, J =7.0 Hz), 7.22–7.53 (10H, m); ^{13}C NMR (CDCl3, 50 MHz): δ = 2.4, 25.1, 28.0, 47.3, 65.5, 83.3, 126.8, 127.0, 128.0, 129.0, 146.0, 147.0, $[\alpha]_D^{30}$ = – 30 (c = 1.0, CH_2Cl_2); lit.[123] $[\alpha]_D^{28}$ = –32.3 (c = 1.0, CH_2Cl_2).

3.4.2 General procedures

General Procedure 3.4.2.I. Survey of organocatalysts for Michael addition of acetone on β- silylmethylene malonate 75

Acetone (220 μL, 3 mmol, 12 equiv) was added to a stirred mixture of silylmethylene malonate **75** (77 mg, 0.25 mmole, 1 equiv) and organocatalyst (0.075 mmol, 0.3 equiv) in NMP (1 mL) at 0 °C. After 1-7 days at room temperature (28 °C), the reaction mixture was diluted with water and extracted with EtOAc/hexane (1/1). 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 **79a** (9 mg - 68 mg, 10%-75%).

General Procedure 3.4.2.II. Survey of additives with organocatalysts 63/64/11 for optimization of Michael addition of acetone on 75

Acetone (220 μL, 3 mmol, 12 equiv) was added to a stirred mixture of silylmethylene malonate **75** (77 mg, 0.25 mmole, 1 equiv), organocatalyst (0.075 mmol, 0.3 equiv) and the

desired additive (0.0125-0.075 mmol, 0.05-0.3 equiv) in NMP/DMF/Toluene (1 mL) at −10 °C. After 5-10 days at −10 or 4 °C, the reaction mixture was diluted with water and extracted with EtOAc/hexane (1/1). 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 **79a** (4 mg - 80 mg, 4%-88%).

General Procedure 3.4.2.III. Michael addition of methyl ketones on 75 using organocatalyst 63 and additive TFA

Respective methyl alkyl ketone (1-6 mmol, 2-12 equiv) was added to a stirred mixture of silylmethylene malonate **75** (153 mg, 0.5 mmole, 1 equiv), pyrrolidine **63** (23 mg, 0.15 mmol, 0.3 equiv) and trifluoroacetic acid (4 μL, 0.05 mmol, 0.1 eqiuv) in NMP (2 mL) at -10 °C. After 3-7 days at −10 °C, the reaction mixture was diluted with water and extracted with EtOAc/hexane (1/1). 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 **79a-k** (76-94%).

General Procedure 3.4.2.IV. Michael addition of methyl ketones on 75 using (D,L)-proline or pyrrolidine for the preparation of racemic Michael product (±)-**79a-k**

Respective methyl alkyl ketone (1-6 mmol, 2-12 equiv) was added to a stirred mixture of silylmethylene malonate **75** (77 mg, 0.25 mmole, 1 equiv), (D,L)-proline or pyrrolidine (0.075 mmol, 0.3 equiv) in NMP (1 mL) at 28°C. After 5-10 days at 28 °C, the reaction mixture was diluted with water and extracted with EtOAc/hexane (1/1). 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 (±)-**79a-k**.

Ethyl (3*S*)-3-dimethylphenylsilyl-2-ethoxycarbonyl-5-oxohexanoate 79a: Prepared from **75** (153 mg, 0.5 mmol) and acetone (0.44 mL, 6 mmol) according to *General Procedure* **3.4.2.III.** Yield: 138 mg (76%); IR (film): 2981, 1746, 1727, 1427, 1367, 1301, 1250, 1154, 1029, 817 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 0.33 (3 H, s, CH_3Si), 0.32 (3 H, s, CH_3Si), 1.21 (6 H, t, J = 7.2 Hz, 2 × CH_3CH$_2$OCO), 1.97 (3 H, s, COCH_3), 2.29 (1 H, q, J = 6 Hz, SiCH), 2.60 (1 H, dd, J = 5.8, 18.6 Hz, CH_AH$_B$CO), 2.78 (1 H, dd, J = 6.6, 18.6 Hz, CH$_A$$H_B$CO), 3.48 (1 H, d, J = 5.6 Hz, CHCHSi), 4.00-4.10 (4 H, m, 2 × CH$_3$CH_2OCO), 7.31 -7.37 (3 H, m, Ph), 7.47-7.53 (2 H, m, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ = –3.5, –3.3, 13.9 (2 C), 20.3, 29.6, 41.7, 51.7, 61.2, 61.3, 127.7 (2 C), 129.1, 134.2 (2 C), 137.1, 169.4, 169.8, 207.6; ESI-HRMS: Found: M^+ + Na, 387.1604. $C_{19}H_{28}O_5SiNa$ requires M^+ + Na 387.1620; $[\alpha]_D^{25}$ = + 4.78 (*c* = 2.31, MeOH); HPLC: Daicel chiralpak AD-H, 2-propanol/ hexane (1/99), flow rate = 1.0 mL/min, t_R(3*S*)-**79a** 13.9 min (95%), t_R(3*R*)-**79a** 21.1 min (5%).

Ethyl (3*S*)-3-dimethylphenylsilyl-2-ethoxycarbonyl-6-methyl-5-oxoheptanoate 79b: Prepared from **185** (153 mg, 0.5 mmol) and methyl isopropyl ketone (0.64 mL, 6 mmol) according to *General Procedure* **3.4.2.III.** Yield: 160 mg (82%); IR (neat): 2975, 1747, 1729, 1368, 1250, 1149, 1033, 819 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 0.33 (3 H, s, CH_3Si), 0.32 (3 H, s, CH_3Si), 0.94 (3 H, d, J = 6.8 Hz, CHMe_AMe$_B$), 0.95 (3 H, d, J = 6.8 Hz, CHMe$_A$$Me_B$), 1.20 (6 H, t, J = 7.2 Hz, 2 × CH_3CH$_2$OCO), 2.29 (1 H, q, J = 6 Hz, SiCH), 2.45 (1 H, septet, J = 6.8 Hz, CHMe$_2$), 2.65 (1 H, dd, J = 6.0, 19.0 Hz, CH_AH$_B$CO), 2.79 (1 H, dd, J = 6.2, 19.0 Hz, CH$_A$$H_B$CO), 3.51 (1 H, d, J = 5.8 Hz, CHCHSi), 4.00-4.11 (4 H, m, 2 × CH$_3$CH_2OCO), 7.25-7.34 (3 H, m, Ph), 7.47-7.53 (2 H, m, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ = –3.5, –3.3, 13.9 (2 C), 18.3 (2 C), 19.9, 38.8, 40.4, 51.8, 61.2, 61.3,

127.7 (2 C), 129.1, 134.2 (2 C), 137.4, 169.5, 169.9, 213.5; ESI-HRMS: Found: M^+ + Na, 415.1902. $C_{21}H_{32}O_5SiNa$ requires M^+ + Na 415.1911; $[\alpha]_D^{25}$ = +7.56 (*c* = 2.91, MeOH); HPLC: Daicel chiralpak AD-H, 2-propanol/ hexane (0.7/99.3), flow rate = 1.0 mL/min, t_R(3*S*)-**79b** 8.9 min (99.72%), t_R(3*R*)-**79b** 15.0 min (0.28%).

Ethyl (3*S*)-3-dimethylphenylsilyl-2-ethoxycarbonyl-7-methyl-5-oxooctanoate 79c: Prepared from **75** (153 mg, 0.5 mmol) and methyl isobutyl ketone (0.312 mL, 2.5 mmol) according to *General Procedure* **3.4.2.III.** Yield: 166 mg (82%); IR (neat): 2957, 1747, 1729, 1368, 1249, 1150, 1111, 1033 and 838 cm^{-1}; ^{1}H NMR 200 MHz, $CDCl_3$): δ = 0.32 (3 H, s, C*H*$_3$Si), 0.33 (3 H, s, C*H*$_3$Si), 0.80 (3 H, d, *J* = 6.4 Hz, CH*Me*$_A$Me$_B$), 0.82 (3 H, d, *J* = 6.4 Hz, CHMe$_A$*Me*$_B$), 1.20 (6 H, t, *J* = 7.2 Hz, 2 × C*H*$_3$CH$_2$OCO), 1.90-2.11 (3 H, m, C*H*$_2$C*H*Me$_2$), 2.29 (1 H, q, *J* = 6 Hz, SiCH), 2.56 (1 H, dd, *J* = 5.8, 18.8 Hz, C*H*$_A$CH$_B$CO), 2.71 (1 H, dd, *J* = 6.2, 18.8 Hz, CH$_A$*H*$_B$CO), 3.50 (1 H, d, *J* = 5.8 Hz, C*H*CHSi), 3.98-4.12 (4 H, m, 2 × CH$_3$C*H*$_2$OCO), 7.3-7.34 (3 H, m, Ph), 7.48-7.53 (2 H, m, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ = –3.4, –3.1, 13.9 (2 C), 20.0, 22.5 (2 C), 24.4, 41.5, 51.4, 51.8, 61.1, 61.3, 127.7 (2 C), 129.0, 134.2 (2 C), 137.3, 169.5, 169.8, 209.4; ESI-HRMS: Found: M^+ + Na, 429.2079. $C_{22}H_{34}O_5SiNa$ requires M^+ + Na 429.2073; $[\alpha]_D^{23}$ = +6.78 (*c* = 2.21, MeOH); HPLC: Daicel chiralpak AD-H, 2-propanol/ hexane (0.7/99.3), flow rate = 1.0 mL/min, t_R(3*S*)-**79c** 8.8 min (98.35%), t_R(3*R*)-**79c** 16.8 min (1.65%).

Ethyl (3*S*)-3-dimethylphenylsilyl-2-ethoxycarbonyl-5-oxoheptanoate 79d: Prepared from **75** (153 mg, 0.5 mmol) and methyl ethyl ketone (0.537 mL, 6 mmol) according to *General Procedure* **3.4.2.III.** Yield: 153 mg (81%); IR (neat): 3070, 2979, 2905, 1748, 1728, 1427, 1369, 1250, 1151, 1111, 1033, 818 cm^{-1}; ^{1}H NMR 200 MHz, $CDCl_3$): δ = 0.31 (3 H, s, C*H*$_3$Si), 0.33 (3 H, s, C*H*$_3$Si), 0.92 (3 H, t, *J* = 7.4 Hz, COCH$_2$*Me*), 1.20 (6 H, t, *J* =

7.2 Hz, 2 × C*H*$_3$CH$_2$OCO), 2.10-2.36 (3 H, m, COC*H*$_2$Me, SiCH), 2.56 (1 H, dd, *J* = 6, 18.4 Hz, SiCHC*H*$_A$CH$_B$CO), 2.72 (1 H, dd, *J* = 6.4, 18.4 Hz, SiCHCH$_A$*H*$_B$CO), 3.48 (1 H, d, *J* = 5.6 Hz, C*H*CHSi), 4.05 (4 H, q, *J* = 7.2 Hz, 2 × CH$_3$C*H*$_2$OCO), 7.3-7.34 (3 H, m, Ph), 7.48-7.53 (2 H, m, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ = –3.4, –3.1, 7.8, 13.9 (2 C), 20.3, 35.6, 40.5, 51.9, 61.2, 61.3, 127.7 (2 C), 129.1, 134.3 (2 C), 137.3, 169.5, 169.9, 210.3; Anal. Calcd for $C_{20}H_{30}O_5Si$: C 63.46, H 7.99 %, Found; C 63.26, H 8.01%. $[\alpha]_D^{27}$ = +5.12 (*c* = 0.86, MeOH); HPLC: Daicel chiralpak AD-H, 2-propanol/ hexane (1/99), flow rate = 1.0 mL/min, t_R(3*S*)-**79d** 15.08 min (96.36%), t_R(3*R*)-**79d** 23.0 min (3.64%).

Ethyl (3*S*)-3-dimethylphenylsilyl-2-ethoxycarbonyl-5-oxooctanoate 79e: Prepared from **75** (153 mg, 0.5 mmol) and methyl propyl ketone (0.638 mL, 6 mmol) according to *General Procedure* **3.4.2.III.** Yield: 167 mg (85%); IR (neat): 3070, 3048, 2962, 2904, 1743, 1727, 1464, 1427, 1369, 1250, 1150, 1111, 1033 and 816 cm^{-1}; ^{1}H NMR 200 MHz, $CDCl_3$): δ = 0.32 (3 H, s, C*H*$_3$Si), 0.33 (3 H, s, C*H*$_3$Si), 0.82 (3 H, t, *J* = 7.4 Hz, COCH$_2$CH$_2$*Me*), 1.20 (6 H, t, *J* = 7.0 Hz, 2 × C*H*$_3$CH$_2$OCO), 1.37-1.56 (2 H, m, COCH$_2$C*H*$_2$Me), 2.04-2.34 (3 H, m, COC*H*$_2$CH$_2$Me, SiCH), 2.57 (1 H, dd, *J* = 6, 18.8 Hz, SiCHC*H*$_A$CH$_B$CO), 2.72 (1 H, dd, *J* = 6.2, 18.8 Hz, SiCHCH$_A$*H*$_B$CO), 3.49 (1 H, d, *J* = 5.6 Hz, C*H*CHSi), 4.00-4.11 (4 H, m, 2 × CH$_3$C*H*$_2$OCO), 7.30-7.34 (3 H, m, Ph), 7.47-7.53 (2 H, m, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ = –3.5, –3.2, 13.6, 13.9 (2 C), 17.2, 20.1, 40.9, 44.4, 51.8, 61.1, 61.3, 127.6 (2 C), 129.1, 134.2 (2 C), 137.3, 169.5, 169.8, 209.7; ESI-HRMS: Found: M^+ + Na, 415.1902. $C_{21}H_{32}O_5SiNa$ requires M^+ + Na 415.1911; $[\alpha]_D^{26}$ = +4.28 (*c* = 0.7, MeOH); HPLC: Daicel chiralpak AD-H, 2-propanol/ hexane (1/99), flow rate = 1.0 mL/min, t_R(3*S*)-**79e** 11.0 min (95.60%), t_R(3*R*)-**79e** 16.7 min (4.40%).

Ethyl (3*S*)-3-dimethylphenylsilyl-2-ethoxycarbonyl-5-oxotetradecanoate 79f: Prepared from **75** (153 mg, 0.5 mmol) and 2-Undecanone (0.513 mL, 6 mmol) according to *General Procedure* **3.4.2.III.**. Yield: 210 mg (88%); IR (neat): 2957, 2927, 2855, 1749, 1730, 1252, 1151, 1112, 1034, 838, 820 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.32 (3 H, s, CH_3Si), 0.33 (3 H, s, CH_3Si), 0.87 (3 H, t, J = 6.4 Hz, $[CH_2]_8CH_3$), 1.10-1.52 (14 H, m, $CH_2[CH_2]_7CH_3$), 1.20 (6 H, t, J = 7.2 Hz, 2 × CH_3CH_2OCO), 2.05-2.23 (2 H, m, $COCH_2[CH_2]_7CH_3$), 2.31 (1 H, q, J = 6 Hz, SiCH), 2.57 (1 H, dd, J = 6.0, 18.6 Hz, CH_AH_BCO), 2.72 (1 H, dd, J = 6.0, 18.6 Hz, CH_AH_BCO), 3.49 (1 H, d, J = 5.6 Hz, CHCHSi), 4.00-4.11 (4 H, m, 2 × CH_3CH_2OCO), 7.30-7.34 (3 H, m, Ph), 7.47-7.52 (2 H, m, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ = –3.4, –3.1, 13.9 (2 C), 14.0, 20.2, 22.6, 23.7, 29.1, 29.2, 29.4 (2 C), 31.8, 40.9, 42.5, 51.8, 61.1, 61.3, 127.7 (2 C), 129.1, 134.2 (2 C), 137.3, 169.5, 169.9, 209.9; ESI-HRMS: Found: M^+ + Na, 499.2840. $C_{27}H_{44}O_5SiNa$ requires M^+ + Na, 499.2856; $[\alpha]_D^{28}$ = +4.81 (*c* = 2.91, MeOH); HPLC: Daicel chiralpak AD-H, 2-propanol/ hexane (0.7/99.3), flow rate = 1.0 mL/min, t_R(3*S*)-**79f** 9.7 min (95.57%), t_R(3*R*)-**79f** 16.6 min (4.43%).

Ethyl (3*S*)-3-dimethylphenylsilyl-2-ethoxycarbonyl-5-oxodecanoate 79g: Prepared from **75** (153 mg, 0.5 mmol) and 2-heptanone (0.356 mL, 6 mmol) according to *General Procedure* **3.4.2.III.** Yield: 197 mg (94%); IR (neat): 2957, 1747, 1729, 1369, 1249, 1152, 1111, 1034, 819 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.33 (3 H, s, CH_3Si), 0.32 (3 H, s, CH_3Si), 0.85 (3 H, t, J = 7.2 Hz, $CH_2[CH_2]_3CH_3$), 1.10-1.50 (6 H, m, $[CH_2]_3CH_3$), 1.20 (6 H, t, J = 7.1 Hz, 2 × CH_3CH_2OCO), 2.13-2.23 (2 H, m, $COCH_2[CH_2]_3CH_3$), 2.31 (1 H, q, J = 6 Hz, SiCH), 2.57 (1 H, dd, J = 6.0, 18.6 Hz, CH_AH_BCO), 2.72 (1 H, dd, J = 6.4, 18.6 Hz, CH_AH_BCO), 3.49 (1 H, d, J = 5.8 Hz, CHCHSi), 4.00-4.11 (4 H, m, 2 ×

CH_3CH_2OCO), 7.26-7.35 (3 H, m, Ph), 7.47-7.52 (2 H, m, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ = –3.5, –3.2, 13.9 (3 C), 20.1, 22.3, 23.4, 31.2, 40.9, 42.4, 51.8, 61.0, 61.2, 127.6 (2 C), 129.0, 134.2 (2 C), 137.3, 169.5, 169.8, 209.8; ESI-HRMS: Found: M^+ + Na, 443.2218. $C_{23}H_{36}O_5SiNa$ requires M^+ + Na, 443.2230; $[\alpha]_D^{25}$ = +1.92 (*c* = 2.61, MeOH); HPLC: Daicel chiralpak AD-H, 2-propanol/ hexane (0.7/99.3), flow rate = 1.0 mL/min, t_R(3*S*)-**79g** 13.5 min (99.82%), t_R(3*R*)-**79g** 23.5 min (0.18 %).

Ethyl (3*S*)-3-dimethylphenylsilyl-2-ethoxycarbonyl-5-oxohexadecanoate 79h:

2-tridecanone (595 mg, 3 mmol), was added to a stirred mixture of silyledene malonate **75** (153 mg, 0.5 mmole, 1 equiv), pyrrolidine **63** (23 mg, 0.15 mmol, 0.3 equiv) and trifluoroacetic acid (4 μL, 0.05 mmol, 0.1 eqiuv) in NMP (2 mL) at 4 °C. After 6 days at 4 °C, the reaction mixture was diluted with water and extracted with EtOAc/hexane (1/1). 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 **79h.**

Yield: 201 mg (80%); IR (neat): 2981, 1748, 1730, 1465, 1367, 1249, 1151, 1111, 1034 819 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 0.32 (3 H, s, SiC*H*$_3$), 0.33 (3 H, s, SiC*H*$_3$), 0.87 (3 H, t, *J* = 6.3 Hz, C*H*$_3$[CH_2]$_{10}$CO), 1.16-1.30 (22 H, m, 2 × -$CO_2CH_2CH_3$, CH_3[C*H*$_2$]$_8CH_2CH_2CO$), 1.34-1.51 (2 H, m, $CH_3[CH_2]_8CH_2CH_2CO$), 2.04-2.44 (3 H, m, $CH_3[CH_2]_9CH_2CO$, SiC*H*), 2.57 (1 H, dd, *J* = 6.0, 18.6 Hz, $CH_3[CH_2]_9CH_2COCH_AH_B$-), 2.71 (1 H, dd, *J* = 6.2, 18.6 Hz, $CH_3[CH_2]_9CH_2COCH_AH_B$-), 3.48 (1 H, d, *J* = 5.8 Hz, C*H*[$CO_2CH_2CH_3$]$_2$), 4.06 (4 H, q, *J* = 7 Hz, 2 × CH_3CH_2OCO), 7.28 -7.33 (3 H, m, Ph), 7.47-7.52 (2 H, m, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ = –3.4, –3.2, 13.8 (2 C), 13.9, 20.3, 22.6, 23.8, 29.1, 29.2, 29.3, 29.4, 29.5 (2 C), 31.8, 40.9, 42.5, 51.9, 61.0, 61.1, 127.6 (2 C),

129.0, 134.2 (2 C), 137.4, 169.4, 169.8, 209.6; Anal. Calcd for $C_{29}H_{48}O_5Si$: C 69.00, H 9.58 %; Found: C, 69.21; H, 9.61%. $[\alpha]_D^{23}$ +4.67 (*c* 1.07, $CHCl_3$); HPLC: Daicel chiralpak AD-H, 2-propanol/ hexane (0.7/99.3), flow rate = 0.6 mL/min, t_R(3*S*)-**79h** 17.2 min (93.55%), t_R(3*R*)-**79h** 27.4 min (6.45%).

Ethyl (3*S*)-3-dimethylphenylsilyl-2-ethoxycarbonyl-7-cyclohexyl-5-oxoheptanoate 79i: Prepared from **75** (153 mg, 0.5 mmol) and 4-cyclohexyl-2-butanone (386 mg, 2.5 mmol), according to *General Procedure* **3.4.2.III.**. Yield: 175 mg (76%); IR (neat): 2980, 1745, 1729, 1448, 1369, 1249, 1151, 1111, 1034, 818 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 0.30 (3 H, s, SiCH_3), 0.32 (3 H, s, SiCH_3), 0.69-0.86 (2 H, m, c-C_6H_{11}), 0.96-1.35 (12 H, m, 2 × $CO_2CH_2CH_3$, *c*-$C_6H_{11}CH_2CH_2CO$, *c*-C_6H_{11}), 1.50-1.61 (5 H, m, c-C_6H_{11}), 2.04-2.33 (3 H, m, *c*-$C_6H_{11}CH_2CH_2CO$, SiCH), 2.57 (1 H, dd, J = 6.0, 18.6 Hz, c-$C_6H_{11}CH_2CH_2COCH_AH_B$-), 2.71 (1 H, dd, J = 6.4, 18.6 Hz, c-$C_6H_{11}CH_2CH_2COCH_AH_B$-), 3.48 (1 H, d, J = 5.6 Hz, CH[$CO_2CH_2CH_3$]$_2$), 4.04 (4 H, q, J = 7.2 Hz, 2 × CH_3CH_2OCO), 7.27 -7.32 (3 H, m, Ph), 7.46-7.50 (2 H, m, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ = –3.5, –3.1, 13.8 (2 C), 20.3, 26.2 (2 C), 26.5, 31.0, 33.0 (3 C), 40.0, 40.9, 51.9, 61.0, 61.1, 127.6 (2 C), 129.0, 134.2 (2 C), 137.4, 169.4, 169.8, 210.0; Anal. Calcd for $C_{26}H_{40}O_5Si$: C 67.79, H 8.75 %. Found: C, 67.75; H, 8.72%; $[\alpha]_D^{23}$ +3.62 (*c* 2.76, $CHCl_3$); HPLC: Daicel chiralpak AD-H, 2-propanol/ hexane (0.7/99.3), flow rate = 1.0 mL/min, t_R(3*S*)-**79i** 14.0 min (95.27%), t_R(3*R*)-**79i** 23.7 min (4.73%).

Ethyl (3*S*)-11-benzyloxy-3-dimethylphenylsilyl-2-ethoxycarbonyl-5-oxoundecanoate 79j: Prepared from **75** (153 mg, 0.5 mmol) and 8-benzyloxy-2-octanone (386 mg, 2.5 mmol), according to *General Procedure* **3.4.2.III.** Yield: 248 mg (92%); IR (neat): 2980, 2936, 2857, 1749, 1729, 1368, 1250, 1151, 1110, 818, 736 cm^{-1}; ^1H NMR (200 MHz,

$CDCl_3$): δ = 0.32 (3 H, s, CH_3Si), 0.33 (3 H, s, CH_3Si), 1.16-1.64 (8 H, m, [CH_2]$_4$CH_2OBn), 1.20 (6 H, t, J = 7.2 Hz, 2 × CH_3CH_2OCO), 2.05-2.23 (2 H, m, COCH_2[CH_2]$_5$OBn), 2.30 (1 H, q, J = 6 Hz, SiCH), 2.56 (1 H, dd, J = 5.8, 18.6 Hz, CH_AH$_B$CO), 2.76 (1 H, dd, J = 6.4, 18.6 Hz, CH$_A$$H_B$CO), 3.43 (2 H, t, J = 5.6 Hz, BnOCH_2), 3.49 (1 H, d, J = 5.6 Hz, CHCHSi), 4.00-4.11 (4 H, m, 2 × CH$_3$CH_2OCO), 4.48 (2 H, s, OCH_2Ph), 7.28-7.34 (8 H, m, Ar), 7.47-7.52 (2 H, m, Ar); ^{13}C NMR (50 MHz, $CDCl_3$): δ = –3.5, –3.2, 13.9 (2 C), 20.1, 23.6, 25.9, 28.9, 29.5, 40.9, 42.4, 51.8, 61.1, 61.3, 70.3, 72.8, 127.4, 127.5 (2 C), 127.6 (2 C), 128.3 (2 C), 129.0, 134.2 (2 C), 137.3, 138.6, 169.5, 169.8, 209.8; ESI-HRMS: Found: M^+ + Na, 563.2819. $C_{31}H_{44}O_6SiNa$ requires M^+ + Na, 563.2799; $[\alpha]_D^{26}$ = +4.95 (*c* = 1.82, MeOH); HPLC: Daicel chiralpak AD-H, 2-propanol/ hexane (5/100), flow rate = 1.0 mL/min, t_R(3*R*)-**79j**11.45 min (4.33%), t_R(3*S*)-**79j** 14.3 min (95.67%).

Ethyl (3*S*)-3-dimethylphenylsilyl-6,6-dimethoxy-2-ethoxycarbonyl-5-oxohexanoate 79k: Prepared from **75** (153 mg, 0.5 mmol) and pyruvaldehyde dimethyl acetal (0.363 mL, 3.0 mmol), according to *General Procedure* **3.4.2.III.**; Yield: 165 mg (78%) ; IR (neat): 3019, 2982, 2834, 1742, 1729, 1251, 1216, 1154, 1073, 1033 ,817 cm^{-1}; ^{1}H NMR 200 MHz, $CDCl_3$): δ = 0.33 (3 H, s, CH_3Si), 0.34 (3 H, s, CH_3Si), 1.19 (3 H, t, J = 7.2 Hz, CH_3CH_2OCO), 1.20 (3 H, t, J = 7.2 Hz, CH_3CH_2OCO), 2.29 (1 H, q, J = 6 Hz, SiCH), 2.76 (1 H, dd, J = 5.8, 19.8 Hz, CH_ACH$_B$CO), 2.88 (1 H, dd, J = 6.2, 19.8 Hz, CH$_A$$H_B$CO), 3.28 (3 H, s, OMe), 3.29 (3 H, s, OMe), 3.49 (1 H, d, J = 6 Hz, CHCHSi), 3.99-4.12 (4 H, m, 2 × CH$_3$CH_2OCO), 4.29 (1 H, s, CHCO), 7.29-7.34 (3 H, m, Ph), 7.48-7.53 (2 H, m, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ = –3.5, –3.3, 13.9 (2 C), 19.5, 36.2, 51.8, 54.3, 54.4, 61.2, 61.3, 103.5, 127.6 (2 C), 129.0, 134.3 (2 C), 137.2, 169.4, 169.7, 204.6; Anal. Calcd

for $C_{21}H_{32}O_7Si$: C 59.41, 7.60%; found C 59.79, H 4.01, N 8.00%. $[\alpha]_D^{27}$ = +4.0 (*c* = 1.75, MeOH); HPLC: Daicel chiralpak AD-H, 2-propanol/ hexane (1/99), flow rate = 1.0 mL/min, t_R(3*S*)-**79k** 30.85 min (92.70%), t_R(3*R*)- **79k** 33.62 min (7.30%).

Ethyl (3*S*)-3-dimethylphenylsilyl -5-oxotetradecanoate 92

A stirred solution of the keto ester **79**f (170 mg, 0.357 mmol) sodium chloride (40 mg, 0.68 mmol) and water (1 mL) in DMSO (40 mL) was heated at 165 °C under nitrogen for 6 h. The reaction mixture was diluted with water (200 mL) and extracted with ether. The organic extract was washed with water and with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, hexane/EtOAc: 95/5) to give the keto ester **92**.

Yield: 123 mg (85%); IR (neat): 2956, 2927, 2855, 1724, 1718, 1216, 1112, 1036, 816, 754 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.29 (3 H, s, C*H*$_3$Si), 0.30 (3 H, s, C*H*$_3$Si), 0.87 (3 H, t, *J* = 6.5 Hz, [CH_2]$_8$C*H*$_3$), 1.10-1.33 (15 H, m, [C*H*$_2$]$_7$CH$_3$, C*H*$_3$CH$_2$OCO), 1.40-1.52 (2 H, m, -CH_2-), 1.87-2.01 (1 H, m, SiCH), 2.12-2.44 (6 H, m, C*H*$_2$COC*H*$_2$, C*H*$_2$CO$_2$Et), 3.95-4.06 (2 H, q, CH$_3$C*H*$_2$OCO), 7.32-7.37 (3 H, m, Ph), 7.46-7.51 (2 H, m, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ = –4.5, –4.3, 14.1, 17.2, 22.7, 23.8, 29.2 (2 C), 29.3 (2 C), 29.4 (2 C), 31.9, 34.7, 42.7, 60.3, 127.8 (2 C), 129.2, 133.9 (2 C), 136.9, 173.6, 210.5; EI-MS: *m*/*z* 389 (M^+-CH_3, 13%), 371 (13), 327 (20), 135 (100), 78 (43); $[\alpha]_D^{25}$ = –6.93 (*c* = 2.31, $CHCl_3$); HPLC: Daicel chiralpak AD-H, 2-propanol/ hexane (1/99), flow rate = 1.0 mL/min, t_R(3*S*)-**92** 9.9 min (94.87%), t_R(3*R*)-**92** 15.3 min (5.13%).

Methyl (3*S*)-3-dimethylphenylsilyl -5-oxotetradecanoate 93

Lithium hydroxide hydrate (18 mg, 0.43 mmol) was added to a stirred solution of the ethyl ester **87** (92 mg, 0.228 mmol) in 5% aqueous methanol (2 mL) at room temperature. After 6h, the solvent was evaporated under reduced pressure and the residue was diluted with water (1 mL), acidified with dil. HCl and extracted with ethyl acetate. The extract was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was esterified with ethereal diazomethane, evaporated the solvent and the residue was chromatographed to give the methyl ester **93**.

Yield: 80 mg (90%); IR (neat): 2952, 2925, 2854, 1736, 1715, 1250, 1112, 816, 774, 701 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.29 (6 H, s, Si[CH_3]$_2$), 0.86 (3 H, t, J = 6.4 Hz, $CH_3CH_2CH_2$-), 1.12–1.38 (12 H, s, br, CH_2[CH_2]$_6$$CH_3$), 1.41–1.50 (2 H, m, $COCH_2CH_2$), 1.87– 2.00 (1 H, m, SiC*H*), 2.12–2.43 (6 H, m, CH_2COCH_2, $CH_2CO_2CH_3$), 3.55 (3 H, s, OCH_3), 7.33–7.36 (3 H, m, Ph), 7.45-7.5 (2 H, m, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ = –4.6, –4.4, 14.0, 17.2, 22.6, 23.7, 29.1, 29.2, 29.3 (2 C), 31.8, 34.5, 42.6 (2 C), 51.4, 127.8 (2 C), 129.2, 133.9 (2 C), 136.8, 173.9, 210.4; $[\alpha]_D^{24}$ = –0.8 (*c* = 0.8, $CHCl_3$); lit.[122] $[\alpha]_D^{21}$ = –0.8 (*c* = 0.79, $CHCl_3$).

Ethyl 2-ethoxycarbonyl-3-Phenyl-2-propenoate 94a

A solution of benzaldehyde (2.54 mL, 25 mmol) and diethyl malonate (3.80 mL, 25 mmol), piperidiniumbenzoate (1g, 5mmol,) in benzene (30 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 **94a**.

Yield: 4.12 g (66%); IR (neat): 2983, 1728, 1630 cm^{-1}; ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 1.28 (3 H, t, *J* = 7.1 Hz, *Me*CH_2OCO), 1.33 (3 H, t, *J* = 7.1 Hz, *Me*CH_2OCO), 4.30 (2 H, q, *J* = 7.1 Hz, MeC*H*$_2$OCO), 4.34 (2H, q, *J* = 7.1, MeC*H*$_2$OCO), 7.30-7.60 (5 H, m, Ar), 7.74 (1H, s, C=C*H*Ar); ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 13.54, 13.80, 61.30, 126.07, 128.48, 129.11, 130.23, 132.58, 141.69, 163.73, 166.29.

Ethyl 2-ethoxycarbonyl-3-Phenyl-2-propenoate 94b

A solution of 4-fluorobenzaldehyde (3.2 mL, 30 mmol) and diethyl malonate (4.56 mL, 30 mmol), piperidiniumbenzoate (1.86 g, 9 mmol,) in benzene (30 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 anhy.$MgSO_4$ and evaporated. The residue was purified by column chromatography on silica using hexane/EtOAc (95/5) to give the diester **94b.**

Yield: 5.58 g (70%); IR (neat): 2983, 2944, 2905, 1729, 1633, 1602, 1509, 1260, 1161, 1064, 835, 757 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.32 (6 H, t, *J*= 7.2 Hz, 2 X C*H*$_3$CH$_2$OCO), 4.31 (4 H, m, 2 X CH$_3$C*H*$_2$OCO), 7.01-7.09 (2 H, m, Ar), 7.41-7.48 (2 H, m, Ar), 7.67 (1 H, s, C=C*H*Ar); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.8, 14.1, 61.6, 61.7, 115.9 (d, *J*=87 Hz) 126.0, 129.1(d, *J* = 12.2 Hz), 131.5 (*J* = 34.2 Hz), 140.7, 161.3, 163.9, 166.4 (*J* = 40.6 Hz),

3.6.3 Reaction of methyl ethyl ketone with diethyl 4-flurobenzylidene malonate

2-Butanone (0.55 mL, 6 mmol, 12 equiv) was added to a stirred mixture of diethyl 4-flurobenzylidene malonate **94b** (133 mg, 0.5 mmole, 1 equiv), pyrrolidine **63** (23 mg, 0.15 mmol, 0.3 equiv) and trifluoroacetic acid (4 μL, 0.05 mmol, 0.1 eqiuv) in NMP (2 mL) at 28 °C. After 5 days, the reaction mixture was diluted with water and extracted with EtOAc/hexane (1/1). 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 a mixture of regioisomeric ketones **95** + **96** (30 mg, 18%), a byproduct **97** (21 mg, 23%) and unreacted diethyl 4-flurobenzylidene malonate (60 mg, 45%).

Ratio of **95:96** = 58:42 (from ^{1}H NMR)

^{1}H NMR (200 MHz, $CDCl_3$) of a mixture **95** and **96** (**95:96**= 58:42): δ = 0.87 (3 H, d, *J* = 7.2 Hz, *Me*CH- from **96**), 0.91 (3 H, t, *J* = 7.2 Hz, CH_3CH_2CO- from **95**), 1.01 (3 H, t, *J* = 7.2 Hz, C*H*$_3$CH$_2$OCO- from **96**), 1.02 (3 H, t, *J* = 7.2 Hz, C*H*$_3$CH$_2$OCO- from **95**), 1.23 (3 H, t, *J* = 7.2 Hz, C*H*$_3$CH$_2$OCO- from **96**), 1.24 (3 H, t, *J* = 7.2 Hz, C*H*$_3$CH$_2$OCO- from **95**), 2.17-2.41 (2 H, m, MeC*H*$_2$CO- from **95**), 2.20 (3 H, s, MeCO- from **96**), 2.80-2.94 (2 H, m, MeCH$_2$COC*H*$_2$- from **95**), 2.96-3.14 (1 H, m, MeCOC*H*- from **96**), 3.65 (1 H, d, *J* = 10 Hz, ArCHC*H*- from **95**), 3.77-4.02 (4 H, m, C*H*$_3$CH$_2$OCO, ArC*H*, ArCHC*H*- from **96**), 4.09-4.23 (2 H, m, C*H*$_3$CH$_2$OCO), 6.89-6.99 (2 H, m, Ar), 7.14-7.24 (2 H, m, Ar).

^{1}H NMR (200 MHz, $CDCl_3$) of **97** δ = 1.16 (3 H, t, *J* = 7.4 Hz, C*H*$_3$CH$_2$CO-), 2.68 (2 H, q, *J* = 7.4 Hz, CH$_3$C*H*$_2$CO-), 6.46 (1 H, d, *J* = 16.2 Hz, CH=C*H*CO-), 7.08 (1 H, d, *J* = 16.2 Hz, C*H*=CHCO-), 7.02-7.13 (1 H, m, Ar), 7.47-7.56 (3 H, m, Ar).

Chapter 4

Synthetic Applications of β-Silyl-δ-keto Esters for Natural Products and Their Analogs

4.1 Introduction

Chiral heterocyclic compounds are widely found as natural products[125] and have a wide range of biological properties including important pharmacological activities. Amongst them, chiral hydroxylated δ-lactones have 'privileged' structures.[126] In many cases they show high efficacy as antibacterial,[127] antiviral[128] anticancer,[129] immunosuppressive,[130] and cholesterol-lowering (HMGR inhibitors) agents.[131] The majority of statin drugs—such as Lipitor **98** and Zocor **99** (**Fig**. **4.1**), for example, contain either a β-hydroxy-δ-lactone moiety or the corresponding open-chain δ-hydroxy carboxylate form (**Fig 4.1**).[132]

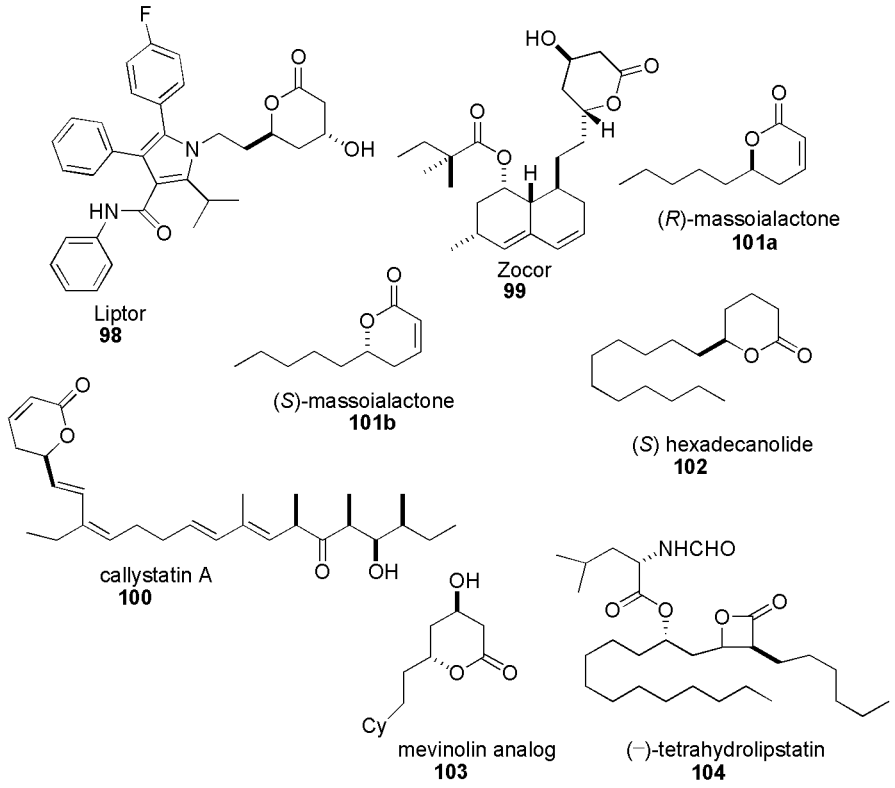


Fig. 4.1 β-hydroxy-δ-lactone based natural products and statin drugs molecules

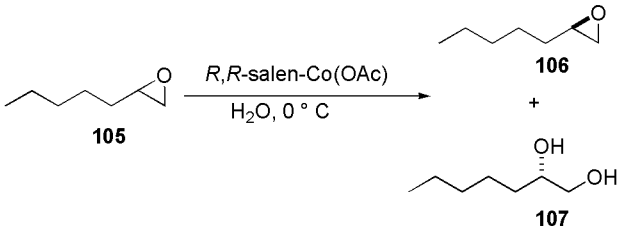
Also, there are several δ-lactones such as massoialactone **101a**, **101b**, hexadecanolide **102** and mevinolin **99** and its analogs **103**, which are well known for their biological activities. In addition, δ-lactones are very useful building blocks for the synthesis of many other

bioactive compounds.[133] One such example is tetrahydrolipstatin **104**, a member of the lipstatin class of β-lactone.

Massoialactone

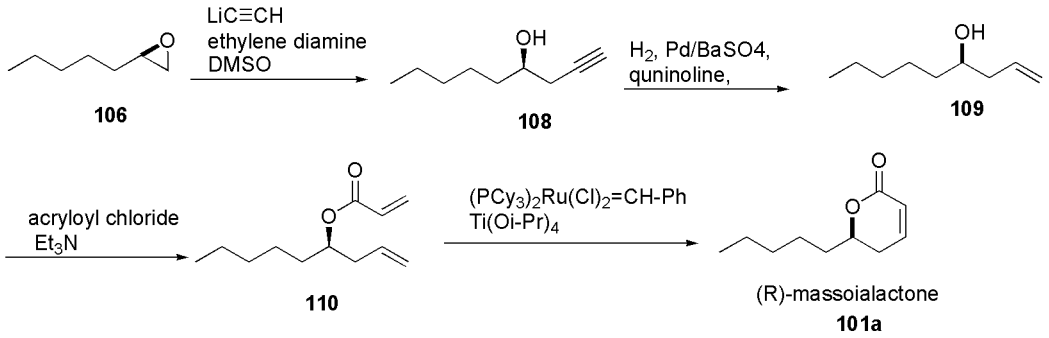
Massiolactone is isolated for the first time from the bark of *Cryptocarya massoia* by Abe[134] in 1937. It is a powerful skin irritant and produces systolic standstill in frog heart muscle.[135] Massioalactone (**Fig 4.1**) is the allomone of the two species of formicine ants belonging to the *Camponotus* genus collected in Western Australia. This lactone has also been isolated from cane molasses and jasmine blossoms as flavour substances. Owing of their specific odour impression and low threshold concentration, they play an important role as flavouring materials. Therefore practical synthesis of this lactone is on demand. A few recent reports for the synthesis of massoialactone **101a,b** (**Fig 4.1**) are briefly discussed in the following.

Kumar et.al.[136] reported the synthesis of both the (*R*) and (*S*)-massoialactone using Jacobsen's hydrolytic kinetic resolution[137] of a terminal epoxide. They started the synthesis from a racemic epoxide **105**. The hydrolytic kinetic resolution was performed on epoxide **105** (**Scheme 4.1**)[136] which gave the *R*-epoxide **106** and a diol **107**. The (*R*)-epoxide was the precursor of (*R*)-massoialactone **101a** whereas the diol **107** was the precursor of (*S*)-massoialactone **101b**.



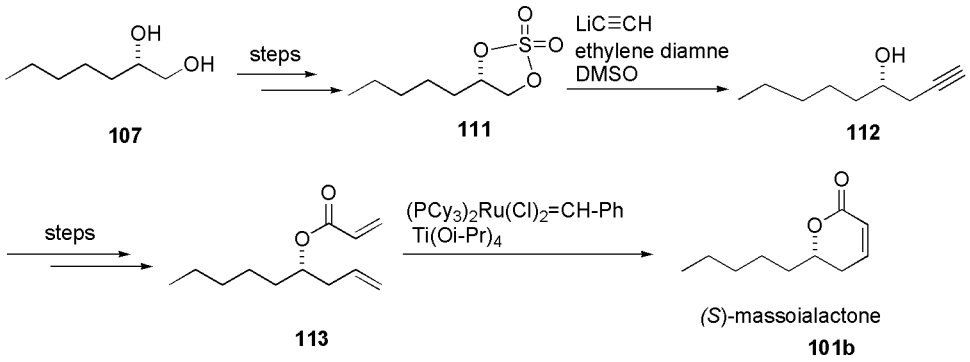
Scheme 4.1

The enantiomerically enriched epoxide **106** was converted to a propargyl alcohol **108** which was transformed to homoallylic alcohol **109**.[136] The alcohol **109** was further esterified to afford the diene **110**. The subsequent ring closing metathesis of the diene gave (*R*)-massoialactone **101a** (**Scheme 4.2**).



Scheme 4.2

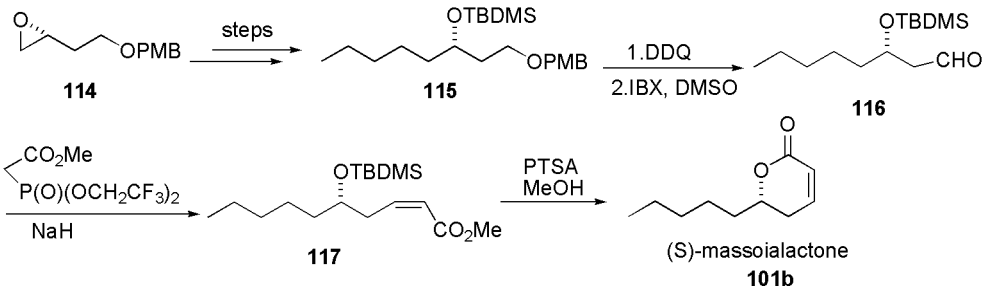
On the other hand the diol **107** was converted to cyclic sulphate **111** which on regioselective ring opening furnished the alcohol **112**. Hydrogenation followed by esterifiaction of the alcohol **112** leads to the diene **113**. Ring closing metathesis of the diene afforded the target molecule (*S*)-massoialactone **101b**.



Scheme 4.3

A recent report[138] described the synthesis of both (*R*) and (*S*)-massoialactones from an epoxide **114**. The synthesis of the (*S*)-massoialactone began with the (*R*) epoxide **114**.

Ring opening of the epoxide **114** followed by the protection of the hydroxyl functionality leads to silyl ether **115**. Removal of one of the protecting group and subsequent oxidation afforded to the aldehyde **116**. Homologation of this aldehyde **116** with methyl(bistrifluoroethyl)phosphonoacetate gave (*Z*)-unsaturated ester **117**. Deprotection of the silyl ether functionality and subsequent lactonisation furnished the target molecule (*S*)-massoialactone **101b** (**Scheme 4.4**). In a similar fashion, the (*R*)-massoialactone was synthesized starting from the (*S*)-epoxide.

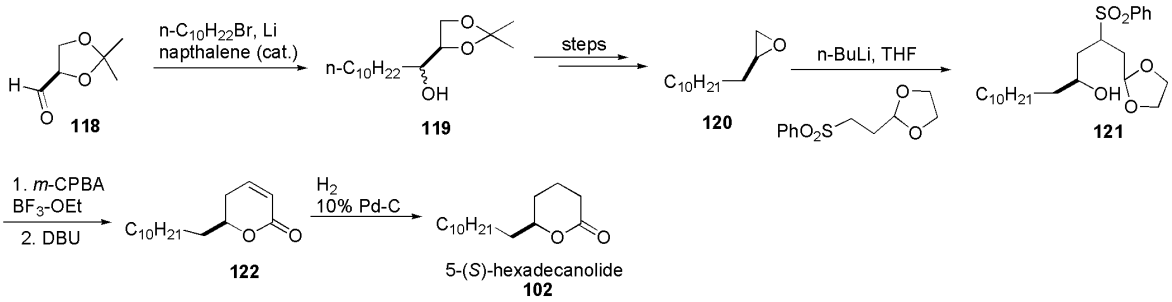


Scheme 4.4

(*S*)-5-Hexadecanolide

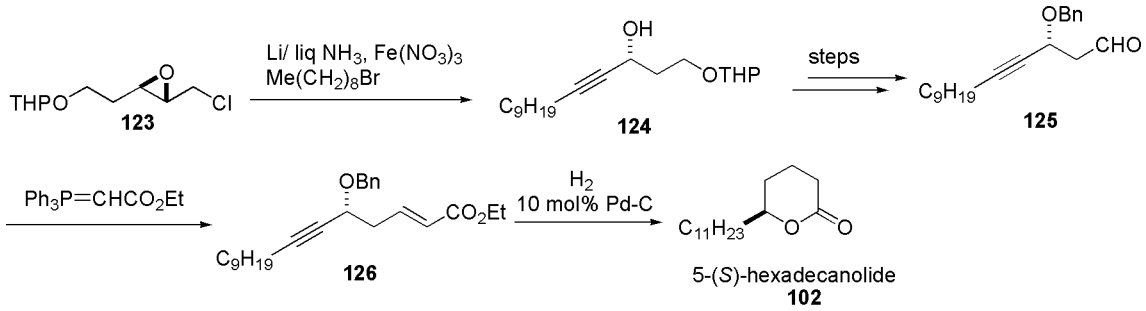
(*S*)-5-hexadecanolide **102** (**Fig 4. 1**) was isolated from the mandibular glands of the oriental hornet, *Vespa* orientalis[139] as a pheromone to stimulate the workers to construct queen cell. This lactone is also found in some fruits, such as apricots and peaches. The important physiological activities of 5-hexadecanolide have led to a number of synthetic procedures reported in the literature. Singh et.al.[140] reported the synthesis of (*S*)-5-hexadecanolide **102** from a mannitol derived aldehyde **118**. The (*R*)-acetonide **118**, synthesized from mannitol, was treated with 1-bromodecane in the presence of lithium and naphthalene to furnish the alcohol **119**. This alcohol was then transformed to a chiral epoxide **120** in four steps. The ring opening of the epoxide provided the hydroxyl acetal

121 which was transformed to an unsaturated δ-lactone **122**. Hydrogentation of the double bond in **122** provided the desired (*S*)-5-hexadecanolide **102** (**Scheme 4.5**).[140]



Scheme 4.5

Sabitha et. al.[141] reported the synthesis of (*S*)-5-hexadecanolide **102** starting from 2,3-epoxy chloride **123**. The epoxy chloride **123** was subjected to base-induced ring opening followed by alkylation resulting to an alkynol **124**. The secondary hydroxyl group of alkynol **124** was protected as benzyl ether and a selective removal of the tetrahydropyranyl protection followed by oxidation of the resulting primary alcohol leads to the aldehyde **125**. The resulting aldehyde **125** underwent Horner-Wadsworth-Emmons reaction gave α, β-unsaturated ester **126**, which on hydrogenation underwent a sequence of reactions finally affording the target molecule **102** (**Scheme 4.6**).[141]

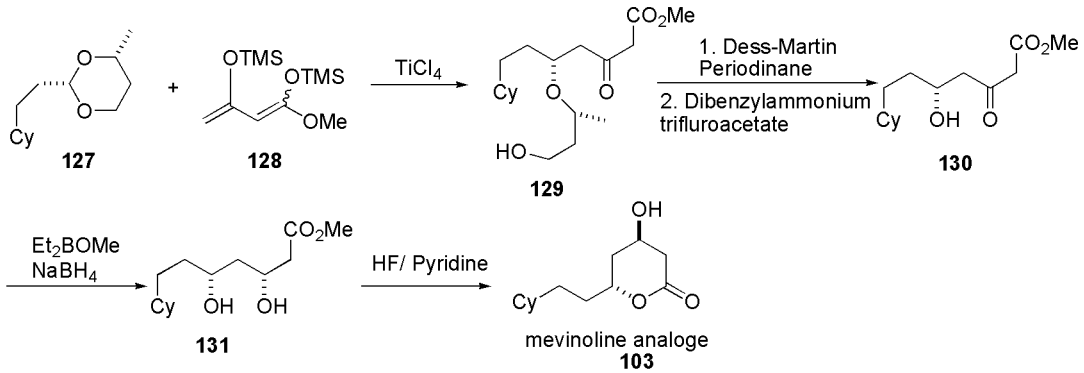


Scheme 4.6

Mevinoline

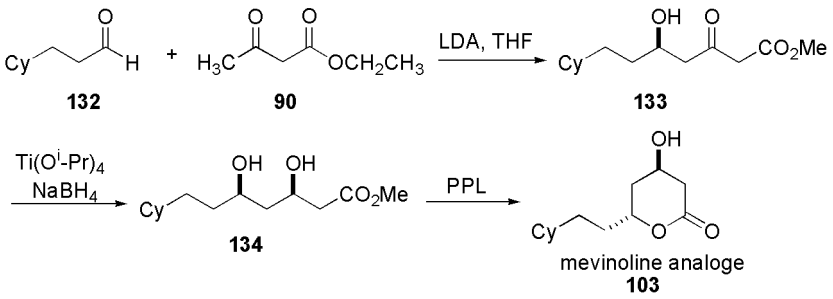
The natural products compactine and mevinolin **99** (**Fig 4.1**)[142]are extremely potent reversible inhibitors of (3*S*)-3-hydroxy-3-methylglutaryl coenzyme A (HMGCoA) reductase, the rate-limiting enzyme in the cholesterol biosynthetic pathway.[131] The beneficial effect displayed by mevinoline **99** in reducing serum cholesterol levels and its consequent potential for the mitigation of antherosclerosis, has elicited much synthetic interest both in the natural product itself and its structurally simplified congeners. Despite its rather simple structure, the lactone moiety of the mevinic acids has proved to be essential for the biological activity of such compounds.[143] For this reasons, many effort have been made to discover and synthesize new analogue of **103** (**Fig 4.1**). In some cases such analogues have proven to be more effective than natural mevinic acids.

Johnson group[144] reported the synthesis of an analogue of mevinoline **103** (R = cyclohexyl i.e. Cy) starting from the acetal **127**. The coupling between acetal and 1,3-bis(trimethylsilyloxy)-1-methoxybuta-1,3-diene **128** gave the alcohal **129**. Removal of the chiral auxiliary afforded the aldol product **130** that was reduced to diol **131**. Saponification and lactonisation gave the desired lactone **103** (**Scheme 4.7**)[144]



Scheme 4.7

Bonini et. al.[145] have achieved the synthesis of mevinoline analoge **103** strating from the aldol product **133**. The key step involves the enzymatic resolution of the *syn* diol. The aldol product **133** was obtained from direct aldol reaction of the acetoacetate **90** with the aldehyde **132** (**Scheme 4.8**). The resulting aldol product **133** was selectively reduced to the *syn* diol **134**. The enzymatic lactonisation of the *syn* diol **134** afforded the desired lactone **103**.[145]



Scheme 4.8

(−)-Tetrahydrolipstatin

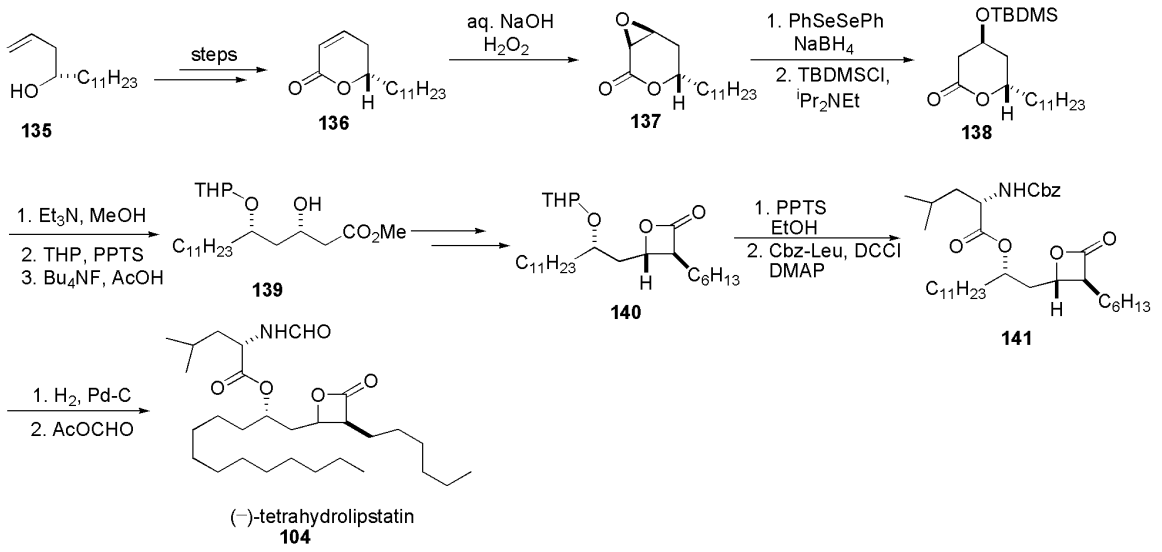
Tetrahydrolipstatin is a microbial agent. It is also known to be a potent and irreversible inhibitor of pancreatic lipase.[146] It was isolated in 1987, from the bacterium *Streptomyces toxytricini*. This lipase enzyme is responsible for the digestion of fat in the diet of humans.[147] The strained β-lactone functionality of **104** is critical to its lipase inhibitory properties. The inactivation mechanism involves an irreversible acylation of the active serine residue of pancreatic lipase by the β-lactone moiety.[148] Therefore it slows down the hydrolysis of triglycerides and absorption of dietary fat by the small intestine. Recent clinical studies have revels that treatment with **104** along with diet modifications has lead to sustained weight loss in humans. Futhermore, tetrahydrolipstatin was recently shown to be a potent fatty acid synthesis (FAS) inhibitor. FAS is an enzyme responsible for the

synthesis of fatty acids in many human carcinomas and is required for tumor cell survival, making FAS inhibitor a promising drug for the treatment of cancer. Hoffman-La Roche Laboratories have introduced (−)-tetrahydrolipstatin under the trade name Xenical® as an anti-obesity agent. The important biological properties along with its unique structural features have stimulated interest in the synthesis of **104**. Some of the important approaches are briefly discussed in the following.

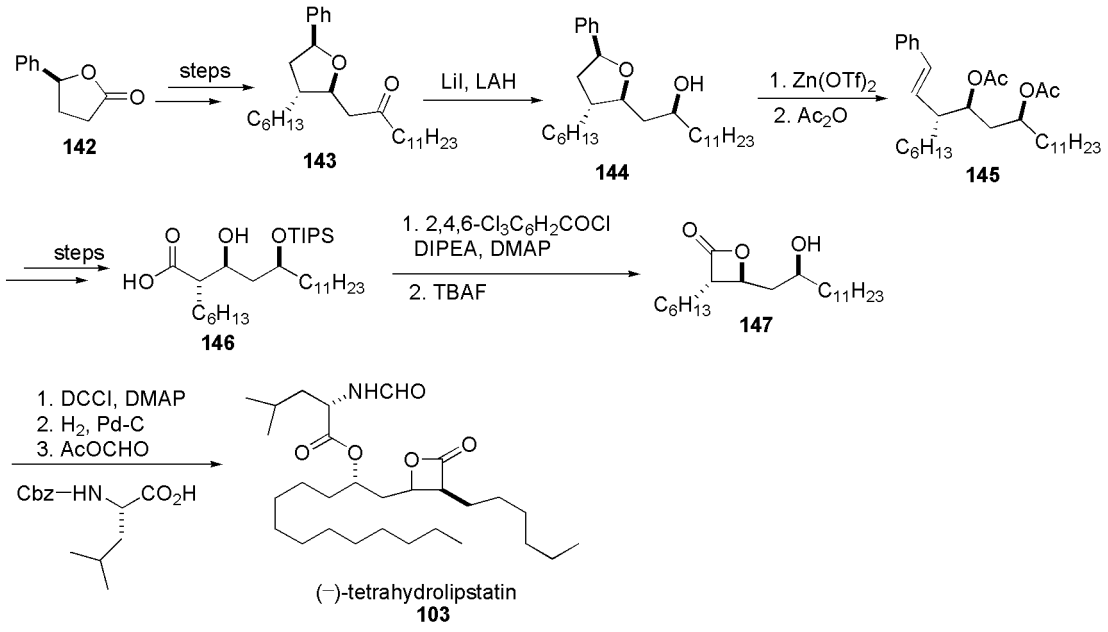
Ghosh et.al.[149] reported the synthesis of **104** strating from a homoallylic alcohol **135**. The alcohol was prepared with 92% ee by Keck's enantioseelective allylation[150] of dodecanal employing a catalytical amount of (*R*)-BINOL and Ti(OPr^i). The alcohol was converted to α,β-unsaturated δ-lactone **136** in two steps which was then converted to the epoxide **137**. Regioselective reduction of the epoxide functionality followed by TBDMS protection lead to the lactone **138**. The lactone **138** was then converted into the β-hydroxy ester **139** in three steps. Asymmetric alkylation, saponifiaction followed by $PhSO_2Cl$ treatment on **139** leads to the β-lactone **140**. The removal of THP protection group followed by esterifiaction with Cbz-leu provided the Cbz derivative **141**. Catalytic hydrogenation of **141** followed by *N*-formylation of the resulting amine with formic acetic anhydride (AcOCHO) furnished the synthetic (−)-tetrahydrolipstatin **104** (**Scheme 4.9**).[149]

The same group[150] has shown the synthesis of **104** starting from the γ-lactone **142**. This lactone was converted to a tetrahydrofuran derivative **143** in two steps. Reduction of the ketone **144** followed by ring opening of the alcohol in presence of Ac_2O leads to diacetoxy styrene derivative **145**. Oxidative cleavage of the styrene moiety resulted into the aldehyde which was further oxidized to the corresponding acid **146**. The hydroxyl acid

146 was then converted to β-lactone **147**. Esterifiaction of this hydroxy β-lactone with Cbz-leuOH followed by catalytic hydrogenation and *N*-formylation of the resulting amine with formic acetic anhydride (AcOCHO) furnished the synthetic (−)-tetrahydrolipstatin **103** (**Scheme 4.10**).[151]

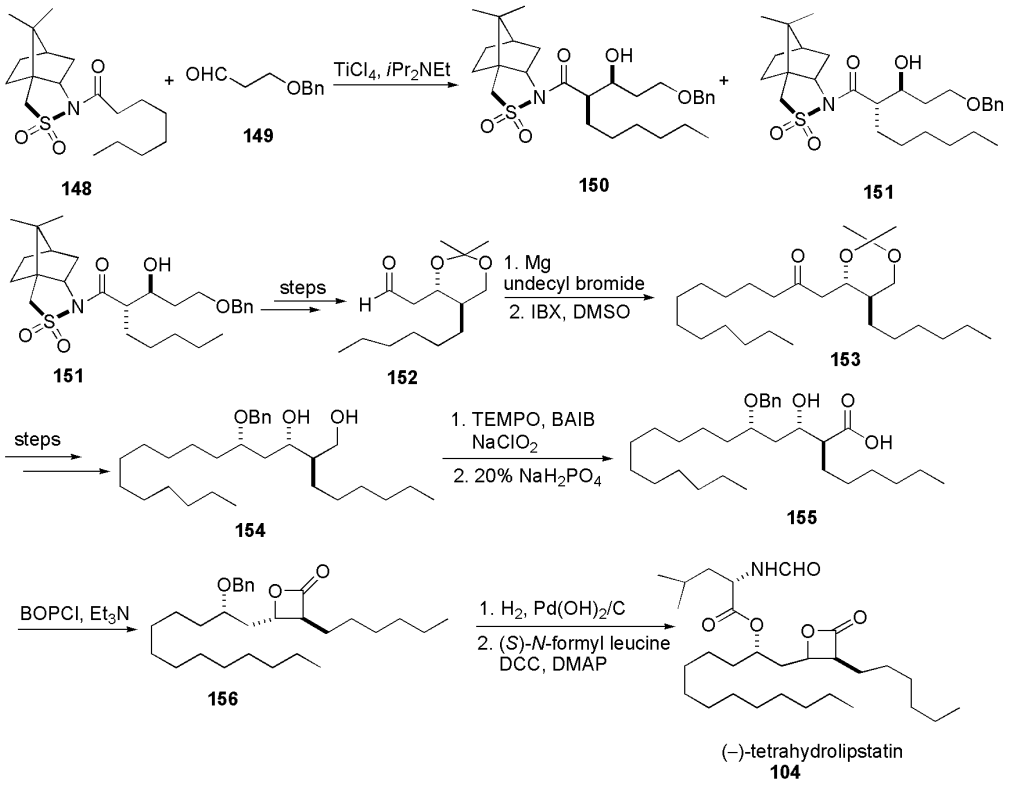


Scheme 4.9



Scheme 4.10

Kumaraswamy et.al.[152] described the synthesis of (−)-tetrahydrolipstatin **103** using Oppolzer's sultam directed aldol reaction as the key step. The synthesis was strated with the anti-aldol product **151** which was obtained by the aldol reaction of acylsultum **148** and benzyoloxy propanal **149**. The reductive cleavage of the **151** followed by oxidation leads to aldehyde **152**, which was treated with a Grignard reagent and the derived alcohol on oxidation leads to the ketone **153**. Reduction of the ketone **153** followed by protection of the hydroxyl group and cleavage of the acetonide furnished the corresponding diol **154**. Chemoselective oxidation of the primary alcohol in **154** with TEMPO and bis(acetoxy)iodobenzene (BAIB) followed by further oxidation of the corresponding aldehydes with perchlorite/ dihydrogen orthophosphate ended up with β-hydroxy acid **155**. The hydroxyl acid **155** was lactonized with bis(2-oxo-3-oxazolidinyl)phosphinic chloride (BOPCl) to the β-lactone **156**. Debenzylation of this β-lactone **156** gave the free alcohol which was coupled with (*S*)-*N*-formylleucine furnished the synthetic (−)-tetrahydrolipstatin **104** (**Scheme 4.11**).[152]



Scheme 4.11

4.2 Present work

Carbonyl compounds having a silyl group at β-position are popular targets because of their versatile nature and are also excellent surrogate for the acetate aldol reaction. We are interested for the asymmetric synthesis of intermediates of type **61** or **62** (**Fig 4.2**) containing a silicon group positioned at β to both a ketone and an ester functionalities because they could be synthons for β-hydroxy-δ-lactone. The asymmetric synthesis of intermediates of type **61 or 62** (**Fig 4.2**) containing a silicon group positioned β to both a carbonyl and ester functionality has already been described in the **Chapter 3**. The dimethyl(phenyl)silyl group was purposely chosen to take advantage of its easy installation, manipulations, unique reactivity, regio- and stereo-chemical control offered by a silicon group in general,[91]and as a masked hydroxyl group[90]. This ketodiesters could be easily converted to β-silyl-δ-keto monoesters **62** (**Fig. 4.2**). The ketoesters can further be

parlayed to β-hydroxy-δ-lactone based natural products and their analogs with well known biological activities. Synthesis of advanced intermediates[120] of some of the natural products like massoialactone **101**, hexadecanolide **102**, mevinolin analogs **103** and tetrahydrolipstatin **104** are discussed below.

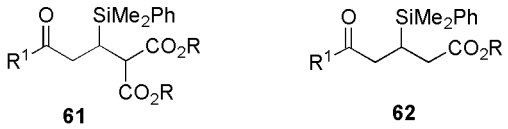
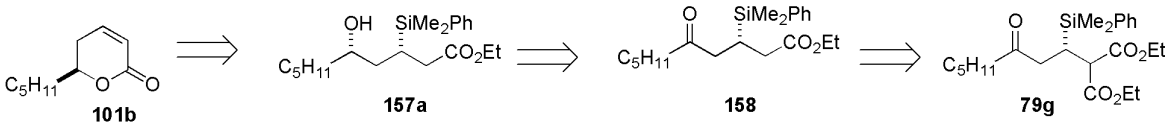


Fig. 4.2

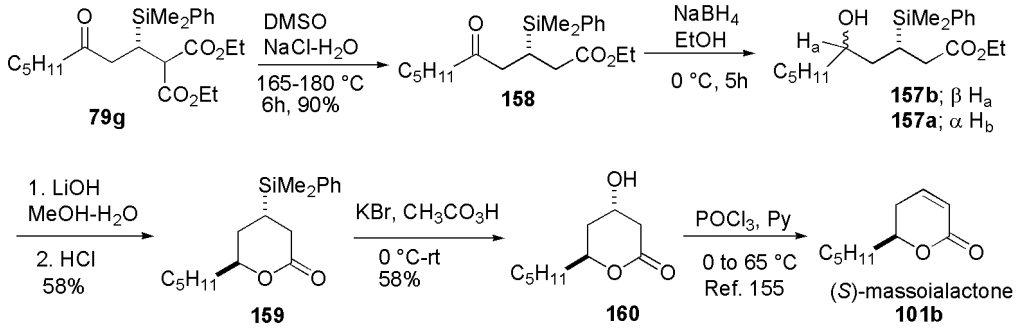
4.2.1 Formal total synthesis of (*S*)-Massoialactone

A number of synthetic procedures are available in the literature for the synthesis of both the natural **101a** and unnatural isomers **101b** of massoialactone as discussed in the introduction part of this chapter. These procedures mainly utilized the chiral pool as the starting material or the resolution of the lactone precursors. The major draw backs are (i) multiple steps and (ii) low yield in the resolution process of the lactone precursor. We formulated[120] an efficient organocatalyzed and silicon directed synthesis of (*S*)-massoialactone **101b**, the antipode of the naturally available one. The retrosynthetic sequence of the (*S*)-massoialactone is shown in scheme (**Scheme 4.12**). The target compound could be achieved from a δ-hydroxy ester **157** through lactonisation reaction. The δ-hydroxy ester **157** could be achieved by a Si-controlled reduction of the ketoester **158**, which can be obtained from the diester **79g**.



Scheme 4.12

The forward synthesis of the known intermediate, the hydroxyl lactone **160**, for the synthesis of (*S*)-massoialactone **101b** is shown in **Scheme 4.13**. The required diester **79g**[115] was obtained by an organocatalytic Michael addition of 2-heptanone on β-silylmethylene malonate **75** as described in **Chapter 3**. The keto diester **79g** was subjected under Krapcho deethoxycarbonylation[121] to give the β-silylated keto ester **158**. This ester was subjected to a silicon-directed stereoselective reduction[153] with sodium borohydride in ethanol at 0 °C to give an inseparable mixture of diastereomeric alcohols **157a** and **157b** (**157a**/**157b** = 80:20). The hydroxy ester mixture was then hydrolyzed and the intermediate hydroxy acids underwent a smooth cyclization to give the major lactone **159**. The dimethyl(phenyl)silyl group in **159** was then converted to the hydroxy group following Fleming oxidation[154] using potassium bromide and peracetic acid with retention of configuration leading to (–)-hydroxy lactone **160** (**Scheme 4.13**), an advanced intermediate for the unnatural massoialactone.[120] The relative and absolute stereochemistry of the hydroxy and the alkyl groups were assigned from the ^{1}H and ^{13}C (**Fig. 4.3** and **Fig. 4.4**) chemical shift values, and comparing the specific rotation value ($[\alpha]_D^{28}$ = –34.7, *c* 1.5, $CHCl_3$; *lit,*[155] $[\alpha]_D$ = +29.4, *c* 1.4, $CHCl_3$ for the antipode of **101b**).



Scheme 4.13

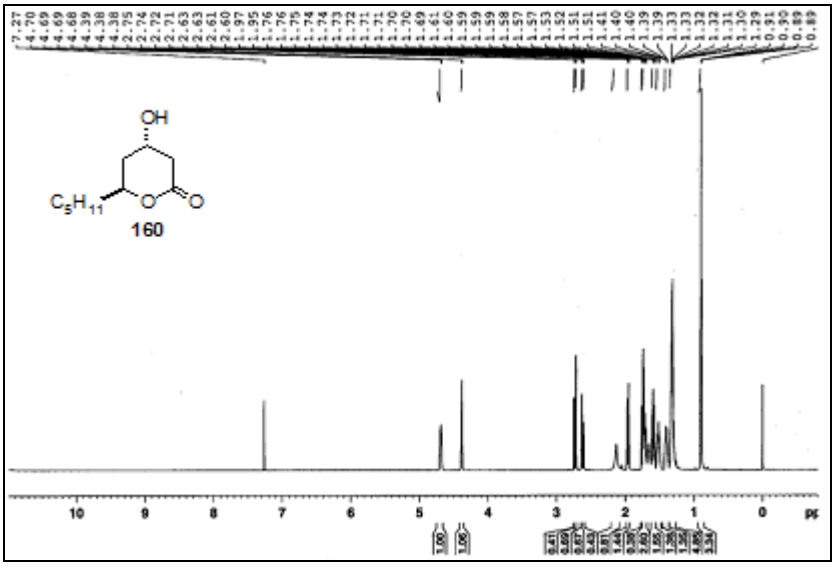


Fig. 4.3. ^{1}H NMR spectrum of 160

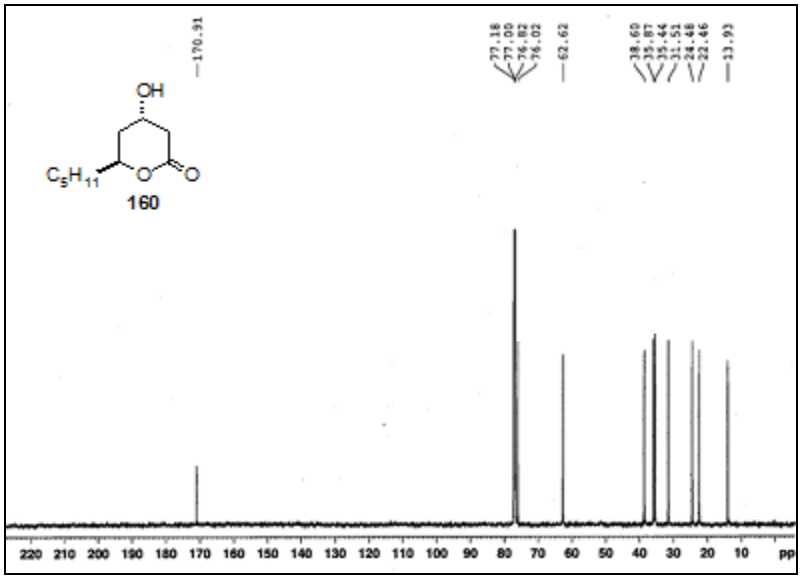
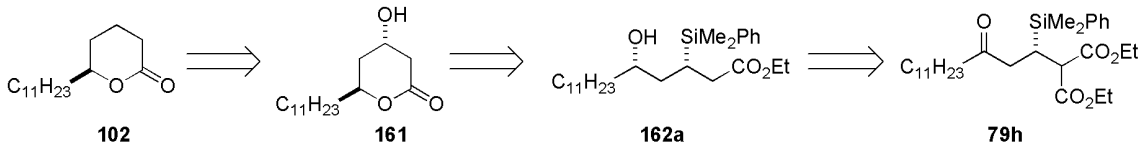


Fig. 4.4. ^{13}C NMR spectrum of 160

4.2.2 Formal total synthesis of (*S*)-5-Hexadecanolide

There are many approaches for the synthesis of the (*S*)-5-hexadecanolide. Many of them require number of protection and deprotection steps. We formulated an efficient route for the synthesis of the target (*S*)-5-hexadecanolide based on the use of β-silyl keto ester. The retrosynthetic strategy is shown in the **Scheme 4.14**. The target compound **102** can be

easily achieved from the hydroxyl lactone **161**, which can be obtained from a δ-hydroxy ester **162a**. This δ-hydroxyester **162a** can be achieved via deethoxycarbonylation of the keto-diester **79h** followed by silicon controlled reduction.

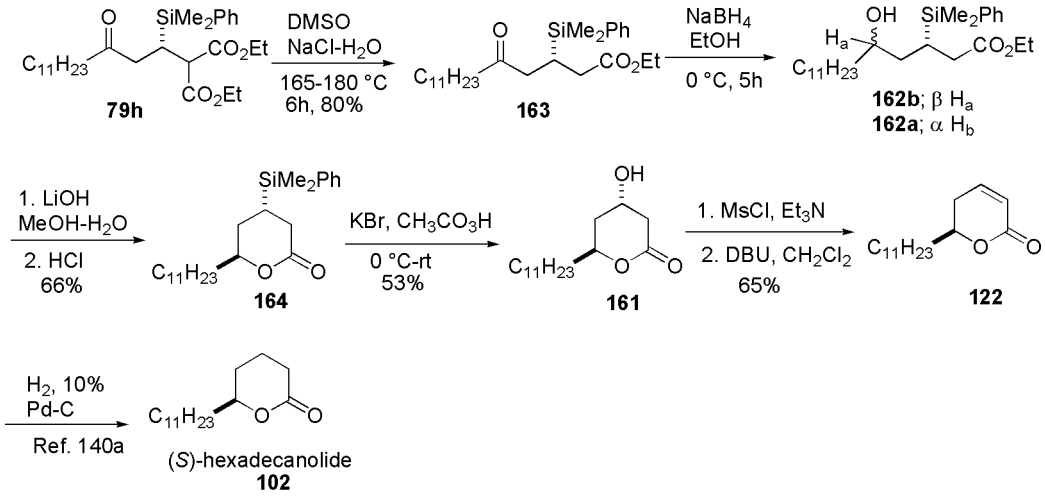


102 **161** **162a** **79h**

Scheme 4.14

The forward synthesis of the known intermediate, the α,β-unsaturated lactone **122**, for the synthesis of (*S*)-5-hexadecanolide is shown in **Scheme 4.15**.[120] The organocatalyzed Michael addition of 2-tridecanone to of β-silylmethelene malonate **75** lead to the ketodiester **79h**[120] with a enantiomeric purity of 87% as described in the **Chapter 3**. This ketodiester **79h** was then converted to β-silylated keto ester **163** by Krapcho deethoxycarbonylation.[118] A silicon-directed stereoselective reduction[153] of the ketoester **163** with sodium borohydride gave an inseparable mixture of diastereoisomeric alcohols (**162a:162b**) with a diasteromeric ratio of 80:20 (**Scheme 4.15**) which was confirmed from ^{1}H NMR spectra. The diastereoisomeric hydroxy ester mixture hydrolyzed with LiOH and the intermediate hydroxy acids lactonized in situ, directly leading to the desired lactone **164** as major product. The dimethyl(phenyl)silyl group in **164** was converted to a hydroxy group following the Tamao–Fleming oxidation[154] using potassium bromide and peracetic acid with retention of configuration leading to the hydroxy δ-lactone **161**. The hydroxy δ-lactone **161** was then converted to mesylate by the treatment of methanesulfonyl chloride and triethylamine. The crude mesylate was treated with DBU in order to obtain the desired unsaturated δ-lactone **122**. The formation of the double bond was confirmed from the ^{1}H NMR and ^{13}C NMR spectra (**Fig 4.5 and Fig 4.6**). The absolute stereochemistry of alkyl

bearing stereocentre of **122** was assigned to be (*S*) by comparing the specific rotation value ($[\alpha]_D^{29}$ = +57, *c* 1, THF; *lit.*[140] $[\alpha]_D^{25}$ = +78.7, *c* 1, THF). This is an advanced intermediate for the synthesis of (*S*)-5-hexadecanolide **102**. This unsaturated lactone has already been converted[140a] to (*S*)-5-hexadecanolide **102** in one step by the hydrogenation.



Scheme 4.15

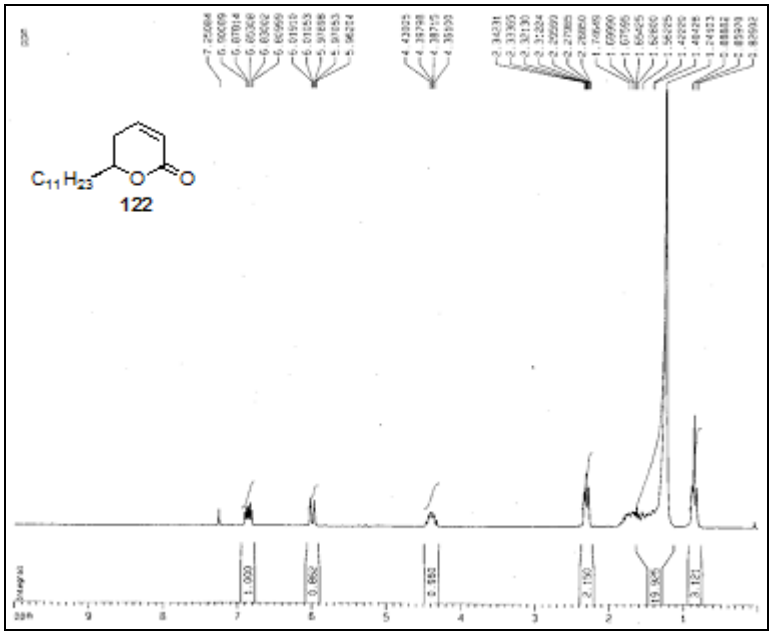


Fig. 4.5. ^{1}H NMR spectrum of 122

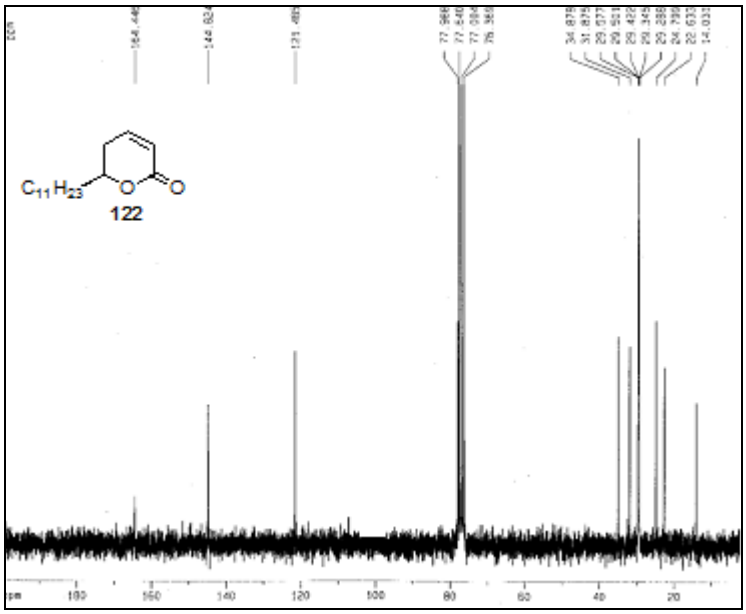
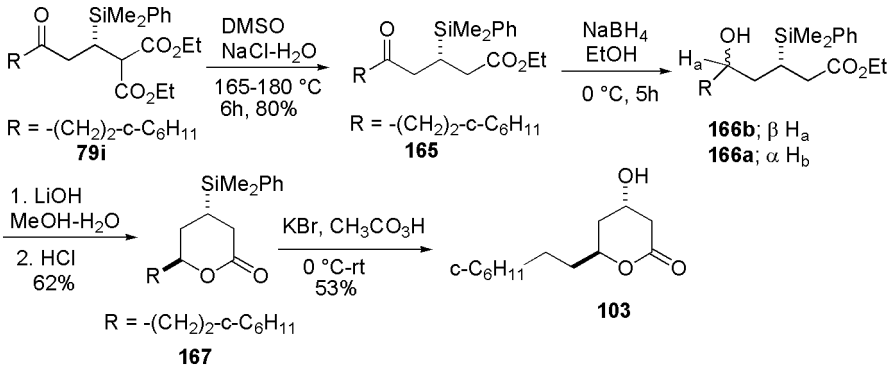


Fig. 4.6. ^{13}C NMR spectrum of 122

4.2.3 Formal total synthesis of enantiomerically pure Mevinolin analog

The mevinolin analoge **103** is a β-hydroxy δ-lactone. Like the synthesis of the other β-hydroxy δ-lactone as described in the previous section, this lactone **103** can be easily achieved from the corresponding ketodiester. This diester **79i**[120] can be obtained from the Michal addition of 4-cyclohexyl-2-butanone on β-silylmethelene malonate **75** as described in the **Chapter 3**. The ketodiester **79i** was subjected to Krapcho deethoxycarbonylation[121] leading to ketoester **165**. A silicon-directed stereoselective reduction[153] of the ketodiester **165** with sodium borohydride gave an inseparable mixture of diastereoisomeric alcohols **166a** and **166b** (**166a**/**166b** ~ 80:20) with high yield (**Scheme 4.16**). The diastereoisomeric hydroxy ester mixture was then hydrolyzed and the intermediate hydroxy acids underwent a smooth cyclization to give the major lactone **167**. The dimethyl(phenyl)silyl group in **167** was then converted to the hydroxy group following Fleming oxidation[154] using potassium bromide and peracetic acid with retention of configuration leading to hydroxy lactone **103** **(Fig 4.7.** and **4.8.**). Lactone **103** is the antipode of a reported mevinolin analog. The

relative and absolute stereochemistry of **103** was further confirmed from the physical and spectral data (Mp 74-75°C, reported[144]72-74°C for the antipode of **103**; $[\alpha]_D^{27}$ = –32.9, *c* 0.94, $CHCl_3$; *lit.*[144] $[\alpha]_D^{25}$ = +29, *c* 0.28, $CHCl_3$ for the antipode of **103**).



Scheme 4.16

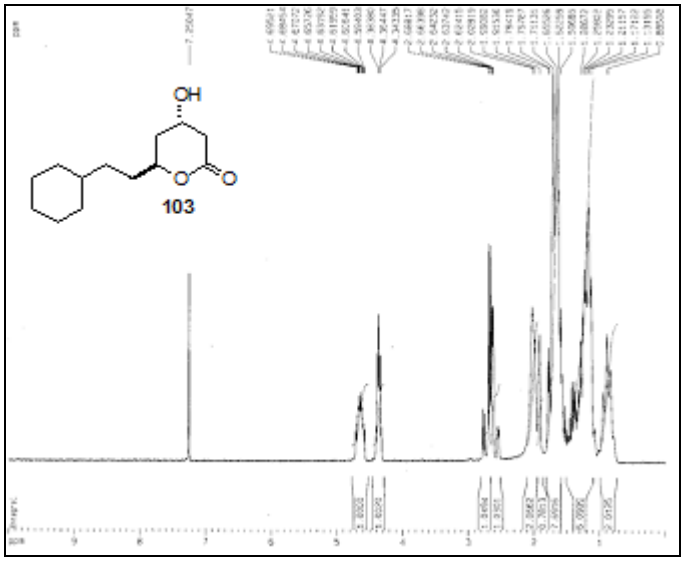


Fig. 4.7. ^{1}H NMR spectrum of 103

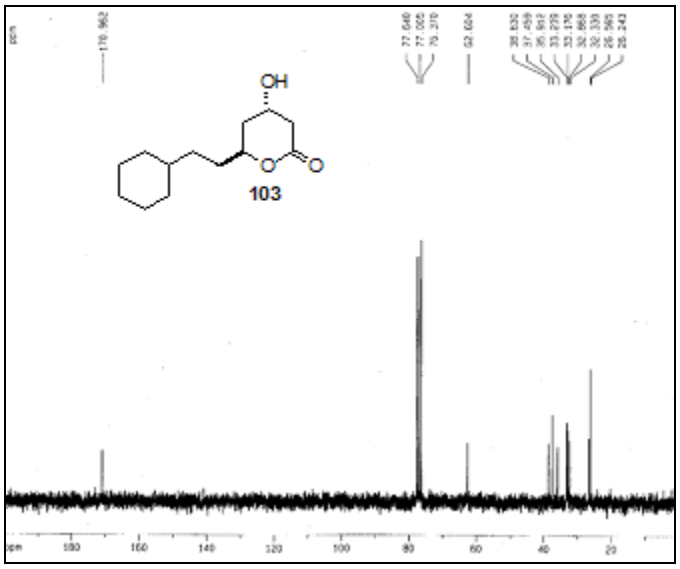
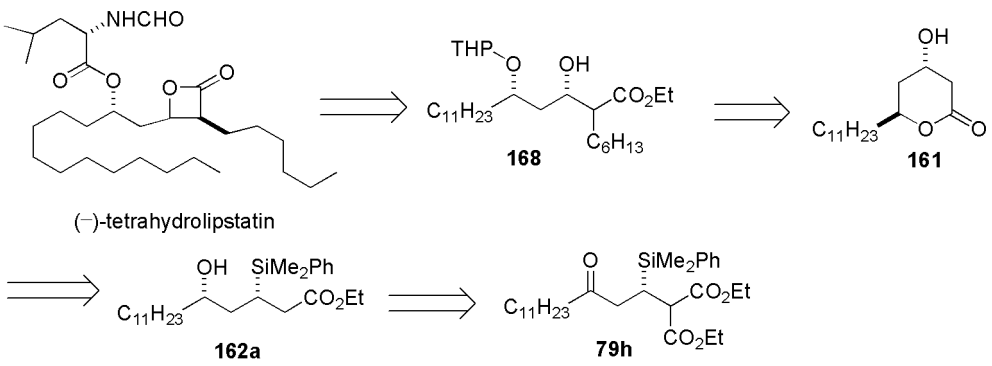


Fig. 4.8. ^{13}C NMR spectrum of 103

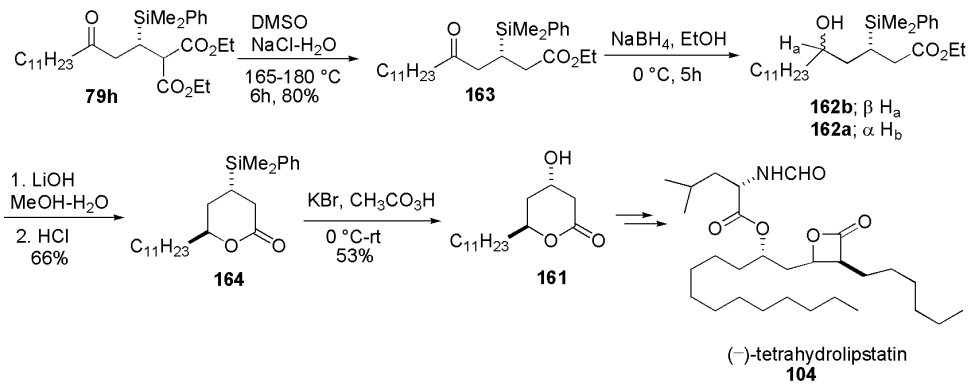
4.2.4 Formal total synthesis of (–)-Tetrahydrolipstatin

There are several methods are available for the synthesis of (–)-tetrahydrolipstatin **104** and some of them are discussed in the introduction part of this chapter. The major drawback in most of the reported syntheses is the synthesis of the optically pure starting material. This prompted us to formulate an efficient and operationally simple route for the synthesis of (–) tetrahydrolipstatin. The retrosynthetic sequence of the (–)-tetrahydrolipstatin **104** is shown in **Scheme 4.17**. The target compound could be achived from a β-hydroxy ester **168**, which can be obtained by the ring opening of the β-hydroxy δ-lactone **161**. The lactone can be easily made from the δ-hydroxy ester **162a**, which can be obtained from the diester **79h**.



Scheme 4.17

The forward synthesis of the known intermediate, the hydroxyl lactone **157**, for the synthesis of **(−)-**tetrahydrolipstatin **104** is shown in **Scheme 4.18**. The ketodiester **79h**[120] was obtained by the organocatalytic Michael addition of β-silylmethelene malonate **75** with 2-tridecanone as described in the **Chapter 3**. The ketodiester **79h** was subjected to Krapcho deethoxycarbonylation[121] leading to ketoester **163** with yield of 80%. A silicon-directed stereoselective reduction[153] of the ketoester **163** with sodium borohydride gave an inseparable mixture of diastereoisomeric alcohols with a diasteromeric ratio of 80:20 (**Scheme 4.18**) which was confirmed from ^{1}H NMR spectra. The diastereoisomeric hydroxy ester mixture hydrolyzed with LiOH and the intermediate hydroxy acids underwent a smooth cyclization to give the major lactone **164**. The dimethyl(phenyl)silyl group in lactone **164** was then converted to the hydroxy group following Fleming oxidation[154] using potassium bromide and peracetic acid with retention of configuration leading to hydroxy lactone **161** (**Fig. 4.9** and **Fig 4.10**). The hydroxyl lactone **161** is the advanced intermediate for **(−)-**tetrahydrolipstatin **104**. The target **(−)-**tetrahydrolipstatin **104** has already been achieved from this hydroxy lactone **157** in a few steps.[149]



Scheme 4.18

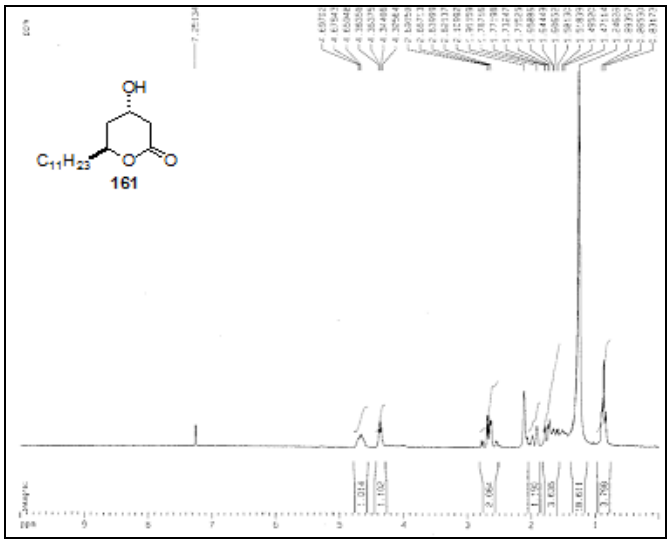


Fig. 4.9. ^{1}H NMR spectrum of 161

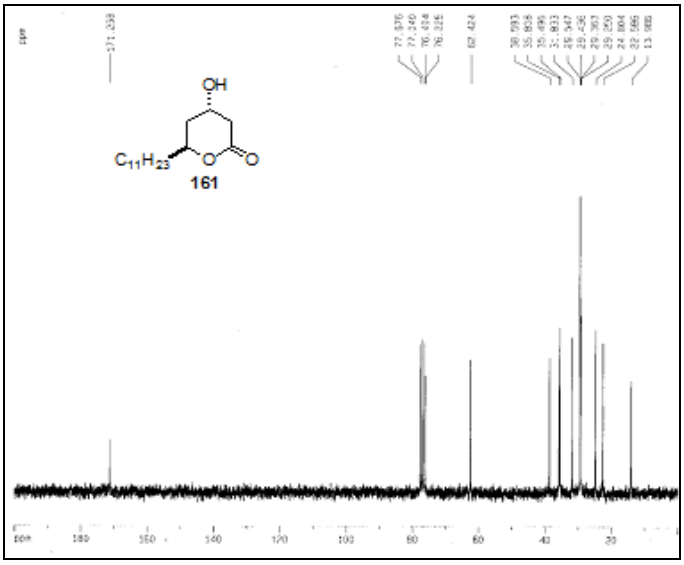


Fig. 4.10. ^{13}C NMR spectrum of 161

4.3 Conclusion

In conclusion, efficient asymmetric synthesis of some natural products and their analogue mainly β-hydroxy δ-lactones based were demonstrated from the easily available β-silylated keto esters. Most of the cases the existing synthetic routs for the above natural products involved multiple steps and several reagents. Sometimes the starting materials and/ or the reagents were to be prepared separately. In comparison, all the reagents and starting materials in our synthesis were easily available. The precursors of β-silylated keto esters are the corresponding β-silylated keto diesters and these diesters are easily available from the organocatalytic Michael addition of β-silylmethelene malonate and the corresponding alkyl methyl ketons. The route provided an efficient alternative method for the synthesis of β-hydroxy δ-lactones with high optical purity. Therefore the synthetic route is easily amenable to the synthesis of other members of the natural products and their analogue from the corresponding β-hydroxy δ-lactones.

4.4 Experimental Section

General Details: As described in **Chapter-2** of this thesis.

Reagents:

$NaBH_4$, Urea-H_2O_2, Methanesulfonyl chloride are commercially available and use as receive. DBU and Et_3N are commercially available and dried over CaH_2 prior to use.

Procedure for the preparation of peracetic acid

Acetic acid (9.4mL, 160 mmol) was added to a stirred urea-hydrogen peroxide complex (8 g, 85 mmol) at 0 °C followed by addition of concentrated H_2SO_4 (0.6 mL). The reaction mixture was allowed to attain to room temperature and stirred for 48 h. The residue was distilled (28 °C/0.1 Torr) to give peracetic acid. Yield: 5.2 g (43%). The strength of this acid was 35% solution in AcOH (as obtained by iodometric titration).

General Procedure **I. Krapcho Deethoxycarbonylation of ketodiesters 79g-i to keto esters 158**, **163**, **165**.

A stirred solution of the keto diester **79g-i** (0.8 mmol) sodium chloride (58 mg, 1.0 mmol) and water (1.5 mL) in DMSO (40 mL) was heated at 165 °C-180 °C under nitrogen for 6 h. The reaction mixture was diluted with water (200 mL) and extracted with ether. The organic extract was washed with water and with brine, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was chromatographed (SiO_2, hexane/EtOAc: 95/5) to give the keto ester **158, 163** and **165** (80-90%).

Ethyl (3*S*)-3-dimethylphenylsilyl -5-oxodecanoate 154

Following the *general procedure* **I**, keto diester **79g** (360 mg, 0.857 mmol) sodium chloride (60 mg, 1 mmol), water (1.5 mL) and DMSO (40 mL) gave the keto ester **158**. Yield: 268 mg (90%); IR (film): 3070, 3019, 2957, 2931, 2872, 1730, 1715, 1216, 1112, 1041, 836, 817, 758 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 0.29 (3 H, s, SiCH_3), 0.32 (3 H, s, SiCH_3), 0.85 (3 H, t, J = 7.3 Hz, $[CH_2]_4CH_3$), 1.28-1.59 (7 H, m, $CH_3[CH_2]_2CH_2CH_2CO$-, CH_3CH_2OCO), 1.38-1.53 (2 H, m, $CO[CH_2]_3CH_2CH_3$), 1.90-2.00 (1 H, m, SiCH), 2.11-2.43 (6 H, m, $CH_2COCH_2[CH_2]_3CH_3$, -$CH_2CO_2CH_2CH_3$), 4.00 (2 H, q, J = 7 Hz, CH_3CH_2OCO), 7.32-7.35 (3 H, m, Ph), 7.45-7.50 (2 H, m, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ = –4.6, –4.3, 13.8, 14.0, 17.2, 22.3, 23.4, 31.2, 34.6, 42.5, 42.6, 60.2, 127.7 (2 C), 129.1, 133.9 (2 C), 136.9, 173.5, 210.0; MS (EI, 70eV): *m*/*z* (%) = 333 (15), 271 (25), 249 (15), 135 (100); $[\alpha]_D^{27}$ = –7.62 (*c* = 0.63, $CHCl_3$).

(4*S*,6*S*)-6-Pentyltetrahydro-4-dimethylphenylsilyl-2*H*-2-pyranone 159

Sodium borohydride (30 mg, 0.78 mmol) was added portion wise to a stirred solution of the keto ester **158** (109 mg, 0.31 mmol) in ethanol (1.5 mL) at 0 ºC. After 5 h, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with dichloromethane. The organic extract was washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure to give an inseparable diastereoisomeric mixture of alcohols **157a** and **157b** (**157a**/**157b** = 80:20) (86 mg). The alcohol mixture was dissolved in 10% aqueous methanol (1 mL) and lithium hydroxide (42 mg 1.0 mmol, 4 equiv.) was added portion-wise to it at room temperature. The reaction mixture was stirred overnight and the solvent was evaporated under reduced pressure. The residue was diluted with water (1 mL),

acidified with dil. HCl and extracted with ethyl acetate. The organic extract was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography to give the lactone **159**.

Yield: 50 mg (53%); IR (film): 3010, 2960, 2931, 2859, 1740, 1427, 1256, 1113, 1064, 834, 812, 701 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 0.32 (6 H, s, Si[CH_3]$_2$), 0.86 (3 H, t, J = 6.5 Hz, [CH_2]$_4$CH_3), 1.25-1.51 (7 H, m, SiCH, CH_2[CH_2]$_3$$CH_3$), 1.59-1.83 (4 H, m, $COCH_2$-, CH_3[CH_2]$_3$CH_2-), 2.22 (1 H, dd, J = 11.2,16.0 Hz, SiCHC$H_A$$H_B$CHOCO), 2.42 (1 H, dd, J = 5.6,16.0 Hz, SiCHC$H_A$$H_B$CHOCO), 3.97-4.09 (1 H, m, CHOCO), 7.35-7.38 (3 H, m, Ph), 7.44-7. 49 (2 H, m, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.6, –5.5, 13.9, 14.9, 22.4, 24.8, 28.0, 29.9, 31.4, 34.9, 78.2, 128.0 (2 C), 129.5, 133.7 (2 C), 135.6, 173.6; ESI-HRMS: Found: M^+ + H, 305.1931. $C_{18}H_{29}O_2Si$ requires M^+ + H 305.1934; $[\alpha]_D^{28}$ = –52.0 (c = 1.75, $CHCl_3$).

(4*S*,6*S*)-6-Pentyltetrahydro-4-hydroxy-2*H*-2-pyranone 160

Potassium bromide (72 mg, 0.6 mmol) was added to a stirred solution lactone **159** (150 mg, 0.49 mmol) peracetic acid (35% solution in acetic acid, 3 mL) at 0 °C followed by H_2O_2 (30%, 0.1 mL). The reaction mixture was allowed to attain to room temperature and stirred for 24 h. The solvent was removed under reduced pressure and the residue was dissolved in dichloromethane. The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography to give lactone **160**.

Yield: 49 mg (54%); IR (film): 3419, 3015, 2956, 2930, 2860, 1715, 1376, 1256, 1035 758 cm^{-1};^1H NMR (700 MHz, $CDCl_3$): δ = 0.90 (3 H, t, J = 7 Hz, [CH_2]$_4$CH_3), 1.28-1.34 (4H, m, CH_2CH_2[CH_2]$_2$CH_3), 1.36-1.43 (1 H, m, CH_2C$H_A$$H_B$[C$H_2$]$_2CH_3$), 1.48-1.55 (1 H, m,

$CH_2CH_AH_B[CH_2]_2CH_3$), 1.57-1.62 (1 H, m, $CH_AH_BCH_2$ $[CH_2]_2CH_3$), 1.69-1.77 (2 H, m, CH_AH_B $CH_2[CH_2]_2CH_3$, $OCHCH_AH_BCHOH$), 1.96 (1 H, m, $OCHCH_AH_BCHOH$), 2.13 (1 H s, br, , OH), 2.62 (1 H, dd, *J* = 4, 18 Hz, CH_AH_BCOO), 2.73 (1 H, dd, *J* = 5, 18 Hz, CH_AH_BCOO), 4.36-4.40 (1 H, m, CHOH), 4.65-4.72 (1 H, m, CHOCO); ^{13}C NMR (175 MHz, $CDCl_3$): δ = 13.9, 22.5, 24.5, 31.5, 35.4, 35.8, 38.6, 62.6, 76.0, 170.9; MS (EI, 70 eV): *m*/*z* (%) = 187 (3) $[M+H]^+$, 169 (2), 140 (7), 115 (79), 97 (100), 73 (42); $[\alpha]_D^{28}$ = –34.7 (*c* = 1.5, $CHCl_3$); *lit.* [155] value for the antipode of **160** $[\alpha]_D$ +29.4 (*c* = 1.4, $CHCl_3$).

Ethyl (3*S*)-3-dimethylphenylsilyl-5-oxohexadecanoate 163

Following the *general procedure* **I**, keto diester **79h** (600 mg, 1.19 mmol) sodium chloride (100 mg, 1.7 mmol), water (2 mL) and DMSO (60 mL) gave the keto ester **163**. Yield: 412 mg (80%); IR (film):2957, 2932, 2871, 1730, 1715, 1212, 1112, 1041, 836, 817, 758 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.29 (6H, s, $Si[CH_3]_2$), 0.86 (3 H, t, *J* = 6.4 Hz, $[CH_2]_{10}CH_3$), 1.16-1.23 (19 H, m, CH_3CH_2OCO-, $COCH_2CH_2[CH_2]_8CH_3$), 1.38-1.53 (2 H, m, $COCH_2CH_2[CH_2]_8CH_3$), 1.87-2.00 (1 H, m, SiCH), 2.11-2.35 (4 H, m, $CH_2COCH_2[CH_2]_9CH_3$), 2.40-2.44 (2 H, m, $CH_2CO_2CH_2CH_3$), 4.00 (2 H, q, *J* = 7 Hz, CH_3CH_2OCO), 7.27-7.35 (3 H, m, Ph), 7.46-7.50 (2 H, m, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ = –4.7, –4.4, 13.8, 13.9, 17.2, 22.5, 23.6, 29.0, 29.1, 29.2, 29.3, 29.4 (2 C), 31.7, 34.5, 42.4, 42.6, 60.0, 127.6 (2 C), 128.9, 133.7 (2 C), 136.9, 173.1, 209.8; ESI-HRMS: Found: M^+ + H, 433.3141. $C_{26}H_{45}O_3Si$ requires M^+ + H 433.3141; $[\alpha]_D^{26}$= –6.0 (*c* = 2.97, $CHCl_3$).

(4*S*,6*S*)-6-Undecyltetrahydro-4-dimethylphenylsilyl-2*H*-2-pyranone 164

Sodium borohydride (88 mg, 2.3 mmol) was added portion wise to a stirred solution of the keto ester **163** (400 mg, 0.92 mmol) in ethanol (4.5 mL) at 0 ºC. After 5 h, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with dichloromethane. The organic extract was washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure to give an inseparable diastereoisomeric mixture of alcohols **162a** and **162b** (**162a**/**162b** = 80/20) (370 mg). The alcohol mixture was dissolved in 10% aqueous methanol (4 mL) and lithium hydroxide (144 mg 3.4 mmol, 4 equiv.) was added portion-wise to it at room temperature. The reaction mixture was stirred overnight and the solvent was evaporated under reduced pressure. The residue was diluted with water (4 mL), acidified with dil. HCl and extracted with ethyl acetate. The organic extract was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography to give the lactone **164**.

Yield: 235 mg (66%); IR (film): 3010, 2960, 2930, 2860, 1741, 1425, 1256, 1113, 1064, 834, 812, 701 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 0.30 (6 H, s, Si[CH_3]$_2$), 0.87 (3 H, t, J = 6.2 Hz, [CH_2]$_{10}$CH_3),1.24 (18 H, bs, [CH_2]$_9$CH_3), 1.33-1.51 (3 H, m, SiCH, CH_2[CH_2]$_9$CH_3), 1.66-1.81 (2 H, m, CHO-CH_2-CHSi), 2.21 (1 H, dd, J = 13, 16 Hz, -CH_AH$_B$COO), 2.42 (1 H, dd, J = 7.6, 16 Hz, CH$_A$$H_B$COO), 3.97-4.09 (1 H, m, CHOCO), 7.33-7.39 (3 H, m, Ph), 7.44-7.49 (2 H, m, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.7, –5.6, 13.8, 14.9, 22.5, 24.9, 27.9, 29.1 (2 C), 29.2, 29.3, 29.4 (2 C), 29.9, 31.7, 34.9, 77.9, 127.8 (2 C), 129.4, 133.6 (2 C), 135.6, 173.0; $[\alpha]_D^{25}$ = –39.9 (c = 1.93, $CHCl_3$).

(4*S*,6*S*)-6-Undecyltetrahydro-4-hydroxy-2*H*-2-pyranone 161

Potassium bromide (88 mg, 0.74 mmol) was added to a stirred solution lactone **161** (235 mg, 0.6 mmol) peracetic acid (35% solution in acetic acid, 4 mL) at 0 °C followed by H_2O_2 (30%, 0.1 mL). The reaction mixture was allowed to attain to room temperature and stirred for 24 h. The solvent was removed under reduced pressure and the residue was dissolved in dichloromethane. The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography to give lactone **161**.

Yield: 80 mg (49%); M.p = 48-51 °C; IR (film): 3420, 3017, 2956, 2930, 2853, 1715, 1376, 1256, 1035 758 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.86 (3 H, t, J = 6.0 Hz, $[CH_2]_{10}CH_3$), 1.47 (18 H, bs, $[CH_2]_9CH_3$), 1.45-2.06 (4 H, m, $CH_2[CH_2]_9CH_3$, -CHOH-CH_2CHOCO), 2.61 (1 H, dd, J = 3.8, 17.6 Hz, CH_AH_BCOO), 2.72 (1 H, dd, J = 5, 17.6 Hz, CH_AH_BCOO), 4.32-4.39 (1 H, m, CHOH), 4.60-4.74 (1 H, m, CHOCO); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 13.9, 22.6, 24.8, 29.3, 29.4, 29.5, (2 C) 29.6 (2 C), 31.8, 35.5, 35.8, 38.5, 62.2, 76.2, 171.3; ESI-HRMS: Found: M^+ + H, 271.2282. $C_{16}H_{31}O_3$ requires M^+ + H 271.2273; $[\alpha]_D^{25}$ = –22.9 (c = 2.1, $CHCl_3$).

(*S*)-6-Undecyl-5,6-dihydro-2(*H*)-pyran-2-one 122

Methanesulfonyl chloride (23 µL, 0.32 mmol) was added to a stirred solution of the hydroxylactone **161** (80 mg, 0.29 mmol) and triethylamine (40 µL, 0.64 mmol) in dichloromethane (2.5 mL) at 0 °C. After 1h, the reaction mixture was quenched with saturated ammonium chloride solution. The reaction mixture was extracted with dichloromethane and the extract was evaporated to give the crude mesylate. The mesylate and DBU (185 µL, 1.24 mmol) were dissolved in dry dichloromethane (1 mL) and the

reaction mixture was stirred overnight. The reaction mixture was diluted with dichloromethane and washed with saturated ammonium chloride solution. The organic layer was separated, dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by silica gel column chromatography to give the unsaturated lactone **122**.

Yield: 47 mg (65%); M.p = 48-51 °C, *lit.*[140b] M.p = 45-47 ° C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.86 (3 H, t, $[CH_2]_{10}CH_3$), 1.24 (20 H, bs, $[CH_2]_{10}CH_3$), 2.26-2.34 (2 H, m, CH_2CHOCO), 4.33-4.46 (1 H, m, CHOCO), 6.00 (1 H, dt, *J* = 1.6, 9.8 Hz, CH_2CH=CHCO), 6.86 (1 H, dt, *J* = 4.4, 9.6 Hz, CH_2CH=CHCO); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.0, 22.6, 24.8, 29.2, 29.3, 29.4 (2 C), 29.5, 29.6 (2 C), 31.9, 34.9, 78.0, 121.5, 144.8, 164.5. $[\alpha]_D^{29}$ +57.0 (*c* 1.0, THF), *lit.*[140a] $[\alpha]_D^{25}$ +78.7 (*c* 1.0, THF).

Ethyl (3*S*)-3-dimethylphenylsilyl-7-cyclohexyl-5-oxoheptanoate 165

Following the *general procedure* **I**, keto diester **79i** (827 mg, 1.79 mmol) sodium chloride (130 mg, 2.24 mmol), water (2 mL) and DMSO (60 mL) gave the keto ester **165**. Yield: 555 mg (80%); IR (film): 2958, 2931, 2871, 1731, 1715, 1216, 1112, 1041, 836, 817, 759 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.29 (6 H, s, $Si[CH_3]_2$), 0.72-0.89 (3 H, m, c-C_6H_{11}), 1.01-1.23 (6 H, m, c-C_6H_{11}, $CO_2CH_2CH_3$), 1.29-1.40 (2 H, m, $COCH_2CH_2C_6H_{11}$), 1.5-1.67 (5 H, m, c-C_6H_{11}), 1.87-2.00 (1 H, m, SiCH), 2.11-2.35 (4 H, m, $CH_2COCH_2CH_2C_6H_{11}$), 2.41-2.50 (2 H, m, $CH_2CO_2CH_2CH_3$), 4.00 (2 H, q, *J* = 7 Hz, CH_3CH_2OCO), 7.30-7.36 (3 H, m, Ph), 7.45-7.50 (2 H, m, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ = –4.6, –4.3, 14.0, 17.3, 26.1 (2 C), 26.5, 31.0, 33.0 (2 C), 34.6, 37.2, 40.1, 42.7, 60.1, 127.7 (2 C), 129.1, 133.9 (2 C), 137.0, 173.3, 210.4; ESI-HRMS: Found: M^+ + Na, 411.2329. $C_{23}H_{36}O_3NaSi$ requires M^+ + Na 411.2331; $[\alpha]_D^{25}$ = –6.4 (*c* 2.64, $CHCl_3$).

(4*S*,6*S*)-6-(2-cyclohexyl)ethyltetrahydro-4-dimethylphenylsilyl-2*H*-2-pyranone 167

Sodium borohydride (115 mg, 3 mmol) was added portion wise to a stirred solution of the keto ester **165** (455 mg, 1.17 mmol) in ethanol (5 mL) at 0 ºC. After 5 h, the reaction mixture was quenched with saturated NH_4Cl solution and extracted with dichloromethane. The organic extract was washed with brine, dried (Na_2SO_4) and evaporated under reduced pressure to give an inseparable diastereoisomeric mixture of alcohols **166a** and **166b** (**166a** /**166b** = 80/20) (394 mg). The alcohol mixture was dissolved in 10% aqueous methanol (4 mL) and lithium hydroxide (170 mg 4 mmol) was added portion-wise to it at room temperature. The reaction mixture was stirred overnight and the solvent was evaporated under reduced pressure. The residue was diluted with water (4 mL), acidified with dil. HCl and extracted with ethyl acetate. The organic extract was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography to give the lactone **167**.

Yield: 250 mg (62%); IR (film): 3011, 2922, 2850, 1743, 1448, 1256, 1113, 1066, 834, 815, 736 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ = 0.32 (6 H, s, Si[CH_3]$_2$), 0.76-0.95 (2 H, m, *c*-C_6H_{11}), 1.01-1.54 (7 H, m, SiCH, CH_2CH_2-*c*-C_6H_{11}, *c*-C_6H_{11}), 1.62-1.83 (9 H, m, SiCHCH_2CHOCO-, CH_2CH_2-*c*-C_6H_{11}, *c*-C_6H_{11}), 2.21 (1 H, dd, *J* = 13, 15.8 Hz, C$H_A$$H_B$COO), 2.42 (1 H, dd, *J* = 5.6, 15.8 Hz, $CH_A$$H_B$COO), 3.94-4.06 (1 H, m, CHOCO), 7.33-7.39 (3 H, m, Ph), 7.39-7.49 (2 H, m, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ = –5.7, –5.6, 14.9, 26.0 (2 C), 26.4, 27.9, 29.9, 32.2, 32.5, 32.9, 33.0, 37.3, 78.4, 127.9 (2 C), 129.4, 133.6 (2 C), 135.6, 173.2; ESI-HRMS: Found: M^+ + H, 345.2236. $C_{21}H_{33}O_2Si$ requires M^+ + H 345.2250; $[\alpha]_D^{23}$= –49.5 (*c* = 2.0, $CHCl_3$).

(4*S*,6*S*)- 6-(2-Cyclohexyl)ethyltetrahydro-4-hydroxy-2*H*-2-pyranone 103

Potassium bromide (102 mg, 0.86 mmol) was added to a stirred solution lactone **167** (232 mg, 0.67 mmol) peracetic acid (35% solution in acetic acid, 4 mL) at 0 °C followed by H_2O_2 (30%, 0.1 mL). The reaction mixture was allowed to attain to room temperature and stirred for 24 h. The solvent was removed under reduced pressure and the residue was dissolved in dichloromethane. The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure. The residue was purified by column chromatography to give lactone **103**.

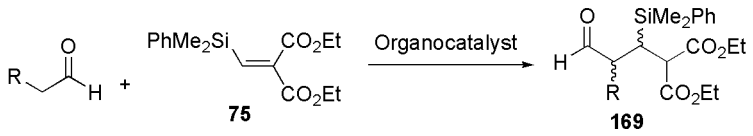
Yield: 78mg, 52%; Mp 74-75 °C, *lit.*[144] Mp 72-74 º C; IR (film): 3419, 3019, 2955, 2930, 2853, 1717, 1066, 758 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.78-0.94 (2 H, m, *c*-C_6H_{11}), 1.00-1.52 (6 H, m, CH_2CH_2-*c*-C_6H_{11}, *c*-C_6H_{11}), 1.57-1.78 (7 H, m, -CHOHCH_2CHOCO-, CH_2CH_2-*c*-C_6H_{11}, *c*-C_6H_{11}), 1.91-2.03 (3 H, m, , *c*-C_6H_{11}, OH), 2.59 (1 H, dd, *J* = 2.8, 17.8 Hz, CH_AH_BCOO), 2.71 (1 H, dd, *J* = 4.8, 17.8 Hz, CH_AH_BCOO), 4.32-4.40 (1 H, m, CHOH), 4.57-4.71 (1 H, m, CHOCO); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.2 (2 C), 26.6, 32.3, 32.9, 33.2, 33.3, 35.9, 37.5, 38.6, 62.6, 76.4, 170.9; $[\alpha]_D^{27}$= –32.9 (*c* = 0.94, $CHCl_3$), *lit.*[144] value for the antipode of **103** $[\alpha]_D^{25}$ = +29 (*c* = 0.28, $CHCl_3$).

Chapter 5

Organocatalyzed Enantioselective Michael Addition of Unmodified Aldehydes to a Silylmethylene Malonate and Their Applications

5.1 Introduction

Organocatalytic asymmetric Michael addition has emerged as a powerful and environmentally friendly tool for the production of enantiomerically pure organic compounds. The direct Michael addition of carbonyl donors by chiral secondary amines via enamine activation represents a particularly attractive route, affording versatile functionalized adducts in an atom-economical manner. Amongst the asymmetric Michael reactions developed in the field of organocatalysis, direct addition of ketones or aldehydes to activated olefins such as nitro olefines have been tested with satisfactory results. However, the addition of the same donors to alkylidene malonates is less successful in terms of generality, efficacy and selectivity. Very recently, a number of efforts have been made by others including us (described in **Chapters 3** and **4**) to address those issues in ketone addition to alkylidene malonates. Initial studies on the use of unmodified aldehydes were not successful to this class of Michael acceptors. Our effort was to develop an organocatalytic Michael addition of enolizable aldehydes to the β-silylmethylene malonate **75** leading to β-silylaldehydes **169** (**Scheme 5.1**). These adducts can easily be transformed into medium-sized rings having skeletal and stereochemically diverse complex structures (**Fig. 5.1**).



Scheme 5.1

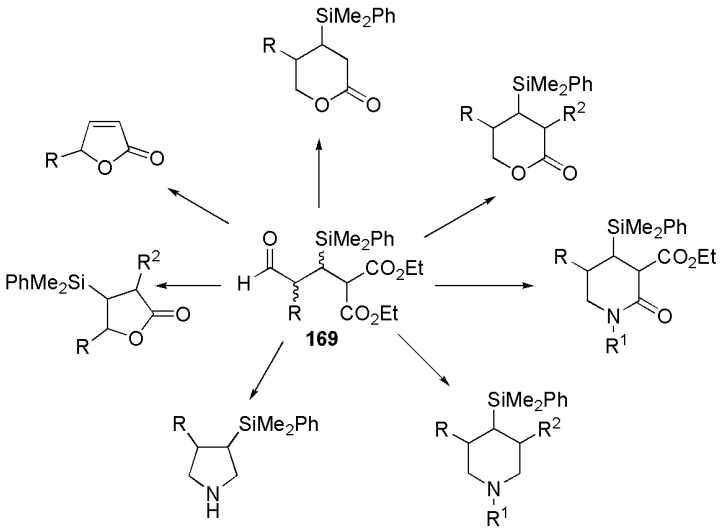
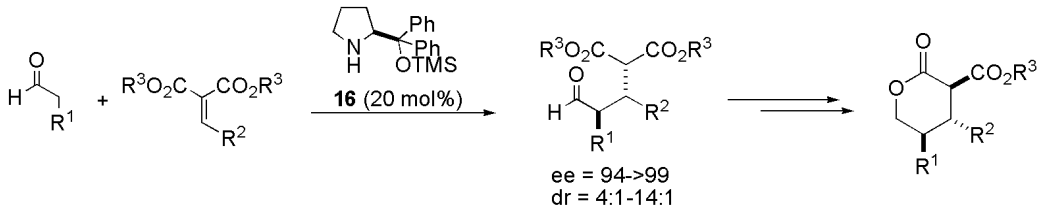


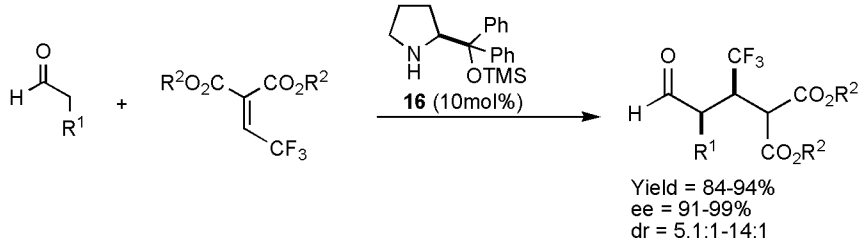
Fig. 5.1 Diverse skeletal types predicted from β-silylaldehyde compounds

Only two successful reports[58,156] have appeared very recently wherein unmodified aldehydes were engaged to add to alkylidene malonates with very high diastereo and enantioselectivity. Cordova and coworkers[58] developed an organocatalytic asymmetric Michael addition reaction which employs unmodified aldehydes and alkylidene malonates (**Scheme 5.2**). This Michael addition of aldehydes to alkylidene malonates were highly chemo- and enantioselective and the corresponding α-aryl- or α-alkyl-β-formyl-substituted malonates were isolated in high yields with up to 14:1 dr and 95 to >99% ee. The reaction worked well for various functionalized aldehydes donors and both aliphatic and aromatic substituted alkylidene malonates could be used as acceptors. Two such β-formyl-substituted malonates were converted to highly substituted δ-lactones with high selectivity.[58]



Scheme 5.2

Very recently Lu et.al.[156] reported the diphenylprolinol silylether **16** catalyzed Michael addition of unmodified aldehydes with trifluoroethylidene malonates (**Scheme 5.3**). The reaction provided β-trifluoromethyl aldehydes with excellent yield (84-94%) and enantioselectivity (91-99%). The reactions of methyl, ethyl, or benzyl 2,2,2-trifluoroethylidene malonates proceeded smoothly with various functionalized aldehydes donors to afford Michael adducts. Some of this β-trifluoromethyl aldehydes were further transformed into 4,4,4-trifluoromethyl butyric acid and trifluoromethyl substituted *δ*-lactones with high enantioselectivity.



Scheme 5.3

5.2 Present work

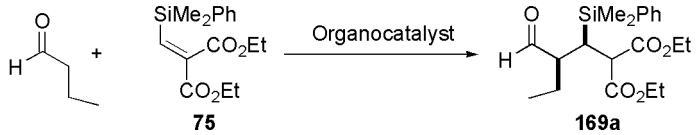
In **chapter 3**, we have shown a highly regioselective Michael addition of alkyl methyl ketones to β-silylmethylene malonate **75** using *N*-(2-pyrrolidinylmethyl)pyrrolidine **63** and TFA combination as the catalyst system of choice and NMP as the solvent.[115] A large number of alkyl methyl ketones with varying steric or electronic natures were reacted with silylmethylene malonate **75** to give exclusively the Michael adducts with excellent yield and high regio- and enantioselectivity.

5.2.1 Addition of aldehydes to β-silylmethylene malonate 75

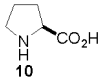
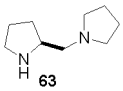
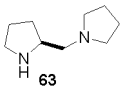
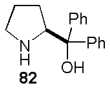
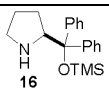
The Michael addition of aldehydes to β-silylmethylene malonate **75** (**Scheme 5.1**) is useful and challenging objective. For this Michael reaction, we choose butyraldehyde as the

model aldehyde and concentrated our efforts on optimizing the yield, diastereo- and enantioselectivity of adduct **169a**. We initially used (*S*)-proline **10** as a catalyst (20 mol%) using 10 equiv of butyraldehyde with respect to substrate **75** in NMP at room temperature, which provided adduct **169a** in moderate yield (42%) and high diastereoselectivity (dr = 96/4) but with very poor enantioselectivity (12.4% ee for the major diastereoisomer) (**Table 5.1**). Since *N*-(2-pyrrolidinylmethyl)pyrrolidine **63** in combination with TFA in NMP[115] gave very good results in the direct addition of alkyl methyl ketones to **75**, we used the same conditions for the butyraldehyde addition. The reaction was very slow with about 20% conversion after 10 days (**Table 5.1**, entry 2). The reaction remained incomplete even when it was carried out at room temperature for over one week. The yield (40%), diastereoselctivity (dr = 80/20) and enantioselectivity (37% ee) for adduct **169a** were also found to be moderate (**Table 5.1**, entry 3). We then moved to the catalysts diphenylprolinol **82** and its silyl ether **16.** Diphenylprolinol **82** was not effectual for this reaction (**Table 5.1**, entry 4) where as its TMS ether **16** was found to be most promising one (**Table 5.1**, entry 5) in terms of the yield and selectivity.

Table 5.1 Screening of catalyst for direct butyraldehyde addition on silylmethylene malonate 75



75 169a

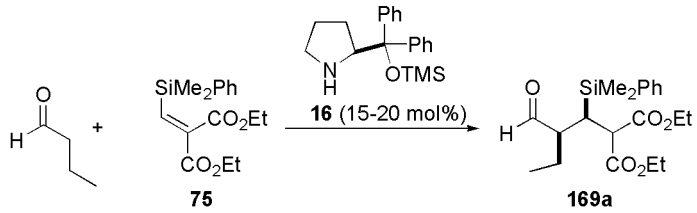
Entry	Catalyst	Catalyst (mol%)/Additive (mol%)	Solvent/temp (°C)/time (days)	d.r[a]	ee (%) (*syn*)[b] (yield %)[c]
1.	 10	20/Nil	NMP/28 /4	96:4	12.4 (42)
2.	 63	30/TFA (10)	NMP/ –10 /5	89:11	ND (ND)
3.	 63	30/TFA (10)	NMP/28 /5	80:20	37.0 (40)
4.	 82	15/Nil	Hexane/28 /7	-----	ND (ND)
5.	 16	15/Nil	$CHCl_3$/28 /3.5	79:21	91.0 (81)

[a] Diastereoisomer ratio (d.r) was determined from the ^{1}H NMR of the crude product; [b] Enantiomeric excess (ee) of the major diastereoisomer (was determined by HPLC using a chiral OD-H column); [c] Yield refers to the mixture of diastereoisomeric products.

We chose diphenylprolinol silyl ether **16** as the catalyst for the addition and carried out a number of experiments in different solvents and under different conditions to obtain the optimum yield, diastereo- and enantioselectivity.[157] The results are summarized in **Table 5.2**. The reaction was carried out in water with 15–20 mol% of **16** at room temperature for 3 days leading to the formation of the product as a mixture of diastereoisomers with moderate selectivity and in 62–64% yield (**Table 5. 2**, entries 1 and 2). The enantiomeric

excess of the major diastereoisomer in these reactions was very high. The reaction was incomplete even after increasing the reaction time as well as fresh addition of butyraldehyde. A significant amount of the homoaldol product[158] of butyraldehyde was also formed, which can be easily removed by chromatographic purification. We also tried the reaction in brine[159] (**Table 5.2**, entry 3) using 15 mol% of catalyst **16** and 30 mol% of acetic acid at room temperature for 5 days. In this case also, the yield was moderate due to incomplete reaction. The diastereoselectivity was high and enantioslectivity of the major diasteromer was also very good. When NMP was used as the solvent, (**Table 5.2**, entry 4) the diastereoselectivity was poor. Acetonitrile as a solvent (**Table 5.2**, entry 5) appeared to be very good as improvement of both the enantioselectivity and diastereoselectivity was observed. But, it required low temperature and longer reaction time in order to achieve these results. Similar results were observed with isopropanol **(Table 5.2**, entry 6) as solvent, but the enantioselectivity was slightly inferior to acetonitrile. No reaction took place when THF (**Table 5.2**, entry 7) was used as the solvent. Halogenated solvents, such as chloroform and dichloromethane were found to be good for this reaction. The reaction in chloroform at room temperature underwent completion in 3.5 days providing the product in 81% yield but the de and ee were only moderate (**Table 5.1**, entry 5). Switching the solvent from chloroform to dichloromethane, significantly improved the diastero and enantioselectivity with slight decrease in yield (**Table 5.2**, entry 8). We then carried out the reaction using catalyst **16** (15 mol%) and a catalytic amount of acetic acid as an additive (**Table 5.2**, entry 9). An improvement in yield and dr was observed without much affecting the enantioselectivity. Increasing the amount of acetic acid or adding benzoic acid as additive did not improve the yield and selectivities (**Table 5.2**, entries 10 and 11).

Table 5.2 Optimization of direct butyraldehyde addition on silylmethylene malonate 75



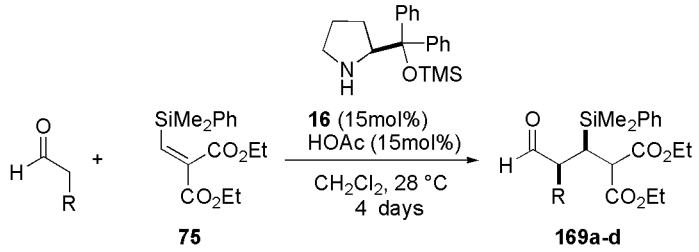
Entry	Additive (mol%)	Solvent/temp (°C)/time (days)	yield (%)[a]	d.r [b]	ee(%)[c] of *syn*-**169a**
1.	Nil	H_2O/28/3	62[d]	70/30	92.3[e]
2.	Nil	H_2O/28/3	64[d]	75/25	97.1
3.	AcOH (30)	Brine/28/5	51[d]	77/23	93.1
4.	AcOH (15)	NMP/28/4	50[d]	60/40	ND[f]
5.	Nil	CH_3CN/4/7	84	83/17	>99[e]
6.	Nil	*i*-PrOH/4/7	86	80/20	93.3[e]
7.	Nil	THF/28/7	NR[g]	-------	-------
8.	Nil	CH_2Cl_2/28/5	67[d]	84/16	>99
9.	AcOH (15)	CH_2Cl_2/28/4	79	86/14	98
10.	AcOH (30)	CH_2Cl_2/28/4	66[d]	83/17	>99
11.	BzOH (15)	CH_2Cl_2/28/6	67[d]	85/15	97

[a] Yield refers to the mixture of diastereoisomeric products; [b] Diastereoisomer ratio (d.r) was determined from the ^{1}H NMR of the crude product; [c] Enantiomeric excess (ee) of the major diastereoisomer (separated by column chromatography) was determined by HPLC using a chiral OD-H column; [d] Incomplete reaction; [e] 20 mol% catalyst was used; [f] ND = Not determined; [g] NR= No reaction.

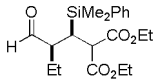
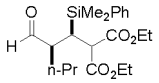
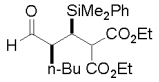
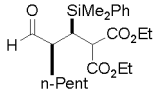
Therefore, we formulated the optimized conditions by using 1 equiv of silylmethylene malonate **75**, 10 equiv of butyraldehyde, a combination of 15 mol% each of **16** and acetic acid as the catalyst system and dichloromethane as the solvent.[157] The reaction mixture was left standing at room temperature for 4 days and gave the adduct **169a** in 79% yield as a mixture of diasteroisomers in a ratio of 86:14. The enantiomeric excess of the major diastereoisomer **169a** was also found to be excellent (98%) as analyzed by HPLC using a chiral stationary phase.

With the optimal catalyst, additive and reaction conditions established with butyraldehyde, we turned our attention to generalize the addition with three more aldehydes. The results are summarized in **Table 5.3**. *n*-Pentanal reacted smoothly with the silylmethylene malonate **75** under the optimized conditions to give the desired product in good yield. The diastereoselectivity was also very high and the enantioselectivity for the major diasteroisomer was excellent (**Table 5.3**, entry 2). *n*-Hexanal and *n*-heptanal also reacted providing the adduct in good yield, high diastereoselectivity and excellent enantioselectivity (**Table5.3**, entries 3 and 4).[157]

Table 5.3 Addition of unmodified aldehydes to silylmethylene malonate 75



75 169a-d

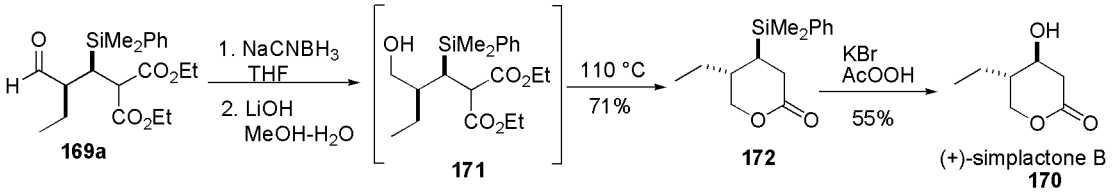
Entry	Aldehyde (10 equiv)	Product	Yield (%) [a] (conversion %) [b]	d.r (*syn*/*anti*)[c]	ee (%)[d] of *syn* isomer
1	*n*-Butanal	 169a	79 (98)	86/14	98
2	*n*-Pentanal	 169b	70 (95)	86/14	98.8
3	*n*-Hexanal	 169c	73 (96)	84/16	>99
4	*n*-Heptanal	 169d	75 (93)	81/19	97.8

[a]Yield refers to the mixture of diastereoisomeric products; [b] The % conversion was based on the disappearance of **75** and determined by ^{1}H NMR of the crude product; [c] Diastereoisomer ratio was determined from the ^{1}H NMR of the crude product; [d] Enantiomeric excess (ee) of the major, that is, *syn*-diastereoisomer (separated by column chromatography) was determined by HPLC using a chiral column.

5.2.2 Determination of sense of asymmetric induction in direct Michael addition of aldehydes to silylmethylene malonate 75

Both, the relative and absolute configurations of the major diastereoisomer **169a** were assigned by converting it to (+)-simplactone B **170**, the antipode of a known and natural valerolactone[160] (**Scheme 5.4**). For this, adduct **169a** was subjected to sodium

cyanoborohydride reduction conditions followed by hydrolysis with lithium hydroxide. The substituted malonic acid intermediate **171** produced was heated at 110 °C which caused decarboxylation and concomitant lactonization leads directly to the desired lactone **172**. The dimethyl(phenyl)silyl group in **172** was then converted to a hydroxy group following the Tamao–Fleming oxidation[154] using potassium bromide and peracetic acid with retention of configuration leading to (+)-simplactone B [157], the antipode of the known (–)-simplactone B as adjudged from the ^{1}H and ^{13}C spectra (**Figs. 5.2** and **5.3**) and specific rotation value ($[\alpha]_D^{24}$ = +22.3, *c* 0.94, $CHCl_3$; *lit*,[160] $[\alpha]_D^{24}$ = –23.0, *c* 0.45, $CHCl_3$) for the antipode of **170**). The relative and absolute configurations of the other products **169b–d** were tentatively assigned in analogy with **169a**.



Scheme 5.4

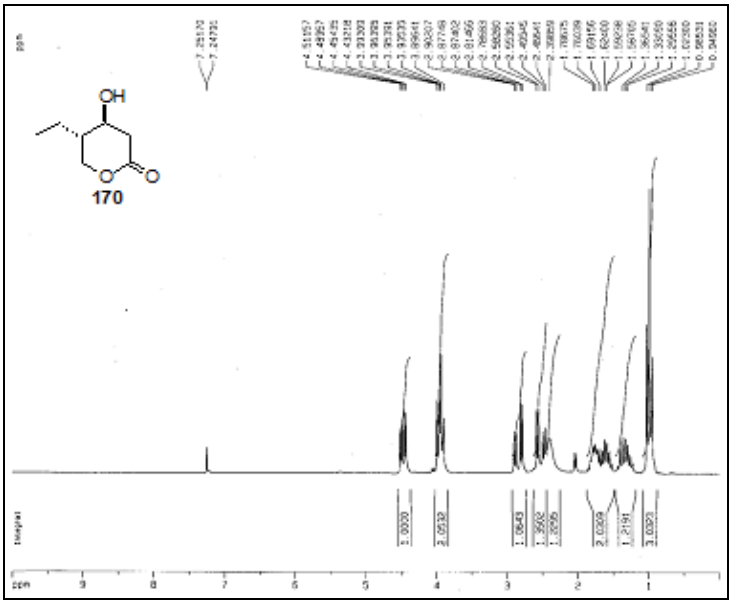


Fig 5.2 ^{1}H NMR of 170

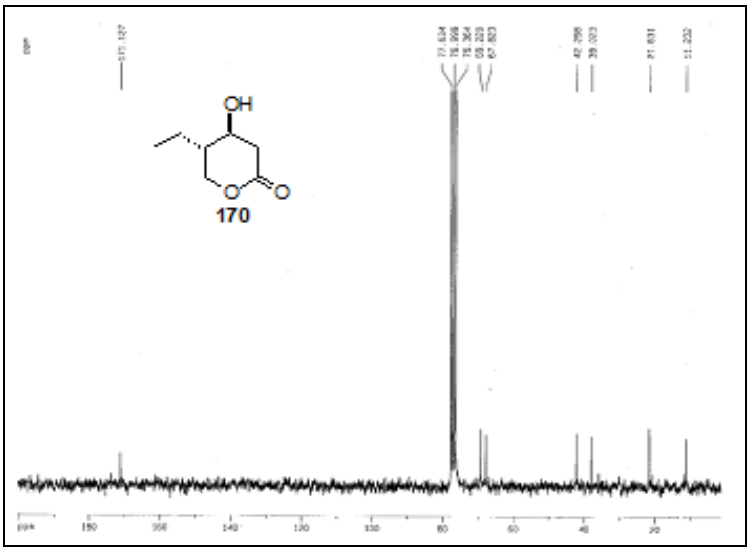
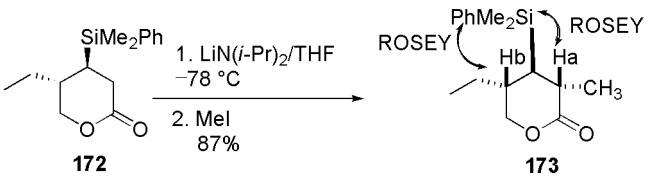


Fig 5.3 ^{13}C NMR of 170

Additional stereochemical centre(s) can easily be introduced to obtain more complex products. For example, the lactone intermediate **172** was methylated to give the lactone **173** where the stereochemistry of the alkylation was controlled by the silicon group. The *trans* relationship between the silyl and methyl groups in **173** was confirmed from the ^{1}H–^{1}H ROESY interaction of both H_a and H_b (**Scheme 5.5**) with the Si–Me and Si–Ph groups.



Scheme 5.5

5.2.3 Proposed mechanism of aldehyde addition to silylmethylene malonate 75

Considering the Michael addition of aldehydes to goes via the enamine intermediate[31,161] of the aldehyde and the chiral pyrrolidine **16**, the stereochemical outcome for the formation of **169a-d** can be explained by the transition state assembly depicted in

Fig. 5.4. Between the two conformational isomeric enamines,[162,163] *S*-trans **174** and *S*-cis **175**, the former is thermodynamically more favoured.[18f] As the *Re*-face of the enamine **174** is efficiently shielded by the bulky trimethylsilyloxy substituent[164] of **16**, the silylmethylene malonate **75** can approach the enamine from the less hindered *Si*-face. Between the two faces of the silylmethylene malonate **75**, *Re*'-face attack would lead to transition state **176a** while *Si*'-face attack would lead to **176b**. The former attack was favoured due to the lesser steric interaction leading to the *syn*-diastereoisomer with an (*R*,*R*)-configuration. The latter transition state suffers from the steric hindrance between the $PhMe_2Si$ and $CHNR_2$ groups. The observed coupling of the trigonal centres with relative topicity Si/Re also follows the general rule proposed by Golin´ski and Seebach.[165] The hydrogen bonding interaction of the malonate carbonyl groups and AcOH can activate **75** as well as lock the conformation of the carbonyl groups, thus demonstrating that a catalytic amount of AcOH can speed up the reaction as well as improve the diastereoselectivity.

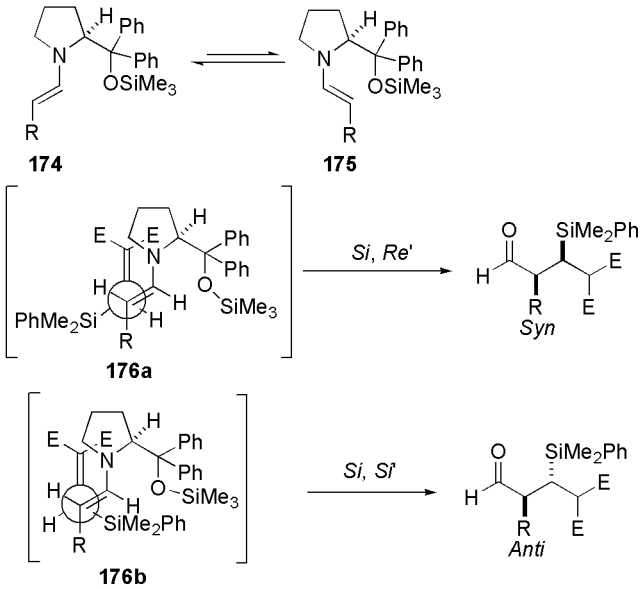


Fig. 5.4 Plausible transition states

5.2.4 Synthesis of a trisubstituted piperidine derivative

The piperidine skeleton is found in the structure of more than half of the alkaloids (**Fig 5.5**) known today.[166,167] They are also found in many natural or synthetic compounds (**Fig 5.5**) with interesting biological activities.[168] Therefore, the search for new and efficient methodologies for the enantioselective synthesis of diversely substituted piperidine derivatives has gained the attention of many synthetic organic chemists.

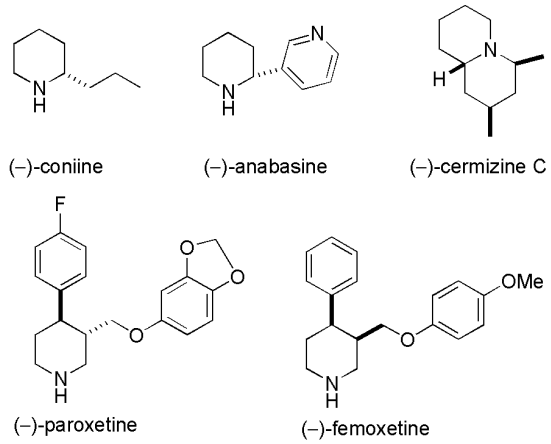
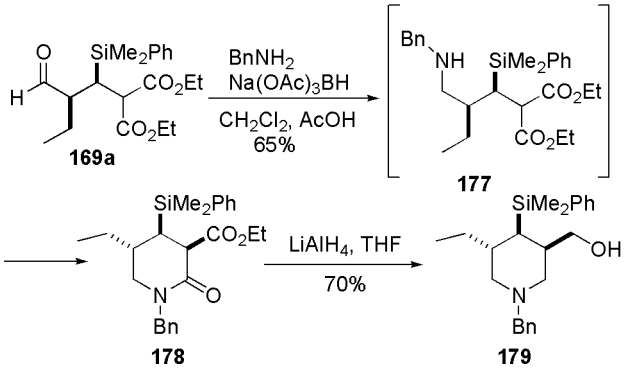


Fig 5.5 Piperidine skeleton based alkaloids and drugs molecules

The β-silyl aldehyde **169a** is the building block of chiral lactam **178**, which can be easily synthesized by a reductive amination–cyclization sequence (**Scheme 5.6**). We applied a tandem procedure of three reaction steps: imine formation, reduction, and lactamization, yielding the lactam **178** in one pot. Reductive amination[169] of the aldehyde group of adduct **169a** with benzylamine and sodium triacetoxyborohydride directly provided the lactam **178** (**Scheme 5.6**). At this stage the minor diastereoisomeric lactam, which had formed due to the minor diastereoisomer present in **169a**, could be eliminated by chromatographic purification. The cis-relative stereochemistry between the silyl and the ethyl ester groups in **178** was confirmed[169] from the coupling constant value (J = 5.8 Hz)

of the protons attached to these centres. Lithium aluminium hydride reduction of pure **178** then provided the 1,3,4,5-substituted piperidine derivative **179**.[157]



Scheme 5.6

5.2.5 Synthesis of some γ-lactone based natural products

Chiral γ-substituted butyrolactones are abundant in nature. They are also valuable intermediates for the synthesis of large variety of molecules containing acyclic and cyclic systems including antibiotics, pheromones, plant growth regulators, antifungal agents and flavor components.[170] A few interesting examples such as avenaciolide **180**, γ-dodecanolactone **181**, protolichesterinic acid **182**, γ-caprolactone **183**, *trans*-quercus lactone **184**, methylenolactocine **185**, rocellaric acid **186**, and blastmycinone **187** are shown in **Fig. 5.6**. In addition, γ-substituted butyrolactones are very useful building blocks for the synthesis of bioactive compounds. Therefore, the syntheses of chiral γ-substituted butyrolactones have been ongoing challenge to the synthetic chemists. A large number methods for their preparation have been reported in the literature. Some of the γ-lactone based natural products such as γ-caprolactone **183**, quercus lactone **184**, and methylenolactocine **185** are targeted by many research groups and their syntheses are discussed below.

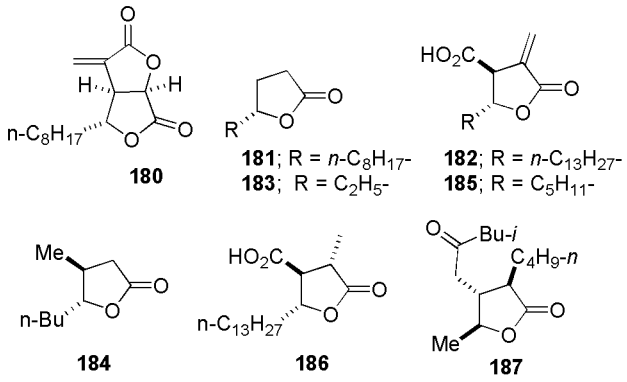
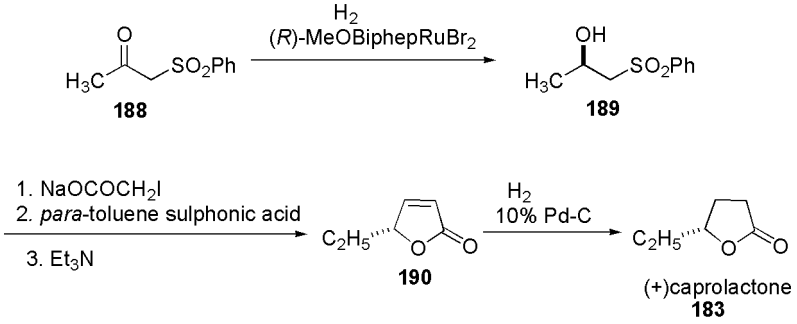


Fig. 5.6 γ-lactone based natural products

5.2.5.I Caprolactone 183

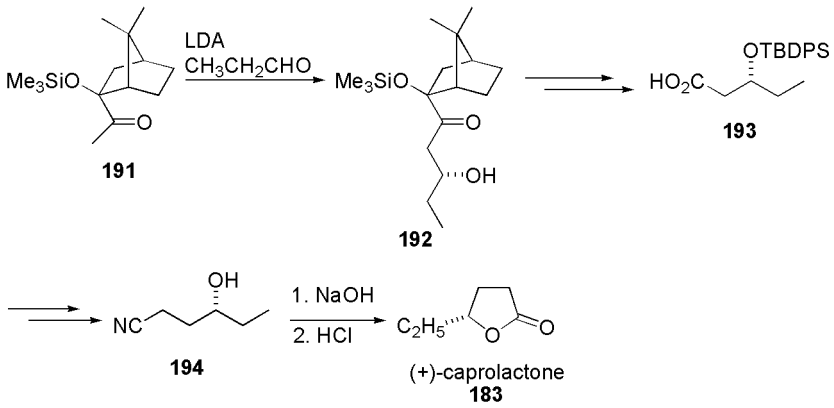
γ-Caprolactone **183** was isolated and identified as a component of the sexual pheromone from the female dermestid beetle *Trogoderma glabrum*,[171] a stored-product pest. The beetle has been reported to respond only the (*R*)-isomer. There are many reports for the synthesis of the γ-caprolactone in literature.

Genêt et.al.[172] reported the synthesis of this lactone from a β-keto sulphone **188** (**Scheme 5.7**). This β-keto sulphone **188** was converted to a β-hydroxy sulphone **189** by an asymmetric catalytic hydrogenation. This β-hydroxy sulphone **189** was then converted to butenolide **190** which on hydrogenation leads to the γ-caprolactone **183**.



Scheme 5.7

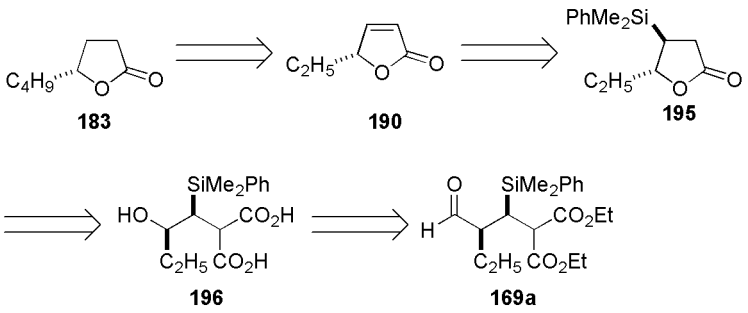
Gil and co-workers[173] achieved the synthesis of γ-caprolactone **183** starting from a bridged bicyclic ketone **191** (**Scheme 5.8**). The aldol reaction of the lithium enolate of the ketone **191** with the propanal afforded the β-hydroxy ketone **192**. Tert-butyldiphenylsilyl ether protection of the hydroxyl functionality followed by cleavage of the auxiliary gave the acid **193** which was then transformed to the hydroxy nitrile **194** in few steps. Subsequent hydrolysis of this nitrile **194** with aqueous base followed by acidification gave the desired lactone **183**.



Scheme 5.8

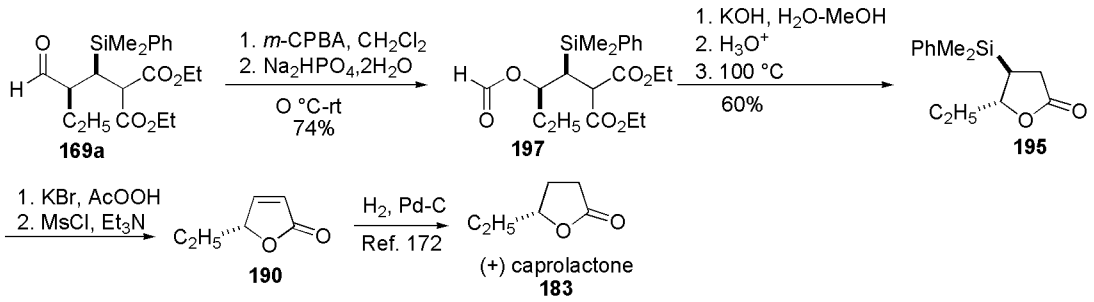
Present synthesis of (+) Caprolactone 183

We have developed a short and efficient route for the synthesis of the (+) caprolactone **183**.[174] The retrosynthetic strategy is shown in the **Scheme 5.9**. The target (+) caprolactone **183** could be achieved from the butenolide **190** which could be obtained from the Si-substituted γ-lactone **195**. This lactone **195** in turn could be obtained from the hydroxy dicarboxylic acid **196**, the synthesis of which might be accomplished from the β-silyl aldehyde **169a**.



Scheme 5.9

The forward synthesis of the known advance intermediate **190**,[172] for the synthesis of (+)-caprolactone **183** is shown in **Scheme 5.10**. The advance intermediate **190**, can be easily obtained by the exploitation of the β-silyl aldehyde **169a**. Organocatalyzed Michael addition of butanal to β-silylmethelene malonate **75** lead to the β-silyl aldehyde **169a**[157] with an enantiomeric purity of 98%. This diasteroisomeric mixture of aldehyde **169a** was subjected to a β-silicon facilitated[174] Baeyer-Villiger oxidation using 3-chloroperoxybenzoic acid leading to an inseparable mixture of diasteroisomeric formates **197**. This formate mixture was then hydrolyzed with KOH in methanol and the resulting hydroxy dicarboxylic acid on heating at 100 °C underwent decarboxylation followed by lactonization finally gave the desired major lactone **195**. The minor diateroisomeric product was eliminated during the chromatographic purification step. The dimethyl(phenyl)silyl group in lactone **195** was converted to hydroxyl group following Fleming[154] oxidation using potassium bromide and peracetic acid with retention of configuration leading to hydroxyl lactone which was then converted into desired butenolide **190** by the treatment with MsCl and Et_3N at 0 °C. The relative and the absolute stereochemistry of the alkyl groups were adjudged from the ^1H and ^{13}C spectra, (**Fig. 5.7** and **5.8**) and specific rotation value ($[\alpha]_D^{25}$= –91.78, *c* 1.46, MeOH; *lit.*[172] $[\alpha]_D^{20}$ = -94 *c* 1.05, CH_2Cl_2).



Scheme 5.10

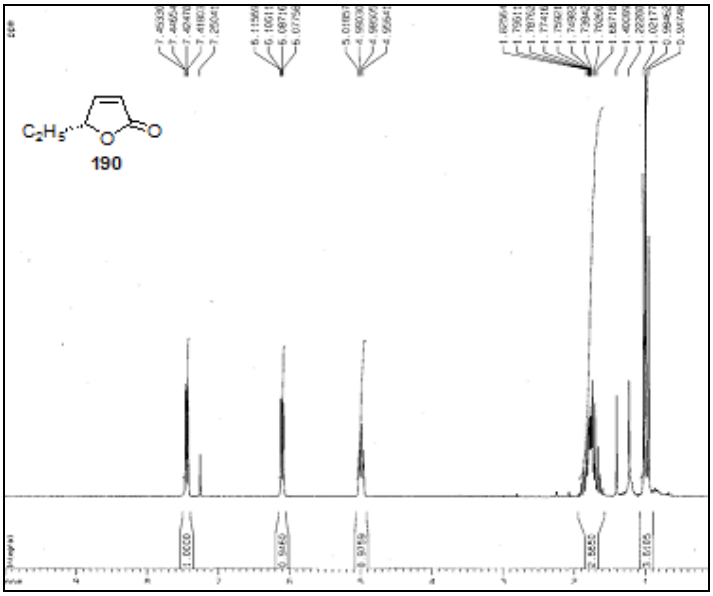


Fig. 5.7. ^{1}H NMR spectrum of 190

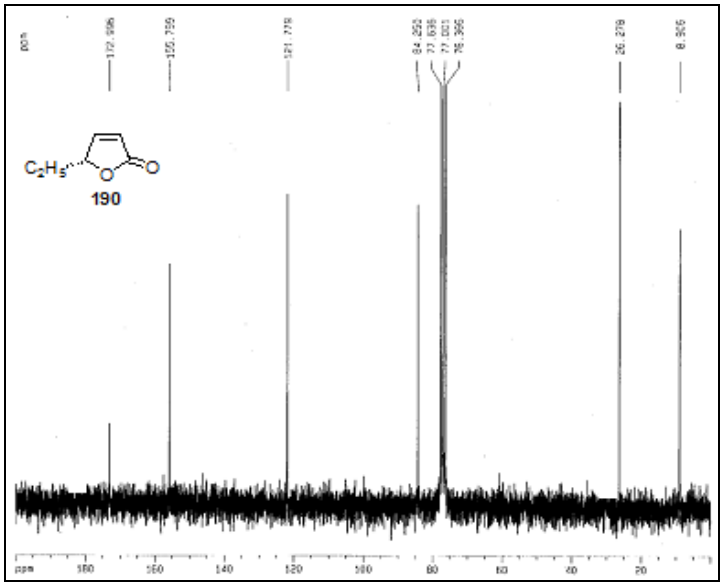
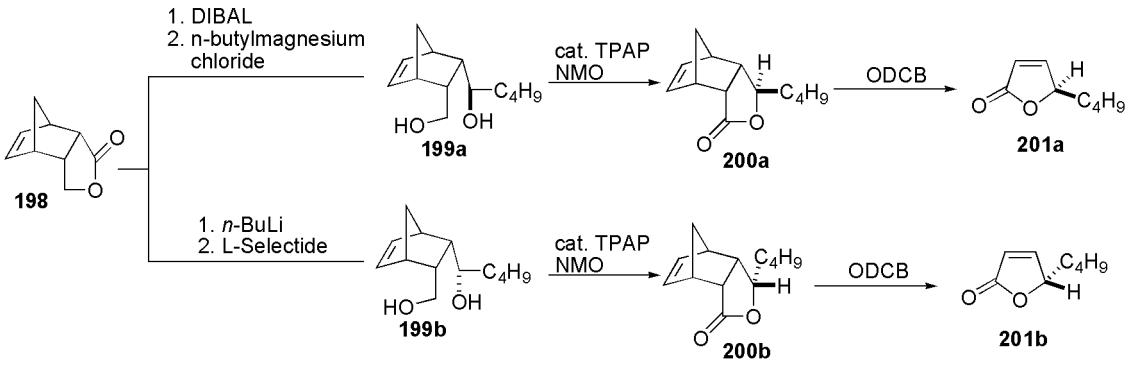


Fig. 5.8. ^{13}C NMR spectrum of 190

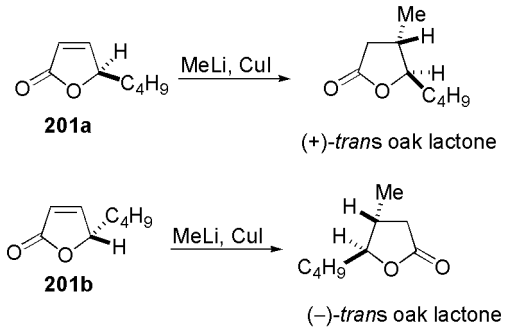
5.2.5.II *trans*-Oak lactone 184

(4*S*,5*R*) *Trans*-isomer of 5-*n*-butyl-4-methyl-4,5-dihydro-2(3*H*)-furanone also known as either the "whiskey" or "oak lactones", is the most important oak derived compound extracted from wood into alcoholic beverages during fermentation and/or maturation. Practical synthesis of this lactone is on demand.

Inomata et.al.[175] reported the synthesis of both the enantiomer of oak lactone **184** starting from a chiral bicyclic lactone **198** (**Scheme 5.11**). The lactone **198** was reduced with diisobutylaluminium hydride (DIBAL) and the resulting aldehyde on reaction with *n*-butylmagnesium chloride leads to a diol **199a**. On the other hand, the lactone **198** was reduced with *n*-butyllithium followed by L-Selectide^{TM} which gave the other isomer of the diol **199b**. Oxidation of this diol with a catalytic amount of tetra-*n*-propylamonium perruthenate (TPAP) in the presence of 4-methylmorpholine N-oxide (NMO) gave the corresponding diasteromeric lactone **200a** and **200b**. Retro-Diels-Alder reaction of the bridged tricyclic lactone **200a** and **200b** in refluxing *o*-dichlorobenzene (ODCB) yielded the enantiomeric 4-butyl-substituted butenolides **201a** and **201b** which were the key intermediates of oak lactones synthesis (**Scheme 5.12**).

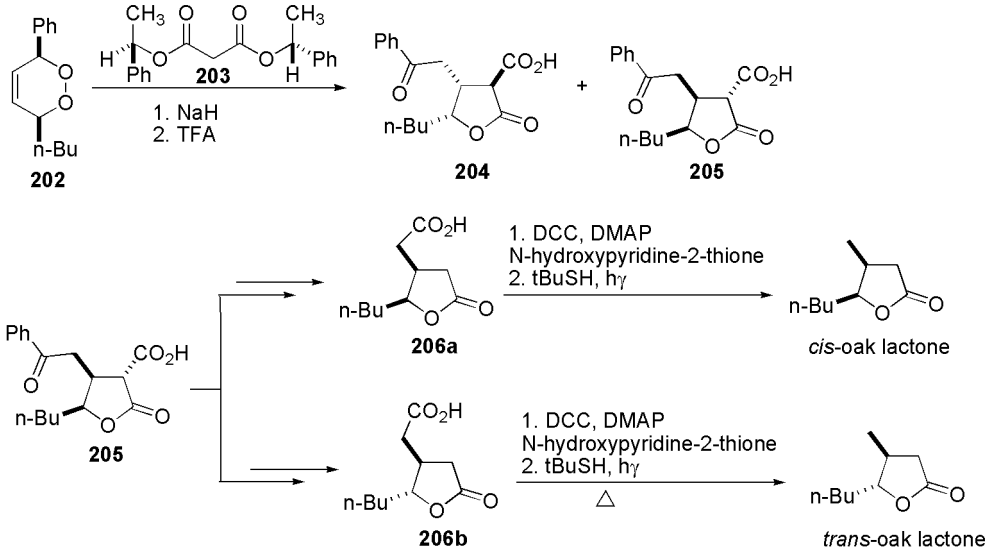


Scheme 5.11



Scheme 5.12

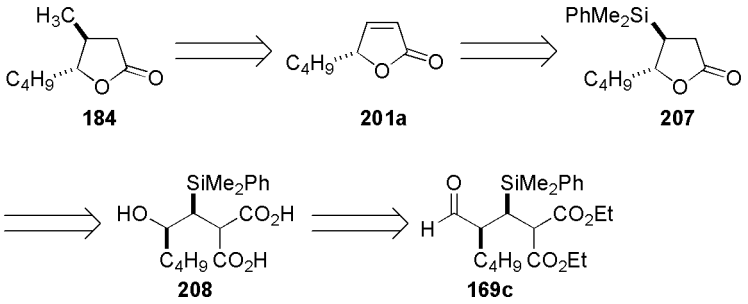
Elsey et.al.[176] have achieved the synthesis of oak lactone **184** starting from a dioxins **202**. Treatment of the dioxins **202** with the anion of a malonate diester **203** followed by the hydrolysis gave the furanones **204** and **205**. Decarboxylation followed by oxidation of the furanones **205** gave the corresponding acids **206a** and **206b** which were further decarboxylated under Barton conditions to give the natural isomers of oak lactone **184** (**Scheme 5.13**).



Scheme 5.13

Present synthesis of (+)-*trans* Oak lactone

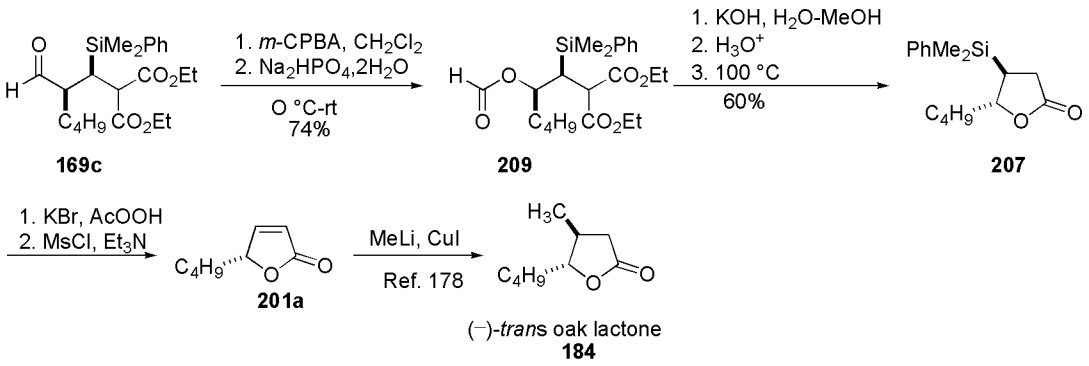
We formulated an efficient organocatalyzed and silicon directed synthesis of (+)-*trans* oak lactone **184**. The retrosynthetic sequence of the (+)-*trans* oak lactone **184** is shown in **Scheme 5.14**. The target compound **184** could be achieved from the butenolide **201a** which could be obtained from the Si-substituted γ-lactone **207**. This lacone **207** in turn could be obtained from the hydroxyl dicarboxylic acid **208**, the synthesis of which might be accomplished from the β-silyl aldehyde **169c**.



Scheme 5.14

The forward synthesis of the known intermediate, the butenolide **201a**,[177] for the synthesis of (–)-*trans* oak lactone **184** is shown in **Scheme 5.15**. The organocatalyzed Michael addition of hexanal to β-silylmethelene malonate **75** lead to the β-silyl aldehyde[153] **169c** with an enantiomeric purity of 99%. This diasteroisomeric mixture of aldehyde **169c** was subjected to a β-silicon facilitated[174] Baeyer-Villiger oxidation using 3-chloroperoxybenzoic acid which gave an inseparable mixture of diasteroisomeric formates **209**. This formate mixture was then hydrolyzed with KOH in methanol and the resulting intermediate hydroxy dicarboxylic acid on heating at 100 °C underwent decarboxylation followed by lactonization gave the desired major lactone **207**. The minor diateroisomer product was eliminated during the chromatographic purification step. The dimethyl(phenyl)silyl group in lactone **207** was converted to hydroxyl group following

Fleming[154] oxidation using potassium bromide and peracetic acid with retention of configuration leading to hydroxyl lactone which was then converted into desired butenolide **201a** by the treatment with MsCl and Et_3N at 0 °C. The relative stereochemistry of the alkyl groups was assigned from the ^1H and ^{13}C chemical shift value (**Fig 5.9** and **Fig. 5.10**) and the absolute stereochemistry by comparing the specific rotation value ($[\alpha]_D^{28} = -101.85$, *c* 2.16, $CHCl_3$; *lit.*[178] $[\alpha]_D^{25} = -101$, *c* 1.2)



Scheme 5.15

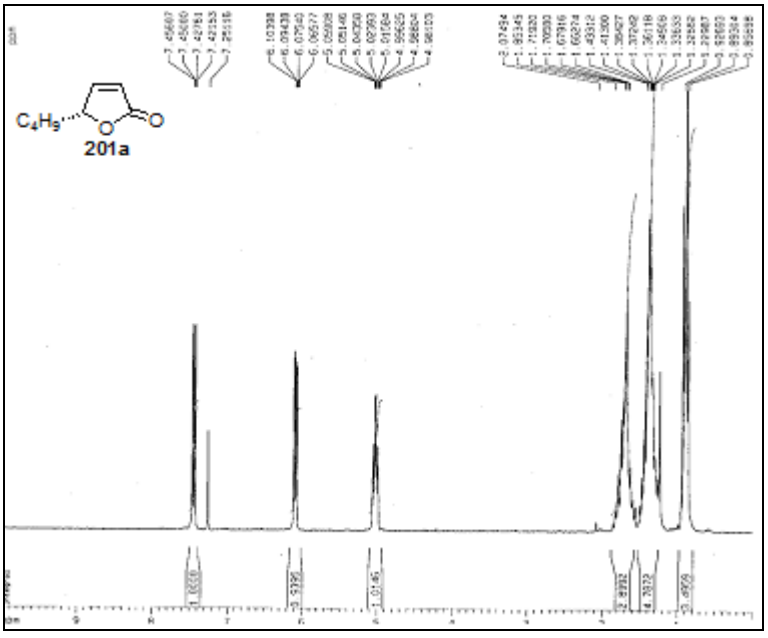


Fig. 5.9. ^1H NMR spectrum of 201a

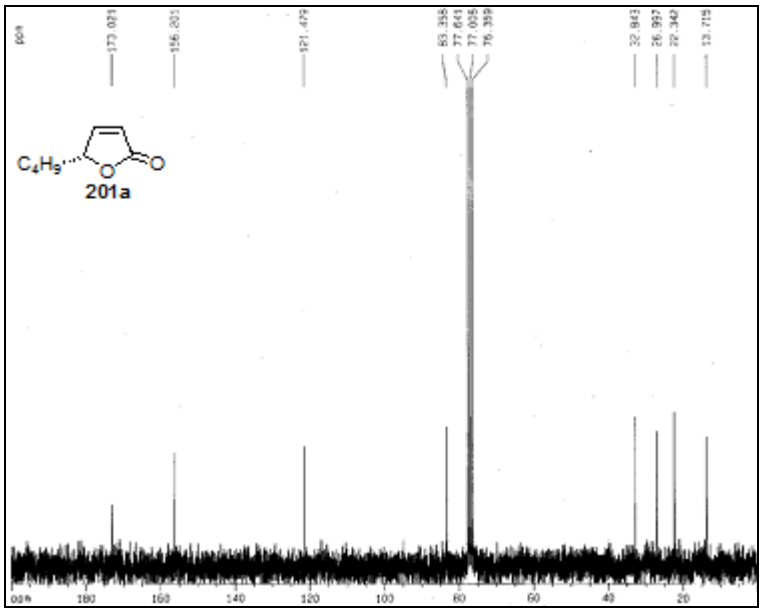
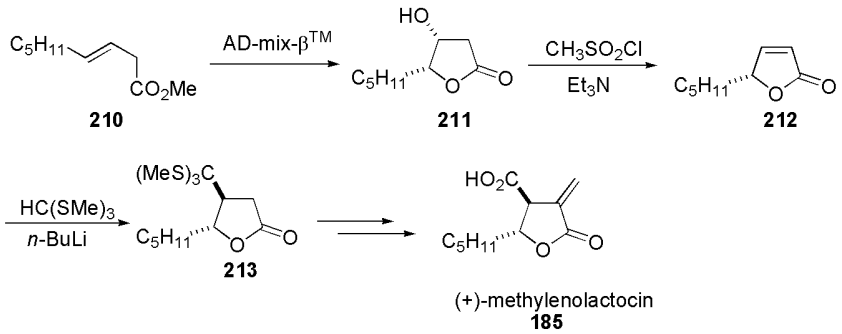


Fig. 5.10. ^{13}C NMR spectrum of 201a

5.2.5.III Methylenolactocin 185

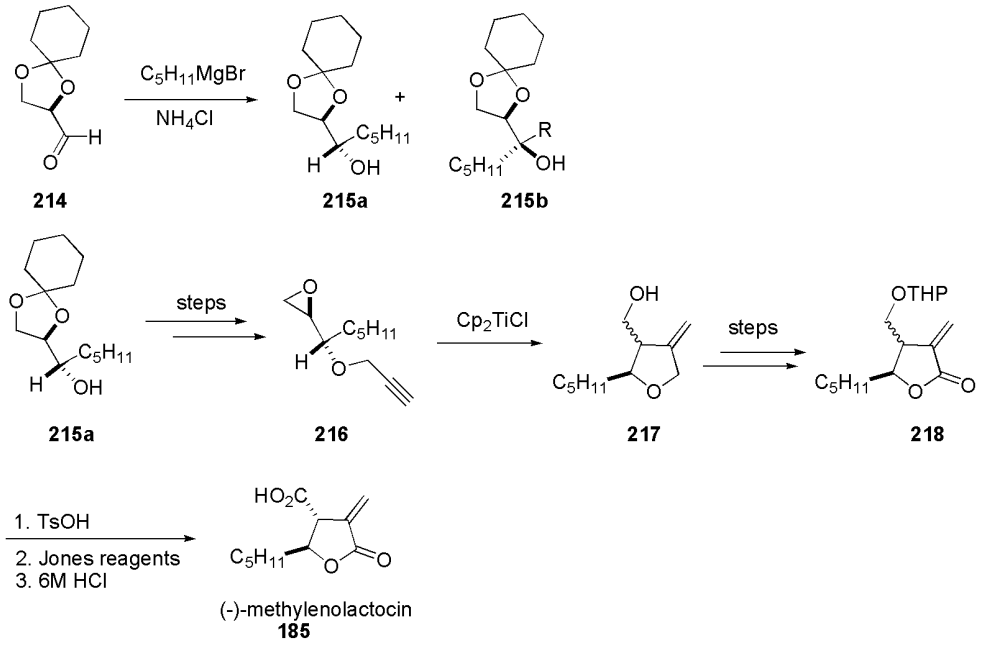
Methylenolactocin **185** is belongs to the paraconic acid family. It was isolated from culture filtrate of *penicilium* sp.[179] It is effective in inhibiting the growth of gram positive bacteria.

Bruckner et.al.[180] reported the synthesis of methylenolactocin **185** strating from a β,γ-unsaturated carboxylic ester **210**. The asymmetric dihydroxylation of the unsaturated ester **210** ended up with the hydroxyl lactone **211** which was then converted to the corresponding butenolide **212**. This butenolide **212** was then transformed to a β,γ-substituted lactone **213** which was hydrolyzed with a Lewis acid followed by reaction with Stile's reagent furnished the desired (+)-methylenolactocin **185** (**Scheme 5.16)**



Scheme 5.16

Roy and co-workers[181] reported the synthesis of (–)-methylenolactocin **185** from the (*R*)-2,3-O-cyclohexylidene glyceraldehyde **214**. This aldehyde **214** was converted to diasteromeric alcohol **215a** and **215b** by the action of pentyl magnesium bromide. One of the alcohol **215a** was then transformed to an epoxide **216** which was subjected to radical cyclization reaction using Cp_2TiCl leading to a tetrahydrofuran **217**. This tetrahydrofuran **217** was then converted to the lactone **218**. Deprotection of the primary alcohol followed by oxidation of the alcohol functionality in the lactone **218** ended up with the target compound (–)-methylenolactocin **185** (**Scheme 5.17**)

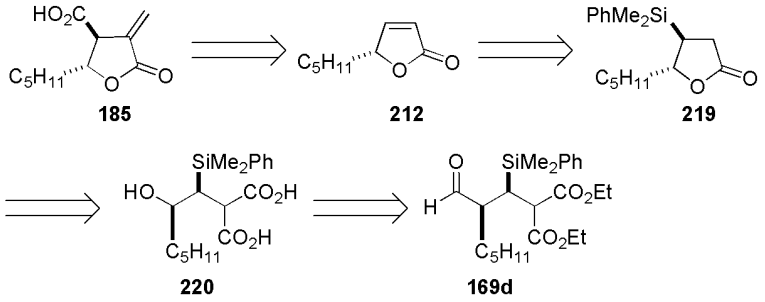


Scheme 5.17

Present synthesis of (+)-Methylenolactocin 185

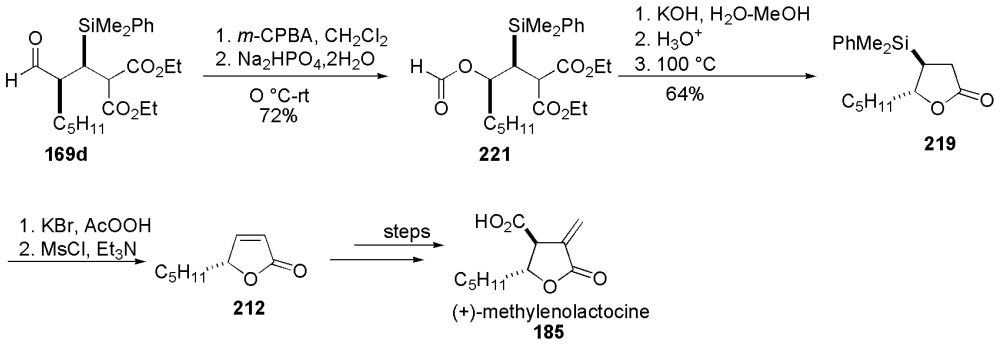
We formulated a straightforward and simple route for the synthesis of the target (+)-methylenolactocin **185** based on the use of β-silyl aldehyde **169d**. The retrosynthetic strategy is shown in the **Scheme 5.18**. The target compound **185** could be easily achieved from the butenolide 212 which in turn could be obtained from the Si-substituted γ-lactone **219** where $PhMe_2Si$ group is considered as the mask hydroxyl group. This lactone **219**

could be prepared from the hydroxy malonic acid derivative **220** which could be obtained from the β-silyl aldehyde **169d**.



Scheme 5.18

The forward synthesis of the known advance intermediate **212**, for the synthesis of (+)-methylenolactocin **185** is shown in **Scheme 5.19**. The β-silyl aldehyde **169d**[157] was obtained as diasteroisomeric mixture (81:19) from the Michael addition of n-heptanal to β-silylmethelene malonate **75**. This diasteroisomeric mixture of aldehyde was then transformed to an inseparable diasteroisomeric formate mixture **221** by a silicon controlled Baeyer-Villiger oxidation using 3-chloroperoxybenzoic acid. This formate mixture was then hydrolyzed with KOH in methanol and the intermediate hydroxy dicarboxylic acid on heating at 100 °C underwent decarboxylation followed by lactonization gave the desired major lactone **219**. The minor diasteroisomer product was eliminated during the chromatographic purification step. The dimethyl(phenyl)silyl group in **219** was then converted to the hydroxy group following Fleming oxidation[154] using potassium bromide and peracetic acid with retention of configuration leading to hydroxy lactones. The butenolide **212**[174] was then accomplished from the hydroxyl lactone by the treatment of MsCl and Et_3N at 0 °C. The absolute stereochemistry was confirmed from the spectral data (**Fig. 5.11** and **Fig. 5.12**) and the optical rotation value. ($[\alpha]_D^{25}$ = –93.28, *c* 2.53, $CHCl_3$; *lit.*[180] $[\alpha]_D^{25}$ = -90.1, *c* 1.36, $CHCl_3$).



Scheme 5.19

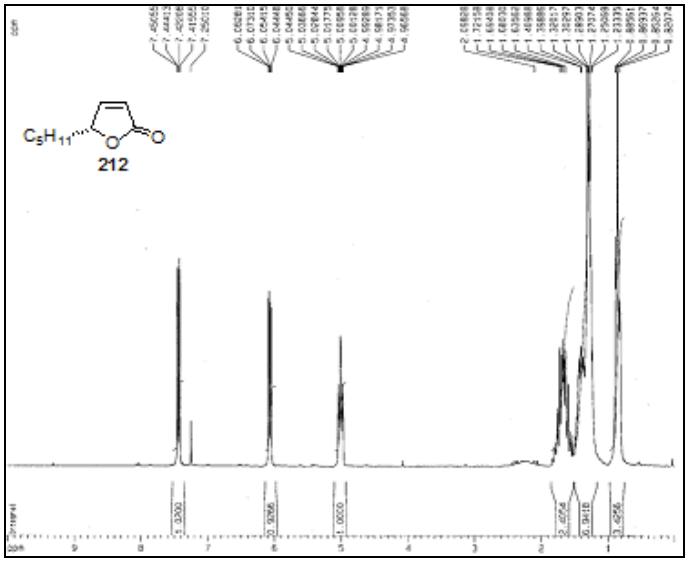


Fig. 5.11. ^{1}H NMR spectrum of 212

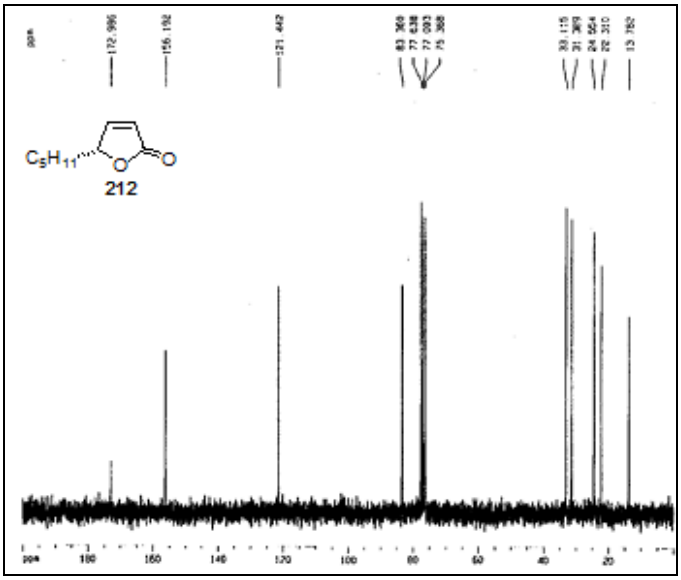


Fig. 5.12. ^{13}C NMR spectrum of 212

5.3 Conclusion

In conclusion, we have developed an organocatalytic asymmetric Michael addition of unmodified aldehydes to a silylalkylidene malonate with high diastereo- and excellent enantioselectivity. The resulting β-silyl aldehydes have been transformed into skeletally diverse *N* and O-heterocyclic compounds with embeded functionalities. The total synthesis (+)-simplactone B has been achieved from one of the adducts and some of the adducts have been transformed to γ-alkyl-butenolides those are known to be the advance intermediates for the synthesis of few natural products.

5.4 Experimental Section:

Reagents: HPLC grade NMP, CH_2Cl_2, $CHCl_3$ were used as received. Butanal, pentanal, hexanal, heptanal are commercially available, and distilled prior to use. $LiAlH_4$, $NaBH_4$, $NaCNBH_3$, $Na(OAc)_3BH$, *m*-CPBA (70%) are commercially available, and use as receive. $BnNH_2$ is commercially available and dried over CaH_2 prior to use.

HPLC: Enantiomeric excess (ee) determinations were carried out by HPLC using a JASCO (JASCO PU-2080) instrument fitted with Daicel chiralpak AD-H, OD-H columns and UV-2075 detector with λ fixed at 254 nm.

5.4.1 General procedures

General Procedure 5.4.1.I. Survey of organocatalysts for Michael addition of butraldehyde on β-silyledene malonate 75

Butraldehyde (224 μL, 2.5 mmol, 10 equiv) was added to a stirred mixture of silyledene malonate **75** (77 mg, 0.25 mmole, 1 equiv) and organocatalyst (0.037-0.075 mmol, 0.15-0.3 equiv) in solvents (0.5 mL) at 0 °C or -10 °C. After 3.5-7 days at room temperature (28 °C) or -10 °C, the reaction mixture was diluted with water and extracted with EtOAc/hexane (1/1). 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 **169a** (38 mg - 77mg, 40%-81%).

General Procedure 5.4.1.II. Michael addition of aldehydes to β-silyledene malonate 75 using organocatalyst 16 and AcOH additive

General Procedure **5.4.1.II.**: Respective aldehydes (5 mmol, 10 equiv) was added to a stirred mixture of silylmethylene malonate **75** (153 mg, 0.5 mmole, 1 equiv),

diphynylprolinol silyl ether **16** (25 mg, 0.075 mmol, 0.15 equiv) and acetic acid (4 μL, 0.075 mmol, 0.15 eqiuv) in dichloromethane (1 mL) at 0 °C. After 4 days at 28 °C, the reaction mixture was diluted with water and extracted with EtOAc/hexane (1/1). 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 **169a-d** (73-79%).

General Procedure 5.4.1.III. Michael addition of aldehydes to β-silyledene malonate 75 for the preparation of racemic Michael products (±)-**169a-d using (D,L)-proline**

General Procedure **5.4.1.III.**: Respective aldehydes (2.5 mmol, 10 equiv) was added to a stirred mixture of silylmethylene malonate **75** (77 mg, 0.25 mmole, 1 equiv), (D,L)-proline (9 mg, 0.075 mmol, 0.3 equiv) in NMP (1 mL) at 28 °C. After 5 days at 28 °C, the reaction mixture was diluted with water and extracted with EtOAc/hexane (1/1). 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 (±)-**169a-d**.

Ethyl (3*R*,4*S*)-3-dimethylphenylsilyl-2-ethoxycarbonyl-4-formylhexanoate 169a

Prepared from silylmethylene malonate **75** (153 mg, 0.5 mmol) and *n*-butanal (0.45 mL, 5 mmol) according to *General Procedure* **5.4.1.II.** Yield: 149 mg (79%). Diastereoisomer ratio (*syn*/*anti* = 86/14) was determined from ^{1}H NMR of the crude product. Data for *syn*-**169a**: IR (film): 3071**,** 2981, 2937, 2877, 1745, 1725, 1462, 1427, 1252, 1110, 909, 820 cm^{-}1; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.34 (3 H, s, CH_3Si) , 0.42 (3 H, s, CH_3Si), 0.79 (3 H, t, J = 7.4 Hz, $CHCH_2CH_3$), 1.17-1.27 (6 H, m, 2 × CH_3CH_2OCO), 1.35-1.72 (2 H, m, $CHCH_2CH_3$), 2.29 (1 H, t, J = 5.2 Hz, SiC*H*), 2.33-2.43 (1 H, m, $CHCH_2CH_3$), 3.52 (1 H, d, J = 5.0 Hz, C*H*CHSi), 4.01-4.14 (4 H, m, 2 × CH_3CH_2OCO), 7.24-7.35 (3 H, m, Ph),

7.53 -7.58 (2 H, m, Ph), 9.53 (1 H, d, J = 2.0 Hz, CHC*H*O); ^{13}C NMR (50 MHz, $CDCl_3$): δ = –2.4, –1.4, 12.4, 13.9 (2 C), 21.6, 26.7, 51.4, 53.7, 61.5, 61.6, 127.7 (2 C), 129.1, 134.0 (2 C), 138.6, 169.6 (2 C), 204.1. ESI-HRMS: Found: M^+ + H, 379.1935, requires M^+ + H $C_{20}H_{31}O_5Si$ 379.1941; HPLC of *syn* 1**69a**: Daicel chiralpak OD-H, 2-propanol/ hexane (0.3/99.7), flow rate = 0.6 mL/min, t_R = 23.58 min (99%), t_R = 52.15 min (1%).

Ethyl (3R,4S)-3-dimethylphenylsilyl-2-ethoxycarbonyl-4-formylheptanoate 169b

Prepared from silylmethylene malonate **75** (153 mg, 0.5 mmol) and *n*-pentanal (0.5 mL, 5 mmol) according to *General procedure* **5.4.1.II.** Yield: 137 mg (70%). Diastereoisomer ratio (*syn*/*anti* = 86/14) was determined from the ^{1}H NMR of the crude product. Data for *syn*-**169b**: IR (film): 3070, 3048, 2957, 2933, 2872, 1748, 1730, 1730, 1464, 1427, 1249, 1153, 1110, 1030, 819 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.35 (3 H, s, C*H*$_3$Si), 0.42 (3 H, s, C*H*$_3$Si), 0.76 (3 H, t, J = 7.1 Hz, $CHCH_2CH_2CH_3$), 1.14–1.29 (8 H, m, 2 × CH_3CH_2OCO, $CHCH_2CH_2CH_3$), 1.33–1.40 (2 H, m, $CHCH_2CH_2CH_3$), 2.26 (1 H, t, J = 5.2 Hz, SiC*H*), 2.52–2.43 (1 H, m, C*H*$CH_2CH_2CH_3$), 3.53 (1 H, d, J = 5.2 Hz, C*H*CHSi), 4.00–4.13 (4 H m, 2 × CH_3CH_2OCO), 7.32–7.35 (3 H, m, Ph), 7.53–7.58 (2 H, m, Ph), 9.52 (1 H, d, J = 2.2 Hz, CHC*H*O); ^{13}C NMR (50 MHz, CDCl3): δ = – 2.3, –1.4, 13.7, 13.8 (2C), 20.9, 26.9, 30.6, 51.3, 51.6, 61.4, 61.6, 127.7 (2C), 129.0, 134.0 (2C), 138.6, 169.6 (2C), 204.1; ESI-HRMS: Found: M^+ + H, 393.2104, requires M^+ + H $C_{21}H_{33}O_5Si$ 393.2097; HPLC of *syn*-**169b**: Daicel chiralpak OD-H, 2-propanol/ hexane (0.4/99.6), flow rate = 0.4 mL/min, t_R = 27.27 min (99.4%), t_R = 57.39 min (0.6%).

Ethyl (3*R*,4*S*)-3-dimethylphenylsilyl-2-ethoxycarbonyl-4-formyloctanoate 169c

Prepared from silylmethylene malonate **75** (153 mg, 0.5 mmol) and *n*-hexanal (0.6 mL, 5 mmol) according to *General Procedure* **5.4.1.II.**. Yield: 148 mg (73%). Diastereoisomer ratio (*syn*/*anti* = 84/16) was determined from ^{1}H NMR of the crude product. Data for ***syn*-169c**: IR (film): 3070, 3048, 2958, 2872, 2721, 1745, 1726, 1465, 1427, 1251, 1110, 912, 820 cm^{-1}. ^{1}H NMR (200 MHz**,** $CDCl_3$): δ = 0.35 (3 H, s, CH_3Si), 0.42 (3 H, s, CH_3Si), 0.78 (3 H, t, J = 6.2 Hz, CH[CH_2]$_3$CH_3), 1.12-1.39 (12 H, m, 2 × C$H_3$$CH_2$OCO, CH[C$H_2$]$_3$$CH_3$), 2.27 (1 H, t, J = 5.2 Hz, SiC*H*), 2.37-2.51 (1 H, m, C*H*[CH_2]$_3$$CH_3$), 3.53 (1 H, d, J = 5.0 Hz, C*H*CHSi), 4.01-4.17 (4 H, m, 2 × CH_3CH_2OCO), 7.32-7.35 (3 H, m, Ph), 7.53-7.58 (2 H m, Ph), 9.52 (1 H, d, J = 2.0 Hz, CHC*H*O); ^{13}C NMR (50 MHz, $CDCl_3$): δ = –2.5, –1.4, 13.8, 13.9 (2 C), 22.4, 26.9, 28.2, 29.8, 51.3, 51.8, 61.4, 61.6, 127.7 (2 C), 129.0, 134.0 (2 C), 138.7, 169.6 (2 C), 204.2; ESI-HRMS: Found: M^+ + H, 407.2236, requires M^+ + H $C_{22}H_{35}O_5Si$ 407.2254; HPLC of *syn* **169c**: Daicel chiralpak AD-H, 2-propanol/ hexane (0.3/99.7), flow rate = 0.5 mL/min, t_R = 34.56 min (99.5%), t_R = 37.36 min (0.5%).

Ethyl (3*R*,4*S*)-3-dimethylphenylsilyl-2-ethoxycarbonyl-4-formylnonanoate 169d

Prepared from silylmethylene malonate **75** (153 mg, 0.5 mmol) and *n*-heptanal (0.71 mL, 5 mmol) according to *General Procedure* **5.4.1.II.** Yield: 157 mg (75%). Diastereoisomer ratio (*syn*/*anti* = 81/19) was determined from ^{1}H NMR of the crude product. Data for ***syn*-169d**: IR (film): 3070, 3048, 2957, 2930, 2858, 1745, 1727, 1465, 1427, 1250, 1152, 1110, 1029, 819 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.34 (3 H, s, CH_3Si), 0.42 (3 H, s, CH_3Si), 0.80 (t, J = 6.2 Hz, 3 H, CH[CH_2]$_4$CH_3), 1.10-1.57 (14 H, m, 2 × C$H_3$$CH_2$OCO, CH[C$H_2$]$_4$$CH_3$), 2.66 (1 H, t, J = 5.2 Hz, SiC*H*), 2.42-2.47 (1 H, m, C*H*[CH_2]$_4$$CH_3$), 3.53

(1 H, d, *J* = 5.2 Hz, C*H*CHSi), 4.01-4.17 (4 H, m, 2 × CH_3CH_2OCO), 7.31-7.37 (3 H, m, Ph), 7.52-7.58 (2 H, m, Ph), 9.51 (1 H, d, *J* = 2.2 Hz, CHC*H*O); ^{13}C NMR (50 MHz, $CDCl_3$): δ = –2.4, –1.4, 13.9 (3 C), 22.3, 26.9, 27.4, 28.5, 31.5, 51.3, 51.8, 61.4, 61.6, 127.8 (2 C), 129.0, 134.0 (2 C), 138.7, 169.7 (2 C), 204.2; ESI-HRMS: Found: M^+ + H, 421.2415, requires M^+ + H $C_{23}H_{37}O_5Si$ 421.2410; HPLC of *syn* **169d**: Daicel chiralpak AD-H, 2-propanol/ hexane (0.4/99.6), flow rate = 0.6 mL/min, t_R = 18.63 min (98.9%), t_R = 37.36 min (1.1%).

(4*S*,5*S*)-5-Ethyltetrahydro-4-dimethylphenylsilyl-2H-2-pyranone 172

Acetic acid (0.26 mL) was added to a stirred solution of aldehyde **169a** (94.5 mg, 0.25 mmol) in THF (1 mL) at 0 °C followed by the addition of sodium cyanoborohydride (22 mg, 0.35 mmol). The reaction mixture was allowed to return to room temperature and stirred overnight. Brine (1 mL) was added to the reaction mixture and the pH was adjusted to 7 by adding saturated $NaHCO_3$ solution. The reaction mixture was extracted with CH_2Cl_2 and the organic extract was dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was dissolved in 10% aqueous methanol (3.5 mL) after which lithium hydroxide (42 mg, 1.0 mmol) was added to the solution at room temperature. After being left overnight, the solvent was evaporated under reduced pressure and the residue was diluted with water (1 mL), acidified with dil HCl and extracted with ethyl acetate. The organic extract was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was heated under an argon atmosphere at 110 °C for 0.5 h cooled to room temperature and purified by column chromatography to give lactone **172** as a single diastereoisomer.

Yield: 47.0 mg (71%); IR (film): 3069, 2960, 2876, 1746, 1427, 1378, 1257, 1112, 1045, 832, 815, 774, 737 cm^{-1}; ^{1}HNMR (200 MHz, CDCl3): δ = 0.34 (6 H, s, $[CH_3]_2Si$), 0.81 (3 H, t, J = 7.2 Hz, CH_2CH_3) 0.97– 1.05 (1 H, m, Si*H*CH_2CO-), 1.19–1.41 (2 H, m, CH_2CH_3), 1.71–1.83 (1 H, m, $CH_3CH_2CHCH_2O$-), 2.26 (1 H, dd, J = 11.2, 15.6 Hz, $SiCHCH_AH_BCO$-), 2.42 (1 H,dd, J = 7, 5.4 Hz, $SiCHCH_AH_BCO$-), 3.95 (1 H, dd, J = 4, 11.6 Hz, CH_AH_BOCO), 4.09 (1 H, dd, J = 3.8, 11.6 Hz, CH_AH_BOCO), 7.35–7.40 (3 H, m, Ph), 7.46–7.50 (2 H, m, Ph); ^{13}C NMR (50 MHz, CDCl3): δ = –5.4, –5.1, 11.4, 23.0, 27.1, 29.5, 35.5, 69.6, 128.0 (2C), 129.6, 133.7 (2C), 135.8, 174.2; ESI-HRMS: Found: M^+ + Na, 285.1281, requires M^+ + Na $C_{15}H_{22}NaO_2Si$ 285.1292; $[\alpha]_D^{26}$ = +46.0 (c = 1.34, $CHCl_3$). HPLC: Daicel chiralpak AD-H, 2-propanol/ hexane (1/99), flow rate = 1.0 mL/min, t_R = 15.65 min (98.5%), t_R = 19.17min (1.5%).

(4*S*,5*S*)-5-Ethyltetrahydro-4-hydroxy-2H-2-pyranone 170

Potassium bromide (54 mg, 0.46 mmol) was added to a stirred solution of lactone **172** (100 mg, 0.38 mmol) and peracetic acid (35% solution in acetic acid, 3 mL) at 0 °C followed by H_2O_2 (30%, 0.1 mL). The reaction mixture was allowed to return to room temperature and stirred for 24 h. The solvent was removed under reduced pressure and the residue was dissolved in dichloromethane. The organic phase was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was purified by column chromatography to give lactone **170**.

Yield: 32 mg (55%); IR (film): 3437, 3019, 2967, 2933, 2881,1731, 1241, 1054, 910, 760, 733 cm^{-1}; ^{1}HNMR (200 MHz, CDCl3): δ = 0.98 (3 H, t, J = 7.6 Hz, CH_2CH_3), 1.22–1.43 (1 H, m, $CH_3CH_2CHCH_2O$), 1.52–1.85 (2 H, m, CH_2CH_3), 2.4 (br s, OH), 2.52 (1 H, dd, J

= 5.8, 17.4 Hz, CH_AH$_B$COO), 2.89 (1 H, dd, J = 5.0, 17.6 Hz, CH$_A$$H_B$COO), 3.89–3.99 (2 H, m, C$H_A$$H_B$OCO), 4.46 (1 H, dd, J = 4.4, 11.4 Hz, CHOH). 13C NMR (50 MHz, CDCl3): δ = 11.2, 21.6, 38.0, 42.3, 67.8, 69.2, 171.1; $[\alpha]_D^{28}$ = +22.3 (c = 0.94, $CHCl_3$) *lit.*[160] value for the antipode of **170**; $[\alpha]_D^{25}$ = – 23 (c = 0.45, $CHCl_3$).

(3R,4S,5S)-5-Ethyltetrahydro-4-dimethylphenylsilyl-3-methyl-2H-2-pyranone 173

n-Butyl lithium (0.21 mL, 1.6 M in hexane, 0.33 mmol) was added to a stirred solution of diisopropylamine (0.05 mL, 0.33 mmol) in THF (1 mL) at –78 °C and the solution was stirred at 0 °C for 0.5 h. The reaction mixture was cooled to –78 °C and a solution of the lactone **172** (88 mg, 0.33 mmol) in THF (0.5 mL) was added to it. After 1.5 h stirring under these conditions, methyliodide (0.1 mL, 1.6 mmol) was added to the reaction mixture and allowed to return to room temperature. After being left overnight, the reaction mixture was diluted with water and extracted with 1:1 hexane–ethyl acetate. The organic extract was washed with brine and dried over Na_2SO_4. The solvent was evaporated and the residue was purified to give the methylated lactone **173**.

Yield: 79 mg, (87%); IR (film): 3070, 2960, 2880, 1746, 1427, 1370, 1252, 1112, 1030, 832, 817, 772, 735 cm^{-1}; ^{1}H NMR (200 MHz, CDCl3): δ = 0.39 (6 H, s, $[CH_3]_2$Si), 0.66-0.86 (4 H, m, $CH_2C$$H_3$, SiCH), 1.10 (3 H, d, J = 6.6 Hz, COCHCH_3), 1.13–1.51 (2 H, m, CH_2CH_3), 1.65–1.82 (1 H, m, $CH_3CH_2C$$H$$CH_2$O-), 2.37–2.53 (1 H, m, $CH_3C$$H$COO), 3.88 (1 H, dd, J = 3.0, 11.4 Hz, CH_AH$_B$COO), 4.09 (1 H, dd, J = 2.4, 11.6 Hz, CH$_A$$H_B$COO), 7.34–7.38 (3 H, m, Ph), 7.47–7.52 (2 H, m, Ph); ^{13}C NMR (50 MHz, CDCl3): δ = –3.8, –3.6, 11.3, 17.0, 27.4, 31.6, 34.2, 36.9, 67.8, 128.0 (2 C), 129.5, 133.7 (2 C), 136.7, 176.8;

ESI-HRMS: Found: M^+ + Na, 299.1449, requires M^+ + Na $C_{16}H_{24}NaO_2Si$ 299.1438; $[\alpha]_D^{26}$ = +37.2 (*c* = 0.78, $CHCl_3$).

(3*R*,4*S*,5*S*)-1-Benzyl-4-dimethylphenylsilyl-5-ethyl-2-oxopiperidine-3-carboxylic acid ethyl ester 178

Sodium triacetoxyborohydride (85 mg, 0.4 mmol) was added to a stirred solution of the aldehyde **169a** (94.5 mg 0.25 mmol) and benzylamine (30 μL, 0.25 mmol) in CH_2Cl_2 (2 mL) at 0 °C followed by the addition of acetic acid (15 μL, 0.25 mmol). The reaction mixture was allowed to return to room temperature and stirred overnight. The reaction mixture was diluted with saturated $NaHCO_3$ solution and extracted with ethyl acetate. The organic extract was dried over Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography followed by crystallization to give lactam **178** as a white crystalline solid and as a single diastereoisomer.

Yield: 68 mg (65%); M.p. = 92–93 °C; IR: 3068, 3000, 2961, 2917, 2874, 1731, 1659, 1428, 1252, 1215,1183, 1113, 755 cm^{-1}; ^{1}H NMR (200 MHz, CDCl3): δ = 0.30 (3 H s, CH_3Si), 0.32 (3 H, s, CH_3Si), 0.58 (3 H, t, *J* = 7.3 Hz, CH_2CH_3), 1.02–1.16 (2 H, m, CH_2CH_3), 1.24 (3 H t, *J* = 7.1 Hz, CH_3CH_2OCO), 1.65 (2 H, m, SiC*H*,$CH_3CH_2CHCH_2N$) 2.83–3.04 (2 H, m, NCH_ACH_BCH), 3.35 (1 H, d, *J* = 6 Hz, $COCHCO_2CH_2CH_3$), 4.01–4.21 (2 H, m, CH_3CH_2OCO), 4.35 (1 H, d, *J* = 14.6 Hz, NCH_AH_BPh), 4.66 (1 H, d, *J* = 14.6 Hz, NCH_AH_BPh), 7.17–7.28 (5 H, m, Ar), 7.31–7.38 (3 H, m, Ph), 7.48– 7.52 (2 H, m, Ph), ^{13}C NMR (50 MHz, CDCl3): δ = – 4.7, –4.6, 11.4, 13.9, 27.1, 27.8, 36.2, 49.0, 49.5, 50.4, 61.4, 127.4, 127.8 (2C), 128.3 (2C), 128.5 (2C), 129.4, 134.0 (2C), 136.3, 136.8, 168.3,

171.3; Anal. Calcd for $C_{25}H_{33}NO_3Si$: C, 70.88; H, 7.85; N, 3.31%. Found; C, 70.46; H, 8.11; N, 3.46%.; $[\alpha]_D^{27} = -19$ (*c* = 1.0, $CHCl_3$).

(3*R*,4*S*,5*S*)-(1-Benzyl-4-dimethylphenylsilyl-5-ethylpiperidine-3-yl)-methanol 179

A solution of lactam ester **178** (78 mg, 0.18 mmol) in THF (3 mL) was added dropwise to a stirred suspension of LiAlH4 (35 mg, 0.9 mmol) in THF (3 mL) at 0 °C. The reaction mixture was heated at reflux overnight. A solution of sodium hydroxide (2 M, 3 mL) was added to the reaction mixture and stirred for 30 min. The reaction mixture was diluted with Rochelle's salt solution (20 mL) and extracted with ethyl acetate. The organic extract was washed with brine and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography to give piperidine alcohol **179**.

Yield: 46 mg (70%); IR (film): 3377, 2957, 2929, 2898, 2873, 2803, 1454, 1427, 1249, 1110, 1028 816, 754, 699 cm^{-1}; ^1H NMR (200 MHz, CDCl3): δ = 0.34 (3 H, s, C*H*$_3$Si), 0.35 (3 H, s, C*H*$_3$Si), 0.71 (3 H, t, *J* = 7.3 Hz, CH_2CH_3), 0.89 (1 H, t, *J* = 5 Hz, SiCH), 1.31–1.52 (2 H, m, C*H*$_2$CH$_3$), 1.55–1.70 (1 H, m, $CH_3CH_2CHCH_2N$), 1.84–1.96 (1 H, m, $OHCH_2CH$), 2.12– 2.46 (5 H, m, NC*H*$_2$CH, NC*H*$_2$CHCH$_2$OH, CH$_2$O*H*), 3.34–3.63 (4 H, m, NC*H*$_2$Ph), 7.26–7.35 (8 H m, Ph, Ar), 7.48–7.53 (2 H m, Ph); ^{13}C NMR (50 MHz, CDCl3): δ = – 2.5, – 1.9, 12.2, 27.0, 29.4, 36.3, 37.5, 55.7, 57.4, 63.2, 67.9, 127.2, 127.8 (2 C), 128.2 (2 C), 128.9, 129.0 (2 C), 133.7 (2 C), 137.5, 139.1.; ESI-HRMS: Found: M^+ + H, 368.2385, requires M^+ + H $C_{23}H_{34}NOSi$ 368.2404; $[\alpha]_D^{26} = +5.0$ (*c* = 2.36, $CHCl_3$).

(2*R*,3*S*)-(1,1)-Bis(ethoxycarbonyl)-2-dimethylphenylsilylpentan-3-yl formate 197

A solution of 3-chloroperoxybenzoic acid (~70%) (375 mg, 1.5 mmol, 1.5 equiv) in dichloromethane (10 mL) was pre-dried over anhydrous $MgSO_4$ and added to a stirred mixture of the respective aldehydes **169a** (378 mg,1 mmol, 1 equiv) and $Na_2HPO_4, 2H_2O$ (356 mg, 2 mmol, 2 equiv) in dichloromethane (7 mL) at 0 °C. The reaction mixture was brought to room temperature and stirred under those conditions for 4 h. The reaction mixture was quenched with aqueous sodium metabisulfite solution and extracted with dichloromethane. The combined organic extract was washed with $NaHCO_3$ solution followed by water and brine, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica using hexane/EtOAc (95/5) as eluent to give the desired formate esters **197**.

Yield: 299 mg (76%); Diastereoisomer ratio (*syn*/*anti* = 86/14) was determined from ^{1}H NMR of the crude product. IR (film): 3070, 3047, 2956, 2932, 2872, 1747, 1729, 1373, 1178, 1110, 1033, 820 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.33 (3 H, s, C*H*$_3$Si), 0.44 (3 H, s, C*H*$_3$Si), 0.67 (3 H, t, *J* = 7.3 Hz, OCHCH$_2$C*H*$_3$), 1.20-1.28 (6 H, m, 2 × C*H*$_3$CH$_2$OCO), 1.35-1.67 (2 H, m, OCHC*H*$_2$CH$_3$), 2.25 (1 H, q, *J* = 3.6 Hz, SiCH), 3.65 (1 H, d, *J* = 3.6 Hz, SiCHC*H*), 4.00-4.21 (4 H, m, 2 × CH$_3$C*H*$_2$OCO), 5.12-5.19 (1 H, m, SiCHC*H*OCO), 7.32-7.35 (3 H, m, Ph), 7.64-7.59 (2 H, m, Ph), 7.96 (1 H, s, OCO*H*). ^{13}C NMR (50 MHz, $CDCl_3$): δ = –3.5, –1.6, 9.3, 13.8, 13.9, 27.1, 30.6, 50.2, 61.2, 61.5, 74.9, 127.7 (2 C), 129.0, 134.0 (2 C), 138.7, 160.4, 169.7, 170.0; $[\alpha]_D^{25}$ = + 12.46 (*c* = 3.7, $CHCl_3$).

(4*S*,5*R*)-5-Ethyl-dihydro-4-dimethylphenylsilylfuran-2(3*H*)-one 195

Potassium hydroxide (280 mg, 5 mmol, 5 equiv) was added to a stirred solution of the formyl esters **197** (394 mg, 1 mmol) in methanol (7 mL) at room temperature. After 12 h, the solvent was evaporated under reduced pressure and the residue was diluted with water (2 mL), acidified with dil. HCl and extracted with ethyl acetate. The organic extract was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was heated at 110 °C under nitrogen for 5 h, cooled to room temperature and purified by column chromatography on silica using hexane/EtOAc (95/5) as eluent to give the desired butyrolactones **195** as a single diastereoisomer.

Yield: 160 mg (65%); IR (film): 3019, 2957, 2930, 2871, 1774, 1426, 1372, 1176, 1111, 821 cm^{-1}, ^1H NMR (200 MHz, $CDCl_3$): δ = 0.35 (6 H, s, $[CH_3]_2Si$), 0.94 (3 H, t, J = 7.3 Hz, CH_2CH_3), 1.46-1.69 (3 H, m, CH_2CH_3, SiC*H*), 2.28-2.62 (2 H, m, $SiCHCH_AH_BCO$), 4.23-4.33 (1 H, m, C*H*OCO), 7.34-7.48 (5 H, m, Ph); ^{13}C NMR (50 MHz, $CDCl_3$): δ = –4.8, –4.5, 9.8, 28.3, 29.0, 31.8, 84.6, 128.1 (2 C), 129.7, 133.5 (2 C), 135.4, 176.9; ESI-HRMS: Found: M^+ + Na, 271.1130, requires M^+ + Na $C_{14}H_{20}NaO_2Si$ 271.1128; $[\alpha]_D^{25}$ = +31.8 (c = 0.66, $CHCl_3$).

(*R*)-5-Ethyl-2*(*5H*)*-furanone 190

Potassium bromide (143 mg, 1.2 mmol, 1.2 equiv) was added to a stirred solution lactones **195** (248mg, 1 mmol) in peracetic acid (6 mL of a 35% solution in acetic acid) at 0 °C followed by addition of H_2O_2 (30%, 0.15 mL). The reaction mixture was allowed to attain to room temperature and stirred for 24 h. The solvent was removed under reduced pressure and the residue was dissolved in dichloromethane. The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure to give the crude hydroxyl lactones.

Methanesulfonyl chloride (50 µL, 0.65 mmol) was added to a stirred solution of the crude hydroxylactone (0.6 mmol) and triethylamine (168 µL, 1.2 mmol) in dichloromethane (4 mL) at 0 °C. After 1 h, the reaction mixture was quenched with saturated ammonium chloride solution. The reaction mixture was extracted with dichloromethane and the extract was evaporated to give the crude butenolide which was purified by column chromatography to give the pure **190**.

Yield: 51 mg (75%); IR (film): 3018, 2957, 2931, 2860, 1754, 1600,1465, 1334, 1163, 1096, 1024, 819 and 756 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.98 (3 H, t, *J* = 7.4 Hz, CH_2CH_3), 1.59-1.89 (2 H, m, CH_2CH_3), 4.95-5.01 (1 H, m, CHOCO), 6.09 (1 H, dd, *J* = 5.7 Hz, *J* = 1.9 Hz, CH=CHCO), 7.43 (1 H, dd, *J* = 5.7 Hz, *J* = 1.3 Hz, CH=CHCO). ^{13}C NMR (50 MHz, $CDCl_3$): δ 8.9, 26.3, 84.2, 121.8, 155.8, 173.0; $[\alpha]_D^{24}$ = –91.8 (*c* = 1.46, MeOH) *lit.*[172] $[\alpha]_D^{20}$ = -94 (*c* = 1.05, CH_2Cl_2).

(2R,3S)-1,1-bis(ethoxycarbonyl)-2-dimethylphenylsilylheptan-3-yl formate 209

A solution of 3-chloroperoxybenzoic acid (~70%) (375 mg, 1.5 mmol, 1.5 equiv) in dichloromethane (10 mL) was pre-dried over anhydrous $MgSO_4$ and added to a stirred mixture of the respective aldehydes **165c** (406 mg,1 mmol, 1 equiv) and $Na_2HPO_4, 2H_2O$ (356 mg, 2 mmol, 2 equiv) in dichloromethane (7 mL) at 0 °C. The reaction mixture was brought to room temperature and stirred under those conditions for 4 h. The reaction mixture was quenched with aqueous sodium metabisulfite solution and extracted with dichloromethane. The combined organic extract was washed with $NaHCO_3$ solution followed by water and brine, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica using hexane/EtOAc (95/5) as eluent to give the desired formate esters **209**.

Yield: 312 mg (74%). Diastereoisomer ratio (*syn*/*anti* = 84/16) was determined from ^{1}H NMR of the crude product. IR (film): 3070, 3047, 2958, 2934, 2873, 1748, 1729, 1373, 1178, 1111, 1033, 820 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.33 (3 H, s, C*H*$_3$Si), 0.44 (3 H, s, C*H*$_3$Si), 0.71 (3 H, t, *J* = 6.6 Hz, OCH[CH_2]$_3$C*H*$_3$), 0.96-1.07 (4 H, m, OCHCH_2[C*H*$_2$]$_2$CH_3), 1.20-1.28 (6 H, m, 2 × C*H*$_3$CH_2OCO), 1.35-1.67 (2 H, m, OCHC*H*$_2$[CH_2]$_2$CH_3), 2.24 (1 H, q, *J* = 3.6 Hz, SiCH), 3.65 (1 H, d, *J* = 3.6 Hz, SiCHC*H*), 4.00-4.21 (4 H, m, 2 × CH_3C*H*$_2$OCO), 5.12-5.19 (1 H, m, SiCHC*H*OCO), 7.32-7.35 (3 H m, Ph), 7.64-7.59 (2 H, m, Ph), 7.94 (1 H, s, OCO*H*); ^{13}C NMR (50 MHz, $CDCl_3$): δ = –3.6, –1.5, 13.7, 13.9, 14.0, 22.1, 27.0, 31.0, 33.9, 50.2, 61.2, 61.5, 73.8, 127.8 (2C), 129.0, 134.0 (2 C), 138.8, 160.3, 169.7, 169.9. $[\alpha]_D^{25}$ = + 12.8 (*c* 1.64, $CHCl_3$).

(4*S*,5*R*)-5-butyl-dihydro-4-dimethylphenylsilyl furan-2(3*H*)-one 207

Potassium hydroxide (280 mg, 5 mmol, 5 equiv) was added to a stirred solution of the formyl esters **209** (422 mg, 1 mmol) in methanol (7 mL) at room temperature. After 12 h, the solvent was evaporated under reduced pressure and the residue was diluted with water (2 mL), acidified with dil. HCl and extracted with ethyl acetate. The organic extract was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was heated at 110 °C under nitrogen for 5 h, cooled to room temperature and purified by column chromatography on silica using hexane/EtOAc (95/5) as eluent to give the desired butyrolactones **207** as a single diastereoisomer.

Yield: 165 mg (60%); IR (film): 3019, 2957, 2932, 2859, 1774, 1427, 1254, 1210, 1112, 836, 758 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.36 (6 H s, [CH_3]$_2$Si), 0.83 (3 H, t, *J* = 7.0 Hz, [CH_2]$_3$C*H*$_3$), 1.17-1.31 (3 H, m, alkyl), 1.36-1.52 (3 H, m, alkyl), 1.62-1.72 (1 H, m, SiC*H*), 2.27-2.61 (2 H, m, SiCHC*H*$_A$*H*$_B$CO), 4.27-4.38 (1 H, m, C*H*OCO), 7.31-7.48 (5

H, m,). ^{13}C NMR (50 MHz, $CDCl_3$): δ = –4.8, –4.5, 13.7, 22.2, 27.7, 29.0, 31.8, 35.8, 83.5, 128.1 (2 C), 129.8, 133.5 (2 C), 135.5, 176.9; ESI-HRMS: Found: M^+ + Na, 299.1449, requires M^+ + Na $C_{16}H_{24}NaO_2Si$ 299.1443; $[\alpha]_D^{25}$ = +49.0 (*c* = 1.51, $CHCl_3$).

(*R*)-5-Butyl-2*(*5H*)*-furanone 201a

Potassium bromide (143 mg, 1.2 mmol, 1.2 equiv) was added to a stirred solution lactones **207** (276 mg, 1 mmol) in peracetic acid (6 mL of a 35% solution in acetic acid) at 0 °C followed by addition of H_2O_2 (30%, 0.15 mL). The reaction mixture was allowed to attain to room temperature and stirred for 24 h. The solvent was removed under reduced pressure and the residue was dissolved in dichloromethane. The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure to give the crude hydroxyl lactones. Methanesulfonyl chloride (50 µL, 0.65 mmol) was added to a stirred solution of the crude hydroxylactone (0.6 mmol) and triethylamine (168 µL, 1.2 mmol) in dichloromethane (4 mL) at 0 °C. After 1 h, the reaction mixture was quenched with saturated ammonium chloride solution. The reaction mixture was extracted with dichloromethane and the extract was evaporated to give the crude butenolide which was purified by column chromatography to give the pure **201a**.

Yield: 64 mg (77%); IR (film): 3019, 2959, 2933, 2863, 1755, 1600,1466, 1335, 1164, 1097, 1024, 819 and 754 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.89 (3 H, t, *J* = 6.9 Hz, $[CH_2]_3CH_3$), 1.25-1.51 (4 H, m, $CH_2[CH_2]_2CH_3$), 1.55-1.85 (2 H, m, $CH_2[CH_2]_2CH_3$), 4.98-5.05 (1 H, m, CHOCO), 6.08 (1 H, dd, *J* = 5.7 Hz, *J* = 1.9 Hz, C*H*=CHCO), 7.44 (1 H, dd, *J* = 5.8 Hz, *J* = 1.2 Hz, CH=C*H*CO). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.7, 22.3, 27.0, 32.8, 83.4, 121.5, 156.2, 173.0; $[\alpha]_D^{24}$ = –101.8 (*c* = 2.16, $CHCl_3$) *lit.*[178] $[\alpha]_D^{25}$ = –101 (*c* = 1.2, $CHCl_3$).

(2R,3S)-1,1-bis(ethoxycarbonyl)-2-dimethylphenylsilyl octan-3-yl formate 221

A solution of 3-chloroperoxybenzoic acid (~70%) (375 mg, 1.5 mmol, 1.5 equiv) in dichloromethane (10 mL) was pre-dried over anhydrous $MgSO_4$ and added to a stirred mixture of the respective aldehydes **169d** (421 mg,1 mmol, 1 equiv) and $Na_2HPO_4, 2H_2O$ (356 mg, 2 mmol, 2 equiv) in dichloromethane (7 mL) at 0 °C. The reaction mixture was brought to room temperature and stirred under those conditions for 4 h. The reaction mixture was quenched with aqueous sodium metabisulfite solution and extracted with dichloromethane. The combined organic extract was washed with $NaHCO_3$ solution followed by water and brine, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by column chromatography on silica using hexane/EtOAc (95/5) as eluent to give the desired formate esters **221**.

Yield: 314 mg(72%). Diastereoisomer ratio (*syn*/*anti* = 81/19) was determined from ^{1}H NMR of the crude product. IR (film): 3070, 3047, 2955, 2930, 2871, 1746, 1730, 1372, 1176, 1111, 1033, 821 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.33 (3 H, s, C*H*$_3$Si), 0.44 (3 H, s, C*H*$_3$Si), 0.76 (3 H, t, *J* = 6.8 Hz, OCH[CH_2]$_4$C*H*$_3$), 0.94-1.20 (6 H, m, OCHCH_2[C*H*$_2$]$_3$CH_3), 1.22-1.35 (6 H, m, 2 × C*H*$_3$CH_2OCO), 1.39-1.57 (2 H, m, OCHCH_2[CH_2]$_3$CH_3), 2.23 (1 H, q, *J* = 3.6 Hz, SiCH), 3.60 (1 H, d, *J* = 3.6 Hz, SiCHC*H*), 3.98-4.21 (4 H, m, 2 × CH_3C*H*$_2$OCO), 5.16-5.25 (1 H, m, SiCHC*H*OCO), 7.32-7.35 (3 H, m, Ph), 7.54-7.58 (2 H, m, Ph), 7.94 (1 H, s, OCO*H*); ^{13}C NMR (50 MHz, $CDCl_3$): δ –3.6, –1.5, 13.7, 13.8, 13.9, 22.3, 24.5, 30.9, 31.2, 34.0, 50.2, 61.2, 61.5, 73.8, 127.7 (2 C), 129.0, 134.0 (2 C), 138.8, 160.2, 169.7, 169.9; $[\alpha]_D^{23}$ = + 9.73 (*c* 1.85, $CHCl_3$).

(4*S*,5*R*)-5-pentyl-dihydro-4-dimethylphenylsilyl furan-2(3*H*)-one 219

Potassium hydroxide (280 mg, 5 mmol, 5 equiv) was added to a stirred solution of the formyl esters **221** (437 mg, 1 mmol) in methanol (7 mL) at room temperature. After 12 h, the solvent was evaporated under reduced pressure and the residue was diluted with water (2 mL), acidified with dil. HCl and extracted with ethyl acetate. The organic extract was dried over Na_2SO_4 and evaporated under reduced pressure. The residue was heated at 110 °C under nitrogen for 5 h, cooled to room temperature and purified by column chromatography on silica using hexane/EtOAc (95/5) as eluent to give the desired butyrolactones **219** as a single diastereoisomer.

Yield: 185 mg (64%); IR (film): 3019, 2956, 2933, 2859, 1773, 1428, 1254, 1210, 1111, 836, 757 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 0.36 (6 H, s, $[CH_3]_2Si$), 0.84 (3 H, t, J = 6.5 Hz, $[CH_2]_4CH_3$), 1.13-1.32 (5 H, m, alkyl), 1.37-151 (3 H, m, alkyl), 1.62-1.72 (1 H, m, SiC*H*), 2.27-2.62 (2 H, m, $SiCHCH_AH_BCO$), 4.27-4.37 (1 H, m, CH), 7.36-7.48 (5 H, m,); ^{13}C NMR (50 MHz, $CDCl_3$): δ –4.8, –4.4, 13.8, 22.3, 25.3, 29.0, 31.3, 36.1, 83.6, 128.2 (2 C), 129.8, 133.7 (2 C), 135.5, 177.0; ESI-HRMS: Found: M^+ + Na, 313.1598, requires M^+ + Na $C_{17}H_{26}NaO_2Si$ 313.1600; $[\alpha]_D^{25}$ = +45.12 (c = 0.82, $CHCl_3$).

(*R*)-5-Pentyl-2*(*5H*)*-furanone 212

Potassium bromide (143 mg, 1.2 mmol, 1.2 equiv) was added to a stirred solution lactones **219** (290 mg, 1 mmol) in peracetic acid (6 mL of a 35% solution in acetic acid) at 0 °C followed by addition of H_2O_2 (30%, 0.15 mL). The reaction mixture was allowed to attain to room temperature and stirred for 24 h. The solvent was removed under reduced pressure and the residue was dissolved in dichloromethane. The organic phase was dried (Na_2SO_4) and evaporated under reduced pressure to give the crude hydroxyl lactones.

Methanesulfonyl chloride (50 µL, 0.65 mmol) was added to a stirred solution of the crude hydroxylactone (0.6 mmol) and triethylamine (168 µL, 1.2 mmol) in dichloromethane (4 mL) at 0 °C. After 1 h, the reaction mixture was quenched with saturated ammonium chloride solution. The reaction mixture was extracted with dichloromethane and the extract was evaporated to give the crude butenolide which was purified by column chromatography to give the pure **212**.

Yield: 70 mg (76%); IR (film): 3018, 2957, 2931, 2858, 1752, 1600,1465, 1334, 1163, 1095, 1024, 819, 757 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 0.85 (3 H, t, *J* = 6.5 Hz, $[CH_2]_4CH_3$), 1.16-1.48 (6 H, m, $CH_2[CH_2]_3CH_3$), 1.53-1.83 (2 H, m, $CH_2[CH_2]_3CH_3$), 4.96-5.04 (1 H, m, CHOCO), 6.06 (1 H, dd, *J* = 5.6 Hz, *J* = 1.9 Hz, CH=CHCO), 7.43 (1 H, dd, *J* = 5.7 Hz, *J* = 1.3 Hz, CH=CHCO). ^{13}C NMR (50 MHz, $CDCl_3$): δ 13.8, 22.3, 24.6, 31.4, 33.1, 83.4, 121.4, 156.2, 173.0; $[\alpha]_D^{24}$ = –93.28 (*c* 2.53, $CHCl_3$) *lit*[180]. $[\alpha]_D^{25}$ = –90.1 (*c* = 1.76, $CHCl_3$).

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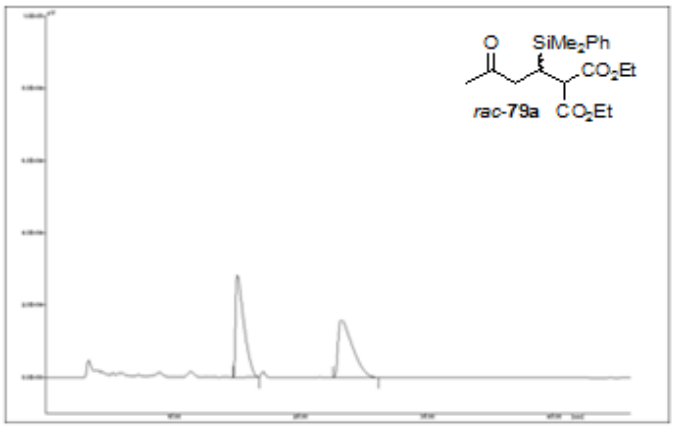
APPENDIX

HPLC Chromatograph for products 79a-k and 169a-d

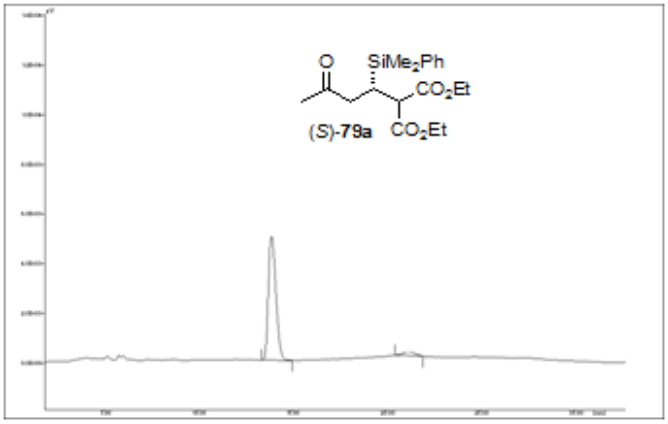


File name : rc-oc-122B088.CH3

Injection Date :31-Mar-2009 16:34:10

Control Method :RNC1

Name	RT	Area[µV.Sec]	%Area	Corr.Area
(*S*)-**79a**	15.100	1210468.500	49.981	1210468.50
(*R*)-**79a**	23.325	1211393.750	50.019	1211393.75

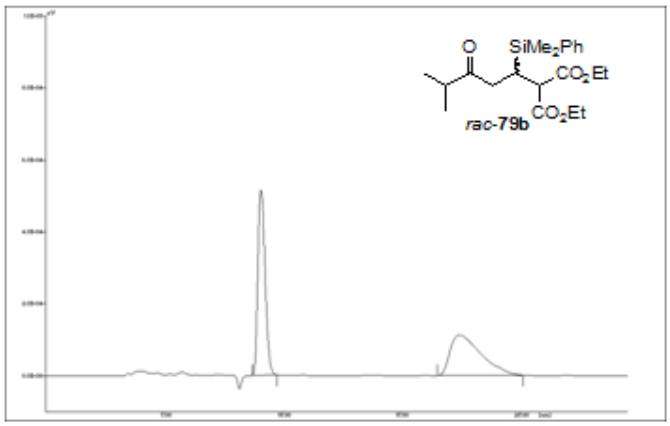


File name : RC-0C-36B033.CH3

Injection Date :18-Jul-2008 11:35:22

Control Method :RNC1

Name	RT	Area[µV.Sec]	%Area	Corr.Area
(*S*)-**79a**	13.883	1210468.500	94.903	129201.57
(*R*)-**79a**	21.100	6939.365	5.097	6939.37

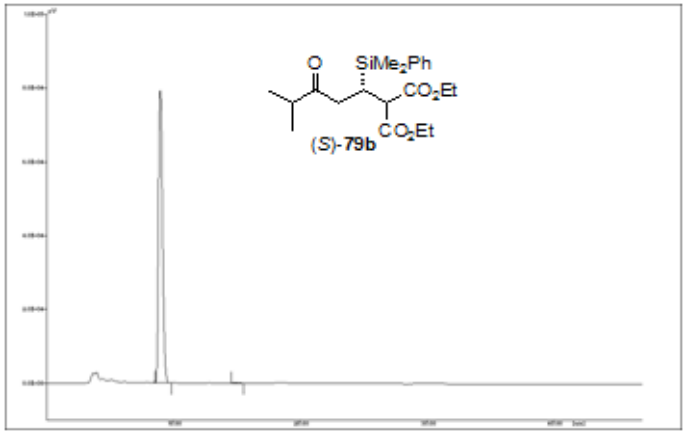


File name : rc-oc-105B076.CH3

Injection Date :15-Jan-2009 14:39:54

Control Method :RNC1

Name	RT	Area[µV.Sec]	%Area	Corr.Area
(*S*)-**79b**	9.058	1007467.000	50.202	1007467.00
(*R*)-**79b**	17.425	999362.000	49.798	999362.00

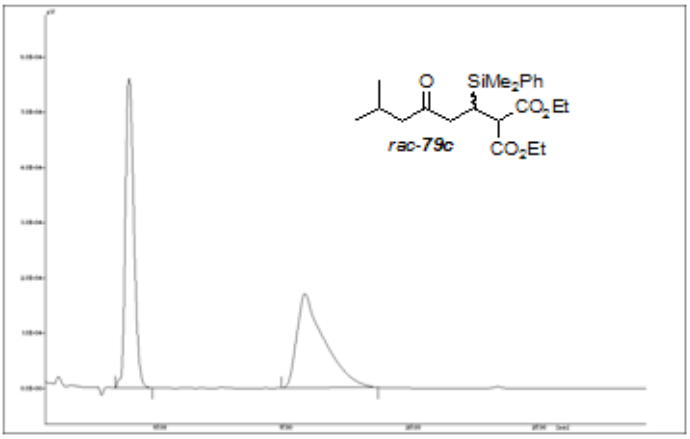


File name : rc-oc103B022.CH3

Injection Date :11-Nov-2008 14:40:44

Control Method :RNC1

Name	RT	Area[µV.Sec]	%Area	Corr.Area
(*S*)-**79b**	8.933	1513453.640	99.718	1513453.64
(*R*)-**79b**	15.067	4282.500	0.282	4282.50

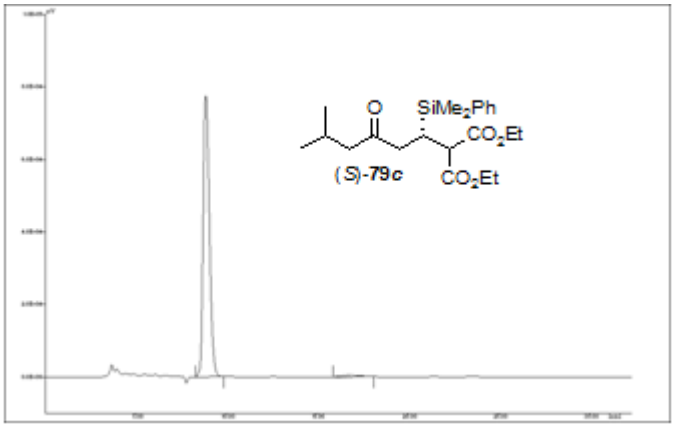


File name : rc-oc74B019.CH3

Injection Date :10-Nov-2008 16:44:52

Control Method :RNC1

Name	RT	Area[µV.Sec]	%Area	Corr.Area
(*S*)-**79c**	8.825	1218762.500	49.020	1218762.50
(*R*)-**79c**	15.775	1267497.500	50.980	1267497.50

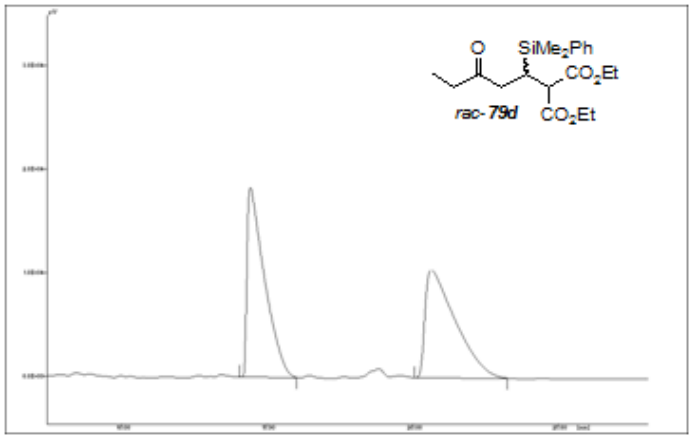


File name : rc-oc-97B017.CH3

Injection Date :10-Nov-2008 15:46:50

Control Method :RNC1

Name	RT	Area[µV.Sec]	%Area	Corr.Area
(*S*)-**79c**	8.825	1700961.930	98.348	1700961.93
(*R*)-**79c**	16.800	28572.000	1.652	28572.00

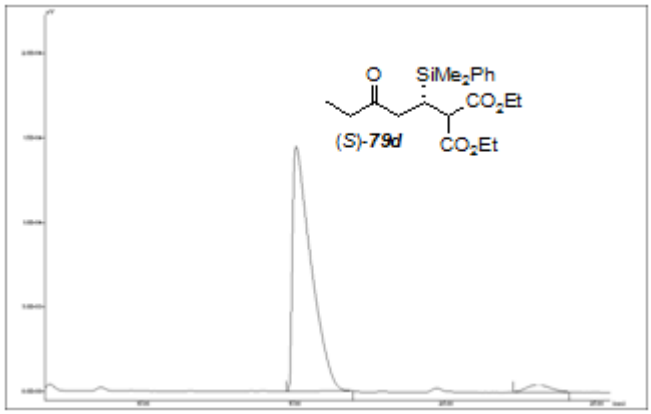


File name : rc-oc-196B127.CH3

Injection Date : 8-Jun-2009 15:47:18

Control Method :RNC1

Name	RT	Area[µV.Sec]	%Area	Corr.Area
(*S*)-**79d**	14.408	737686.500	50.086	737686.50
(*R*)-**79d**	20.625	735148.955	49.914	735148.96

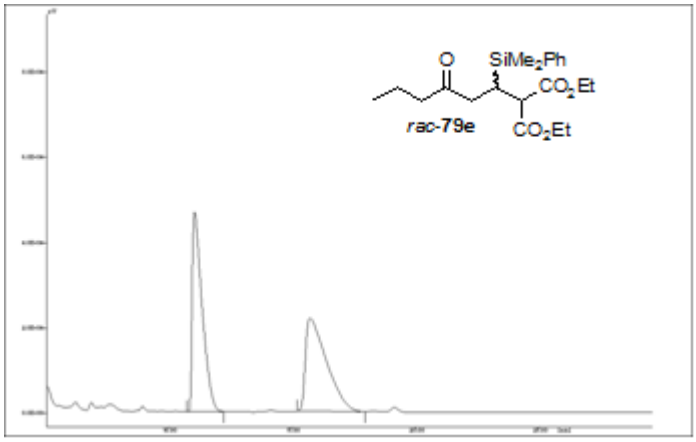


File name : rc-oc-197B129.CH3

Injection Date : 8-Jun-2009 17:09:10

Control Method :RNC1

Name	RT	Area[µV.Sec]	%Area	Corr.Area
(*S*)-**79d**	15.083	598863.500	96.363	598863.50
(*R*)-**79d**	23.058	22603.000	3.637	22603.00

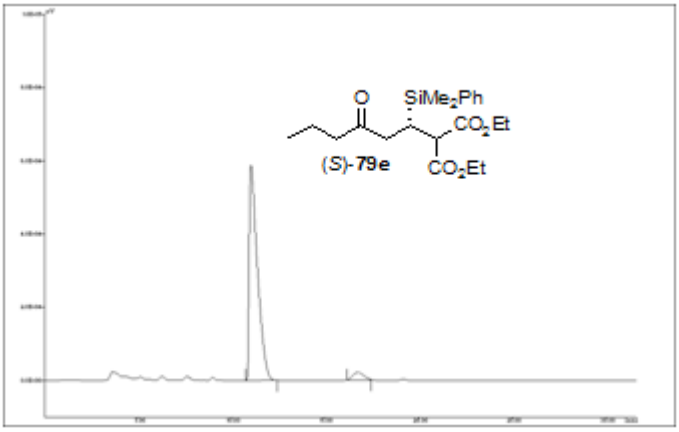


File name : rc-oc-206B130.CH3

Injection Date :16-Jun-2009 11:11:54

Control Method :RNC1

Name	RT	Area[µV.Sec]	%Area	Corr.Area
(*S*)-**79e**	11.042	1237518.235	49.402	1237518.23
(*R*)-**79e**	15.725	1267481.500	50.598	1267481.50

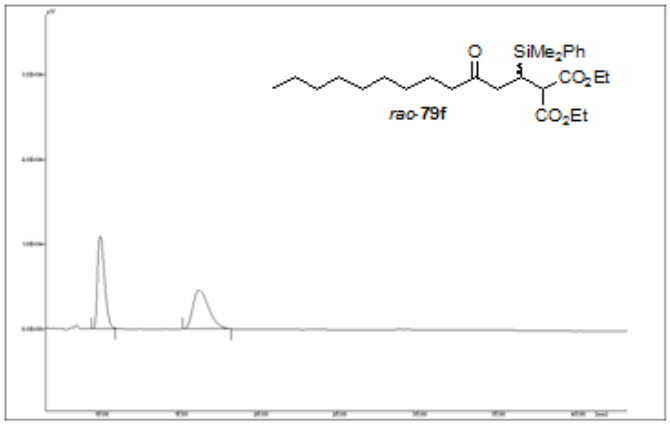


File name : rc-oc-207B131.CH3

Injection Date :16-Jun-2009 11:43:00

Control Method :RNC1

Name	RT	Area[µV.Sec]	%Area	Corr.Area
(*S*)-**79e**	11.000	1683900.993	95.588	1683900.99
(*R*)-**79e**	16.708	77729.750	4.412	77729.75

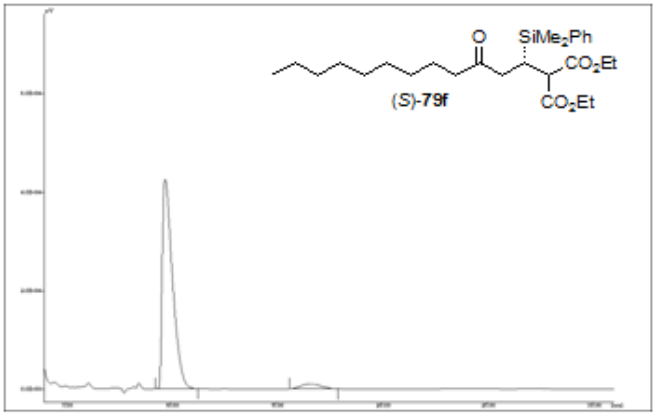


File name : rc-oc-82B011.CH3 racemic

Injection Date :10-Nov-2008 12:08:56

Control Method :RNC1

Name	RT	Area[µV.Sec]	%Area	Corr.Area
(*S*)-**79f**	9.942	305331.113	50.057	305331.11
(*R*)-**79f**	16.175	304632.000	49.94	304632.00

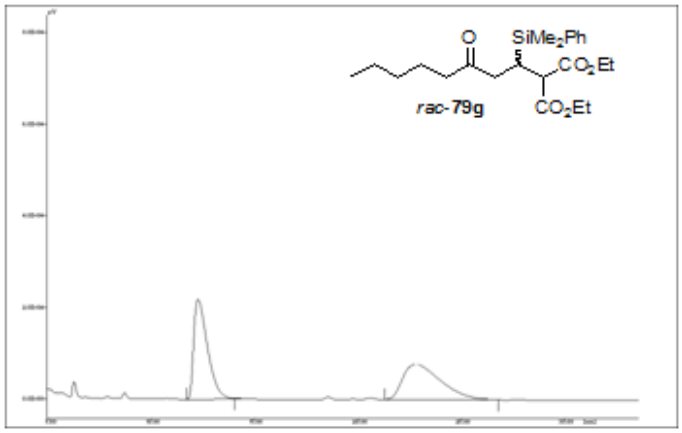


File name : rc-oc-100B013.CH3

Injection Date :10-Nov-2008 13:29:08

Control Method :RNC1

Name	RT	Area[µV.Sec]	%Area	Corr.Area
(*S*)-**79f**	9.700	1362785.608	95.572	1362785.61
(*R*)-**79f**	16.575	63135.250	4.428	63135.25

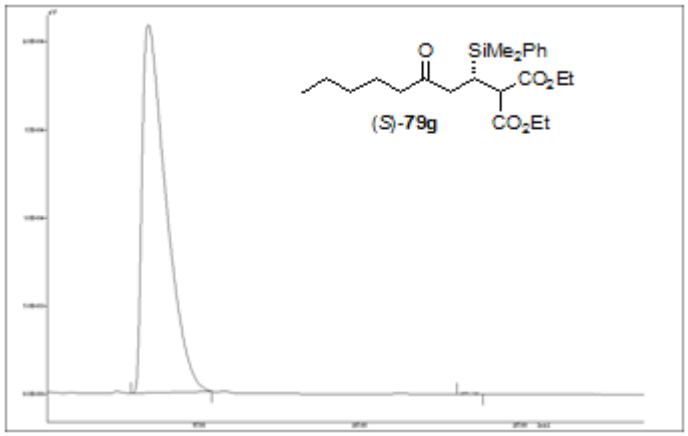


File name : RC-0C-77B060.CH3

Injection Date : 4-Sep-2008 16:29:58

Control Method :RNC1

Name	RT	Area[µV.Sec]	%Area	Corr.Area
(*S*)-**79g**	12.233	968044.688	50.231	968044.69
(*R*)-**79g**	22.758	959157.231	49.769	959157.23

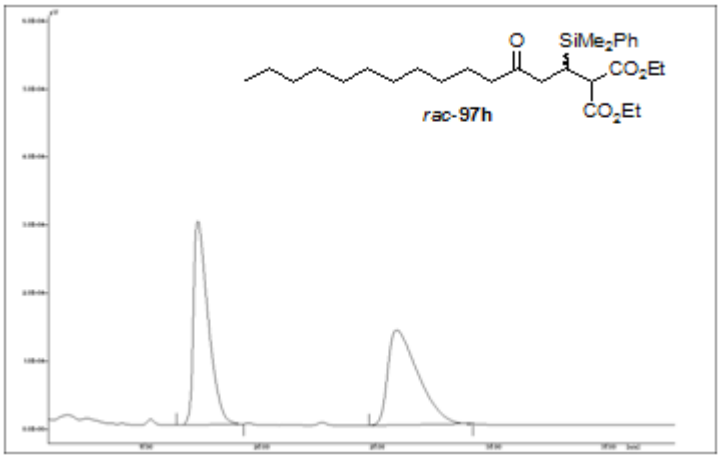


File name : rc-oc95B020.CH3

Injection Date :10-Nov-2008 17:15:10

Control Method :RNC1

Name	RT	Area[µV.Sec]	%Area	Corr.Area
(*S*)-**79g**	13.458	1056546.031	99.823	1056546.03
(*R*)-**79g**	23.458	1877.250	0.177	1877.25

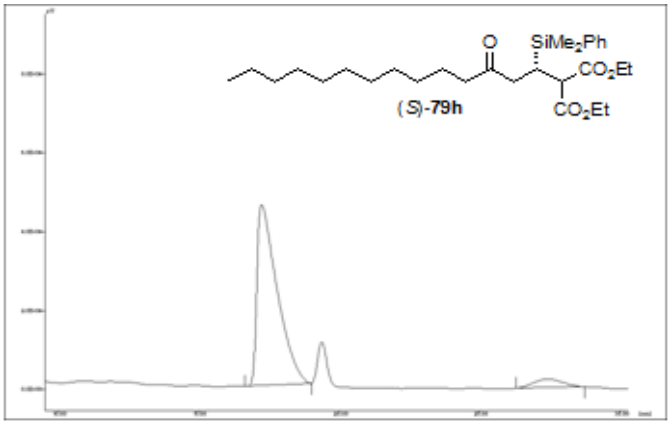


File name : rc-oc-406B027.CH3

Injection Date :28-Dec-2010 18:02:30

Control Method :RC-OC-B

Name	RT	Area[µV.Sec]	%Area
(*S*)-**79h**	17.275	1269880.151	50.535
(*R*)-**79h**	25.883	1242999.987	49.465

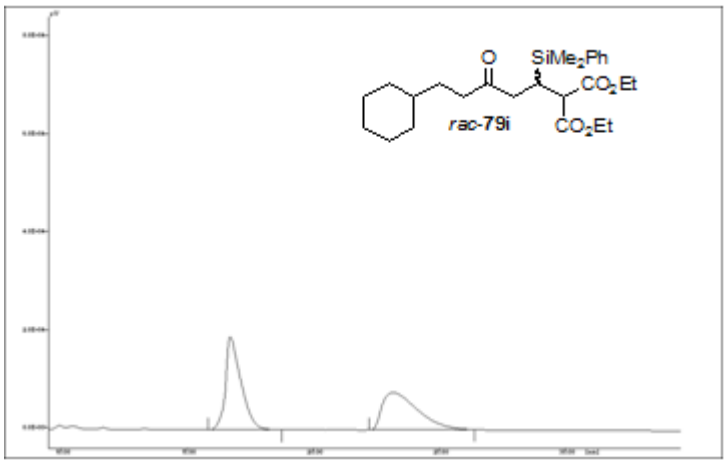


File name : rc-oc-406B026.CH3

Injection Date :28-Dec-2010 17:31:26

Control Method :RC-OC-B

Name	RT	Area[µV.Sec]	%Area
(*S*)-**79h**	17.217	2239563.644	93.545
(*R*)-**79h**	27.417	154532.500	6.45

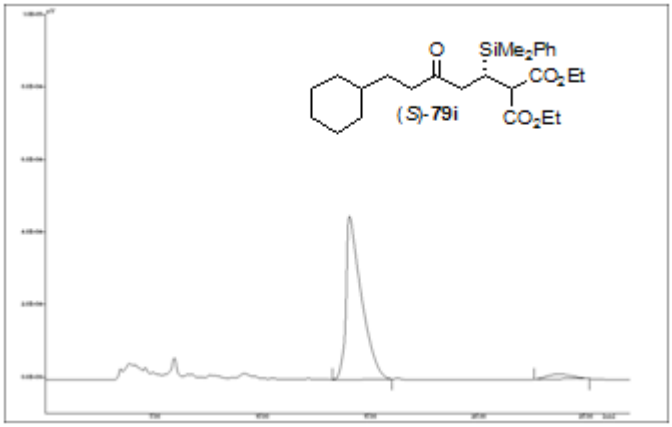


File name : rc-oc-393B014.CH3

Injection Date :26-Nov-2010 11:20:18

Control Method :RC-OC-B

Name	RT	Area[µV.Sec]	%Area
(*S*)-**79i**	16.683	784097.000	51.652
(*R*)-**79i**	23.133	733954.500	48.348

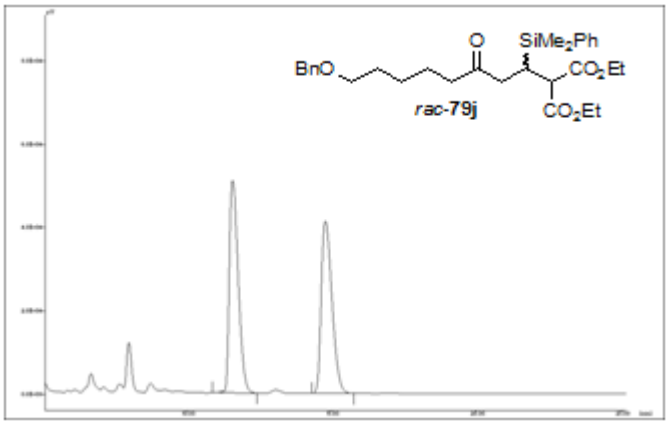


File name : rc-oc-394B015.CH3

Injection Date :26-Nov-2010 11:56:14

Control Method :RC-OC-B

Name	RT	Area[µV.Sec]	%Area
(*S*)-**79i**	14.075	2154982.250	95.266
(*R*)-**79i**	23.792	107094.750	4.734

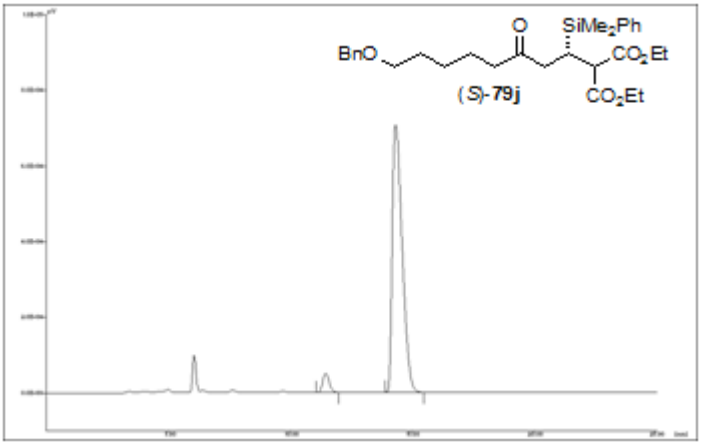


File name : rc-oc-125B099.CH3 racemic

Injection Date :23-Jan-2009 14:22:34

Control Method :RCOCB

Name	RT	Area[µV.Sec]	%Area	Corr.Area
(*S*)-**79j**	11.567	1026440.500	50.423	1026440.50
(*R*)-**79j**	14.767	1009222.750	49.577	1009222.75

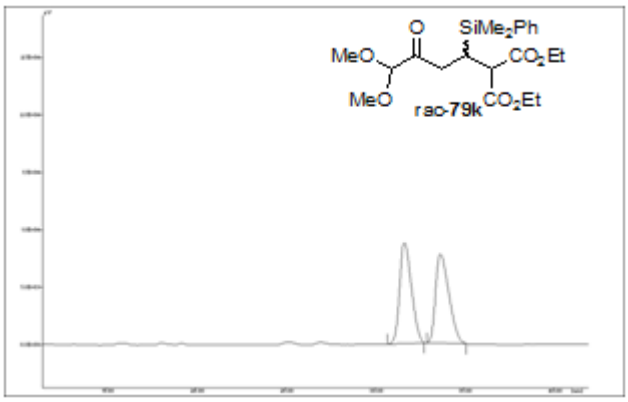


File name : rc-oc-125B101.CH3

Injection Date :23-Jan-2009 15:18:00

Control Method :RCOCB

Name	RT	Area[µV.Sec]	%Area	Corr.Area
(*S*)-**79j**	11.450	84874.500	4.333	84874.50
(*R*)-**79j**	14.308	1873794.750	95.667	1873794.75

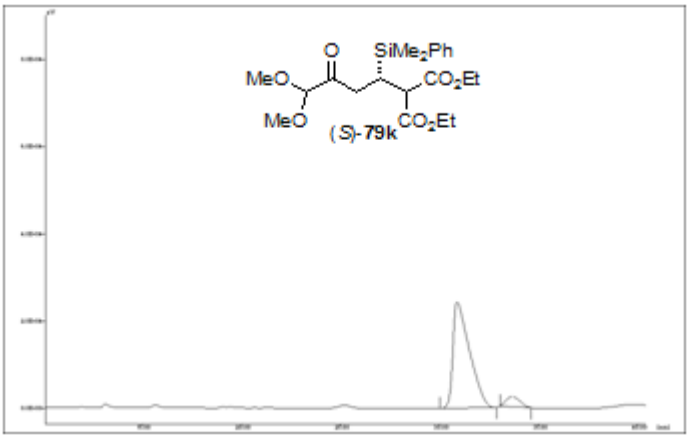


File name : rc-oc-149B106.CH3

Injection Date : 7-May-2009 12:58:18

Control Method :RNC1

Name	RT	Area[µV.Sec]	%Area	Corr.Area
(*S*)-**79k**	31.617	387575.227	49.914	387575.23
(*R*)-**79k**	33.650	388909.750	50.086	388909.75

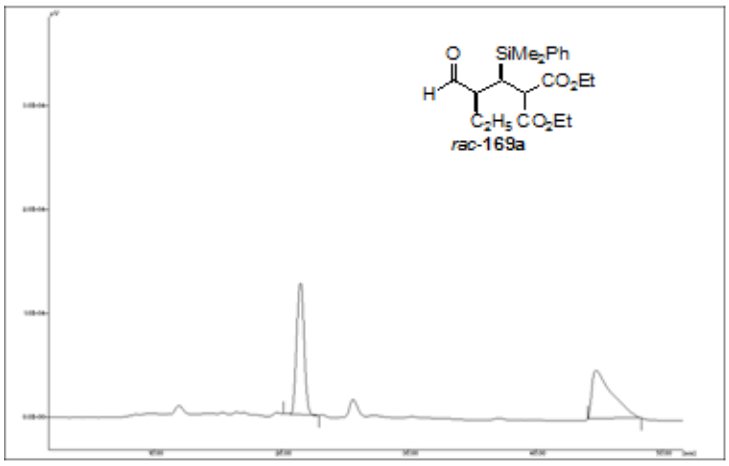


File name : rc-oc-149B107.CH3

Injection Date : 7-May-2009 13:41:26

Control Method :RNC1

Name	RT	Area[µV.Sec]	%Area	Corr.Area
(*S*)-**79k**	30.850	1372157.724	92.704	1372157.72
(*R*)-**79k**	33.625	107992.000	7.296	107992.00

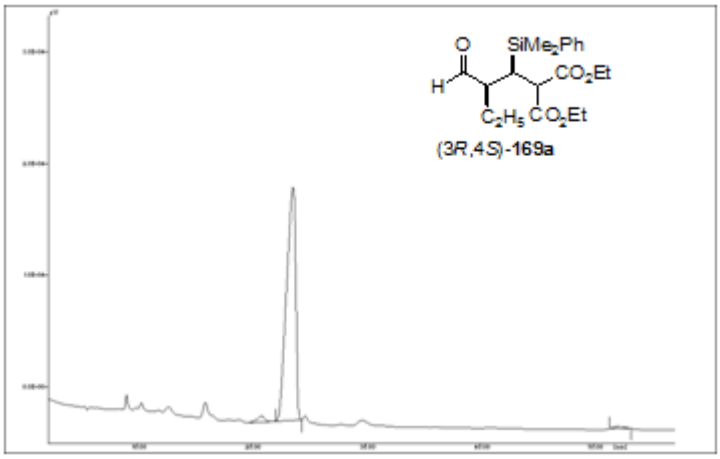


File name : rc-oc-racb195.CH3

Injection Date :24-Aug-2009 11:10:44

Control Method :RC-OC4B

Name	RT	Area[µV.Sec]	%Area	Corr.Area
(3*R*,4*S*)-**169a**	21.442	472602.840	48.860	472602.84
(3*S*,4*R*)- **169a**	44.717	494655.750	51.140	494655.75

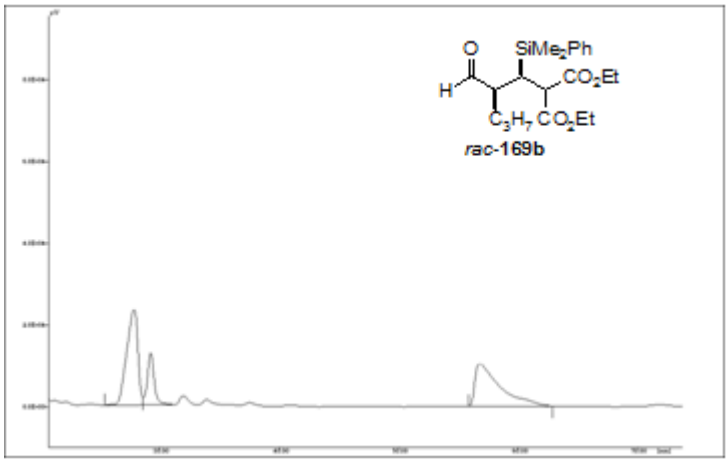


File name : rc-oc-275B217.CH3

Injection Date :11-Sep-2009 19:44:06

Control Method :RC-OC4B

Name	RT	Area[µV.Sec]	%Area	Corr.Area
(3*R*,4*S*)-**169a**	23.583	1097104.500	98.813	1097104.50
(3*S*,4*R*)- **169a**	52.150	13177.500	1.187	13177.50

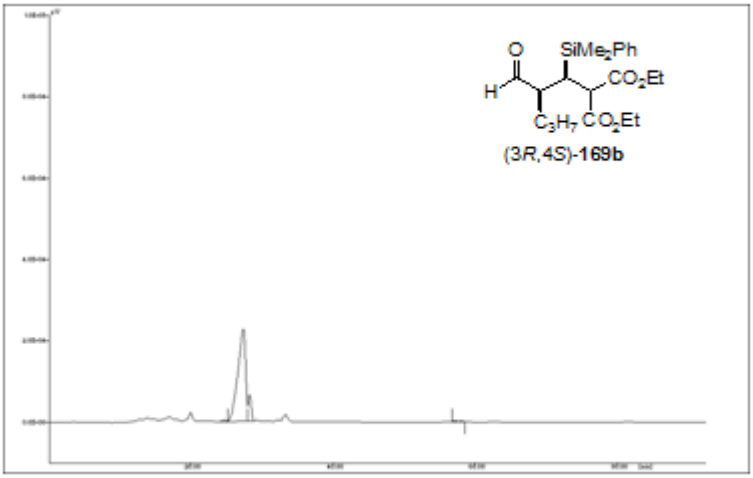


File name : rc-oc-325B043.CH3

Injection Date :14-Jan-2010 13:11:40

Control Method :RC-OC-B2010

Name	RT	Area[µV.Sec]	%Area	Corr.Area
(3*R*,4*S*)-**169b**	27.825	1447229.987	49.431	1447229.99
(3*S*,4*R*)- **169b**	56.733	1480546.250	50.569	1480546.25

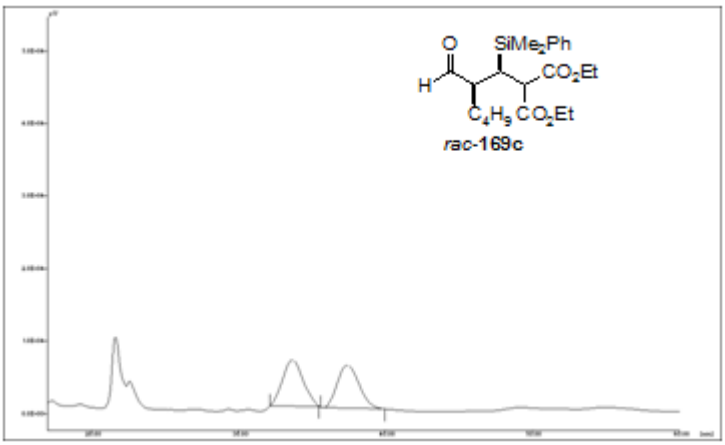


File name : rc-oc-330B045.CH3

Injection Date :14-Jan-2010 15:45:58

Control Method :RC-OC-B2010

Name	RT	Area[µV.Sec]	%Area	Corr.Area
(3*R*,4*S*)-**169b**	27.275	1575635.838	99.391	1575635.84
(3*S*,4*R*)- **169b**	57.392	9653.000	0.609	9653.00

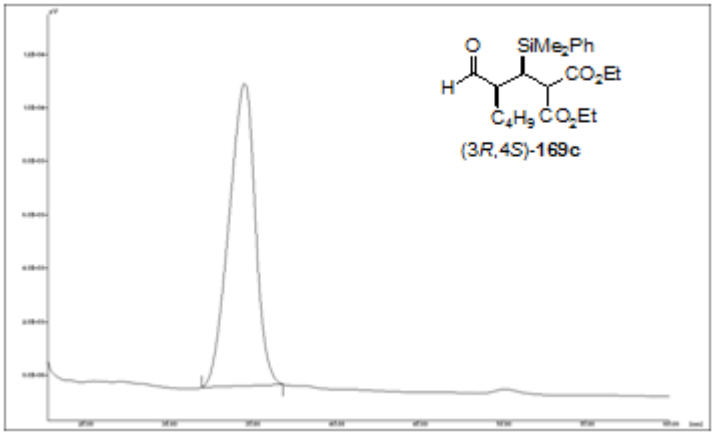


File name : rc-oc-280B041.CH3

Injection Date :16-Oct-2009 14:07:24

Control Method :RC-OC-6B

Name	RT	Area[µV.Sec]	%Area	Corr.Area
(3*R*,4*S*)-**169c**	33.625	614136.750	50.946	614136.75
(3*S*,4*R*)- **169c**	37.367	591334.478	49.054	591334.48

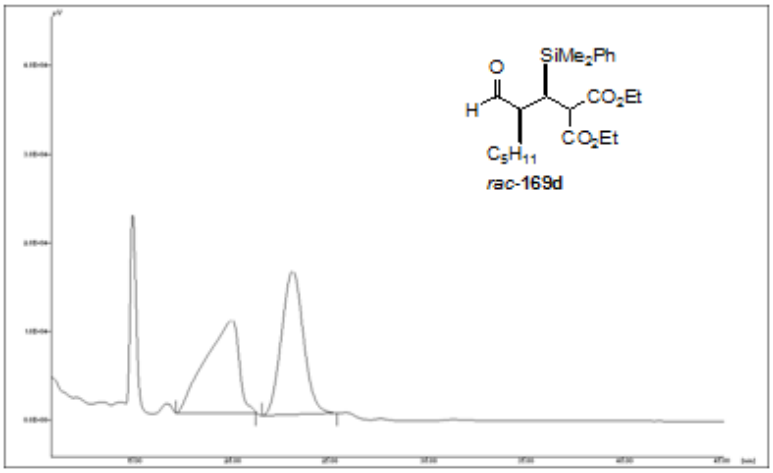


File name : rc-oc-286B039.CH3

Injection Date :16-Oct-2009 11:47:58

Control Method :RC-OC-6B

Name	RT	Area[µV.Sec]	%Area	Corr.Area
(3*R*,4*S*)-**169c**	34.558	1206630.000	100.000	1206630.00
(3*S*,4*R*)- **169c**	------	---------	----------	----------

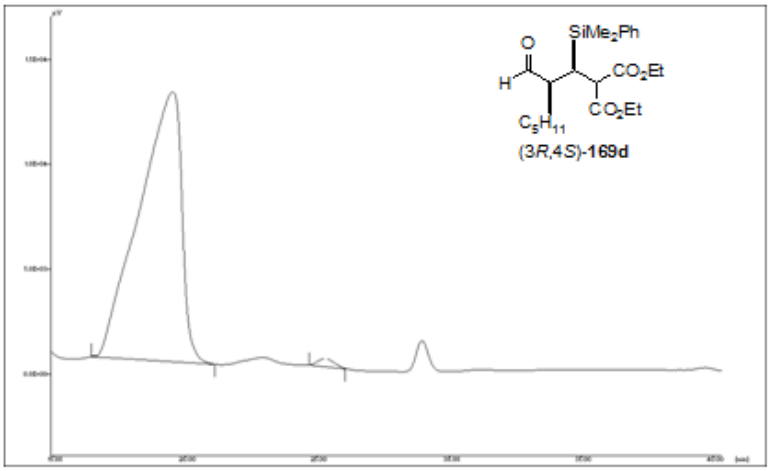


File name : rc-oc-283B034.CH3

Injection Date :15-Oct-2009 12:18:28

Control Method :RC-OC4B

Name	RT	Area[µV.Sec]	%Area	Corr.Area
(3*R*,4*S*)-**169d**	20.017	1203343.029	49.459	1203343.03
(3*S*,4*R*)- **169d**	23.125	1229651.541	50.541	1229651.54



File name : rc-oc-291B046.CH3

Injection Date :20-Oct-2009 18:43:22

Control Method :RC-OC4B

Name	RT	Area[µV.Sec]	%Area	Corr.Area
(3*R*,4*S*)-**169d**	20.017	1203343.029	49.459	1203343.03
(3*S*,4*R*)- **169d**	23.125	1229651.541	50.541	1229651.54

LIST OF PUBLICATIONS

1. **Chowdhury, R.;** Ghosh, S. K. Organo-catalyzed Enantioselective synthesis of some β-Silyl γ- Alkyl γ- Butyrolactones as Intermediates for Natural products. *Tetrahedron: Asymmetry*, **2011**, *22* 1895–1900.
2. **Chowdhury, R.;** Ghosh, S. K. Enantioselective Route to β-Silyl-δ-keto Esters by Organocatalyzed Regioselective Conjugate Addition of Methyl Ketones to a Silylmethylene Malonate and Their Use in the Syntheses of Natural Product Intermediates. *Synthesis* **2011**, 1936-1945. (Invited article for the special issue Organocatalysts)
3. **Chowdhury, R.;** Ghosh, S. K. Organocatalytic Michael addition of aldehydes to a β –silylmethylene malonate to form intermediates for the enantioselective synthesis of hydroxylated valerolactones and piperidines. *Tetrahedron: Asymmetry*, **2010**, *21*, 2696–2702.
4. **Chowdhury, R.;** Ghosh, S. K. Highly Regio- and Enantioselective Organocatalytic Conjugate Addition of Alkyl Methyl Ketones to a β-Silylmethylene Malonate. *Org.Lett.* **2009,** *11*, 3270-3273.
5. **Chowdhury, R.;** Ghosh, S. K. Sequential Double Olefination of 2-(Arylmethylidene)-2-phosphonoacetonitrile with Dimsyl Lithium and Aldehydes: A Domino Route to Densely Substituted1,3-Butadienes. *Eur. J.Org.chem*. **2008**, 3868-3874.