Chapter 1
Introduction

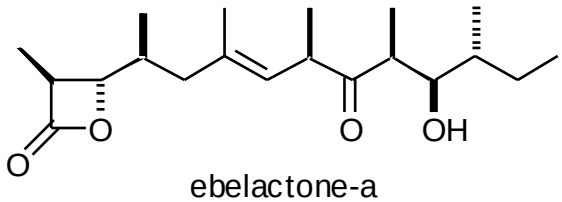
1.1 The Target Molecule

1.1.1 Introduction

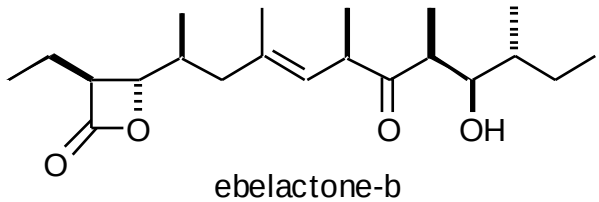
Ebelactone-a was isolated in 1980 by the Umezawa group from a cultured strain of soil actinomycetes (MG7-G1) closely related to *Streptomyces aburaviensis,*[1] and its structure was later determined by the same group by X-ray crystallographic analysis of its *p*-bromobenzoate derivative.[2] Ebelactone-a is an antibiotic of low toxicity and, together with its homologue ebelactone-b, is a potent esterase and lipase inhibitor.[1,2] Since lipase is the key enzyme required for the absorption of dietary triglycerides, such compounds may be useful for prophylaxis or therapeutics of hyperlipidemia and obesity.[3-5] Ebelactone-a also inhibits *N*-formylmethionine aminopeptidases located on the cell membrane of various animal cells and hence enhances immune responses.[1,2] Its action in inhibiting cutinases produced by fungal pathogens also gives it a potential rôle in protecting plants against fungal attack.[6]

Evidence suggests that it is the β–lactone group that is the biologically active feature of the molecule, and ebelactones a and b have similar structures to other biologically active β-lactones such as lipstatin,[7] tetrahydrolipstatin,[8] esterastin,[9] valilactone[10] and obafluorin[11] (see figure 1.1).

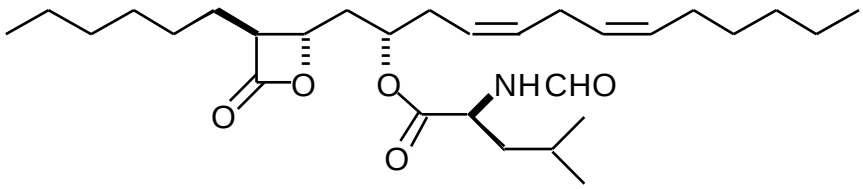
Ebelactone-a is a challenging synthetic problem. It has seven stereogenic centres, an *E*-double bond and a sensitive β-lactone group. Much work has already been carried out in this group towards the synthesis of ebelactone-a (see chapter 2), with the aim of using organosilicon chemistry to control *all* the relative stereochemistry,[12] accepting that this would



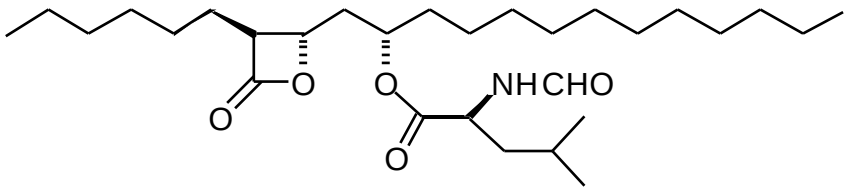
ebelactone-a



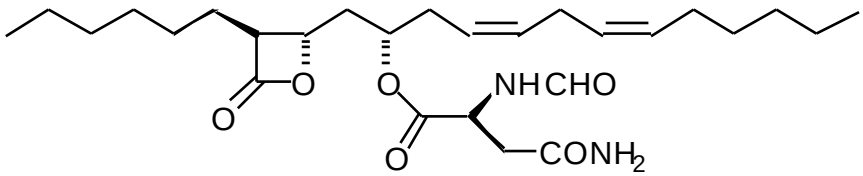
ebelactone-b



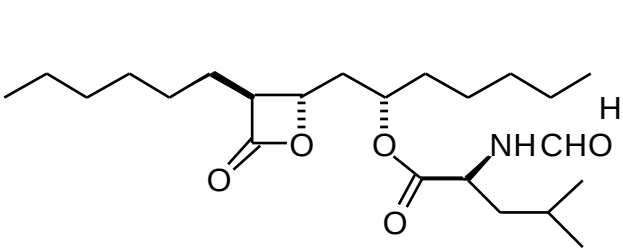
lipstatin



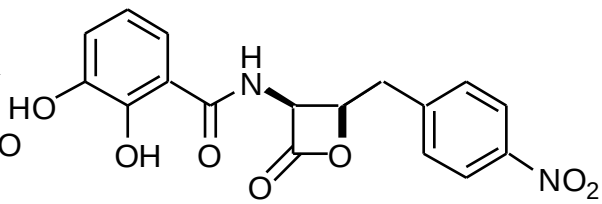
tetrahydrolipstatin



esterastin



valilactone



obafluorin

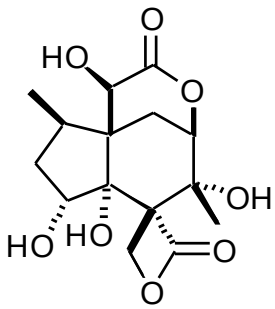
Figure 1.1

inevitably lead to a less efficient synthesis than other routes [notably Paterson's synthesis (see section 1.3)[13,14]]. It has now been shown in principle that silicon chemistry could be used to solve all the stereochemical features of the synthetic problem, but the yields have not always been found to be good, so the approach has now shifted to using silicon chemistry only where it is in fact a good solution, and using other methods where they result in a higher efficiency.

1.2 β-Lactones

1.2.1 Introduction

β-Lactones (2-oxetanones) have recently been the subject of much synthetic effort[4,15] due to their widespread natural occurrence and biological interest,[16] their utility as synthetic intermediates[5,17] and their employment as monomers for the preparation of biodegradable polymers.[18] Some recent syntheses of naturally occurring β-lactones with similar structures to ebelactone-a are mentioned below.[4,5,13,14,19-34]



anisatin

The first naturally occurring β-lactone to be isolated was anisatin in 1952,[35] though it was not characterised until thirteen years later.[36] However, it was not until the 1980's that the vast majority of the large number of naturally occurring β-lactones were discovered. This is no doubt due to the susceptibility of the β-lactone ring towards attack by nucleophiles (see section 1.2.2.3) and hence the difficulty of isolating these interesting compounds.

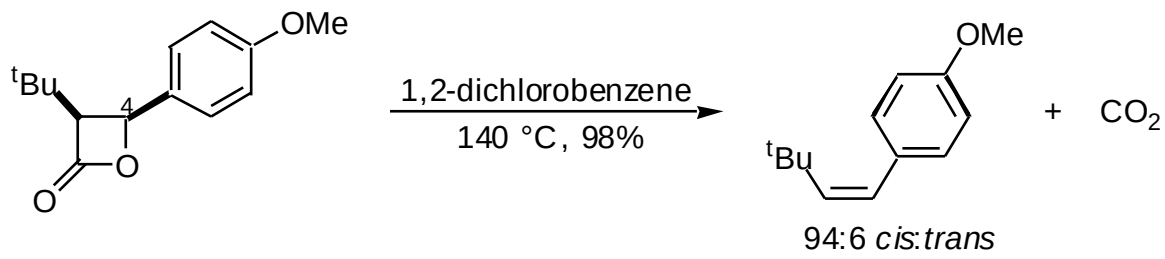
Naturally occurring β-lactones may be classified roughly into terpenoid β-lactones (such as anisatin), α-amino-β-lactones (such as obafluorin) and fatty acid and polyketide-like β-lactones (such as ebelactone-a) (see figure 1.1).[16] We consider below some of the reactions of β-lactones and then some synthetic approaches in the literature to β-lactone-containing compounds.

1.2.2 Reactions of β-Lactones

The high strain in the 4-membered ring leads to chemistry rather different from that of normal esters/lactones.[37] This lies behind the features of β-lactone chemistry described below.

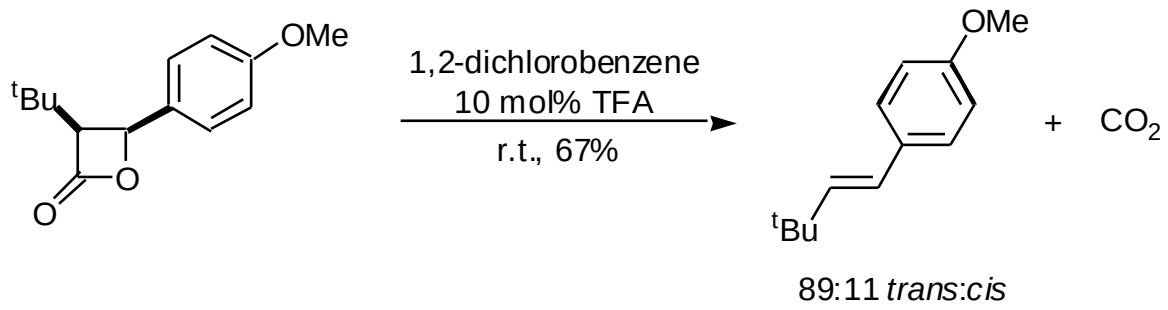
1.2.2.1 Decarboxylation

β-lactones undergo thermal decomposition at elevated temperatures by loss of carbon dioxide in a stereospecifically *cis* fashion. The mechanism was previously thought to be a concerted [2+2] cycloreversion,[38] but this is disallowed by the Woodward-Hoffmann rules and the consensus now is that the mechanism is probably concerted though highly asynchronous, involving a planar transition structure with high zwitterionic character.[39-41] Thermal decarboxylation takes place faster from *trans* derivatives than from *cis* derivatives,[40] and is very dependent on the particular substituent at the C4 position in the ring (e.g., see scheme 1.1).[41]



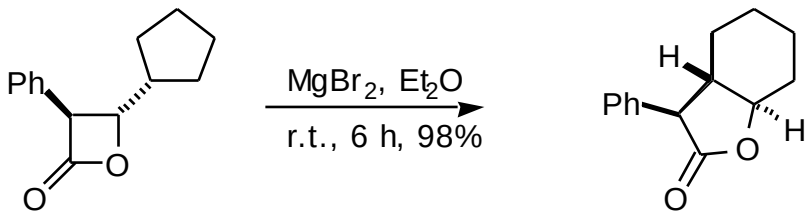
Scheme 1.1

On the other hand, acid-catalysed decarboxylation can take place with inversion,[42] and is a faster reaction (e.g., scheme 1.2). The ease with which acid-catalysed decarboxylation can occur restricts the conditions under which β-lactones can be formed and used in a synthetic procedure. On the positive side, though, β-lactone decarboxylation has found many synthetic applications.[43]



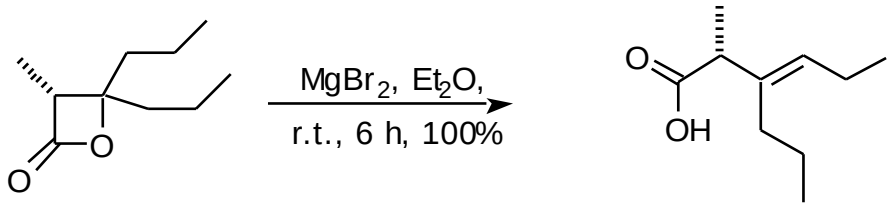
Scheme 1.2

1.2.2.2 Rearrangement



Scheme 1.3

β-Lactones which are unsubstituted or monosubstituted at C4 undergo dyotropic Wagner-Meerwein[44,45] rearrangement in a stereospecific fashion to give γ-lactones under Lewis acid catalysis[46] (preferably with magnesium bromide[45,47]) (scheme 1.3).[48] β-Lactones disubstituted at C4 do not undergo ring expansion but instead E_1-type ionisation-elimination takes place to give β,γ-unsaturated carboxylic acids (scheme 1.4).[49]



Scheme 1.4

Where the molecule contains further functionality, more complex behaviour can be observed under Lewis acid conditions.[50]

1.2.2.3 Nucleophilic Attack

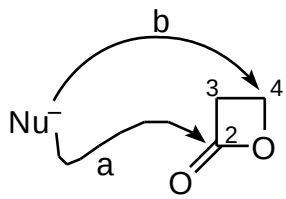
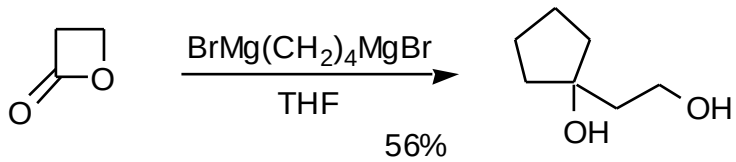
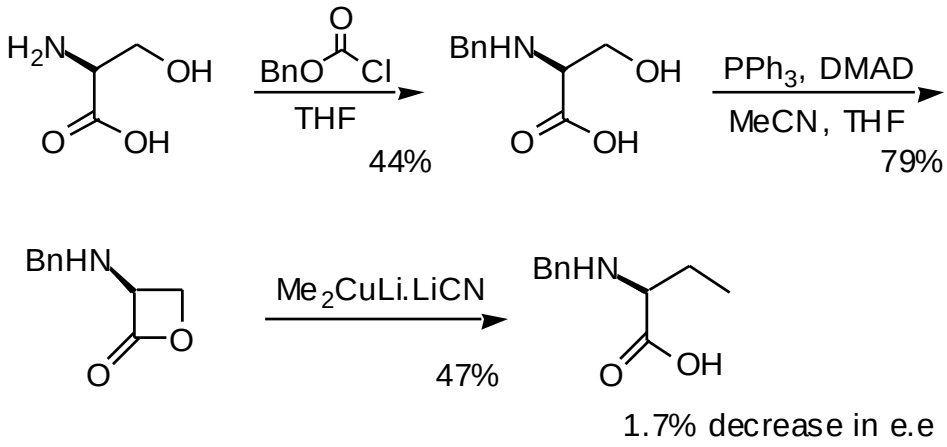


Figure 1.2

β-Lactones are ambident electrophiles, electrophilic at carbons 2 and 4, corresponding to nucleophilic attack *a* or *b* respectively (figure 1.2). Mode *a* is preferred by organolithium and organomagnesium reagents,[51] whereas organocuprates prefer to attack by mode *b*.[52] Both processes have been much used in synthesis (see scheme 1.5 for a mode *a* example[53] and scheme 1.6 for a mode *b* example[54]).

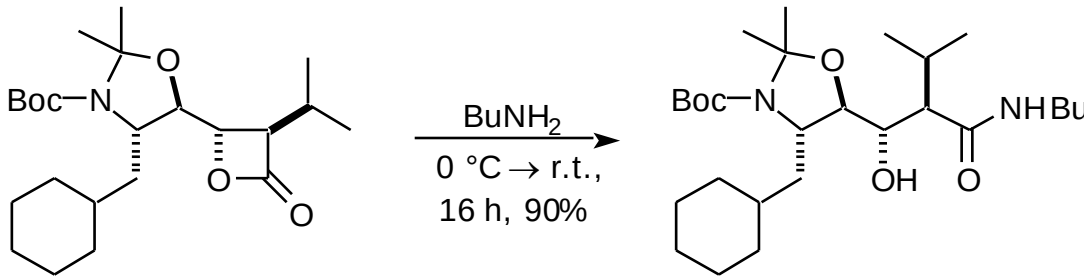


Scheme 1.5



Scheme 1.6 (DMAD = dimethyl azodicarboxylate)

It is more difficult to summarise the behaviour of heteronucleophiles towards β-lactones, as the product obtained depends on the nature of the particular nucleophile, the substrate and the solvent.[55] However, synthetic applications have been found. (e.g., see scheme 1.7 where butylamine is the nucleophile, attacking in mode *a*.[56])

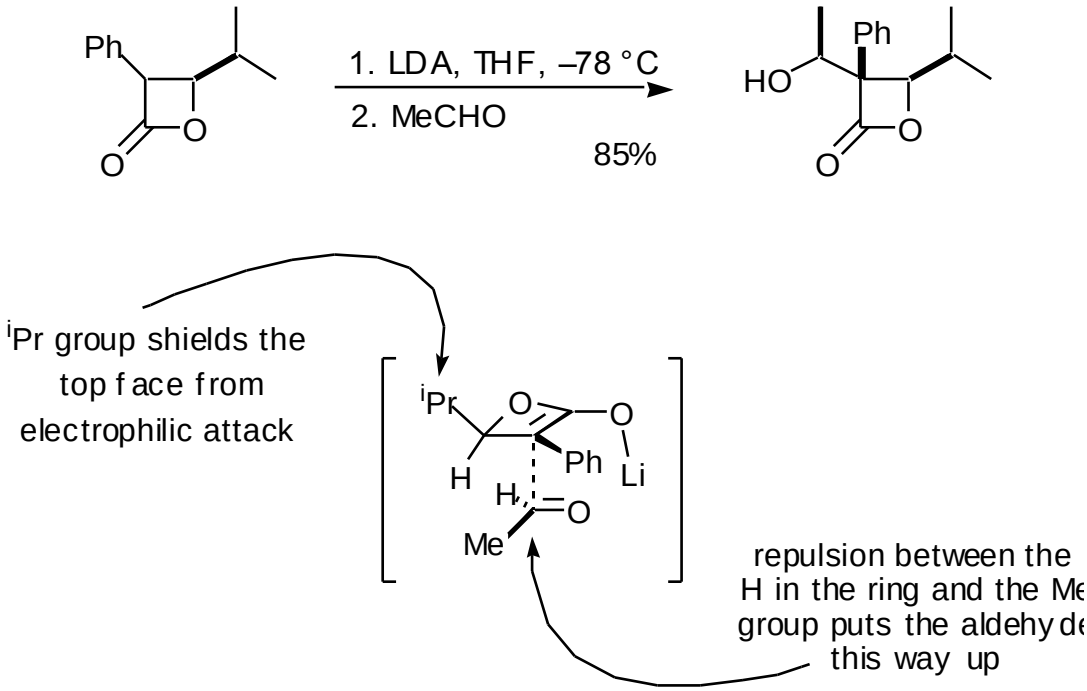


Scheme 1.7

1.2.2.4 Enolate Formation and Reaction

β-Lactone enolates are extremely useful intermediates in organic synthesis. The α-proton is labile, and treatment of α-substituted β-lactones with LDA at –78 °C leads to enolates which react with various common electrophiles (e.g., alkyl, allyl and propargyl halides,[57] and aldehydes.[58]) In the case of β-substituted β-lactones, electrophilic attack on the

enolate takes place predominantly from the less bulky side of the enolate. Hence, addition to aldehydes leads to diastereoselective aldol reactions and the control of three stereogenic centres in a single operation.[58,59] The proposed transition structure is shown for a typical reaction in scheme 1.8.



Scheme 1.8

Mulzer found that in base β-lactones are epimerised at the α-centre without any ring opening and with no scrambling at the β-position (scheme 1.9). This result is surprising because a free enolate ion such as **1** is not likely to be an intermediate, since under the reaction conditions spontaneous isomerisation (β-elimination) would be expected to take place to give the acrylate **2** (scheme 1.9).

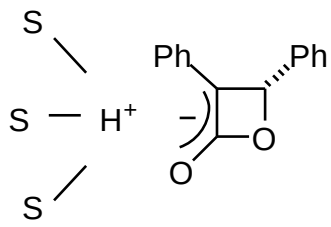
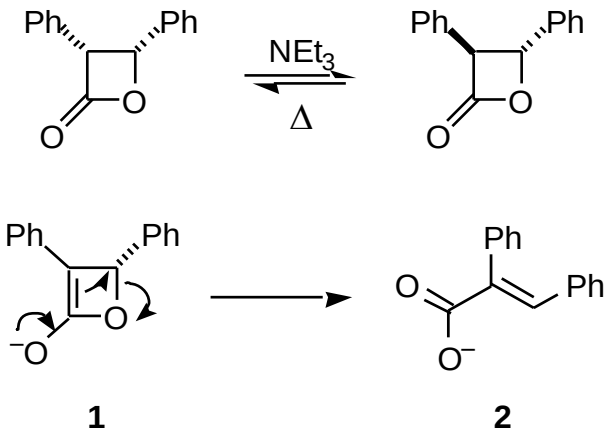


Figure 1.3 (S = solvent)



Scheme 1.9

Thus, it has been suggested that the anion is held as a contact ion-pair with the proton, tightly associated with solvent molecules (figure 1.3).[60]

Another possible explanation that has been offered is that enolate **1** *is* the intermediate, but that it is stabilised with respect to ionisation by the rigidity of the β-lactone ring, which keeps the p-orbitals of the carbonyl group and the α-carbon atom at right angles to the σ-orbital of the C-O bond, thus preventing the low-energy pathway for C-O bond cleavage by assistance from the negative charge (see figure 1.4).[57]

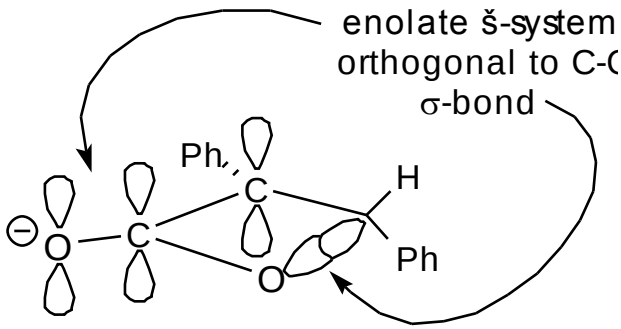
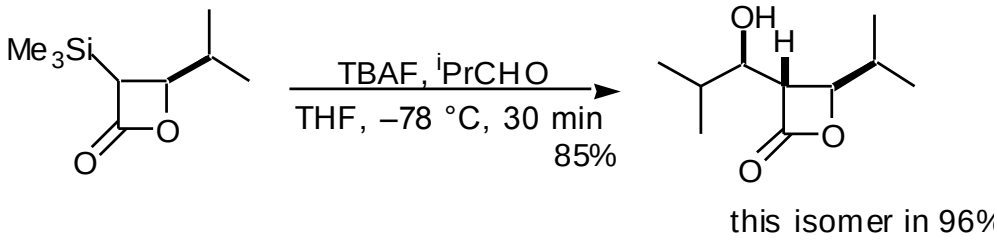


Figure 1.4

α-Unsubstituted β-lactone enolates give poor yields in alkylation reactions, but Mead has developed a way around this difficulty by incorporating a silyl substituent at the α-position and

then using a one-step desilylation-alkylation reaction,[61] or a one-step desilylation-aldol reaction[62] which took place in a stereoselective fashion (see scheme 1.10).



Scheme 1.10

1.2.2.5 Conclusion

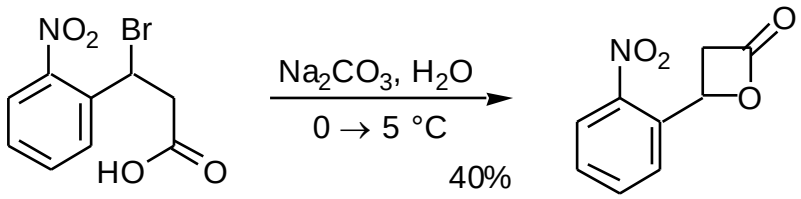
The consequences for our synthesis of the reactivity of β-lactones described in the above sections are straightforward: once the β-lactone functionality is in place in our molecule, we shall need to avoid acidic conditions, heat and nucleophiles. This will dictate that the lactonisation step must come relatively late in the synthetic scheme and that the lactone will need to be carried through earlier steps in the open form as a protected hydroxyacid.

1.2.3 Synthesis of β-Lactones

Many different approaches to the synthesis of β-lactones have been explored, and some of the more important are considered below.[4,63]

1.2.3.1 Cyclisation of β-Halocarboxylic Acid Salts

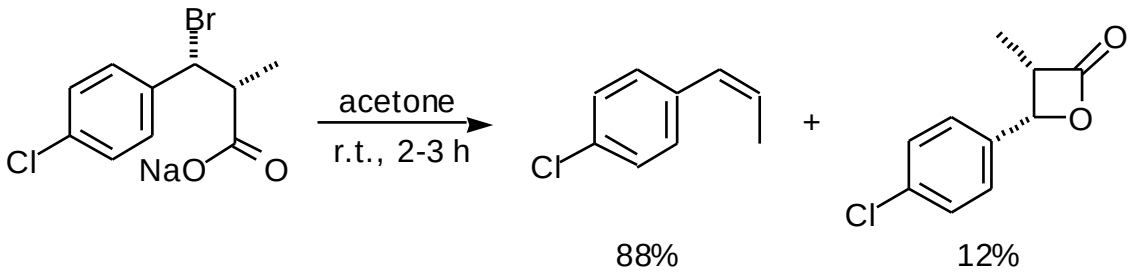
β-Lactones have been known in the laboratory since 1883 when Einhorn obtained β-lactone **4** by treatment of β-bromocarboxylic acid **3** with base (scheme 1.11).[64] Since then, this class of reaction has been developed, allowing reaction in aqueous or non-aqueous media, the acid salt being prepared by a mild base and the cyclisation taking place at room



3 **4**

Scheme 1.11

temperature.[37,65] The mechanism is S_N2 attack of the carboxylate anion on the β-carbon atom, and hence the reaction proceeds with inversion at this centre.[66] Alkenes are frequently a major by-product of the reaction, and the process is little used nowadays (scheme 1.12).[67]

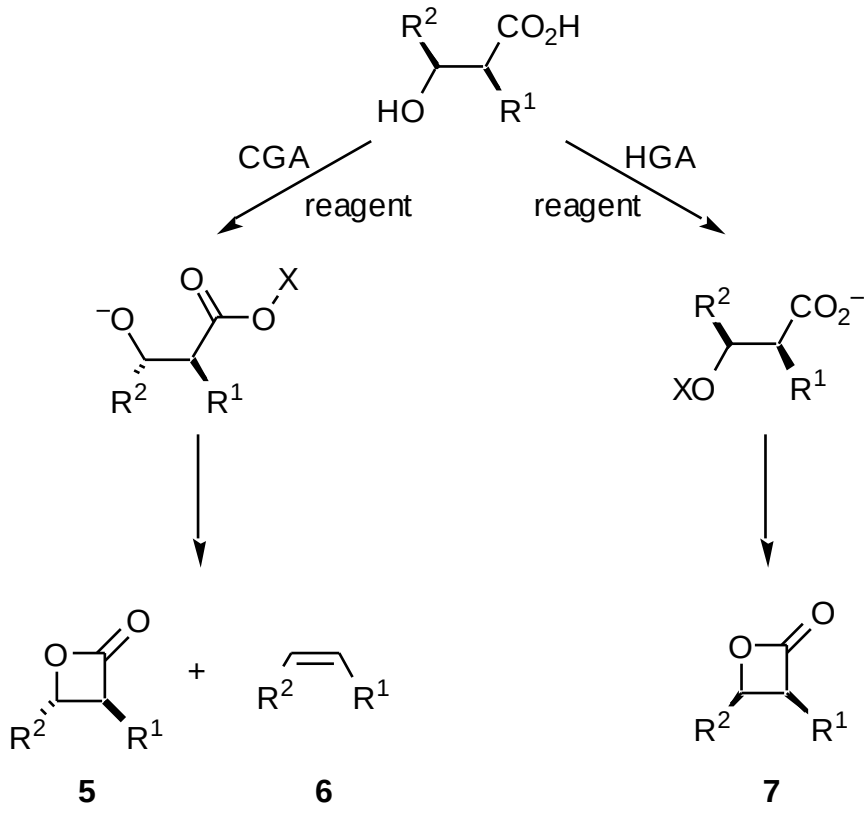


Scheme 1.12

1.2.3.2 Cyclisation of β-Hydroxycarboxylic Acids

Much more important in modern β-lactone synthesis is cyclisation of β-hydroxycarboxylic acids by means of carboxyl-group-activating (CGA) or, less commonly, hydroxyl-group-activating (HGA) reagents. The former lead to retention of configuration at the β-carbon atom (and hence lactone **5**) and the latter to inversion (lactone **7**), as shown in scheme 1.13.[68,69]

Alkene **6** is produced by a Grob fragmentation (decarboxylation).[70] Under Mitsunobu conditions,[71] Mulzer has shown that *cis* or *trans* lactones can be formed according to the stereochemistry of the starting hydroxyacid and the nature of the substituents R^1 and R^2.[68,69]

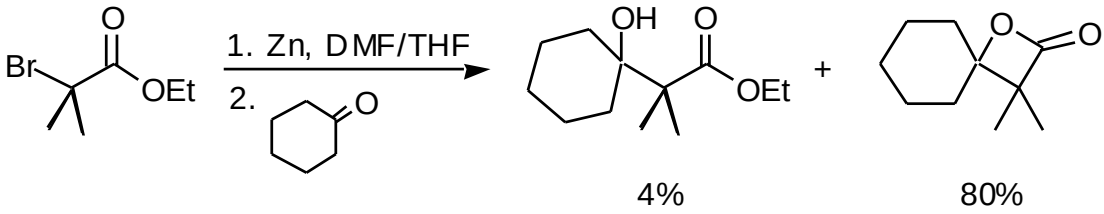


Scheme 1.13

This has been used in the synthesis of serine β-lactones, which are precursors to α-amino acids.[72]

Many reagents have been used to effect β-lactonisation of hydroxyacids, including ethyl chloroformate in pyridine,[73] various carbodiimide reagents,[74] tosyl chloride in pyridine,[75] *p*-bromobenzenesulfonyl chloride in pyridine,[76] and methanesulfonyl chloride with sodium carbonate in dichloromethane.[77] However, by far the most successful and widely-used reagent today is benzenesulfonyl chloride in pyridine.[78] Under these latter conditions, retention of configuration is obtained and the reagents are compatible with a wide variety of substituents. The reaction is carried out at sub-zero temperature to inhibit thermal decarboxylation (see section 1.2.2.1), and acid-catalysed decarboxylation is avoided by using pyridine as the solvent. Many modern syntheses of β-lactones use this reaction to form the β-lactone ring.[4] This is almost certainly how we will close the β-lactone ring in our ebelactone-a synthesis.

Recently Schick has developed conditions under which certain β-hydroxyester products of aldol reactions undergo spontaneous intramolecular cyclisation to give β-lactones (see scheme 1.14).[79]



Scheme 1.14

1.2.3.3 [2+2] Cycloaddition Reactions

Thermal cycloaddition of ketenes to carbonyl compounds appears at first sight to be disallowed by the Woodward-Hoffmann rules, but if the p-orbital on the carbon atom of the carbonyl compound develops overlap to the p_Z orbital of the terminal carbon atom of the ketene, while the p-orbital on the oxygen atom of the carbonyl compound develops overlap to the p_Y orbital of the central carbon atom of the ketene, then attack on the ketene is effectively antarafacial and thus the process is allowed (see figure 1.5) and gives a β-lactone.[80]

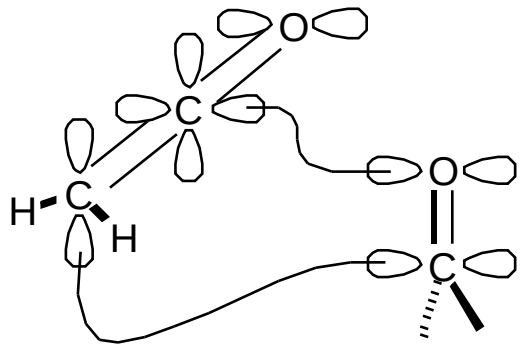
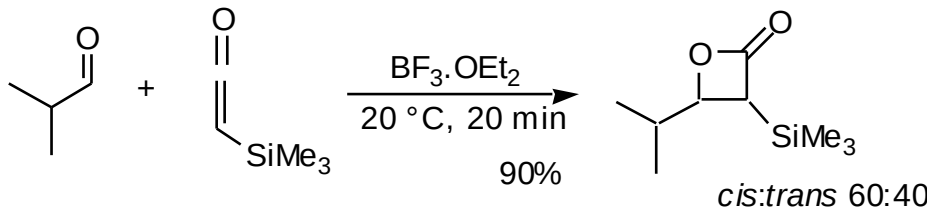


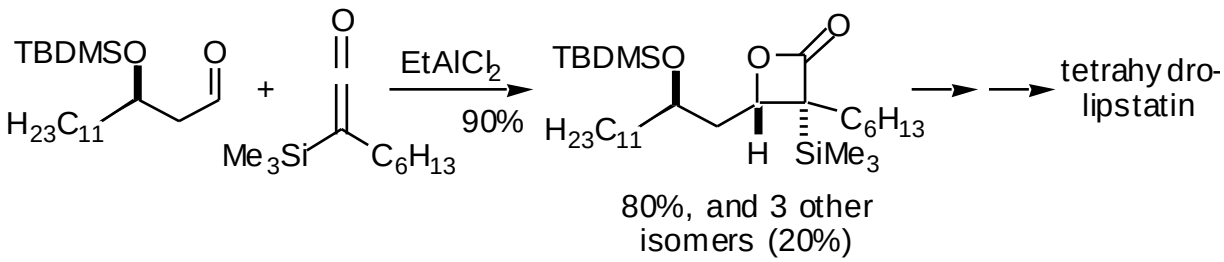
Figure 1.5

The difficulty with this approach to β-lactones is the instability of ketenes; however, there are many examples of [2+2] cycloadditions involving ketenes generated *in situ*.[81] Trialkylsilylketenes are remarkably stable compounds and can be stored at –20 °C for lengthy periods, and [2+2] cycloadditions with these lead to α-silyl-β-lactones with moderate *cis* selectivity, which can be improved by using aluminium-based Lewis acids.[82] (See scheme 1.15[83])



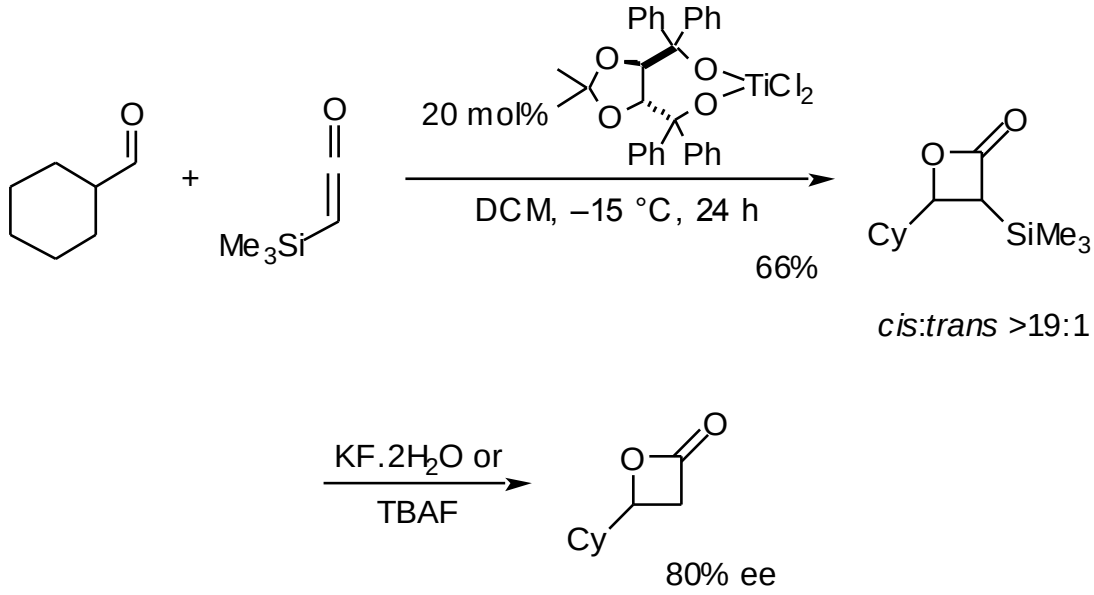
Scheme 1.15

The difficulty of preparation of alkyl(trimethylsilyl)ketenes restricts their common use in synthesis, though Kocienski has developed catalytic enantioselective [2+2] cycloaddition reactions of achiral aldehydes with (trimethylsilyl)ketene using enantiomerically pure methylaluminoimidazoles,[84] and has used chelation-controlled[85] diastereoselective cycloadditions in his syntheses of lipstatin,[20] tetrahydrolipstatin (scheme 1.16),[23,27] and most recently panclicins A-E.[86]



Scheme 1.16

Also recently, Romo has used Seebach's and Narasaka's dichlorotitanium-TADDOL catalysts to perform asymmetric [2+2] cycloadditions of silylketenes and achiral aldehydes with good enantioselectivity (e.g., scheme 1.17).[87]

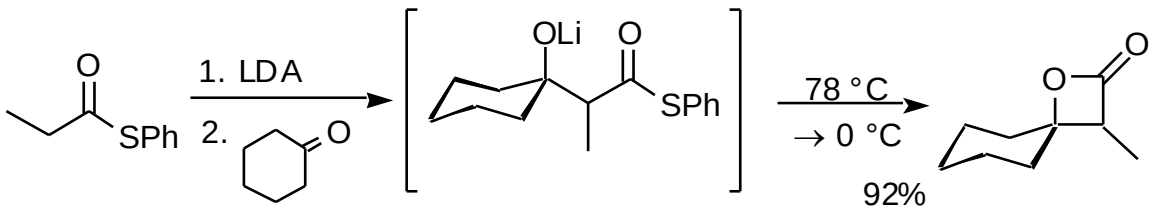


Scheme 1.17

1.2.3.4 Other Methods

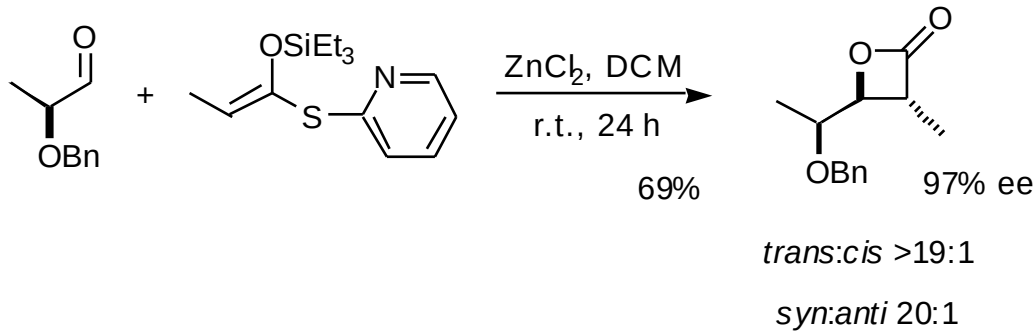
Most modern β-lactone syntheses follow either the oxygen-acyl bond lactonisation method from hydroxyacids or the [2+2] cycloaddition approaches, but there are numerous other routes to β-lactones,[5] such as halolactonisation of β,γ-unsaturated acids,[88] epoxidation of allenes[89] or reaction of propargylic alcohols with chromium carbene complexes.[90] Several concise approaches to optically active β-lactones have been reported in recent years, and some of these are described below along with other important methods.

Following on from work of Masamune,[91] Danheiser has developed a method starting from thiol esters (scheme 1.18).[92] The thiol ester enolate takes part in an aldol reaction with a carbonyl compound, and on warming the lactone forms spontaneously.



Scheme 1.18

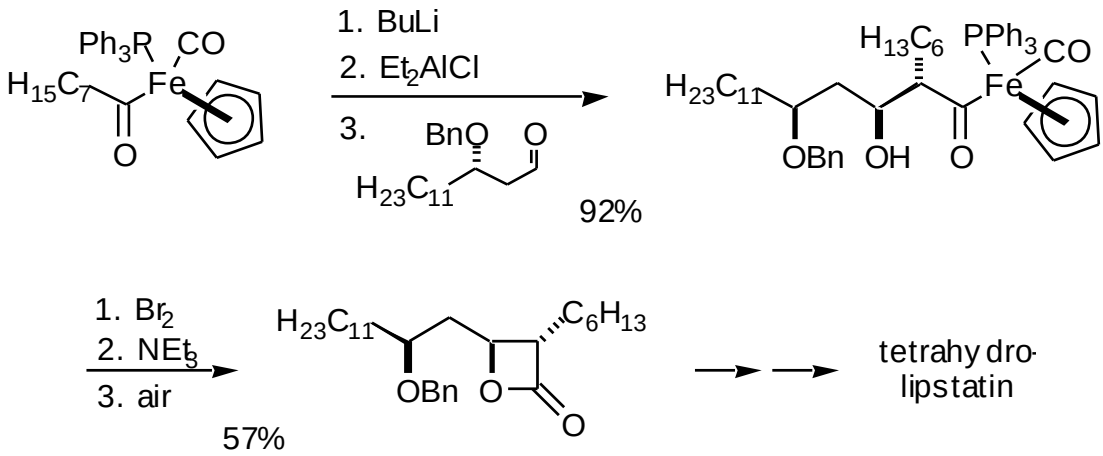
This has been applied to homochiral aldehydes,[93] and by using a tandem Mukaiyama aldol-lactonisation reaction, Romo has developed a diastereoselective route to racemic *trans*-3,4-disubstituted β-lactones which when applied to optically active aldehydes gives β-lactones with high enantiomeric excesses (scheme 1.19).[94]



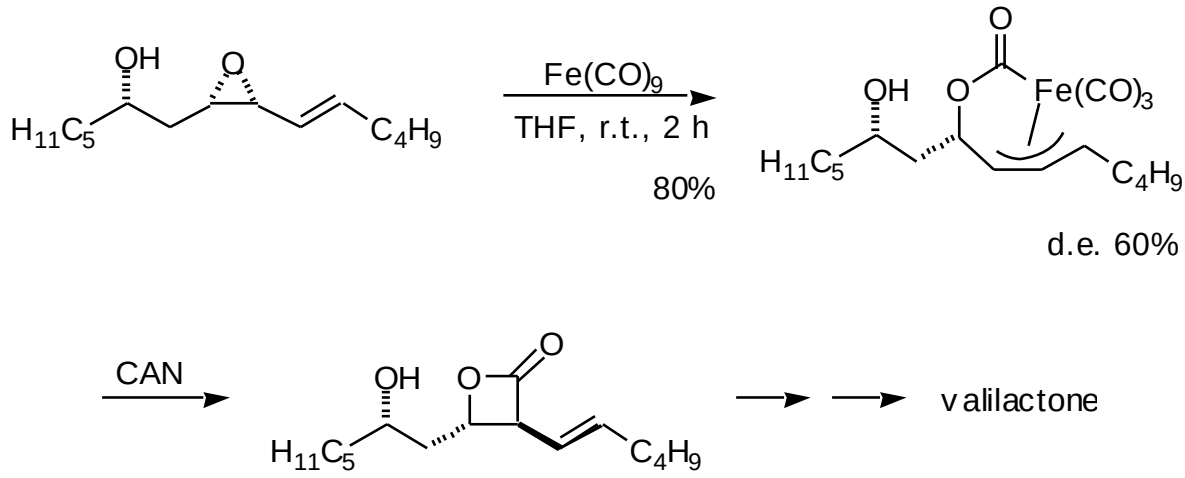
Scheme 1.19

Davies has used an iron chiral auxiliary [$CpFe(CO)(PPh_3)$] in aldol condensations to give *syn* or *anti* β-hydroxy-iron-acyls, which are treated with bromine to give the corresponding *cis* or *trans* β-lactones.[19] This approach was used in his synthesis of tetrahydrolipstatin (scheme 1.20).[23]

Also using iron chemistry, Ley has treated vinylepoxides with ironpentacarbonyl or diironnonacarbonyl to give π-allyltricarbonyliron-lactone complexes, which on oxidation with ceric ammonium nitrate give β-lactones.[95] This approach has led to a total synthesis of (–)-valilactone (scheme 1.21).[31]



Scheme 1.20

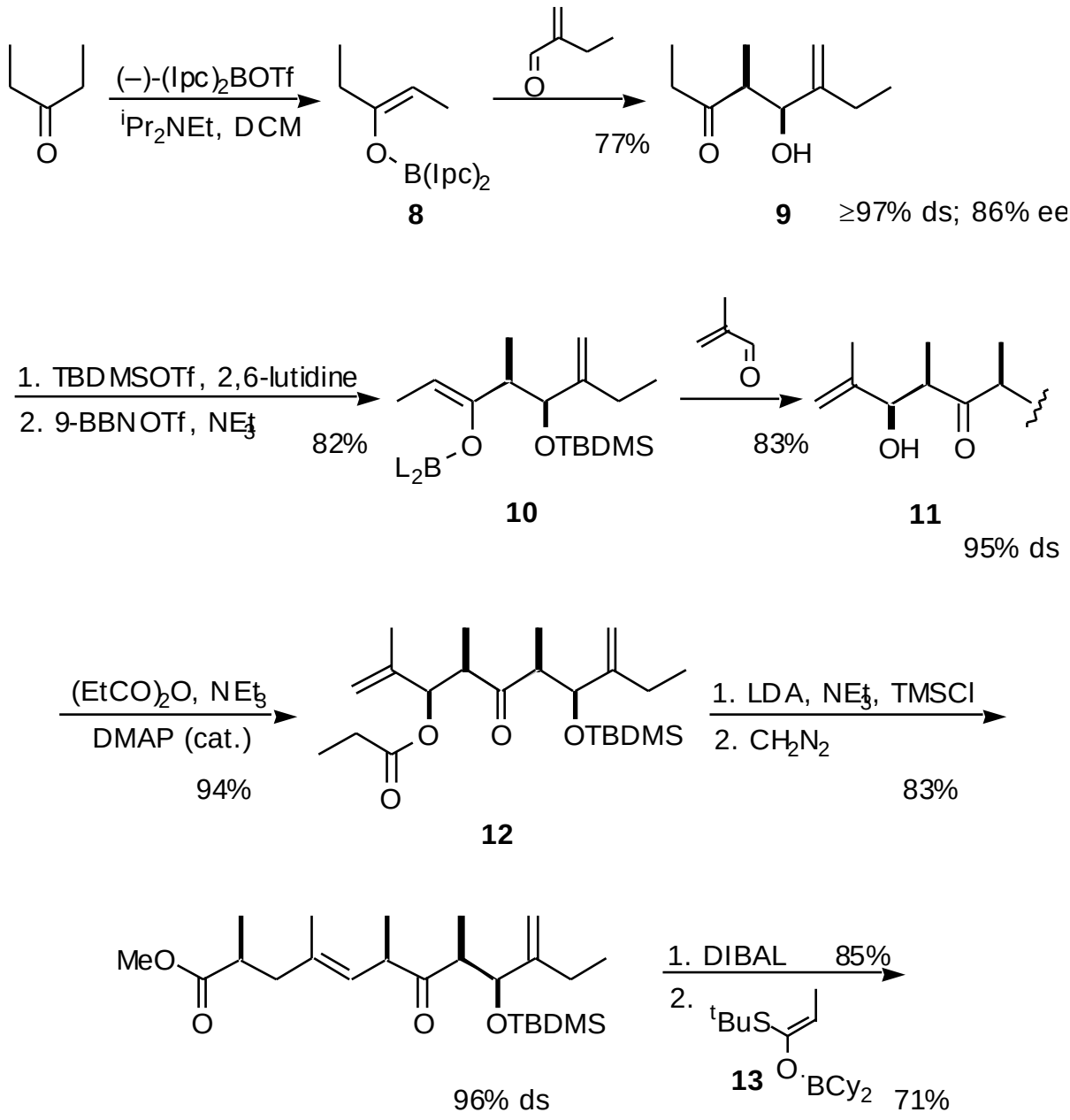


Scheme 1.21

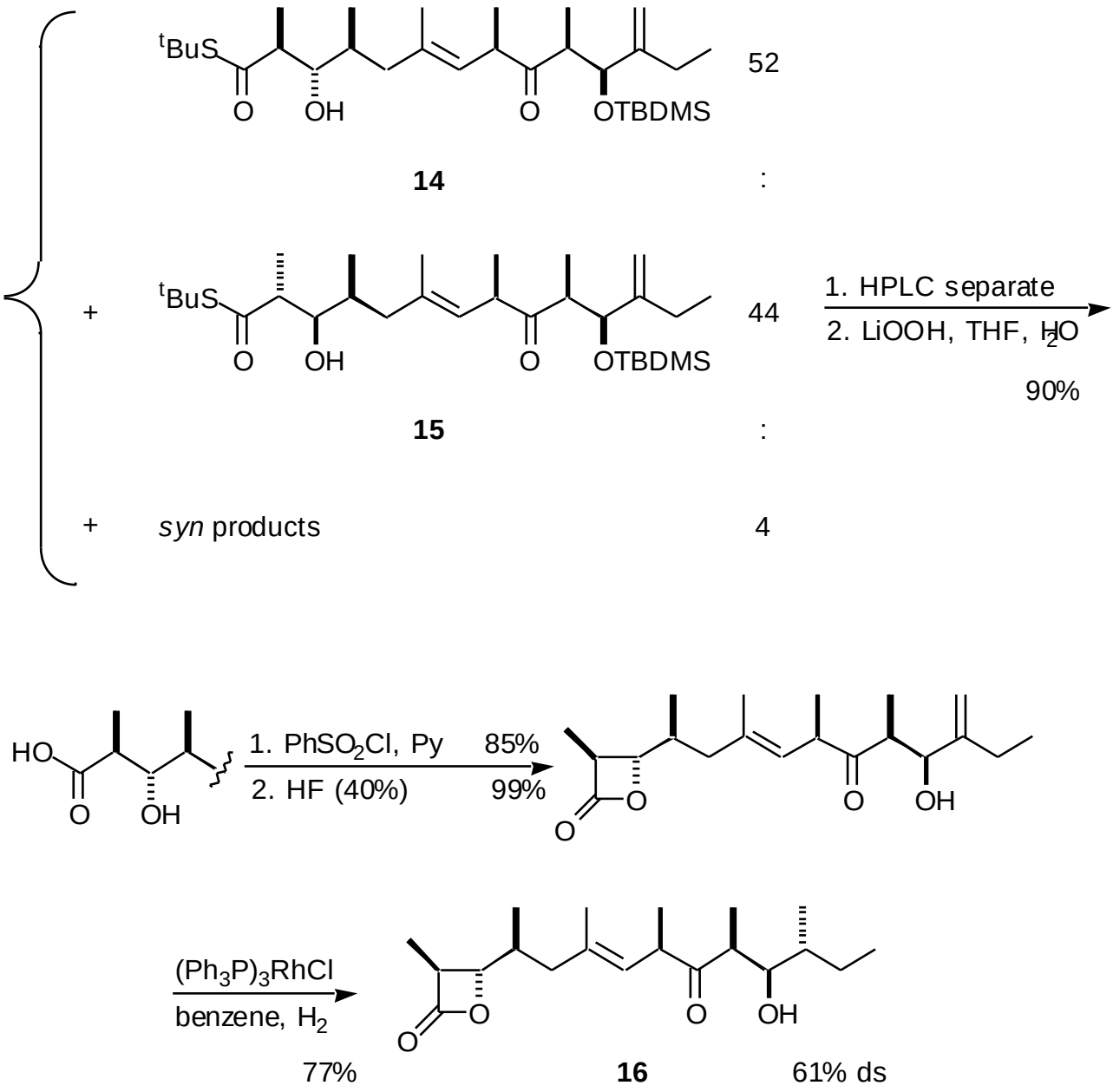
1.3 Paterson Synthesis of Ebelactone-a

The only synthesis of ebelactone-a reported to date is that by Paterson and Hulme. In 1990, they published a racemic synthesis,[13] and this was followed in 1995 by syntheses of (–)-ebelactone-a and (–)-ebelactone-b using the same approach.[14] Paterson used his boron enolate aldol methodology[96] as the basis of his ebelactone syntheses (schemes 1.22a and 1.22b).

Z-Boron enolate **8** was made from diethyl ketone by using the chiral boron reagent (–)-diisopinocampheylboron triflate, and on reaction with 2-ethylacrolein the *syn* aldol product **9** was formed (scheme 1.22a and b) (see chapter 4 for a discussion of the stereochemistry of aldol reactions). Formation of the *Z*-boron enolate **10** on the other side of the ketone, and reaction with methacrolein led similarly to the all-*syn* adduct **11** in good yield, and this was esterified to give the *O*-propionate **12**. Carefully controlled conditions then enabled the


(–)-(Ipc)2BOTf
iPr2NEt, DCM
B(Ipc)2
8
77%
9
≥97% ds; 86% ee
1. TBDMSOTf, 2,6-lutidine
2. 9-BBNOTf, NEt3
82%
L2B
OTBDMS
10
83%
11
95% ds
(EtCO)2O, NEt3
DMAP (cat.)
94%
12
1. LDA, NEt3, TMSCl
2. CH2N2
83%
MeO
96% ds
1. DIBAL 85%
2.
tBuS
13
BCy2
71%

Scheme 1.22a



Scheme 1.22b

authors to achieve an Ireland-Claisen[97] ester enolate rearrangement without protection of the ketone functionality at C9. DIBAL reduction to the aldehyde was followed by aldol condensation with boron enolate **13** to give hydroxy thioesters **14** and **15** in a 54:46 ratio, which were separated by means of HPLC. Gentle hydrolysis, lactonisation, deprotection and selective hydrogenation of the allylic alcohol functionality (with poor stereocontrol) led to (–)-ebelactone-a **16** in 4% overall yield (12 steps).

Strengths of the synthetic plan are its efficiency, selectivity and versatility (for example, ebelactone-b was made by Paterson with little additional effort).[14] Weaknesses are the poor diastereoselectivity for the *anti*-aldol reaction used to set up C2-C3, and the linear nature of the synthesis (a convergent synthesis with the same number of steps and similar yields would give a much higher overall yield).

1.4 General Organosilicon Chemistry

1.4.1 Introduction and The Nature of the C-Si Bond

In recent years, organosilicon chemistry has become increasingly important in organic synthesis.[98-100] Many classes of organosilicon compounds have been extensively studied and widely used in synthesis. A brief overview is given here of some of the most important features of organosilicon chemistry.

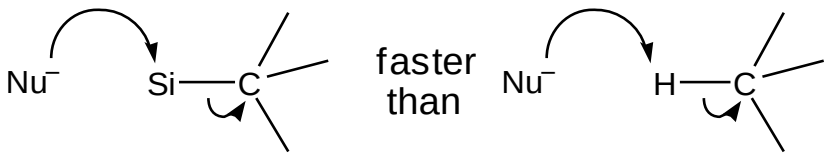


Figure 1.6

The synthetic utility of organosilicon reagents stems from the nature of the carbon-silicon bond. Silicon has a Pauling electronegativity of 1.8 (*cf* carbon 2.5 and hydrogen 2.1) so that the C-Si bond is polarised towards the carbon, but only weakly so. Hence, organosilanes are relatively inert compared to other organometallic compounds, frequently enabling C-Si bonds to be taken through a long synthetic sequence without disruption. However, the C-Si

Bond	C-Si	C-C	C-H	Si-O	Si-F
Bond Enthalpy /kJ mol^{-1}	318	348	412	374	582

Table 1.1

bond is more polarised and weaker than most C-H bonds, and together with the high strength (and hence ready formation) of Si-O and Si-Hal bonds this means that halogen or oxygen nucleophiles much more readily attack the electropositive silicon than they do a hydrogen atom (figure 1.6 and table 1.1). This means that silyl groups can frequently be removed highly selectively.

Another important feature of the C-Si bond is its ability to stabilise a positive charge β to silicon. This hyperconjugative stabilisation is much more effective than that provided by C-C or C-H bonds, and is due to overlap of the bonding molecular orbital of the C-Si bond with the empty p-orbital of the carbocation (figure 1.7). There are two reasons why this so-called "β-

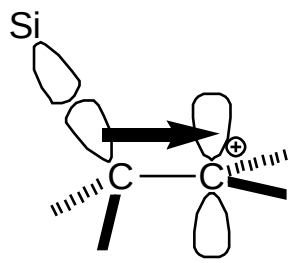


Figure 1.7

effect" is greater for C-Si bonds than it is for C-C or C-H bonds: firstly, the greater polarisation in the direction of carbon for the C-Si bond means that the coefficient of the molecular orbital on carbon is greater, leading to more efficient overlap with the empty p-orbital. Secondly, since the bonding molecular orbital of the C-Si bond is closer in energy to the empty p-orbital than are the corresponding C-C or C-H orbitals, overlap leads to greater

stabilisation (see figure 1.8). This β-effect frequently leads to regio- or stereospecificity in reactions where a stabilised β-silyl carbocation is an intermediate.

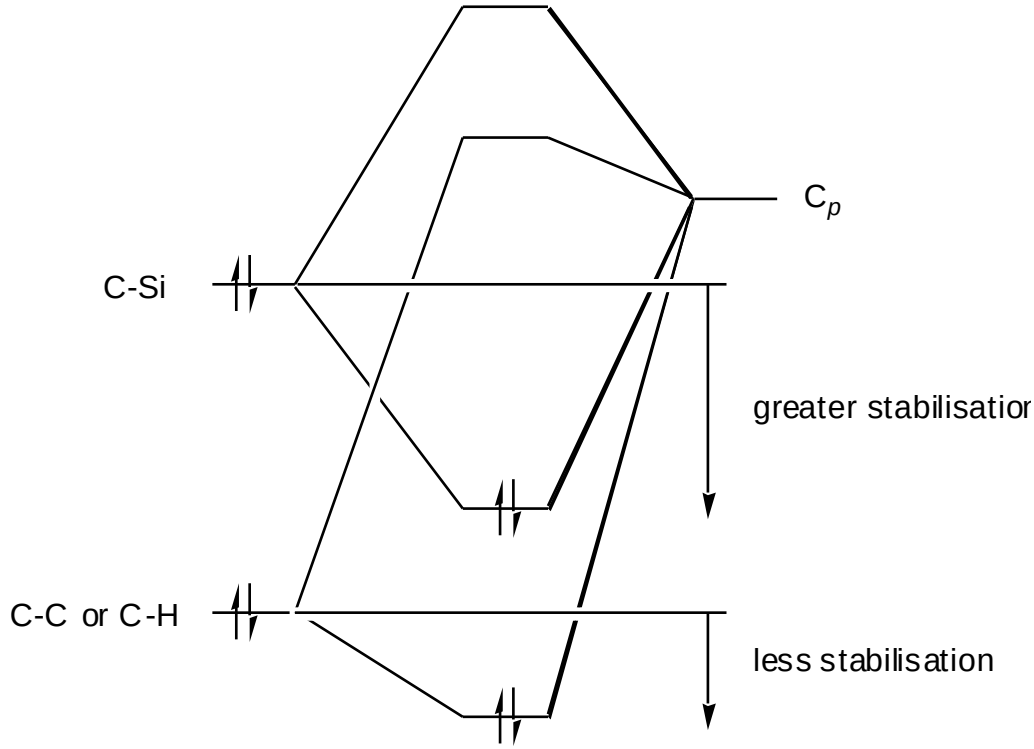


Figure 1.8 (not to scale)

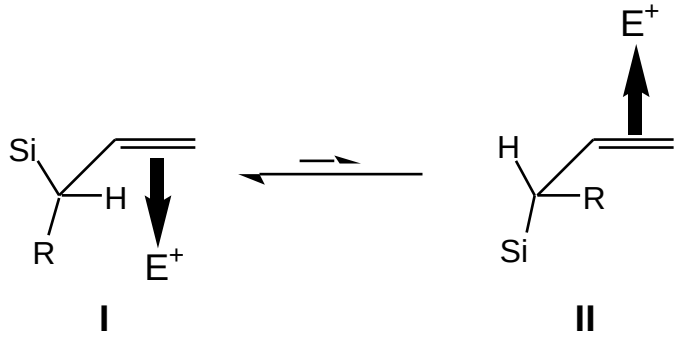
Some examples of organosilicon chemistry which take advantage of these properties and which have relevance to the work described in this thesis are discussed briefly below.

1.4.2 Electrophilic Attack Directed by Silicon

1.4.2.1 Introduction

The stereochemical outcome of electrophilic attack on a double bond adjacent to a stereogenic centre carrying a silyl group, an alkyl group and a hydrogen atom is dependent on the conformation of the allylsilane unit when it attacks the electrophile. We expect that the bulky silyl group will not eclipse the double bond in any low energy conformation, and so if

there is a choice between a small hydrogen atom (confomation **I**) and a more bulky alkyl group (conformation **II**) (scheme 1.23), then we would expect most of the molecules to exist in conformation **I** because there the steric crowding is less.



Scheme 1.23

Thus, electrophilic attack will take place with the molecule predominantly in conformation **I**. We expect attack of the electrophile (E^+) to be *anti* to the silicon for steric (and possibly electronic) reasons. Hence, electrophilic attack takes place in an *anti* fashion.

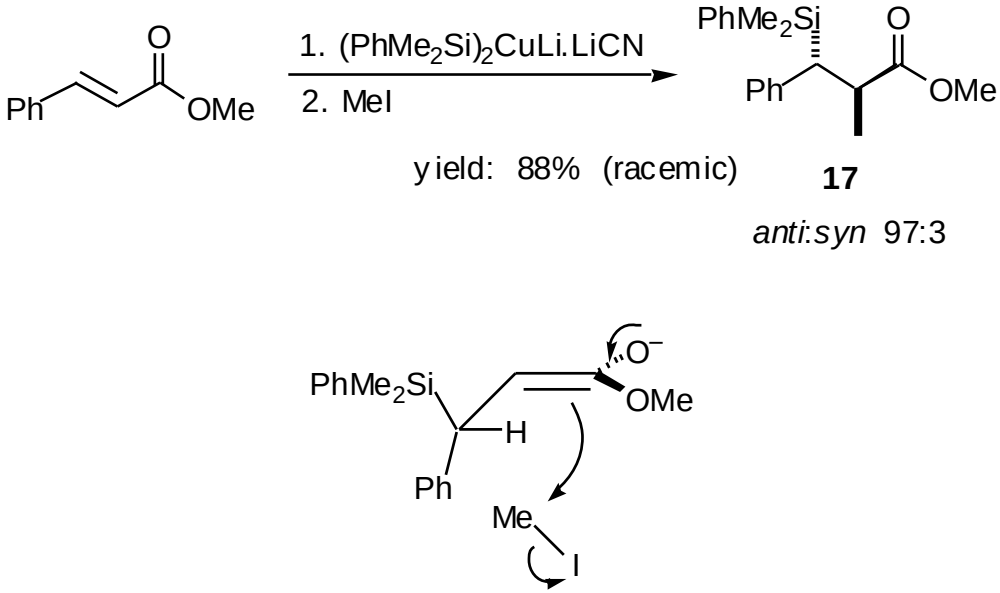
Three common uses of this stereoselectivity in organosilicon chemistry are described below using example reactions from the literature.

1.4.2.2 Alkylation of β-Silyl Enolates

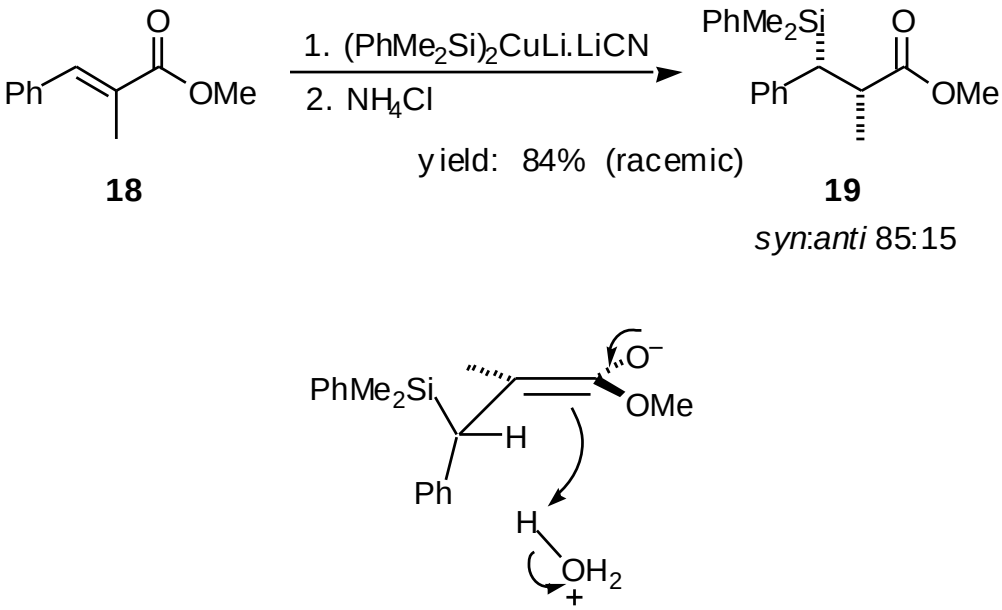
The *anti* compound **17** is formed with excellent diastereoselectivity by alkylation of β-silyl enolates[101] (scheme 1.24). On the other hand, starting with the ester **18** with the methyl group already present, forming the β-silyl enolate, and then quenching puts the *proton anti* to the silyl group and thus leads to the *syn* compound **19** predominantly (scheme 1.25). Hence, both the *anti* and the *syn* compounds are readily available by this method.

1.4.2.3 Hydroboration of Allylsilanes

Hydroboration provides another way of using the directing properties of silicon to

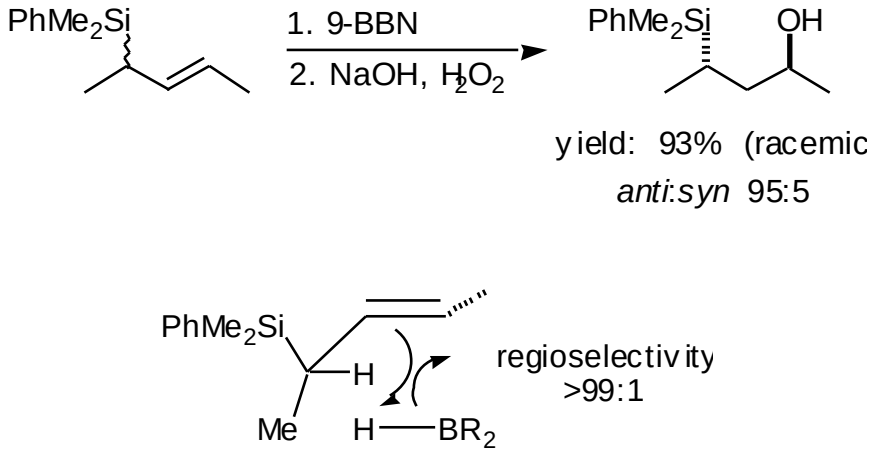


Scheme 1.24



Scheme 1.25

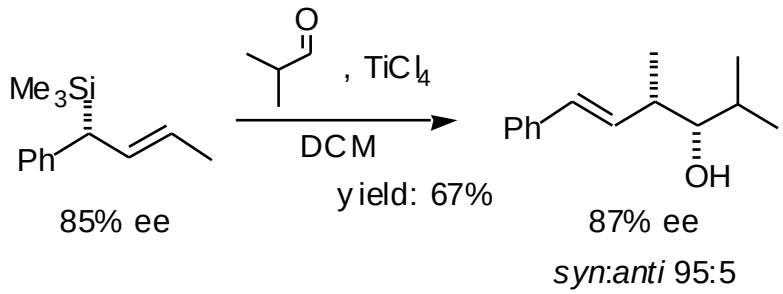
introduce groups with high diastereoselectivity without losing the silyl group in the process. The geometry of the double bond determines the relative stereochemistry of the product (e.g., scheme 1.26).[102]

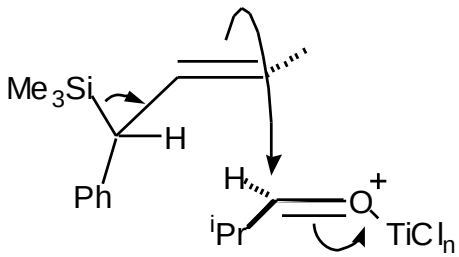


Scheme 1.26

1.4.2.4 S_E2' Reaction of Allyl- and Allenylsilanes

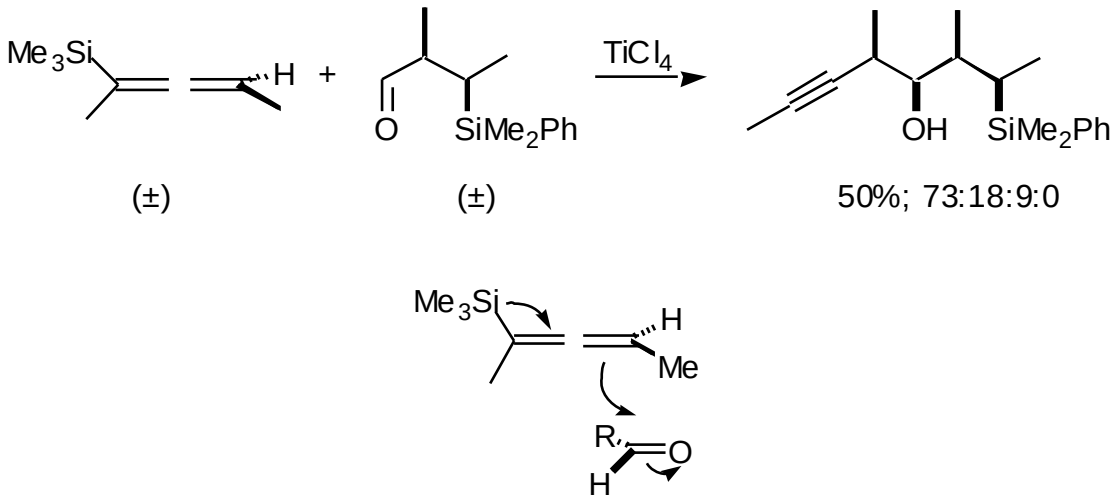
Regiospecific reaction of allylsilanes with many electrophiles takes place to give an allylic rearrangement and an overall *anti* product, usually possessing an *E* double bond. This





Scheme 1.27

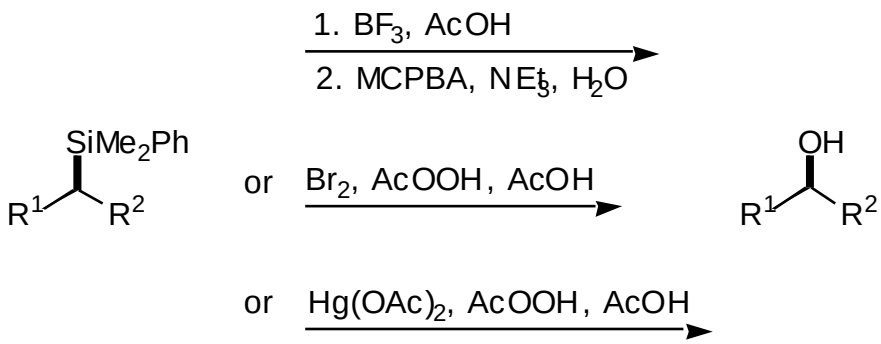
constitutes transfer of chirality two carbon atoms down the molecule, the silyl group being lost in the process (e.g., scheme 1.27).[103,104] Allenylsilanes react in an S_E2' manner with *anti* selectivity (e.g., scheme 1.28).[105]



Scheme 1.28

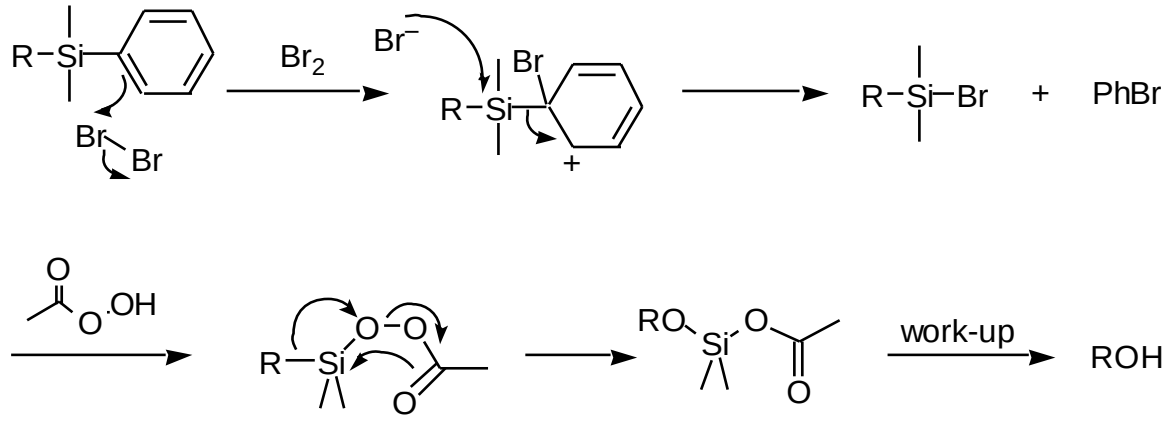
1.4.3 The Dimethyl(phenyl)silyl Group as a Masked Hydroxyl

An extremely useful transformation of the dimethyl(phenyl)silyl group is the one-pot conversion to a hydroxyl group with retention of configuration (scheme 1.29).[106,107]



Scheme 1.29

Several different conditions are available for this transformation, and can be used depending on what other functionality exists in the molecule. The likely mechanism for the reaction using bromine (the others are analogous) is shown in scheme 1.30.



Scheme 1.30

The phenyl group undergoes electrophilic attack by bromine (*ipso* attack is favoured because the carbocation thus formed is β to silicon and therefore stabilised), and this is followed by nucleophilic attack by bromide ion on the silicon, leading to loss of bromobenzene. Peracetic acid displaces the bromide ion from the silicon, and rearrangement takes place with migration of the alkyl group from silicon to oxygen with retention of configuration. Hydrolysis gives the alcohol.

Thus, a dimethyl(phenyl)silyl group can be used to control the stereochemistry in a synthetic sequence, and then at a suitable point be "unmasked" to reveal a hydroxyl group. While it is carried through as a dimethyl(phenyl)silyl group, in contrast to other methods of alcohol protection, there is no possibility of chelation (since the silicon atom has no lone pairs), it is electropositive rather than electronegative, it is potentially much more bulky sterically and it can take part in all of the interesting silicon chemistry described in this section.