

**ASYMMETRIC SYNTHESIS USING SUGARS
AS HOMOCHIRAL AUXILIARIES**

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To my beloved husband, Fahrul Zaman, my four beautiful little girls,
Farhanah, Farhah, Fathiah and Fatini.....

To my loving parents, especially my mom who had always been there
whenever I needed her most.

**I have always believed that our journey through life is never
complete without stumbling into milestones and setbacks. But
these misfortunes as most may call them are only divine tests from
Allah to make us better and stronger individuals**

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ABSTRACT

The development of the area of asymmetric synthesis has increased interests of many organic chemists. Asymmetric synthesis simply means the selective generation of new chirality elements by action of chiral reagents in which many are found naturally. In this study, the addition reaction of enones with *N*-bromosuccinimide (NBS) in series of primary alcohol was observed and produced bromoalkoxy adducts as major products as well as their diastereomers which made up the portion of the minor isomers. The major adducts were isolated by direct recrystallisation of the crude products. 2-Methyl-1-propanol and 1-propanol were found to demonstrate the highest selectivity in the addition reaction and gave diastereomic ratio of 15.3:1 and 13:1 respectively. The formation of the major adducts increases with increasing molecular weight of the alcohol. The bromoalkoxylation of the major adducts may be due to predominant formation of gauche conformation of the substituents on the two stereogenic centres. This may have contributed to the lower steric hindrance and a lower potential energy. The removal of the sugar auxiliary from the bromoalkoxy derivatives was successfully performed using trifluoroacetic acid and ethane-1,2-diol to yield mixtures of acetal and tetraacetylglucose. Trifluoroacetic acid was observed to be an excellent reagent in the removal of the sugar auxiliary. The tetraacetylglucose was removed from the acetal, by treatment with *p*-toluenesulphonic acid in methanol to produce pure acetal as a colourless oil. The bromoalkoxy adducts were characterized using infrared (IR) and nuclear magnetic resonance (¹H-NMR) spectroscopies.

ABSTRAK

Perkembangan di dalam bidang sintesis asimetrik telah menarik minat ramai para ahli kimia kimia organik. Sintesis asimetrik bermaksud pemilihan penghasilan suatu elemen kiral baru melalui tindak balas oleh agen kiral yang boleh di dapati dengan banyaknya di alam semulajadi. Di dalam kajian ini, tindakbalas penambahan enon dengan *N*-bromosuksinimida (NBS) telah menghasilkan aduk bromoalkoksi sebagai hasil utama bersama dengan diastereomer sebagai hasil sampingan. Aduk utama dapat dituliskan melalui penghabluran semula hasil mentah. 2-Metil-1-propanol dan 1-propanol telah menghasilkan kepilihan yang tertinggi di dalam tindak balas penambahan dengan nisbah diastereomer sebanyak 15.3:1 dan 13:1. Kepilihan terhadap hasil utama bromoalkoksi mungkin disebabkan oleh konformasi *gauche* yang diambil oleh kumpulan penukarganti pada kedua-dua pusat kiral. Ini membawa kepada pengurangan halangan sterik dan tenaga potensi pada aduk utama. Asid trifluoroasetik merupakan bahan yang paling sesuai untuk mengeluarkan molekul auksiliari gula dari aduk bromoalkoksi dan menghasilkan campuran asetal dan tetraasetalglukosa. Tetraasetalglukosa telah dipisahkan dari campuran tersebut melalui tindakbalas dengan acid *p*-toluenasulfonik di dalam metanol untuk menghasilkan minyak asetal tulen. Kesemua aduk bromoalkoksi telah dicirikan dengan menggunakan spektroskopi inframerah dan resonans magnet nucleus ($^1\text{H-NMR}$).

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LIST OF SYMBOLS

C	-	carbon
°C	-	degree Celcius
d	-	doublet
dd	-	doublet of doublet
m	-	multiplet
s	-	singlet
t	-	triplet
q	-	quartet
CDCl ₃	-	deuterated chloroform
cm ⁻¹	-	reciprocal centimeters (wavenumber)
δ	-	chemical shift
g	-	gram
H	-	hydrogen
HCl	-	hydrochloric acid
¹ H-NMR	-	proton Nuclear Magnetic Resonance
IR	-	infrared
<i>J</i>	-	coupling constant
KBr	-	potassium bromide
CSA	-	camphorsulphonic acid
CBz	-	carbobenzoxy group

L	-	litre
max	-	maximum
MHz	-	MegaHertz
Me ₂ CO	-	acetone
Me	-	methyl
mmol	-	millimol
m.p.	-	melting point
NaOMe	-	sodium methoxide
O	-	oxygen
OAc	-	acetate
%	-	percent
TLC	-	thin layer chromatography
TMS	-	tetramethylsilane
TFA	-	trifluoroacetic acid
ν	-	wavenumber

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CHAPTER I

INTRODUCTION

1.1 Research Background

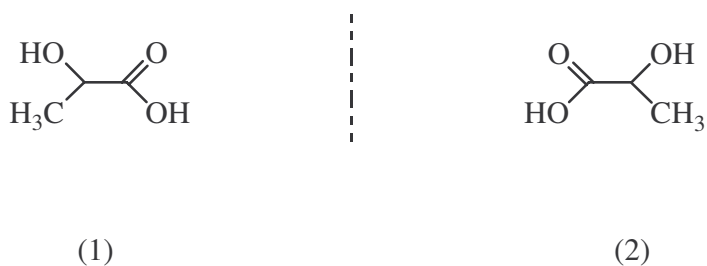
The environment we live in is surrounded by stereoisomerism and chirality which remains oblivious to most of us [1]. The fact that many organic compounds which are found naturally, or synthesized by man in the laboratory are chiral. Chemists working with perfumes, cosmetics, nutrients, flavours, pesticides, vitamins and pharmaceuticals require access to enantiomerically pure compounds [2]. In the pharmaceutical industry, by 1990 more than half of the drugs available on the market worldwide were chiral. About 90 percent were natural products or semi-synthetic derivatives. Enantiomeric compounds have different tastes and odours [3]. Hence, it is obvious that two enantiomers would be considered different when screened for pharmacological activity, as in some cases, it could mean between life and death if the manufactured drug were not enantiomerically pure [4].

It was Emil Fischer in 1894, who had clearly outlined the concept of asymmetric synthesis based upon his experiments in the conversion of one sugar to its next higher homolog via the cyanohydrin reaction, relating this process directly to the biochemical process for the production of optically active sugars in plants [5]. His work now forms the basis for the modern asymmetric synthesis.

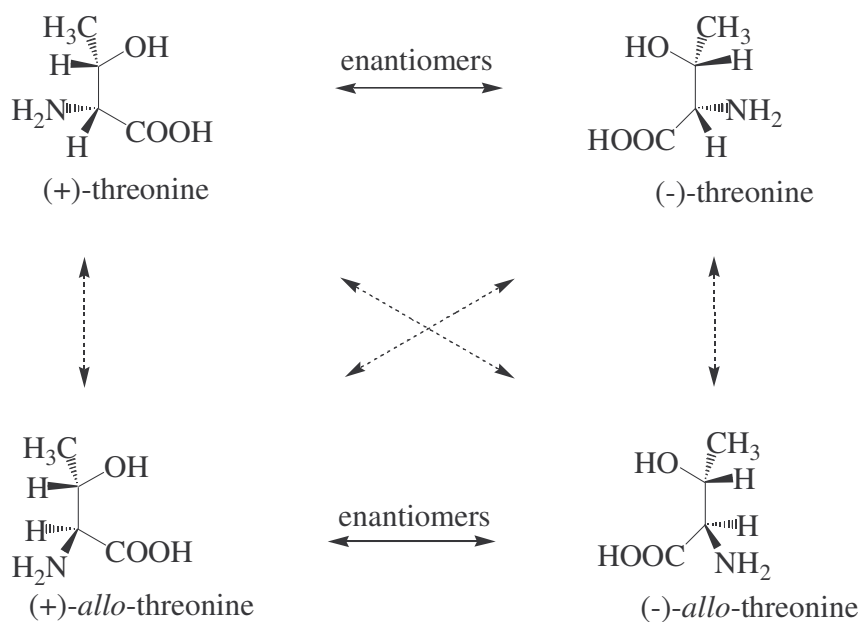
An asymmetric synthesis is defined as a synthesis in which an achiral unit in an ensemble of substrate molecules is converted to a chiral unit such that the possible stereoisomers are formed in unequal amounts [6]. It is a process which converts a prochiral unit into a chiral unit so that unequal amounts of stereoisomeric products results. The reactants include only the usual chemical reagents and also solvents, catalysts and physical forces such as circularly polarized light [7]. It is actually a reaction or reaction sequence that selectively creates one configuration of one or more new stereogenic elements by the action of a chiral reagent or auxiliary, acting on heterotopic faces, atoms or groups of a substrate. The stereoselectivity is primarily influenced by the chiral catalyst, reagent, or auxiliary, despite any stereogenic elements that may be present in the substrate [8].

Another fundamental of symmetry property of three-dimensional objects is chirality. Asymmetric synthesis involves the formation of chiral molecules. An object is said to be chiral if it cannot be superimposed upon its mirror image [6]. A chiral object lacks all the second order symmetry elements such as the mirror plane (σ), center of symmetry (i) and rotation reflection axis (S). In chemistry, the term is applied to the entire molecule and not to contain parts of molecule. A chiral compound may be either racemic or nonracemic [8]. In a chemical context, chirality is applied to the three-dimensional structure of a molecule.

Asymmetric synthesis is not complete without the formation of enantiomers. Enantiomers refer to pairs of stereoisomers with the highest level of similarity. When their formulas are written down according to the same convention, internuclear distances are identical. Enantiomers however, may differ in the direction in which they rotate the plane of polarized light [9]. The conventional character of distinguishing enantiomers must be emphasized. A typical statement describing the difference between dextrorotatory and levorotatory lactic acid is: when their formulas are depicted according to the same convention whereby hydrogen is remote from the viewer, the sequence of the groups hydroxy, carboxy and methyl is anticlockwise as (*R*) for the dextrorotatory (1) and clockwise for the levorotatory (2) enantiomer as (*S*). This phenomenon of optical activity provides the basis for the nomenclature of enantiomers. Hence (1) which rotates the plane of polarized light clockwise is denoted as (+)-(*R*)-lactic acid and the enantiomer (*S*) which rotates the plane of polarized light anticlockwise is denoted as (-)-(*S*)-lactic acid [10].



There are only two possible stereoisomers of a chiral compound containing one stereogenic unit, the (+) –and– (–)-enantiomers if there are n stereogenic units there will be 2^n stereoisomers. There are two possibilities arising either as mirror images of each other, in which they are enantiomers, or they are called diastereomers. An example provided by the four possible stereoisomers of the amino acid threonine is as shown in Figure 1.1.



Note: [\longleftrightarrow] = diastereomers

Figure 1.1: Four possible stereoisomers of the amino acid threonine.

A pair of enantiomer which has identical physical properties, except for their opposite signs of optical rotation can be separated. This feature provides the basis for the resolution of chiral compounds. In this procedure a racemic mixture is derivatised by reaction with enantiomerically pure compounds which leads to a mixture of two diastereomers. The diastereomers can be separated by fractional crystallisation or distillation as a result of their different physical properties [11].

1.2 Method for the Formation of Chiral Compounds

Before considering in detail the different approaches to asymmetric synthesis, it is worth looking briefly at all the methods available to obtain chiral compounds in a non-racemic form.

1.2.1 Use of Naturally Occurring Chiral Compounds as Building Blocks.

The steps in this method will generally not involve the stereogenic centre(s) required for the product and care has to be taken that there is no chance of racemisation during the sequence. In some cases the stereogenic centre may undergo reaction as long as this proceeds with retention of chirality, an S_N2 substitution being a common example. This approach to chiral compound is easily recognised since no new stereogenic units are formed. The stereogenic units are directly derived from the starting material.

The first application involves an amino acid as chiral starting material in the synthesis of unnatural amino acids. (*S*)-serine (3) is converted into its *N*-protected analogue (4). Under Mitsunobu conditions the primary hydroxyl is displaced giving (5). This strained β -lactone undergoes S_N2 ring-opening when treated with a wide variety of Grignard reagents in the presence of Cu(I) salts. To complete the synthesis of the unnatural amino acid, the CBz group is removed to give the enantiomerically pure product (6) [12]. The synthesis of pure product (6) is shown in Figure 1.2.

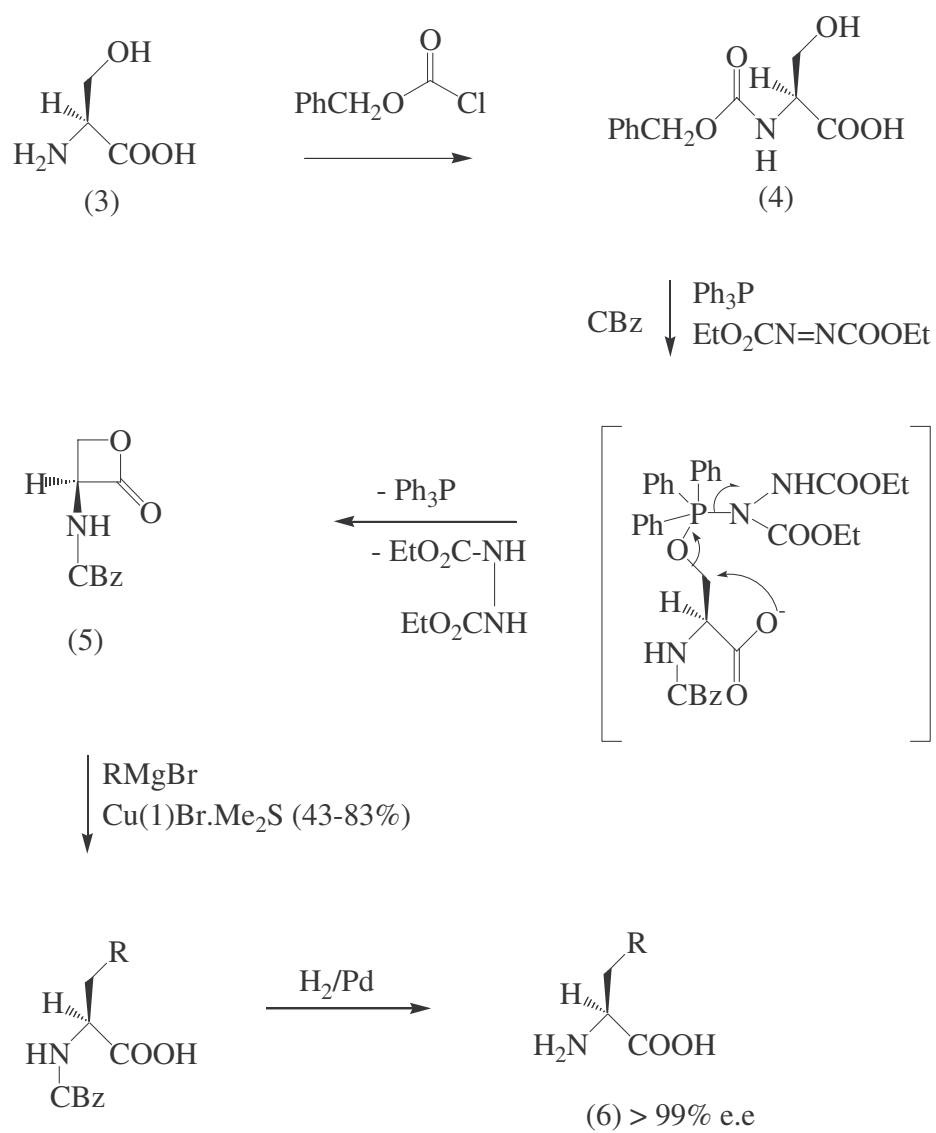


Figure 1.2: Synthesis of Unnatural Amino Acids

1.2.2 Resolution

Resolution is considered the classical method of obtaining enantiomerically pure products which relies on the different physical properties of diastereomers. If the racemic compound which is to be resolved is derivatised by reaction with a naturally occurring enantiomerically pure compound. Only then the resulting diastereomeric compounds may be separated most commonly by crystallization but also by chromatography, and then separately treated to liberate the two enantiomers. If we represent the substrate to be resolved by S and the resolving agent by A*, then the overall process is shown in Figure 1.3.

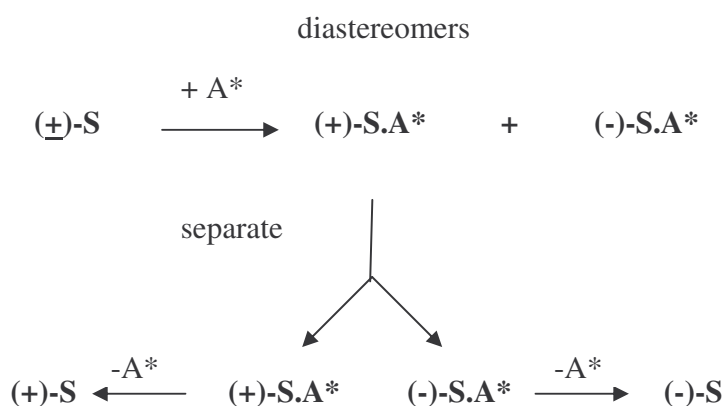
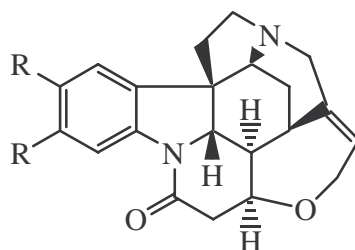


Figure 1.3: Resolution of (+)-S

The resolving agent is recovered unchanged after this procedure and can be reused repeatedly. Because of the need to obtain crystalline adducts which are readily broken down to their components again, the ionic salts formed between amines and acids either carboxylic or sulphonic, are ideal for resolution. Many amines were resolved by formation of salts and organic acids were resolved with bases such as quinine,

cinchonine and the highly toxic alkaloids brucine (7) and strychnine (8). Reliable resolution methods have been worked for many other types of compounds and these have provided most cost-effective way to obtain enantiomerically pure compounds on a large scale [12].



(7) R = OMe

(8) R = H

Resolution of enantiomers may also be performed by the covalent attachment of an enantiomerically pure compound more commonly used as a chiral auxiliary, followed by separation of the diastereomers. A popular choice for chiral auxiliary ketones and lactones is (+)-(*R,R*)-2,3-butanediol, whose is illustrated by the synthesis of a fragment of (+)-latrunculin B (11). The synthesis of latrunculin B (11) begins with alkylation of the racemic lactone (9) to give diastereomers in a 1:1 ratio each consisting of an equal mixture of both enantiomers. The chiral diol is installed to the *ortho*-ester of the lactone, which results in the equilibrium of the *syn* isomer in a ratio of 6:1. At this point the diastereomers of the major and isomer can be separated by HPLC, which also serves to remove the minor *syn* products. Ozonolysis of (10) gives the aldehyde whose two stereogenic centres become C-8 and C-11 of (+)-latrunculin B (11). The absolute configuration of these centres could be predicted in advance, so a crystalline derivative was made to allow an X-ray determination of the structure. Since the absolute configuration of the (*R,R*)-2,3-butanediol is known with certainty, that of the *ortho*-ester could be inferred with confidence [13]. Synthesis of compound (11) is shown in Figure 1.4.

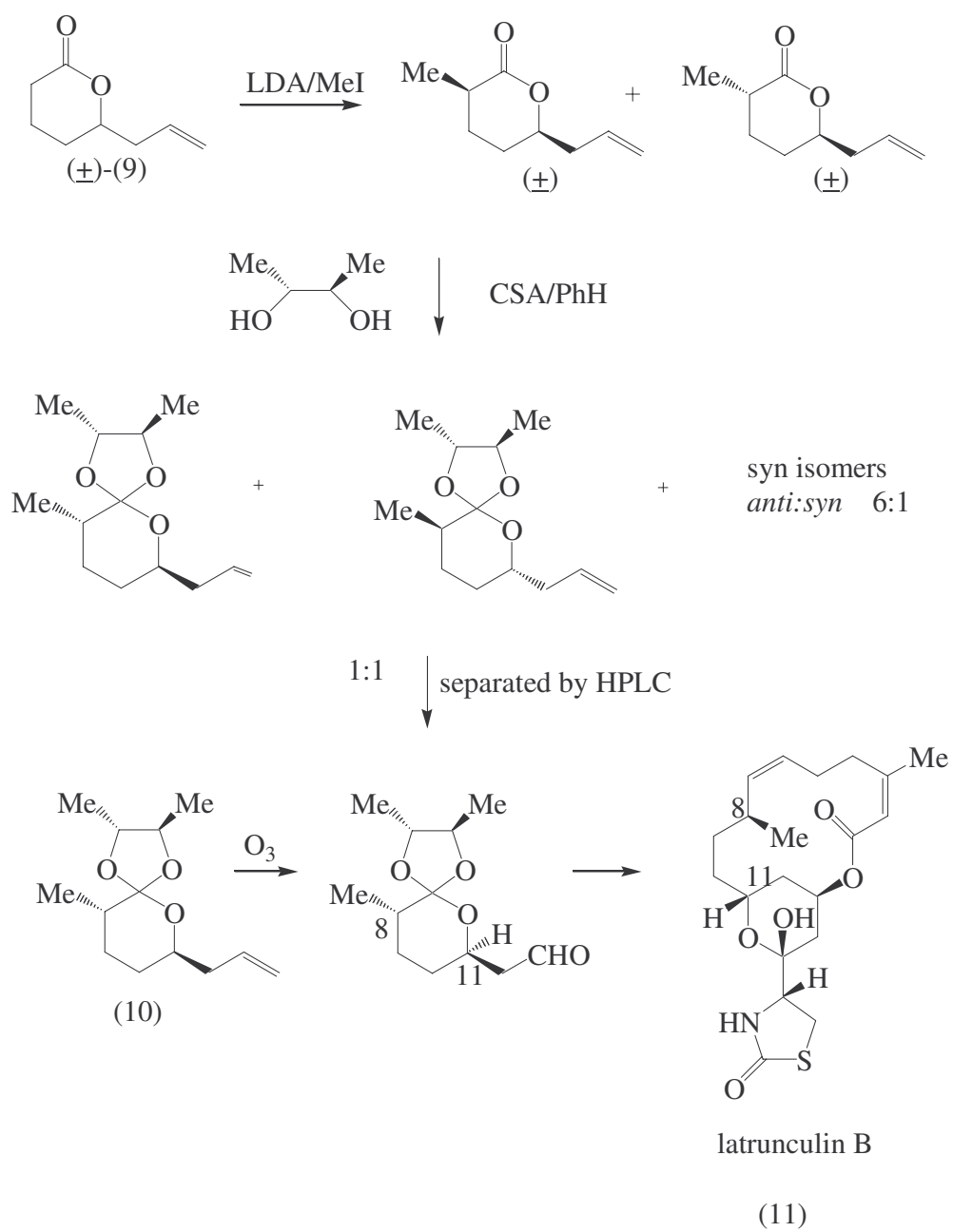


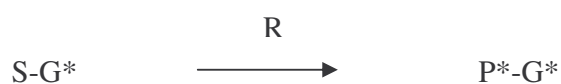
Figure 1.4: Synthesis of Latrunculin B (11).

1.2.3 Methods Of Asymmetric Synthesis

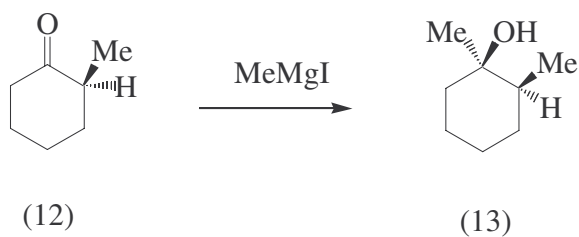
As mentioned earlier, asymmetric synthesis involves the formation of a new stereogenic unit in the substrate under the influence of a chiral group ultimately derived from a naturally occurring chiral compound. The known methods can be conveniently divided into four major classes, depending on how this influence is exerted. The classes are as follows.

1.2.3.1 First Generation Methods or Substrate-Controlled Methods.

For the first generation method, the reaction is directed intramolecularly by a stereogenic unit already present in the chiral substrate. The new stereogenic unit is formed by a reaction with an achiral reagent at a diastereotopic site controlled by a nearby stereogenic unit. To explain the reaction, the substrate which reacts is represented as S, the chiral directing group as G, the reagent as R, the product as P-G and chirality by *, the overall process becomes:



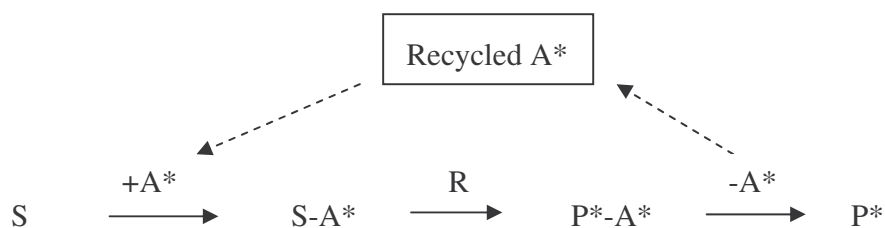
A good example is provided by the addition of methyl Grignard reagent to (*S*)-2-methylcyclohexanone (12) to give (13). The addition reaction to the carbonyl group is influenced by the adjacent stereogenic centre in accordance to Cram's rule.



A disadvantage in this method is the need for an enantiomerically pure material. This is because we are not forming a product from an achiral substrate but merely adding an additional stereogenic unit to an already enantiomerically pure substrate.

1.2.3.2 Second-Generation or Auxiliary-Control Methods

For this method, control is again achieved intramolecularly by a chiral group in the substrate. The difference is only the directing group. The ‘chiral auxiliary’ is now deliberately attached to an achiral substrate in order to direct the reaction of an incoming molecule and can be removed once it has served its purpose. Retaining the same symbols as above and representing the auxiliary by A, we have:



This approach has a feature in which two possible products resulting from the alternative modes of reaction with R are not enantiomers but diastereomers as a result of the presence of the additional stereogenic centre of the auxiliary. The undesired diastereomer of the initial product can be removed by crystallisation or chromatography

so that after the removal of the auxiliary, the final product is obtained in very high enantiomeric excess. An example is the methylation of methylcyclohexanone *via* its imine formed with the methyl ether of (*S*)-phenylalaninol to give (14) as shown in Figure 1.5. Most of the new asymmetric synthesis methods introduced in the last 20 years are the second-generation type.

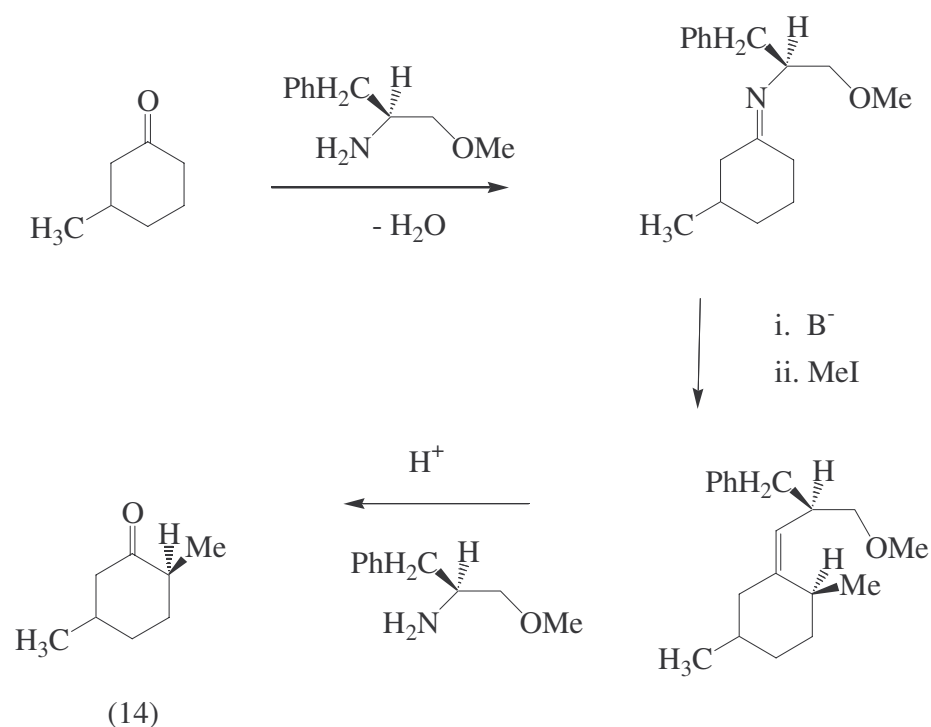
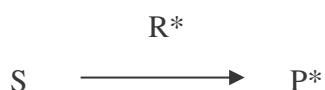


Figure 1.5: Methylation of Cyclohexanone (14).

1.2.3.3 Third-Generation or Reagent-Controlled Methods

This method involves a direct conversion of an achiral substrate to the chiral product by use of a chiral reagent in which the control of the reaction is intermolecular.



However, the range of reactions for which effective chiral reagents exist is somewhat limited. An example is provided by the hydroboration of 1-methylcyclohexene as in Figure 1.6, using isopinocampheyl-borane (15) derived from (+)- α -pinene to give alcohol (16) with two adjacent stereogenic centres [11].

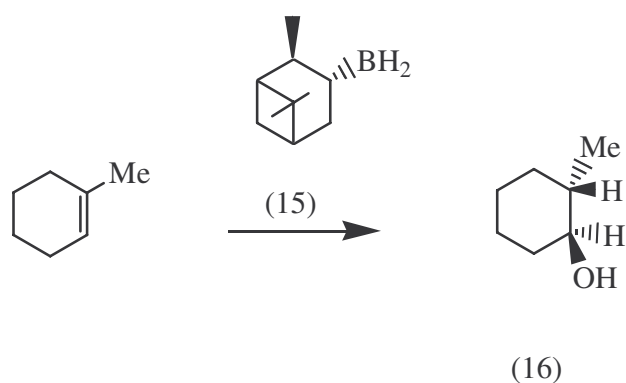
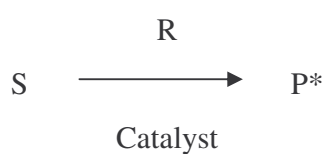


Figure 1.6: Hydroboration of 1-Methylcyclohexene (16).

1.2.3.4 Fourth Generation or Catalyst-Controlled Method

This method involves the use of a chiral catalyst to direct the conversion of an achiral substrate directly to a chiral product with an achiral reagent [11]. The control of the reaction is also intermolecular;



An example is the asymmetric synthesis conjugate addition of a thiophenol to methylcyclohexenone to give (17) catalysed by the alkaloid cinchonidine as shown in Figure 1.7.

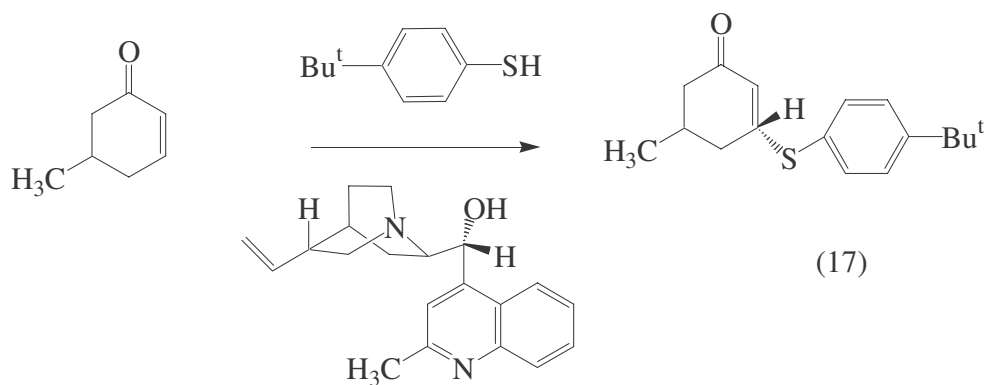


Figure 1.7: Conjugate Addition of a Thiophenol To Cyclohexenone (17).

1.3 Natural Starting Material for The First Generation Method Of Asymmetric Synthesis

Virtually all the known methods of asymmetric synthesis are ultimately based on the pool of naturally occurring enantiomerically pure compounds such as amino acids, terpenes and sugars produced by living organisms. There are a few examples of first-generation asymmetric synthesis in which part of the starting compound is actually built into the final product and serves to direct the formation of the new stereogenic centres. The syntheses below are divided into three groups on the basis of the chiral starting material used.

1.3.1 Sugars

The plant kingdom provides enantiomerically pure sugars which can be converted by standard methods into more interesting compounds. Avenaciolide (24), a naturally occurring α -methylene lactone with cytotoxic properties has been synthesised. Fraser-Reid and Anderson had successfully synthesised compound (24) from glucose. All but one of the carbons and the two of the five stereogenic centres of glucose are used. Glucose reacts with 2,2-dimethoxypropane to give diisopropylidene- α -D-glucopyranose (18). Oxidation of the remaining hydroxyl and Horner-Emmons reaction of the resulting ketone gives (19) which then is reduced stereoselectively to (20). Compound (20) now contains all the stereogenic centres of the target molecules in their correct absolute configuration. Next is the selective cleavage of the pendant ketal group, homologation of the aldehyde (21), cleavage of the vicinal diol to (22), hydrolysis of the remaining ketal with concomitant lactonisation giving (23). Finally, oxidation of the lactol and installation of the *exo*-methylene group to give avenaciolide (24) which is

essentially, enantiomerically pure. The synthesis of avenaciolide (24) is shown in Figure 1.8.

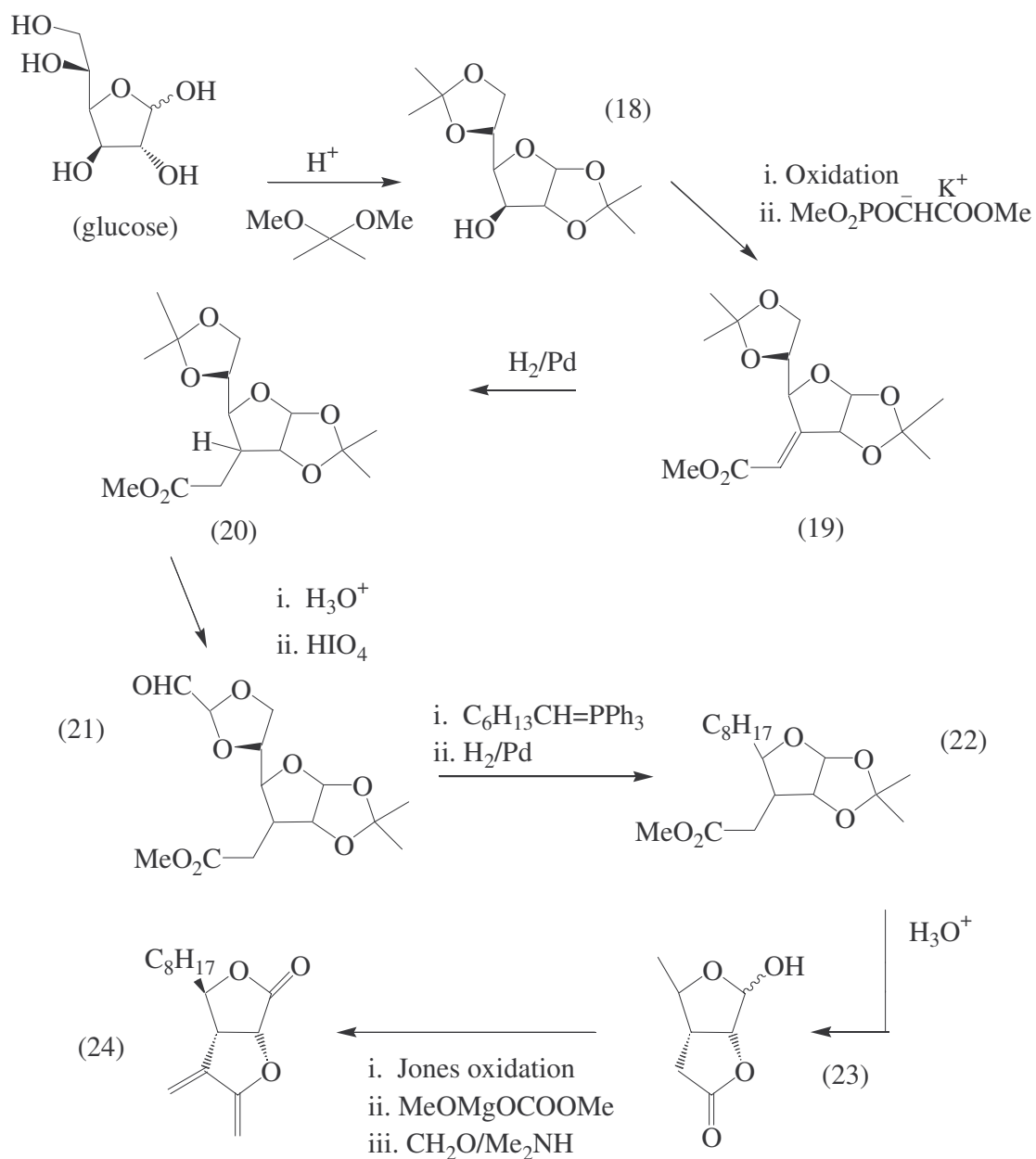


Figure 1.8: Synthesis of Avenaciolide (24).

1.3.2 Amino Acids

In this example, shows how asymmetry may be 'grown' along a carbon chain by the use of 1,2-diastereoselection. The starting material is (*S*)-glutamic acid whose monosodium salt is the famous flavour enhancer. Diazotization of (*S*)-glutamic acid results in the loss of N₂ with formation of strained α -lactone (25) via an internal S_N2 displacement followed by a second S_N2, giving α -lactone (26) with an overall retention. Conversion to unsaturated lactone or butenolide (27) is standard. Lithium dimethylcuprates adds with 1,2-diastereoselection exclusively *anti* to the silyloxymethyl substituent, and the resulting enolate undergoes electrophilic hydroxylation *anti* to the newly formed stereocentre giving (28). Compound (29) is converted to (31) via epoxide (30) and the same reaction was repeated to form (31). Compound (31) has no fewer than five stereogenic centres, four of the installed under the direction of the original centre from glutamic acid. The butenolide (27) was used as a chiral template to propagate the asymmetry of glutamic acid along the chain [15]. Figure 1.9 shows synthesis of derivative of monosodium glutamate (32).

1.3.3 Terpenoids

These are popular chiral starting materials because they are cheap, available in bulk and chemically versatile. So far the synthetic sequences have been linear. In a convergent synthesis, the two or more fragments to be joined must be enantiomerically pure to avoid impossible difficulties with diastereomeric mixtures. This point is illustrated by the synthesis of natural enantiomer of the antibiotic milbemycin β_3 , in which the ultimate sources of chirality are the odiferous terpenoid (-)-(3*S*)-citronellol and the carbohydrate (+)-mannitol. However, on the synthesis of lactone (37), which

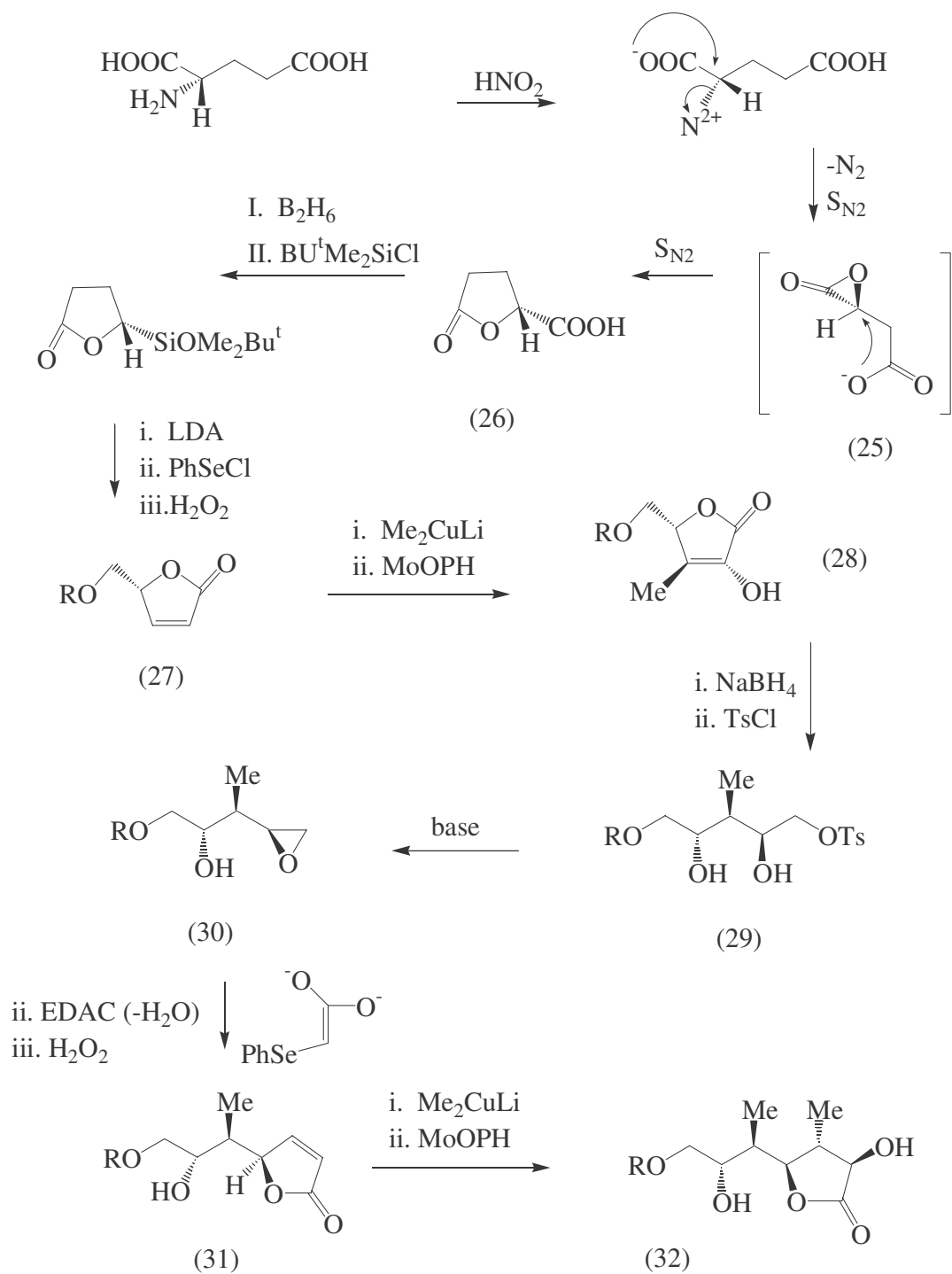


Figure 1.9: Synthesis of Derivative of Monosodium Glutamate (32).

constitutes the C₂₁-C₂₅ section of milbemycin β₃. (3*S*)-citronellol is dehydrated to (33) and selectively ozonised at the more electron-rich double bond, giving aldehyde (34). Jones oxidation of (34) furnished acid (35). The key reaction is the iodolactonisation of (35). This will cause the molecule to adopt a chair-like conformation with the methyl group in an equatorial position. Ring closure to (36) occurs with very high diastereomeric (15:1), and therefore enantiomeric excess. Finally the iodide is reduced under radical conditions to give the C₂₁-C₂₅ lactone (37) [16]. Figure 1.10 shows synthesis of lactone (37) from (3*S*)-citronellol.

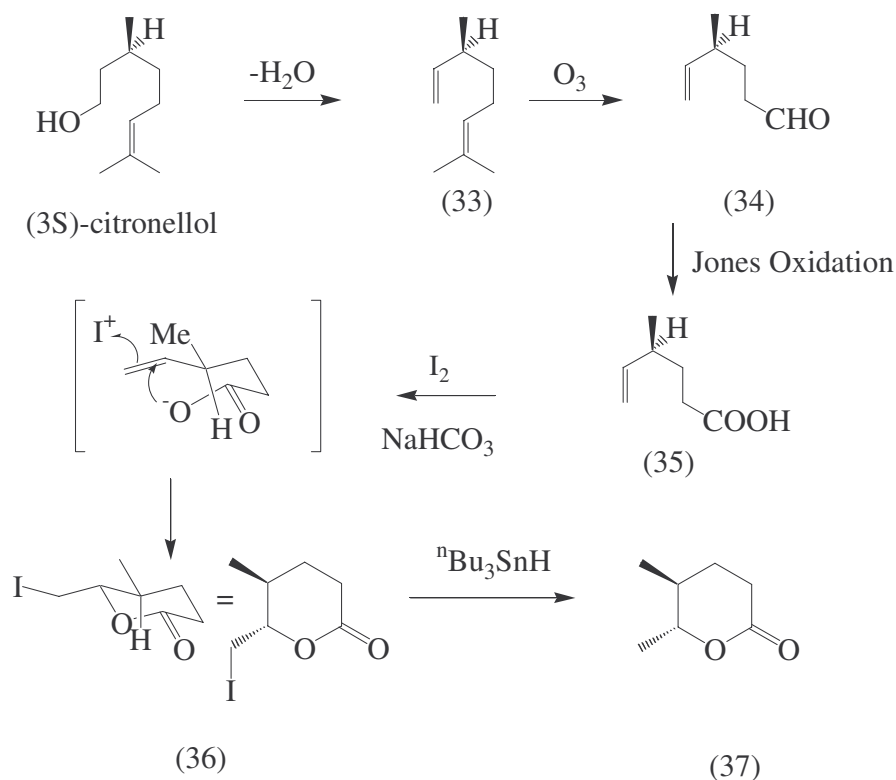


Figure 1.10: Synthesis of Lactone (37) from (3*S*)-Citronellol.

1.3.4 Hydroxy Acids

HR 780 (39) is an inhibitor of enzyme HMG CoA reductase and straightforward asymmetric synthesis based on hydroxyl acid was chosen for this. This enzyme is used for the treatment of atherosclerosis. The synthesis of HR 780 (40) begins with (*S*)-malic acid, which is transformed into (38). The ester function is homologated by a directed Claisen condensation to hydroxyl ketoester (39). The second stereogenic centre is then installed by a stereospecific reduction of the ester to give (40). The reason for the selectivity is that the reductant is delivered intramolecularly by the neighbouring hydroxyl, leading to an excellent 3-diastereoselection [17,18]. The rest of the synthesis is relatively standard as in Figure 1.11.

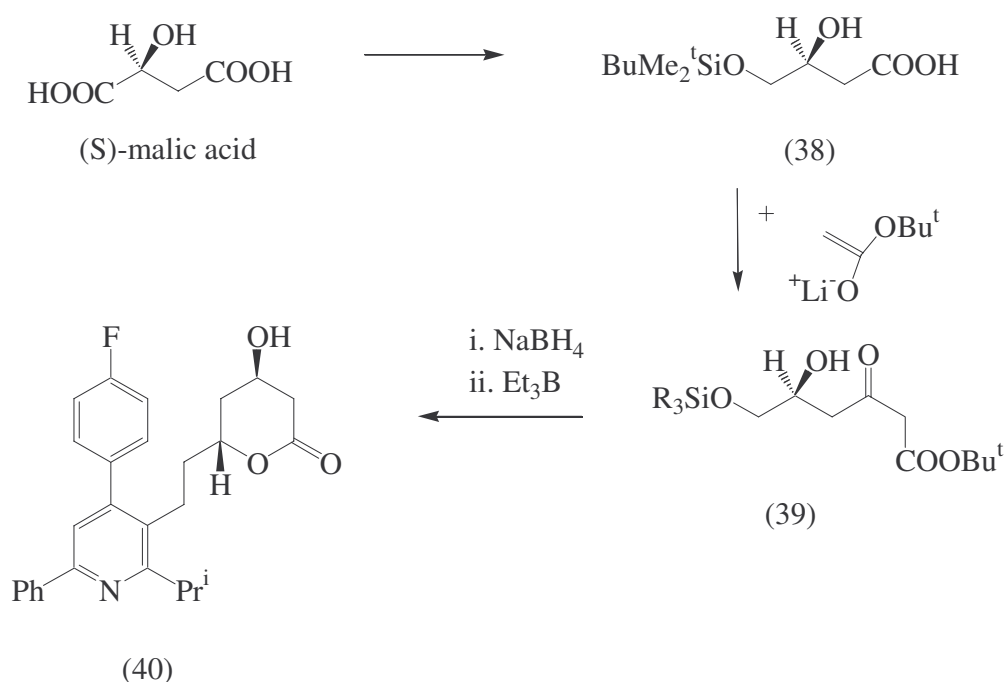


Figure 1.11: Synthesis of HR 780 (40).

1.4 Second-Generation Method of Asymmetric Synthesis

As mentioned earlier, second-generation methods of asymmetric synthesis use a chiral auxiliary which comprises of three steps. They are installation of the enantiomerically pure auxiliary on the substrate, reaction with an achiral reagent producing the two possible diastereomers in unequal amount and lastly, removal of the auxiliary without racemisation.

The second-generation that will be described further is divided into two main groups are as follows;

1.4.1 Nucleophiles Bearing a Chiral Auxiliary

An example of this mode of asymmetric synthesis is the synthesis of α -amino anions. The tetrahydroisoquinoline nucleus is found in thousands of alkaloids, many of which are of great medicinal importance. Methods have been developed to produce a valuable asymmetric synthesis of such systems which is based on an (*S*)-valine-derived chiral auxiliary, abbreviated to VBE. The methylene group adjacent to the nitrogen can be metallated with strong base to give an α -amino anion in which the lithium cation is chelated by the two heteroatoms of the chiral auxiliary [18] as shown in Figure 1.12.

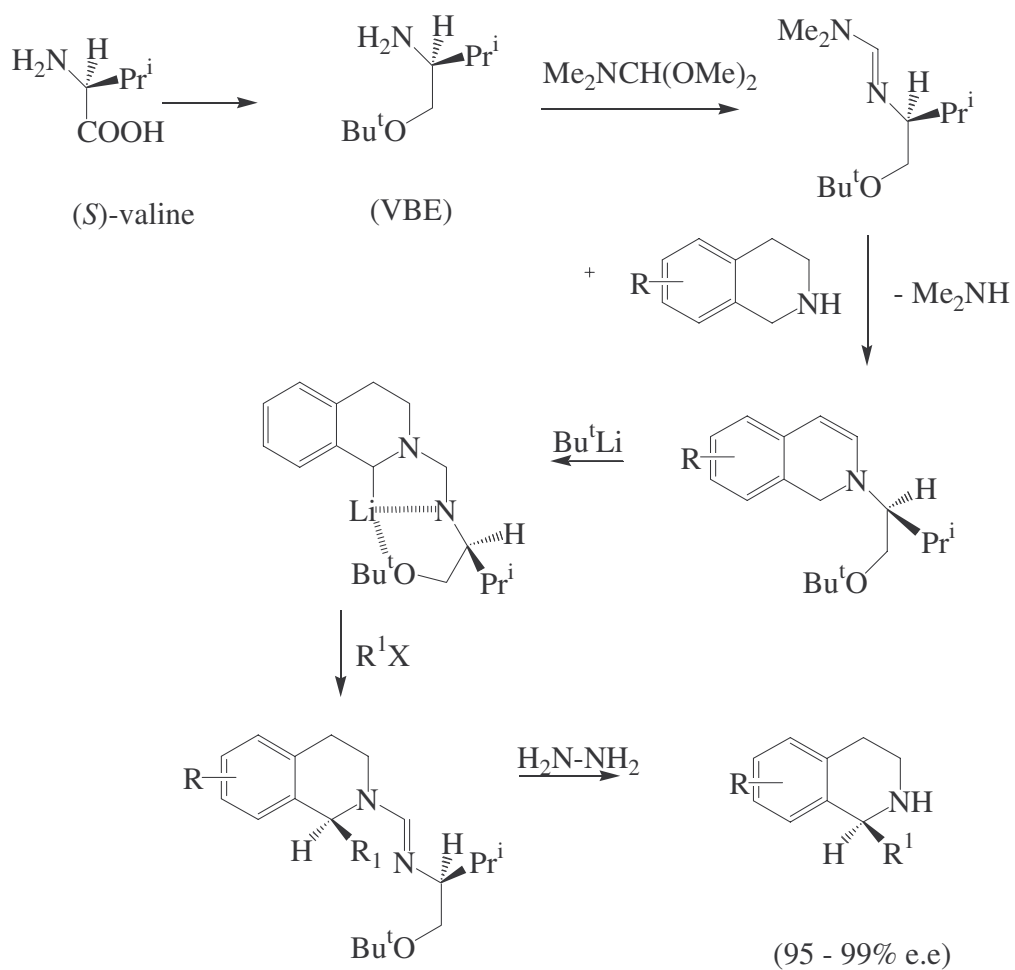


Figure 1.12: Asymmetric Synthesis Using Nucleophile as A Chiral Auxiliary.

1.4.2 Electrophile Bearing Chiral Auxilliary

The Meyers oxazoline auxiliary provides an efficient means of performing Michael addition to prochiral alkenes with excellent diastereofacial selectivity. As shown below this allows convenient acces to chiral β -alkylated acids. It has been known

for sometime that aromatic rings substituted with oxazolines are attacked in a Michael fashion by alkyllithium reagents. An asymmetric version of the reaction has been reported more recently by Meyers, and like so many other second-generation asymmetric syntheses, it relies on internal metal chelation to induce the necessary diastereofacial selectivity. The typical example is the conversion of compound (41) to (42) in Figure 1.13.

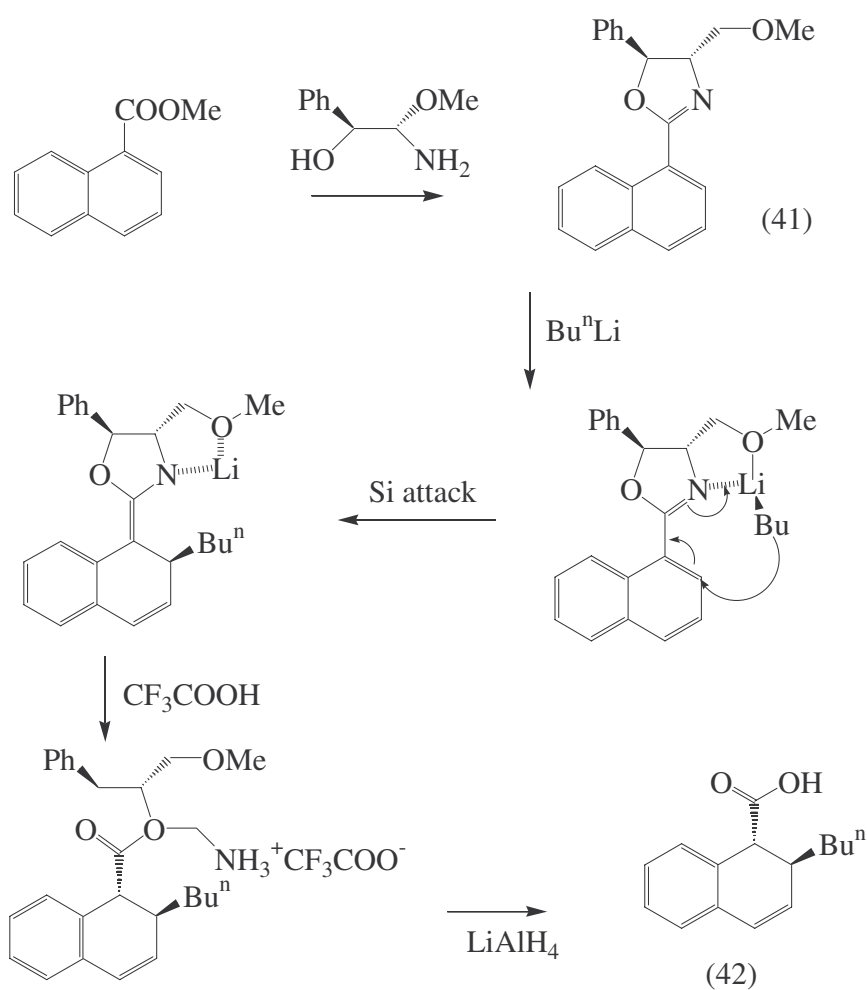
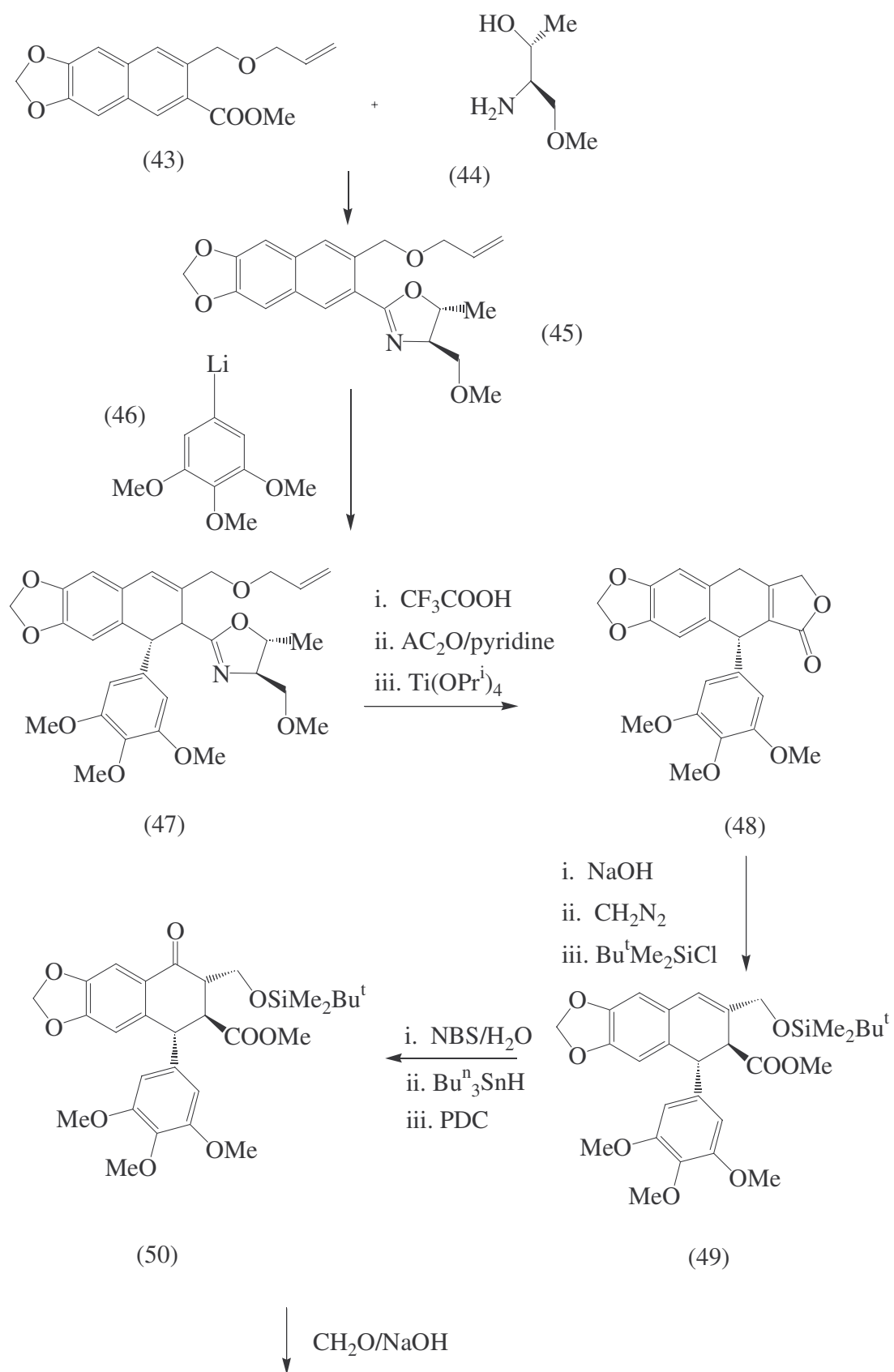


Figure 1.13: Conversion of (41) to (42) via Internal Metal Chelation.

1.5 Synthetic Application of Asymmetric Synthesis

1.5.1 Synthesis of (-)-Podophyllotoxin (55)

One of the important discoveries made by natural product chemist Kupchan was the unusual lignan a derivative of podophyllotoxin (47), which has clinical applications as a powerful and selective antineoplastic. The problem of synthesising it asymmetrically is solved by using the chiral oxazoline auxiliary. The starting material for the synthesis is the highly substituted achiral naphthalene (43). The ester group of (43) reacts with the chiral amino alcohol (44) derived from threonine to give the oxazoline (45), which reacts with aryllithium (46) diastereoselectively, affording intermediate dihydronaphthalene (47) as a mixture of diastereomers. Removal of the auxiliary and allyl group gives lactone (48). On hydrolysis, the double bond migrates back into conjugation with the ring, affording (49) after silylation and esterification. The double bond is transformed *via* the bromohydrin to ketone (50), which is epimeric at two of its three stereogenic centres with the final molecule. Hydroxymethylation gives (51), followed by a retro-aldol reaction to afford (52). The ketone group of (52) is reduced to the desired compound and the analysis is completed by inverting the centre adjacent to the lactone carbonyl by protonation of the enolate. Separation of the two epimers (53) and (54), followed by desilylation gives (-)-podophyllotoxin (55) with a high enantiomeric excess of 93-94% as shown in Figure 1.14 [20].



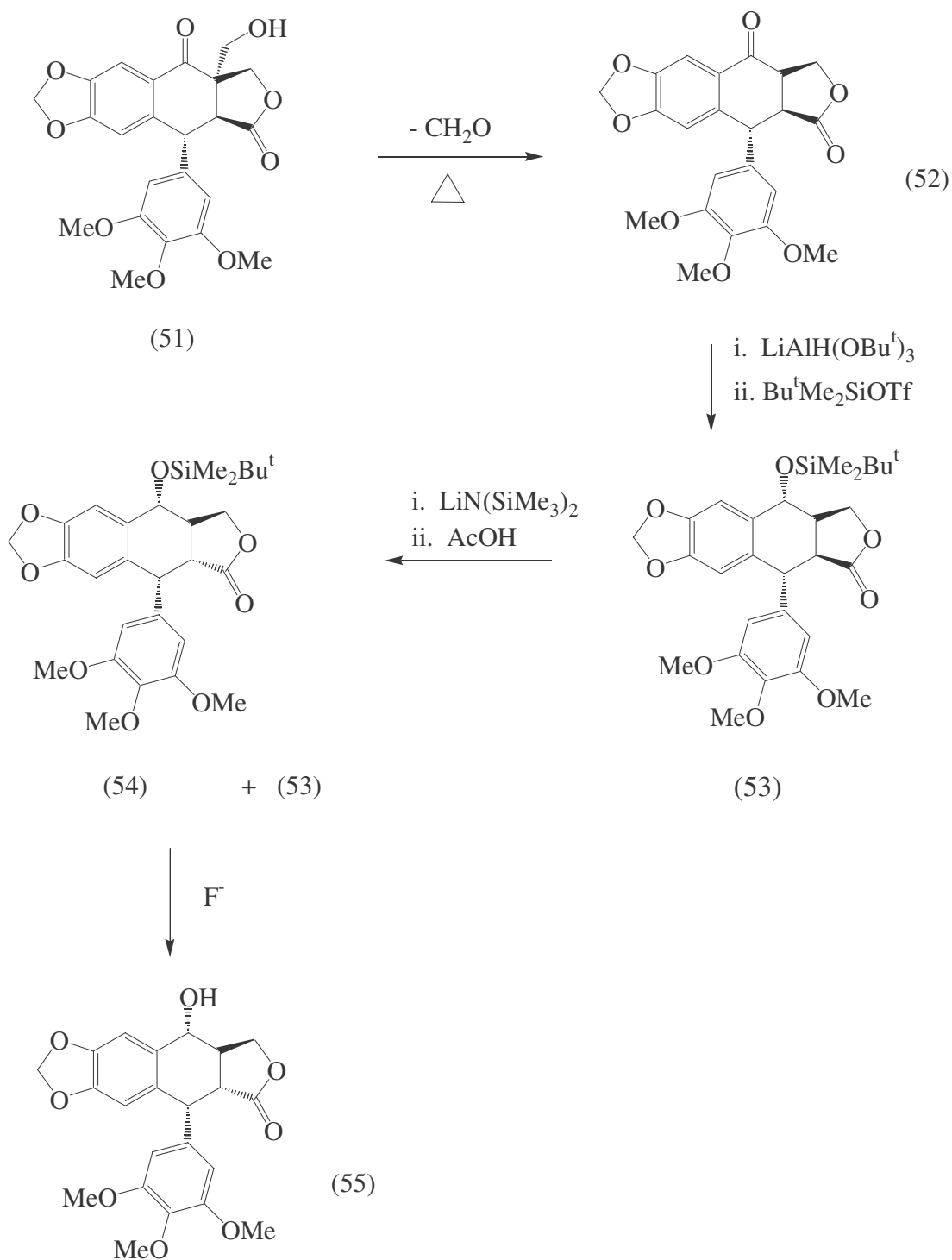
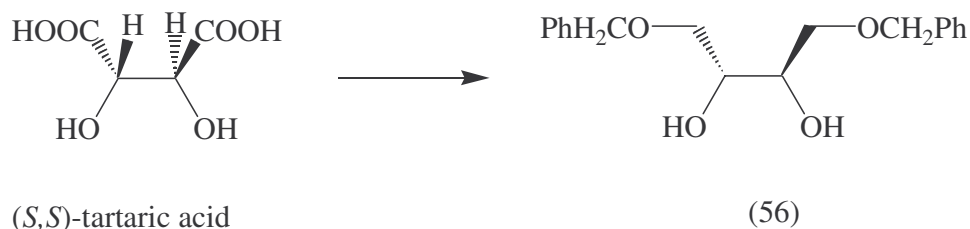


Figure 1.14: Synthesis of (-)-Podophyllotoxin (55).

1.5.2 Synthesis of (*R*)-Muscone (61)

Muscone is one of the components of the anal gland secretion of the civet cat, and despite its provenance, is much valued in perfumery for its 'musky' odour. The synthesis here illustrates an unusual concept in asymmetric synthesis which uses a chiral protecting group as an auxiliary. The chiral auxiliary (56) was synthesised by standard means from unnatural (*2S*, *3S*)-tartaric acid.



Cheap and readily available cyclopentadecanone is α -brominated to (57) and ketalised with (56). The resulting alpha-bromoketal (58) subjected to base induced elimination of HBr, giving (59). The key asymmetric step is now at hand. The Simmons-Smith cyclopropanation proceeds with very high facial selectivity, giving almost entirely the diastereomer (60). The result is rationalised on the basis of zinc chelation by the oxygens of the ketal in which the chiral diol may be recovered for reuse, and followed by reductive opening of the cyclopropane ring under Birch conditions, and reoxidation of the alcohol back to the ketone to form the (*R*)-muscone (61) [21]. The synthesis of (*R*)-muscone (61) is shown in Figure 1.15.

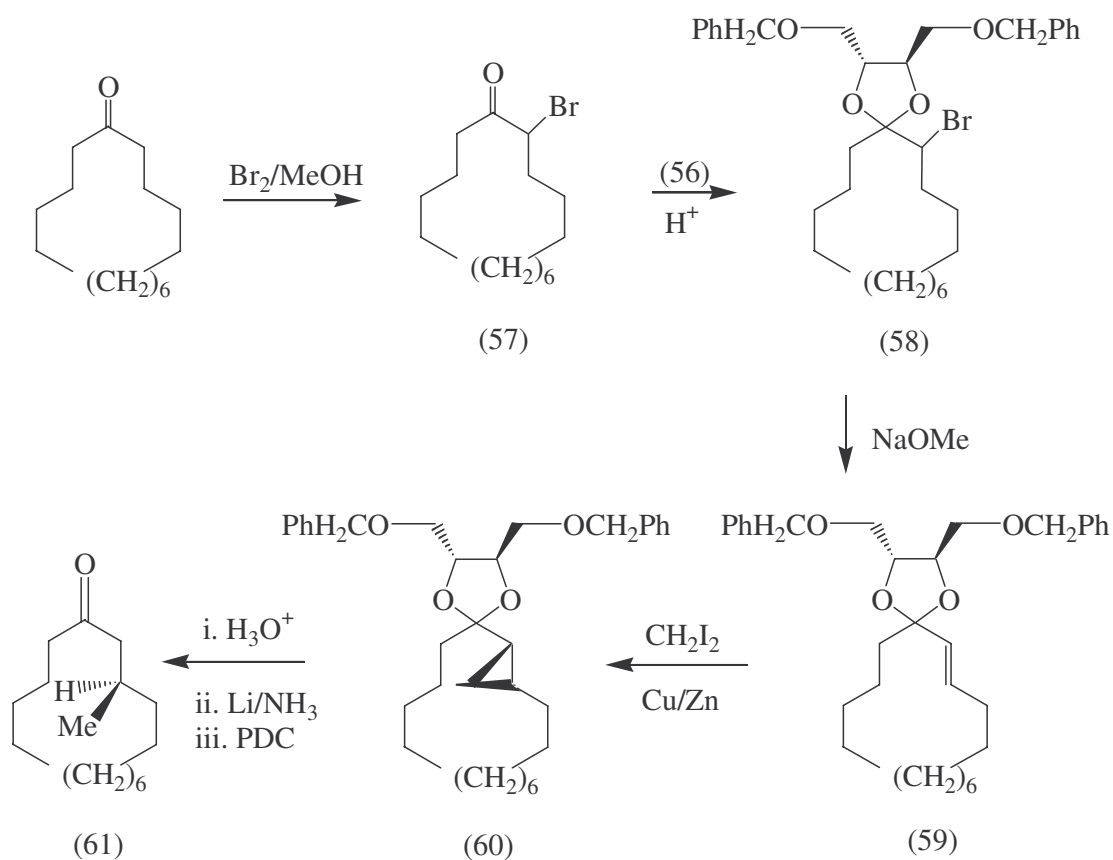


Figure 1.15: Synthesis of (*R*)-Muscone (61).

1.6 Aim of Research

To prove that sugars utilised in the experiments performed were suitable stereodirectors for the reactions of asymmetric synthesis using the second-generation or auxiliary method. The ability of the sugars to produce the desired enantiomers in high enantiomeric excess will also be measured. The experiments performed were used to

determine which of the alcohols used will give the best in term of selectivity in the additions reactions.

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