Chapter 1: Synthetic studies towards D(+) biotin

Section 1: Total synthesis of biotin: A review

Section 2   Attempted synthesis of biotin

Section 3   Formal synthesis of biotin

Chapter 2   Development of some useful synthetic methodologies

Section 1   Deprotection of oxathioacetals

Form-A

CERTIFICATE

Certified that the work incorporated in the thesis entitled "**Synthetic studies Towards D(+)-Biotin And Development Of Useful Synthetic Methodologies**" by **Ms. Priti Soni** was carried out by her under my supervision. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

December 2003
PUNE

S. P. Chavan
Research Guide

TO MY SISTER

Acknowledgements

Priti Soni

1. All melting points and boiling points are uncorrected and the temperatures are in the centigrade scale.

2. All solvents were distilled before use. Petroleum ether refers to the fraction boiling in the range of 60-80°C.

3. Organic layers were dried over anhydrous sodium sulfate.

4. TLC analysis was carried out on glass plates using silica gel GF-254 and the plates were analyzed by keeping in iodine or under UV light.

5. In cases where chromatographic purification was done, silica gel (60-120 mesh) was used as the stationary phase.

6. IR spectra were recorded on Perkin-Elmer Infrared Spectrophotometer Model 68B or on Perkin-Elmer 1615 FT Infrared spectrophotometer.

7. ^{1}H NMR and ^{13}C NMR were recorded on **Bruker AC-200** (50 MHz) or **Bruker MSL-300** (75 MHz) or **Bruker DRX-500** (125 MHz). Figures in parentheses refer to ^{13}C frequencies. Tetramethyl silane was used as the internal standard.

|	
Ac	Acetyl
acac	acetoacetate
AIBN	2,2-Azobis(isobutyronitrile)
Ar	Aryl
BMS	Boron dimethyl sulfide
Bu	Butyl
^{t}Bu	*tert*-Butyl
CAN	Ceric ammonium nitrate
DBU	1,8-Diazabicyclo[5,4,0]undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
DHP	Dihydropyran
DIBAL-H	Diisobutyl aluminium hydride
DMAP	N,N-Dimethyl amino pyridine
DMF	N,N-Dimethyl formamide
DMS	Dimethyl sulphate
DMSO	Dimethyl sulfoxide
EDC	Ethylene dichloride
Et	Ethyl
HMDS	Hexamethyldisilazane
LDA	Lithium diisopropyl amide
mCPBA	m-Chloroperbenzoic acid
Me	Methyl
Ms	Methane sulfonyl
NCS	N-Chlorosuccinamide
NMO	N-Methyl morpholine N-oxide
PDC	Pyridinium dichromate
PCC	Pyridinium chlorochromate
Pd/C	Palladized carbon
PPTS	Pyridinium p-toluene sulfonate
Ph	Phenyl
PPh$_3$	Triphenyl phosphine
p TSA	p-Toluene sulfonic acid
^{i}Pr	Isopropyl
Py	Pyridine
TBAF	Tetrabutyl ammonium fluoride
TFA	Trifluoroacetic acid
TFAA	Trifluroacetic anhydride
TLC	Thin Layer Chromatography
THF	Tetrahydrofuran
TBDMSCl	*tert*-Butyldimethylsilyl chloride
Ts	Tosyl
TBHP	*tert*-butyl hydrogen peroxide
TBTH	tri-n-butyltin hydride
TMSOTf	Trimethylsilyl triflate
TBSOTf	t-Butyldimethylsilyl triflate

The thesis entitled "**Synthetic Studies Towards D(+)-Biotin And Development of Useful Synthetic Methodologies**" is divided into two chapters. The first chapter deals with D(+)-biotin synthesis while the second chapter details development of some novel methodologies.

Chapter 1: Deals with general introduction, recent reports on D(+)-biotin and attempted methods towards D(+)-biotin which culminated in the formal synthesis of D(+)-biotin.

Biotin is one of the water-soluble B-complex vitamins. It plays an essential role as a coenzyme in carboxylation reactions related to biochemical processes such as a glucogenesis and fatty acid biosynthesis. It is widely used in poultry feeds for rapid growth of chicks and healthy hatching of eggs. The main resources of biotin are liver, kidney, pancreas, yeast, milk, and egg yolk. Biotin deficiency in poultry and swine causes a series of severe symptoms. These deficiencies are corrected by using biotin as a feed additive. Hence it is commercially important molecule.

Although a number of syntheses of biotin are known, no practical synthesis was available. There was thus a need for a novel and more practical synthesis of biotin.

Section 1:

1
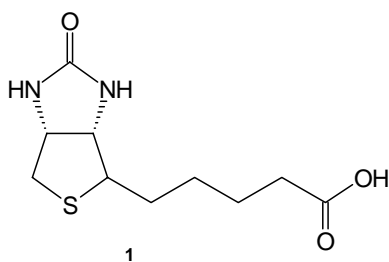
This section presents a general introduction to D(+)-biotin (**1**)along with a brief account about its isolation, biosynthesis. Greater emphasis has been given to the total synthesis and thus all recent syntheses of the compound to this date have been reviewed.

Section 2: Attempted synthesis of D(+)-biotin:

The main emphasis in this section are various approach and the development of simple, non hazardous route to 5,5-fused system which is present in biotin skeleton, from cheaply available starting material i.e.,fumaric acid and L-cysteine

Scheme 1 :
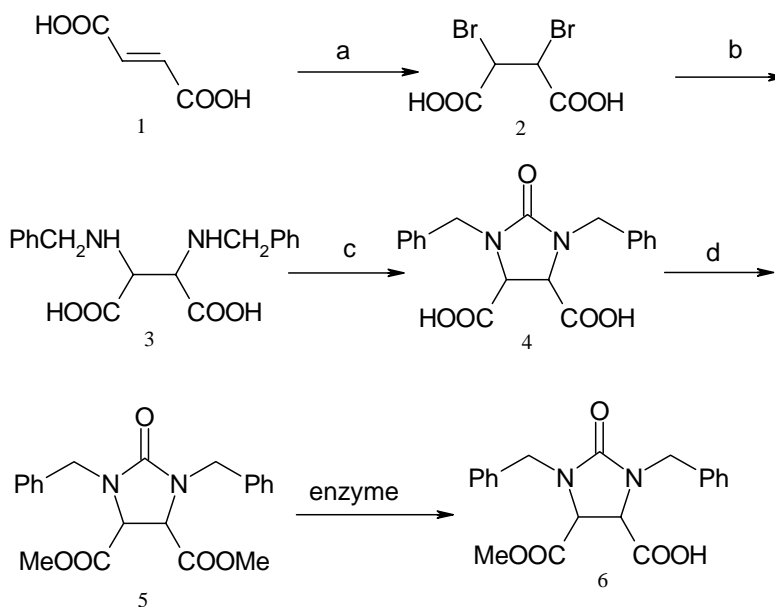
Conditions : *a) Br₂, water, reflux, 90 %; b) PhCH₂NH₂, MeOH, reflux, 90 %; c) triphosgene, toluene, NaOH, H₂O, 90 %; d) SOCl₂, CH₃OH, rt, 12 h*

In accordance with the planned synthesis, fumaric acid was converted to its known dibromosuccinic acid **2** by refluxing fumaric acid and bromine in water. Dibromosuccinic acid **2** was refluxed with benzylamine (10 eq) for 7 h to furnish dibenzylsuccinic acid **3** in quantitative yields. Dibenzylsaccinic acid was refluxed with triphosgene in toluene and aqueous NaOH to furnish **4** in 90 % yield. Diacid **4** was converted to diester in methanol by using thionylchloride at room temperature. With desired diester in hand there was a need to hydrolyze one of the ester groups selectively so that meso diacid could be converted to chiral monoester **6**.

Selective hydrolysis of the diester was attempted by using PLE, PPL, Lipase enzymes under different conditions. But none of these enzymes were found to be suitable for this transformation. The diester did not get hydrolysed and it was recovered as such.

In yet another approach as shown in **scheme 2** methoxy ureide **7** was treated with sodium sand to furnish **8**. Compound **8** was then treated with octyloxyacetylene under various conditions but desired addition product **9** was not formed.

Scheme 2 :
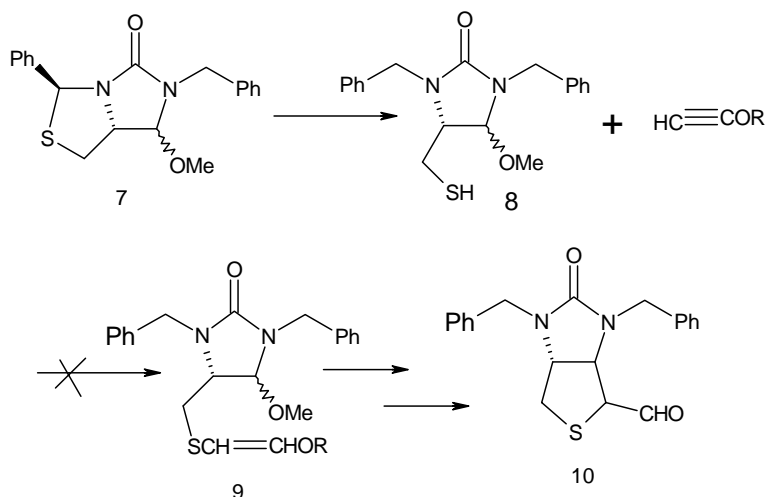
It was thought of making **9** by different route. As shown in scheme **3**, compound **8** was treated with bromoacetaldehyde diethylacetal to furnish **11**. It was then treated with n-BuLi. with the hope to get desired acetylene **12** which in turn could be converted to the olefin **13**. However the reaction was not clean and the desired acetylene could not be obtained.

Scheme 3 :
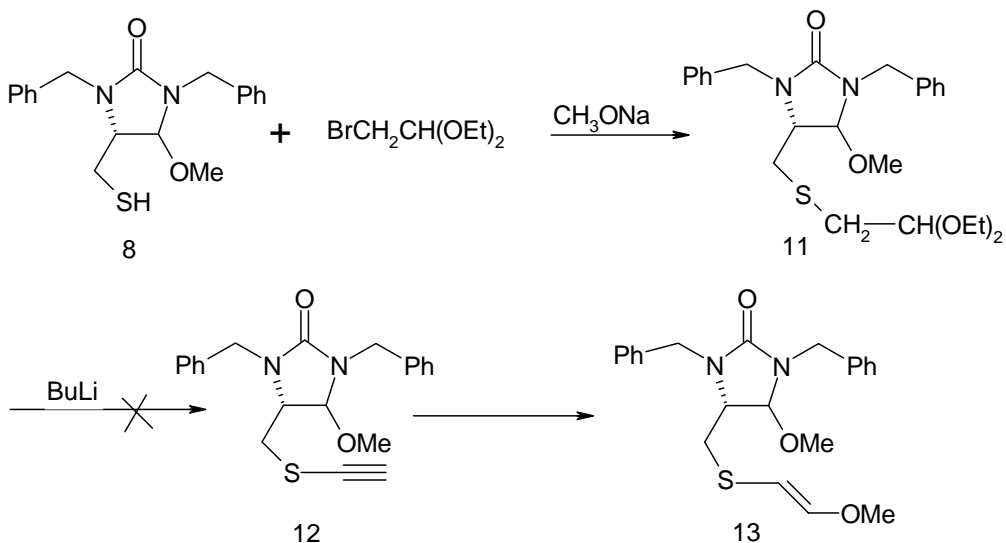
Section 3 : Formal synthesis of biotin.

This section deals with various approaches towards acid .

As shown in **scheme 4** cysteine hydrochloride hydrate was converted to hydantoin3 which in turn was reduced with sodium borohydride to furnish methoxy ureide **7**. It was then treated with PhSH and subjected for C-S bond cleavage with Li/naphthalene to give the radical anion. The radical anion was quenched with CO_2 with a view to obtain the desired intermediate acid **15**. But reaction was not clean and a mixture of products was obtained.

Scheme 4 :
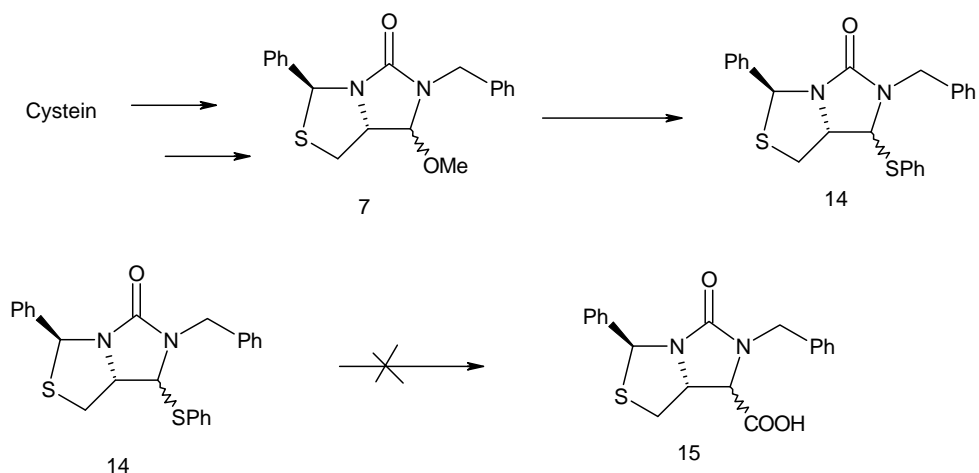
In another approach it was thought of making the acid **15** from aldehyde **16**

Scheme 5
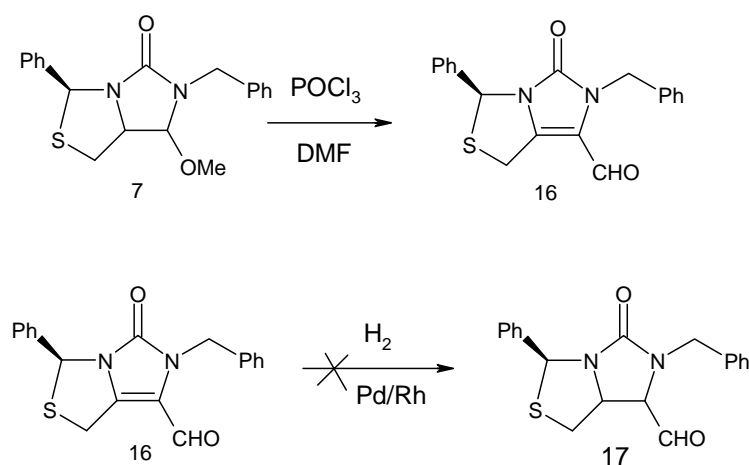
As shown in **scheme 5**, methoxy ureide **7** was converted to conjugated aldehyde **16**. Attempted hydrogenation of the olefine to the corresponding dihydro derivative could not be accomplished

The key intermediate acid **15** was then prepared by condensation of methoxy uriede **7** with silylenol ether **19** followed by its cleavage with TBHP. Acid **15** is converted to **21** by using ethylchloroformate. Further cleavage of C-S bond of **21** is done with tributyltin hydride, **Scheme 6,** to furnish **22**, which can be converted to thiolactone **23**.

Scheme 6 :
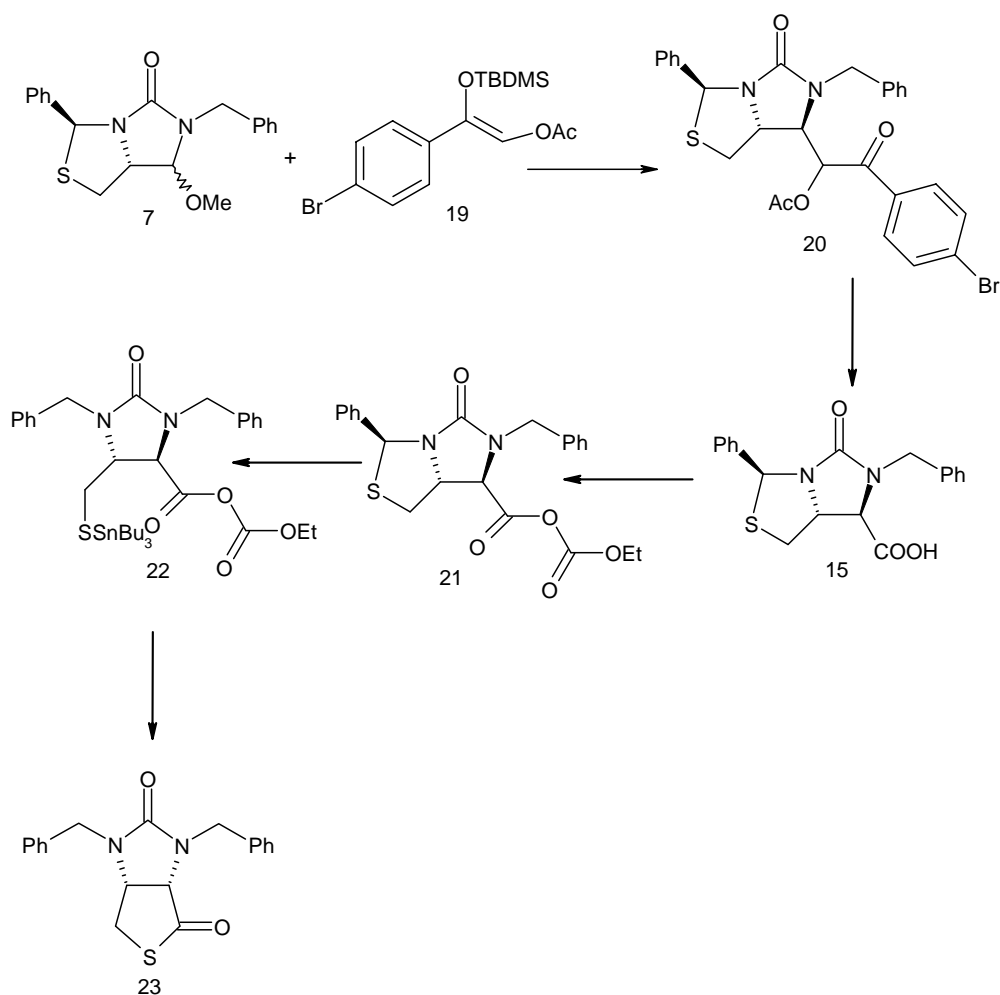
Chapter II: Development of useful synthetic methodologies

This chapter is further divided into two sections

Section 1: Unmasking of carbonyls from oxathioacetals.

Carbonyl compounds were regenerated from corresponding oxathioacetals *via* equilibrium exchange with glyoxylic acid and Amberlyst-15 as the heterogeneous catalyst, under solvent free conditions.

CHOCOOH
A-15

R, R' = alkyl, aryl, H
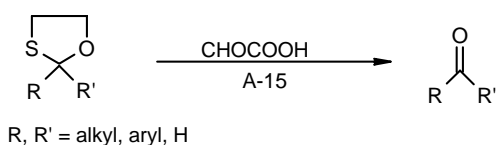
Scheme 2: Deprotection of thioacetals using glyoxylic acid and Amberlyst-15

The reaction is fast and the product is isolated by a simple aqueous workup. A wide variety of oxathioacetals derived from ketones and aldehydes were shown to undergo facile deprotection under these conditions.

Present protocol is efficient, rapid, nonhazardous, solvent free and therefore should find widespread utility in organic synthesis.

Section 2: Functional group transformations:
(a) Unmasking of carbonyls from acetals and oximes

The identification of a mild and chemoselective aqueous glyoxylic acid for the deprotection of acetals and oximes formed the basis of this investigation. Glyoxylic acid is readily available commercially as 50% aqueous solution and can be used as such.

Scheme 3: Deprotection of acetals and oximes at room temp.

CHOCOOH
RT

R, R' = alkyl, aryl, H
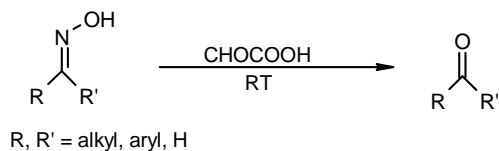
Thus this method can be used   selectively to deprotect acetals and oximes in presence of other protecting group such as TBDMS ether in a multifunctional compound. This

R, R' = alkyl, aryl, H
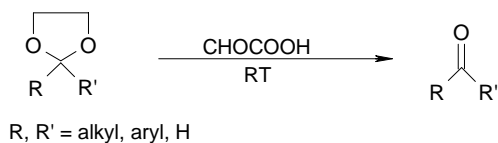
method is high yielding, fast, clean, safe, cost-effective, and therefore most suitable for practical organic synthesis.

(b) Deprotection of OTHP ethers:

Alcohols were regenerated from corresponding OTHP ethers by using glyoxylic acid. The reaction is fast and the product is isolated by a simple aqueous workup. A wide variety of THP ethers were shown to undergo facile deprotection under these conditions.

1.1.1 Introduction

The Chemistry of Biotin dates back to 1936 when it was isolated by Kogl[1] from egg yolk. A few years later it was also isolated from beef liver[2] and from milk concentrate.[3] It is also known as anti-egg white injury factor, bios IIB, vitamin H *etc*. Chemically biotin is (+)-*cis*-hexahydro-2-oxo-1*H*-thieno[3,4-d]-imidazole-4-valeric acid.

D(+)-Biotin **1**

Biotin is one of the water-soluble B-complex group of vitamins. In bound form it is distributed widely as a cell constituent of animal and human tissues. The main sources of biotin are liver, kidney, pancreas, egg yolk, yeast and milk. A high content of biotin in cow's milk occurs in early lactation. It is al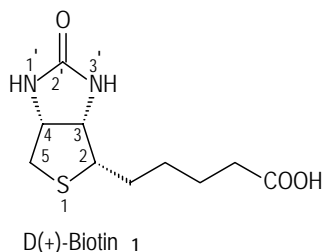so present in different plant materials, especially in seeds, pollen, molasses, rice, mushroom, fresh vegetables and in some fruits. Moist fish contain biotin in small amounts.

Biochemically, biotin functions as a cofactor for enzymes principal to carboxylation reactions. These reactions are involved in important biochemical processes *e.g.,* gluconeogenesis and fatty acid synthesis.

1.1.1a Structure determination:

The empirical formula for biotin $C_{10}H_{16}N_2O_3S$ was established in 1941 and the full structure in 1942 by du Vigneaud.[4,5] The structure was confirmed by the first total synthesis of biotin in Merck Laboratories by Harris and coworkers in 1945.[6] The absolute configuration was established more than 20 years later by X-ray crystallographic analysis.[7]

Biotin has three contiguous chiral carbon atoms and therefore, four diastereomeric racemic forms are possible, of which only (+)-biotin **1** is biologically active, while, *epi, allo* and *epi-allo*-biotin **I**, **II**, and **III** respectively and their enantiomers are biologically inactive. Of the four diastereomeric racemic forms, only D(+)-biotin occurs in nature whereas other isomers are of synthetic origin.
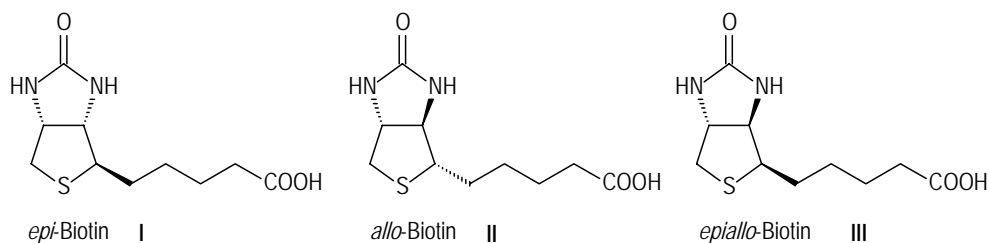
In 1976 two groups redetermined the crystal structure of biotin and results reported were in agreement with the previous ones, but more accurate.[8] According to these data, ureido ring is planar while the thiophane ring has an envelope conformation **IV**. The valeric acid side chain is not fully extended but twisted and there is a strong interaction between C_6 and $N_{3'}$, a feature of importance in determining the biochemical reactivity of biotin. This envelope conformation **IV** of thiophane ring is also found in solution as shown by Glassel and Marquet.[9]
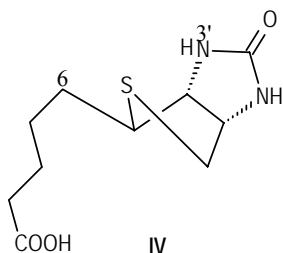
1.1.1b Biosynthesis:

A number of fungi and bacteria synthesize biotin from pimelic acid by a metabolic pathway, whose last step involves the conversion of dethiobiotin to biotin. This pathway has been thoroughly investigated.[10-13] All the intermediates from pimelic acid to dethiobiotin are formed by classical biochemical reactions. Recently Marquet and coworkers solved the elucidation of the mechanism for the transformation of dethiobiotin to biotin. Evidence has been presented that the biosynthesis of biotin *Aspergillus niger* and *E. Coli* proceeds by the introduction of sulfur at C_1 and C_4 of dethiobiotin without apparent involvement of C_2 and C_3.[14,15] A more recent study clearly demonstrates that sulfur is introduced at C_4 of dethiobiotin with loss of the 4 pro *S* hydrogen atom. Since the configuration of biotin at C_3 is *S*, it follows that sulfur is introduced with retention of configuration at C_4, prochiral center of dethiobiotin.

1.1.1c Biotin Deficiency:

Because of biosynthesis by intestinal flora, a deficiency of biotin seldom occurs in humans. In rare cases, biotin deficiency when inducted, results in dermatitis, a loss of appetite, nausea, vomiting, depigmentation, alopecia, weight loss, anemia, elevated blood

cholesterol and depression.[16] These symptoms can be reversed by giving biotin at the level of adult requirement, 150-300 µg/dose. Recently a rare life threatening genetic defect in biotin metabolism, that is biotin-dependent-carboxylase deficiency, has been determined in a small number of young children. Johnson *et al*[17] reported: "A diet which is marginally deficient in the vitamin biotin may cause sudden unexpected death of young broiler chickens when they are exposed to stress. Chickens affected with this disorder have low levels of biotin in their livers. In condition of biotin insufficiency, we postulate that a similar disorder, triggered by mild stress may occur in the human infants". They used radiochemical technique to measure the biotin content of 204 livers obtained from infants at autopsy. The levels of biotin in the livers of infants who had died of sudden infant death syndrome (SIDS; cot death) were significantly lower than those in livers of infants of similar age, who had died of explicable causes. These findings support an association of biotin with SIDS.

In poultry, biotin is an essential vitamin for normal growth, feed conversion, and reproduction as well as healthy skin, feathers and bones. Biotin deficiency in poultry causes reduced growth rate, impaired feed conversion, reduced feed intake, perosis and other deformities causing leg-weakness, poor feathering and food dermatitis. In broilers, a biotin deficiency causes breast blisters, fatty liver and kidney syndrome, parrot beak and death. Biotin deficiency also causes dramatic symptoms in swine, *e.g.* Reduced growth rate, dermatitis, excessive hair loss, furry tongue, food tensions, stiff-legged gait, squatness, and hind-leg spasms. These deficiencies are corrected by using biotin as a feed additive for poultry and swine.

1.1.1d Uses:

It is used in pharmaceutical preparation of ointments, tonics, *etc*. It is also used in poultry for rapid growth of chicks and healthy hatching of eggs.

In recent years a utilization of strong biotin avidin complex has emerged in biochemistry as an important and versatile method for isolation, localization, immunoassay and drug delivery.[18a] It has been recently recognized that biotin finds use in cosmetic[18b] and it administered orally for brittle nails.

Avidin-Biotin system in immunochemistry:[19]

One of the most useful interactions in immunochemistry involves the specific binding of water-soluble vitamin: biotin, to the egg white protein avidin. Avidin is a tetramer containing four identical subunits of molecular weight 15,000. Each subunit contains a high

affinity binding site for biotin with a dissociation constant of approximately 10-15 M. The binding is undisturbed by extremes of pH buffer salts or even chaotropic agents, such as guanidine hydrochloride (up to 3 M). The strength of the avidin biotin interaction has provided the researcher with a unique tool for use in immunoassays, receptor studies, immunocytochemical staining and protein isolation.

The avidin biotin system is particularly well suited for use as a bridging or sandwich system in association with antibody-antigen interactions. The biotin molecule can easily be activated and coupled to either antigens or antibodies, usually with complete retention of activity. Subsequently avidin can be conjugated with enzymes, fluorochromes, ferritin or colloidal markers and used as high affinity secondary reagents, which can greatly increase the sensitivity of an assay. In addition, since only one conjugate preparation is required for many different assays, the biotin-avidin system can be very attractive for use in immunological procedures. The following are some of the biotin derivatives in use.

a). Biotin derivatives as gelators of organic solvents: [20]

V
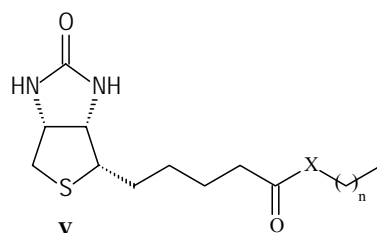
X = NH, n = 15, 11, 10, 7, 5, 2

The recovery of spilled solvents, disposal of used cooking oil and novel drug delivery systems have been suggested as possible applications for gelling compound. Several of these compounds are capable of forming stable gels with a variety of organic solvents.

b). Biotin derivatives as anti HIV protease inhibitors: [21]

VI
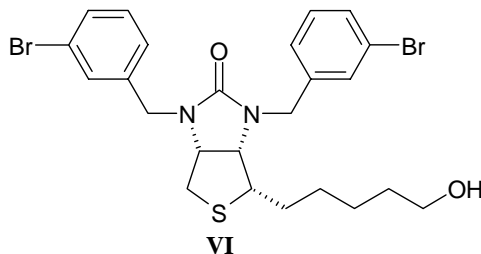
Several bis-*N*-alkylated (+)-biotin derivatives were synthesized and evaluated for activities against HIV-1 protease. The most potent inhibitor, **VI** has K_i of 0.50 mM and antiviral IC_{90} of 7mM.The (+)-biotin analogues in general have good translations from enzymic K_i to

antiviral cell assay IC_{90}. Other derivatives of biotin also like *N*-hydroxysuccinimidobiotin, sulfosuccinimidobiotin,*N*-iodoacetyl-*N*-biotinylhexylenediamine,biotinhydrazide, immobilized biotin, biotincellulose of biotin are commonly used derivatives in different applications.

Biotin possesses a deceptively simple-looking structure. Its skeleton consists of a bi-heterocyclic core, to which is attached a carboxybutyl side chain. The heterocyclic system comprises a cyclic urea and a tetrahydrothiophene ring (which will subsequently be called thiophane). It further possesses three contiguous stereocenters on the thiophane ring in the all-*cis* configuration. Because of the fundamental and commercial importance, biotin has, ever since it was discovered, attracted the attention of both academic and industrial synthetic chemists.

A continuous endeavor over a period of more than 50 years has now resulted in more than 40 original contributions on the total synthesis of biotin. Many of earlier syntheses known were lengthy involving a number of steps, without any stereochemical control. Then there was a drought of published information for 20 years when no significant progress in biotin synthesis was made. However, the recent recognition of the importance of biotin in poultry, biochemistry and pharmaceutical formulations, revived the interest in this molecule, and this is evident by a boom in a number of international patents (around 50) between 1970-2000. The above figure excludes the applications of biotin in biochemistry and related subjects.

Some of the recent syntheses are discussed briefly since the syntheses of biotin were already reviewed by R. B. Tejwani and Amar Gopal of this laboratory,[22] as well as is reviewed by De Clercq in 1997. [23] This section is mostly restricted to syntheses reported after 1992. However the classical Hoffmann La Roche synthesis that till date is the commercially practiced technology with modifications is described.

Schemes constitute the vehicle of the synthetic chemist. They are conceived so that the chemist can grasp the important stages in each shown sequence. Relevant experimental conditions are listed, including yields when they have been clearly reported in the original literature. The following stereochemical designations are used in the schemes: an unprefixed Arabic numeral is used for achiral molecules and for chiral molecules which possesses the correct enantiomeric configuration for eventual conversion into (+)-biotin; the opposite enantiomeric configuration is indicated by prefix *ent* and racemic mixtures by
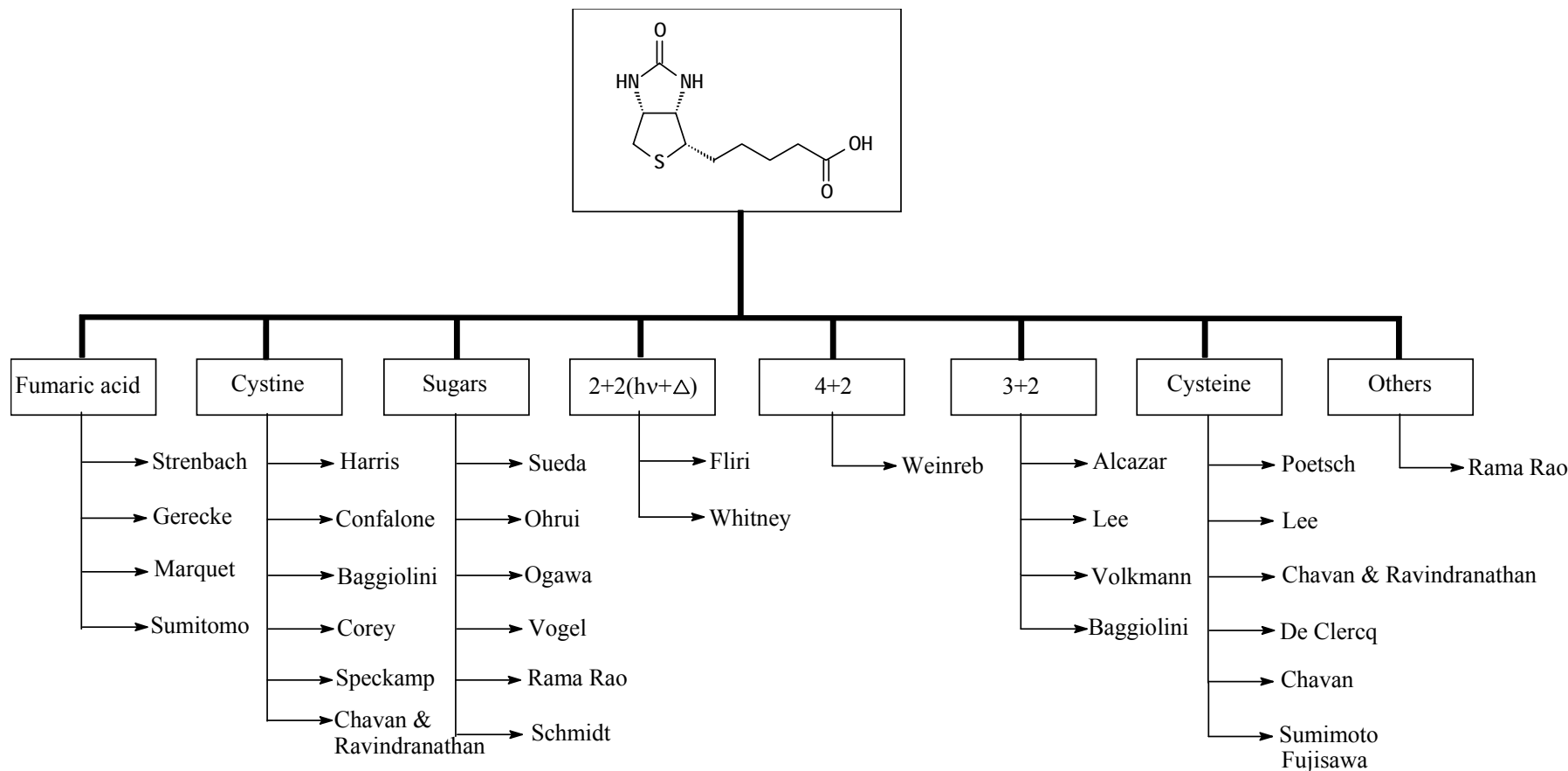
the prefix *rac*. Throughout the section/thesis, the atom numbering along the thiophane nucleus shown below will be used:
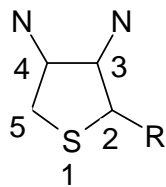
1.1.2 Earlier Approaches

Chart 1 shows Up to date approaches for biotin synthesis starting from different starting materials.

Chart 1:[23]

Fumaric acid	Cystine	Sugars	2+2(hv+△)	4+2	3+2	Cysteine	Others
Strenbach	Harris	Sueda	Fliri	Weinreb	Alcazar	Poetsch	Rama Rao
Gerecke	Confalone	Ohrui	Whitney		Lee	Lee	
Marquet	Baggiolini	Ogawa			Volkmann	Chavan & Ravindranathan	
Sumitomo	Corey	Vogel			Baggiolini	De Clercq	
	Speckamp	Rama Rao				Chavan	
	Chavan & Ravindranathan	Schmidt				Sumimoto Fujisawa	

Hoffmann-La Roche's Lactone-Thiolactone approach:

In 1946 Goldberg, Strenbach[24] described the total synthesis of (+)-biotin starting from cheaply available fumaric acid (see Scheme 1).

Scheme 1: Goldberg, M. W. *et al* US Pat. 2,489232, Nov. 22, 1949; Chem. Abstr. 1951, 45, 184.
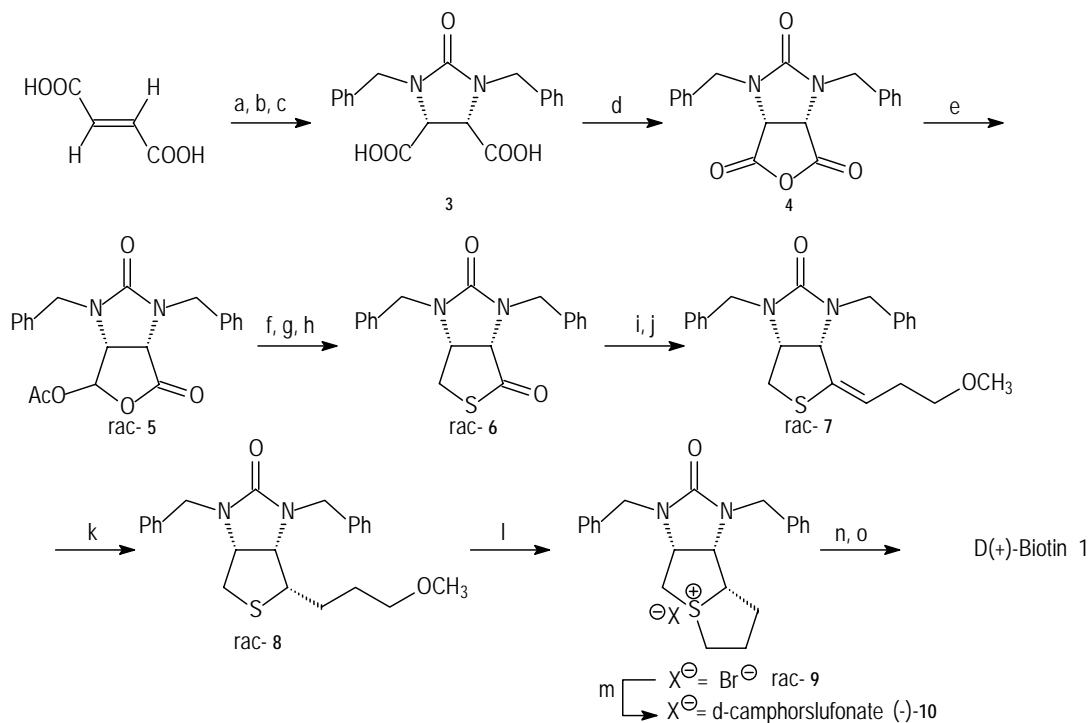
Conditions: **a**) Br_2, H_2O, 90% yield ;**b**)$BnNH_2$, MeOH, 90 % yield; **c**) $COCl_2$, DCM; **d**) Ac_2O; **e**) Zn, AcOH, H_2O; **f**) Ac_2O ; **g**) $HCl-H_2S$; **h**) Zn dust, H_2S, AcOH; **I**) $MeO(CH_2)_3MgCl$, ether; **j**) H_2SO_4; **k**) $H_2/RaNi$; **l**) HBr; **m**) camphorsulphonate; **n**) HBr reflux.

Fumaric acid is converted into the cyclic anhydride **4** *via* a four step sequence involving bromination of fumaric acid to yield *meso*-dibromo succinic acid, double substitution of the latter with benzyl amine, formation of the cyclic ureide **3** with phosgene, followed by formation of anhydride **4** upon treatment of **3** with acetic anhydride. At this stage *cis* relation of the vicinal amino groups at C_3 and C_4 centers are fixed. In the second stage, the thiophane nucleus is formed by conversion of *meso*-**4** into thiolactone **6**. This involves reduction of anhydride **4** with zinc in acetic acid, treatment of the resultant acetoxy lactone **5** with hydrogen sulfide, and its further reduction with zinc to yield thiolactone **6** in racemic form. In the third stage, part of the carboxy butyl chain of biotin is introduced *via* Grignard reaction with subsequent dehydration to from the exocyclic olefin **7** with undefined double-bond stereochemistry. Catalytic hydrogenation of the latter yields **8** with

the desired all *cis* relative configuration, at centers C_2, C_3 and C_4. In the fourth stage ether **8** is converted into the thiophanium salt **9** by treatment with hydrobromic acid (HBr). At this point, resolution is effected by conversion of bromide **9** into the diastereomeric sulfonate salt **10** which are readily separated in

excellent yield by simple fractional crystallization. In the final stage of the synthesis the side chain is accomplished by reaction of diastereomer (-)-**10** with sodium diethyl malonate. In this important step selective attack is observed at the least hindered primary center of the trimethylene thiophanium moiety. Finally heating with conc. hydrobromic acid effected hydrolysis, subsequent decarboxylation, and debenzylation all in one operation to furnish biotin.

Several intermediates in the above scheme, and in particular, thiolactone **6** has been obtained later in racemic or homochiral form by other groups then constituting new formal synthesis of *rac*-biotin or (+)-biotin respectively.

Several other groups have also used the establishment of stereocenter 2 *via* catalytic hydrogenation of an exocyclic olefin subsequently. The use of benzyl groups as protective groups in the imidazolidothiophane and related intermediates has been commonly utilized in almost all-later synthesis.

Sumitomo modification :

Scheme 2: Goldberg, M. V. *et al US Patent* 3, 876, 856, April **1975;** *Chem Abstr.* **1974**, 80, 95951z.
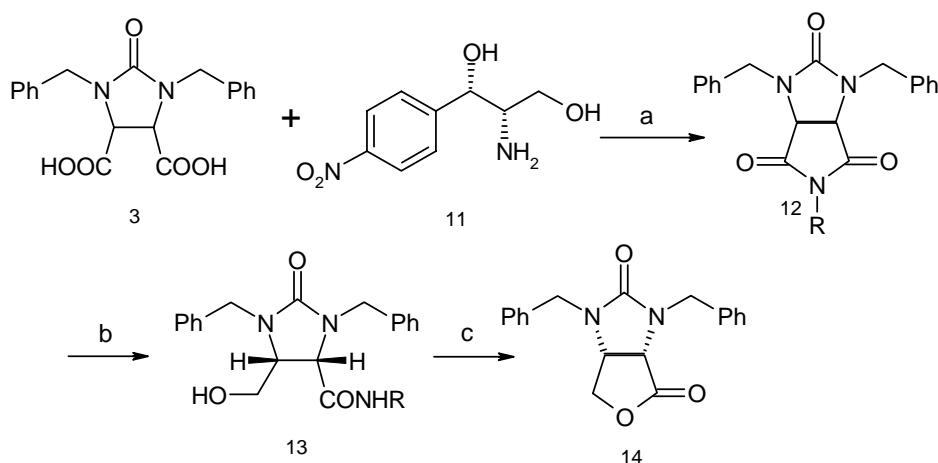

Conditions: a) reflux; b) NaBH$_4$; c) HCl, reflux.

In 1975 Sumitomo chemists[25] replaced the optical resolution-reduction sequence of the Sternbach synthesis by an efficient asymmetric conversion of the prochiral cis acid **3** to the optically active lactone **14**. The acid reacts with the optically active dihydroxyamine **11** to give quantitatively the chiral imide **12**. Sodium borohydride reduces stereoselectively the optically pure hydroxyamide **13**. Hydrolysis then yields the lactone **14**.

Eyer's approach

More recently Eyer *et al* [27] have developed an alternative Wittig sequence starting from thiolactone **15**. The sequence of reactions involves reduction with diisobutyl aluminium hydride (DIBAL-H) to the corresponding hydroxy derivative, which is directly converted to phosphonium salt **16** with triphenylphosphine hydrogen tetrafluoroborate. Condensation of the corresponding ylide with methyl 5-oxopentanoate gave **17** in fair yield (Scheme 3).

Scheme 3: Eyer, M. *et al* Eur. Pat. Appl. EP 0 387 747, 19 Sept. 1990; Chem. Abstr. **1991**, 114, 81435t
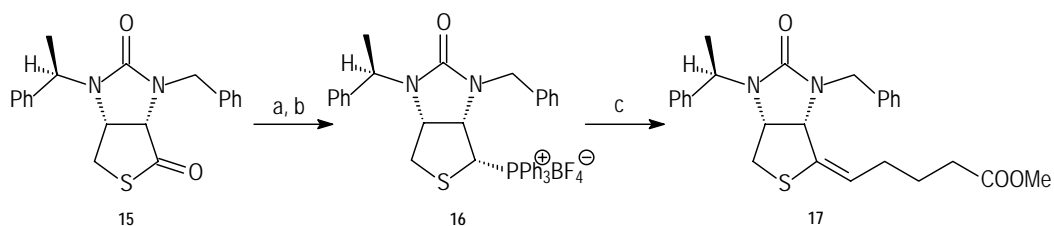

Conditions: ***a***) *(Me$_2$CHCH$_2$)$_2$AlH, PhCH$_3$, -70 ^{o}C;* ***b***) *Ph$_3$P-HBF$_4$, CH$_3$CN, reflux, 97%;* ***c***) *KO^{t}Bu, THF, OHC(CH$_2$)$_3$CO$_2$Me, THF, 65%.*

Senuma's approach

Senuma and co workers reported[28] an alternative method for the industrial resolution of hydroxyl lactone **18** in 1990. (Scheme 4). It involves the direct resolution of the hydroxy lactone *rac*-**18** (*trans*-epimer) with optically active amines. Thus the reaction of *rac*-**18** with cinchonidine readily gave the cinchonidine salt of **19a** in 45% yield with an optical purity evaluated at more than 98%. Upon acidification, the salt readily underwent cyclization to give a 42% overall yield of **18**. Evaporation of the mother liquor of the salt afforded after acidification *ent*-**18** in 36% yield. The undesired enantiomer is readily converted to *meso*-diacid **3** by facile oxidation with sodium chlorite. To find a more

practical and inexpensive resolving agent applicable for industrial use, the authors also examined the optical resolution of *rac*-**18** with various *N*-alkyl-*D*-glucamines.

**Scheme 4:** Senuma, M. *et al Chem.Pharm.Bull.* **1990**, *38*, 882.
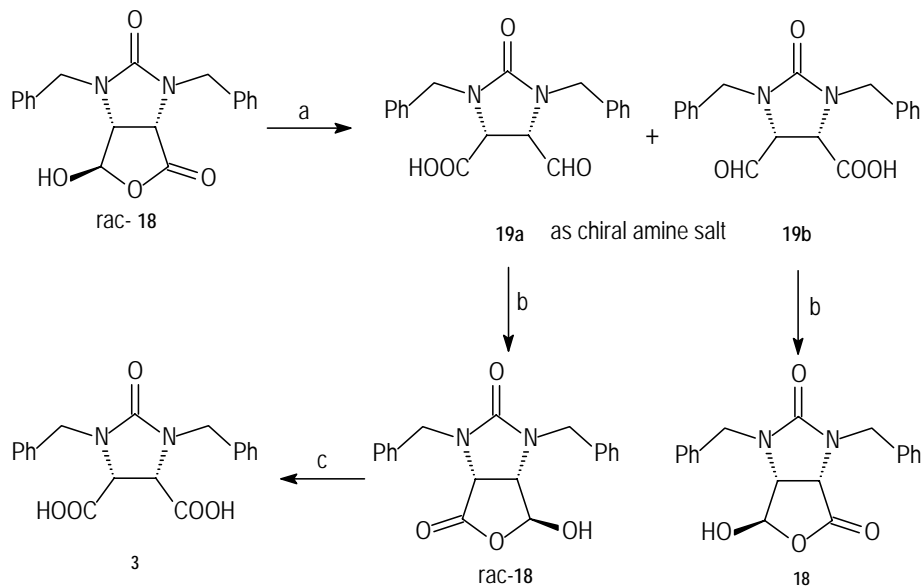
*Conditions: **a**) Cinchonidine:45% of precipitated salt or N-n-butyl-D-glucosamine derivative: 46% of precipitated salt; **b**) HCl; **c**). NaClO₂, 87%.*

Matsuki's approach

The further development of efficient asymmetric strategies in the context of the original Hoffmann-La Roche scheme culminated in 1993 by Matsuki and co-workers report on the highly enantioselective reduction of *meso*-1,2-dicarboxylic anhydride to yield optically active lactones using Noyori's lithium aluminium hydride-ethanol-1,1'-bis-2-naphthol complex (BINAL-*H*).[29] When applied to *meso*-**4**, the desired lactone **20** was directly obtained in 76% yield with 90% *ee*, which was enriched to 95% *ee* by recrystallization from benzene/cyclohexane (Scheme 5).[30]

Scheme 5: Matsuki, K. *et al Tetrahedron Lett.* **1993**, *34*, 1167.
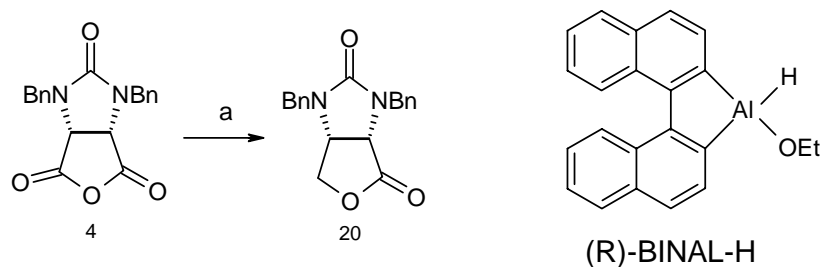
*Condition: a) (R)-BINAL-H, -78 °C to rt., THF, 76%.*

Although the chiral recognition mechanism is not clear, the general mechanism proposed by Noyori can be applied[30] to explain outcome of the reaction.

Garrity's approach

Another interesting asymmetric approach has been developed by chemists at Lonza that center about the hydrogenation of furoimidazole derivative **24** (Scheme 6).[31] The synthesis of this intermediate **24** involves a straightforward four-step sequence starting from tetronic acid. Treatment of the latter with the diazonium salt derived from aniline leads to diazo compound **22** which is converted into **24** *via* reaction with a primary amine such as (*S*)-1-phenylethyl amine followed by reduction to **23** and subsequent imidazolone ring formation with ethyl chloroformate.[32] It is interesting to note that both **24** and *ent*-**24** can lead to the diastereomer with the desired (3*S*, 4*R*)-configuration depending on the hydrogenation conditions:

1. Rhodium on alumina in DMF for **24** (54% yield of crystalline **25**) and

2. Palladium on carbon in acetic acid for *ent*-**24**(54% yield).[33]

Scheme 6: Mc Garrity, J. *et al* Eur. Pat. Appl. EP 0 270 076, 8 June, 1988; Chem. Abstr. **1988**, *109*, 128718b.
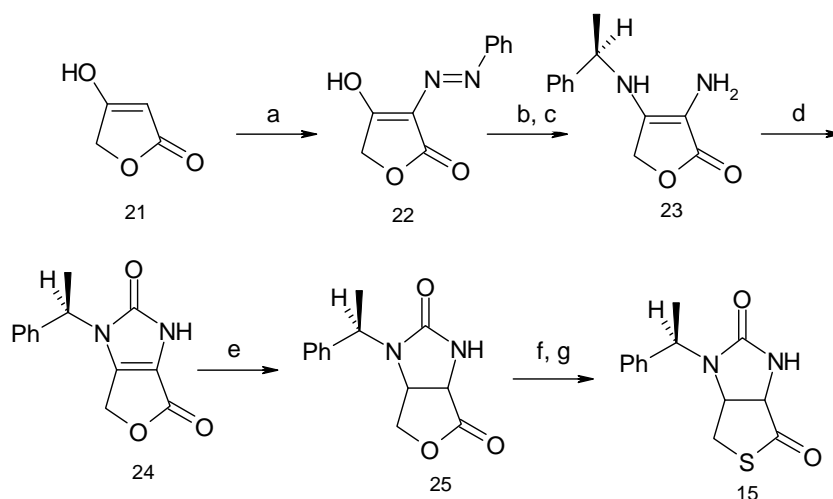

Conditions: a) PhNH$_2$, NaNO$_2$, HCl, 92%; b) (R)-PhCH(NH$_2$)CH$_3$, B(OEt)$_3$, PhCH$_3$, 80 °C; c) H$_2$, Pt/C, EtOAc, 40 bar, 84%; d) ClCOOEt, Et$_3$N, THF, Et$_3$N, CH$_3$CN, reflux, 66%; e) H$_2$, Rh/Al$_2$O$_3$, DMF, 40 bar, 54%; f) NaH, DME, PhCH$_2$Br; g). CH$_3$COSK, CH$_3$CON(CH$_3$)$_2$, 150 °C, 69%.

A further dramatic improvement has been claimed very recently when the hydrogenation was performed in the presence of a rhodium complex and a chiral ferrocenylphosphine ligand

(Scheme 7).[33, 34] The reduction of achiral **26** into **27** (95% yield; 90% *ee*) constitutes a second example in which the chirality is introduced involving a catalytic pathway.

**Scheme 7:** Mc Garrity, J. *et al* Eur. Pat. Appl. EP 624 587 17th Nov. 1994; Chem. Abstr. **1995**, *122*, 81369q.

24 R = (structure, H, Ph) **25** (98%, de)

26 R = -CH$_2$Ph **27** (90% ee)
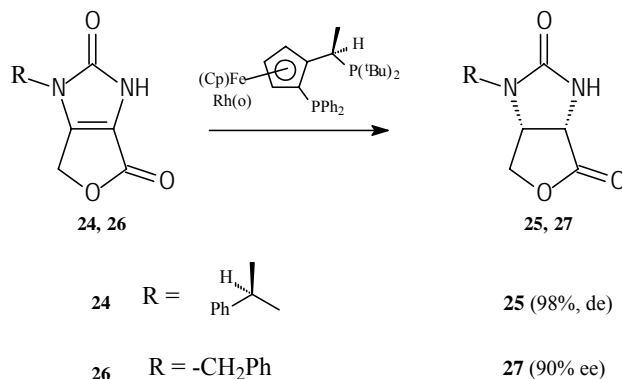
Condition: a) Rh(0)= [Rh(norbornadiene)Cl]$_2$, chiral ligand, PhCH$_3$, 70 ^{o}C, H$_2$, 50 bar, 95%.

Kinoshita's approach

In 1983 Kinoshita group[35] described a six-step synthesis of **28**. In 1986 Bates and Rosenblum described[36] the chlorination of **28** with *N*-chlorosuccinamide stereoselectively and further converted it to deoxybiotin **2** in racemic form (Scheme 8).

**Scheme 8:** Kinoshita, M. *et al J. Org. Chem.* **1986**, *51*, 3447
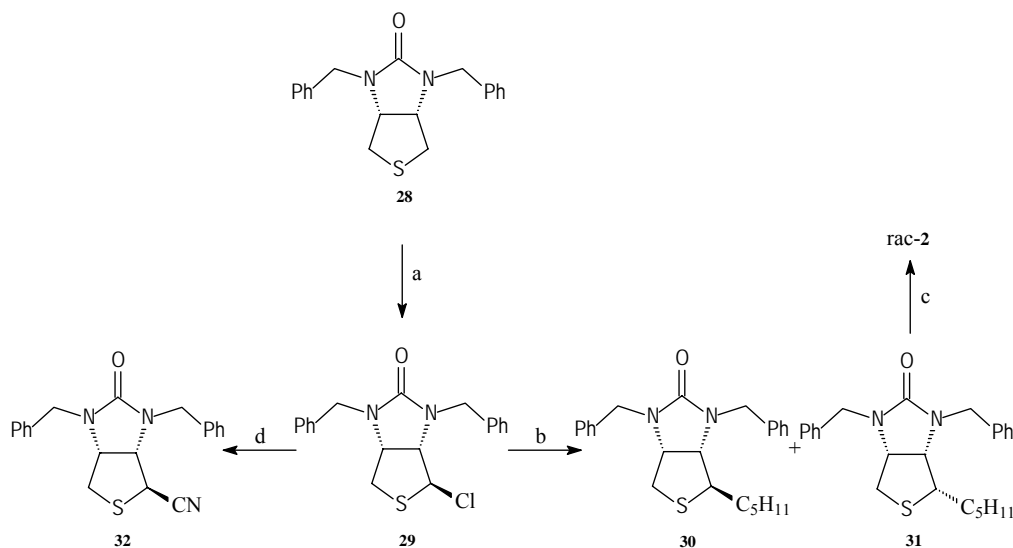
Conditions: a) NCS, PhH, 100%; b) n-pentyl(Me)CuLi (mol of LiCl/mol of R$_2$CuLi=1), -60 ^{o}C, ether, 53%; c) Na, liq. NH$_3$ or HBr (48%); d) NaCN.

Bihovsky's approach

Bihovsky and Bodepudi[37] succeeded in resolving **33** as shown in Scheme 9. The resolution was accomplished by separation of the diastereomeric alkoxy derivative **34a** and **34b** that were obtained by reaction of *rac*-**29** with optically active secondary alcohols. The most efficient alcohol was (*S*)(+)-mandelic acid, since the diastereomers could be readily separated by crystallization. Acid hydrolysis of **34b** led to (+)-**33** and hence to (+)-**6**, *via* oxidation or to **29** *via* treatment with HCl.

Scheme 9: Bihovsky, R. et al *Tetrahedron* **1990**, *46*, 7667
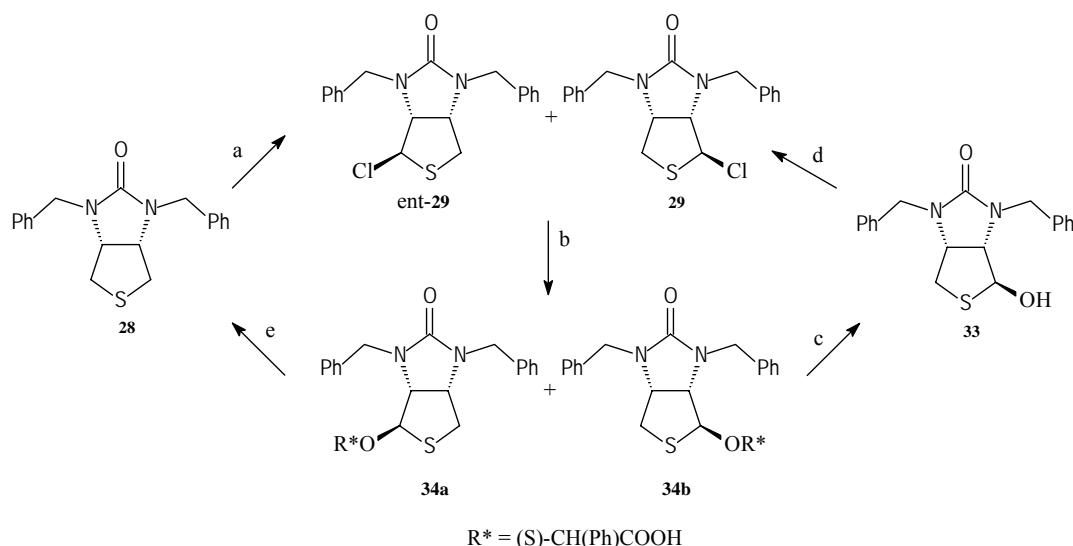
R* = (S)-CH(Ph)COOH

Conditions: a) NCS; b) R*-OH = (S)-(+)-mandelic acid, 75%; diastereomer separation by crystallization; CCl$_4$, reflux, 33% isolated with R* = -CH(Ph)COOH; c) H$_2$SO$_4$/dioxane; d) HCl, CHCl$_3$; e) Et$_3$SiH, CF$_3$COOH.

Yamano's approach

Successful enzyme catalyzed kinetic resolutions were reported by Yamano *et al.* (Scheme 10). [38] A variety of commercially available enzymes and microorganisms were investigated in order to effect the enantioselective hydrolysis of the ester **35**, which was obtained by conventional acylations of *rac*-**33**.

In a second approach, the same group found that direct resolution of alcohol **33** was accomplished *via* acylation with the lipoprotein from *Pseudomonas aeruginosa* TE 3285 in toluene.[39] Curiously, addition of molecular sieves (MS) 4A° to the reaction mixture

Scheme 10: Yamano, T. *et al Bull. Chem. Soc. Jpn.* **1993**, *66*, 1456
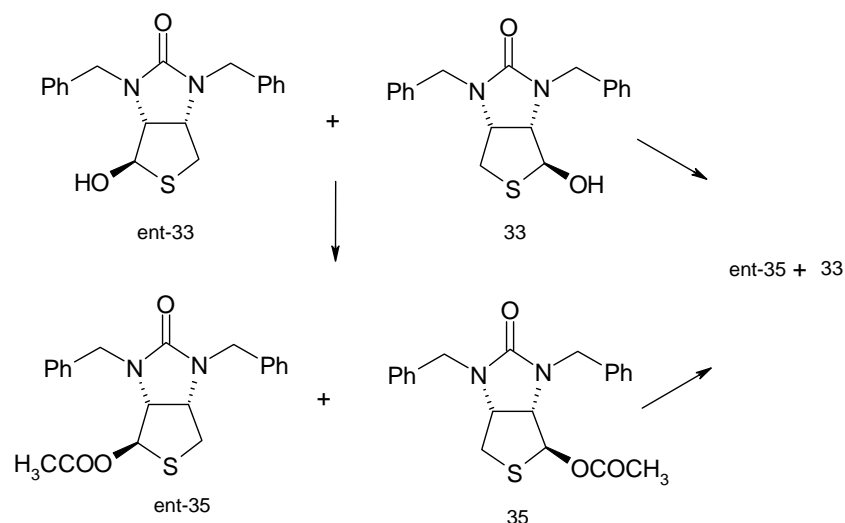
*Conditions: **a**) Ac$_2$O, pyridine, 98%; **b**) Streptomyces rochei var. volubilis; 27% conversion; 92 and 94% ee after crystallization; **c**) LIP (P.aeruginosa TE3285; TOYOBO immobilized lipase), 0.3% H$_2$O, 4A^o molecular sieves (MS), PhCH$_3$, vinyl acetate; 56% conversion; 99 and 99.8% ee after crystallization of alcohol.*

improved the reactivity, while at the same time as addition of a small amount of water was found to be beneficial for the reaction.

Speckamp's approach

In a joint effort, Speckamp and co workers and Poetsch and Casutt have used the intramolecular version of the condensation of silyl enol ether with *N*-acyliminium intermediate to effect the ring closure of thio ether **37** to the thiophane nucleus (Scheme 11)[40a, b] from the known intermediate **36**. The intermediate **36** is readily available from L-cysteine. Reduction with DIBAL-H led to the formation of corresponding hydroxy imidazolidinone (10:1) ratio of *cis*:*trans* diastereomers. Coupling with appropriate α-chloro ketone furnished the thioether, which was converted into the ethoxy derivative **37**. The crucial cyclization step involved the use of ethyl(trimethylsilyl)acetate/tetra-*n*-butylammonium fluoride for the *in situ* enol ether formation and addition of trimethylsilyltriflate (TMSOTf) to induce the cyclization. This led to a 78% yield of the two diastereomers **38** and **39** (3:2 ratio). The probable mechanism for the cyclization may

be attributed to chair like transition state to yield **38** possessing the required all *cis* configuration whereas the formation of a diastereomer **39** by boat like confirmation can be explained.

Scheme 11: Speckamp, W. N. and coworkers *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2391
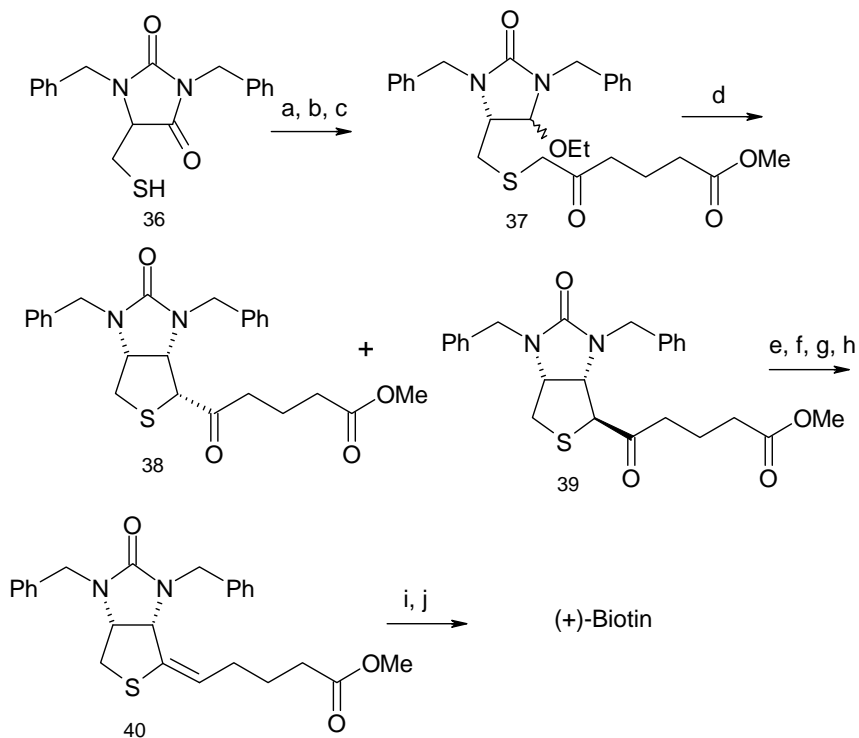
Conditions: a) DIBAL-H, THF, -70°C, 1h; **b**) MeO$_2$C(CH$_2$)$_3$C(O)CH$_2$Cl, Et$_3$N, 4h; **c**) H$_2$SO$_4$/EtOH, methyl orange, pH=3.1, 0 ^{o}C, 2h, 72%. **d**) 2.1 eq. of (TMS)CH$_2$CO$_2$Et, 0.03 eq. of TBAF, THF, -78°C to 25°C, 18h, then 1.5eq. of TMSOTf, DCM, -78 ^{o}C, 1h, 78%; **e**) NaBH$_4$, MeOH, 25°C; **f**). MeSO$_2$Cl, Et$_3$N, DCM; **g**) DBU, 60°C, 2h; **h**) KOH/MeOH, 2h, 87%; **i**) H$_2$ (10 bar), 10% Pd/C, 2-propanol, 50°C, 18h; **j**) 48% HBr, 100 ^{o}C, 2h, 85%.

The loss of stereochemical control does not influence however, the further conversion into biotin. In deed, the mixture is converted to the same exocyclic olefin **40** *via* sodium borohydride reduction, mesylation, 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) elimination and saponification. Final conversion of **40** to biotin proceeds in the usual way.
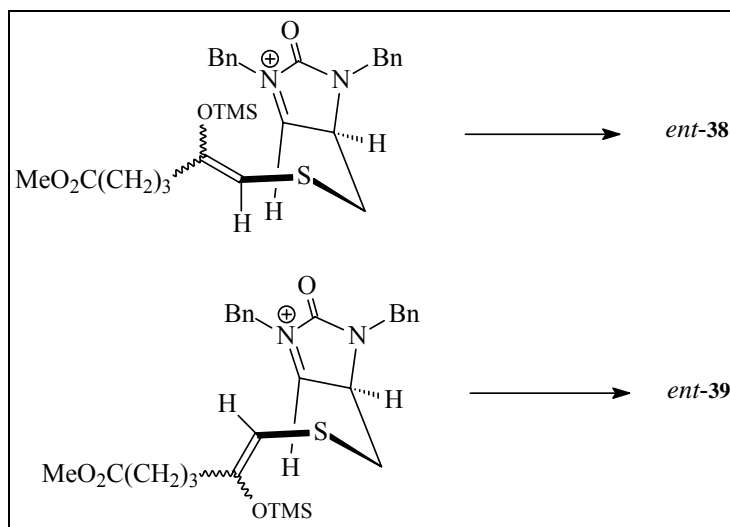
Chavan's approach

Independently, our group has reported the biotin synthesis on similar lines of *N*-acyliminium cyclisation shown in Scheme 12. [41]

Conversion of thioaldehyde **43** to the corresponding silyl enol ether followed by trialkyl silyl triflate mediated cyclization in the presence of *p*-nitrobenzaldehyde as thiophenol scavenger lead to the thermodynamically more stable thiophane aldehyde **44**. The synthesis of aldehyde **43** involves reduction of hydantoin ester **41** to yield the cyclic hemiacetal **42**, which is further converted to **43** by treatment with thiophenol. The transformation of **44** into biotin involved first Wittig reaction with the 4-carbon ylide , followed by deconjugation with base to yield the exocyclic olefin **45**. Further catalytic hydrogenation led to dibenzyl biotin methyl ester **46**, which on treatment with 48% HBr furnished D (+)-biotin.

Scheme 12: Chavan, S. P. *et al* US patent 5,274,107; Chem. Abstr. **1994**, *120*, 217097t; *J. Org. Chem.* **2001**, 66, 6197.
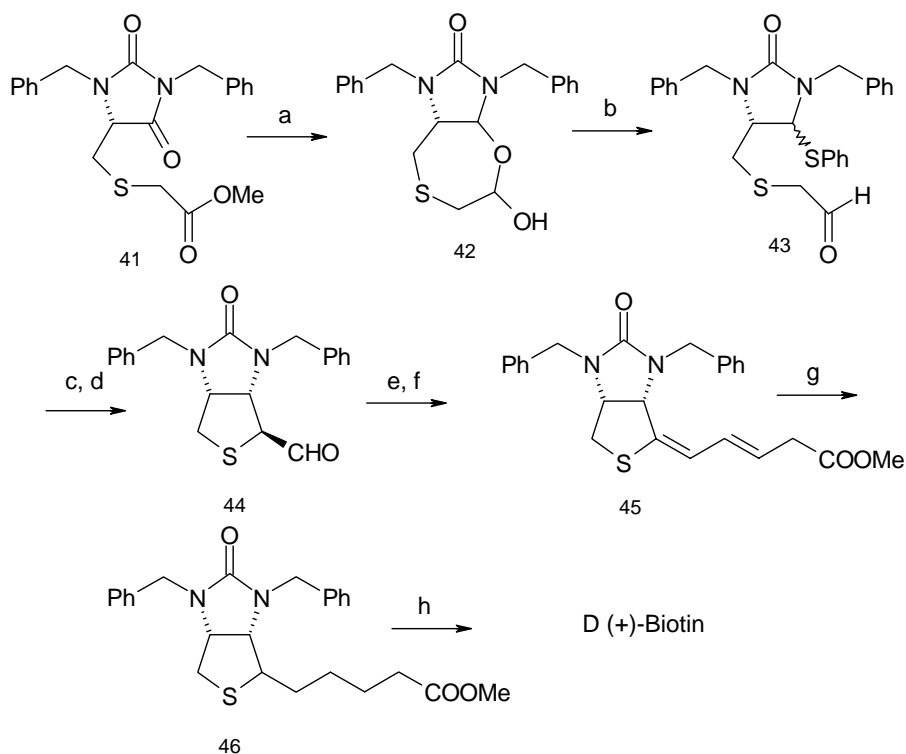
Conditions: a) *DIBAL-H, PhCH₃, 72%;* ***b***) *p-TsOH, PhSH, 70%;* ***c***) *^{t}BuMe₂SiCl, DBU, DCM;* ***d***) *^{t}BuMe₂SiOTf (cat.), p-NO₂PhCHO, DCM, 87%;* ***e***) *Ph₃P=CH-CH=CH-CO₂Me, DCM;* ***f***) *DBU, DCM, 86%;* ***g***) *H₂ (3 bar), Pd/C, MeOH 92%;* ***h***) *48% HBr.*

Amongst the other approaches towards D (+)-biotin some of them are briefly described as follows:

Seki's approach

Very recently Seki *et al* reported[42] a facile synthesis of D (+)-biotin by using Fukuyama coupling of carbonyl compounds.

Scheme 13 : Fukuyama, T. and coworkers *Tetrahedron Lett.* **2000**, *41*, 5099.
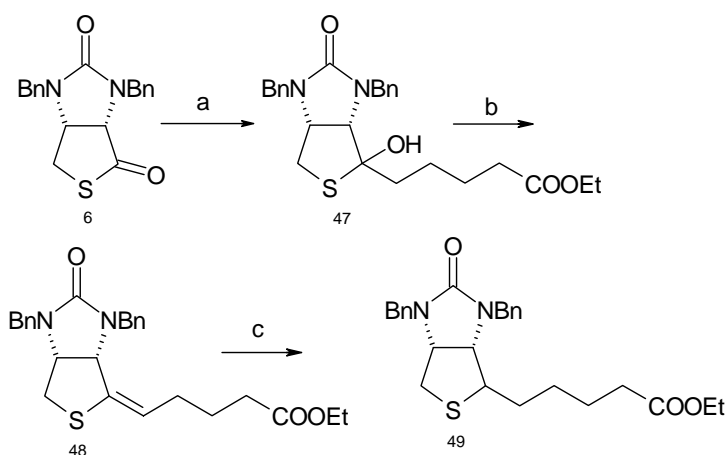
Conditions: a) *IZn(CH₂)₄CO₂Et (3 eq), PdCl₂(PPh₃)₂ (10 mol%), THF, toluene, DMF, 20 °C, 35h;* ***b***) *pTSA, toluene, 20 °C, 18h, 86%;* ***c***) *H₂, (70 atms), Pd/C, EtOH, 100 °C, 3h, 91%;* ***d***) *i) 48% aq. HBr, reflux, 48h;* ***ii***) *ClCOOEt, NaOH;* ***iii***) *HCl, 80%.*

The known thiolactone **6** with zinc reagent in presence of PdCl₂(PPh₃)₂ in mixed solvent at 20 °C for 35 h gave alcohol **47** which without purification was allowed to react with *p*TSA in toluene at 20°C to furnish the known olefin **48** in 86% yield. The final conversion of **48** into (+)-biotin **1** further involved catalytic hydrogenation and debenzylation. The coupling reaction with thiolactone was further modified [42b] by using zinc reagent in presence of Pd/C to furnish 48 in 94 % yield. To avoid problem of high cost of the palladium catalyst, seki et al [42c] used NiBr₂(PPh₃)₂/DMF instead of Pd catalyst to furnish **48** in 81 % yield.

Mioskowski's approach

Mioskowski and co workers [43] reported the synthesis of the diastereomers of dethiobiotin using the conjugate addition of 4-phenyloxazolidin-2-one to a nitroalkene (Scheme 16).

Nitroalkene **53** was prepared according to the sequence described in scheme 16. Commercially available 7-bromoheptanenitrile was converted in three efficient steps into known methyl 7-nitroheptanoate **51**.

Scheme 14: Mioskowski, C. and coworkers *Eur. J. Org. Chem.* **2000**, 3575
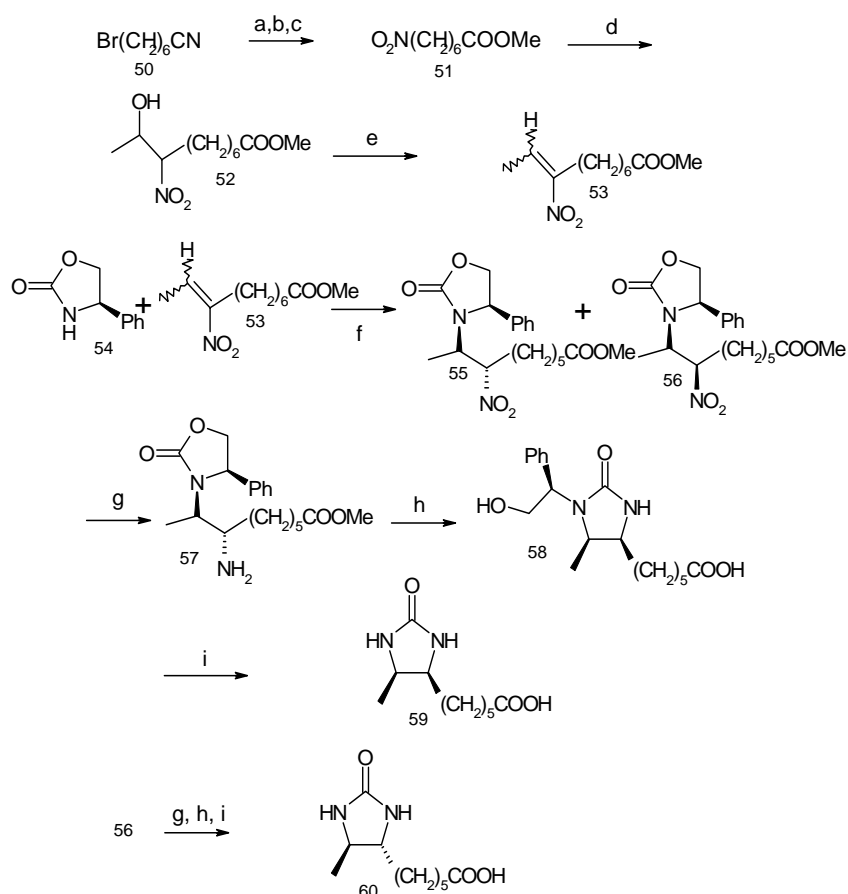
Conditions: a*) H₂SO₄, MeOH, 40h, reflux, 66%; **b**) NaI, acetone, 30h, reflux, 94%; **c**). AgNO₂, ether, 3 days, rt, 80%; **d**) CH₃CHO, KOH, MeOH, 19h, 0 °C, 84%; **e**) **i**) DMAP, Ac₂O, ether, 16h, rt; **ii**) DMAP, basic alumina, 4h, reflux, 63%; **f**) **i**) ᵗBuOK, 18-crown-6 (cat.), THF, 0 °C, 20 min, **ii**) -78 °C, 45 min;*

iii) AcOH, 74%. g). HCO$_2$NH$_4$, Pd/C, MeOH, 3 days, 72%; h) KOH, MeOH, 16h, reflux, 89%; i) H$_2$, Pd(OH)$_2$/C, MeOH, H$_2$SO$_4$(cat), 2 days 63%.

Henry reaction of **51** with acetaldehyde followed by elimination of hydroxy group by converting it into its acetate with Ac$_2$O followed by basic alumina yielded nitroalkene **53** as a 90:10 (*E*) and (*Z*) isomers. Conjugate addition of the potassium salt generated from either (*R*)-**54** or (*S*)-**54** by treatment with potassium *tert*-butoxide in THF in the presence of 0.1 eq of 18-crown-6, with nitroalkene **53** was performed. Only two diastereomeric adducts were formed (85:15) and the two diastereomers were separated by column chromatography.

The adducts **55** and **56** and their enantiomers *ent*-**55** and *ent*-**56** obtained from (*S*)-4-phenyloxazoldin-2-one were then all converted into the dethiobiotin methyl ester or into its stereoisomers. Treatment of **55** with ammonium formate in the presence of palladium on carbon in methanol afforded the corresponding amine **57**. Heating this compound at reflux with potassium hydroxide in methanol led to the more stable imidazolidinone **58**. And finally the imidazolidinone **58** was subjected to hydrogenolysis to get imidazolidinone **59**. The same sequence was carried out for nitro compound **56** as summarized in the above scheme.

Li Dengs approach

Scheme 15: Li Deng and coworkers, *Synthesis* **2001,** 11, 1737.
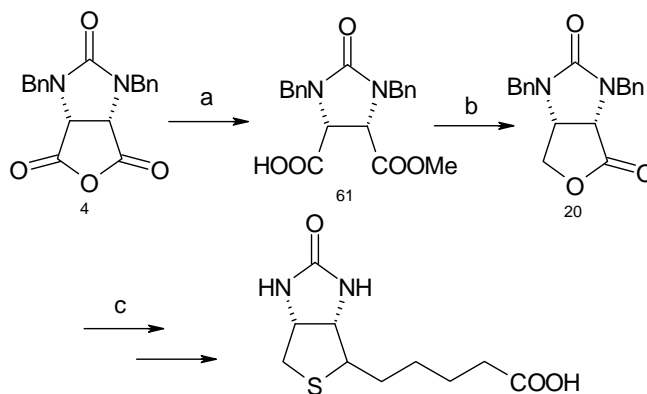
*Conditions : **a**) DHDQ-PHN; **b**) cyanuric chloride NMM, NaBH$_4$.*

Li Deng and coworkers reported [44] catalytic asymmetric synthesis of biotin in 2001. The key steps involve a catalytic, highly enantioselective and quantitative desymmetrization of

a meso cyclic anhydride followed by a one pot chemoselective reduction to form the optically active lactone intermediate in the Goldberg-Sternbach biotin synthesis.

Masahikos approach

Masahiko Seki and co-workers reported [45] key intermediate for biotin from Aspartic acid. The aldol reaction of an N-Cbz-3-amino-4-butanolide4, derived from L-aspartic acid, with formaldehyde gave the trans-disubstituted 3-amino-4-butanolide **65** stereoselectively. Following protection of the hydroxyl group of **65**, amidation and oxidation provided the

Scheme 16 : Seki, M. *et al Synthesis* **2002**, 3, 316
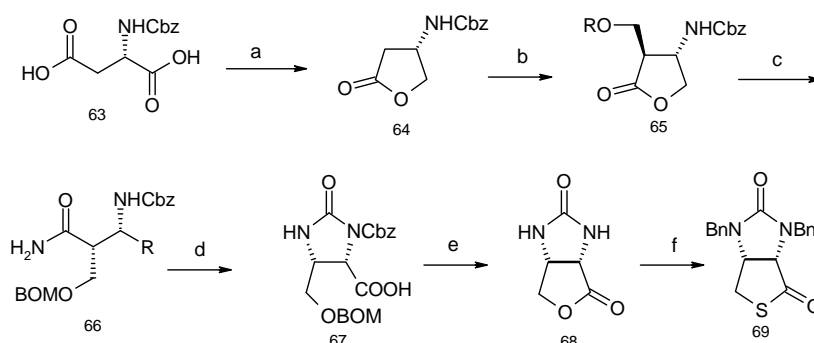
Conditions : *a*) *Ac₂O, NaBH₄,; b*) *LDA, HCHO; c*) *BOMCl, NH₄OH; d*) *Jones reagent, NaOCl, NaOH; e*) *Pd/C, H₂; f*) *BnBr, NaH, DMF; AcSK, DMF.*

substituted L-asparagine derivative **66**. The Hoffmann rearrangement of **66** with NaOCl in the presence of NaOH and subsequent hydrogenation gave the bicyclic lactone **58**, which upon dibenzylation and thionation, gave the thiolactone **6**, a key intermediate for the synthesis of biotin.

Very recently Masahiko Seki [45] and co-workers reported synthesis of biotin in 25 % overall yield over 11 steps from L-cysteine. The contiguous asymmetric centers at C-3a and C-6a were formed through a novel and highly stereoselective Lewis base-catalyzed cyanosilylation of amino aldehyde to provide anti-O-TMS-cyanohydrin **73** with high stereoselectivity and in high yield (anti/syn=92:8, 96%). Treatment of **73** with a di-Grignard reagent, 1,4-bis(bromomagnesio)butane, followed by carbon dioxide, efficiently installed the 4-carboxybutyl chain at C-4 to give keto acid **74**. The final cyclization to

bicyclic compound **76**, a precursor to **77**, was realized by a palladium-catalyzed intramolecular allylic amination of *cis*-allylic carbonate *6b* that was elaborated from **75**.

Scheme 17: Seki, M. *et al* *J. Org. Chem.* **2002,** 67, 5527-5536.
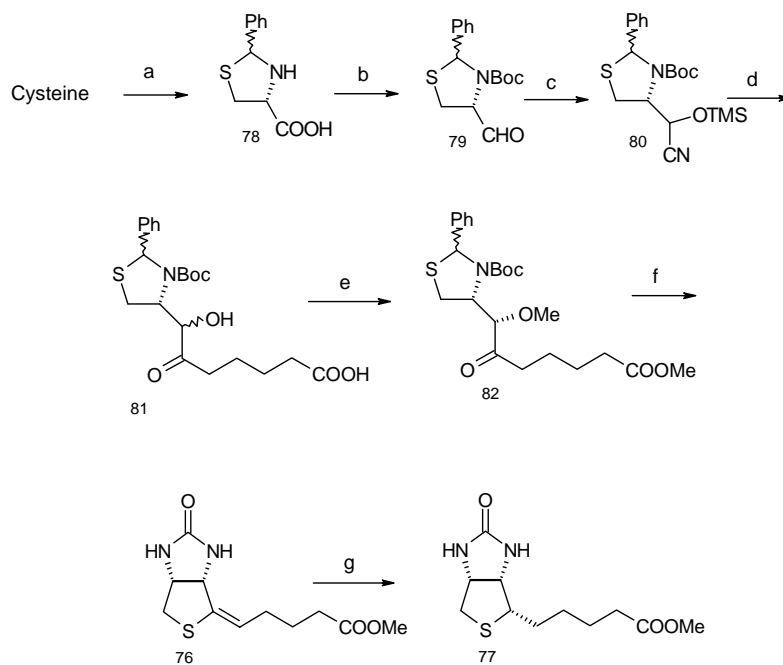
Conditions : ***a*)** *PhCHO, AcOK;* ***b*)** *SOCl₂; (ii) Ca(BH₄)₂; (iii) (Boc)₂O, Na₂CO₃; (iv) SO₃-Py* ***c*)** *TMSCN;* ***d*)** *Mg, 1,4-dibromobutane; CO₂;* ***e*)** *CH₂N₂;* ***f*)** *(i) AcCl, MS 4A; (ii) KOCN; (iii) Pd(OAc)₂P(OEt)₃, Bu₄NCl;* ***g*)** *H₂, Pd(OH)₂/C, AcOEt.*

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1.2.1 Introduction

D(+)-Biotin[1a] (**1**) has gained importance of late, after the development of certain complexes with avidin, streptavidin and has emerged in biochemistry as an important method for isolation, localization, immunoassay and drug delivery.
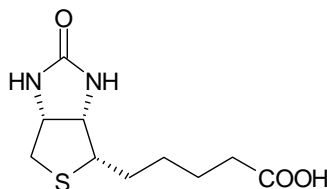
In pharmaceutical industry also D (+)-Biotin has immense commercial importance. Especially in the tonics prescribed for young children. It has been established[1g] that young children who lack biotin, when subjected to stress, die of what is commonly called "cot-death" or **SIDS** (**S**udden **I**nfant **D**eath **S**yndrome). Use of D(+)-Biotin is very popular and is on the rise the western world (US and Europe) and it is extensively used in the poultry industry and animal husbandry. However, in India the use of D(+)-Biotin is not to such an extent because of its prohibitive price. Currently the requirement D(+)-Biotin formulated in India is met thro' imports.

Although a number of syntheses[2] of biotin are known (see Chapter 1 Section 1), most of them are not practical enough to be commercialized. There was thus a need to develop a more practical route to D(+)-biotin. Keeping this view in mind, efforts were directed towards development of a practical synthesis of D(+)-biotin.

This section details the efforts towards this end. This low volume, high priced item was chosen as the molecule of interest. The synthesis of D(+)-Biotin which bears three contiguous chiral centers at C_2-, C_3-, C_4- on tetrahydro thiophane group poses a synthetic a challenge to organic chemists. One of the key factors to develop a practical synthesis is the ready availability of the starting material at economical rates. In the present synthetic route chosen the choice of starting material was fumaric acid, which is commercially readily available.

1.2.2 Retrosynthetic analysis:

Our synthetic endeavor is described in retrosynthetic scheme. According to this scheme bicyclic skeleton **2** was the key intermediate which in turn could be accessed from acid **4**.

Meso acid **4** could be converted to chiral monoester **8** by selective hydrolysis of its diester by using enzyme.

Scheme 1 : Retrosynthetic analysis :
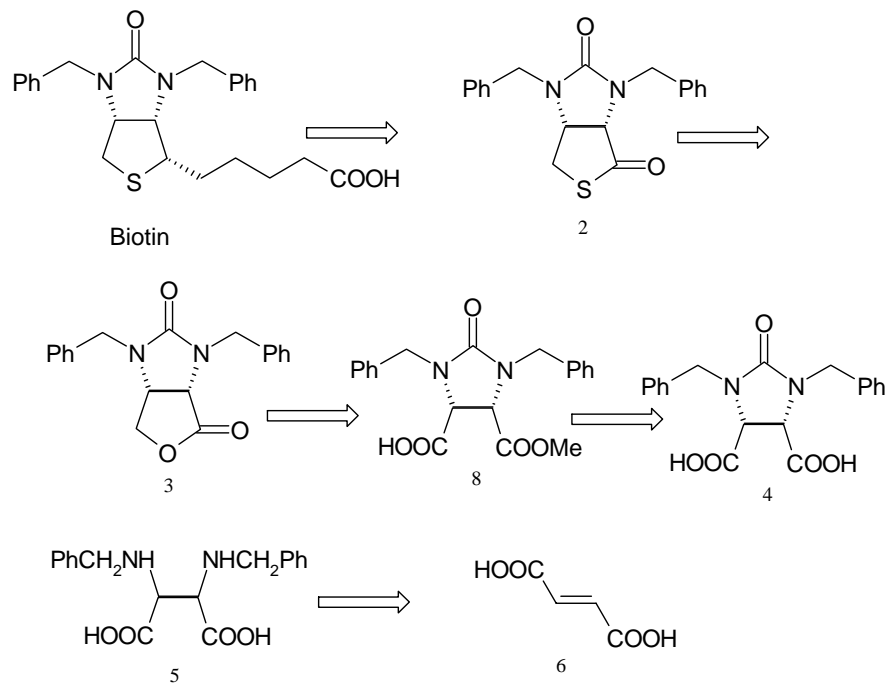
1.2.3 Results and discussions :

In accordance with the planned synthesis, fumaric acid was converted to its known dibromosuccinic acid **11** by refluxing fumaric acid and bromine in water. [3] Dibromosuccinic acid **11** was refluxed with benzylamine (10 eq) for **7** h to furnish dibenzylsuccinic acid **5** in quantitative yields. [4] Dibenzylsuccinic acid was refluxed with triphosgene in toluene and aqueous NaOH to furnish **4** in 90 % yield. Diacid **4** was converted to diester **7** in methanol by using thionylchloride at room temperature. With desired diester **7** in hand there was a need to hydrolyze one of the ester groups selectively so that meso diacid could be converted to chiral monoester **8**.

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Scheme 2 :
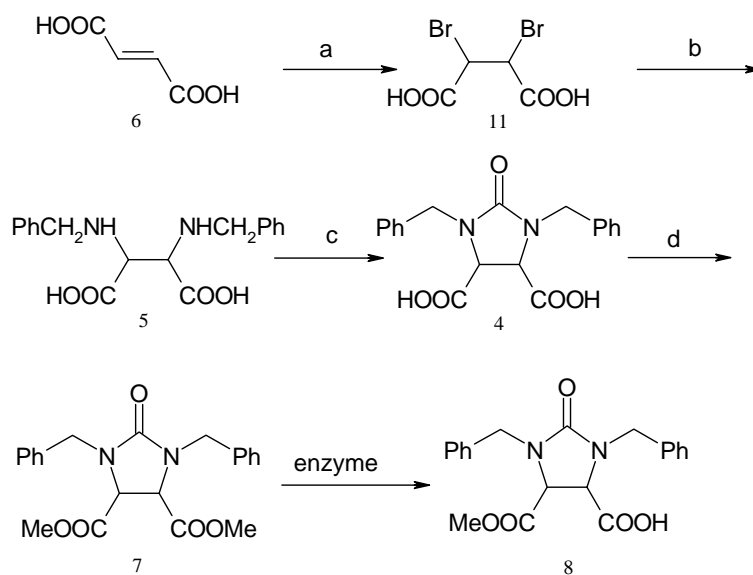
Conditions : a) Br₂, water, reflux, 90 %; b) PhCH₂NH₂, MeOH, reflux, 90 %; c) triphosgene, toluene, NaOH, H₂O, 90 %; d) SOCl₂, CH₃OH, rt, 12 h, 90%.

The use of enzymes for the hydrolysis is an important tool to obtain chiral compounds. Various lipases and esterases are reported [5] to catalyze enantioselective hydrolysis of meso-cyclopent-1,4-diacetate **3a** in aqueous buffer medium to afford **3c** of high enantiopurity in high yields.

Scheme 3:
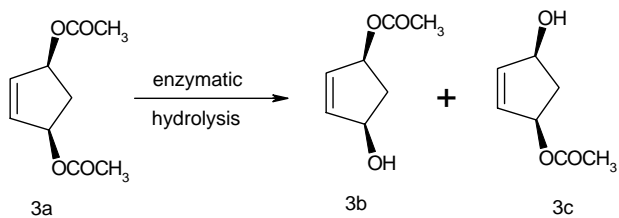
Selective hydrolysis of the diester **7** was attempted by using PLE, PPL, Lipase enzymes under different conditions. A systematic study of hydrolysis of diester with these enzymes is described in table **1**. Diester **7** (50 mg) and 5 mg of enzyme was shacked in 5 ml of solvent. But none of these enzymes were found to be suitable for this transformation. The diester **7** did not get hydrolysed and it was recovered as such.

Table 1 : Enzyme hydrolysis.

No	Enzyme	Solvent	water	Time
1	PLE	Ethanol 2.5 ml	2.5	7 days
2	PLE	Methanol 2.5	2.5	7 days
3	PLE	Acetone 0.5	4.5	7 days
4	PLE	DMF 0.5	4.5	7 days
5	PPL	Ethanol 2.5	2.5	7 days
6	PPL	Methanol 2.5	2.5	7 days
7	PPL	Acetone 0.5	4.5	7 days
8	PPL	DMF 0.5	4.5	7 days
9	Lipase	Ethanol 2.5	2.5	7 days
10	Lipase	Methanol 2.5	2.5	7 days
11	Lipase	Acetone 0.5	4.5	7 days

1.2.4 Present Work :

The desire to imitate nature and living organisms in their extraordinary ability to build complex ring systems with complete regio and stereo control makes studies towards ring construction of fundamental interest in synthetic organic chemistry. Contemporary methods of ring construction encompass basic reactions, which may be categorized as those involving cationic, radical and anionic intermediates.

The main objective of this section is to develop 5, 5 fused system, which is present in biotin skeleton by using ionic cyclization reaction as the key step.

1.2.5 Retrosynthetic Analysis :

Our synthetic endeavor is described in retrosynthetic scheme **4**. According to this scheme,

Scheme 4 : Retrosynthetic analysis:
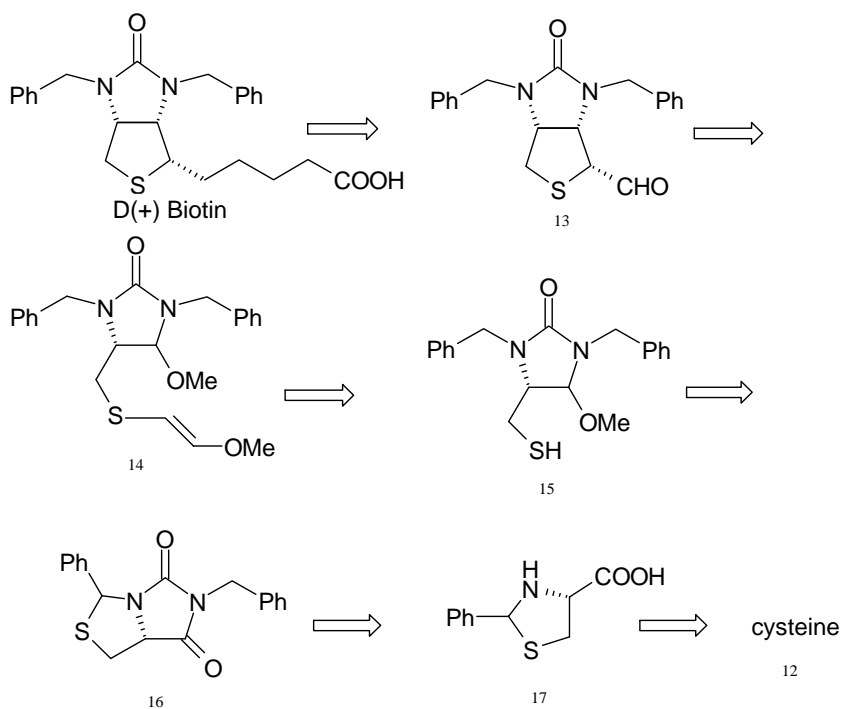
5, 5-fused bicyclic skeleton **13** was the key intermediate which in turn could be accessed from the cyclization of **14**. The success of the synthetic route depended heavily and hinged on the ease of availability of appropriately substituted **14** from hydantoin **16**.

1.2.6 Results and Discussions :

In accordance with the planned synthesis, cysteine hydrochloride hydrate was converted to its known 4-(*R*) – carboxy-2-phenylthiazolidine **17** with benzaldehyde in the presence of KOAc. A one-pot addition of isocyanate to secondary amine followed by dehydration under acidic conditions furnished the compound imidazolidinone **16** in 90 % yield. Reduction of imidazolidinone with sodium borohydride gave hydroxy imidazolidine **18** in almost quantitative yield. Treatment of hydroxy imidazolidine **18** with methanol at room temperature under acidic conditions (*p*TSA) furnished methoxy imidazolidine **19** in 95 % yield. C-S bond of methoxy imidazolidine was cleaved with Na- sand to furnish **15** in 70 % yield.

Scheme 5 :
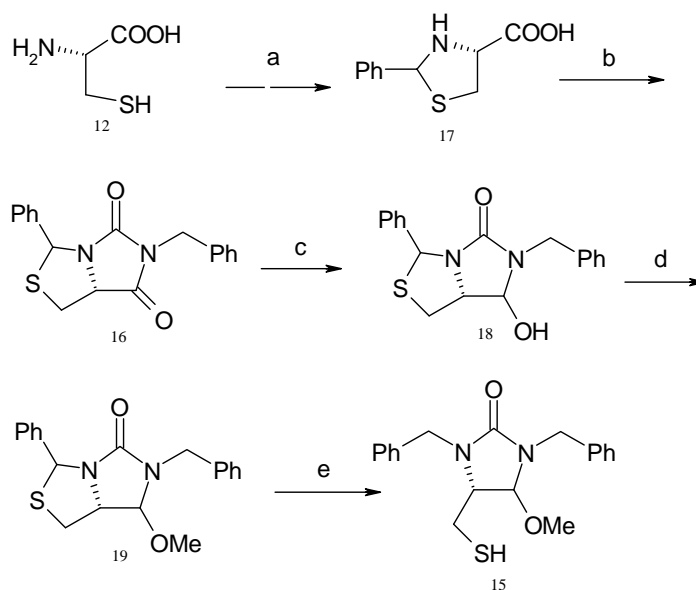
Conditions : *a) PhCHO, KOAc, CH$_3$OH:H$_2$O (1:1), rt, 6h, 98%; b) BnNCO, DCM, 60 min, conc. HCl, 60 min, 90%; c) NaBH$_4$, CH$_3$OH, rt,1h, 90% d) MeOH, pTSA (cat), 15 min, 99 %*

With the desired mercapto compound **15** in hand, there was a need to alkylate it. Addition reaction of thiol with acetylene are well known in literature. [7] As shown in scheme **6,** compound **15** was heated with octyloxyacetylene in toluene with catalytic amount of AIBN. But unfortunately under free radical conditions, unstable mercapto compound **15** was transformed to olefin **21**, instead of forming the desired addition product **14**.

Scheme 6 :
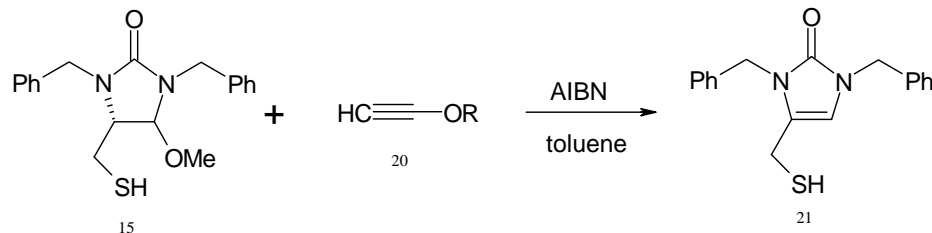
It was thought of preparing the addition product under basic medium in which starting material is stable. Accordingly, compound **15** was refluxed with excess of octyloxyacetylene in dry methanol and sodium methoxide under argon for 24 hours. But desired addition product was not formed even after refluxing for 24 hours.

Scheme 7 :
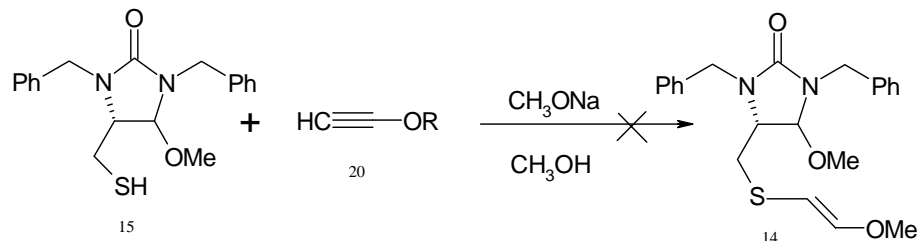
It was then thought of making olefin **14** by a different route. As shown in scheme **8**, thiol **15** was refluxed with bromoacetaldehyde diethylacetal and sodium methoxide in methanol to furnish **21** in 70% yield. Alkylated compound **21** was then treated with n-BuLi with the

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hope to get desired acetylene **22** which in turn could be converted to the olefin **14**. However, the reaction was not clean and the desired acetylene could not be obtained.

Scheme 8 :
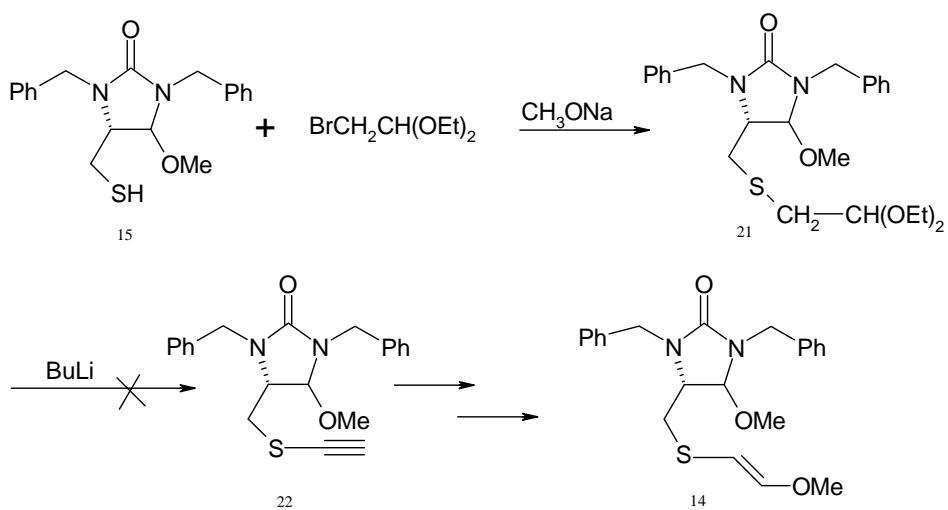
1.2.7 Experimental

1.   Preparation 4-(*R*)-carboxy-2-phenylthiazolidine (17): [6]
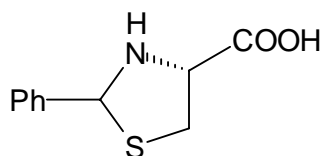
To a solution of L-cysteine hydrochloride hydrate (60g, 0.34 mol), in water (525 mL) and potassium acetate (36g, 0.37 mol) was added. After a solution was obtained, 95% of methanol (525 mL) was added; followed by immediate addition of benzaldehyde (44.2g, 0.42 mol) in one portion. The product thiazolidine soon began to crystallize. The reaction mixture was kept at 25 °C for three hours and an additional three hours at 0 °C. The product was filtered, washed with methanol, and dried to afford thiazolidine as white solid.

Yield	72.0g (98%).
Mol. Formula	$C_{10}H_{11}NO_2S$, white solid
M.P.	155 °C (Lit [3] 159-160 °C)
Optical Rotation	$[\alpha]_D = -133°$ (c=1, DMSO); (Lit [3] $[\alpha]_D = -133.51°$)
IR (KBr, cm^{-1})	3040, 2960, 2700-2400 (NH_3^+), 1600-1550 (CO_2^-) 1360.
Mass (m/z)	209(M^+ 34), 170(39), 164(65), 137(100),
^{1}H NMR (DMSO-d$_6$, 200MHz)	3.50-3.30 (m, 2H, CH_2); 4.40-4.0 (m, 1H, CHCOOH); 5.80 (s, 1H, CH); 6.80 (m, 1H, NH)); 7.40 (m, 5H).

2. 6-Benzyl-3-phenyl(3S, 7aR)perhydroimidazo[1,5-c][1,3]-thiazol-5,7-dione (16):
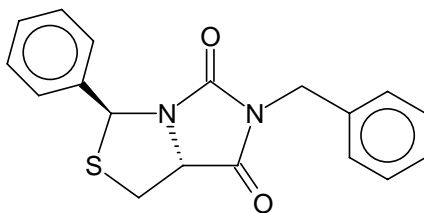
In a 500 mL two necked round bottom flask filled with nitrogen, (20.0g, 95.6 mmol) thiazolidine carboxylic acid **17** was placed in 150 mL of anhydrous THF. To this suspension, a solution of (15.2g, 114.3 mol) benzyl isocyanate in 50 mL of THF was added drop wise within 20 min. The reaction mixture was stirred for 1 h, at 60 ^{o}C. Subsequently it was cooled to 0 ^{o}C and conc. HCl (20.0 mL) was added and the reaction mixture was allowed to stir for 90 min at 60 ^{o}C. Then the reaction mixture was cooled to 0 ^{o}C and water was added and extracted with ethyl acetate. The combined organic layers were dried over anhyd. Na_2SO_4, filtered and concentrated under reduced pressure. After triturating with methanol the hydantoin **16** was obtained as a white crystalline solid [m.p 78 ^{o}C] (27.8g, 90%).

Mol. Formula	$C_{18}H_{16}N_2O_2S$
M.P	78°C, white solid. (Lit[8] 79-80 ^{o}C)
Optical Rotation	$[\alpha]_{365} = +1010^o$ (c=1, $CHCl_3$); $[\alpha]_D = -250^o$ (c=1.08, $CHCl_3$)
IR ($CHCl_3$, cm^{-1})	3040, 2960, 1720, 1700, 1510, 1420, 1230, 1050.
^{1}H NMR(CDCl$_3$, 200MHz)	3.17 (dd, 1H, J = 7.82, 11.2Hz); 3.30 (dd, 1H, J = 6.81, 11.2Hz); 4.52 (t, 1H, J = 7.32Hz); 4.68 (s, 2H); 6.43 (s, 1H); 7.39 (m, 10H).
^{13}C NMR (CDCl$_3$, 125 MHz)	33.2(t), 42.81(t), 65.19(d), 65.82(d), 126.36(d), 127.41(d), 127.91(d), 128.05(d), 125.15(d), 128.28(d), 128.42 (d), 128.48 (d), 128.72(d), 128.80(d), 135.44(s), 139.04(s), 158.54(s, C=O), 171.0(s, C=O).
Mass (m/z)	325(M+1, 30), 324(M$^+$ 100), 323(M-1, 40), 291(9), 278(4), 233(28), 162(22), 145(5), 132(8), 122(14), 117(39), 104(9), 91 (38), 77(10), 65(8), 55(7).

Analysis

	Carbon	Hydrogen	Nitrogen	Sulphur
Calc.:	66.64	4.97	8.64	9.88
Found:	66.30	5.17	8.43	9.55

3. 6-Benzyl-7-hydroxy-3-phenyl(3*S*, 7a*R*)perhydroimidazo[1,5-*c*][1,3]-thiazol-5-one (18):
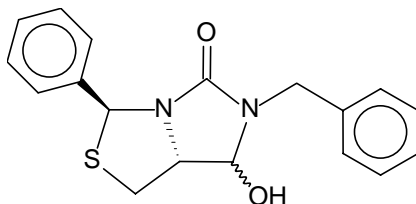
The imidazolidinone **16** (32.4g, 0.1 mmol) was taken in aq. THF or methanol (300 mL) and cooled to 0 °C. Sodium borohydride (5.6g, 0.15mol) was added gradually in small portions at a time. After addition of sodium borohydride was over, the reaction mixture was brought to room temperature. Stirring was continued for additional half an hour. The reaction mixture was quenched with water and the contents were extracted with ethyl acetate. The combined layers were washed with water (100 mL), brine (100 mL) and dried over anhyd. Na_2SO_4 and filtered. After concentration of the organic layer under reduced pressure a white crystalline solid of hydroxy imidazoline **18** was obtained in 90 % yield.

Yield   29 g   (90%).

Mol. Formula $C_{18}H_{18}N_2O_2S$, white solid.

M.P.   113 °C

Optical Rotation $[\alpha]_D = +52.58°$ (c=1, $CHCl_3$)

IR (in $CHCl_3$, cm^{-1})   3400, 3010, 2960, 1700, 1510, 1438, 1310, 1239, 1160, 959.

^{1}H NMR ($CDCl_3$, 200MHz) 2.92 (dd, 1H, J = 6.83, 11.72 Hz); 3.23 (d, 1H, J = 10.26 Hz, -O<u>H</u>, D_2O exchangeable); 3.33 (dd, 1H, J = 5.37, 11.72 Hz); 4.18 (d, 1H, J = 15.14 Hz); 4.19 (m, 1H, J = 5.37, 6.83 Hz,-C<u>H</u>-CH-OH); 4.78 (d, 1H, J = 15.14 Hz);

5.04 (dd, 1H, J= 6.84, 10.26 Hz, N-C$\underline{H}$-OH, D_2O exchangeable); 6.38 (s, 1H); 7.30 (m, 8H); 7.40 (m, 2H).

^{13}C NMR (CDCl$_3$, 125 MHz)	31.60(t), 43.83(t), 64.37(d), 66.03(d), 77.74(d), 126.08(d), 127.93(d), 128.03(2C, d), 128.34(2C, d), 128.41(2C, d), 128.55 (2C, d), 136.40(s), 140.98(s), 159.55(s, C=O).

Mass (m/z)	326(M$^+$, 25), 308(19), 280(13), 192(9), 187(19), 160(6), 147(5), 132(27), 121(36), 104(23), 91(100), 77(14), 65(6)

Analysis :

	Carbon	Hydrogen	Nitrogen	Sulphur
Calc.:	66.23	5.56	8.58	9.82
Found:	66.10	5.17	8.20	9.72

4. 6-Benzyl-7-methoxy-3-phenyl(3S, 7aR)perhydroimidazo[1,5-c][1,3]-thiazol-5-one (19):
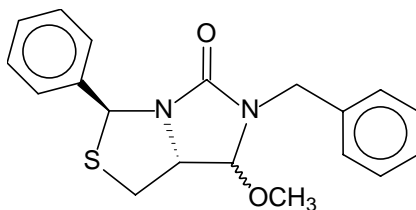
The hydroxy imidazolidine **18** (32.6g, 0.1mol) was dissolved in anhydrous methanol (300 mL) and to this solution catalytic amount of *p*TSA was added and the reaction mixture was stirred for 10 min at room temperature. After completion of the reaction (by TLC) the reaction mixture was quenched with Na$_2$CO$_3$ and filtered. Removal of solvent and extraction with EtOAc furnished the methoxy hydantoin **19** in almost quantitative yield.

Yield	33.8g (99%).

Mol. Formula	C$_{19}$H$_{20}$N$_2$O$_2$S, white solid.

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M.P.	83 °C

Optical Rotation	$[\alpha]_D = -210^o$ (c=1, CHCl$_3$)

IR (in CHCl$_3$, cm^{-1})	2930, 1705, 1510, 1420, 1360, 1236, 1160, 1005.

^{1}H NMR (CDCl$_3$, 200MHz) 2.55 (t, 1H, J = 9.75 Hz); 3.13 (dd, 1H, J = 4.87, 12.19 Hz); 4.0 (dd, 1H, J = 4.87, 9.75 Hz); 3.30 (s, 3H); 4.21 (d, 1H, J = 15.14 Hz); 4.65 (s, 1H); 4.90 (d, 1H, J = 15.14 Hz); 6.45 (s, 1H); 7.38 (m, 10H).

^{13}C NMR (CDCl$_3$, 125 MHz) 36.39(t), 44.60(t), 52.96(q), 64.79(d), 65.37(d), 86.87(d), 126.0(d), 127.65(d), 127.73(d), 127.82(d), 128.13(d), 128.29(2C, d), 128.42(d), 128.55(d), 128.70(d), 136.12(s), 141.36(s),160.01(s, C=O).

Mass (m/z) 340(M$^+$, 24), 309(6), 294(54), 240(6), 203(19), 187(5), 174(13), 144(6), 132(42), 121(8), 106(33), 91(100), 77(13),

Analysis :   :

	Carbon	Hydrogen	Nitrogen	Sulphur
Calc.:	67.03	5.92	8.23	9.42
Found:	67.10	5.87	8.56	8.90

5. 1,3-benzyl-4-methoxy-5-sulfanylmethyltetrahydro-1*H*-2-imidazolone (15) [9]
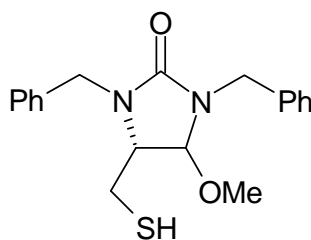
Methoxy imidazolidinone **19** (3 g, 10 mmol) was stirred at rt with sodium sand (1.15g, 50 mmol) in THF for 3-4 hours. Progress of the reaction was monitored by using TLC. After completion of the reaction, reaction mixture was quenched with methanol. Organic solvent was evaporated and reaction mixture was extracted with ethylacetate. After evaporation of ethyl acetate, the residue was column chromatographed using 30 % ethyl acetate : Pet ether.

Yield   80%

Mol. Formula $C_{19}H_{22}N_2O_2S$

^{1}H NMR (CDCl$_3$, 200MHz)   2.5 (2H, m); 3.06 (3H, S); 4.06 (m, 2H); 4.53 (s, 1H); 4.88 (m, 2H); 7.31(m, 10H).

6.   1,3-dibenzyl-4-(2,2-dimethoxyethylsulphanylmethyl)-5-methoxytetrahydro-1*H*-2-imidazolone : (21) [9]
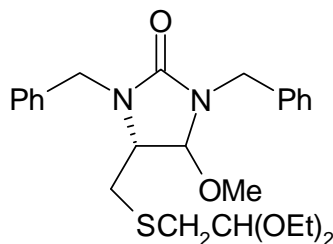
Methoxy imidazolidine **15** (3.14g, 10mmol) was stirred with sodium sand 91.15 g, 50 mmol) in THF for 3-4 hours. After completion of the reaction, reaction mixture was quenched with methanol. The reaction mixture was then refluxed with bromoacetaldehyde diethylacetal (1.7 g, 1mmol) for 6 h. The progress of the reaction was monitored by using TLC. After completion of reaction, reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was dried over anhydrous Na$_2$SO$_4$, filtered and evaporated at reduced pressure. The residue was column chromatographed using 30 % ethyl acetate : pet ether as eluent.

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Yield	70 %
Molecular formula	$C_{23}H_{30}N_2O_4S$
IR (in $CHCl_3$, cm^{-1})	3400, 2950, 1700, 1510, 1430, 1230, 1150, 950.
^1H NMR ($CDCl_3$, 200MHz)	1.12 (m, 6H), 2.43 (m, 2H), 2.80 (m, 1H), 3.0 (s, 3H), 3H), 3.40 (m, 6H), 4.02 (m, 2H), 4.37 (m, 1H), 4.4 (s, 1H), 4.87 (m, 2H), 7.58 (m, 10H)
^{13}C NMR ($CDCl_3$, 50MHz)	15.57, 33.36, 35.34, 44.68, 45.41, 52.36, 57.14, 62.32, 88.38, 1.3.60, 128.74, 137.16, 158.44.

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7. a) Viehe, H. G. Chemistry of acetylenes _ New York, Marcel Dekker INC. **1969**. b) Brandsma L. Synthesis of acetylenes, allenes and cumulenes _ Elsevier Science Publishers, **1981**.

8. Poetsch, E.; Casutt, M., Chimia **1987**, *41*, 148.

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1.3.1 Introduction :

Although a variety of syntheses of D(+)-biotin are known (see chapter-1:Section-1) most of them are not practical enough to be commercialized. Hence, there was a need to develop a more practical route to D(+)-biotin. Keeping this view in mind, efforts were directed towards development of a practical synthesis of D(+)-biotin from L-cysteine *via N*-acyliminium intermediate. Several approaches to D(+)-biotin hitherto reported employ inexpensive chiral substrates such as amino acids, sugars and other as starting materials. Amongst them, L-cysteine, in particular possesses a promising potential as a chiral building block, since it contains thiol and amine moieties of the correct stereochemistry as required for D(+)-biotin. From this standpoint, L-cysteine has been one of the most useful starting materials for D(+)-biotin synthesis.

1.3.2 Retrosynthetic Analysis :

Scheme 1 :
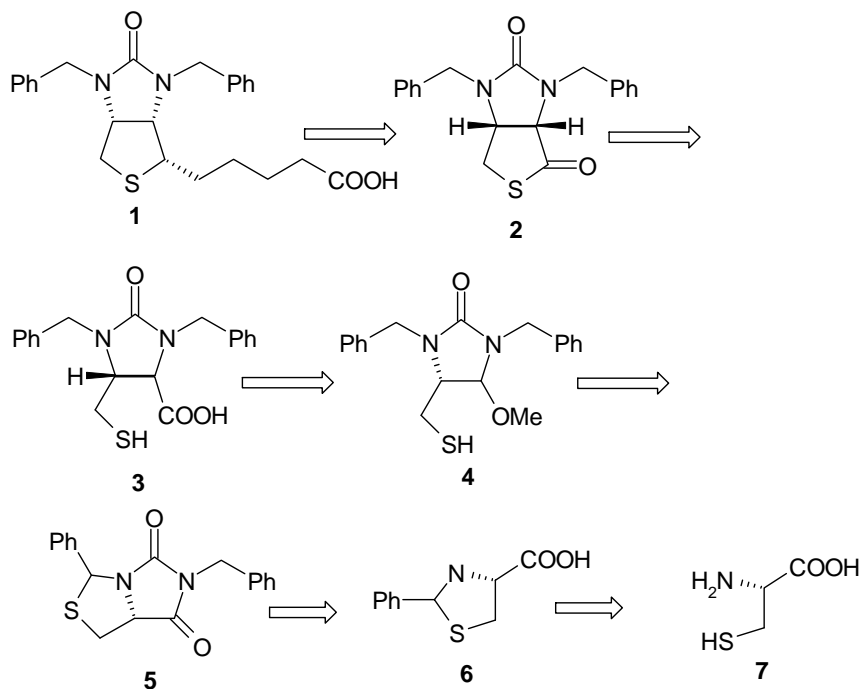
Retrosynthetic analysis revealed acid **3** as the key intermediate, which in turn could be accessed from inexpensive, commercially available starting material cysteine.

In accordance with the planned synthesis, hydroxy imidazolidine **8** was prepared from cysteine hydrochloride hydrate. Cysteine hydrochloride hydrate **7** was converted to its 2 phenyl-thiazolidine-4 carboxylic acid **6** by condensation with benzaldehyde, in the presence of KOAc. A one pot addition of benzylisocyanate followed by dehydration furnished imidazolidinone in 90 % yield. Reduction of amide carbonyl using NaBH$_4$ in CH$_3$OH provided hydroxy imidazolidine **8** in quantitative yield. Hydroxy imidazolidine **8** was converted into methoxy imidazolidine by stirring in methanol and catalytic amount of *p*TSA.

Scheme 2 :
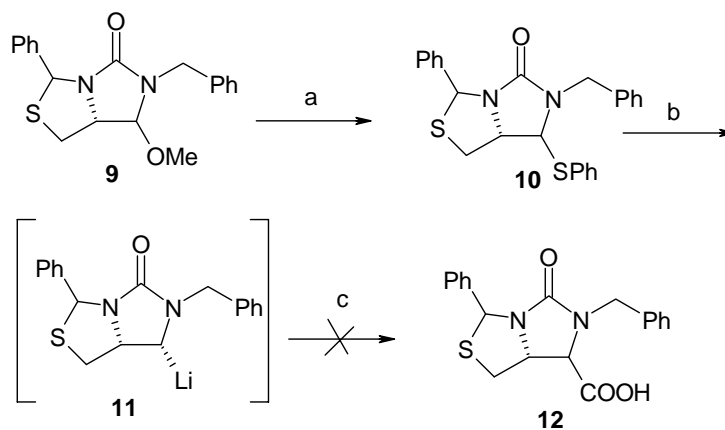
Conditions : a) PhSH, pTSA, 70 %; b) Li/naphthalene, THF, -78 °C; c) CO$_2$

As shown in above scheme methoxy imidazolidine 9 was treated with PhSH and catalytic amount of *p*TSA to furnish thio derivative **10**.

With desired compound **10** in hand there was a need to cleave selectively one of the C-S bond to furnish radical anion **11** which could be quenched with CO$_2$ to obtain desired acid. Accordingly, substrate **10** was treated with Li/naphthalene at -78 °C in different stoichiometric ratios ranging from two equivalents to four equivalents to cleave selectively one of the C-S bonds. But unfortunately reaction was not clean and a mixture of products was obtained.

In yet another approach it was thought of making the acid **4** from aldehyde **14**.

Scheme 3 :
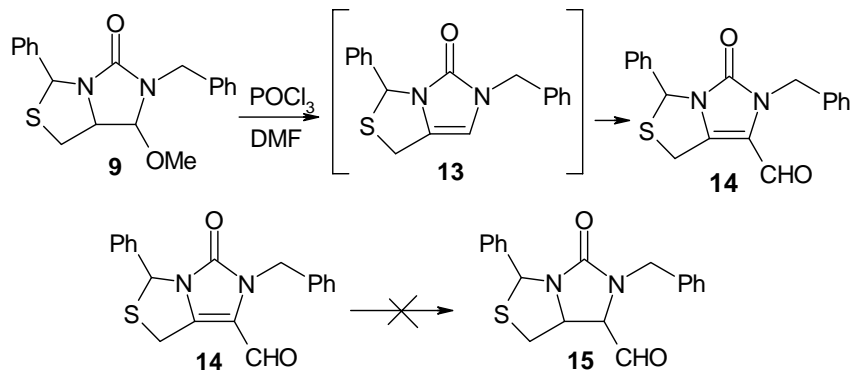
as shown in scheme **3** methoxy imidazolidine **9** was treated with POCl₃ and DMF to furnish conjugated aldehyde **14** in 70% yield. Unsaturated aldehyde was subjected for hydrogenation under various conditions with various catalysts (**table 1**). Several attempts to convert **14** to **15** met with failure and the starting material was recovered unchanged.

Table 1 : Hydrogenation of aldehyde 12

Catalyst	H₂ Pressure (psi)	Solvent	Temp. (°C)	Time (hr.)
Pd/C	800	MeOH	80-100	24
Pd/C	1000	DMF	80-100	24
Ru/Al₂O₃	800	MeOH	80-100	25
Ru/Al₂O₃	1000	DMF	80-100	23
Rh/ Al₂O₃	800	MeOH	80-100	25
Rh/ Al₂O₃	1000	DMF	80-100	24

1.3.3 Present Work

Enol ethers:

Silyl enol ethers in combination with Lewis acids like TMSOTf or BF$_3$.OEt$_2$ are excellent nucleophiles for the intermolecular C-C bond formation.

Application of *N*-acyliminium ions in the synthesis of some natural products:

Some of the following biologically active compounds were reported in literature by using acyliminium chemistry as the key step.

Scheme 4:

D(+)-Biotin[4]   (-)Xenovenine[1] Epibatidine[2]   Stemoamide[3]
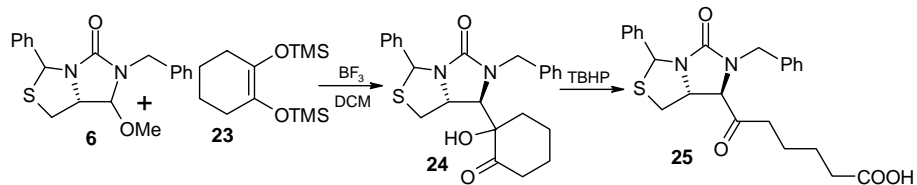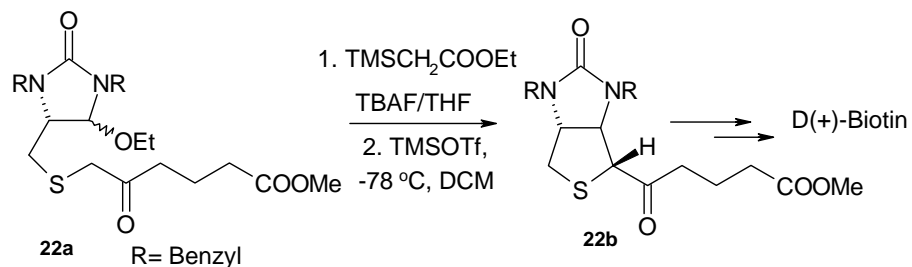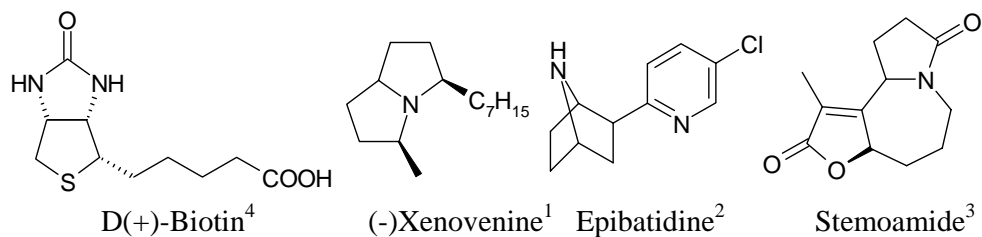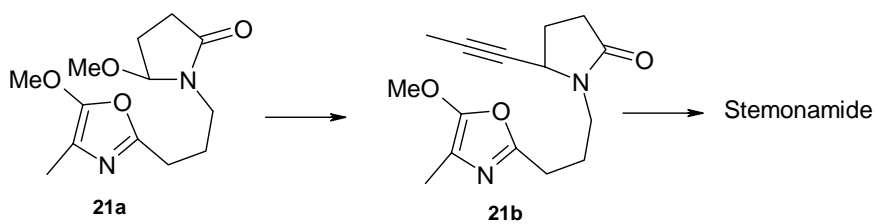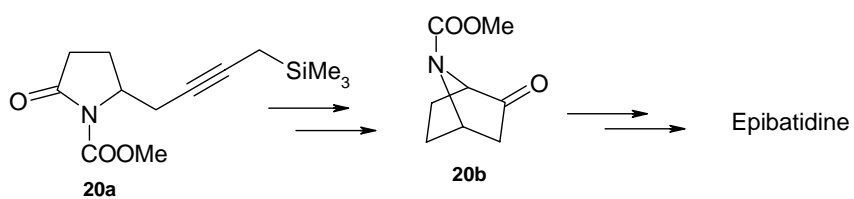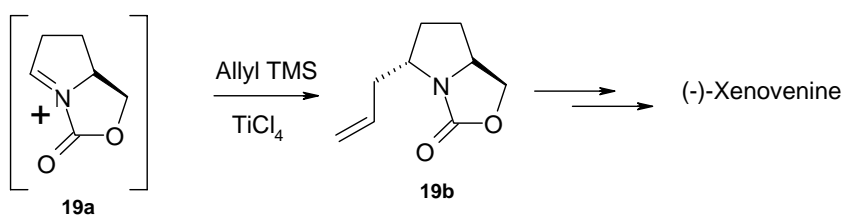
1.3.4 Results and Discussion

Scheme 5 :
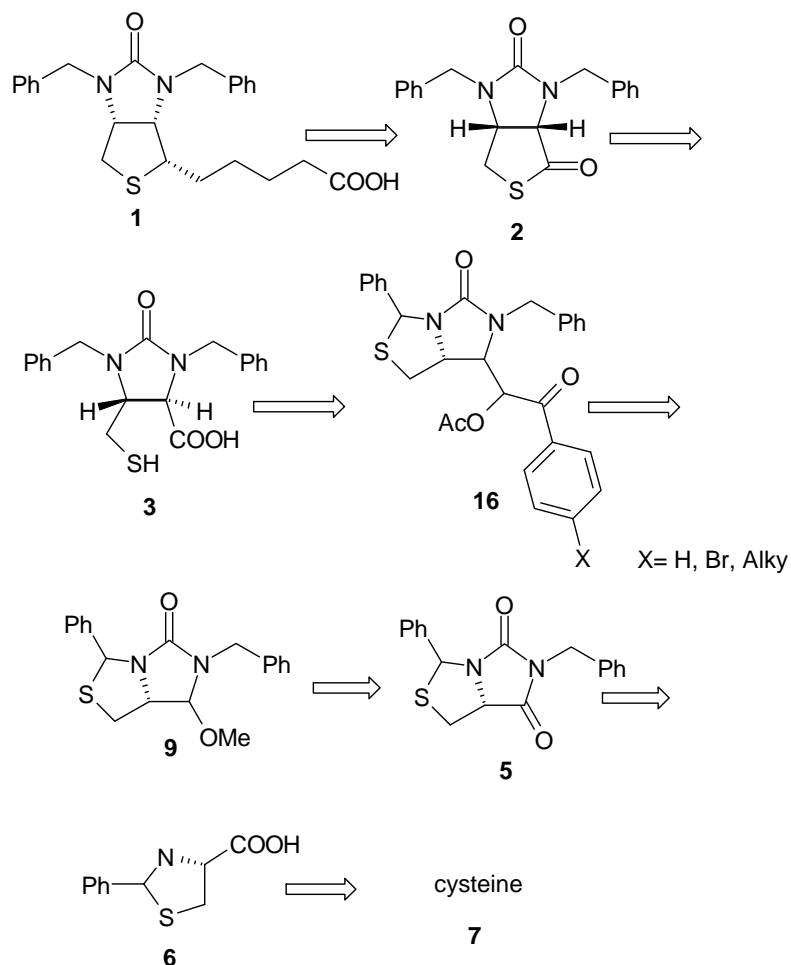
Retrosynthetic analysis revealed methoxy imidazolidine **9** an intermediate that on C-C bond formation could be a probable approach towards biotin. In accordance with the planned synthesis methoxy imidazolidine **9** was prepared from cysteine **7**. The methoxy imidazolidine **9** could serve as an ideal substrate for the amidoalkylation at C7-position via *N*-acyliminium ion. Thus the reaction of methoxy imidazolidine **9** with 1.5 eq of silylenol ether **19**, in the presence of 1.3 eq of BF_3 as a Lewis acid at 0 to 25 ^{o}C proceeded smoothly to give the 7-substituted imidazolidine **16** in excellent yield. Silylenol ether **19** was inturn prepared from *p*-bromo phenacyl bromide **17**.

Scheme 6 :
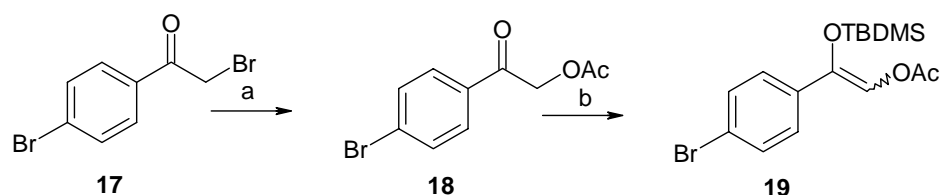
Conditions: *a) acetic acid, KF, DMF, 95 % yield ; b) TBDMSCl, DBU, DCM. 85 % yield*

p-Bromo phenacyl bromide was stirred with 2 eq of acetic acid in DMF in the presence of 2 eq of KF to furnish p-bromophenacyl acetyl **18** in quantitative yields. The acetyl derivative **18** was then refluxed with 2 eq of TBDMSCl in dry DCM and 2 eq of DBU to furnish silyl enol ether **19** in excellent yields.

Scheme 7 :
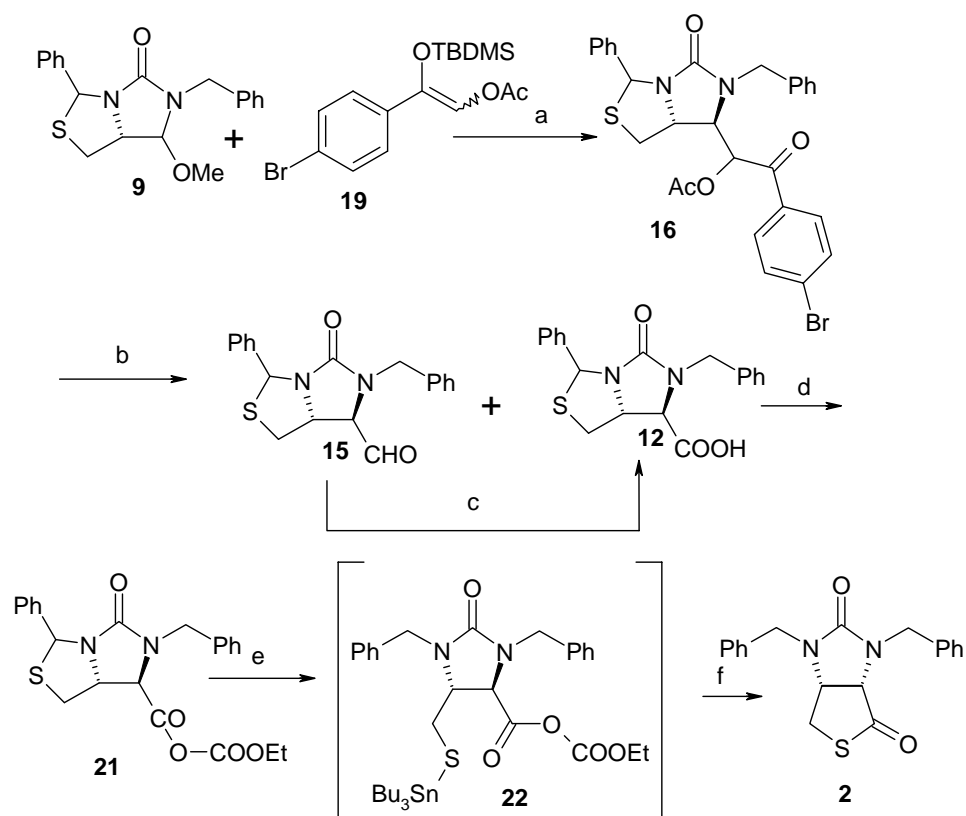
Conditions : *a) DCM, BF$_3$.Et$_2$O 0 ^{o}C, 10 min, 70 %; b) TBHP (1.2 eq), KOH, MeOH, 20 min, 70% c) KMnO$_4$ (1eq) acetone, 10 min, 0 ^{o}C, 60 % d) ethylchloroformate (1.2 eq), pyridine (1.3 eq), DCM, 3 h, 85%. e) tributyltinhydride, AIBN, toluene, reflux, 6 h, f) pyridine, reflux, 48 h*

To cleave C-C bond of condensed product **16**, it was treated with TBHP in methanolic KOH. However 0-10 % aldehyde **15** was also formed along with acid **12**. Aldehyde was separated from the reaction mixture and further oxidized to acid by using KMnO$_4$ .With desired acid **12** in hand, there was a need to cleave the C-S bond and cyclise to get the thiolactone. It was thought of cleaving the C-S bond by using tributyltin hydride.

Tri n-butyltin hydride as reducing agent:

Among the various methods employed, the most common is the reductive cleavage of alkyl halide or alcohol derivative to generate carbon-centered radicals that are further used in inter- or intramolecular reactions. The disadvantage of this approach is that the C-C bond is formed at the expense of the loss of functionality (R-X to R^1-H). However, it is possible to retain functionality at the initial radical center simply by generating the radical from an acid derivative (RCOOH to R^{1}C(O)R^3) or a carbonyl derivative (R^{1}C(O)R to R^{2}R^{1}COH).

Gutierrez et al[5] established that *tri*-n-butyltin hydride in the presence of AIBN [azobis(isobutyronitrile)] as an initiator was effective for desulfurization of dithiolanes and that this process involved a stepwise radical chain reaction.

Recently it has been shown by Fallis et al[6] that aldehydes or ketones protected as 1,3-oxathiolanes[7] and 5-oxo-1,3-thiolanes undergo facile S_H2 cleavage of C-S bond in a reaction with stannyl radicals.

Scheme 8: *Tetrahedron Lett.* **1988**, *29*, 897
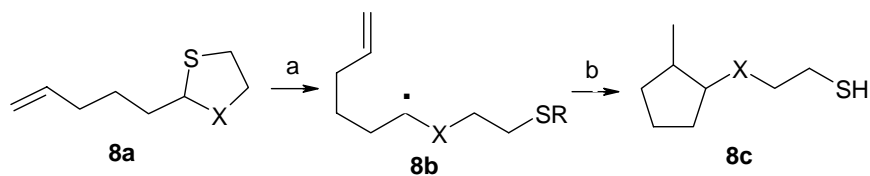
Conditions: a) Tri-n-butyltin hydride, AIBN, benzene, reflux; b) NaOH, aq. EtOH.

Scheme 9: *Tetrahedron Lett.* **1989**, *30*, 3283
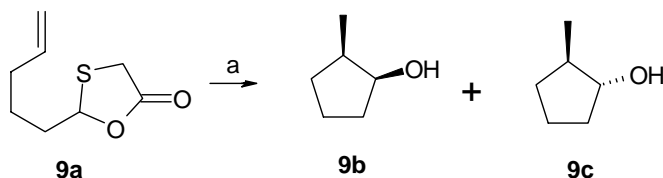
Condition: *a) Tri-n-butyltin hydride, AIBN, benzene, reflux.*

Based on the above literature precedents reductive cleavage of carbon-sulphur bond of compound **10a** employing above-mentioned condition was attempted.

Scheme 10:
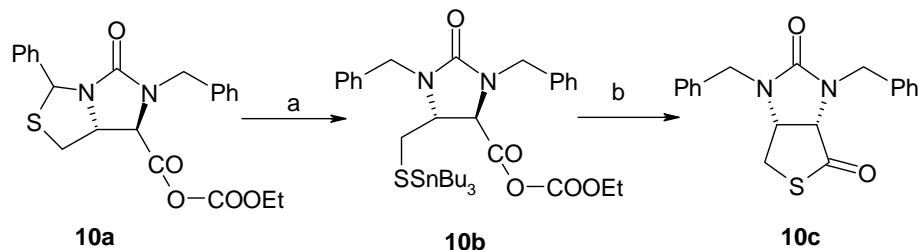
Conditions: *a) Tri-n-butyltin hydride, AIBN, toluene, reflux. b) pyridine, reflux.*

Thus compound **10a** was treated with *tri*-n-butyltin hydride in the presence of catalytic amount of radical initiator [azobis (isobutyronitrile)] (AIBN) in toluene at elevated temperature for 30-45 min. It was gratifying to note that under these conditions cleavage of C-S bond was achieved. Intermediate 10b was further cyclised by refluxing with pyridine for 48 hours.

In conclusion short and efficient synthesis of D(+)-biotin intermediate, thiolactone has been achieved starting from naturally available amino acid *viz*, L-cysteine hydrochloride hydrate involving *N*-acyliminium ion chemistry.

1.3.5 Experimental Section :

1. 6 Benzyl-3-phenyl 7-phenylsulfonyl tetrahydro-imidazo[1,5-*c*] thiazo-5one. (10)
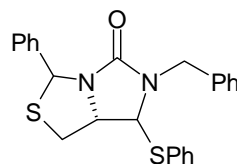
Methoxy ureide **9** (4.14 g, 10 mmol) was dissolved in thiophenol (20 ml) and solution was cooled to 0 °C. To this was then added catalytic amount of *p*TSA (20 mg, 0.1 mmol) and the mixture was stirred at 0 °C for 5 min. Mixture of DCM (20ml) and water (5ml) was then added, organic layer was separated washed with NaOH solution , dried over anhydrous sodium sulphate and filtered. Rotary evaporation of solvent under reduced pressure and chromatographic purification (15 % Ethylacetate :Petether) afforded 3 gm of benzyl-3-phenyl 7-phenylsulfonyl tetrahydro-imidazo[1,5-*c*] thiazo-5one.

Yield	3 g (70 %)
Mol Formula	$C_{24}H_{22}N_2OS_2$
IR(CHCl$_3$, cm^{-1})	970, 1070, 1210, 1415, 1585, 1690, 2400, 3020.
^{1}H NMR (CDCl$_3$, 200 MHz)	2.5 (1H, t); 3.12 (1H, m); 4.1 (1H, m) 4.4 (1H, m); 4.46 (1H, m); 6.27 (1H, s); 6.82 (2H, s), 7.38 (13 H, m).
^{13} C NMR (CDCl$_3$, 75 MHz)	36.7, 44.13, 64.57, 65.5, 66.62, 127.38, 134, 140, 158.43.
Mass (m/z)	419, 310, 328, 219, 192.

Analysis:

	Carbon	Hydrogen	Nitrogen	Sulphur
Calc.:	68.87	5.30	6.69	15.32
Found:	68.10	5.00	6.56	15.00

2.   6   benzyl-5-oxo-3-phenyl-5,6-dihydro-1*H*-imidazo[1,5-*c*]thiazole-7-carbaldehyde. (14)
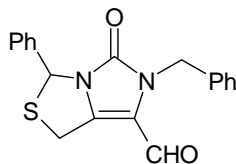
5 ml of DMF and POCl$_3$ (3 g, 20 mmol) were cooled at -5 C in two necked round bottom flask under argon. To this solution methoxy ureide **9** (6 g, 20 mmol) dissolved in DMF was added through dropping funnel dropwise. Reaction mixture was stirred at room temperature for 12 hours. Reaction was quenched with ice cold water with vigourous stirring. Product precipitated out as yellow solid. Recrystallisation from methanol provided aldehyde (4 g) in 70 % yield.

Yield	4 g (70%)
Mol Formula	C$_{19}$H$_{16}$N$_2$O$_2$S
M.P	108 ^{o}C
IR(CHCl$_3$, cm^{-1})	668, 1440, 1663, 1715, 3018.
^{1}H NMR (CDCl$_3$, 200 MHz)	4.25 (m, 2H); 5.2 (m, 2H); 6.27 (s,1H); 7.4 (m, 10H); 9.4 (s, 1H).
^{13}C NMR (CDCl$_3$, 75 MHz)	27.02, 45.82, 63.32, 127.097, 137, 141, 148.26, 174.95.
Mass (m/z)	338, 337, 308, 226, 148, 132.

Analysis:

	Carbon	Hydrogen	Nitrogen	Sulphur
Calc.:	67.84	4.79	8.33	9.53
Found:	67.10	4.37	8.06	9.30

3 Acetic acid 2-(4-bromo-phenyl)-2-oxo-ethyl ester. (18)
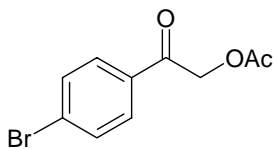
p- Bromo phenacyl bromide (2.8 g, 1 mmol) was stirred with KF (91.16 g, 2 mmol) and acetic acid (0.12 g, 2 mmol) for 15 min. at room temperature. Reaction was monitored by TLC. After completion of the reaction, reaction mixture was quenched with water. Product precipitated out as white solid. It was filtered and dried to furnish 2.5 g of acetic acid 2-(4-bromo-phenyl)-2-oxo-ethyl ester

Yield	2.5 g (96 % yield)
MP	78 ^{o}C
Mol Formula	$C_{10}H_9BrO_3$
IR(CHCl$_3$, cm^{-1})	1070, 1217, 1580, 1690, 1740, 3020, 3436
^{1}H NMR (CDCl$_3$, 300 MHz)	2.2 (3H, s); 5.25 (2H, s); 7.6 (2H, d, J = 8.2 Hz); 7.8(2H, d, J= 8.2 Hz)
^{13} C NMR (CDCl$_3$, 200 MHz)	20.87, 66.19, 129.67, 132.54, 170.48, 191.46.
Mass (m/z)	256, 256, 177, 118.

Analysis:

	Carbon	Hydrogen	Bromine
Calc.:	46.72	3.53	31.08
Found:	46.60	3.51	31.00

4. Acetic acid 2-(4-bromo-phenyl)-2-(tert-butyl-dimethyl-silanyloxy)-vinyl ester. (19)
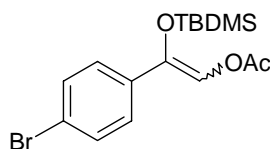
Acetic acid 2-(4-bromo-phenyl)-2-oxo-ethyl ester **18** (2.6 g, 1 mmol) was refluxed with TBDMSCl (2.25 g, 1.5 mmol) and DBU (2.5 g, 1.5 mmol) in dry DCM for 10 hours. Reaction was monitored with TLC. After completion of the reaction, reaction mixture was quenched with water and extracted with DCM. Organic layer was removed, dried over Na_2SO_4, filtered and solvent was removed under reduced pressure. Crude product was purified by column chromatography (SiO_2) to furnish 3 gm of silylenol ether acetic acid 2-(4-bromo-phenyl)-2-(tert-butyl-dimethyl-silanyloxy)-vinyl ester in 80 % yield.

Yield	3 g (80 % yield)
Mol Formula	$C_{16}H_{23}BrO_3Si$
^{1}H NMR (CDCl$_3$, 300 MHz)	0.0 (6H, s); 0.8 (9H, s); 2.1 (3H, s); 6.6 (1H, s); 7.04 (2H, d, J=15 Hz)); 7.28(2H, d, J= 15 Hz)
^{13} C NMR (CDCl$_3$, 500 MHz)	-4.52, 18.16, 20.29, 25.42, 120.03, 126.35, 131.11, 166.4
Mass (m/z)	370, 311, 245, 176, 186.

Analysis:

	Carbon	Hydrogen	Bromine
Calc.:	51.75	6.24	21.52
Found:	51.30	6.17	21.46

5. Acetic acid 1-(6-benzyl-5-oxo-3-phenyl-tetrahydro-imiazo[1,5-*c*]thiazol-1-yl)-2-(4-bromo-phenyl)-2-oxo-ethyl ester. (16)
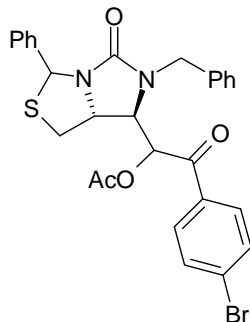
To a solution of methoxy ureide **9** (6.52 g, 20 mmol) in DCM (200ml) was added silylenol ether **15** (7.5 g, 40 mmol). Then the solution was cooled to 0 ^{o}C and Lewis acid BF$_3$.Et$_2$O (2.84 g, 20 mmol) was added dropwise. The reaction mixture was stirred at 0 ^{o}C for 10 min, and it was quenched with saturated ammonium chloride (50 ml). The organic layer was separated, dried, filtered, concentrated under reduced pressure and the residue thus obtained was purified by column chromatography (SiO$_2$) provided acetic acid 1-(6-benzyl-5-oxo-3-phenyl-tetrahydro-imiazo[1,5-*c*]thiazol-1-yl)-2-(4-bromo-phenyl)-2-oxo-ethyl ester (**16**) in 70 % yield in form of viscous colorless liquid.

Yield	9 g (70 %)
MP	85 ^{o}C, white solid.
Mol Formula	C$_{29}$H$_{25}$BrN$_2$O$_4$S
IR(CHCl$_3$, cm^{-1})	977, 1071, 1216, 1415, 1587, 1690, 1745, 2400, 3019.
^{1}H NMR (CDCl$_3$, 500 MHz)	2.2(3H, s); 2.4 (1H, t, J= 9.9 Hz); 3.1 (1H, dd, J=9.9 Hz, 10.33 Hz); 3.8 (1H, d, J= 5.57 Hz); 4 (2H, m); 5 (1H, d, J= 15.1 Hz); 6.1 (1H, d, J= 5.17 Hz); 6.5 (1H, s); 7.4 (10H, m); 7.6(2H, d, J= 8.3 Hz); 7.8 (2H,d, J=8.3 Hz)
^{13} C NMR (CDCl$_3$, 50 MHz)	20.73, 37.02, 46.91, 57.90, 61.60, 65.74, 74.17, 128, 136, 142, 160.51, 170.15, 195.18.
Mass (m/z)	565, 466, 404, 392, 355, 334, 325, 309, 291, 279, 261, 243.

Analysis:

	Carbon	Hydrogen	Nitrogen	Sulphur	Bromine
Calc.:	59.47	4.46	4.95	5.67	14.13
Found:	59.08	4.41	4.75	5.32	13.98

6. 6-Benzyl-5 oxa-3 phenyl-tetrahydro-imidazo[1,5-*c*]thiazole-7-carboxylic acid (12) [8]
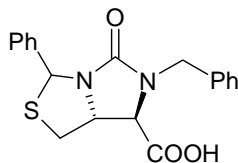
To an alkaline solution of methanol (0.336g, 6 mmol of KOH was dissolved in 10 mL of methanol) was added compound **16** (1g, 2 mmol). The solution was cooled to 0 ^{o}C and then 70% *t*-butylhydrogen peroxide (0.216 g, 2.4 mmol) was added dropwise. The reaction mixture was stirred for an additional 30 min. After stirring for 30 min the methanol was removed and the aqueous layer was extracted with ethylacetate. Organic layer and aqueous layers were separated.

The aqueous layer was acidified to pH 3 and extracted with ethylacetate. Evaporation of the solvent under reduced pressure furnished 6-benzyl-5-oxa-3-phenyl-tetrahydro-imidazo[1,5-c]thiazole-7-carboxylicacid   (0.280 g, 1.5 mmol) in 75% yield.

Yield	0.280 g
MP	183 ^{o}C (Lit 183 ^{o}C)
Mol Formula	$C_{19}H_{18}N_2O_3S$
IR(CHCl$_3$, cm^{-1})	1013, 1215, 1296, 1587, 1681, 2560, 3019.
^{1}H NMR (CDCl$_3$, 200 MHz)	2.49 (1H, m); 3.09 (1H, m); 3.72 (1H, s); 4.07 (2H, m); 5 (1H, d, J=14.8 Hz); 7.25 (10H, m).
^{13}C NMR (CDCl$_3,$ 75 MHz)	36.92, 46.11, 58.17, 62.54, 65.04, 128.08, 160.39, 171.75.
Mass (m/z)	355, 325, 243, 165, 149, 131.

7. 6-Benzyl-5 oxa-3 phenyl-tetrahydro-imidazo[1,5-*c*]thiazole-7-carboxylic acid ethyl formate. (21) [8]
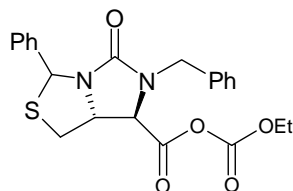
Ethyl chloroformate (0.170 g, 1.8 mmol) was added to a solution of (0.535 g, 15 mmol) of 1,3-dibenzyl-2-oxo-5-mercaptomethyl-imidazoline-4-carboxylic acid in a mixture of 5 ml of DCM and pyridine (0.142 g, 1.8mmol) at 5 $^{\circ}$C and the mixture was stirred for 3 hours. Reaction was quenched with water. It was then washed twice with 5 ml of 1N hydrochloric acid at a time, dried over sodium sulphate, filtered and concentrated under reduced pressure to furnish 0.500 g of compound benzyl-5 oxa-3 phenyl-tetrahydro-imidazo[1,5-*c*]thiazole-7-carboxylic acid ethyl formate. (21)

Yield	0.5 g, (80%)
Mol Formula	$C_{22}H_{22}N_2O_5S$
IR(CHCl$_3$, cm^{-1})	1020, 1205, 1300, 1580, 1680, 1730, 1800, 2550, 3020.
^{1}H NMR (CDCl$_3$, 200 MHz)	1.3 (3H, m); 2.57(1H, m); 3.15 (1H, m); 3.79 (1H, m); 4.17(4H, m); 5.1 (1H, d, J=16 Hz); 6.45 (1H, s); 7.3 (10H, m).
[13] C NMR (CDCl$_3$, 75 MHz)	36.85, 46.1, 58, 61, 62, 65, 127, 135, 141, 159, 167.

Analysis:

	Carbon	Hydrogen	Nitrogen	Sulphur
Calc.:	61.96	5.20	6.57	7.52
Found:	61.77	5	6.35	7.32

8. 1,3-dibenzyltetrahydrothieno[3,4-*d*]imidazole-2(3*H*), 4-dione. (2) [8]
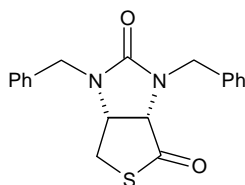
Compound **21**, (0.500 g) was refluxed with tributyltin hydride (0.500 g) and catalytic amount of AIBN (0.01g) in dry toluene. Reaction was monitored with TLC. After completion of the reaction pyridine was added and reaction mixture was further refluxed for 48 hours. Reaction was monitored by TLC. After completion of the reaction 10 % HCl (10 ml) was added to the reaction mixture. Organic layer was separated, dried over Na_2SO_4, solvent was removed under reduced pressure.The residue was chromatographed on silica gel, using Ethylacetate: Petether (9:1). 1,3-dibenzyltetrahydrothieno[3,4-*d*]imidazole-2(3*H*), 4-dione with a melting point of 120 ^{o}C was obtained.

Yield	0.045 g, (15%)
MP	120 ^{o}C (lit 121 ^{o}C)
Mol Formula	$C_{19}H_{18}N_2O_2S$
IR($CHCl_3$, cm^{-1})	1010, 1200, 1300, 1590, 1685, 1800, 2540, 3030.
^{1}H NMR (CDCl$_3$, 200 MHz)	3.3 (2H, m); 3.81(1H, d, J=8Hz); 4.1 (1H, m); 4.32 (2H, m); 4.7(1H, d, J=16Hz); 5 (1H, d, J=16 Hz); 7.3 (10H, m).
^{13}C NMR (CDCl$_3$, 75 MHz)	32.41, 44.62, 45.62, 56.05, 62.66, 127.58, 137.3, 158.16, 205.69.
Mass (m/z)	338, 247, 156, 124, 96.

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2.1 Protecting Groups In Organic Chemistry :

2.1.1 Introduction

When a chemical reaction is to be carried out selectively at one reactive site in a multifunctional compound other reactive sites must be temporarily blocked. For this reason such blocking functions have been developed for nearly hundred years by numerous researchers of the disciplines of organic chemistry and consequently solutions to the existing problems were devised; making use of various synthetic transformations. It was Fischer, who among his many important contributions to chemistry, first realized that the application of protecting functions is often a necessity for a successful synthesis. Thus he introduced the isopropylidene acetal in carbohydrate chemistry[1] and for the first time used both the chloroacetyl moiety and a urethane, namely the ethoxycarbonyl group as *N*-terminal protection group in the selective synthesis of peptides. [2]

It was not until 1932, that the decisive break-through for the invention of easily and selectively removable protecting groups was achieved by the use of benzoyloxycarbonyl (Z, Cbz) group in peptide synthesis[3] and thereby opened up this new field of organic chemistry which has resulted in highly selective construction of polyfunctional molecules through the extensive use of protecting groups. The studies aiming at the successful total synthesis of pallytoxin[4] the most complex compound known to date, provide an impressive example of this. Today therefore, protecting group chemistry is more important than ever. [5]

2.1.2 Carbonyl protecting groups :

The carbonyl function as present in aldehydes and ketones is probably the most versatile functional group in organic chemistry and a great deal of work has been done on the protection and deprotection of aldehyde and ketone groups. In the course of complex syntheses, for instance in the total syntheses of natural products, carbonyl groups often must be protected against nucleophilic attack e.g. by organometallic compounds, reduction, oxidation and also deprotection by strong bases. To achieve this aim, the carbonyl functions generally are transformed into suitable acetals, thioacetals, hydrazones, oximes and cyanohydrins. In addition they can be converted to enamines, enol ethers and silylenol ethers. Most of the protecting groups can be removed by treatment with acids. In particular, the oxygen acetals and ketals are readily cleaved by acidic hydrolysis and are stable to

oxidants and heavy metal ions. In contrast, thioacetals are cleaved by a wide range of oxidants and under neutral conditions by mercury (II), silver (I) or copper (II) salts. Due to the pronounced differences in reactivity between the different carbonyl groups, in many cases a reactive carbonyl group may be protected selectively in the presence of less reactive one.

The order of reactivity of the carbonyl group in general is aldehydes (aliphatic > aromatic) > acyclic ketones and cyclohexanones > cyclopentanones > aromatic ketones.

The most commonly used protecting groups are the acyclic and cyclic acetals and the acyclic or cyclic thioacetals. These protecting groups have opened a field in the electrophilic substitution at the carbonyl carbon, "Umpolung of the reactivity," a general class of reactions in synthesis, consists of process which reverse temporarily the characteristic reactivity, nucleophilic or electrophilic, of an atom or group. One such process results in the transformation of the normally electrophilic carbon of a carbonyl group into a nucleophilic carbon. This inversion of the normal polarization of a functional group has come to be known as umpolung, introduced by Corey and Seebach. [6]

Generally the carbonyl compounds are protected in the presence of acids with an alcohol, diol, thiol or dithiol. The following lines are for the protection and deprotection of carbonyl compounds.

2.1.3 Oxathiolanes:

The properties of oxygen and sulfur compounds are combined in the cyclic 1,3-oxathiolanes. These are formed by acid catalyzed reaction of carbonyl compounds with mercaptoethanol to give corresponding 1,3-oxathianes. Due to combined properties of oxygen and sulfur acetals, they can be cleaved with mercury salts and are also labile towards acids than the sulfur analogs. (ease of deprotection O,O acetals > O, S acetals > S, S acetals).

Oxathioacetals have gained prominence as protecting group in functional group transformations, carbon-carbon bond formation by virtue of their stability and ability to act as an acyl anion equivalent.[7] Eliel has established the use of oxathiolanes as acyl anion equivalent for the synthesis of chiral alcohols.

The electronegativity of oxygen naturally polarizes the carbonyl group so that the carbon atom is electrophilic and provides acylation (C), however generation of the subsequent anion (D) i.e. acyl anion is difficult under normal circumstances.

Scheme 1

But reversal of this natural polarity of masked carbonyl groups lead to formyl (CH=O) and acyl (RC=O) anions. As indicated in scheme 2, the sulfur stabilized anionic reagents are equivalent to acyl anions which implies that they can be used effectively to reverse the characteristic electrophilicity of a carbonyl carbon (symmetrization of reactivity, reversible umpolung).

Protected carbonyl group is acyl anion equivalent or metalated masked carbonyls, which can react with various electrophiles. These acyl anion equivalents are responsible for the formation of additional asymmetric centre in the molecule.

2.1.4 Preparation of Oxathiolanes:

Oxathiolanes can be prepared by a variety of different methods: for example , by treating aldehyde or ketone with 2-mercaptoethanol in the presence of mild catalyst, $ZnCl_2$ and sodium sulphate, [8] TMSCl-NaI, [9] SO_2, [10] trimethylsilyl triflate, [11] silyl ethers and phenyl sulfide. [12] Most commonly used method is use of one equivalent of boron trifluoride to equimolar mixture of carbonyl compound and 2-mercaptoethanol in ether. [13]

All oxathioacetals were prepared by using boron trifluoride and characterized by IR, ^{1}H-NMR, and Mass spectra. IR spectrum showed the absence of carbonyl absorption. In ^{1}H-NMR, the signals at δ 3 is the indication of protons adjacent to sulphur atom and at δ 4 are the indication of protons adjacent to oxygen atom.

2.1.5 Deprotection of Oxathiolanes:

The standard method for the deprotection of oxahiolanes is the acid-catalysed hydrolysis. Deprotection of 1,3-oxathiolanes using Raney Nickel [14] needs harsh conditions and is contaminated with by products in some cases because of radical reaction pathway. Hydrolysis by mineral acids requires drastic conditions to give the ketones in moderate yields. [15] Reaction using isoamyl nitrite [16] or chloramine T [17] afford the parent carbonyl compound under mild reaction conditions. The Corey's method (NCS-AgNO₃) [18] which was applied for deprotection of 2-hydroxy-alkyl-1,3-oxathiolanes furnished the desired alpha hydroxyl aldehydes in moderate yields (62-65%). The use of conventional mercuric chloride for the deprotection of the same type of 1,3-oxathiolane gave the corresponding aldehyde in 54% yield. [19] A variety of 2-substituted 1,3-oxathiolanes were deprotected to carbonyl groups and phenylvinyl sulfides with benzyne induced fragmentation. [20] Benzyne was generated by decomposing 2-carboxybenzene diazonium chloride in the presence of propylene oxide (HCl scavenger). A recent method uses silvernitrite-iodine system for the deprotection of oxathiolanes. [21] Deprotection of oxathiolanes using cat. TMSOTf and in presence of p-nitrobenzaldehyde and polymer supported nitrobenzaldehyde to carbonyl group (scheme 2) in high yields has been reported by our group. [22a] In both the cases equivalent amount of oxathiolane of p-nitrobenzaldehyde is formed as a byproduct, which

was separated by column chromatography. A late study on deprotection of oxathioacetals from our group also reported facile deprotection of activated oxathioacetals by use of TMSOTf alone. [22b] Since one equivalent of p-nitrobenzaldehyde was sacrificed for converting one equivalent of oxathiolane, it was felt necessary to devise a protocol for regeneration of p-nitrobenzaldehyde from its oxathiolane efficiently without the use of heavy metals as oxidants. Hence H_2O_2 in acetonitrile was used for deprotection of oxathiolane of *p*-nitrobenzaldehyde, which has been published recently. [23]
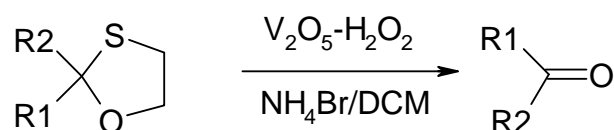
Ref: J. Chem. Soc. Perkin Trans. 1, **2002**, 1026.
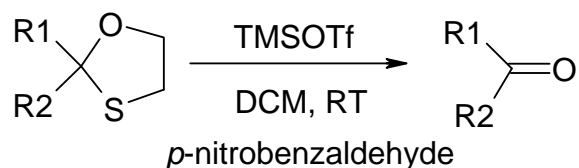
Ref : J. Chem. Soc. Chem. Commun. **1994**, 1937.

Scheme 2: Cleavage of oxathioacetals to carbonyl compounds

2.1.6 Present Work:

Oxathioacetals are frequently used to protect carbonyl compounds in the course of total syntheses and hence several reagents[24] have been developed for their deprotection to this end. Some of them include mercuric cyanide, [25] SeO_2/H_2O_2. [26] However most of these methods involve use of toxic, corrosive reagents and oxidants in anhydrous solvents at elevated temperature. Despite the growing awareness of the need for "green chemistry" many chemists still use environmentally unacceptable reagents and sophisticated conditions. The identification of a mild and chemoselective glyoxylic acid and Amberlyst-15 [27] for the deprotection of oxathioacetals formed the basis of this investigation. Glyoxylic acid is readily available at low cost and requires no special handling.

2.1.7 Results and Discussion:

This section deals with our efforts towards development of efficient protocol for the deprotection of oxathioacetals.

Oxathioacetals are efficiently deprotected by an equilibrium driven exchange with glyoxylic acid in the presence of Amberlyst-15 as the catalyst both under microwave conditions as well as at room temperature

R, R$_1$ = Alkyl, Aryl, H
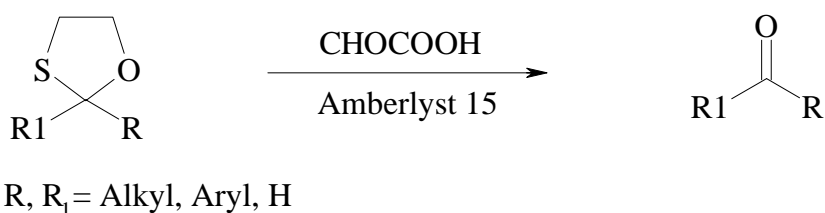
Scheme 3: Cleavage of oxathioacetals using glyoxalic acid and Amberlyst-15

Microwave enhanced reactions due to their efficiency, short time and operational simplicity have gained in popularity. Our group has recently published [28] Wolf rearrangement by using microwave. The origin of the heating effect [29] produced by the microwaves arises from the ability of an electric field to exert a force on charged particles. When a substance or molecule is irradiated with microwaves it rotates to align itself with the applied field. The frequency of molecular rotation is similar to the frequency of microwave radiation and consequently the molecule continually attempts to realign itself with the changing field and energy is absorbed.
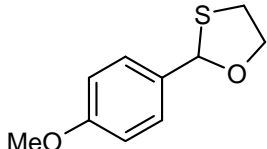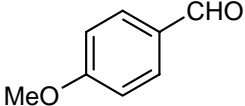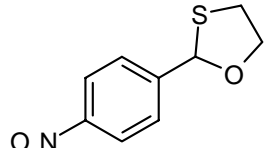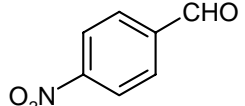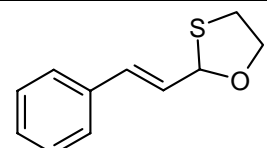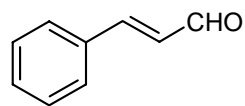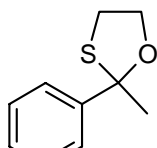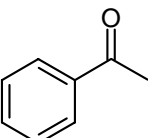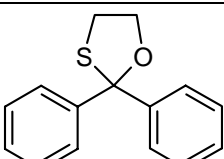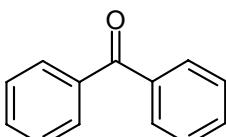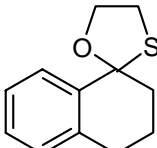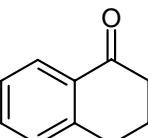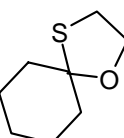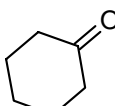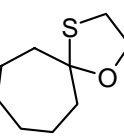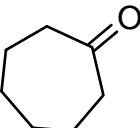
In liquid systems, microwave primarily heat a material by inducing rotation of polar molecules to align and relax at a given frequency, in the field of the electromagnetic radiation. It is the energy dissipated during such collisions that leads to the heating effect. So when a solvent is heated using microwaves, the heat is generated within the reaction medium rather than being transferred from an external source. This leads to a situation where the reaction medium is hotter than the walls of the vessel, resulting in non-nucleated super heating of the reaction medium.
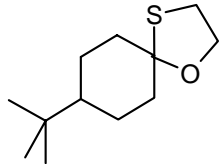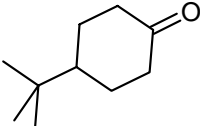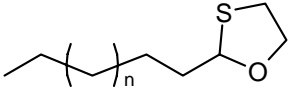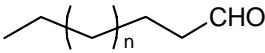
Under such conditions, the reaction can exist at temperatures above its boiling point without physical boiling, even in an open system. As the temperature increases, the rate of reaction increases and it is this effect, coupled with the efficient heating processes induced by microwaves, that leads to the many observed enhancements in reduced reaction times, increased yield and improved extraction efficiency.

We have found a distinct rate enhancement under microwave conditions where reactions were completed in just 1 to 3 min as compared to few hours required at room temperature. The experimental procedure is very simple and involves stirring the oxathioacetal (1 mmole) with glyoxylic acid (10 mmole) and Amberlyst 15 (0.125g) in open vessel at room temperature for few hours or irradiating in a domestic microwave oven for few minutes. The reaction is fast and the product is isolated by a simple aqueous workup. A wide variety of oxathioacetals derived from ketones and aldehydes were shown to undergo facile deprotection under these conditions **table 1**. Oxathioacetal of cycloheptanone was deprotected in 3 min in microwave oven. The cycloheptanone thus obtained was characterized by IR and ^{1}H NMR. In IR spectra peak at 1710 cm^{-1}, confirmed the presence of carbonyl group and peak at δ 2.4 for 4 H atoms adjacent to carbonyl group in ^{1}H NMR and absence of peaks in region δ 3-4 clearly indicate deprotection of oxathiolane.

From the table it is evident that oxathioacetals of ketones in conjugation with arene ring are deprotected faster than normal ketones. Oxathioacetals of aromatic aldehydes are deprotected with equal ease, **table 1** (entries 1, 2, 3) . It is observed that electron donating substituents on the arene ring (entry 1) facilitate oxathioacetal deprotection whereas electron withdrawing substituents (entry 2) retard it. However, this has no detrimental effect on the yield of the product. As expected oxathioacetals of aliphatic aldehydes were resistant to the reagent at room temperature, however, the reaction proceeds only at high temperature (entry 10).

Table 1: Deprotection of oxathioacetals :

N	Substrate	product	Th T/hr	Th Yield	MW T/min	MW Yield
1			6	92	1	94
2			7	93	2	95
3			7	92	1.5	93
4			7	93	1.5	94
5			7	93	1.5	93
6			7	94	2	94
7			10	92	3	94
8			10	93	3	94

9			10	94	3	94
10		.CHO	3 [a]	80	6	78

a = at 80 $^{\circ}$C, n = 5

2.1.8 Conclusion :

A mild and highly efficient transformation of oxathioacetals to the corresponding carbonyl compounds was achieved. This protocol is metal free, high yielding, fast, clean, safe and inexpensive and hence a "green" one.

2.2 Deprotection of acetals:

2.2.1 Introduction :

The protection-deprotection sequence is probably the most encountered functional group transformation in organic synthesis. Among the plethora of groups typically employed for protecting aldehydes and ketones, cyclic acetals and ketals enjoy a cardinal position, as exemplified by the numerous and ingenious methods devised for their attachment and removal. Some examples include p-TsOH/acetone, [30a] TiCl$_4$/LiI, [30b] HClO$_4$/CH$_2$Cl$_2$, [30c] LiCl/DMSO[30d] and Pd. [30e] However, many of these methods involve, use of corrosive reagents and require the reactions to be performed at elevated temperatures. Hence several milder methods that use neutral conditions have also been developed. [31] These include the use of phosphorous iodides, [32] transition metals and other Lewis acids, [33] oxidative methodologies [34] and other generally less acidic techniques; each of which have their own respective strengths. Selective methods for cleavage of acetals in presence of other acid labile protective group such as TBDMS has also been reported by using FeCl$_3$ [35] and Bi(NO$_3$)$_3$ [36] but latter is restricted to acyclic acetals. These methods lead to poor yields in cases where acetals that are not in conjugation with double bond or arene ring. All of the systems developed to date show some practical or synthetic limitations including the use of inaccessible or sensitive reagents, harsh or toxic reaction conditions or utility with a limited range of substrates.
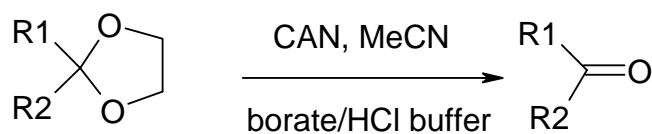
Ref : Angew. Chem. Int. Ed. **1999**, *38*, 3207
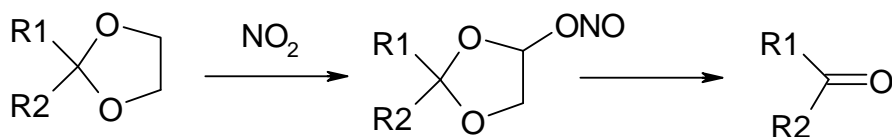
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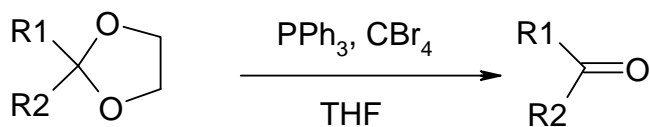
Ref: Chem. Commun. **1996**, 341.

Scheme 4

2.2.2 Present Work :

The identification of a mild and chemoselective aqueous glyoxylic acid for the deprotection of acetals formed the basis of this investigation. Organic reactions in water without the use of any harmful organic solvents are of great current interest, because water is an easily available, economical, safe, and environmentally benign solvent. Glyoxylic acid is readily available commercially as 50% aqueous solution and can be used as such.

Intrigued by the presence of bifunctionality *viz* acid as well as reactive aldehyde in glyoxylic acid, which is incidentally the smallest bifunctional organic molecule, it was anticipated that both the functionalities could be utilized and exploited for functional group transformations of carbonyl compounds. The activated aldehyde could serve as an excellent acceptor in the presence of the internal acid and would be able to transform acetals to the corresponding carbonyl compounds was the premise of this study. We wish to report that glyoxylic acid is an efficient reagent for the selective deprotection of acetals derived from ketones and aldehydes.

2.2.3 Results and Discussions :

The experimental procedure is very simple and involves stirring the acetal with 50% glyoxylic acid at room temperature.

R, R' = alkyl, aryl, H

Scheme 5
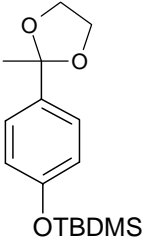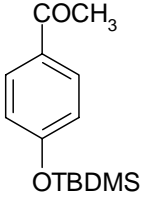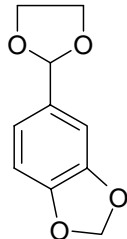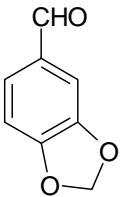
The reaction is fast and product is readily isolated by a simple work up. Glyoxylic acid is commercially available as 50% aqueous solution and requires no special handling.

The reactions are performed in aqueous medium without using any additional organic solvent. The results of this study are summarized in **table 2**.
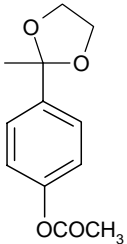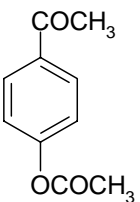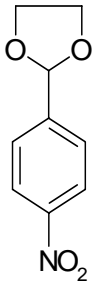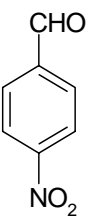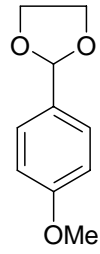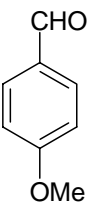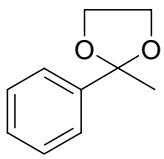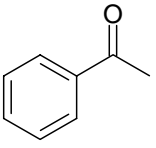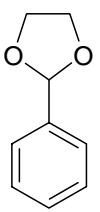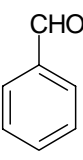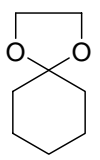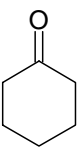
From **table 2,** it is evident that the acetals derived from aromatic as well as simple ketones were smoothly deprotected at room temperature. The acetals derived from aldehydes in conjugation with double bond or arene ring also underwent deprotection with equal ease. Lack of reactivity was observed with t-butyl dimethyl silyl (TBDMS) ethers derived from phenols. To demonstrate the chemoselectivity of this reagent we prepared the TBDMS ether (entry 1). Methylenedioxy ether (entry 2) and OAc (entry 3) are also stable under these reaction conditions. Mildness of our methodology is evident in selective deprotection of acetals in the presence of silyl ethers.
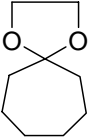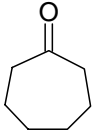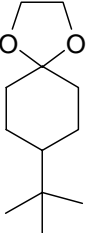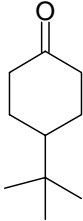
However when THP ethers and oximes were exposed to glyoxylic acid, they got deprotected with equal ease and it was not possible to deprotect acetals selectively in the presence of these functionalities. Due to the ease with which oximes got deprotected we explored our method further for the deprotection of oximes and THP ethers.

Table 2: Deprotection of acetals.

No.	Substrate	Product	T/h	Yield
1			1	95
2			1	96

3			1	94
4			1.2	93
5			1	95
6			1	93
7			1	92
8			1.5	91

| 9 | | | 1.5 | 92 |
| 10 | | | 1.5 | 92 |

2.2.4 Conclusion :

Facile deprotection of acetals was achieved by using glyoxylic acid in aqueous medium. This method is solvent free, high yielding, fast, clean, safe and inexpensive. An exciting feature of this methodology is that acetals can be deprotected selectively in presence of other acid labile groups like OTBDMS.

2.3 Deprotection of oximes :

2.3.1 Introduction:

Oxime derivatives are often used to purify, characterize and protect aldehydes and ketones, so the regeneration of the parent carbonyl compound is important. Oximes can also be synthesized from non-carbonyl compounds and thus their conversion to carbonyl compounds constitutes a useful synthesis of the latter. [37] The classical method for deprotection of oximes viz. hydrolytic cleavage requires the use of strong mineral acids. Although literature enumerates quite a number of methods for the conversion of oximes into carbonyl groups, careful scrutiny of the reaction procedures reveals some shortcomings or other in most of the procedures. Benzaldoxime for example [38] was deoximated in poor yield by PCC, [39] in 35 % yield by PCC-H$_2$O$_2$, [40] in 56 % yield by triethyl ammonium chlorochromate [41] and in 72 % yield by chromic anhydride-chlorotrimethyl silane. [42] Methods so far developed to regenerate carbonyl compounds from oximes consist of acid catalysed [43] or oxidative [44] or reductive reactions. [45] Most of the methods involve reagents that are often hazardous or very toxic, expensive or not readily available. [46-56] They need to be freshly prepared or the reaction require drastic conditions, long reaction times and tedious work up. With increasing environmental concerns, it is imperative that new environment friendly reagents be developed.
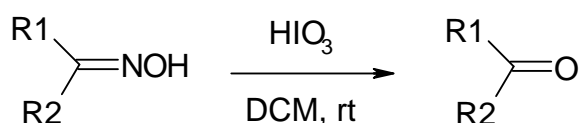
Ref : Tetrahedron Lett. **2002**, 43, 4023.
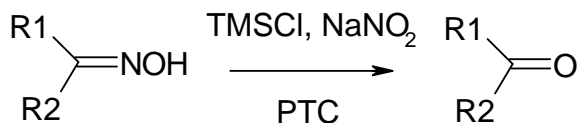
Ref : Tetrahedron Lett. **1990**, 43, 4023.

R1\R2C=NOH →[Raney nickel, boric acid][H_2/ acetone] R1\R2C=O
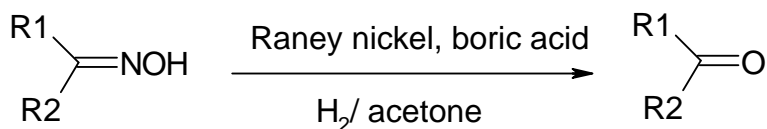
Ref : J. Org. Chem. **1984**, 49, 1654.

Scheme 6

2.3.2 Present Work:

In continuation of our work on deprotection of oxathioacetals we have observed that

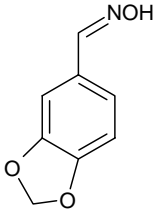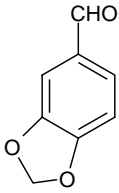R\R'C=N-OH →[CHOCOOH][RT] R\R'C=O
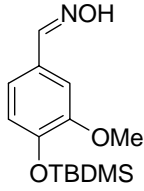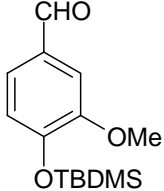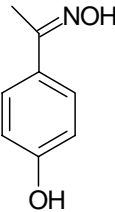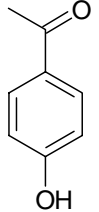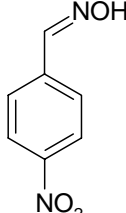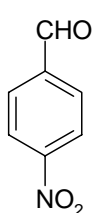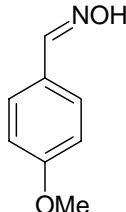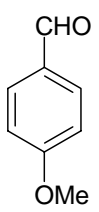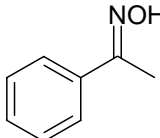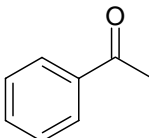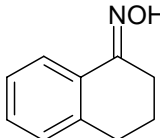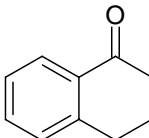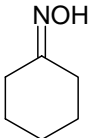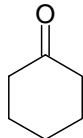
R, R' = alkyl, aryl, H
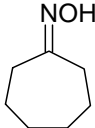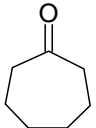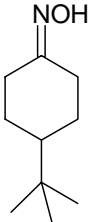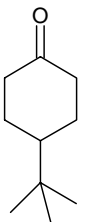
Scheme 7

glyoxylic acid is an efficient reagent for the selective deprotection of oximes derived from ketones and aldehydes **scheme 7**. The experimental procedure is very simple and involves stirring the oxime with 50% glyoxylic acid at room temperature. The reaction is fast and product is isolated by a simple aqueous work up. The reactions are performed in aqueous medium without using any additional organic solvent. The carbonyl compounds thus obtained were sufficiently pure and required no additional purification. The results of this study are summarized in **table 3**.

Oximes derived from aromatic as well as simple ketones were smoothly deprotected at room temperature. Mildness of our methodology is evident in selective deprotection of oximes in the presence of silyl ethers. We were able to selectively deprotect the oxime group without affecting the TBDMS group in almost quantitative yield (entry 1). Thus this method can be used to selectively deprotect oximes in presence of TBDMS ether in a multifunctional compound.

Table 3: Deprotection of oximes.

No	Substrate	Product	t/h	Yield
1			1	96
2			1	94
3			1.2	94
4			1	95
5			1	94
6			1	94
7			1.5	93

8			1.5	92
9			1.5	90
10			1	92

2.3.3 Conclusion :

A mild and highly efficient transformation of oximes to the corresponding carbonyl compounds was achieved in aqueous medium. The present protocol can be used for the deprotection of oximes of complex and sensitive molecules. The chemoselectivity of the present protocol can be used to deprotect oximes in the presence of other labile functionalities like OTBDMS.

2.4 Deprotection of THP ethers :

2.4.1 Introduction :

The protection and deprotection of alcohols is a common event in a multi-step organic syntheses and tetrahydropyranylation (THP) is one of the most frequently employed methods. The THP ethers are attractive because they are less expensive, easy to deprotect and are stable enough to strong basic media, oxidative conditions, reduction with hydrides and reaction involving Grignard reagents. Generally the methods used for the removal of THP ethers employ aqueous reaction media acidified with mineral acids, or non-aqueous media acidified with organic acids. [57] The weaker acids, invariably require higher temperature. [58] Other reagents for the hydrolysis of THP ethers are amberlyst-15, [59] $MgBr_2$, [60] Me_2AlCl, [61] $(NCSBu_2Sn)_2O$, [62] $PPh_3.Br_2$, [63] etc. There are few examples, which make use of aqueous, or nonaqueous neutral reaction conditions [64] and most of these methods involve some costly and toxic reagents or formation of considerable amount of side products. Corey *et. al.* has reported in a synthetic sequence [65] deprotection of THP ether by using acetic acid in THF-water. However this reaction is not generalized. Reaction conditions are mild as reaction is reported at 40 ^{o}C, but the time required for the reaction to go to completion is 40 hrs. The identification of a mild aqueous glyoxylic acid for the deprotection of THP ethers under solvent free conditions formed the basis of this investigation. Deprotection of THP ether is fast and goes to completion in few hours. 50% Aqueous solution of glyoxylic acid is environmentally benign reagent readily available at a low cost & is fairly stable.

$$\xrightarrow[\text{90 °C}]{\text{LiCl/DMSO}} \text{ROH}$$
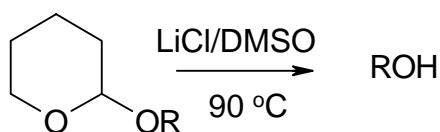
Ref: J. Org. Chem. **1996**, 61, 6038.

$$\xrightarrow[\text{MeOH}]{\text{AlCl}_3} \text{ROH}$$
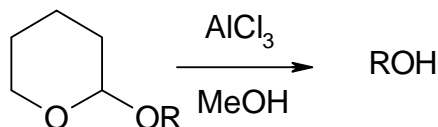
Ref: Tetrahedron Lett. **2002**, 43, 1143.

Scheme 8

2.4.2 Results and Discussions :

Glyoxylic acid is an efficient reagent for the deprotection of THP ethers. The experimental procedure is simple and involves stirring the THP ethers with 50% glyoxylic acid. The reaction is fast and product is isolated by a simple aqueous work up. Glyoxylic acid is commercially available as 50% aqueous solution and requires no special handling. The reactions are performed in aqueous medium without using any additional organic solvents. The hydroxyl compounds thus obtained were sufficiently pure and required no additional purification. The result of this study is summarized in **table 4**.
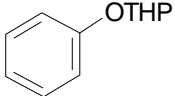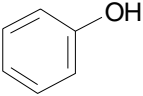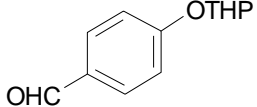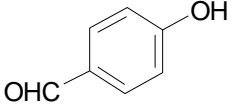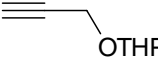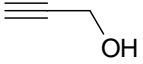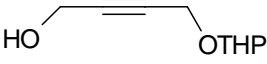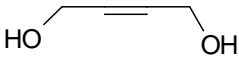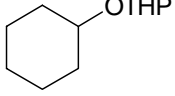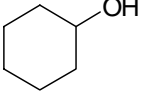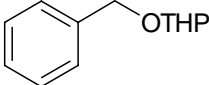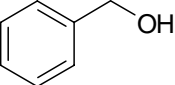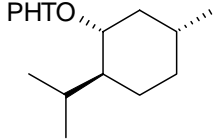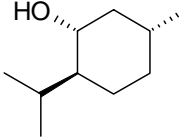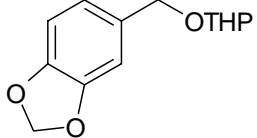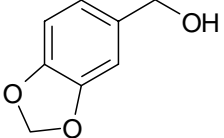
THP ethers derived from aromatic hydroxy group were smoothly deprotected at room temperatures, whereas, THP ethers derived from simple alcohols were deprotected only at elevated temperatures. Lack of reactivity was also observed with methylenedioxy ethers (entry 11).

$$\text{THP-O-R} \xrightarrow{\text{CHOCOOH}} \text{ROH}$$

R= alkyl, aryl
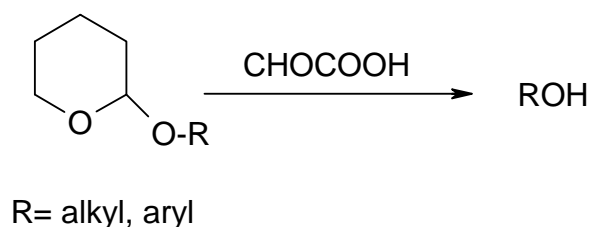
Scheme 9

Table 4: Deprotection of THP ethers

No.	Substrate	Product	Time h	Temp °C	Yield %
1			7	rt	90
2			7	rt	91

	Substrate	Product	Time	Temp	Yield
3	OTHP (phenyl)	OH (phenyl)	6	rt	90
4	OHC–C6H4–OTHP	OHC–C6H4–OH	7	rt	90
5	alkyne–CH2–OTHP	alkyne–CH2–OH	5	80	91
6	HO–CH2–C≡C–CH2–OTHP	HO–CH2–C≡C–CH2–OH	5	80	92
7	cyclohexyl–OTHP	cyclohexyl–OH	6	80	90
8	benzyl–OTHP	benzyl–OH	5	80	91
9	PHTO–menthyl	HO–menthyl	5	80	92
10	PHTO–[CH2]10–OTHP	HO–[CH2]10–OH	6	80	92
11	piperonyl–CH2–OTHP	piperonyl–CH2–OH	5	80	90

rt: room temperature

2.4.3 Conclusion :

Facile deprotection of THP ether was achieved by using glyoxylic acid in aqueous medium. Good to excellent yields of the alcohol were obtained. Short reaction time, higher yields and simple workup procedure are the main features of this method.

2.4.4 Experimental :

**General procedure for the preparation of oxathiolanes:**

To a stirred, refluxing solution of 25 mmol of carbonyl compound and 25 mmol of 2-mercaptoethanol in 20 ml anhydrous ether was added dropwise over 15 min period, 3.08 ml (25 mmol) of $BF_3.Et_2O$. After an additional hour of being heated under reflux, the solution was allowed to cool, washed with 20 ml of 0.1 M NaOH solution and once with 10 ml saturated brine and dried. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography.

**General procedure for deprotection of oxathioacetals :**

A mixture of oxathioacetal (10mmol) and glyoxylic acid (100mmol) with Amberlyst-15 (0.125 g) was stirred at room temperature or irradiated in microwave oven. Progress of the reaction was monitored by TLC. After the completion of the reaction, reaction mixture was extracted with ether. The ether extract was washed with 10ml $NaHCO_3$ (20%) solution and dried over anhydrous Na_2SO_4 and filtered. Evaporation of the solvent under reduced pressure gave pure carbonyl compound.

Following compounds were prepared and characterized according to above method:

1. Oxathiolane of *p*-methoxy benzaldehyde:
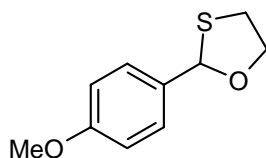
|	
Mol. Form	$C_{10}H_{12}OS$
IR (neat, cm^{-1})	845, 940, 1020, 1160, 1220, 1460, 1510, 1580, 1600, 2850, 2900.
^{1}H NMR (200 MHz, CDCl$_3$)	3 (m, 2H); 3.76 (s, 3H); 3.8 (m, 1H); 4.4 (m, 1H); 5.96 (s, 1H); 6.8 (m, 2H); 7.23 (m, 2H).

2. Oxathiolane of *p*-nitobenzaldehyde
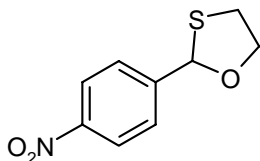
|	
Mol. Form	$C_9H_9NO_3S$
IR (neat, cm^{-1})	835, 860, 985, 1020, 1225, 1350, 1530, 1615, 2890, 3040
^{1}H NMR (200 MHz, CDCl$_3$)	3.25 (m, 2H); 4 (m, 1H); 4.55 (m, 1H); 6.1 (s, 1H); 7.6 (m, 2H); 8.6 (m, 2H).
Mass (m/z)	211, 89, 77, 60

3. Oxathiolane of cinnamaldehyde:
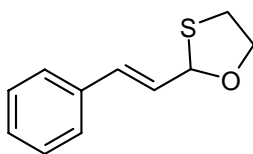
|	
Mol. Form	$C_{11}H_{12}OS$
Pale yellow liquid	
IR (neat, cm^{-1})	540, 700, 770, 970, 1060, 1140, 1210, 1270, 1450, 1500, 1600, 2860, 2930, 3020.
^{1}H NMR (200 MHz, CDCl$_3$)	3.2 (m, 2H); 3.9 (m, 1H); 4.4 (m, 1H); 5.7 (m, 1H); 6.3 (m, 1H); 6.7 (m, 1H); 7.3 (m, 5H).

4. Oxathiolane of acetophenone [66]
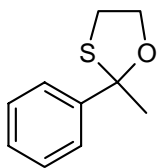
| Mol. Form	$C_{10}H_{12}OS$
Colourless liquid	
IR (neat, cm^{-1})	870, 920, 1030, 1070, 1100, 1220, 1310, 1380, 1440, 1610, 2860, 2960, 3080.
^{1}H NMR (200 MHz, CDCl$_3$)	1.88 (s, 3H); 3 (m, 2H); 4 (m, 2H); 7.3 (m, 5H).
Mass (m/z)	180, 165, 149, 133, 121, 115, 105, 91, 77, 69, 60, 51.

5. Oxathiolane of benzophenone [66]
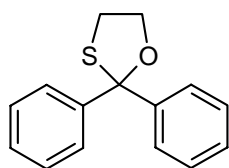
Mol. Form	$C_{15}H_{14}OS$
Viscous liquid	
IR (neat, cm^{-1})	925, 1030, 1065, 1110, 1315, 1485, 1620, 2860, 2980
^{1}H NMR (200 MHz, CDCl$_3$)	3 (s, 2H); 4.03 (t, 2H); 7.3 (m, 10H).

6. Oxathiolane of tetralone
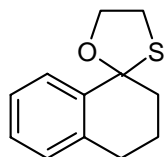
Mol. Form	$C_{12}H_{14}OS$
Colourless viscous liquid	
IR (neat, cm^{-1})	835, 945, 1070, 1155, 1275, 1380, 1450, 2860, 2930.
^{1}H NMR (200 MHz, CDCl$_3$)	1.71 (m, 4H); 2.4 (m, 2H); 3 (m, 2H); 4 (m, 1H); 4.36 (m, 1H); 7 (m, 3H); 7.3 (m, 1H).

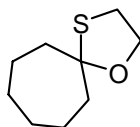**7**. Oxathiolane of cyclohexanone [66]
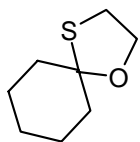
Mol. Form	$C_8H_{14}OS$

Pale yellow liquid

IR (neat, cm^{-1})   580, 620, 780, 1080, 1180, 1250, 1280, 1350, 1450, 2980

^{1}H NMR (200 MHz, CDCl$_3$)   1.5 (m, 6H); 2.1(m, 4H); 3.1(t, 2H); 4.25 (t, 2H).
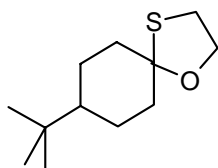
8. Oxathiolane of cycloheptanone [66]

Mol. Form	$C_9H_{16}OS$

IR (neat, cm^{-1})   540, 760, 860, 960, 1030, 1070, 1160, 1200, 1230, 1270, 1360, 1460, 2850, 2920.

^{1}H NMR (200 MHz, CDCl$_3$)   1.5 (m, 8H); 2 (m, 4H); 3(m, 2H); 4.8(m, 2H).

Mass(m/z)   172, 165, 157, 144, 129, 115, 102, 95, 89, 79, 68.

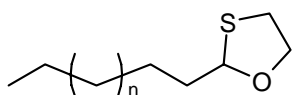**9**. Oxathiolane of *p tert*-butyl cyclohexanone:

Mol. Form	$C_{12}H_{22}OS$

Viscous liquid

IR (neat, cm^{-1})	550, 640, 820, 840, 920, 1060, 1080, 1150, 1300, 1450, 2840.
^{1}H NMR (200 MHz, CDCl$_3$)	0.75 (m, 9H); 1.6 (m, 7H); 3 (m, 2H); 4.1 (m, 2H)

10. Oxathiolane of decanal

Mol. Form	C$_{12}$H$_{24}$OS
Colourless liquid	
IR (neat, cm^{-1})	550, 650, 820, 960, 1030, 1100, 1170, 1200, 1230, 1480, 2930
^{1}H NMR (200 MHz, CDCl$_3$)	1.3 (m,19 H); 3.2 (m,2H); 4.0 (m,1H); 4.5 (m,1H); 5.2 (m, 1H)

General procedure for preparation of acetals :

25 mmol of carbonyl compound and 25 mmol of ethylenediol in 50 ml anhydrous benzene and catalytic amount of *p*TSA was refluxed in an round bottom flask with Dean-Stark reflux condenser for 6-8 hours. Reaction was monitored by TLC. After completion of the reaction, reaction mixture was quenched with NaHCO$_3$ solution. The organic layer was separated, dried over anhydrous Na$_2$SO$_4$, filtered and the solvent was removed under reduced pressure and the crude residue was purified by column chromatography.

General procedure for deprotection of acetals :

A mixture of acetal (10 mmol) and 50% glyoxylic acid (10 ml) was stirred at room temperature. Progress of the reaction was monitored by TLC. After the completion of the reaction, reaction mixture was extracted with ether. The ether extract was washed with 10 ml NaHCO$_3$ (20%) solution and dried over anhydrous Na$_2$SO$_4$ and filtered. Evaporation of the solvent under reduced pressure gave pure carbonyl compound.
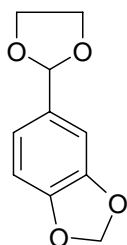
1. tert-Butyl-dimethyl-[4-(2-methyl-[1,3]dioxolane-2-yl)-phenoxy]-silane.

Mol. Form	$C_{16}H_{26}O_3Si$

Colourless liquid

IR (neat, cm^{-1}) 560, 820, 910, 1017, 1060, 1090, 1217, 1276.

^{1}H NMR (200 MHz, CDCl$_3$) 0.1 (m,6H); 0.9 (m, 9H); 1.5 (s, 3H); 3.6 (s, 2H); 3.9 (s, 2H); 6.75 (m, 2H); 7.2 (m, 1H); 7.75 (m, 1H).
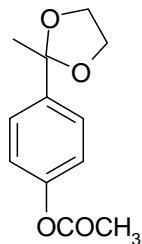
2. Acetal of piperonal
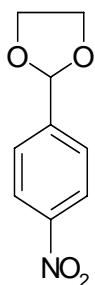

Mol. Form	$C_{10}H_9O_4$

Colourless liquid

IR (neat, cm^{-1}) 580, 920, 1030, 1130, 1380, 1400, 1510, 1610, 2940.

^{1}H NMR (200 MHz, CDCl$_3$) 4 (m, 4H); 5.7 (s, 1H); 5.9 (s, 2H); 6.8 (m, 3H).
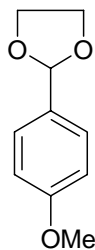
3. Acetic acid 4-(2-methyl-[1,3]dioxolan-2-yl)-phenyl ester.

Mol. Form $C_{12}H_{14}O_4$

IR (neat, cm^{-1})   780, 855, 910, 1200, 1460, 1510, 1600,

1730, 2960.

^{1}H NMR (200 MHz, CDCl$_3$)   1.5 (s, 3H); 2.1 (s, 3H); 3.6 (m, 2H); 3.8
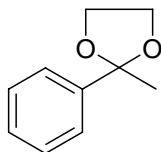
(m, 2H); 6.8 (m, 2H); 7.4 (m, 2H)

4. Acetal of *p*-nitro benzaldehyde

Mol. Form $C_9H_9NO_4$

IR (neat, cm^{-1}) $C_9H_9NO_4$

^{1}H NMR (200 MHz, CDCl$_3$)   4.1 (m, 4H); 5.9 (s, 1H); 7.6 (m, 2H); 8.25
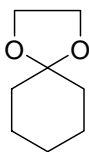
(m, 2H)

5. Acetal of *p*-methoxy benzaldehyde:

|	
Mol. Form	$C_{10}H_{12}O_3$
IR (neat, cm^{-1})	900, 980, 1046, 1216
^{1}H NMR (200 MHz, CDCl$_3$)	3.75 (s, 3H); 4 (s, 2H); 4.1 (s, 2H); 5.75 (s, 1H); 6.9 (m, 2H); 7.4 (m, 2H).

6. Acetal of acetophenone

|	
Mol. Form	$C_{10}H_{12}O_2$
IR (neat, cm^{-1})	1017, 1060, 1094, 1217, 1275
^{1}H NMR (200 MHz, CDCl$_3$)	1.6 (s, 3H); 3.75 (m, 2H); 4 (m, 2H); 7.4 (m, 5H)

7. Acetal of cyclohexanone.

Mol. Form	$C_8H_{14}O_2$
IR (neat, cm^{-1})	881, 944, 1041, 1085, 1215.9, 1384.5
^{1}H NMR (200 MHz, CDCl$_3$)	1.4 (m, 2H); 1.6 (m, 8H); 3.8 (s, 4H)

8.Acetal of cycloheptanone.
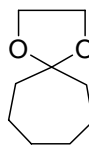
Mol. Form $C_9H_{16}O_2$

IR (neat, cm^{-1})   890, 940, 1100, 1215, 1390

^{1}H NMR (200 MHz, CDCl$_3$)   1.5-1.8 (m, 14 H); 3.9 (s, 4H)

9. Acetal of *p-tert* butyl cyclohexanone
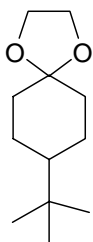
Mol. Form $C_{12}H_{22}O_2$

IR (neat, cm^{-1})   906, 945, 1038, 1103, 1216.8, 1366.

^{1}H NMR (200 MHz, CDCl$_3$)   0.75 (s, 9H); 1.25 (m, 2H); 1.5 (m, 2H);

   1.75 (m, 5H); 3.9 (s, 4H).

General procedure for preparation of oximes :

1gm of the carbonyl compound was stirred with 1 gm of hydroxylaminehydrochloride and 1 gm of pyridine in 5 ml of methanol, for 3-4 hours. Reaction was monitored by TLC.

After completion of the reaction, ice cold water was added in the reaction mixture. Oxime precipitated out was filtered and dried.

General procedure for deprotection of oximes :

A mixture of oxime (10 mmol) and 50% glyoxylic acid (10 ml) was stirred at room temperature. Progress of the reaction was monitored by TLC. After the completion of the reaction, reaction mixture was extracted with ether. The ether extract was washed with 10 ml NaHCO$_3$ (20%) solution and dried over anhydrous Na$_2$SO$_4$ and filtered. Evaporation of the solvent under reduced pressure gave pure carbonyl compound.

**1.** 4-(tert-Butyl-dimethyl-silanyloxy)-3-methoxy-benzaldehyde oxime.
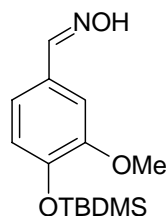
|	
Mol. Form	$C_{14}H_{23}NO_3Si$
Viscous liquid	
IR (CHCl$_3$, cm^{-1})	520, 870, 940, 1034, 1216, 1254, 1304, 1515, 1600, 3280.
^{1}H NMR (200 MHz, CDCl$_3$)	0.1 (m, 6H); 0.8 (m, 9H); 3.75 (s, 3H); 6.75 (m, 2H); 7.1 (m, 1H); 8 (s, 1H).

2. Oxime of *p*-methoxybenzaldehyde
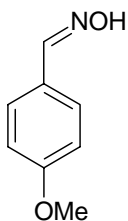
|	
Mol. Form	$C_8H_8NO_2$
MP.	50 ^{o}C
IR (CHCl$_3$, cm^{-1})	875, 954, 1032.4, 1173, 1216, 1254, 1304, 1515, 1608, 3305.
^{1}H NMR (200 MHz, CDCl$_3$)	3.8 (s, 3H); 6.9 (m, 2H); 7.5 (m, 2H); 8.1 (s, 1H).

3. Oxime of acetophenone
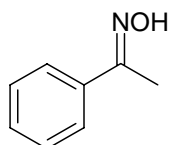
| Mol. Form	C_8H_9NO
M.P.	58 ^{o}C
IR (CHCl$_3$, cm^{-1})	924, 1005.7, 1080, 1217, 1302, 1370, 1446, 1498, 1633, 3303.
^{1}H NMR (200 MHz, CDCl$_3$)	2.25 (s, 3H); 7.3 (m, 3H); 7.5 (m, 2H).

4. Tetralone oxime
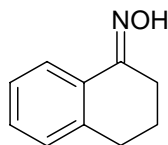
Mol. Form	$C_{10}H_{11}NO$
M.P.	90 ^{o}C
IR (CHCl$_3$, cm^{-1})	896, 992, 1216, 1449, 1664, 2860, 2936, 3246.
^{1}H NMR (200 MHz, CDCl$_3$)	1.5 (m, 6H); 2.1(m, 2H); 2.4 (m, 2H).

5. Oxime of cyclohexanone
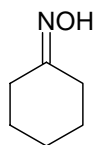
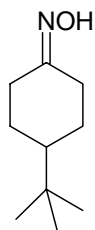| Mol. Form	$C_6H_{11}NO$
M.P.	90 ^{o}C
IR (CHCl$_3$, cm^{-1})	896, 992, 1216, 1449, 1664, 2860, 2936, 3246.
^{1}H NMR (200 MHz, CDCl$_3$)	1.5 (m, 6H); 2.1(m, 2H); 2.4 (m, 2H).

6. Oxime of cycloheptanone
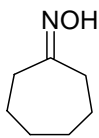
|	
Mol. Form	$C_7H_{13}NO$
M.P.	35 ^{o}C
IR (CHCl$_3$, cm^{-1})	990, 1216, 1360, 1630, 2869, 2957, 3017, 3260
^{1}H NMR (200 MHz, CDCl$_3$)	1.5 (m, 8H); 2.55 (m, 4H).

7. Oxime of *p-tert* butyl cyclohexanone

|	
Mol. Form	$C_{10}H_{18}NO$
M.P.	125-127 ^{o}C
IR (CHCl$_3$, cm^{-1})	668, 758.9, 988, 1215, 1367, 1660, 2870, 2955, 3018, 3270.
^{1}H NMR (200 MHz, CDCl$_3$)	0.75 (m, 9H); 1.2 (m, 3H); 1.5 (m, 1H); 1.9 (m, 3H); 2.4 (m, 1H); 3.25 (m, 1H).

8. Oxime of piperonal
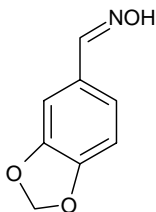
| Mol. Form	$C_8H_7NO_3$
M.P.	146 ^{o}C
IR (CHCl$_3$, cm^{-1})	669, 758, 1042, 1215, 1253, 1450, 1505, 1605, 3019, 3368.
^{1}H NMR (200 MHz, CDCl$_3$)	5.9 (s, 2H); 6.7-7.2 (m, 3H); 7.9 (s, 1H).

9. *p* acetoxy acetophenone

COCH$_3$

OCOCH$_3$
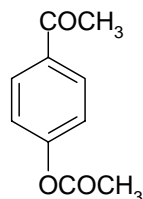
| Mol. Form	$C_{10}H_{10}O_3$
IR (CHCl$_3$, cm^{-1})	580, 720, 810, 920, 1020, 1050, 1250, 1300, 1400, 1620, 1720, 1750, 2900, 3020.
^{1}H NMR (200 MHz, CDCl$_3$)	2.25 (s, 3H); 2.6 (s, 3H); 7.2 (m, 2H); 8 (m, 2H).

10. *p* OTBDMS acetophenone
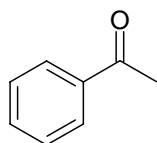
COCH$_3$

OTBDMS
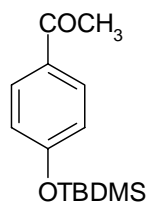
Mol. Form	$C_{14}H_{22}O_2Si$
IR (CHCl$_3$, cm^{-1})	580, 740, 820, 880, 1050, 1150, 1200, 1280, 1360, 1570, 1650, 1675, 1775, 3000, 3060.
^{1}H NMR (200 MHz, CDCl$_3$)	0.1 (s, 6H); 1 (s, 9H); 7 (m, 2H); 7.8 (m, 2H).

11. *p*-nitrobenzaldehyde:
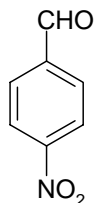
Mol. Form	$C_7H_5NO_3$
M.P.	105 ^{o}C
IR (CHCl$_3$, cm^{-1})	740, 820, 850, 1100, 1200, 1350, 1450, 1520, 1600, 1710, 2850, 3020
^{1}H NMR (200 MHz, CDCl$_3$)	8.07 (d, 2H, J= 8.6 Hz); 8.4 (d, 2H, J= 8.6 Hz); 10.16 (s, 1H).

12. *p*-methoxybenzaldehyde:
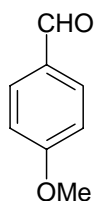
Mol. Form	$C_8H_8O_2$
IR (CHCl$_3$, cm^{-1})	840, 1180, 1210, 1350, 1510, 1600, 1690, 2840, 3010
^{1}H NMR (200 MHz, CDCl$_3$)	3.85 (s, 3H); 6.9 (d, 2H); 7.86 (d, 2H); 9.9 (s, 1H).

13. Acetophenone

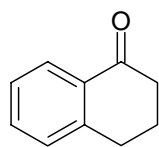| Mol. Form	C_8H_8O
IR (CHCl$_3$, cm^{-1})	580, 740, 820, 880, 1050, 1150, 1200, 1280, 1360, 1380 ,1450, 1570, 1650, 1775, 3000, 3060
^{1}H NMR (200 MHz, CDCl$_3$)	2.57 (s, 3H); 7.56 (m, 3H); 8(m, 2H).

14. Benzaldehyde
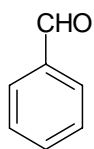
Mol. Form	C_7H_6O
IR (CHCl$_3$, cm^{-1})	780, 850, 880, 920, 1200, 1480, 1500, 1600, 1700, 2950.
^{1}H NMR (200 MHz, CDCl$_3$)	7.5-7.8 (m, 5H); 9.8 (s, 1H)

15.Tetralone

Mol. Form	$C_{10}H_{10}O$
IR (CHCl$_3$, cm^{-1})	880, 960, 1210, 1340, 1520, 1600, 1680, 1770, 3000.
^{1}H NMR (200 MHz, CDCl$_3$)	2.1 (m, 2H); 2.65 (t, 2H, J= 6.27Hz); 2.95 (t, 2H, t, 2H, J= 7Hz); 7.25 (q, 2H, J= 7Hz); 7.45 (dt, 1H, J=1Hz, 7Hz); 8 (dd, 1H, J=1Hz, 7Hz).

16.Cycloheptanone:
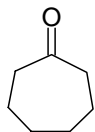
Mol. Form	$C_7H_{12}O$
IR (CHCl$_3$, cm^{-1})	820, 880, 910, 1050, 1120, 1410, 1710
^{1}H NMR (200 MHz, CDCl$_3$)	1.71 (s, 8H); 2.48 (m, 4H).

17. Cyclohexanone:

Mol. Form	$C_6H_{10}O$
IR (CHCl$_3$, cm^{-1})	720, 820, 860, 900, 1000, 1060, 1125, 1320, 1420, 1710, 2850, 3000
^{1}H NMR (200 MHz, CDCl$_3$)	1.7 (s, 6H); 2.5 (m, 4H).

18. *p t*-butyl cyclohexanone :
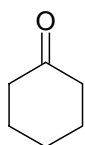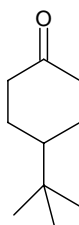

Mol. Form	$C_{10}H_{18}O$
IR (CHCl$_3$, cm^{-1})	720, 850, 1020, 1050, 1125, 1400, 1710, 2840, 3000.
^{1}H NMR (200 MHz, CDCl$_3$)	0.9 (s, 9H); 1.4 (m, 4H); 2.1 (m, 1H); 2.3 (m, 4H).

19. Piperonal:
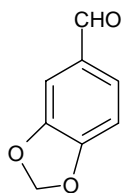
Mol. Form	$C_8H_6O_3$
IR (CHCl$_3$, cm^{-1})	810, 933, 1040, 1098, 1216, 1448, 1503, 1600, 1688, 2785, 2900, 3020
^{1}H NMR (200 MHz, CDCl$_3$)	6.1 (s, 2H); 6.9 (m, 1H); 7.3 (m, 2H); 9.8 (s, 1H).

20. Cinnamaldehyde:
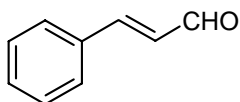
|	
Mol. Form	C_9H_8O
IR (CHCl$_3$, cm^{-1})	780, 980, 1080, 1200, 1450, 1510, 1620, 1690, 2920, 3020.
^{1}H NMR (200 MHz, CDCl$_3$)	6.7 (m, 2H); 7.5 (m, 5H); 9.7 (s, 1H).

**General procedure for preparation of OTHP ethers :**

1 mol of the hydroxyl compound was stirred with 1.2 mol of dihydropyrane and 0.01gm of *p*TSA in 25 ml dry DCM for 6-7 hours. Reaction was monitored by TLC. After completion of the reaction, reaction mixture was quenched with $NaHCO_3$ solution. Organic layer was separated, dried over $NaSO_4$, filtered and evaporated under reduced pressure. The crude residue thus obtained was purified by column chromatography.

General procedure for deprotection of OTHP ethers :

A mixture of OTHP ether (10 mmol) and 50% glyoxylic acid (10 ml) was stirred at room temperature (or refluxed at 80 ^{o}C). Progress of the reaction was monitored by TLC. After the completion of the reaction, reaction mixture was extracted with ether. The ether extract was washed with 10 ml $NaHCO_3$ (20%) solution and dried over anhydrous Na_2SO_4 and filtered. Evaporation of the solvent under reduced pressure gave pure carbonyl compound.

1. 2-p-Tolyloxy-tetrahydro-pyran
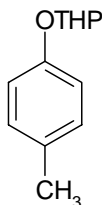
Mol. Form	$C_{12}H_{16}O_2$
IR (CHCl$_3$, cm^{-1})	967, 1036, 1124, 1220, 1355, 1442, 2871, 2945, 3347
^{1}H NMR (200 MHz, CDCl$_3$)	1.5 (m, 6H); 2.2 (s, 3H); 3.4 (m, 1H); 3.8 (m, 1H); 5.25 (s, 1H); 6.8 (m, 4H).

2. 2-Phenoxy-tetrahydro-pyran
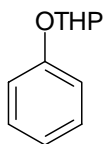
Mol. Form	$C_{11}H_{14}O_2$
IR (CHCl$_3$, cm^{-1})	1002, 1100, 1200, 1480, 1615, 2934
^{1}H NMR (200 MHz, CDCl$_3$)	2 (m, 6H); 3.6 (m, 1H); 4.1 (m, 1H); 5.5 (m, 1H); 7.3 (m, 5H).

3. 4-(Tetrahydro-pyran-2-yloxy)-benzaldehyde
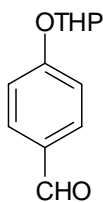
Mol. Form	$C_{12}H_{14}O_3$
IR (CHCl$_3$, cm^{-1})	960, 1026, 1112, 1350, 1440, 1770, 2870, 2957.
^{1}H NMR (200 MHz, CDCl$_3$)	1.5-2 (m, 6H); 3.7 (m, 2H); 5.5 (s, 1H); 7 (m, 2H); 7.8 (m, 2H); 9.9 (s, 1H).

4. 4-(Tetrahydro-pyran-2-yloxy)-but-2-yn-1-ol
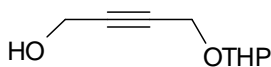
Mol. Form	$C_9H_{14}O_3$
IR (CHCl$_3$, cm^{-1})	666, 902, 1058, 1202, 1353, 1442, 1728, 2118, 2944, 3289.
^{1}H NMR (200 MHz, CDCl$_3$)	1.6 (m, 6H); 3 (s, 1H); 3.5 (m, 1H); 3.8 (m, 1H); 4.3 (m, 4H); 4.8 (s, 1H).

5. 2-Cyclohexyloxy-tetrahydro-pyran
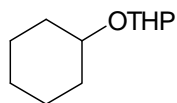
Mol. Form	$C_{11}H_{19}O_2$
IR (CHCl$_3$, cm^{-1})	570, 870, 967, 1036, 1124, 1220, 1355, 1442, 2870.
^{1}H NMR (200 MHz, CDCl$_3$)	1.5 (m, 16H); 3.5 (m, 2H); 3.8 (m, 1H); 4.75 (s, 1H).

6. 2-Benzyloxy-tetrahydro-pyran

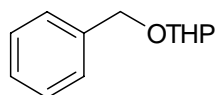|	
Mol. Form	$C_{12}H_{16}O_2$
IR (CHCl$_3$, cm^{-1})	590, 1020, 1208, 1384, 1454, 1496, 1606, 2870
^{1}H NMR (200 MHz, CDCl$_3$)	1.6 (m, 6H); 3.5 (m, 1H); 3.9 (m, 1H); 4.5 (m, 1H); 4.7 (m, 2H); 7.3 (m, 5H).

7. Di-OTHP of decandiol
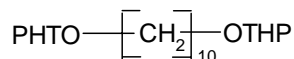
Mol. Form	$C_{20}H_{38}O_4$
IR (CHCl$_3$, cm^{-1})	590, 735, 860, 960, 1032, 1120, 1210, 1305, 1432.
^{1}H NMR (200 MHz, CDCl$_3$)	1.5 (m, 28H); 3.3 (m, 2H); 3.4 (m, 2H); 3.7 (m, 2H); 3.8 (m, 2H); 4.5 (s, 2H).

8. 5-(Tetrahydro-pyran-2-yloxymethyl)-benzo[1,3]dioxole
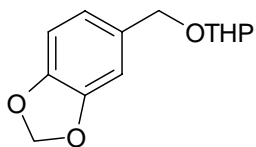
Mol. Form	$C_{13}H_{16}O_4$
IR (CHCl$_3$, cm^{-1})	1035, 1119, 1215, 1384, 1444, 1504, 1609, 945, 3017, 3436.
^{1}H NMR (200 MHz, CDCl$_3$)	1.6 (m, 6H); 3.5 (m, 1H); 3.9 (m, 1H); 4.45 (m, 1H); 4.65 (m, 1H); 5.9 (s, 2H); 6.75 (m, 3H).

9. Menthol-OTHP
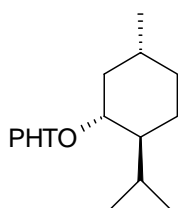
Mol. Form	$C_{15}H_{27}O_2$
IR (CHCl$_3$, cm^{-1})	560, 880, 900, 1020, 1220, 1360, 1435, 2860.
^{1}H NMR (200 MHz, CDCl$_3$)	1 (m, 12 H); 1.4 (m, 2H); 1.8 (m, 8H); 2.1 (m, 1.5 H); 2.4 (m, 0.5); 3.3 (m, 0.5); 3.5 (m, 1.5 H); 3.9 (m, 2H); 4.6 (s, 0.5H); 4.8 (s, 0.5H).

10. Phenol
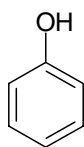
Mol. Form C_6H_6O

IR (neat, cm^{-1})   1044, 1384, 1596, 3020, 3435

^{1}H NMR (200 MHz, CDCl$_3$)   7.2 (m,5H).

11. p-Hydroxy benzaldehyde

OH

CHO
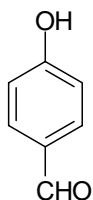
Mol. Form $C_7H_6O_2$

IR (neat, cm^{-1})   830, 1030, 1160, 1490, 1700, 2872, 3027,

3086.

^{1}H NMR (200 MHz, CDCl$_3$)   6.9 (m, 2H); 7.7 (m, 2H); 9.8 (s, 1H).

12. Propargyl alcohol

OH
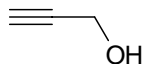
Mol. Form $C_3H_4O_2$

IR (neat, cm^{-1})   647, 915, 1028, 1229, 1417, 1634, 2120,

2928, 3294

^{1}H NMR (200 MHz, CDCl$_3$)   2.5 (s, 1H); 4.3 (m, 2H).

13. 2 Butyn 1,4 diol

HO   OH
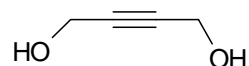
Mol. Form $C_4H_6O_2$

IR (neat, cm^{-1})   920, 1030, 1231, 1400, 1630, 3300.

^{1}H NMR (200 MHz, CDCl$_3$)   4.2 (s, 4H).

14. Benzyl alcohol
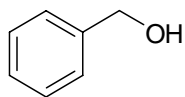
Mol. Form	C_7H_8O
IR (neat, cm^{-1})	735, 1021, 1079, 1208, 1454, 1496, 1606, 1811, 1952, 2874, 3087, 3341
^{1}H NMR (200 MHz, CDCl$_3$)	4.5 (s, 2H); 7.3 (m, 5H).

15. 1,10 Decane diol
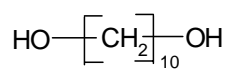
Mol. Form	$C_{10}H_{22}O2$
IR (neat, cm^{-1})	550, 910, 1020, 1230, 1417, 1600, 2870, 3300.
^{1}H NMR (200 MHz, CDCl$_3$)	1.3-1.5 (m, 16H); 3.6 (m, 4H).

16. Menthol
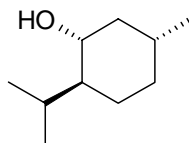
Mol. Form	$C_{10}H_{18}O$
IR (neat, cm^{-1})	555, 640, 910, 1230, 1415, 3290.
^{1}H NMR (200 MHz, CDCl$_3$)	0.9 (m, 6H); 1.6 (m, 1H); 1.9 (m, 1H); 2.2 (m, 1H); 3.4 (m, 1H)

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