SYNTHETIC STUDIES TOWARD PSEUDOTHEONAMIDES, HERBARUMIN III, BICYCLIC THIOHYDANTOINS AND OXAZOLIDINONE-5-ONE

A THESIS

SUBMITTED FOR THE DEGREE OF
DOCTOR OF PHILOSOPHY
(IN CHEMISTRY)
TO

PUNE UNIVERSITY
BY

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FEBRUARY 2006

DEDICATED TO MY BELOVED PARENTS AND BROTHERS

DECLARATION

The research work embodied in this thesis has been carried out at National Chemical Laboratory, Pune under the supervision of **Dr. M. K. Gurjar**, Deputy director, and Head, Division of Organic Chemistry: Technology, National Chemical Laboratory, Pune – 411 008.This work is original and has not been submitted part or full, for any degree or diploma of this or any other University.

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CERTIFICATE

The research work presented in this thesis entitled "Synthetic studies toward Pseudotheonamides, Herbarumin III, Bicyclic thiohydantoins and Oxazolidinone-5-one" has been carried out under my supervision and is a bonafide work of **Mr. Sukhen Karmakar**. This work is original and has not been submitted for any other degree or diploma of this or any other University.

Pune-8
Date: 10-02-06

Dr. M. K. Gurjar
(Research Guide)

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Sukhen Karmakar

ABBREVIATIONS

Ac_2O	----------	Acetic anhydride
AcOH	----------	Acetic acid
AIBN	----------	2,2'-Azobisisobutyronitrile
All	----------	Allyl
$BF_3.OEt_2$	----------	Boron trifluoride diethyl ether complex
Bn	----------	Benzyl
Boc	----------	*tert*-Butoxy carbonyl
Boc_2O	----------	Di-*tert*-butyl dicarbonate
n-BuLi	----------	*n*-Butyl lithium
nBu_3SnH	----------	*n*-Tributyltin hydride
Bu^t	----------	*tert*-butyl
CSA	----------	Camphorsulphonic acid
Cbz	----------	Benzyloxy carbonyl
DCC	----------	Dicyclohexylcarbodiimide
DDQ	----------	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	----------	Diethyl azodicarboxylate
DMF	----------	*N,N*-Dimethylformamide
DMSO	----------	Dimethyl sulfoxide
DPP-Cl	----------	Diphenylphoshonic chloride
DCM	----------	Dichloromethylene
DMAP	----------	*N,N*-Dimethylamino pyridine
EDCI	----------	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochlorode
Et_3N	----------	Triethylamine
Et_2O	----------	Diethyl ether
EtOAc	----------	Ethyl acetate
EtOH	----------	Ethanol
Fmoc	----------	9-Fluorenylmethoxycarbonyl
HOBt	----------	1-Hydroxybenzotriazole hydrate
Im	----------	Imidazole
LiHMDS	----------	Lithium hexamethyl disiloxane

Me	----------	Methyl
MeI	----------	Methyl iodide
MeOH	----------	Methanol
Ms	----------	Methanesulfonyl
NMM	----------	*N*-Methylmorpholine
NMO	----------	*N*-Methylmorpholine *N*-oxide
Pd/C	----------	Palladium on Carbon
Ph	----------	Phenyl
PMB	----------	*p*-Methoxybenzyl
PMB-Cl	----------	*p*-Methoxybenzyl chloride
Py	----------	Pyridine
PTSA	----------	*p*-Toluenesulfonic acid
PhSTMS	----------	Phenylthiotrimethylsilane
PhtNH	----------	Phthalimide
TBS	----------	*tert*-Butyldimethylsilyl
TBSCl	----------	*tert*-Butyldimethylsilyl chloride
THF	----------	Tetrahydrofuran
TsCl	----------	*p*-Toluenesulfonyl chloride
TFA	----------	Trifluroacetic acid
TPP	----------	Triphenylphosphine
TFFA	----------	Trifluroacetic acetic anhydride

General remarks

- ^{1}H NMR spectra were recorded on AC-200 MHz, MSL-300 MHz, AV-400 MHz and DRX-500 MHzspectrometers using tetramethylsilane (TMS) as an internal standard. Chemical shifts have been expressed in ppm units downfield from TMS.
- ^{13}C NMR spectra were recorded on AC-50 MHz, MSL-75 MHz, AV-100 MHz, and DRX-125 MHz spectrometers.
- EI Mass spectra were recorded on Finngan MAT-1020 spectrometer at 70 *eV* using a direct inlet system.
- Infrared spectra were scanned on Shimadzu IR 470 and Perkin-Elmer 683 or 1310 spectrometers with sodium chloride optics and are measured in cm−1.
- Optical rotations were measured with a JASCO DIP 370 digital polarimeter.
- Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected.
- All reactions were monitored by Thin Layer chromatography (TLC) carried out on 0.25 mm E-Merck silica gel plates (60F-254) with UV light, I2 and anisaldehyde in ethanol as development reagents.
- All solvents and reagents were purified and dried by according to procedures given in Vogel's Text Book of Practical Organic Chemistry. All reactions were carried out under Nitrogen or Argon atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise specified. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.
- All evaporations were carried out under reduced pressure on Buchi rotary evaporator below 40 °C.
- Silica gel (60-120) mesh used for column chromatography was purchased from ACME Chemical Company, Mumbai, India.

Contents

CHAPTER - 1

SECTION–I

A novel application of a [3+2] cycloaddition reaction for the synthesis of the piperazinone ring system of the pseudotheonamide A_1 and A_2

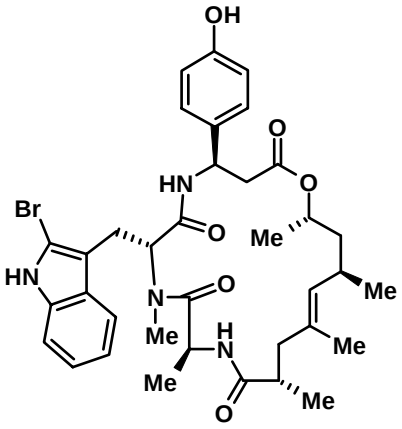
Introduction

Marine organisms are the most productive sources of bioactive compounds including peptides, alkaloids, terpenoids, fatty acid, lipids and steriods. Among them sponges are the rich sources of structurally unusual biological active peptides.[1] The exact origin of these compounds is not understood but microsymbiotins living in the sponges may have the crucial role as well as the sponge cells themselves may produces these valuable natural products. Sponges are widely found from pole to pole and from intertidal zones to deep waterthese are simple cell aggregates, which are usually considered as "most undeveloped multicellular animals". Thus sponges provide the accommodation for many organism brittle stars, bivalves, gastropods, crustaceans, and annelid worms are common guests. In addition to these macroorganisms, bacteria, blue-green algae, and dinoflagellates are observed in many species.[2] It is therefore reasonable to believe that some sponge metabolites are produced by the symbiotic microorganisms. In fact, certain classes of compounds are structurally identical. The isolation, characterization and evaluation of biological activity of peptides from marine sponges are a paramount important area of research from long time back. These peptides exhibit pronounced activities such as insectidal, antimicrobial, antiviral, antitumor, tumor promotive, anti-inflammatory and immunosuppressive action. Some of these peptides act as effective drugs or as a lead compound in drug discovery while others have proven useful in studies directed towards the elucidation of biochemical pathways.[3]

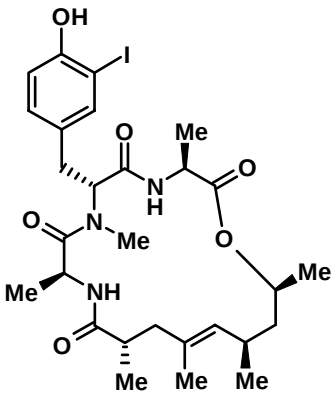
Today, a vast numbers of challenging complex peptide molecules have been isolated and fully characterized from bioactive sponges and this is because of the advancement of reverse phase HPLC, chiral chromatography and development of characterization techniques by spectroscopy especially 2D NMR and FAB mass.

Bioactive sponge peptides

Jaspamide (**1**) and geodiamolide A (**2**) the first bioactive peptides from sponges of the order Choristida (*Jaspls* sp.)[4] were cyclic depsipeptides sharing similar structural features: presence of an 11-carbon hydroxy acid and a halogenated aromatic amino acid.



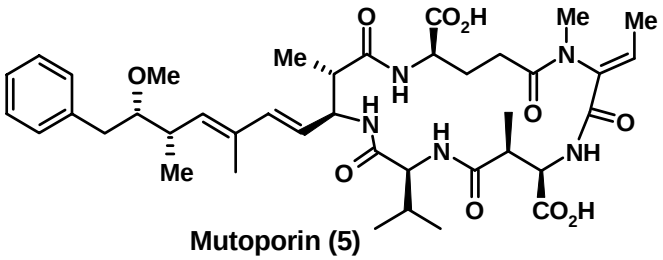
Jaspamide (1)



Geodiamolide A (2)

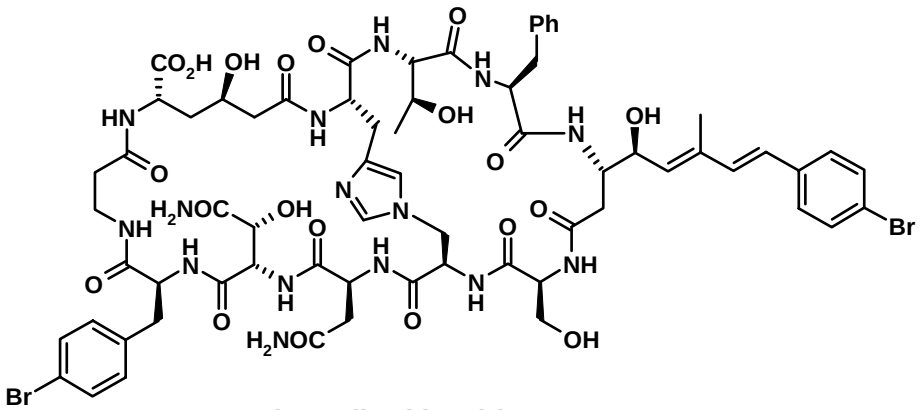
Sponges of two genera *Discodermia* and *Theonella* of lithistida have proved to be a rich source of bioactive metabolites. Most of the secondary metabolites reported from the sponges of this order are nitrogenous *viz.*, isocyano or amino sesquiterpenes, indole derivatives, tetramic acids and peptides.[5] Similarity between metabolites of lithistid sponges and those isolated from the blue-green algae raised the question of the true producer of these metabolites.[6] It had been proposed that soft bodies sponges have a higher probability of containing bioactive compounds than those with hard bodies, because they need chemical defense against predators. However, *Discodermia kiiensis* and calyculin-containing *D. calyx,* which not only have hard bodies, but also epiphytes, contain large amount of bioactive metabolites. This is the case for other sponges of the order lithistida. Discodermins[7] were the first bioactive peptides isolated from marine sponges, from *Discodermia kiiensis* as antimicrobial constituents. They are tetradecapeptides with the *N*-terminus blocked by a formyl group and the *C*-terminus lactonized with the ninth (Thr) residue from the *N*-terminus.

Motuporin (**5**)[8] has been isolated from the Papua New Guinean *Theonella swinhoei* (Lithistida sponge). It is a cyclic pentapeptide with potent inhibitory activity against protein phosphatase. This peptide may provide direct evidence for the participation of symbiotic blue-green algae in the biosynthesis of cyclic peptides from sponges.



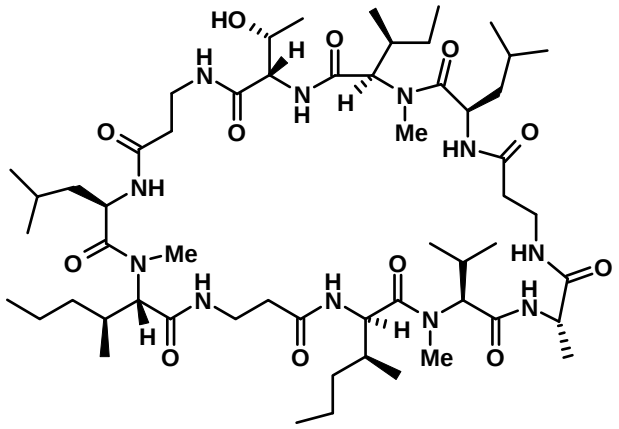
Mutoporin (5)

Theonellamide F (**6**),[9] an antifungal and cytotoxic cyclic dodecapeptide, exhibits a characteristic structural feature, especially because of the presence of a histidinoalanine bridge. Another unusual amino acid, (3*S*,4*S*,5*E*,7*E*)-3-amino-4-hydroxy-6-methy1-8-(*p*-bromophenyl)-5,7-octadienoic acid (Aboa), was interesting in view of biogenetic considerations, since closely related amino acid, 3-amino-9-methoxy-2,6,8-trimethyl-l0-phenyl-decadienoic acid (Adda) is found in microcystins,[10] hepatotoxic cyclic peptides, and (2*S*,3*R*,5*S*)-3-amino-2,5,9-trihydroxy-10-phenyldecanoic acid (Ahad) is contained in scytonemin A,[11] a peptide with calcium antagonistic activity, both of which were reported from blue-green algae. Also a biogenetically related δ-hydroxy acid was found in cryptophycin,[12] a cytotoxic peptide from a blue-green algae. To date, β-amino acids of these classes have never been encountered in peptides from bacteria, fungi, or plants. Therefore, it is likely that a symbiotic blue-green alga (algae) play(s) important parts in the production of theonellamide F.



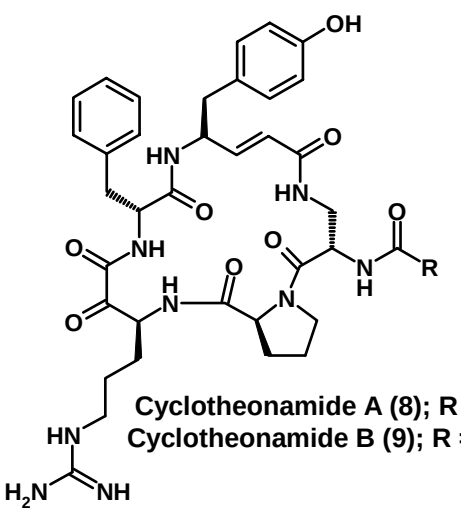
Theonellamide F (6)

Higa *et al*., reported[13] the isolation of three new cyclic peptides, barangamides B, C, and D (**7**) and a new depsipeptide, theonellapeptolide IIe along with known theonellapeptolides Ia, Id, Ie, IId from the sponge *Theonella swinhoei* collected in Baranglompo Island, Indonesia.

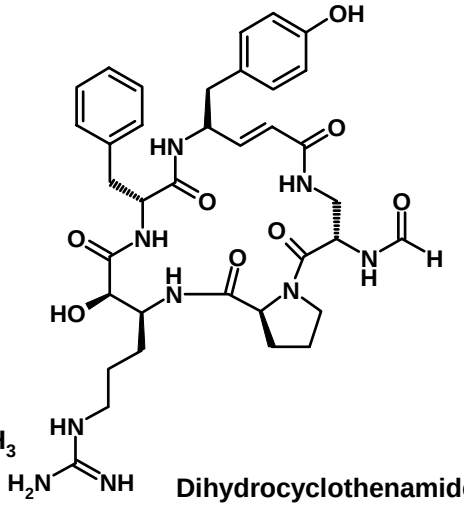


Barangamide D (7)

The cyclotheonamide A (**8**) and B (**9**) were isolated from the marine sponge *Theonella swinhoei* collected off Hachijo-jima Island, 300 km south of Tokyo, and are unusual cyclic peptides containing two new amino acids, α-ketohomoarginine (k-Arg) and vinylogoustyrosine (v-Tyr).[14]

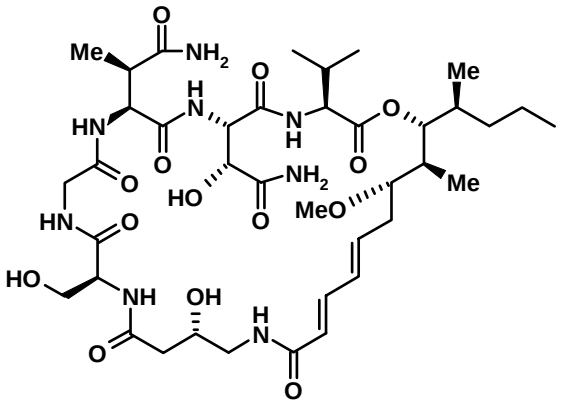


Cyclotheonamide A (8); R = H
Cyclotheonamide B (9); R = CH_3



Dihydrocyclothenamide A (10)

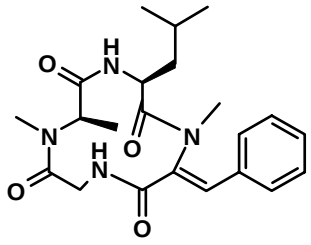
Recently, another bioactive cyclic peptide, nagahamide A (**11**), was isolated from the marine sponge, *Theonella swinhoei* by Fusetani *et al.*[15] It was characterized by seven-residue depsipeptide containing three unusual amino acids and a polyketide acid. The structural features of nagahamide A, especially the presence of the polyketide acid with a terminal (*E,E)*-dienoic moiety, were unprecedented among the peptides from natural sources.



Nagahamide A (11)

Peptide conformation and its effect on biological activities

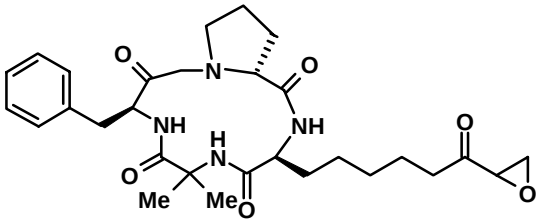
The significant pharmacology diversity is the function of peptide structure and conformation, which are in turn dictated by constituted amino acids, many of which are nonribosomal amino acids. These non-coded or nonribosomal amino acids include D-series amino acids, *N*-alkylated and α,β-dehydro amino acids. Nonribosomal amino acids can have certain degree of effects on the secondary structure of the peptide. As for example, *N*-Me residues commonly found in the natural peptide molecules exhibiting reduced preferences for the *trans* conformations normally assumed by secondary amides and this effect can lead to biological relevant β-turn structures similar to those often induced by proline residues.[16] *N*-substituted peptides may also show enhanced hydrophobicity and improved stability to proteolytic enzymes, which can increase bioavailability and therapeutic potential. Fungal metabolite such as tentoxin (**12**), cyclosporine,[17] marine sponge natural products such as the jaspamides (**1**), keramamides, motuporins (**5**) are all having *N*-methyl residues and show pronounced biological activity.



Tentotoxin (12)

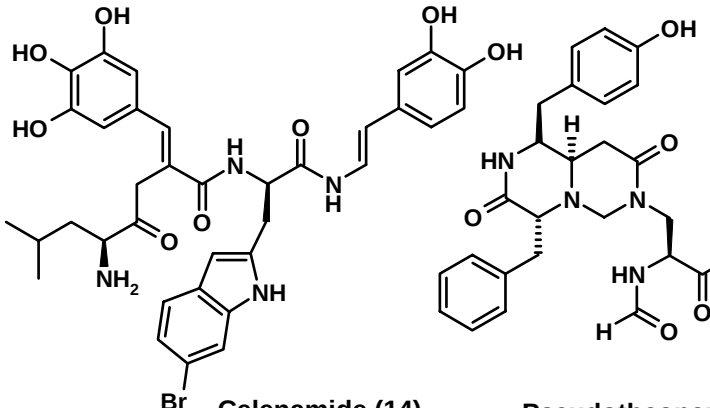
Non-ribosomal amino acid of the category α,α-disubstituted amino acid residues, such as Aib and α-ethyl alanine[18] are frequently found in natural bioactive peptide molecule These non-coded amino acid residues rigidify the peptide backbone through the formation

of helixes and β-turns.[19] These organized structures are responsible for the interesting biological activity of the peptaibols.[20] α,α-disubstituted residues are also found in bioactive peptide chalmydocin (**13**).[21]

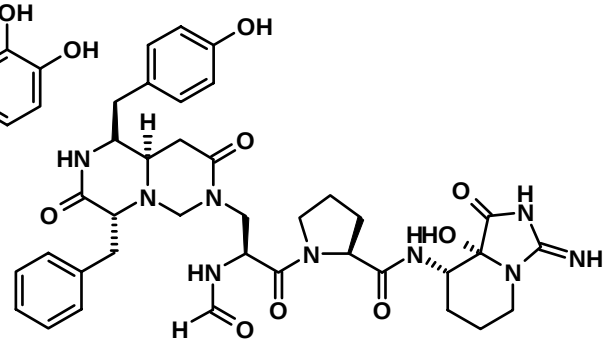


chalmydocin (13)

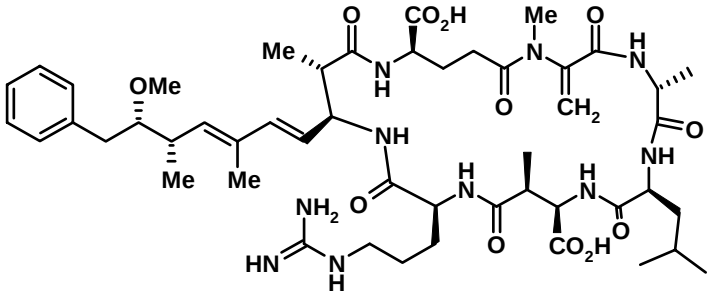
Another important nonribosomal amino acid residues, dehdydroamino acid (Dhaa), are widely found in natural peptides. Dhaa residues also have rigidifying effect on peptide backbone, which can increase peptide-receptor affinity by reducing the entropic costs of binding.[22] According to conformational energy calculations, dehydro residues allow conformations that are not permitted with saturated residues.[23] Dehydropeptides show increased stabilities to degradative enzymes. Dhaa residues sometimes occur in active sites and in naturally occurring enzyme inhibitors, where they may serve as electrophiles in nucleophilic addition reaction.[24] There are a large numbers of peptides having Dhaa residues such as celenamide (**14**),[25] microcystin LR (**16**),[10] nudularin,[26] theoneolamide F (**6**), pseudotheonamide D (**19**), pseudotheonamide C (**20**).[27] Sometimes Dhaa residues are masked by intramolecular Michael addition, giving rise to elaborate macrocyclic structures such as pseudotheonamide A_1 (**17**), A_2 (**18**) and B (**15**).[27]



Celenamide (14)



Pseudotheonamide B (15)

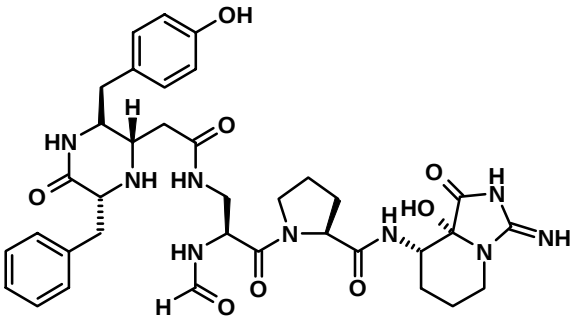


Microcystin LR (16)

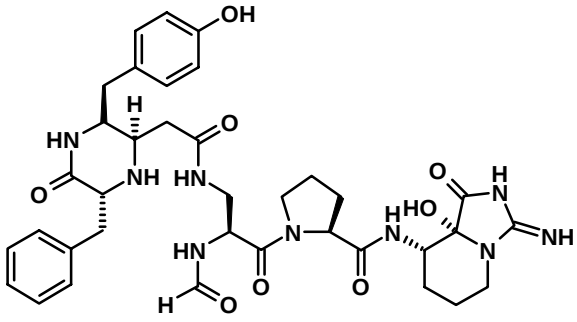
Cyclic structures reduce peptide conformational freedom and often result in high receptor binding affinities by reducing unfavorable entropic effects. For this reasons the cyclic peptides often make promising lead compounds in drug discovery.[28]

Examination of the extract of *T. swinhoei* sample led to isolate six new peptides related to the cyclotheonamides: pseudotheonamides A_1 (**17**), A_2 (**18**), B (**15**), C (**20**), D (**19**) and dihydrocyclotheonamide A (**10**).[27] Significantly, they possess potent inhibitor activity against serine proteases including thrombin, trypsin and plasmin. Pseudotheonamides A_1 (**17**), A_2 (**18**) and B (**15**) possess the rare piperazinone and piperadinoiminoimidazolone rings system.

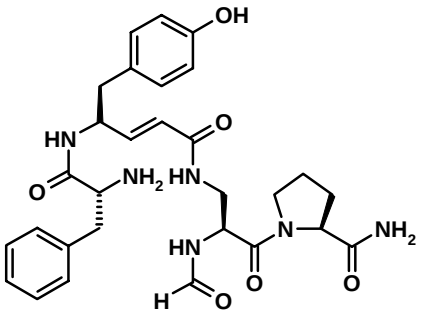
Because of structural features and pronounced biological activity, we started our research work towards the synthesis of pseudotheonamide A_1 (**17**) and A_2 (**18**). Although several methods are reported in the literature[37] to construct piperazinone ring system, we interested to develop a conceptually new idea for the preparation of fully substituted piperazinone ring system.



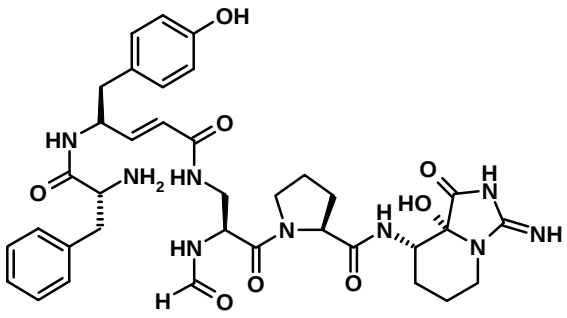
Pseudotheonamide A_1 (17)



Pseudotheonamide A_2 (18)



Pseudotheonamide D (19)



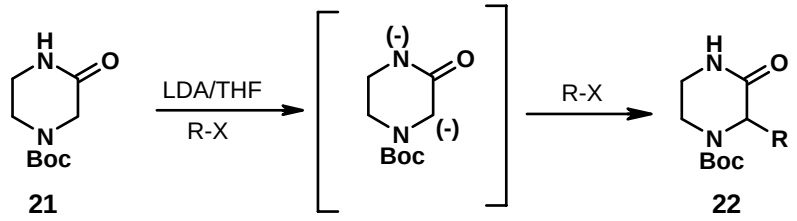
Pseudotheonamide C (20)

Brief overview on various methods for the construction of piperazinone ring system

The piperazinone ring is similar to a conformationally constrained peptide and could lead to improved receptor binding interaction due to reduced entropy. It serves as an effective and versatile template for the construction of biologically active molecules.[29-31] Therefore, many methods have been developed for the synthesis of piperazinones with substitution at different ring positions. Few important methods are summarized below:

Rsne and his co-workers[32] prepared 3-substituted piperazinone derivative (**22**) by the alkylation of protected piperazinone dianion.

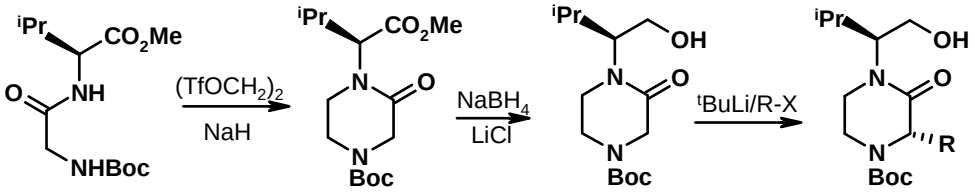
Scheme 1



21 **22**

Quirion and *et al*., [33] prepared 3-alkyl substituted-2-oxopiperzinone **26** during the efficient synthesis of conformationally constrained peptidomimetics. The method involves a direct diastereoselective alkylation of the *N*-(hydroxyalkyl)-2-oxopiperazine **25**, prepared in three steps from methyl L-leucinate.

Scheme 2

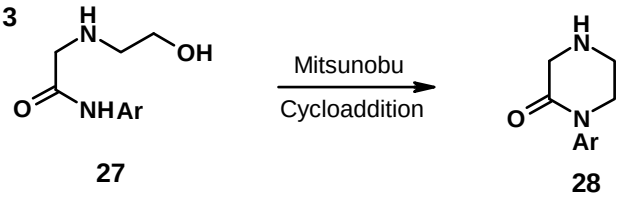


23 **24** **25** **26**

Weissman *et al.,*[34] reported a practical two-pot synthesis of *N*-arylpiperazinones **28** from the corresponding aniline. The key transformation is a selective intramolecular

Mitsunobu cyclodehydration of an amido alcohol **27**. A series of *N*-arylpiperazinones were prepared in good yield (Scheme 3).

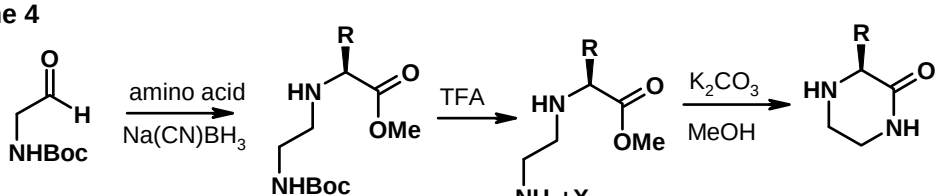
Scheme 3



27 **28**

Hansen and his co-workers[35] devised a new protocol for synthesis of piperazinone ring and showed its application in the synthesis of constrained mimetics of the growth hormone secretagogue NN703. This method involves base medium cyclisation of δ-amino ester **31** to form piperazinone derivative **32** (Scheme 4)**.**

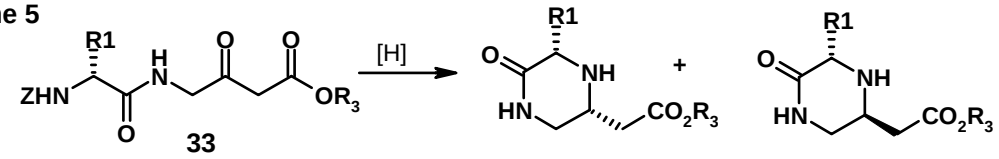
Scheme 4



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

Muñiz *et al.* reported[36] the stereoselective generation of 3,5-disubstituted and 3,5,6-trisubstituted 2-oxopiperazine by intramolecular reductive amination of β-keto esters derived from Z-Xaa-Gly-OH and Z-Xaa-Yaa-OH dipeptides, respectively (Scheme 5).

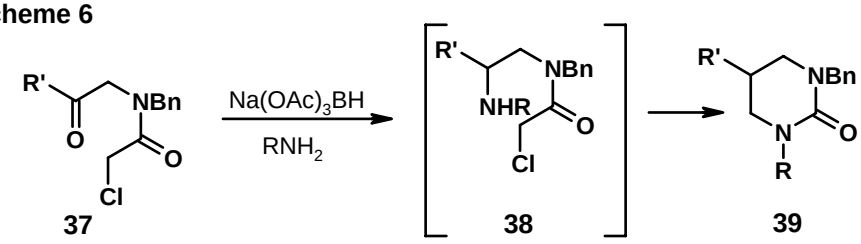
Scheme 5



33 **35** **36**

Dinsmore *et al.*,[37] synthesized 2-piperzinones **39** by a tandem reductive coupling and SN_2–cyclisation of a 2-chloro-N-(2-oxoalkyl) acetamide **38** and a primary amine. The method is convenient for diversity-oriented synthesis, since a wide variety of amines may be used in the ring forming reaction to produce *N*-substituted piperazinones (Scheme 6).

Scheme 6

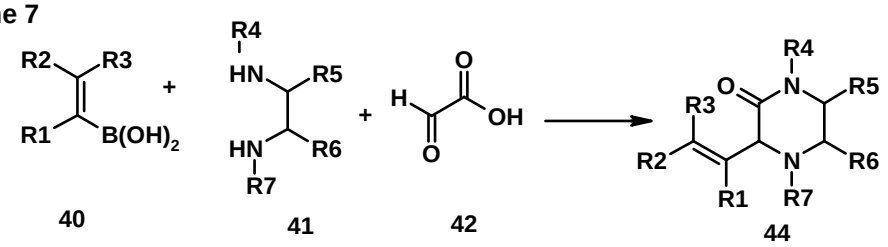


37 **38** **39**

Petasis and his coworkers[38] have discovered that alkenyl, aryl and heteroaryl

boronic acids react with 1,2-diamines and glyoxylic acid to give directly in one step the corresponding 2-oxopiperazines. Similarly, the use of monoprotected 1,2-phenylenediamine leads to benzopiperazinones (1,2,3,4-tetrahydroquinoxalin-2-ones)

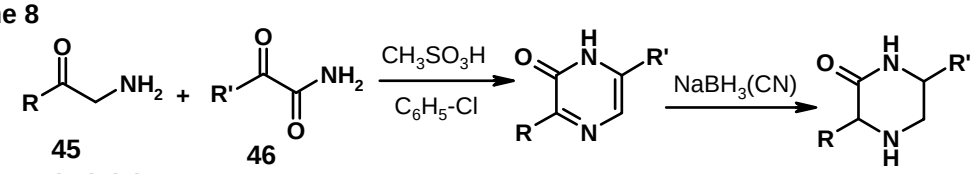
Scheme 7



40 41 42 44

Horne *et al.,*[39] constructed 3,5 and 3,6-linked pyrazinones and their reduction to the requisite piperazinones with sodium cyanoborohydride in the total synthesis of marine sponge bisindole alkaloids dihydrohamacanthins (Scheme 8).

Scheme 8

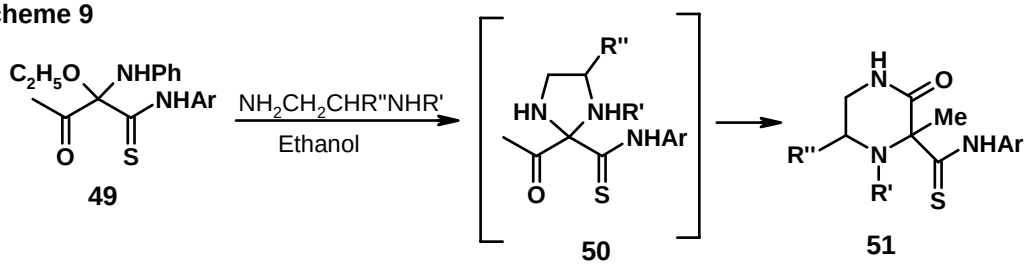


45 46 47 48

R, R'= indolyl group

Piperazinone derivatives were prepared by reactions of 2-anilino-2-ethoxy-3-oxothiobutanoic acid anilide **49** with aliphatic 1,2-diamines. An unusual ring expansion of the intermediate 1,3-diazines leads to 1,4-diazines[40] **51** (Scheme 9).

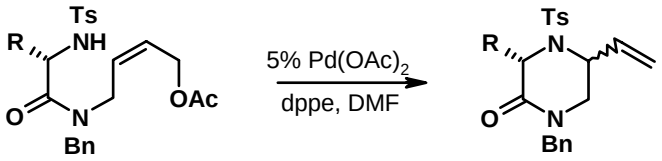
Scheme 9



49 50 51

Polia *et al.,*[41] have developed synthetic route toward 3,5-disubstituted piperazinones **53**. The method relies upon a 6-*exo* intramolecular process between a sulfonylated nitrogen atom of amino acid derivative and a η^3-allyl-palladium moiety. Cyclization process generates the two possible (*cis* and *trans*) diastereoisomers, whose ratio depends on the amino acid employed. The bulkier the acid residue, the higher the observed *cis*: *trans* ratio.

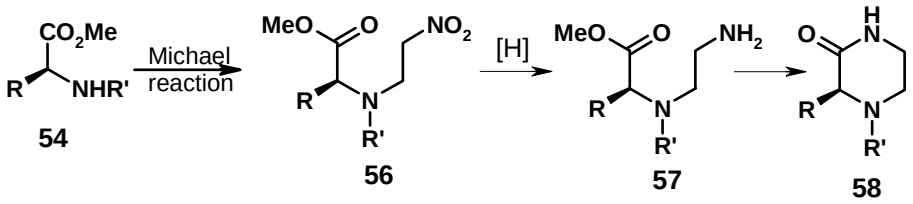
Scheme 10



52 **53**

Polliniet *et al.*,[42] reported the synthesis of 2-piperzininones bearing variable substituents at the C-3 position of the heterocyclic nucleus. The method involves spontaneous intramolecular amide bond formation of δ-amino ester **57** obtained from intermolecular Michael addition of amine **54** and nitroethylene followed by reduction of NO_2 group to provide oxopiperazine nucleus **58** (Scheme 11).

Scheme 11



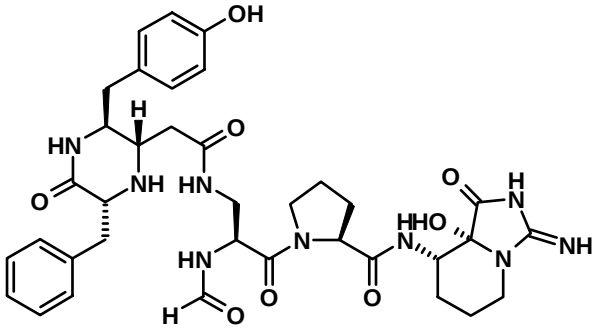
54 **56** **57** **58**

CHAPTER - 1

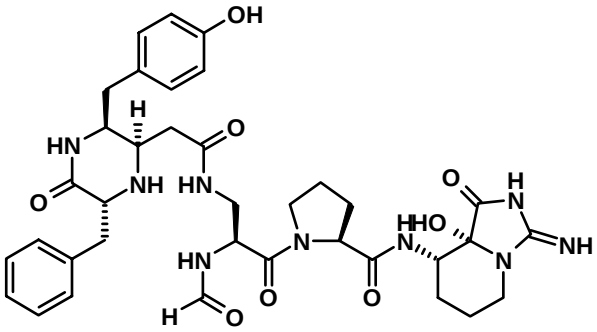
SECTION – II

An approach towards piperadinoiminoimidazolone ring system: Synthesis of bicyclic thiohydantoins

Recently, six new peptides pseudotheonamides A_1 (**17**), A_2 (**18**), B (**15**), C (**20**), D (**19**), and dihydrocyclotheonamide related to the cyclotheonamides have been isolated from the marine sponge *Theonella swinhoei*.[17] Significantly, they possess potent inhibitor activity against serine proteases including thrombin, trypsin and plasmin. Pseudotheonamides A_1 (**17**) and A_2 (**18**) possess in their structural framework the rare piperazinone and piperadinoiminoimidazolone rings system.



Pseudotheonamide A_1 (17)



Pseudotheonamide A_2 (18)

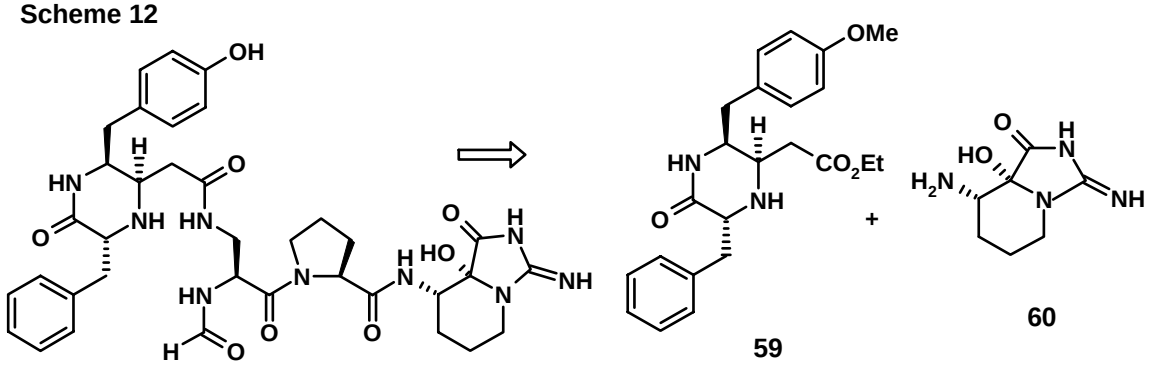
The structures and absolute stereochemistries of pseudotheonamide A_1 (**17**) and A_2 (**18**) were established by exhaustive interpretation of spectroscopic data such as the ^1H, ^{13}C NMR, COSY, HMQC, HOHAA, HMBC and HR-FABMS.[17] Both the peptides, pseudotheonamide A_1 (**17**) and A_2 (**18**) are linear pentapeptide, embracing the rare piperazinone and piperadinoiminoimidazolone ring systems, proline and 2,3-diamino acid residues. Compounds **17** and **18** are two epimers differing at the chiral center Tyr C_β, with absolute configurations (*S)* and (*R*) respectively.

The lack of sufficient amount of sample from natural source to complete biological activity evaluation coupled with interesting structural parameters, we undertook the

synthetic investigation of two natural products pseudotheonamide A_1 and A_2.

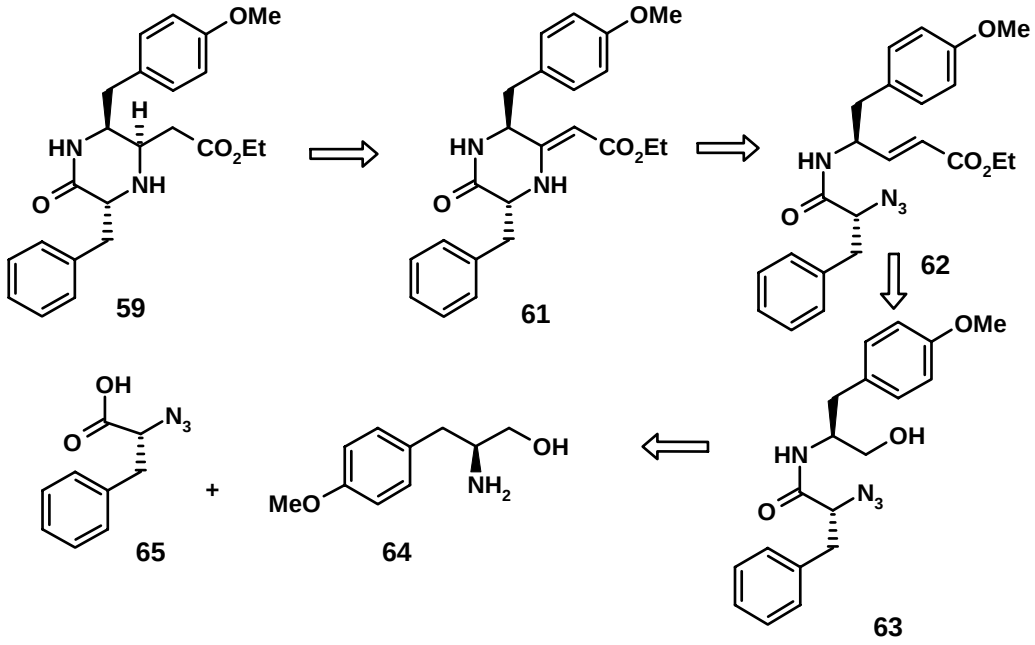
The retrosynthesis of pseudotheonamide A_2 (**18**) began with the disconnection strategy of amide bonds leading to piperazinone derivative (**59**) and piperadinoimino-imidazolone derivative (**60**) as the key fragments (Scheme 12).

Scheme 12



Our first concern was to develop a synthetic scheme for the piperazinone ring moiety. We wish to develop an intramolecular [3+2] cycloaddition between azide and α,β–unsaturated ester as delineated in Scheme13, as a proposed strategy.

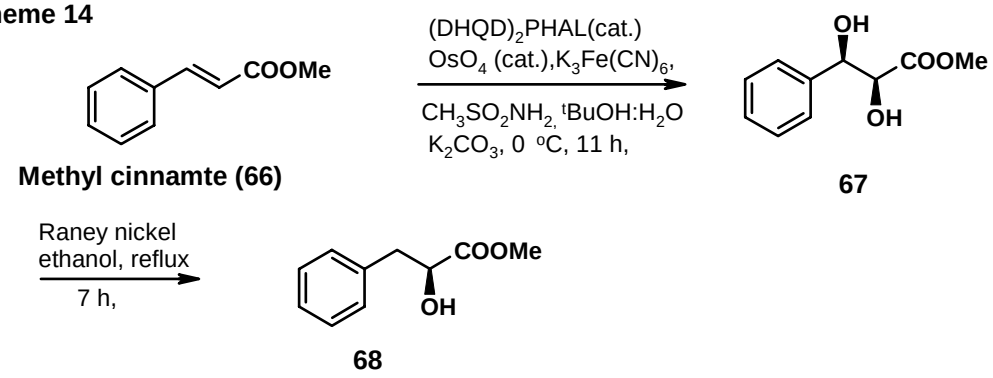
Scheme 13



The preparation of (*R*)-2-azido-3-phenylpropanoic acid (**65**) was contemplated *via* the Sharpless asymmetric dihydroxylation (ADH)[43] as a key step. Accordingly, methyl cinnamate was subjected to ADH reaction by using $(DHQD)_2PHAL$ as a chiral ligand, and OsO_4 and $K_3Fe(CN)_6/K_2CO_3$ as oxidants in *t*-BuOH and water mixture to afford the diol

67. The spectral and optical rotation data of **67** were identical with the reported values.[44] By refluxing **67** with Raney nickel (KALCAT®)[45] in a degassed ethanol, the benzylic OH group was selectively reduced to afford compound **68**. The ^{1}H, ^{13}C NMR spectra and elemental analysis confirmed the assigned structure. For example, in the ^{1}H NMR spectrum, the two double-doublets were located at 3.12 and 3.02 ppm (each integrating for one proton assigned) due to benzylic methylenes. The peak at 4.47 ppm (double-doublet) was due to the methine proton bearing the hydroxyl group. Rest of the protons resonated at their expected chemical shift values. The structure was further confirmed by the ^{13}C NMR spectrum, where benzylic carbon appeared at 40.2 ppm (Scheme 14).

Scheme 14



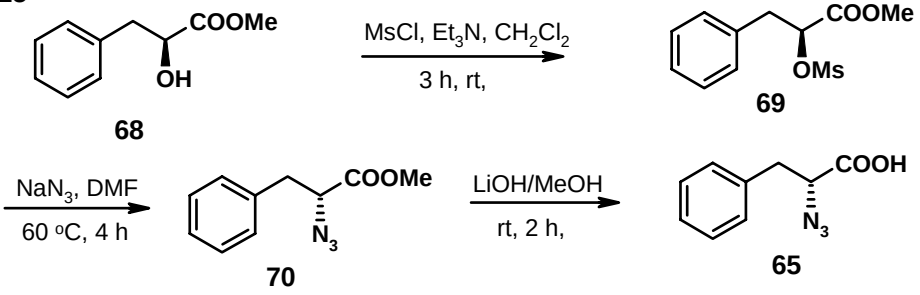
Methyl cinnamte (66)

67

68

Treatment of compound **68** with methanesulphonyl chloride and Et_3N in CH_2Cl_2 furnished the sulphonate derivative **69**. The presence of mesyl group was evident from the singlet located at 2.74 ppm in the ^{1}H NMR spectrum of **69**. The S_N2 displacement of OMs of **69** by N_3 was carried out by using sodium azide in DMF to afford the azide **70**. The structure of **70** was confirmed by the ^{1}H, ^{13}C NMR, IR spectra and by elemental analysis. In the ^{1}H NMR spectra of both **69** and **70**, the resonance due to H-3 were clearly apparent as a double-doublet where as the chemical shifts of all other protons were comparable, that due to H-2 showed an upfield shift of 1.09 ppm. In the ^{13}C NMR spectrum, signal due to C-2 was located at 63.1 ppm along with other signals at their expected positions. In addition, the IR spectrum exhibited a characteristic absorption at 2110 cm^{-1} indicating the presence of N_3 group in compound **70**. Hydrolysis of methyl ester of compound **70** was performed by using LiOH in methanol at room temperature to produce the desired acid **65**. The ^{1}H, ^{13}C NMR spectra and elemental analysis confirmed the structure of **65**. The ^{1}H NMR spectrum of **65** showed the disappearance of methoxyl signal (Scheme 15).

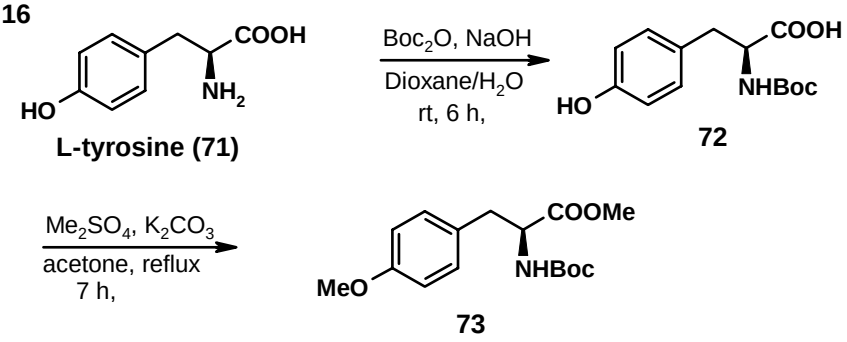
Scheme 15



68 69 70 65

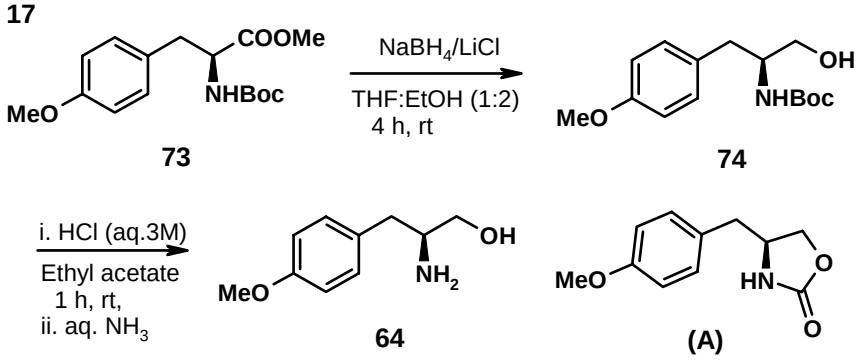
L-Tyrosine (**71**), on treatment with Boc_2O and NaOH in dioxane/H_2O, gave the *N*-Boc derivative (**72**),[46] which was heated under reflux with dimethyl sulphate and K_2CO_3 in dry acetone for 7 h to obtain the methyl tyrosinate derivative **73**. In the ^{1}H NMR spectrum of **73**, the presence of two methoxyl groups were confirmed at 3.70 and 3.72 ppm while *t*-butyl group appeared as a singlet at 1.42 ppm. The structure was further confirmed by the ^{13}C NMR spectrum, where two methoxyl carbons resonated at 51.6 and 54.3 ppm (Scheme 16).

Scheme 16



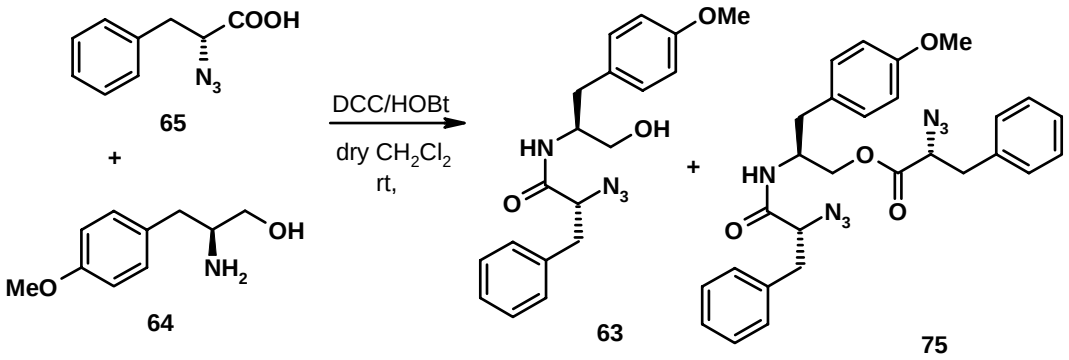
The ester functionality present in **73** was reduced by stirring with $LiBH_4$ [*in situ* prepared from equimolar ratio of LiCl and $NaBH_4$ in THF: C_2H_5OH (1:2)] for 4 h to afford **74**. In the ^{1}H NMR spectrum, apart from the absence of methoxyl group, a multiplet between 3.46-367 ppm due to hydroxylmethyl group appeared. The rest of the signals were in accordance with the proposed structure. In addition, the ^{13}C NMR spectrum of **74** showed only one peak at 54.8 ppm due to aromatic methoxy group. The peak at 63.0 ppm was assigned to methylene carbon. To deprotect the *N*-Boc group from **74**, TFA was used however, the oxazolidinone derivative (**A**) resulted.[47] Therefore, **74** was treated with 3M aqueous HCl in ethyl acetate at room temperature followed by base treatment to furnish *O*-methyl tyrosinol (**64**)[48] supported by the ^{1}H and ^{13}C NMR spectra.

Scheme 17



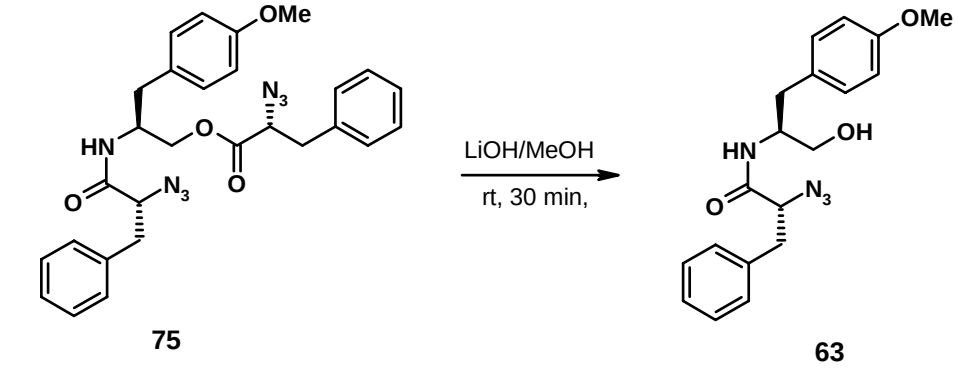
The coupling reaction between the acid (**65**) with amino alcohol (**64**) was performed in the presence DCC/HOBt[49] in CH_2Cl_2 to furnish amide derivative **63** along with the ester **75** in 8:1 ratio. The formation of compound **75** was due to subsequent esterification of **63** with **65** under the reaction condition. However, decreasing the amount of acid with respect to amino alcohol did not change the above ratio. The structures of both **63** and **75** were thoroughly characterized by the ^1H, ^{13}C NMR, IR, mass spectra followed by elemental analysis. In the ^1H NMR spectrum of **63**, the three signals appearing at 2.69 (m, 2H), 3.10 (dd, J = 5.9, 14.4 Hz, 1H), 3.25 (dd, J = 4.8, 14.4 Hz, 1H) ppm were assigned to two benzylic methenes. A double-doublet at 4.18 (J = 4.8, 5.9 Hz) and a multiplet at 4.04 ppm were assigned to two methine protons bearing azido and NH groups. A sharp singlet at 3.78 and a multiplet at 3.46 ppm were due to the methoxyl and hydroxylmethyl groups respectively. All aromatic protons resonated between 6.79-7.45 ppm. In the ^{13}C NMR spectrum, the amide carbonyl carbon appeared at 168.8 ppm. In addition, two benzylic carbons resonated at 36.0 and 38.4 ppm. Rest of the carbon signals were located at the expected positions of the assigned structure. The IR spectrum of **63** exhibited two characteristic absorption peaks at 1665 and 2144 cm^{-1} due to C=O groups of the amide and N_3 respectively. In the mass spectrum, the highest molecular ion peak at *m/z* 365 (M^++1) was observed. The structure of **75** was established by the spectral data. In the ^{13}C NMR spectrum, the signals at 168.1 and 169.9 ppm indicated the presence of carbonyl carbons of amide and ester groups. The three benzylic carbons resonated at 36.4, 37.5 and 38.5 ppm. The rest of the carbon signals appeared at their typical chemical shift values. The IR spectrum exhibited the characteristic absorption peaks at 2160 (N_3), 1753 (C=O of ester group), 1675 (C=O of amide group) cm^{-1} (Scheme 18).

Scheme 18



The hydrolysis of compound 75 **with LiOH in methanol afforded the parent compound** 63**. This hydrolyzed sample was identical with the earlier sample (Scheme 19).**

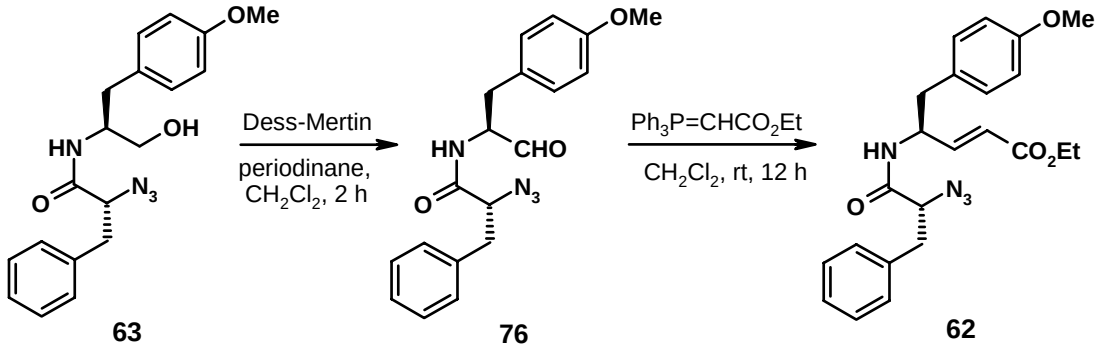
Scheme 19



Our next goal was the installment of a α,β-unsaturated ester system on **63** for which the oxidation with Dess Martin periodinane reagent[50, 51] in CH_2Cl_2 afforded the required aldehyde **76**. The crude aldehyde **76** was immediately treated with excess of ethoxycarbonylmethylenetriphenylphosphorane in CH_2Cl_2 at ambient temperature to furnish the *(E)*-isomer **62**. The structure was determined from the analysis of the ^{1}H, ^{13}C NMR, IR spectra and elemental analysis. The ^{1}H NMR spectrum of **62** showed signals at 1.27 (t, J = 7.17 Hz) and 4.20 ppm due to ethyl ester group. The olefinic proton appeared at 5.62 (double-doublet, J = 1.9, 15.4 Hz) ppm indicating the presence of *trans* double bond. The signals between 6.25-7.40 ppm were due to aromatic and one olefinic proton. Further its ^{13}C NMR spectrum showed olefinic carbons at 121.4 and 146.1 ppm. The two benzylic carbons resonated at 38.0 and 39.3 ppm, while the carbonyl carbons at 165.5 and 167.6 ppm. In the IR spectrum of **62**, the characteristic peaks of N_3, amide and α,β-unsaturated ester appeared at 2108, 1715, and 1659 cm.$^{-1}$ The elemental analysis was satisfactory with

the structure of **62** (Scheme 20).

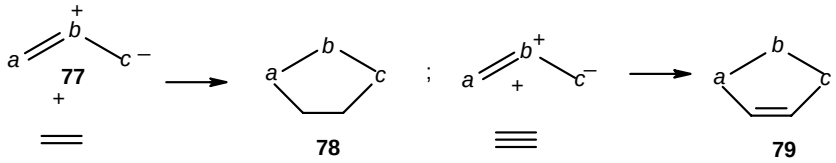
Scheme 20



Short account of 1, 3-dipolar cycloaddition: azides as an useful dipole

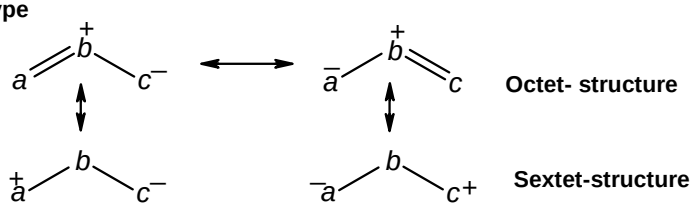
A 1,3-dipole is defined as a structure a-b-c that undergoes 1,3-dipolar cycloaddition reactions with alkene or alkyne (Scheme 21).

Scheme 21

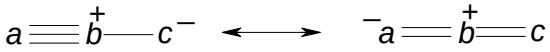


Primarily, 1,3-diploes can be divided into two different types: the allyl anion type and the propargyl/allenyl anion type. In allyl type dipole two possible resonance structures in which the centers have an electron octet, and two structures in which a or c has an electron

Allyl anion type



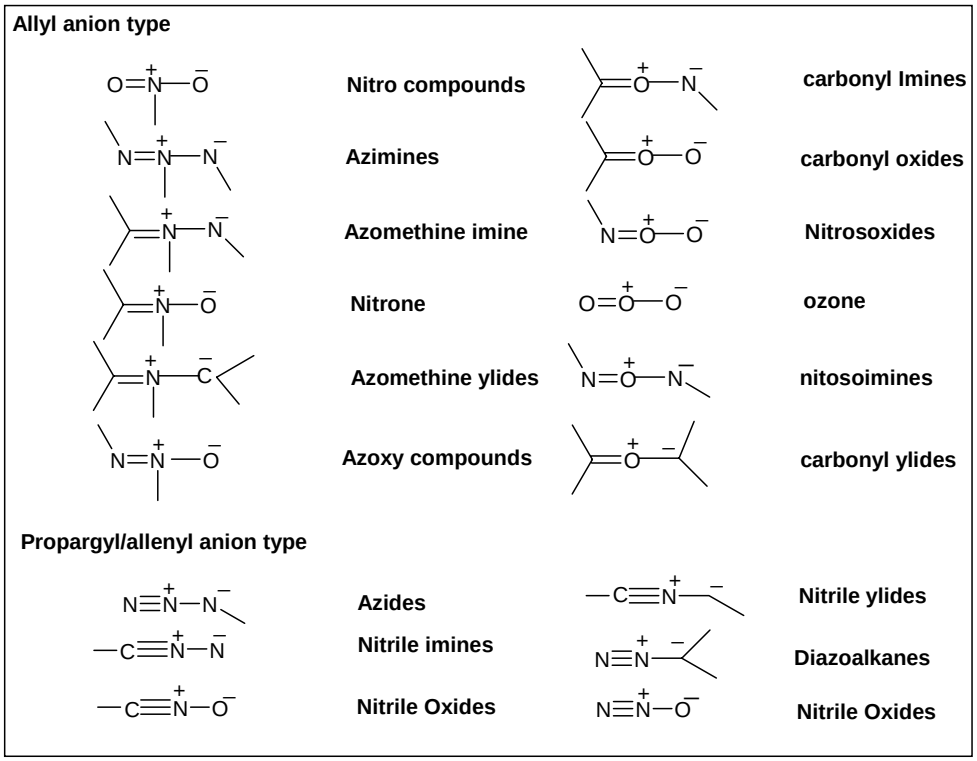
propargyl/allenyl anion type



sextet, can be drawn. The central atom (b) can be nitrogen, oxygen or sulfurthe 1, 3-dipoles consist mainly of elements from main group IV, V and VI. Since parent 1, 3-dipoles consist of elements from the 2nd row, and considering above limitation on the central atom of the dipole, a limited number of structures can be formed by permutations of N, C and O atom. 12 dipoles of allyl anion type and 6 dipoles of propargyl/allenyl type are obtained

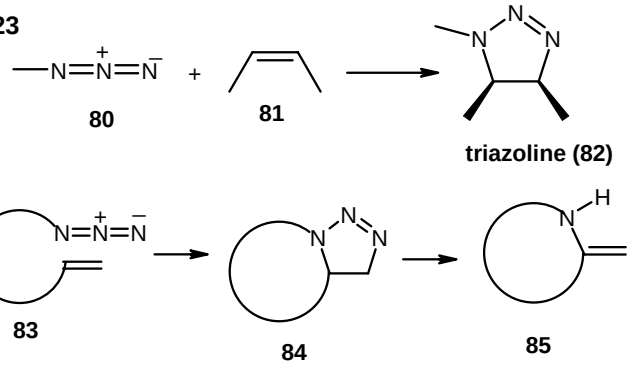
(Chart 1). The 1,3-dipolar reactions of the parent 1,3-dipoles, with alkenes, and alkynes involve 4π electrons from the dipole and 2π electrons from the alkene. The 1,3-dipoles reaction proceeds via a concerted mechanism and it is thermally allowed [$4\pi_s+2\pi_s$]. Thus three p_z orbitals of the 1,3-dipole and two p_z orbitals of the alkene both combine

Chart 1



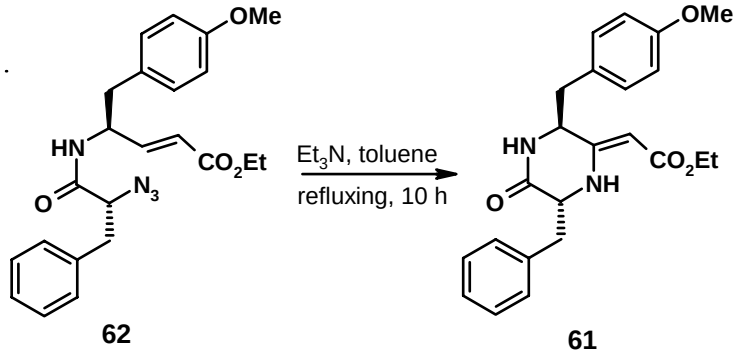
*suprafacially. The 1,3-dipolar reaction of an azide with an alkene leads to the formation of triazoline (**82**). For alkenes containing an EWG substituent high regioselectivity is obtained. The intermolecular 1,3 DC reactions of azide with alkene are most frequently slow at rt and need more time. However, intramolecular 1,3-DC reactions of an azide and olefin are very facile at rt in most of the cases or under heating conditions and resulting trizolines (**84**) on heating eliminates nitrogen to provide nitrogen hetrocycles (**85**).*

Scheme 23



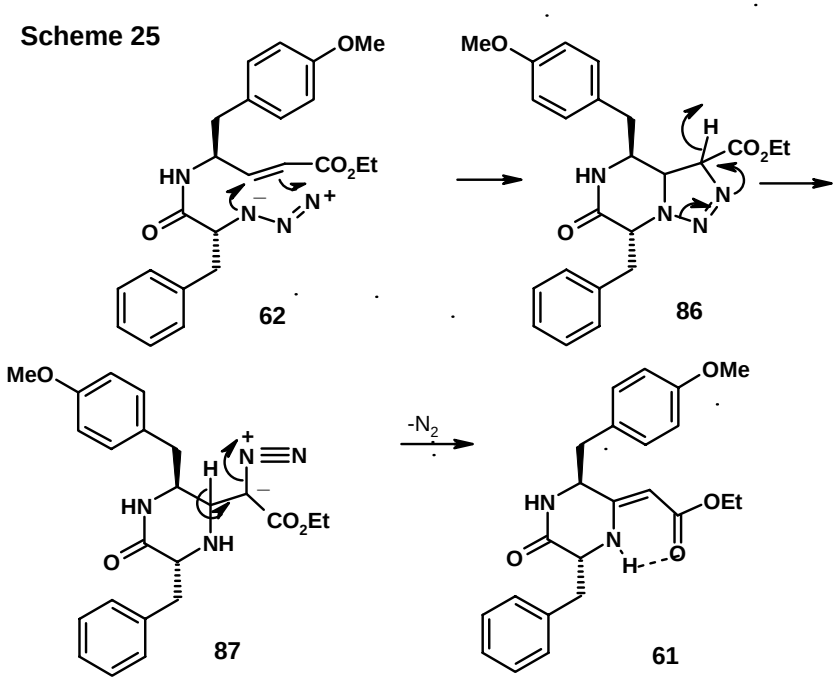
The next key step was the [3+2] intramolecular cycloaddition reaction between the azide and C=C.[52,53] Thus, compound **62** was heated under reflux with catalytic Et_3N in dry toluene. After 6 h, TLC showed two new spots, however, further refluxing for 4 h provided only one major spot. Chromatography on silica gel, the reaction mixture gave **61**.

Scheme 24



It was believed that intramolecular [3+2] cycloaddition under thermal condition between azido group and C=C of **62** initially formed the unstable triazoline intermediate (**86**), which on continuous heating isomerised to the diazoamine derivative **87**. Subsequent elimination of nitrogen gas with concomitant 1,2-H shift[54] formed the vinylogous urethane derivative **61**. The internal hydrogen bonding (as shown in Scheme 25) stabilized the (*Z*)-configuration of exocyclic double bond.[55]

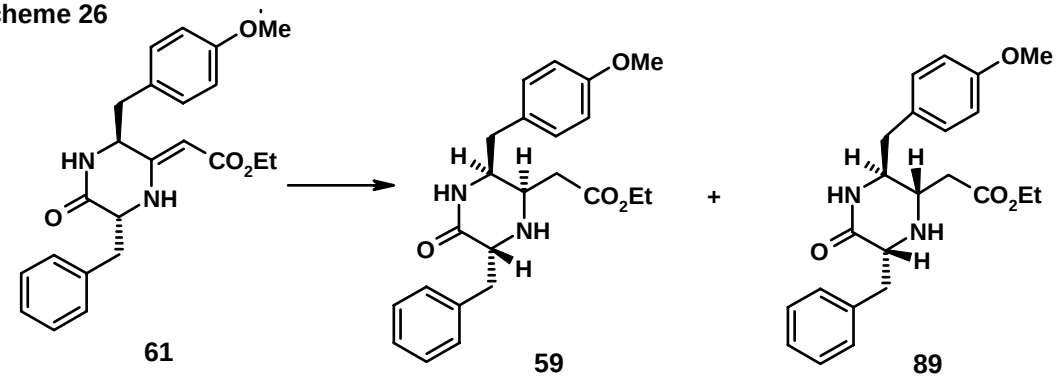
Scheme 25



The structure of **61** was thoroughly investigated by the ^{1}H, ^{13}C NMR, IR, and mass spectra coupled with elemental analysis. For instance, in the ^{1}H NMR spectrum a triplet at 1.25 (J = 7.1 Hz) and a quartet at 4.10 (J = 7.1 Hz) ppm accounted for OCH_2CH_3 group. The olefinic proton appeared as a singlet in the high field region at 4.57 ppm indicating the presence of enamine group. In the ^{13}C NMR spectra, the olefinic carbons (C_α and C_β) were identified at 126.8 and 156.9 ppm. The significant shift of C_β (C_β = 156.9) compared to that of **62** (C_β = 121.1 ppm) was suggested due to nitrogen attached to the double bond. In the IR spectrum of **61**, the characteristic peak due to N_3 group at 2100 cm^{-1} disappeared. The mass spectra exhibited the peak at *m/z* 394 due to M^+ ion.

Our end game was the stereoselective reduction of enamine double bond of **61**. Accordingly, compound **61** was treated with sodium cyanoborohydride[56] in methanol while maintaining the pH at 4.0 with intermittent addition of 5% HCl to furnish a 7:3 mixture of piperazinones **59** and **89**, which were easily separated by silica gel chromatography. To improve the selectivity of reduction, catalytic hydrogenation[57] in the presence of Pt-C was performed. Indeed, the selectivity improved significantly to 9:1 of **59**: **89** (Scheme 26). Both the intermediates are present as the fragments of the natural products **17** and **18**.

Scheme 26



Reagents	ratio of 59: 89	yield (%)
$NaCN(BH)_3$/MeOH pH = 4.0	7:3	90
Pt/C, Methanol, H_2 atm, 50 psi	9:1	94

The structures and relative stereochemistries of **59** and **89** were established the ^{1}H, ^{13}C NMR, IR, NOESY and COSY spectral analysis and elemental analysis. For example, in the ^{1}H NMR spectrum of **89** the peak corresponding to the proton Tyr H_β appeared at 3.00 ppm, and showed coupling (J = 9.0 Hz) with the Tyr H_γ indicating their *trans* relationship. The other two ring protons namely, Tyr H_γ and Phe H_α were identified at 3.38 (dt, J = 2.5, 10.0, 12.5 Hz) and 3.63 (dd, J = 3.5, 9.0 Hz) ppm respectively. Two benzylic protons Phe H_β and Phe $H_{\beta'}$ were resonated at 2.36 and 2.82 ppm as two sets of doublet-doublet with coupling constants 10.2 and 13.7 Hz and remaining two benzylic protons Tyr H_δ and Tyr $H_{\delta'}$ appeared at 2.94 (dd) and 3.43 (dd) (J = 1.5 and 12.5 Hz) ppm, while Tyr H_α and Tyr $H_{\alpha'}$ at 2.42 (dd, J = 7.5, 15.0 Hz) and 2.67 (dd, J = 2.5, 15.0 Hz) ppm. All other peaks also resonated at their typical chemical shift values. The structure of **89** was also supported by its ^{13}C NMR spectrum where two benzylic carbons Tyr C_δ, Phe C_β and Tyr C_α, showed the signals at 37.1, 37.7, 38.6 ppm and three piperazinone ring carbons including Tyr C_β and Tyr C_γ, Phe C_α and methoxyl resonated at 55.2, 55.3, 58.2 and 59.8 ppm. The NOSEY spectrum of **89** showed a strong interaction between Tyr H_β and Phe H_α indicating their *cis*-relationship. This observation in NOSEY and coupling constant value in the ^{1}H NMR ($J_{TyrH\beta,\ TyrH\gamma}$ = 9.0 Hz) evidently confirmed that compound **89** had stereochemical assignment as indicated. Further elemental analysis supported the assigned

structure. Similarly, ^{1}H NMR and ^{13}C NMR of **59** showed the peaks at the expected chemical shift values. In the NOSEY spectrum of **59**, strong interaction between Phe H_{α} and Tyr H_{α} suggested close proximity of one of the protons at α-position of tyrosine residue and Phe Hα. Hence it was confirmed the *trans*-relationship between Phe H_{α} and Tyr H_{β} (Figure 1). Elemental analysis together with mass spectrum data also confirmed its chemical constitutions.

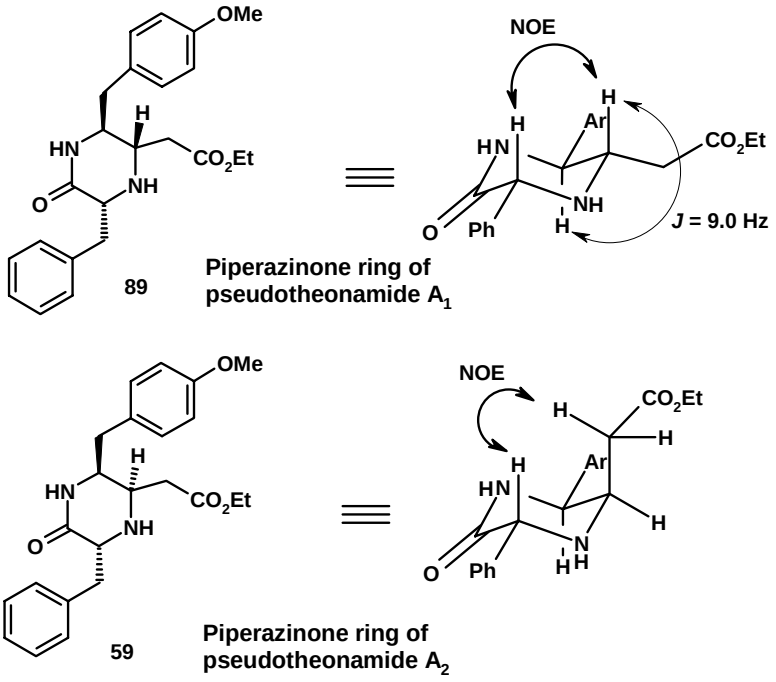
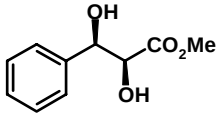


Figure 1: NOE studies on compound **89** and **59**

In conclusion we have developed a stereoselective methods for the synthesis of substituted piperazinone ring by applying thermally allowed [3+2] intramolecular cycloaddition between azido group and activated olefin followed by enamine bond reduction. These particular piperazinone rings synthesized using our protocol are significant part of biologically active natural products pseudotheonamide A_1 and A_2.

Methyl 2(*S*),3(*R*)-dihydroxy-3-phenylpropionate (67):



A mixture of $K_3Fe(CN)_6$ (26.64 gm, 81.0 mmol), K_2CO_3 (11.18 gm, 81.0 mmol), methane sulphonamide (2.08 gm, 27.0 mmol), $(DHQD)_2PHAL$ (216 mg, 0.27 mmol) in *t*-butanol (30 ml) and water (20 ml) was stirred vigorously for 15 min. To this reaction mixture, was added OsO_4 solution (13 mg, 0.54 ml in toluene) and olefin **66** (4.5 gm, 27.0 mmol) at 0 °C and stirred for 11 h. Excess OsO_4 was quenched with Na_2SO_3 solution. *t*-Butanol was evaporated, residue was extracted with ethyl acetate (3x100 ml), dried organic fraction over (Na_2SO_4), concentrated. The residue was purified on silica gel column with petroleum ether: ethyl acetate (1:1) to afford **67** as a white solid (4.35 gm, 80% yield).

Enantiomeric excess of the diol (**67**) was determined by chiral HPLC (analysis condition: column chiral- OJ, MP- 10 % IPA, flow- 1ml/min, λ- 254 nm) and it was found to be 98%.

R_f = 0.3 (45% ethyl acetate/petroleum ether)

Melting point: 85-86 °C; lit.[44] 84-86 °C.

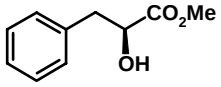
$[\alpha]_D$: + 2.9 (*c* 1.3, C_2H_5OH); lit.[44] $[\alpha]_D$: + 3.4 (*c* 1.19, C_2H_5OH)

^{1}H NMR ($CDCl_3$, 200 MHz): δ 3.05 (br, 2H, 2OH), 3.80 (s, 3H), 4.30 (d, *J* = 2.81 Hz, 1H), 4.99 (d, *J* = 2.81 Hz, 1H), 7.29-7.45 (m, 5H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 52.3, 74.4, 74.9, 126.1, 127.7, 128.1, 139.8, 172.9.

Anal. Calc for $C_{10}H_{12}O_4$: C, 61.22; H, 6.16. Found: C, 61.40; H, 6.03.

Methyl 2(*S*)-hydroxy-3-phenylpropionate (68):



A mixture of **67** (4.10 gm, 20.91 mmol) and Raney nickel (KALCAT$^{(R)}$ 2921) in distilled methanol was vigorously refluxed for 7 h. The suspension was allowed to cool and filtered through a Celite pad. The filtrate was concentrated and the residue purified on silica gel column with ethyl acetate: petroleum ether (1:4) to afford compound **68** (2.25 gm, 60% yield).

R_f = 0.3 (25% ethyl acetate/petroleum ether)

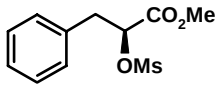
$[\alpha]_D$: -31.47 (*c* 0.8, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.80 (br, 1H, OH), 3.02 (dd, *J* = 6.97, 13.93 Hz, 1H), 3.12 (dd, *J* = 4.18, 13.93 Hz, 1H), 3.78 (s, 3H), 4.47 (dd, *J* = 4.7, 8.5 Hz, 1H), 7.19-7.35 (m, 5H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 40.2, 51.7, 71.1, 126.4, 127.9, 129.1, 136.3, 174.1.

Anal. Calc for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71. Found: C, 66.32; H, 6.23.

Methyl 2(*S*)-methanesulphonyloxy-3-phenylpropionate (69):



To compound **68** (4.0 gm, 22.22 mmol) in dry CH_2Cl_2 (50 ml), were added dry Et_3N (4.8 ml, 33.32 mmol) and $MeSO_2Cl$ (2.8 ml, 33.32 mmol) successively at 0 ^oC and allowed to stir at rt for 3 h. Cold water was added, extracted with CH_2Cl_2 (3x50 ml), dried (over Na_2SO_4), concentrated. The residue was chromatographed on SiO_2 column with ethyl

acetate: pet ether (1:4) to afford **69** as a light yellow solid (5.54 gm, 95% yield).

R_f = 0.3 (25% ethyl acetate/petroleum ether)

$[\alpha]_D$: -28.70 (*c* 1.70, $CHCl_3$)

Melting point: 55 °C

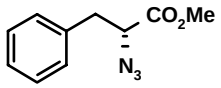
IR (ν_{max}, $CHCl_3$): 1605, 1759, 2957, 3032 cm^{-1}

^1H NMR ($CDCl_3$, 200 MHz): δ 2.74 (s, 3H), 3.12 (dd, *J* = 8.67, 14.44 Hz, 1H), 3.23 (dd, *J* = 8.71, 14.44 Hz, 1H), 3.77 (s, 3H), 5.16 (dd, *J* = 4.31, 8.74 Hz, 1H), 7.25 (m, 5H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 37.8, 37.9, 52.3, 78.1, 127.1, 128.3, 129.2, 134.6, 168.4.

Anal. Calc for $C_{11}H_{14}O_5S$: C, 51.16; H, 5.42; S, 12.40; found: C, 51.39; H, 5.61; S, 12.45.

Methyl 2(*S*)-azido-3-phenylpropionate (70):



A mixture of **69** (5.50 gm, 21.32 mmol) and NaN_3 (4.15 gm, 63.96 mmol) in dry DMF (20 ml) was stirred at 60 °C for 4 h. Water was added, and extracted with ether (3x100 ml). The combined organic fraction was thoroughly washed with water, dried over Na_2SO_4, concentrated. The residue was purified on silica gel column with ethyl acetate: petroleum ether (1:19) to afford **70** as a yellowish coloured liquid (3.93 gm, 90% yield).

R_f = 0.6 (25% ethyl acetate/petroleum ether)

$[\alpha]_D$: +18.59 (*c* 1.1, $CHCl_3$)

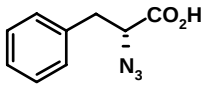
IR (ν_{max}, $CHCl_3$): 1436, 1456, 1496, 1747, 2110, 2929, 3031 cm^{-1}

^1H NMR ($CDCl_3$, 200 MHz): δ 3.05 (dd, *J* = 8.22, 14.10 Hz, 1H), 3.19 (dd, *J* = 5.29, 14.10 Hz, 1H), 3.82 (s, 3H), 4.07 (dd, *J* = 5.42, 8.80 Hz, 1H), 7.24-7.37 (m, 5H)

^{13}C NMR ($CDCl_3$, 50 MHz): δ 37.5, 52.3, 63.1, 127.1, 128.5, 129.1, 135.9, 170.1

Anal. Calc for $C_{10}H_{11}N_3O_2$: C, 58.53; H, 5.40; N, 20.48. Found: C, 58.15; H, 5.61; N, 21.10.

2(*S*)-Azido-3-phenylpropionic acid (65):



To a stirred solution of **70** (3.80 gm, 18.53 mmol) in methanol (30 ml) and water (2 ml), was added LiOH (0.66 gm, 27.80 mmol) at rt and stirred for 2 h. Methanol was evaporated, residue dissolved in water (25 ml). The aqueous layer was washed with ether

(2x50 ml) to remove organic impurity. Aqueous fraction was acidified with 2N HCl, extracted with ethyl acetate (4x125 ml). Organic layer was dried over Na_2SO_4, concentrated and crude product was purified on silica gel column to afford **65** (3.36 gm, 95% yield) as a colorless liquid.

$[\alpha]_D$: + 28.70 (*c* 2.40, $CHCl_3$)

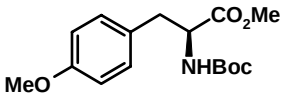
IR (ν_{max}, $CHCl_3$): 1219, 1265, 1455, 1497, 1441, 1604, 1720, 2116, 3031 cm^{-1}

^1H NMR ($CDCl_3$, 200 MHz): δ 3.00 (dd, *J* = 4.85, 14.06 Hz, 1H), 3.25 (dd, *J* = 4.85, 14.06 Hz, 1H), 4.14 (dd, *J* = 5.03, 8.98 Hz, 1H), 7.27-7.35 (m, 5H), 10.60 (brs, 1H, COOH).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 37.2, 62.8, 127.1, 128.5, 129.0, 135.5, 175.0.

Anal. Calc for $C_9H_9N_3O_2$: C, 56.54; H, 4.74; N, 21.98. Found: C, 56.83; H, 4.12; N, 22.21.

Methyl 2(S)-[(*tert*-butoxycarbonyl)amino]-3-(4-methoxyphenyl)-propanoate (73):



To a solution of L-tyrosine (10.0 gm, 55.24 mmol) in a mixture of dioxane (125 ml) and aqueous NaOH (10.18 gm, 181.8 mmol, 40 ml), was added Boc_2O (15 ml, 72.72 mmol) at 0°C and stirred for 6 h at rt. Dioxane was removed, acidified with saturated $KHSO_4$, extracted with ethyl acetate (3x200 ml). The combined organic fraction was washed with water and brine, dried over Na_2SO_4, concentrated to afford **72** (14.90 gm, 96% yield.), which was used for further step.

To a solution of **72** (12.0 gm, 42.70 mmol) in dry acetone (250 ml), Me_2SO_4 (7 ml, 69.6 mmol) and K_2CO_3 (11.78 gm, 85.4 mmol) were added and refluxed for 7 h. It was filtered, concentrated the combined fractions to afford a residue, which was purified on silica gel column with ethyl acetate: petroleum ether (3:17) to afford **73** (10.82 gm, 82% yield).

R_f = 0.5 (20% ethyl acetate/petroleum ether)

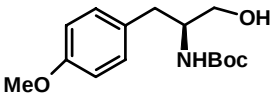
$[\alpha]_D$: + 42.82 (*c* 1.0, $CHCl_3$)

^1H NMR ($CDCl_3$, 200 MHz): δ 1.42 (s, 9H), 3.01 (m, 2H), 3.70 (s, 3H), 3.77 (s, 3H), 4.53 (m, 1H), 5.02 (brs, 1H, NH), 6.81 (d, *J* = 8.15 Hz, 2H), 7.10-7.14 (m, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 27.8, 36.8, 51.6, 54.0, 54.3, 79.1, 113.5, 120.8, 127.7, 129.8, 154.7, 158.2, 172.0.

Anal. Calc for $C_{16}H_{23}NO_5$: C, 62.12; H, 7.49; N, 4.53. Found: C, 62.40; H, 7.53; N, 4.03.

2(*S*)-[(*tert*-butoxycarbonyl)amino]-3-(4-methoxyphenyl)-propanol (74):



LiCl (2.76 gm, 64.64 mmol) and $NaBH_4$ (2.38 gm, 64.64 gm) were successively added to a stirred solution of **73** (10 gm, 32.0 mmol) in a mixture of EtOH (150 ml) and THF (75 ml) at rt and stirred for 4 h. The reaction mixture was neutralised with dropwise addition of 20% acetic acid. Solvent was evaporated, residue dissolved in ethyl acetate and extracted with ethyl acetate (3x150 ml). The combined organic fractions were washed with saturated $NaHCO_3$, brine, dried over Na_2SO_4, concentrated, and purified on silica gel column with ethyl acetate: petroleum ether (1:20) to give **74** (8.45 gm, 93% yield).

R_f = 0.4 (50% ethyl acetate/petroleum ether)

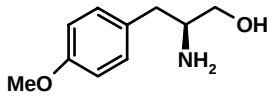
$[\alpha]_D$: - 21.66 (*c* 1.50, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.40 (s, 9H), 2.75 (dd, J = 7.41, 13.13 Hz, 1H), 3.10 (m, 1H), 3.46-3.67 (m, 2H), 3.77 (s, 3H), 4.50 (m, 1H), 5.01 (d, *J* = 6.10, 1H, NH), 6.70 (d, *J* = 8.76 Hz, 2H), 7.10 (m, 2H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 28.0, 36.5, 53.5, 54.8, 63.0, 79.0, 113.5, 121.0, 130.0, 155.9, 157.8.

Anal. Calc for $C_{15}H_{23}NO_4$: C, 64.04; H, 8.24; N, 4.98. Found: C, 64.54; H, 8.52; N, 4.13.

2(*S*)-amino-3-(4-methoxyphenyl)-propanol (64):



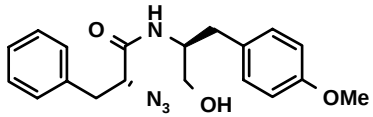
To a solution of **74** (5.0 gm, 17.79 mmol) in ethyl acetate (50 ml), was added 3N HCl (40 ml) and the reaction mixture was stirred for 1 h at rt. It was basified with aqueous NH_3 solution and extracted with ethyl acetate (3x100 ml). The organic fraction was concentrated to afford **64** as a white solid, which was used for further step without purification (3.05 gm, 95% yield).

$[\alpha]_D$: + 42.82 (*c* 1.0, $CHCl_3$)

^{1}H NMR ($CDCl_3$, 500 MHz): δ 2.20 (brs, 3H, NH_2, OH), 2.50 (dd, *J* = 8.81, 13.23 Hz, 1H), 2.75 (dd, *J* = 5.29, 13.66 Hz, 1H), 3.10 (m, 1H), 3.40 (dd, *J* = 7.47 10.70 Hz, 1H), 3.65 (dd, *J* = 3.66, 10.70 Hz, 1H), 3.80 (s, 3H), 6.85 (d, *J* = 8.64 Hz, 2H), 7.10 (d, *J* = 8.64 Hz, 2H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 39.5, 54.2, 55.1, 65.9, 113.9, 130.0, 130.8, 158.1.

2(*S*)-[[2(*R*)-azido-3-phenyl]propanoyl]amino-3-(4-methoxyphenyl)-propanol (63):



To a mixture of **65** (3.00 gm, 15.70 mmol) and **64** (2.86 gm, 15.70 mmol) in dry CH_2Cl_2 (175 ml), was successively added HOBt (2.54 gm, 18.84 mmol) and DCC (3.88 gm, 18.84 mmol) at 0 °C and stirred at rt for 4 h. The by-product was removed by filtration on Celite pad. The combined filtrate was washed with dilute HCl, saturated $NaHCO_3$ and brine successively. The organic layer was dried (Na_2SO_4), and concentrated to afford crude product mixtures. The residue was chromatographed on silica gel to afford **63** (4.04 gm) and **75** (0.50 gm) in the ratio of 8:1 (overall yield 82%).

Hydrolysis of dipeptide ester (75):

A mixture of **75** (1.00 gm, 1.89 mmol) and LiOH (54 mg, 2.26 mmol) in MeOH (10 ml) and water (2 ml) was stirred for 30 min. Methanol was evaporated, residue dissolved in water, washed with ether. Aqueous part was acidified with 2M HCl, extracted with ethyl acetate (3x50 ml), dried over Na_2SO_4, concentrated. The crude product was purified on silica gel column with ethyl acetate: pet ether (1:4) to afford **63** (0.61 gm, 92% yield).

Physical data for dipeptide alcohol (63):

R_f = 0.5 (50% ethyl acetate/petroleum ether)

Melting point: 78-80 °C

$[\alpha]_D$: - 41.40 (*c* 1.3, $CHCl_3$)

IR (ν_{max}, $CHCl_3$): 725, 1027, 1206, 1215, 1535, 1665, 2144, 2359, 3035, 3402 cm^{-1}.

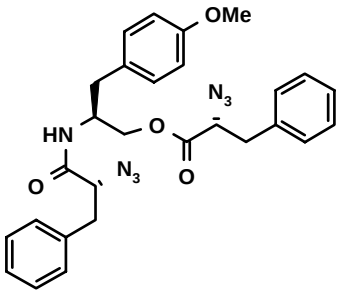
^1H NMR ($CDCl_3$, 200 MHz): δ 2.69 (m, 2H), 3.10 (dd, *J* = 6.6, 14.4 Hz, 1H), 3.25 (dd, *J* = 5.9, 14.4 Hz, 1H), 3.50 (m, 2H), 3.78 (s, 3H), 4.04 (m, 1H), 4.18 (dd, *J* = 4.8, 5.9 Hz, 1H), 6.29 (d, *J* = 6.4 Hz, 1H), 6.79 (d, *J* = 8.0 Hz, 2H), 7.03 (d, *J* = 8.0 Hz, 2H), 7.30-7.45 (m, 5H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 36.0, 38.4, 52.9, 55.1, 63.2, 65.4, 114.1, 127.2, 128.6, 129.2, 129.5, 130.1, 136.1, 158.4, 168.8.

EIMS *m/z*: 354 (M^+)

Anal. Calc for $C_{19}H_{22}N_4O_3$: C, 64.39; H, 6.26; N, 15.81 found: C, 64.01; H, 5.94; N, 14.61.

[2(*S*)-[[2 (*R*)-azido-3-phenyl]propanoyl]amino-3-(4-methoxyphenyl)]-yl-2(*R*)-3-phenyl-propanoate (75):



R_f = 0.75 (50% ethyl acetate/petroleum ether)

Melting point: 125-127 °C

$[\alpha]_D$: - 41.40 (*c* 0.85, $CHCl_3$)

IR (ν_{max}, $CHCl_3$): 1562, 1675, 1753, 2153, 2160, 3075 cm^{-1}

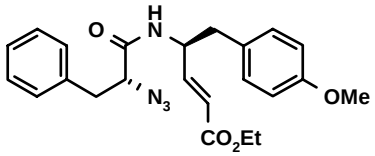
^1H NMR ($CDCl_3$, 200 MHz): δ 2.49-2.70 (m, 2H), 2.89-3.01 (m, 2H), 3.13 (ddd, *J* = 2.61, 5.41, 13.82 Hz, 1H), 3.21-3.27 (m, 1H), 3.77 (s, 3H), 3.95-4.41 (m, 4H), 4.27-4.32 (m, 1H), 6.20 (br, 1H, NH), 6.78-6.80 (m, 2H), 6.89 (d, *J* = 8.28 Hz, 1H), 6.96 (d, *J* = 8.28 Hz, 1H), 7.20-7.33 (m, 10H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 36.4, 37.5, 38.5, 49.4, 55.2, 63.3, 67.5, 67.8, 114.3, 127.4, 128.7, 128.9, 129.2, 129.6, 129.9, 136.1, 158.1, 168.1, 169.9.

EIMS *m/z*: 527 (M^+)

Anal. Calc for $C_{28}H_{29}N_7O_4$: C, 63.75; H, 5.54; N, 18.58. Found: C, 63.09; H, 5.31; N, 18.31.

Ethyl 4(*S*)-[[2-(*R*)-azido-3-phenyl]propanoyl]amino-5-(4-methoxyphenyl)-2(*E*) pentenoate (62):



To a solution of **63** (2.0 gm, 5.60 mmol) in dry CH_2Cl_2 (30 ml), was added Dess Martin periodinane reagent (3.56 gm, 8.39 mmol) and stirred for 2 h. Water was added and extracted with CH_2Cl_2 (3x50 ml), concentrated to obtain crude product **76**, which was used for further step without characterization (1.69 gm, 85% crude yield).

A mixture of aldehyde **76** (1.69 gm, 4.80 mmol) and ethoxycarbonylmethylene triphenylphosphorane (4.18 gm, 12.00 mmol) in dry CH_2Cl_2 (40 ml) was stirred at rt for 12 h. Solvent was evaporated to leave the residue, which was purified on silica gel column

with ethyl acetate: petroleum ether (1:4) to afford **62** as a white solid (1.26 gm, 90% yield).

R_f = 0.4 (50% ethyl acetate/petroleum ether)

Melting point: 145-146 °C

$[\alpha]_D$: - 14.44 (*c* 2.65, $CHCl_3$)

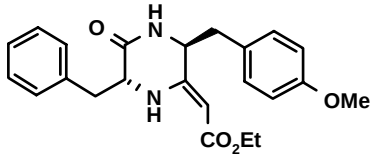
IR (ν_{max}, $CHCl_3$): 730, 1013, 1148, 1223, 1513, 1659, 1715, 2108, 2959, 3316 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ 1.27 (t, *J* = 7.17 Hz, 3H), 2.70-3.10 (m, 3H), 3.20 (dd, *J* = 4.39, 13.58 Hz, 1H), 3.76 (s, 3H), 4.10-4.23 (m, 3H), 4.80 (m, 1H), 5.62 (dd, *J* = 1.9, 15.4 Hz, 1H), 6.25 (d, *J* = 9.07 Hz, 1H), 6.72-6.66 (m, 4H), 7.00 (d, *J* = 9.08 Hz, 1H), 7.15-7.40 (m, 5H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ 14.1, 38.0, 39.3, 50.6, 54.8, 60.2, 64.8, 113.8, 121.4, 127.1, 128.5, 129.3, 130.2, 135.8, 146.1, 158.5, 165.5, 167.6.

Anal. Calc for $C_{23}H_{26}N_4O_4$: C, 65.39; H, 6.20; N, 13.26 Found: C, 65.72; H, 6.04; N, 13.52.

(Z)-Ethyl 2-[(3*S*,6*R*)-3-(4-methoxybenzyl)-6-benzyl-5-oxopiperazin-2-ylidene]acetate (61):



Compound **62** (1.0 gm, 2.36 mmol) in dry toluene (40 ml) was vigorously refluxed in presence of few drops of Et_3N. After 10 h, solvent was evaporated to leave dark brown residue, which was purified on SiO_2 column with ethyl acetate: pet ether (1:1) to afford **61** (522 mg, 56% yield) as a white solid.

R_f = 0.6 (75% ethyl acetate/petroleum ether)

Melting point: 153-154 °C

$[\alpha]_D$: +37.35 (*c* 1.5, $CHCl_3$)

IR (ν_{max}, $CHCl_3$): 689, 1027, 1162, 1243, 1514, 1611, 1666, 1794, 2918, 3013, 3216 cm^{-1}.

^1H NMR ($CDCl_3$, 200 MHz): δ 1.25 (t, *J* = 7.1 Hz, 3H), 2.89 (m, 3H), 3.28 (m, 2H), 3.78 (s, 3H), 3.89 (m, 1H), 4.10 (q, *J* = 7.1 Hz, 2H), 4.57 (s, 1H), 6.82 (m, 3H), 7.03 (d, *J* = 7.1 Hz, 2H), 7.10-7.25 (m, 2H), 7.26-7.40 (m, 3H), 8.68 (s, 1H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 14.4, 38.0, 42.7, 54.6, 55.0, 58.5, 80.6, 114.0, 126.8, 127.0, 128.5, 129.3, 131.0, 136.1, 156.7, 159.0, 170.0 (2C)

EIMS (*m/z*): 394 (M^+)

Anal. Calc for $C_{23}H_{26}N_2O_4$: C, 70.00; H, 6.50; N, 7.10 found: C, 69.24; H, 6.46; N, 6.43.

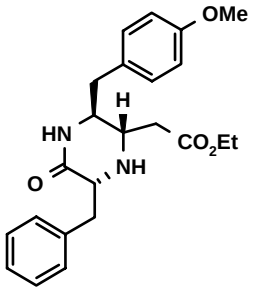
Reduction of enamine double bond of 61by sodium cyanoborohydride:

To a mixture of solution of **61** (150 mg, 0.38 mmol) in dry MeOH (10 ml), was added $Na(CN)BH_3$ (34 mg, 0.57 mmol) followed by trace amount of bromocresol green indicatorthe reaction mixture was stirred at 0 °C under N_2 atmosphere. To this resulting green solution, 5% HCl in MeOH was added drop wise until solution maintained a yellow color. Stirring was continued under this condition for 2 h, when TLC (75% ethyl acetate in pet ether) showed the complete disappearance of starting material and two major spots appeared. NaOH solution (3 ml) was added, extracted with CH_2Cl_2 (2x15 ml), organic layers were dried (over Na_2SO_4), concentrated to afford crude products mixture. Silica gel column chromatography allowed to separating two products. The faster moving spot was eluted with 35% ethyl acetate/petroleum ether and slower one with 37% ethyl acetate/petroleum ether (total yield: 135 mg, 90% yield, compound **59**: 94 mg, compound **89**: 41 mg; ratio 7:3 of **59:89**).

Reduction of enamine double bond of 61 by platinum charcoal:

A mixture of **61** (100 mg, 0.25 mmol) and 5% platinum adsorbed in charcoal (20mg) in dry methanol (20 ml) was shaken at 50 *psi* hydrogen atmosphere at rt in Paar Shaker for 6 h. The reaction mixture was filtered over Celite and washed the residue with methanol. The combined organic fractions were concentrated to afford the mixture of two diastereomers, which was separated by silica gel column chromatography [total yield: 94 mg, 94%; Compound **59**: 84 mg; compound **89**: 10 mg; ratio 9:1 of **59:89**].

Ethyl 2-[(2*S*,3*S*,6*R*)-3-(4-methoxybenzyl)-6-benzyl-5-oxopiperazin-2-yl]acetate (89):



R_f = 0.4 (75% ethyl acetate/petroleum ether)

$[\alpha]_D$: - 7.47 (*c* 2.20, $CHCl_3$)

IR (ν_{max}, $CHCl_3$): 702, 754, 1031, 1178, 1247, 1454, 1612, 1666, 1732, 3215 cm^{-1}

^1H NMR (500 MHz, $CDCl_3$): δ 1.15 (t, *J* = 6.2 Hz, 3H), 2.36 (dd, *J* = 10.2, 13.7 Hz, 1H),

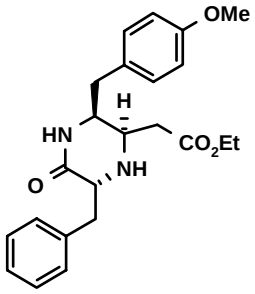
2.42 (dd, *J* = 7.5, 15.0 Hz, 1H), 2.67 (dd, *J* = 2.5, 15.0 Hz, 1H), 2.82 (dd, *J* = 10.0, 13.7 Hz, 1H), 2.94 (dd, *J* = 2.5, 12.5 Hz, 1H), 3.00 (dt, *J* = 2.5, 9.0, 12.5 Hz, 1H), 3.38 (dt, *J* = 2.5, 10.0, 12.5 Hz, 1H), 3.43 (dd, *J* = 2.5, 12.5 Hz, 1H), 3.63 (dd, *J* = 3.5, 9.0 Hz, 1H), 3.82 (s, 3H), 4.01 (q, *J* = 6.25 Hz, 2H), 5.57 (s, 1H), 6.88 (d, *J* = 8.0 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 2H), 7.29 (m, 5H)

^{13}C NMR (125 MHz, CDCl3): δ 14.1, 37.1, 37.7, 38.6, 55.2, 55.3, 58.2, 59.8, 60.8, 114.8, 126.6, 128.6, 129.4, 130.2, 138.2, 159.1, 170.7 (2C).

Anal. Calc for $C_{23}H_{28}N_2O_4$: C, 69.68; H, 7.12; N, 7.07 found: C, 69.01; H, 7.46; N, 7.87.

EIMS: *m*/*z* 397 (M^++1).

Ethyl 2-[(2*R*,3*S*,6*R*)-3-(4-methoxybenzyl)-6-benzyl-5-oxopiperazin-2-yl]acetate (59):



R_f = 0.3 (75% ethyl acetate/petroleum ether)

$[\alpha]_D$: - 16.3 (*c* 2.30, $CHCl_3$)

IR (ν_{max}, $CHCl_3$): 702, 754, 1031, 1178, 1247, 1454, 1612, 1666, 1732, 3215 cm^{-1}

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.20 (t, *J* = 7.2 Hz, 3H), 2.52 (dd, *J* = 5.5, 15.1 Hz, 1H), 2.53 (dd, *J* = 10.2, 15.1 Hz, 1H), 2.62 (dd, *J* = 9.6, 15.1 Hz, 1H), 2.74 (dd, *J* = 4.1, 13.8 Hz, 1H), 2.85 (dd, *J* = 10.32, 13.88 Hz, 1H), 3.32 (dd, *J* = 3.0, 13.8 Hz, 1H), 3.65 (m, 1H), 3.76 (dd, *J* = 2.8, 9.6 Hz, 2H), 3.81 (s, 3H), 4.07 (m, 2H), 5.66 (s, 1H), 6.88 (d, *J* = 8.3 Hz, 2H), 7.09 (d, *J* = 8.3 Hz, 2H), 7.22-7.28 (m, 3H) 7.29-7.35 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1, 33.7, 36.4, 38.1, 49.2, 55.3, 56.5, 55.7, 60.9, 114.6, 126.7, 128.1, 128.6, 129.4, 130.1, 138.1, 158.9, 170.9, 171.2.

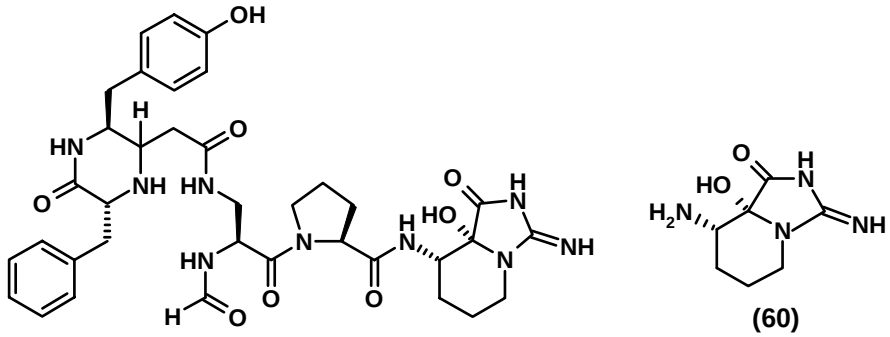
EIMS: *m*/*z* 397 (M^++1).

Anal. Calc for $C_{23}H_{28}N_2O_4$: C, 69.68; H, 7.12; N, 7.07. Found: C, 69.23; H, 7.54; N, 7.30.

CHAPTER - 2

Synthetic studies towards pseudotheonamide D

After successfully synthesizing the piperazinone ring systems of pseudotheonamide A_1 (**17**) and A_2 (**18**),[58] we next directed our attention towards the synthesis of piperadinoiminoimidazolone ring (**60**), which was found to be a novel core structure.

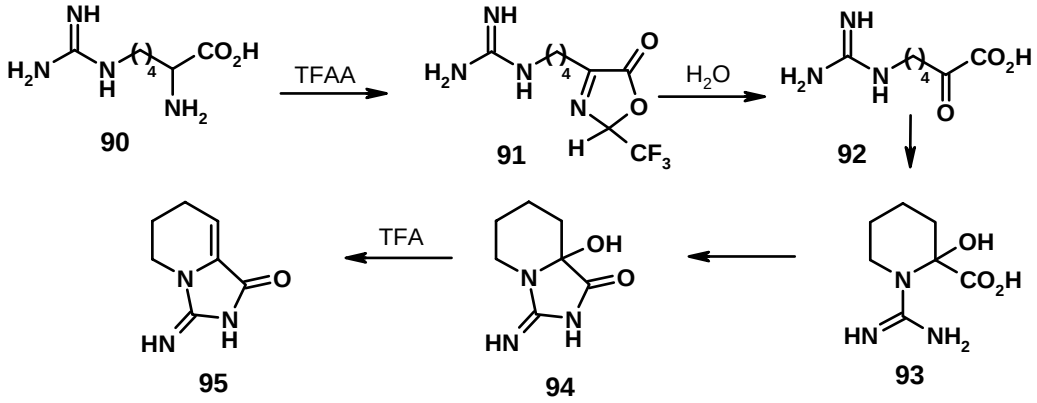


(60)

β_H = Pseudotheonamide A_1 (17); α_H = Pseudotheonamide A_2 (18)

Literature survey revealed that synthesis of piperadinoiminoimidazolone type ring system is unprecedented except only one report by Steglich *et al.*[59] Their work involves treatment of homoarginine (**90**) with trifluroacetic anhydride leading to 2-trifluromethyl-3-oxazolin-5-one (**91**), which in turn was hydrolyzed to yield α-keto acid **92** under mild conditions. The α-keto acid **92** was converted into **94** and **95** (Scheme 27).

Scheme 27

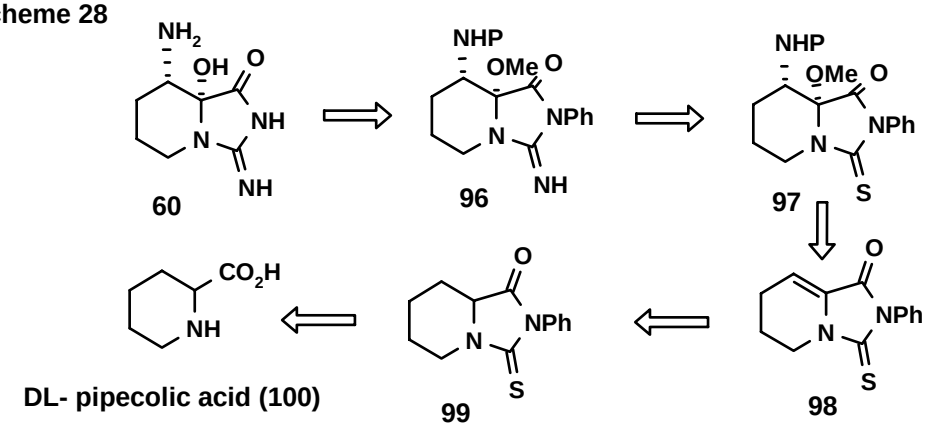


Although Steglich work is useful, we have in structure **60**, an additional amino

group on cyclohexane ring to deal with. Furthermore, Steglich route is fraught with difficulties and therefore a new synthetic strategy was warranted.

Inspired by the piperadinoiminoimidazolone core structure of pseudotheonamide, the retrosynthetic analysis was first designed as shown in Scheme 28 starting from pipecolic acid (**100**). Installment of two desired substituents was envisaged from asymmetric amino hydroxylation reaction on the double bond of compound **98**, whose synthesis was proposed by selenium chemistry. Finally, conversion of thiocarbonyl to imine and deprotection would lead to piperadinoiminoimidazolone ring of natural products pseudotheonamide A_1 and A_2 (Scheme 28)

Scheme 28

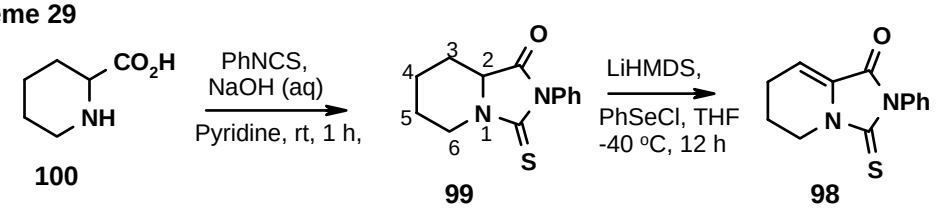


Treatment of DL-pipecolic acid (**100**) with phenylthioisocyanate[60] in aqueous sodium hydroxide solution and pyridine gave the bicyclic thiohydantoin derivative **99**. The structure of compound **99** was confirmed from the ^{1}H, ^{13}C NMR, IR spectra and elemental analysis. For example, in the ^{1}H NMR spectrum, five aromatic protons resonated between 7.28-7.25 ppm as multiplets while the methine proton appeared at 4.90 ppm as a double-doublet (J = 2.36, 12.65 Hz). The rest of the protons were found at the expected chemical shift values. The ^{13}C NMR spectrum revealed thiocarbonyl and carbonyl carbons at 179.1 and 172.4 ppm respectively. In the IR spectrum, the characteristic absorption peaks at 1500 and 1752 cm^{-1} were due to C=S and C=O respectively.

Our next concern was to install a double bond at 2,3-position of **99** by applying

selenium chemistry.[61] Compound **99** was treated with LiHMDS in dry THF at –20 °C followed by addition of PhSeCl to afford the unsaturated derivative **98**. The structure of **98** was confirmed by the ^{1}H NMR spectrum and elemental analysis. For instance, in the ^{1}H NMR spectrum, olefinic proton was located at 6.28 ppm as a triplet (J = 4.36 Hz). The rest of the spectrum was in complete agreement with the assigned structure (Scheme 29).

Scheme 29



It was assumed that when lithium enolate of **99** was treated with an excess of PhSeCl (2.3 eqv), initially α-selenated derivative **101** formed as evident by the isolation and characterization. Selenation of the selenide **101** by a second equivalent of electrophiles, giving rise to unstable intermediate **106** that quickly eliminates with the assistance of the nitrogen lone pair to form *N*-acyliminium ion **107**. Finally, prototopic displacement assisted by chloride ion gave the olefin **98**. The essential requirement of the chloride ion for prototopic displacement was proved by Rubio's experiment[61b] with similar type of substrate (Figure 2).

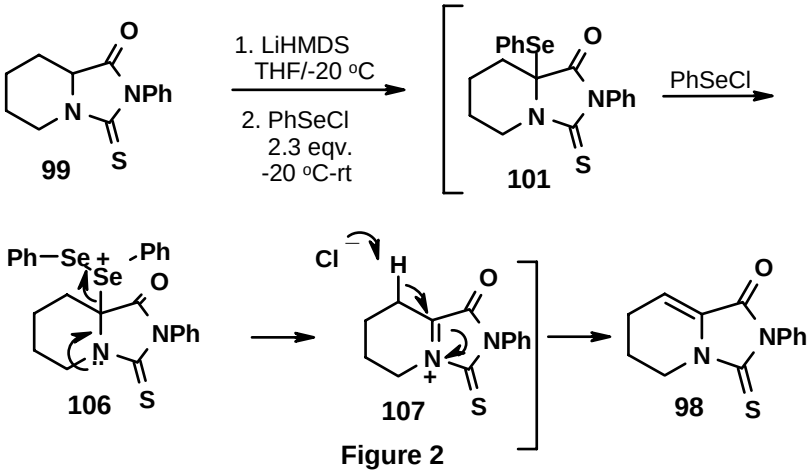


Figure 2

We isolated the intermediate organo selenium compound **101** in the crystalline form by quenching the reaction mixture with NH_4Cl solution after 2 h followed by silica gel chromatographic purification. The structure of **101** was determined based on single X-ray crystallographic studies. [The details of crystal data and structure refinement (Table 1), bond lengths and bond angles (Table 2) and torsion angle (Table 3), are given at the end of

this section] The ORTEP diagram of **101** was given in Figure 3.

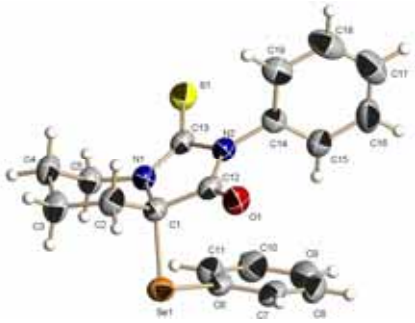
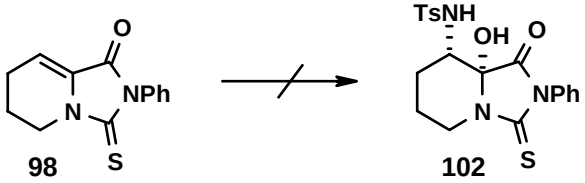


Figure 3: ORTEP diagram of compound 101

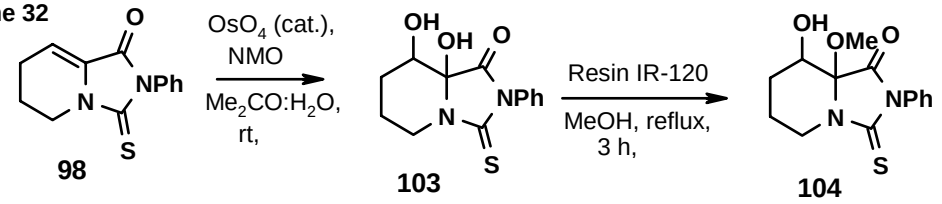
Compound **98** was subjected Sharpless asymmetric aminohydroxylation[62] (AAH) reaction by using chloramin-T, chiral ligand $(DHQ)_2PHAL$, and catalytic oxidant $K_2Os(OH)_4$ but it did not work (Scheme 30).

Scheme 30



This promoted us to devise a new synthetic strategy involving Sharpless ADH[43] followed by SN_2 displacement of 3-OH group with amine. Accordingly, compound **98** was treated with catalytic OsO_4 and *N*-methyl morpholine-*N*-oxide in acetone/water mixture to furnish the diol **103**. Compound **103** was characterized by the ^1H, ^{13}C NMR spectra and elemental analysis. Tertiary hydroxyl group of **103** was selectively protected as methyl ether by refluxing with methanol and Amberlite IR-120 (H^+) resin to give **104** (Scheme 32). The structure of **104** was confirmed by its ^1H, ^{13}C NMR spectra coupled with elemental analysis. In the ^1H NMR spectrum of **104**, methine proton bearing hydroxyl group appeared at 4.78 (dd, J = 3.96, 13.50 Hz) ppm. Methoxyl group resonated as a sharp singlet at 3.30 ppm, while resonance for the aromatic protons were located between 7.26-7.48 ppm as multiplets. The structure was further analyzed by its ^{13}C NMR spectrum, where carbonyl and thiocarbonyl resonated at 170.8 and 182.0 ppm respectively while methoxyl group at 51.2 ppm. The rest of the carbons appeared at their typical chemical shift values.

Scheme 32



The structure of **104** was confirmed by single X-ray crystallographic data. [The details of crystal data and structure refinement (Table 4), bond lengths and bond angles (Table 5) and torsion angles (Table 6) are provided at the end of this section.] The ORTEP diagram of **104** is shown in Figure 4.

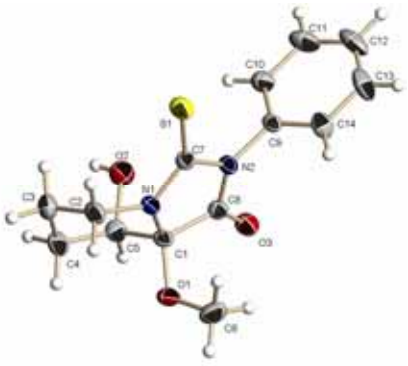
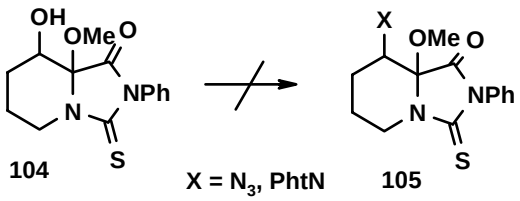


Figure 4: ORTEP diagram of compound 104

The next concern was the displacement of OH with azido. However, this displacement turned out to be a difficult proposition. Direct conversion of OH to N_3 under Mitsunobu[63] reaction condition using hydrazoic acid, TPP and DEAD[64] resulted in the recovery of starting material. Use of phthalimide[65] or diphenylphosphoryl azide[66] was not successful (Scheme 33).

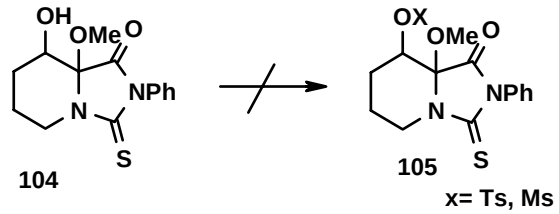
Scheme 33



Reagents and conditions	Results
1. HN_3/TPP/DEAD THF, RT	Starting material recovered
2. PhtNH, TPP, DEAD, THF, RT	Starting material recovered
3. $(PhO)_2PON_3$, DEAD, TPP, THF, RT	Starting material recovered

Next, logical strategy would be the displacement of *O*-sulphonate with nitrogen nucleophile. However, all our efforts to transform **104** into the tosylate or mesylate derivative were not successful (Scheme 34). The failure to effect either direct displacement of OH to azido as well as to form *O*-sulphonate derivative was attributed to both steric as well as electronic factors.

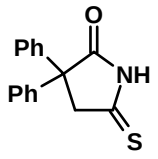
Scheme 34



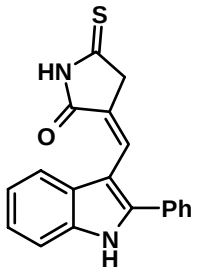
Reagents and conditions	Results
1. TsCl, Pyridine, CH_2Cl_2, rt	Starting material recovered
2. MsCl, Et_3N, CH_2Cl_2, rt	Starting material recovered

With the negative results in hand and during the literature search, it has been found that there has been much interest in the synthesis and properties of derivatives of 2-thiohydantoins, which are useful synthetic intermediates and have also found application as therapeutics[67] as well as fungicides and herbicides.[68] Furthermore, several 5-arylidene-3-aryl thiohydantoins and their nueleosides show potent activity against herpes simplex virus (HSV),[69] the human immunodeficiency virus (HIV),[70] and the leukemia subpanel.[71] In addition, the biological activity of hydantoins nucleus containing a urea moiety is responsible for a array of biological activities such as antiarrhythmic,[72] antihypertensive,[73] antiviral,[74] antineoplastic,[75] anticonvulsant,[76] and antimycobacterial.[77] For instance, 5,5-diphenyl-2-thiohydantoin (DPTH, **106**), a sulphur analogue of antiepileptic drug phenytoin (5,5-diphenylhydantoin DPH), has been suggested to be a potential hypolipidemic agent[78] and a potent goitrogenic compound.[79] Its prominent activities were reported as being

inhibitory against thyroxine-stimulated response in mitochondria and being hypolipidemic.[80] Another important thiohydantion derivative 5-(2-phenyl-3′-indolal)-2-thiohydantion (**107**)[81] was found to be highly anti-HIV agent like AZT.



106

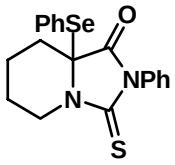


107

Although our work of synthesis of piperadinoiminoimidazolone ring system was failed, we were able to achieve a protocol for the synthesis of new novel bicyclic thiohydantoin derivatives including **98**, **103** and **104**, which may show promising biological activities.

In conclusion, our work towards synthesis of piperadinoiminoimidazolone ring (**60**) of pseudotheonamide A_1 and A_2 contributed to a straight forward protocol to access the substituted bicyclic 2-thiohydantions, which may show pronounced biological activity.

Table 1. Crystal data and structure refinement for **101.**



Empirical formula	$C_{19}H_{18}N_2OSSe$
Formula weight	401.37
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhomic, *P*bca
Unit cell dimensions	a = 14.684(4) Å α = 90°, b = 15.397(4) Å β = 90°, c = 16.276(4) Å γ = 90°.
Volume	3679.9(15) $Å^3$
Z, Calculated density	8, 1.449 Mg/m^3
Absorption coefficient	2.162 mm^{-1}
F(000)	1632
Crystal size	0.59 x 0.32 x 0.01 mm
Theta range for data collection	2.29 to 24.99°
Limiting indices	-17<=h<=17, -18<=k<=18, -19<=l<=19
Reflections collected / unique	21795 / 3231 [R(int) = 0.0438]
Completeness to theta = 24.99	99.8 %
Max. and min. transmission	0.9704 and 0.3620
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3231 / 0 / 217
Goodness-of-fit on F^2	1.042
Final R indices [I>2sigma(I)]	R1 = 0.0417, wR2 = 0.0878
R indices (all data)	R1 = 0.0674, wR2 = 0.0979
Largest diff. peak and hole	0.379 and -0.160 e. $Å^{-3}$

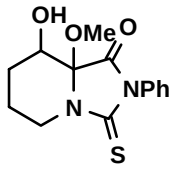
Table 2. Bond lengths [Å] and angles [deg] for **101**.

S(1)-C(13)	1.650(3)	C(13)-N(1)-C(1)	113.3(2)
Se(1)-C(6)	1.916(4)	C(13)-N(1)-C(5)	126.2(3)
Se(1)-C(1)	2.002(3)	C(1)-N(1)-C(5)	119.6(3)
O(1)-C(12)	1.207(3)	C(12)-N(2)-C(13)	111.2(3)
N(1)-C(13)	1.331(4)	C(12)-N(2)-C(14)	123.2(3)
N(1)-C(1)	1.445(4)	C(13)-N(2)-C(14)	125.5(3)
N(1)-C(5)	1.464(4)	N(1)-C(1)-C(12)	102.3(3)
N(2)-C(12)	1.381(4)	N(1)-C(1)-C(2)	111.4(3)
N(2)-C(13)	1.411(4)	C(12)-C(1)-C(2)	113.0(3)
N(2)-C(14)	1.438(4)	N(1)-C(1)-Se(1)	112.4(2)
C(1)-C(12)	1.504(4)	C(12)-C(1)-Se(1)	109.8(2)
C(1)-C(2)	1.530(4)	C(2)-C(1)-Se(1)	107.9(2)
C(2)-C(3)	1.528(5)	C(3)-C(2)-C(1)	111.0(3)
C(3)-C(4)	1.511(5)	C(4)-C(3)-C(2)	111.2(3)
C(4)-C(5)	1.517(4)	C(3)-C(4)-C(5)	11.7(3)
C(6)-C(7)	1.378(5)	N(1)-C(5)-C(4)	108.7(3)
C(6)-C(11)	1.382(5)	C(7)-C(6)-C(11)	119.9(4)
C(7)-C(8)	1.380(5)	C(7)-C(6)-Se(1)	120.6(3)
C(8)-C(9)	1.367(6)	C(11)-C(6)-Se(1)	119.5(3)
C(9)-C(10)	1.353(6)	C(6)-C(7)-C(8)	119.6(4)
C(10)-C(11)	1.386(5)	C(9)-C(8)-C(7)	120.3(4)
C(14)-C(15)	1.365(5)	C(10)-C(9)-C(8)	120.3(4)
C(14)-C(19)	1.368(5)	C(9)-C(10)-C(11)	120.6(4)
C(15)-C(16)	1.389(6)	C(6)-C(11)-C(10)	119.3(4)
C(16)-C(17)	1.343(7)	O(1)-C(12)-N(2)	125.8(3)
C(17)-C(18)	1.354(7)	O(1)-C(12)-C(1)	127.8(3)
C(18)-C(19)	1.387(6)	N(2)-C(12)-C(1)	106.3(3)
C(6)-Se(1)-C(1)	96.50(14)	N(1)-C(13)-N(2)	106.7(3)
N(2)-C(13)-S(1)	124.4(3)	C(15)-C(14)-C(19)	120.3(4)
C(15)-C(14)-N(2)	119.2(3)	C(16)-C(17)-C(18)	120.5(5)
C(19)-C(14)-N(2)	120.5(3)	C(17)-C(18)-C(19)	120.3(5)
C(14)-C(15)-C(16)	119.4(4)	C(14)-C(19)-C(18)	119.2(4)
C(17)-C(16)-C(15)	120.3(5)		

Table 3. Torsion angles [deg] for **101.**

C(13)-N(1)-C(1)-C(12)	-1.2(3)	C(8)-C(9)-C(10)-C(11)	0.2(7)
C(5)-N(1)-C(1)-C(12)	-170.7(3)	C(7)-C(6)-C(11)-C(10)	-0.6(6)
C(13)-N(1)-C(1)-C(2)	119.8(3)	Se(1)-C(6)-C(11)-C(10)	178.9(3)
C(5)-N(1)-C(1)-C(2)	-49.7(4)	C(9)-C(10)-C(11)-C(6)	0.2(7)
C(13)-N(1)-C(1)-Se(1)	-118.9(3)	C(13)-N(2)-C(12)-O(1)	-175.8(3)
C(5)-N(1)-C(1)-Se(1)	71.6(3)	C(6)-C(7)-C(8)-C(9)	-0.1(6)
C(6)-Se(1)-C(1)-N(1)	60.4(2)	C(7)-C(8)-C(9)-C(10)	-0.3(7)
C(6)-Se(1)-C(1)-C(12)	-52.8(2)	C(8)-C(9)-C(10)-C(11)	0.2(7)
C(6)-Se(1)-C(1)-C(2)	-176.4(2)	C(7)-C(6)-C(11)-C(10)	-0.6(6)
N(1)-C(1)-C(2)-C(3)	47.7(4)	C(8)-C(9)-C(10)-C(11)	0.2(7)
C(12)-C(1)-C(2)-C(3)	162.2(3)	C(7)-C(6)-C(11)-C(10)	-0.6(6)
Se(1)-C(1)-C(2)-C(3)	-76.2(3)	Se(1)-C(6)-C(11)-C(10)	178.9(3)
C(1)-C(2)-C(3)-C(4)	-53.3(4)	C(9)-C(10)-C(11)-C(6)	0.2(7)
C(2)-C(3)-C(4)-C(5)	57.4(4)	C(14)-N(2)-C(12)-C(1)	-178.5(3)
C(13)-N(1)-C(5)-C(4)	-116.1(4)	C(13)-N(2)-C(12)-C(1)	3.0(3)
C(1)-N(1)-C(5)-C(4)	52.0(4)	C(14)-N(2)-C(12)-C(1)	-178.5(3)
C(3)-C(4)-C(5)-N(1)	-53.6(4)	N(1)-C(1)-C(12)-O(1)	177.6(3)
C(1)-Se(1)-C(6)-C(7)	96.9(3)	C(2)-C(1)-C(12)-O(1)	57.7(4)
C(1)-Se(1)-C(6)-C(11)	96.9(3)	Se(1)-C(1)-C(12)-O(1)	-62.9(4)
C(11)-C(6)-C(7)-C(8)	0.5(6)	N(1)-C(1)-C(12)-N(2)	-1.1(3)
Se(1)-C(6)-C(7)-C(8)	-178.9(3)	C(2)-C(1)-C(12)-N(2)	-121.0(3)
C(6)-C(7)-C(8)-C(9)	-0.1(6)	Se(1)-C(1)-C(12)-N(2)	118.4(2)
C(7)-C(8)-C(9)-C(10)	-0.3(7)	C(1)-N(1)-C(13)-N(2)	3.0(4)
C(1)-N(1)-C(13)-S(1)	-175.7(2)	C(5)-N(1)-C(13)-N(2)	171.7(3)
C(5)-N(1)-C(13)-S(1)	-7.1(5)	C(13)-N(2)-C(14)-C(19)	84.9(4)
C(12)-N(2)-C(13)-N(1)	-3.8(4)	C(19)-C(14)-C(15)-C(16)	-0.7(6)
C(14)-N(2)-C(13)-N(1)	177.8(3)	C(14)-C(15)-C(16)-C(17)	0.5(7)
C(12)-N(2)-C(13)-S(1)	175.0(2)	C(15)-C(16)-C(17)-C(18)	0.2(8)
C(14)-N(2)-C(13)-S(1)	-3.4(5)	C(16)-C(17)-C(18)-C(19)	-0.7(7)
C(12)-N(2)-C(14)-C(15)	84.5(4)	C(15)-C(14)-C(19)-C(18)	0.2(6)
C(13)-N(2)-C(14)-C(15)	-97.3(4)	N(2)-C(14)-C(19)-C(18)	178.0(3)
C(12)-N(2)-C(14)-C(19)	-93.4(4)	C(17)-C(18)-C(19)-C(14)	0.6(6)

Table 4. Crystal data and structure refinement for 104



Empirical formula	$C_{14}H_{16}N_2O_3S$
Formula weight	292.35
Temperature	293(2) K
Wavelength	0.71073 Å
Crystal system, space group	Orthorhombic, Pbca
Unit cell dimensions	a = 8.5492(8) Å, α = 90°. b = 16.1087(15) Å, β = 90°. c = 20.6230(19) Å γ = 90°.
Volume	2840.1(5) $Å^3$
Z, Calculated density	8, 1.367 Mg/m^3
Absorption coefficient	0.237 mm^{-1}
F(000)	1232
Crystal size	0.61 x 0.16 x 0.10 mm
Theta range for data collection	1.97 to 25.00°
Limiting indices	-10<=h<=10, -19<=k<=19, -24<=l<=24
Reflections collected / unique	23399 / 2500 [R(int) = 0.0429]
Completeness to theta = 25.00	99.8 %
Max. and min. transmission	0.9779 and 0.8701
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2500 / 0 / 197
Goodness-of-fit on F^2	1.403
Final R indices [I>2sigma(I)]	R1 = 0.0733, wR2 = 0.1320
R indices (all data)	R1 = 0.0777, wR2 = 0.1336
Largest diff. peak and hole	0.259 and -0.175 e. $Å^{-3}$

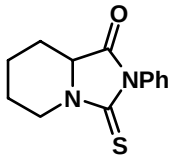
Table 5. Bond lengths [Å] and angles [deg] for **104**.

S(1)-C(7)	1.644(3)	N(1)-C(1)-C(5)	110.3(3)
O(1)-C(1)	1.394(4)	C(8)-C(1)-C(5)	110.3(3)
O(1)-C(6)	1.423(4)	N(1)-C(2)-C(3)	109.9(3)
O(2)-C(5)	1.416(4)	C(4)-C(3)-C(2)	112.1(3)
O(3)-C(8)	1.212(4)	C(3)-C(4)-C(5)	111.6(3)
N(2)-C(8)	1.360(4)	O(2)-C(5)-C(4)	113.0(3)
N(2)-C(7)	1.411(4)	O(2)-C(5)-C(1)	104.0(3)
N(2)-C(9)	1.438(4)	N(1)-C(7)-N(2)	106.8(3)
N(1)-C(7)	1.342(4)	N(1)-C(7)-S(1)	128.6(2)
N(1)-C(1)	1.453(4)	N(2)-C(7)-S(1)	124.5(2)
N(1)-C(2)	1.457(4)	O(3)-C(8)-N(2)	126.9(3)
C(1)-C(8)	1.520(4)	O(3)-C(8)-C(1)	126.1(3)
C(1)-C(5)	1.524(4)	N(2)-C(8)-C(1)	107.0(3)
C(2)-C(3)	1.515(5)	C(14)-C(9)-C(10)	120.8(3)
C(3)-C(4)	1.514(5)	C(14)-C(9)-N(2)	120.7(3)
C(4)-C(5)	1.523(5)	C(10)-C(9)-N(2)	118.4(3)
C(9)-C(14)	1.363(5)	C(9)-C(10)-C(11)	119.3(4)
C(9)-C(10)	1.372(5)	C(12)-C(11)-C(10)	120.2(4)
C(10)-C(11)	1.375(5)	C(11)-C(12)-C(13)	120.4(4)
C(11)-C(12)	1.355(6)	C(12)-C(13)-C(14)	119.9(4)
C(12)-C(13)	1.368(6)	C(9)-C(14)-C(13)	119.2(4)
C(13)-C(14)	1.382(5)	C(7)-N(1)-C(2)	125.8(3)
C(1)-O(1)-C(6)	115.3(3)	C(1)-N(1)-C(2)	119.0(3)
C(8)-N(2)-C(7)	111.5(3)	O(1)-C(1)-N(1)	113.2(3)
C(8)-N(2)-C(9)	124.1(3)	O(1)-C(1)-C(8)	114.6(3)
C(7)-N(2)-C(9)	123.8(2)	N(1)-C(1)-C(8)	101.5(2)
C(7)-N(1)-C(1)	112.6(2)	O(1)-C(1)-C(5)	107.0(2)

Table 6. Torsion angles [deg] for **104**

C(6)-O(1)-C(1)-N(1)	-61.9(4)	C(9)-N(2)-C(8)-C(1)	-172.0(3)
C(6)-O(1)-C(1)-C(8)	53.8(4)	O(1)-C(1)-C(8)-O(3)	53.9(4)
C(6)-O(1)-C(1)-C(5)	176.4(3)	N(1)-C(1)-C(8)-O(3)	176.2(3)
C(7)-N(1)-C(1)-O(1)	130.2(3)	C(5)-C(1)-C(8)-O(3)	-66.9(4)
C(2)-N(1)-C(1)-O(1)	-67.1(4)	O(1)-C(1)-C(8)-N(2)	-126.0(3)
C(7)-N(1)-C(1)-C(8)	7.0(3)	N(1)-C(1)-C(8)-N(2)	-3.7(3)
C(2)-N(1)-C(1)-C(8)	169.7(3)	C(5)-C(1)-C(8)-N(2)	113.3(3)
C(7)-N(1)-C(1)-C(5)	-110.0(3)	C(8)-N(2)-C(9)-C(14)	-101.5(4)
C(2)-N(1)-C(1)-C(5)	52.7(4)	C(7)-N(2)-C(9)-C(14)	87.9(4)
C(7)-N(1)-C(2)-C(3)	109.3(4)	C(8)-N(2)-C(9)-C(10)	76.5(4)
C(1)-N(1)-C(2)-C(3)	-50.9(4)	C(7)-N(2)-C(9)-C(10)	-94.1(4)
N(1)-C(2)-C(3)-C(4)	49.8(4)	C(14)-C(9)-C(10)-C(11)	-1.5(6)
C(2)-C(3)-C(4)-C(5)	-54.9(4)	N(2)-C(9)-C(10)-C(11)	-179.5(3)
C(3)-C(4)-C(5)-O(2)	-60.3(4)	C(9)-C(10)-C(11)-C(12)	-0.7(6)
C(3)-C(4)-C(5)-C(1)	55.4(4)	C(10)-C(11)-C(12)-C(13)	2.2(7)
O(1)-C(1)-C(5)-O(2)	-167.4(3)	C(11)-C(12)-C(13)-C(14)	-1.6(7)
N(1)-C(1)-C(5)-O(2)	69.1(3)	C(10)-C(9)-C(14)-C(13)	2.0(5)
C(8)-C(1)-C(5)-O(2)	-42.2(3)	N(2)-C(9)-C(14)-C(13)	180.0(3)
O(1)-C(1)-C(5)-C(4)	71.4(4)	C(12)-C(13)-C(14)-C(9)	-0.5(6)
N(1)-C(1)-C(5)-C(4)	-52.2(4)		
C(8)-C(1)-C(5)-C(4)	-163.5(3)		
C(1)-N(1)-C(7)-N(2)	-7.5(3)		
C(2)-N(1)-C(7)-N(2)	-168.8(3)		
C(1)-N(1)-C(7)-S(1)	172.5(2)		
C(2)-N(1)-C(7)-S(1)	11.2(5)		
C(8)-N(2)-C(7)-N(1)	4.8(3)		
C(9)-N(2)-C(7)-N(1)	176.4(3)		
C(8)-N(2)-C(7)-S(1)	-175.2(2)		
C(9)-N(2)-C(7)-S(1)	-3.6(4)		
C(7)-N(2)-C(8)-O(3)	179.7(3)		
C(9)-N(2)-C(8)-O(3)	8.1(5)		
C(7)-N(2)-C(8)-C(1)	-0.4(3)		

Cyclotetramehylene-3-phenyl-2-thiohydantion (99):



To a solution of DL-pipecolic acid (5.00 gm, 38.7 mmol) in water (30 ml), was added pyridine (5.8 ml). The reaction mixture was basified with 10% aqueous NaOH to pH 9.0 and PhNCS (7.0 ml, 58.1 ml) was added dropwise over 20 min periods under stirring condition. Portion wise 10% NaOH solution was added in between to maintain the pH at 9.0. The turbid reaction mixture was stirred for an additional 1 h. The solution was extracted with ethyl acetate (3x50 ml), the organic fraction washed with water and brine, dried over Na_2SO_4, concentrated. Crude product was purified on silica gel column with petroleum: ethyl acetate (5:1) as eluent to furnish **99** (8.58 gm, 90% yield) as a yellowish white solid.

R_f = 0.4 (25% ethyl acetate/petroleum ether)

Melting point: 146-147 °C

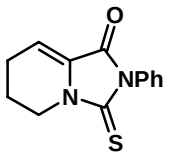
IR (ν_{max}, $CHCl_3$): 1210, 1243, 1265, 1346, 1378,1442, 1500, 1596,1752, 2859, 2947, 3062 cm^{-1}

^1H NMR ($CDCl_3$, 200 MHz): δ 1.52-1.68 (m, 3H), 1.89 (m, 1H), 2.08 (m, 1H), 2.34-2.39 (m, 1H), 3.12 (dt, *J* = 3.38, 12.49, 16.03 Hz, 1H), 4.07 (dd, 4.43, 11.26 Hz, 1H), 4.90 (dd, *J* = 2.36, 12.65 Hz, 1H), 7.28-7.55 (m, 5H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 22.2, 24.4, 27.6, 43.4, 59.8, 128.0, 128.5, 132.9, 172.4, 179.1.

Anal. Calc for $C_{13}H_{14}N_2OS$: C, 63.41; H, 5.69; N, 11.38; S, 13.08. Found: C, 63.27; H, 6.44; N, 11.41; S, 13.47.

Cyclotetramethylene-5-ene-3-phenyl-2-thiohydantion (98):



To a solution of **99** (4.00 gm, 16.26 mmol) in THF (50 ml), was added LiHMDS (24.4 ml, 1.0 M in THF) drop wise at - 40 °C under N_2 atmosphere. After stirring for 45

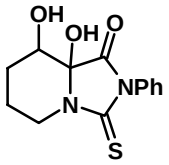
min, the reaction mixture was cannulated over a solution of PhSeCl (7.78 gm, 40.65 mmol) in THF (40 ml). Stirring was continued for 1 h under this condition and left at rt for 12 h. The reaction mixture was quenched with saturated NH_4Cl and extracted with ethyl acetate (3x100 ml). The organic fraction was washed with brine, dried (Na_2SO_4) and concentrated. The residue was purified over a silica gel column with petroleum ether: ethyl acetate (5:1) to afford **98** (2.77 gm, 70% yield).

R_f = 0.5 (25% ethyl acetate/petroleum ether)

^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.04-2.09 (m, 2H), 2.41-2.46 (m, 2H), 4.01(m, 2H), 6.28 (t, *J* = 4.36 Hz, 1H), 7.30-7.50 (m, 5H)

Anal. Calc for $C_{13}H_{12}N_2OS$: C, 63.91; H, 4.95; N, 11.47; S, 13.2. Found: C, 63.31, H, 4.32; N, 11.21; S, 13.37.

Cyclotetramethylene-5,6-dihydroxy-3-phenyl-2-thiohydantion (103):



To a solution of **98** (0.50 gm, 2.04 mmol) in a mixture of acetone: water (10:1), was added OsO_4 solution (0.7 ml in toluene) and stirred at rt for 7 h. The excess OsO_4 was quenched with solid Na_2SO_3 and subsequent stirring for 45 min. The organic solvent was removed to leave the residue, which was extracted with ethyl acetate (3x50 ml), the organic fraction was dried (Na_2SO_4), concentrated, purified on silica gel column with petroleum: ether (1:1) to afford **103** (0.24 gm, 43% yield).

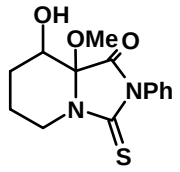
R_f = 0.4 (75% ethyl acetate/petroleum ether)

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.78-183 (m, 4H), 2.98 (dt, *J* = 3.97, 12.97, 16.56 Hz, 1H), 3.53-3.63 (m, 1H), 4.35 (dd, *J* = 4.74, 13.30 Hz, 1H), 6.96-7.15 (m, 5H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 23.6, 26.6, 42.8, 69.4, 81.9, 125.9, 128.2, 128.9, 131.1, 172.6, 178.8.

Anal. Calc for $C_{13}H_{14}N_2O_3S$: C, 56.10; H, 5.07; N, 10.06; S, 11.52. Found: C, 56.32; H, 5.23; N, 10.13; S, 11.52.

Cyclotetramethylene-5-methoxy-6-hydroxy-3-phenyl-2-thiohydantion (104):



Compound **103** (0.20 gm, 0.71 mmol) and Amberlite IR-120 (H^+) resin (1.2 gm) in dry methanol was refluxed for 4 h. It was filtered, and concentrated. The crude product was purified on silica gel column with petroleum ether: ethyl acetate (7:3) as eluent to afford **104** as a white crystalline solid (0.19 gm, 91% yield).

R_f = 0.6 (75% ethyl acetate/petroleum ether)

Melting point: 123-125 °C

^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.57 (m, 1H), 1.83 (m, 1H), 2.01 (m, 2H), 3.14 (dt, *J* = 3.21, 12.44, 16.08 Hz, 1H), 3.30 (s, 3H), 4.21 (m, 1H), 4.78 (dd, *J* = 3.96, 13.50 Hz, 1H), 7.26-7.29 (m, 2H), 7.44-7.48 (m, 3H).

^{13}C NMR ($CDCl_3$, 50 MHz): δ 18.2, 26.6, 40.8, 51.9, 68.2, 90.8, 128.5, 129.1, 129.2, 170.8, 182.0.

Anal. Calc for $C_{14}H_{16}N_2O_3S$: C, 57.53; H, 5.36; N, 9.58; S, 10.95. Found: C, 57.86; H, 6.25; N, 9.83; S, 11.02

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