SYNTHETIC STUDIES TOWARDS D(+)-BIOTIN AND DEVELOPMENT OF SOME USEFUL SYNTHETIC METHODOLOGIES

THESIS

SUBMITTED TO THE

UNIVERSITY OF PUNE

FOR THE DEGREE OF

DOCTOR OF PHILOSOPHY

(IN CHEMISTRY)

BY

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APRIL 2001

Form-A

CERTIFICATE

Certified that the work incorporated in the thesis entitled **"Synthetic Studies Towards D(+)-Biotin And Development Of Some Useful Synthetic Methodologies"** *by* ***Mr CH. AMAR GOPAL*** was carried out by him under my supervision. Such material as has been obtained from other sources has been duly acknowledged in the thesis.

April 2001
PUNE

S. P. Chavan
Research Guide

With Love

To My Parents

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Acknowledgements

It gives me great pleasure to express my deep sense of esteem and gratitude to my research guide, Dr. Subhash P. Chavan, for his inspiring guidance, never diminishing encouragement, support and his complete dedication during the progress of my work.

I am thankful to Dr. T. Ravindranathan (former head) Organic Chemistry: Technology division for his deep interest and valuable suggestions. I also thank Dr. M. K. Gurjar, Head, OCT for his valuable suggestions.

On a personal basis I am indebted to Dr. S. K. Kamat and Dr. Kalkote who had helped me all along to speed up my research work. My feelings go beyond limit to thank Mrs. Latha Sivadasan and Mrs. Kamalam Balakrishnan, for their affection, valuable help, suggestions and the memorable moments I shared with them during my stay at OCT division.

When it comes to friends, thank you seems a very simple word to envelope all the support and encouragement given to me by Tripura, Devadas, Raghunath, Ramesh, Srinivas Hotha, Geetha who had propped me up when I tended to lean during my trying times. Special thanks are due to Ramakrishna who had helped tremendously in the compilation of this thesis.

I would like to thank all my friends who brightened my gloomiest days by their presence especially Tejwani, Shubhada, Venkat, Ethiraj, Chitra, Anil, Sivappa, Shivasankar, Kharul, Ramesh kale, Pasupathy, Praveen, Shambhaji, Dushyant, Mahesh, Pallavi, Swapna, Sanjay, Vikas, Boddu Gowd, Sreekanth, Laha, Sahoo, Murugan, Adhikari, Subramanyam, my REC juniors Krishna, Eku, Nagaprasad, Subbarao, Vasudev, Mahesh, Siddarth, DPS Reddy, Sarita, Bulbule, Mahesh patil, Vishal Mahajan, Rajgopal, Sowmya, Eswar, Nirmalya, Anirban, Bhagawat.

I also take this opportunity to thank the senior scientists in our division Dr. V. H. Deshpande, Dr. (Mrs) R.D. Wakharkar, Bhanu Chanda, Dr. R. J. Lahoti, Dr. (Mr & Mrs) Joshi, Mr. I. Shivakumar, Dr. Borate and Mr. Ramalingam.

I would also like to acknowledge all the staff members of NMR, Microanalysis, Special Instruments Lab and also Library staff for their assistance during my course work.

This also gives me an opportunity to thank my sisters and brothers in law for their constant encouragement and my parents for their unstinting support.

Finally I thank CSIR, New Delhi, for financial support and also Dr. Paul Ratnasamy, Director NCL for allowing me to work here and submit my work in the form of this thesis.

NCL, Pune CH. Amar Gopal

General Remarks

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^{o}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

Abstract

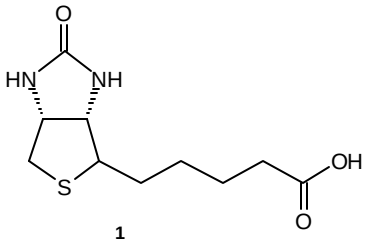
*The thesis entitled "**Synthetic Studies Towards D(+)-Biotin And Development of Some Useful Synthetic Methodologies**" is divided into two chapters. The first chapter with D(+)-biotin synthesis while the second chapter details development of some novel methodologies.*

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

Sec 1:

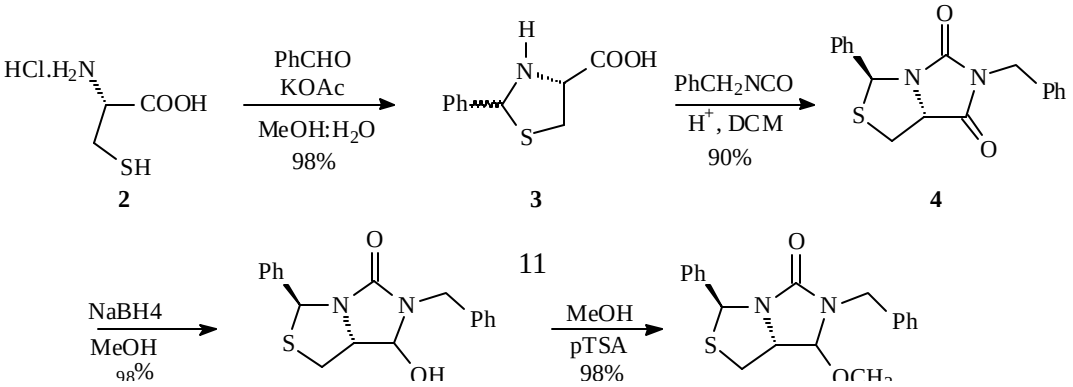


1

*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 synthesis of the compound to this date has been reviewed.*

***Sec 2:** Reductive cleavage of C-S bond of thiazolidine derivative **3** and its elaboration to D(+)-biotin:*

The main emphasis in this section are modification of our earlier 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., L-cysteine (**2**) and attempts to elaborate 5,5-fused system to D(+)-biotin.*

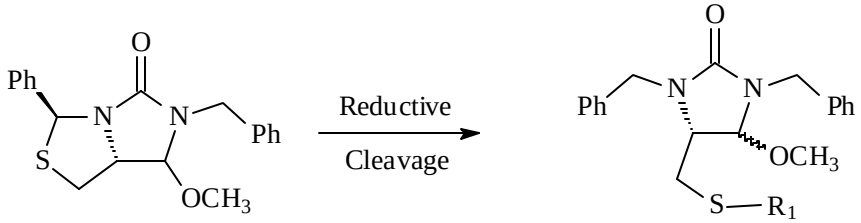
***Scheme 1**:*

*Accordingly cyclic acid **3** of L-cysteine on treatment with benzyl isocyanate under acidic conditions using conc.HCl furnished hydantoin **4** in 90% yield. Reduction of hydantoin with sodium borohydride yielded hydroxy hydantoin **5** in quantitative yield, this hydroxy hydantoin subsequently converted to methoxy hydantoin **6** by treating with methanol and catalytic amount of pTSA in quantitative yield.*

*Reductive cleavage of C-S bond of methoxy bicyclic hydantoin **6** was successfully achieved by three different methods.*

1. *Tributyltin hydride*
2. *Lithium/Arene*
3. *Zn/sat. NH_4Cl*

Scheme 2:

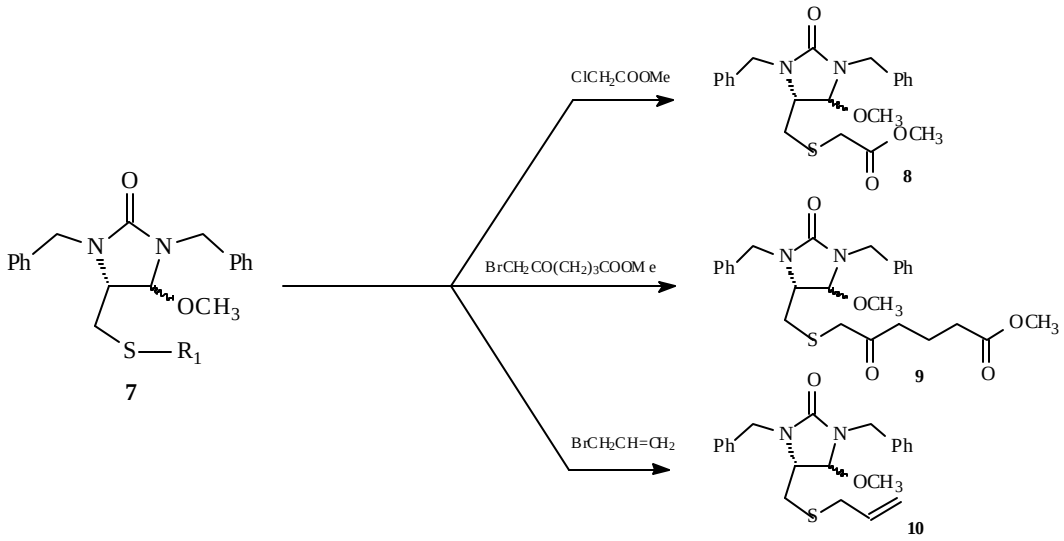


6 **7**

R_1 = H, $SnBu_3$

*Thus treatment of thiol generated with different alkyl halides under K_2CO_3 as a base at room temperature furnished S-alkylated compounds (for example **8**-**10**) in 50-70% yields. These are important synthons for the synthesis of D(+)-biotin. Conversion of these synthons to D(+)-biotin is described in the following sections.*

***Scheme 3**:*

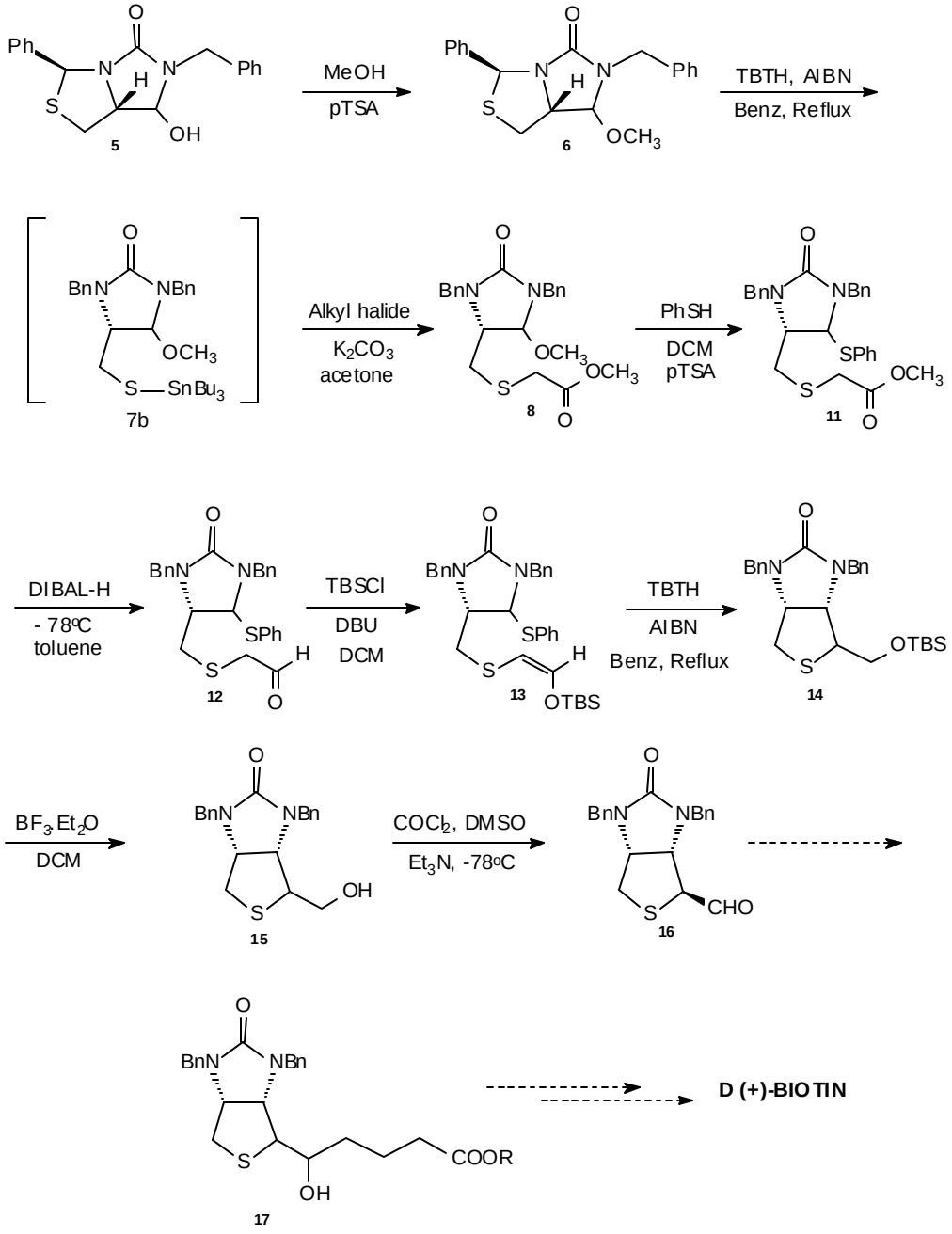

ClCH2COOMe
BrCH2CO(CH2)3COOMe
BrCH2CH=CH2
Ph
N
O
OCH3
S
R1
OCH3
8
9
10

7

Sec 3a: *Radical cyclisation for the synthesis of 5,5-fused system:*

This section deals with conversion of crucial intermediate ***8*** *to 5,5-fused cyclic aldehyde* ***16*** *by radical approach.*

Scheme 4*:*



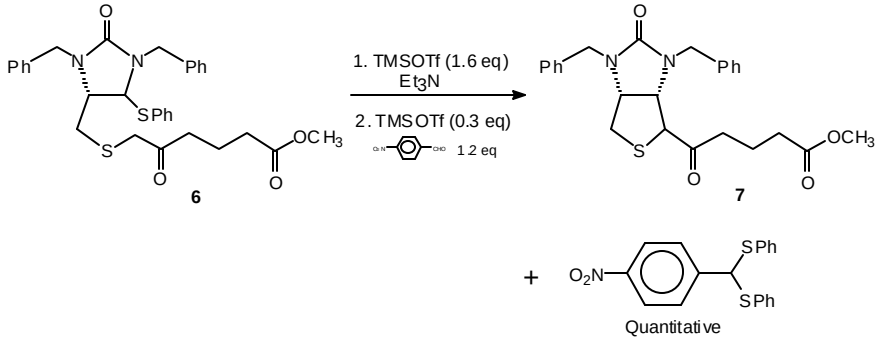
Thiophenoxy ester ***11*** *was reduced to aldehyde* ***12*** *in 78% yield. Aldehyde* ***12*** *was converted to its t-butylsilloxyenol ether* ***13*** *in 80% using TBDMSCl and*

DBU. TBS enol ether ***13*** *was subjected to radical cyclisation using TBTH in refluxing benzene and AIBN as the catalyst. Here the noteworthy feature is the formation of 5,5-cis fused system but formation exclusively trans side chain as against expected all cis stereochemistry. The resulting ether was subjected to deprotection of TBDMS group with* $BF_3.Et_2O$*. Swern oxidation of the corresponding alcohol furnished (-)cycloaldehyde* ***16*** *in 50% overall yield. (* $[\alpha]_D$ *= - 60°; c= 0.78,* $CHCl_3$*). The conversion of the aldehyde to biotin will be detailed in this section. Some of the other approaches towards generation of S-alkylated aldehyde* ***12*** *are also presented in this section.*

Section 3b*: Ionic cyclisation for the synthesis of 5,5-fused system*

In another attempt the full side chain was appended to thiol obtained from ***6****. The crucial cyclisation was performed through the silyl enol ether in the presence of p-nitrobenzaldehyde as a thiol scavenger in the presence of TMSOTf as a catalyst to furnish* ***18*** *in 65% yield and the thio acetal of p-nitrobenzaldehyde was obtained in 97% yields.*

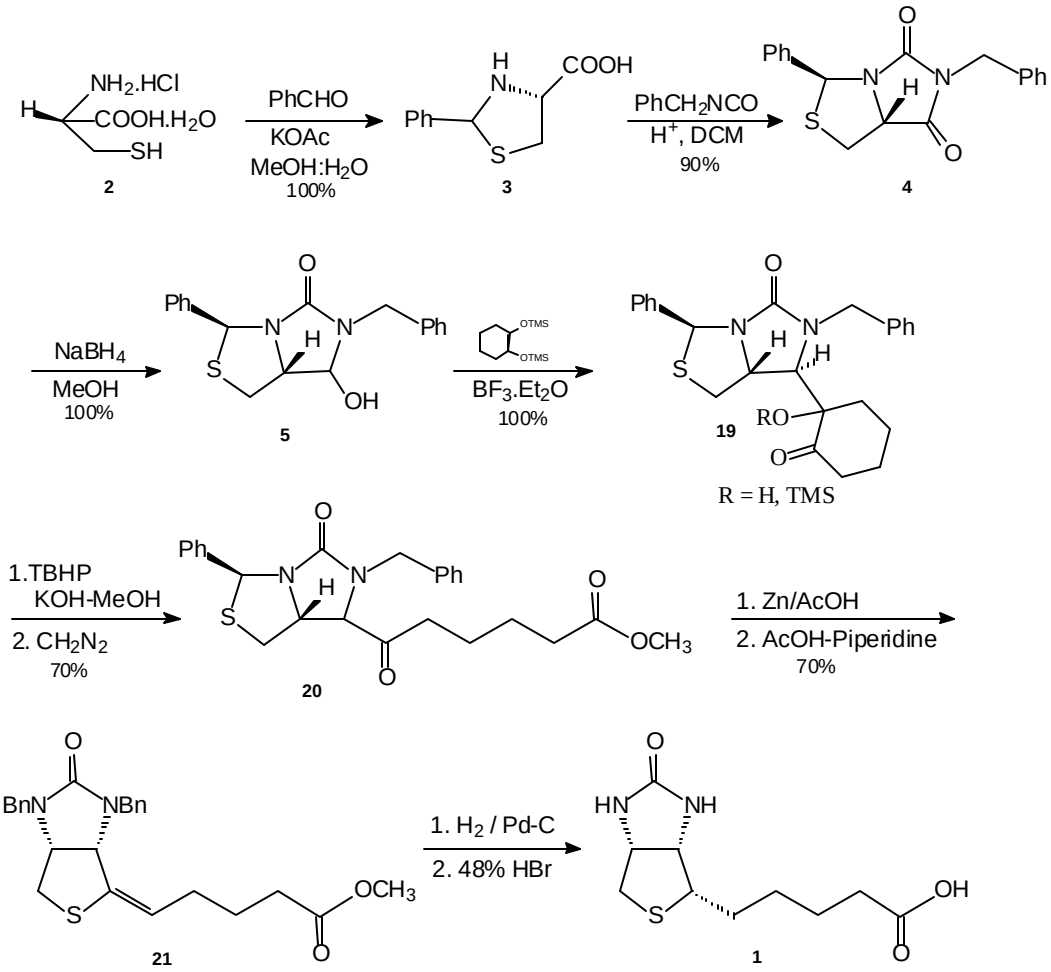
Scheme 5*:*



Sec 4: *Stereospecific synthesis of D(+)-biotin.*

This section deals with the development of efficient method of nucleophilic substitution at C-7 position of hydroxy hydantoin ***5****, and its further elaboration. Following this protocol one of the best total synthesis of D(+)-biotin from L-cysteine hydrochloridehydrate has been achieved in 9 steps in an overall yield of approx. 24%.*

Scheme 6:



*Thus thiazolidine carboxylic acid **3** when treated with benzyl isocyanate under acidic conditions furnished single diastereomer in 90% yield. Reduction of hydantoin with sodium borohydride furnished the aminol **5** in quantitative yield.*

*The crucial condensation was attempted using 1,2-bis(trimethylsilyloxy)cyclohexene as a nucleophile and BF_3Et_2O as a Lewis acid to furnish 7-substituted imidazolidines **19** in quantitative yield. This was further subjected to Baeyer-Villiger Oxidation under basic condition (TBHP in alkaline MeOH) followed by hydrolysis of lactone occurred, esterification of the resultant keto acid with diazomethane furnished the keto ester **20** in 70% yield. Reductive cleavage of C-S bond with Zn / AcOH and the cyclisation of the resulting keto thiol with piperdinylacetate furnished olefin **21** in 60% yield. Hydrogenation of the olefin **21** with palladium charcoal in methanol at 200 psi at elevated temperature (70°C) resulted in the formation of dibenzyl*

biotin in quantitative yield. Debenzylation with 48% HBr yielded D(+)-biotin ***1*** *in 70%. Thus one of the short and elegant synthesis of D(+)-biotin has been achieved.*

Chapter 2: *deals with development of useful synthetic methodologies*

Sec 1: *Diastereoselective synthesis of protected trans 1,2-diamines.*

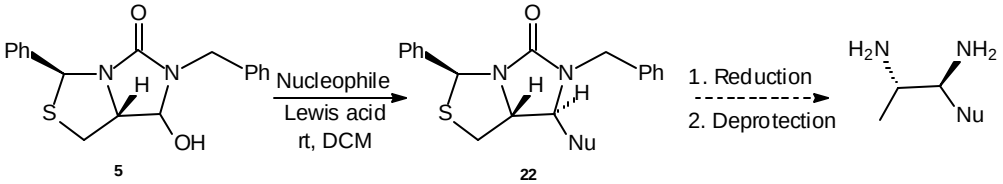
This section presents a brief introduction of 1,2-diamines and its applications in organic synthesis.

Vicinal diamines are important synthons in organic chemistry. Although a variety of methods exist for the preparation of symmetrical cis and trans diamines, surprisingly very little is known about unsymmetrical trans diamines. Trans 1,2-diamines were achieved by condensation of aminol ***5*** *with different nucleophiles. Trimethyl sillylenol ethers and tin derivatives have been demonstrated very good nucleophiles for the above reaction to furnish 7-substituted imidazolidinones* ***22*** *in excellent selectivity as well as yields.*

The present approach for preparing unsymmetrical vicinal trans diamines is efficient and easy to perform when compared to existing methods.

Scheme 7 *:*

Trans diamines are important chirons and chiral auxiliaries in catalytic asymmetric organic synthesis.

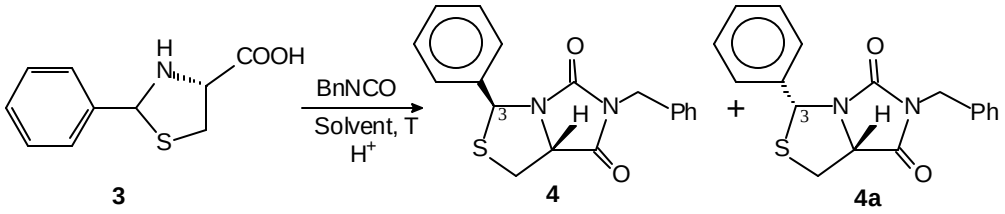


5 **22**

Our protocol provides an access to diastereomerically pure protected trans diamines.

Sec 2: *Unusual epimerisation of trans hydantoin: A novel route to convert the natural amino acids to an unnatural derivatives:*

Scheme 8 *:*



3 **4** **4a**

This section provides a reactivity profile of thiazolidine carboxylic acid ***3*** *with benzyl isocyanate and describes conditions for the exclusive formation of only one diastereomer.*

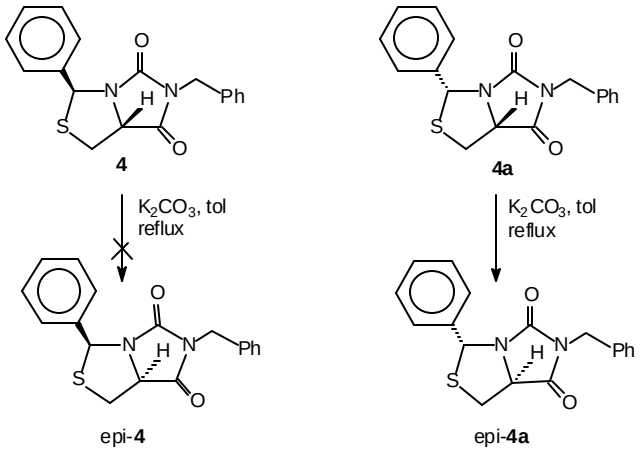
When thiazolidine carboxylic acid ***3*** *was treated with benzylisocyanate followed by conc.HCl in THF as a solvent at refluxing temperature only one diastereomer i.e.,*

*Hydantoin-**4** was obtained. However when the same reaction was carried out at room temperature with pTSA as catalyst a mixture of two diastereomers **4, 4a** in 60:40 ratio were obtained.*

Based on X-ray, NMR and chemical studies indicate these two diastereomers differ orientation of proton at C-3 position only.

*Interestingly complete epimerisation of Hydantoin at C-7 position of **4a** was observed when the hydantoin was treated with a base but not in the case of thermodynamically stable Hydantoin **4**. Thus **4a** could be converted exclusively on treatment with K_2CO_3 in refluxing toluene to hydantoin **4a'** (epi-**4**) which is the enantiomer of hydantoin **4.** It is noteworthy that the stereo chemistry at C-7 position is exactly opposite to that present in **4** or **4a.** Formation of **4a'** (epi-**4**) has been confirmed by spectral analysis as well as polarimetric studies. Thus utilizing the above results one can potentially convert natural amino acids (viz., cysteine, serine) into unnatural amino aicds through the formation of hydantoins.*

***Scheme 9**:*

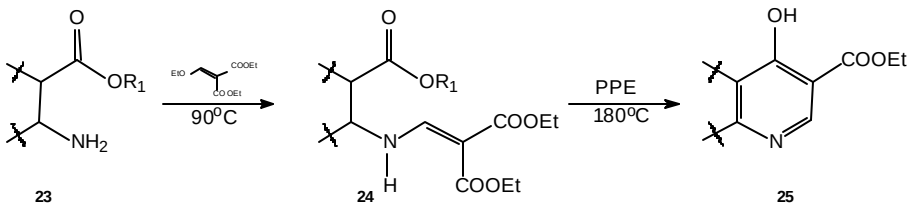


Sec 3: *Preparation of [2,3-b]thienopyridines using dehydrating agents like Polyphosphate ester or P_2O_5-Methane sulphonic acid:*

Thieno [2,3-b]pyridines and its derivatives are clinically useful drugs for the treatment of a broad spectrum of human harmone dependent diseases. Most of these thienopyridine derivatives are used therapeutically as gonadotropin releasing harmones.

In this section polyphosphate ester was effectively utilized for the conversion of enamines of formula ***24*** *to*

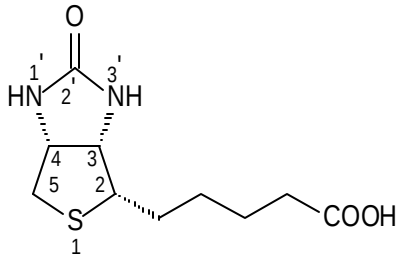
[2,3-b]thienopyridines ***25*** *in good to moderate yields in very short period of reaction time. The superiority of the current protocol over the existing protocols is detailed in this section.*



23 **24** **25**

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**

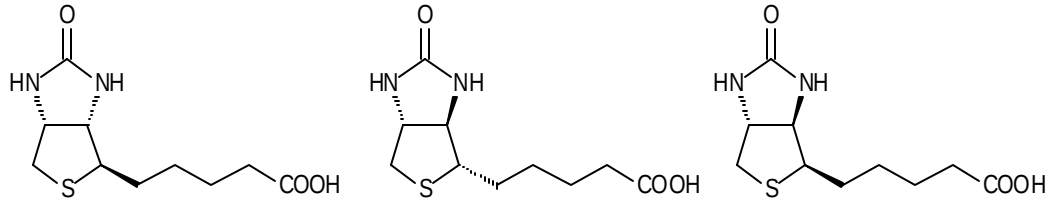
Biotin is one of the water-soluble B-complex group of vitamins. In bound form it is distributed widely as a cell constituent of animal and human tissues. The main sources of biotin are liver, kidney, pancreas, egg yolk, yeast and milk. A high content of biotin in cow's milk occurs in early lactation. It is also 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:

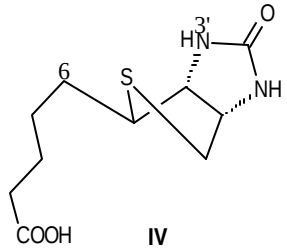
The empirical formula for biotin $C_{10}H_{16}N_2O_3S$ was established in 1941 and the full structure in 1942 by du Vigneaud.[4,5] The structure was confirmed by the first total synthesis of biotin in Merck Laboratories by Harris and coworkers in 1945.[6] The absolute configuration was established more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



epi-Biotin **I** *allo*-Biotin **II** *epiallo*-Biotin **III**

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]



IV

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 ìg/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.

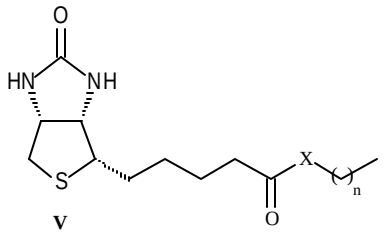
Avidin-Biotin system in immunochemistry:[19]

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]

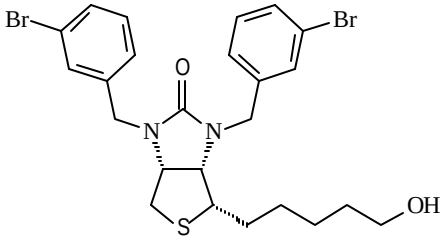


V

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

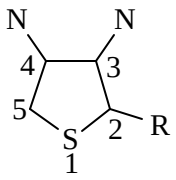
Several bis-*N*-alkylated (+)-biotin derivatives were synthesized and evaluated for activities against HIV-1 protease. The most potent inhibitor, **VI** has K_i of 0.50 mM and antiviral IC_{90} of 7mM. The (+)-biotin analogues in general have good translations from enzymic K_i to antiviral cell assay 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 up to 1992 were already reviewed by R. B. Tejwani of this laboratory,[22] as well as is reviewed by De Clercq in 1997[23] the current 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.

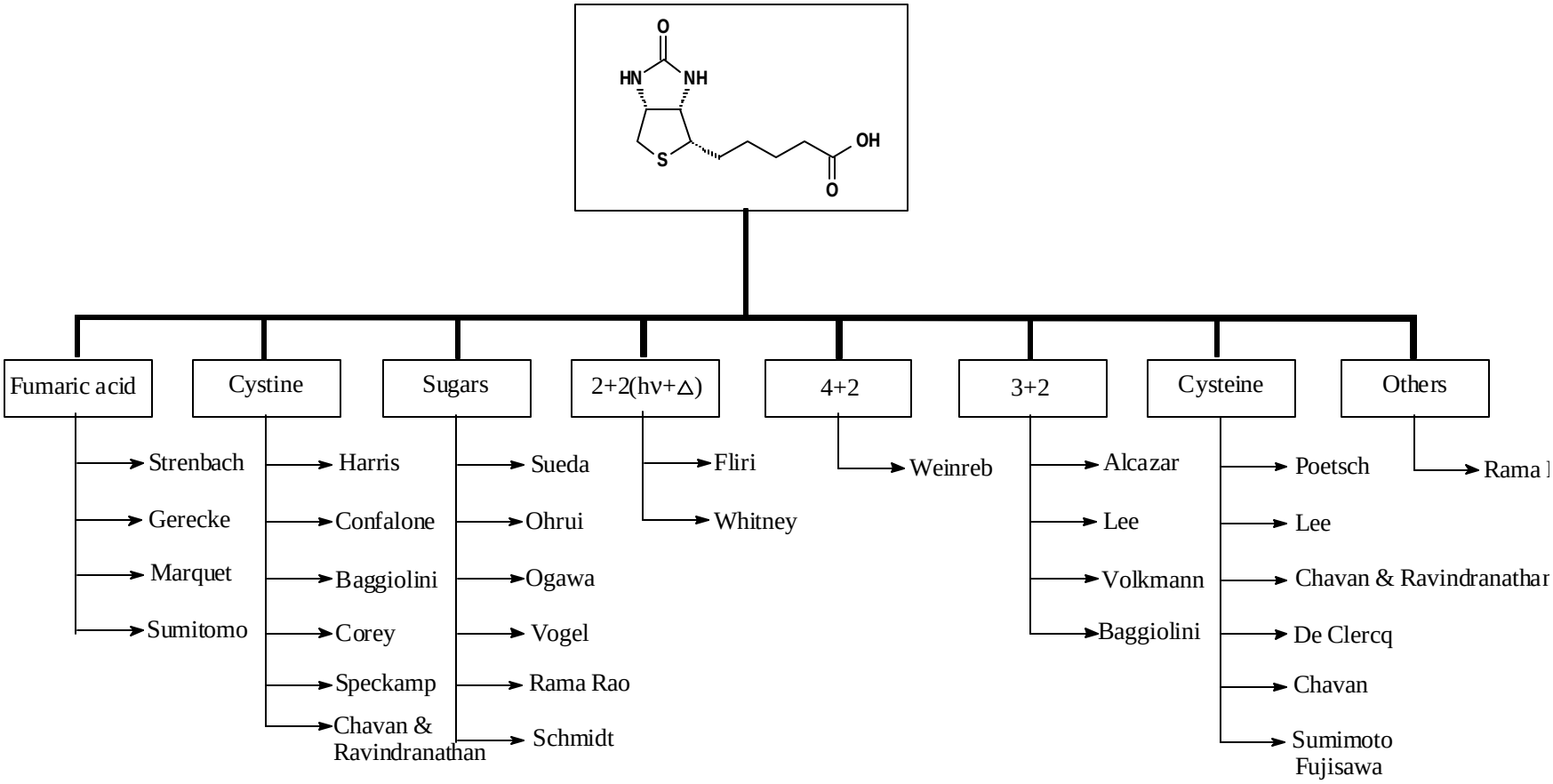
Schemes constitute the vehicle of the synthetic chemist. They are conceived so that the chemist can grasp the important stages in each shown sequence. Relevant experimental conditions are listed, including yields when they have been clearly reported in the original literature. The following stereochemical 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.

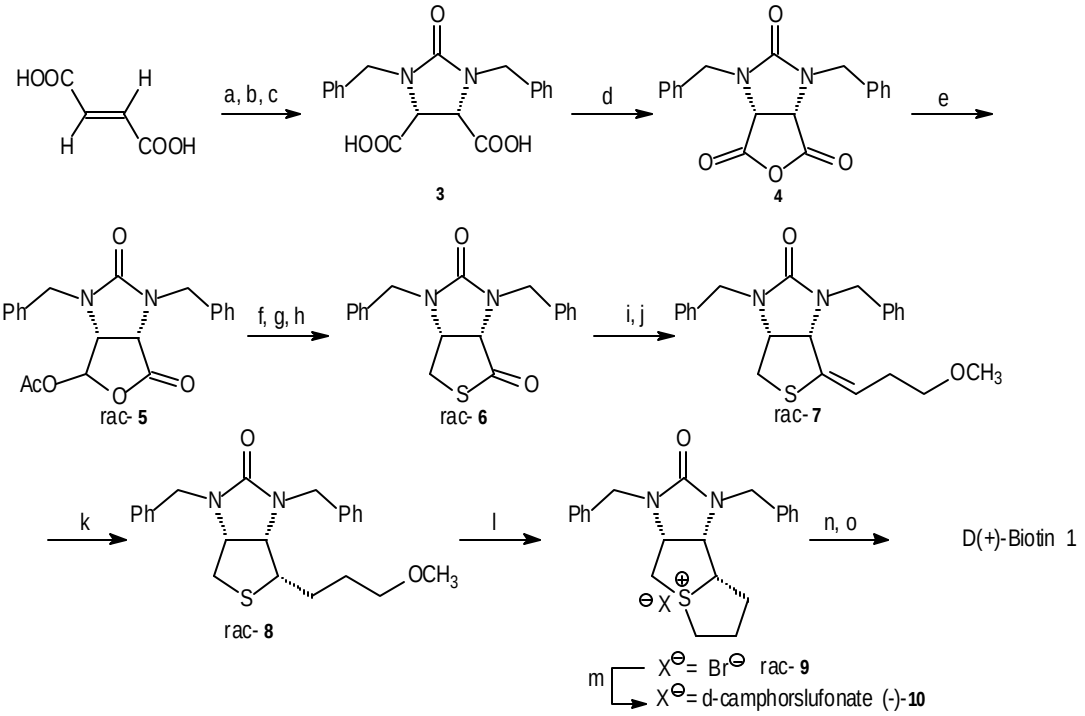
Chart 1:[23]



Hoffmann-La Roche's Lactone-Thiolactone approach:

In 1946 Goldberg, Strenbach[24-26] described the total synthesis of (+)-biotin starting from cheaply available fumaric acid (see Scheme 1).

Scheme 1: Pat. 2,489232, Nov. 22, 1949; Chem. Abstr. **1951**, 45, 184.



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

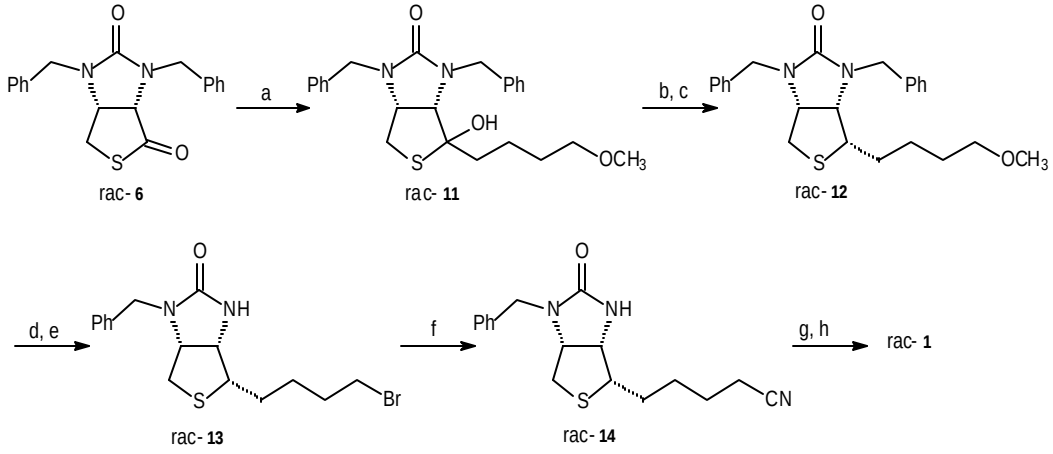
thiophanium salt **9** by treatment with hydrobromic acid (HBr). At this point, resolution is effected by conversion of bromide **9** into the diastereomeric sulfonate salt **10** which are readily separated in excellent yield by simple fractional crystallization. In the final stage of the synthesis 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.

Another approach by Goldberg[25] described a route in which the thiophanium salt were not involved. The conversion of thiolactone **6** into *rac*-biotin involved a sequence of eight steps (Scheme 2).

Scheme 2: US Pat. 2,489235, Nov. 22, 1949; Chem. Abstr. **1951**, 45, 186a.



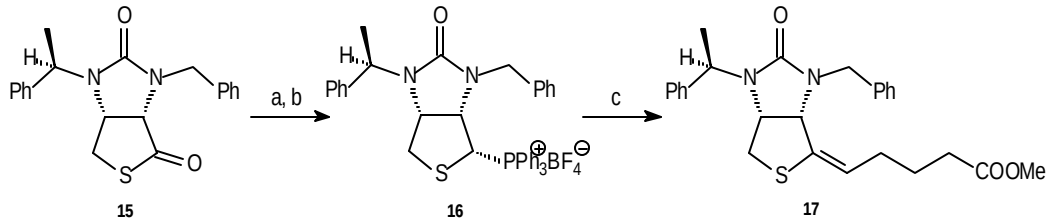
Conditions: ***a****) $CH_3O(CH_2)_4Br$, Mg, ether; PhH;* ***b****. HOAc, reflux;* ***c****) H_2, Pd/C, MeOH;* ***d****) Na, liq.NH_3;* ***e****) HBr, HOAc, 90 °C;* ***f****) KCN, H_2O;* ***g****) NaOH, H_2O/MeOH;* ***h****) Na, liq. NH_3*

Thus Grignard reaction of **6** with 4-methoxybutyl bromide furnished the alcohol **11**. Dehydration of **11** followed by catalytic hydrogenation yielded **12**. Removal of one benzyl group with sodium in liquid ammonia and conversion of the terminal methoxy alkyl group into the corresponding bromide **13** and

its one carbon homologation with potassium cyanide furnished **14**, whose basic hydrolysis resulted in the formation of the corresponding carboxylic acid. Subsequent debenzylation with sodium in liq. Ammonia furnished (±)-biotin.

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).

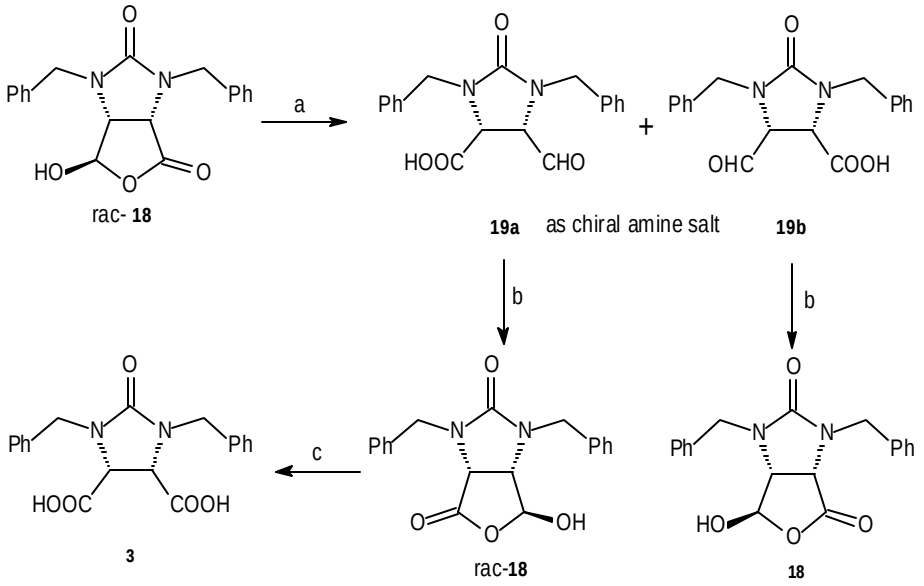
Scheme 3: Eur. Pat. Appl. EP 0 387 747, 19 Sept. 1990; Chem. Abstr. **1991**, 114, 81435t



Conditions: ***a***) *$(Me_2CHCH_2)_2AlH$, $PhCH_3$, -70 ^0C;* ***b***) *Ph_3P-HBF_4, CH_3CN, reflux, 97%;* ***c***) *KO^tBu, THF, $OHC(CH_2)_3CO_2Me$, THF, 65%.*

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.

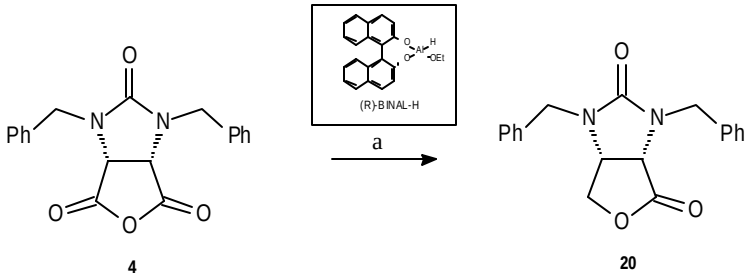
Scheme 4: *Chem.Pharm.Bull.* **1990**, *38*, 882.



Conditions: ***a****) Cinchonidine:45% of precipitated salt or N-n-butyl-D-glucosamine derivative: 46% of precipitated salt;* ***b****) HCl;* ***c****). $NaClO_2$, 87%.*

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: *Tetrahedron Lett.* **1993**, *34*, 1167.



90% ee (95% ee after crystallisation)

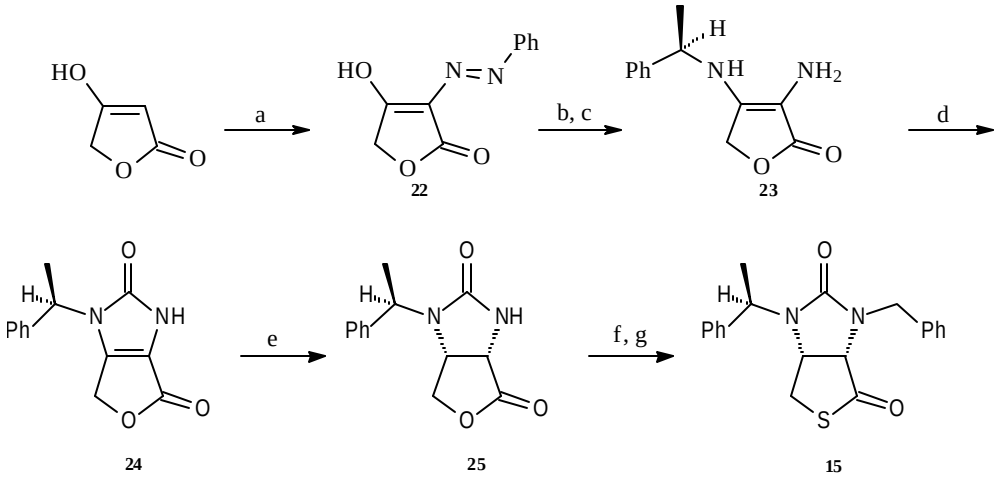
Condition: ***a****) (R)-BINAL-H, -78 °C to rt., THF, 76%.*

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

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]

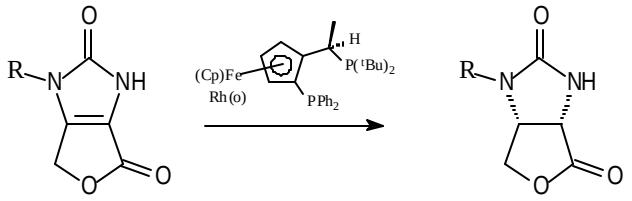
Scheme 6: Eur. Pat. Appl. EP 0 270 076, 8 June, 1988; Chem. Abstr. **1988**, *109*, 128718b.



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_3N, THF, Et_3N, CH_3CN, reflux, 66%;* ***e****) H_2, Rh/Al_2O_3, DMF, 40 bar, 54%;* ***f****) NaH, DME, $PhCH_2Br$;* ***g****). CH_3COSK, $CH_3CON(CH_3)_2$, 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: Eur. Pat. Appl. EP 624 587 17th Nov. 1994; Chem. Abstr. **1995**, *122*, 81369q.



24, 26 **25, 27**

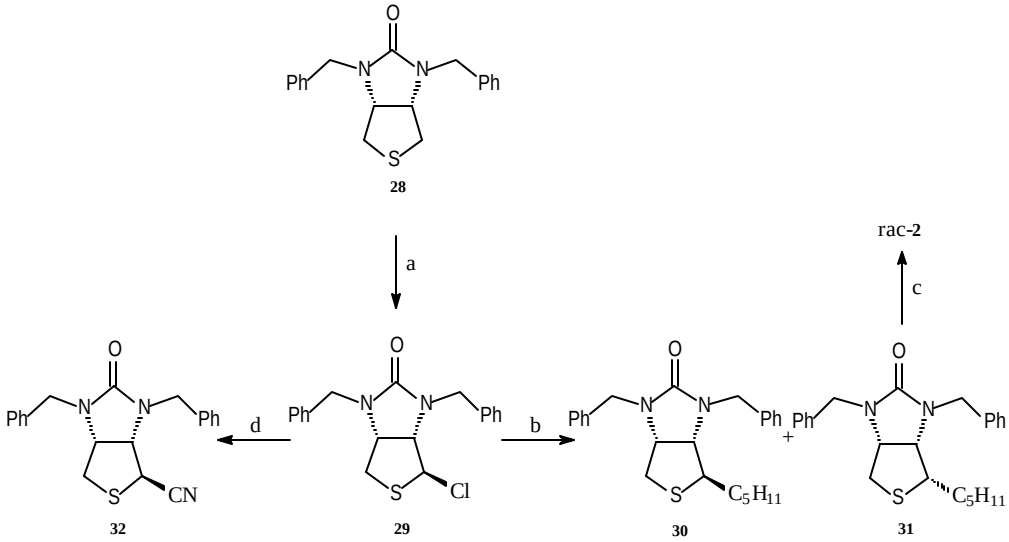
24 R =  **25** (98%, de)

26 R = -CH_2Ph **27** (90% ee)

Condition: a) *Rh(0)= [Rh(norbornadiene)Cl]$_2$, chiral ligand, $PhCH_3$, 70 °C, H_2, 50 bar, 95%.*

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: *J. Org. Chem.* **1986**, *51*, 3447



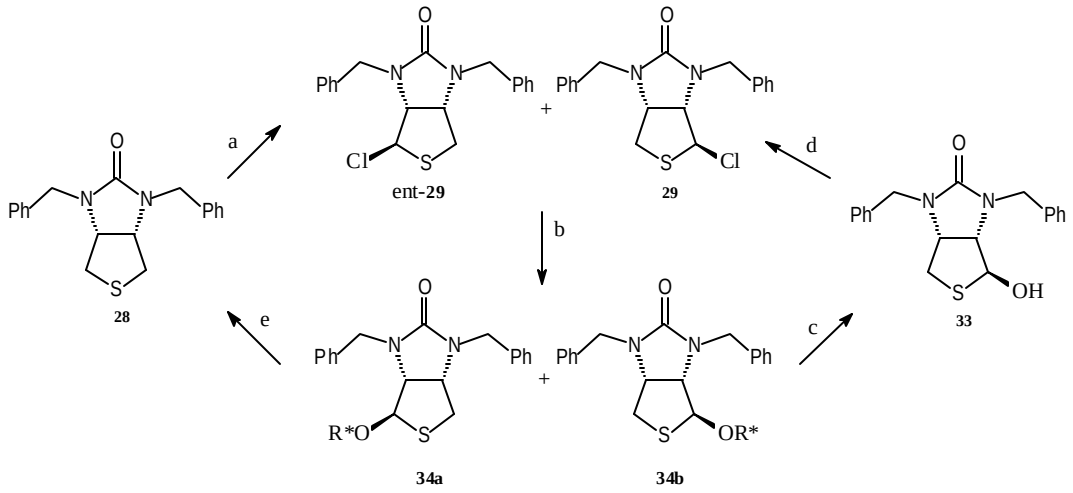
28

32 **29** **30** **31**

Conditions: a) *NCS, PhH, 100%;* ***b)*** *n-pentyl(Me)CuLi (mol of LiCl/mol of RCuLi=1), -60 °C, ether, 53%;* ***c)*** *Na, liq. NH_3 or HBr (48%);* ***d)*** *NaCN.*

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.

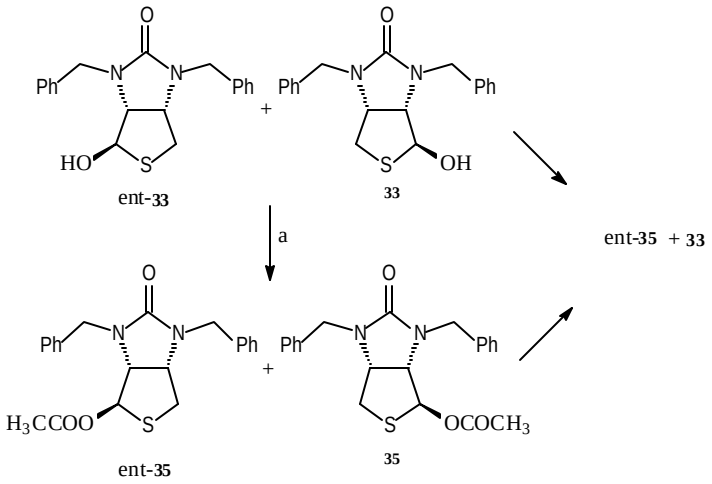
Scheme 9: *Tetrahedron* **1990**, *46*, 7667



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_2SO_4*/dioxane;* ***d****) HCl,* $CHCl_3$*;* ***e****)* Et_3SiH*,* CF_3COOH*.*

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**.

Scheme 10: *Bull. Chem. Soc. Jpn.* **1993**, *66*, 1456

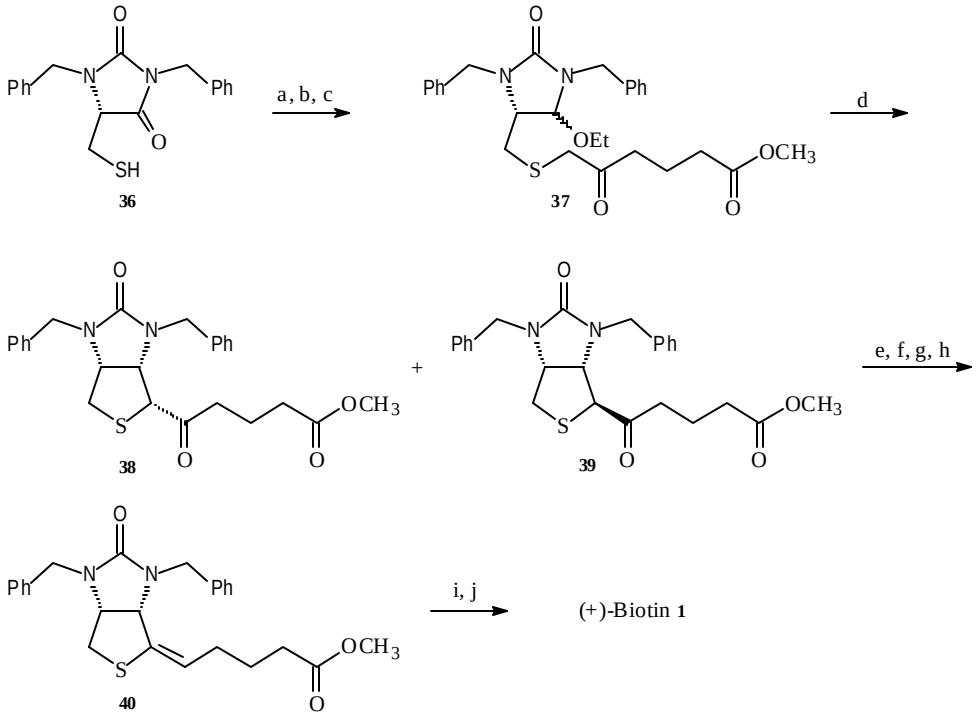


Conditions: ***a****)* Ac_2O*, pyridine, 98%;* ***b****) Streptomyces rochei var. volubilis; 27% conversion; 92 and 94% ee after crystallization;* ***c****) LIP (P.aeruginosa TE3285; TOYOBO immobilized lipase), 0.3%* H_2O*, 4A° molecular sieves (MS),* $PhCH_3$*, vinyl acetate; 56% conversion; 99 and 99.8% ee after crystallization of alcohol.*

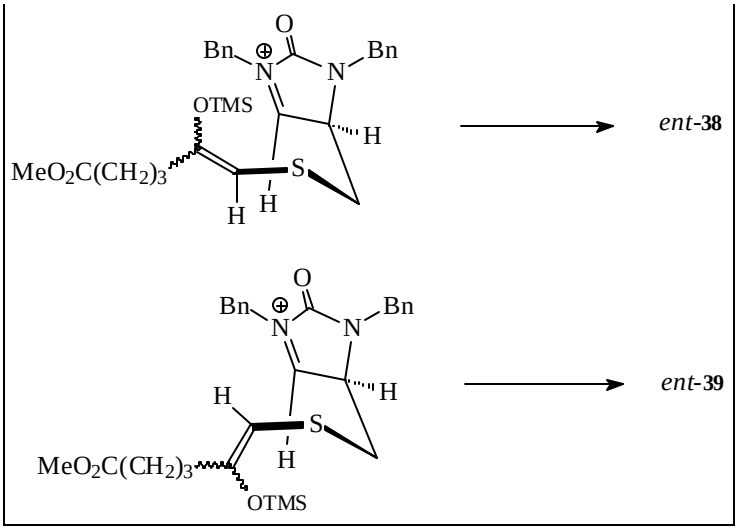
In a second approach, the same group found that direct resolution of alcohol **33** was accomplished *via* acylation with the lipoprotein from *Pseudomonas aeruginosa* TE 3285 in toluene.[39] Curiously, addition of molecular sieves (MS) 4A° to the reaction mixture improved the reactivity, while at the same time as addition of a small amount of water was found to be beneficial for the reaction.

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 á-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: *Angew. Chem. Int. Ed. Engl.* **1995**, *34*, 2391



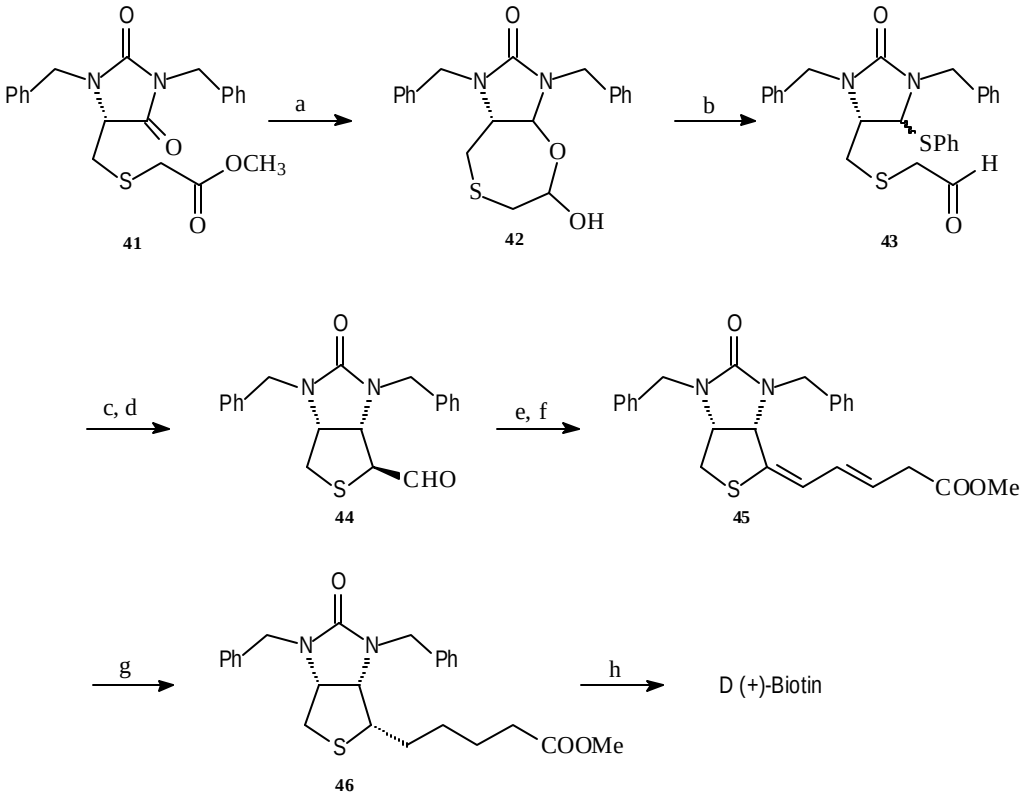
Conditions: ***a****) DIBAL-H, THF, -70°C, 1h;* ***b****) $MeO_2C(CH_2)_3C(O)CH_2Cl$, Et_3N, 4h;* ***c****) H_2SO_4/EtOH, methyl orange, pH=3.1, 0 °C, 2h, 72%.* ***d****) 2.1 eq. of $(TMS)CH_2CO_2Et$, 0.03 eq. of TBAF, THF, -78°C to 25°C, 18h, then 1.5eq. of TMSOTf, DCM, -78 °C, 1h, 78%;* ***e****) $NaBH_4$, MeOH, 25°C;* ***f****). $MeSO_2Cl$, Et_3N, 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 °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.

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

Scheme 12: US patent 5,274,107; Chem. Abstr. **1994**, *120*, 217097t



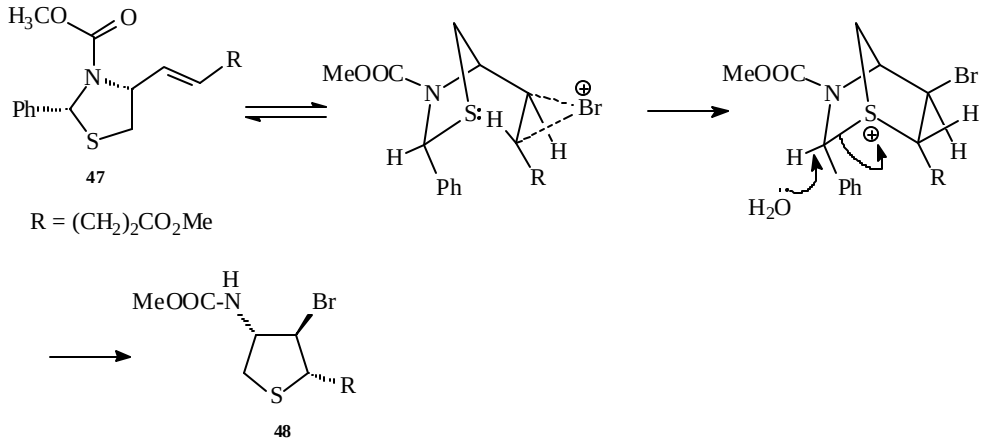
Conditions: ***a****) DIBAL-H, $PhCH_3$, 72%;* ***b****) p-TsOH, PhSH, 70%;* ***c****) $^tBuMe_2SiCl$, DBU, DCM;* ***d****) $^tBuMe_2SiOTf$ (cat.), pNO_2PhCHO, DCM, 87%;* ***e****) $Ph_3P=CH-CH=CH-CO_2Me$, DCM;* ***f****) DBU, DCM, 86%;* ***g****) H_2 (3 bar), Pd/C, MeOH 92%;* ***h****) 48% HBr.*

Conversion of thioaldehyde **43** to the corresponding silyl enol ether followed by trialkyl triflate mediated cyclization in the presence of *p*-nitrobenzaldehyde as thiophenol scavenger leads 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.

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

In 1975, Confalone and co-workers reported an interesting approach in which bromination of olefin **47** resulted in a spectacular and stereospecific rearrangement (Scheme 13).[42]

Scheme 13: *J. Am. Chem. Soc.* **1975**, *97*, 5936



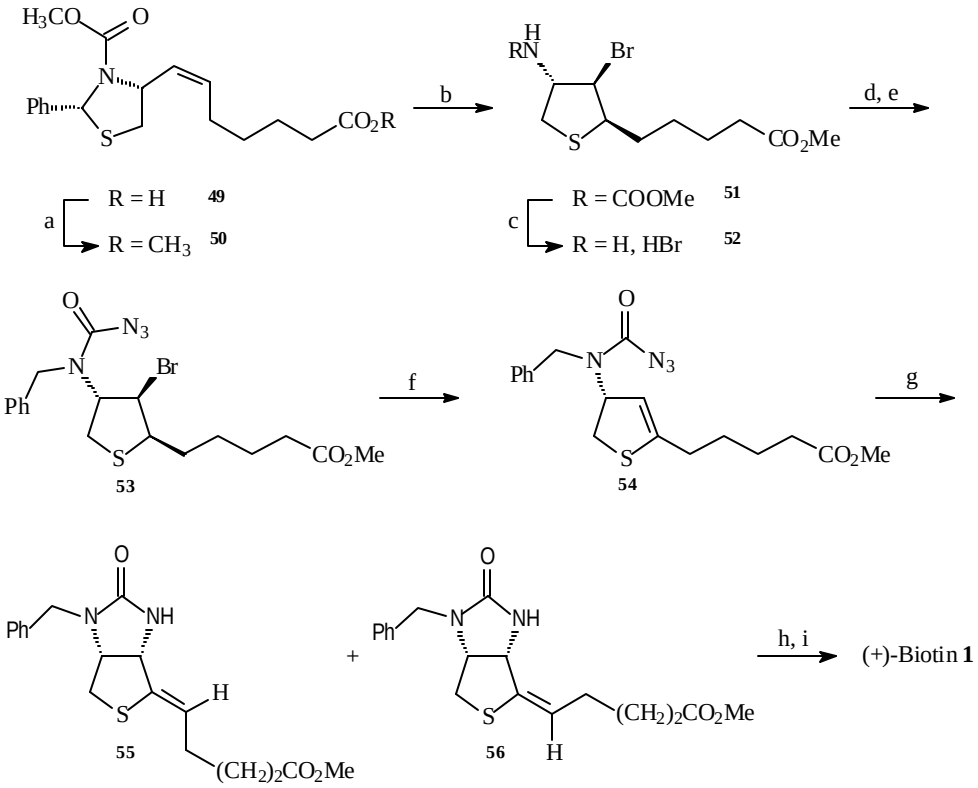
It is interesting to note here that the rearrangement occurring upon bromination of **47** is stereospecific.

In 1993 and 1994 De Clercq[43] described two different approaches of biotin based on a thermal intramolecular 1,3-dipolar cycloaddition of a carbamoyl azide to an alkene. The approach described in Scheme 14 fully takes advantage of the stereochemical outcome of the above mentioned rearrangement (Scheme 13).[42] Indeed, when the methyl ester **50** was brominated in the presence of water, bromide **51** was obtained as the sole isomer. The amino group in **51** was further converted into the benzylated carbamoyl azide **53** *via* cleavage of the urethane to yield **52**, followed by *N*-benzylation by reductive amination, and introduction of the acyl azide group. When bromide **53** was treated with DBU, the expected E2 elimination product **54** was obtained in excellent yield. The projected intramolecular 1,3-dipolar cycloaddition was effected by treatment of **54** at high temperature in an autoclave. This led to a mixture of (*E*)- and (*Z*)- exocyclic olefins **55** and **56** that were further converted into biotin in the usual way (Scheme-14).

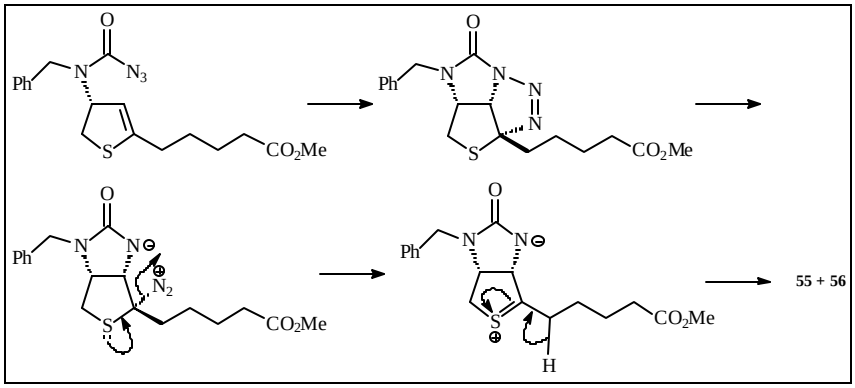
The second approach involved the intramolecular cycloaddition of the benzylated carbamoyl azide **61** (Scheme 15).[44, 45] When this reaction was effected in water as solvent at 145 ^{o}C (autoclave), a mixture of the two monobenzylated forms of biotin **62** and **63** was directly obtained. According to De Clercq the mechanism of this transformation would involve formation of a triazoline, subsequent formation to yield a betaine, nitrogen expulsion with assistance of the proximal sulfur with the

concomitant formation of tricyclic sulfonium intermediate, and final nucleophilic attack of water to form the carboxylic side chain of biotin.

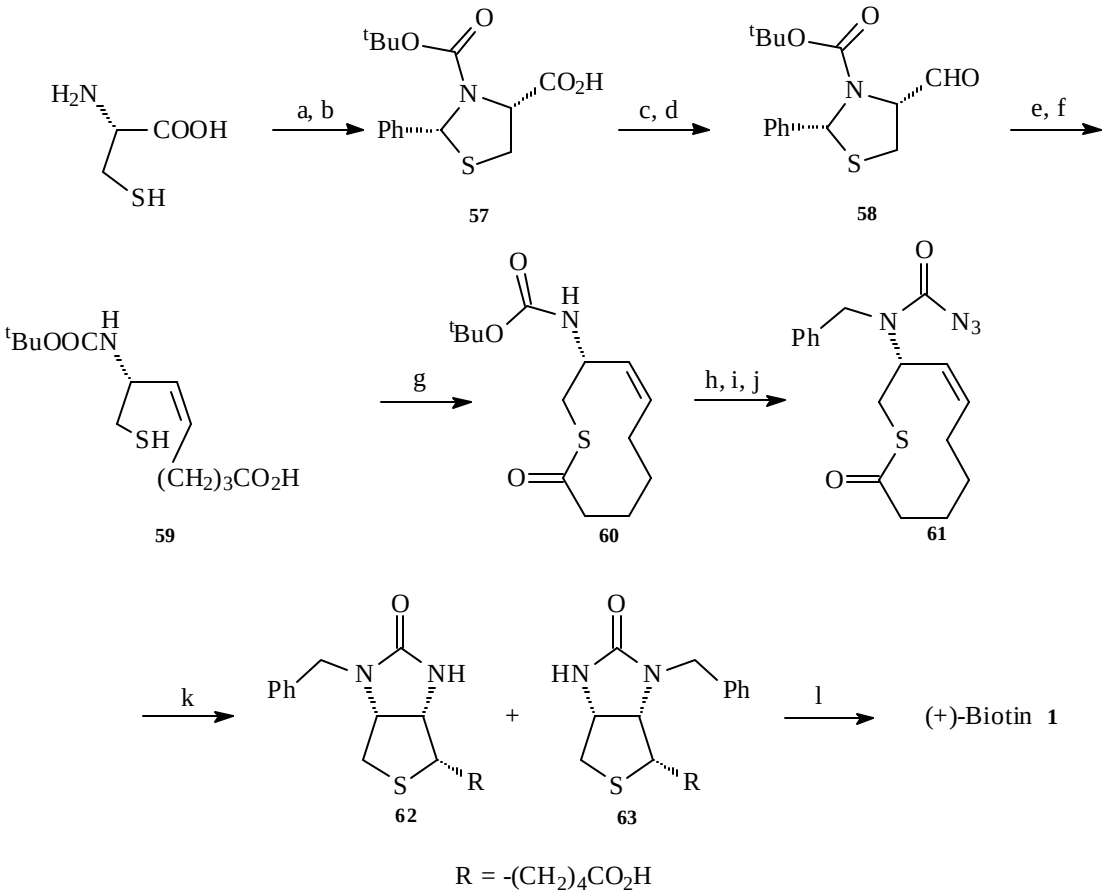
Scheme 14: *Tetrahedron Lett.* **1993**, *34*, 4365



Conditions: ***a)*** *CH_2N_2, Et_2O, 0 °C, 99%;* ***b)*** *Br_2, $CHCl_3$, H_2O, rt, 65%;* ***c)*** *HBr, HOAc, 85%;* ***d)*** *PhCHO, $NaCNBH_3$, THF, H_2O, rt;* ***e)*** *$COCl_2$, DBU, DCM, 0 °C, NaN_3, acetone/H_2O, rt, 54%;* ***f)*** *DBU, THF, reflux, 95%;* ***g)*** *autoclave, DCM, 150 °C, 3h, 78%;* ***h)*** *H_2 (4 bar), $Pd(OH)_2$/C, EtOAc, rt;* ***i)*** *HBr (48%), reflux, 78%.*

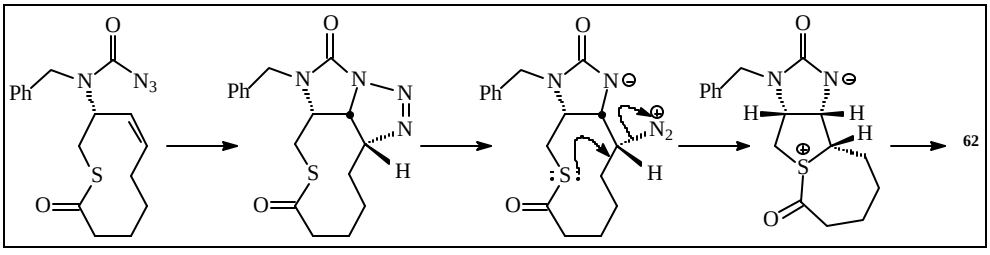


Scheme 15: *Tetrahedron Lett.* **1994**, *35*, 2615



$R = -(CH_2)_4CO_2H$

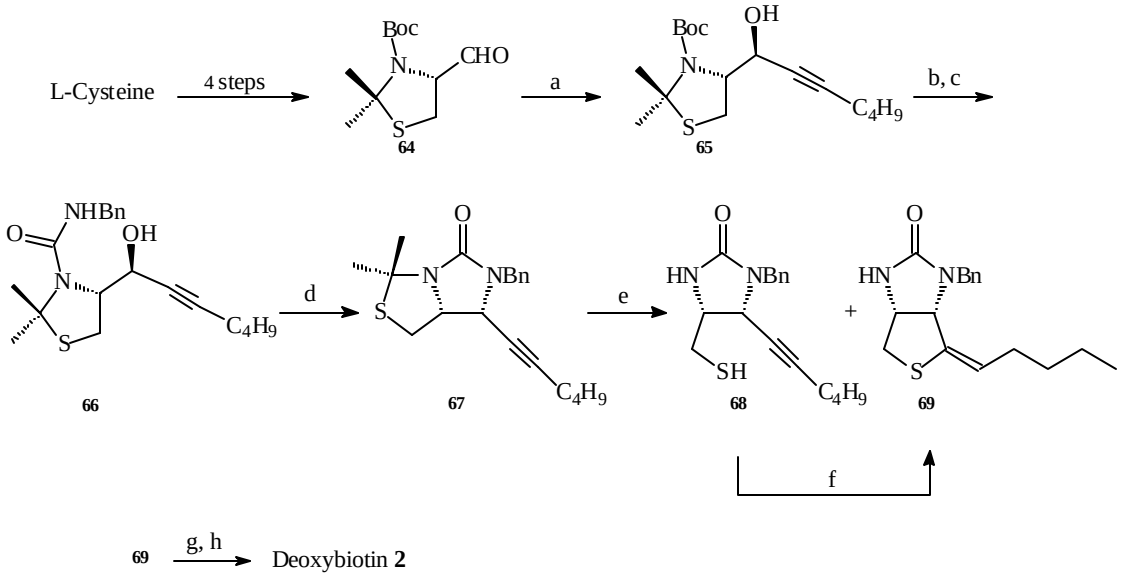
Conditions: ***a****) PhCHO, KOAc, H_2O, EtOH, rt;* ***b****) $(Boc)_2O$, NaOH, H_2O, dioxane, 80%;* ***c****) Me_2S/BH_3, THF;* ***d****) $(COCl)_2$, DMSO, -60 °C, Et_3N, 66%;* ***e****) $[Ph_3P(CH_2)_5COOH]Br$, 2eq. of LDA, THF, rt, 1h;* ***f****) Na liq.NH_3, H_3O^+, 78%;* ***g****) $PhOP(O)Cl_2$/DMF, DCM, rt, 24%;* ***h****) HCl, Et_2O, 0 °C;* ***i****) PhCHO, $NaCNBH_3$, THF/H_2O (pH=4), 0 °C;* ***j****) $COCl_2$, DBU, NaN_3, acetone/H_2O, rt; 40%;* ***k****) H_2O, autoclave, 145 °C, 2h, 42%;* ***l****) HBr (48%), reflux, 2h, 85%.*



In 1994 Fujisawa and coworkers reported an interesting approach to (+)-deoxybiotin from L-cysteine (Scheme 16).[46]

The synthesis involves the diastereoface discrimination in the addition of an acetylide to chiral aldehyde **64**. The compound **64** is obtained from L-cysteine *via* a known four-step sequence involving thiazolidine formation, N-urethane protection, esterification and reduction with DIBAL-H.[47]

Scheme 16: *J. Org. Chem.* **1994**, *59*, 5865

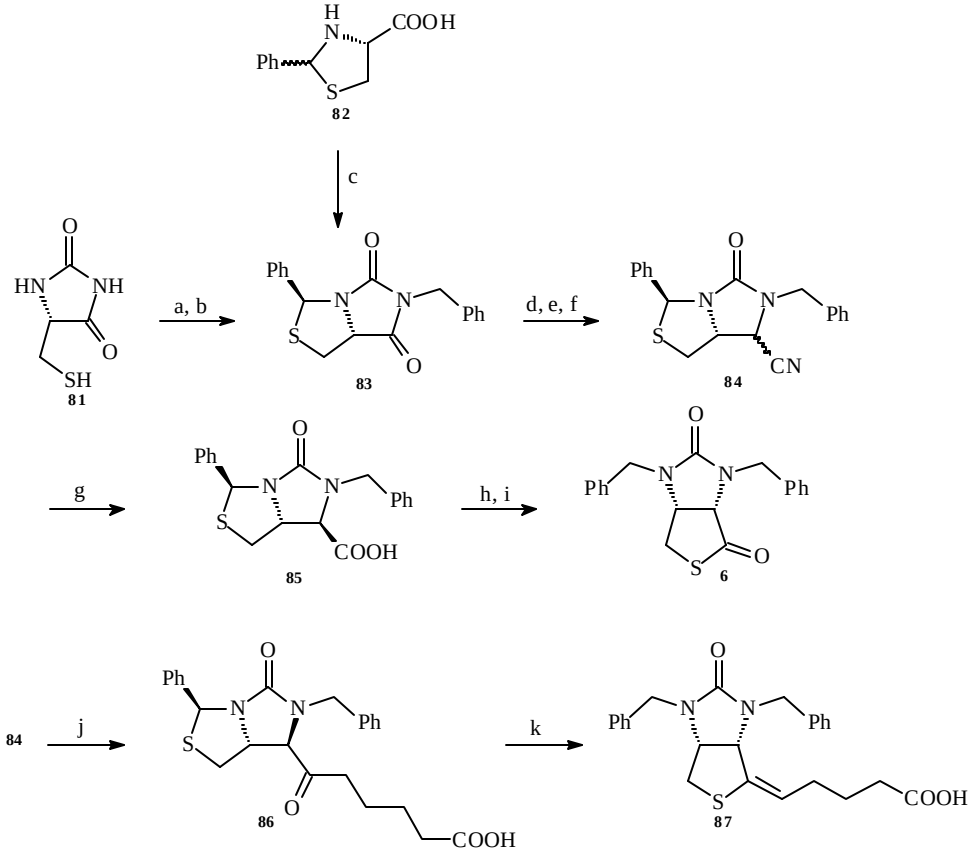


Conditions: ***a)*** *$C_4H_9C\equiv C$-ZnCl, Et_2O, 10h, 86%;* ***b)*** *p-TsOH, MeOH, 35 °C, 11h;* ***c)*** *$PhCH_2NCO$, C_5H_5N, 0 °C, 70%;* ***d)*** *KH, (5eq), p-TsCl, HMPA (30 eq), THF, 86%;* ***e)*** *p-TsOH, MeOH/H_2O, 40 °C, 15h (O_2 free!!)* ***68*** *(65%),* ***69*** *(23%);* ***f)*** *CsOH, H_2O/THF (10:1), 40 °C, 50%;* ***g)*** *H_2 (10 bar), Pd/C, 2-propanol/H_2O (6:1), 40°C;* ***h)*** *HBr (47%), reflux, 73%.*

When the chlorozinc acetylide derived from 1-hexyne was condensed with aldehyde **64**, the propargylic alcohol **65** was obtained as the sole isomer in very good yield. The high selectivity is rationalized in terms of chelation-control model in which the metal is chelated by the aldehyde and carbamate oxygens. Introduction of the amino group at C3 in the required configuration resulted from an internal S_N2 displacement *via* potassium hydride treatment of the tosylated alcohol **66**. The latter was obtained from **65** after hydrolysis and formation of the mixed urea. Deprotection of the acetonide in **67** with 1 eq. of p-toluenesulphonic acid (p-TsOH) led to the cyclized thiophane **69** (23% yield !) along with thiol **68** in 65% yield. Further cyclization of **68** presented a regiochemical problem, since an undesired six membered isomer was formed in addition to desired **69**. The final conversion of **69** into (+)-deoxybiotin **2** further involved catalytic hydrogenation and debenzylation.

In 1987 Poetsch and Casutt reported[48] shortest enantiospecific sequence to (+)-biotin (Scheme 17).

Scheme 17: *Chimia* **1987**, *41*, 148

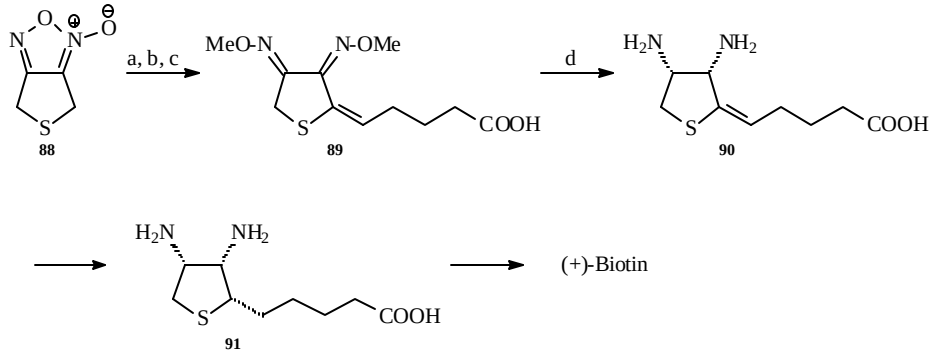


Conditions: ***a****) PhCHO, $POCl_3$, $PhCH_3$;* ***b****) $PhCH_2Cl$, K_2CO_3, DMF, 79%;* ***c****) $PhCH_2NCO$, acetone, HCl, DCM, 85%;* ***d****) $NaBH_4$, THF/H_2O;* ***e****) 1,1'-carbonyldiimidazole, THF;* ***f****) CH_3I, DMF; KCN, DMF, 78%;* ***g****) KOH, EtOH, H_2O, 91%;* ***h****) Zn, AcOH;* ***i****) N,N'-dicyclohexylcarbodiimide, C_5H_5N, p-TsOH; 70%;* ***j****) $Br(CH_2)_4Br$, Mg, THF, CO_2, HCl, 65%;* ***k****) Zn, AcOH; piperidine, AcOH, 70%.*

The crucial intermediate in the synthesis is nitrile **84**. This is obtained from the bicyclic thiazolidine hydantoin **83** *via* selective reduction and cyanide introduction on the activated 1-(alkoxycarbonyl) imidazole derivative. The starting material **83** is obtained either from the readily available hydantoin **81**[49] or from the known thiazolidine carboxylic acid **82**.[50] Two different routes were developed that allow the conversion **84** into biotin. The direct Grignard reaction on **84** led to **86** followed by reductive opening of the thiazolidine leads to an intermediate thiol that is cyclized using piperidine acetate/acetic acid to yield the biotin precursor **87**. Alternatively nitrile **84** is converted to the thermodynamically more stable acid which after reductive cleavage furnished the corresponding thiol acid, which was further cyclized to thiolactone **6**.

Quite recently an interesting short and enantioselective synthesis of (+)-biotin has been claimed by Kurimoto *et al*[51] Starting from **88**, the carboxybutyl chain is introduced *via* condensation with 5-oxopentanoic acid (Scheme 18).

Scheme 18: JP 06 263 752, Sept 20, 1994; Chem. Abstr. **1995**, *122*, 81011s



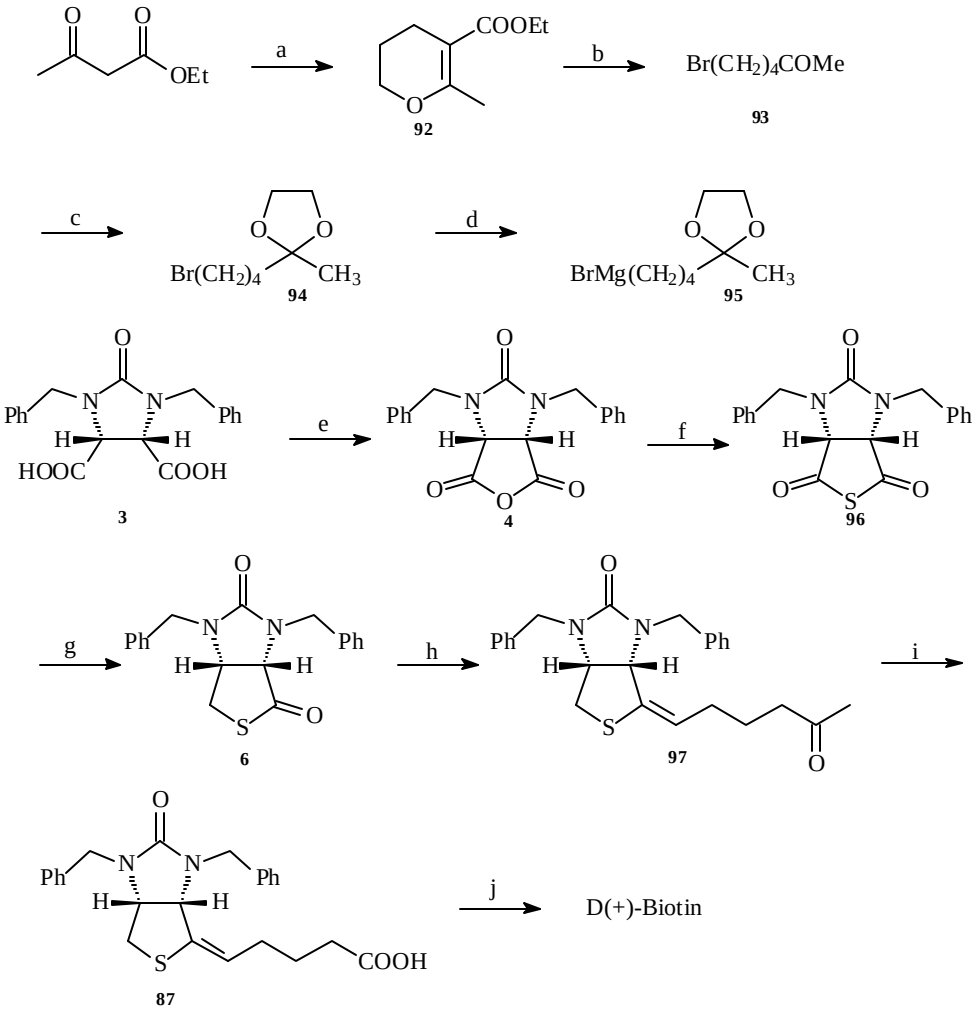
Conditions: a) LDA, $OHC(CH_2)_3CO_2H$; **b**) PhNHNHPh; **c**) methylation; **d**) BH_3/THF, norephedrine.

After reduction of the furoxan ring with hydrazobenzene and methylation, acid **89** is obtained. When the latter is reduced with borane-THF complex in the presence of norephedrine the *cis*-3,4-diamino derivative **90** is formed. The diamine **90**, *via* a known precursor **91**, is converted to (+)-biotin.

In 2000 Chen and co workers reported[52] an efficient and enantioselective synthesis of D(+)-biotin using BINAL-*H* reduction of *meso*thioanhydride **26** (Scheme 19).

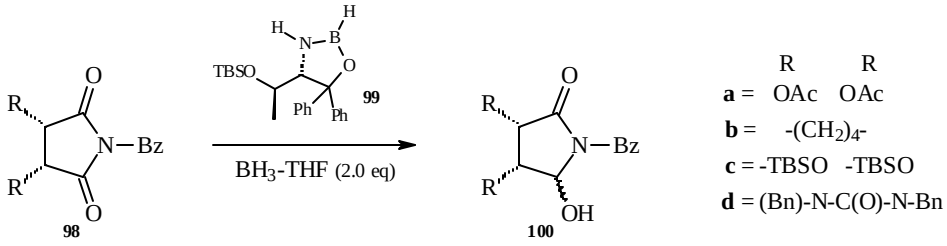
The synthesis starts with *cis*-1,3-dibenzyl-2-imidazolidine-4,5-dicarboxylic acid **3**. The key steps are the enantioselective reduction of meso-1,2-dicarboxylicthio anhydride **96** to prepare the (3a*S*, 6a*R*)-thiolactone **6**, and the introduction of the C_6 side chain at C_2 in **6** *via* a modified Grignard reaction. This novel synthesis proceeded in six steps starting from **3** to afford **1** with 21% overall yield.

Scheme 19: *Synthesis*, **2000**, 2004



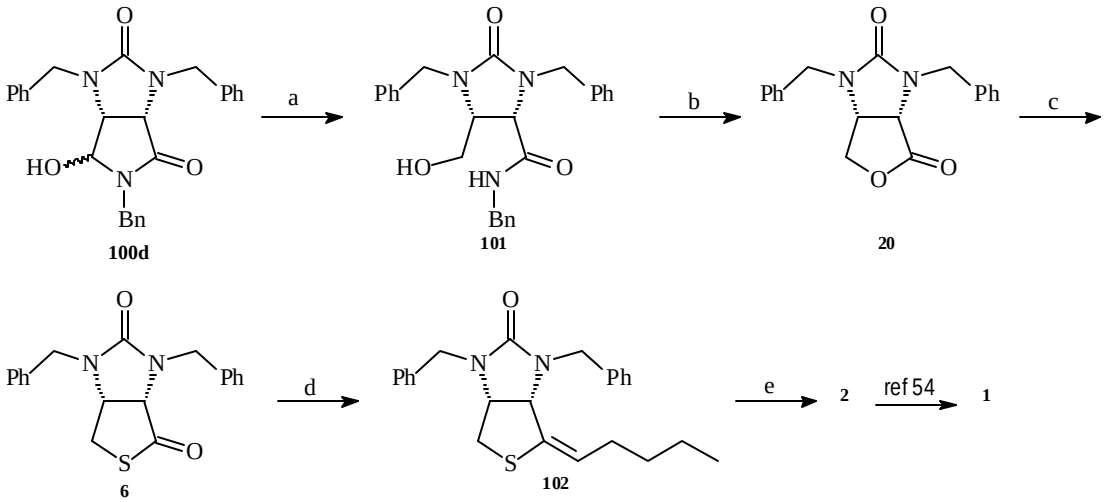
Conditions: ***a)*** *1-Bromo-3-chloropropane, K_2CO_3, toluene, 80 °C, 94%;* ***b)*** *47% HBr, NaBr, H_2SO_4, 50 °C, 86%;* ***c)*** *$(CHOH)_2$, TsOH, toluene, reflux, 92%;* ***d)*** *Mg, THF, rt;* ***e)****. Ac_2O, 83% H_3PO_4 (cat.), reflux, 98%;* ***f)*** *$Na_2S.9H_2O$, THF, H_2O, rt, 49%;* ***g)*** *(R)-BINAL-H, THF, -78 °C to rt, 83%;* ***h)*** ***95****, THF, reflux, then 30% H_2SO_4, 60 °C, 82%;* ***i)*** *I_2, KI, 10% NaOH, dioxane, 60 °C, 75%;* ***j)*** *75% HCOOH, CH_3SO_3H, 10% pd/c, reflux, 85%.*

In 1999 Shimazu and coworkers[53] reported stereo controlled reduction of *meso*-imides using oxazaborolidine.



The known *meso*-imide **98** was reduced using oxazaborolidine derived from L-threonine and borane-THF complex **99** to give lactams **100a-d** in high enantiomeric purity. This methodology was successfully applied to the synthesis of (+)-deoxybiotin in an enantio controlled manner in good overall yield.

Scheme 20: *Tetrahedron Lett.* **1999**, *40*, 8873

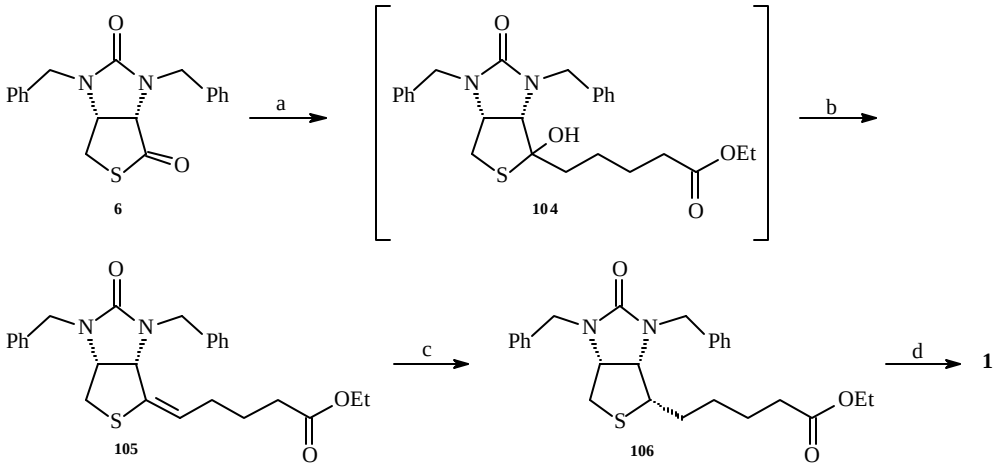


Conditions: ***a)*** *$NaBH_4$ (4.0 eq), THF-H_2O (10:1), 71%;* ***b)*** *2N H_2SO_4-1,4-dioxane (8:1), 0 ^oC, 92%;* ***c)*** *CH_3COSK, DMF, 150 ^oC, 87%;* ***d)*** *n-$C_5H_{11}MgBr$, THF, AcOH, reflux, 82%;* ***e)*** ***i)*** *Pd black, H_2, 40 ^oC, ^iPrOH-H_2O (6:1), 90%;* ***ii)*** *Na liq. NH_3, THF, 62%.*

The hydroxy lactam **100d** was reduced with $NaBH_4$ to give hydroxy amide **101** in 71% yield and the subsequent treatment with sulfuric acid gave the lactone **20** in 92% yield. Thiolactone **6** formation was carried out as described in the literature[55] in 87% yield. The side chain was introduced by the addition of a Grignard reagent followed by treatment with acetic acid gave **102** in 82% yield. Stereospecific hydrogenation of double bond and further *N*-debenzylation with Na in liq. NH_3 gave (+)-deoxybiotin **2** in 62% yield.

Very recently Seki *et al* reported[56] a facile synthesis of D(+)-biotin by using Fukuyama coupling[57] of carbonyl compounds.

Scheme 21: *Tetrahedron Lett.* **2000**, *41*, 5099



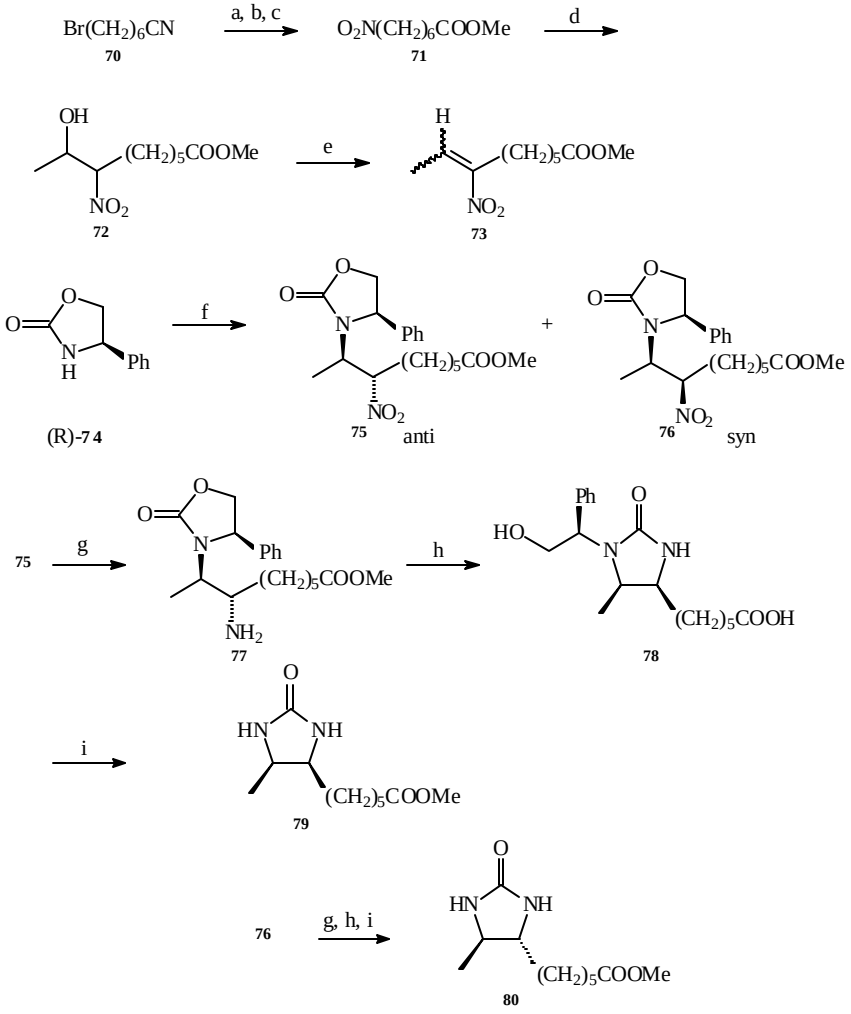
Conditions: a) *IZn(CH$_2$)$_4$CO$_2$Et* ***103*** *(3 eq), PdCl$_2$(PPh$_3$)$_2$ (10 mol%), THF, toluene, DMF, 20 ^{o}C, 35h;* ***b)*** *pTSA, toluene, 20 ^{o}C, 18h, 86%;* ***c)*** *H$_2$, (70 atms), Pd/C, EtOH, 100 ^{o}C, 3h, 91%;* ***d) i)*** *48% aq. HBr, reflux, 48h;* ***ii)*** *ClCOOEt, NaOH;* ***iii)*** *HCl, 80%.*

The known thiolactone **6** with zinc reagent **103** in presence of $PdCl_2(PPh_3)_2$ in mixed solvent at 20 ^{o}C for 35 h gave alcohol **104** which without purification was allowed to react with pTSA in toluene at 20^{o}C to furnish the known olefin **105** in 86% yield. The final conversion of **105** into (+)-biotin **1** further involved catalytic hydrogenation and debenzylation.

Very recently after completion of the present work Mioskowski and co workers[58] reported the synthesis of the diastereomers of dethiobiotin using the conjugate addition of 4-phenyloxazolidin-2-one to a nitroalkene (Scheme 22).

Nitroalkene **73** was prepared according to the sequence described in scheme 22. Commercially available 7-bromoheptanenitrile was converted in three efficient steps into known methyl 7-nitroheptanoate **71**. Henry reaction of **71** with acetaldehyde followed by elimination of hydroxy group by converting it into its acetate with Ac_2O followed by basic alumina yielded nitroalkene **73** as a 90:10 (*E*) and (*Z*) isomers. Conjugate addition of the potassium salt generated from either (*R*)-**74** or (*S*)-**74** by treatment with potassium *tert*-butoxide in THF in the presence of 0.1 eq of 18-crown-6, with nitroalkene **73** was performed. Only two diastereomeric adducts were formed (85:15) and the two diastereomers were separated by column chromatography.

Scheme 22: *Eur. J. Org. Chem.* **2000**, 3575



Conditions: ***a)*** *H_2SO_4, MeOH, 40h, reflux, 66%;* ***b)*** *NaI, acetone, 30h, reflux, 94%;* ***c)****. $AgNO_2$, ether, 3 days, rt, 80%;* ***d)*** *CH_3CHO, KOH, MeOH, 19h, 0 °C, 84%;* ***e) i)*** *DMAP, Ac_2O, ether, 16h, rt;* ***ii)*** *DMAP, basic alumina, 4h, reflux, 63%;* ***f) i)*** *^{t}BuOK, 18-crown-6 (cat.), THF, 0 °C, 20 min,* ***ii)*** ***73****, -78 °C, 45 min;* ***iii)*** *AcOH, 74%.* ***g)****. HCO_2NH_4, Pd/C, MeOH, 3 days, 72%;* ***h)*** *KOH, MeOH, 16h, reflux, 89%;* ***i)*** *H_2, $Pd(OH)_2$/C, MeOH, H_2SO_4(cat), 2 days 63%.*

The adducts **75** and **76** and their enantiomers *ent*-**75** and *ent*-**76** obtained from (*S*)-4-phenyloxazoldin-2-one were then all converted into the dethiobiotin methyl ester or into its stereoisomers. Treatment of **75** with ammonium formate in the presence of palladium on carbon in methanol afforded the corresponding amine **77**. Heating this compound at reflux with potassium hydroxide in methanol led to the more stable imidazolidinone **78**. And finally the imidazolidinone **78** was subjected to hydrogenolysis to get imidazolidinone **79**. The same sequence was carried out for nitro compound **76** as summarized in the above scheme.

1.1.3 References

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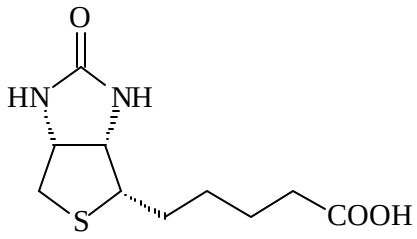
1.2.1 Introduction

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.



1

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.

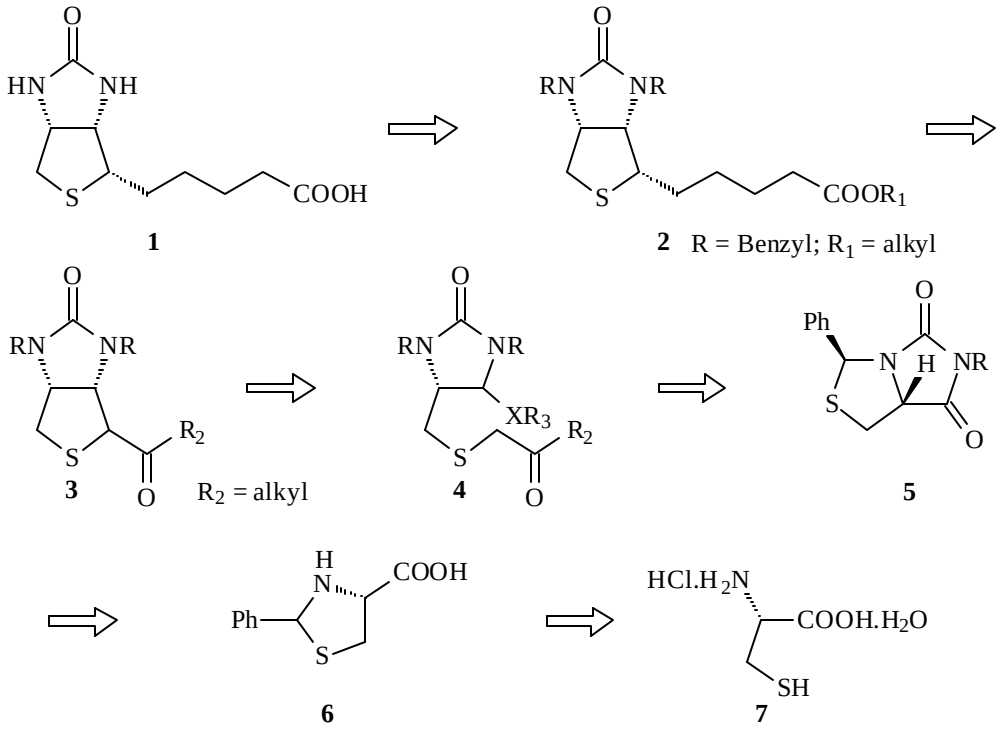
Although a number of syntheses[2] of biotin are known (see Chapter 1 Section 1), most of them are not practical enough to be commercialized. There was thus a need to develop a more practical route to D(+)-biotin. Keeping this view in mind, efforts were directed towards development of a practical synthesis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

1.2.2 Retrosynthetic analysis

Our synthetic endeavor is described in retrosynthetic scheme 1. According to this scheme 5,5 fused bicyclic skeleton **3** was the key intermediate which in turn could be accessed from the cyclization of **4**. The success of the synthetic route depended heavily and hinged on the ease of availability of appropriately substituted **4** from hydantoin **5**.

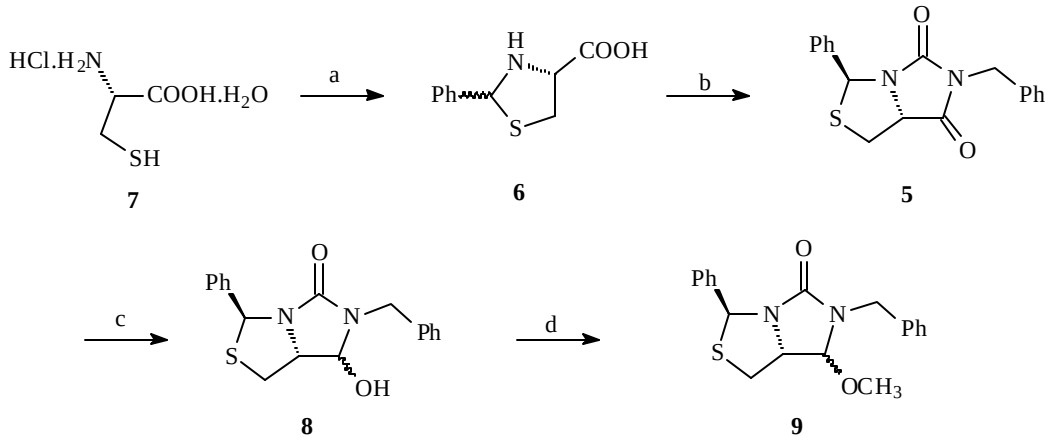
Scheme 1:



1.2.3 Results and Discussion

In accordance with the planned synthesis, cysteine hydrochloride hydrate (**7**) was converted to its known 4-(*R*)-carboxy-2-phenylthiazolidine (**6**)[3] with benzaldehyde in the presence of potassium acetate. A one-pot addition of isocyanate to secondary amine followed by dehydration under acidic conditions furnished the compound imidazolidinone **5** in 90% yield.

Scheme 2:

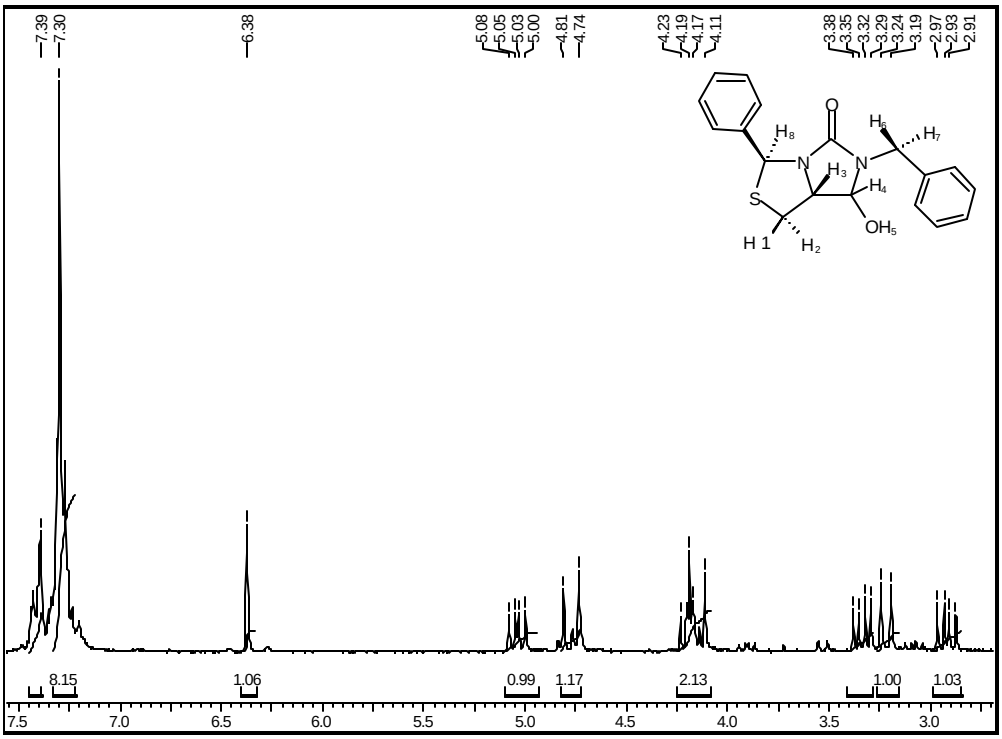


7 **6** **5**

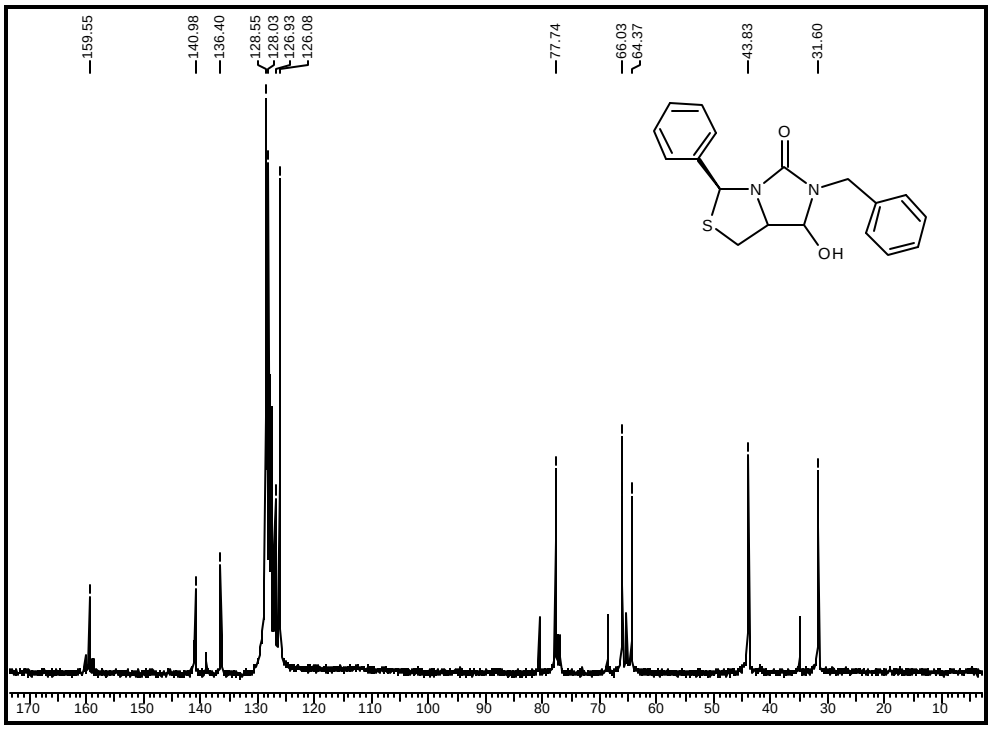
8 **9**

***Conditions**: **a**) PhCHO, KOAc, MeOH:H2O (1:1), rt, 6h, 98%; **b**) BnNCO, DCM, 60 min, Conc. HCl, 60 min, reflux, 90min, 90%. **c**) NaBH4, MeOH, 0 °C to rt, 1h, 98%; **d**) MeOH, pTSA (catalytic), 15 min, 98%.*

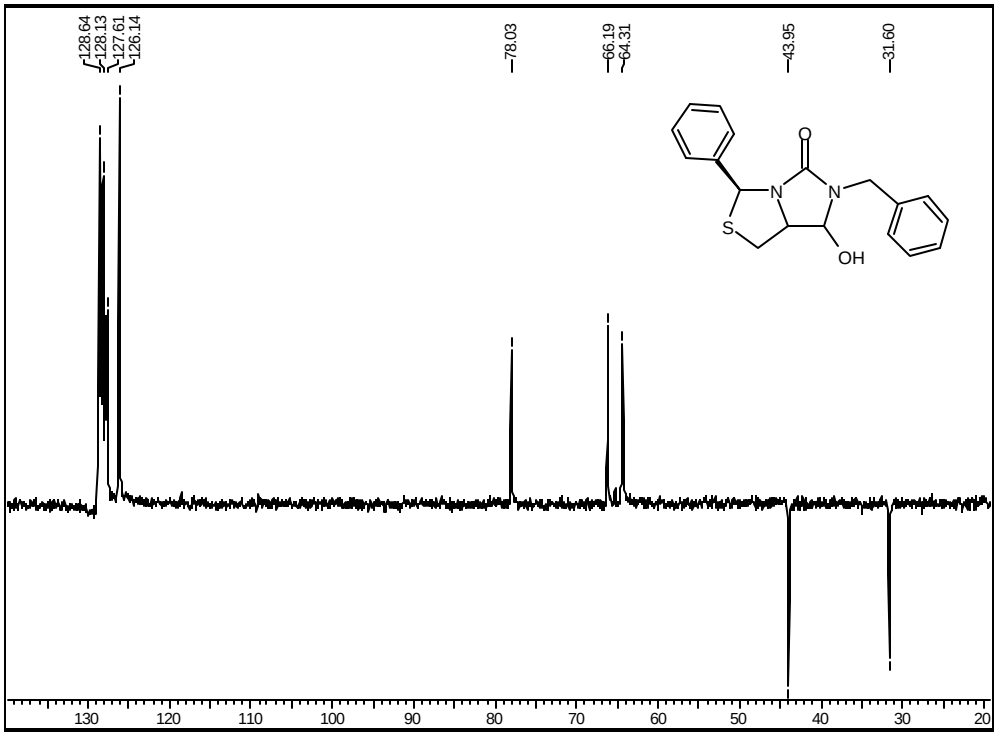
Reduction of imidazolidinone **5** with sodium borohydride gave hydroxy imidazolidine **8** in almost quantitative yield. IR spectrum of hydroxy imidazolidine exhibited presence of –OH stretching at 3300. Mass spectrum of compound **8** showed molecular ion peak at 326.



^{1}H NMR spectrum of compound **8** ($CDCl_3$, 200 MHz)



^{13}C and DEPT NMR spectra of hydroxy imidazolidine **8** ($CDCl_3$, 125MHz)



^1H NMR spectra of aminol **8** revealed a multiplet at δ 7.4 for two protons and another multiplet at ä 7.3 integrating for eight protons which were assigned to the 10 aromatic protons. A singlet at

ä 6.38 was assigned to benzylidine proton, doublet of doublet at ä 5.04 (J = 6.84, 10.26 Hz) for one proton was assigned to H_4 proton, doublets at ä 4.78, 4.18 (J = 15.14 Hz) were assigned for two benzylic protons (H_6, H_7), multiplet at ä 4.19 (J = 5.37, 6.83 Hz) for one proton was assigned for H_3, doublet of doublet at ä 3.33 (J = 5.37, 11.72 Hz) for one proton was assigned to H_2 proton, doublet at ä 3.23 (J = 10.26 Hz) was assigned for hydroxy proton H_5 (D_2O exchangeable), and doublet of doublet at ä 2.92 (J = 6.84, 11.72 Hz) for one proton was assigned to H_1 proton.

Treatment of hydroxy imidazolidine **8** with methanol at room temperature under acidic conditions (pTSA) furnished methoxy imidazolidine **9**. Absence of broad singlet at 3300 cm^{-1} in IR spectrum and presence of singlet for three protons at ä 3.31 indicated incorporation of methoxy group.

With desired methoxy imidazolidine **9** in hand there was a need to cleave the C-S bond and alkylation of mercapto compound with alkyl halide to get the appropriately functionalized desired system for the proposed 5,5-fused system of D(+)-biotin. The conventional method of reductive cleavage of C-S bond employing Zn/AcOH[4] led to the formation of undesired olefin obtained by elimination of the alcohol.

A systematic study of reductive cleavage of C-S bond with various reagents was undertaken. This mainly comprises of three types of reagents which are described as follows:

The use of free radical reactions for the formation of carbon-carbon bonds is now an important tool in the design of total synthesis.[5]

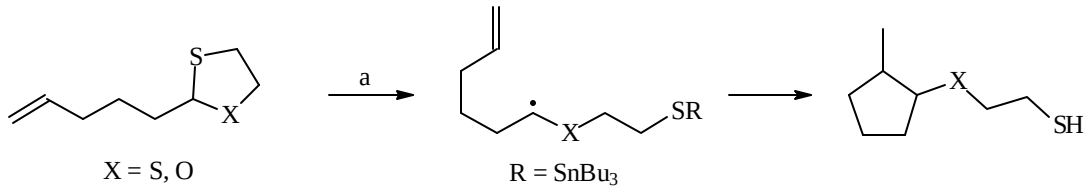
I. Tri n-butyltin hydride as reducing agent:

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 $R^1C(O)R^3$) or a carbonyl derivative ($R^1C(O)R$ to R^2R^1COH).

Gutierrez et al[6] 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[7] that aldehydes or ketones protected as 1,3-oxathiolanes[8] and 5-oxo-1,3-thiolanes undergo facile S_H2 cleavage of C-S bond in a reaction with stannyl radicals.

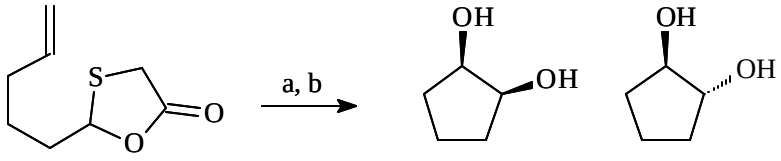
Scheme 3: *Tet. Lett.*, **1988**, *29*, 897



10 **11** **12**

***Condition**: **a**) Tri-n-butyltin hydride, AIBN, benzene, reflux.*

Scheme 4: *Tet. Lett.*, **1989**, *30*, 3283

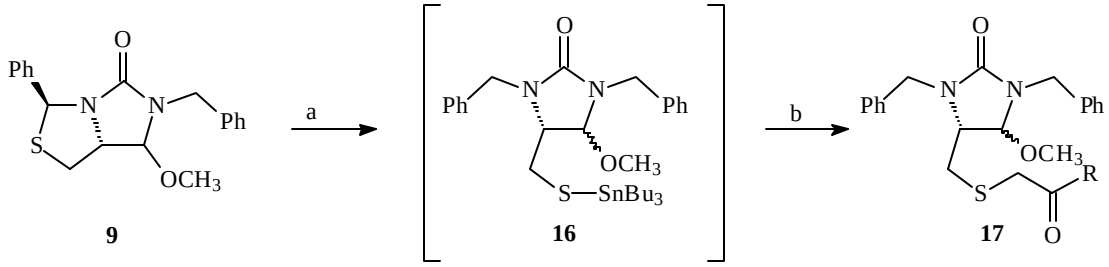


13 **14** **15**

***Conditions**: **a**) Tri-n-butyltin hydride, AIBN, benzene, reflux; **b**) NaOH, aq. EtOH.*

Based on the above literature precedents reductive cleavage of carbon-sulphur bond of methoxy imidazolidine **9** employing above-mentioned condition was attempted.

Scheme 5:

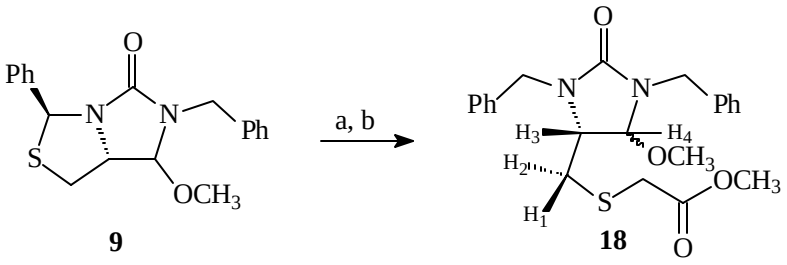


9 **16** **17**

***Conditions**: **a**) Tri-n-butyltin hydride, AIBN, benzene, reflux; **b**) Chloroketone, anhyd. K_2CO_3, acetone, rt, 12h.*

Thus methoxy imidazolidine **9** was treated with *tri*-n-butyltin hydride in presence of catalytic amount of radical initiator [azobis (isobutyronitrile)] (AIBN) in benzene at elevated temperature for 30-45 min. It was gratifying to note that under these conditions cleavage of C-S bond was achieved. This constitutes one of the novel approach to cleave C-S bond in imidazolidine type moiety. Unstable nature of S-$SnBu_3$ compound necessitated isolation as the S-alkyl compounds **17** obtained after alkylation with chloroketone/ester under anhydrous conditions with potassium carbonate as a base and acetone as a solvent. In the case of methyl chloroacetate as alkylating agent 80% of *S*-alkylated **18** product was obtained. It was discovered that the alkylation reaction did not proceed in the absence of potassium carbonate.

Scheme 6:



9 **18**

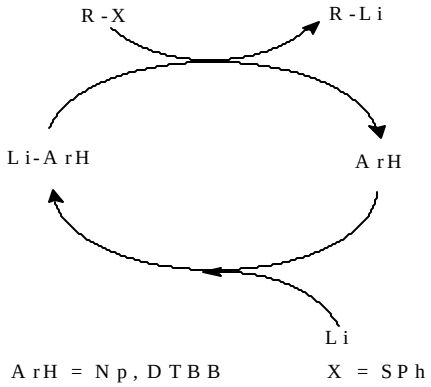
***Conditions**: **a**) Tri-n-butyltin hydride, AIBN, benzene, reflux; **b**) Methyl chloroacetate, anhyd. K_2CO_3, acetone, rt, 12h, 83%.*

The ^1H NMR of S-alkylated compound **18** indicated the presence of a singlet at ä 4.50 for one proton (H_4). The doublet of doublet at ä 2.80 (J = 3.7, 14Hz) and 2.53 (J = 7.5, 14Hz) were assigned to H_1 and H_2. Correspondingly quintet (ddd) (J = 3.7, 7.5 Hz) was also observed for H_3 proton at ä 3.4. Singlets at ä 3.1 for three protons and another one at ä 3.0 for two protons were assigned to methoxy and methylene protons α-to methyl ester group respectively. Aromatic and methyl ester protons appeared at their expected chemical shifts. Mass spectrum of *S*-alkylated compound **18** exhibited M^+ peak at 414 lending further evidence for the proposed structure.

Having successfully achieved the reductive cleavage by radical method other reductive methods to cleave C-S bond were also explored.

II. Li/Arene as reducing agent:

Organolithium compounds are very useful intermediates in synthetic organic chemistry mainly in carbon-carbon bond forming processes by reaction with carbon electrophiles. Among the different methods to prepare this type of organometallic compound, the most versatile is probably *via* halogen-lithiation exchange, bromine and chlorine being the most commonly used halogens. For this purpose commercially available lithium is in general reactive enough to perform this transformation unless the reaction has to be carried out at low temperature. In this case it is necessary to activate the metal. One way to get very active lithium is to dissolve the metal in a stoichiometric amount of an arene, almost always using tetrahydrofuran as solvent. Among the arenes, naphthalene (Np) and 4,4'-di-*tert*-butylbiphenyl (DTBB) are the most frequently used for electron transfer.

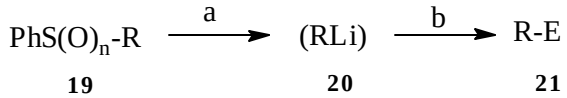


Few years ago Yus and coworkers[9] have demonstrated the use of catalytic amount of an arene in the lithiation of functionalized chlorinated precursors is a very powerful method to prepare unstable functionalized organolithium compounds[10] under very mild conditions.

Lithiation of phenylsulfides[11] allows the preparation of unsubstituted[12] and α-functionalized organolithium compounds.

In 1994 Yus *et al*[13] for the first time demonstrated a reductive desulfonylation, and desulfinylation reaction of sulfones and sulfoxides respectively using an arene catalyzed lithiation, which represents both a new type of reactivity of sulfones and sulfoxides, as well as a new route for organolithium reagents.

Scheme 7: *Tetrahedron,* **1995,** *51*, 2699



n = 1,2

R = Et, $-CH_2-CH=CH_2$, ^iPr, $PhCH_2$

E^+ = iPrCHO, PhCHO, Et_2CO

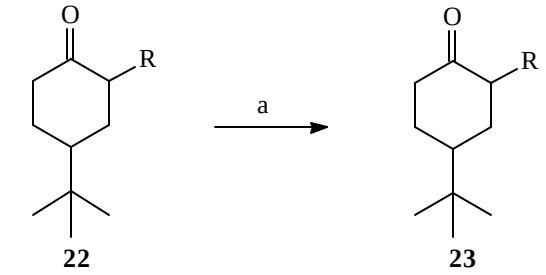
***Conditions**: **a**) Li powder, $C_{10}H_8$ cat (8 mol%); **b**) E^+, THF, -78 °C to 20 °C then H_2O*

Taking cue from the above report reductive cleavage of C-S bond of methoxy imidazolidine was attempted under the conditions mentioned. Thus methoxy imidazolidine **9** was subjected to the treatment with lithium naphthalide at –78 °C in THF and further *S*-alkylation with methyl chloroacetate under basic condition the furnished the corresponding *S*-alkylated compound **18** in 74% yield.

III. Zn/NH_4Cl as reducing agent:

Holton *et al*[14] has developed a novel and very mild method for the reductive desulfurization of α-phenylthio and α-phenylslfinyl carbonyl compounds using zinc metal and aqueous ammonium chloride solution at room temperature.

Scheme 8: *J. Org. Chem.***1987**, *52*, 2317

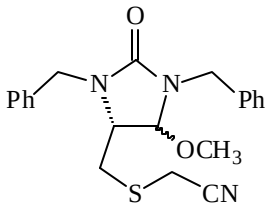


22 **23**

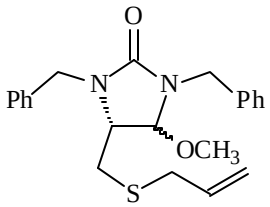
R = SPh or SOPh R = H

***Condition**: **a**) Zinc, aq.sat NH_4Cl:THF (1:1), 32h, 94%.*

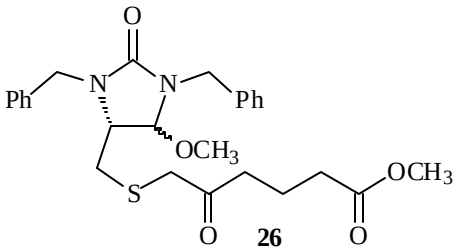
Attempted reductive cleavage of C-S bond of methoxy imidazolidine **9** under Holton's conditions and further *S*-alkylation under basic condition yielded same intermediate **18** as mentioned earlier in 63% yield. By changing the alkyl halide and using any one of the above three methods compounds of the formulae **18, 24-26** were also prepared. The following table 1 summarizes the results obtained by employing the three methods.



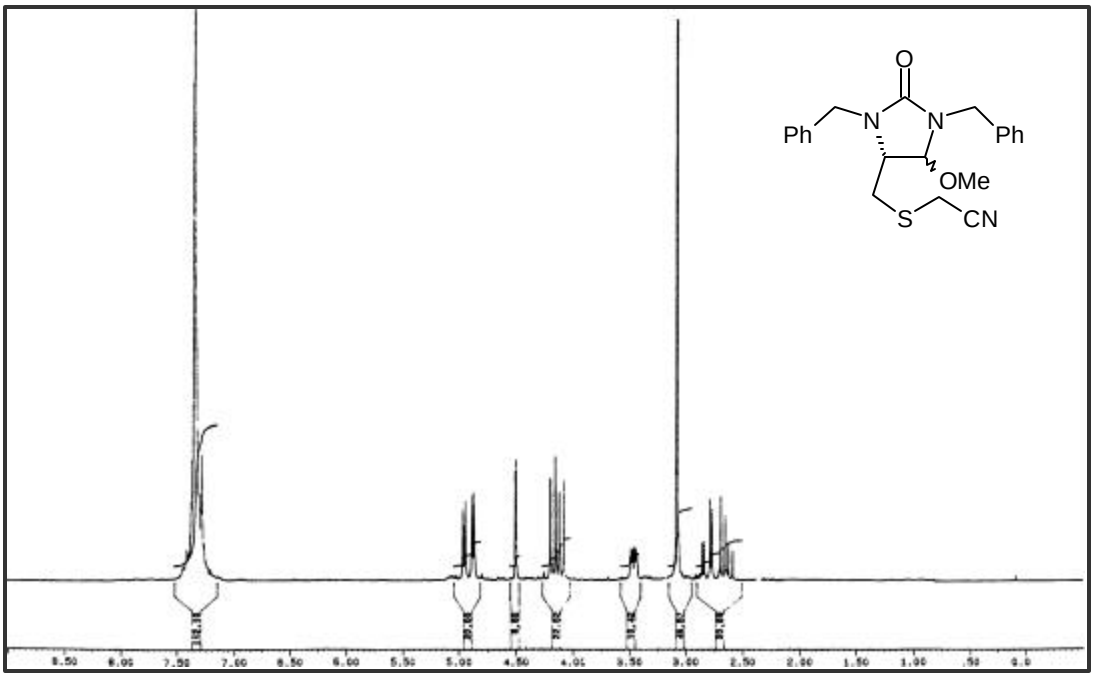
24



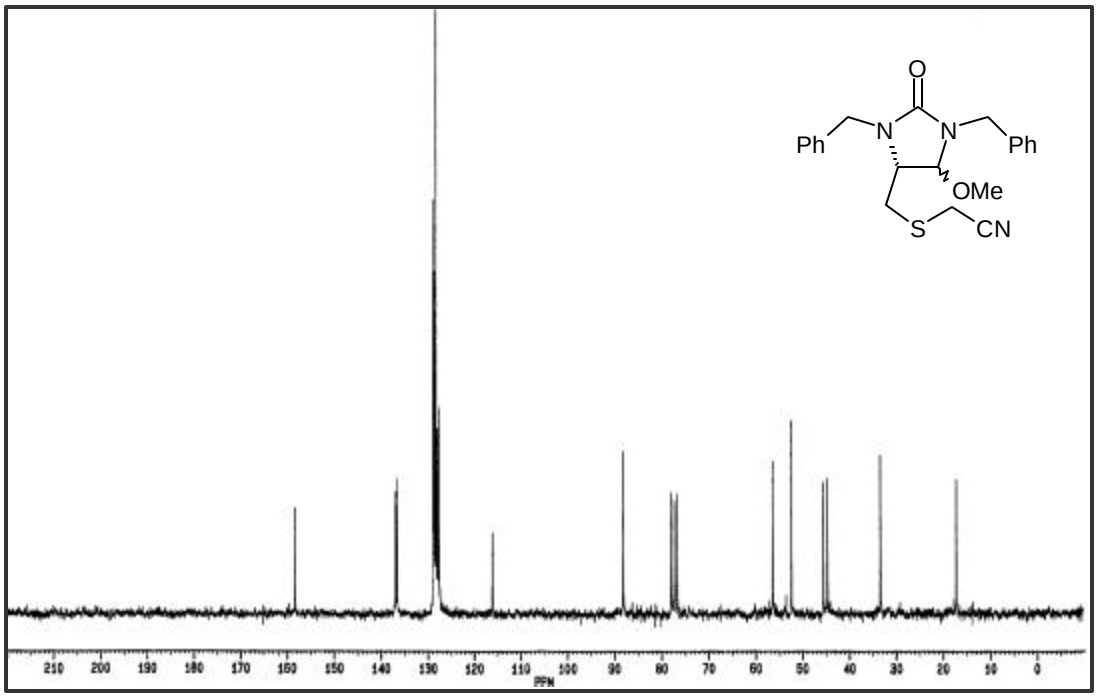
25



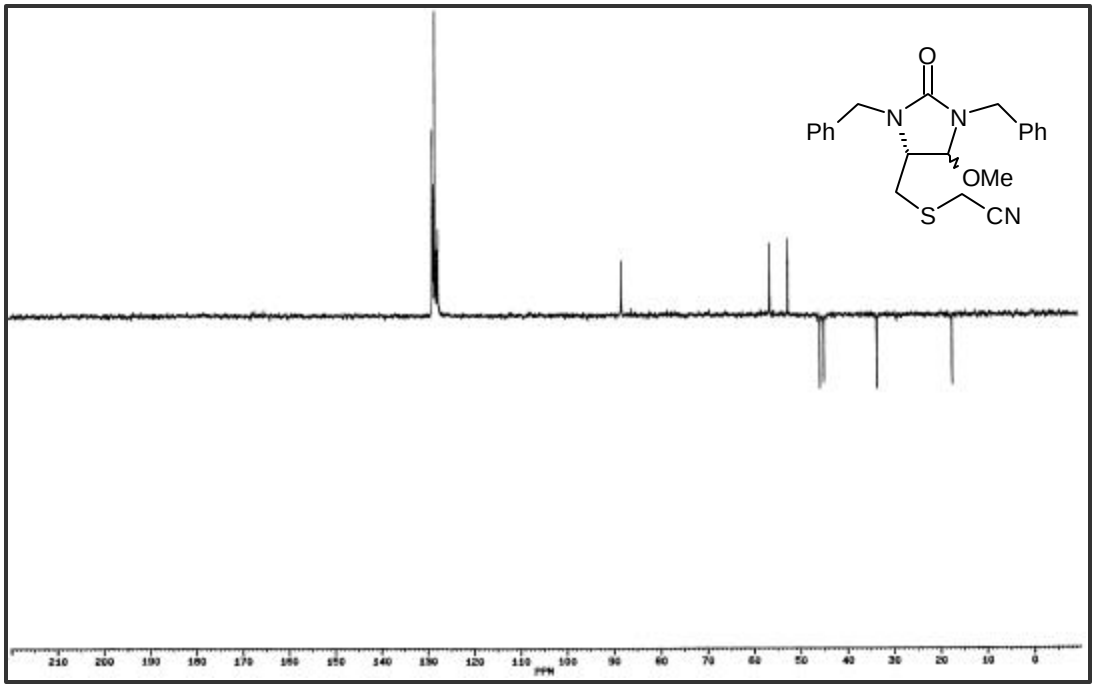
26

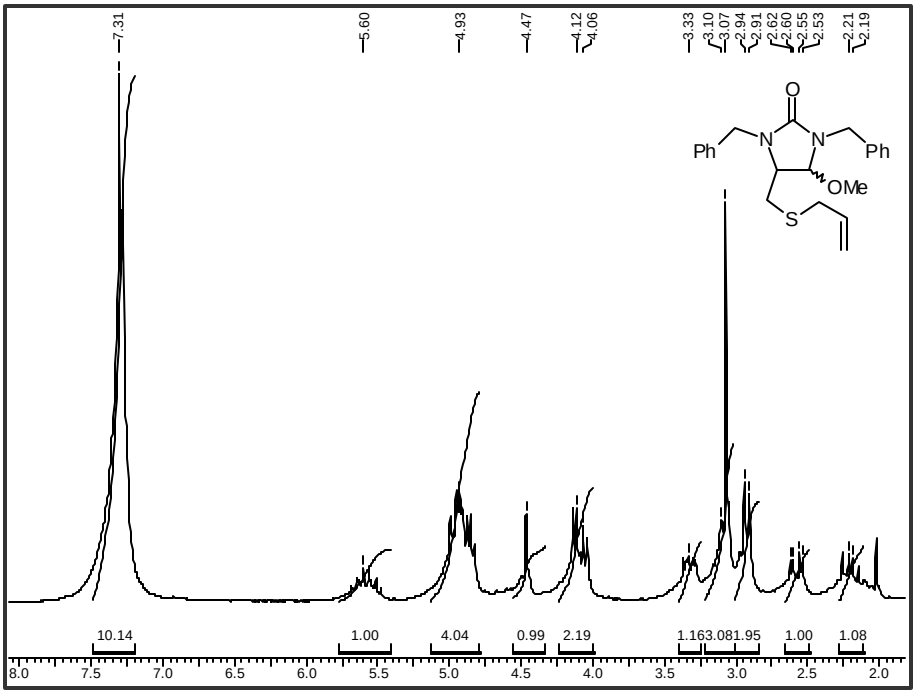


^{1}H NMR spectrum of compound **24** ($CDCl_3$, 200 MHz)

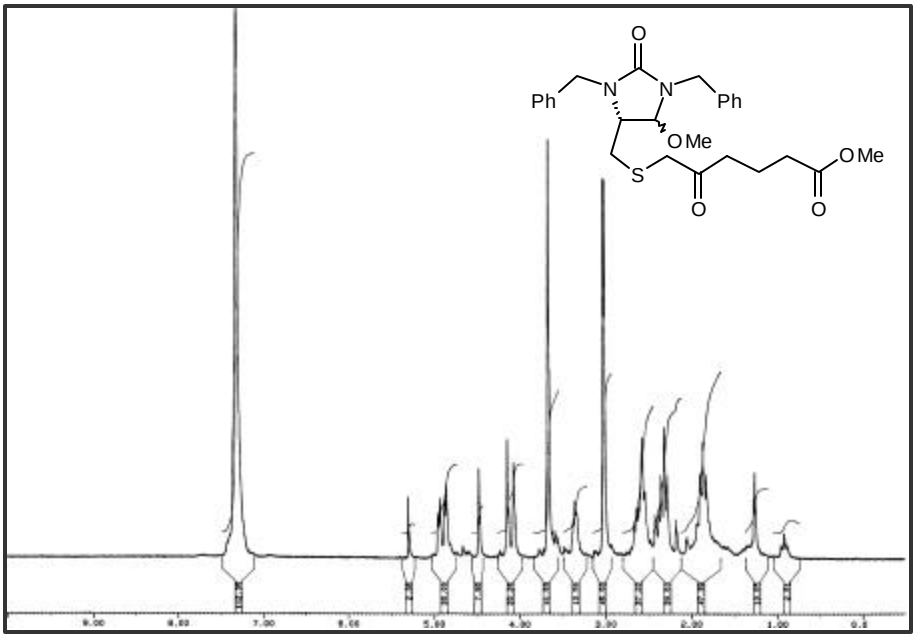


^{13}C & DEPT NMR spectra of compound **24** ($CDCl_3$, 50 MHz)

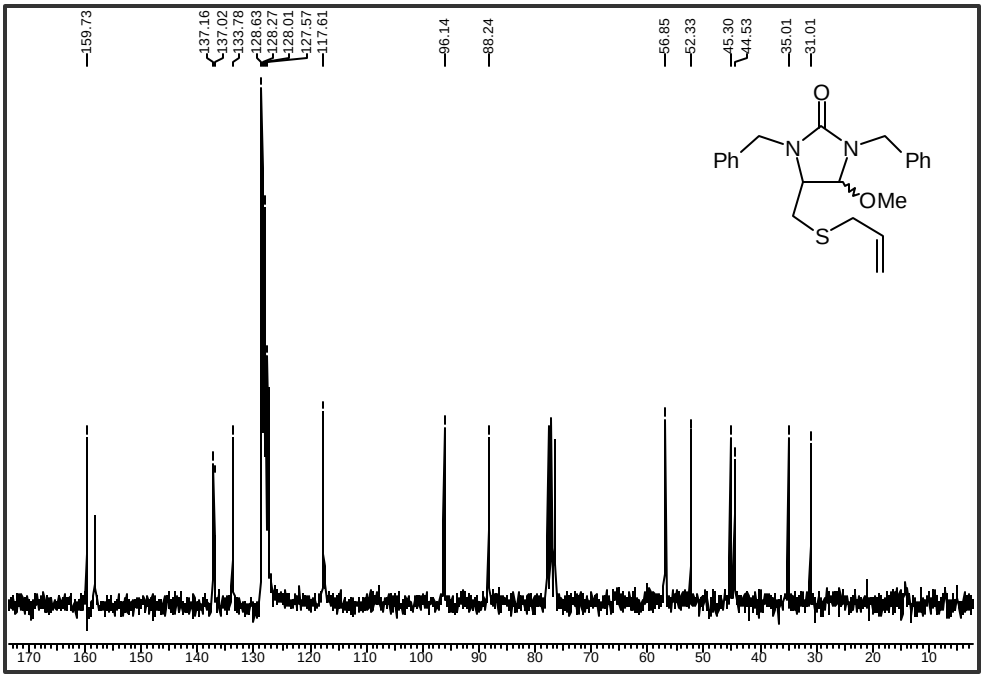




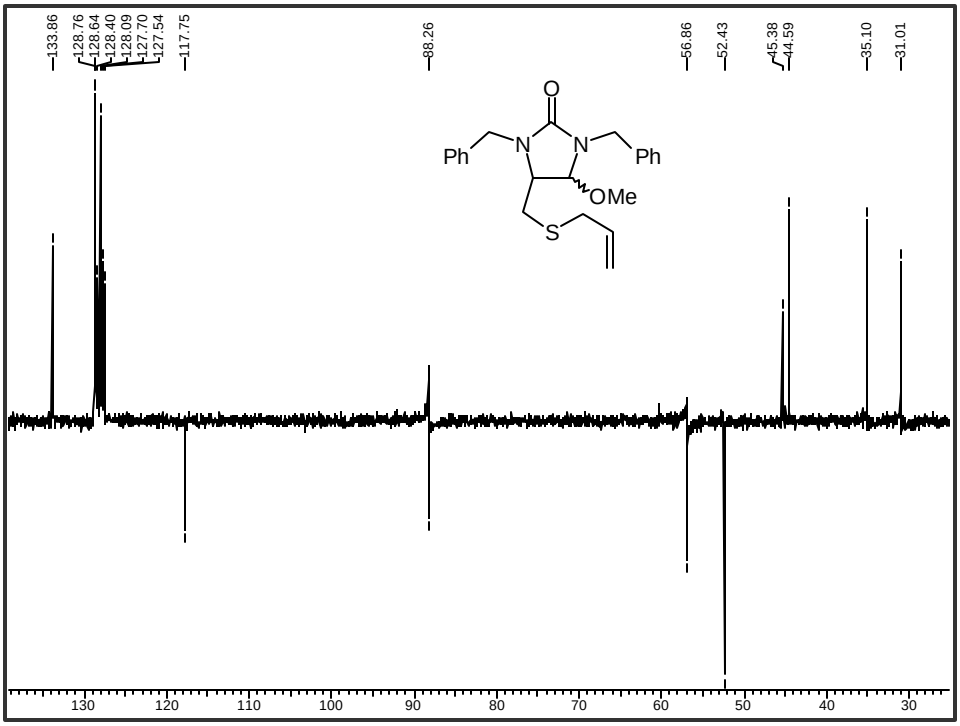
^{1}H NMR spectrum of compound **25** ($CDCl_3$, 200 MHz)

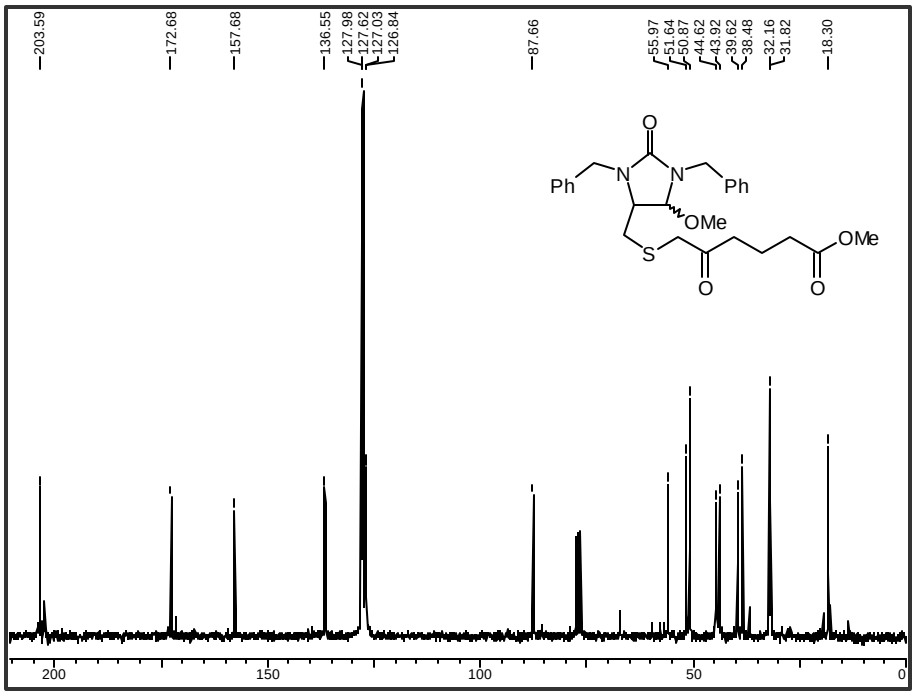


^{1}H NMR spectrum of compound **26** ($CDCl_3$, 200 MHz)

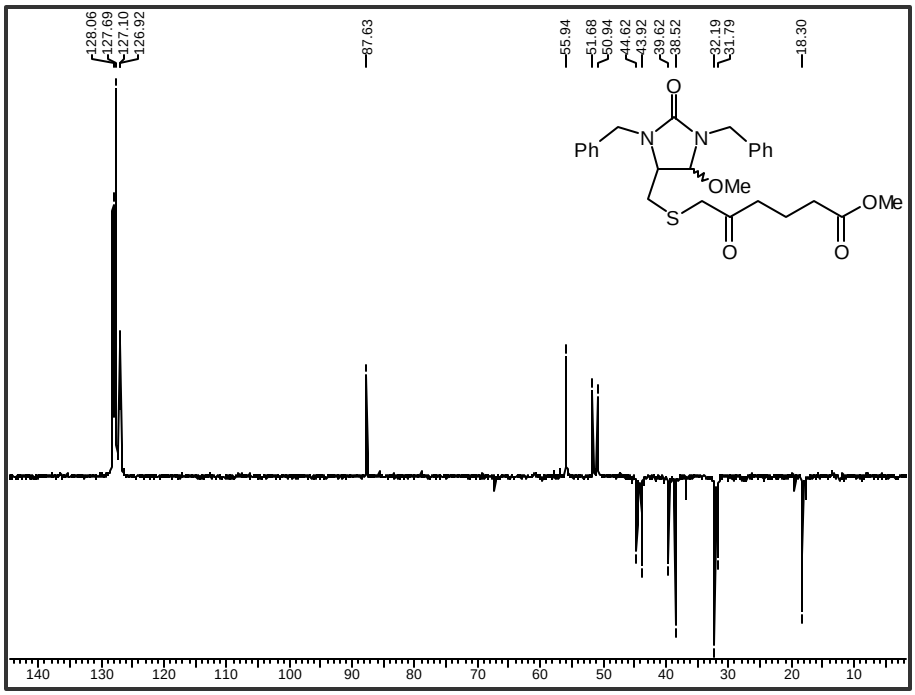


^{13}C & DEPT NMR spectra of compound **25** ($CDCl_3$, 50 MHz)





^{13}C & DEPT NMR spectra of compound **26** (CDCl3, 50MHz)



All these alkylated derivatives are very useful intermediates for constructing 5,5-fused system which is present in D(+)-biotin skeleton. (for details see Chapter 1 Section 3)

Table 1: Comparison of formation of S-alkylated compounds with various reducing systems.

	Alkylating Agent (% of yield)			
	$ClCH_2COOMe$	$ClCH_2C(O)(CH_2)_3COOMe$	$ClCH_2CN$	$ClCH_2CH=CH_2$
Method A[1]	80%	70%	78%	85%
Method B[2]	74%	64%	76%	80%
Method C[3]	63%	58%	70%	73

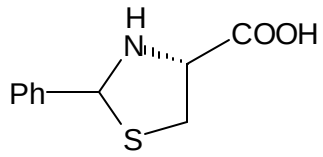
[1] Reduction of C -S bond was achieved with tri n-butyltin hydride.
[2] Reduction of C -S bond was achieved with lithium naphthalide.
[3] Reduction of C-S bond was achieved with zinc and aq. saturated NH_4Cl.

Results from the above table 1 clearly establish the superiority of the n-tributyltin hydride as an efficient reagent in effecting reductive cleavage of C-S bond as compared to Li/Arene or Zn/NH_4Cl(sat)

In conclusion reductive cleavage of C-S bond of methoxy imidazolidine was successfully achieved by three independent methods and this intermediate is converted to S-alkylated compounds **18**, **24-26** which are required for biotin skeleton are useful precursors for intramolecular ionic or radical ring closure to obtain 5,5 -fused system.

1.2.4 Experimental

1. Preparation 4-(*R*)-carboxy-2-phenylthiazolidine (6):[3]



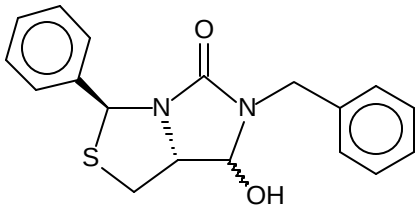
To a solution of L-cysteine hydrochloride hydrate (60g, 0.34 mol), in water (525 mL) and potassium acetate (36g, 0.37 mol) was added. After a solution was obtained, 95% of methanol (525 mL) was added; followed immediate addition of benzaldehyde (44.2g, 0.42 mol) in one portion. The product thiazolidine soon began to crystallize. The reaction mixture was kept at 25 ^{o}C for three hours and an additional three hours at 0 ^{o}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 ^{o}C (Lit [3] 159-160 ^{o}C)
Optical Rotation	:$[\alpha]_D$ = -133^{o} (c=1, DMSO)
IR (KBr, cm^{-1})	: 3040, 2960, 2700-2400 (NH_3^+), 1600-1550 (CO_2^-) 1360.
^{1}H NMR (DMSO-d_6, 200MHz)	: 3.50-3.30 (m, 2H, CH_2); 4.40-4.0 (dd, 1H, CHCOOH); 5.80 (s, 1H, CH); 6.80 (bm, 1H, NH)); 7.40 (m, 5H).
Mass (m/z)	: 209(M^+ 34), 170(39), 164(65), 137(100), 77(10), 65(8), 55(7).

2. 6-Benzyl-3-phenyl(3*S*, 7a*R*)perhydroimidazo[1,5-c][1,3]-thiazol-5,7-dione (5):

For the preparation of the above compound please see chapter 2: section 2.

3. 6-Benzyl-7-hydroxy-3-phenyl(3*S*, 7a*R*)perhydroimidazo[1,5-c][1,3]-thiazol-5-one (8):



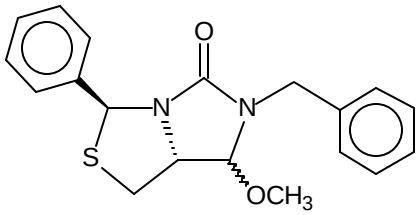
The imidazolidinone **5** (32.4g, 0.1 mmol) was taken in aq. THF or methanol (300 mL) and cooled to 0 ^{o}C. Sodium borohydride (5.6g, 0.15mol) was added gradually in small portions at a time. After addition of sodium borohydride was over, the reaction mixture was brought to room temperature. Stirring 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 under reduced pressure a white crystalline solid of hydroxy hydantoin **8** was obtained in almost quantitative yield.

Yield	: 32.5g (99%).
Mol. Formula	: $C_{18}H_{18}N_2O_2S$, white solid.
M.P.	: 113 ^{o}C
Optical Rotation	:$[\alpha]_D$ = +52.58^{o} (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, 11.72Hz); 3.23 (d, 1H, J = 10.26Hz, -OH, D_2O exchangeable); 3.33 (dd, 1H, J = 5.37, 11.72Hz); 4.18 (d, 1H, J = 15.14Hz); 4.19 (m, 1H, J = 5.37, 6.83Hz, -CH-CH-OH); 4.78 (d, 1H, J = 15.14Hz); 5.04 (dd, 1H, J = 6.84, 10.26Hz, N-CH-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(3*S*, 7a*R*)perhydroimidazo[1,5-c][1,3]-thiazol-5-one(9):



The hydroxy imidazolidine **8** (32.6g, 0.1mol) was dissolved in anhydrous methanol (300 mL) and to this solution catalytic amount of pTSA 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_2CO_3 and filtered. Removal of solvent and extraction with EtOAc furnished the methoxy hydantoin **9** in almost quantitative yield.

Yield : 33.8g (99%).

Mol. Formula : $C_{19}H_{20}N_2O_2S$, white solid.

M.P. : 83 ^oC

Optical Rotation :$[\alpha]_D = -210^o$ (c=1, $CHCl_3$)

IR (in $CHCl_3$, cm^{-1}) : 2930, 1705, 1510, 1420, 1360, 1236, 1160, 1005.

^1H NMR ($CDCl_3$, 200MHz) : 2.55 (t, 1H, J = 9.75Hz); 3.13 (dd, 1H, J = 4.87, 12.19Hz); 4.0 (dd, 1H, J = 4.87, 9.75Hz); 3.30 (s, 3H); 4.21 (d, 1H, J = 15.14Hz); 4.65 (s, 1H); 4.90 (d, 1H, J = 15.14Hz); 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), 65(6).

Analysis :

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

General procedure for the reductive cleavage of C-S bond of methoxy imidazolidine 9:

A). By using tri-n-butyltin hydride:

A solution of methoxy hydantoin (34.0g, 0.1mol), tributyltin hydride (34.9g, 0.12mol) and AIBN (50 mgs) in dry benzene (400 mL) was refluxed for 30 min with addition of few crystals (10 mgs) of AIBN at the end of every 10 min. The progress of the reaction was monitored by using TLC. After completion of reaction, organic solvent was evaporated and the residue was stirred with chloro compound (0.1mol) and anhydrous potassium carbonate (41.4g, 0.3mol) in anhydrous acetone (100 mL) for 10-12 hrs at room temperature. After filtration and evaporation of organic solvent, the residue was column chromatographed using 35% EA: Pet.ether as eluent to furnish S-alkylated compounds.

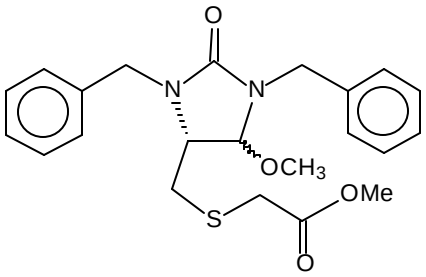
B). By using Li/Arene:

To cooled (-78 ^{o}C) suspension of lithium (0.0347g, 0.011 mmol) and naphthalene (0.0034 g; 0.026 mmol) in tetrahydrofuran (20 mL) was added methoxy imidazolidine **9** (0.340g, 1 mmol) in tetrahydrofuran (10 mL) and stirred for 3 hrs. The reaction was quenched with water as an electrophile and temperature of the reaction was raised to 20 ^{o}C during 1 hr. The reaction mixture was filtered through celite and extracted with ethylacetate. On evaporating the organic solvent the residue was subjected to alkylation with chloro compounds as mentioned in method A.

C). By using Zn/sat. NH_4Cl:

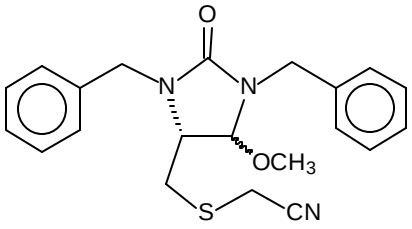
To a solution of methoxy imidazolidine **9** (0.34g, 1 mmol) in THF (7 mL) was added activated zinc (2g, 30.5 mmol) and saturated aqueous ammonium chloride solution (7 mL). The mixture was stirred vigorously at 25 ^{o}C under nitrogen atmosphere. Progress of the reaction was monitored by TLC, which indicated that no unreacted **9** remained after 12h. The reaction mixture was diluted with water (20 mL) and extracted with ethyl acetate (2x30 mL). The organic layer was extracted with two 20 mL portions of saturated aqueous sodium bicarbonate solution, dried over anhydrous Na_2SO_4, filtered and evaporated. The crude mass was subjected for S-alkylation with halo alkanes as mentioned in method A.

5. 1,3-Dibenzyl-2-oxo-5-(3-carbomethoxycarbonyl-2-thiapropyl)-4-methoxy-imidazolidine (18):



Yield	: 38.6g (80%).
Mol. Formula	: $C_{22}H_{26}N_2O_4S$, viscous liquid.
M.P./B.P.	: Highly viscous liquid
Optical Rotation	:$[\alpha]_D = -18.4^0$ (c=1.04, $CHCl_3$)
IR (neat, cm^{-1})	: 3006, 2930, 1725, 1701, 1450, 1358, 1234, 1077.
^1H NMR ($CDCl_3$, 200MHz)	: 2.50 (dd, 1H, J = 8.3, 12.50Hz); 2.71 (dd, 1H, J = 4.16, 12.50Hz); 2.87 (s 2H); 3.01 (s, 3H); 3.58 (dd, 1H, J = 4.16, 8.3Hz); 3.64(s, 3H); 4.0 (d, 1H, J = 15.46Hz); 4.31 (d, 1H, J = 15.46Hz); 4.52 (d, 1H, J = 15.34Hz); 4.57 (s, 1H); 5.11 (d, 1H, J = 15.46Hz); 7.36 (m, 10H).
Mass (m/z)	: 414(M^+, 1), 399(1), 382(3), 309(5), 295(15), 277(10), 203(2), 181(5), 161(4), 132(5), 117(2), 105(6), 91(100), 77(4), 65(14).

6. 1,3-Dibenzyl-2-oxo-5-(3-cyano-2-thiapropyl)-4-methoxy-imidazolidine (24):



Yield	: 29.7g (78%).
Mol. Formula	: $C_{21}H_{23}N_3O_2S$ (381)
M.P./B.P.	: Highly viscous liquid

Optical Rotation : $[\alpha]_D = +49.73^o$ (c=1, $CHCl_3$)

IR (neat, cm^{-1}) : 2925, 2230, 1703, 1463, 1359, 1237, 1077.

^1H NMR ($CDCl_3$, 200MHz) : 2.62 (dd, 1H, J = 7.54, 11.32Hz); 2.80 (dd, 1H, J = 3.89, 11.32Hz); 3.03 (s, 3H); 3.05 (s, 2H); 3.45 (m, 1H); 4.15 (dd, 2H, J =15.10Hz); 4.50 (d, 1H, J = 1.3Hz); 4.90 (dd, 2H, J = 15.10Hz); 7.35 (m, 10H).

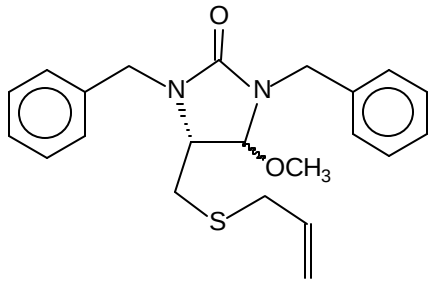
^{13}C NMR ($CDCl_3$, 50 MHz) : 17.12(t), 33.3(t), 44.6(t), 45.5(t), 52.3(q), 56.3(d), 88.1(d), 116.0(s), 127.5(d), 127.8(2C, d), 128.2(3C, d), 128.5(2C, d), 128.8(2C, d), 136.4(s), 136.8(s), 158.2 (s, C=O).

Mass (m/z) : 381(M^{+1}, 1), 361(1), 349(1), 295(18), 277(4), 269(4), 257(1), 233(4), 204(3), 187(3), 177(15), 162(3), 149(4), 134(6), 121(9), 106(10), 91(100), 77(4), 65(13).

Analysis :

	Carbon	Hydrogen	Nitrogen	Sulphur
Calc.:	66.12	6.08	11.01	8.41
Found:	66.30	5.85	10.82	8.95

7. 1,3-Dibenzyl-2-oxo-5-(2-thiapentyl-4ene)-4-methoxy-imidazolidine (25):



Yield : 32.5g (85%).

Mol. Formula : $C_{22}H_{26}N_2O_2S$ (382)

M.P./B.P. : Highly viscous liquid

Optical Rotation : $[\alpha]_D = +41.3^o$ (c=1, $CHCl_3$)

IR (neat, cm^{-1}) : 3062, 3026, 2922, 1709, 1620, 1494, 1424, 1356, 1224, 1094, 1029.

^1H NMR ($CDCl_3$, 200MHz) : 2.21 (dd, 1H, J = 9.28, 13.68Hz); 2.58 (dd, 1H, J = 3.90, 13.68Hz); 2.93 (d, 2H, J = 7.33Hz); 3.07 (s, 3H); 3.33 (m, 1H, J = 3.90, 9.28Hz); 4.08 (d, 1H, J = 15.62Hz); 4.10 (d, 1H, J = 15.14Hz); 4.47 (d, 1H, J = 0.97Hz); 4.91 (m, 4H); 5.58 (m, 1H); 7.29 (m, 10H).

^{13}C NMR ($CDCl_3$, 50 MHz) : 30.92(d), 35.01(d), 44.53(q), 52.34(2C, t), 56.77(t), 88.24(t), 117.53(t), 127.36(d), 127.48(d), 127.61(d), 127.94(d), 128.21 (2C, d), 128.46(2C, d), 128.67(d), 133.78(d), 137.02(s), 137.16(s), 159.73(s, C=O).

Mass (m/z) : 382(M^{+1}, 1), 362(1), 351(1), 295(18), 277(4), 269(4), 257(1), 233(4), 162(3), 149(4), 134(6), 121(9), 106(10), 91(100), 77(4), 65(13).

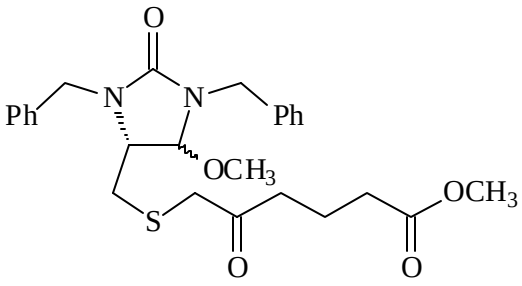
Analysis :

	Carbon	Hydrogen	Nitrogen	Sulphur
Calc.:	69.08	6.85	7.32	8.38
Found:	69.30	6.25	7.65	8.59

8. Methyl 6-(1,3-dibenzyl-5-methoxy-2-oxotetrahydro-1H-4-imidazolylmethyl-sulfanyl)-5-oxohexanoate (26):

Yield : 33.9g (70%).

Mol. Formula : $C_{26}H_{32}N_2O_5S$ (484)



M.P./B.P. : Highly viscous liquid

Optical Rotation : $[\alpha]_D$ = +49.9^0 (c=1.26, $CHCl_3$)

IR ($CHCl_3$, cm^{-1}) : 3019, 3001, 2948, 1733, 1716, 1700, 1445, 1366, 1317, 1202, 1172, 1078, 754.

^{1}H NMR ($CDCl_3$, 200MHz) : 1.98 (m, 2H); 2.41 (m, 3H), 2.60 (m, 3H); 3.03 (s, 5H); 3.42 (m, 1H); 3.74 (s, 3H); 4.15 (d, 2H, J =15.10Hz); 4.50 (d, 1H, J = 1.3Hz); 4.93 (dd, 2H, J = 15.10Hz); 7.30(m, 10H).

Mass (m/z) : 484(M^{+1}, 1), 453(1), 421(1), 341(5), 308(7), 295(26), 277(56), 257(8), 233(4), 187(21), 162(3), 129(29), 91(100), 77(4), 65(13)

1.2.5 References

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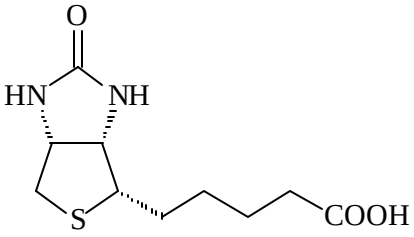
1.3.1 Introduction

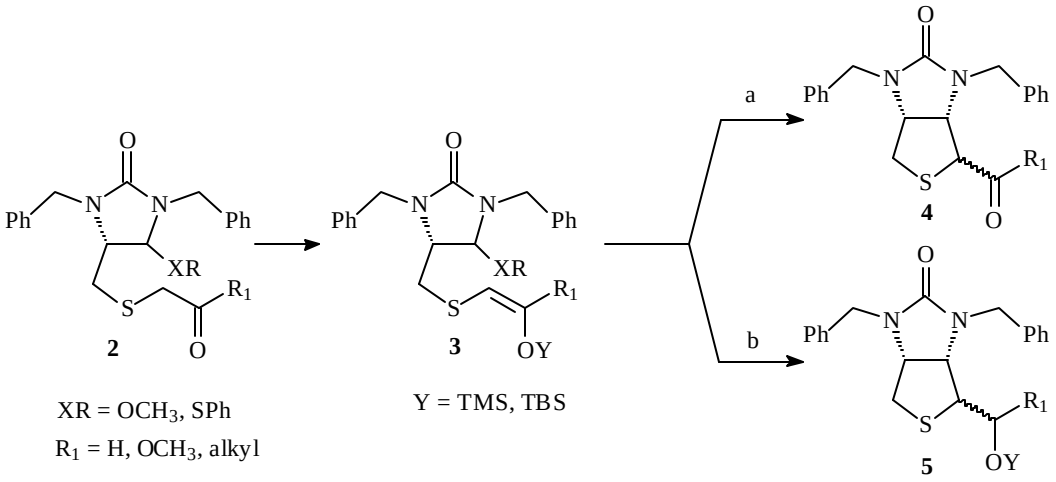
The desire to imitate nature and living organisms in their extraordinary ability to build complex ring systems with complete *regio* and *stereo* control makes ring construction a fundamental interest in synthetic organic chemist. Contemporary methods of ring construction encompass basic reactions, which may be categorized as those involving cationic, radical and anionic intermediates, as well as metal catalyzed and pericyclic reactions (cycloadditions, electrocyclic reactions and pericyclic rearrangements).



1

The main objective of this section is to develop 5,5-fused system, which is present in D(+)-biotin skeleton by using either by radical or ionic cyclization reaction as a key step.

Scheme 1:

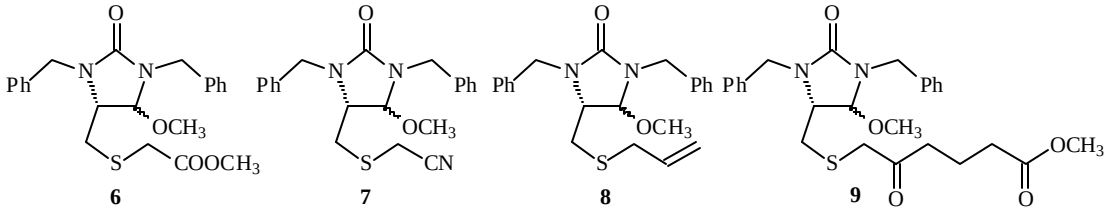


***Conditions: a**) Ionic cyclization (X= OCH_3, SPh); **b**) Radical cyclization (X= SPh)*

1.3.2 Results and Discussion

Having successfully achieved the synthesis of optically active *S*-alkylated imidazolidines **6-9** (see Chapter 1 section:2) attention was focused on the conversion of these intermediates to 5,5-fused systems as the framework of (+)-biotin.

Scheme 2:

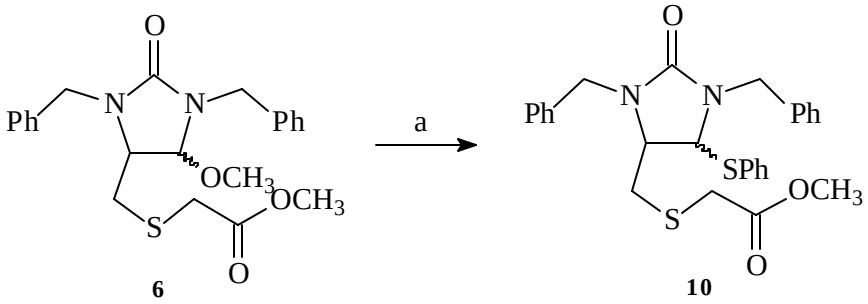


The formation of five membered rings using radical cyclization has been used extensively in the last few years for the synthesis of target molecules.

It is well documented in the literature[1] that *N*-acylamine radical could be generated by treatment of phenylthio, methylthio with tri n-butyl tin hydride in the presence of catalytic amount of AIBN. The radical was shown to add olefin and to allene.

The methoxy imidazolidine derivative **6** was converted to its phenylthio ether **10** *via* iminium ion by use of thiophenol under acidic conditions[1] (pTSA).

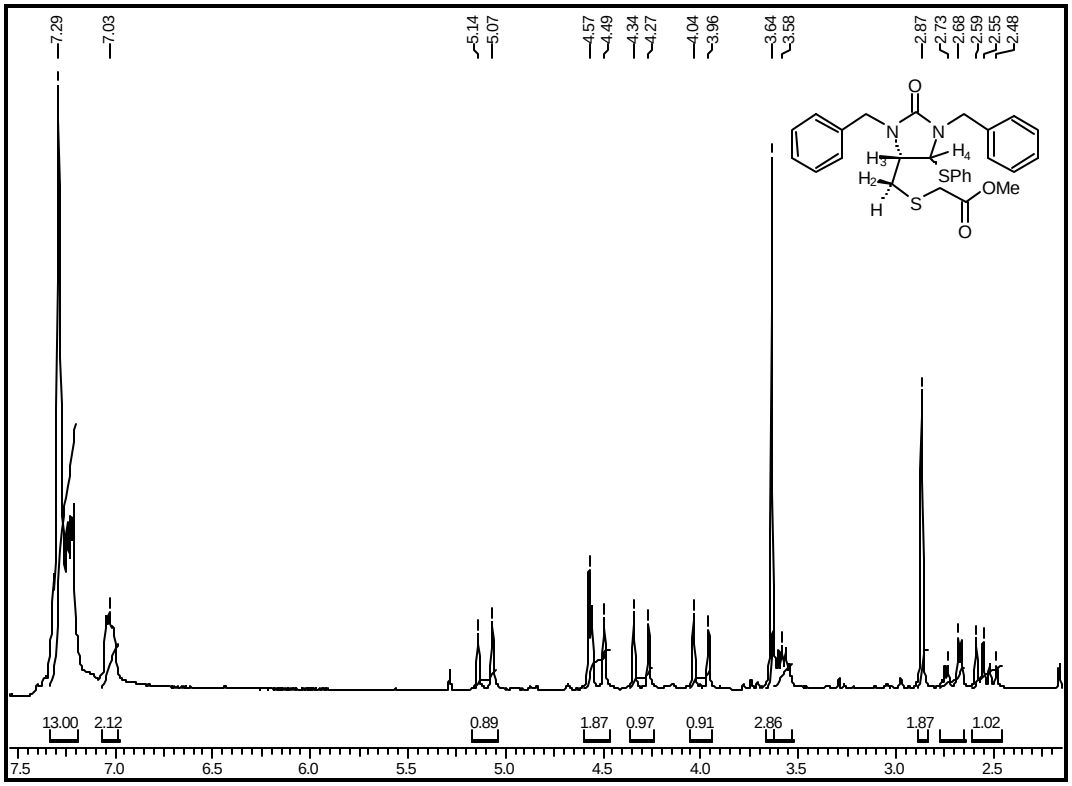
Scheme 3:



***Condition**: **a**) PhSH, pTSA(cat), 0 °C, 10 min*

The ^{1}H NMR of *S*-alkylated compound **10** indicated presence of doublets at δ 5.11 (J = 14.65 Hz), 4.53 (J = 13.78 Hz); 4.31 (J = 15.14 Hz) and 4.0 (J = 15.14 Hz) for four of *N*-benzylic protons, and singlet at δ 4.57 for one proton (H_4). The doublet of doublet at δ 2.71 (J = 3.7, 14.0 Hz) and 2.54 (J = 7.5, 14Hz) were assigned to H_1 and H_2. Correspondingly quintet (ddd) (J = 3.7, 7.5 Hz) was also observed for H_3 proton at δ 3.58 while singlets at 3.1 for three protons and another one at δ 3.0 for two protons were assigned to methoxy and methylene protons α-to methyl ester group

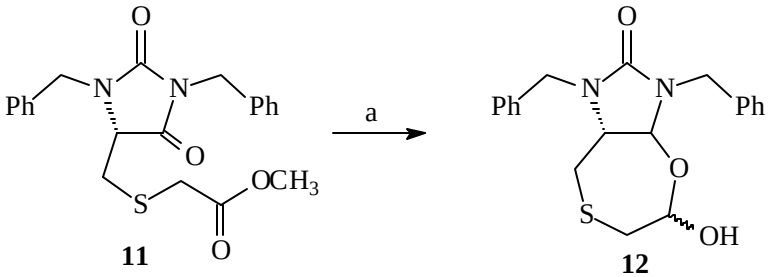
respectively. Aromatic and methyl ester protons appeared at their expected chemical shifts. Mass spectrum of *S*-alkylated compound **10** exhibited M^+ peak at 414.



^{1}H NMR Spectrum of compound **10** ($CDCl_3$, 200MHz).

It was thought worthwhile to attempt DIBAL-H reduction directly on ester **6**/**10** or nitrile **7**. Earlier study from our laboratory revealed that an analogues reaction had been successfully performed where hydride reduction of keto ester **11** furnished lactol **12**[2] (Scheme 4).

Scheme 4:

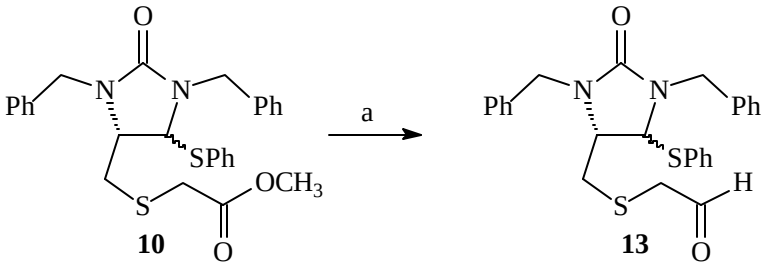


11 **12**

***Condition**: **a**) DIBAL-H, toluene, -78 °C, 2h, 72%.*

Thus the reduction of thiophenoxy methyl ester **10** was effected using 1.2 eq of diisobutyl aluminum hydride in toluene at –78 ºC for 90 min to furnish the phenylthio aldehyde **13** as a colorless viscous liquid (78%).

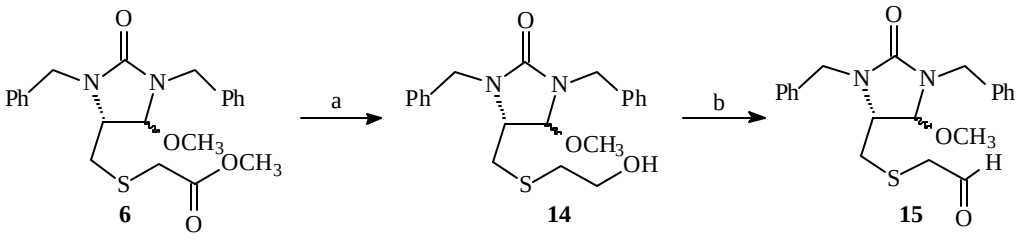
Scheme 5:



***Condition**: **a**) DIBAL-H, toluene, -78 ºC, 90 min, 78%.*

The methoxy aldehyde **15** was also prepared from methoxy imidazolidine ester **6** by sodium borohydride reduction and pyridinium dichromate (PDC) oxidation of primary alcohol in dichloromethane at room temperature. Normally esters are not reduced by sodium borohydride at room temperature. We have developed a methodology[3,4] where sulfur assisted reduction were shown to reduce esters to the corresponding alcohols. Thus when the ester **6** was subjected to reduction with sodium borohydride in methanol at room temperature, the alcohol **14** was obtained in excellent yields.

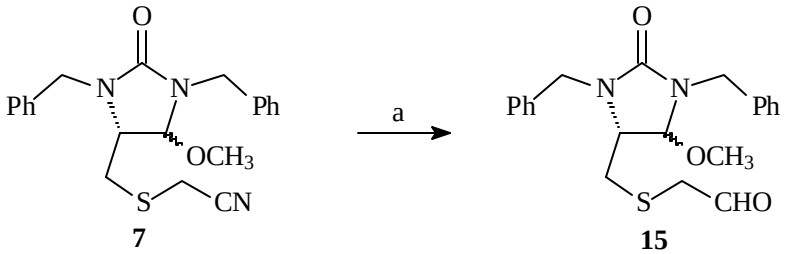
Scheme 6:



***Conditions**: **a**) NaBH4, EtOH or MeOH, rt, 3h, 95%; **b**) Pyridinium dichromate, DCM, rt, 3h, 60%.*

In another approach the phenyl thio acetonitrile **7** derivative was also reduced to aldehyde **15** by using DIBAL-H at –60 ºC.

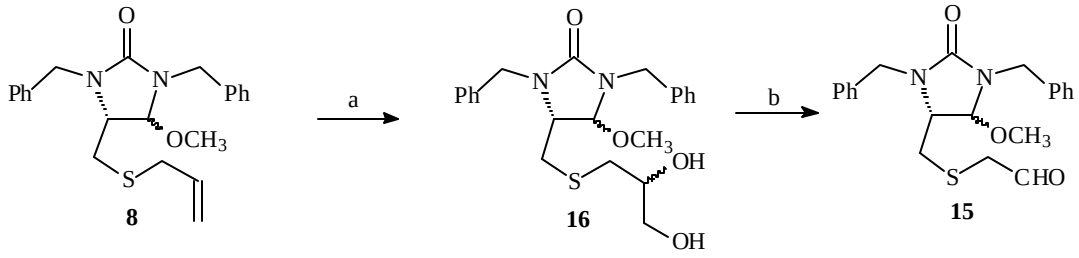
Scheme 7:



***Condition**: **a**). DIBAL-H, -60 °C, 3h, then –10 °C to rt, sat.NH_4Cl, 1h, 46%.*

In an another alternative approach to obtain the above aldehyde **15**, the allylic imidazolidine derivative **8** was dihydroxylated under non-sulphur oxidative conditions.[5] *i.e.* by using catalytic amount of osmium tetraoxide (OsO_4), potassium ferricyanide and potassium carbonate in *t*-butanol-water (1:1). The dihydroxy derivative **16** was effectively cleaved by using sodium metaperiodate in aq. methanol (MeOH:H_2O-9:1) in ten minutes to furnish the desired aldehyde.

Scheme 8:



***Conditions**: **a**) OsO_4, $K_3Fe(CN)_6$, K_2CO_3, ^{t}-BuOH:H_2O(1:1), 12h, 83%; **b**) $NaIO_4$ (1.5eq), MeOH:H_2O (1:1), 10 min, 60%.*

Aldehyde and N-CO-N carbonyl stretchings were observed at 1710 and 1700 cm^{-1} respectively in IR spectrum of aldehyde **13**, The proton NMR spectral analysis of aldehyde **13** exhibited triplet at δ 9.2 (*J* = 4Hz) for aldehydic proton while a doublet at δ 2.85 (*J* = 4Hz) was assigned to SCH_2-CHO. ^{13}C NMR spectrum of **13** displayed doublet at 192.60 for aldehydic carbon. Presence of a peak at M^+-109 as parent peak in the mass spectrum of aldehyde confirmed presence of SPh and fragmentation confirmed the assigned structure of **13**.

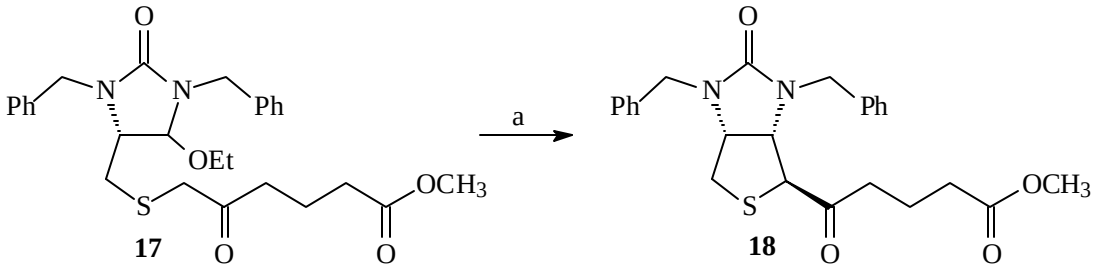
Having achieved the preparation of S-alkylated compounds, the next challenge was to bring the ring closure of aldehyde **13** to get 5,5-fused system.

1.3.2a Ionic Cyclization approach:

Sulphides are well known to complex with Lewis acids. Mori *et al* [6] summarized that selective complexation and generation of iminium ion followed by intramolecular trapping of the ionic intermediate by silyl enol ether led to chemo selective C-C bond formation.

Speckamp and co workers and Poetsch and Casutt[7] have used the intramolecular version of the condensation of silyl enol ether with N-acyliminium intermediate to effect the ring closure of thio ether **17** for the construction of the thiophane nucleus **18**.

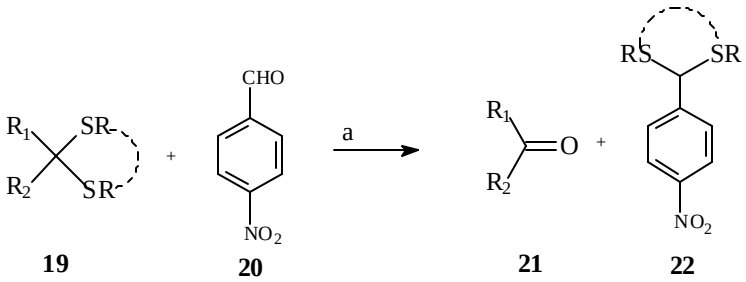
Scheme 9:



***Condition**: **a**) 2.1 eq. of (TMS)CH_2CO_2Et, 0.03 eq. of TBAF, THF, -78 °C to 25 °C, 18h, then 1.5eq. of TMSOTf, DCM, -78 °C, 1h, 78%.*

It was also demonstrated by our group[8] that catalytic anhydrous practically irreversible transthioacetalisation methodology involving a double transfer of oxygen and alkanethiol is a convenient and efficient method for the deprotection of thioacetals (scheme 10). Further a novel methodology for the construction of 5,5-fused system of biotin was also developed in our group (scheme 11).

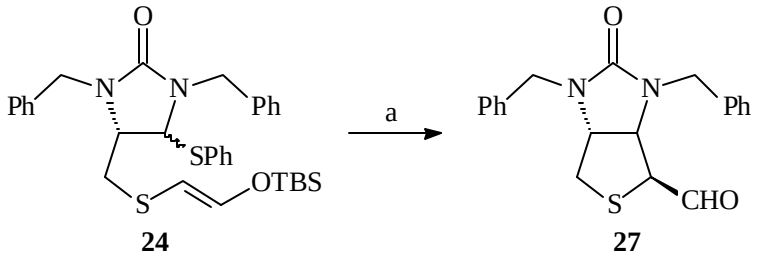
Scheme 10:



19 **20** **21** **22**

***Condition**: **a**) p-Nitrobenzaldehyde, DCM, TBSOTf, 5 min, 95%.;*

Scheme 11:

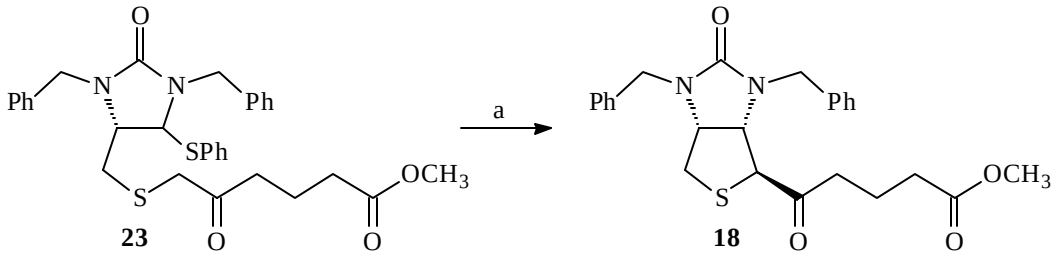


24 **27**

***Condition**: **a**) TMSOTf, DCM, rt, 1-4h, 88-100%.*

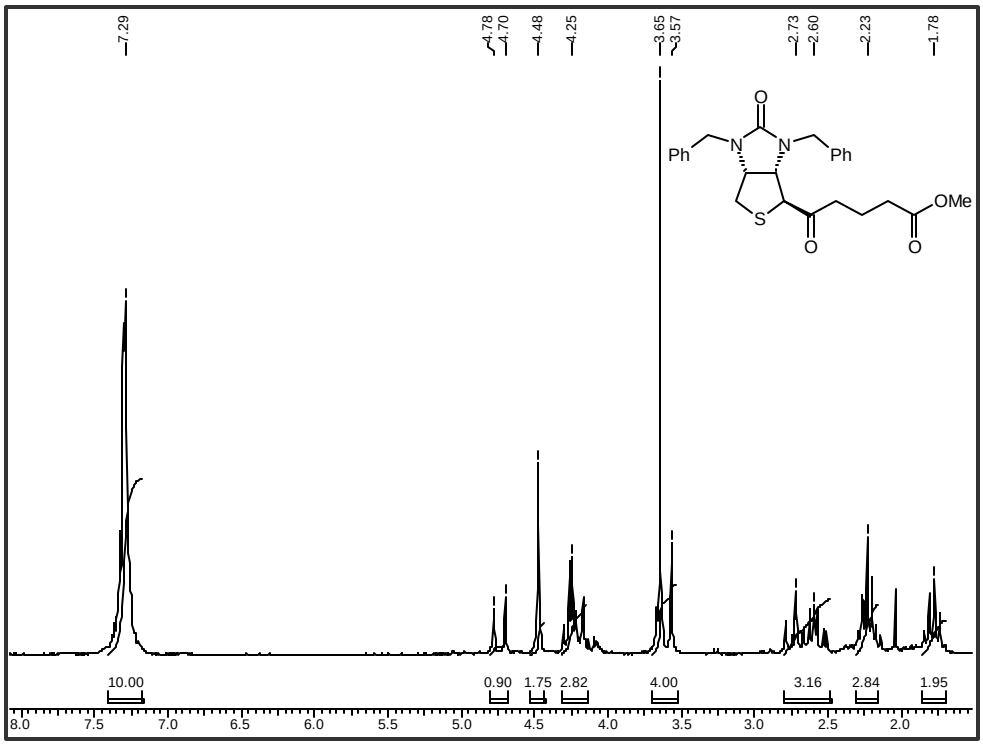
It was thought worthwhile to attempt cyclization of silyl enol ether of intermediate **23** by using methodology developed by our group.

Scheme 12:

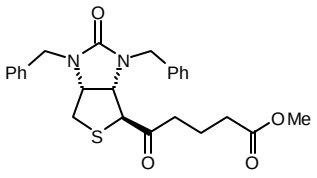


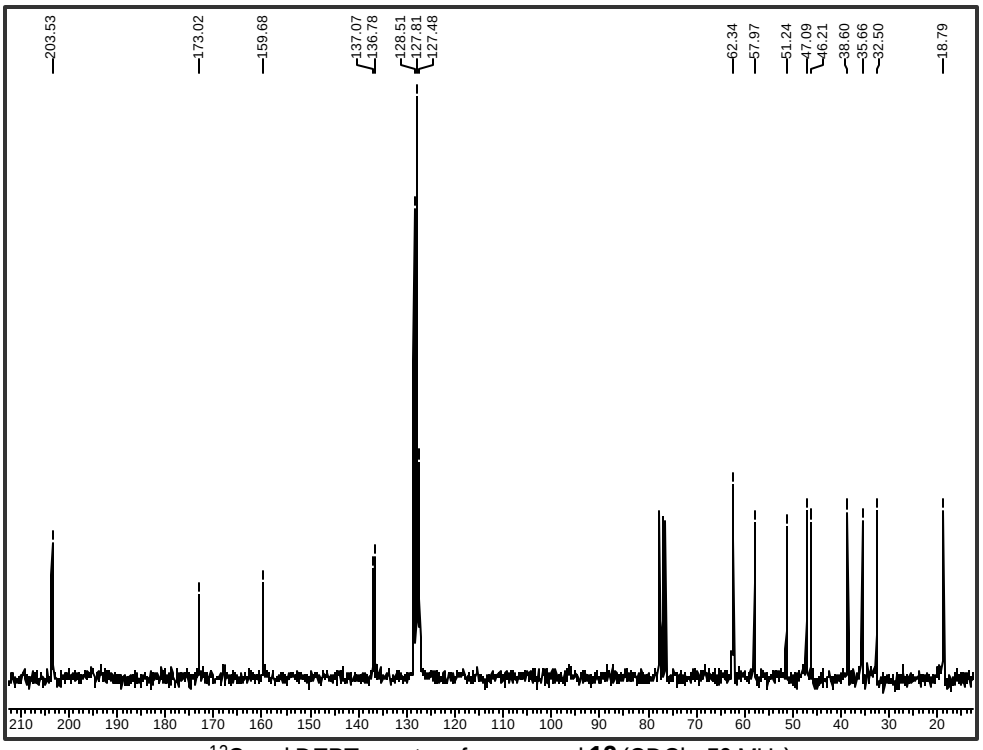
***Condition**: **a**) TMSOTf (1.5eq), Et_3N, DCM, -40 °C, 2h then –20 °C, p-nitrobenzaldehyde(1eq), TMSOTf (cat), 10min, 65%.*

Thus thioketone **23**, when subjected to enol ether formation and *in situ* cyclization in presence of *p*-nitrobenzaldehyde and catalytic amount of TMSOTf, furnished the cyclized product **18** in 65% yield. Thus it was clearly demonstrated that the protocol developed by us earlier works well with the substrate **23**.

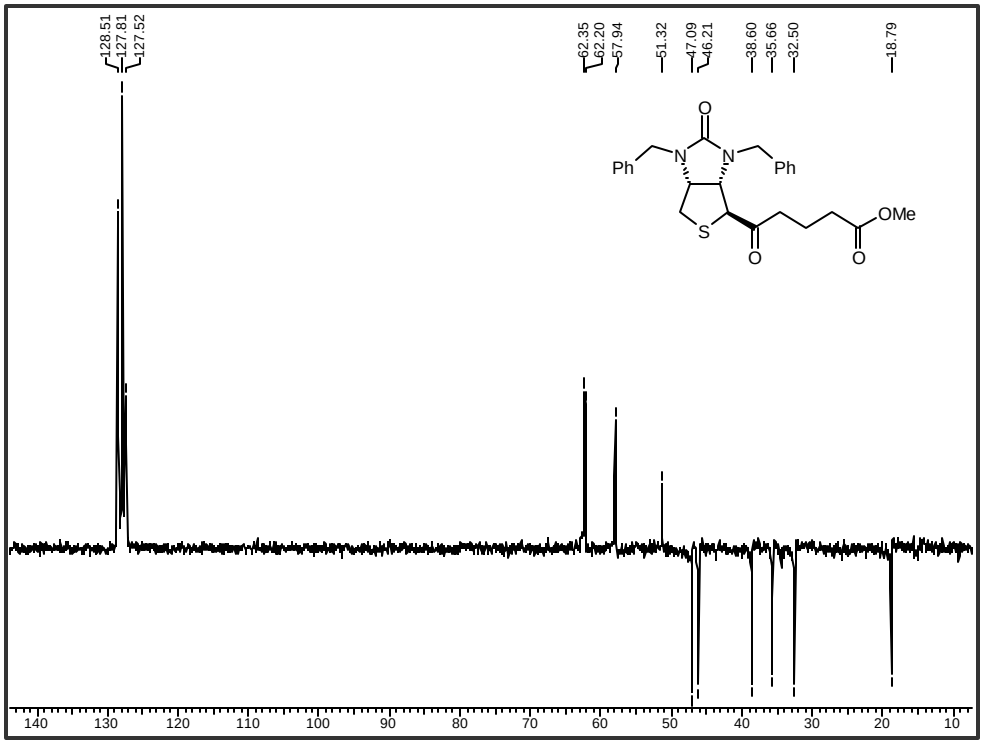


^{1}H NMR spectrum of compound **18** ($CDCl_3$, 200 MHz)





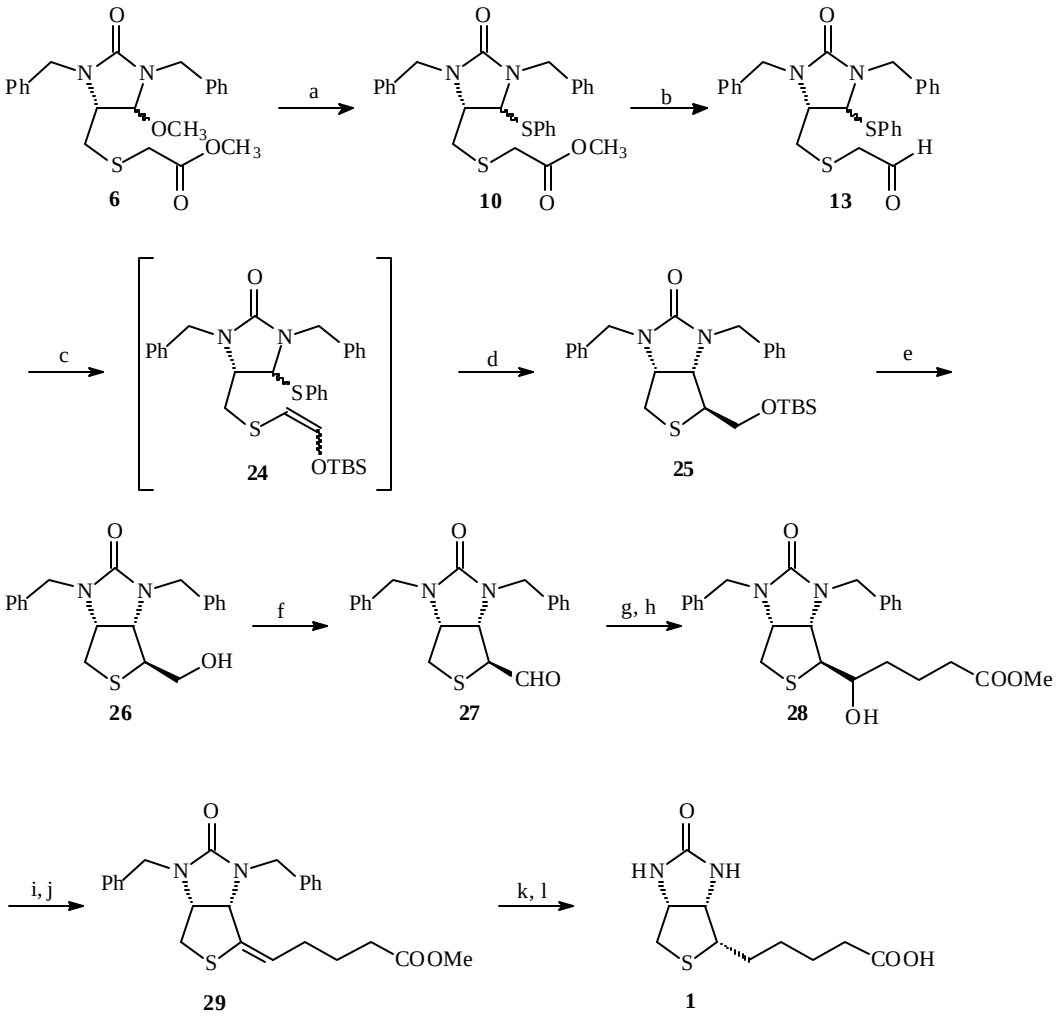
^{13}C and DEPT spectra of compound **18** ($CDCl_3$, 50 MHz)



1.3.2b Radical approach for 5,5-fused system:

α-Acylamine radical could be generated by treatment of phenylthio, methylthio with tributyl tin hydride in the presence of azobis(isobutyronitrile) (AIBN). The radical was shown to add intramolecularly to olefin and allene.[9]

Scheme 13:



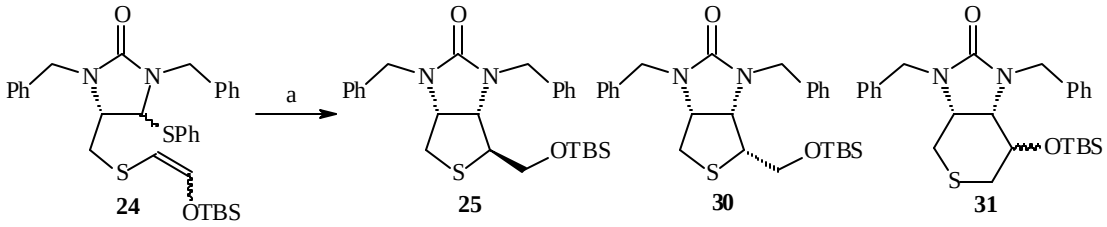
***Conditions**: **a**) PhSH, pTSA(cat), 10 min, 93%; **b**) DIBAL-H, -78 °C, 2h, 78%; **c**) TBSCl, DBU, DCM, reflux, 30 min, 80%; **d**) Tri-n-butyltin hydride, AIBN, benzene, reflux, 4h, 53%; **e**) $BF_3.Et_2O$, $CHCl_3$, 2h, 75%; **f**) $(COCl)_2$, DMSO, DCM, Et_3N, 2.5h, 61%; **g**) Mg, $BrCH_2CH_2CH_2Br$, 12h, then cooled –15 °C, CO_2, 2h, rt; **h**) CH_2N_2, 15 min, 76%; (two steps); **i**) MsCl, Et_3N, DCM, 3h; **j**) DBU, 60 °C, 12h, 80% (two steps); **k**) H_2, Pd-C, 200psi, 65 °C, 6h, 99%; **l**) HBr(47%), reflux, 5h, 75%.*

Several instances are reported in literature where enol ethers have been used in carbon-carbon bond formation in radical fashion. It was decided to harness the propensity of α-acylamine radical in intramolecular cyclization to silyl enol ether. Accordingly the silyl enol ether **24** was obtained in 70%

yield when aldehyde **13** was subjected to tert-butyl dimethylsilyl chloride (TBDMSCl, 1.2eq) and diazabicylo[5.4.0]undec-7-ene (DBU, 1.0eq) in dichloromethane at refluxing temperature. Appearance of two doublets one at δ 6.45 with coupling constant 11.72, and another at δ 6.25 with coupling constant 5.37 Hz of ^{1}H NMR spectrum of **24** suggested that olefin exists as a mixture *trans* and *cis* isomers in 3:1 ratio respectively.

The silyl enol ether **24** has the functionalities well set to undergo free radical cyclization. Thus, when the silyl enol ether **24** was refluxed with *tri* n-butyltin hydride (TBTH) and catalytic amount azobis (isobutyro) nitrile (AIBN) under inert atmosphere, a single product was obtained in 53% yield which was eventually shown to be the desired 5,5-fused system **25**. No trace of diastereomer **30** or regio isomer **31** was isolated.

Scheme 14:

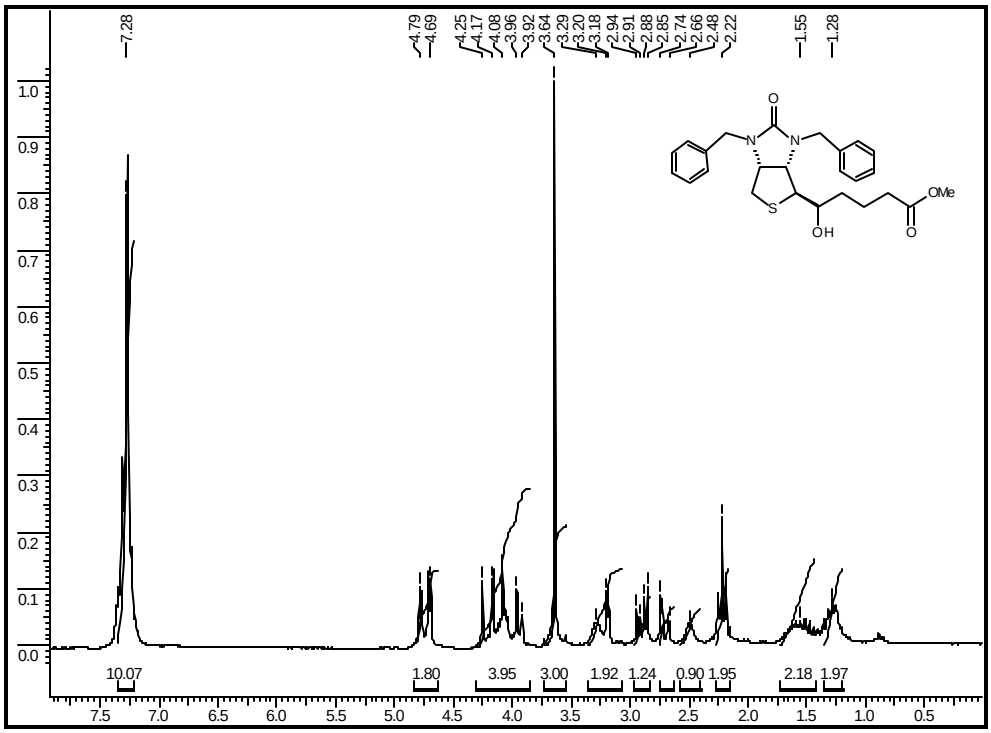


Deprotection of silyl enol ether **25** using $BF_3.Et_2O$ in $CHCl_3$ furnished primary alcohol **26** in 78% yield. ^{1}H NMR of **26** displayed broad singlet at δ 2.20 for O<u>H</u> which disappeared on addition of D_2O. Presence of stretching at 3412 cm^{-1} in IR spectrum confirmed the presence of hydroxy group. Alcohol **26** was oxidized to bicyclic aldehyde **27** in 60% yield under Swern oxidative conditions. Though the aldehyde **27** had the incorrect stereochemistry, it could be rectified during homologation at later stages. Having achieved the bicyclic framework of (+)-biotin with a suitable functionality, the attention was focused to introduce the side chain of biotin. Thus Grignard reaction of aldehyde **27** with 1,3-propane dimagnesium dibromide, followed by carbon dioxide quench[10] at –15 ^oC and esterification with diazomethane furnished bicyclo hydroxy methyl ester **28** in 76% yield.

The ^{1}H NMR spectrum of compound **28** displayed multiplets at δ 1.29 and δ 1.55 assigned to two β,γ methylene protons of the ester group. Triplet at δ 2.22 for the two protons were assigned to methylene group adjacent to ester moiety. Singlet at δ 3.64 for 3 protons is assigned for methoxy group of ester.

^{13}C NMR showed five carbons at δ 20.97, 33.48, 36.07, 36.23, 46.27, 46.82 which appeared as triplets and four carbons at δ 51.52, 62.39, 65.65, 71.63 which appeared as doublets and one

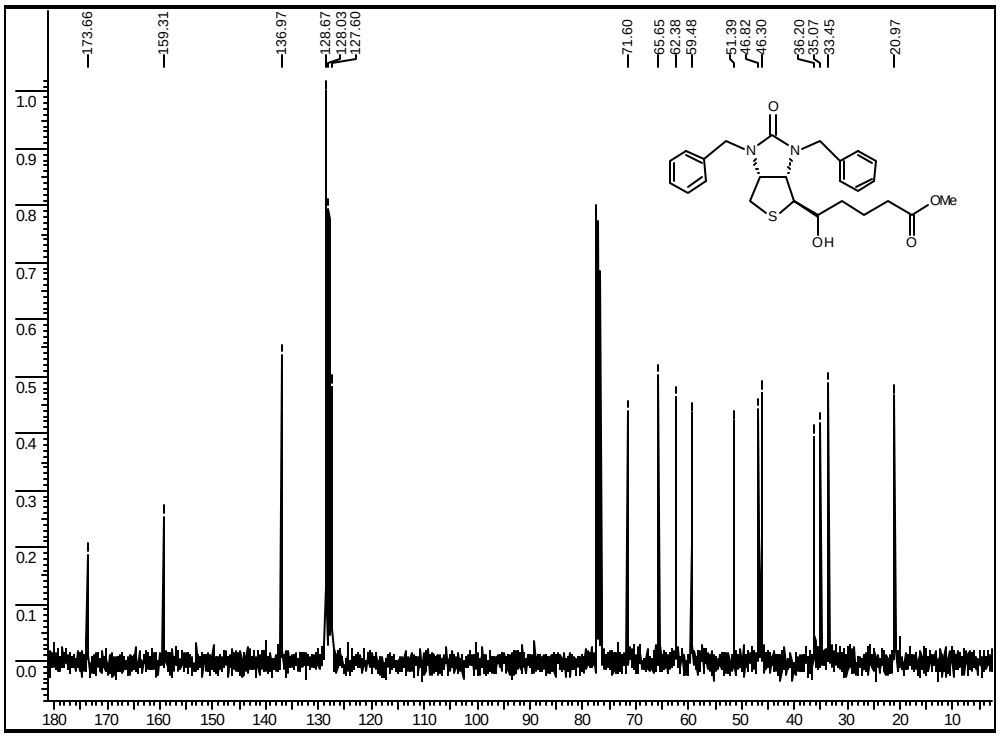
carbon at δ 59.49 as a quartet indicated incorporation of side chain in bicyclic compound **28**. Mass spectrum M^+ at 452 and fragmentation confirmed the assigned structure of hydroxy ester **28**.



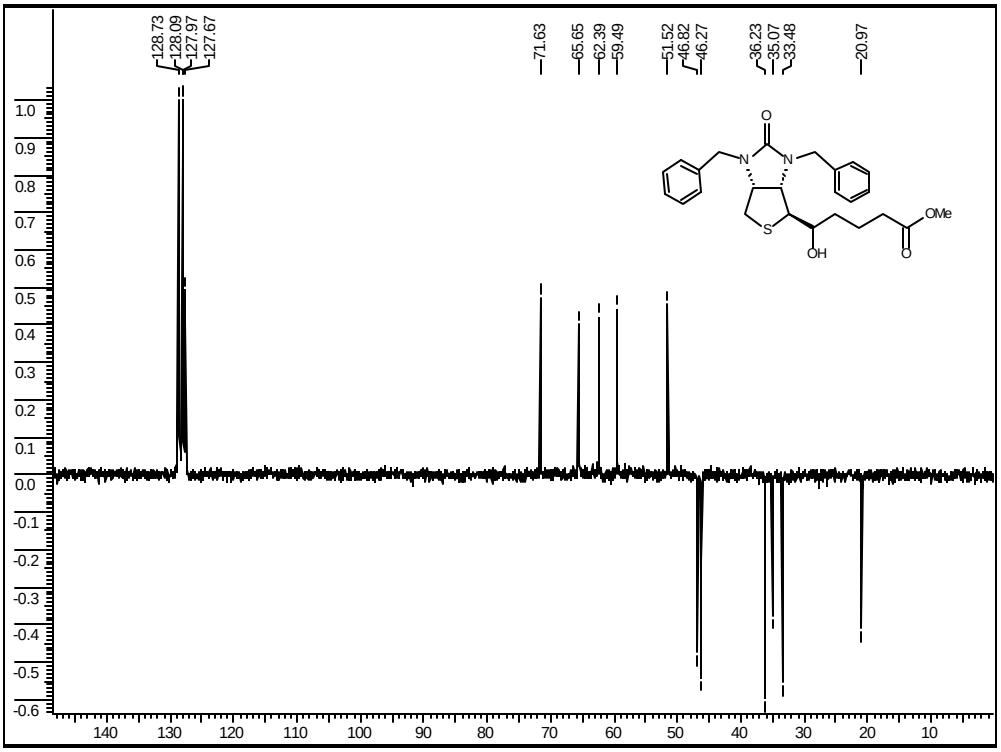
The ^{1}H NMR spectrum of compound **28** ($CDCl_3$, 200 MHz)

The hydroxy ester derivative **28** was converted to its mesylate with methane sulphonyl chloride and triethyl amine at 0 ^oC for 3h. The crude mesylate was subjected to elimination using diaza bicyclo [5.4.0]undec-7-ene (DBU) at 60 ^oC to furnish known olefin **29** in 80% yield. Stereospecific hydrogenation was carried out in the presence of 10% palladium black gave *N*,*N*-dibenzyl biotin methyl ester in quantitative yield. Removal of N-benzyl groups was conducted with aq. HBr (47%) at reflux temperature afforded (+)-biotin **1**, which was characterized as methyl ester (reflux for 2h in methanol in cat. amount of H_2SO_4 in 95% yield) had $[\alpha]_D$ = +78^o (as compared to $[\alpha]_D$ = +81^o for an authentic sample).

In conclusion two different cyclization methods (ionic as well as radical) for 5,5 fused system which is required for D(+)-biotin have been developed and successfully employed to achieve an elegant biotin synthesis.

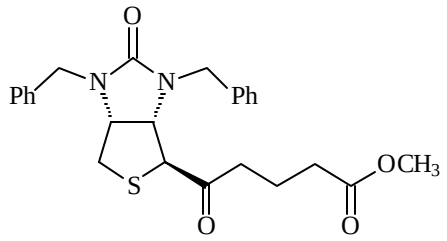


^{13}C & DEPT NMR Spectra of compound **28** ($CDCl_3$, 50 MHz)



1.3.3 Experimental

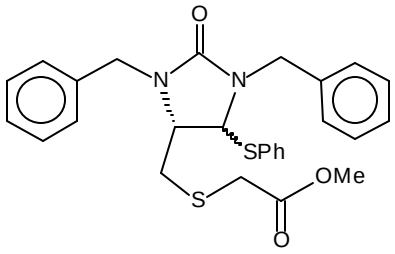
1. Preparation of compound 18:



The thio ketone **23** (0.56g, 1 mmol) was taken in a 100 mL two necked flask along with 40 mL of anhydrous dichloromethane under nitrogen. The flask was cooled to –40 ^{o}C and triethyl amine (0.26g, 2 mmol) was added at –40 ^{o}C. To this solution TMSOTf (0.33g, 1.5 mmol) in 5 mL of DCM was added dropwise and the stirring was continued for 2h maintaining the same temperature. After completion of 2h, the reaction mixture was brought to –20 ^{o}C, a solution of p-nitrobenzaldehyde (0.15g, 1 mmol) in 5 mL of DCM and catalytic amount of TMSOTf was added at –20 ^{o}C. After 10 min, saturated $NaHCO_3$ solution (5 mL) was added. Dichloromethane layer was separated washed with water (2x10 mL), dried over anhyd. Na_2SO_4 filtered. Removal of solvent under reduced pressure and column chromatography over silica gel with 35% EA: pet.ether furnished cyclized keto ester **18** (0.29g, 65%) as a pale yellow solid and thioacetal of 4-nitrobenzaldehyde thioacetal **22** (0.34g, 97%).

Yield	: 0.29g (65%).
Mol. Formula	: $C_{25}H_{28}N_2O_3S$, pale yellowish solid.
Optical Rotation	: $[\alpha]_D$ = - 15.82^{o} (c=0.88; $CHCl_3$)
IR ($CHCl_3$, cm^{-1})	: 3023, 2943, 1731, 1693, 1449, 1359, 1323, 1237, 1064, 753.
^{1}H NMR ($CDCl_3$, 200MHz)	: 1.78 (m, 2H); 2.23 (m, 3H); 2.60 (m, 2H), 2.73 (m, 1H); 3.57 (s, 1H); 3.65 (s, 3H); 4.25 (m, 3H); 4.48 (s, 2H), 4.76 (d, 1H, *J* = 15Hz); 7.29 (m, 10H).
Mass (m/z)	: 452(M^+1), 421(3), 339(1), 277(100), 129(10), 91(23).

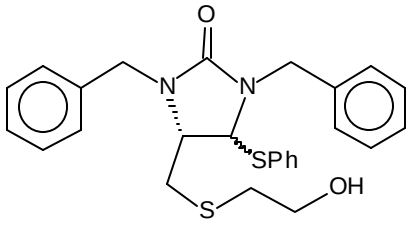
2. 1,3-Dibenzyl-2-oxo-5-(3-carbomethoxycarbonyl-2-thiapropyl)-4-phenylthio-imidazolidine (10):



Methoxy ureide **6** (4.14g, 10 mmol) was dissolved in thiophenol (20 mL) and solution was cooled to 0 ^{o}C. To this was then added catalytic amount of pTSA (20mgs, 0.1 mmol) and the mixture was stirred at 0 ^{o}C for 5 min. Mixture of DCM (20 mL) and water (5 mL) was then added, organic layer was separated, washed with brine (5 mL), dried over anhyd. Na_2SO_4 and filtered. Rotary evaporation of solvent under reduced pressure and chromatographic purification (20% EA: Pet.ether) afforded 4-phenylthio ureide **10**.

Yield	: 4.70g (93%).
Mol. Formula	: $C_{27}H_{28}N_2O_3S_2$, Viscous liquid.
Optical Rotation	: $[\alpha]_D$ = - 19.36^{o} (c=0.98; $CHCl_3$)
IR (neat, cm^{-1})	: 3030, 2920, 2875, 1725, 1695, 1583, 1495, 1420, 1386, 1365, 1064
^{1}H NMR ($CDCl_3$, 200MHz)	: 2.53 (dd, 1H, J = 14, 7.5Hz); 2.70 (dd, 1H, J = 14, 3.7 Hz); 2.9 (s, 2H); 3.60 (ddd, 1H, J = 3.7, 7.5Hz); 4.0 (d, 1H, J = 15.5Hz); 3.65 (s, 3H); 4.3 (d, 1H, J = 15.3Hz); 4.53 (d, 1H, J = 15Hz); 4.57 (d, 1H, J = 3.7Hz); 5.1 (d, 1H, J = 15Hz); 7.09 (m, 3H); 7.28 (m, 12H).
Mass (m/z)	: 383(M^+-109, 18), 277(100), 264(7), 187(7), 110(7), 91(54).

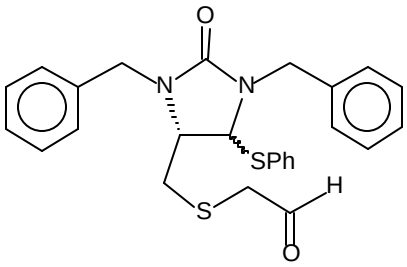
3. 1,3-Dibenzyl-2-oxo-5-(4-hydroxy-2-thiabutyl)-4-phenylthio-imidazolidine (14):



The thiophenyl ester **10** (4.14g, 10 mmol) was dissolved in methanol (20 mL) and solution was cooled to 0 ^{o}C. To this was then added sodium borohydride (0.57g, 15 mmol) in portions, and the reaction mixture was stirred at room temperature for 3h. After completion of reaction (by TLC) the methanol was removed and extracted with EtOAc. The organic layer was washed with water (20 mL), and brine (20 mL), dried over anhyd. Na_2SO_4 and filtered. Rotary evaporation of the solvent, and column chromatographic purification with 30% EA:Pet.ether afforded alcohol in 95% yield.

Yield	: 3.52g (90%).
Mol. Formula	: $C_{26}H_{28}N_2O_2S_2$, Viscous liquid.
Optical Rotation	: $[\alpha]_D$ = - 26.34^{o} (c= 0.96, $CHCl_3$).
IR (neat, cm^{-1})	: 3406, 2924, 1688, 1451, 1359, 1235, 1076.
^{1}H NMR ($CDCl_3$, 200MHz)	: 2.36 (dd, 1H, J = 7.3, 13.7Hz); 2.40 (dt, 2H, J = 1.7, 5.9Hz); 2.5 (dd, 1H, J = 3.7, 13.7Hz); 3.44 (t, 2H, J = 5.9Hz); 3.54 (m, 1H, J = 3.4, 3.7, 7.3Hz); 3.98 (d, 1H, J = 15.38Hz); 4.32 (d, 1H, J = 14.89Hz); 4.42 (d, 1H, J = 15.38Hz); 4.56 (d, 1H, J = 3.42Hz); 5.11 (d, 1H, J = 14.89Hz); 6.98 (m, 2H); 7.31 (m, 13H).
Mass (m/z)	: 355(M^+-109, 18), 277(100), 264(7), 187(7), 110(7), 91(54).

4. 1,3-Dibenzyl-2-oxo-5-(3-formyl-2-thiopropyl)-4-phenylthio imidazolidine (13):



From ester 10**:**

Thiophenyl ester 10 **(2.21g, 4.37 mmol) was taken in a 100 mL two-necked round bottom flask along with 30 mL of anhydrous toluene under an atmosphere of argon. The flask was cooled to –78 ^{o}C and DIBAL-H (0.68g, 4.8 mmol) was added slowly at –78 ^{o}C and was stirred for 2 h. After 2 h (TLC) it was quenched with 2.0 mL of MeOH and 2.0 mL of water. The solution was**

then stirred for half an hour and the white solid was filtered. The filtrate was evaporated under reduced pressure and the

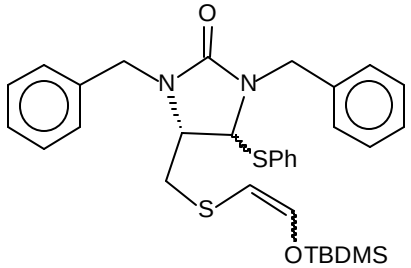
residue taken in EtOAc and washed with water. The organic layer was then dried over anhyd. Na_2SO_4, filtered and the product obtained was chromatographed on silica gel with 25% EA:Pet.ether to yield the product aldehyde 13 **(1.57g) in 78% as a colorless viscous liquid.**

From alcohol 14**:**

Alcohol 14 **(0.464, 1 mmol) was dissolved in dichloromethane (20 mL) and the solution was cooled to 0 °C. To this was then added pyridinium dichromate (PDC) (1.13g, 3 mmol) in portions, and the reaction mixture was stirred for 3h. After completion of reaction the reaction mixture was filtered through celite. Rotary evaporation of solvent and column chromatographic (SiO_2) purification with 30% EA:Pet.ether afforded aldehyde** 13 **(0.28g) in 60% yield as a colorless viscous liquid.**

Mol. Formula	: $C_{26}H_{26}N_2O_2S_2$, Viscous liquid.
Optical Rotation	: $[\alpha]_D$ = - 26.7° (c= 0.9, $CHCl_3$).
IR (neat, cm^{-1})	: 3010, 2900, 1710, 1700, 1600, 1580, 1495, 1450, 1390, 1140, 1070.
^1H NMR ($CDCl_3$, 200MHz)	: 2.32 (m, 2H); 2.80 (d, 2H, J = 3.6Hz); 3.45 (m, 1H); 3.94 (d, 1H, J = 15.2Hz); 4.27 (d, 1H, J = 15.2Hz); 4.40 (d, 1H, J = 15.2Hz); 4.48 (d, 1H, J = 4Hz); 5.10 (d, 1H, J = 15.2Hz); 7.13 (m, 15H); 9.14 (t, 1H).
Mass (m/z)	: 353(M^+-109, 5), 294(6), 149(5), 141(7), 132(14), 91(100), 84(11), 77(17), 69(13), 65(18).

5. 1,3-Dibenzyl-2-oxo-5-[(3E, 3Z)-4-tert-butyldimethylsilyloxy-2-thiabut-3-enyl]-4-phenylthio imidazolidine (24):



A solution of *t*-butyldimethylsilyl chloride (0.255g, 1.69 mmol) in anhydrous DCM (5 mL) was added *via* syringe to a solution of aldehyde **13** (0.650g, 1.41 mmol) in DCM (20 mL). After 5 min DBU (0.28g, 1.3 mmol) was added drop wise and mixture was heated to reflux. After 30 min (TLC) the

reaction mixture was concentrated and purified by column chromatography by using 10% EA:Pet.ether.

Yield : 0.65g (80%).

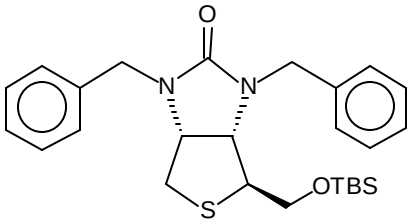
Mol. Formula : $C_{32}H_{40}N_2O_2S_2Si$, semi solid.

IR (neat, cm^{-1}) : 2910, 2840, 1695, 1600, 1595, 1450, 1420, 1375, 1210, 1100, 940.

^1H NMR ($CDCl_3$, 200MHz) : 0.1 (s, 6H); 0.8 (s, 9H); 2.20 (dd, 1H, J = 7, 13Hz); 2.40 (dd, 1H, J = 4, 13Hz); 3.40 (m, 1H); 3.90 (d, 1H, J = 15Hz); 4.20 (d, 1H, J = 15Hz); 4.30 (d, 1H, J = 15Hz); 4.55 (d, 1H, J = 3.5Hz); 5.0 (d, 1H, J = 15Hz); 5.15 (d, 1H, J = 11.6Hz); 6.56 (d, 1H, J = 11.6Hz); 7.0 (m, 3H); 7.35 (m, 12H).

Mass (m/z) : 467(M^+-109, 5), 277(40), 203(7), 110(29), 91(100), 73(28), 65(13).

6. 1,3-Dibenzyl-4-(1-tert-butyldimethylsilyloxy methyl)-1H-tetrahydrothieno-[3,4-d]imidazole-2(3H)-one (25):



A solution of phenylthio enol ether **24** (0.30g, 0,52 mmol), tributyltin hydride (0.18g, 0.63 mmol) and AIBN (catalytic) in dry benzene (20 mL) was refluxed for 4h with addition of few crystals of AIBN at the end of 2h. After removal of benzene under reduced pressure, crude product thus obtained was purified by column chromatography (SiO_2) (10% EA: Pet.ether) to furnish the bicyclic silyl ether **25** as a viscous liquid.

Yield : 0.13g (53%).

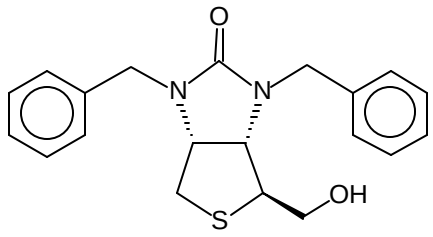
Mol. Formula : $C_{26}H_{36}N_2O_2SSi$, viscous liquid.

Optical Rotation : $[\alpha]_D$ = +46.2° (c= 1.09, $CHCl_3$).

IR (neat, cm^{-1}) : 2910, 2840, 1690, 1600, 1580, 1495, 1460, 1360, 1250, 1100.

^{1}H NMR ($CDCl_3$, 200MHz)	: 0.01 (s, 6H); 0.78 (s, 9H); 2.90 (d, 2H, J = 2 Hz); 3.28 (dd, 1H, J = 4.8, 8.12 Hz); 3.40 (dd, 1H, J = 8.12, 10.1 Hz CH_2-OTBS); 3.50 (dd, 1H, J = 4.8, 10.1 Hz C$\underline{H}_2$-OTBS); 4.09 (m, 2H); 4.17 (d, 1H, J = 15 Hz); 4.24 (d, 1H, J = 15 Hz); 4.75 (d, 1H, J = 15.4 Hz); 4.80 (d, 1H, J = 15.4 Hz); 7.25 (m, 10H).
Mass (m/z)	: 468(M^+, 8), 453(21), 435(4), 411(90), 91(100).

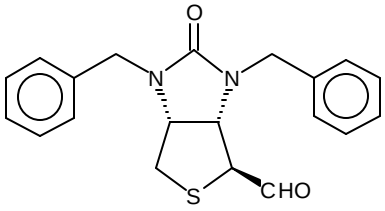
7. 1,3-Dibenzyl-4-(1-hydroxymethyl)-1H-tetrahydrothieno-[3,4-d]-imidazol-2-(3H)-one (26):



TBDMS ether **25** (0.312g, 0.66 mmol) was dissolved in anhydrous dichloromethane (10 mL) and stirred under nitrogen atmosphere. To this solution was added borontrifluoride etherate (0.473g, 3.3 mmol). After stirring at room temperature (2h) the reaction mixture was neutralized with 1M $NaHCO_3$ solution and extracted with DCM (2X10 mL). Combined organic layers were washed with water (2X10 mL), brine, dried over anhyd. Na_2SO_4, filtered and chromatographed (SiO_2) to furnish the alcohol **26** as viscous liquid.

Yield	: 0.177g (75%).
Mol. Formula	: $C_{20}H_{22}N_2O_2S$, viscous liquid.
Optical Rotation	: $[\alpha]_D$ = +60.38° (c=2, $CHCl_3$)
IR (neat, cm^{-1})	: 3400, 2910, 1690, 1600, 1505, 1480, 1380, 1260, 1100.
^1H NMR ($CDCl_3$, 200MHz)	: 2.2 (bs, 1H, D_2O exchangeable); 2.69 (dd, 1H, J = 4.6, 10.6Hz); 2.71 (dd, 1H, J = 5.1, 10.6Hz); 3.30 (s, 2H); 3.83 (d, 1H, J = 8.1Hz); 4.01 (m, 2H); 4.07 (d, 1H, J = 15Hz); 4.08 (d, 1H, J = 15.4Hz); 4.71 (t, 2H, J = 15.1Hz); 7.30 (m, 10H).
MS (m/z)	: 354(M^+, 22), 307(7), 277(23), 263(20), 187(9), 149(7), 91(100), 65(13), 57(10)

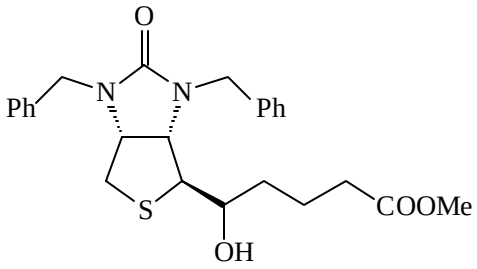
8. 1,3-Dibenzyl-4-formyl-1H-tetrahydrothieno-[3,4-d]-imidazol-2(3H)-one (27):



To a flame dried 50 mL round bottom flask equipped with a magnetic stirrer and nitrogen atmosphere was added dichloromethane (5 mL, freshly distilled over P_2O_5). The flask was cooled to –78 °C and oxalyl chloride (0.050g, 0.395 mmol) was added, followed by DMSO (0.061g, 0.790 mmol). After the mixture was stirred at –78 °C, a solution of alcohol **26** (0.070g, 0.197 mmol) in DCM (2 mL) was added by syringe. The resulting cloudy solution was stirred at –78 °C for 1h. Et_3N (0.12g, 1.185 mmol) was added and the milky white solution was stirred for 30 min at –78 °C. Reaction mixture was allowed to warm gradually to ambient temperature. After 2h, water (10 mL) was added and the organic layer was separated, was subsequently washed with saturated aq. NH_4Cl (2 mL), aq. $NaHCO_3$ (2 mL), and brine (5 mL). Organic layer was dried over anhyd. Na_2SO_4, filtered and rotary evaporated under reduced pressure and chromatographic purification of the residue (25% EA:Pet.ether) furnished aldehyde **27**.

Yield	: 0.043g (61%).
Mol. Formula	: $C_{20}H_{20}N_2O_2S$, solid
M.P.	: 140-141°C
Optical Rotation	:$[\alpha]_D$ = -62.4° (c=0.75, $CHCl_3$)
IR (neat)	: 3120, 2940, 1720, 1695, 1605, 1595, 1500, 1450, 1250.
^{1}H NMR ($CDCl_3$, 200MHz)	: 2.29 (dd, 1H, J = 4.7, 13.15Hz); 2.68 (dd, 1H, J = 4.7, 13.15Hz); 3.59 (s, 1H); 4.11 (dd, 1H, J = 4.7, 7.78Hz); 4.16 (d, 1H, J = 15.4Hz); 4.34 (d, 1H, J = 7.9Hz); 4.36 (d, 1H, J = 15.4Hz); 4.47 (d, 1H, J = 15.4Hz); 4.68 (d, 1H, J = 15.4Hz); 7.25 (m, 10H); 9.13 (s, 1H).
MS (m/z)	: 352(M^+, 5), 323(5), 277(93), 264(6), 91(100), 65(6).

9. Preparation of compound 28:

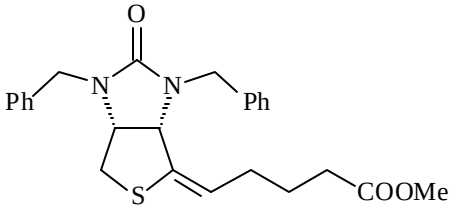


Under nitrogen atmosphere, magnesium (0.061g, 2.54 mmol) turnings were initially introduced into THF (10 mL) and the mixture was heated to boiling. A solution of dibromopropane (0.516g, 2.54 mmol) in THF (10 mL) was added to this suspension during 30 min. The reaction mixture was heated to reflux for 45 min and subsequently stirred at room temperature for 12h. It was then cooled to –15 ^{o}C. A solution of cyclic aldehyde **27** (0.18g, 0.51 mmol) in THF (10 mL) was added drop wise in the course of 30 min at a temperature between –14 to –16 ^{o}C. After stirring for 10 minutes the reaction vessel was evacuated and charged with CO_2 atmosphere. To this reaction mixture solid carbon dioxide (~1g) was added. After 1h, dil. HCl (1N, 5 mL) was added and the reaction mixture was extracted with EtOAc. The combined organic layers were washed with water (20 mL), brine (20 mL). Organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure and the crude product was subjected to esterification with diazomethane. Chromatographic purification of the residue (50% EA: Pet. ether) furnished hydroxy methyl ester **28** as a viscous liquid.

Yield	: 0.176g (76%)
Mol. Formula	:.$C_{25}H_{30}N_2O_4S$, viscous liquid.
Optical Rotation	: $[\alpha]_D$ = +62.13^{o} (c=1.24, $CHCl_3$)
IR (neat, cm^{-1})	: 3310, 3032, 2928, 1743, 1700, 1440, 1342, 1231, 1079, 789.
^{1}H NMR ($CDCl_3$, 200MHz)	: 1.25 (m, 2H); 1.59 (m, 2H); 2.22 (t, 2H, J == 7.32Hz); 2.70 (dd, 1H, J == 2.44, 12.21Hz); 2.91 (dd, 1H, J = 1.47, 12.21Hz); 3.20 (m, 1H, J = 1.47Hz); 3.28 (bs, 1H); 3.64 (s, 3H); 3.94 (dd, 1H, J = 7.81, 8.30Hz); 4.06 (m, 2H); 4.12 (d, 1H, J = 15.62Hz); 4.21 (d, 1H, J = 15.63Hz); 4.73 (d, 1H, J = 15.14Hz); 4.75 (d, 1H, J = 15.14Hz); 7.28 (m, 10H).
^{13}C NMR ($CDCl_3$, 125 MHz)	: 20.97(t), 33.48(t), 35.07(t), 36.23(t), 46.27(t), 46.82(t), 51.52(q), 59.49(d), 62.39(d), 65.65(d), 71.63(d), 127.51(d), 127.60(d), 127.97(2C, d), 128.03(2C, d), 128.61(2C, d), 128.67(2C, d), 136.97 (2C, s), 159.31(s, C=O), 173.66(s, C=O).

Mass (m/z) : 454(M^+, 5), 407(4)), 363(11), 324(33), 277(55), 233(11), 187(21), 149(14), 91(100), 65(11).

10. *Cis*-2-oxo-1,3-Dibenzyl-4(4-carbomethoxybutyl-1-idene)hexahydro-1H-thieno [3,4-d]imidazole (29):



The hydroxy ester **28** (0.1g, 0.22 mmol) was taken in a 25 mL two-necked round bottomed flask under nitrogen atomosphere and DCM (10 mL) was added to it. The flask was cooled to 0 ^oC and to it mesyl chloride (0.075g, 0.66 mmol) and triethyl amine (0.68g, 6.6 mmol) were added and the solution stirred for 5 h at room temperature. After completion of reaction, the reaction mixture further was diluted with DCM (10 mL) and the organic layer was washed with water (10 mL) and brine (10 mL). Dichloromethane layer was separated, dried over anhyd. Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was treated with diazabicyclo[5.4.0]undec-7-ene (DBU)(0.067g, 0.44 mmol) and heated to 60 ^oC for 12h. After completion of reaction (monitored by TLC) the reaction mixture was cooled to 0 ^oC and quenched with dil HCl (2N, 10 mL) and extracted with ethyl acetate. The combined organic layers was washed with water (5 mL), brine (5 mL) and dried over anhyd. Na_2SO_4 and filtered. The organic layer was concentrated under vacuum and the residue was chromatographed over silica gel with 35% EA:Pet.ether to yield olefin **29** in 80% yield.

Yield : 0.076g, 80%

Optical Rotation : $[\alpha]_D = +195.22^o$ (c=0.64, $CHCl_3$) [lit.[12] $[\alpha]_D = +211^o$ (c=1, $CHCl_3$)

IR (cm^{-1}, in $CHCl_3$) : 3032, 2928, 1743, 1701, 1634, 1440, 1415, 1342, 1219, 1143, 1079, 789.

^1H NMR ($CDCl_3$, 200MHz) : 1.72 (m, 2H); 2.12 (m, 2H); 2.31 (t, 2H, J = 7.3Hz); 3.05 (dd, 1H, J = 9.2, 10.2Hz); 3.12(dd, 1H, J = 4.4, 10.2Hz); 3.70 (s, 3H); 4.05 (d, 1H, J = 15.4Hz); 4.10 (ddd, 1H, J = 4.4, 7.3, 9.5Hz); 4.25 (d, 1H, J = 15.1Hz); 4.30 (d, 1H, J = 7.32Hz); 4.85 (d, 1H, J = 15.4 Hz); 5.01 (d, 1H, J = 16.0Hz); 5.54 (t, 1H, J = 7.3Hz); 7.35 (m, 10H).

Mass (m/z) : 436(M^{+1}, 1), 422(1), 405(1), 345(1), 309(45), 263(37), 187(6), 173(4), 158(4), 143(5), 132(17), 117(8), 105(25), 91(100), 77(10), 65(6).

1.3.4 References

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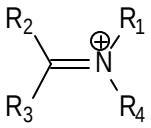
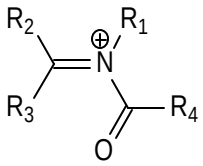
1.4.1 Introduction

Progress in the art of organic synthesis in the last three decades has been achieved by marked advances in *chemo*-, *regio*-, and stereoselectivity of classical and newly developed reagents. Well known in the former respect are the Mannich reagent **1** and the amido-alkylating reagent **2** of which the also called *N*-acyliminium ion- had been designed primarily to allow Mannich type condensations with primary amines.



1



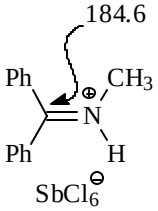
2

It soon appeared, however, that the *N*-acyliminium ion has highly versatile reaction characteristics in a much broader sense, which is now reflected in an impressive number of synthetic applications. Most of these reactions are of the intermolecular type and have been reviewed comprehensively. [1]

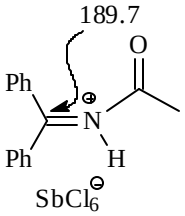
1.4.1a Reactivity Of *N*-Acyliminium *Vs* Iminium Ions:

The presence of strongly electron withdrawing carbonyl group leads one to expect that the imino carbon atom in the amidoalkylation reagent **2** is more electron poor than in the Mannich reagent **1**. Recently, this expectation was borne out for iminium salts **3** and **4** by comparison of their ^{13}C NMR spectra.[2] Substitution of an *N*-methyl by an *N*-acetyl group leads to a down field shift of the imino carbon absorption of about 5 ppm. The carbamate derived *N*-acyliminium ion **5** exhibits it imino carbon absorption also around 190 ppm.

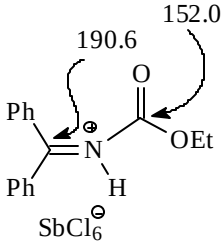
Scheme 1:



3



4



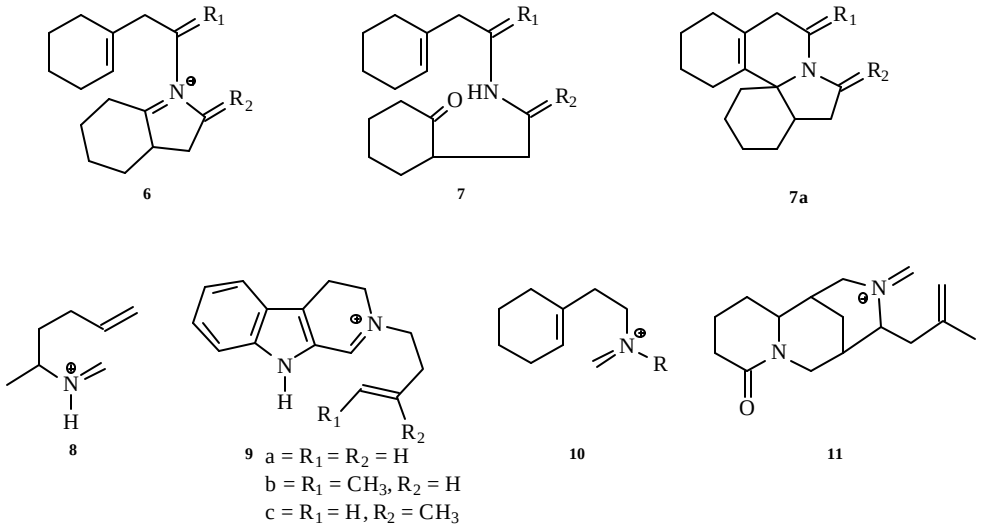
5

Thus, one may anticipate that *N*-acyliminium ions are more electrophilic, *i.e.,* more reactive than iminium ions.[3] However quantitative data, *i.e.*, mechanistic and/or kinetic investigations with intentional comparison of reactivities of the two types of reagents have not been published so far.

Quantitatively, it is known that in intermolecular arylation, Mannich reagents only react with strongly activated aromatic (phenols)[4] compounds whereas amidoalkylation even succeeds with extremely poor nucleophiles like nitrobenzene.

A nice illustration of the difference in reactivity in intramolecular reactions is the result on olefin cyclizations obtained in Erythrina alkaloid synthesis. Both acyliminium ions **6** (R_1 = O, R_2 = H_2[5] and R_1 = R_2 =O)[6] generated from the respective keto amides **7** gave expected cyclization product **7a**. In contrast, attempted ring closure of iminium salt **6** (R_1 = R_2 = H_2) led to unidentifiable products.[6] Other iminium systems such as **8**[7], **9a**[8] and **9b**[7] also failed to undergo cyclization.

Scheme 2:

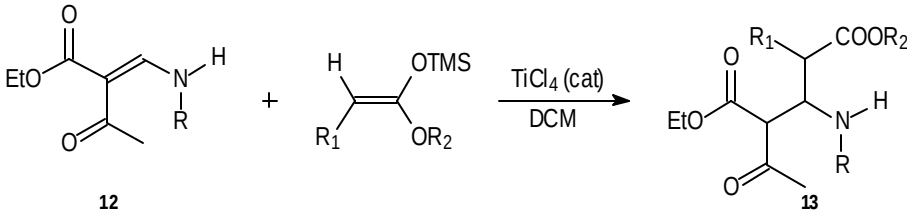


Care must be taken, however not to overestimate the reactivity difference between **1** and **2** since cyclisation **9c**[8] and **10**,[9] where tertiary carbenium ions occur as intermediate, proceed smoothly. Even **11**[10] has been reported to cyclize in good yield, despite the low nucleophilicity of a mono substituted double bond. Therefore, the actual difference in reactivity between iminium and *N*-acyliminium ions are not always obvious. One should realize here that these olefin cyclization reactions are in principle reversible processes, the reverse reaction being a Grob fragmentation.[11] The product of an *N*-acyliminium olefin cyclisation, being an amide is much less susceptible to fragmentation, than the product of an iminium-olefin cyclization, which is an amine. Therefore, the greater usefulness of *N*-acyliminium ion cyclizations in organic synthesis may primarily be attributed to their irreversibility.

Recently, it was experimentally demonstrated that *N*-acyliminium ions posses a higher reactivity profile as compared to the iminium species. A recent intermolecular example is found in the ketene

acetal addition[12] to **12** which proceeds rapidly to **13** in case of R = Cbz. An acyl group on the nitrogen atom is crucial for the reaction to take place since *N*-alkyl versions are inert under the given reaction conditions.

Scheme 3:



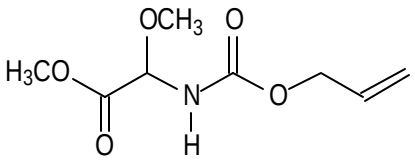
1.4.1b Experimental Conditions:

Protic acids-formic acid-as well as Lewis acids have been used to effect C-C bond formation. Evidently for sensitive nucleophiles such as enol ethers, alkenyl silanes or organometallic derivatives, *e.g.,* organo cuprates, the use of protic acid is only possible if the rate of bond formation is sufficiently high as compared to the alternative nucleophilic decomposition which in practice limits the reaction to the intramolecular variant. In the Lewis acid mode a number of studies are concerned with the effects of different catalysts. From these data it is inferred that the majority of reactions $BF_3.Et_2O$, $SnCl_4$, and $TiCl_4$ are superior in terms of convenience and results. In a few cases metal halides such as $FeCl_3$, $ZnBr_2$ and $MgBr_2$ or $LiClO_4$ are also used.

1.4.1c Stereo Control:

The mechanistic pathway for *N*-acyliminium reactions does not allow direct control of the desired stereochemistry. A recent example is found in the reaction of optically pure (+)-**14** with three types of nucleophiles, in all cases the completely racemized products being obtained.[13] Moreover upon mixing **14** with $BF_3.Et_2O$ without a carbon nucleophile present, the starting material was almost completely racemized within 24h at room temperature. Thus any desired effect should be brought about *via* indirect technique such as the use of chiral pool starting materials or with the aid of chiral auxiliaries.

Scheme 4:



14

1.4.1d Preparation of chiral and achiral precursors:

Various methods are known in literature for the preparation of cyclic as well as acyclic *N*-acyliminium intermediates. This section briefs only methods available for cyclic acyliminium ions. The various methods are:

1. a). Hydride addition to C=O of lactams and imides.[14]
   b). Enantiocontrolled reduction of meso-imides.[15]
2. Addition of RMgBr or RLi to imides[16]
3. Chemical oxidation at α-CH in cyclic amines and lactams.[17]
4. Electrochemical oxidation and decarboxylation at α-CH in cyclic amines and lactams.[18]
5. Ring closure of linear amides.[19]
6. Bicyclic oxylactams.[20]
7. Addition to enamide and pyridinium type compounds.[21]
8. Addition to enantiopure unsaturated alkoxylactams.[22]
9. Sugar and amino acid type starting materials.[23]

1.4.1e Carbon-Carbon bond formation of cyclic *N*-acyliminium intermediates:

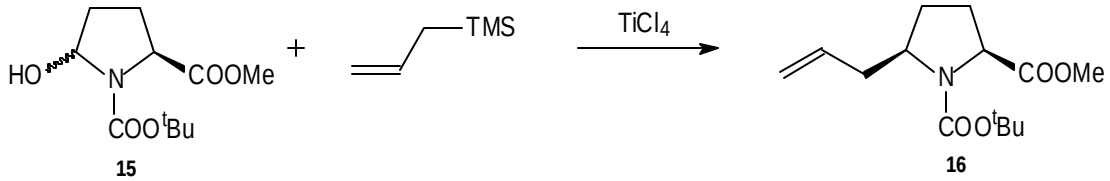
Carbon-Carbon bond formation of cyclic *N*-acyliminium intermediates can be performed in both intramolecular and intermolecular fashion. Emphasis will be placed upon the intermolecular C-C bond formation of cyclic *N*-acyliminium intermediates.

Since the majority of intermolecular applications deal with (chiral) substituted precursors a number of studies have been aimed at the optimization of the factors determining the stereo control.

a. Alkenyl silanes and stannanes as nucleophiles:

Highest *cis*-selectivity has been found in the $TiCl_4$/allyl TMS reaction to intermediate **15**.

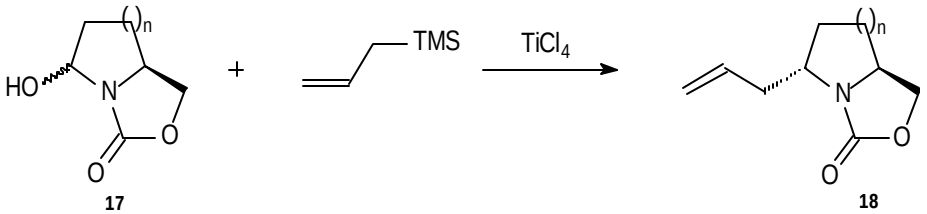
Scheme 5:



15 **16**

Interestingly in the case of cyclic intermediate **17** high *trans*-selectivity is observed.[24]

Scheme 6:



17 n = 1,2 **18** n = 1,2

b. Organocuprates:

In contrast to the previously mentioned *cis*-addition in pyroglutamate type precursors **15** the organocopper nucleophiles favor a high *trans*-selectivity.[25]

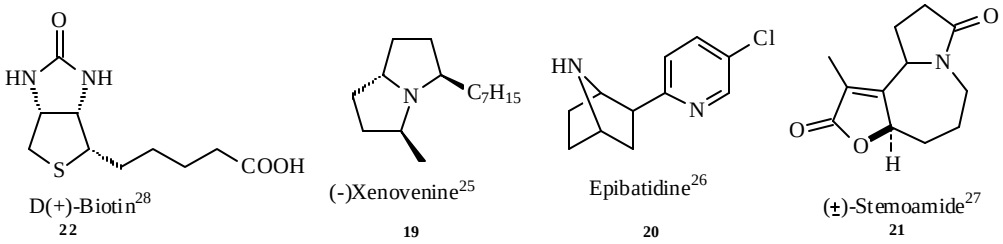
c: Enol ethers:

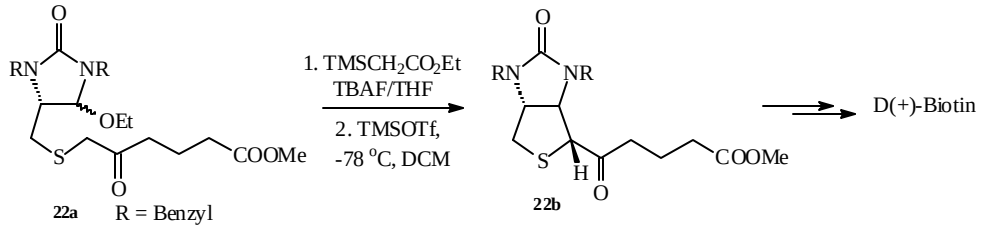
Silyl enol ethers in combination with Lewis acids like TMSOTf or $BF_3.OEt_2$ are excellent nucleophiles for the intermolecular C-C bond formation.

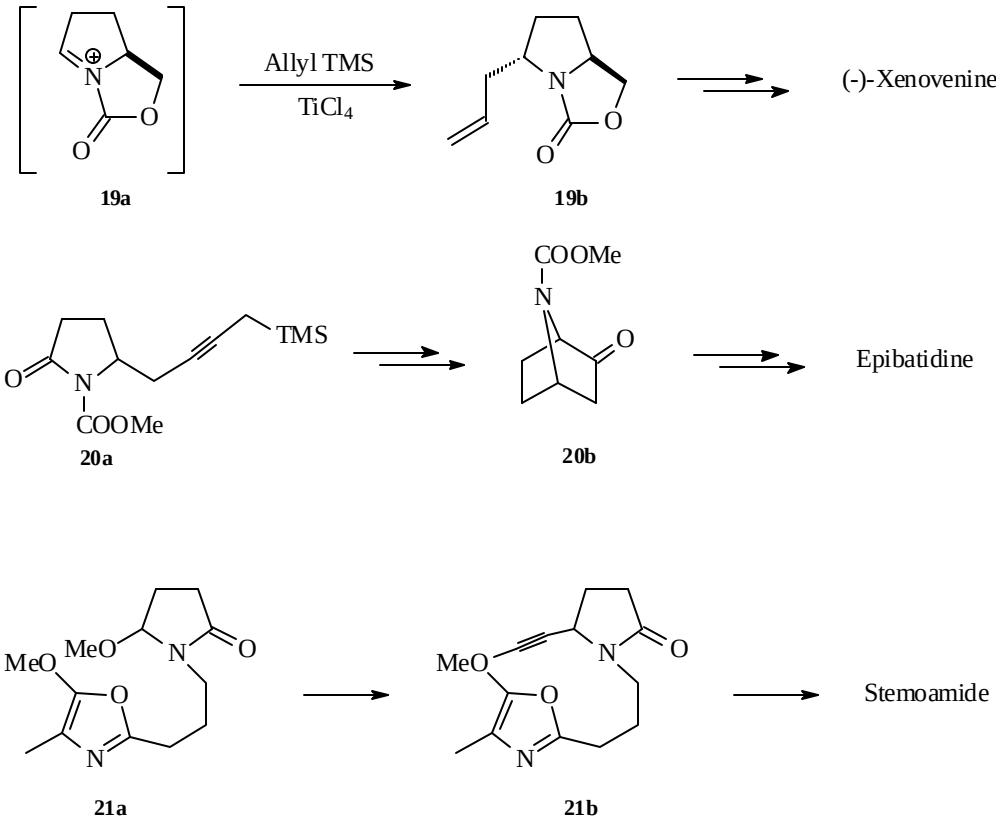
1.4.1f Application of *N*-acyliminium ions in the synthesis of some natural products:

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

Scheme 7:





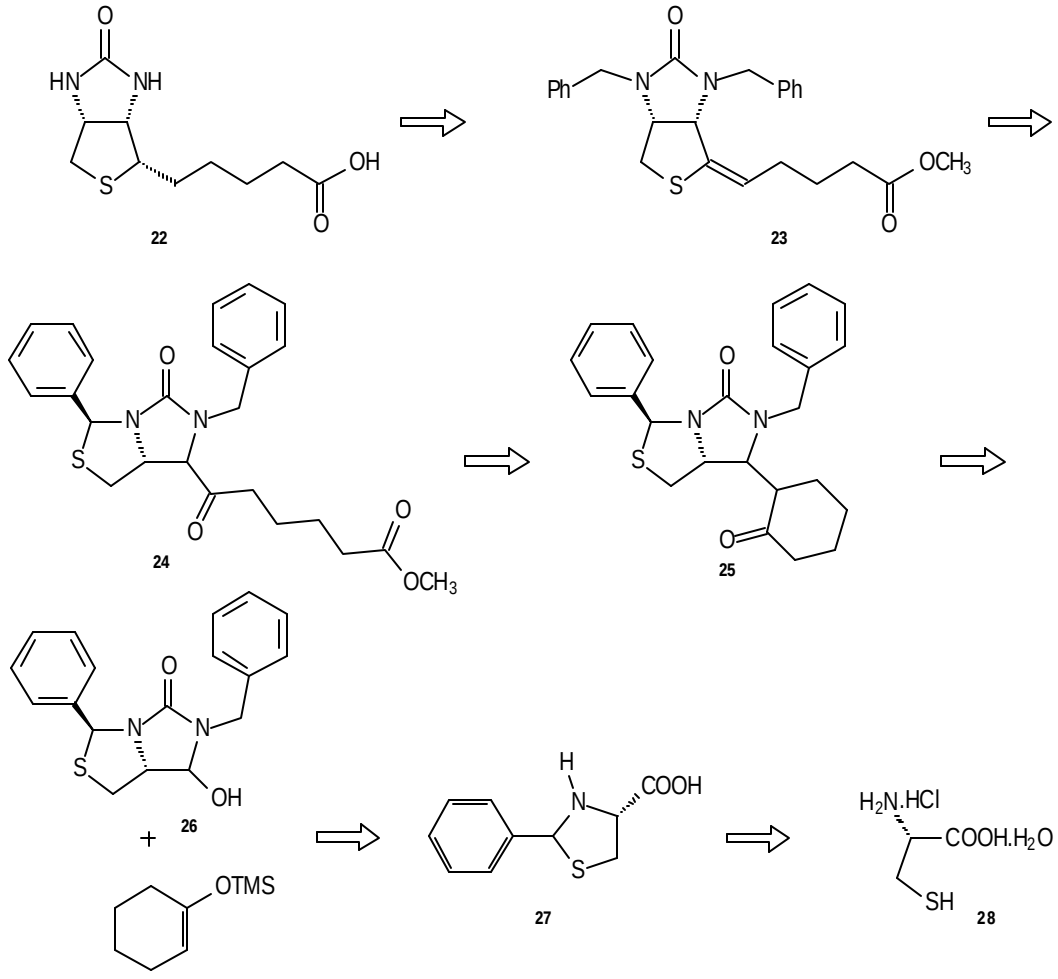

Allyl TMS
TiCl4
(-)-Xenovenine
19a
19b
TMS
COOMe
Epibatidine
20a
20b
MeO
Stemoamide
21a
21b

1.4.2 Present Work

Although a variety of syntheses of D(+)-biotin were known (see chapter-1:Section-1) most of them are not practical enough to be commercialized. 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 (+)-biotin hitherto reported employ inexpensive chiral substrates such as amino acids, sugars and so on as starting materials. Among them L-cysteine, in particular possesses potential as a chiral building block, since it contains thiol and amine moieties of the correct stereochemistry. From this standpoint, L-cysteine has been one of the most useful starting materials for (+)-biotin.

1.4.3 Results and Discussion

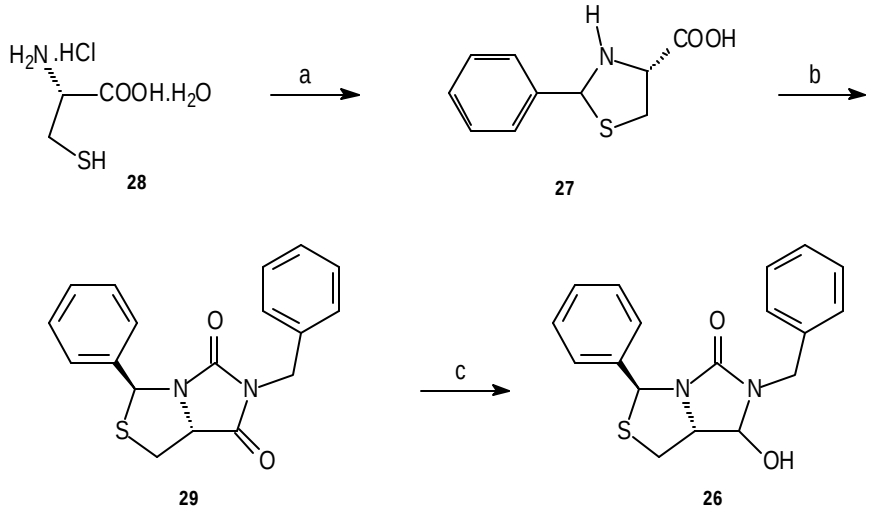
Scheme 8:



Retrosynthetic analysis (Scheme-8) revealed hydroxy imidazolidine **26** an intermediate which on C-C bond formation could be a probable approach towards D(+)-biotin. This scheme also revealed compound **24** as the key intermediate which could be accessed from inexpensive, commercially available starting materials.

In accordance with the planned synthesis, 7-hydroxy imidazolidine **26** was prepared from cysteine hydrochloride hydrate (**28**) (see chapter 1:section 2). Cysteine hydrochloride hydrate (**28**) was converted to its 2-phenyl-thiazolidine-4-carboxylic acid (**27**) by condensing with benzaldehyde, in the presence of KOAc.[30a] A one-pot addition of benzylisocyanate followed by dehydration furnished imidazolidinone **29** in 90% yield.[30b] Reduction of amide carbonyl using $NaBH_4$ in methanol provided hydroxy imidazolidine **26** in quantitative yield.

Scheme 9:

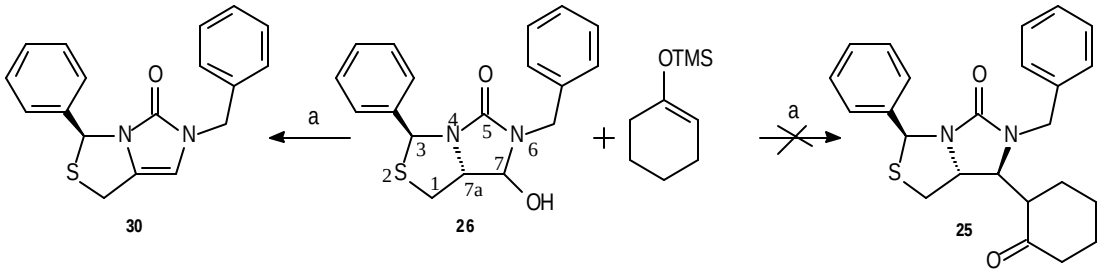


***a**) PhCHO, KOAc, MeOH:H_2O (1:1), 3 h, 98%.; **b**) BnNCO, THF, conc.HCl, 60 °C, 3 h, 90%.; **c**) $NaBH_4$, MeOH, 0 °C, 1 h, 98%.*

The hydroxy imidazolidine **26** would serve as an ideal substrate for the amidoalkylation at C_7- position *via N*-acyliminium ion.

Initial experiments of amidoalkylation of hydroxy imidazolidine **26** with nucleophiles such as 1-trimethylsilyloxy cyclohexene was attempted in the presence of $SnCl_4$ as a Lewis acid at –78 °C which failed to provide 7-substituted imidazolidine **25**. Instead olefin **30** was obtained as the sole product. Formation of **30** was established by its spectral analysis.

Scheme 10:



Condition: a) *$SnCl_4$(5eq), DCM, -78 °C to room temp., 5h, 95%*

Using other Lewis acids such as $SnCl_4$, $TiCl_4$ or $BF_3.OEt_2$ and 1-trimethylsilyloxy cyclohexene we examined amidoalkylation with hydroxy imidazolidine **26** and results are summarized in Table-1.

Table-1:[a] Amidoalkylation of hydroxy imidazolidine **26**

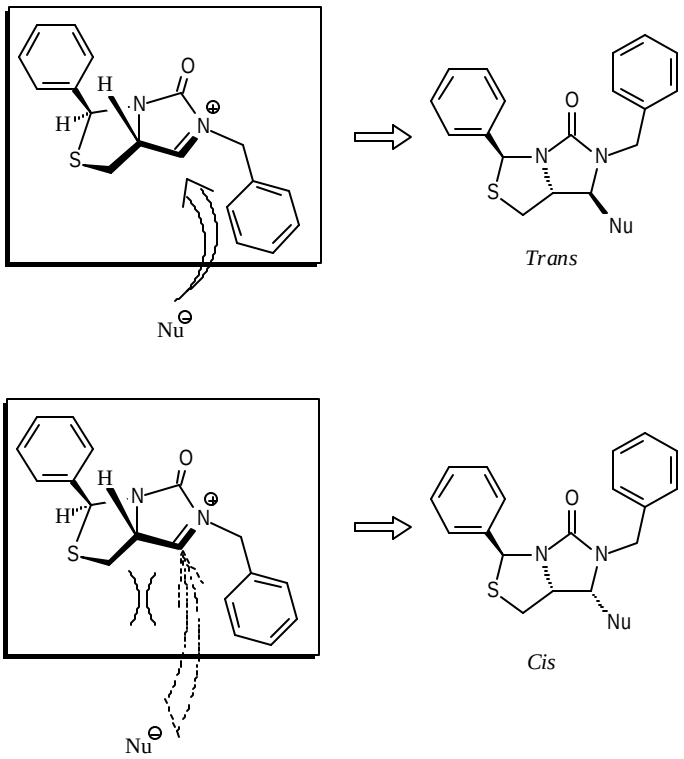
Entry	Nucleophile[b] (eq)	Lewis acid (eq)	Temp. (T / °C)	Time (min)	Formation of products in %		Yield (%)
					25	30	
1	5	$SnCl_4$ (5)	-78 to 25	300	-	100	96
2	5	$SnCl_4$ (3)	-78 to 25	300	-	100	98
3	5	$TiCl_4$ (3)	-78 to 25	300	-	100	95
4	5	$TiCl_4$ (2)[c]	-50 to 25	180	-	100	98
5	5	$TiCl_4$ (2)[c]	-30 to 0	300	10	90	-
6	5	$BF_3.OEt_2$ (3)	-78 to -40	120	-[d]	-[d]	-
7	5	$BF_3.OEt_2$ (3)	-20 to 0	60	50	50	-
8	3	$BF_3.OEt_2$ (3)	0 to 25	30	100	-	88
9	1.5	$BF_3.OEt_2$ (1.3)	0 to 25	10	100	-	>98

a. All reactions were performed with 1.0 eq of hydroxy imidazolidine **26**.
b. 1-Trimethylsilyloxy cyclohexene.
c. 1.0 M solution in dichloromethane
d. Starting material recovered.

After lot of experimentation, conditions were established for successful C-C bond formation using $BF_3.Et_2O$ as the Lewis acid. Thus the reaction of hydroxy imidazolidine **26** with 1-trimethylsilyloxy cyclohexene (1.5 eq) in the presence of 1.3 eq. of $BF_3.Et_2O$ as a Lewis acid at 0 to 25 °C proceeded smoothly to give the 7-substituted imidazolidine **25** in excellent yield. From the above table-1 it is evident that strong Lewis acids such as $TiCl_4$ and $SnCl_4$ neat as well as solution in dichloromethane were less effective. The reaction proceeds with high degree of diastereoselectivity to give the

corresponding 7-substituted imidazolidine **25** as a single diastereomer. The stereochemistry at C_7 position with respect to C_{7a} could be tentatively assigned as *trans* because the nucleophile attack should take place from the sterically less hindered convex face of the bicyclic imidazolidine group as depicted in Scheme 11.

Scheme 11:

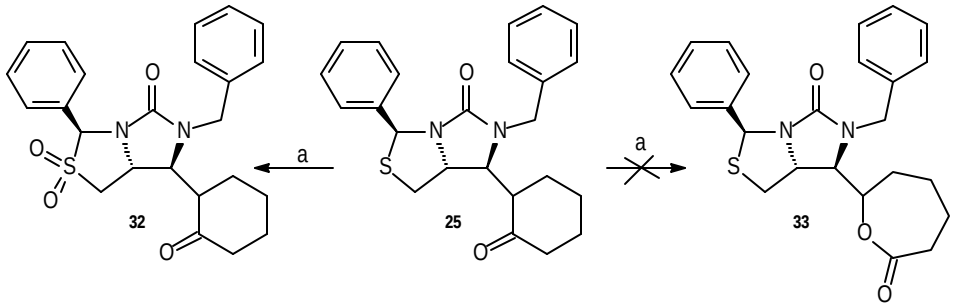


The *trans* stereochemistry was further confirmed by NMR spectroscopy.[31] The coupling constant between C_7H and $C_{7a}H$ is less than 1Hz which indicates the stereochemistry to be *trans*.

^1H NMR spectrum of **25** revealed a multiplet at δ 7.38 integrating for 10 protons and it was assigned to the 10 aromatic protons. Singlet at δ 6.37 for one proton was assigned to the benzylidine proton (C_3H). IR spectrum showed presence of peak at 1715 cm^{-1} confirming presence of ketone functionality.

Having confirmed the structure of compound **25** as a first step, a Baeyer-Villiger oxidation was performed on compound **25** to effect the 7membered lactone formation of cyclohexanone moiety. However the reaction failed to give the desired product, instead furnished sulphone **32** in 80% yield. Appearance of characteristic peaks at 1315, 1220, 1150 cm^{-1} in IR spectrum confirmed the formation of sulphone.

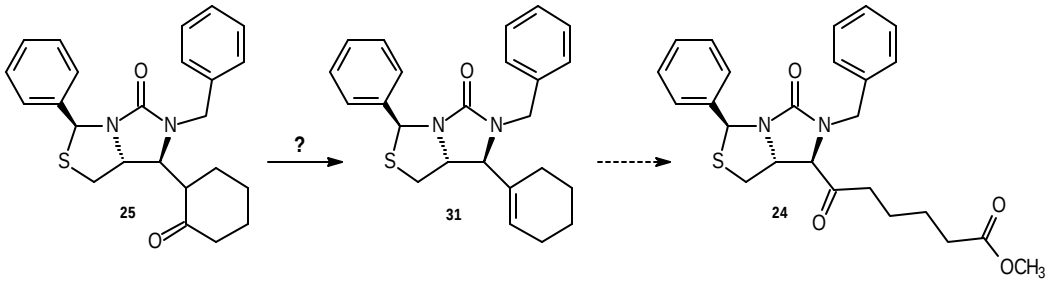
Scheme 12:



***a**) mCPBA, DCM, rt., 12h, 80%.*

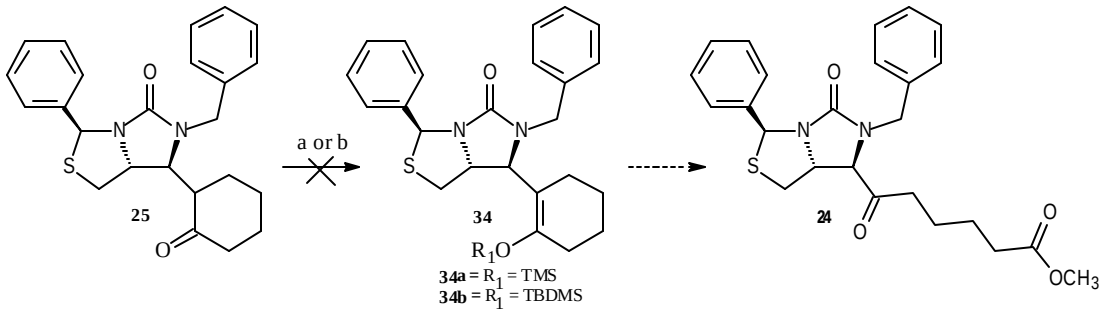
With the desired 7-substituted imidazolidine **25** in hand there was a need to elaborate it to cyclohexene moiety which in turn could be converted, to keto ester **24** by dihydroxylation, oxidation of diol and esterification of keto acid. Accordingly, ketone **25** was subjected to $NaBH_4$ reduction. Surprisingly, the reaction did not go to completion with invariably recovery of **25**. The alcohol thus obtained was subjected to elimination reaction employing under acidic as well as under basic conditions. However, under these conditions the olefin **31** could not be obtained. Alternatively, it was proposed to convert ketone **25** regioselectively under thermodynamic conditions to furnish enol ether **34** which could be readily converted into keto ester **24**.

Scheme 13:



All attempts to convert **25** to its corresponding silyl enol ether (**34a** or **34b**) met with failure.

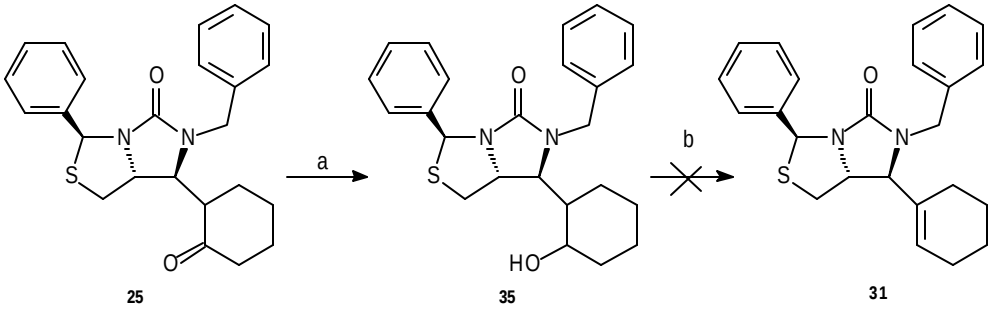
Scheme 14:



Conditions: ***a****) TMSCl/Et*$_3$*N/DCM rt or reflux;* ***b****) TBDMSCl/Et*$_3$*N/DCM, rt or reflux*

Failure to prepare the desired TMS/TBS enol ether(s) of the 7-substituted imidazolidine **25** led to the exploration of an alternative pathway to achieve the desired end. Thus compound **25** when subjected to sodium borohydride reduction in methanol at room temperature furnished 80% yield of hydroxy compound **35**.

Scheme 15:

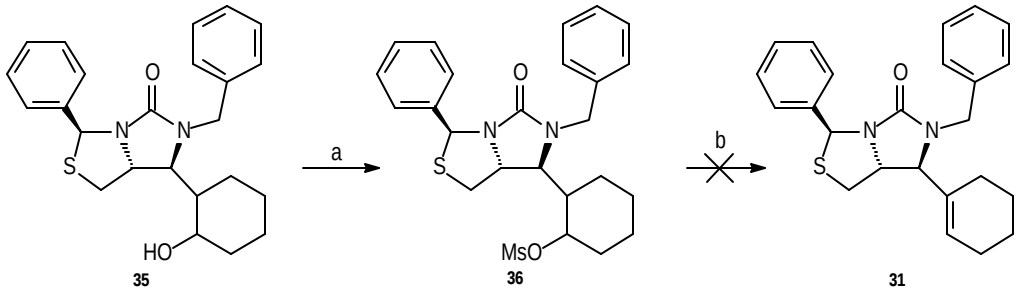


Conditions: a*) NaBH*$_4$*, MeOH, rt, 30 min, 80%.;* ***b****) pTSA, benzene, reflux, 24h.*

The IR spectrum confirmed the presence of hydroxy group at 3423cm^{-1}. Having confirmed structure of the hydroxy compound **35**, dehydration under acidic condition was attempted on compound **35** in order to get cyclohexene moiety **31**. Thus the cyclohexanol **35** was treated with pTSA, benzene under reflux in order to effect dehydration. However the reaction failed to give the desired product with the recovery of the starting material.

In an another attempt the hydroxy compound **35** was further converted to the mesylate **36** in order to eliminate it under basic conditions to give cyclohexene derivative, which could be converted to the keto ester **24**. Mesylation proceeded smoothly to give corresponding mesylate **36** in 90% yield.

Scheme 16:



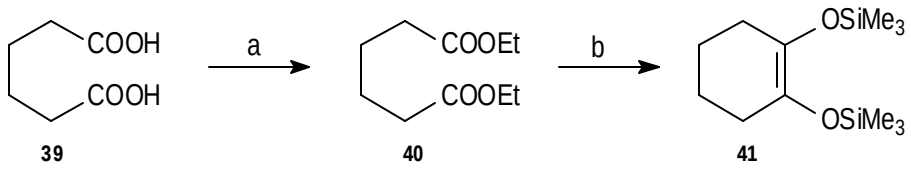
Conditions: ***a****) $MeSO_2Cl$, DCM, DMAP, pyridine, rt, 12h, 90%;* ***b****) **i**) DBU, benzene, rt or reflux.; **ii**) KO^tBu in toluene or DMF at rt or reflux.*

IR spectrum indicated the absence of hydroxy group and ^1H NMR confirmed the presence of mesyl group incorporation with a peak at δ 3.62. However refluxing the mesylate **36** in DBU/ benzene failed to furnish the required product **31**. Attempted elimination of the mesylate **36** was when subjected to KO^tBu/toluene or KO^tBu/DMF failed to furnish the desired product, with the recovery of starting material **36**. (see Scheme 16)

Having had discouraging results in converting the cyclohexanone derivative **25** to cyclohexene derivative **31**, it was thought that the amidoalkylation with appropriate nucleophile such 1,2-bis(trimethylsilyloxy)cyclohexene can be performed on hydroxy imidazolidine **26**. The resultant

α-hydroxy ketone could be selectively and readily cleaved to furnish the desired keto acid. Hence 1,2-bis(trimethylsilyloxy)cyclohexene (**41**) was prepared according to reported procedure[32] in 64% yield.

Scheme 17:

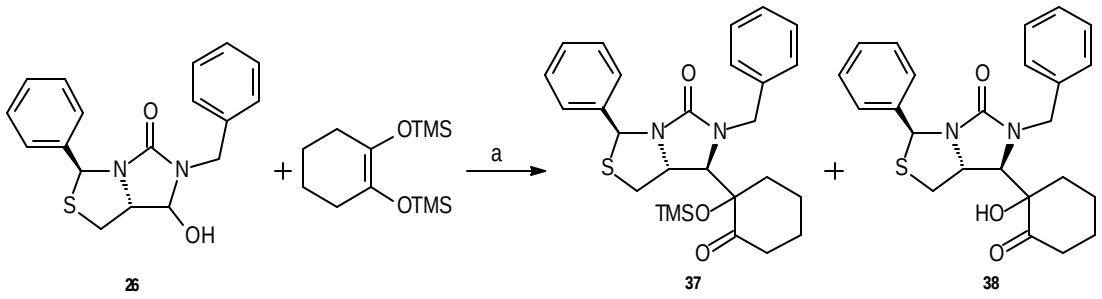


39 40 41

***Conditions: a**) $SOCl_2$, EtOH, rt, 3h, 98%; **b**) Na, TMSCl, toluene, reflux, 24h, 75%.*

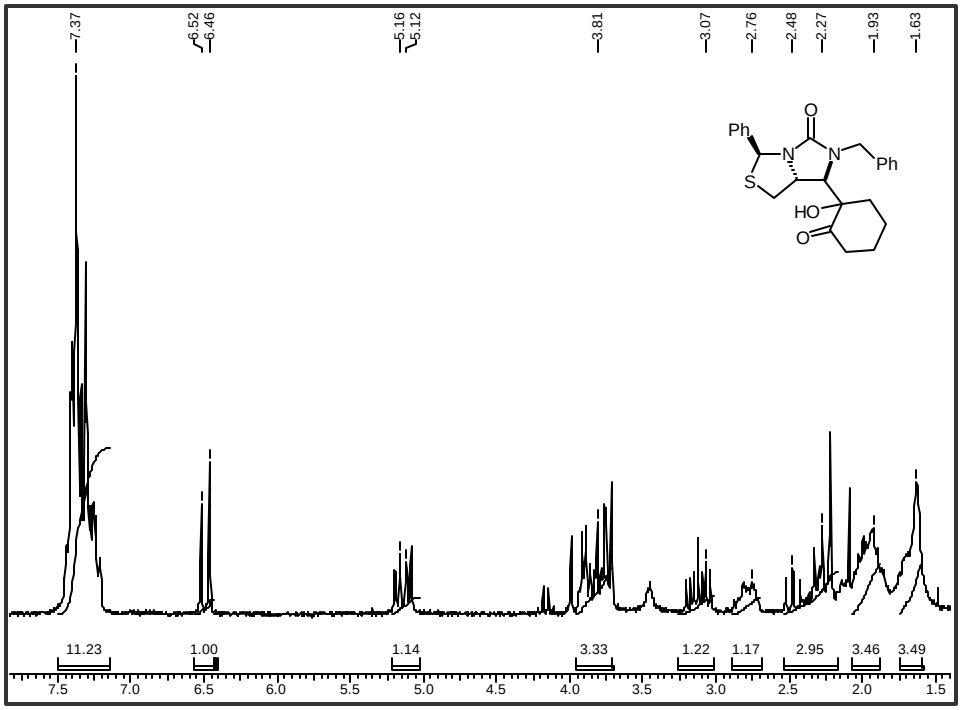
Amidoalkylation of compound **26** was attempted with 1,2-bis(trimethylsilyloxy)-cyclohexene (**41**) by using $BF_3.OEt_2$ as a Lewis acid, under the conditions developed earlier led to the formation of two compound **37** and **38** in 76% and 22% yield. The ^1H NMR of major compound showed the presence of trimethylsilyl (TMS) group apart from those of the imidazolidine and cyclohexanone moieties. In the ^{13}C NMR spectrum the presence of a quartenary carbon at 79 ppm was indicative of the formation of **37**. Finally the major compound was found to be 6-benzyl-7(1-trimethylsilyloxy-2-oxocyclohexyl)-3-phenyl-(3*S*, 7*S*, 7a*R*)-perhydroimidazo[1,5-C][1,3]thiazol-5-one (**37**) as confirmed by mass spectroscopy with a peak appearing at 494. Hence the structure was assigned to be **37**. The other minor compound **38** showed the presence of hydroxy group at 3443cm^{-1} in IR spectrum. In mass spectrum peak at 422 confirmed the structure of minor compound to be **38**.

Scheme 18:

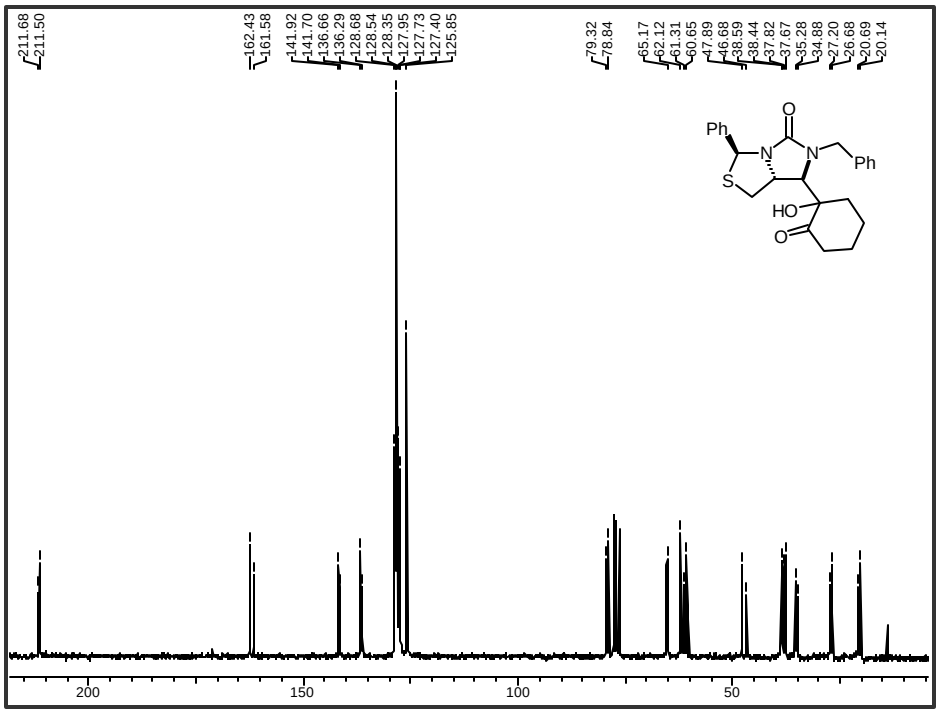


26 37 38

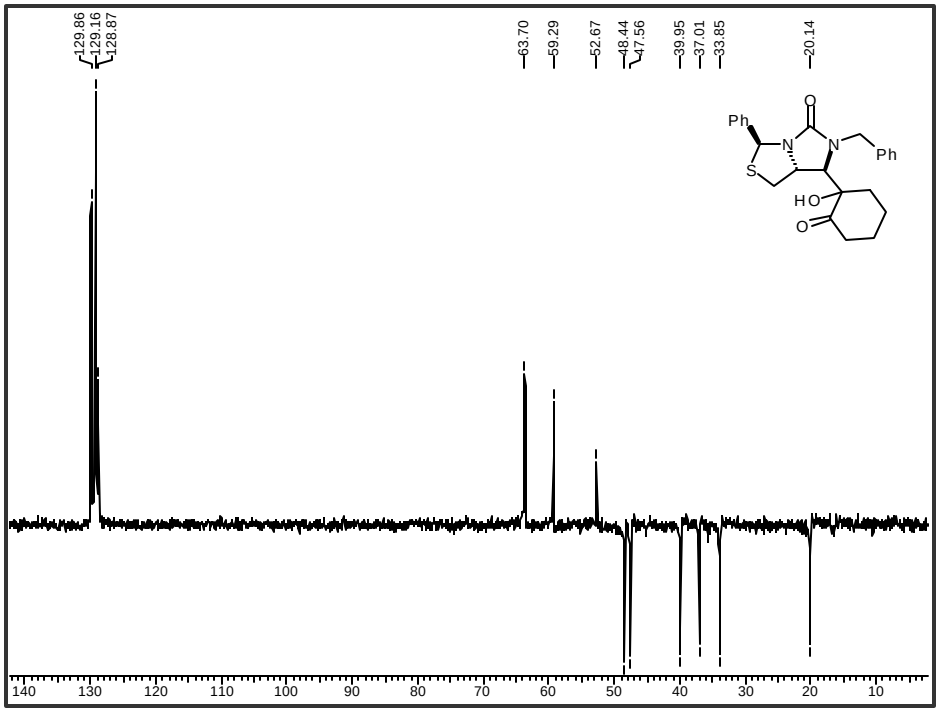
***Condition: a**) $BF_3.OEt_2$, DCM, 0 °C to rt., 10*min.*76%(**37**), 22%(**38**).*



^{1}H NMR spectrum of compound **38** ($CDCl_3$, 200 MHz)

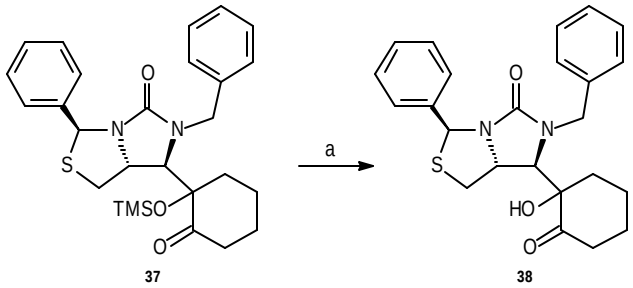


^{13}C and DEPT NMR spectra of compound **38** ($CDCl_3$, 50 MHz)



Deprotection of TMS group of compound **37** proceeded smoothly under alkaline methanol to furnish hydroxy compound **38** in 96% yield.

Scheme 19:

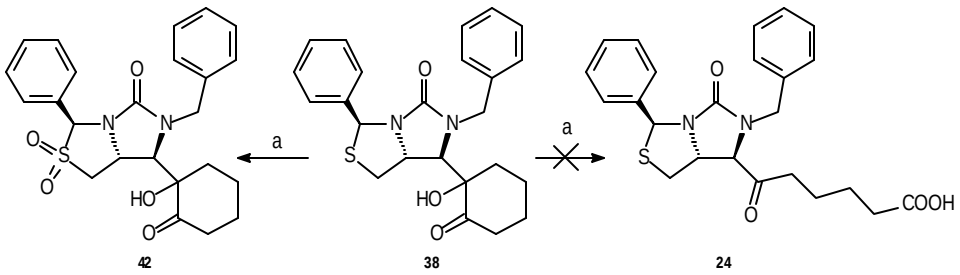


37 38

Condition: a*) 5.0eq KOH, MeOH, rt, 30* min*, 96%*

Oxidative cleavage of α-hydroxy ketone **38** with sodium metaperiodate gave only sulphone **42** (confirmed by IR) instead of desired keto acid. Having unsuccessful in cleaving the α-hydroxy ketone to the keto-acid, challenging task was to cleave the C-C bond without oxidizing the sulphur. One of the ways of effecting this cleavage could be the peroxide mediated cleavage under basic conditions where S does not get oxidized. Accordingly it was decided to perform the reaction with the readily available 30% H_2O_2 in the presence of base.[33]

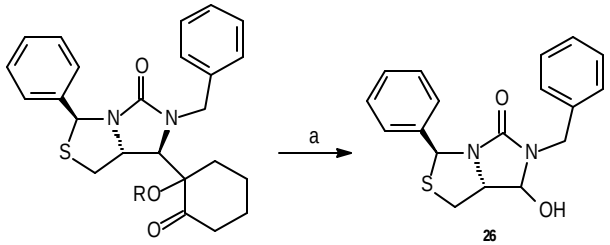
Scheme 20:



42 38 24

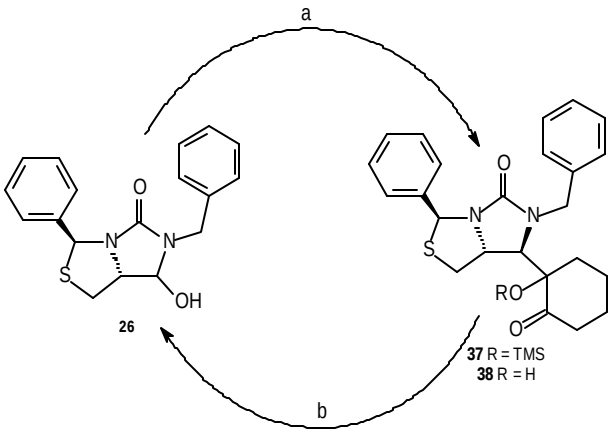
Condition: a*) $NaIO_4$, MeOH-H_2O (9:1), rt, 10 min.*

Scheme 21:



Condition: a) *H_2O_2, $NaHCO_3$, THF:H_2O (9:1), 5h, 70%*

Scheme 22:



Conditions: a) ***41***, *$BF_3.OEt_2$, DCM, 10* min, *98%* ***b)*** *H_2O_2, $NaHCO_3$, THF:H_2O (9:1), 5h, 70%*

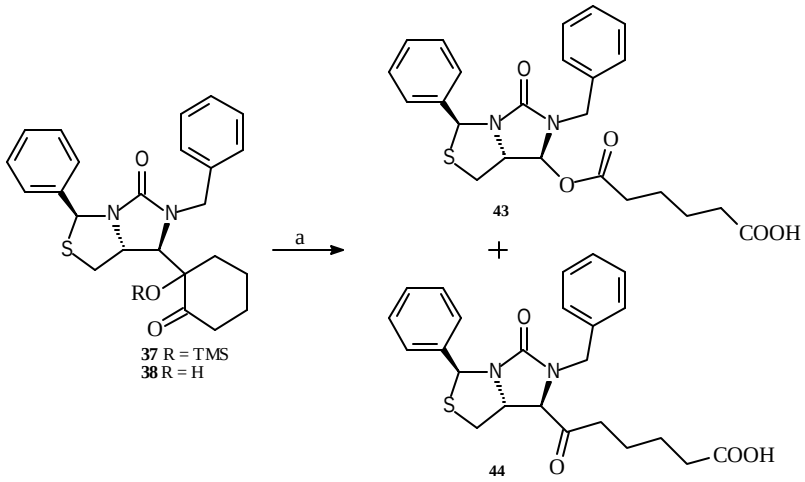
Accordingly both the compounds **37** and **38** were subjected separately to Bayer-Villiger oxidation with 30% hydrogen peroxide and $NaHCO_3$ as a base in 9:1 ratio of THF and water. It is interesting to note that under these conditions hydroxy imidazolidine **26** was obtained in 70% yield. The identity of **26** was established by comparison with authentic compound.

A point worthy of note is that by employing one set of condition one can convert **26** to **37** and **38** involving a C-C bond formation while the reverse reaction can be brought about by performing the reaction with peroxide under basic condition. Interestingly the conversion of **37** to **26** involves a series of four sequential reactions involving desilylation, insertion of oxygen, cleavage of α-hydroxy ketone followed by Baeyer-Villiger oxidation to furnish an ester which in turn is then hydrolyzed under the reaction conditions to furnish **26**. Considering four domino reactions occur in one pot the total yield of 70% is indicative of the high efficiency of the reaction. From the above study it is clear that depending on the choice of reagents one can readily interconvert **26** and **37/38.**

Since it was found to be difficult to control the reaction with H_2O_2 it was thought worthwhile investigating the reaction of compound **37** or **38** with different peroxides under basic conditions.

t-Butylhydrogen peroxide is one of the best source of oxygen atom when one considers the combined features of economics, selectivity and safety. The reaction of **37** or **38** with *t*-butylhydrogen peroxide (>2.5eq) in alkaline methanol furnished two acids in 80:20 ratio. The crude acids were esterified with diazomethane for the characterization purpose. The major isomer showed the presence of two ester carbonyls at δ 173.4 and δ 170.9 along with ureido carbonyl at δ 158.4ppm in ^{13}C NMR spectrum. Presence of molecular ion peak in mass spectrum at 468 suggests that the structure of compound to be **43**. The minor isomer in its ^{13}C NMR showed peaks appearing at δ 206.3, 173, 160 ppm for keto, ester and ureido carbonyls respectively. Molecular ion peak at 452 suggests that the structure of minor isomer to be **44**.

Scheme 23:



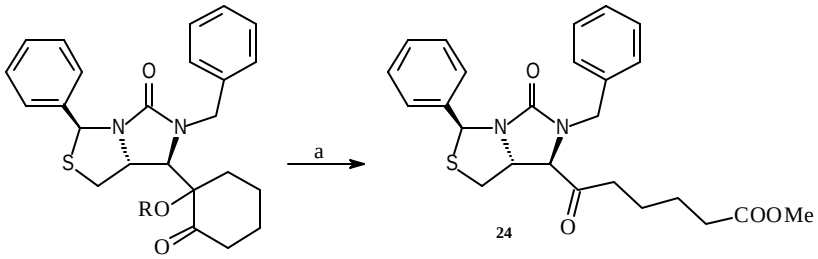
***Condition: a**) TBHP (2.5eq), KOH, MeOH, 20*min, *80 %(**43**) and 20 %(**44**).*

The structure of major isomer was further confirmed by subjecting it with sodium borohydride reduction. Upon borohydride reduction the compound **43** yielded hydroxy imidazolidine **26** in 80% yield.

Above result clearly suggests that the formation of compound **43** is due to over oxidation of compound **44**. In order to control the reaction and suppressing the side reaction the reaction was

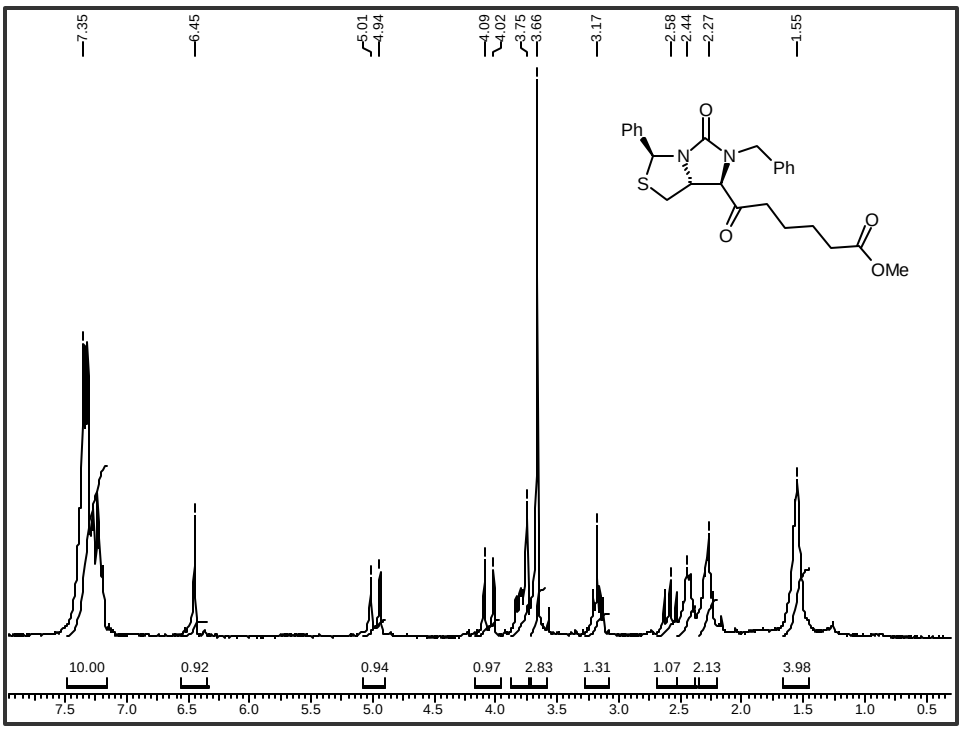
performed under different conditions by varying the stoichiometry of peroxide as well as base. Performing the same reaction for the cleavage of C-C bond with less equivalents of *t*-butylhydrogen peroxide (TBHP) (~1.2-1.4 eq.) in alkaline methanol, surprisingly the reaction proceeded smoothly in 20 min to furnish keto acid **44**. Finally exclusive formation of compound **44** from **37**/**38** was observed by using 1.2 eq of TBHP in alkaline methanol at 0 ^{o}C for 20 min in 75% yield. The acid **44** was converted to its methyl ester by treating with diazomethane.

Scheme 24:

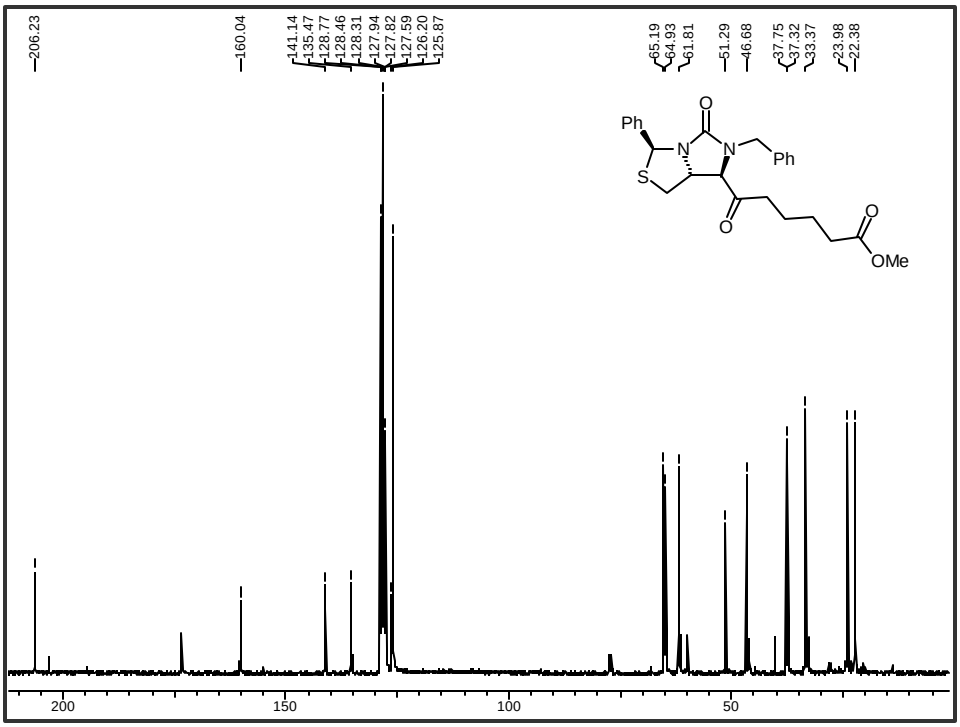


37 R = TMS
38 R = H

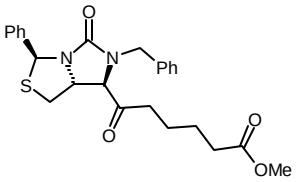
Condition: a*) TBHP (1.2eq), KOH, MeOH, 20*min*, 75%.*

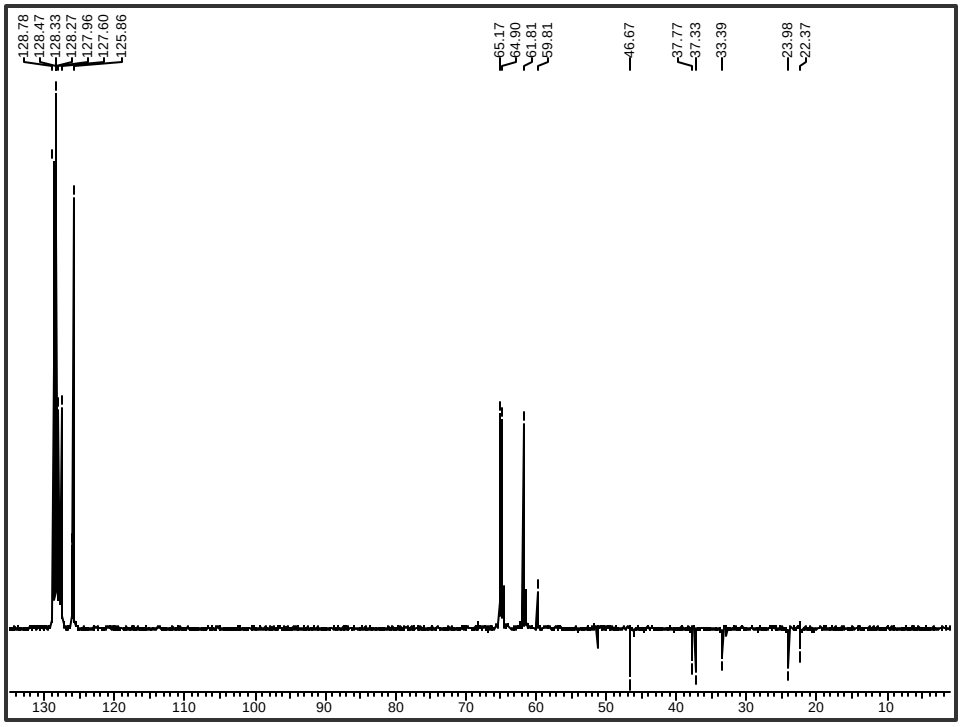


^{1}H NMR Spectrum of compound **24** ($CDCl_3$, 200 MHz)



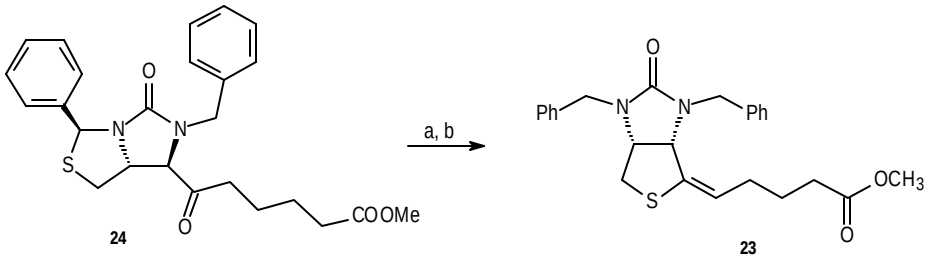
^{13}C and DEPT NMR spectra of compound **24** ($CDCl_3$, 50 MHz)



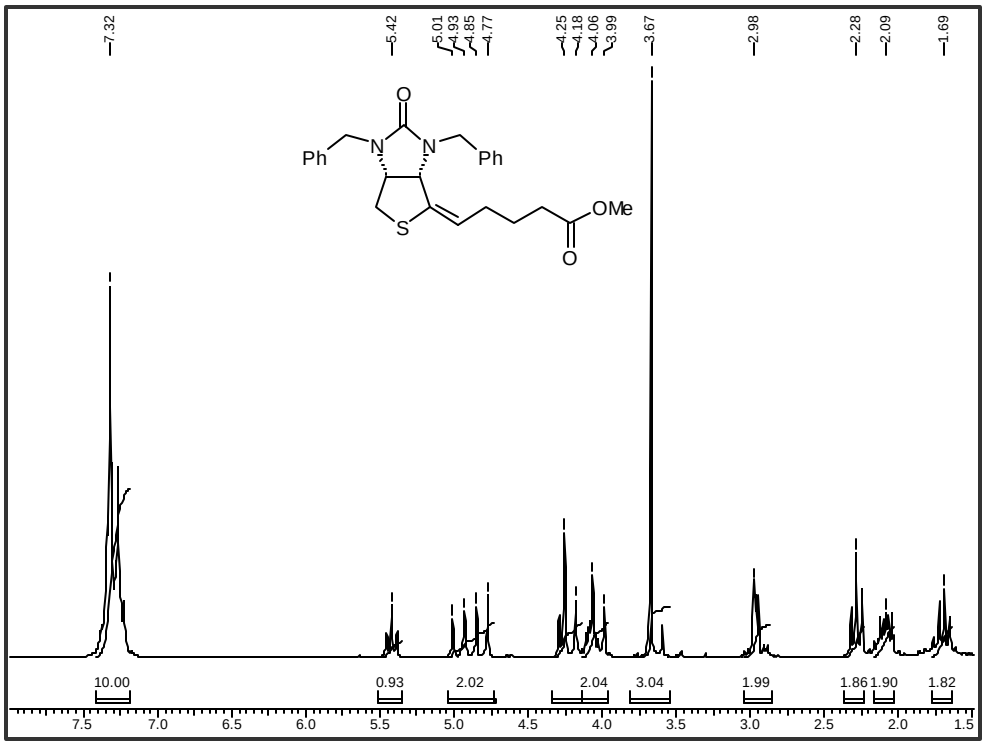


Reductive cleavage of carbon-sulphur bond of keto ester **24** with zinc in glacial acetic acid[34] gave crude thiol. Due to the unstable nature of the thiol, it was further subjected with piperidenyl acetate in acetic acid to yield known biotin precursor **23**.

Scheme 25:



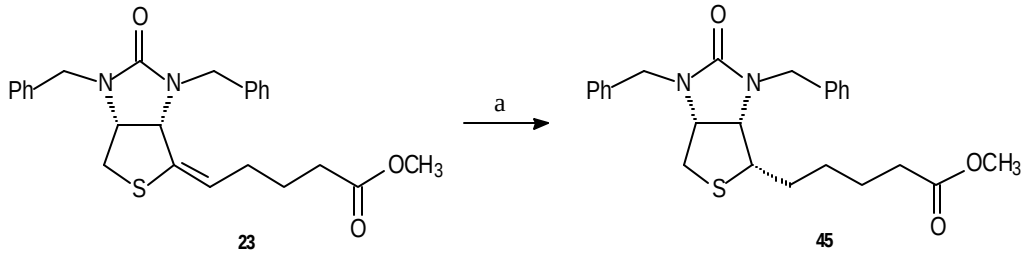
***Conditions: a**) Zn, AcOH(glacial), 80 °C, 5h.; **b**) Piperdine, AcOH, 100 °C, 90*min, *70%(two steps)*



^{1}H NMR spectrum of compound **23** ($CDCl_3$, 200 MHz)

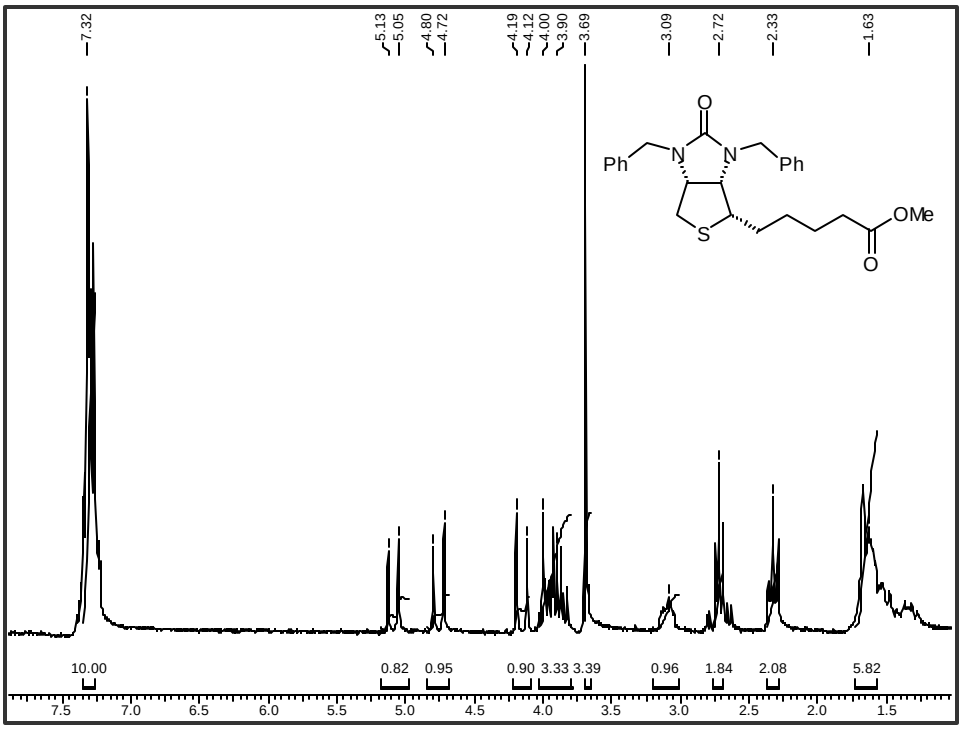
The ^{1}H NMR spectrum of compound **23** revealed a characteristic triplet at δ 5.54 (J = 7.3Hz) integrating for one proton which was assigned to the olefinic proton.

Scheme 26:



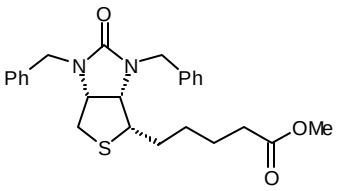
***Condition: a**) H_2/Pd-C, MeOH, 70 °C, 8h, 99%.*

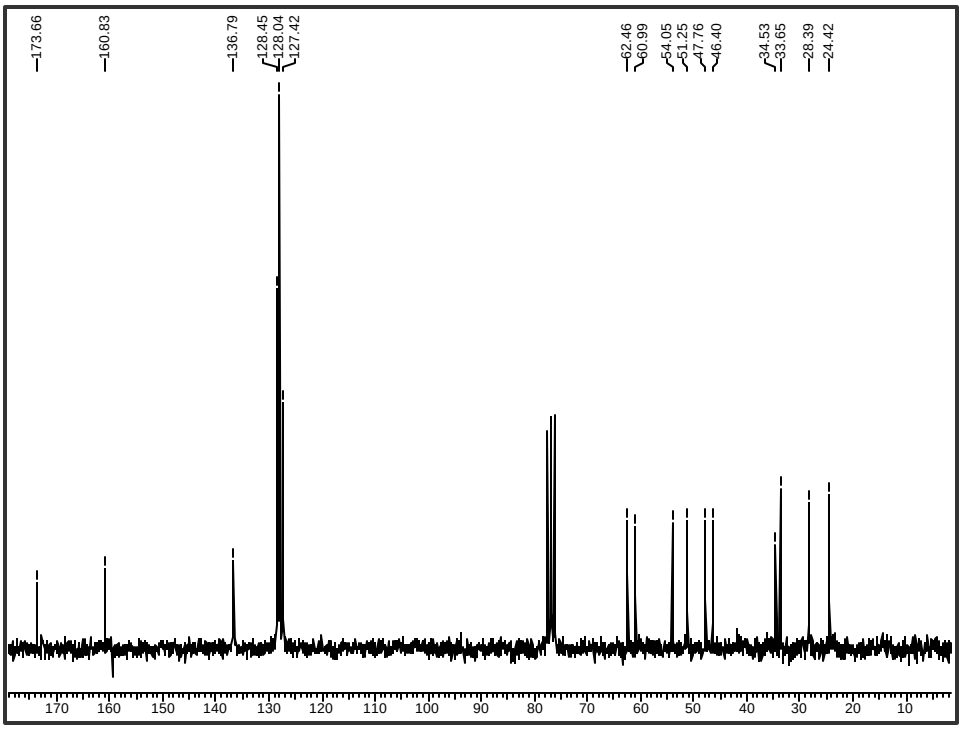
Catalytic hydrogenation of compound **23** palladised charcoal (10%) in methanol at 70 ^{o}C under hydrogen pressure (200 *psi*) for 8 h in autoclave gave all *cis N,N*-dibenzyl biotin methyl ester **45** in almost quantitative yield.



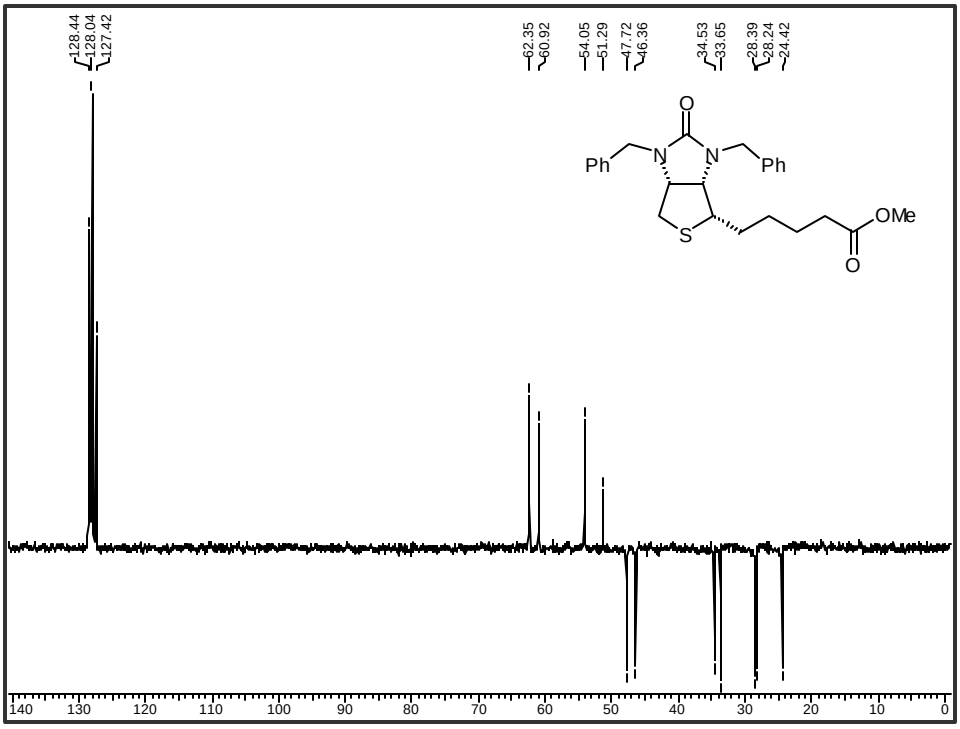
^{1}H NMR spectrum of compound **45** ($CDCl_3$, 200 MHz)

Two benzyl groups appeared as four doublets at δ 4.05, 4.25, 4.85 and 5.01 ppm (J =15.4 Hz). The IR spectrum showed absence of double bond at 1634 cm^{-1}.

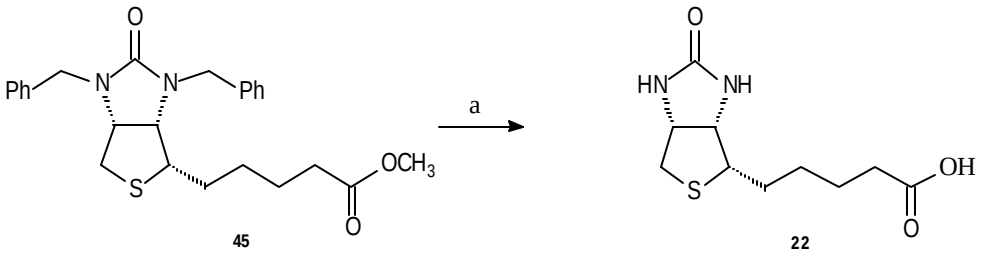




^{13}C and DEPT NMR spectra of compound **45** ($CDCl_3$, 50 MHz)



Scheme 27:



***Condition: a**) 47% aq. HBr, reflux, 4h, 70%.*

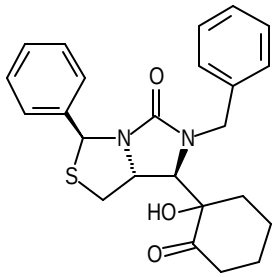
The compound **45** was converted to D(+)-biotin (**22**) according to reported procedure[35] through the removal of the benzyl protective groups in 70% yield. The product obtained by the present method revealed identity with an authentic sample with respect to m.p., IR, ^{1}H NMR, mass spectra and specific rotation. (see experimental section)

1.4.4 Conclusions

1. A short and efficient enantioselective synthesis of D(+)-biotin has been achieved starting from naturally available amino acid *viz.,* L-cysteine hydrochloride hydrate involving *N*-acyliminium ion chemistry involving only 10 steps.
2. The products obtained (except intermediate **23**) are all solids and the reaction sequence is simple to perform and p roceed in very good yields.
3. Nucleophilic addition of enol ethers to *N*-acyliminium ion of hydroxy imidazolidine **26** under Lewis acid conditions is reported for the first time and is probably one of the simplest steps towards the total synthesis of D(+)-biotin.
4. A non sulphur oxidative Bayer-Villiger oxidation method for cyclic α-hydroxy ketones to keto acids was developed under alkaline methanol conditions.
5. Most importantly this method is even better than the method developed by us earlier from practical point of view and has the following salient features:
    - **Novelty**
    - **Simplicity**
    - **Ease of operation**
    - **Short reaction time**
    - **Non-anhydrous conditions.**
    - **Potentially industrially feasible method. (Large scale)**

1.4.5 Experimental

1. 6-benzyl-7-(1-hydroxy-2-oxocyclohexyl)-3-phenyl-(3*S*, 7*R*, 7a*R*)-perhydroimidazo-[1,5-C][1,3]- thiazole-5-one (38):



To a solution of compound 6-benzyl-7-hydroxy-3-phenyl-(3*S*, 7a*R*)-perhydroimidazo-[1,5-C][1,3]thiazol-5-one of formula **26** (6.52 g, 20 mmol) in dichloromethane (200 mL) was added 1,2-bistrimethylsilyloxy cyclohexene (10.3 g, 40 mmol). Then the solution was cooled to 0 ^{o}C, and Lewis acid $BF_3.Et_2O$ (2.84 g, 20 mmol) was added dropwise. The reaction mixture was stirred at 0 ^{o}C for 10 min, and the reaction mixture was quenched with saturated ammonium chloride (50 mL). The organic layer was separated, dried, filtered, concentrated under reduce pressure and the residue thus obtained on column purification with ethylacetate:pet.ether (20:80) as eluent provided compound 6-benzyl-7-(1-trimethylsilyloxy-2-oxocyclohexyl)-3-phenyl-(3*S*, 7*R*, 7a*R*) -perhydroimidazo[1,5-C][1,3]thiazole-5-one of formula **37** (viscous liquid, 15.0 g, 30.4 mmol) in 76% yield. And with ethyl acetate: pet.ether (25:75) as eluent provided the compound 6-benzyl-7-(1-hydroxy-2-oxocyclohexyl)-3-phenyl-(3*S*, 7*R*, 7a*R*)-perhydroimidazo[1,5-C][1,3]thiazole-5-one of formula **38** (highly viscous liquid, 1.86 g, 4.4 mmol) in 22% yield.

Yield	: 15.0g (76% of **37**) and 1.86g (22% of **38**)
Mol. Formula	: $C_{24}H_{26}N_2O_3S$ (422)
M.P.	: 72 ^{o}C
Optical Rotation	: $[\alpha]_D$ = - 211 (c=1.18; $CHCl_3$).
IR (cm^{-1}, in $CHCl_3$)	: 3443, 2939, 2861, 1705, 1415, 1352, 11 75, 1115, 1043, 839, 698.

^{1}H NMR ($CDCl_3$, 200 MHz) : 1.63 (m, 3H); 1.93 (m, 3H); 2.0-2.45 (m, 3H); 2.76 (m, 1H); 3.07 (m, 1H); 3.81 (m, 3H); 5.13 (dd, 1H, J = 15.6Hz); 6.46 (s, 1/2H); 6.52 (s, 1/2H); 7.37 (m, 10H).

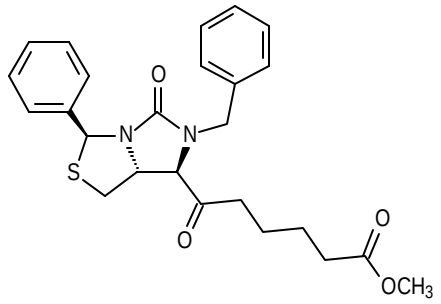
^{13}C NMR ($CDCl_3$, 75 MHz) : 20.2(t), 26.8(t), 34.8(t), 37.9(t), 38.3(t), 47.0(t), 60.3(d), 61.9(d), 64.9(d), 78.9(s), 125.8(d), 127.3(d), 127.6(d, 2c), 127.9(d, 2c), 128.3(d, 2c), 128.4(d), 128.5(d), 138.4(s), 141.7(s), 161.9(s, C=O), 211.5(s).

Mass(m/z) : 422(M^+, 1), 405(1), 309(32), 263(23), 142(6), 132(7), 121(6), 91(100), 77(19), 65(5).

Analysis

	Carbon	Hydrogen	Nitrogen	Sulphur
Calc.:	68.22	6.20	6.63	7.59
Found:	68.35	6.30	7.12	8.10

2. Methyl 6-[6-benzyl-5-oxo-3-phenyl-(3*S*, 7a*R*)-perhydroimidazo[1,5-c][1,3]thiazol-7yl]-6-oxohexanoic acid (44):



To an alkaline solution of methanol (0.336g, 6 mmol of KOH was dissolved in 10 mL of methanol) was added compound **38** (0.844g, 2 mmol). The solution was cooled to 0 ºC and then 70% *t*-butylhydrogen peroxide (0.216g, 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. The aqueous layer was acidified to pH 3 and extracted with ethylacetate. Evaporation of the solvent under reduced pressure furnished the compound 6-benzyl-5-oxo-3-phenyl-(3*S*, 7a*R*)-perhydroimidazo[1,5-c][1,3]thiazol-7yl]-6-oxohexanoic acid **44** (0.657g, 1.5 mmol) in 75% yield (after acid-base treatment). This acid was characterized as its methyl ester.

Yield : 0.657g (75%).

Mol. Formula : $C_{25}H_{28}N_2O_4S$, viscous liquid.

Optical Rotation : $[\alpha]_D = -162.5^o$ (c=1, $CHCl_3$)

IR (cm^{-1}, in $CHCl_3$) : 3030, 2949, 1731, 1728, 1716, 1444, 1415, 1359, 1222, 1157, 914, 732.

^1H NMR($CDCl_3$, 200MHz) : 1.55 (m, 4H); 2.27 (m, 2H); 2.44 (m, 2H); 2.58 (dd, 1H, J = 9.3, 10.3Hz); 3.17 (dd, 1H, J = 7.82, 11.2Hz); 3.66 (s, 3H); 3.75 (s, 1H); 3.80 (dd, 1H, J = 6.3, 9.0 Hz); 4.06 (d, 1H, J = 14.65); 4.98 (d, 1H, J = 14.65Hz); 6.45 (s, 1H); 7.38 (m, 10H).

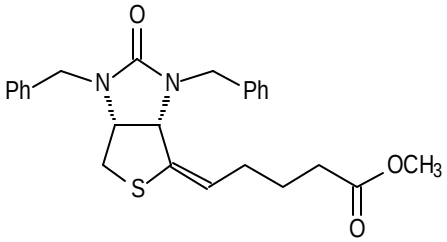
^{13}C NMR ($CDCl_3$, 125 MHz) : 22.38(t), 23.98(t), 33.37(t), 37.32(t), 37.75(t), 46.67(t), 59.87(q), 61.81(d), 64.93(d), 65.19(d), 125.87(d), 127.59(d), 127.71(d), 127.94(d), 128.31(d, 2C), 128.46(d, 2C), 128.78(d, 2C), 135.47(s), 141.14(s), 160.04(s, C=O), 173.30s, C=O), 206.30(s, C=O).

Mass (m/z) : 452(M^{+1}, 4), 421(3), 309(14), 263(7), 233(6), 187(5), 132(6), 121(5), 91(100), 77(10), 65(6), 55(5).

Analysis :

	Carbon	Hydrogen	Nitrogen	Sulphur
Calc.:	66.34	6.23	6.19	7.08
Found:	65.82	6.32	6.41	7.10

3. *Cis*-2-oxo1,3-dibenzyl-4(4-carbomethoxybutyl-1-idene)hexahydro-1H-thieno-[3,4-d]imidazole (23):



The keto ester **24** (0.452g, 1 mmol) was dissolved in glacial acetic acid (10 mL), and zinc dust (0.975g, 15 mmol) was added in portions at room temperature under nitrogen atmosphere. After addition was complete, the reaction mixture was heated to 80 ^oC for 5h. After completion of the

reaction (monitored by TLC) the reaction mixture was filtered through celite and the filtrate was concentrated to 2 mL. To this solution piperidine (0.176g, 1.5 mmol) was added and the reaction mixture was heated to 100 ^{o}C for 90 min. After completion of reaction, the reaction mixture was quenched with dil. HCl (10 mL) and extracted with ethyl acetate. The combined organic layers were washed with brine, dried over anhyd. Na_2SO_4, filtered and concentrated under reduced pressure. Column chromatography of the residue over silica gel using ethyl acetate:pet.ether (35:65) mixture as eluent furnished the olefin **23** as pale yellow viscous liquid.

Yield : 0.310 g, (70%)

Mol. Formula : $C_{25}H_{28}N_2O_3S$, viscous liquid.

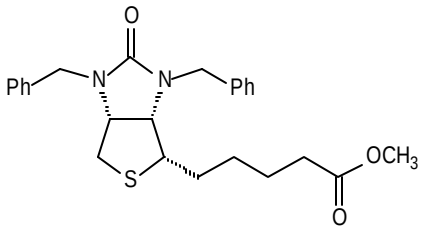
Optical Rotation : $[\alpha]_D = +194^{o}$ (c=1, $CHCl_3$)

IR (cm^{-1}, in $CHCl_3$) : 3032, 2928, 1743, 1701, 1634, 1440, 1415, 1342, 1219, 1143, 1079, 789.

^{1}H NMR($CDCl_3$, 200MHz) : 1.72 (m, 2H); 2.12 (m, 2H); 2.31 (t, 2H, J = 7.3Hz); 3.05 (dd, 1H, J = 9.2, 10.2Hz); 3.12(dd, 1H, J =4.4, 10.2Hz); 3.70 (s, 3H); 4.05 (d, 1H, J = 15.4Hz); 4.10 (ddd, 1H, J = 4.4, 7.3, 9.5Hz); 4.25 (d, 1H, J = 15.1Hz); 4.30 (d, 1H, J =7.32Hz); 4.85 (d, 1H, J =15.4 Hz); 5.01(d, 1H, J = 16.0Hz); 5.54 (t, 1H, J = 7.3Hz); 7.35 (m, 10H).

Mass (m/z) : 436(M^{+1}, 1), 422(1), 405(1), 345(1), 309(45), 263(37), 187(6), 173(4), 158(4), 143(5), 132(17), 117(8), 105(25), 91(100), 77(10), 65(6).

4. Methyl 5-[1,3-dibenzyl-2-oxo(3a*S*, 4*S*, 6a*R*)-perhydrothieno[3,4-d]imidazol-4-yl]-pentanoate (45):



A mixture of olefin **23** (0.30g, 0.68 mmol) and 10% palladium on charcoal (36mg) in methanol (50 mL) was hydrogenated (200 *psi*) for 8 h. Filtration of the catalyst and removal of the solvent under reduced pressure furnished a residue which was purified by column chromatography (20:80

ethylacetate:pet.ether) to furnish methyl 5-[1,3-dibenzyl-2-oxo(3a*S*, 4*S*, 6a*R*)-perhydrothieno-[3,4-d]imidazol-4-yl]pentanoate (**45**) as a white solid.

Yield : 0.295g, 99%.

Mol. Formula : $C_{25}H_{30}N_2O_3S$, white solid.

M.P. : 78 ^oC

Optical Rotation :$[\alpha]_D$ = - 42.13^o (c=1.05, $CHCl_3$)

IR (neat) : 3028, 2932, 2840, 1741, 1698, 1448, 1440, 1425, 1347, 1198, 1134, 1081, 792.

^1H NMR($CDCl_3$, 200MHz) : 1.67 (m, 6H); 2.33 (t, 2H); 3.10 (m, 1H); 3.69 (s, 3H); 3.90 (m, 3H); 4.15 (d, 1H, J = 15.4Hz); 4.75 (d, 1H, J = 15.6Hz); 5.10 (d, 1H, J =15.4Hz); 7.32 (m, 10H).

^{13}C NMR ($CDCl_3$, 125 MHz) : 24.42(t), 28.14(t), 28.29(t), 33.65(t), 34.53(t),, 46.40(t), 47.76(t), 51.25(d), 54.05(d), 60.99(d), 62.46(q), 127.42(d, 2C), 128.04(d, 4C), 128.45(d, 4C), 136.79(s, 2C); 160.83(s, C=O), 173.66(s, C=O).

Mass (m/z) : 438(M^+, 8), 347(13), 277(31), 265(13), 240(9), 187(18), 149(4), 91(100), 77(3), 65(9).

Analysis :

	Carbon	Hydrogen	Nitrogen	Sulphur
Calc.:	68.46	6.89	6.38	7.31
Found:	68.15	6.39	6.24	8.13

1.4.6 References

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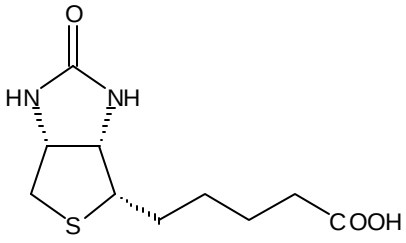
    b). Goldberg, M. W.; Strenbach, L. H. USP 2,489,235. Nov. 22, 1949. Chem. Abstr. **1951**:*45*, 186a.

2.1.1 Introduction

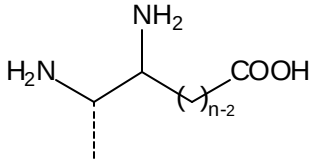
Many natural products that have valuable biological properties contain a 1,2-diamine moiety. D(+)-biotin (vit. H) also poses 1,2-diamine as the key functionality in its structure. In recent years several synthetic diamine derivatives have also been employed as medicinal agents especially in chemotherapy. Their utility in organic synthesis has also increased considerably recently, especially in the field of catalytic asymmetric synthesis. Hence, interest in these compounds brought about numerous studies aimed at the design of efficient diastereo and enantiospecific routes to 1,2-diamines. This section briefs the occurrence of natural products containing 1,2-diamine functionality as well as their biological and therapeutical properties, followed by application of vicinal diamines and their derivatives as tools in organic synthesis and finally some important methods of preparation of these compounds.

2.1.1a Vicinal Diamines in Natural Products:

Biotin **1** (or Vitamin H),[1] which is an essential cofactor to carboxylaze-catalyzed reactions, is one of the compounds found in nature that contain the 1,2- diamine moiety in their skeleton. A large number of natural products, especially peptides contain a n, n+1 diamino carboxylic acid substrate such as **2**. 2,3-Diamino propanoic acid is a constituent of several peptide antibiotics such as edeines[2] and tuberactomycin derivatives.



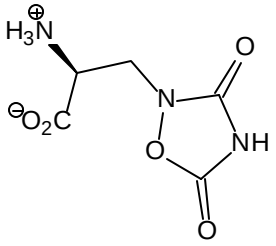
D(+)-Biotin **1**



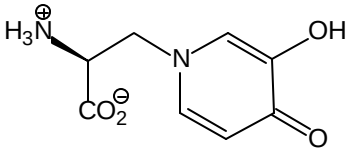
n, n+1-Diaminocarboxylic acid **2**

The bleomycins, first isolated in 1966[3] are a family of glycopeptides containing the 2,3-diaminopropanamide moiety. These are chemotherapeutic agents used for the clinical treatment of malignant lymphomas and squamous cell carcinomas.[4] β-(Methylamino)-L-alanine is a neurotoxin that has been linked to the so-called Guam disease.

Neuroexcitatory quisqualic acid,[5] mimosine and the isoxazlinone alanine derivatives[6] also all include the 2,3-diamino propanoic residue. Amphomycin,[7] aspartomycin,[8a] streptonigrin[8b] lavendamycin,[8c] glumamycin and antrimycin are potent antibacterial peptides incorporating the 2,3-diamino butanoic acid residue.

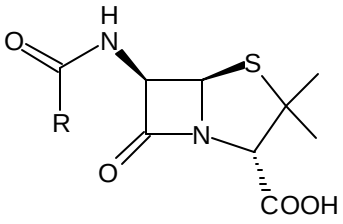


L-Quisqualic acid **3**

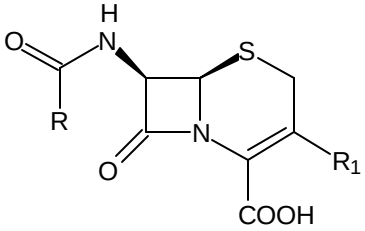


Mimosine **4**

The well-known antibiotics pencillins **5** and cephalosporins **6** also contain 2,3-diamino carboxylic acid unit, incorporated into the penam and cepham structures respectively.



Penicillins **5**

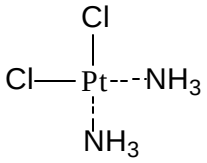


Cephalosporins **6**

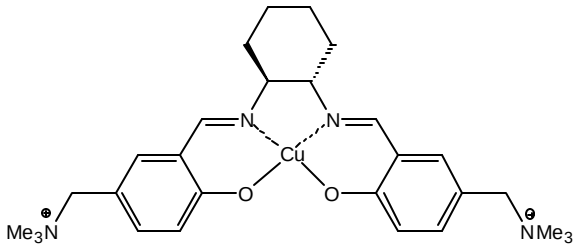
2.1.1b Applications In Medicinal Chemistry:

The 1,2- diamine functionality can be found in various compounds, displaying a broad spectrum of biological activity. In 1989 Michalson and Szmuszkoviz reviewed medicinal agents incorporating the 1,2- diamine unit.[9] Among these one can cite, for instance, antiarrhythmics, antidepressant agents, anthypertensives, antipsychotics, analgesics, anti anxiety agents and anticancer drugs.

Anti tumor properties of cisplatin [cis-diaminedichloropaltinum (II)] were serendipitously discovered by Rosenberg in the mid 1960s.[10] In recent years, metal complexes of salen Schiff's bases such as **8** were reported to bind selectively with DNA was observed in several cases. These studies could lead to development of artificial restriction enzymes or antitumor drugs.



cis-Platin **7**



8

Several compounds that incorporate the 1,2- diamine moiety such as EDTA can strongly chelate metal ions to form stable complexes. This property has been employed in particular in the field of nuclear medicine, since the complexes of metallic radioactive isotopes can be used as imaging agents.

2.1.1c Vicinal Diamines In Organic Synthesis:

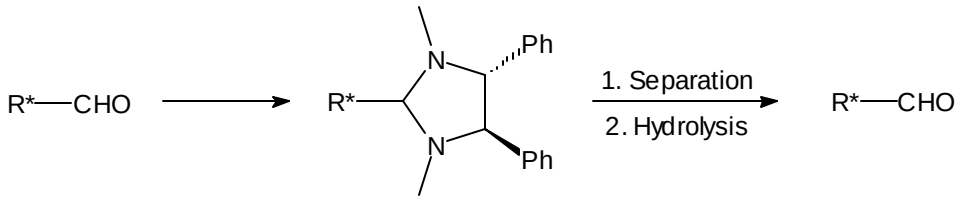
1,2-Diamino compounds are valuable synthetic intermediates for the preparation of heterocycles.[11] Diamines such as TMEDA are widely used as additive to stabilize and activate organometallic reagents and inorganic salts.

Chiral non-racemic vicinal diamines have received increasing attention during the last decades. Indeed, enantiomerically pure 1,2-diamines and their derivatives are particularly useful as chiral auxiliaries or ligands, and they have found tremendous applications in stereoselective synthesis. In their field, chiral C_2-symmetric 1,2-diamine[12] and their various derivatives offer especially great promise as new reagents for enantioselective synthesis. The utility of chiral vicinal diamines is briefly described.

1. Resolution of racemates and determination of *ee*:

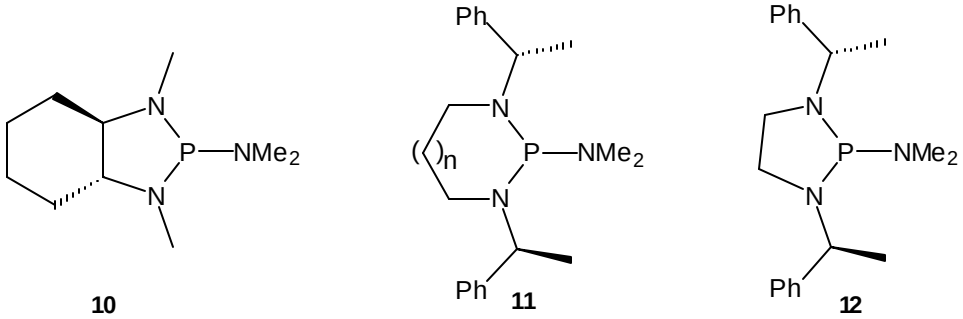
Mangeney and Alexakis *et al.*[13] have demonstrated the utility of symmetrical vicinal diamines as interesting compounds that can be utilized as resolving agents for chiral aldehydes.

Scheme 1: *Tetrahedron Lett.* **1988**, *29*, 2677



9

Later, the same authors later also introduced phosphorus derivatives such as which were obtained from C_2-symmetric diamines, for the determination of the enantiomeric composition of chiral alcohols, thiols, and amines by ^{31}P, ^{1}H, ^{13}C, and ^{19}F NMR spectroscopy.



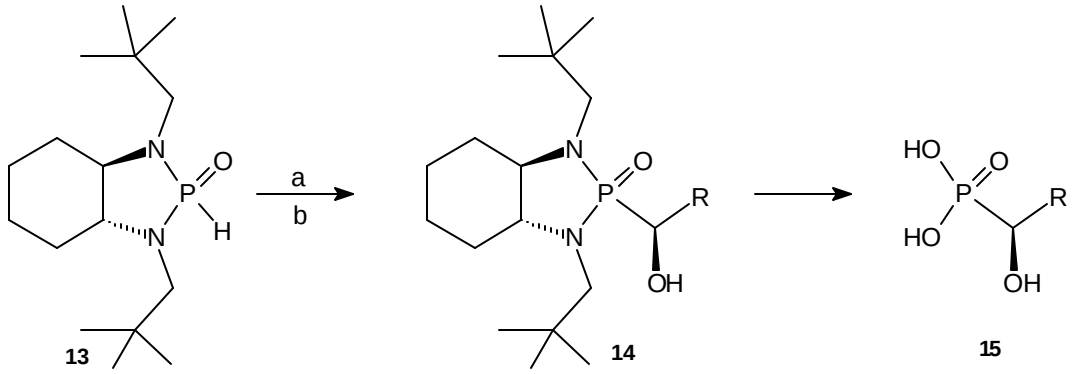
10 **11** **12**

2. As chiral auxiliaries in diastereoselective synthesis:

Several chiral auxiliaries derived from 1,2- diamines have been employed in highly stereoselective reactions. For example phosphonamides, imidazolidin-2-ones, diazaborolidines and aminals have been demonstrated as efficient chiral auxiliaries in diastereoselective synthesis.

Spilling *et al.* [14a] have recently described the stereoselective synthesis of α-hydroxyphosphonic acids **15** from the chiral bicyclic phosphonamide **13**. The rigidity of these bicyclic systems is probably important in dictating the levels of asymmetric induction observed.

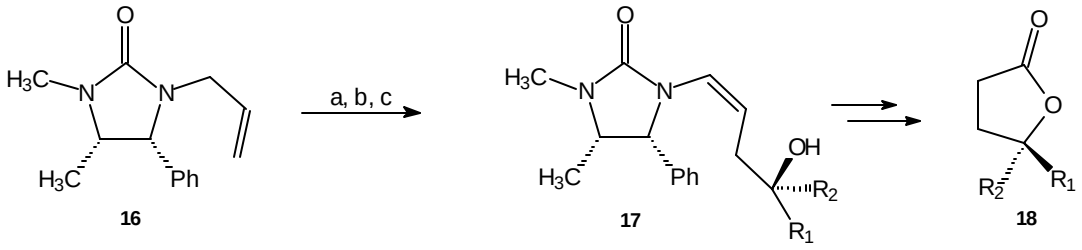
Scheme 2: *Tetrahedron: Asymmetry* **1994**, *5*, 499



Conditions: ***a****) $^{i}Pr_2NLi$, THF;* ***b****) RCHO, THF, -70 °C.*

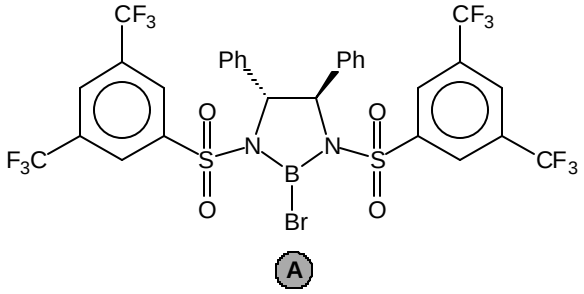
Helmchen *et al.* [14b] described the homoaldol addition of the titanium compound obtained from N-alkyl urea **16** with aldehydes or ketones. This reaction afforded alcohols **17** (*de*=88-96%, *de*>98% after crystallization) which were then converted to γ-lactones **18**.

Scheme 3: *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 898



Conditions: ***a****) n-BuLi, -78 °C;* ***b****) $(Et_2N)_3TiCl$, -20 °C;* ***c****) R_1R_2CO.*

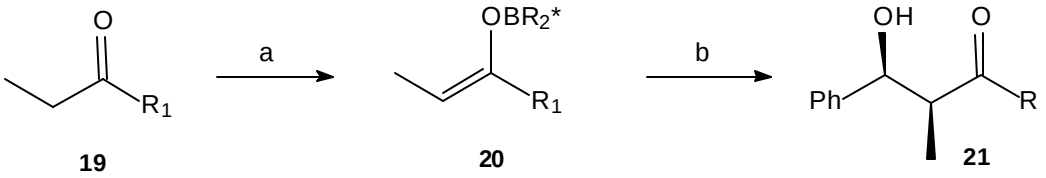
Corey *et al.* [15] have developed enantioselective protocols that make use of chiral, boron–containing chiral auxiliaries derived from 1,2-diphenylethylene diamine.



For example the enantioselective synthesis of either of *syn* or *anti* aldol products by using diazaborolidine [A] was described. The divergence in stereochemistry was attributed to the

intermediacy of boron enloates of either E- or Z- configuration depending of the ester structure.

Scheme 4: *Pure Appl. Chem*., **1992**, *62*, 1209



19 **20** **21**

93%

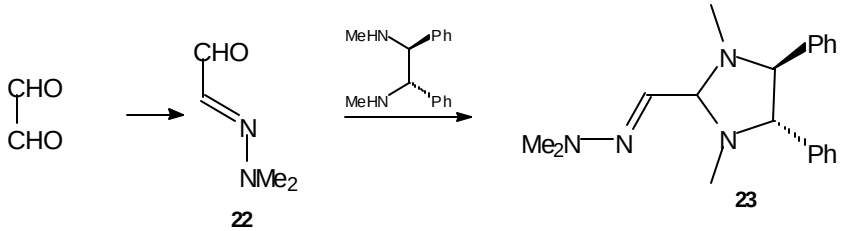
If R = SPh, *Syn*:*anti* = 99:1
R = O^{t}Bu, *Syn*:*anti* = 1:99

Conditions: a) (A) , ^{i}Pr$_2$NEt, DCM, -40 °C; ***b)*** PhCHO, -78 °C.

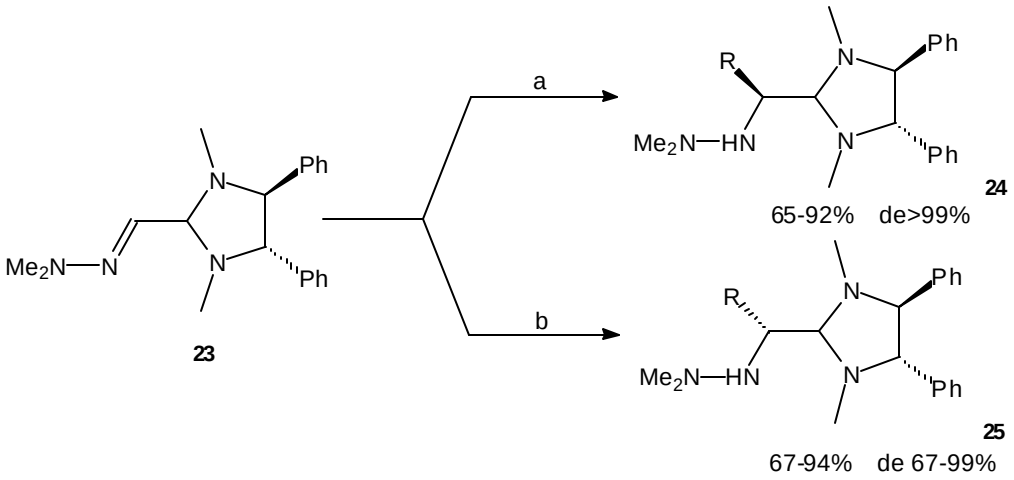
The same diazaborolidine **A** was also used to promote other diastereo and enantioselective processes, such as the reaction of a thiopropionate ester with aldmines to afford anti-β-aminothioesters,[16] a Darzen's reaction that led mainly to anti-α-bromo-β-hydroxy ester,[17] and an Ireland Claisen rearrangement of achiral allylic esters.[18]

Alexakis and Mangeney *et al.* [19] utilized chiral aminals obtained from aldehydes and C_2-symmetric 1,2-diamines as chiral auxilliaries and demonstrated their utility in exerting impressive stereo control as depicted in scheme 5.

Scheme 5: Synthesis , **1995**, 1038



22 **23**



23 24 25

Conditions: ***a****) RLi, -70 °C, THF;* ***b****) RMgX, rt, Et_2O.*

3. Vicinal Diamines and their derivatives as chiral ligands in asymmetric synthesis:

The most widely used ligands incorporating a vicinal diamine moiety are derivatives of 1,2-diphenylethylene diamine and of 1,2-diamino cyclohexanone. All these chiral compounds are used increasingly in various reactions such as:

- Alkylation of aldehydes
- Aldol reactions
- Conjugate addition of organometallic reagents to α,β-unsaturated carbonyl compounds
- Diels-Alder reactions
- Cyclopropanation
- Enantioselective protonation of enolates
- Deprotections with chiral lithium amides
- Epoxidation, dihydroxylation and aziridination
- Reduction of prochiral carbonyl compounds

In conclusion the utility of enantiomerically pure vicinal diamines and their derivatives as chiral auxiliaries and ligands in asymmetric synthesis is evident by the variety of diverse reaction they are able to catalyze in highly efficient manner.

The following section deals with their reported methods for the synthesis of optically active vicinal diamines.

2.1.1d Reported methods for Vicinal Diamines:

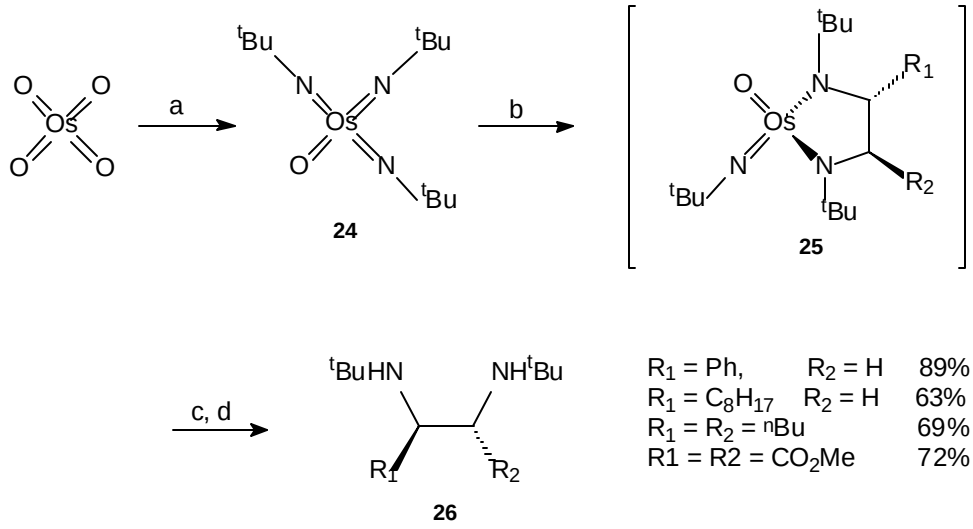
Various methods are available for the synthesis of 1,2-diamines. These methods can be divided mainly into four categories:

A. *The one in which the two nitrogen atoms are introduced concomitantly on the carbon skeleton.*
B. *Compound(s) already containing one of the final two nitrogen atoms of the target 1,2-diamine.*
C. *Compound(s) that already have both nitrogen atoms and finally*
D. *Synthesis starting from two nitrogen containing substrates and involves the formation of the C_1-C_2 bond.*

A. Simultaneous Introduction of two nitrogen atoms:

In 1977 Sharpless *et al.*[20a] showed that the triimidoosmium complex **24** reacted with monosubstituted and disubstituted E-olefins through a stereospecific *cis* addition to give vicinal diamines.

Scheme 6: *J. Am. Chem.Soc.***1977**, *99*, 3420



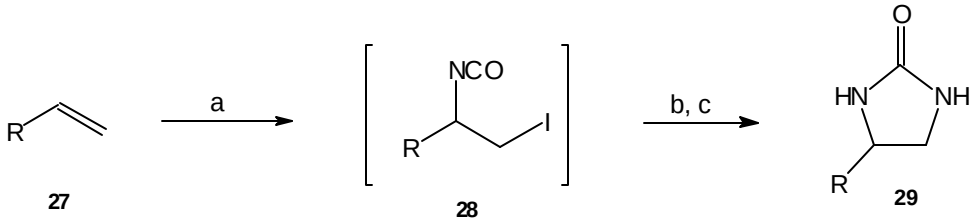
Conditions: ***a****) $^{n}Bu_3P=N^{t}Bu$, 45%;* ***b****) $R_1CH=CHR_2$;* ***c****) LAH, Et_2O;* ***d****) NaOH, H_2O.*

Drawbacks:

1. The complex **24** must be prepared beforehand from OsO_4, which is an expensive reagent. Also OsO_4 is required in stoichiometric amounts.
2. Complex **24** is unreactive towards disubstituted Z-olefins.
3. This method is applicable only for the preparation of secondary N-tert-butyl substituted *anti* 1,2-diamines.

Substituted imidazolidine-2-ones can be considered as protected form of 1,2-diamines. In 1983 Ghomi and Orr[20b] published a simple preparation of 4-substituted imidazolidin-2-ones.

Scheme 7: *Chem. Ind.*, **1983**, 928



Conditions: ***a****) AgNCO, I_2, Et_2O, -5 ^{o}C;* ***b****) NH_3;* ***c****) aq. HCl (3%), reflux, 12h.*

Drawbacks:

Moderate yields.

No examples concerning poly-substituted alkenes were demonstrated.

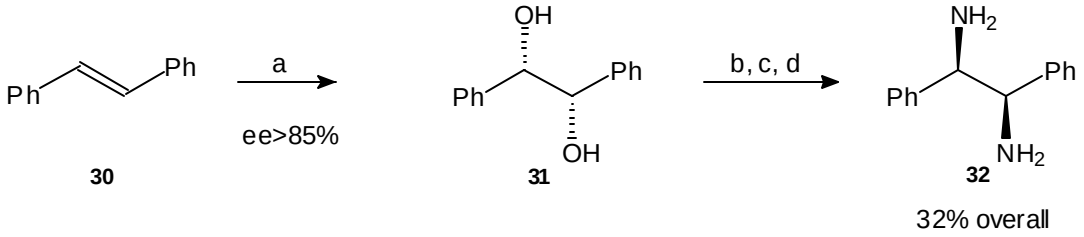
It involves use of stoichiometric quantities of silver isocyanate

Taking into account of the recent developments of catalytic asymmetric epoxidation,[21] of catalytic asymmetric dihydroxylation,[22] and of catalytic aminohydroxylation[23] a "catalytic asymmetric diamination" may appear in near future.

Osmium catalyzed asymmetric dihydroxylation allows access to various enantiomerically pure

1,2-diols which can be converted by several methods into enantiopure vicinal diamines (scheme 8).

Scheme 8: *Chem. Rev.*, **1994**, *94*, 2483



Conditions: ***a****) OsO_4, acetone, NMO, H_2O, DHQ-CLB;* ***b****) TsCl, Pyr, 0 °C to rt, 4d;* ***c****) NaN_3, DMF, 90 °C, 5h;* ***d****) LAH, Et_2O, 35 °C, 2h, rt, 12h.*

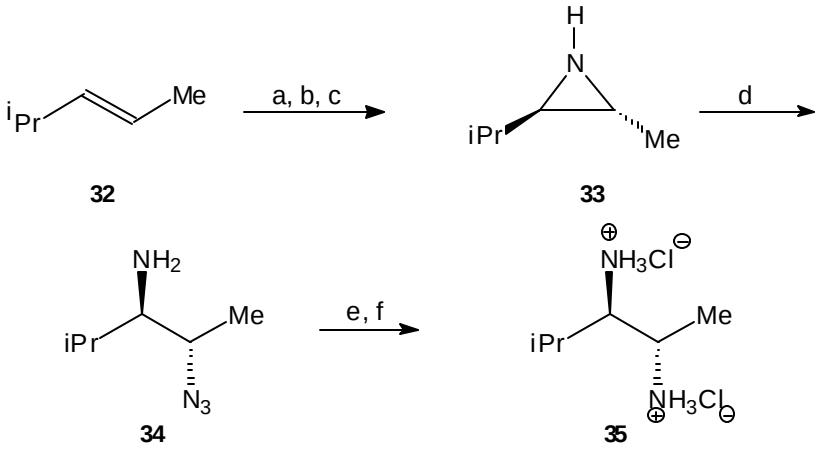
B. Compound containing already one nitrogen in the target molecule:

I. Vicinal diamines from aziridines:

Numerous methods have been reported for the preparation of 1,2-diamines stereoselectively by the opening of aziridines by nucleophiles containing nitrogen atom.

In 1967 Shift and Swern[24a] disclosed a strategy that provides access to either *syn* or *anti* 1,2-diamines *via* the intermediacy of aziridines, obtained from olefins, being opened by the azide ion (scheme 9).

Scheme 9: *J. Org. Chem.*, **1967**, *32*, 511



Conditions: ***a****) INCO;* ***b****) MeOH;* ***c****) KOH, MeOH;* ***d****)* NaN_3*, EtOH;* ***e****)* H_2*, Pt;* ***f****) HCl*

Advantages:

Stereoselective synthesis of vicinal diamines are readily accessed.

Both *syn* and *anti* diamines can be prepared depending on the geometry of olefin.

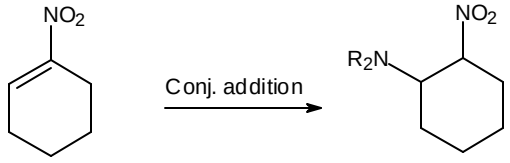
Drawbacks:

a. Yields are low
b. Ketones by products may be formed during the reaction with iodineisocyanate by an elimination-hydrolysis mechanism.[24b]
c. Loss of product can also occur bec ause of volatility of aziridines and their solubility in water.

II. Conjugate addition of a nitrogen nucleophile on nitroalkene:

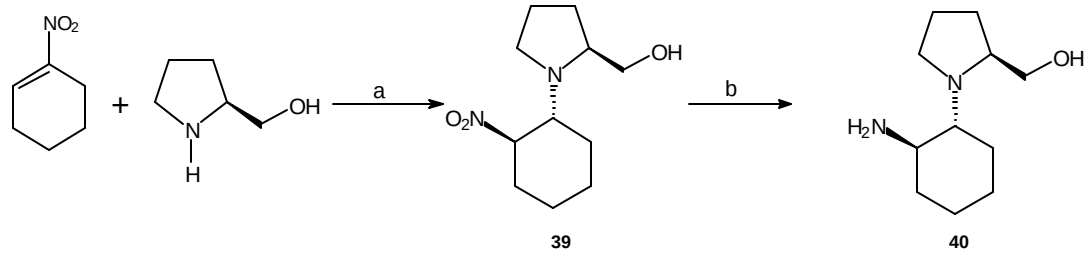
The conjugate addition of a nitrogen nucleophile on a nitroalkene affords a compound that may serve as a precursor of vicinal diamine, since nitro group can be readily reduced to an amine by a variety of reagents. The stereochemical outcome of the addition of amines to (2-nitropropenyl)benzene was studied by Southwick and Anderson,[25] who reported that the *syn* adducts were formed predominantly under thermodynamic conditions (scheme 10).

Scheme 10: *J. Am. Chem. Soc.*, **1957**, *79*, 6222



The reaction of various chiral amines with nitroalkanes was evaluated by Sturgess *et al*.[26] The reaction of (*S*)-2-pyrrolidinyl methanol **38** with 1-nitrocyclohexene afforded a single product in both excellent stereoselectivity and yield; it's nitro group was then reduced with samarium diiodide in methanol, under conditions that prevent epimerization.

Scheme 11: *Tetrahedron Lett.*, **1993**, *34*, 43



39 **40**

trans: cis > 99:1

***Conditions:* a** *) DCM, rt, 30 min;* **b** *) SmI_2, MeOH, THF, 90%.*

Strecker Condensation:

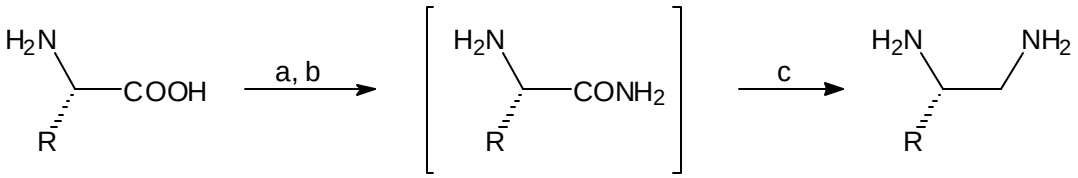
To introduce a carbon and a nitrogen atom simultaneously at a carbonyl compound one can use the Strecker condensation or the related Bucherer-Berg reaction. In the later case hydantoin is formed. Both reactions have been applied to the synthesis of products containing nitrogen functionalities on vicinal carbon atoms of α-amino ketones.[27]

C. Vicinal Diamines from compound having both nitrogen atoms:

a. Reduction of α-amino amides or α-amino nitriles:

The reduction of amides derived from natural α-amino acids is a convenient way to obtain monosubstituted vicinal diamines.[28] For example, Brunner *et al.* synthesized diamines **43** in this manner with high degree of enantiomeric purity (scheme 12).[29]

Scheme 12: *J. Med. Chem. Chim. Ther.* **1985**, *20*, 509

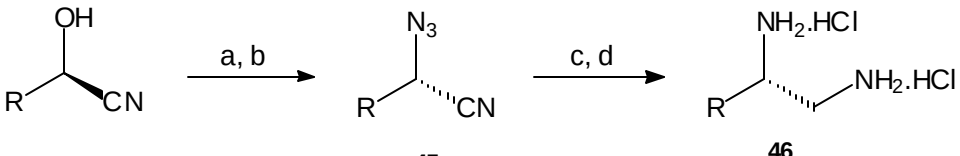


41 **42** **43**

Conditions: ***a****) $SOCl_2$, MeOH;* ***b****) NH_3, MeOH;* ***c****) LAH, THF.*

Effenberger *et al.* [30a] took advantage of the ready access to optically active cyanohydrins **44** in their synthesis of monosubstituted 1,2-diamines **46**, which also made use of a nucleophilic substitution by sodium azide.

Scheme 13: *Tetrahedron: Asymmetry* **1996**, *7*, 607



44

ee = 82-99%

R = ^{t}Bu, cyclohexyl, cyclohexenyl

45

46

23-76%

ee = 85-99%

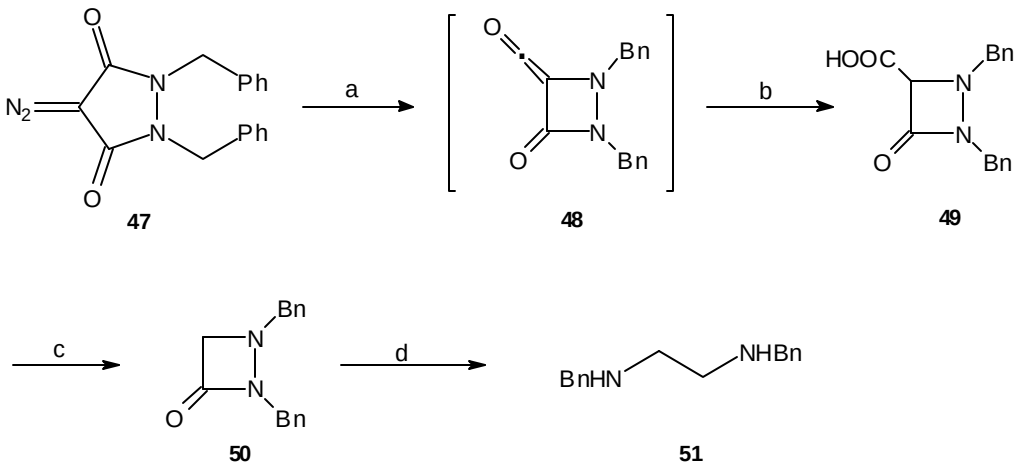
Conditions: ***a****) TsCl, Pyr;* ***b****) NaN_3, crown ether, DMF;* ***c****) LAH, THF;* ***d****) HCl, Et_2O.*

1,2-diamines have also been prepared by reduction of optically active α-aminonitriles obtained from asymmetric Strecker reaction.[30b]

From 1,2-dizetidinones:

The cleavage of the *N-N* bond of 1,2-diazetidine should lead to the corresponding 1,2-diamine was the premise of this study. In 1984 Moody *et al.*,[31] obtained 1,2-di(benzylamino)ethane (**51**) from the reduction of diazetidinone **50** with diborane in THF. The diazetidinone itself had been prepared from the photochemical ring construction of α-diazopyrazolidine-3,5-dione (**47**).

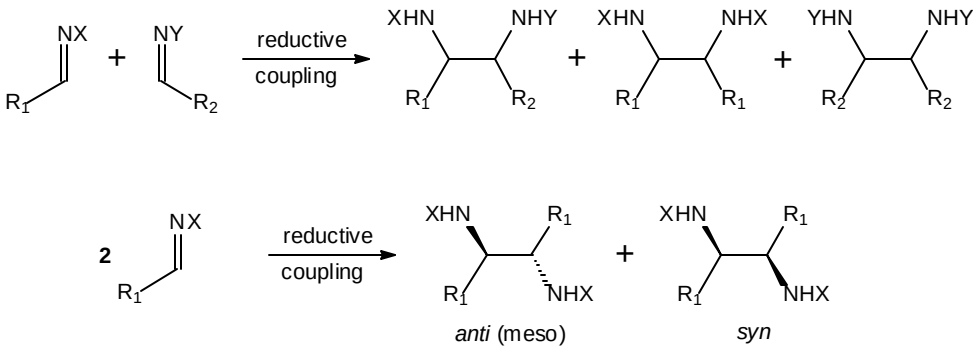
Scheme 14: *J. Chem. Soc. Chem. Commun.*, **1984**, 754



Conditions: ***a****) hõ,-N₂;* ***b****) H₂O, 50%;* ***c****) Benzene, reflux;* ***d****) Diborane, THF.*

D. Diamines from C-C bond formation:

In principle the reductive coupling of imines (with the help of a metal or of a metallic complex) seems a simple way to prepare vicinal diamines. Infact it is usually applied only to the synthesis of symmetrical diamines, since one can expect to obtain a mixture of products from the coupling of two different imines.



Various conditions have been utilized to couple imines, which lead to variable proportions of *anti* (*meso*) and *syn* diamines.

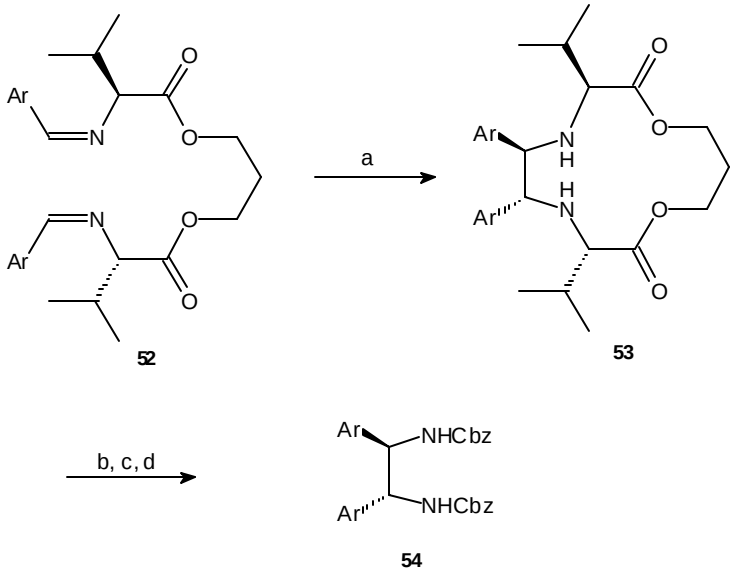
Reductive coupling of aryl N-alkyl imines can be performed in good yields by photoreduction[32] or by electrolysis.[33]

Low valent titanium reagents were utilized by Seebach *et al.*[34] as well as Roskamp and Petersen[35] to prepare unsubstituted vicinal diamines with moderate to good *anti* selectivity.

Recently reductive couplings that use SmI_2,[36] indium,[37] and ytterbium[38] were reported and intramolecular coupling of unsymmetrical dibenzylidene sulfamides mediated either by zinc activated by chloro trimethylsilane or by samarium diiodide. The cyclic sulfamides obtained were easily converted into the corresponding unsymmetrical 1,2-diaryl-1,2-diamines by Pansare and co workers.[39] Aluminum, an inexpensive, stable, easy to handle non toxic material was used in conjuction with KOH[40] for the coupling of aldimines.

Shono *et al.*[41] described a stereoselective synthesis of (*R*,*R*)-1,2-diaryl ethylene diamines **54** by the reductive intramolecular coupling of chiral, aromatic bisimines **52**, derived from (*S*)-valine methyl ester in the presence of zinc. A three-carbon chain linkage between the two-valine moieties afforded the best selectivity. The presence of electron donating groups at *para* position of aryl group increased the selectivity (scheme 15).

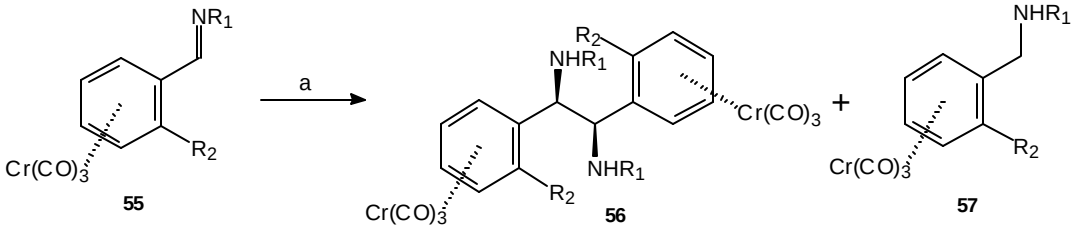
Scheme 15: *J. Org. Chem.*, **1995**, *60*, 3980



Conditions: ***a****) Zn, MsOH, THF, 0 °C;* ***b****) NaOH, aq. EtOH;* ***c****) $Pb(OAc)_4$, H_2O;* ***d****) CbzCl.*

Very recently Uemura *et al.*[42] have demonstrated that only *syn* diamines **56** were formed during the samarium diiodide mediated coupling of enantiomerically pure tricarbonyl(benzaldimine) chromium complexes **55**, along with variable amount of amines **57.**

Scheme 16: *Synlett* **1997**, 51



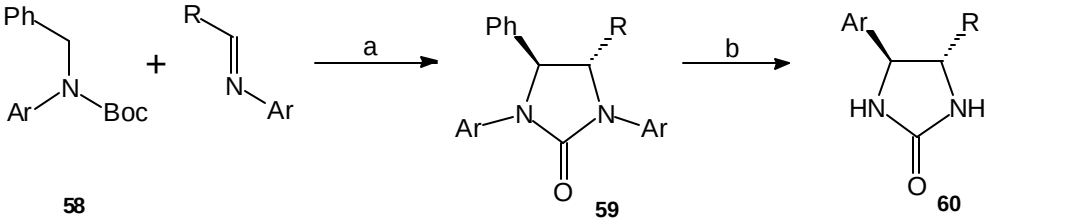
55 **56** **57**

***Condition: a**) SmI$_2$, THF, 0 ^{o}C, 2h.*

In 1996 Kise *et al.*[43] have reported the stereoselective synthesis of *trans*-imidazolidin-2-ones by the reaction of the carbanion of *N*-benzyl-*N*-Boc para anisidine **58** with imine which are derived from *para* anisidine and do not have an exchangeable proton. Very good stereoselectivities were obtained, either in diethyl ether or in THF depending on the substrate. Treatment of the adducts **59** with CAN afforded in good yields the unprotected *trans*-imidazolidinones **60**, which are precursors of 1,2-diamines.

This method was limited to the preparation of adducts, substituted only by aryl or *tert*-butyl groups and also only in racemic form. However, an enantioselective version of this process was soon reported by Beak *et al.*[44] They showed that the reaction of **58** with n-BuLi in toluene, in the presence of (-)-sparteine, followed by addition of *N*-benzylideneaniline yielded *trans* imidazolidinone (*R,R*)-**60** as the major adduct with a 73% enantiomeric excess.

Scheme 17:



58

Ar = p-MeOC$_6$H$_4$
R = aryl, 2-furyl

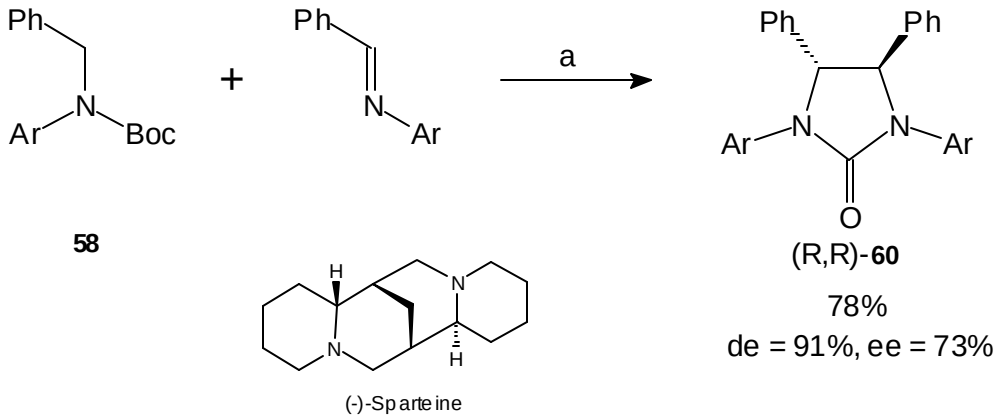
59

64-92%
de > 98%
de = 18% (R = 2-furyl)

60

70-82%
de > 98%
de = 18% (R = 2-furyl)

***Conditions: a**). sec-BuLi, -78 ^{o}C, THF; **b**). CAN.*



Condition: a) *n-BuLi, -78 °C, toluene, (-)-Sparteine.*

Although a variety of methods exist in literature most of them describe the synthesis of C-2 symmetric diamines. However the ubiquitous character of the 1,2-diamino moiety and the increasing interest in vicinal diamines brought about search for new methods for their preparation especially stereoselective ones.

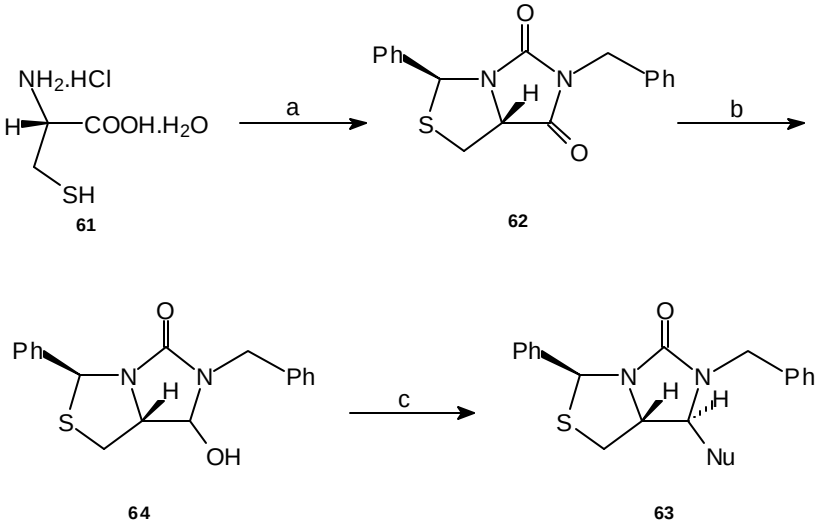
In connection with the synthesis of D(+)-bioitn we were interested in the synthesis of vicinal diamines starting from naturally available amino acid *viz*., L-cysteine. The following presentation describes our efforts towards this endeavor.

2.1.2 Present Work

Literature survey revealed that stereoselective synthesis of unsymmetrical vicinal diamines has very limited reported methods.

It was proposed to control the stereochemistry by performing the reaction on bicyclic rigid substrate. The 5,5-fused bicyclic hydantoin **62** was the substrate which would meet these requirement as the stereochemistry of the rigid bicyclic framework would allow the nucleophilic attack to occur from the convex side of the bicyclic structure either exclusively/predominantly thereby, would lead to a good to excellent stereoselectivity.

Scheme 18:



***Conditions: a**) Ref. 43; **b**) $NaBH_4$, MeOH, 0 °C to rt; **c**) Nucleophile, Lewis Acid, DCM.*

In order to test this hypothesis the bicyclic hydantoin **62** was prepared[45] from cysteine and was further reduced to the aminol **64**. This alcohol or it's ether can serve as very good precursors for acyliminium cation. It was decided to trap the carbocation with variety of nucleophiles.

The present scheme describes a simple route to stereoselective synthesis of unsymmetrical diamines based on the above concept. Thus cysteine hydrochloride hydrate was converted to hydantoin **62**. Further reduction of **62** with sodium borohydride furnished the compound **64** which served as source of acylammonium cation. Treatment of **64** with a variety of

nucleophiles furnished **63** with excellent stereoselectivity and yields. Elaboration of **63** by usual chemical transformation would lead to unsymmetrical diamines.

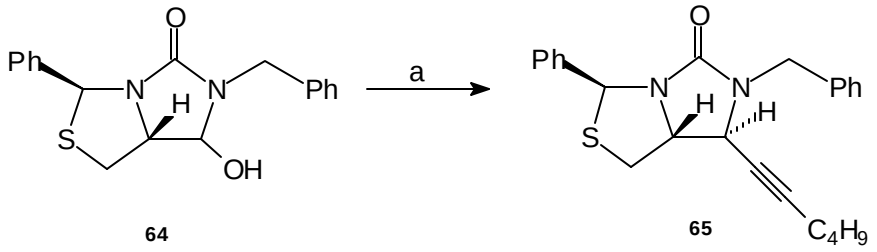
It was also decided to screen various trimethylsilyl enol ethers as well as tributyltin derivatives in the present study as the nucleophiles in order to establish the synthetic utility of this methodology. These vicinal diamines would serve as important chiral auxiliaries for catalytic asymmetric synthesis.

If successful the synthesis of these unsymmetrical diamines would certainly be advantageous over the earlier reported methods.

2.1.3 Results and discussion

A variety of nucleophiles were treated with aminol **64** in the presence of Lewis acid to yield 7-substituted imidazolidinones in excellent yields as well as stereochemistry (see Scheme 19).

Scheme 19:



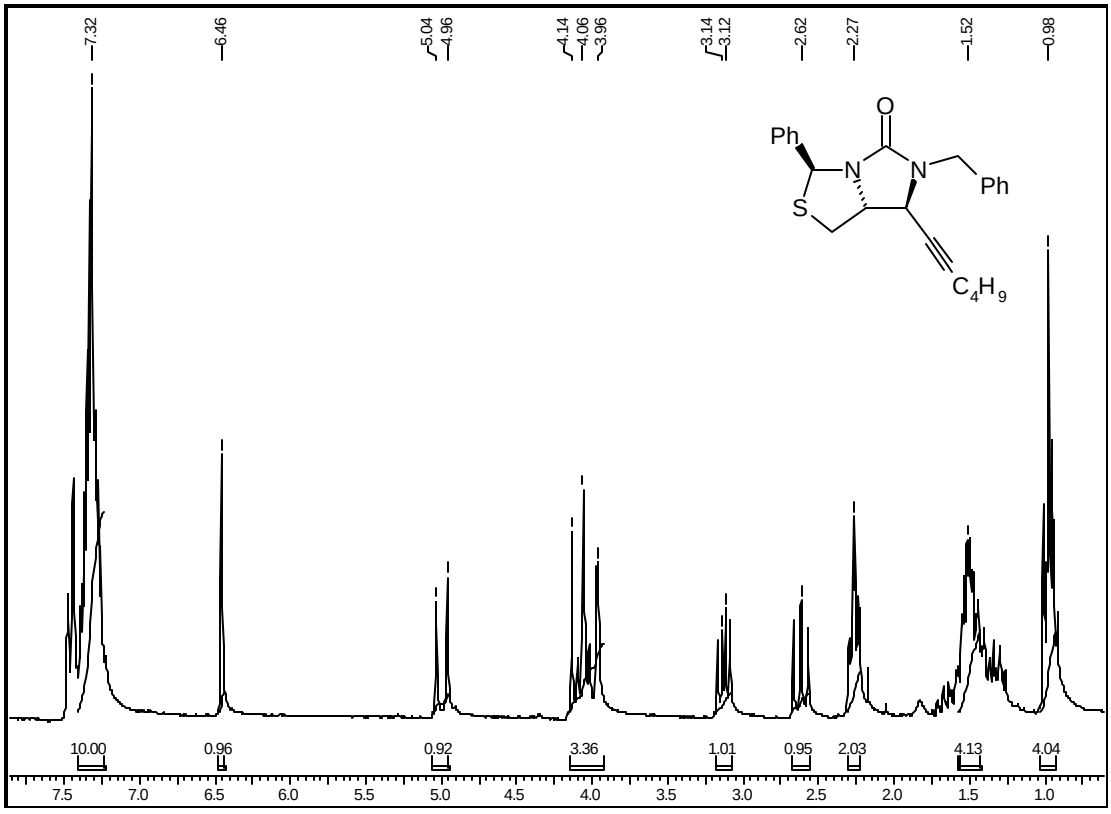
64 **65**

***Condition: a**) 1-tributyltin-1-hexyne, $BF_3.Et_2O$, DCM.*

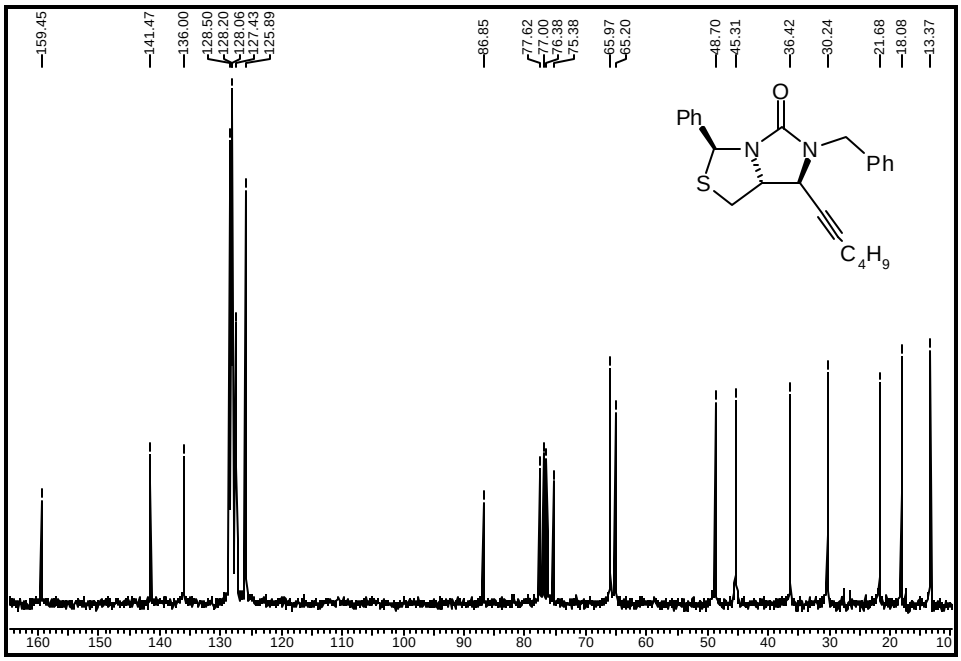
In a typical procedure a mixture of 1eq. of hydroxy hydantoin **64**, 2eq. of nucleophile [for example

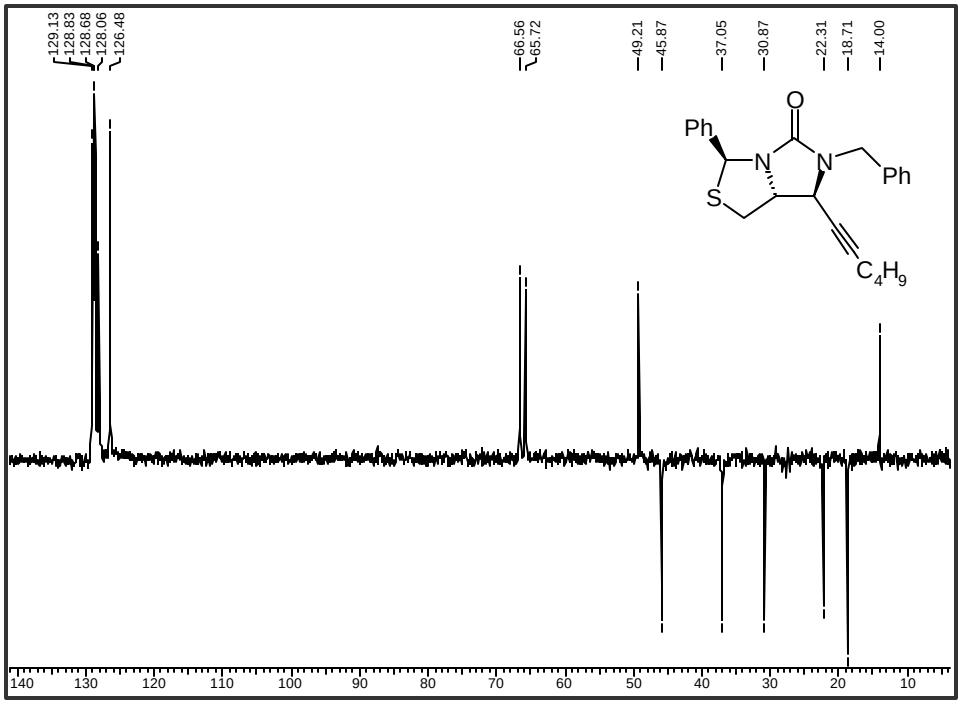
1-tributyltin-1-cyclohexyne (**78**)] was taken in dichloromethane, and cooled to 0 ^oC. Lewis acid *viz*., $BF_3.Et_2O$ 1eq. was added dropwise. The reaction mixture was stirred at 0 ^oC for 10 min (and the reaction mixture was quenched with saturated NH_4Cl) to furnish the 7-substituted hydantoin **65** in almost quantitative yields. After a lot of experimentation it was concluded that the sequence of addition of the reactants and the reagent was critical and crucial for the success of this reaction.

The product **65** isolated by column chromatography was characterized by NMR, IR, Mass, and elemental analysis. IR spectrum confirmed the incorporation of triple bond moiety by the presence of a peak at 2117 cm^{-1} ascribed to the triple bond. ^{1}H NMR indicated presence of two protons as a triplet at δ 2.27 corresponding to the α- to the triple bond in hexyne. The other four protons appeared at δ 1.50 as a multiplet. Presence of triplet at δ 0.98 for three protons confirmed the incorporation of n-hexyne moiety. Mass spectroscopy indicated molecular ion peak at 390. ^{13}C NMR also confirmed the presence of two quarternary carbons at δ 76.0 and 87.5 ppm. Three methylene carbons appeared at δ 18.7, 22.3, 30.9 ppm. The spectral analysis revealed the exclusive formation of only one isomer.



^{1}H NMR spectrum of compound **65** ($CDCl_3$, 200 MHz)

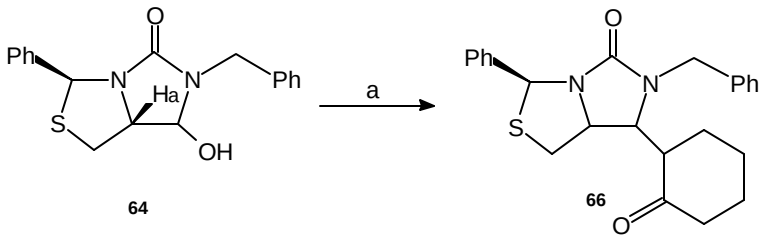




^{13}C and DEPT spectra of compound **65** ($CDCl_3$, 50MHz)

It was also found that the trimethylsilyl enol ether derivatives such as 1-trimethylsilyloxy-1-cylcohexene (**75**) also can be utilized as efficient nucleophiles to trap the acylammonium carbocation in the C-C bond formation with excellent stereocontrol.

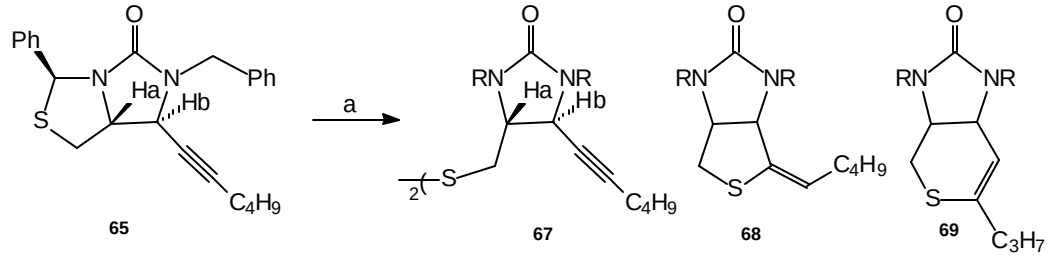
Scheme 20:



Condition: a*) 1-trimethylsilyloxy-1-cyclohexene (**75**), $BF_3.OEt_2$, DCM.*

The product **65** when subjected to tributyltin hydride reduction in presence of AIBN in refluxing benzene gave exclusively dimer compound **67** instead of desired **68** or **69**. Exclusive formation of dimer can be explained the ^1H NMR analysis. The protons H_a and H_b exhibited a coupling constant J = 1.45 Hz thus establishing the *trans* stereochemistry. [46]

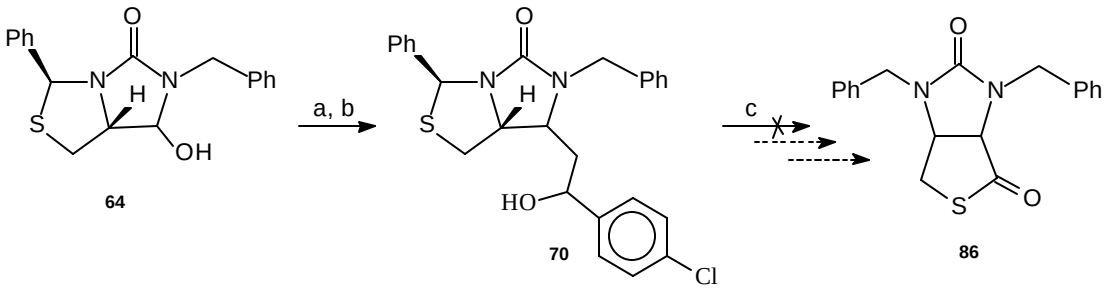
Scheme 21:



Condition: a*) Tributyltin hydride, AIBN, benzene, reflux.*

In order to establish the generality of the above protocol it was also decided to screen a wide variety of other enol ethers as well. Thus the *p*-chloroacetophenone enol ether was subjected to aldol reaction as depicted in the above scheme 21 in order to obtain the 7-substituted hydantoin. Having achieved the synthesis of **70** it was decided to convert it to thiolactone **86**. However the hydroxy compound **70** failed to undergo dehydration under acidic conditions.

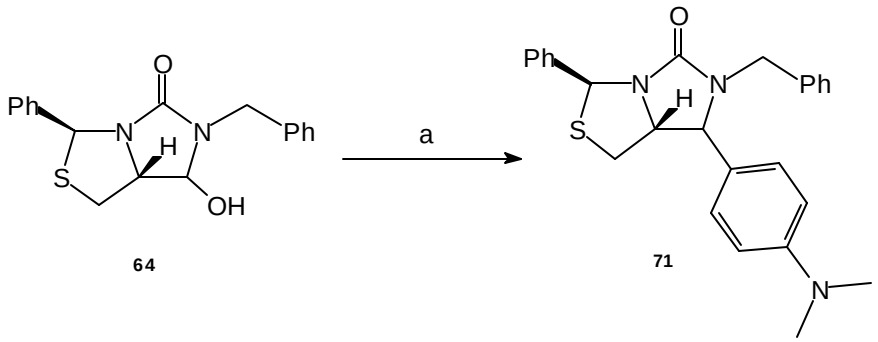
Scheme 22:



***Conditions: a**) 1-Trimethylsilyloxy-4'-chlorostyrene, $BF_3.OEt_2$, DCM; **b**) $NaBH_4$, MeOH, rt; **c**). Dehydration.*

Another important observation was the case participation of electron rich aromatics such as *N,N*-dimethyl aniline **79** as a nucleophile to furnish the corresponding , 7-substituted hydantoin **71**. The formation of **71** was confirmed by IR, NMR and spectral analysis.

Scheme 23:



***Condition: a**) N,N-Dimethylaniline, $BF_3.OEt_2$, DCM.*

Therefore, it was concluded that these acyliminium reactions proceed well with trimethylsilyl enol ethers and tributyltin hexyne. In order to test the generality of this reaction a wide variety of nucleophiles were reacted with the hydroxy hydantoin **64**. The results are tabulated in table-1. From the table-1 it is evident that a wide variety of nucleophiles participated exceedingly well in this reaction with excellent stereocontrol. However certain alkoxy enol ethers and alkoxy benzene failed to react with **64** when subjected under similar conditions (scheme 24).

Scheme 24:

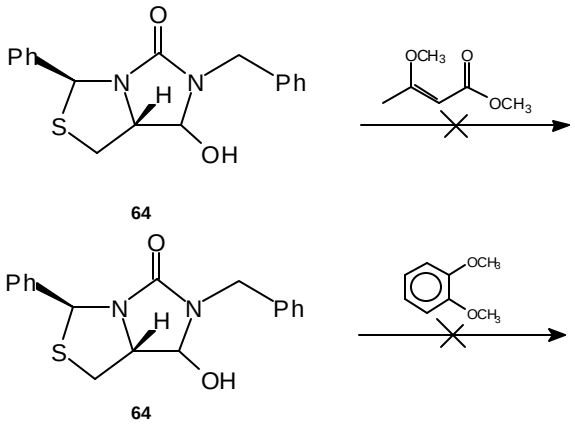
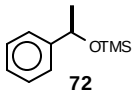
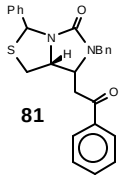
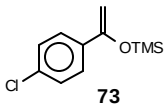
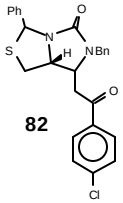
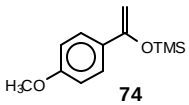
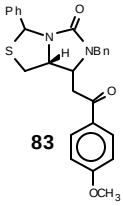
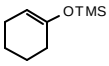
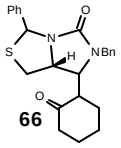
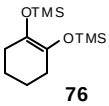
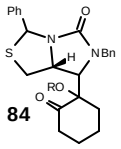
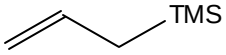
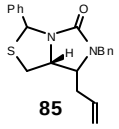
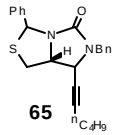
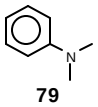
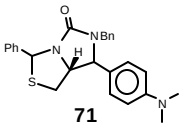
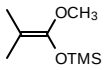
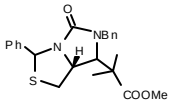


Table-1:

S.No	Nucleophile	Product	Yield
1.	 **72**	 **81**	98
2.	 **73**	 **82**	98
3.	 **74**	 **83**	98
4.	 **75**	 **66**	98
5.	 **76**	 **84**	98
6.	 **77**	 **85**	98
7.	 **78**	 **65**	98
8.	 **79**	 **71**	50

9.	 **80**	 **86**	98

2.1.5 Conclusion:

- For the first time C-C bond formation with different nucleophiles using acyliminium ion of hydroxy hydantoin **64** was successfully performed in excellent yields as well as selectivity.
- It provides one of the easiest route for the preparation of unsymmetrical 1,2-*trans* diamines.
- The rigidity of the bicyclic framework is instrumental in imparting a high degree of stereocontrol.
- This methodology has also been used for the preparation of chiral intermediates for the synthesis of D(+)-biotin.

2.1.4 Experimental

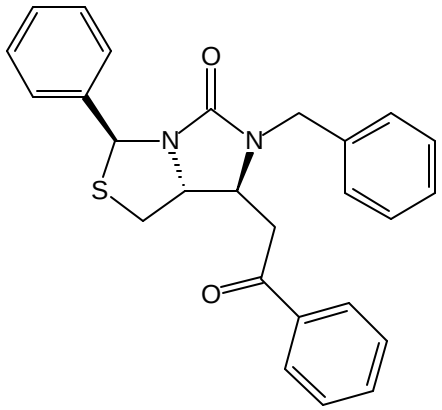
The trimethyl silyloxy enol ethers were prepared according to reported method. [47]

General procedure for the preparation of 7-substituted hydantoins:

To a solution of compound 6-benzyl-7-hydroxy-3-phenyl-(3*S*, 7a*R*)-perhydroimidazo-[1,5-C][1,3]thiazol-5-one (**64**) (1 mmol) in dichloromethane (10 mL) was added nucleophile (2 mmol) and the solution was cooled and stirred at 0 ^{o}C. Borontrifluoride etherate ($BF_3.Et_2O$) (1 mmol) was added dropwise. The reaction mixture was stirred at 0 ^{o}C for 10 min, and the reaction mixture was quenched with saturated ammonium chloride (10 mL). The organic layer was separated, dried over anhyd. Na_2SO_4, concentration and

column purification with ethylacetate:pet.ether (15:85) as eluent provided 7-substituted hydantoins as viscous liquid in almost quantitative yield.

1. 6-Benzyl-7-(1-hydroxy-2-oxocyclohexyl)-3-phenyl-(3*S*, 7*S*, 7a*R*)-perhydroimidazo-[1,5-c] [1,3] thiazol-5-one (81):



Mol. Formula : $C_{26}H_{24}N_2O_2S$ (428)

M.P./B.P. : Highly viscous liquid

Optical Rotation : $[\alpha]_D$ = - 104.22 (c=0.9; $CHCl_3$).

IR ($CHCl_3$, cm^{-1}) : 3060, 3015, 2924, 1705, 1441, 1378, 1348, 1249, 1216, 698.

^1H NMR ($CDCl_3$, 200 MHz) : 2.66 (t, 1H, J = 9.3Hz); 3.30 (m, 3H); 3.75 (dd, 1H, J = 5.9, 8.8Hz)); 3.92 (dd, 1H, J = 3.9, 9.3Hz); 4.14 (d, 1H, J = 15.2Hz); 4.85 (d, 1H, J = 15.1Hz); 6.44 (s, 1H); 7.39 (m, 13H); 7.85 (d, 2H, J = 8.79Hz).

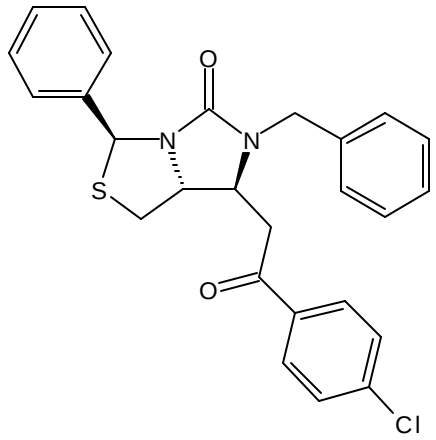
^{13}C NMR ($CDCl_3$, 75.5MHz) : 37.2(t), 40.7(t), 45.5(t), 54.1(d), 65.6(d), 66.0(d), 126.3(d, 3c), 127.5(d, 3c), 127.8(d, 3c), 128.3(d, 3c), 128.7(d, 3c), 133.6(s), 136.6(s), 141.7(s), 160.1(s), 197.3(s).

Mass(m/z) : 428(M^+, 6), 395(23), 382(34), 337(10), 323(10), 291(16), 277(81), 263(10), 214(10), 187(39), 144(39), 132(67), 121(25), 105(100), 91(25), 77(4).

Analysis

	Carbon	Hydrogen	Nitrogen	Sulphur
Calc.:	72.87	5.64	6.54	7.48
Found:	72.37	5.84	6.34	7.88

2. 6-Benzyl-7-[2-(4-chlorophenyl)-2-oxomethyl]-3-phenyl-(3*S*, 7*S*, 7a*R*)-perhydroimidazo- [1,5-c][1,3] thiazol-5-one (82):



Mol. Formula : $C_{26}H_{23}ClN_2O_2S$ (462.9)

M.P./B.P. : Highly viscous liquid

Optical Rotation : $[\alpha]_D$ = -111.36 (c=1.2; $CHCl_3$).

IR ($CHCl_3$, cm^{-1}) : 3063, 3031, 1699, 1688, 1588, 1447, 1421, 1381, 1220, 1209, 1090, 699.

^1H NMR ($CDCl_3$, 200 MHz) : 2.68 (dd, 1H, J = 9.3, 10.3Hz) ; 3.09 (dd, 1H, J = 9.6, 17.5Hz); 3.31 (dd, 1H, J = 4.6, 10.3Hz) ; 3.43 (dd, 1H, J = 6.3, 9.1Hz) ; 3.51 (m, 1H); 3.92 (dd, 1H, J = 3.9, 9.3Hz) ; 4.16 (d, 1H, J = 15.14Hz) ; 4.81 (d, 1H, J = 15.14Hz) ; 6.45 (s, 1H) ; 7.26 (m, 10H) ; 7.39 (d, 2H, J = 8.8Hz) ; 7.76 (d, 2H, J = 8.8Hz).

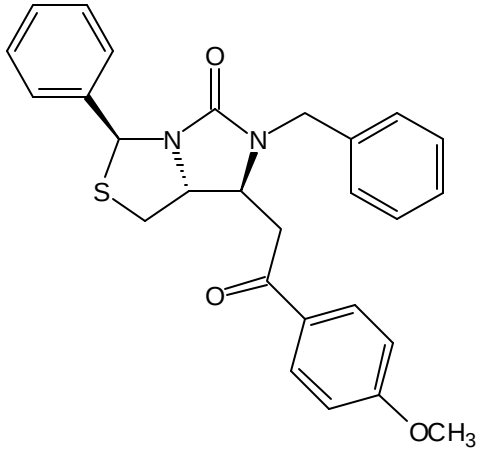
^{13}C NMR ($CDCl_3$, 75.5MHz) : 37.1(t), 40.3(t), 45.2(t), 55.3(d), 66.3(d), 66.8(d), 114.2(d), 126.1(d, 2C), 127.3(d), 127.5(d, 2C), 128.1(d, 2C), 128.5(d, 2C), 128.7(d, 2C), 129.3(s), 130.7(d, 2C), 137.1(s), 139.4(s), 142.4(s), 160.8(s), 196.8(s).

Mass(m/z) : 463(M^+, 1), 35(5), 309(12), 308(36), 277(7), 187(10), 135(91), 121(15), 104(12), 91(100), 77(41), 65(17).

Analysis :

	Carbon	Hydrogen	Nitrogen	Sulphur
Calc.:	67.45	5.01	6.05	6.93
Found:	67.56	5.31	6.13	6.48

3. 6-Benzyl-7-(1-hydroxy-2-oxocyclohexyl)-3-phenyl-(3*S*, 7*S*, 7a*R*)-perhydroimidazo-[1,5-c][1,3] thiazol-5-one (83):



Mol. Formula : $C_{27}H_{26}N_2O_3S$ (458)

M.P./B.P. : Highly viscous liquid

Optical Rotation : $[\alpha]_D$ = -105 (c=1; $CHCl_3$).

IR ($CHCl_3$, cm^{-1}) : 3098, 3016, 2925, 1711, 1441, 1352, 1309, 1248, 1167.

^1H NMR ($CDCl_3$, 200 MHz) : 2.67 (dd, 1H, J = 8.7, 10.8Hz) ; 3.15 (dd, 1H, J = 9.4, 17.4Hz); 3.34 (m, 2H) ; 3.77 (m, 3H) ; 3.88 (s, 3H) ; 4.16 (d, 1H, J =15.14Hz) ; 4.86 (d, 1H, J = 15.14Hz) ; 6.46 (s, 1H) ; 6.93 (d, 2H, J = 8.79Hz) ; 7.31 (m, 10H) ; 7.83 (d, 2H, J = 8.79Hz).

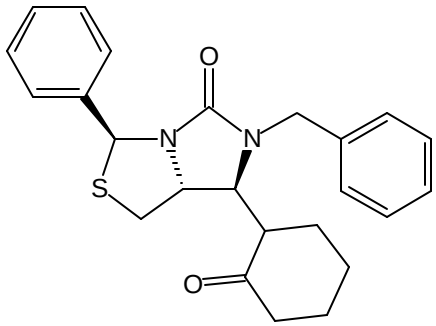
^{13}C NMR ($CDCl_3$, 75.5MHz) : 37.5(t), 40.7(t), 45.6(t), 54.6(d), 55.4(q), 65.9(d), 66.3(d), 113.9(d), 126.4(d, 2c), 127.6(d), 127.7(d, 2c), 128.1(d, 2c), 128.3(d, 2c), 128.7(d, 2c), 129.5(s), 130.3(d, 2c), 137.0(s), 142.0(s), 160.2(s), 163.9(s), 195.7(s).

Mass(m/z) : 458(M^+, 1), 457(M^+-1, 2), 425(6), 412(5), 335(2), 309(8), 308(24), 277(5), 187(8), 135(89), 121(11), 104(12), 91(100), 77(41), 65(17).

Analysis

	Carbon	Hydrogen	Nitrogen	Sulphur
Calc.:	70.72	5.71	6.11	6.99
Found:	71.12	5.82	6.63	5.90

4. 6-Benzyl-7-(2-oxocyclohexyl)-3-phenyl-(3*S*, 7*S*, 7a*R*)-perhydroimidazo[1,5-c][1,3]- thiazol-5-one (66):



Mol. Formula : $C_{24}H_{26}N_2O_2S$ (406)

M.P./B.P. : Highly viscous liquid

Optical Rotation : $[\alpha]_D$ = - 246 (c=1.3; $CHCl_3$).

IR ($CHCl_3$, cm^{-1}) : 3143, 3112, 3085, 3062, 2935,2862, 1715, 1701, 1492, 1439, 1352, 1129, 912.

^1H NMR ($CDCl_3$, 200 MHz) : 1.65 (m, 2H) ; 1.9-2.1 (m, 4H) ; 2.32 (t, 2H, J = 9.3Hz) ; 2.56 (m, 1H, J = 4.5, 6.7, 11.2Hz) ; 2.65 (dd, 1H, J = 9, 10Hz) ; 3.33 (dd, 1H, J = 6, 10Hz) ; 3.64 (dd, 1H, J = 6.1, 7.6, 9Hz) ; 3.87 (dd, 1H, J = 2, 4.7, 12.5Hz) ; 4.12 (d, 1H, J = 15.12Hz) ; 4.70 (d, 1H, J = 15.12Hz) ; 6.37 (s, 1H) ; 7.38 (m, 10H).

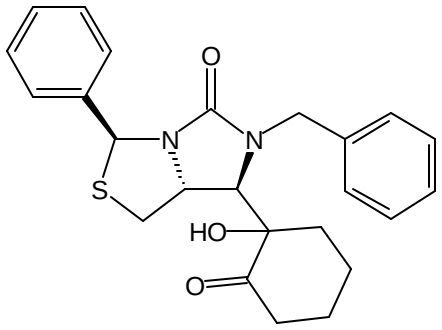
^{13}C NMR ($CDCl_3$, 75.5MHz) : 24.2(t), 26.5(t), 26.9(t), 38.1(t), 42.0(t), 46.5(t), 50.5(d), 57.4(d), 63.5(d), 66.0(d), 125.3(d), 127.2(d), 127.5(d, 2C), 128.05(d), 128.1(d, 2c), 128.2(d), 128.5(d, 2c), 137.1(s), 146.3(s), 160.2(s, C=O), 208.7(s).

Mass(m/z) : 406(M^+, 91), 373(92), 360(42), 332(10), 309(10), 281(8), 269(15), 263(32), 241(9), 132(17), 117(8), 106(11), 91(100), 83(11), 77(16), 65(8), 55(7).

Analysis :

	Carbon	Hydrogen	Nitrogen	Sulphur
Calc.:	70.90	6.45	6.89	7.89
Found:	69.05	7.12	5.46	6.87

5. 6-Benzyl-7-(1-hydroxy-2-oxocyclohexyl)-3-phenyl-(3*S*, 7*S*, 7a*R*)-perhydroimidazo-[1,5-c][1,3] thiazol-5-one (84b):



Mol. Formula : $C_{24}H_{26}N_2O_3S$ (422)

M.P. : 45 °C

Optical Rotation : $[\alpha]_D$ = - 211 (c=1.18; $CHCl_3$).

IR ($CHCl_3$, cm^{-1}) : 3421, 2939, 2861, 1705, 1415, 1352, 11 75, 1115, 1043, 839, 698.

^1H NMR ($CDCl_3$, 200 MHz) : 1.63 (m, 3H) ; 1.86 (m, 3H) ; 2.0-2.45 (m, 3H) ; 2.73 (m, 1H) ; 3.05 (m, 1H) ; 3.80 (m, 3H) ; 5.05 (dd, 1H, J = 15.6Hz); 6.35 (s, 1/2H) ; 6.45 (s, 1/2H) ; 7.32 (m, 10H).

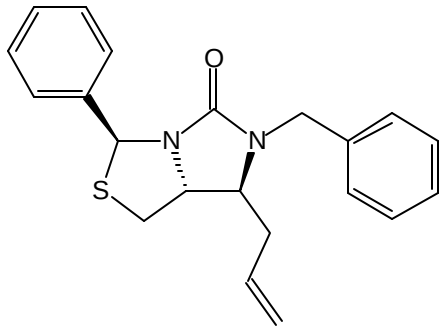
^{13}C NMR ($CDCl_3$, 75.5MHz) : 20.2(t), 26.8(t), 34.8(t), 37.9(t), 38.3(t), 47.0(t), 60.3(d), 61.9(d), 64.9(d), 78.9(s), 125.8(d), 127.3(d), 127.6(d, 2c), 127.9(d, 2c), 128.3(d, 2c), 128.4(d), 128.5(d), 138.4(s), 141.7(s), 161.9(s, C=O), 211.5(s).

Mass(m/z) : 422(M^+, 1), 405(1), 309(32), 263(23), 142(6), 132(7), 121(6), 91(100), 77(19), 65(5).

Analysis

	Carbon	Hydrogen	Nitrogen	Sulphur
Calc.:	68.22	6.20	6.63	7.59
Found:	67.35	6.30	6.22	8.40

6. 7-Allyl-6-benzyl-3-phenyl-(3*S*, 7*S*, 7a*R*)-perhydroimidazo[1,5-c][1,3]-thiazol-5-one (85):

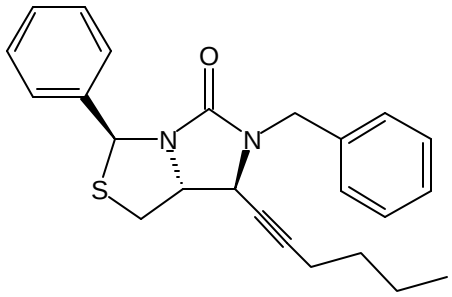


Mol. Formula	: $C_{21}H_{22}N_2OS$ (350)
M.P./B.P.	: Highly viscous liquid
Optical Rotation	: $[\alpha]_D$ = -233.98 (c=1.02 ; $CHCl_3$).
IR ($CHCl_3$, cm^{-1})	: 3062, 3026, 2922, 1709, 1620, 1494, 1424, 1356, 1224, 1094, 1029.
^1H NMR ($CDCl_3$, 200 MHz)	: 2.44 (m, 2H) ; 2.55 (dd, 1H, J = 9, 10Hz) ; 3.07 (dd, 1H, J = 6, 10Hz) ; 3.35 (m, 1H) ; 3.8 (m, 1H) ; 4.08 (d, 1H, J = 15.14Hz) ; 4.96 (d, 1H, J = 15.14Hz) ; 5.18 (m, 2H) ; 5.76 (m, 1H) ; 6.46 (s, 1H) ; 7.32 (m, 10H).
^{13}C NMR ($CDCl_3$, 75.5MHz)	: 35.9(t), 36.9(t), 44.7(t), 56.1(d), 63.9(d), 65.0(d), 118.8(t), 125.5(d), 127.1(d, 2c), 127.3(d, 2c), 127.6(d, 2c), 128.0(d, 2c), 128.4(d), 131.9(d), 136.2(s), 141.8(s), 159.7(s, C=O).
Mass(m/z)	: 350(M^+, 67), 309(77), 303(75), 277(13), 263(60), 213(9), 187(4), 170(4), 132(23), 117(9), 104(8), 91(100), 77(7), 65(6).

Analysis :

	Carbon	Hydrogen	Nitrogen	Sulphur
Calc.:	71.97	6.33	7.97	9.15
Found:	72.21	6.62	7.72	8.49

7. 6-Benzyl-7(1-hexynyl)-3-phenyl(3*S*, 7*S*, 7a*R*)-perhydroimidazo[1,5-c][1,3]- thiazol-5-one (65):

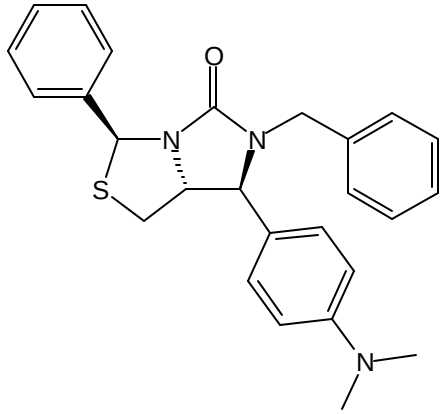


Mol. Formula	: $C_{24}H_{26}N_2OS$ (390)
M.P.	: 54 °C
Optical Rotation	: $[\alpha]_D$ = -169.08 (c=1 ; $CHCl_3$).
IR ($CHCl_3$, cm^{-1})	: 3011, 2956, 2929, 2865, 2210, 2117, 1710, 1439, 1359, 1218.
^1H NMR ($CDCl_3$, 200 MHz)	: 0.98 (t, 3H, J = 7.32Hz) ; 1.50 (m, 4H) ; 2.27 (dt, 2H, J = 1.95, 6.8Hz) ; 2.62 (dd, 1H, J = 10.3Hz) ; 3.12 (dd, 1H, J = 6.3, 10.4Hz) ; 3.96 (d, 1H, J = 1.5Hz) ; 4.06 (dd, 1H, J = 6.3, 9.0Hz) ; 4.10 (d, 1H, J = 14.7Hz) ; 5.0 (d, 1H, J = 14.7Hz) ; 6.46 (s, 1H) ; 7.32 (m, 10H).
^{13}C NMR ($CDCl_3$, 50MHz)	: 14.0(q), 18.7(t), 22.3(t), 30.9(t), 37.0(t), 45.9(t), 49.3(d), 65.8(d), 66.6(d), 76.0(s), 87.5(s), 125.8(d), 126.5(d), 127.4(d), 127.8(d), 128.0(d), 128.2(d), 128.5(d), 128.7(d), 128.8(d), 129.1(d), 136.6(s), 142.1(s), 160.1(s, C=O).
Mass(m/z)	: 390(M^+, 14), 348(22), 269(13), 258(22), 211(15), 177(9), 166(9), 155(15), 132(41), 117(15), 105(54), 91(100), 77(28), 65(6).

Analysis :

	Carbon	Hydrogen	Nitrogen	Sulphur
Calc.:	73.81	6.71	7.17	8.21
Found:	72.86	7.10	6.98	7.98

8. 6-Benzyl-7-(4-*N*,*N*-dimethylaminophenyl)-3-phenyl-(3*S*, 7*S*, 7a*R*)-perhydroimidazo- [1,5-c][1,3] thiazol-5-one (71):



Mol. Formula : $C_{26}H_{27}N_3OS$ (429)

M.P./B.P. : Highly viscous liquid

Optical Rotation : $[\alpha]_D$ = -123.75 (c=0.5 ; $CHCl_3$).

IR ($CHCl_3$, cm^{-1}) : 3020, 2924, 2 855, 1708, 1596, 1495, 1440, 1349, 698.

^1H NMR ($CDCl_3$, 200 MHz) : 2.61 (dd, 1H, J = 10.2Hz) ; 2.85 (s, 6H) ; 3.16 (dd, 1H, J = 6, 10.2Hz) ; 3.87 (d, 1H, J = 15.12Hz) ; 3.92 (dd, 1H, J = 6, 9.3Hz) ; 4.94 (d, 1H, J = 15.12Hz) ; 5.03 (s, 1H) ; 6.47 (s, 1H) ; 6.73 (d, 2H, J = 8.9Hz) ; 7.08 (m, 2H) ; 7.29 (m, 10H).

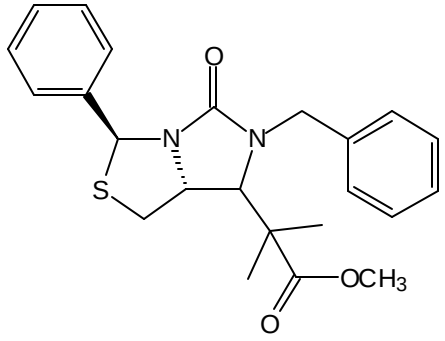
^{13}C NMR ($CDCl_3$, 75.5MHz) : 37.3(t), 45.2(t), 51.2(q), 51.5(q), 54.3(d), 66.1(d), 66.5(d), 113.3(d), 126.7(d, 2C), 127.6(d), 127.9(d, 2C), 128.5(d, 2C), 128.7(d, 2C), 128.9(d, 2C), 129.5(s), 130.3(d, 2C), 137.5(s), 138.3(s), 142.6(s), 160.5(s).

Mass(m/z) : 429(M^+, 1), 414(1), 383(1), 354(2), 338(1), 309(1), 308(2), 254(2), 187(2), 106(100), 91(22), 77(35), 65(13).

Analysis :

	Carbon	Hydrogen	Nitrogen	Sulphur
Calc.:	72.69	6.34	9.78	7.46
Found:	72.21	6.62	10.24	6.83

9. Methyl-2-[6-benzyl-5-oxo-3-phenyl-(3*S*, 7a*R*)-perhydroimidazo[1,5-c][1,3]thiazol-7-yl]-2-methyl propanoate (86):



Mol. Formula : $C_{23}H_{26}N_2O_3S$ (410)

M.P./B.P. : Highly viscous liquid

Optical Rotation : $[\alpha]_D$ = -216.86 (c=1.1 ; $CHCl_3$).

IR ($CHCl_3$, cm^{-1}) : 3022, 2982, 2946, 1711, 1439, 1417, 1359, 1138, 704.

^1H NMR ($CDCl_3$, 200 MHz) : 1.22 (s, 3H) ; 1.27 (s, 3H) ; 2.20 (dd, 1H, J = 9.52, 10.3Hz) ; 2.91 (dd, 1H, J = 5.86, 10.3Hz) ; 3.58 (s, 3H) ; 3.6 (m, 2H) ; 3.82 (d, 1H, J = 14.66Hz) ; 5.07 (d, 1H, J = 14.66Hz) ; 6.43 (s, 1H) ; 7.31 (m, 10H).

^{13}C NMR ($CDCl_3$, 75.5MHz) : 20.7(q), 21.3(q), 37.5(t), 46.1(s), 47.1(t), 51.8(d), 62.6(q), 62.6(d), 65.1(d), 125.5(d, 2c), 127.2(d, 2c), 127.5(d, 2c), 127.7(d), 128.0(d, 2c), 128.3(d), 136.1(s), 141.5(s), 161.5(s, C=O), 175.8(s, C=O).

Mass(m/z) : 410(M^+, 7), 379(1), 364(3), 319(1), 309(19), 263(23), 187(4), 132(8), 117(14), 91(100), 65(6), 55(2).

Analysis :

	Carbon	Hydrogen	Nitrogen	Sulphur
Calc.:	67.29	6.38	6.82	7.81
Found:	67.03	6.96	7.13	6.63

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2.2.1 Introduction

The capability to design and construct new proteins with tailor made structural and functional properties is a goal that is currently being vigorously pursued.[1] The rapid developments that have taken place pertaining to protein synthesis have not been matched with knowledge relating to the relationship between the primary sequence and its folding profile.

A promising approach towards protein design would be to take advantage of detailed information pertaining to structural ensembles colleted from protein crystallographic database.

Proteins with altered functions can be created from existing molecules by modification either by genetic manipulations involving addition or deletion of specific amino acid residue at the genomic level or particularly in the case of relatively small peptides, by chemical methods, through side chain alteration or by backbone modification. Although protein modification by gene manipulation finds ample illustration, there are only a few examples by proteins where new functional molecules have been created through side chain alteration.

Since the rigidity and flexibility of the protein molecule is manifested largely in its backbone and even marginal changes in the peptide backbone may lead to conformers with altered biological profiles. Indeed, in the past 10-15 years, design and synthesis of backbone modified pseudopeptides or peptide isosteres containing numerous surrogates of the amide carbonyl (C=O), the amide nitrogen (-NH) or both groups (-CO-NH-) has emerged as popular endeavor in peptide chemistry and is fast becoming the most popular approach to overcome the poor solubility, lack of oral absorption and marginal ability to cross the blood-brain barrier in the use of peptides as therapeutic agents. The resulting protease resisting analogues, and in some cases as potent protease inhibitors.

The peptide backbone $(\text{-NH-CHR-CO-})_n$- comprises three repeating elements, -NH, -CHR- and –CO. Modification of the backbone would mean a change at any one of these elements or a combined (-CO-NH-) unit of the peptide. The most challenging task synthetically appears to be modification at á-carbon in the peptide backbone. Unfortunately so far this transformation has involved arduous synthetic endeavors. It is no wonder that there are only a few examples of backbone modification at the á-carbon in peptides and there is only one example of backbone modification in proteins involving none other than the most common L to D isomer change.

Modification of the peptide backbone leads primarily to an increase in the biological half-life in comparison with that of parent compounds, and only secondarily, if at all to restrictions in confirmation.

The unnatural enantiomer of an enzyme operates on an achiral substrate and yields an achiral product (such as carbonic anhydride) should be fully functional *in vivo*. This may have important potential therapeutic applications. D-enzymes are expected to be long lived *in vivo* (in an L-protein biosphere) because they would be resistant to naturally occurring protease that would in general attack only proteins made up of L-amino acids.

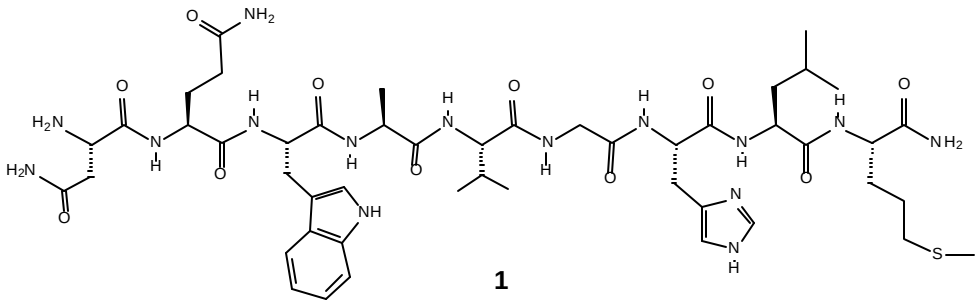
D-protein molecules have other potentially practical applications. At the present time D-enzymes and D-proteins in general are accessible only by chemical synthesis. Recent innovations in the total chemical synthesis of proteins should considerably increase the utility of this approach to the preparation of protein enantiomer.[2]

2.2.1a Importance of D-isomers

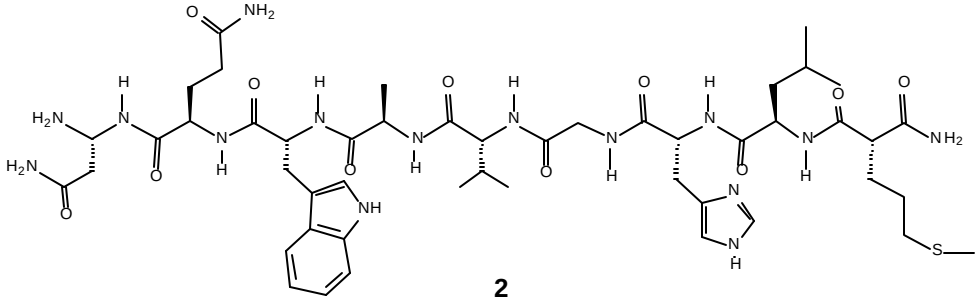
Retro Inverse Isomers:

Approach for changing the peptide backbone is the use retro-inverse modification.[3] In this method the L-amino acids of a peptide are exchanged for D-amino acids, and simultaneously the direction of the peptide is reversed.

The retro-inverse modification itself does not contain any conformational restrictions when compared with the native peptide. For example,



1

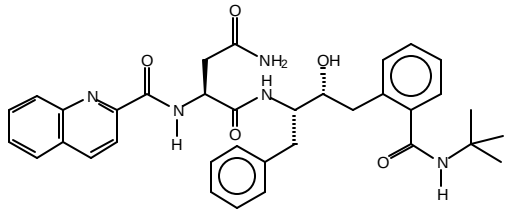


2

The C-terminal nonapeptide **1**, which has the full agonist activity of bombesin and the retro-inverse isomer **2** with modified end groups, which does not bind to the receptor.

2.2.1b Applications

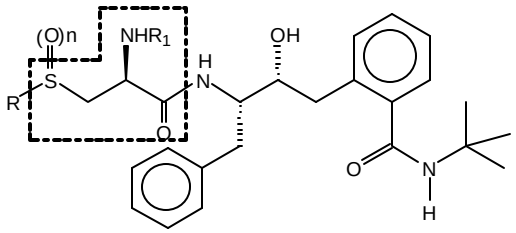
1. Human immunodeficiency virus type 1 (HIV-1) protease, an essential enzyme in the life cycle of HIV, remains an exciting target for anti AIDS (Acquired Immuno Deficiency Syndrome) chemotherapeutic agents. Considerable effort has been spent on attempts to find potent, orally bio-available, peptidomimetic inhibitors of this enzyme. The Lilly group[4] recently reported lead compound LY 289612 **3** for above purpose.



LY 289612 **3**

Recently Jungheim *et al.*.[5] introduced "D-amino acid concept" for better structure activity relationship studies of parent LY 289612. A number of Damino acids were screened for their ability to act as mimics of the quinaldic amide aspargine moiety found in lead inhibitor LY 289612. A brief SAR was developed in order to optimize the nitrogen substituents on D-amino acids found to date were

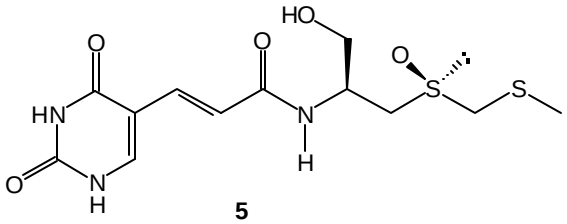
S-arylcysteine analogues. The majority of these compounds are potent HIV protease inhibitors and several of these compounds possess potent antiviral activity, significantly more potent than lead structure LY 289612.



4 R = alkyl or aryl

R_1 = acetyl or mesyl

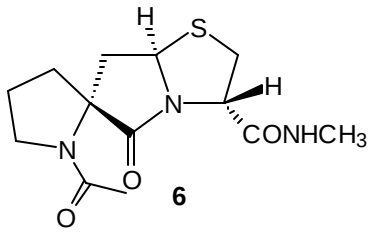
2. *Other biologically important compounds with D-configuration:*



5

Sparsomycin[6] **5** has attracted considerable attention because of its unusual chiral dithioacetal

S-oxide moiety as well as it's anti tumor activity. Besides its anti tumor activity Sparsomycin also exhibits activity against various bacteria, fungi, and viruses.



6

A novel highly constrained spiro-bicyclic system **6**[7] has been developed to mimic the type I â -turn, a secondary structural feature found in many bioactive peptides. This system simultaneously restricts three (Φ, ψ_2, and Φ_3) of the four torsional angles that characterize the type II β-turn peptidomimetic.

2.2.2 Reported methods for the preparation of D-amino acids

In general the most frequently used methods for the synthesis of optically active amino acids have encompassed chiral glycine enolates, chiral phase transfer catalysis, manipulation of natural amino acids and asymmetric hydrogenation of dehydro-amino acids. Most recently there have been several syntheses of optically active amino acids based on biocatalytic kinetic hydrolytic resolution of racemic substrates.

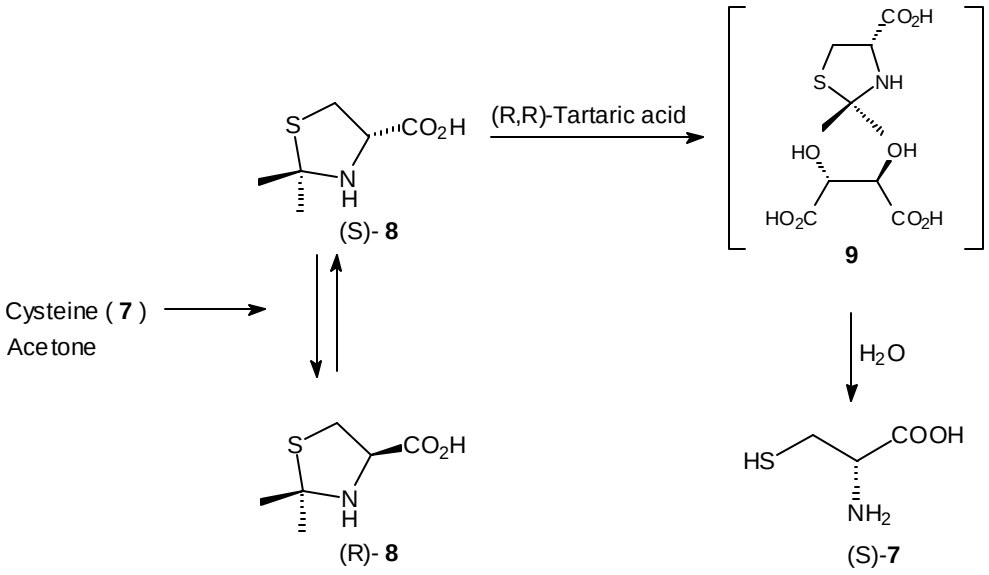
1. Kinetic Resolution of Racemates:

a). Chemical Methods:

Cyclic amino acids can be recemized smoothly by heating in carboxylic acid with an aldehyde as catalyst. Protonated Schiff's bases are proposed as intermediates of this epimerization. In combination with enantioselective salt precipitation using (*R,R*)- or (*S,S*)-tartaric acid Shiraiwa and co workers[8] have applied this principle for the deracemization of amino acids.

For example (*R/S*)-cysteine **7** was transformed with acetone/AcOH to 2,2-dimethyl thiozolidine-4-carboxylic acid **8** in the presence of salicylaldehyde, the salt **9** was precipitated in high yield. Hydrolysis gave (*S*)-cysteine **7** in 98% *ee* in 80% overall yield.

Scheme 1: *Bull. Chem. Soc., Jpn.*, **1989**, *62*, 109



Using the same method (*S*)-proline (80%) and pipecolic acid (70%) were obtained in optically pure form.

b). Use of Hydrolytic Enzymes:

Hydrolytic enzymes are especially well suited for the kinetic resolution of racemic amino acid derivatives. This method has therefore found numerous industrial applications.

The different approaches are best classified according to the bond cleaved by enzymatic assistance. The major processes are amide or nitrile hydrolysis by *aminopeptidase* or *nitrilases* cleavage of *N*-acyl groups by *acylases* and ester hydrolysis by *lipase* or *protease*.

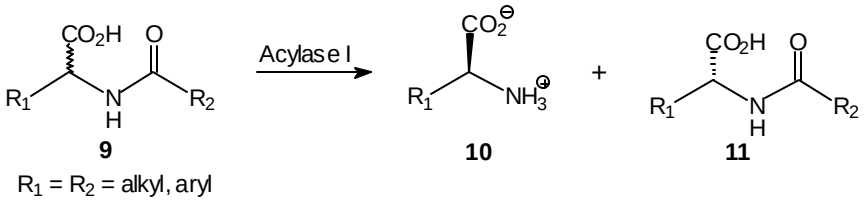
Enantioselective hydrolysis of *N*-acyl amino acids catalyzed by Acylase I

Whitesides *et al.*[9] described the use of Acylase I enzyme as catalyst for the kinetic resolution of

á-amino acids range of substrates accepted by each enzyme, factors influencing the

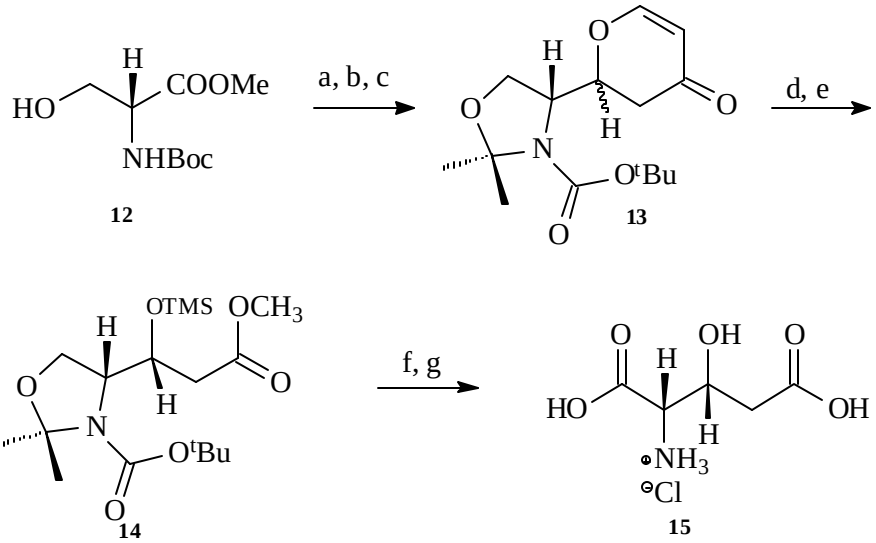
activities and stabilities of the enzymes and methods for the preparative scale resolution of representive compounds. Both L- and D- amino acid product were obtained with high (generally > 90%) enantiomeric excess.

Scheme 2: *J. Am. Chem. Soc.,* **1989**, *111*, 6354



2. From (R)-amino acid to (S)-amino acid derivatives: [10]

Scheme 3: *Tetrahedron Lett.,* **1984**, *25*, 5855



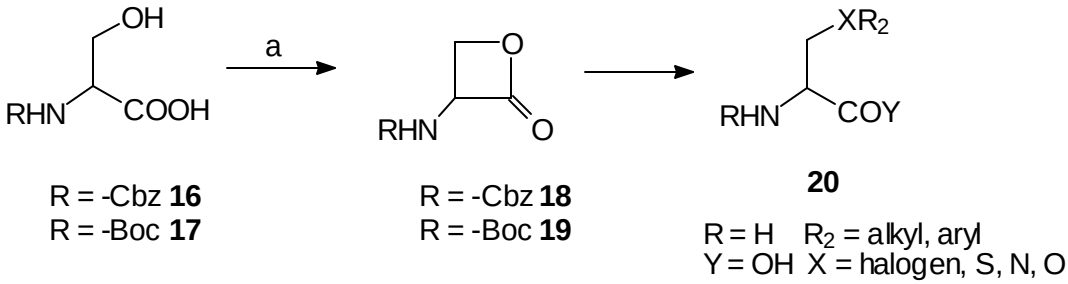
Conditions: ***a****) DMP, cat. TsOH;* ***b****) DIBAL-H, -78 °C;* ***c****) 1-Methoxy-3-(trimethylsiloxy)-1,3-butadiene, cat. 2% of EUFOD or 5% $ZnCl_2$ in DCM, HCl, DCM;* ***d****) $NaIO_4$, cat. RuO_2, H_2O, NaOH; then HCl, CH_2N_2;* ***e****) Et_2NTMS, flash chromatography;* ***f****) MeOH, cat. TsOH;* ***g****) $KMnO_4$, aq. NaOH, HCl.*

Condensation of *N*-Boc-D-serine methyl ester (**12**) with 2,2-dimethoxy propane in the presence of pTSA resulted in a 60% yield of oxazolidine ester, controlled reduction of ester

with DIBAL-H at –78 °C gave the aldehyde. Lewis acid mediated cyclocondensation of Danishefsky's diene to aldehyde furnished compound **13**. Oxidative degradation of **13** with $NaIO_4$ + cat. RuO_2, followed by formate hydrolysis, esterification with diazomethane and TMS-ether formation resulted compound **14**. Deprotection of **14** with pTSA-methanol gave diol, selective oxidation of diol with basic $KmnO_4$ followed by treatment of HCl resulted threo-*p*-hydroxy-*L*-glutamic acid (**15**).

3. From D-serine to D-cysteine derivatives:[11]

Scheme 4: *J. Am. Chem. Soc.,* **1985**, *107*, 7105



R = -Cbz **16**
R = -Boc **17**

R = -Cbz **18**
R = -Boc **19**

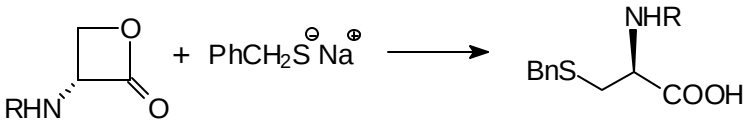
20

R = H R_2 = alkyl, aryl
Y = OH X = halogen, S, N, O

***Condition**: **a**) Ph_3P/DMAD/THF/ -78 °C.*

Pure enantiomers of *N*-(benzyloxycarbonyl) serine (**16**) or *N*-(tert-butoxy carbonyl)serine (**17**) are cyclized without racemization to *N*-protected á-amino-â-lactones **18** and **19** in 60-72% yield by using modified Mitsunobu conditions (PPh_3 and dimethyl azido carboxylate). Treatment of â-lactones with a variety of halogen, oxygen, sulfur or nitrogen nucleophiles gave pure enantiomers of *N*-protected â-substituted alanines **20** in high yield. Only hard nucleophiles (*e.g.,* methoxide) attack these lactones at carbonyl position (scheme 4).

Scheme 5:



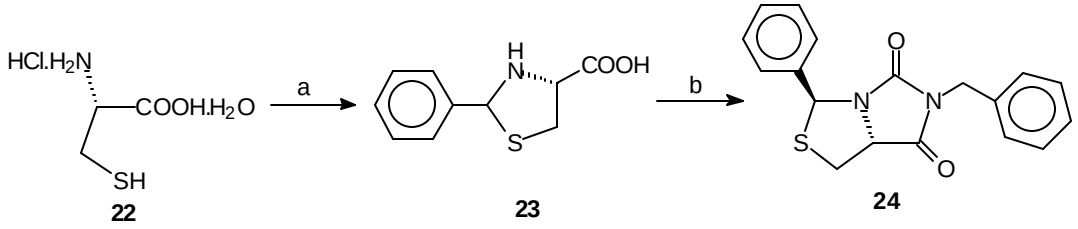
18 **21**

***Condition: a**). DMF, 22 °C, 30 min, 65%.*

2.2.3 Present Work

During our enantioselective synthesis of D(+)-biotin there was a need to prepare imidazolidinone **24** of thiazolidine-4-carboxylic acid **23** (see Chapter I). It was reported[12] that treatment of thiazolidine-4-carboxylic acid **23** with BnNCO in THF at elevated temperature furnished the corresponding urea which on dehydration with conc. HCl furnished desired imidazolidinone **24** in good yield and excellent stereo control.

Scheme 6:



22 **23** **24**

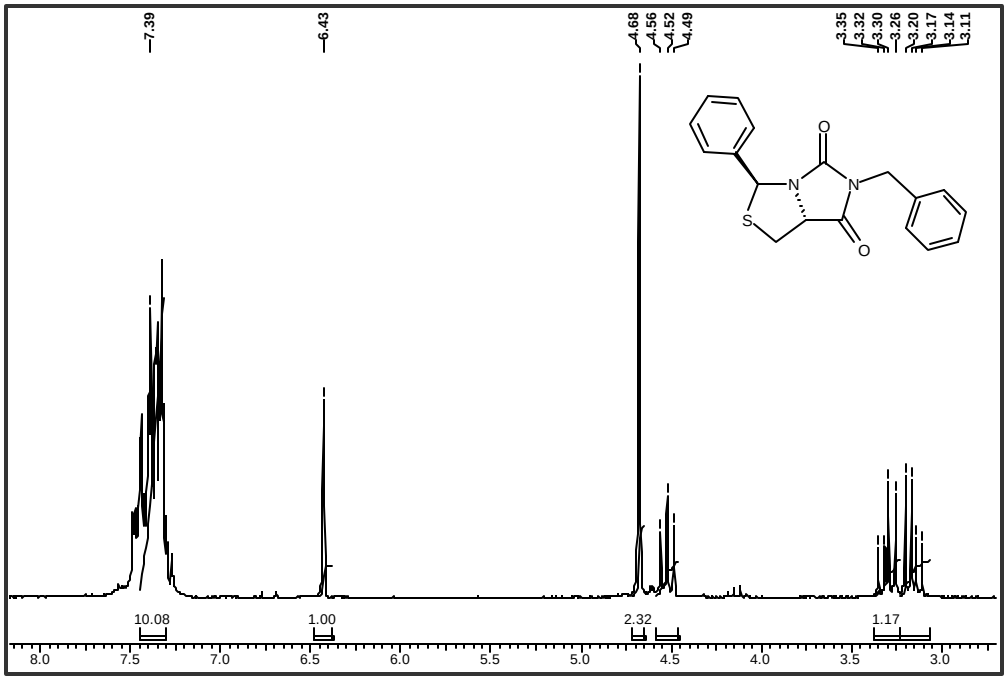
Conditons: ***a****) PhCHO, KOAc, MeOH:H2O (1:1), 5h, 99%;* ***b****) BnNCO, THF, con.HCl, 3h, 90%.*

It was thought worthwhile investigating the reaction of thiazolidine-4-carboxylic acid with benzyl isocyanate by changing solvent, temperature and performing the reaction under mild acidic conditions.

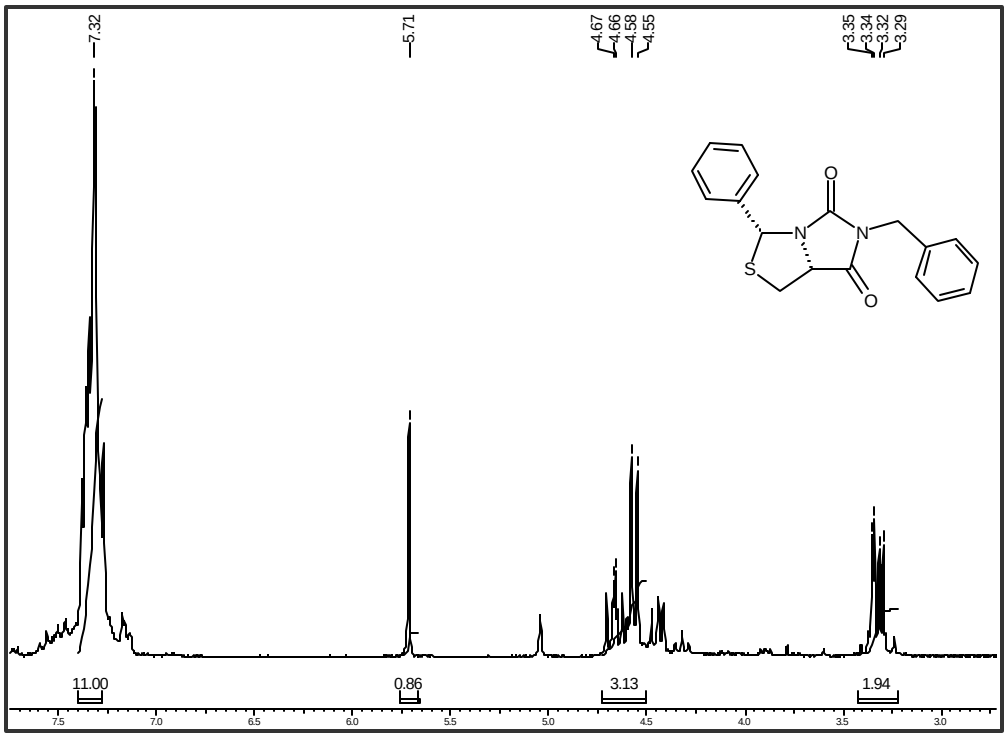
2.2.4 Results and Discussion

Following the reported procedure preparation of imidazolidinone **24** was carried out with benzyl isocyanate, pTSA in THF at ambient temperature for 12 h. When thiazolidine-4-carboxylic acid was treated with benzylisocyanate followed by Conc.HCl in THF as a solvent at 60 ^{o}C, only one diastereomer *i.e.,* hydantoin **24** was exclusively obtained. With a view to perform the above reaction conditions the reactions was carried out at room temperature with pTSA as the catalyst, a mixture of diastereomers (hydantoin **24**, hydantoin **25**) in 2:1 ratio were obtained in 90% yield. The ratio of these diastereomers remained unaltered when the reaction was performed in different solvents as well as at different temperatures.

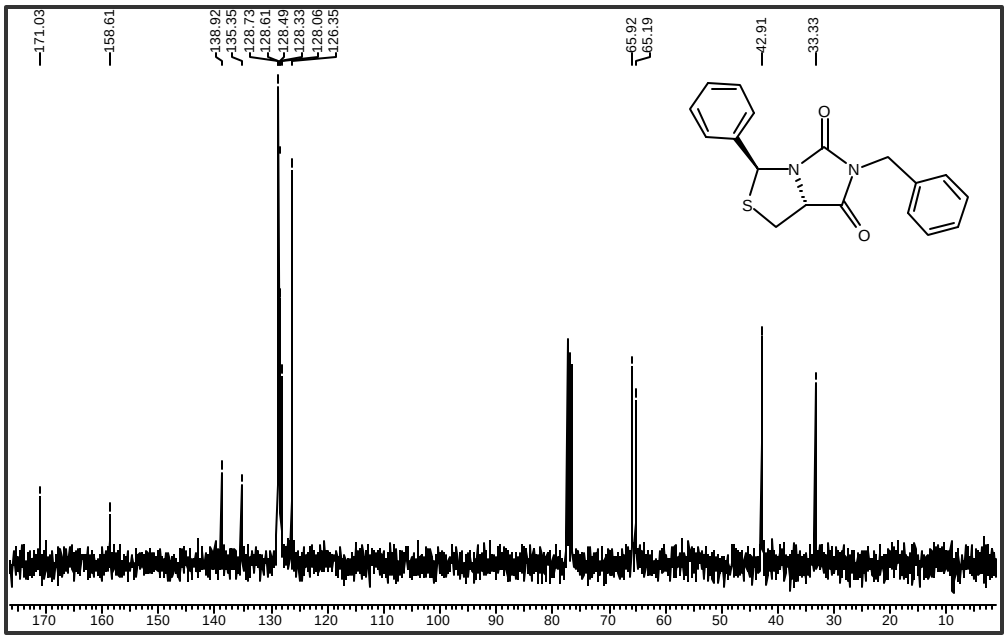
^{1}H NMR spectra of the two diastereomers are tabulated in Table-1. IR spectrum showed peaks at 1720, 1700 cm^{-1} indicating presence of carbonyls of amide, ureido groups respectively.^{13}C NMR showed singlet at ppm 171.0, 158.5 for major diastereomer (hydantoin **24**) and in the case of minor diastereomer (hydantoin **25**) at ppm 169.5, 153.2 for amide, ureido carbonyl groups respectively.



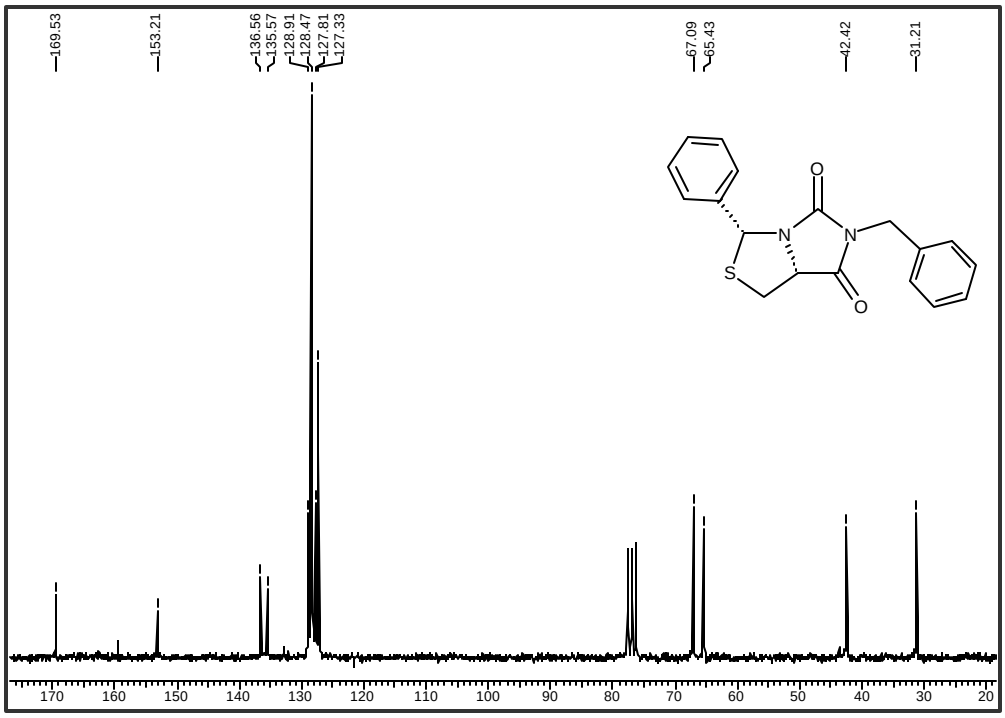
^{1}H NMR spectrum of Hydantoin **24** ($CDCl_3$, 200 MHz)



^{1}H NMR spectrum of Hydantoin **25** ($CDCl_3$, 200 MHz)



^{13}C NMR and DEPT spectrum of Hydantoin **24** ($CDCl_3$, 125 MHz)



^{13}C and DEPT NMR spectra of Hydantoin **25** ($CDCl_3$, 125 MHz)

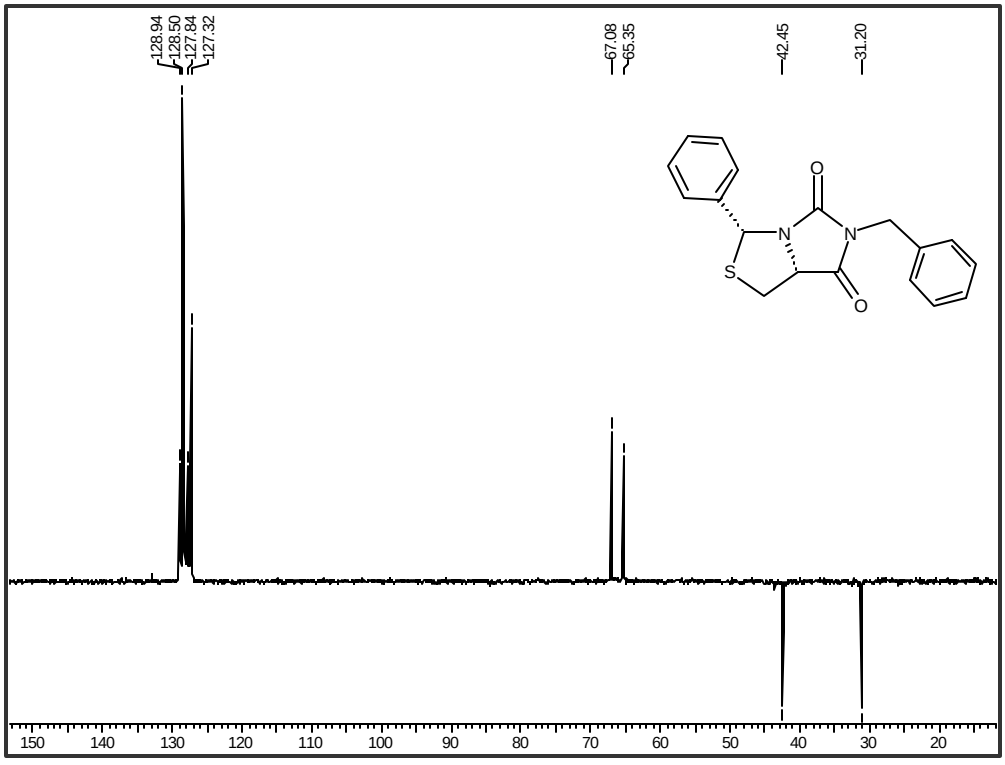
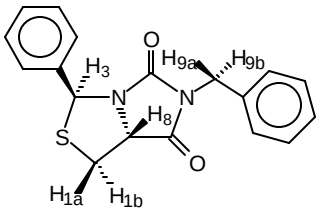
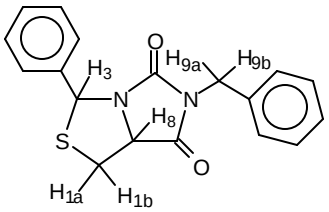
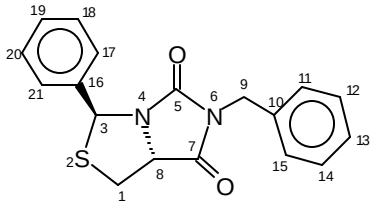
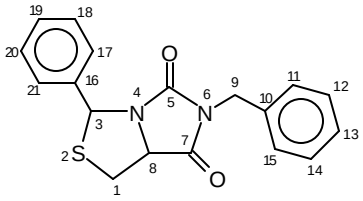


Table 1: ^{1}H NMR Chemical shifts (δ_H in ppm) for hydantoin **24** and hydantoin **25** in $CDCl_3$.

Proton	**Hydantoin 24**	**Hydantoin 25**
		
Aromatic	7.39 (m)	7.32 (m)
H_3	6.43 (s)	5.71 (s)
H_{9a}/H_{9b}	4.68 (s)	4.61 (d, J = 14.2 Hz)
H_{9b}/H_{9a}	4.68 (s)	4.50 (d, J = 14.2 Hz)
H_8	4.52 (t, J = 7.3 Hz)	4.67 (dd J = 7.3, 9.0 Hz)
H_{1a} (cis)	3.30 (dd, J = 6.81, 11.2 Hz)	3.37 (dd, J = 7.3, 11.2 Hz)
H_{1b} (trans)	3.17 (dd, J = 7.82, 11.2 Hz)	3.29 (dd, J = 9.0, 11.2 Hz)

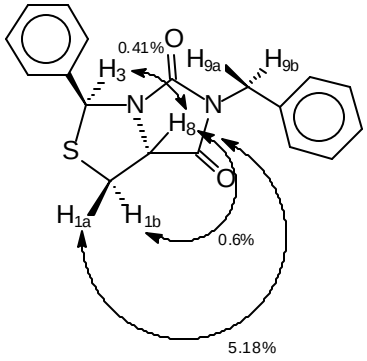
m: multiplet; t: triplet; dd: double doublet; d: doublet; s: singlet

Table 2: ^{13}C NMR Chemical shifts (δ_C in ppm) for hydantoin **24** and hydantoin **25** in $CDCl_3$.

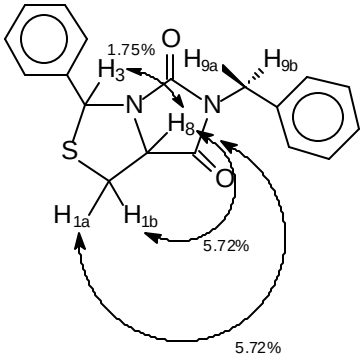
Carbon	**Hydantoin 24**	**Hydantoin 25**
		
C-9	33.2	31.2
C-1	42.8	42.4
C-8	65.2	65.4
C-3	65.8	67.1
C-10	135.4	135.6
C-16	139.0	136.7
C-5 (N-CO-N)	158.5	153.2
C-7 (N-CO-C)	171.0	169.5

The absolute configuration of hydantoin **24** was reported by Casutt *et al.*.[12] as 6-benzyl-3-phenyl(3*S*, 7a*R*)perhydroimidazo[1,5-c][1,3]-thiazol-5,7-dione. In the case of minor diastereomer (hydantoin **25**) the stereochemistry was established by using NOE and chemical studies.

i. NOE studies:



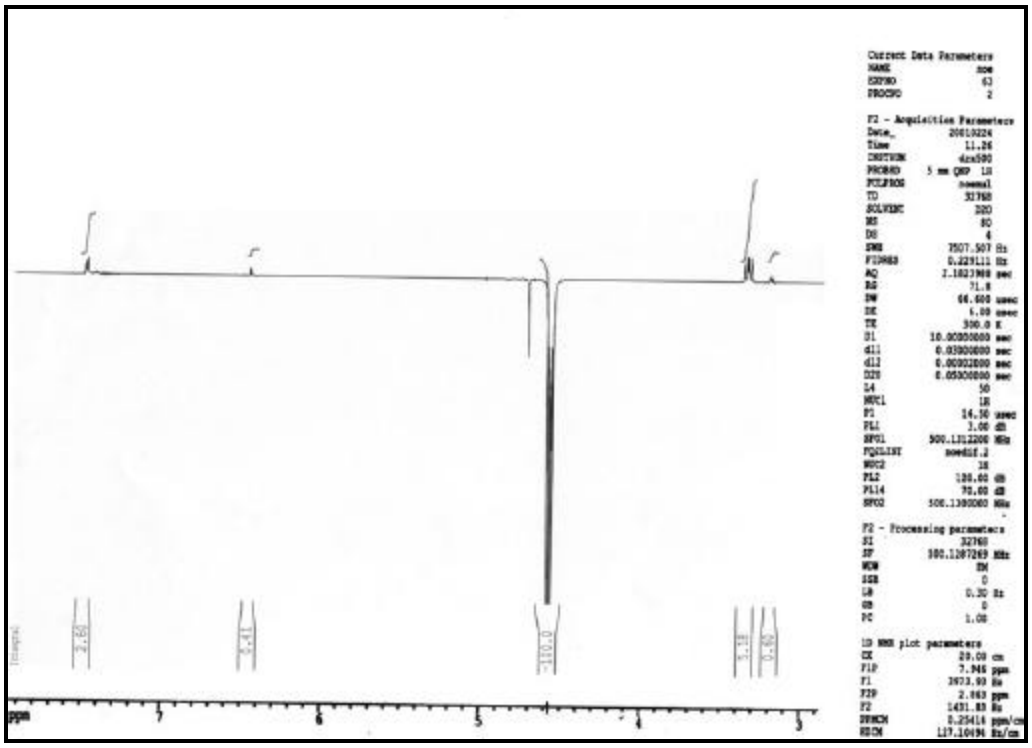
Hydantoin **24**



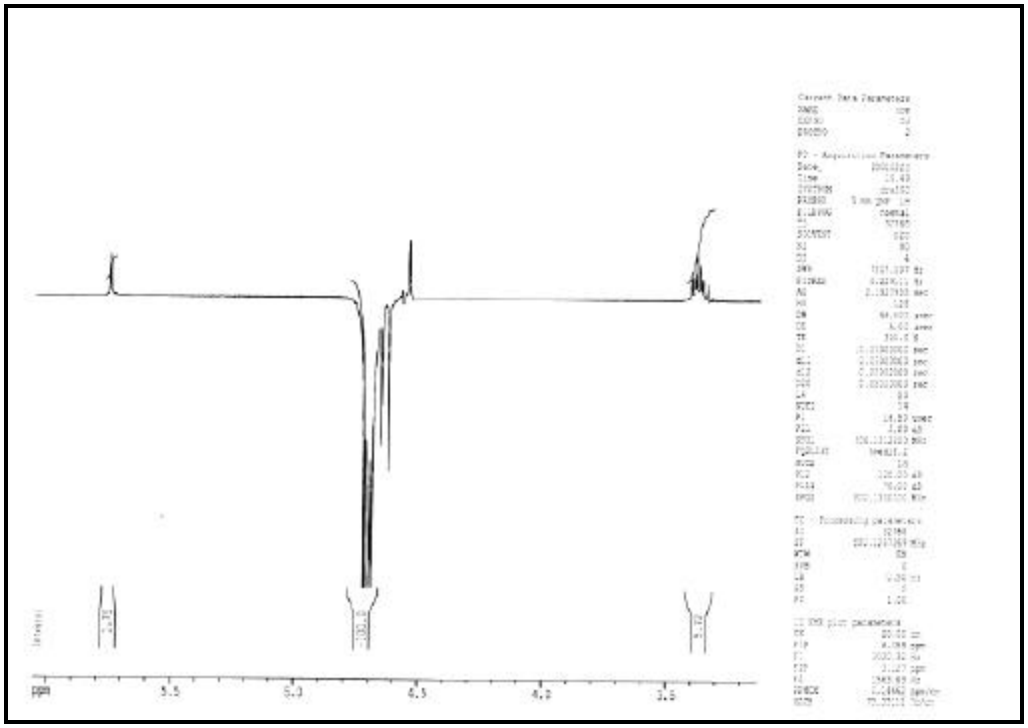
Hydantoin **25**

Irradiation of H_8 in hydantoin **24** allows the assignment of the *cis* configuration for H_{1a} at 3.30 ppm, (5.18% of NOE), *trans* configuration for H_{1b} at 3.17 ppm, (0.6% NOE) and for H_3 at 6.43 ppm (0.41% NOE).

An identical reasoning was applied to hydantoin **25**. Thus irradiation of H_8 in hydantoin **25** allows the stereochemical assignment for H_3 at 5.71 ppm (1.75% NOE) to be *cis* with respect to H_8. However based on NOE results the H_{1a} and H_{1b} stereochemical assignments could not be done due to their identical enhancements.



NOE spectrum of hydantoin **24** (Irradiation of H_8)



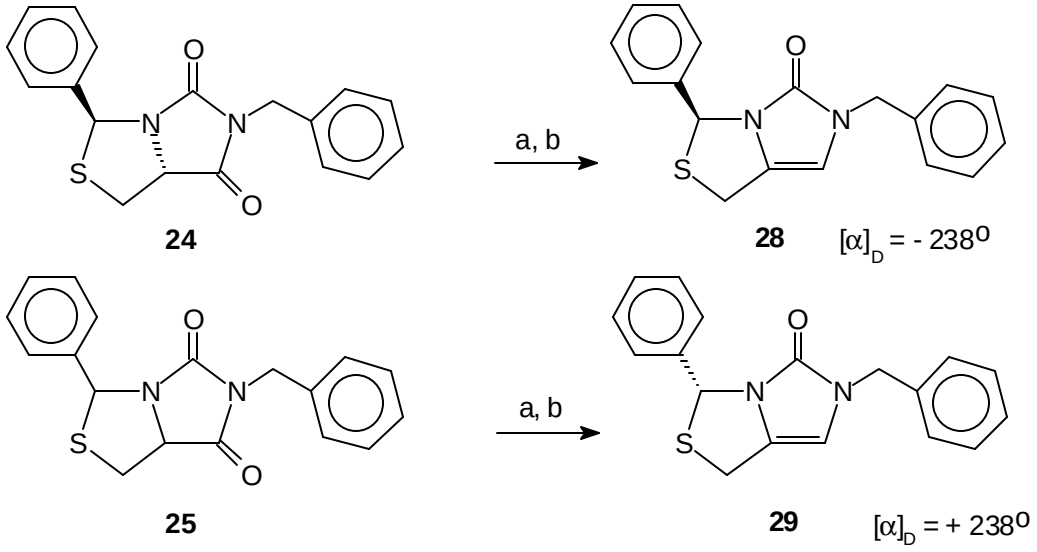
NOE spectrum of hydantoin **25** (Irradiation of H_8)

ii. Chemical Studies:

The diastereomeric relationship of hydantoin **24** and hydantoin **25** was established as follows:

Hydantoin **24** and hydantoin **25** were separately subjected to sodium borohydride reduction to the respective aminols and further subjected to dehydration with pTSA in dichloromethane at room temperature for 4h. This treatment in both cases gave the enantiomeric olefins **28** and **29**. This finding clearly established that the two diastereomers have opposite configuration only at C_3-position.

Scheme 7:



24 **28** $[\alpha]_D = -238^o$

25 **29** $[\alpha]_D = +238^o$

***Conditions: a**) NaBH$_4$, MeOH, 0 ^{o}C to rt; **b**). Conc. HCl, DCM, rt.*

NOE and chemical studies suggest that the diastereomers **24** & **25** differ in absolute stereochemistry at C_3-position as 3(*S*) and 3(*R*) for hydantoin **24** and hydantoin **25** respectively. This result was further confirmed by using X-ray crystallographic analysis of hydantoin **25**.

Based on above studies (NMR, Chemical and X-ray analysis) the absolute configuration of hydantoin **25** is 6-benzyl-3-phenyl(3*R*, 7a*R*)perhydroimidazo[1,5-c][1,3]-thiazol-5,7-dione.

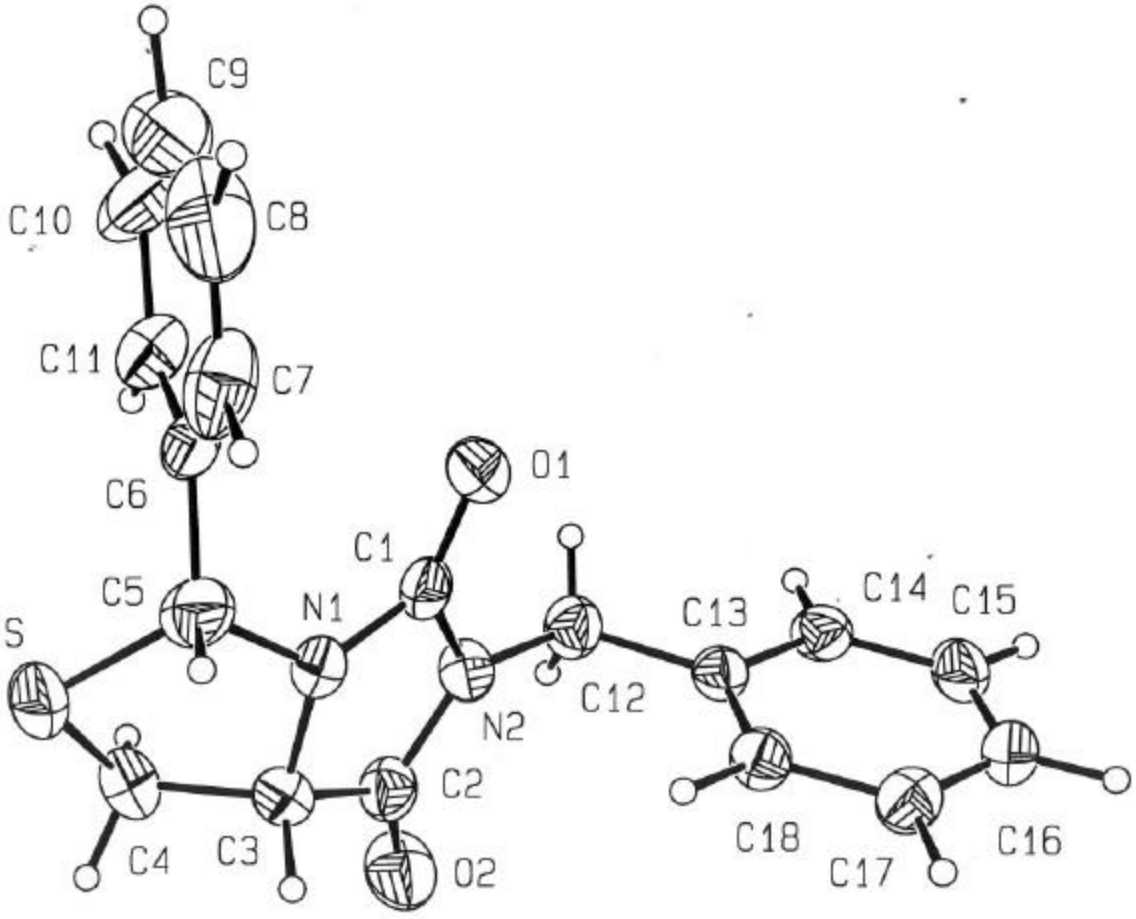
iii. Single Crystal X-ray analysis of second isomer (hydantoin 25):

Single crystals of hydantoin **25** were grown using methanol:water (3:1) by slow cooling at room temperature.

Table 3: Crystal, Data Collection and Refinement Parameters

Formula	$C_{18}H_{16}N_2O_2S$
FW	324.4
Crystal size, mm	0.18x 0.22x 0.40
Crystal color	Colorless
Crystal mount	On glass fiber w/silicone glue
a, Å	10.7970 (16)
b, Å	5.8810 (11)
c, Å	12.4611 (7)
â, deg	95.3927 (12)
V, Å^3	788.5
cell detn, refls	4177
cell detn, 2è range, deg	3,59
d(calcd), g cm^{-3}	1.37
space group	$P2_1$
Z	2
F000	340
radiation	MoKá, graphic monochromated
ë,Å	0.7107
Temp, K	293
Linear abs coeff, mm^{-1}	0.21
diffractometer	Mercury CCD
scan technique	Omega
2 è range, deg	4-50
h,k,l ranges	-12, 12; -7, 7; -14, 14
absorption correction	Multi-scan empirical
absorption range	0.89 – 1.00
refl means	6264
unique refls	1532
R for merge	0.027
data with 1>3.0a(I)	1013
solution method	Direct method
parameters refined	216
R for 1>3.0a(I)	0.039
GOF	1.70
Largest /ó	0.00
Final diff map, e Å^3	-0.15(3), +0.11(3)
programs	NRC 386 (PC version of NRCVAX)[a]
Scattering factors	Internat. Table for Crystallography, Vol 4
H atom treatment	Idealized (C-H = 0.95 Å)

[a] NRCVAX-An Interactive Program System for Structure Analysis, E. J. Gabe, Y. Lepage, J. P. Charland, F. L., Lee, and P. S. White. *J. Appl. Cryst. 22*, 383, **1989.**



X-ray structure of hydantoin 25

Table 4: Atomic Parameters x, y, z and Biso

Atom	x	y	z	Beq/Biso
S1	0.4679(6)	0.8953(20)	0.3885(5)	10.7(5)
S2	0.4448(3)	0.7213(10)	0.3582(3)	8.56(19)
O1	0.8160(3)	0.9625(8)	0.2553(24)	5.96(18)
O2	0.4724(3)	1.2489(9)	0.0624(3)	7.33(20)
N1	0.6113(3)	0.8297(9)	0.2326(3)	4.33(17)
N2	0.6618(3)	1.1443(9)	0.1467(3)	4.38(17)
C1	0.7089(4)	0.9717(10)	0.2179(3)	4.19(20)
C2	0.5368(4)	1.1221(11)	0.1211(4)	4.76(23)
C3	0.4957(4)	0.9138(11)	0.1785(3)	4.99(23)
C4	0.4081(4)	0.9606(14)	0.2650(4)	7.1(3)
C5	0.5949(5)	0.6842(12)	0.3237(4)	6.3(3)
C6	0.6985(4)	0.6713(12)	0.4126(3)	4.74(23)
C7	0.7693(7)	0.4772(12)	04251(5)	7.6(3)
C8	0.8623(10)	0.4615(22)	0.5085(10)	12.0(7)
C9	0.8805(9)	0.636(3)	0.5784(9)	13.0(8)
C10	0.8130(9)	0.8261(22)	0.5670(5)	11.0(6)
C11	0.7210(5)	0.8433(12)	0.4842(4)	6.30(3)
C12	0.7387(4)	1.3244(11)	0.1081(3)	4.89(21)
C13	0.7975(4)	1.2719(10)	0.0062(3)	4.01(20)
C14	0.8748(4)	1.4343(10)	-0.0334(3)	4.55(21)
C15	0.9321(4)	1.3947(12)	-0.1250(4)	5.25(24)
C16	0.9148(4)	1.1943(12)	-0.1810(4)	4.91(23)
C17	0.8367(4)	1.0336(11)	-0.1437(4)	5.23(24)
C18	0.7780(4)	1.0696(10)	0.0501(4)	4.41(20)
H3	0.458	0.778	0.128	5.3
H4a	0.325	0.913	0.236	7.1
H4b	0.421	1.082	0.291	7.1
H5	0.583	0.506	0.293	7.0
H7	0.754	0.320	0.379	8.0
H8	0.918	0.312	0.523	10.4
H9	0.943	0.592	0.637	9.8
H10	0.827	0.921	0.625	11.0
H11	0.668	0.956	0.473	6.7
H12a	0.800	1.337	0.162	6.0
H12b	0.683	1.425	0.091	6.0
H14	0.890	1.548	0.006	5.3
H15	0.983	1.481	-0.152	5.9
H16	0.959	1.137	-0.243	5.8
H17	0.821	0.866	-0.184	5.9
H18	0.725	0.927	-0.020	5.0

Table 5:

Selected bond distances:

S1-S2	1.111(13)
S1-C4	1.659(8)
S2-C4	1.845(9)
S1-C5	2.070(9)
S2-C5	1.730(7)
O1-C1	1.207(6)
O2-C2	1.216(7)
N1-C1	1.370(7)
N1-C3	1.450(6)
N1-C5	1.446(7)
N2-C1	1.412(7)
N2-C2	1.364(6)
N2-C12	1.455(7)
C2-C3	1.506(9)
C3-C4	1.525(7)
C5-C6	1.501(7)
C6-C7	1.375(10)
C6-C11	1.356(9)
C7-C8	1.381(15)
C8-C9	1.348(24)
C9-C10	1.335(22)
C10-C11	1.369(11)
C12-C13	1.505(6)
C13-C14	1.389(7)
C13-C18	1.388(8)
C14-C15	1.369(6)
C15-C16	1.374(9)
C16-C17	1.376(8)
C17-C18	1.396(6)

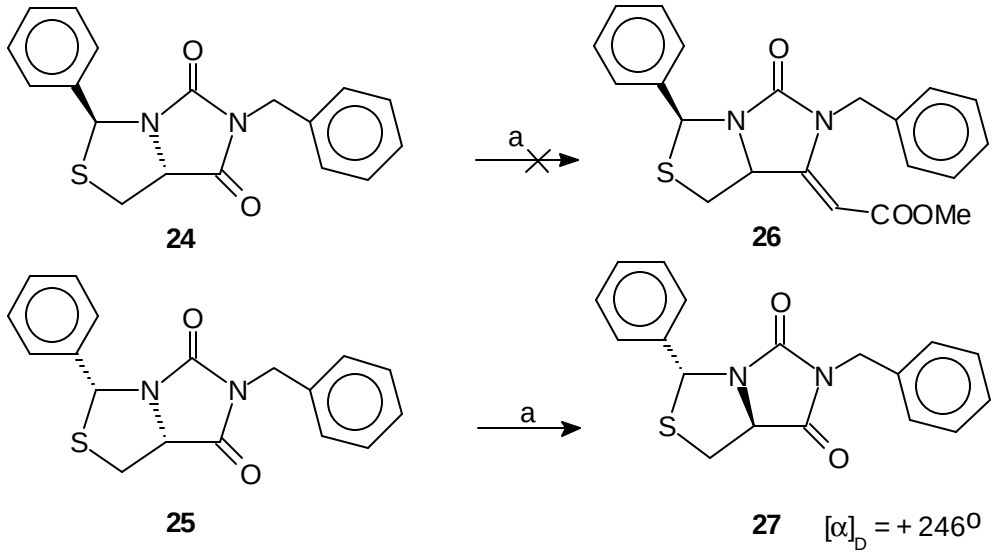
Selected Bond Angles:

C4-S1-C5	89.5(4)	C5-C6-C11	121.6(6)
C4-S2-C5	95.2(3)	C7-C6-C11	118.7(5)
C1-N1-C3	111.7(5)	C6-C7-C8	119.9(8)
C1-N1-C5	128.1(4)	C7-C8-C9	119.2(9)
C3-N1-C5	113.8(4)	C8-C9-C10	121.6(9)
C1-N2-C2	111.7(4)	C9-C10-C11	119.5(9)
C1-N2-C12	123.2(4)	C6-C11-C10	121.0(7)
C2-N2-C12	125.1(4)	N2-C12-C13	115.4(5)
O1-C1-N1	129.9(5)	C12-C13-C14	118.3(5)
O1-C1-N2	123.5(5)	C12-C13-C18	123.2(4)
N1-C1-N2	106.6(4)	C14-C13-C18	118.5(4)
O2-C2-N2	125.4(5)	C13-C14-C15	120.9(5)
O2-C2-C3	127.4(4)	C14-C15-C16	121.3(5)
N2-C2-C3	107.2(5)	C15-C16-C17	118.4(4)
N1-C3-C2	102.6(4)	C16-C17-C18	121.3(5)
N1-C3-C4	107.2(4)	C13-C18-C17	119.6(5)
C2-C3-C4	114.8(5)		
C3-C4-S1	113.7(4)		
C3-C4-S2	101.4(5)		
S1-C4-S2	36.5(5)		
N1-C5-C6	118.2(4)		
N1-C5-S1	94.9(5)		
N1-C5-S2	107.9(4)		
C6-C5-S1	102.5(4)		
C6-C5-S2	118.2(4)		
S1-C5-S2	32.5(4)		
C5-C6-C7	119.6(6)		

iv. Unusual epimerization of hydantoin 25 at C_8 position:

During our enantiospecific synthesis of D(+)-biotin, hydantoin **24** was reduced to the corresponding derivative with sodium borohydride in methanol at room temperature (Chapter 1: Section 2). Prompted by the successful reduction of amide carbonyl of hydantoin **24**, it was decided to functionalise the amide carbonyl of hydantoin **24** with phosphorus ylide (Wittig reaction). The reaction of hydantoin **24** with ethyl triphenyl phosphonoacetate salt, anhydrous K_2CO_3 in toluene under refluxing conditions failed to furnish the olefin. When the same reaction was done with hydantoin **25** no formation of the olefin could be observed, instead it furnished hydantoin **27** in 96% yield corresponding to epimerization at C_8-position.

Scheme 8:



24 **26**

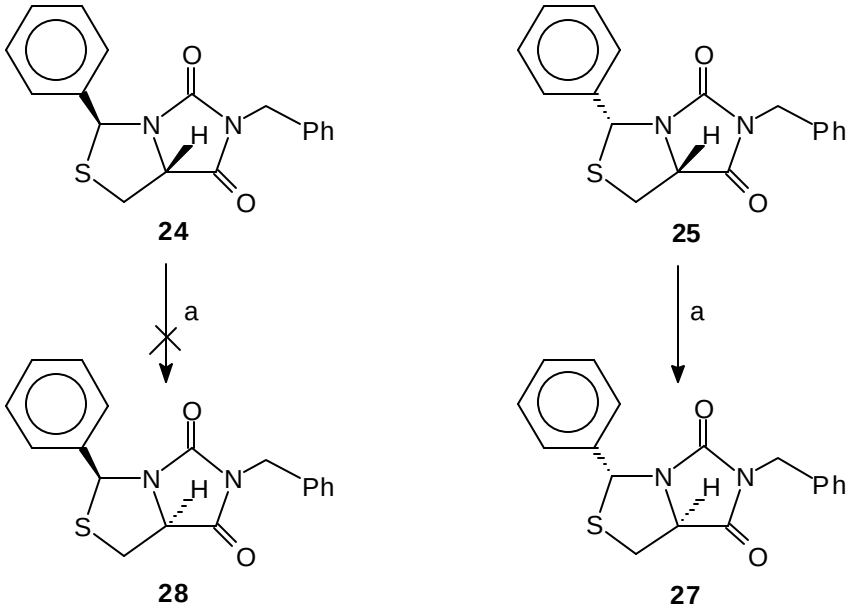
25 **27** $[\alpha]_D = +246^o$

***Conditions: a**) [$Ph_3PCHCOOMe$]Br, K_2CO_3, toluene, reflux, 5h.*

^{1}H NMR showed a singlet at δ 6.43 integrating for one proton assigned for H_9, singlet at δ 4.68 for two protons assigned for benzylic protons and triplet at δ 4.52 (J = 7.32Hz) for one proton was assigned for H_8. Two doublet of doublets at δ 3.30 (J = 6.81, 11.2Hz) and δ 3.17 (J = 7.82, 11.2Hz) integrating for one proton each were assigned to the methylene protons á to the sulphur. Thus the ^{1}H NMR spectrum of hydantoin **27** thus obtained was identical with the ^{1}H NMR of hydantoin **24**. Additionally **27** was also identical with **24** by TLC. The polarimetric studies revealed it to exhibit the almost same magnitude of rotation but in opposite direction. All these facts clearly establish that hydantoin **27** is an enantiomer of hydantoin **24**.

Having established the formation of **27** during Wittig reaction it was also established that hydantoin **25** clearly can be transformed (epimerised) to **27** by treatment with anhydrous K_2CO_3 in refluxing toluene whereas **24** resisted similar transformation. It is noteworthy that the stereochemistry in hydantoin **27** at C_8-position was exactly opposite to that present in hydantoin **24** or hydantoin **25**. Thus the stereochemistry of hydantoin **27** has been confirmed by spectral analysis as well as polarimetric studies.

Scheme 9:



Condition: a) *K_2CO_3, Toluene, reflux.*

The epimerization of proton at C_8 takes place only in the case of hydantoin **25** can be explained by the support of theoretical studies also. The first calculations were performed with hydantoin **24** using the crystal structure as a starting geometry. The hydantoins (hydantoin **24** and hydantoin **25**) geometry were optimized by using semi empirical PM3 method using HyperChem for windows (Developed by Hypercube, Inc, CANADA, the programme was implemented on a Microsoft Pentium-II computer)

v. Geometrical optimization studies:

1. Hydantoin 24:

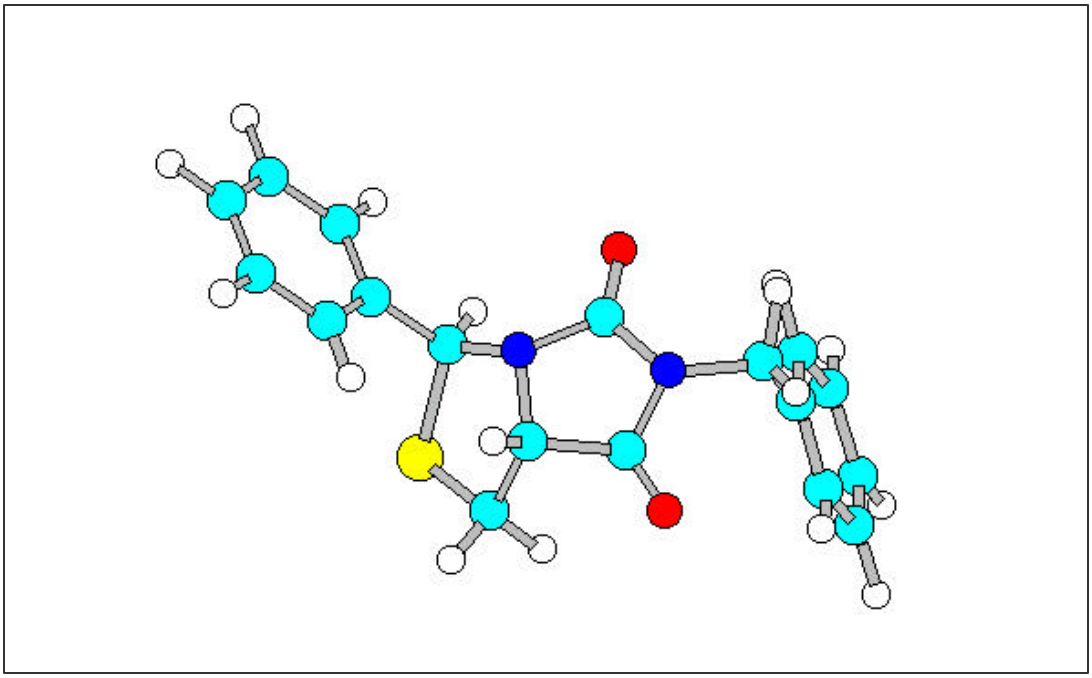
Conditions:
Geometry optimization, Semi Empirical, molecule = hydantoin **24** PM3
Polak-Ribiere optimizer
Convergence limit = 0.0100000 Iteration limit = 50

Accelerate convergence = YES
Optimization algorithm = Polak-Ribiere
Criterion of RMS gradient = 0.0100 kcal/(A mol) Maximum cycles = 585
RHF Calculation:

Singlet state calculation
Number of electrons = 116
Number of Double Occupied Levels = 58

Charge on the System = 0
Total Orbitals = 108

Starting PM3 calculation with 108 orbitals



Geometry optimized structure of hydantoin **24**

E=-4331.6309 Grad=0.009 Conv=YES(510 cycles 1077 points) [Iter=1 Diff=0.00000]

ENERGIES AND GRADIENT
Total Energy = - 80171.7417748 (kcal/mol)
Total Energy = - 127.759252052 (a.u.)
Binding Energy = - 4331.6306608 (kcal/mol)
Isolated Atomic Energy = - 75840.1111140 (kcal/mol)
Electronic Energy = - 609076.9480605 (kcal/mol)
Core-Core Interaction = 528905.2062857 (kcal/mol)

Heat of Formation = -10.4606608 (kcal/mol)

Gradient = 0.0089454 (kcal/mol/Ang)

NET CHARGES AND COORDINATES

Atom	Z	Charge	Coordinates(Angstrom) x	y	z	Mass
1	6	0.264673	1.59525	0.78040	0.90525	12.01100
2	7	-0.067001	2.83667	0.05332	0.85568	12.01100
3	6	0.266555	3.92018	0.96460	0.56985	12.01100
4	6	-0.090075	1.91388	2.27380	0.80143	12.01100

5	7	-0.062386	3.41611	2.31961	0.70534	12.01100
6	6	-0.037149	3.93056	3.39554	-0.18930	12.01100
7	16	-0.019234	2.51826	3.96115	-1.25978	12.01100
8	6	-0.184678	1.26409	2.95468	-0.40199	12.01100
9	8	-0.332263	5.07299	0.65853	0.34142	12.01100
10	8	-0.310514	0.51520	0.25227	1.05589	12.01100
12	6	-0.090399	4.53795	4.51043	0.61041	12.01100
13	6	-0.065629	3.83170	5.17380	1.61562	12.01100
14	6	-0.104055	4.43789	6.19562	2.33732	12.01100
15	6	-0.087354	5.74993	6.56480	2.06069	12.01100
16	6	-0.103043	6.45743	5.90774	1.05989	12.01100
17	6	-0.076032	5.85718	4.88284	0.33768	12.01100
18	6	0.018881	2.93782	-1.41135	0.65742	12.01100
19	6	-0.139592	2.75927	-1.82950	-0.77054	12.01100
20	6	-0.078866	3.86577	-1.92352	-1.61612	12.01100
21	6	-0.105947	3.70074	-2.33411	-2.93424	12.01100
22	6	-0.087617	2.43477	-2.65521	-3.41272	12.01100
23	6	-0.107190	1.33132	-2.56710	-2.57044	12.01100
24	6	-0.080845	1.49061	-2.15699	-1.25150	12.01100
11	1	0.118004	1.62604	2.79350	1.74912	12.01100
25	1	0.117265	4.70921	2.97199	-0.87277	1.00800
26	1	0.099543	0.82886	2.22298	-1.10800	1.00800
27	1	0.101337	0.42253	3.59599	-0.08325	1.00800
28	1	0.104326	2.79416	4.89672	1.83593	1.00800
29	1	0.105022	3.87839	6.71149	3.12460	1.00800
30	1	0.104154	6.22469	7.37084	2.62962	1.00800
31	1	0.106058	7.49093	6.19526	0.84012	1.00800
32	1	0.109422	6.42592	4.36527	-0.44452	1.00800
33	1	0.080283	3.93046	-1.72670	1.03783	1.00800
34	1	0.078537	2.17055	-1.88270	1.30432	1.00800
35	1	0.120344	4.86573	-1.67305	-1.24006	1.00800
36	1	0.106880	4.57097	-2.40533	-3.59515	1.00800
37	1	0.104251	2.30719	-2.97885	-4.45095	1.00800
38	1	0.106418	0.33440	-2.82248	-2.94461	1.00800
39	1	0.117915	0.61920	-2.09191	-0.58818	1.00800

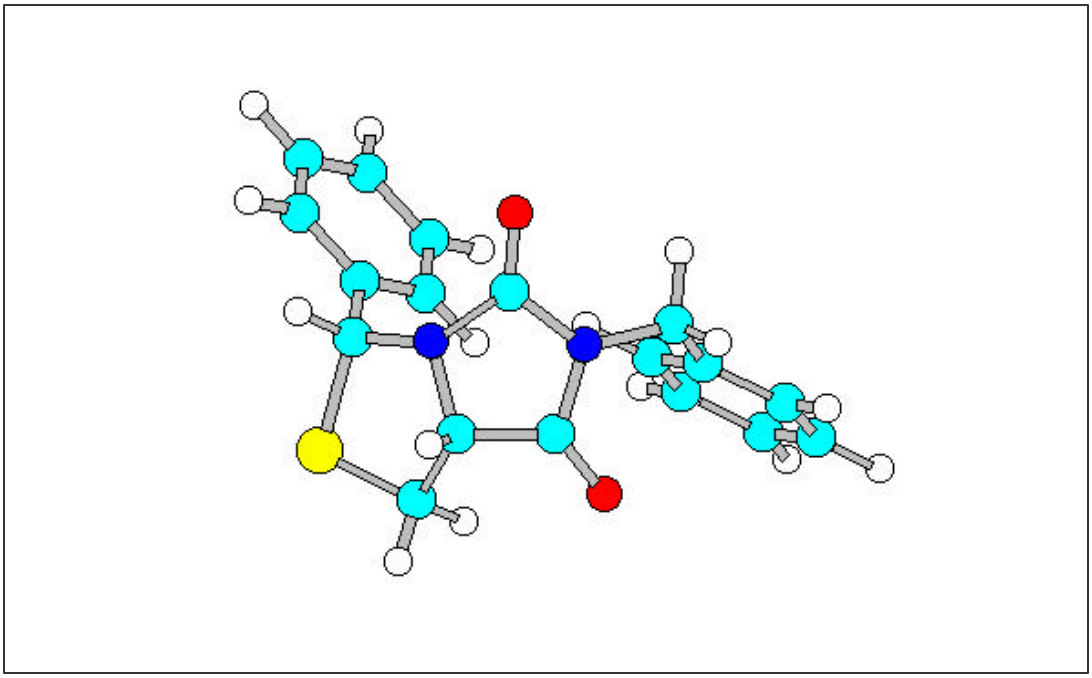
Dipole (Debyes)	x	y	z	Total
Point-Chg.	0.009	1.006	0.105	1.011
sp Hybrid	-0.426	-0.896	0.045	0.993
pd Hybrid	0.000	0.000	0.000	0.000
Sum	-0.417	0.109	0.149	0.456

2. hydantoin 25:

Geometry optimization, Semi Empirical, molecule = hydantoin **25**, PM3
PolakRibiere optimizer
Convergence limit = 0.0100000 Iteration limit = 50
Accelerate convergence = YES

Optimization algorithm = Polak-Ribiere
Criterion of RMS gradient = 0.0100 kcal/(A mol) Maximum cycles = 585
RHF Calculation:

Singlet state calculation
Number of electrons = 116
Number of Double Occupied Levels = 58
Charge on the System = 0
Total Orbitals = 108



Geometry optimized structure of hydantoin **25**

E=-4328.4233 Grad=0.009 Conv=YES (281 cycles 609 points) [Iter=1 Diff=0.00000]

ENERGIES AND GRADIENT
Total Energy = - 80168.5 344507 (kcal/mol)
Total Energy = - 127.754140957 (a.u.)
Binding Energy = - 4328.4233367 (kcal/mol)
Isolated Atomic Energy = - 75840.1111140 (kcal/mol)
Electronic Energy = - 629532.1441142 (kcal/mol)
Core-Core Interaction = 549363.6096635 (kcal/mol)

Heat of Formation = -7.2533367 (kcal/mol)

Gradient = 0.0093844 (kcal/mol/Ang)

NET CHARGES AND COORDINATES

Atom	Z	Charge	Coordinates(Angstrom) x	y	z	Mass
1	6	0.260381	1.59743	1.40307	1.79036	12.01100
2	7	-0.077775	2.95432	0.92431	1.82934	14.00700
3	6	0.266348	3.86602	2.00159	1.49412	12.01100
4	6	-0.090917	1.63486	2.90875	1.52805	12.01100
5	7	-0.076545	3.09918	3.22805	1.35616	14.00700
6	6	-0.025580	3.36839	4.26066	0.31224	12.01100
7	16	-0.018970	1.75262	4.66035	-0.52675	32.06400
8	6	-0.182339	0.82738	3.33821	0.30893	12.01100
9	8	-0.313571	5.07465	1.90531	1.47848	15.99900
10	8	-0.301551	0.63289	0.69985	1.99455	15.99900
12	6	-0.099520	4.43678	3.94547	-0.68924	12.01100
13	6	-0.086696	4.38559	2.81932	-1.51355	12.01100
14	6	-0.096478	5.38381	2.59305	-2.45375	12.01100
15	6	-0.081524	6.44247	3.48607	-2.57980	12.01100
16	6	-0.098196	6.50301	4.60590	-1.75767	12.01100
17	6	-0.066002	5.50705	4.83620	-0.81560	12.01100
18	6	0.014242	3.32935	-0.50137	1.71345	12.01100
19	6	-0.112134	2.95152	-1.14240	0.41063	12.01100
20	6	-0.077911	2.31864	-2.38725	0.43193	12.01100
21	6	-0.097124	1.99757	-3.03046	-0.75794	12.01100
22	6	-0.093500	2.30093	-2.43536	-1.97781	12.01100
23	6	-0.098280	2.92537	-1.19322	-2.00384	12.01100
24	6	-0.115777	3.25024	-0.54814	-0.81595	12.01100
11	1	0.119008	1.28914	3.45873	2.43864	1.00800
25	1	0.111250	3.65838	5.17314	0.88946	1.00800
26	1	0.095216	0.64016	2.49526	-0.38231	1.00800
27	1	0.107359	-0.17064	3.71152	0.60205	1.00800
28	1	0.108164	3.56434	2.09162	-1.42116	1.00800
29	1	0.105210	5.33440	1.70470	-3.09271	1.00800
30	1	0.105135	7.22753	3.30551	-3.32140	1.00800
31	1	0.106654	7.33822	5.30829	-1.84905	1.00800
32	1	0.108621	5.56667	5.72013	-0.16886	1.00800
33	1	0.088417	4.42610	-0.57943	1.86159	1.00800
34	1	0.075133	2.84616	-1.02521	2.56384	1.00800
35	1	0.109829	2.07001	-2.85975	1.38979	1.00800
36	1	0.106002	1.50250	-4.00691	-0.73292	1.00800
37	1	0.105271	2.04780	-2.94242	-2.91460	1.00800
38	1	0.104270	3.16554	-0.71899	-2.96153	1.00800
39	1	0.113879	3.74373	0.43650	-0.86013	1.00800

Dipole (Debyes)	x	y	z	Total
Point-Chg.	0.158	0.619	-0.865	1.076
sp Hybrid	-0.109	-1.234	-0.086	1.242
pd Hybrid	0.000	0.000	0.000	0.000
Sum	0.048	-0.615	-0.951	1.134

Based on above calculations it is evident that hydantoin **24** is thermodynamically more stable product on the other hand hydantoin **25** is kinetically formed. The hydantoin **25** undergoes facile epimerization under basic conditions to form thermodynamically more stable product **24**

Thus, utilizing the above results one can potentially convert natural amino acids (*viz* cysteine, serine) into unnatural amino acids thro the formation of hydantoins.

2.2.5 Conclusions

In conclusion thiazolidine-4-carboxylic acid reacts with benzyl isocyanate stereoselectively at elevated temperature to produce hydantoin **24** *i.e.,* 6-benzyl-3-phenyl(3*S*, 7a*R*)perhydroimidazo [1,5-c][1,3]-thiazol-5,7-dione and nonstereoselectively at ambient temperature to produce mixture (66:33 ratio) of the C_3 epimers of 6-benzyl-3-phenyl(3*R/S*, 7a*R*)perhydroimidazo[1,5-c][1,3]-thiazol-5,7-diones.

Selective epimerization at C_8 of 6-benzyl-3-phenyl(3*R*, 7a*R*)perhydroimidazo[1,5-c][1,3]-thiazol-5,7-dione (hydantoin **25**) was shown to occur under very mild basic conditions using K2CO3 as a base. This result would lead to synthesis of unnatural amino acids from natural amino acids thro the formation of hydantoins.

2.2.6 Experimental

Preparation of hydantoins 24 and 25:

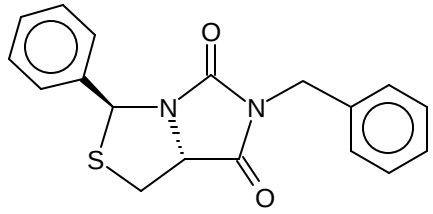
Method A:

In a 500 mL two necked round bottom flask filled with nitrogen, (20.0g, 95.6 mmol) thiazolidine carboxylic acid **23** was placed in 150 mL of anhydrous THF. To this suspension, a solution of (15.2g, 1.143 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 this 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 **24** was obtained as a white crystalline solid [m.p 78 ^{o}C (Lit[12] 79-80 ^{o}C)] (27.8g, 90%).

Method B:

In a 100 mL two necked round bottom flask (2.0g, 9.56 mmol) thiazolidine carboxylic acid **23** was placed in 50 mL of anhydrous acetone in an atmosphere of nitrogen . To this suspension, a solution of (1.52g, 11.43 mmol) benzyl isocyanate in 15 mL of acetone was added drop wise within 10 min. and stirred for 6 h. Catalytic amount (10 mg) of pTSA was added and stirring was continued for overnight. After completion of reaction, acetone was removed and the contents were extracted with ethyl acetate. The combined organic layers were dried over anhyd. Na_2SO_4 filtered and concentrated under reduced pressure. The crude product was purified by column chromatography eluting with 15% ethyl acetate and pet. ether gave white solid [hydantoin **24**, 1.85g (59.6%)]. Further elution with 25% ethyl acetate and pet. ether gave white crystalline solid [hydantoin **25**, 0.93g (30%)].

1. 6-Benzyl-3-phenyl(3*S*, 7a*R*)perhydroimidazo[1,5-c][1,3]-thiazol-5,7-dione (24):

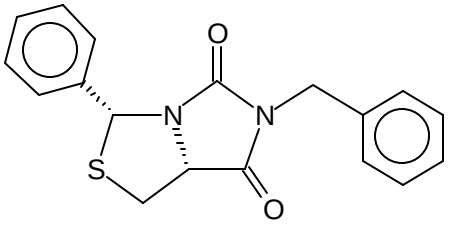


Mol. Formula	: $C_{18}H_{16}N_2O_2S$
M.P.	: 78 ^oC, white solid.
Optical Rotation	:$[\alpha]_{365}$ = +1010^o (c=1, $CHCl_3$); $[\alpha]_D$ = -250^o (c=1.08, $CHCl_3$)
IR ($CHCl_3$, cm^{-1})	: 3040, 2960, 1720, 1700, 1510, 1420, 1230, 1050.
^1H NMR($CDCl_3$, 200MHz)	: 3.17 (dd, 1H, J = 7.82, 11.2Hz); 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

2. 6-Benzyl-3-phenyl(3*R*, 7a*R*)perhydroimidazo[1,5 -c][1,3]-thiazol-5,7-dione (25):

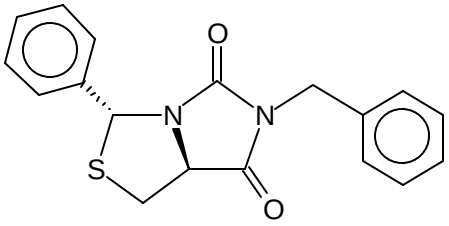


Mol. Formula	: $C_{18}H_{16}N_2O_2S$
M.P.	: 144 ^oC, white solid.
Optical Rotation	:$[\alpha]_{365}$ = -325^o (c=1, $CHCl_3$); $[\alpha]_D$ = -86.13^o (c=1.03, $CHCl_3$)
IR ($CHCl_3$, cm^{-1})	: 3040, 2960, 1720, 1700, 1510, 1420, 1230, 1050.
^1H NMR($CDCl_3$, 200MHz)	: 3.29 (dd, 1H, J = 9.0, 11.2Hz); 3.37 (dd, 1H, J = 7.3, 11.2Hz); 4.50 (d, 1H, J = 14.2Hz); 4.61 (d, 1H, J = 14.2Hz); 4.67 (dd, 1H, J = 7.3, 9.0Hz); 5.71 (s, 1H); 7.32 (m, 10H).
^{13}C NMR ($CDCl_3$, 125 MHz)	: 31.2(t), 42.4(t), 65.4(d), 67.0(d), 127.2(d), 127.3(d), 127.7(d, 2C), 127.8(d), 128.4(d, 2C), 128.5(d), 128.8(d), 128.9(d), 135.6(s), 136.6(s), 153.2(s, C=O), 169.5(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:	66.15	5.17	8.34	9.43

3. 6-Benzyl-3-phenyl(3*R*, 7a*S*)perhydroimidazo[1,5-c][1,3]-thiazol-5,7-dione (27):



Procedure: 0.30g, (0.93 mmol) of 6-Benzyl-3-phenyl(3*S*, 7a*S*)perhydroimidazo[1,5-c][1,3]-thiazol-5,7-dione (**25**) and 0.38 (2.79 mmol) of anhydrous potassium carbonate in 20 mL of dry toluene was refluxed for 5h . Reaction was monitored by TLC. After completion of reaction, the reaction mixture was filtered and toluene was concentrated under reduced pressure. The crude viscous mass was washed with water and extracted with ethyl acetate. The combined organic layers were dried over anhyd. Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography eluting with 10% ethyl acetate and pet. ether gave white solid [hydantoin **27**, 0.29g (96%)].

Mol. Formula	: $C_{18}H_{16}N_2O_2S$, white solid.
M.P.	: 70 ^oC
Optical Rotation	:$[\alpha]_D$ = +246.19^o (c=0.94, $CHCl_3$)
IR (neat)	: 3040, 2960, 1720, 1700, 1510, 1420, 1230, 1050.
^1H 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).

2.2.7 References

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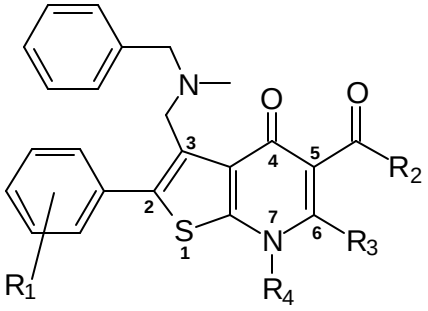
2.3.1 Introduction

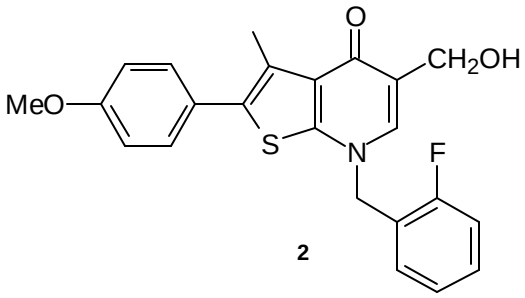
Chemical interest in the thienopyridine system arises from the fact that a thiophene ring (susceptible to facile electrophilic substitution, but resistant to nucleophilic substitution) is fused to a pyridine ring (susceptible to facile nucleophilic substitution, but resistant to electrophilic substitution).



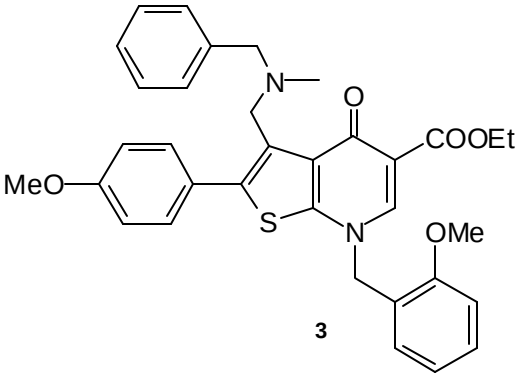
1

Thieno[2,3-b]pyridines and its derivatives are clinically useful drugs[1] for the treatment of a broad spectrum of human hormone dependent diseases.[1] Most of these thieno[2,3-b]pyridine derivatives are used therapeutically as gonadotropin releasing hormones.[1] Especially compounds having the basic structure **1** (R^1 = substituted alkoxy, C_{1-8} alkanoylamino; R^2 = alkyl, alkoxy, cycloalkyloxy, 6-membered *O*-containing heterocyclic group; R^3 = H, alkyl and their salts; R^4 = H, substituted $-CH_2Ar$) are widely used in medicinal chemistry.

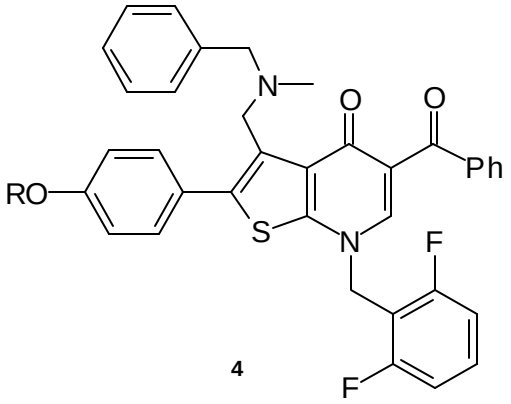
Some of the derivatives of this basic structure are given below.



2



3

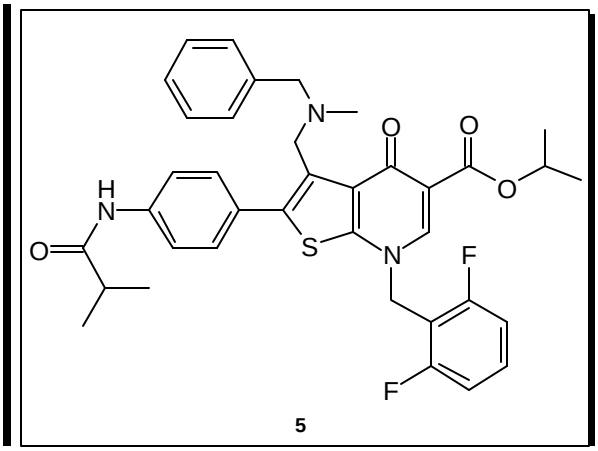


4

R = H, $CH_2CH=CH_2$, $CH_2C(CH_3)=CH_2$

These drug molecules are used for the treatment of several hormone dependent diseases like prostatic cancer, cancer of uterine cervix, breast cancer, pituitary adenomayoma of uterus, endometriosis, precocious puberty, amenorrhea, premenstrual syndrome, polycystic ovary syndrome acne vulgaris, as a fertility controlling agent in both sexes, a contraceptive of male or female, an ovulation-inducing agent of female, an infertility treating agent, and for modulating oestrous cycles in animals in the field of animal husbandry, an agent for improving the quality of edible meat or promoting the growth of animals and as an agent for spawning promotion in fish.

The synthesis of compound **5** was undertaken as a part of project in this present work. This compound **5** is another important derivative[1] of thieno[2,3-b]pyridines and is useful as the gonadotropin releasing hormone antagonist.



5

2.3.1a The Gonadotropins:

The gonadotropins are protein hormones produced by the anterior pituitary and by the placenta. Those of pituitary origin consist of follicle stimulating hormones (FSH), Luteining hormone (LH) and Luteotrophic hormone (probably identical with prolactin or lactogenic hormone). The urine of postmenopausal women is a particularly rich source of gonadotropins and extracts from such urine contains both FSH and LH activities, normally referred to as human menopausal gonadotropin (HMG).

Gonadotropins arise from basophilic cells of the anterior pituitary. Peripherally situated cells are responsible for the production of FSH, while the centrally located basophiles are considered to be the source of LH.

2.3.1b Biological activity:

The sequence of ovarian changes occurring during the normal menstrual cycle is governed by the release of gonadotropins from the anterior pituitary, which in turn is dependent on hypothalamic control. FSH is responsible for the growth of the follicle, which produces oestrogen and stimulates endometrial growth in the uterus. Then LH, possibly in combination with FSH, induces the carpus luteum which secretes progesterone and oestrogen which induces the secretary phase of the endometrium. The steroids produced during this cycle of events react by a feedback mechanism on the anterior pituitary hypothalamus to control the further release of gonadotropin.

In the male, FSH causes growth of the seminiferous tubules and maintains spermatogenesis, while LH promotes the secretion of androgens by the interstitial cells (Leydig cells).

2.3.2 Earlier approaches for thieno[2,3-b]pyridines

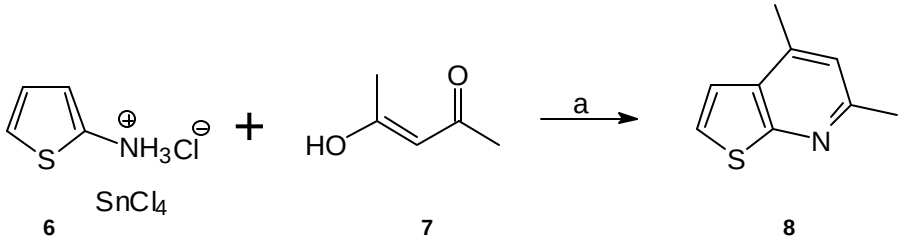
The synthesis of compound **5** has only been reported in the patent so far.[1] However the basic structure of this molecule which is the thieno[2,3-b]pyridine derivative has been synthesized and the literature survey for the preparation of these kind of derivatives are given below.

William's approach:

Steinkopf and Lutzkendorf [3] first reported the synthesis of these thieno[2,3-b] pyridines with very low yields (5%). The low yield was not surprising in view of the sensitivity of 2-amino thiophene even to such mild oxidizing agents as atmospheric oxygen. Therefore, William *et al*. [4] selected a type of

reaction that would not involve hydrogen removal and hence employed 2amino thiophene stannihydrochloride (**6**) as starting material. This compound **6** was condensed with acetylacetone using Koenigs and Mengel's procedure, [5] thus obtained 4,6-dimethylthieno[2,3-b]pyridine (**8**) in 80% yield.

Scheme 1:



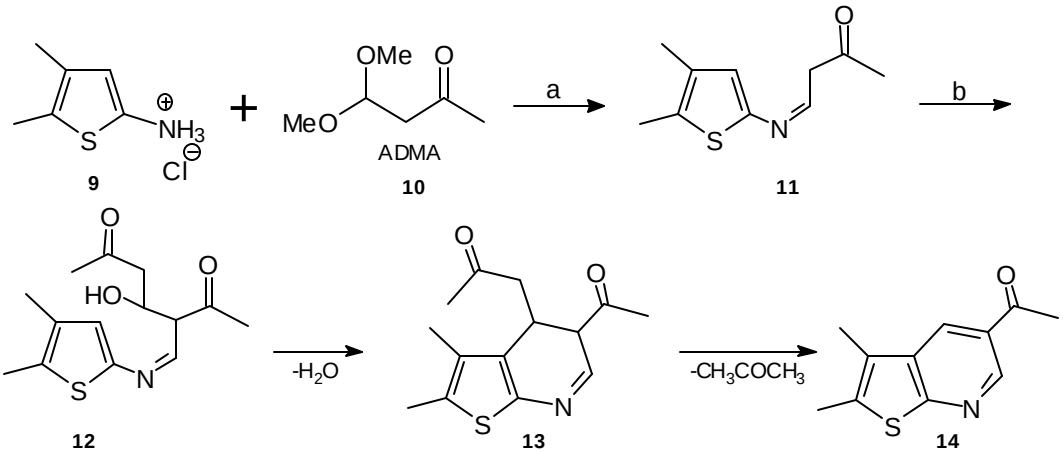
6 **7** **8**

Condition: a) *H_2SO_4, NaOH.*

Klemm's Approach:

Klemm, L.H. *et al.*[6] in 1967 reported a sequence of condensation-cyclisation reactions of 2-amino thiophenes for a practical synthesis of thieno[2,3-b]pyridines. According to their procedure, the 2-amino salt of thiophene **9** was converted to the Schiff's base **11** by using acetoacetaldehyde dimethylacetal (ADMA) in ethanolic hydrochloric acid. Further this Schiff's base **11** was condensed with a second molecule of acetoacetaldehyde to give the ketol **12**. Acid catalyzed dehydration followed by cyclisation gave **13**. Reverses Michael reaction further lead to **14**.

Scheme 2:



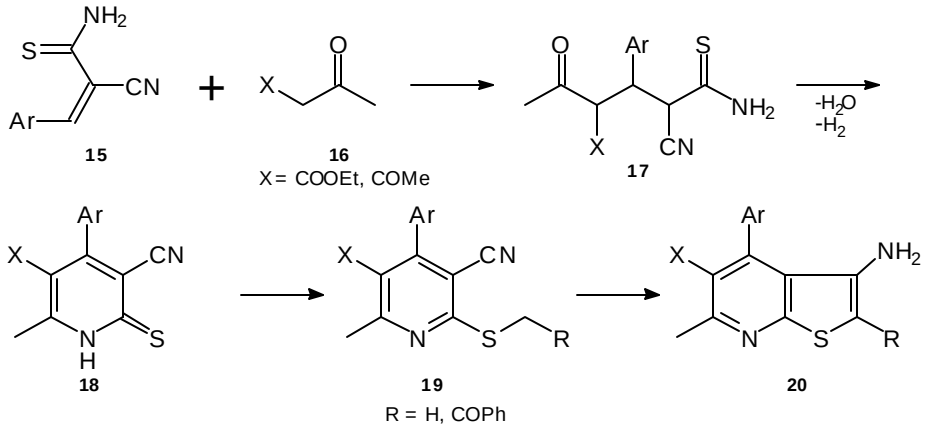
9 **10** **11** **12** **13** **14**

Conditions: a) *HCl, EtOH;* ***b)*** *ADMA.*

Elfahham's Approach:

Elfahham *et al.*[7] effectively utilized readily obtainable arylmethylene cyanothioacetamide **15** and condensed it with ethyl acetoacetate to develop a novel procedure for the synthesis of thieno[2,3-b]pyridine derivatives. Arylmethylene cyanothioacetamide **15** was reacted with ethyl acetoacetate or acetylacetone to give the corresponding 3-cyano-2-(1H)-pyridinethione derivative **18**, which was been alkylated at sulfur atom and cyclized into the corresponding thieno[2,3-b]pyridine derivative **20**.

Scheme 3:



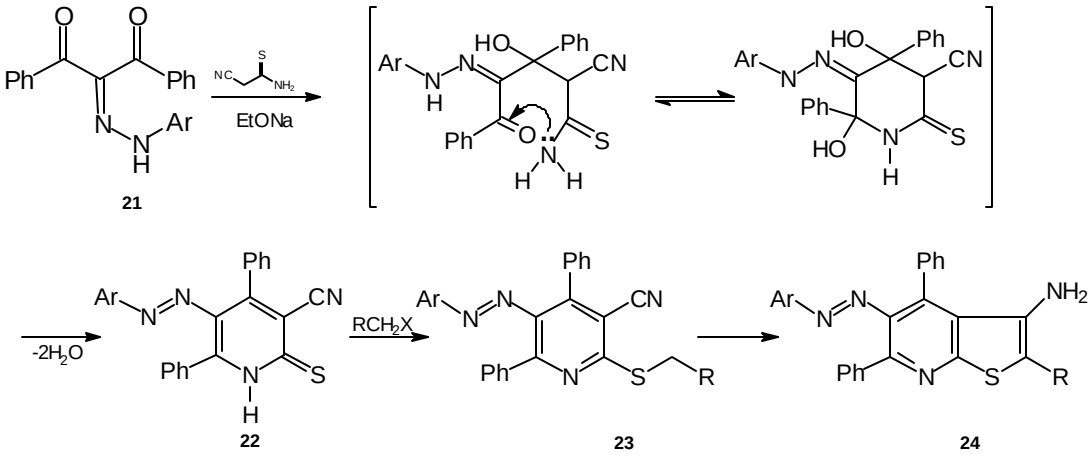
The formation of **18** from the reaction of **15** with **16** is assumed to proceed *via* Michael type addition of the methylene function in **16** to the activated double bond in **15**. Subjecting the potassium salt of **18** to the alkylating agents such as methyliodide afforded the corresponding S-alkyl derivatives **19**. However, **20** was directly isolated using phenacyl bromide as alkylating agent,

Elgemeie's Approach:

Elgemeie *et al.*[8] in 1992 reported another synthetic route for the synthesis of thieno[2,3-b]pyridines utilizing cyanothioacetamide and 2-aryl-hydrazono-1,3-diphenyl propane-1,3-diones (**21**) as starting components.

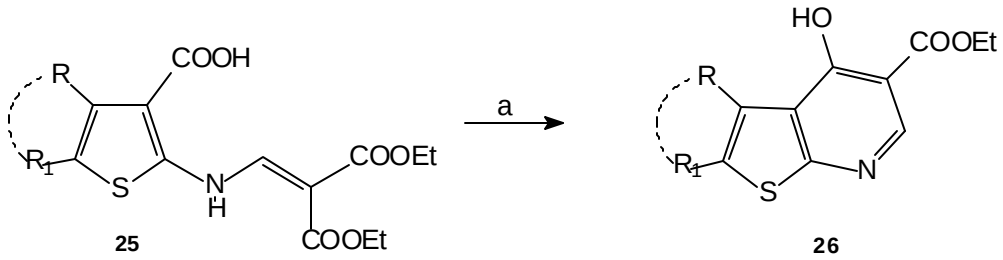
Dibenzoylmethane was coupled with aryldiazonium chlorides in ethanol containing sodium acetate to afford the corresponding monoaryl hydrazone derivatives **21** which inturn was reacted with cyanothioacetamide in ethanol-sodium ethoxide to give the 3-cyanopyridine-2-(1H)-thiones (**22**). Compound **22** was then reacted with ethyliodide in methylene chloride -sodium hydroxide to afford the corresponding 8-ethyl derivatives **23**. When **23** was treated with phenacyl bromide in ethanol-NaOEt, the thieno[2,3-b]pyridine derivative **24** was obtained.

Scheme 4:



Scheme 5:

In 1999 Fukuoka reported[9] synthetic route for the synthesis of thieno[2,3-b]pyridines from substituted thieno enamine carboxylic acid using dehydrating agents.

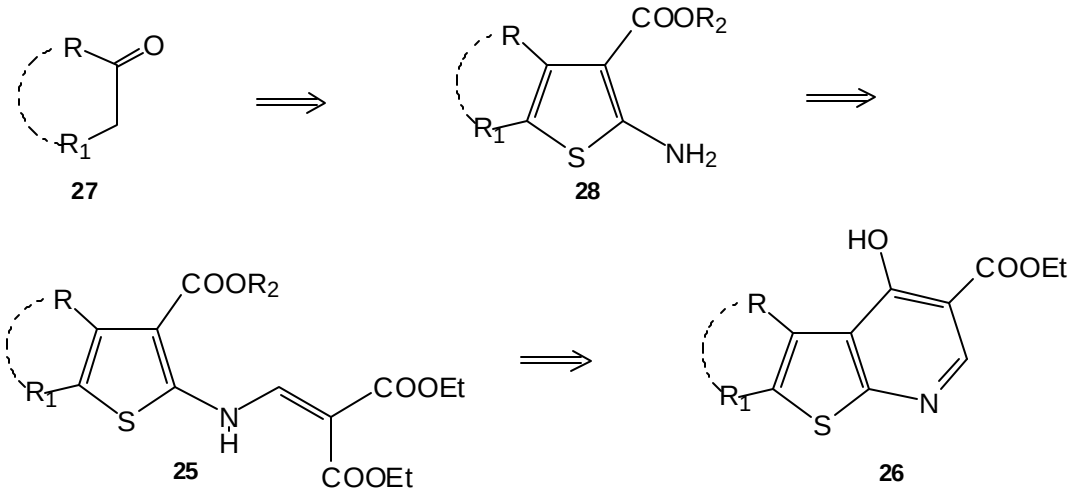


***Condition**: **a**) PPE, 150°C or P_2O_5-CH_3SO_3H, 30min, 70-80%*

2.3.3 Present Work

Literature survey revealed that cyclization of thieno substituted enamine esters is a novel reaction with the only one report[9] being that of cyclization of thieno substituted enamine acid to give the corresponding thieno[2,3-b]pyridines.

Scheme 5:

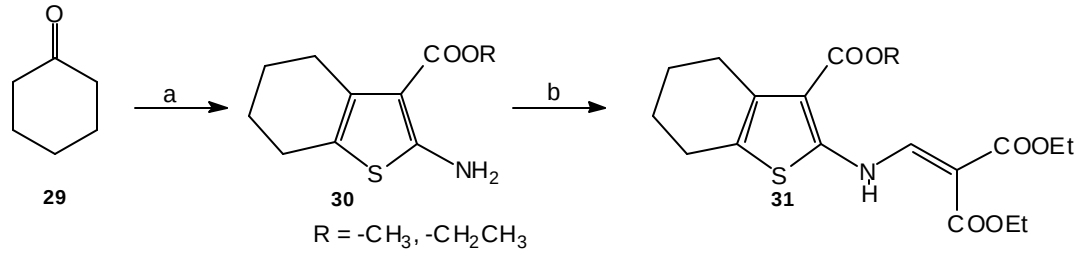


In the present scheme, a simple route to thienopyridines of thienosubstituted enamine ester of formula **25** with dehydrating reagent(s) was proposed to furnish the thieno[2,3-b]pyridine in good to moderate yields. Thienoenamines **28** were prepared by known method reported in literature.[9] These thienopyridines serve as a crucial intermediates for various drugs and drug intermediate which possess various excellent gonadotropin releasing hormone antagonizing activity, and are useful for preventing or treating sex hormone dependent diseases.

2.3.4 Results and Discussion

A direct efficient and convenient methodology for the synthesis of a variety of thieno[2,3-b]pyridines from substituted thieno enamine ester in the presence of dehydrating agents like PPE or $MeSO_3H$-P_2O_5 complex has been developed.

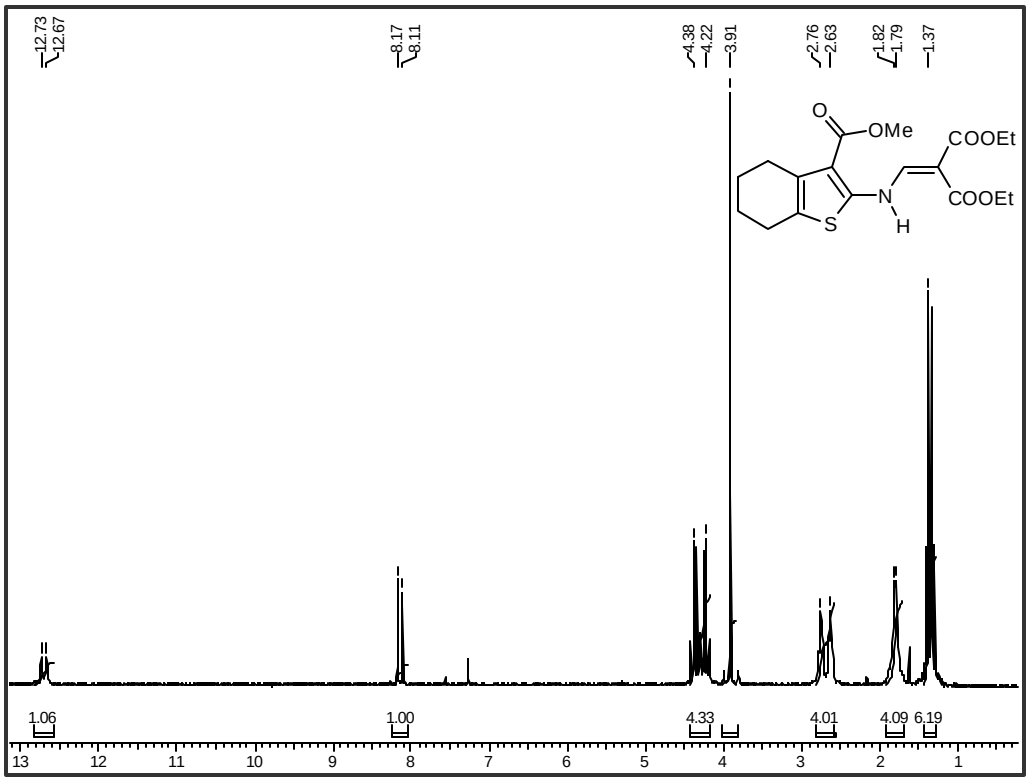
Scheme 6:



***Conditions**: **a**)(**i**) $CNCH_2COOR$, NH_4OAc, AcOH, benzene, reflux, 24hrs.; **ii**) S, Et_2NH, EtOH, 60 °C, 2hrs. **b**) Ethoxymethylene diethyl malonate, 90 °C, 90 min.*

The synthesis of the substrates is delineated as follows:

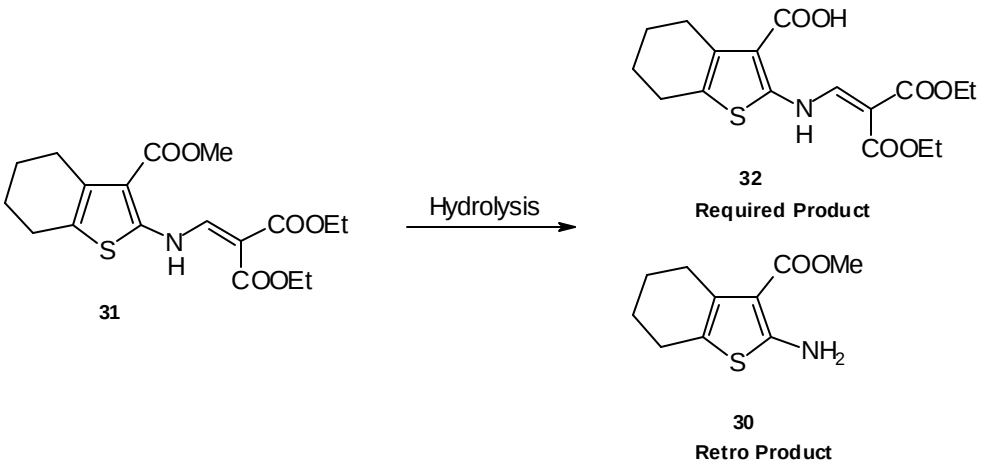
Cyclohexanone **29** was subjected to Knoevenagel condensation with cyanomethyl acetate in the presence of ammonium acetate and acetic acid. The crude product thus obtained, without isolation was then treated with sulfur in the presence of diethyl amine to give the thiophene derivative **30** in moderate yields (50-59%). ^{1}H NMR and IR spectral analysis confirmed the structure of this thiophene derivative. IR spectrum showed the presence of amine and ester at 3351 and 1651cm^{-1} respectively. ^{1}H NMR indicated the presence of the methyl moiety with the appearance of a singlet at δ 3.91. The cyclohexyl group protons appeared multiplets at δ 1.37, 2.63 and 2.76 for 4, 2 and 2 protons amine proton appeared as a broad singlet at δ 6.1. The thiophene derivative **30** was further converted to enamine **31** by condensing with diethylethoxymethylene malonate at 120 °C. IR and NMR once again confirmed the identity of the product. ^{1}H NMR spectrum displayed the required olefinic proton at δ 8.14 with the amine proton resonating at δ 12.70. The downfield shift of the proton is indicative of an intramolecular hydrogen bonding. The presence of two sets of quartets at δ 4.22 and δ 4.38 indicated the incorporation of the diethyl malonate moiety.



^{1}H NMR spectrum of compound **31** ($CDCl_3$, 200MHz)

The enamine **31** was then subjected to hydrolysis by a variety of reagents the details of which are given below. In most of the cases during hydrolysis with KOH led to the formation of retro Michael product *i.e.,* **30** (amino ester) instead of the expected acid. Finally after lot of experimentation the hydrolysis was achieved in moderate yields by treating with KOH and DMSO (60-65%).

Scheme 7:



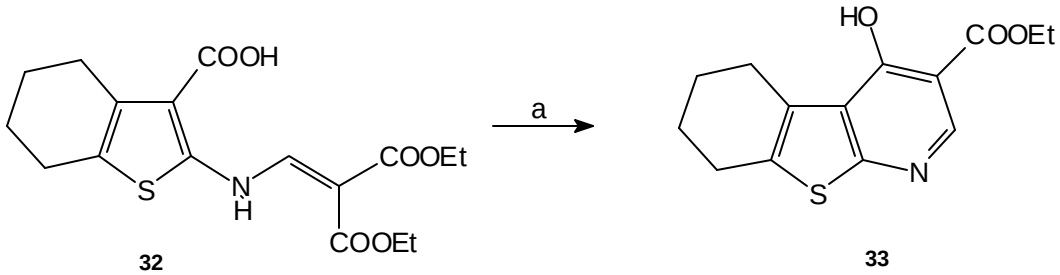
Different conditions were tried for the hydrolysis of aromatic ester and results are summarized in table 1:

Table 1:

Sl.No.	Reagents used	Temperature	Result
1	KOH/EtOH/Dioxane	60-70 ^{o}C	Retro
2	KOH/EtOH/Dioxane	Room temp.	Retro
3	KOH/EtOH	60-70 ^{o}C	Retro
4	KOH/EtOH	Room temp.	Retro
5	KOH/MeOH	Room temp.	Retro
6	KOH/THF(aq)	Room temp.(40h)	Starting material
7	KOH/THF(aq)	Refluxing (24h)	50% conversion
8	KOH/DMSO	60-70 ^{o}C	Product

Finally required acid **32** was achieved with KOH in DMSO at 60 ^{o}C. The compound **32** was then subjected to a cyclization reaction using PPE to yield thieno[2,3-b]pyridine **33** in 65% yields. IR spectrum showed the presence of hydroxy group at 3430cm^{-1} and the ester carbonyl at 1692cm^{-1}. ^{1}H NMR indicated a shift in the proton adjacent to nitrogen from δ 8.20 to δ 8.84 indicative of the formation of thienopyridine ring. The hydroxy proton appeared at δ 12.11 as a singlet. The disappearance of one of the ester moiety also confirmed the formation of the pyridine moiety.

Scheme 7:

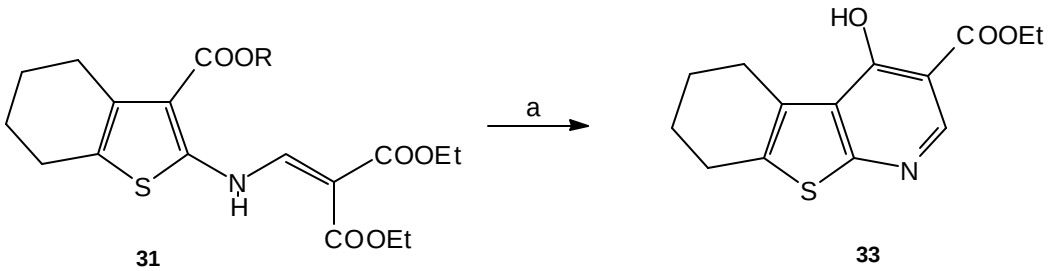


32 **33**

***Condition**: **a**) Polyphosphate ester, 180^{o}C, 10 min*

Having problems with low yields in hydrolysis of enamine carboxylate ester it was proposed to attempt directly conversion of **31** to **32**. Accordingly it was decided to perform PPE cyclization on enamine ester **31** itself. Gratifyingly when **31** was subjected to the cyclization in the presence of PPE or methanesulphonic acid-phosphoric acid (CH_3SO_3H-P_2O_5) complex good to moderate yields of the thieno[2,3-b]pyridine **33** was observed.

Scheme 8:



31 **33**

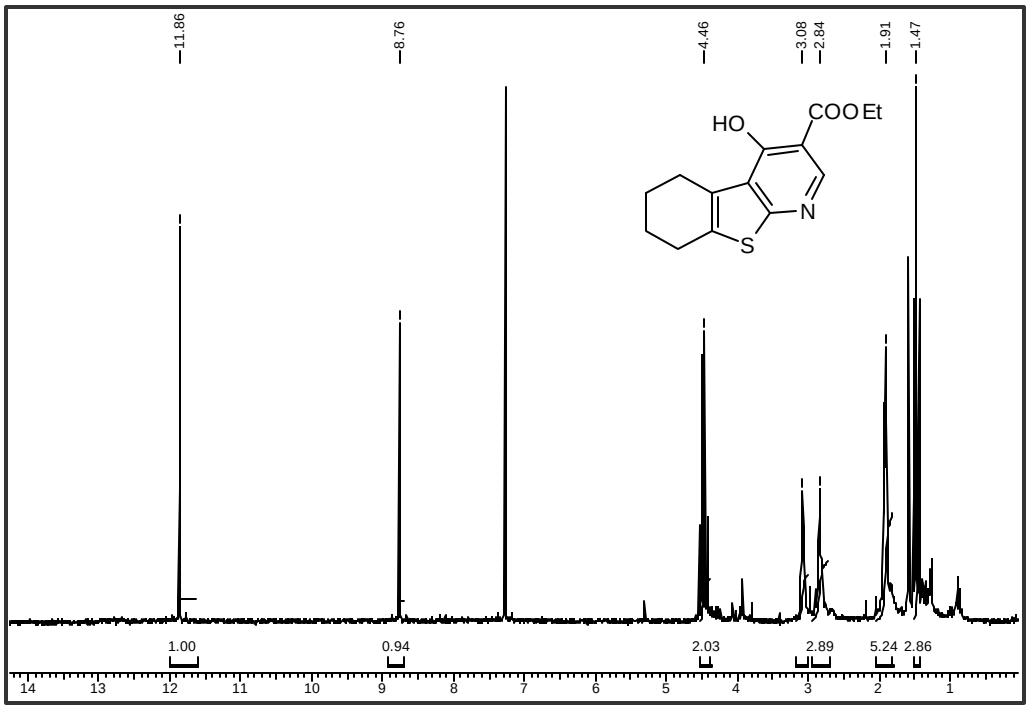
R = $-CH_3$, $-CH_2CH_3$

***a**) Polyphosphate ester, 180°C, 10 min. or P_2O_5-Methanesulphonic acid complex, 110°C, 30 min.*

In a typical reaction as shown in the above scheme PPE or $MeSO_3H$-P_2O_5 complex (10 mL of $MeSO_3H$ was treated with 1 g of P_2O_5 at 100-110 °C for 40 min) was treated with substituted thieno enamine ester **25** at 110 °C for 30 min to furnish the thieno[2,3-b]pyridine **26** in 60-70% yield as a yellow solid.

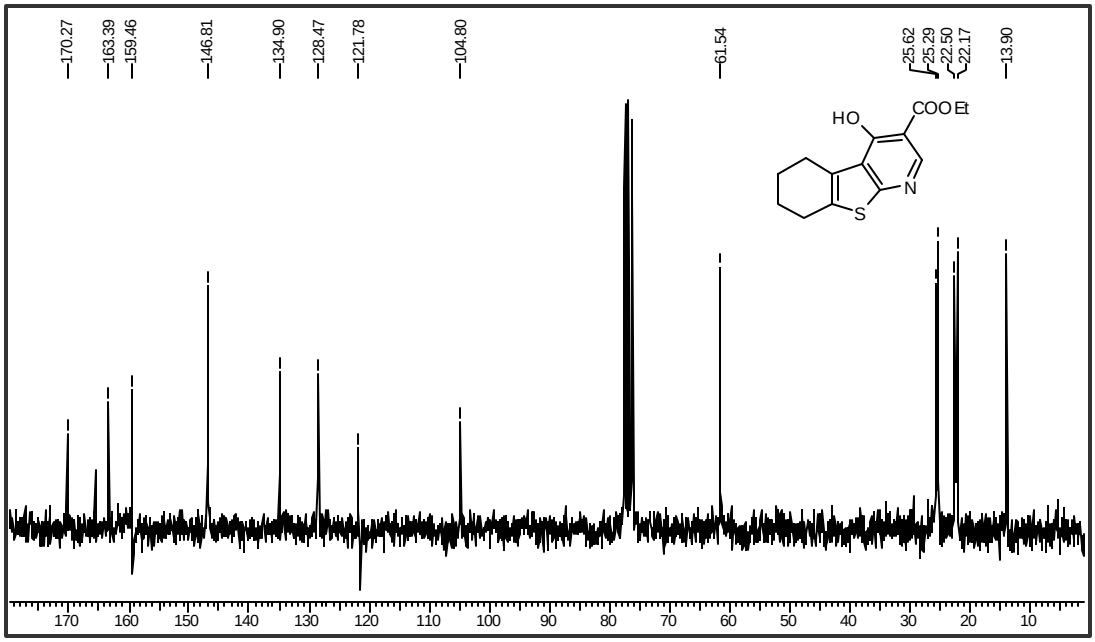
The thieno[2,3-b]pyridines for example **44** is an important basic skeleton for the synthesis of compounds like **5** and its derivatives which are effective drugs for treatment of hormone and sex hormone dependent diseases like prostatic cancer, breast cancer *etc.,*

The product **33** thus formed was characterized by IR, ^{1}H NMR, ^{13}C NMR and Mass spectroscopy. IR spectrum showed the presence of hydroxy group at 3430 cm^{-1} and the ester carbonyl at 1692 cm^{-1}. ^{1}H NMR indicated a downfield shift in the proton adjacent to nitrogen from δ 8.14 to δ 8.76 due to the formation of thienopyridine ring. The hydroxy proton appeared appreciably downfield and resonated at δ 11.86 as singlet indicative of intramolecular hydrogen bonding thereby confirming the structure. Also disappearance of one of the ester moiety was observed. In ^{13}C NMR (DEPT) appearance of a doublet at δ 146.8 indicates presence of cyclized product. In the mass spectrum a peak at 277 (M^+ 35) was observed lending further support to the proposed structure.



^{1}H NMR Spectrum of compound **33** ($CDCl_3$, 200MHz)

In order to test the generality of above methodology a variety of substituted thiophene enamine esters were prepared and subjected to cyclisation with dehydrating agents. The results have been summarized in Table-3. This methodology of cyclisation of enamine ester was found to be effective with *tri* and *tetra* substituted thiophene derivatives. Noteworthy feature of the present methodology is that it obviates the need to hydrolyze the ester group present at G3 position in thiophene system. Another interesting point is that even enamine of methyl anthranilate furnished ethyl 4-hydroxy-3-quinoline carboxylate in excellent yield. All the products formed were purified by column chromatography and the thienopyridines were characterized by spectral analysis like IR, ^{1}H NMR, ^{13}C NMR and Mass.



^{13}C NMR and DEPT spectra of compound **33** (CDCl3, 75MHz)

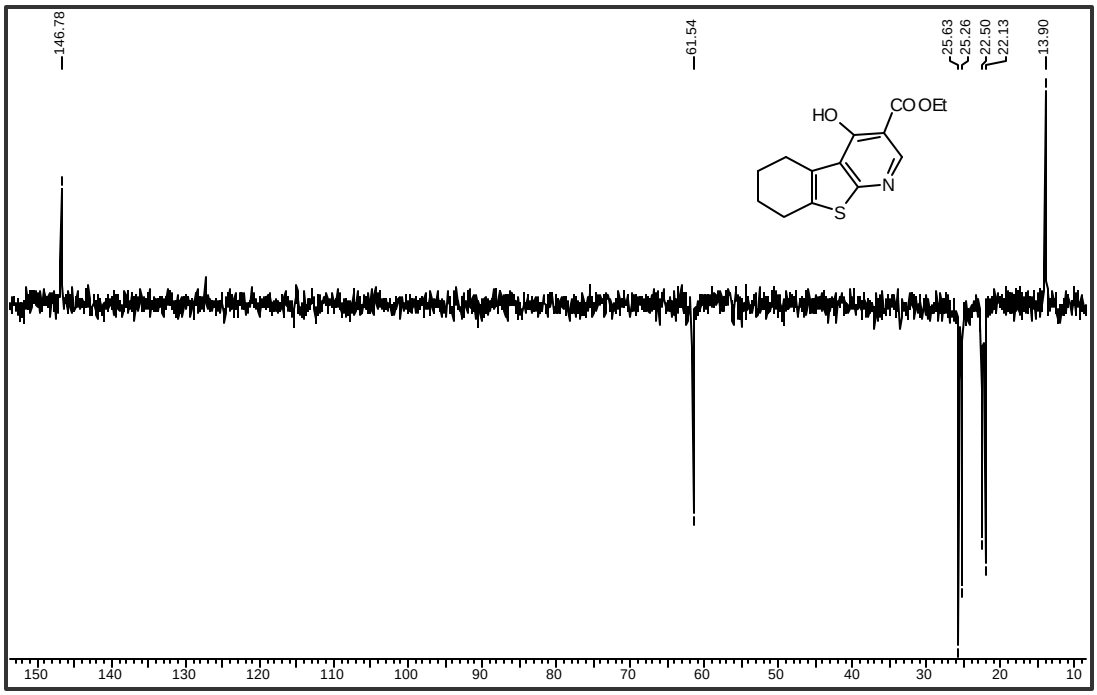
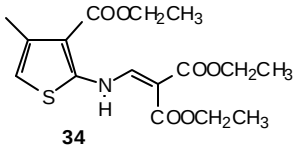
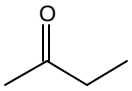
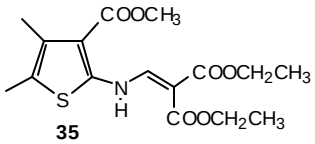
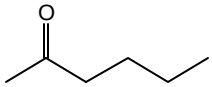
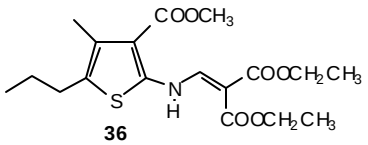
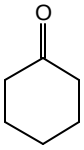
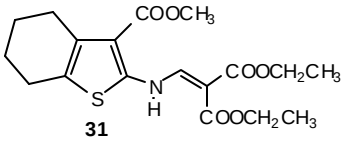
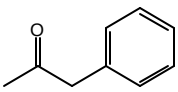
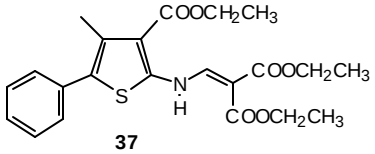
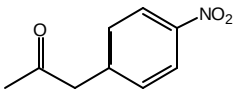
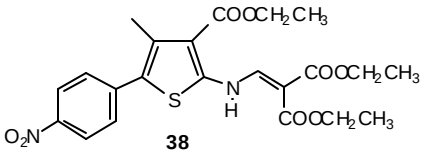
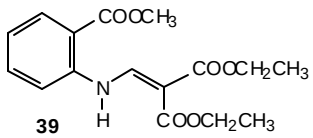
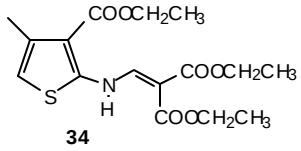
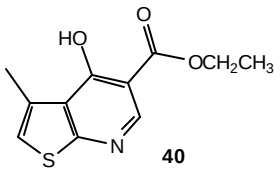
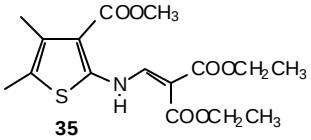
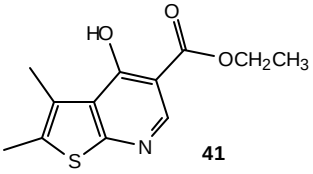
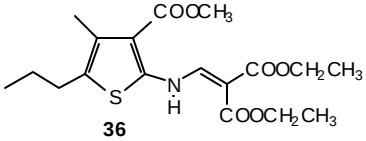
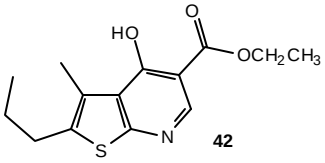
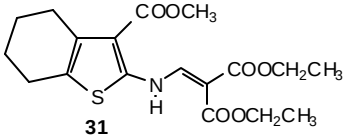
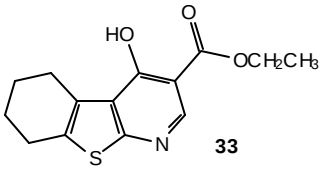
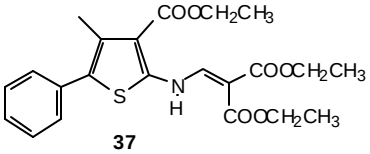
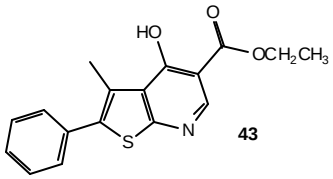
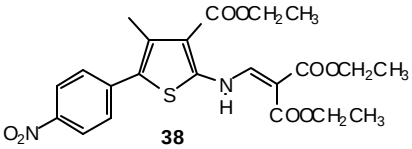
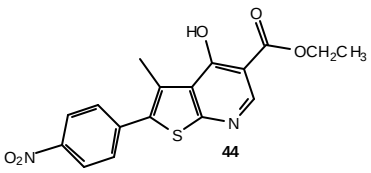
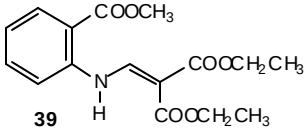
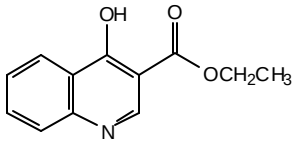


Table 2: Preparation of enamines from ketones.

Entry No.	Ketone	Enamine	Yield (%)
1.		 **34**	55
2.		 **35**	54
3.		 **36**	58
4.		 **31**	61
5.		 **37**	54
6.		 **38**	55
7.	--	 **39**	94*

* From methylanthranilate.

Table 3: Preparation of thieno[2,3-b]pyridines from enamines

Entry No.	Enamine	Thienopyridines	Yield (%)	
			A	B
1.	 **34**	 **40**	48	51
2.	 **35**	 **41**	45	50
3.	 **36**	 **42**	52	53
4.	 **31**	 **33**	58	58
5.	 **37**	 **43**	65	70
6.	 **38**	 **44**	60	63
7.	 **39**	 **45**	87	90

A. PPE as a dehydrating agent; **B**. P_2O_5-CH_3SO_3H complex as a dehydrating agent.

2.3.5 Conclusion

In conclusion, the core moiety of many gonadotropin hormones and drug molecules *viz.,* thieno[2,3-b]pyridines were readily achieved from substituted thieno enamines by using dehydrating agents like PPE / CH_3SO_3H-P_2O_5 complex. The present methodology not only reduces one step but also obviates the need to have acid which in turn are obtained in low-moderate yields without consistency. The yields obtained are moderate-good and compare well with the two steps.

2.3.6 Experimental

General procedure for the preparation of diethyl 2-[3-alkoxy carbonyl(4,5-substituted alkyl)-2-thienylaminomethylene]malonates:

a) A mixture of ketone (0.05 mol), ethyl cyanoacetate (0.05 mol), ammonium acetate (0.01 mol), acetic acid (0.04 mol) and benzene (100 mL) was refluxed for 24 h, and the water formed in the reaction was removed azeotropically by using Dean-Stark apparatus. After cooling, the reaction mixture was concentrated under reduced pressure. The residue was partitioned between dichloromethane and an aqueous sodium hydrogen carbonate solution. The organic layer was washed with aqueous NaCl solution and was dried over anhydrous Na_2SO_4 followed by filtration and concentration of the solvent under reduced pressure.

b) To an ethanolic solution of the residue was added sulfur (0.05 mol) and diethylamine (0.05 mol). The mixture was stirred at 60 ^oC for 2 h and then concentrated and the residue was extracted with ethyl acetate. The organic layer was dried over anhyd. Na_2SO_4, and further concentrated under reduced pressure. The residue thus obtained was chromatographed on silica gel using 20% EA;Pet.ether as eluent and, the product thus obtained was crystallized from ether-hexane to obtain yellowish orange crystals in ~50% yield.

c) To diethyl ethoxymethylene diethylmalonate (0.06 mol) which was taken in 100 mL round bottom flask was added the amine compound (0.06 mol). The mixture was stirred for 2 h at 120 ^oC. After cooling, ether was added to the reaction mixture to precipitate the crystals. The crystals were collected by filtration and washed once with ether, the ether layer also yielded the pale yellow-to-yellow crystals after concentration. The combined yield of the product from ketone was 45-55%.

Preparation of Polyphosphate ester (PPE): [10]

To a solution of anhydrous diethyl ether (300 mL) and alcohol free chloroform (150 mL) was added phosphorus pentoxide (150g). The mixture was then refluxed under nitrogen for 4 days. The resulting solution was decanted and concentrated to syrup on rotary evaporator. Final traces of solvent were removed by heating for 36 h at 40 ^{0}C under vacuum to obtain a viscous liquid of PPE.

General Procedure for the preparation of thienopyridines:

By using polyphosphate ester:

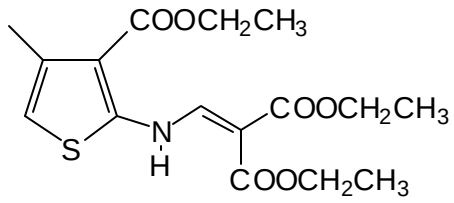
To polyphosphoric ester (PPE) (1.5 mL) was added enamine ester **25** (0.25 mmol) in small portions at 190 ^{0}C with stirring. The mixture was stirred for 10 minutes at the same temperature. The reaction mixture was poured into ice water, and then extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish the crude cyclized product **26** which was chromatographed to furnish the pure compound as a yellow solid in 45-87% yield.

By using P_2O_5-CH_3SO_3H complex:

To P_2O_5-CH_3SO_3H complex (1.5 mL) was added enamine ester **25** (0.25 mmol) in small portions at 110 ^{0}C with stirring. The mixture was stirred for 30 minutes at the same temperature. The reaction mixture was poured into ice water, and then extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over anhydrous sodium sulphate, filtered and concentrated under reduced pressure to furnish the crude cyclized product **26** which was chromatographed to furnish the pure compound as a yellow solid in 50-90% yield.

Substituted enamines:

1. Diethyl 2-(4-methyl-3-ethyloxycarbonyl-2-thienylaminomethylene)malonate (34):



Mol. Formula : $C_{16}H_{21}NO_6S$ (355)

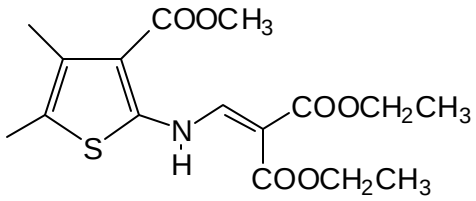
M. P. : 63 ^{O}C, Yellow colored solid

IR (cm^{-1}, in $CHCl_3$) : 3019, 2984, 2933, 1708, 1681, 1594, 1548, 1406, 1381, 1287, 1206, 1144

^{1}H NMR ($CDCl_3$, 200 MHz) : 1.36 (t, 3H, J = 7.2Hz); 1.38 (t, 6H, J = 7.3Hz); 2.37 (s, 3H); 4.2 (q, 2H, J = 7.2Hz); 4.42 (q, 4H, J = 7.3Hz); 7.52 (s, 1H); 8.22 (d, 1H, J = 13.2Hz); 12.65 (d, 1H, J = 13.18Hz)

Mass (m/z) : 355 (M^+, 39), 309(100), 295(5), 280(54), 264(5), 235(4), 220(4), 207(49), 191(81), 164(25), 139(22), 124(8), 109(4).

2. Diethyl 2-(4,5-dimethyl-3-methyloxycarbonyl-2-thienylaminomethylene)malonate (35):



Mol. Formula : $C_{16}H_{21}NO_6S$ (355)

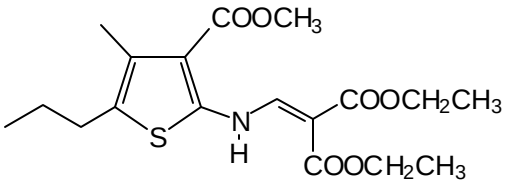
M. P. : 68 ^{O}C, Yellow colored solid

IR (cm^{-1}, in $CHCl_3$) : 3019, 2984, 2937, 1709, 1598, 1440, 1409, 1379, 1297,1208, 1083

^{1}H NMR ($CDCl_3$, 200 MHz) : 1.35 (t, 3H, J = 7.4Hz); 1.37 (t, 3H, J = 7.4Hz); 2.26 (s, 3H); 2.28 (s, 3H); 3.93(s, 3H); 4.25 (q, 2H, J = 7.4Hz); 4.40 (q, 2H, J = 7.4Hz); 8.16 (d, 1H, J = 13.2Hz); 12.70 (d, 1H, J = 13.2Hz)

Mass (m/z) : 355 (M^+, 32), 309(100), 294(19), 278(10), 236(8), 222(16), 205(52), 177(74), 153(14), 144(9), 123(8), 97(7).

3. Diethyl 2-(4-methyl-3-methyloxycarbonyl-5-propyl-2-thienylaminomethylene) malonate (36):



Mol. Formula : $C_{18}H_{25}NO_6S$ (383)

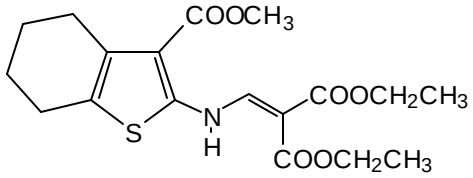
M. P. : 84 ^{O}C, Yellow colored solid

IR (cm^{-1}, in $CHCl_3$) : 3018, 2961, 2934, 1710, 1668, 1597, 1441, 1408, 1379, 1297, 1070

^{1}H NMR ($CDCl_3$, 200 MHz) : 0.96 (t, 3H, J = 7.1Hz); 1.34 (t, 3H, J = 7.3Hz); 1.36 (t, 3H, J = 7.3Hz); 1.60 (m, 2H); 2.23 (s, 3H); 2.62 (t, 2H); 3.93 (s, 3H); 4.34 (q, 4H, J = 7.3Hz); 8.14 (d, 1H, J = 13.18Hz); 12.68 (d, 1H, J =.18Hz)

Mass (m/z) : 383 (M^+, 15), 351(10), 337(100), 322(18), 308(95), 295(44), 276(31), 264(12), 232(25), 204(59), 190(14), 176(13), 163(13), 148(14), 121(11), 109(10), 97(12)

4. Diethyl 2-[3-methyloxycarbonyl-4,5,6,7-tetrahydrobenzo[b]thiophen-2-ylamino-methylene)malonate (31):



Mol. Formula : $C_{18}H_{23}NO_6S$ (381)

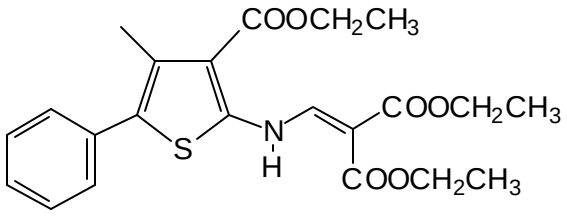
M. P. : 94 ^{O}C, Yellow colored solid

IR (cm^{-1}, in $CHCl_3$) : 3018, 2983, 2941, 1708, 1670, 1598, 1408, 1381, 1269, 1207, 1075, 1027, 755.

^{1}H NMR ($CDCl_3$, 200 MHz) : 1.37 (t, 6H, J = 7.3Hz); 1.82 (m, 4H); 2.71 (m, 4H); 3.91 (s, 3H); 4.22 (q, 2H, J = 7.3Hz); 4.38 (q, 2H, J = 7.3Hz)); 8.14 (d, 1H, J = 13.18Hz); 12.70 (d, 1H, J = 13.18Hz)

Mass (m/z) : 381 (M^+, 62), 335(100), 302(26), 285(9), 276(12), 230(61), 203(100), 170(9), 147(9), 121(6).

5. Diethyl 2-(3-ethyloxycarbonyl-4-methyl-5-phenyl-2-thienylaminomethylene) malonate (37):



Mol. Formula : $C_{22}H_{25}NO_6S$ (431)

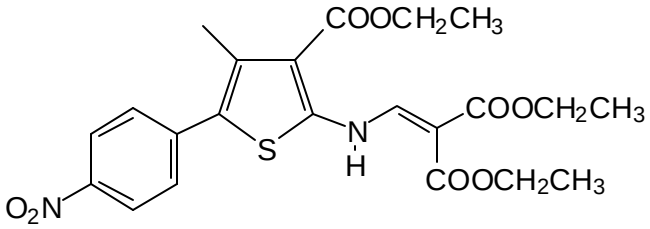
M. P. : 110 ^{O}C, Yellow colored solid

IR (cm^{-1}, in $CHCl_3$) : 3019, 2982, 2932, 1671, 1596, 1408, 1380, 1347, 1298,1202, 1062, 756.

^{1}H NMR ($CDCl_3$, 200 MHz) : 1.35 (t, 6H, J = 7.2Hz); 1.37 (t, 3H, J = 7.5Hz); 2.37 (s, 3H); 4.25 (q, 2H, J = 7.2Hz); 4.40 (q, 2H, J = 7.2Hz); 4.50 (q, 2H J = 7.2Hz); 7.54 (m. 5H); 8.26 (d, 1H, J = 13.18Hz); 12.76 (d, 1H, J = 13.18Hz)

Mass (m/z) : 431 (M^+, 100), 387(36), 385(78), 352(23), 339(21), 312(77), 267(56), 239(76), 225(36), 210(26), 171(27), 115(30), 91(30).

6. Diethyl 2-[3-ethyloxycarbonyl-4-methyl-5-(4-nitrophenyl)-2-thienylaminomethylene] malonate (38):



Mol. Formula : $C_{22}H_{24}N_2O_8S$ (476)

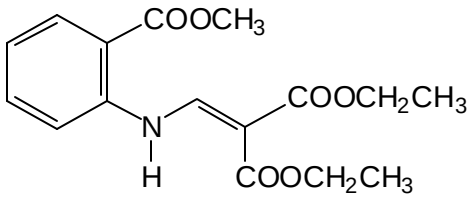
M. P. : 143 ^{O}C, Yellow solid

IR (cm^{-1}, in $CHCl_3$) : 3018, 2986, 1704, 1630, 1590, 1427, 1410, 1312, 1253, 1116, 1083, 755.

^{1}H NMR ($CDCl_3$, 200 MHz) : 1.35 (t, 9H, J = 7.1Hz); 2.45 (s, 3H); 4.25 (q, 2H, J = 7.1Hz);

4.40 (q, 2H, J = 7.1Hz); 4.50 (q, 2H, J = 7.1Hz); 7.60 (dd, 2H, J_1 =J_2 = 8.9Hz); 8.20 (d, 1H, J = 13.18 Hz); 8.30 (dd, 2H, J_1 =J_2 = 8.7Hz); 12.85 (d, 1H, J = 13.18Hz)

7. Diethyl 2-(2-methyloxycarbonylanilinomethylene)malonate (39):



Mol. Formula : $C_{16}H_{19}NO_6$ (321)

M. P. : 48 ^{O}C, Pale yellow crystalline solid

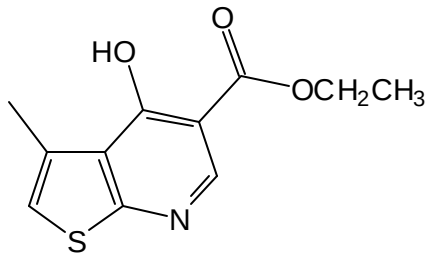
IR (cm^{-1}, in $CHCl_3$) : 3015, 2984, 1704, 1590, 1426, 1312, 1243, 1083, 755.

^{1}H NMR ($CDCl_3$, 200 MHz) : 1.35 (t, 3H, J = 7.2Hz); 1.37 (t, 3H, J = 7.2Hz); 3.97 (s, 3H); 4.26 (q, 2H, J = 7.2Hz); 4.38 (q, 2H, J = 7.2Hz); 7.10 (dd, 1H, J_1=J_2= 8.3Hz); 7.40 (d, 1H, J = 8.3Hz); 7.55 (dd, 1H, J = 7.33, 8.3Hz); 8.05 (d, 1H, J = 7.31Hz); 8.53 (d, 1H, J = 13.18 Hz); 12.70 (d, 1H, J = 13.18Hz)

Mass (m/z) : 321 (M^+, 56), 276(24), 260(100), 202(15), 188(66), 172(48), 143(43), 116(34), 89(23), 77(14).

Thieno[2,3-b]pyridines:

1. Ethyl 4-hydroxy-3-methylthieno[2,3-b]pyridine-5-carboxylate (40):



Mol. Formula : $C_{11}H_{11}NO_3S$ (237)

M. P. : 131 ^{O}C, Yellow colored solid

IR (cm^{-1}, in $CHCl_3$) : 3028, 2873, 2354, 1170, 1328, 1214, 1180, 758, 663.

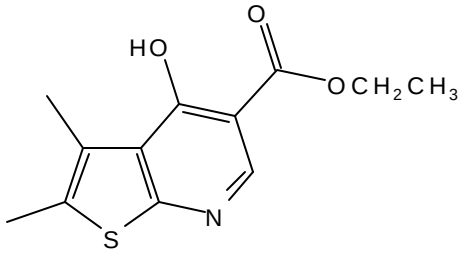
^{1}H NMR ($CDCl_3$, 200 MHz) : 1.47 (t, 3H, J = 7.32Hz); 2.63 (s, 3H); 4.47 (q, 2H, J = 7.32Hz); 6.93 (s, 1H); 8.83(s, 1H); 12.04 (bs, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz) : 14.40 (q); 17.54 (q); 62.10 (t); 105.13 (s); 120.15 (d); 123.21 (s); 132.27 (s); 148.62 (d); 165.17 (s); 168.34 (s); 170.84 (s, C=O).

Mass (m/z) : 237 (M^+, 63), 191(100), 163(100), 149(15), 130(10), 109(7), 85(7), 65(8), 57(10).

Analysis		Carbon	Hydrogen	Nitrogen	Sulphur
	Calc.:	55.68	4.67	5.90	13.51
	Found:	55.76	4.90	6.12	13.05

2. Ethyl 4-hydroxy-2,3-dimethylthieno[2,3-b]pyridine-5-carboxylate (41):



Mol. Formula : $C_{12}H_{13}NO_3S$ (251)

M. P. : 133 ^{O}C, Yellow colored solid

IR (cm^{-1}, in $CHCl_3$) : 3019, 1666, 1215, 1191, 758, 669.

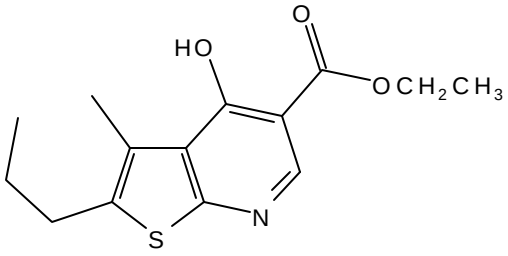
^{1}H NMR ($CDCl_3$, 200 MHz) : 1.48 (t, 3H, J = 7.28Hz); 2.46 (s, 3H); 2.53 (s, 3H); 4.47 (q, 2H, J = 7.28Hz); 8.77 (s, 1H); 12.02 (bs, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz) : 13.41 (q); 14.07 (q); 14.40 (q); 61.64 (t); 105.01 (s); 126.62 (s); 130.26 (s); 131.84 (s); 147.24 (d); 161.29 (s); 163.67 (s); 170.77 (s, C=O).

Mass (m/z) : 251 (M^{+}, 30), 205(86), 185(6), 177(100), 153(17), 144(31), 121(9), 89(9), 77(8), 65(10), 59(16).

Analysis		Carbon	Hydrogen	Nitrogen	Sulphur
	Calc.:	57.35	5.21	5.57	12.76
	Found:	5718	5.23	5.83	12.38

3. Ethyl 4-hydroxy-3-methyl-2-propylthieno[2,3-b]pyridine-5-carboxylate (42):



Mol. Formula : $C_{14}H_{17}NO_3S$ (279)

M. P. : 135 ^{O}C, Yellow colored solid

IR (cm^{-1}, in $CHCl_3$) :3023, 2860, 2348, 1169, 1214, 1180, 758, 668.

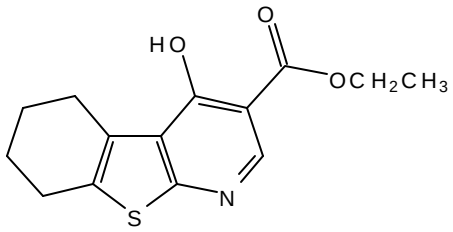
^{1}H NMR ($CDCl_3$, 200 MHz) : 1.02 (t, 3H, J = 7.28Hz); 1.48 (t, 3H); 1.71 (m, 2H); 2.54 (s, 3H); 2.80 (t, 2H); 4.50 (q, 2H, J = 7.28Hz); 8.75 (s, 1H); 12.0 (bs, 1H).

^{13}C NMR ($CDCl_3$, 75 MHz) : 13.74 (q, 2C); 14.18 (q); 24.25 (t); 29.95 (t); 61.60 (t); 105.01 (s); 122.84 (s); 126.26 (s); 137.83 (s); 147.28 (d); 159.85 (s); 163.97 (s); 170.77 (s, C=O).

Mass (m/z) : 279 (M^{+}, 40), 233(78), 227(11), 213(7), 204(100), 198(25), 184(22), 152(64), 121(14), 97(11).

Analysis		Carbon	Hydrogen	Nitrogen	Sulphur
	Calc.:	60.19	6.13	5.01	11.48
	Found:	59.97	6.14	4.95	11.21

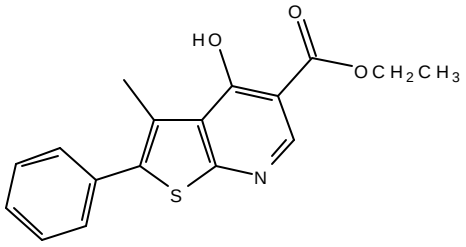
4. Ethyl 4-hydroxy-5,6,7,8-tetrahydrobenzo[4,5]thieno[2,3-b]pyridine-3-carboxylate (33):



Mol. Formula	: $C_{14}H_{15}NO_3S$ (277)
M. P.	: 146 ^{O}C, Yellow colored solid
IR (cm^{-1}, in $CHCl_3$)	: 3019, 2857, 2350, 1668, 1214, 1186, 758, 668.
^{1}H NMR ($CDCl_3$, 200 MHz)	: 1.48 (t, 3H, J= 7.28Hz); 1.91 (m, 4H); 2.84 (m, 2H); 3.08 (m, 2H); 4.46 (q, 2H, J= 7.28Hz); 8.76 (s, 1H); 11.86 (s, 1H).
^{13}C NMR ($CDCl_3$, 75 MHz)	: 13.90 (q); 22.17 (t); 22.50 (t); 25.29 (t); 25.62 (t); 61.54 (t); 104.84 (s); 121.78 (s); 128.47 (s); 134.90 (s); 146.81 (d); 159.46(s); 163.39 (s); 170.27 (s, C=O).
Mass (m/z)	: 277 (M^+, 35), 231(54), 203(100), 170(11), 149(23), 115(7), 89(5).

Analysis		Carbon	Hydrogen	Nitrogen	Sulphur
	Calc.:	60.63	5.45	5.05	11.56
	Found:	60.45	5.67	5.24	11.08

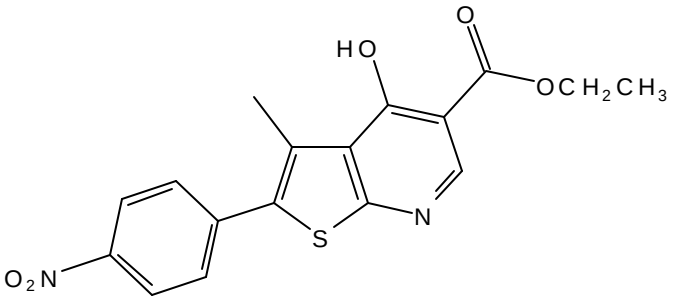
5. Ethyl 4-hydroxy-3-methyl-2-phenylthieno[2,3-b]pyridine-5-carboxylate (43):



Mol. Formula	: $C_{17}H_{15}NO_3S$ (313)
M. P.	: 168 ^{O}C, Yellow colored solid
IR (cm^{-1}, in $CHCl_3$)	: 3418, 3018, 2928, 1682, 1597, 1376, 1214, 1187, 758.
^{1}H NMR ($CDCl_3$, 200 MHz)	: 1.48 (t, 3H, J = 7.36Hz); 2.68 (s, 3H); 4.46 (q, 2H, J = 7.36Hz); 7.63 (m, 5H); 8.83 (s, 1H); 12.14 (s, 1H).
^{13}C NMR ($CDCl_3$, 75 MHz)	: 13.99 (q); 14.39 (q); 64.27 (t); 106.61 (s); 127.01 (s); 128.08 (s); 129.07 (d, 2C); 129.69 (s, 3C); 130.61 (s); 139.99 (s); 141.57(d); 154.14 (s); 168.03 (s); 168.99 (s, C=O).
Mass (m/z)	: 313 (M^+, 40), 267(100), 239(86), 238(52), 210(14), 198(11), 186(12); 171(10); 151(12), 121(10), 91(2), 77(3).

Analysis	Carbon	Hydrogen	Nitrogen	Sulphur
Calc.:	65.16	4.82	4.47	10.23
Found:	64.85	4.92	4.69	9.69

6. Ethyl 4-hydroxy-3-methyl-2-(4-nitrophenyl)thieno[2,3-b]pyridine-5-carboxylate (44):



Mol. Formula : $C_{17}H_{14}N_2O_5S$ (358)

M. P. : 180 ^{O}C, Yellow colored solid

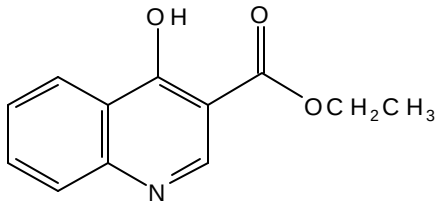
IR (cm^{-1}, in $CHCl_3$) :2922, 2855, 1692, 1603, 1458, 1375, 1349.

^{1}H NMR ($CDCl_3$, 200 MHz) : 1.49 (t, 3H, J = 7.36Hz); 2.69 (s, 3H); 4.52 (q, 2H, J = 7.36Hz); 7.68 (d, 2H, J = 8.79 Hz); 8.33(d, 2H, J = 8.79 Hz); 8.87 (s, 1H); 12.25 (s, 1H).

Mass (m/z) : 358 (M^+, 48), 312(100), 284(14), 267(9), 238(74), 210(19), 177(13), 139(13).

Analysis		Carbon	Hydrogen	Nitrogen	Sulphur
	Calc.:	56.98	3.94	7.82	8.95
	Found:	56.87	3.96	7.34	9.23

7. Ethyl 4-hydroxy-3-quinoline carboxylate (45):



Mol. Formula : $C_{12}H_{11}NO_3$ (217)

M. P. : 183^{O}C, white solid

IR (cm^{-1}, in $CHCl_3$)	: 3161, 3129, 2855, 1699, 1620, 1550, 1528, 1460, 1375, 1289, 758.
^1H NMR ($CDCl_3$, 200 MHz)	: 1.48 (t, 3H, J = 7.33Hz); 4.42 (q, 2H, J = 7.33Hz); 7.61 (dd, 1H, J = 6.60, 8.06 Hz); 7.83 (d, 1H, J = 8.06 Hz); 7.87 (dd, 1H, J = 6.6, 8,06 Hz); 8.34 (d, 1H, J = 8.06); 8.76 (d, 1H, J = 5.86 Hz); 12.37 (bs, 1H).
Mass (m/z)	: 217(M^+, 29), 172(11), 171(100), 143(25), 116(17), 115(50), 89(56), 76(15), 63(16), 53(14).

2.3.7 References

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