STEREOSELECTIVE TOTAL SYNTHESES OF MACROCYCLIC DEPSIPEPTIDE CRYPTOPHYCIN−24, (−)−GALANTINIC ACID AND DEVELOPMENT OF HETEROGENEOUS CATALYSED SYNTHETIC METHODOLOGIES

A THESIS SUBMITTED FOR
THE DEGREE OF DOCTOR OF PHILOSOPHY
(IN CHEMISTRY)

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BY
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With

Sadhguru's blessings

Dedicated To

My Father….

DECLARATION

I hereby declare that the research work embodied in this thesis is the result of investigations carried out by me at Indian Institute of Chemical Technology, Hyderabad, under the supervision of Dr. J. S. Yadav, Director, Indian Institute of Chemical Technology, CSIR, Hyderabad–500 007, India. This work is original and has not been submitted in part or full, for any degree or diploma to this or any other university.

Place: Hyderabad, **K. V. PURNIMA**

Date: 30th June, 2011. **(Candidate)**

CERTIFICATE

I hereby certify that the entire work embodied in this thesis has been carried out by **Mrs. Venkata Purnima Kamaraju** under our supervision at Indian Institute of Chemical Technology, Hyderabad. I state that no part or full has been submitted elsewhere for any degree or diploma.

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Venkata Purnima Kamaraju

GENERAL REMARKS

1. All reactions were carried out in oven or flame–dried glassware with magnetic stirring under nitrogen atmosphere using dry, freshly distilled solvents, unless otherwise noted.
2. Commercially available compounds were used as received unless otherwise indicated.
3. All evaporations were carried out under reduced pressure on Buchi rotary evaporator or Heidolph rotary evaporator below 45 °C.
4. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm Merck Kiesel gel 60 F254 plates with UV light, iodine, 7% ethanolic phosphomolybdic acid–heat and 2.5% methanolic anisaldehyde (with 1% AcOH and 3.3% conc. H_2SO_4)–heat as developing agents.
5. Acme's silica gel 60–120 mesh or 100–200 mesh was used for flash column chromatography.
6. Yields refer to chromatographically and spectroscopically homogeneous materials unless otherwise stated.
7. IR spectra were recorded as neat liquids using ALPHA FT–IR Spectrometer (Bruker).
8. NMR spectra were recorded using $CDCl_3$ as solvent on UNITY–INOVA–500 MHz Varian, Avance–300 MHz Bruker, UNITY–400 MHz Varian and Gemini−200 MHz Varian spectrometers using TMS as internal standard or the solvent signals as secondary standards and the chemical shifts are shown in δ scale.
9. Multiplicities of ^{1}H NMR signals are designated as s (singlet), d (doublet), t (triplet), q (quartet), ABq (AB quartet), br (broad), m (multiplet, for unresolved lines), br s (broad singlet) etc.
10. ^{13}C NMR spectra were recorded on 100 and 75 MHz spectrometers with complete proton decoupling.
11. Mass spectra were recorded on a Micromass VG Autospec–M and Micromass QuattroLC mass spectrometers. Mass spectra were obtained under electro spray ionisation (ESI).

12. High Resolution Mass Spectra were measured using above mentioned mass spectrometers at 5 or 7K resolution using polyethylene glycol as an internal reference compound.
13. Accurate mass measurement was performed on Q STAR XL Hybrid mass spectrometer (Applied Biosystems, USA).
14. Optical rotations were measured with a digital Horiba–SEPA–300 polarimeter.
15. All solvents and reagents were purified and dried according to procedures given in Vogel's Text Book of Practical Organic Chemistry or Purification of Laboratory Chemicals (3^{rd} Edition) by Perrin and Armarego.

CONTENTS

Section C: The silver salt of 12−tungstophosphoric acid: A mild and selective catalyst for the synthesis of β-ketoesters *via* carbene insertion

ABBREVIATIONS

Ac	:	Acetyl
aq.	:	Aqueous
Ar	:	Aryl
(*S*)−BINAP	:	(S)- (−)-2,2'-Bis(diphenylphosphino)-1'1-binaphthyl
Bn	:	Benzyl
Boc	:	*tertiary*– Butyloxycarbonyl
^{n}Bu	:	*normal*–Butyl
Bz	:	Benzoyl
Calcd	:	Calculated
Cbz	:	Benzyloxycarbonyl
Cp	:	Cyclopentadienyl
m–CPBA	:	*meta*–Chloroperbenzoic acid
CSA	:	Camphor–10–sulfonic acid
DBU	:	1,8-Diazabicyclo[5.4.0]undec-7-en
DCC	:	N,N'-Dicyclohexyl-Carbodiimide
DDQ	:	2,3–Dichloro–5,6–dicyanobenzoquinone
DIBAL–H	:	Diisobutylaluminium hydride
DIPEA	:	*N*,*N*–Diisopropylethylamine
2,2−DMP	:	2,2−dimethoxy propane
DMAP	:	4–Dimethylaminopyridine
DMD	:	dimethyldioxirane
DMF	:	*N*,*N*–Dimethylformamide
DMP	:	Dess–Martin periodinane
DMSO	:	Dimethyl sulfoxide
DNA	:	Deoxyribonucleic acid
dr	:	Diastereomeric ratio
EDCI	:	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EI−MS	:	Electron impact mass spectrometry
ESI–MS	:	Electrospray ionization mass spectrometry
Et	:	Ethyl

Et_3N	:	Triethylamine
EtOAc	:	Ethyl acetate
EtOH	:	Ethyl alcohol
FDPP	:	pentafluorophenyl diphenylphosphinate
GTP	:	Guanosine-5'-triphosphate
GDP	:	Guanosine-5'-diphosphate
h	:	Hour
HOAt	:	Hydroxy azabenzotriazole
HOBt	:	Hydroxy benzotriazole
HRMS	:	High resolution mass spectrometry
NBS	:	*N*−bromo succinimide
Hz	:	Hertz
IR	:	Infrared
LC−MS	:	Liquid chromatography mass spectrometry
LDA	:	Lithium diisopropylamide
Me	:	Methyl
min	:	Minute(s)
MeOH	:	Methyl alcohol
MOM	:	Methoxy methyl
Ms	:	Methanesulfonyl (mesyl)
4 Å MS	:	4 Å Molecular sieves
MHz	:	Megahertz
NaHMDS	:	Soduim bis(trimethylsilyl)amide
NMO	:	*N*− Methylmorpholine-*N*-Oxide
NMR	:	Nuclear magnetic resonance
Ph	:	Phenyl
PMB	:	*para*–Methoxybenzyl
PPTS	:	Pyridinium *p*-toluenesulfonate
^{i}Pr	:	*iso*–Propyl
quant.	:	Quantitative
Red-Al	:	Sodium bis(2–methoxyethoxy)aluminium hydride

rt	:	Room temperature
R_f	:	Retardation factor
TBAF	:	Tetra–*n*–butylammonium fluoride
TBAI	:	Tetra–*n*–butylammonium iodide
TBDPSCl	:	*tertiary*–Butyldiphenylsilyl chloride
TBHP	:	*tertiary* –Butylhydroperoxide
TBSCl	:	*tertiary*–Butyldimethylsilyl chloride
TBSOTf	:	*tertiary* –Butyldimethylsilyl trifluoromethanesulfonate
TEMPO	:	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl, or (2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl
TESOTf	:	Triethylsilyl trifluoromethanesulfonate
TFA	:	Trifluoro acetic acid
THP	:	Tetrahydropyran
TIPSOTf	:	Triisopropylsilyl trifluoromethanesulfonate
TMS	:	Tetramethylsilane
TLC	:	Thin layer chromatography
TPP	:	Triphenylphosphine
p−TSA	:	*p*–Toluenesulfonic acid

SYNOPSIS

CHAPTER–I

INTRODUCTION

Cancer is one of the most notorious health problems worldwide. Cancer can occur in almost any cell. It begins with damaged DNA, the "building block of life" that controls all cell functions, which reins the entire function of the body. Cells with damaged DNA can divide rapidly or outlive normal cells.

Cell division is arguably one of the most complex and demanding processes undertaken by the body. During cell division, the cell must completely duplicate its internal components, including the whole of its DNA, such that it can form two identical daughter cells. Once duplication of the internal components has been completed, the cell must then order its DNA into two identical sets of chromosomes and separate them into two distinct parcels at opposite ends of the cell, ready to form two nuclei, the cell is then ready to split into the two new daughter cells. This ordering and relocation of the genetic material, which takes about an hour, is known as mitosis,[1] and falls into five distinct phases.

This cell division is more frequent in cancer cells than normal cells. Most of the time, the body's immune system recognizes these damaged cells and destroys them. However, if this normal process does not happen, a *tumor* can grow. Most cancers form a tumor but some, like leukemia, do not. So the inhibitors target is Tubulin, which is a hetero−dimer of α-tubulin and β-tubulin which forms long, dynamic polymers which associate to tube shaped microtubules.

Microtubles are eukaryotic cellular structures involved in the movement of positioning of chromosomes during mitosis as well as the movement of vesicles and organelles within these cells. The dynamic nature of the equilibrium between microtubules and tubulin along with their involvement in cell division has made them an important target in anticancer research.

Anti cancer agents constitute an important topic of current research all over the world. The major classes of antimicrotubular drugs, commonly known as spindle poisons are grouped according to their site of action on tubulin. Some of the agents have been shown to act as clinically useful anticancer agents.[2] The wide variety of antimicrotubular drugs in nature can be appreciated with excellent activity with such complex structures (Figure 1). Some examples of antimicrotubular drugs are

Halichondrin−B (**1**), [3] Discodermolide (**2**),[4] Taxol (**3**),[5] Vinblastine (**4**),[6] Cryptophycins (Figure 3), Dolastatin−15 (**5**),[7] Okadaic acid (**6**),[8] etc.

Figure 1

Interference with microtubule dynamics is the common and most important chemotherapeutic property of an anticancer drug. Most of anticancer agents interact with tubulin at one of the three major binding sites (Figure 2) either at the paclitaxel site, at the *vinca* domain or at the colchicine binding site.[9,10] All compounds binding at the paclitaxel site (e.g. taxanes, epothilones, and discodermolide) inhibit microtubule depolymerisation at high agent concentration and thus have a stabilising effect on microtubules. In contrast, all agents binding at, or near, the *vinca* domain (e.g. vinblastine, vincristine, cryptophycins, dolastatins, and hemiasterlins) or at the colchicine site (e.g. combretastatine, 2-methoxyestradiol, and methoxybenzene sulfonamide) inhibit microtubule polymerisation at a high concentration.[11]

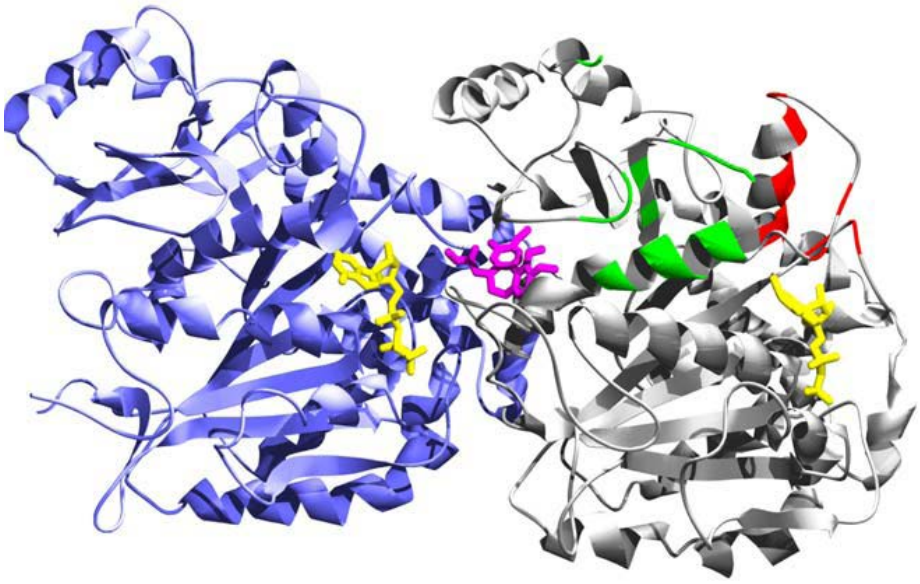


Figure 2: X−ray structure of tubulin, viewing the three major binding sites of antimitotic agents on β-tubulin: light blue = α-tubulin; grey = β-tubulin; red = proposed 'peptide site' (binding site of cryptophycins, overlapping with the *vinca* domain), green = paclitaxel binding site, [12] purple = colchicine at its binding site between α- and *β*-tubulin, [13] yellow = GTP/GDP.

Unlike paclitaxel−site binding agents, the latter two classes of compounds inhibit nucleotide exchange and GTP hydrolysis on β−tubulin, thus preventing microtubule assembly.[10] At low drug concentrations, both tubulin−stabilising and tubulin−destabilising agents suppress microtubule dynamics without affecting microtubule mass, and ultimately lead to a block in cell division.

The bioactivity of cryptophycins is based on their ability to interact with tubulin. Cryptophycins have a much higher affinity towards tubulin than other mitosis inhibitors.[14] These cryptophycins bind the tubulin at the *vinca* domain. It seems likely that epoxide-containing cryptophycins covalently bind to tubulin by nucleophilic attack of an amino acid side chain to the epoxide.

Cryptophycins are a class of macrocyclic depsipeptides produced as secondary metabolites from *Nostoc* sp. strains ATCC 53789, isolated by Schwartz and coworkers.[15] Although, the Schwartz group has established the structure; no details of the absolute stereochemistry was demonstrated. Subsequently, a variety of cytotoxins were isolated by Moore *et al* from a crude lipophilic extract of *Nostoc* sp. GSV 224 with their absolute stereochemistry.[16a] These cryptophycins have demonstrated extreme cytotoxicity against yeast of the genus *Cryptococcus,* which frequently infect immunodeficient [16] persons suffering from diseases such as AIDS and cancer so the name cryptophycins was given. These cyclic depsipeptides are remarkably potent against tumor cell lines.[16b]

Cryptophycin A (**7**) and B (**8**) exhibit cytotoxic IC_{50} values of 5 and 7 pg/mL, respectively against KB cells. In 1994, arenastatin A (**12**) (renamed as cryptophycin−24), another member of the cryptophycin family, was isolated by Kobayashi *et al.* from the Okinawa marine sponge *Dysidea arenaria*. It also exhibits cytotoxicity with IC_{50} value of 5 pg/mL against KB cells.[17] In 1995, Moore *et al* have discovered that the synthetically derived cryptophycin 8 (**14**) is more active *in vivo* than (**7**) (Figure 3a,b).[18] Later on, cryptophycin−52 (**13**) and −55 (**15**) have also been tested, with positive results.[19]

Figure 3a: Structures of Cryptophycins

Figure 3b: Structures of Cryptophycins

Contemporary works:

The significant clinical potentials of cryptophycins and their low natural abundance have made them attractive synthetic targets. Consequently, there have been some reports on the total synthesis of cryptophycins following multi−step synthetic sequences. For the retrosynthetic analysis cryptophycins can be disconnected into four units or fragments. Unit A is the only polyketide derived molecular fragment, which provides the greatest synthetic challenge. Unit B is a Tyrosine derivative, where as unit C and D correspond to (*R*)-3-amino-2-methyl-propanoic acid or β-alanine or 3-amino-2,2-dimethylpropanoic acid and (*S*)-2-hydroxy-4-methylvaleric (*L*-leucic) acid, respectively (Figure 4).

Figure 4

First total synthesis by Tius′s group:

Tius′s group[16c] have reported the first relative and absolute stereochemistry for cryptophycins in 1994. Their synthetic approach is illustrated in Scheme 1.

Scheme 1

The synthesis began with the DIBAL-H reduction of enolate **27**, which was prepared from commercially available dihydro cinnamaldehyde **28** and trimethyl phosphonoacetate. Sharpless′ asymmetric epoxidation on the allyl alcohol followed by opening of epoxide **26** yielded diol **25**. Diol **25** was brominated at benzylic position leading to unstable bromide, which was immediately dehydro brominated by exposure

to DBU to afford acetonide compound **24**. Hydrolysis of the acetonide **24** followed by tosylation of primary hydroxyl alcohol, convertion of the secondary alcohol as its silyl ether, displacement of the tosylate by cyanide and DIBAL-H reduction provided aldehyde **23**, which upon Horner−Emmons homologation afforded the protected fragment A **18** of cryptophycin−I. This was coupled with tyrosine derivative, which was prepared from commercially available D-tyrosine in five steps. Unit C **21** was prepared from (*S*)-(+)-3-hydroxy-2-methyl propanoate **22** in four steps. Unit D **20** was obtained by allylation on *L*−leucic acid. The coupling of C and D was accomplished with DCC and DMAP followed by deprotection of allyl ester to give CD subunit **19**. The ester linkage between **19** and **17** was installed with DCC to produce *seco* compound **16**. Macrolactamisation followed by epoxidation with m-CPBA led to a mixture (2:1) of cryptophycin−1 and the corresponding (*S*,*S*)-*trans*−epoxide.

Gardinier′s approach:

The Leahy−Gardinier[20] synthesis of cryptophycin−1 started with Evans′ aldol reaction of (*R*)-mandelaldehyde derivative **39** that furnished the aldol adduct **38**, which was converted to **37**. Tishchenko reduction of C_5 keto group in compound **37** generated compound **36** (Scheme 2). The conversion of **36** to unit A precursor **31** was accomplished by oxidative cleavage of terminal alkene to aldehyde followed by Horner−Emmons homologation using Masamune−Roush conditions. Unit C was prepared from compound **35** and coupled with Tyrosine derivative **33** and then L−leucic acid benzyl ester **32** was coupled to generate peptidic subunit **30**. Coupling of unit A **31** with BCD subunit **30** was carried out under Yamaguchi conditions and macrolactamisation furnished the macrolide **29**. Finally β–epoxide was generated with a modification in Sharpless′ procedure to reach the target molecule **7**.

The limitation for this procedure is that the Evans′ aldol reaction is sensitive to scale. On larger scale, increasing quantities of the undesired isomer **41** was generated; therefore this reaction was limited to a 2 g scale only.

Scheme 2

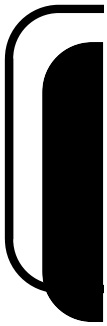
Tius′s approach:

Tius *et al* [21] have synthesized fragment A **42** from (*S*)-*E*-3-pentene-2-ol **47** *via* a [2,3] Wittig rearrangement (Scheme 3). Exposure of **47** to propargyl bromide and base under phase transfer conditions led to the allyl propargyl ether **46**. Anionic Wittig rearrangement afforded the compound **45**. Protection of C−5 alcohol as the silyl ether, selective hydroboration of the terminal alkyne followed by oxidation afforded the aldehyde **44**. Horner−Emmons homologation and selective ozonolysis of the electron rich double bond yielded the aldehyde **43**. Wittig reaction of **43** with benzylidene triphenylphosporane led to an E/Z mixture of styrenes that were isomerized to the stable *E*−geometrical isomer **42** by PhSH and VAZO 88.

Scheme 3

After the succesful synthesis of cryptophycin fragment A they started the total synthesis of cryptophycin−1. Tius *et al* [22] synthesis relies on Hetero Diels−Alder reaction, intramolecular Michael addition and Horner−Emmons reactions as a key strategy (Scheme 4). This synthesis was started with (*R*)-methyl mandelate derivative **55** as the sole source of asymmetry, which was combined with diene **56** in a magnesium bromide−catalyzed hetero−Diels−Alder reaction. Acid catalyzed cleavage of the ethoxyethyl protecting group in **54** was followed by intramolecular Michael addition of the hydroxyl to give bicyclic products **53a** and **53b**. Epimerization of **53b** and reduction

with L−selectride, protection of aldehyde resulted compound **52**, which was subjected to Horner−Emmons reaction that led to unit A precursor **51**. Coupling of unit A **51** with tyrosine derivative **50** and CD subunit **19** yielded compound **48**, which was subjected to macrolactomisation and a modified Sharpless′ procedure to accomplish the target molecule cryptophycin−1.



Scheme 4

White′s approach:

White and co-workers[23] reported a synthesis of unit A based on asymmetric crotyl boration reaction (Scheme 5). The synthesis commenced from 1,3- propanediol which was converted to aldehyde **61** in two steps. Brown's asymmetric crotyl boration

followed by oxidation led to homoallylic alcohol **60**. Protection of secondary hydroxyl group as its silyl ether followed by ozonolysis yielded the aldehyde **59**. Horner−Emmons reaction of **59** with diethyl benzyl phosphonate gave the (*E*)− isomer **58** as the exclusive product. Selective deprotection of the primary silyl ether followed by oxidation afforded the aldehyde **23** which upon Horner−Emmons homologation with (*t*−butoxycarbonylmethylene) triphenylphosphorane afforded the protected fragment A **57** of cryptophycin.

Scheme 5

Furuyama and Shimizu′s approach:

Furuyama and Shimizu have achieved the synthesis [24] of unit A by applying palladium catalyzed reductive opening of optically active alkenyl oxirane. PMB derivative of 3-hydroxy propanal **67** upon Wittig olefination and subsequent DIBAL-H reduction provided the allyl alcohol **66**. Sharpless′ epoxidation of **66** followed by Swern oxidation afforded the aldehyde **65**. Wittig olefination of **65** with benzylidene triphenylphosphorane at −100°C to room temperature led to the *Z*−olefin **64**. Palladium mediated reduction−isomerization converts *cis*-isomer **64** to *trans*-isomer **63**. PMB deprotection using $AlCl_3$ gave the diol, followed by protection of both the hydroxyl groups as silyl ether and selective deprotection of primary silyl ether afforded **62**. Swern oxidation followed by Horner−Emmons homologation accomplished the unit A **18** (Scheme 6).

Scheme 6

Eli Lilly Company′s approach:

Chemists at Eli Lilly company [25] have described a successful chemoenzymatic synthesis of unit A, which involves enzymatic resolution, Baeyer−Villiger oxidation and Horner−Emmons homologation as key steps (Scheme 7). (*R*)−Carvone **74** was bioreduced with *Trigonopsis variabilis* (ATCC 10679) using glucose as a carbon source to produce alcohol **73** (98% ee). Protection of free hydroxyl group as its TBS ether followed by ozonolysis and Criegee rearrangement provided the compound **72**.

Scheme 7

Alcohol in compound **72** was oxidized to ketone **71**, followed by Baeyer-Villiger oxidation and deprotection of silyl ether to afford the alcohol **70**, and its regioisomer in 98:2 ratio. Cleavage of lactone in **70** with DIBAL-H followed by Horner−Emmons homologation provided the diol **69**. Oxidation of the primary alcohol to aldehyde followed by addition of PhMgBr gave diastereomeric benzylic alcohols **68** which were dehydrated with Ms_2O and Et_3N to afford the unit A of cryptophycin **18**.

Ghosh′s appoach:

A. K. Ghosh and co-workers [26] have reported a very unconventional strategy for the synthesis of cryptophycin B which involved ester-derived titanium-enolate-mediated *syn*-aldol reaction to set the stereocentres at C-5 and C-6 of fragment A.

Scheme 8

Acylation of (+)-(1*R*,2*S*)-1-(*N*-tosylamino)-2-indanol with *trans*-4-phenyl -3-butenoic acid using DCC and DMAP afforded the ester **82**. Reaction of the titanium

enolate of **82** with 3-benzyloxy propanal **83** at −78°C furnished the aldol adduct **81** as a single diastereomer. Reduction of **81** with LAH afforded the diol, which upon selective protection of the primary hydroxyl as its tosylate afforded **80**. The replacement of tosyl group in **80** with hydrogen provided the alcohol **79**. Protection of secondary hydroxy as its silyl ether followed by debenzylation afforded the alcohol **78**. PCC oxidation and Horner−Emmons olefination provided the silyl protected Unit A of cryptophycin **77**, which was coupled with Tyrosine derivative to afford the amide **76**. Amide **76** was coupled with CD subunit **19** under Yamaguchi conditions resulting in compound **75**. Macrocyclization under Yamaguchi conditions followed by epoxidation with DMD furnished the cryptophycin−B in 3:1 mixture of epoxides (Scheme 8).

Georg′s approach:

Georg group [27] have made clever use of the Noyori asymmetric hydrogenation in order to control the absolute stereochemistry at C_5 of unit A. Methyl 5-benzyloxy-3-oxopentanoate **88** was hydrogenated in presence of (*S*)−BINAP/$RuBr_2$ to give the (*R*)-alcohol **87** in 97% ee, which upon Frater alkylation afforded the product **86** with 90% *de*. The benzyl ether in **86** was converted to its silyl ether and the ester group was transformed to aldehyde that led to compound **59**. The aldehyde **59** was altered to the unit A **88** in the similar sequence as in Scheme 9.

Scheme 9

In 2001, Georg group have reported a total synthesis of cryptophycin−24 *via* acyl-β-lactam macrolactamization. This synthesis was started with esterification of the

secondary alcohol **94** with leucic acid segment **95** that yielded compound **93**. The *p*-methoxybenzyl ether was deblocked and oxidized followed by reaction with neutral phosphorane that produced the *t*-butyl ester **91**. Deprotection of the *t*-butyl ester followed by coupling with aminoacylazetidinone **92** furnished compound **90**. Deprotection of silyl group followed by macrolactamization provided macrolide **89**. Finally, phenyl group was introduced under Heck conditions and epoxidation with DMD accomplished cryptophycin−24.

Scheme 10

Georg and Tripathy[29] have published another approach to cryptophycin−24 which relies ring closing metathesis and asymmetric dihydroxylation as key strategy. A Heck reaction of compound **105** with iodobenzene gave styrene derivative **104**, followed by asymmetric dihydroxylation to furnish the stereogenic *syn*-diols **103** with 95% *de*. The diol **103** was converted to corresponding epoxide **102** *via* the cyclic orthoformate and *O*-formyl bromohydrin, by treating with potassium carbonate. The primary alcohol was oxidized and subjected to Tebbe olefination to form the terminal olefin. Deprotection of the silyl ether accomplished the homoallylic alcohol unit A precursor **98**, which was coupled with peptidic subunit **97** under Yamaguchi conditions

to obtain diene **96**. The peptidic subunit was prepared from tyrosine derivative **101**, β-alanine methyl ester **100** and L-luecic acid *t*-butyl ester **99**. Ring closing metathesis was applied to diene **96** to complete the target molecule (Scheme 11).

Scheme 11

Larchevêque′s approach:

Larchevêque and his co-workers[30] have reported a synthesis of cryptophycin fragment A with four stereogenic centres which relies on Sharpless′ epoxidation and HWE reactions as a key strategy. They envisioned the synthesis could be started with (*R*)-methyl mandelic acid derivative **114**, which was reduced to the aldehyde with DIBAL-H. An *O*−silyl protected magnesium alkynide was then added diastereoselectively to give compound **113**. The triple bond was reduced with Red−Al

under Denmark conditions to furnish *trans*−double bond **112**, which was converted to epoxide **111** with 95:5 *de* under Sharpless′ conditions. Epoxide was opened with trimethylaluminium to give **110**, which was submitted to a diol−epoxide transformation that accomplished the stereogenic epoxide **109** with net retention of configuration at the former stereogenic hydroxyl group. The epoxide was opened with cyanide to provide nitrile **108** followed by the protection of free hydroxy group to its silyl ether and the nitrile group was reduced to aldehyde **107** with DIBAL-H. This aldehyde **107** was subjected to HWE reaction to finish the synthesis of fragment A **106** (Scheme 12).

Scheme 12

Raghavan′s approach:

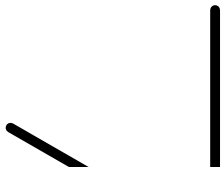
Raghavan and his co-worker have reported a synthesis[31] of fragment A of cryptophycin−3. The key step involves the regio and stereoselective transformation of an unsaturated ester to bromohydrin *via* anchimeric assistance by the sulfinyl group. Their synthesis was commenced from alcohol **120**, which was prepared from the oxazolidinone and methacraloyl chloride. Swern oxidation followed by Wittig olefination using Still's phosphonate afforded the *cis*−ester **119** as a predominant product. The sulfide upon oxidation afforded equimolar, inseparable mixture of sulfoxides which were treated with NBS to yield the bromohydrins **118** as a mixture. The debromination of bromohydrin afforded sulfoxide followed by the reduction of carbomethoxy group with DIBAL-H furnished aldehyde. Two−carbon homologation by

subjecting the aldehyde to treatment with methyl (triphenyl phosphoranylidene) acetate afforded the *trans*−ester **117**. Compound **117** was submitted to Pummerer reaction followed by sodium bicarbonate workup to yield the aldehyde **116**. Wittig reaction of aldehyde revealed the mixture of *cis*− and *trans*−isomer, which were isomerized to *trans*-isomer with thiophenol to accomplish the dienolate **115** (Scheme 13).

Scheme 13

Sewald′s approach:

Two short synthetic approaches reported towards cryptophycin unit A [32] **121** consist of a catalytic asymmetric dihydroxylation as the sole source of chirality, while all further stereogenic centres are introduced under substrate control (Scheme 14a). The key step of the first route is a vinylogous Mukaiyama aldol addition, which introduces α, β-unsaturated ester moiety **121** with defined configuration at the α-carbon atom. This synthesis was commenced from (*E*)-4-phenylbut-3-enoic acid **128**, which was converted to its methyl ester **127**. Asymmetric dihydroxylation of **127** under concomitant lactonization gave β-hydroxylactone **126**. α- Methylation with LDA yielded compound **125** without any O-methylation. Opening of lactone gave its methyl ester and resulted diol was protected as acetonide by treatment with 2,2-dimethoxypropane, methanol, and Amberlyst-15 to furnish **124**. The ester **124** was converted to aldehyde **123** with DIBAL-H. The magnesium bromide diethyl etherate mediated vinylogous Mukaiyama aldol addition of (*E*,*Z*)-(1-*tert*-butoxybuta- 1,3-dienyloxy)trimethylsilane **122** to aldehyde **123** gave unit A precursor **121** with 95% *de*.



Scheme 14a

Due to moderate yield in aldol addition step and synthesis of silyl ketone acetal, they investigated an alternative root to prepare **121**. The Heck allylation of aldehyde **123** with allyltributylstannane gave homoallylic alcohol **129** with 98% *de* (Scheme 14b). A cross metathesis reaction with homoallylic alcohol **129** and *t*-butylacrylate **130** was carried out to accomplish the unit A precursor **121**.

Scheme 14b

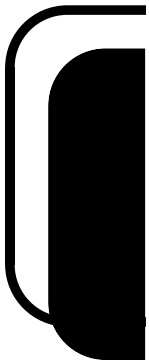
Utilizing this short synthesis Sewald *et al* [33] have synthesized cryptophycin−52 and its three analogues. The synthetic route consists of macrocyclization of the *seco*-depsipeptide based on ring closing metathesis and Yamaguchi esterification.

PRESENT WORK

The prosperity of biological functions and their importance prompted us to initiate a program aimed at the total synthesis of cryptophycin−24.

In recent days, Prins cyclization has become a powerful synthetic tool for the construction of carbocyclic and heterocyclic compounds such as multi−substituted tetrahydropyrans.[34] Owing to its high stereoselectivity, it has found wide applications for the synthesis of polyether antibiotics and other complex natural products [35] that contain multi-substituted tetrahydropyran backbones. The utility of this method lies in its ability to simultaneously form carbon-carbon bonds and introduce hetero-functionality in a predictable and stereocontrolled manner. A variety of heteroatom-stablized carbocations have been cyclized including oxenium, thienium, and iminium carbocations. The cyclization proceeds through the addition of dioxenium cations onto unactivated olefins resulting in the formation of 4-hetero-substituted pyranosides. Our group has made a significant effort to explore the utility of Prins cyclization in the synthesis of various polyketide intermediates and applied it to the total synthesis of some natural products.[36] In the ongoing program on the utilization of the highly stereoselective Prins cyclization reaction for the synthesis of polyketide motifs, the total synthesis of cryptophycin−24 (arenastatin A) was undertaken.

Retrosynthetic strategy for the cryptophycin−24 has been summarized in Scheme 15. We have envisaged that total synthesis of cryptophycin−24 can be achieved by macrocyclization based on ring closing metathesis. Initial bond disconnection at the conjugated alkene suggests coupling employing ring closing metathesis in the diene **132**, which upon selective epoxidation with 1,2 *syn*-diols provides access to target molecule. It was predicted that diene **132** could be obtained by esterification between the polyketide unit **129** and depsipeptide unit **97** under Yamaguchi conditions.



Scheme 15: Retrosynthetic analysis of cryptophycin−24

The key fragment **129** with 1,3-diol system could be achieved from homoallylic alcohol **135** involving Prins cyclization, stereoselective phenyl Grignard reaction and Wittig reaction as key steps. The polyketide unit **129** can be prepared from **133**, which could be derived from the 2,4,5,6-tetrasubstituted tetrahydropyran **134** *via* ring opening and stereoselective phenyl Grignard reaction followed by few functional group manipulations. The tetrasubstituted tetrahydropyran **134** could be easily constructed through the Prins cyclization of homoallylic alcohol **135** and aldehyde **83**. The homoallylic alcohol **135** could be obtained from (*S*)-benzyl glycidyl ether **136** by regioselective opening of epoxide and Birch reduction, where as the aldehyde **83** was prepared from 1,3-propanediol.

Synthesis of Cryptophycin−24:

Our synthesis commenced from benzyl glycidyl ether **140**, which was prepared from *epi*-chlorohydrin **139** and benzyl alcohol in 88% yield. Jacobsen kinetic resolution of benzyl glycidyl ether **140** using (*R*,*R*)−(salen)Co(II) precatalyst, AcOH and H_2O (0.51 eq.) for 22 h resulted in (*S*)−benzyl glycidyl ether **136** in 46% yield. The analytical data of compound **136** were in good agreement with the reported values.[37]

Scheme 16

Regioselective opening of epoxide **136** with propynyllithium, formed on treatment of condensed propyne gas with *n*-BuLi, in the presence of $BF_3.OEt_2$ in THF at –78 °C resulted in homopropargyl alcohol **141** in 86% yield (Scheme 16). Formation of product was ascertained from ^{1}H NMR spectrum, where the absence of epoxide protons and presence of methyl protons along with the other required protons confirmed the product. In addition to this, a signal at *m/z* 204 in the EI–MS spectrum of compound

141 that corresponds to the $[M+H]^+$ was additional support for the formation of the product.

Birch reduction of **141** using Na in liquid NH_3 furnished dihydroxy *trans*-olefin **135** in 6 h in 86% yield. [38] In ^1H NMR spectroscopy, appearance of a multiplet at δ 5.61−5.35 integrating two protons, a multiplet at δ 2.14 integrating three protons along with the other required protons confirmed the conversion. Signal at *m/z* 116 in the EI–MS spectrum which corresponds to the $[M]^+$ further justified the product.

Aldehyde required for the Prins cyclization is prepared from 1,3-propanediol as shown in Scheme 17. Monoprotection of commercially available 1,3-propanediol with benzyl bromide and sodium hydride in 6 h gave 3-benzyloxy propanol **142** in 70% yield. Appearance of signals at δ 7.29 as multiplet integrating for 5 protons corresponding to Ph*H* and a singlet integrating for 2 protons at δ 4.5 corresponding to OCH_2Ph group in the ^1H NMR spectrum of compound **142** confirmed the monoprotection. In addition to this, a signal at *m/z* 167 in the ESI–MS spectrum of compound **142** that corresponds to the $[M+H]^+$ was additional support for the formation of the product. The alcohol **142** was oxidized with PCC in 4 h to furnish 3-benzyloxy propanal **83** in quantitative yield which was taken forward to next reaction, after a flash column chromatography, without any further characterization.

Scheme 17

Now the two components were ready for the Prins cyclization. The crucial Prins cyclization was achieved by subjecting the *trans*-homoallylic alcohol **135** and three eq. of 3-benzyloxy propanal **83** in the presence of TFA in CH_2Cl_2 to obtain trifluoroacetate **143**. Constant persuasion of thin layer chromatography showed the complete consumption of homoallylic alcohol after 4 h. After work up, the crude trifluoroacetate **143** on hydrolysis with K_2CO_3 in methanol yielded desired tetrasubstituted pyran **134**

in 65% yield (Scheme 18). Stereochemistry was assumed to be in anticipated line as it was well examined and established previously.[36]

Scheme 18

Formation of Prins product was ascertained from its ^{1}H NMR and mass spectrum. The ^{1}H NMR spectrum of compound **134** showed 3 methyl protons integrating at δ 0.99 as doublet. Presence of equatorial proton around δ ~2.0 was the additional proof for the structure. In addition to this, high resolution ESI mass spectrum carrying a signal at *m/z* 303.1564 corresponding to $[M+Na]^{+}$ (calcd 303.1572) was also in good agreement with the successful formation of the prins product.

Proposed mechanism for Prins cyclisation:

Figure 5: Formation of the *syn*−THP ring

A plausible mechanism for the *syn*−selectivity is shown in Figure 5. Competition exists between the sterically stable and favored transition state T.S1 and unstable T.S−2, which is having 1,3-diaxial interactions.[39] The favored T.S−1 leads to the conventional *syn*−isomer **A** whereas T.S−2 leads to *anti*−isomer **B**. In both cases, axial nucleophilic attack by the external nucleophile at the 4-position is prevented. Obviously, *syn*−isomer is major product, which comes from favored transition state.

The primary hydroxyl group of compound **134** was selectively protected as its tosylate using *p*-TSCl and triethyl amine in CH_2Cl_2 in 82% yield. The ^{1}H NMR spectrum of compound **144** exhibited signals at δ 7.75 and 7.25 for additional phenyl protons as doublet that indicated 2,4-disubstituted phenyl ring and δ 2.42 for methyl protons in tosyl group. It was further confirmed by its ESI mass spectrum, which showed a $[M+H]^+$ peak at *m/z* 435.2 (Scheme 19).

Scheme 19

The secondary hydroxyl group in compound **144** was protected as MOM ether with MOM−Cl and DIPEA in CH_2Cl_2 for 6 h to afford compound **145** in 76% yield (Scheme 19). The compound **145** was evidenced by the ^{1}H NMR spectrum, in which the additional signals appeared at δ 4.68−4.53 for −OC*H*$_2$OCH$_3$ protons and δ 3.33 for −OCH$_2$OC*H*$_3$ protons. In addition to this, a signal at *m/z* 501 in the ESI–MS spectrum of compound **145** that corresponds to the $[M+Na]^+$ was additional support for the formation of the product.

The primary tosyl group in **145** was converted to iodo by treatment of tosylated compound with NaI in acetone under reflux conditions for 24 h to give the respective iodo compound **146** in 86% yield. The reaction was confirmed from ^{1}H NMR spectrum

and ^{13}C NMR spectrum of iodo compound which shows the absence of tosyl group. ESI mass spectrum of **146**, which showed a $[M+Na]^+$ peak at *m/z* 457.0, was also in good concurrence with the successful formation of **146**.

The iodo compound **146** was exposed to potassium *t*-butoxide [40] in dry THF and a subsequent rearrangement on silica gel [36d] gave the key unstable alkene intermediate **147** in 55% yield. Appearance of characteristic peaks for trisubstistuted alkene at δ 4.69−4.60 as a multiplet for 1H and CH_3 at δ 1.71 as a singlet in ^{1}H NMR spectrum ensured the formation of compound **147**. A peak at *m/z* 329.1 $[M+Na]^+$ in the ESI−MS, indicated the formation of desired compound.

Scheme 20

Ozonolysis of the alkene **147** gave the corresponding aldehyde **148**, which was taken forward to next reaction, without any further characterization. Intially, we attempted this phenyl Grignard reaction without chelation control. Surprisingly, there was no selectivity in this reaction, and resulted in mixture of inseparable diastereomers. Then we was endeavored this reaction with temperature variation, which was also unsuccessful. Afterwards, we overcame this problem *via* chelation controlled reaction. The adjacent chiral hetero atom was used to chelate the aldehyde. We predicted that the magnesium diethyletherate could be a good chelating agent to yield the desired selectivity.

The crude aldehyde **148** was subjected to phenylmagnesium bromide in presence of magnesium bromide diethyl etherate in CH_2Cl_2 at –78 °C that produced exclusively *syn*−selective alcohol **133**, in 72% overall yield.[41] Ideal support for the formation of the product was obtained from the ^{1}H NMR spectrum of the compound **133** showing signals corresponding to additional phenyl moiety at δ 7.18−7.38 and benzylic proton at δ 4.73. High resolution ESI mass spectrum carrying a signal at *m/z* 439.2075 corresponding to $[M+Na]^+$ (calcd 439.2096) was also in good agreement with the formation of the compound **133** (Scheme 20). The stereochemistry of the newly generated chiral centre carrying the phenyl group was further more confirmed by transforming **133** into compound **129** in advance steps.

Figure 6: Chelation model for 1,2 *syn*−selectivity

Chelation controlled with metal co-ordination has been illustrated in Figure 6. Initially, Magnesium bromide chelates with aldehyde and the adjacent protected oxygen as showed in Newmann projection. The most stable conformation will then be attacked by the nucleophile from the least hindered side, here the hydrogen. After nucleophile attack the product was in stable conformation which leads to 1,2-*syn* diols.

MOM group was deprotected in compound **133** with 10 mol% of *p*-TSA in methanol under reflux conditions to afford the corresponding diol **149** in 65% yield. Disappearance of the characteristic peaks in ^{1}H NMR corresponding to−OC H_2OCH_3 group along with all other signals indicates the deprotection of MOM group. A peak at

m/z 395.2 $[M+Na]^+$ in the ESI-MS, gave the extra support for the formation of compound **149** (Scheme 21).

Scheme 21

The diol was protected as acetonide with 1,2-dimethoxypropane in the presence of catalytic amount of PPTS in CH_2Cl_2 as solvent for 3 h to afford compound **150** in 92% yield.The formation of compound **150** was characterized by ^{1}H NMR, which showed the appearance of peaks at δ 1.45 as singlet for 3H and δ 1.39 as singlet for 3H corresponding to two methyl groups in acetonide. The *J* coupling of 8.8 Hz of the acetonide ring protons of **150** confirmed the *R*−stereochemistry of the new chiral centre. Appearance of peaks at δ 27.2, 27.1 in the ^{13}C NMR spectrum of the compound **150** suggested the successful protection. In addition to this, a signal at *m/z* 435 in the ESI–MS spectrum which corresponding to $[M+Na]^+$ also supported the formation of the product.

Scheme 22

The acetate in **150** was hydrolyzed with 1.5 eq. of K_2CO_3 in methanol for 2 h to yield alcohol **151** in quantitative yield. Debenzylation of **151**, using 5 mol% Pd/C in methanol at room temperature under hydrogen atmosphere for 3 h gave the desired compound **152** in 82% yield. The absence of aromatic protons and benzylic protons signals in the ^{1}H NMR spectrum of compound **152** was also in concurrence with the debenzylation of **151**. ESI mass spectrum (*m/z* 303.2 $[M+Na]^+$) analysis was also in accordance with the expected compound.

Scheme 23

Selective oxidation of primary hydroxyl group in **152** with TEMPO and iodo benzene diacetate in CH_2Cl_2 afforded desired aldehyde, which was subjected to next reaction without further purification. Wittig olefination [42] of the resulting aldehyde with excess C_1−ylide generated *insitu* with the reaction of ICH_3PPh_3 and potassium *t*-butoxide gave the target fragment A of cryptophycin **129** in 76% yield. Appearance of characteristic peak for olefin protons at δ 5.79−5.61 and 5.04−4.92 along with other peaks in the ^{1}H NMR spectrum ensured the formation of compound **129**. Peaks at *m/z* 277 $[M+H]^+$ and 299 $[M+Na]^+$ in ESI mass spectrum analysis was also in accordance to the successful formation of the desired compound. A high resolution ESI mass spectrum consisting of a signal at *m/z* 299.1625 corresponding to $[M+Na]^+$ (calcd 299.1623) further justified the structural assainment.

Preparation of Depsipeptide Subunit:

The preparation of depsipeptide subunit was started with (*D*)-*N*-Boc-tyrosine methyl ester **138**. Methylation of the phenol group of commercially available (*D*)-*N*-Boc-tyrosine methyl ester **138** with DMS and potassium carbonate afforded compound **153** in 96% yield. Appearance of characteristic peaks at δ 3.77 as singlet corresponding to 3H of –OC*H*$_3$ group in the ^{1}H NMR spectrum indicated the formation of compound **153**. In addition to this, the ESI mass spectrum of the compound **153** carrying a signal at *m/z* 332 corresponding to $[M+Na]^+$ lent support for the efficient transformation.

The removal of *N*−Boc protecting group in **153** was achieved with TFA in CH_2Cl_2 at room temperature for 3 h to provide free amine, which was subjected to subsequent amide formation with acryloyl chloride in presence of DIPEA in CH_2Cl_2 to furnish the compound **154** in 82% yield. The appearance of characteristic peaks for olefin along with other peaks in the ^{1}H NMR spectrum ensured the formation of **154**. Additional carbonyl signal was observed at δ 164.8 in the ^{13}C NMR spectrum of the

compound **154**. High resolution ESI mass spectrum carrying a signal at *m/z* 264.1233 corresponding to $[M+H]^+$ (calcd 264.1233) was also in agreement to the successful formation of the compound **154** (Scheme 24).[43]

Scheme 24

The methyl ester in **154** was hydrolyzed with $LiOH.H_2O$ in 4 h to afford the acid **101** in 90% yield. The disappearance of the methyl peaks at δ 3.76 in the ^1H NMR spectrum indicated the acid **101**. Peaks at *m/z* 248.1 $[M-H]^+$, 249.1 $[M]^+$ in ESI mass specrtum confirmed the ester hydrolysis.

β−Alanine methyl ester was prepared from β−alanine **155** with $SOCl_2$ in refluxing methanol to yield β−alanine methyl ester hydrochloride **156** in 90% yield, which was neutralized and coupled with acid **101** using EDCI and HOAt in CH_2Cl_2 in presence of DIPEA as base in 12 h to give compound **137** in 92% yield.[29] Some sort of recemization was observed when HOBt was used instead of HOAt which was determined by rotation.[44] The appearance of signals at δ 2.47−2.24 as multiplet with 2H integration for −COC H_2 and δ 3.55−3.43, 3.35−3.23 as two multiplets with 1H integration for NH−CH_2 and in ^{13}C NMR spectrum additional signal at δ 172.3, which is characteristic peak for carbonyl indicates the formation of amide bond. In addition to this, the high resolution ESI mass spectrum of the compound **137** carrying a signal at *m/z* 335.1602 corresponding to $[M+H]^+$ (calcd 335.1601) lent support for the efficient transformation.

Scheme 25

The methyl ester of compound **137** was hydrolyzed with $LiOH.H_2O$ in THF: methanol: water (2:2:1) in 4 h to afford the acid **157** in 87% yield. The disappearance of peak corresponding to methyl ester in ^1H NMR spectrum of **157** indicated the hydrolysis of methyl ester. Further support was obtained from ESI mass spectrum (*m/z* 342.9 $[M+Na]^+$).

L-Leucic acid *t*-butyl ester **159** was prepared from L-leucic acid **158** treated with acetyl chloride to make free −OH to −OAc. This crude acetate was converted to *t*-butyl ester with *t*-butanol, DCC and DMAP to afford the compound **159** in 81% yield. The appearance of peaks in acetyl region δ 2.10 as singlet for 3H and δ 1.46 as singlet for 9H of *t*-Bu group indicated the formation of product **159**. ^{13}C NMR spectrum was also in accordance with the expected compound (Scheme 26).

The acetyl group in **159** was hydrolyzed with 2.0 eq. of K_2CO_3 in methanol at room temperature in 15 min to provide the L-leucic acid *t*-butyl ester **99** in 90% yield.[45] The disappearance of peak corresponding to acetyl group in ^1H NMR and IR spectrums indicates the removal of acetyl group.

Scheme 26

The L-leucic acid *t*-butyl ester **99** and acid **157** were coupled with DCC and DMAP in CH_2Cl_2 to furnish the desire depsipeptide **160** in 82% yield. The appearance of peaks corresponding to L-leucic acid *t*-butyl ester **99** at δ 1.48 as singlet for 9H of *t*-butyl group along with all other protons in ^{1}H NMR spectrum of **160** indicated the formation of desired compound. Signal at *m/z* 513.2554 in the high resolution ESI mass spectrum of the compound **160** corresponding to $[M+Na]^+$ (calcd 513.2576) further justified the formation of the strctural assianment.

The *t*-butyl ester of **160** was hydrolyzed with TFA in CH_2Cl_2 to afford the acid **97** in quantitative yield, which was taken forward to the next step without further purification and characterization. The acid was coupled with alcohol **129** employing Yamaguchi conditions with 2,4,6−trichloro benzoyl chloride in presence of DIPEA and DMAP in THF to afford the compound **132** in 80% overall yield.[29] The additional olefin peaks resonated at δ 5.54−4.83, five aromatic protons at δ 7.32−7.21 and also acetonide protons at δ 1.45 as singlet for 3H and δ 1.38 as singlet for 3H characterized the compound **132**. It was further characterized by its ^{13}C NMR with four carbonyl signals along with other relative peaks indicating the succesful formation of ester. Presence of signals at *m/z* 693 and 715 corresponding to $[M+H]^+$ and $[M+Na]^+$ respectively in the LC mass spectrum further supported the formation of the product. In addition to this, a signal at *m/z* 715.3578 corresponding to $[M+Na]^+$ (calcd 715.3570) in the high resolution ESI mass spectrum also suggested the success of the reaction.

Scheme 27

This diene **132** was treated with 10 mol% Grubbs′ second generation catalyst in refluxing CH_2Cl_2 to afford the cyclic product **161** in 75% yield (Scheme 3). [22] The disappearance of the signal corresponding to terminal vinylic protons along with other required signals indicated the formation of compound **161**. In the LC mass spectrum, peak at *m/z* 687.4 $[M+Na]^+$ also supported the formation of the RCM product. High resolution ESI mass spectrum carrying a signal at *m/z* 687.3238 corresponding to $[M+Na]^+$ (calcd 687.3257) was also in good agreement with the formation of the product.

Scheme 28

The cyclized product **161** was treated with TFA in CH_2Cl_2 for 4 h to afford the diol **131** in 80% yield. The disappearance of the signal corresponding to acetonide

protons along with other required signals indicated the formation of diol **131**. ^{13}C NMR spectrum and a peak at *m/z* 647.2 $[M+Na]^+$ in ESI mass spectrum ensured the formation of desired compound. A high resolution ESI mass spectrum consisting of a signal at *m/z* 647.2918 corresponding to $[M+Na]^+$ (calcd 647.2944) further justified the success of the reaction.

The *syn*−diols in **131** were converted to epoxide in three sequential steps in 65% yield. At first diol was treated with trimethoxy orthoformate in presence of PPTS in CH_2Cl_2, followed by acetyl bromide in CH_2Cl_2 to produce the anticipated bromohydrin formate, which was taken on to the last step without purification. The formation of epoxide was achieved with powdered $KHCO_3$ in a mixture of DME/ethanol/methanol (6:4:1) at 40 °C for 6 h.[22] The ^1H NMR and ^{13}C NMR of target molecule of cryptophycin−24 (arenastatin A) were identical in all respects to the reported data.[18]

Our synthetic cryptophycin−24 (**12**) showed specific rotation $[\alpha]_D$ = + 52.6 (*c* 0.75, $CHCl_3$); lit. value: $[\alpha]_D$ = + 48 (*c* 0.090, $CHCl_3$),[29] $[\alpha]_D$ = + 49 (*c* 0.63, $CHCl_3$).[18]

The LC mass spectrum of compound **12** showed a signal at *m/z* 629 corresponding to $[M+Na]^+$ and in addition to this, the high resolution ESI mass spectrum carrying a signal at *m/z* 629.2827 corresponding to $[M+Na]^+$ (calcd 629.2838) also supported for the formation of target molecule.

In conclusion, we have proved the versatility of the Prins cyclisation in natural product synthesis by achieving the stereoselective synthesis of cryptophycin−24 (arenastatin A). Stereoselective Grignard reaction, Yamaguchi esterification, Amide bond formation, Ring closing metathesis and a diol−epoxide transformation were the other key steps.

EXPERIMENTAL SECTION

(±)−2−[(Benzyloxy)methyl]oxirane (140):

To a suspension of NaH (60%, 3.3 g, 138.8 mmol) in anhydrous THF (120 mL) was added benzyl alcohol (7.5 g, 69.4 mmol) in THF (20 mL) at 0 °C over 20 min. and allowed the reaction mixture to warm to room temperature. After 30 min. the mixture was again cooled to 0 °C and *epi*-chlorohydrin **139** (5.44 mL, 69.4 mmol) was added drop wise over 10 min. After stirring the reaction mixture at room temperature for 4 h, quenched carefully with saturated NH_4Cl solution (70 mL) at 0 °C. Extracted with EtOAc (2×100 mL) and combined organic layers were washed with brine (50 mL) and concentrated under reduced pressure. The residue on column chromatography afforded benzyl glycidyl ether **140** (10.0 g, 88% yield) as colorless oil.

***R*f :** 0.6 (SiO_2, 20% EtOAc in petroleum ether).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35−7.28 (m, 5H), 4.60 (d, 1H, J = 12.0 Hz), 4.55 (d, 1H, J = 12.0 Hz), 3.76 (dd, 1H, J = 11.2, 2.8 Hz), 3.42 (dd, 1H, J = 11.2, 5.8 Hz), 3.14−3.05 (m, 1H), 2.78 (dd, 1H, J = 4.5, 4.2 Hz), 2.60 (dd, 1H, J = 4.5, 2.5 Hz).

^{13}C NMR (75 MHz, $CDCl_3$) : δ 137.8, 128.0, 127.3, 72.8, 70.4, 50.3, 43.5.

MASS (ESIMS): *m/z* (%) 165 (100) $[M+H]^+$.

(*S*)−2−[(Benzyloxy)methyl]oxirane (136):

To the (*R*,*R*)−(salen) Co(II) precatalyst (294 mg, 0.48 mmol, 0.5 mol %) in a flask was charged sequentially with (±)−benzyl glycidyl ether **140** (16.0 g, 97.5 mmol) and AcOH (117 mg, 1.9 mmol, 0.02 equiv) at room temperature. After the reaction mixture turned from a red suspension to a dark brown solution, the flask was cooled to 0 °C and THF (1.0 mL) followed by H_2O (1.32 g, 53.6 mmol, 0.55 equiv) were added. The reaction mixture was allowed to warm to room temperature over 2 h and stirred at rt for an additional 20 h. Purification by column chromatography gave unreacted (*S*)−benzyl glycidyl ether **136** (7.36 g, 46% yield) as colorless oil.

R_f : 0.6 (SiO_2, 20% EtOAc in petroleum ether).

$[\alpha]_D$: + 5.1 (*c* 2.0, $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35−7.28 (m, 5H), 4.60 (d, 1H, *J* = 12.0 Hz), 4.55 (d, 1H, *J* = 12.0 Hz), 3.76 (dd, 1H, *J* = 11.2, 2.8 Hz), 3.42 (dd, 1H, *J* = 11.2, 5.8 Hz), 3.14−3.05 (m, 1H), 2.78 (dd, 1H, *J* = 4.5, 4.2 Hz), 2.60 (dd, 1H, *J* = 4.5, 2.5 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 140.0, 128.5, 127.8, 73.3, 70.9, 50.9, 44.3.

ESI−MS : *m/z* (%) 165 (100) $[M+H]^+$.

(*S*)−1−(Benzyloxy)hex− 4−yn−2−ol (141):

Under nitrogen atmosphere, a solution of *n*−butyl lithium in hexane (47.8 mL, 124.3 mmol, 2.6 M solution in hexane) was added to a solution of propyne (4.97 g, 124.3 mmol) in THF (90 mL) at−78 ° C and the mixture was stirred for 15 min. Then, $BF_3.OEt_2$ (8.76 g, 62.2 mmol) was added to the solution and the stirring was continued for 15 min at −78° C. Finally a solution of epoxide **136** (10.2 g, 62.2 mmol) in dry THF (30 mL) was added and after stirring the reaction mixture for 2 h at−78 ° C, the reaction was quenched by adding saturated aqueous NH_4Cl solution (50 mL). The reaction mixture was extracted with ethyl acetate (2×100 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvents resulted in crude alcohol, which was purified by column chromatography to afford pure alcohol **141** (11.1 g, 86%) as colorless oil.

R_f : 0.45 (SiO_2, 20% EtOAc in petroleum ether).

$[\alpha]_D^{25}$: + 13.8 (*c* 2.0, $CHCl_3$).

IR (neat): ν_{max} 3422, 2917, 2865, 1449, 1107, 744 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38−7.20 (m, 5H), 4.55 (s, 2H), 3.86 (m, 1H), 3.55 (dd, 1H, *J* = 9.4, 4.3 Hz), 3.45 (dd, 1H, *J* = 9.4, 6.5 Hz), 2.41−2.23 (m, 3H, including OH), 1.78 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 137.5, 128.9, 127.2, 77.7, 74.5, 73.0, 72.8, 68.8, 46.0, 23.8.

EI−MS: *m/z* (%) 204 (100) $[M+H]^+$.

(2*S*,4*E*)−4−Hexene−1,2−diol (135):

To a blue solution of sodium metal (9.4 g, 411.7 mmol) in 250 mL of NH_3 was added drop wise a solution of **141** (10.5 g, 51.0 mmol) in THF (50 mL) at –78° C. During the addition of compound, the blue color of the reaction mixture was maintained by adjusting the speed of the addition. After addition of the whole compound the reaction mixture was stirred for 6 h at –33° C. The reaction mixture was quenched with NH_4Cl and let the ammonia to be completely evaporated. The mixture was then diluted with water and extracted with diethyl ether. Organic layer was dried (Na_2SO_4) and concentrated. Column chromatography of the crude product gave the compound **135** (5.13 g, 86%) as viscous liquid.

$\boldsymbol{R_f}$ **:** 0.2 (SiO_2, 80% EtOAc in petroleum ether).

$\boldsymbol{[\alpha]_D}$**:** + 9.0 (*c* 2.0, $CHCl_3$).

IR (neat): ν_{max} 3389, 2927, 1646, 1444, 1075 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 5.61−5.35 (m, 2H), 3.71−3.57 (m, 2H), 3.40 (dd, 1H, *J* = 11.1, 7.1 Hz), 3.18 (br s, 2H), 2.14 (m, 2H), 1.67 (d, 3H, *J* = 6.0 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 128.1, 126.5, 72.2, 65.8, 36.9, 17.7.

EI−MS: *m/z* (%) 116 (100) $[M]^+$.

3−(Benzyloxy)propan−1−ol (142):

To the suspension of NaH (2.6 g, 65.78 mmol) in dry THF (35 mL) cooled to 0° C was added 1,3-propanediol (5.0 g, 65.78 mmol) in THF (130 mL) in a dropwise manner. The reaction mixture was stirred at room temperature for 30 min. and cooled to 0° C. After addition of BnBr (7.77 mL, 65.78 mmol), reaction was left to room temperature and stirred for 6 h, cooled to 0° C and quenched with saturated NH_4Cl solution (60 mL) carefully. Then added EtOAc (150 mL), organic layer was separated,

washed with H_2O (3×30 mL) and brine solution (30 mL) and dried *in vacuo*. Column chromatography of crude product afforded **142** as colorless oil (6.65 g, 70%) along with 18% recovered starting material.

***R*f :** 0.6 (SiO_2, 30% EtOAc in petroleum ether).

IR (neat): ν_{max} 3377, 2927, 2861, 1452, 1093, 1024, 738, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.32−7.28 (m, 5H), 4.50 (s, 2H), 3.75 (t, 2H, J = 5.7 Hz), 3.63 (t, 2H, J = 5.7 Hz), 2.17 (brs, 1H, O*H*), 1.86−1.84 (m, 2H).

ESI−MS: *m/z* (%) 167.0 (100) $[M+H]^+$.

3−(Benzyloxy)propanal (83):

Freshly prepared pyridinium chlorochromate (7.7 g, 36.0mmol) was added portion wise to a solution of alcohol **142** (4 g, 24.0 mmol), activated molecular sieves(4 g) and silica gel (4 g) in dry CH_2Cl_2 (50 mL) at 0° C under nitrogen atmosphere. The turbid solution was allowed to warm to room temperature and stirred for 4 h. When TLC analysis shows that most of the starting material is consumed, the solids suspended in the reaction and the chromium species are removed by filtration through a pad of silica gel and the pad is washed with ether. The organic phases were concentrated, followed by purification by column chromatography afforded the pure aldehyde **83** (3.55 g, quant.) as colorless oil. This aldehyde was taken forward to next step with any further characterization.

***R*f :** 0.4 (SiO_2, 10% EtOAc in petroleum ether).

(2*S*,3*R*,4*S*,6*S*)−2−(2−(Benzyloxy)ethyl)−6−(hydroxymethyl)−3−methyltetrahydro−2H−pyran−4− ol (134):

Trifluoroacetic acid (10 mL, 129 mmol) was added slowly to a solution of the homoallylic alcohol **135** (1.5 g, 12.9 mmol) and aldehyde **83** (6.34 g, 38.7 mmol) in CH_2Cl_2 (10 mL) at room temperature under nitrogen atmosphere to give the triflouroacetate. The reaction mixture was stirred for 6h and then saturated sodium hydrogen carbonate solution (200 mL) was added and pH was adjusted to >7 by addition of triethylamine. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×70 mL) and the organic layers were combined and the solvent was removed under reduced pressure to obtain trifluoroacetate **143** which was used in the next reaction without purification.

The residue was dissolved in methanol (20 mL) and stirred with potassium carbonate (3.56 g, 25.8 mmol) for 2h. The methanol was then removed under reduced pressure and water (20 mL) was added. The mixture was extracted with CH_2Cl_2 (3×30 mL) and the combined organic layers were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Purification of the crude by column chromatography on silica gel yielded **135** (2.35 g, 65%) as light yellow liquid.

***R*$_f$:** 0.2 (SiO_2, 60% EtOAc in petroleum ether).

[α]$_D^{25}$: –13.5 (*c* 1.0, $CHCl_3$).

IR (neat): ν_{max} 3401 (br, OH), 2923, 2859, 1733, 1453, 1372, 1248, 1092, 1054, 744, 699, 628 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35−7.18 (m, 5H), 4.49 (ABq, 2H, *J* = 12.4 Hz), 3.64−3.38 (m, 5H), 3.31 (td, 1H, *J* = 9.9, 4.9 Hz), 3.17 (td, 1H, *J* = 9.9, 2.4 Hz), 2.12−1.90 (m, 2H), 1.82 (dd, 1H, *J* = 12.4, 4.9 Hz), 1.69−1.54 (m, 1H), 1.39−1.12 (m, 3H), 0.99 (d, 3H, *J* = 6.6 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 128.3, 127.5, 77.9, 75.6, 73.1, 72.9, 66.7, 65.8, 43.9, 36.6, 33.1, 12.7.

ESI−MS: *m/z* (%) 281.2 (80) $[M+H]^+$, 303.2 (100) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{16}H_{24}O_4Na$ 303.1572; found 303.1564.

((2*S*,4*S*,5*R*,6*S*)−6−(2−(Benzyloxy)ethyl)−4−hydroxy−5−methyltetrahydro−2H−pyran−2−yl)methyl 4−methylbenzenesulfonate (144):

To a solution of diol **134** (2.10 g, 7.50 mmol) in dry CH_2Cl_2 (30 mL) was added triethyl amine (1.56 mL, 11.25 mmol) in one portion followed by *p*-TSCl (1.42 g, 7.50 mmol) in three portions at 0 °C. The reaction mixture was stirred for 8 h while slowly bringing it up to room temperature. It was quenched with the saturated NH_4Cl solution (15 mL), diluted with CH_2Cl_2 (30 mL), washed with brine (15 mL), dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification of the crude by silica gel column chromatography afforded tosyl compound **144** (2.66 g, 82%) as colorless oil.

***R*$_f$:** 0.6 (SiO_2, 50% EtOAc in petroleum ether).

[α]$_D^{25}$: − 30.0 (*c* 1.0, $CHCl_3$).

IR (neat): ν_{max} 3423, 2923, 2857, 1359, 1176, 1186, 1095, 973, 815, 743, 669, 556 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, 2H, *J* = 8.0 Hz), 7.33-7.22 (m, 7H), 4.44 (ABq, 2H, *J* = 12.4 Hz), 3.96 (dd, 1H, *J* = 10.8, 6.6 Hz), 3.89 (dd, 1H, J = 9.9, 4.1 Hz), 3.57−3.46 (m, 3H), 3.28 (td, 1H, *J* = 10.8, 4.9 Hz), 3.08 (td, 1H, *J* = 9.4, 2.2 Hz), 2.42 (s, 3H), 1.99−1.86 (m, 2H), 1.56−1.47 (m, 1H), 1.29−1.12 (m, 3H), 0.95 (d, 3H, *J* = 6.6 Hz).

^{13}C NMR (75MHz, $CDCl_3$): δ 144.7, 138.5, 132.9, 129.7, 128.3, 127.9, 127.5, 127.4, 77.9, 72.98, 72.93, 72.5, 71.8, 66.5, 43.6, 36.8, 33.0, 21.6, 12.6.

ESI−MS: *m/z* (%) 435.2 (100) $[M+H]^+$.

((2*S*,4*S*,5*S*,6*S*)−6−(2−(Benzyloxy)ethyl)−4−(methoxymethoxy)−5−methyltetrahydro−2H−pyran−2−yl)methyl 4−methylbenzenesulfonate (145):

To a solution of alcohol **144** (2.5 g, 5.75 mmol) in anhydrous CH_2Cl_2 (20 mL) at 0 °C were added DIPEA (2.55 mL, 14.45 mmol) and MOM-Cl (0.69 mL, 8.64 mmol) successively and the mixture was stirred for 6h at room temperature and then quenched by adding water (10 mL) and extracted with CH_2Cl_2 (3×12 mL). The organic extracts were washed with brine (10 mL), dried over anhydrous Na_2SO_4 and concentrated under vacuum to remove the solvent and the crude was purified by column chromatography to afford the pure product **145** (2.09 g, 76%).

***R*$_f$:** 0.7 (SiO_2, 20% EtOAc in petroleum ether).

[α]$_D^{25}$: − 6.5 (*c* 1.0, $CHCl_3$).

IR (neat): ν_{max} 2923, 2853, 1456, 1361, 1176, 1096, 1035, 973, 814, 739, 698, 666, 554 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74 (d, 2H, *J* = 8.3 Hz), 7.36−7.22 (m, 7H), 4.68 (d, 1H, *J* = 6.7 Hz), 4.53 (d, 1H, *J* = 6.7 Hz), 4.44 (ABq, 2H, *J* = 12.0 Hz), 3.98−3.86 (m, 2H), 3.56−3.44 (m, 3H), 3.33 (s, 3H), 3.20 (td, 1H, *J* = 10.5, 4.5 Hz), 3.11 (td, 1H, *J* = 9.0, 2.2 Hz), 2.43 (s, 3H), 2.05−1.89 (m, 2H), 1.56−1.44 (m, 1H), 1.37−1.09 (m, 2H), 0.93 (d, 3H, *J* = 6.0 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 144.6, 138.6, 129.7, 128.3, 127.9, 127.5, 127.4, 95.3, 78.4, 78.1, 72.9, 72.4, 71.9, 66.5, 55.5, 41.7, 34.0, 33.1, 21.5, 12.8.

ESI−MS: *m/z* (%) 501.2 (100) $[M+Na]^+$.

(2*S*,3*S*,4*S*,6*S*)−2−(2−(Benzyloxy)ethyl)−6−(iodomethyl)−4−(methoxymethoxy)−3−methyltetrahydro−2H−pyran (146):

To a solution of tosyl compound **145** (1.9 g, 6.34 mmol) in dry acetone (10 mL) were added sodium iodide (1.2 g, 7.93 mmol) at room temperature. The reaction mixture was allowed to reflux under stirring for 24 h. The acetone was removed under vacuum and the resultant mixture was diluted with ethyl acetate, washed with water and brine, dried (Na_2SO_4) and concentrated under reduced pressure. Purification of the residue by column chromatography gave iodide **146** (1.48 g, 86%) as colorless clear oil.

***R*_f :** 0.3 (SiO_2, 10% EtOAc in petroleum ether).

$[\alpha]_D^{25}$: +14.5 (*c* 1.0, $CHCl_3$).

IR (neat): ν_{max} 2923, 2853, 1147, 1096, 1033, 739, 697 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38−7.23 (m, 5H), 4.75 (d, 1H, *J* = 7.3 Hz), 4.61 (d, 1H, *J* = 7.3 Hz), 4.57−4.50 (m, 2H), 3.76−3.62 (m, 2H), 3.40−3.25 (m, 5H), 3.23−3.11 (m, 3H), 2.25 (ddd, 1H, *J* = 11.7, 4.3, 1.4 Hz), 2.09− 2.01 (m, 1H), 1.68−1.60 (m, 1H), 1.41−1.30 (m, 1H), 1.27−1.20 (m, 1H), 0.89 (d, 3H, *J* = 6.5 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 138.6, 128.2, 127.7, 127.4, 95.3, 78.5, 78.1, 74.6, 73.0, 66.7, 55.5, 41.7, 37.9, 33.3, 12.8, 8.9.

ESI−MS: *m/z* (%) 457.0 (100) $[M+Na]^+$.

(3*S*,4*R*)−2−(2−(Benzyloxy)ethyl)−4−(methoxymethoxy)−3,6−dimethyl−3,4−dihydro−2H− pyran (147) :

To a solution of iodide **146** (1.3 g, 3.00 mmol) in dry THF (10 mL), was added *t*-BuOK (0.66 g, 6.01 mmol) in one portion at 0 °C. The resultant mixture was allowed

to stir for 30min and it was quenched by the addition of saturated NH_4Cl solution (5 mL). The organic layer was separated and water layer was extracted with Et_2O (2×25 mL). Solvents were evaporated and residue was purified by silica gel column chromatography with a gradient elution of ethyl acetate: hexane, (5:95) to furnish the pure olefin **147** (498 mg, 55%) as colorless oil.

***R*$_f$:** 0.6 (SiO_2, 10% EtOAc in petroleum ether).

IR (neat): ν_{max} 3014, 2969, 2930, 2886, 1215, 1097, 1035, 759 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.41−7.23 (m, 5H), 4.72 (d, 1H, *J* = 7.0 Hz), 4.69−4.60 (m, 2H), 4.53 (s, 2H), 3.86 (td, 1H, *J* = 8.5, 3.1 Hz), 3.76 (d, 1H, *J* = 6.2 Hz), 3.71−3.56 (m, 2H), 3.39 (s, 3H), 2.09−1.88 (m, 2H), 1.81−1.69 (m, 4H), 1.00 (d, 3H, *J* = 6.6 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 152.3, 138.5, 128.2, 127.5, 127.4, 96.6, 95.1, 76.2, 74.8, 72.9, 66.6, 55.4, 37.0, 32.3, 19.8, 15.0.

ESI−MS: *m/z* (%) 329.1 (100) $[M+Na]^+$.

(4*R*,5*S*,6*R*,7*R*)−4−(2−(Benzyloxy)ethyl)−7−hydroxy−6−(methoxymethoxy)−5−methyl−7−phenylheptan−2−one (133):

Ozone was bubbled through a solution of **147** (450 mg, 1.45 mmol) in CH_2Cl_2 (12 mL) at –78 °C until completion of starting material was observed in TLC. The reaction mixture was purged with N_2 to remove the excess ozone and cooled to 0 °C, dimethyl sulfide (2.16 mL, 2.93 mmol) was added, and the mixture was stirred for 1h. The mixture was concentrated *in vacuo*. After diluted with water, the reaction mixture was extracted with Et_2O (2×25 mL).The combined organic layers were washed with brine solution, dried over Na_2SO_4, concentrated under reduced pressure and the crude aldehyde **148** was subjected to the next reaction without further purification and characterization.

The solution of unpurified aldehyde **148** in dry CH_2Cl_2 (10 mL) cooled to –78 °C then $MgBr_2.Et_2O$ (0.55 g, 2.18 mmol) was added portion wise with in 20min. The reaction mixture was allowed to stir for 20min at –78 °C. Then phenyl magnesium bromide (0.72 mL, 2.18 mmol) 3M solution in diethyl ether was added drop wise to the reaction mixture. The mixture was continued to stir for 45min. until the starting material had been consumed. The reaction mixture was quenched by addition of saturated NH_4Cl solution (6 mL) and the solvent was evaporated. The residue was taken in ethyl acetate (25 mL) and the organic layer was washed with water (15 mL) followed by brine (15 mL) and dried over anhydrous Na_2SO_4. The solvent was evaporated under reduced pressure. Purification by column chromatography afforded the pure product **133** (435 mg, 72% yield in 2 steps) as viscous liquid.

***R*$_f$:** 0.3 (SiO_2, 20% EtOAc in petroleum ether).

$[\alpha]_D^{25}$: – 53.0 (*c* 1.0, $CHCl_3$).

IR (neat): ν_{max} 3442 (br, OH), 2926, 2856, 1724, 1454, 1378, 1275, 1240, 1108, 1027, 763, 706, 618 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.38−7.18 (m, 10H), 4.93 (td, 1H, *J* = 8.0, 2.9 Hz), 4.73 (d, 1H, *J* = 6.6 Hz), 4.67 (d, 1H, *J* = 6.6 Hz), 4.56 (d, 1H, *J* = 8.0 Hz), 4.33 (s, 2H), 3.53 (d, 1H, *J* = 8.0 Hz), 3.46 (s, 3H), 3.32−3.25 (m, 2H), 1.93 (s, 3H), 1.84−1.73 (m, 1H), 1.49−1.33 (m, 3H), 0.92 (d, 3H, *J* = 6.6 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ 170.4, 140.6, 138.1, 128.5, 128.2, 128.0, 127.6, 127.4, 127.1, 126.5, 99.2, 86.9, 75.3, 73.0, 72.9, 66.6, 56.0, 38.1, 31.8, 21.0, 10.1.

LCMS: *m/z* (%) 439.2 (100) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{24}H_{32}O_6Na$ 439.2096; found 439.2075.

(3*S*,4*R*,5*R*,6*R*)−1−(Benzyloxy)−5,6−dihydroxy−4−methyl−6−phenylhexan−3−yl (149):

Compound **133** (420 mg, 1.00 mmol) was dissolved in methanol (15 mL) and added *p*-TSA (17 mg, 0.10 mmol). The reaction mixture was refluxed for 6 h. Then the methanol was removed under reduced pressure and water (30 mL) was added. The mixture was extracted with CH_2Cl_2 (3×30 mL) and the combined organic layers were dried (Na_2SO_4) and the solvent was removed under reduced pressure. Purification of the crude by column chromatography on silica yielded diol **149** (240 mg, 65%) as colorless liquid.

$\boldsymbol{R_f}$ **:** 0.2 (SiO_2, 50% EtOAc in petroleum ether).

$\boldsymbol{[\alpha]_D}$**:** − 46.3 (*c* 0.55, $CHCl_3$)

IR (neat): ν_{max} 3445, 2924, 2854, 1718, 1631, 1384, 1275, 1244, 1113, 1024, 706 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.31−7.13 (m, 10H), 4.91 (m, 1H), 4.57 (d, 1H, *J* = 8.3 Hz), 4.37 (q, 2H, *J* = 11.8 Hz), 3.55 (d, 1H, *J* = 8.1Hz), 3.37−3.28 (m, 2H), 1.97 (s, 3H), 1.75−1.53 (m, 1H), 1.43−1.32 (m, 2H), 0.98 (d, 3H, *J* = 6.7 Hz).

ESI−MS : *m/z* (%) 395.2 (100) $[M+Na]^+$.

(3*S*,4*S*)−1−(Benzyloxy)−4−((4*R*,5*R*)−2,2−dimethyl−5−phenyl−1,3−dioxolan−4−yl)pentan−3−yl acetate (150):

To a solution of diol **149** (215 mg, 0.57 mmol) in dry CH_2Cl_2 (3 mL) were added 2,2−DMP (0.14 mL, 1.16 mmol) and PPTS (12 mg, 0.05 mmol) sequentially at room temperature. Then the reaction was stirred for 3 h and quenched with saturated $NaHCO_3$ solution (4 mL). The double layer was extracted with CH_2Cl_2 (2×10 mL), and washed with water (5 mL) and brine (2 mL). The organic extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel to give **150** (220 mg, 92%).

$\boldsymbol{R_f}$**:** 0.3 (SiO_2, 20% EtOAc in petroleum ether).

$\boldsymbol{[\alpha]_D^{25}}$**:**− 10.7 (*c* 0.75, $CHCl_3$).

IR (neat): ν_{max} 2981, 2928, 2858, 1737, 1372, 1237, 1103, 1026, 752, 699 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34−7.15 (m, 10H), 4.88−4.83 (m, 1H), 4.65 (d, 1H, *J* = 8.6 Hz), 4.29 (ABq, 2H, *J* = 12.2 Hz), 3.74 (dd, 1H, *J* = 8.6, 3.5 Hz), 3.27−3.20 (m, 1H), 3.16−3.09 (m, 1H), 1.99−1.82 (m, 4H), 1.75−1.62 (m, 2H), 1.45 (s, 3H), 1.39 (s, 3H), 1.00 (d, 3H, *J* = 7.3 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 170.1, 137.8, 128.6, 128.4, 128.4, 128.3, 128.3, 127.6, 127.5, 127.0, 108.7, 82.9, 80.9, 73.1, 72.9, 66.8, 37.1, 30.4, 27.2, 27.1, 21.0, 9.3.

ESI−MS: *m/z* (%) 435.8 (100) $[M+Na]^+$.

(3*S*,4*S*)−4−((4*R*,5*R*)−2,2−Dimethyl−5−phenyl−1,3−dioxolan−4−yl)pentane−1,3−diol (152):

To a solution of compound **150** (200 mg, 0.48 mmol) in methanol (5 mL) were added potassium carbonate (134 mg, 0.97 mmol) at room temperature. Then the reaction was stirred for 2 h and removed the solvent. The residue was diluted with CH_2Cl_2 (2×10 mL), and washed with water (5 mL) and brine (2 mL). The organic extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was chromatographed on silica gel to give alcohol **151** in quantitative yield.

To a stirred solution of alcohol (180 mg, 0.48 mmol) in MeOH (5 mL) 5% Pd/C (25 mg) was added under H_2 at room temperature. The stirring was continued for 3 h .The resulting heterogeneous mixture was filtered through celite pad and filtrate was concentrated under reduced pressure to dark brown oil, which was purified by column chromatography with a gradient elution of ethyl acetate−hexanes (5:95) to furnish the compound **152** (112 mg, 82%) as light yellowish syrup.

***R_f*:** 0.2 (SiO_2, 50% EtOAc in petroleum ether).

$[\alpha]_D^{25}$: − 6.0 (*c* 0.54, $CHCl_3$).

IR (neat): ν_{max} 3452, 2924, 2854, 1458, 1382, 1047, 759 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37−7.21 (m, 5H), 4.73 (d, 1H, *J* = 8.5 Hz), 4.00 (d, 1H, *J* = 8.5 Hz), 3.77−3.60 (m, 3H), 3.23−3.04 (br s, 1H), 2.92−2.71 (br s, 1H), 1.76−1.67 (m, 1H), 1.59−1.49 (m, 5H), 1.46 (s, 3H), 1.02 (d, 3H, *J* = 6.4 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 137.3, 128.5, 128.2, 126.6, 108.6, 82.7, 79.8, 74.6, 61.4, 37.3, 35.7, 27.0, 26.9, 10.4.

ESI−MS: *m/z* (%) 303.2 (100) $[M+Na]^+$.

(2*S*,3*S*)−2−((4*R*,5*R*)−2,2−Dimethyl−5−phenyl−1,3−dioxolan−4−yl)hex−5−en−3−ol(2*S*,3*S*)−2−((4*R*,5*R*)−2,2−dimethyl−5−phenyl−1,3−dioxolan−4−yl)hex−5−en−3−ol (129):

Diol **152** (100 mg, 0.35 mmol) was dissolved in CH_2Cl_2 (5 mL) was added TEMPO (16 mg, 0.10 mmol) and BAIB (172 mg, 0.53 mmol) at room temperature. Stirring was allowed until TLC indicated complete conversion of the starting material to product. The reaction mixture was quenched by addition of saturated $Na_2S_2O_3$ solution (5 mL). The reaction mixture was then extracted with ethyl acetate (2×30 mL). The combined organic layers were dried over anhydrous Na_2SO_4 and concentrated. The crude aldehyde was taken forward to next reaction, without any further purification and characterization.

Methyl triphenyl phosphoniumbromide was evacuated with toluene three times and then dried on a vacuum pump for 1h at room temperature. Dry THF (15 mL) was added to a flask containing the dry methyl triphenyl phosphoniumbromide (719 mg, 1.78 mmol) and potassium tertiary butoxide (179 mg, 1.60 mmol) at 0 °C, which was turned to yellow. The suspension warmed to room temperature for 2h. The yellow suspension is then cooled to 0 °C and the crude aldehyde in THF (5 ml) was added drop wise. The mixture was removed from the ice bath and stirred at room temperature for 4h. The reaction was quenched with aq. sat. NH_4Cl (10 mL) and the solvents were removed and extracted with EtOAc (2×30 mL). Combined organic extracts were

washed with brine (20 mL), concentrated *in vacuo* and subjected the residue to column chromatography to afford the pure alcohol **6** (75 mg, 76%) as colorless oil.

R_f **:** 0.5 (SiO_2, 30% EtOAc in petroleum ether).

$[\alpha]_D^{25}$ **:** − 3.0 (*c* 1.0, $CHCl_3$).

IR (neat): ν_{max} 3458, 2980, 2926, 1641, 1454, 1375, 1233, 1036, 757, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40−7.25 (m, 5H), 5.79−5.61 (m, 1H), 5.04−4.92 (m, 2H), 4.77 (d, 1H, *J* = 9.0 Hz), 4.09 (dd, 1H, *J* = 9.0, 2.0 Hz), 3.64−3.54 (m, 1H), 2.32−2.20 (m, 2H), 2.19−2.09 (m, 1H), 1.83−1.72 (m, 1H), 1.56 (s, 3H), 1.49 (s, 3H), 1.07 (d, 3H, *J* = 6.9 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 137.6, 134.8, 128.5, 128.3, 126.7, 117.8, 108.7, 82.6, 79.9, 73.6, 39.5, 36.1, 27.2, 27.0, 10.7.

ESI−MS: *m/z* (%) 277 (50) $[M+H]^+$, 299 (50) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{17}H_{24}O_3Na$ $[M+Na]^+$ 299.1623 found 299.1625.

2(*R*)−*tert*−Butoxycarbonylamino−3−(4−methoxy−phenyl)−propionic acid methyl ester (153):

To a dry flask containing **138** (5.0 g, 16.9 mmol) in dry Acetone (400 mL) was added K_2CO_3 (4.6 g, 33.8 mmol), and then Me_2SO_4 (1.8 mL, 20.2 mmol). The mixture was refluxed for 8 h, cooled to rt, and the solvent removed *in vacuo*. The residue was dissolved in EtOAc (200 mL), washed with water (200 mL), and the aq. layer extracted with EtOAc (100 mL). The combined organic layers were dried with Na_2SO_4, filtered, concentrated *in vacuo*, and the crude material purified by flash chromatography (15% EtOAc/Hex) to afford the dimethylated product **153** (5.02 g, 96%) as a white solid.

R_f **:** 0.6 (SiO_2, 30% EtOAc in petroleum ether).

$[\alpha]_D$**:** − 56.5 (*c* 1.0, $CHCl_3$).

IR (neat): ν_{max} 3372, 2973, 1714, 1512, 1364, 1249, 1170, 1033, 828 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.99 (d, 2H, *J* = 8.0 Hz), 6.78 (d, 2H, *J* = 8.0 Hz), 4.86 (d, 1H, *J* = 8.0 Hz), 4.53−4.44 (m, 1H), 3.77 (s, 3H), 3.70 (s, 3H), 3.03−2.98 (m, 2H), 1.42 (s, 9H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3, 158.5, 130.2, 127.8, 113.9, 79.8, 55.1, 54.4, 52.1, 37.4, 28.2.

ESI−MS: *m/z* (%) 332 (100) $[M+Na]^+$.

2(*R*)−Acryloylamino−3−(4−methoxy−phenyl)−propionic acid methyl ester (154):

To a flask containing the **153** (6.4 g, 20.7 mmol) was added CH_2Cl_2 (50 mL), and TFA (50 mL). The solution was stirred for 3 h at room temperature then concentrated, and the residue diluted with ether (200 mL) and extracted with 1N HCl (3×100 mL). The combined acidic extracts were basified (pH~10) with solid Na_2CO_3 and extracted with CH_2Cl_2 (3×100 mL). The combined organic extracts were dried with Na_2SO_4, and concentrated *in vacuo* to afford the desired free amine as colorless oil in quantitative. This was used directly in the subsequent step without further purification.

To a dry flask containing crude amine in CH_2Cl_2 (70 mL), cooled to 0^oC, was added DIPEA (9.0 mL, 51.6 mmol) followed by the dropwise addition of acroylyl chloride (1.67 mL, 20.6 mmol). The mixture was stirred for 2 h at rt and diluted with EtOAc (200 mL) and washed successively with 1N HCl (2×100 mL), sat. Na_2CO_3 and brine. The organic layer was dried with Na_2SO_4, filtered and concentrated *in vacuo* to afford the acylated product, methyl *N*−acryloyl−*O*−methyl−D−tyrosinate **154** (4.46 g, 82%) as colorless oil.

R_f : 0.3 (SiO_2, 30% EtOAc in petroleum ether).

$[\alpha]_D$: − 122 (*c* 1.0, $CHCl_3$).

IR (neat): ν_{max} 3320, 2924, 2853, 1742, 1659, 1533, 1515, 1248, 1178, 1031, 812, cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 6.94 (d, 2H, *J* = 8.4 Hz), 6.76 (d, 2H, *J* = 8.4 Hz), 6.29 (dd, 1H, *J* = 16.9, 1.3 Hz), 6.07 (dd, 1H, *J* = 16.9, 10.1 Hz), 5.98 (d, 1H, *J* = 7.1 Hz), 5.66 (dd, 1H, *J* = 10.1, 1.3 Hz), 4.88 (m, 1Hz), 3.76 (s, 3H), 3.74 (s, 3H), 3.09 (t, 2H, *J* = 5.2 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9, 164.8, 158.6, 130.1, 127.5, 127.1, 113.9, 55.1, 53.2, 52.3, 36.8.

ESI−MS: *m/z* (%) 264 (52) $[M+H]^+$, 286 (100) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{14}H_{18}NO_4$ $[M+H]^+$ 264.1233, found 264.1233.

2(*R*)−Acryloylamino−3−(4−methoxy−phenyl)−propionic acid (101):

To a flask containing **154** (4.40 g, 16.41 mmol) was added THF (20 mL), MeOH (20 mL), water (10 mL), and $LiOH.H_2O$ (758 mg, 18.0 mmol). The mixture was stirred for 4 h at rt, then concentrated to a volume of 50 mL and acidified (pH ~ 2) with 1N aq. $NaHSO_4$. The aq. solution was extracted with CH_2Cl_2 (3×100 mL), and the combined organic extracts dried with Na_2SO_4, filtered, and concentrated *in vacuo* to afford the desired product **101** as a colorless amorphous solid (3.74 g, 90%).

R_f : 0.1 (SiO_2, 100% EtOAc).

$[\alpha]_D$: −53.7 (*c* 1.05, $CHCl_3$).

IR (KBr): ν_{max} 3452, 3351, 2922, 2850, 1657, 1618, 1518, 1251, 1177, 1030, 807 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ 7.49 (d, 1H, *J* = 7.1 Hz), 7.09 (d, 2H, *J* = 8.1 Hz), 6.72 (d, 2H, *J* = 8.1 Hz), 6.29−6.09 (m, 2H), 5.52 (dd, 1H, *J* = 9.4, 2.0 Hz), 4.60−4.49 (m, 1H), 3.73 (s, 3H), 3.12 (dd, 1H, *J* = 13.7, 4.7 Hz), 2.97 (dd, 1H, *J* = 13.7, 6.4 Hz).

ESI−MS : *m/z* (%) 248.1 (100) $[M-H]^+$, 249.1 (14) $[M]^+$.

(*R*)−Methyl-3-(2−acrylamido−3−(4−methoxyphenyl)propanamido)propanoate (137):

To a stirred solution of β-alanine **155** (1 g, 11.2 mmol) in methanol (10 mL) was added $SOCl_2$ (2.4 mL, 33.6 mmol) dropwise at 0 °C under nitrogen atmosphere. The reaction mixture was allowed to reflux for 24 h, then concentrated and azeotroped with toluene (3×10 mL) then dried on a vacuum pump for 1 h at room temperature to obtaine β-alanine HCl salt **156** (1.4 g, 90%).

To a stirred solution of the β-alanine HCl salt **156** (300 mg, 2.15 mmol) in CH_2Cl_2 (5 mL) was added DIPEA (0.44 mL, 2.58 mmol) dropwise at 0°C. This reaction mixture was allowed to stir for 15 min at rt, then acid **101** (479 mg, 1.92 mmol) in dry CH_2Cl_2 (8 mL) was added followed by HOAt (264 mg, 1.92 mmol), EDCI.HCl (684 mg, 2.30 mmol) and DIPEA (0.33 mL, 1.92 mmol) successively. After being stirred at room temperature for 12 h, the mixture was diluted with water (4 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined extracts were washed with 1 N HCl (3 mL), water (3 mL), $NaHCO_3$ (3 mL), brine (3 mL) and finally dried over anhydrous Na_2SO_4. Then the organic extract was concentrated under reduced pressure and chromatographed on silica gel with EtOAc−petroleum ether (1:1) as eluant to give **137** (642 mg, 92%) as pale yellow solid.

***R*$_f$:** 0.5 (SiO_2, 100% EtOAc).

[α] $_D$: − 13.0 (*c* 1.0, $CHCl_3$).

IR (KBr): ν_{max} 3254, 2926, 1740, 1649, 1618, 1555, 1515, 1252, 1179, 1030, 986, 832 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.08 (d, 2H, *J* = 8.6 Hz), 6.77 (d, 2H, *J* = 8.6 Hz), 6.57 (d, 1H, *J* = 7.5 Hz), 6.41 (t, 1H, *J* = 5.6 Hz), 6.28 (dd, 1H, *J* = 16.9, 1.3 Hz), 6.12 (dd, 1H, *J* = 16.9, 10.0 Hz), 5.66 (dd, 1H, *J* = 10.0, 1.3 Hz), 4.65−4.55 (m, 1H), 3.77 (s, 3H),

3.62 (s, 3H), 3.55−3.43 (m, 1H), 3.35−3.23 (m, 1H), 3.06 (dd, 1H, *J* = 13.4, 5.4 Hz), 2.87 (dd, 1H, *J* = 13.4, 8.6 Hz), 2.47−2.24 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 172.3, 170.7, 165.0, 158.4, 130.3, 130.1, 128.3, 127.0, 113.8, 55.0, 54.7, 51.6, 37.9, 34.6, 33.4.

ESI−MS: *m/z* (%) 335.0 (27) $[M+H]^+$, 357.0 (100) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{17}H_{23}N_2O_5$ $[M+H]^+$ 335.1601, found 335.1602.

(*R*)−3−(2−Acrylamido−3−(4−methoxyphenyl)propanamido)propionic acid (157):

To a flask containing **137** (1.5 g, 4.49 mmol) was added THF (8 mL), methanol (8 mL), water (4 mL), and LiOH (207 mg, 4.94 mmol). The mixture was stirred for 4 h at rt, then concentrated to a volume of 50 mL and acidified (pH ~ 2) with 1N aq. $NaHSO_4$. The aq. solution was extracted with CH_2Cl_2 (3×100 mL), and the combined organic extracts dried with Na_2SO_4, filtered, and concentrated *in vacuo* to afford the desired product **157** as a colorless amorphous solid (1.25 g, 87%).

***R*$_f$:** 0.1 (SiO_2, 100% EtOAc).

IR (KBr): ν_{max} 3361, 3263, 2924, 1722, 1655, 1547, 1512, 1250, 1192, 1034, 803, 682, 524 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, 1H, *J* = 7.9 Hz), 7.59−7.49 (m, 1H), 7.08 (d, 2H, *J* = 8.6 Hz), 6.74 (d, 2H, *J* = 8.4 Hz), 6.29−6.12 (m, 2H), 5.54 (dd, 1H, *J* = 9.2, 2.8 Hz), 4.58 (q, 1H, *J* = 7.1 Hz), 3.75 (s, 3H), 3.44−3.26 (m, 2H), 2.98 (dd, 1H, *J* = 13.5, 7.3 Hz), 2.85 (dd, 1H, *J* = 13.5, 6.6 Hz), 2.45−2.27 (m, 2H).

ESI−MS: *m/z* (%) 342.9 (100) $[M+Na]^+$.

(*S*)−*tert*−Butyl 2−acetoxy−4−methylpentanoate (159):

To compound **158** (2 g, 15.1 mmol) was added acetyl chloride (10 mL) at 0 °C. The reaction mixture was then refluxed at 60 °C for 4 h. Excess acetyl chloride was removed under vacuum. Diethyl ether was added, and the solution was washed with water. The organic layer was dried and evaporated under vacuum. The residue was used in the next step without further purification. The residue and *tert*−butyl alcohol (2.45 g, 33.1 mmol) were dissolved in CH_2Cl_2 (30 mL), DMAP (607 mg, 5.0 mmol) and DCC (4.1 g, 20.0 mmol) in CH_2Cl_2 (10 mL) were added at 0 °C. The reaction mixture was stirred at room temperature for 12 h. Then, the urea was filtered and the organic layer was washed with water. The organic layer was dried and evaporated under reduced pressure. The crude residue was purified by flash column chromatography (15% EtOAc in *n*−hexane) to give compound **159** as yellow oil (2.82 g, 81%).

***R*_f :** 0.5 (SiO_2, 10% EtOAc in petroleum ether).

IR (neat): ν_{max} 2962, 2874, 1746, 1371, 1229, 1163, 1076, 846, 768 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.81 (dd, 1H, *J* = 9.0, 4.5 Hz), 2.10 (s, 3H), 1.81−1.66 (m, 2H), 1.62−1.51 (m, 1H), 1.46 (s, 9H), 0.97 (d, 3H, *J* = 6.7 Hz), 0.91 (d, 3H, *J* = 6.0 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 170.5, 169.8, 81.8, 71.4, 39.6, 27.8, 24.5, 22.9, 21.5, 20.6.

(*S*)−*tert*−Butyl 2−hydroxy−4−methylpentanoate (99):

To a solution of compound **159** (400 mg, 17.4 mmol) in methanol (3 mL) was added potassium carbonate (48 mg, 34.8 mmol) at room temperature. The resulting solution was stirred for 15 min. Then the reaction mixture was monitored with TLC,

diluted with diethyl ether (50 mL), and washed with water (2×15 mL) and brine (20 mL). The organic extract was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give **99** (294 mg, 90%).

***R*f :** 0.4 (SiO_2, 10% EtOAc in petroleum ether).

IR (neat): ν_{max} 3470, 2926, 2857, 1728, 1462, 1369, 1256, 1141, 1086, 846, 763 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$) : δ 4.00 (t, 1H, *J* = 6.4 Hz), 2.81−2.61 (br s, 1H), 1.97−1.82 (m, 1H), 1.56−1.42 (m, 11H), 0.96 (d, 3H, *J* = 2.2 Hz), 0.94 (d, 3H, *J* = 2.4 Hz).

(*S*)−*tert*−Butyl-2−(3−((*R*)−2−acrylamido−3−(4−ethoxyphenyl)propanamido) propanoyloxy)−4−methylpentanoate (160):

To a stirred solution of acid **157** (4.6 g, 14.37 mmol) in CH_2Cl_2 (25 mL) was added DCC (3.24 g, 15.81 mmol) at 0 °C. After being stirred for 5 min at the same temperature, compound **99** (2.70 g, 14.37 mmol) in CH_2Cl_2 (25 mL) was cannulated and stirred for another 30 min. Then DMAP (174 mg, 1.43 mmol) was added and stirring was continued for 8 h at same temperature. The reaction mixture was next diluted with CH_2Cl_2 (200 mL), washed with water (2×30 mL), brine (30 mL) and dried over anhydrous Na_2SO_4. The organic solution was concentrated under reduced pressure and chromatographed on silica gel with EtOAc− petroleum ether (6:4) as eluant to give **160** (5.5 g, 82%) as pale yellowish solid.

***R*f:** 0.4 (SiO_2, 50% EtOAc in petroleum ether).

$[\alpha]_D^{25}$: − 30.4 (*c* 0.97, $CHCl_3$).

IR (KBr): ν_{max} 3266, 2961, 1746, 1653, 1559, 1513, 1372, 1245, 1157, 1072, 840, 704, 529 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.06 (d, 2H, *J* = 8.6 Hz), 6.84–6.73 (m, 3H), 6.40 (d, 1H, *J* = 7.7 Hz), 6.26 (dd, 1H, *J* = 16.9, 1.5 Hz), 6.07 (dd, 1H, *J* = 16.9, 10.1 Hz), 5.61 (dd, 1H, *J* = 10.1, 1.5 Hz), 4.90 (dd, 1H, *J* = 9.4, 4.1 Hz), 4.70–4.61 (m, 1H), 3.76 (s, 3H), 3.62–3.42 (m, 2H), 3.11–2.93 (m, 2H), 2.49 (t, 2H, *J* = 7.1 Hz), 1.78–1.63 (m, 2H), 1.60–1.45 (m, 10H), 0.94 (d, 3H, *J* = 6.4 Hz), 0.92 (d, 3H, *J* = 6.6 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 170.7, 170.5, 164.8, 158.4, 130.5, 130.3, 126.9, 113.9, 82.8, 71.5, 55.1, 54.3, 39.5, 37.7, 35.2, 34.3, 28.0, 24.7, 22.9, 21.6.

ESI–MS: *m/z* (%) 491.1 (76) $[M+H]^+$.

HRMS (ESI): Calcd for $C_{26}H_{38}N_2O_7Na$ $[M+Na]^+$ 513.2576, found 513.2554.

(*S*)–((2*S*,3*S*)–2–((4*S*,5*R*)–2,2–Dimethyl–5–phenyl–1,3–dioxolan–4–yl)hex–5–en–3–yl)2–(3–((*R*)–2–acrylamido–3–(4–methoxyphenyl)propanamido)propanoyloxy)–4–methylpentanoate (132):

CF_3CO_2H (2 mL) was added dropwise to a stirred solution of **160** (115 mg, 0.23 mmol) in CH_2Cl_2 (3 mL) at room temperature and allowed to stir for 4h. The resulting mixture was concentrated *in vacuo* and azeotroped with dry CH_2Cl_2 (3×5 mL). This crude acid **97** was dissolved in dry THF (5 mL) and added DIPEA (0.13 mL, 0.70 mmol) at 0 °C after 5min stirring, 2,4,6– trichloro benzoylchloride (0.43 mL, 0.28 mmol) was added slowly and stirred for 2h at room temperature. The reaction mixture was again cooled to 0 °C then a solution of alcohol **129** (65 mg, 0.23 mmol) and DMAP (63 mg, 0.51 mmol) in dry THF (3 mL) was added over the period of 15min. The resulting reaction mixture was allowed to stir for 18 h at rt. Then the reaction was quenched with saturated aqueous NH_4Cl solution, solvent was removed under reduced pressure. The aqueous layer was extracted with ethyl acetate (2×40 mL). The organic layer was separated and washed with water, brine, dried over Na_2SO_4 and concentrated

under reduced pressure. The crude product was purified by column chromatography to afford **132** (130 mg, 80%).

***R*$_f$:** 0.3 (SiO_2, 50% EtOAc in petroleum ether).

$[\alpha]_D^{25}$: −12.6 (*c* 0.95, $CHCl_3$).

IR (KBr): ν_{max} 3285, 2924, 2853, 1742, 1653, 1513, 1375, 1245, 1173, 1037, 757 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.32−7.21 (m, 5H), 7.02 (d, 2H, *J* = 8.5 Hz), 6.73 (d, 2H, *J* = 8.5 Hz), 6.46−6.40 (m, 1H), 6.24−6.15 (m, 2H), 6.00 (dd, 1H, *J* = 17.0, 10.9 Hz), 5.55 (d, 1H, *J* = 9.7 Hz), 5.49−5.39 (m, 1H), 4.93−4.83 (m, 3H), 4.80 (d, 1H, *J* = 17.0 Hz), 4.65−4.57 (m, 2H), 3.77 (dd, 1H, *J* = 9.7, 2.4 Hz), 3.70 (s, 3H), 3.53−3.45 (m, 1H), 3.41−3.31 (m, 1H), 3.02−2.92 (m, 2H), 2.48−2.38 (m, 2H), 2.21−2.12 (m, 2H), 1.91−1.81 (m, 1H), 1.67−1.56 (m, 2H), 1.45 (s, 3H), 1.38 (s, 3H), 1.30−1.22 (m, 1H), 1.02 (d, 3H, *J* = 7.3 Hz), 0.84 (d, 3H, *J* = 6.0 Hz), 0.79 (d, 3H, *J* = 6.0 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 171.1, 170.7, 170.5, 164.8, 158.4, 137.6, 132.4, 130.4, 130.2, 128.6, 128.3, 126.8, 126.6, 118.2, 113.8, 108.8, 81.8, 80.3, 76.2, 71.0, 55.1, 54.3, 39.4, 37.6, 35.3, 35.2, 34.1, 33.8, 27.1, 27.0, 24.5, 23.0, 21.2, 9.7.

LC−MS: *m/z* (%) 693.4 (100) $[M+H]^+$, 715.4 (46) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{39}H_{52}N_2O_9Na$ 715.3570; found 715.3578.

(3*S*,10*R*,16*S*,*E*)−16−((*S*)−1−((4*S*,5*R*)−2,2−Dimethyl−5−phenyl−1,3−dioxolan−4−yl)ethyl)−3−isobutyl−10−(4−methoxybenzyl)−1,4−dioxa−8,11−diazacyclohexadec−13−ene−2,5,9,12−tetraone (161):

Grubbs' second generation catalyst (10.17 mg, 10 mol%) in dry CH_2Cl_2 was added to the refluxing solution of diene **132** (120 mg, 0.172 mmol) in CH_2Cl_2 (100 mL) under nitrogen atmosphere. The reaction mixture was allowed to stir for another 2 h under reflux condition. After completion of starting material, the reaction mixture was

concentrated under *vacuo* and purified with column chromatography to afford the cyclized product **161** (85 mg, 75%).

***R*$_f$:** 0.45 (SiO_2, 50% EtOAc in petroleum ether).

$[\alpha]_D^{25}$: +33.0 (*c* 1.75, $CHCl_3$).

IR (KBr): ν_{max} 3403, 3280, 2927, 1748, 1727, 1665, 1519, 1377, 1242, 1180, 1033, 699 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35−7.22 (m, 5H), 7.04 (d, 2H, *J* = 8.3 Hz), 6.89 (t, 1H, *J* = 5.2 Hz), 6.73 (d, 2H, *J* = 9.0 Hz), 6.46 (ddd, 1H, *J* = 15.1, 10.5, 4.5 Hz), 5.69 (d, 1H, *J* = 8.3 Hz), 5.55 (dd, 1H, *J* = 15.1, 1.5 Hz), 4.97 (ddd, 1H, *J* = 9.0, 6.7, 2.2 Hz), 4.77 (dd, 1H, *J* = 10.5, 4.5 Hz), 4.69−4.61 (m, 2H), 3.73 (d, 1H, *J* = 3.0 Hz), 3.70 (s, 3H), 3.46−3.33 (m, 2H), 3.08 (dd, 1H, *J* = 14.3, 5.2 Hz), 2.92 (dd, 1H, *J* = 14.3, 7.5 Hz), 2.50−2.47 (m, 2H), 2.35 (ddd, 1H, *J* = 14.3, 5.2, 2.2 Hz), 2.19−1.97 (m, 1H), 1.77 (td, 1H, *J* = 7.5, 3.0 Hz), 1.69−1.51 (m, 2H), 1.43 (s, 3H), 1.39 (s, 3H), 1.31−1.19 (m, 1H), 1.06 (d, 3H, *J* = 6.7 Hz), 0.84 (d, 3H, *J* = 6.7 Hz), 0.76 (d, 3H, *J* = 6.0 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 172.5, 170.7, 170.2, 165.5, 158.4, 141.4, 137.4, 130.1, 128.7, 128.6, 128.5, 126.5, 124.8, 113.9, 109.0, 82.3, 80.1, 75.6, 71.0, 55.1, 54.1, 39.6, 36.8, 35.4, 35.1, 34.1, 32.3, 27.1, 26.9, 24.3, 22.8, 21.3, 9.5.

LC−MS: *m/z* (%) 665.4 (30) $[M+H]^+$, 687.4 (100) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{37}H_{48}N_2O_9Na$ 687.3257; found 687.3238.

(3*S*,10*R*,16*S*,*E*)−16−((2*R*,3*R*,4*R*)−3,4−Dihydroxy−4−phenylbutan−2−yl)−3−isobutyl−10−(4−methoxybenzyl)−1,4−dioxa−8,11−diazacyclohexadec−13−ene−2,5,9,12−tetraone (131):

CF_3CO_2H (1 mL) was added drop wise to a stirred solution of **161** (80 mg, 0.12 mmol) in CH_2Cl_2 (2 mL) at 0 °C and stirring was continued for 4 h at room

temperature. The resulting mixture was concentrated *in vacuo* and azeotroped with dry CH_2Cl_2 (3×5 mL). The solid residue was chromatographed on silica gel with EtOAc−petroleum ether (8:2) as eluant to give **131** (60 mg, 80%) as white solid.

R_f: 0.2 (SiO_2, 100% EtOAc).

$[\alpha]_D^{25}$: + 3.0 (*c* 1.0, $CHCl_3$).

IR (KBr): ν_{max} 3412, 2925, 1740, 1670, 1515, 1247, 1174, 1005, 702 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36−7.21 (m, 5H), 7.03 (d, 2H, *J* = 8.4 Hz), 6.92 (t, 1H, *J* = 5.8 Hz), 6.72 (d, 2H, *J* = 8.3 Hz), 6.60 (br t, 1H, *J* = 10.9 Hz), 5.93 (d, 1H, *J* = 7.5 Hz), 5.61 (d, 1H, *J* = 15.1 Hz), 5.03 (t, 1H, *J* = 9.2 Hz), 4.82 (dd, 1H, *J* = 9.8, 2.8 Hz), 4.66−4.51 (m, 2H), 3.73−3.65 (m, 4H), 3.54−3.40 (m, 1H), 3.25−3.23 (m, 1H), 3.07 (dd, 1H, *J* = 13.9, 5.8 Hz), 2.86 (dd, 1H, *J* = 13.9, 7.3 Hz), 2.67−2.41 (m, 4H), 2.18−2.04 (m, 1H), 1.71 (td, 1H, *J* = 13.9, 10.1, 4.5 Hz), 1.63−1.50 (m, 1H), 1.45−1.31 (m, 2H), 1.93 (d, 3H, *J* = 6.9 Hz), 0.87 (d, 3H, *J* = 6.6 Hz), 0.80 (d, 3H, *J* = 6.4 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 172.2, 170.8, 170.7, 165.8, 158.3, 142.2, 140.5, 130.0, 128.6, 128.5, 128.2, 126.9, 124.6, 113.9, 76.4, 75.8, 74.8, 70.9, 55.1, 54.4, 39.6, 37.9, 35.8, 35.0, 34.0, 32.3, 24.4, 22.9, 21.4, 9.3.

ES−MS: *m/z* (%) 625 (90) $[M+H]^+$, 647 (100) $[M+Na]^+$.

HRMS (ESI): calcd for $C_{34}H_{44}N_2O_9Na$ 647.2944; found 647.2918.

Cryptophycin−24 (arenastatin A) (12):

To a solution of diol **131** (50 mg, 0.08 mmol) in CH_2Cl_2 (1 mL), trimethylorthoformate (0.35 mL, 0.32 mmol) and PPTS (3 mg, 0.01 mmol) were added at room temperature. The mixture was stirred for 1h, and then filtered through a layer of silica gel, washed with 80% ethyl acetate in hexane. The solvents were evaporated and the residue was evacuated at the vacuum pump for 30min. The residue was dissolved in

1 mL of CH_2Cl_2 and 0.15 mL of acetyl bromide in CH_2Cl_2 (0.85 M) was added dropwise at room temperature. After 2 h stirring at room temperature reaction mixture was quenched with 1 mL of aqueous saturated sodium bicarbonate solution. The organic layer was separated and aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, the solvents were evaporated and the residue was evacuated at the pump for 30min. This residue was dissolved in a solvent mixture of 0.6 mL of dimethoxy ethane, 0.4 mL of ethanol and 0.1 mL of methanol. Freshly powdered potassium bicarbonate (40 mg, 0.4 mmol) was added to the reaction mixture at rt. This heterogeneous mixture was stirred vigorously at 40 ^oC for 6h. Then the reaction mixture was diluted with ethyl acetate (5 mL) and filtered through a layer of silica gel. The solvents were evaporated and the residue was purified on column chromatography to obtained cryptophycin-24 (**12**) (31 mg, 65 % yield) as amorphous solid.

***R*$_f$**: 0.4 (SiO_2, 100% EtOAc).

$[\alpha]_D^{25}$: + 52.6 (*c* 0.75, $CHCl_3$).

IR (KBr): ν_{max} 3401, 3281, 2923, 2854, 1736, 1653, 1516, 1458, 1374, 1246, 1179, 1063, 1037, 996, 888, 821, 751, 698 cm^{-1}.

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39−7.31 (m, 3H), 7.27−7.22 (m, 2H), 7.11 (d, 2H, *J* = 7.9 Hz), 7.00−6.94 (m, 1H), 6.81 (d, 2H, *J* = 8.9 Hz), 6.69 (ddd, 1H, *J* = 14.8, 10.9, 4.9 Hz), 5.69 (d, 1H, *J* = 15.8 Hz), 5.62 (d, 1H, *J* = 7.9 Hz), 5.20 (dd, 1H, *J* = 11.9, 5.9 Hz), 4.89 (dd, 1H, *J* = 10.9, 3.9 Hz), 4.77−4.70 (m, 1H), 3.78 (s, 3H), 3.68 (d, 1H, *J* = 1.9 Hz), 3.56−3.48 (m, 1H), 3.47−3.38 (m, 1H), 3.15 (dd, 1H, *J* = 14.8, 5.9 Hz), 3.02 (dd, 1H, *J* = 14.8, 7.9 Hz), 2.92 (d, 1H, *J* = 7.2 Hz), 2.60−2.52 (m, 3H), 2.48−2.39 (m, 1H), 1.84−1.76 (m, 1H), 1.72−1.65 (m, 2H), 1.34−1.27 (m, 1H), 1.15 (d, 3H, *J* = 6.9 Hz), 0.84 (d, 3H, *J* = 5.9 Hz), 0.83 (d, 3H, *J* = 5.9 Hz).

^{13}C NMR (75 MHz, $CDCl_3$): δ 172.8, 170.6, 165.3, 158.5, 141.1, 136.7, 130.1, 128.7, 128.5, 128.4, 125.6, 125.2, 114.1, 75.8, 71.8, 63.0, 59.0, 55.2, 54.1, 40.6, 39.5, 36.7, 35.1, 34.1, 32.4, 24.3, 22.8, 21.2, 13.5.

LC−MS: *m/z* (%) 629.2 (100) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{34}H_{42}N_2O_8Na$ 629.2827, found 629.2838.

REFERENCES

1. Jordan, A.; Hadfield, J. A.; Lawrence, N. J.; McGown, A. T. *Med. Res. Rev*. **1998**, *18*, 259–296.
2. Eißler, S.; Stoncius, A.; Nahrwold, M.; Sewald, N. *Synthesis* **2006**, *22*, 3747−3789.
3. Rizvi, S. A.; Tereshko, V.; Kossiakoff, A.; Kozmin, S.; *J. Am. Chem. Soc.*, **2006,** *128*, 3882−3883.
4. Gunasekera, S. P.; Gunasekera, M.; Longley, R. E.; Schulte, G. K. *J. Org. Chem*. **1990**, *55*, 4912−4915.
5. Lama, K. S. *Trends in Microbiology* **2007,** *15*, 279−289.
6. Cormier, A.; Marchand, M.; Ravelli, R. B. G.; Knossow, M.; Gigant, B. *Scientific Report* **2008**, *9*, 1101−1106.
7. Pettit, G. R.; Xu, J. P.; Hogan, F.; Williams, M. D.; Doubek, D. L.; Schmidt, J. M.; Cerny, R. L.; Boyd, M. R. *J. Nat. Prod.* **1997**, *60*, 752−754.
8. Aicher, T. D.; Buszek, K.R.; Fang, F.G.; Forsyth, C.J.; Jung, S.H.; Kishi, Y.; Matelich, M.C.; Scola, P.M.; Spero, D.M.; Yoon, S.K. *J. Am. Chem. Soc*. **1992**, *114*, 3162−3164.
9. (a) Jordan, M. A.; Wilson, L. *Nat. Rev. Cancer* **2004**, *4*, 253. (b) Jordan, A.; Hadfield, J. A.; Lawrence, N. J.; McGown, A. T. *Med. Res. Rev.* **1998**, *18*, 259−296. (c) Giannakakou, P.; Sacket, D.; Fojo, T. *J. Natl. Cancer Inst.* **2000**, *92*, 182−183.
10. Hamel, E. *Peptide Sci.* **2002**, *66*, 142−160.
11. Mitra, A.; Sept, D. *Biochemistry* **2004**, *43*, 13955−13962.
12. Löwe, J.; Li, H.; Downing, K. H.; Nogales, E. *J. Mol. Biol.* **2001**, *313*, 1045−1057.
13. Ravelli, R. B.; Gigant, B.; Curmi, P. A.; Jourdain, I.; Lachkar, S.; Sobel, A.; Knossow, M. *Nature* **2004**, *428*, 198−202.
14. Panda, D.; Ananthnarayan, V.; Larson, G.; Shih, C.; Jordan, M. A.; Wilson, L. *Biochemistry* **2000**, *39*, 14121.
15. (a) Schwatrz, R. E.; Hirsch, C. F.; Sesin, D. F.; Flor, J. E.; Chartrain, M. Fromtling, R. E.; Harris, G. H.; Salvatore, M. J.; Liesch, J. M.; Yudin, K. *J. Ind.*

Microbiol. **1990**, *5*, 113−118. (b) Hirsch, C. F.; Liesch, J. M.; Salvatore, M. J.; Schwatrz, R. E.; Sesin, D. F. U.S. Patent 4, 946, 835, August 7, 1990.

16. (a) Trimurtulu, G.; Ohtani, I.; Patterson, G. M. L.; Moore, R. E.; Corbett, T. H.; Valeriote, F. A.; Demchik, L. *J. Am. Chem. Soc.* **1994**, *116*, 4729−4737. (b) Smith, C. D.; Zhang, X.; Mooberry, S. L.; Patterson, G. M. L.; Moore, R. E. *Cancer Res.* **1994**, *54*, 3779−3784. (c) Barrow, R. A.; Hemscheidt, T.; Liang, J.; Paik, S.; Moore, R. E.; Tius, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 2479−2490.
17. (a) Kobayashi, M.; Aoki, S.; Ohyabu, N.; Kurosu, M.; Wang, W.; Kitagawa, I. *Tetrahedron Lett.* **1994**, *35*, 7969−7972. (b) Koiso, Y.; Morita, K.; Kobayashi, M.; Wang, W.; Ohyabu, N.; Iwasaki, S. *Chem. Biol. Interact.* **1996**, *102*, 183−191. (c) Kobayashi, M.; Wang, W.; Ohyabu, N.; Kurosu, M.; Kitagawa, I. *Chem. Pharm. Bull.* **1995**, *43*, 1598−1600.
18. Trimurtulu, G.; Ogino, J.; Heltzel, C. E.; Husebo, T. L.; Jensen, C. M.; Larsen, L. K.; Patterson, G. M. L.; Moore, R. E.; Mooberry, S. L.; Corbett, T. H.; Valeriote, F. A. *J. Am. Chem. Soc.* **1995**, *117*, 12030−12049.
19. (a) Shih, C.; Teicher, B. A. *Curr. Pharm. Des.* **2001**, *7*, 1259−1276. (b) Menon, K.; Alvarez, E.; Forler, P.; Phares, V.; Amsrud, T.; Shih, C.; Al−Awar, R. S.; Teicher, B. A. *Cancer Chemother. Pharmacol.* **2000**, *46*, 142−149. (c) Liang, J.; Moore, R. E.; Moher, E. D.; Munroe, J. E.; Alawar, R. S.; Hay, D. A.; Varie, D. L.; Zhang, T. Y.; Aikins, J. A.; Martinelli, M. J.; Shih, C.; Ray, J. E.; Gibson, L. L.; Vasudevan, V.; Polin, L.; White, K.; Kushner, J.; Simpson, C.; Pugh, S.; Corbett, T. H. *Invest. New Drugs* **2005**, *23*, 213−224.
20. Gardinier, K. M.; Leahy, J. W. *J. Org. Chem*. **1997**, *62*, 7098−7099.
21. Liang, J.; Hoard, D. W.; Khau, V. V.; Martinelli, M. J.; Moher, E. D.; Moore, R. E.; Tius, M. A. *J. Org. Chem*. **1999**, *64*, 1459−1463.
22. Li, L. H.; Tius, M. A. *Org. Lett*. **2002**, *4*, 1637−1640.
23. White, J. D.; Hong, J.; Robarge, L. A. *J. Org. Chem.* **1999**, *64*, 6206−6216.
24. Furuyama, M.; Shimizu, I. *Tetrahedron: Asymmetry* **1998**, *9*, 1351−1357.
25. Varie, D. L.; Brennan, J.; Briggs, B.; Cronin, J. S.; Hay, D. A.; Rieck, J. A. III; Zmijewski, M. J. *Tetrahedron Lett.* **1998**, *39*, 8405−8408.
26. Ghosh, A. K.; Bischoff, A. *Org. Lett.* **2000**, *2*, 1573−1575.

27. Ali. S. M.; Georg, G. I. *Tetrahedron Lett.* **1997**, *38*, 1703−1706.

28. Eggen, M.; Nair, S. K.; Georg, G. I. *Org. Lett.* **2001**, *3*, 1813−1815.

29. Tripathy, N. K.; Georg, G. I. *Tetrahedron Lett.* **2004**, *45*, 5309−5311.

30. Pousset, C.; Haddad, M.; Larchevêque, M. *Tetrahedron* **2001**, *57*, 7163−7167.

31. Raghavan, S.; Tony, K. A. *J. Org. Chem.* **2003**, *68*, 5002–5005.

32. Eißler, S.; Markus, N.; Neumann, B.; Stammler, H. G.; Sewald, N. *Org. Lett*. **2007**, *9*, 817−819.

33. Eißler, S.; Borner, T.; Markus, N.; Sewald, N. *Chem. Eur. J.* **2009**, *15*, 11273–11287.

34. (a) Barry, C. St. J.; Crosby, S. R.; Harding, J. R.; Hughes, R. A.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett*. **2003**, *5*, 2429−2432. (b) Yang, X. −F.; Mague, J. T.; Li, C. J. *J. Org. Chem*. **2001**, *66*, 739−747. (c) Yadav, J. S.; Reddy, B. V. S.; Sekhar, K. C.; Gunasekar, D. *Synthesis* **2001**, *6*, 885−888. (d) Yadav, J. S.; Reddy, B. V. S.; Reddy, M. S.; Niranjan, N. *J. Mol. Catal. A: Chem*. **2004**, *210*, 99−103. (e) Yadav, J. S.; Reddy, B. V. S.; Reddy, M. S.; Niranjan, N.; Prasad, A. R. *Eur. J. Org. Chem*. **2003**, *9*, 1779−1783.

35. (a) Aubele, D. L.; Wan, S.; Floreancig, P. E. *Angew. Chem. Int. Ed.* **2005**, *44*, 3485−3488. (b) Barry, C. S.; Bushby, N.; Harding, J. R.; Willis, C. S. *Org. Lett*. **2005**, *7*, 2683−2686. (c) Cossey, K. N.; Funk, R. L. *J. Am. Chem. Soc*. **2004**, *126*, 12216−12217. (d) Crosby, S. R.; Harding, J. R.; King, C. D.; Parker, G. D.; Willis, C. L. *Org. Lett*. **2002**, *4*, 3407−3410. (e) Marumoto, S.; Jaber, J. J.; Vitale, J. P.; Rychnovsky, S. D. *Org. Lett*. **2002**, *4*, 3919−3922. (f) Kozmin, S. A. *Org. Lett*. **2001**, *3*, 755−758. (g) Jaber, J. J.; Mitsui, K.; Rychnovsky, S. D. *J. Org. Chem*. **2001**, *66*, 4679−4686. (h) Kopecky,D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc*. **2001**, *123*, 8420−8421. (i) Rychnovsky, S. D.; Thomas, C. R. *Org. Lett*. **2000**, *2*, 1217−1219. (j) Rychnovsky, S. D.; Yang, G.; Hu, Y.; Khire, U. R. *J. Org. Chem*. **1997**, *62*, 3022−3023. (k) Su, Q.; Panek, J. S. *J. Am. Chem. Soc.* **2004**, *126*, 2425−2430.

36. (a) Yadav, J. S.; Reddy, M. S.; Rao, P. P.; Prasad, A. R. *Tetrahedron Lett.* **2006**, *47*, 4397−4401. (b) Yadav, J. S.; Reddy, M. S.; Prasad, A. R. *Tetrahedron Lett.* **2006**, *47*, 4937−4941. (c) Yadav, J. S.; Reddy, M. S.; Prasad, A. R. *Tetrahedron*

Lett. **2006**, *47*, 4995−4998. (d) Yadav, J. S.; Reddy, M. S.; Rao, P. P.; Prasad, A. R. *Synlett* **2007**, 2049−2052, and the references cited therein.

37. Furrow, M. E.; Schaus, S. E.; Jacobsen, E. N. *J. Org. Chem.* **1998**, *68*, 6776−6777.
38. Yadav, J. S.; Reddy, M. S.; Prasad, A. R. *Tetrahedron Lett.* **2005**, *46*, 2133−2136.
39. Chan, K. P.; Seow, A. H.; Loh, T. P. *Tetrahedron Lett.* **2007**, *48*, 37–41.
40. Fuwa, H.; Okamura, Y., Natsugari, H. *Tetrahedron* **2004**, *60*, 5341−5352.
41. Brabander, J. D.; Vandewalle, M. *Synthesis* **1994**, 855−865.
42. (a) Nicolaou, K. C.; Harter, M. W.; Gunzner, J. L.; Nadin. A. *Liebigs Ann.***1997**, 1283−1301. (b) Ghosh. S.; Kumar, T. P. *J. Org. Chem.* **2010**, *75*, 2107–2110
43. (a) Hulme, A. N.; Rosser, E. M. *Org. Lett*. **2002**, *4*, 265−267. (b) McCubbin, J. A.; Maddess, M. L.; Lautens, M. *Org. Lett*. **2006**, *8*, 2993−2996.
44. Ghosh, A. K.; Xu, C. X. *Org. Lett*. **2009**, *11*, 1963−1966. and the references cited therein.
45. Yang, D.; Li, B.; Ng, F.; Yan, Y.; Qu, J.; Wu, Y. *J. Org. Chem*. **2001**, *66*, 7303–7312.

CHAPTER–II

INTRODUCTION

Galantin−I[1] is a peptide antibiotic isolated from culture broth of *Bacillius puluifaciensis* by Shoji and co-workers. Galantin−I is a mixture of congeners differing at the fourth amino acid residue from *N*-terminal, which are the D-ornithine **1a** (orn) and D-lysine **1b** (lys) residues (orn / lys=9/1) (Figure 1). This is effective against Gram positive, Gram negative and acid−fast bacteria and inactive against fungi and yeast. The water soluble antibiotic contains glycine, alanine, ornithine, lysine and few more ninhydrin−positive components. (−)−Galantinic acid, a non proteinogenic amino acid, was isolated from galantin I by the use of ion−exchange chromatography and preparative paper electrophoresis and was originally assigned the structure **2**. The structure of galantin−I and galantinic acid were revised by Ohfune and co-workers who also reported the first synthesis of galantinic acid (Figure 2).[2,3]

Figure 1

Figure 2

Ohfune *et al* in their efforts aiming at the total synthesis of galantin−I showed that the proposed structure **1** was different from natural galantin−I by comparing the ^{1}H NMR and MS of the synthetic and natural product and this has lead them to reinvestigate the structure of natural galantin−I. The galantinic acid residue present in natural galantin−I was found to undergo cyclization during the chemical degradation condition with retention of its C−3 configuration to give the artifact **2**. The data suggested that the correct structure of galantinic acid was not the cyclic form **2** but the acyclic form **5**. The structure of galantin−I was revised to structure **4**.

Contemporary works:

Galantinic acid has been an attractive target for synthetic chemists due to its unique structure with dense functionality and also interesting bioactivity.

Ohfune′s approach:

Ohfune *et al* [3] reported a total synthesis of (−)−galantinic acid starting from serinal derivative **11**, which was subjected to Wittig−Horner reaction followed by reduction to yield the allyl alcohol. The olefin was converted to epoxide with *m*−CPBA

to give the desired epoxy alcohol **10**. The alcohol was oxidized and treated with C_2−ylide to give α, β-unsaturated ester, which was cleaved reductively to give β, γ-unsaturated ester **9**. The cyclisation of **9** gave lactone **7** in moderate yield accompanied by undesired α, β-(*E*)-unsaturated ester **8**. Epoxidation of lactone **7** with *t*-BuOOH in presence of catalytic amount of aqueous benzyl trimethyl ammonium hydroxide (Triton B) gave epoxy lactone **6** stereoselectively, which was opened and inverted the obtained alcohol by oxidation and reduction to get 1,3-*anti* hydroxyl groups with moderate stereoselectivity. The undesired isomer was separated by column chromatography after conversion as silyl ether. Finally, exposure to TFA accomplished galantinic acid in moderate yield (Scheme 1).

Scheme 1

Ikota′s approach:

Ikota *et al* [4] started from D−ribono lactone **15** which was transformed into the 2-pyrrolidine derivative **14** in 11 steps. The β−keto ester **13** was obtained from **14** by treatment with lithio-*t*-butyl acetate. The keto group in **13** was reduced with $NaBH_4$ in the presence of LiCl to yield the β−hydroxy esters **12** in a ratio (1,3-*anti*:*syn*) 1.9:1 respectively. The desired 1,3-*anti* isomer of **12** was separated by converting it into its silyl ether derivative. Deprotection of all other protecting groups afforded (−)-galantinic acid **5** (Scheme 2).

Scheme 2

Apurba Datta′s approach:

Apurba *et al* [5] synthesized the *N*-Boc-galantinic acid ethyl ester **16** from L-serine, which was converted to a functionalized derivative **20** involving chelation controlled addition of Grignard reagent. Then the alkene group in **20** was converted to aldehyde **19** followed by Reformatasky reaction to give 3:2 mixture of diastereomers of compound **18**. The hydroxyl group in **18** was further oxidized to ketone **17** and finally, stereoselective reduction of the ketone *via* intramolecular hydride delivery, followed by deprotection of silyl ether linkage furnished the target molecule **16** (Scheme 3).

Scheme 3

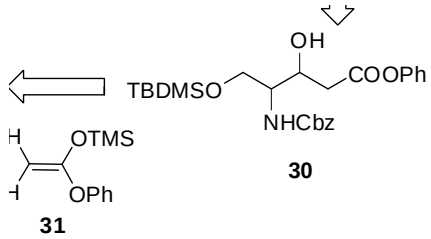
Campagne′s approach:

Campagne and his co-workers[6] reported the synthesis of *N*-(*Z*)-galantinic butyl ester **21** by using the Lewis acid catalyzed acetoacetate aldol−type reaction on a protected serinal **24**. The reaction of serinal with dienolate **25** in the presence of 10% of $Eu(fod)_3$ led to the formation of the vinylogous aldol product **23** with 9:1 diastereoselectivity. The dioxinone ring in **23** was opened by refluxing in *n*-butanol to give the keto alcohol **22**. Stereoselective reduction of ketone **22** using Evans′ protocol was accomplished galantinic acid butyl ester **21** with 98:2 diastereoselectivity (Scheme 4).

Scheme 4

Kiyooka′s approach:

Kiyooka and his group[7] synthesized the *N*-Cbz-galantinic acid **26** from protected L-serinal derivative **32** employing chiral oxazaborolidine promoted asymmetric aldol reaction (Scheme 5). The aldol reaction between **32** and silyl nucleophile **31** in presence of (*S*)-oxazaborolidinone furnished the *syn*-aldol product **30** in 10:1 (*dr*) ratio. The diastereomers were separated by column chromatography and protected as its acetonide, followed by the reduction of ester group to give alcohol **29**. The primary alcohol was oxidized followed by aldol reaction with **28** in presence of (*R*)-oxazaborolidinone to give 1,3-*anti*-diol unit **27**. Deprotection of other groups in compound **27** gave the *N*-Cbz-galantinic acid **26.**



30

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Scheme 5

Pradeep Kumar′s approach:

Pradeep Kumar and his co-workers[8] have reported (−) -galantinic acid **5** from commercially available 1,3-propanediol, which was converted to allyl alcohol **38** in 3 stabilized steps. This allyl alcohol was epoxidized under Sharpless asymmetric epoxidation conditions to give epoxide **37**.

Scheme 6

The *trans*-selective opening of the epoxide **37** was achieved with perchloric acid to afford the triol, which was subsequently protected with benzaldehyde dimethyl acetal to give 1,3 and 1,2 benzylidene compounds in 9:1 ratio. The desired 1,3-benzylidene **36**

was isolated by column chromatography. The PMB-ether in **36** was cleaved and the secondary hydroxy group was converted to azide under Mitsunobu conditions to give compound **35.** Compound **35** was converted to α, β-unsaturated ester, followed by asymmetric dihydroxylation to give diol **34**. The diol was transformed to cyclic sulfite **33** with thionyl chloride. The cyclic sulfite **33** was opened with $NaBH_4$ followed by acidic hydrolysis and reduction of azide to give the target molecule **5** (Scheme 6).

Raghavan′s approach:

Raghavan and his co-workers[9] reported a synthesis of galantinic acid derivative starting from *epi*-chlorohydrin **44**. The reaction of **44** with PMB protected homopropargyl alcohol using Yamaguchi protocol followed by hydrolytic kinetic resolution afforded the optical pure epoxide **43**. Opening of epoxide with thiophenol, conversion of PMB ether to silyl ether, subsequent reduction of triple bond with $LiAlH_4$ and oxidation of sulfide with $NaIO_4$ yielded an equimolar inseparable mixture of sulfoxides **42**. Treatment of epimeric sulfoxides **42** with NBS in presence of water afforded bromohydrin **41** as inseparable mixture. Oxidation of sulfoxide to sulfone, conversion of bromide to azide and the formation of epoxide **40** with sulfone as a leaving group, yielded the protected galantinic acid **39** in another five steps (Scheme 7).

Scheme 7

Gademann′s approach:

Gademann and his co-workers[10] reported the synthesis of galantinic acid from hydroxyl aminoacid **47**, which was readily prepared from protected serine **48**. Claisen condensation of **47** with lithiated *t*-butyl acetate gave the hydroxyketoester **46.** The keto

group in **46** was stereoselectively reduced to give **45** subsequent deprotection of all functional groups led to compound **5** (Scheme 8).

Scheme 8

PRESENT WORK

A retrosynthetic analysis for (−)-galantinic acid **5** based on chiron approach with diastereoselective allylic addition as the prominent strategy is pictorially presented in Scheme 9. We envisioned that the synthesis of galantinic acid could be achieved by employing stereoselective allylation as a key strategy to make this route more feasible and simple.

Scheme 9

The homoallylic alcohol **49** can be obtained from **50** by converting terminal olefin to aldehyde followed by stereoselective allylation. Compound **50** could be achieved from homoallylic alcohol **51a** *via* S_N2 substitution of benzyl amine followed

by protections. The homoallylic alcohol **51a** was prepared from (*R*)-2,3-*O*-isopropylidine glyceraldehyde **52** which was prepared from commercially available D−mannitol **53**.

In direct reciprocation of retrosynthetic analysis, we commenced our synthesis from D-mannitol **53**. The cheap and commercially easy availability with high enantiomeric purity and having C_2 symmetry were the strong incentives to start from D-mannitol. The foremost step was the conversion of D-mannitol **53** into 1,2,5,6-di-*O*-isopropylidine-D-mannitol **54** using 2,2–dimethoxy propane and cat. *p*-TSA in dry DMSO as shown in Scheme 10.

Scheme 10

The treatment of diacetonide D-mannitol **54** with $NaIO_4$, and sat. $NaHCO_3$ in CH_2Cl_2 at 0 °C for 8 h afforded the (*R*)-2,3-*O*-isopropylidineglyceraldehyde **52** in quantitative yield.[11] In the ^{1}H NMR spectrum of **52** the characteristic aldehyde proton resonated at δ 9.70 and two methyl protons appeared as two singlets at δ 1.45 and 1.40 confirming the formation of the product.

Scheme 11

The next endeavor was the stereoselective allyl addition to the aldehyde **52**. Accordingly**,** the compound **52** was treated with allyl bromide, in presence of activated zinc dust and saturated NH_4Cl, which gave the mixture of diastereomers **51a** and **51b** in in 92% yield with 95:5 ratio (*anti* : *syn*) (Scheme 11). The required diastereomer was separated by column chromatography. In the ^{1}H NMR, appearance of allylic protons peaks at δ 5.90–5.79 for one proton and δ 5.20–5.11 for two protons as multiplets attributed vinylic group. A signal at *m/z* 195 corresponding to $[M+Na]^+$ in the ESI mass

spectrum also confirmed the formation of the product. In supplement to this, a signal at *m/z* 195.0998 corresponding to $[M+Na]^+$ (calcd 195.0997) in the high resolution ESI mass spectrum also proved the efficient transformation.

This reaction is called as Barbier type reaction; this stereoselective Barbier reaction installed the single chiral center of the target compound with appropriate stereochemistry. A brief discussion on Barbier reaction and the rational for the stereochemical outcome is discussed herein. The nucleophilic addition of allyl and propargyl halides in the presence of metals like Zn, In and Sn to a carbonyl electrophile is called Barbier reaction. The advantage of Barbier reaction is two fold: 1) Unlike other reagents which have to be generated from alkyl or propargyl halides mediated by Zinc powder beforehand, there is no necessity to the prior generation of the organometal in the Barbier protocol. 2) Use of water (salt) as co solvent makes this reaction as a two−phase system and also makes an attractive green protocol. Under such conditions,[12] intermediate radical ion formed by an electron transfer mechanism $[CH_2=CHRX].-Zn.^+$, is thought to interact with the carbonyl compound. The proposed transition state for this Barbier type reaction, with geometric characteristics is similar to that of the corresponding structure in the SN_2 displacement (Figure 3).[13]

In the transition state, the substituted carbon atom (α carbon) of the allylic moiety interacts with an aldehyde molecule adsorbed on the zinc metal surface. The rigid arrangement of transition state, having a cyclic structure, favors the *threo*−form owing to minor interactions between the methyl group linked to the allyl (α carbon) atom and the bulky R groups of the aldehyde. Adsorbed carbonyl compounds can interact with the zinc metal to give radical anion and then, by desorption radical species.[14,15] The hypothesis of a transition state with a cyclic structure might be explained by the moderate *threo*−selective allylation on aldehyde.

Proposed Reaction Mechanism:

Figure 3

The *anti*−diastereoselectivity may be explained by Felkin−Ann model (Figure 3) with the addition of allyl metal expected at the less hindered side of the carbonyl group in the staggered model of Newman projection. The moderate diastereoselectivity (95:5, *anti:syn*) can be explained by the steric size difference between R_L and R_M, which are large and moderate groups respectively. In addition, the steric differentiation of two groups is limited due to the formation of 1,3−dioxolane ring. Since the *syn*−isomer is formed as minor product and also the reaction is performed in aqueous medium, the chelation control model is ruled out.

Scheme 12

The alcohol of **51a** was treated with benzyl bromide and NaH in dry THF at 0^{o}C and warmed to room temperature to afford **55** in 90% yield (Scheme 12). The newly introduced protons corresponding to benzyl group in ^{1}H NMR of **55** resonated at δ 4.60−4.61 as multiplet for benzylic protons and another multiplet at δ 7.39−7.20 for aromatic protons, while the rest of the protons appeared at the expected chemical shifts. Thus the product was confirmed. A signal at *m/z* 263 and 285 corresponding to $[M+H]^{+}$ and $[M+Na]^{+}$ in the EI mass spectrum of the compound **55** also confirmed the formation of the product.

Acetonide deprotection of the compound **55** on reaction with 2N HCl in THF at room temperature for 3 h afforded diol **56** in 90% yield. Disappearance of signals corresponding to acetonide group and presence of the remaining signals at their respective chemical shift values in the ^{1}H NMR spectrum of the compound **56** clarified the deprotection. A signal at *m/z* 245 corresponding to $[M+Na]^{+}$ in the EI mass spectrum of the compound **56** also confirmed the formation of the product.

The diol **56** was subjected to selective protection of primary alcohol using BnBr in the presence of dibutyltin oxide [16,17] in benzene under reflux to produce the compound **57** in 88% yield (Scheme 13). In ^{1}H NMR of compound **57** the benzylic and phenyl protons are doubled, which confirm the presence of newly introduced protons. EIMS of compound **57** $[M+Na]^{+}$ shows a peak at 335.1 giving further confirmation of the product.

Scheme 13

The free OH group in **57** was treated with $MeSO_2Cl$ in presence DIPEA in anhydrous CH_2Cl_2 at 0 °C for 3h to afford the corresponding mesyl ester **58** in 82% yield. Appearance of a singlet at δ 2.96 in the ^{1}H NMR spectrum of the compound **58** integrating for 3 protons that corresponds to –OMs group lent support for the mesylation and the rest of the protons were observed at their respective chemical shift values. In addition to this, a signal at *m/z* 413 corresponding to the $[M+Na]^{+}$ in the EI

mass spectrum of the compound **58** was also in very good agreement with this conversion.

After that we envisioned to replace the mesyl group with azide. Several experiments were carried out for this transformation by using sodium azide in different solvent media at various temperature but these efforts were unsuccessful (Scheme 14). Finally, we accomplished this conversion with benzylamine in solvent free conditions.

Scheme 14

The mesyl ester **58** was subsequently heated with benzylamine [18] (excess) at 120 °C under solvent free condition for 12 h to afford the desired amino compound **59** in 85% yield. The S_N2 substitution was a smooth affair, even though the mesylate group is sterically flanked by benzylic groups (Scheme 15). Disappearance of the signal corresponding to –OMs group in the ^{1}H NMR spectrum of the compound **59** was the prime support for the successful transformation and the rest of the protons were observed at their respective chemical shift values. ESI mass spectrum of compound **59** showed a signal at *m/z* 402 corresponding to $[M+H]^+$. A high resolution ESI mass spectrum consisting of a signal at *m/z* 402.2438 corresponding to $[M+H]^+$ (calcd 402.2433) further justified the success of the reaction.

Scheme 15

The free NH−proton in **59** was protected with CBZ−chloride in aq. ethanol for 3 h at 0 °C and warmed to room temperature to afford the corresponding carbamate derivative **50** in 90% yield. The integration of peaks at δ 7.33−6.99 region and δ 5.14−4.89 were increased that correspond to the CBZ group and indicate the formation

of **50**. A high resolution ESI mass spectrum consisting of a signal at *m/z* 558.2620 corresponding to $[M+Na]^+$ (calcd 558.2620) further justified the success of the reaction.

Scheme 16

Then the double bond in **50** was dihydroxylated with osmium tetroxide to give diol that was cleaved with sodium periodate to give the aldehyde in a pure form. We proceeded to the next chelation−controlled diastereoselective allylation without any further purification and analytical characterization of the aldehyde. Thus, the aldehyde was treated with allyl(tributyl)stannane in the presence of magnesium bromide[19] in CH_2Cl_2 at 0 °C to give the corresponding homoallylic alcohol as a mixture of isomers **49a** and **49b** in 72% overall yield in 9:1 ratio. The desired major 1,3−*anti*−adduct **49a** was easily separated by column chromatography from the undesired isomer (Scheme 16). Appearance of the characteristic peaks of olefin at δ 5.89–5.65, and δ 5.20–4.92 and another signal at δ 1.67–1.45 corresponding to the methylene group demonstrated the formation of the product **49a**. In addition to this, a broad signal at 3453 cm^{-1} in the IR spectrum of the compound **49a** also suggested the presence of –OH functionality. High resolution ESI mass spectrum carrying a signal at *m/z* 602.2854 corresponding to $[M+Na]^+$ (calcd 602.2882) was also in excellent agreement with the formation of the product.

This stereoselective allylation can be explained via asymmetric induction model involving preferred stereo-electronically controlled addition of nucleophile.[20] Furthermore, transition states **Ts–I** and **Ts–II** shown in Figure 4 can be invoked in order to explain the stereochemistry of products **A** and **B**, assuming that interactions of the substituents of the oxocarbenium ion and the allyl tributyl tin must be minimized. Then, the preferential formation of the *anti* adduct can be rationalized through a transition state (**Ts–I**) on the basis of stereoelectronic and steric considerations.

Figure 4: Asymmetric induction model for 1,3 *anti*−chelation

The homoallylic alcohol **49a** was treated with a catalytic amount of osmium tetroxide to give the 1,2−diol, which was oxidatively cleaved with $NaIO_4$ in THF–H_2O (5:1) to afford the aldehyde. The aldehyde was oxidized to an acid **60** with $NaClO_2$ and $NaH_2PO_4.2H_2O$ in *t*-BuOH at room temperature, in 85% yield (Scheme 17).

Scheme 17

The ^{1}H NMR spectrum of compound **60** showed the appearance of signal at δ 2.51−2.24 corresponding to the methylene group next to carboxyl group. Peaks at *m/z* 620.3 $[M+Na]^+$ in LC−MS further ensured the formation of **60**. High resolution ESI

mass spectrum carrying a signal at *m/z* 620.2646 corresponding to $[M+Na]^+$ (calcd 620.2624) was also in excellent agreement with the formation of the product.

Debenzylation and CBZ deprotection in **60** was achieved with 10% Pd/C in methanol at room temperature under hydrogen atmosphere. After 8 h stirring, the desired compound **5** was obtained in 86% yield. The ^{1}H NMR and specific rotation of our synthetic product **5** matched with those reported for the natural product (−)−galantinic acid.[2,3]

The LC mass spectrum of compound **5** showed a signal at *m/z* 194 corresponding to $[M+H]^+$. In addition to this, the high resolution ESI mass spectrum carrying a signal at *m/z* 216.0839 corresponding to $[M+Na]^+$ (calcd 216.0847) was also in support for the formation of the product.

In conclusion, we have described a simple, convenient and efficient approach for the synthesis of (−)−Galantinic acid **5** involving a sequence of reactions starting from (*R*)-2,3-*O*-isopropylidine glyceraldehydes with high stereoselectivity. Readily available starting material at low cost and simple experimental conditions in this approach makes it a useful and attractive process for the total synthesis of (−)−Galantinic acid **5**.

EXPERIMENTAL SECTION

(1*S*,2*S*)−1,2−Bis((*R*)−2,2−dimethyl−1,3−dioxolan−4−yl)ethane−1,2−diol (54):

To a mixture of D-mannitol **53** (10.0 g, 54.94 mmol) and *p*-TSA catalytic amount (5 mg) in dry DMSO (15 mL), was added 2,2-dimethoxypropane (13.6 mL, 109.88 mmol) at 0°C under nitrogen atmosphere. The resulting reaction mixture was gradually warmed to ambient temperature and allowed to stir for 8 h. The complete conversion of the starting material was confirmed by TLC. Then the reaction mixture was partitioned between water and ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to obtain the crude product which was purified by column chromatography to obtain the pure product **54** (10.0 g, 70%) as a white solid.

***R*$_f$:** 0.5 (SiO_2, 50% EtOAc in petroleum ether).

IR (neat): ν_{max} 3330, 2987, 2935, 1372, 1214, 1068 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 4.10 (m, 4H), 3,94 (q, 2H), 3.68 (t, 2H, J = 4.8 Hz), 2.71 (br, 2H, −OH), 1.40 (s, 6H), 1.34 (s, 6H).

EI−MS: *m/z (%)* 248 $[M-14]^+$, 190 (3), 102 (45), 73 (15), 59 (43), 43 (100).

(*R*)−2,3−*O*−Isopropylideneglyceraldehyde (52):

To a stirred solution of D-mannitol diacetonide **54** (7.0 g, 2.0 mmol) in CH_2Cl_2, was added 3.0 mL of aq. saturated sodium bicarbonate solution at 0 °C and then added sodium metaperiodate (11.7 g, 54.6 mmol) as portion wise over 15 min. The reaction mixture was stirred for 8 h at ambient temperature. After completion of reaction, the

reaction mixture was filtered and concentrated under reduced pressure to afford the crude aldehyde **52** as colorless liquid in quantitative yield.

$\boldsymbol{R_f}$ **:** 0.6 (SiO_2, 50% EtOAc in petroleum ether).

^{1}H NMR (300 MHz, $CDCl_3$): δ 9.70 (s, 1H), 4.35 (m, 1H), 4.10 (m, 2H), 1.45 (s, 3H), 1.40 (s, 3H).

(*S*)−1−((*R*)−2,2−Dimethyl−1,3−dioxolan−4−yl)but−3−en−1− ol (51a):

To a mixture of activated zinc dust (5.5 g, 84.6 mmol) in 30ml of dry THF under nitrogen atmosphere, was added a solution of (*R*)−glyceraldehyde **52** (5.5 g, 42.3 mmol) in 25 mL THF at 0 °C followed by allyl bromide (7.15 mL, 84.6 mmol) drop wise over 10 min. The reaction mixture was stirred for 4 h at 0 °C. After completion of the reaction (monitored by TLC), the reaction mixture was quenched by addition of saturated aqueous ammonium chloride (17 mL) at 0 °C over 30 min. After being stirred for 1 h, the reaction mixture was filtered and the filtrate was concentrated under vacuum. The crude product was partitioned between water and ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and evaporated. The residue was further purified by column chromatography to afford the pure compound **51a** (7.75 g, 87%) as yellowish oil.

$\boldsymbol{R_f}$ **:** 0.5 (SiO_2, 30% EtOAc in petroleum ether).

$[\alpha]_D$: +5.58 (*c* 0.5, MeOH).

IR (neat): ν_{max} 3454 (br), 2986, 1375, 1214, 1064 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 5.90−5.79 (m, 1H), 5.20−5.11 (m, 2H), 4.07−3.91 (m, 3H), 3.82−3.75 (m, 1H), 2.38−2.15 (m, 2H), 1.39 (s, 3H), 1.33 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 133.8, 118.3, 109.0, 78.0, 70.2, 65.1, 37.5, 26.4, 25.2.

ESI−MS: *m/z* (%) 195 (100) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_9H_{16}O_3Na$ $[M+Na]^+$ 195.0997, found 195.0998.

(4*R*)−4−[(1*S*)−1−(Benzyloxy)but−3−en−1−yl]−2,2−dimethyl−1,3−dioxolane (55):

A solution of **51a** (5.5 g, 31.9 mmol) in dry THF (20 mL) was added to a stirred solution of NaH (1.53 g, 38.3 mmol) in anhyd THF (40 mL) at 0 °C under N_2, and the mixture was stirred for 20 min. BnBr (4.6 mL, 38.3 mmol) was added, and the mixture was stirred for 4 h at rt. The reaction was then quenched with ice−cold NH_4Cl (20 mL) at 0 °C, and the mixture was concentrated and then diluted with H_2O (50 mL). The aqueous layer was extracted with EtOAc (3×30 mL), and the combined organic layers were washed with brine (30 mL), dried (Na_2SO_4), and concentrated. The residue was further purified by column chromatography to give pure compound **55** (7.5 g, 90%) as yellowish oil.

***R*$_f$**: 0.6 (SiO_2, 20% EtOAc in petroleum ether).

[α]$_D$: + 36.0 (*c* 0.01, $CHCl_3$).

IR (neat): ν_{max} 3069, 3031, 2985, 2931, 1454, 1375, 1212, 1072, 915, 854, 739 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.39−7.20 (m, 5H), 5.92−5.78 (m, 1H), 5.18−5.03 (m, 2H), 4.60 (ABq, 2H, *J* = 11.3 MHz), 4.09−3.99 (m, 2H), 3.91−3.82 (m, 1H), 3.58−3.51 (m, 1H), 2.50−2.27 (m, 2H), 1.41 (s, 3H), 1.35 (s, 3H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 138.1, 134.2, 128.2, 128.1, 127.9, 127.6, 127.2, 117.3, 108.9, 78.9, 77.2, 72.5, 66.1, 35.5, 26.4, 25.2.

ESI−MS: *m/z* (%) 263.0 (40) $[M+H]^+$, 285.1 (100) $[M+Na]^+$.

(2*R*, 3S)−3−(Benzyloxy)hex−5−ene−1,2−diol (56):

To a stirred solution of acetonide **55** (1.0 g, 3.81 mmol) in THF (15 mL) was added 2 M HCl (1 mL) at 0 °C. The mixture was stirred for 3 h at room temperature, then cooled to 0 °C and neutralized with solid $NaHCO_3$ (0.168 g, 2 mmol). The solvent

was removed *in vacuo* and diluted with H_2O (20 mL). The aqueous layer was extracted with EtOAc (3×20 mL) dried (Na_2SO_4) and concentrated. The residue was further purified by flash chromatography to give pure **56** (0.76 g, 90%) as yellowish oil.

***R*$_f$**: 0.4 (SiO_2, 50% EtOAc in petroleum ether).

[α]$_D$: +16.0 (*c* 0.1, $CHCl_3$).

IR (neat): ν_{max} 3413 (br, OH), 2923, 2860, 1451, 1078, 915, 740 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.37−7.21 (m, 5H), 5.92−5.77 (m, 1H), 5.20−5.05 (m, 2H), 4.72−4.41 (m, 2H), 3.78−3.49 (m, 4H), 2.52−2.29 (m, 2H), 2.21−1.90 (br s, 1H), 1.65−1.40 (br s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 138.1, 134.2, 128.4, 127.8, 117.6, 80.3, 72.4, 72.3, 63.2, 35.0.

ESI−MS: *m/z* (%) 245.2 (100) $[M+Na]^+$.

(2*R*,3*S*)−1,3−Bis(benzyloxy)hex−5−en−2−ol (57):

Bu_2SnO (2.06 g, 8.30 mmol) and Bu_4NI (696 mg, 1.89 mmol) were added to a stirred solution of compound **56** (1.67 g, 7.55 mmol) in benzene (150 mL) at rt. The flask was then fitted with a Dean–Stark trap (filled with 4−Å molecular sieves) and a reflux condenser. The trap was filled with benzene, and the mixture was heated to reflux until H_2O evolution appeared to be complete. The mixture was cooled to rt., and BnBr (1.08 mL, 9.04 mmol) was added. The resulting yellow solution was refluxed for 18 h. The mixture was then diluted with Et_2O (50 mL) and washed with 10% $Na_2S_2O_3$ (50 mL). The layers were separated, and the aqueous phase was extracted with Et_2O (3×50 mL). The combined organic layers were washed with H_2O (30 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel chromatography to give ether **57** (2.06 g, 88%) as colorless oil.

***R*$_f$:** 0.5 (SiO_2, 30% EtOAc in petroleum ether).

[α]$_D$: +14.0 (*c* 1.0, $CHCl_3$).

IR (neat): ν_{max} 3453 (br, OH), 3030, 2923, 2863, 1454, 1384, 1092, 1027, 913, 740, cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.43−7.18 (m, 10H), 5.93−5.76 (m, 1H), 5.18−5.02 (m, 2H), 4.68−4.42 (m, 4H), 3.82−3.72 (m, 1H), 3.62−3.46 (m, 3H), 2.50−2.20 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 134.8, 128.3, 128.2, 127.8, 127.7, 127.5, 117.2, 79.0, 73.3, 72.1, 71.3, 71.0, 35.0.

EI−MS: *m/z* (%) 335.1 (100) $[M+Na]^+$.

(2*R*,3*S*)−1,3−Bis(benzyloxy)hex−5−en−2−yl Methanesulfonate (58):

$MeSO_2Cl$ (0.86 mL, 11.06 mmol) was added to a stirred solution of compound **57** (3.15 g, 10.06 mmol) and DIPEA (5.24 mL, 15.09 mmol) in anhydrous CH_2Cl_2 (15 mL) at 0 °C. The mixture was stirred for 3 h at room temperature then neutralized with K_2CO_3 (1.65 g, 12 mmol). The resulting mixture was stirred for 15 min then washed with H_2O (2×15 mL), and extracted with CH_2Cl_2 (2×25 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4), and concentrated. The residue was further purified by column chromatography to give pure compound **58** (3.2 g, 82%) as pale yellow oil.

***R*$_f$:** 0.5 (SiO_2, 30% EtOAc in benzene).

$[\alpha]_D$: +2.0 (*c* 0.2, $CHCl_3$).

IR (neat): ν_{max} 3030, 2922, 2858, 1454, 1353, 1174, 1097, 919, 741, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41–7.18 (m, 10H), 5.90–5.73 (m, 1H), 5.21–5.12 (m, 2H), 4.89–4.80 (m, 1H), 4.64–4.44 (m, 4H), 3.79–3.69 (m, 3H), 2.96 (s, 3H), 2.48–2.14 (m, 2H).

EI−MS: *m/z* (%) 413.1 (100) $[M+Na]^+$.

(2*S*,3*S*)−*N*−Benzyl−1,3−bis(benzyloxy)hex−5−en−2−amine (59):

A mixture of compound **58** (2.5 g, 6.41 mmol) and $BnNH_2$ (10.5 mL, 96.15 mmol) was heated to 120 °C. After 12 h, the mixture was cooled to room temperature, and diluted with EtOAc. The resulting mixture was washed with aq $NaHCO_3$ and brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was further purified by column chromatography to give compound **59** (2.0 g, 85%) as yellowish oil.

R_f : 0.4 (SiO_2, 30% EtOAc in petroleum ether).

$[\alpha]_D$: + 7.5 (*c* 0.1, $CHCl_3$).

IR (neat): ν_{max} 3063, 3029, 2923, 2853, 1454, 1095, 913, 738, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40−7.18 (m, 15H), 5.92−5.72 (m, 1H), 5.19−4.98 (m, 2H), 4.68−4.41 (m, 4H), 3.89−3.49 (m, 5H), 2.92−2.87 (m, 1H), 2.59−2.22 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 140.7, 138.5, 138.2, 135.4, 134.3, 129.6, 128.9, 128.4, 128.3, 128.2, 128.1, 127.7, 127.6, 127.5, 127.4, 126.7, 116.8, 78.9, 73.1, 72.2, 69.5, 58.4, 52.0, 35.0.

ESI−MS: *m/z (%)* 402.2 (100) $[M+H]^+$.

HRMS (ESI): Calcd for $C_{27}H_{32}NO_2$ $[M+H]^+$ 402.2433, found 402.2438.

Benzyl benzyl[(2*S*,3*S*)−1,3−bis(benzyloxy)hex−5−en−2−yl]carbamate (50):

Compound **59** (1.3 g, 3.25 mmol) was dissolved in EtOH: H_2O (10:1; 10 mL) and the mixture was stirred at 0°C. Solid $NaHCO_3$ (1.09 g, 13 mmol) and CbzCl (0.56 mL, 3.9 mmol) were added, and the mixture was stirred for 3 h at 0 °C and then diluted with H_2O (20 mL). The resulting mixture was concentrated and extracted with EtOAc

(2×25 mL). The combined organic layers were washed with brine (20 mL), dried Na_2SO_4, and concentrated *in vacuo*. The residue was further purified by column chromatography to give compound **50** (1.48 g, 90%) as yellowish oil.

$\boldsymbol{R_f}$ **:** 0.4 (SiO_2, 20% EtOAc in petroleum ether).

$\boldsymbol{[\alpha]_D}$ **:** – 4.5 (*c* 0.1, $CHCl_3$).

IR (neat): ν_{max} 3064, 3030, 2922, 2853, 1697, 1454, 1243, 1103, 914, 736, 697 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ 7.33−6.99 (m, 20H), 5.96−5.65 (m, 1H), 5.14−4.89 (m, 4H), 4.69−4.41 (m, 3H), 4.40−4.07 (m, 4H), 3.92−3.33 (m, 3H), 2.48−2.14 (m, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 139.4, 137.9, 136.5, 134.3, 134.1, 128.2, 128.0, 127.7, 127.6, 127.4, 127.0, 126.5, 117.4, 78.5, 72.8, 72.5, 69.2, 67.2, 59.4, 49.7, 35.8.

ESI−MS: *m/z* (%) 536.2 (30) $[M+H]^+$, 558.2 (100) $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{35}H_{37}NO_4Na$ $[M+Na]^+$ 558.2620, found 558.2620.

Benzyl benzyl[(2*S*,3*S*,5*R*)−1,3−bis(benzyloxy)−5−hydroxyoct−7−en−2−yl] carbamate (49a):

To a solution of compound **50** (0.7 g, 1.30 mmol) in acetone–H_2O (3:1, 10 mL) were added OsO_4 (0.5 mol%) and NMO (0.46 g, 3.92 mmol) at rt. The mixture was stirred for 6 h, and then the reaction was quenched with solid $NaHSO_4$ (0.94 g, 7.84 mmol) and the mixture was stirred for 15 min. Solid particles were separated by filtration and the filtrate was dried (Na_2SO_4) and concentrated. The residue was dissolved in THF–H_2O (4:1, 10 mL), and $NaIO_4$ (0.84 g, 3.92 mmol) was added. After 30 min, the mixture was filtered, dried (Na_2SO_4), and concentrated to give the crude aldehyde. A solution of this crude aldehyde (0.6 g, 1.1 mmol) in anhydrous CH_2Cl_2 (15 mL) was treated with $MgBr_2 \cdot Et_2O$ (0.53 g, 3.31 mmol) and allyl(tributyl)stannane (0.51 mL, 1.65 mmol) at 0 °C, and the mixture was stirred for 3 h. The mixture was then

washed with 2 M HCl solution (5 mL) and extracted with CH_2Cl_2 (2×25 mL). The combined organic layers were dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography to give compound **49a** (0.40 g, 64%) as yellowish oil.

R_f : 0.4 (SiO_2, 30% EtOAc in petroleum ether).

$[\alpha]_D$: – 6.2 (*c* 0.75, $CHCl_3$).

IR (neat): ν_{max} 3453(br, OH), 3063, 3030, 2920, 2854, 1692, 1452, 1414, 1241, 1067, 913, 734, 696 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ 7.40−6.98 (m, 20H), 5.89−5.65 (m, 1H), 5.20−4.92 (m, 4H), 4.71−3.92 (m, 8H), 3.80−3.63 (m, 1H), 3.62−3.34 (m, 2H), 2.19−1.94 (m, 2H), 1.67−1.35 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 157.0, 139.1, 136.4, 134.6, 128.8, 128.7, 128.3, 128.2, 128.1, 128.0, 127.8, 127.6, 127.4, 127.0, 126.6, 117.7, 77.0, 73.0, 72.7, 69.1, 67.8, 67.2, 60.0, 50.0, 42.5, 37.5.

LC–MS: *m/z* (%) 580.3 $[M+H]^+$, 602.3 $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{37}H_{41}NO_5Na$ $[M+Na]^+$ 602.2882, found 602.2854.

(3*S*,5*S*,6*S*)−6−[Benzyl(benzyloxycarbonyl)amino]−5,7−bis(benzyloxy)−3−hydroxyheptanoic Acid (60):

To a solution of compound **49a** (0.5 g, 0.86 mmol) in acetone–H_2O (3:1, 5 mL) were added OsO_4 (0.5 mol%) and NMO (0.30 g, 2.59 mmol) at rt. The mixture was stirred for 6 h, and the reaction was quenched with solid $NaHSO_4$ (0.62 g, 5.18 mmol) and the mixture was stirred for 15 min. Solid particles were separated by filtration, and the filtrate was dried with Na_2SO_4 and concentrated *in vacuo*. The residue was dissolved in THF/H_2O (4:1, 5 mL), and $NaIO_4$ (0.55 g, 2.59 mmol) was added. After 30 min, the mixture was filtered, dried with Na_2SO_4, and concentrated to give the crude

aldehyde. To a solution of this crude aldehyde (0.43 g, 0.74 mmol) in *t*−BuOH (5 mL) were added $NaClO_2$ (0.73 g, 8.14 mmol) and 20% aq. $Na_2H_2PO_4 \cdot 2H_2O$ (5 mL) at 0 °C, and the mixture was stirred for 4 h at room temperature. The mixture was then diluted with EtOAc (5 mL) and washed with 5 M aq. NaH_2PO_4 (1 mL). The organic layer was dried with Na_2SO_4 and concentrated, and residue was purified by flash column chromatography to afford compound **60** (0.43 g, 85%) as yellowish oil.

R_f : 0.1 (SiO_2, EtOAc).

$[\alpha]_D$: – 6.0 (*c* 0.23, $CHCl_3$).

IR (neat): ν_{max} 3435 (br, OH), 3029, 2923, 2854, 1693, 1454, 1243, 1103, 738, 697 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.63–7.06 (m, 20H), 5.13 (br s, 2H), 4.79–4.04 (m, 8H), 3.74–3.41 (m, 3H), 2.51–2.24 (m, 2H), 1.80–1.46 (m, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ 157.2, 138.8, 137.5, 136.2, 128.4, 128.2, 128.0, 127.8, 127.7, 127.6, 127.0, 126.8, 77.1, 73.1, 72.8, 70.1, 69.0, 67.5, 59.8, 49.9, 41.5, 37.2.

LC–MS: *m/z* (%) 620.3 $[M+Na]^+$.

HRMS (ESI): Calcd for $C_{36}H_{39}NO_7Na$ $[M+Na]^+$ 620.2624; found 620.2646.

(–)−Galantinic Acid (5):

To a solution of acid **60** (0.23 g, 0.38 mmol) in MeOH (10 mL) was added 10% Pd/C (0.01 g) under H_2 atmosphere, and the mixture was stirred for 8 h. The mixture was then filtered and concentrated to give a residue that was purified on Dowex 50W×4, eluting with 1 M aq NH_3, to give target molecule **5** (0.06 g, 86%) as colorless solid.

$[\alpha]_D$: – 28.2 (*c* 0.5, H_2O).

IR (KBr): ν_{max} 3448, 2923, 2851, 1637, 1458, 1215, 759 cm^{-1}.

^{1}H NMR (400 MHz, D_2O): δ 4.26–4.17 (m, 1H), 3.94–3.89 (m, 1H), 3.78 (dd, *J* = 4.3, 12.3 Hz, 1H), 3.64 (dd, *J* = 7.0, 12.3 Hz, 1H), 3.18 (ddd, *J* = 4.3, 7.0, 7.0 Hz, 1H), 2.59–2.44 (m, 2H), 1.68–1.55 (m, 2H).

LC−MS: *m/z* (%) 194.1 $[M+H]^+$, 216.1 $[M+Na]^+$.

HRMS (ESI): Calcd for $C_7H_{15}NO_5Na$ $[M+Na]^+$ 216.0847, found 216.0839.

REFERENCES

1. Shoji, j.; Sakajaki, R.; Koizumi, K.; Mayama, M.; Matsurra, S. J. *J. Antibiot.* **1975**, *28*, 122−125.
2. Sakai, N.; Ohfune, Y. *Tetrahedron Lett.* **1990**, *31*, 4151−4154.
3. Sakai, N.; Ohfune, Y. *J. Am. Chem. Soc*. **1992**, *114*, 998−1010.
4. Ikota, N. *Heterocycles* **1991**, *32*, 521−528.
5. Kumar, J. S. R.; Datta, A. *Tetrahedron Lett.* **1999**, *40*, 1381−1384.
6. Moreau, X.; Campagne, J. *Tetrahedron Lett.* **2001**, *42*, 4467−4469.
7. Kiyooka, S.; Goh, K.; Nakamura, Y.; Takesue, H.; Hena, M. A. *Tetrahedron Lett.* **2000**, *41*, 6599−6603.
8. Kumar, P.; Pandey, S. K.; Kandula, S.V. *Tetrahedron Lett.* **2004**, *45*, 5877−5879.
9. Raghavan, S.; Ramakrishna Reddy, S. *J. Org. Chem.* **2003**, *68*, 5754−5757.
10. Bethuel, Y.; Gademann, K. *Synlett* **2006,** *10*, 1580−1582.
11. Mu, Q.; Tang,W.; Li, C.; Lu, Y.; Sun, H.; Zheng,H.; Hao, X.; Zheng, Q.; Wu, N.; Lou, L.; Xu, B. *Heterocycles* **1999**, 2969−2976.
12. (a) Marton, D.; Stivanello, D; Tagliavini, G.; *J. Org. Chem*. **1996**, *61*, 2731−2737; (b) Christian, p.; Jean, L. L.; *J. Org. Chem*. **1985**, *50*, 910−912; (c) Petrier, C.; Einhorn, J.; Luche, J. L.; *Tetrahedron Lett*. **1985**, *26*, 1449−1452; (d) Cathy, E.; Jean, L. L.; *J. Organomet. Chem*. **1987**, *322*, 177−183; (e) Carogiglio, T.; Marton, D.; Tagliavini, G.; *Organometalics* **1992**, *11*, 2961−2963; (f) Gyldenfaldt, F. V.; Morton, D.; Tagliavini, G.; *Organometalics* **1994**, *13*, 906−913.
13. Moiano, A.; Periacas, M. A.; Riera, A.; Luche, J. L.; *Tetraheron Lett*. **1990**, *31*, 7619−7622.
14. De Souya−Barboza, J. C.; Luche, J.L.; Patrier, C.; *Tetrahedron Lett*. **1987**, *28*, 2013−2016.
15. Rodriguez, A.; Nomen, M.; Spur, B. W.; Godfroid, J. J. *Tetrahedron Lett*. **1999**, *40*, 5161−5164.
16. Rama Rao, A. V.; Mysorekar, S. V.; Gurjar, M. K.; Yadav, J. S. *Tetrahedron Lett*. **1987**, *28*, 2183−2186.
17. Quinn, K. J.; Smith, A. G.; Cammrano, C. M. *Tetrahedron 2007, 63*, 4881−4886.

18. Prashad, M.; Kim, H. Y.; Lu, Y.; Liu, Y.; Har, D.; Repic, O.; Blacklock T. J.; Giannousis. P. *J. Org. Chem*. **1999**, *64*, 1750−1753.
19. For use of magnesium bromide diethyl etherate in allylstannane reaction, see: (a) Lee, E.; Jeong, E. J.; Kang, E. J.; Sung, L. T.; Hong, S. K. *J. Am. Chem. Soc*. **2001**, *123*, 10131−10132. (b) Keck, G. E.; Abbott, D. E. *Tetrahedron Lett*. **1984**, 25, 1883−1886.
20. Brabander, J. D.; Vandewalle, M. *Synthesis* **1994**, 855−865.

CHAPTER–III

Section - A

INTRODUCTION

Heterogeneous catalysts in organic synthesis:

In the recent years, in view of the emerging importance to more environmental awareness in chemical and pharmaceutical industries, development of environmentally benign organic reactions have become a crucial and demanding research area in modern organic chemical research.[1] Due to environmental awareness, chemists are allocated toward 'green chemistry' which by definition is to design, develop and implement chemical products and processes to reduce or eliminate the use and generation of substances hazardous to human health and the environment.

In this progression originated the heterogeneous catalysis, which is one of the fine areas for clean and green chemistry. The heterogeneous solid acids are advantageous over conventional homogeneous acid catalysts as they can be easily recovered from the reaction mixture by simple filtration and can be reused after activation or without activation, thereby making the process economically viable. In many cases, heterogeneous catalysts can be recovered with only minor changes in activity and selectivity so that they can be conveniently used in continuous flow reactions. These are particularly attractive as they often lead to the formation of large quantities of products with the use of only small amounts of catalysts, which can be easily separated by simple filtration.[1b]

Among various heterogeneous catalysts, heteropoly acids are most attractive because of their unique properties such as well−defined structure, Bronsted acidity, possibility to modify their acid–base and redox properties by changing their chemical composition (substituted HPAs), ability to accept and release electrons, high proton mobility etc.[2] Heteropoly acids (HPAs) are environmentally friendly and economically feasible solid acids owing to their high catalytic activities and reactivities, ease of handling, allow cleaner reactions in comparison to conventional catalysts, non−toxicity and experimental simplicity and hence regarded as green catalysts.[3]

The heteropoly compounds more frequently utilized are the Keggin-type ones. The Keggin-type heteropoly acids typically represented by the formula $H_{8-x}[XM_{12}O_{40}]$, where X is the heteroatom (e.g., P^{5+} or Si^{4+}), x is its oxidation state and M is the addenda atom (usually Mo^{6+} or W^{6+}), form an important class of catalysts, and among

them $H_3PW_{12}O_{40}$, $H_3PMo_{12}O_{40}$ and $H_4SiW_{12}O_{40}$ [4] are the most common. However, they are readily soluble in polar solvents. The solubility problem can be overcome by changing these HPAs into their corresponding salts, which are generally insoluble in polar solvents. The Keggin-type heteropoly acids such as 12-molybdophosphoric and 12-tungstophosphoric acids can be modified by the addition of different transition metal ions.[5] These ions can either be positioned outside the Keggin unit (KU) in the secondary structure in the form of cations, or directly replace molybdenum or tungsten in the anion.[6] These ions sometimes have a considerable effect on the catalytic behaviour, being directly involved in the oxidation mechanism, influencing the redox properties of the catalyst [7] or modifying its acid-base properties.[8]

Among the heteropoly acids, tungstophosphoric acid is one of the less expensive and commercially available catalyst. 12-Tungstophosphoric acid (TPA, F.W: $H_3PW_{12}O_{40}$) has been extensively studied as super acid catalyst for many organic reactions and it has found industrial application in several processes.[9]

Here in we modified the 12-tungstophosphoric acid to its Cu salt by the addition of copper salts. As per experimental procedure initially the 12-tungstophosphoric acid ($H_3PW_{12}O_{40}$) was converted to its Barium salt by addition of $BaSO_4$. Later it was converted to its copper salt with $CuSO_4 \cdot 5H_2O$. Thus, the chemical composition of the Cu salt of 12-tungstophosphoric acid (TPA) is $Cu_{1.5}PW_{12}O_{40}$.The retention of Keggin structure after exchange of Cu ions is confirmed by XRD and FT−IT analysis.

Cyclopropanation of alkenes via C-H insertion:

The synthesis of chiral cyclopropanes remains a considerable challenge, especially due to the fact that cyclopropane rings are often found in a variety of natural products and biologically active compounds.[10] Organic chemists have always been fascinated by the cyclopropane subunit,[11] which has played and continues to play a prominent role in organic chemistry.[12] Its strained structure, interesting bonding characteristics, and value as an internal mechanistic probe have attracted the attention of the physical organic community. Cyclopropane ring is found in a wide variety of naturally occurring compounds including terpenes, pheromones, fatty acid metabolites and unusual amino acids (Figure 1).[13]

Figure 1

Cyclopropane subunits also occur in many natural products of primary and secondary metabolism. Naturally occurring and synthetic cyclopropanes bearing simple or complex functionalities are endowed with a large spectrum of biological properties, including enzyme inhibition and insecticidal, antifungal, herbicidal, antimicrobial, antibiotic, antibacterial, antitumour and antiviral activities.[14] For example, they constitute a common structural motif in pyrethroids,[15] the antidepressant, tranylcypromine,[16] papain and cysteine protease inhibitors,[17] potential antipsychotic substances,[18] anti−HIV agents [19] and marine lactones.[20]

Indeed, the strain associated with the three−membered ring allows cyclopropanes to undergo a variety of synthetically useful ring−opening reactions [21] and also serve as versatile synthetic intermediates for the preparation of functionalized cycloalkanes [22] and acyclic compounds.[23] In recent years, most of the synthetic efforts involving cyclopropanes have focused on the enantioselective synthesis of these compounds.

Transition-metal-catalysed decomposition of diazoalkanes:

The cyclopropanation of olefins using the transition-metal-catalysed decomposition of diazoalkanes is one of the most extensively studied reactions in the organic chemist's arsenal.[24] Indeed, the synthesis of cyclopropanes by transition-metal-mediated carbene transfer from aliphatic diazo compounds to carbon-carbon double bonds is not only a major method for the preparation of cyclopropanes, but is also

among the best developed and most general methods available to the synthetic organic chemist.[25]

The catalytic cycle of the carbenoid cyclopropanation reaction is outlined in Scheme 1, involving interaction of the catalyst with the diazo precursor to afford a metallocarbene complex as the central intermediate with concomitant release of nitrogen and subsequent transfer of the carbene to an olefin. Enantiocontrol in the carbene-transfer step may be achieved by chiral ligands surrounding the metal centre of the catalyst.

The most exhaustively studied diazo reagents for intermolecular cyclopropanation reactions are the α-diazoesters. Particularly, Ethyl diazoacetate is an important two-carbon synthon for organic chemistry.[26] It is sensitive, flammable and toxic its use as a large-scale, industrial commodity is limited due to safety concerns. Simple α-diazoesters have been prepared and reacted *insitu* in the presence of the metal catalyst and the alkene.[27]

Cyclopropanation of styrene with ethyl diazoacetate often serves as the bench−mark reaction for the evaluation of almost any new catalyst.

The metal catalyzed cyclopropanation of alkenes with ethyl diazoacetate is one of the most simple and direct approaches for the preparation of cyclopropanes.[28] The copper complexes have primarily been used as catalysts for the cyclopropanation of alkenes with diazo compounds.[29] Subsequently, rhodium and ruthenium complexes have also been reported for this transformation.[30]

In recent reports iron Lewis acids have been found to give *cis*-cyclopropanes predominantly.[31] However, most of these catalysts are expensive and also difficult to recycle which limit their use in large-scale synthesis. Therefore, the introduction of new

methods involving simple, inexpensive and recyclable catalysts for an efficient and selective cyclopropanation continues to be a challenging endeavor in organic synthesis.

PRESENT WORK

In a model experiment, styrene (**1**) was treated with ethyl diazoacetate (**2**) in the presence of 5 mol% of Cu-TPA in CH_2Cl_2. The reaction was completed in 2.5 h at room temperature and the product, ethyl 2-phenyl-1-cyclopropanecarboxylate was isolated as a mixture of **3a** and **4a** in 90% yield (entry **a**, Table 3, Scheme 2).

Scheme 2

However, the product was obtained as a mixture of **3a** *trans*- and **4a** *cis*-isomers, favoring *trans*-diastereomer **3a**. The diastereomers **3a** and **4a** could be easily separated by column chromatography and were characterized by comparison of their NMR spectra with authentic samples.[30a]

Optimization of reaction condition with different solvent and different mol% of catalyst:

To optimize the reaction conditions, we carried out the cyclopropanation of styrene with ethyl diazoacetate in various solvents by varying the amount of catalyst and the results are summarized in Table 1. The best results were obtained using 5 mol% of the catalyst in CH_2Cl_2.

The effects of various copper(II) salts:

The effects of various copper(II) salts were screened in the cyclopropanation of styrene with ethyl diazoacetate and the results are presented in Table 2.

Noteworthy, cyclopropanation with copper tetrafluoroborate resulted in **3a** and **4a** with poor selectivity (1.2:1 ratio) in 30 min. The best results were obtained using Cu-TPA as the catalyst with high *trans*-selectivity.

Both electron rich and electron deficient styrene derivatives gave cyclopropane carboxylates in high yields. In all cases, the reaction proceeds smoothly at room temperature with high *trans*-selectivity (entries b−d, Table 3).

α-and β-substituted styrene derivatives such as α-methyl styrene and β-methyl styrene gave the corresponding cyclopropane carboxylates in excellent yields but low selectivity with approximately 1:1 ratio of *cis*/*trans*-isomers (entries f and g, Table 3). In addition to this stilbene gave single product (entry h, Table 3).

In addition, treatment of cyclohexene with ethyl diazoacetate gave ethyl bicyclo [4.1.0] heptanes-7-carboxylate in 95% yield. In case of cyclohexene **5**, the product was obtained as a mixture of *endo*- **6a** and *exo*- **7a** isomers, favoring *endo*-isomer (Scheme 3).

Scheme 3

Similarly, cyclooctene, indene and dihydronaphthalene worked well for this cyclopropanation (entries b−d, Table 4).

No allylic insertion was observed in the reactions of cycloalkenes with ethyl diazoacetate. In the absence of catalyst, no reaction was observed between alkene and EDA. The structure of cyclopropanes was established by comparing their NMR, IR and mass spectra with known compounds. The spectral data of all the products were identical with those of authentic samples.[29,30,32]

Reusability:

The advantage of the use of Cu-TPA is that it can be easily recovered and recycled in subsequent runs. Since the reaction mixture is heterogeneous, the catalyst could be easily separated by simple filtration. The recovered catalyst was further washed with ether, dried at 60 °C under reduced pressure and reused in three to four successive runs with only a minimal decrease in activity. For example, styrene and ethyl

diazoacetate in the presence of 5 mol% of Cu-TPA in CH_2Cl_2 gave 90%, 87%, 85% and 80% yields over four cycles.

The chemoselectivity for cyclopropane formation over carbene dimerization was achieved by the use of an excess of alkene and slow addition of the carbene source e.g. ethyl diazoacetate to the reaction mixture. No formation of side products such as diethyl fumarate or diethyl maleate was observed when the reaction was carried out using Cu-TPA. A variety of alkenes including vinyl arenes and few cyclic and acyclic olefins underwent smooth cyclopropanation with ethyl diazoacetate under identical conditions. In most cases, the products were obtained in high yields and with high *trans*-selectivity.

This is an efficient protocol for the cyclopropanation of olefins with ethyl diazoacetate using copper exchanged heteropoly acid (Cu-TPA) as a heterogeneous catalyst. This method offers significant advantages such as high conversions, mild conditions, ease of recovery and reusability of the catalyst, which makes it a useful and attractive strategy for the preparation of cyclopropane carboxylates. The use of heterogeneous catalyst makes this method quite simple, more convenient and environmentally friendly.

EXPERIMENTAL

General procedure for catalyst preparation:

The copper salt of the $H_3PW_{12}O_{40}$ was prepared as precipitate by adding 0.18 g of barium hydroxide (to neutralize the three protons) to the aqueous solution containing 2.0 g of $H_3PW_{12}O_{40}$. Later 0.16 g of $CuSO_4 \cdot 5H_2O$ was added to replace Ba with Cu by eliminating the Ba as $BaSO_4$. Thus the $Cu_{1.5}PW_{12}O_{40}$ salt was recovered from the solution by recrystallization. The catalyst mass was dried at 120 °C for 12 h in an oven and finally calcined at 300 °C for 2 h.

General procedure for preparation of cyclopropanation:

To a stirred solution of alkene (3 mmol) and Cu-TPA (5 mol%) in CH_2Cl_2 (5 mL), ethyl diazoacetate (1 mmol) was added slowly in a dropwise manner. The resulting mixture was stirred at room temperature for the appropriate time (Table 3, 4). After completion, as indicated by TLC, the catalyst was removed by simple filtration and washed with diethyl ether (3×10 mL). The combined organic filtrates were dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by column chromatography on silica gel (Merck, 100–200 mesh) using ethyl acetate: hexane (1:9) as eluant to afforded pure cyclopropane carboxylate.

***trans*−Ethyl 2−phenylcyclopropane−1−carboxylate (3a):**

Liquid, **IR (KBr):** ν_{max} 2985, 2931, 2865, 1720, 1605, 1458, 1369, 1257, 1153, 1070, 1045, 935, 780, 697 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.05–7.32 (m, 5H), 3.99–4.05 (m, 2H), 2.45 (ddd, 1H, *J* = 4.2, 6.4, 9.2 Hz), 1.85 (ddd, 1H, *J* = 4.2, 5.2, 8.4 Hz), 1.53 (ddd, 1H, *J* = 4.4, 5.2, 9.2 Hz), 1.25 (ddd, 1H, *J* = 4.4, 6.4, 8.4 Hz), 1.02 (*t*, 3H, *J* = 6.9 Hz).

EI−MS: *m/z* (%) 190 $[M]^+$, 162, 141, 115, 91, 43.

***cis*−Ethyl 2−phenylcyclopropane−1−carboxylate (4a):**

Liquid, **IR (KBr):** ν_{max} 3059, 2982, 2933, 1728, 1607, 1454, 1381, 1265, 1086, 961, 795, 694 cm^{-1} ;

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.19–7.28 (m, 5H), 3.90 (q, 2H, *J* = 7.1 Hz), 2.59 (ddd, 1H, *J* = 7.4, 8.7, 9.3 Hz), 2.05 (ddd, 1H, *J* = 5.6, 7.8, 9.3 Hz), 1.70 (ddd, 1H, *J* = 5.1, 5.6, 7.4 Hz), 1.33 (ddd, 1H, *J* = 5.1, 7.8, 8.7 Hz), 0.98 (t, 3H, *J* = 7.1 Hz).

EI−MS: *m*/*z* (%) 190 $[M]^+$, 163, 91, 55.

***trans*−Ethyl 2−(4−methylphenyl) cyclopropane−1−carboxylate (3b):**

Liquid, **^{1}H NMR (200 MHz, $CDC1_3$):** δ 7.13−6.90 (m, 4H), 4.14 (q, 2H, *J* = 7.3 Hz), 2.52−2.37 (m, 1H), 2.30 (s, 3H), 1.87−1.75 (m, 1H), 1.61−1.47 (m, 1H), 1.31−1.15 (m, 4H).

***cis*−Ethyl 2−(4−methylphenyl) cyclopropane−1−carboxylate (4b):**

Liquid,**^{1}H NMR (300 MHz, $CDC1_3$):** δ 7.10 (d, 2H, *J* = 7.5 Hz), 7.01 (d, 2H, *J* = 8.3 Hz), 3.87 (q, 2H, *J* = 6.7 Hz), 2.56−2.44 (m, 1H), 2.30 (s, 3H), 2.06− 1.96 (m, 1H), 1.70−1.62 (m, 1H), 1.39−1.21 (m, 1H), 1.01 (t, 3H, *J* = 7.5 Hz).

***trans*−Ethyl 2−(4−methoxyphenyl) cyclopropane−1−carboxylate (3c):**

^{1}H NMR (300 MHz, $CDC1_3$): δ 7.00 (d, 2H, *J* = 8.0 Hz), 6.75 (d, 2H, *J* = 8.0 Hz), 4.12 (d, 2H, *J* = 7.3 Hz), 3.73 (s, 3H), 2.49−2.39 (m, 1H), 1.81−1.72 (m, 1H), 1.58−1.49 (m, 1H), 1.30−1.16 (m, 4H).

***cis*−Ethyl 2−(4−methoxyphenyl) cyclopropane−1−carboxylate (4c):**

^{1}H NMR (300 MHz, $CDC1_3$): δ 7.20 (d, 2H, *J* = 8.3 Hz), 6.81 (d, 2H, *J* = 8.3 Hz), 3.93 (d, 2H, *J* = 6.7 Hz), 3.82 (s, 3H), 2.62−2.47 (m, 1H), 2.12−1.98 (m, 1H), 1.74−1.63 (m, 1H), 1.42−1.25 (m, 1H), 1.09 (t, 3H, *J* = 7.0 Hz).

***trans*-(1*R*,2*R*)-Ethyl 2-(naphthalen-1-yl)cyclopropanecarboxylate (3d):**

^{1}H NMR (200 MHz, $CDC1_3$): δ 8.01−7.64 (m, 3H), 7.60−7.51 (m, 1H), 7.48−7.32 (m, 2H), 7.17 (d, 1H, *J* = 8.0 Hz), 4.18 (q, 2H, *J* = 7.3 Hz), 2.73−2.58 (m, 1H), 2.04−1.91 (m, 1H), 1.72−1.59 (m, 1H), 1.51−1.21 (m, 4H).

***cis*-(1*R*,2*R*)-Ethyl 2-(naphthalen-1-yl)cyclopropanecarboxylate (4d):**

^{1}H NMR (200 MHz, $CDC1_3$): δ 7.87−7.63 (m, 5H), 7.48−7.22 (m, 2H), 3.81 (q, 2H, *J* = 7.3 Hz), 2.79−2.63 (m, 1H), 2.20−2.05 (m, 1H), 1.91 −1.78 (m, 1H), 1.47−1.32 (m, 1H), 0.90 (t, 3H, *J* = 7.3 Hz).

***trans*−Ethyl (1*R*,2*S*)−2−methyl−2−phenylcyclopropane−1−carboxylate (3f):**

^{1}H NMR (200 MHz, $CDC1_3$): δ 7.33−7.11 (m, 5H), 4.26−4.10 (m, 2H), 1.93 (dd, 1H, *J* = 8.8, 5.9 Hz), 1.52 (s, 3H), 1.46−1.36 (m, 2H), 1.31 (t, 3H, *J* = 6.6 Hz).

***cis*−Ethyl (1*R*,2*S*)−2−methyl−2−phenylcyclopropane−1−carboxylate (4f):**

^{1}H NMR (300 MHz, $CDC1_3$): δ 7.26−7.11 (m, 5H), 3.88−3.74 (m, 2H), 1.86 (dd, 1H, *J* = 7.5, 5.2 Hz), 1.76 (t, 1H, *J* = 4.5 Hz), 1.47 (s, 3H), 1.11(dd, 1H, *J* = 7.5, 4.5 Hz), 0.94 (t, 3H, *J* = 6.7 Hz).

***trans*−Ethyl 2−methyl−2−phenylcyclopropane−1−carboxylate (3g):**

^{1}H NMR (200 MHz, CDC1$_3$): δ 7.25−7.18 (m, 2H), 7.16−7.09 (m, 1H), 7.06−7.00 (m, 2H), 4.15 (q, 2H, *J* = 6.7 Hz), 2.36 (dd, 1H, *J* = 6.0, 4.5 Hz), 1.97 (dd, 1H, *J* = 9.0, 4.5 Hz), 1.70−1.58 (m, 1H), 1.35 (d, 3H, *J* = 6.0 Hz), 1.28 (t, 3H, *J* = 6.7 Hz).

***cis*−Ethyl 2−methyl−2−phenylcyclopropane−1−carboxylate (4g):**

^{1}H NMR (200 MHz, CDC1$_3$): δ 7.23−7.10 (m, 5H), 3.85 (q, 2H, *J* = 6.7 Hz), 2.30 (dd, 1H, *J* = 9.0, 6.7 Hz), 2.10−1.99 (m, 1H), 1.78 (dd, 1H, *J* = 9.0, 4.5 Hz), 1.29 (d, 3H, *J* = 6.0 Hz), 0.98 (t, 3H, *J* = 6.7 Hz).

***trans*−2,3−Diphenyl−cyclopropanecarboxylic acid ethyl ester (3h):**

Liquid, **IR (KBr):** ν_{max} 3024, 2924, 2853, 1733, 1448, 1459, 1307, 1191, 1170, 1039, 964, 751, 694 cm^{-1}.

^{1}H NMR (200 MHz, CDCl$_3$): δ 7.11–7.32 (m, 10H), 3.93 (q, 2H, *J* = 7.1 Hz), 3.17 (dd, 1H, *J* = 5.2, 6.9 Hz), 2.88 (dd, 1H, *J* = 6.9, 9.6 Hz), 2.37 (dd, 1H, *J* = 5.0, 9.6 Hz), 1.03 (t, 3H, *J* = 7.1 Hz).

EI−MS: *m*/*z* (%) 267 (10) [M]$^+$, 193 (100), 115 (50).

***endo*−Ethyl bicyclo[4.1.0]heptane−7−carboxylate (6a):**

Liquid, **^{1}H NMR (200 MHz, CDCl$_3$):** δ 4.10 (q, 2H, *J* = 7.1 Hz), 1.91−1.78 (m, 2H), 1.73−1.62 (m, 2H), 1.55−1.41 (m, 2H), 1.39−1.32 (m, 3H), 1.31−1.17 (m, 5H).

***exo*−Ethyl bicyclo[4.1.0]heptane−7−carboxylate (7a):**

Liquid, **^{1}H NMR (200 MHz, $CDCl_3$):** δ 4.08 (q, 2H, *J* = 7.1 Hz), 1.98−1.86 (m, 2H), 1.77–1.66 (m, 2H), 1.59−1.53 (m, 2H), 1.35−1.13 (m, 8H).

***endo*−Bicyclo [6.1.0] nonane−9−caboxylic acid ethyl ester (6b):**

Liquid, **IR (KBr):** ν_{max} 2984, 2923, 2855, 1726, 1449, 1378, 1150 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$): *δ* 4.02–4.19 (q, 2H, *J* = 7.1 Hz), 1.10–1.95 (m, 18H).
EI−MS: *m*/*z* (%) 196 (10) $[M]^+$, 151 (20),108 (15), 97 (25), 81 (100), 67 (55), 55 (40), 41(25).

***exo*−Bicyclo [6.1.0] nonane−9−caboxylic acid ethyl ester (7b):**

Liquid, **IR (KBr):** ν_{max} 2923, 2854, 1723, 1463, 1211, 1180, 1145 cm^{-1}.
^{1}H NMR (200 MHz, $CDCl_3$): *δ* 4.02–4.11 (q, 2H, *J* = 7.1 Hz), 2.0–2.15 (m, 2H), 1.21–1.82 (m, 13H), 0.91–1.18 (m, 3H).
EI−MS: *m*/*z* (%) 196 (10) $[M]^+$, 122 (20), 108 (40), 87 (100), 55 (90), 41 (30).

***endo*−(6c):**

Liquid, **IR (neat):** ν_{max} 2981, 2916, 1721, 1294, 1174, 1141, 760 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35−7.28 (m, 1H), 7.14−7.05 (m, 3H), 4.13 (q, 2H, *J* = 6.7 Hz), 3.27 (dd, 1H, *J* = 17.3, 6.0 Hz), 3.04 (d, 1H, *J* = 17.3 Hz), 2.92 (d, 1H, *J* = 6.0 Hz), 2.41 (td, 1H, *J* = 6.7, 3.0 Hz), 1.27 (t, 3H, *J* = 6.7 Hz), 1.18 (t, 1H, *J* = 3.0 Hz).

EI−MS: *m*/*z* (%) 202 (5) $[M]^+$, 173 (10), 129 (100), 115 (20), 91 (15), 43 (15).

***exo*−(7c):**

Liquid, **IR (neat):** ν_{max} 2980, 2908, 1729, 1473, 1384, 1215, 1181, 1138, 803, 752 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29−7.22 (m, 1H), 7.12−7.04 (m, 3H), 3.80 (q, 2H, *J* = 6.7 Hz), 3.36 (d, 1H, *J* = 16.6 Hz), 3.18 (dd, 1H, *J* = 16.6, 6.7 Hz), 2.95−2.88 (m, 1H), 2.29−2.20 (m, 1H), 1.96 (t, 1H, *J* = 8.3 Hz), 0.94 (t, 3H, *J* = 6.7 Hz).

EI−MS: *m*/*z* (%) 202 (20) $[M]^+$, 173 (45), 129 (100), 77(10), 41(10).

***endo*−Ethyl 1a,2,7,7a−tetrahydro−1H−cyclopropa[β]naphthalene−1−carboxylate (6d):**

Liquid, **IR (KBr):** ν_{max} 2981, 2927, 1726, 1372, 1177, 755, 696 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.31−7.21 (m, 1H), 7.17−6.92 (m, 3H), 4.14 (q, 2H, *J* = 7.3 Hz), 2.74−2.32 (m, 3H), 2.30−1.96 (m, 3H), 1.92−1.70 (m, 1H), 1.28 (t, 3H, *J* = 7.3 Hz).

EI−MS: *m*/*z* (%) 216 (90) $[M]^+$, 205 (10), 187 (50), 141 (45), 128 (100), 115 (90), 88 (35), 39 (10).

exo−Ethyl1a,2,7,7a−tetrahydro−1H−cyclopropa[β]naphthalene−1−carboxylate (7d):

Liquid, **IR (KBr):** ν_{max} 2980, 2927, 2856, 1721, 1300, 1267, 1171, 756, 731cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.22−6.92 (m, 4H), 3.91 (q, 2H, J = 7.3 Hz), 2.87−2.67 (m, 1H), 2.63−2.46 (m, 1H), 2.38 (t, 1H, J = 8.1 Hz), 2.26−2.06 (m, 2H), 2.02−1.82 (m, 2H), 1.05 (t, 3H, J = 7.3 Hz).

EI−MS: *m*/*z* (%) 218 (10) $[M+2]^+$, 171 (30), 143 (80), 130 (100), 116 (30), 89 (10), 39 (10).

REFRENCES

1. (a) Anastas, P. T.; Warner, J. C. *Green Chemistry; Theory and Practice*, Oxford Univ. **1998**. (b) Clark, J. H. *Green Chem.* **1999**, *1*, 1−8. (c) Ono, Y.; Thomas, J. M.; Zamaraev, K.I.; *Eds. Perspectives in catalysis*. Blackwell: London, **1992**.
2. (a) Kozhevnikov, I. V. *Chem. Rev.* **1998**, *98*, 171−198. (b) Okuhara, T.; Mizuno, N.; Misono, M. *Appl. Catal. A: Gen.* **2001,** *222*, 63−77. (c) Yadav, J. S.; Reddy, B. V. S.; Sridhar, P.; Reddy, J. S. S.; Nagaiah, K.; Lingaiah, N.; Saiprasad, P. S. *Eur. J. Org. Chem.* **2004**, 552–557. (d) Lingaiah, N.; Babu, N. S.; Reddy, K. M.; Saiprasad, P. S.; Suryanarayana, I. *Chem. Commun.* **2007**, 278−279.
3. Misono, M.; Ono, I.; Koyano, G.; Aoshima, A. *Pure Appl. Chem*., **2000**, *72*, 1305–1311.
4. (a) Kozhevnikova, E. F.; Quartararo, J.; Kozhevnikov, I. V. *Appl. Catal*. *A* **2003**, *245*, 69–78. (b) Firouzabadi, H.; Jafari, A. A. *J. Iran. Chem. Soc.* **2005**, *2*, 85−114. and references cited therein. (c) Firouzabadi, H.; Iranpoor, N.; Jafari, A. A. *Synlett* **2005**, 299-303. (d) Moffat, J. B. *The Surface and Catalytic Properties of Heteropolyoxometalates*; Kluwer: New York, **2001**.
5. (a) Heravi, M. M., Sadjadi, S., Oskooie, H. A., Shoar, R. H., Bamoharram, F. F. *Molecules*. **2007**, 12, 255−262. (b) Corma, A.; Martínez, A.; Martínez, C. *J. Catal.* **1996**, *164*, 422–432. (c) Mizuno, N.; Misono, M. *Chem. Rev.* **1998,** *98*, 199−217. (d) Yadav, J. S.; Reddy, B. V. S.; Praveenkumar, S.; Nagaiah, K.; Lingaiah, N.; Saiprasad, P. S. *Synthesis* **2004**, 901–904.
6. Cavani, F.; Tanguy, A.; Trifirò, F.; Koutrev1, M. *J. Catal.* **1998**, *174*, 231–241.
7. Akimoto, M.; Tsuchida, Y.; Sato, K.; Echigoya, E. *J. Catal.* **1981**, *72*, 83−94.
8. (a) Ai, M., *J. Catal.* **1981**, *71*, 88−98. (b) Ai, M., *J. Catal.* **1984**, *85*, 324. (c) Ai, M., *J. Catal.* **1989**, *116*, 23.
9. (a) Kozhevnikov, I. V. *Chem. Rev.* **1998**, *98*, 171–198; (b) Okuhara, T.; Mizuno, N.; Misono, M. *Adv. Catal.* **1996**, *41*, 113–252; (c) Kozhevnikov, I. V. *In Catalysis for Fine Chemicals, Catalysis by Polyoxometalates*; Wiley: Chichester, **2002**; Vol. 2, Chapter 7; (d) Misono, M. *Chem. Commun*. **2001**, 1141–1152.
10. (a) Davoren, J. E.; Martin, S. F. *J. Am. Chem. Soc.* **2007**, *129*, 510-511. (b) Srikrishna, A.; Nagamani, S. A.; Jagadeesh, S. G. *Tetrahedron: Asymmetry* **2005**,

16, 1569−1571. (c) Xie, X.; Yue, G.; Tang, S.; Huo, X.; Liang, Q.; She, X.; Pan, X. *Org. Lett*. **2005**, *7*, 4057−4059.

11. (a) Patai, S.; Rappoport, Z. *The Chemistry of the Cyclopropyl Group*; Wiley and Sons: New York, NY, **1987**. (b) *Small Ring Compounds in Organic Synthesis VI*; de Meijere, A., Ed.; Spinger: Berlin, Germany, **2000**, Vol. 207.
12. Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev*. **2007**, *107*, 3117−3179.
13. (a) Salaun, J. *Top. Curr. Chem*. **2000**, *207*, 1−67. (b) Faust, R. *Angew. Chem., Int. Ed*. **2001**, *40*, 2251−2253. (c) Gnad, F.; Reiser, O. *Chem. Rev*. **2003**, *103*, 1603−1623. (d) Keynan S, Hooper NM, Felici A, Amicosante G, Turner, AJ. *Antimicrob. Agents Chemother.* **1995**, *39*, 1629−1631. (e) Trachev, A. V.; Shakirov, M. M.; Raldugin, V. A. *J. Nat. Prod*. **1991**, *54*, 849−853. (f) Seo, T.; Cho, K. W.; Rho, J. R.; Shin, J.; Kwon, B. M.; Bok, S. H.; Song, J. I. *Tetrahedron* **1996**, *52*, 10583−10596. (g) Asai, A.; Hasegawa, A.; Ochiai, K.; Yamashita, Y.; Mizukami, T. J. *Antibiotics* **2000**, *53*, 81−83.
14. Liu, H. W.; Walsh, C. T. *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; John Wiley: New York, NY, **1997**, 959.
15. Nishii, Y.; Maruyama, N.; Wakasugi, K.; Tanabe, Y. *Bioorg. Med. Chem*. **2001**, *9*, 33−39.
16. Csuk, R.; Schabel, M. J.; von Scholz, Y. *Tetrahedron: Asymmetry* **1996**, *7*, 3505−3512.
17. Kumar, J. S.; Roy, S.; Datta, A. *Bioorg. Med. Chem. Lett*. **1999**, *9*, 513−514.
18. Zhang, X.; Hodgetts, K.; Rachwal, S.; Zhao, H.; Wasley, J. W. F.; Craven, K.; Brodbeck, R.; Kieltyka, A.; Hoffman, D.; Bacolod, M. D.; Girard, B.; Tran, J.; Thurkauf, A. *J. Med. Chem*. **2000**, *43*, 3923−3932.
19. (a) Csuk, R.; Kern, A.; Mohr, K. Z. *Naturforsch*. **1999**, 1463−1468. (b) Hogberg, M.; Engelhardt, P.; Vrang, L.; Zhang, H. *Bioorg. Med. Chem. Lett*. **2000**, *10*, 265−268.
20. Mohapatra, D. K.; Datta, A. *J. Org. Chem*. **1998**, *63*, 642−646.
21. Wong, H. N. C.; Hon, M.-Y.; Tse, C.−W.; Yip, Y.−C.; Tanko, J.; Hudlicky, T. *Chem. Rev*. **1989**, *89*, 165−198.

22. For a review on the divinylcyclopropane rearrangement see: (a) Piers, E. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, **1991**, *5*, 971. For a review on the vinylcyclopropane rearrangement see: (b) Hudlicky, T.; Reed, J. W.; In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I, Eds.; Pergamon Press: Oxford, **1991**, *5*, 899.

23. For reviews on cyclopropane opening reactions see: (a) Nonhebel, D. C. *Chem. Soc. Rev*. **1993**, 347−359. (b) Salaun, J. R. Y. *Top. Curr. Chem*. **1988**, *144*, 1−71.

24. (a) Davies, H. M. L.; Antoulinakis, E. *Org. React*. **2001**, *57*, 1−326. (b) Rovis, T.; Evans, D. A. *Prog. Inorg. Chem*. **2001**, *50*, 1−150. (c) Nishiyama, H. Enantiomer **1999**, *4*, 569−574. (d) Singh, V. K.; DattaGupta, A.; Sekar, G. *Synthesis* **1997**, 137−149. (e) Doyle, M. P.; Forbes, D. C. *Chem. Rev*. **1998**, *98*, 911−936.

25. Boche, G.; Lohrenz, J. C. W. *Chem. Rev*. **2001**, *101*, 697−756.

26. (a) Doyle, M. P. *Acc. Chem. Res*. **1986**, *19*, 348−356. (b) Doyle, M. P. *Chem. Rev*. **1986**, *86*, 919−939. (c) Mass, G. *Top. Curr. Chem*. **1987**, *137*, 75−253. (c) Adams, X.; Spero, D. M. *Tetrahedron*, **1991**, *47*, 1765−1808. (d) Padwa, A.; Hotnbuckle, S. F. *Chem. Rev*. **1991**, *91*, 263−309. (e) Padwa, A.; Krumpe, K. E. *Tetrahedron* **1992**, *48*, 5385−5483. (f) Shapiro, E. A.; Kyatkin, A. B.; Ndfodov, Q. M. *Russ. Chem. Rev*. **1993**, *62*, 447−472. (g) Padwa, A.; Austin, D. J. *Angew. Chem*. **1994**, *106*, 1881−1889. (h) Ye, T.; McKervey, M. A. *Chem. Rev*. **1994**, *94*, 1091−1160. (i) Kanemasa, S.; Kanai, T.; Araki, T.; Wada, E. *Tetrahedron Lett*. **1999**, *40*, 5055−5058.

27. (a) Wurz, R. P.; Charette, A. B. *Org. Lett*. **2002**, *4*, 4531−4533. (b) Barrett, A. G. M.; Braddock, D. C.; Lenoir, I.; Tone, H. *J. Org. Chem*. **2001**, *66*, 8260−8263.

28. (a) Dave, V.; Warnhoff, E. W. *Org. React*. **1970,** *18*, 217. (b) Marchand, A. P.; MacBrockway, N. *Chem. Rev*. **1974,** *74*, 431−469. (c) Mass, G. *Topics in Current Chemistry*, **1987,** *137*, Springer-Verlag, 75.

29. (a) Nozaki, H.; Moriuti, S.; Yamabe, M.; Noyori, R. *Tetrahedron Lett*. **1966**, *7*, 59−63. (b) Fraile, J. M.; Garcia, J. I.; Mayoral, J. A. *Chem. Commun*. **1996**, 1319−1320. (d) Lo, M. M. C.; Fu, G. C. *J. Am. Chem. Soc*. **1998**, *120*, 10270−10271.

30. (a) Anciaux, A. J.; Hubert, A. J.; Noels, A. F.; Petiniot, N.; Teyssie, P. *J. Org. Chem*. **1980**, *45*, 695−701. (b) Hubert, A. J.; Noels, A. F.; Anciaux, A. J.; Teyssie, P. *Synthesis* **1976**, 600−602. (c) Doyle, M. P.; VanLeusen, D.; Tamblyn, W. H. *Synthesis* **1981**, 787−789. (d) Callot, H. J.; Piechocki, C. *Tetrahedron Lett*. **1980**, *21*, 3489−3492. (e) Doyle, M. P.; Tawblyn, W. H.; Buhro, W. E.; Dorow, R. L. *Tetrahedron Lett*. **1981**, *22*, 1783-1786. (f) Niimi, T.; Uchida, T.; Irie, R.; Katsuki, T. *Tetrahedron Lett*. **2000**, *41*, 3647−3651. (g) Fukuda, T.; Katsuki, T. *Synlett* **1995**, *8*, 825−826. (h) Tang, W.; Hu, X.; Zhang, X. *Tetrahedron Lett*. **2002**, *43*, 3075−3078. (i) Uchida, T. Irie, R.; Katsuki, T. *Tetrahedron* **2000**, *56*, 3501−3509. (j) Munslow, I. J.; Gillespie, K. M.; Deeth, R. J.; Scott, P. *Chem. Commun*. **2001**, 1638−1639.

31. (a) Seitz, W. J.; Saha, A. K.; Casper, D.; Hossain, M. M. *Tetrahedron Lett*. **1992**, *33*, 7755−7758. (b) Seitz, W. J.; Saha, A. K.; Hossain, M. M. *Organometallics* **1993**, *12*, 2604−2608.

32. Fukuda, T.; Katsuki, T. *Tetrahedron* **1997,** *53*, 7201−7208.

CHAPTER–III

Section - B

INTRODUCTION

1,2,3–Triazoles are potential targets for drug discovery because of their wide range of biological properties such as antibacterial, antiviral, antiepileptic and anti-allergic behavior.[1,2] They are also being used as optical brighteners, light stabilizers, fluorescent whiteners and corrosion retarding agents.[3] Various synthetic methods for the preparation of 1,2,3–triazole derivatives have been developed.

The classical method for the preparation of 1,2,3-triazoles is the Huisgen reaction.[4] However, this uncatalyzed cycloaddition results in products with poor regioselectivity and low yields. The Cu(I)–catalyzed azide–alkyne cycloaddition,[5] one of the most reliable click reactions,[6] has enabled practical and efficient preparation of 1,4-disubstituted-1,2,3-triazoles, from a wide range of substrates with excellent selectivity, which cannot be attained with the traditional Huisgen uncatalyzed thermal approaches.[4] A number of copper(I) sources can be used directly, but in some cases the catalyst is better prepared *insitu* by reduction of Cu(II) salts, which are less costly and often purer than Cu(I) salts. This powerful and reliable Cu-catalyzed 1,3-dipolar cycloaddition has found widespread applications in combinatorial chemistry for drug discovery,[7] material science,[8] and bioconjugation.[9,10] Since triazoles have become progressively more useful and important targets in drugs and pharmaceuticals, the development of simple and efficient methods for their synthesis in a single step operation is desirable.

Proposed catalytic cycle for Cu(I)-catalyzed ligation:

The mechanistic proposal for the catalytic cycle is shown in Scheme 1. It begins unexceptionally with the formation of the copper(I) acetylide **I** (i.e. no reaction is observed with internal alkynes). Then proceeds *via* stepwise annealing sequence from **B-1** to **B-2** to **B-3**; but not directly in sequence B (this is strongly disfavored by extensive density functional theory calculations. According to this, 12-15 kcal-energy is required for concerted [2+3] cycloaddition). This **B-2** proceeds *via* the intriguing six-membered copper-containing intermediate **III**, hence the term “ligation” came for this mechanism (Figure 1).[5b] Finally, cleavage of metal complex leads to the formation of triazoles.

Figure 1

Recently, the use of solid acids as heterogeneous catalysts has received considerable interest in different areas of organic synthesis.[11] The copper salt of heteropoly acid is utilized for the coupling of alkynes with azides *via* 1,3-dipolar cycloaddition. In this section, we have described a novel procedure for the one–pot synthesis of 1,2,3-triazoles from halides, sodium azide and alkynes by means of three component reaction.

PRESENT WORK

In a preliminary experiment, benzyl bromide (**1**) was treated with sodium azide and phenyl acetylene (**2**) in the presence of triethyl amine and 10 mol% of Cu-TPA in DMF. The reaction went to completion in 8 h and the desired product 1-benzyl-4-phenyl-1*H*-1,2,3-triazole **3a** was obtained in 82% yield (Scheme 1).

Scheme 1

Optimization of reaction condition with different solvent and various copper salts:

To know the effect of solvent, the reactions were conducted in various solvents such as acetonitrile, 1,4-dioxane and DMF, but surprisingly, no cycloaddition was observed in 1,4-dioxane. In contrast to acetonitrile, enhanced reaction rates and improved yields were the remarkable features obtained in DMF. This is probably due to the high solubility of sodium azide in DMF. The scope and generality of this process is illustrated with respect to various alkynes, alkyl bromides and sodium azide and the results are presented in Table 2.

The effects of various copper(II) salts such as Cu-TPA, $Cu(acac)_2$, $Cu(OTf)_2$, $Cu(OAc)_2$ and $CuSO_4$ were screened in the reaction of benzyl bromide, sodium azide and phenyl acetylene. Of these copper salts, Cu-TPA was found to give the best conversion (Table 2). However, in the absence of Cu-TPA, the reaction did not give the expected triazole even after long reaction times (8–12 h).

Similarly, other alkynes such as propargyl alcohol, (prop-2-ynyloxy) naphthalene, 1-decyne, *p*-methoxy-phenylacetylene, (prop-2-ynyloxy)benzene and homopropargyl alcohol also reacted effectively with halides and sodium azide under identical conditions to produce 1,2,3-triazoles in good yields (entries b–k, Table 2). Encouraged by the results obtained with benzyl bromide, we turned our attention to various alkyl bromides. Interestingly, (2-bromoethyl) benzene and 1-bromopentane also participated well in this reaction.

Next, we examined the reactivity of 1,3,5-tris(prop-2-ynyloxy)benzene in the three component reaction. Interestingly, the corresponding product, 1,3,5-tris[(1-phenethyl-1*H*-1,2,3-triazol-4-yl)methoxy]benzene **4**, was obtained in 60% yield (Scheme 2).

Scheme 2

Two-component 1,3 dipolar addition:

Furthermore, we have performed two-component coupling reactions between azides and alkynes using Cu-TPA as a catalyst (Scheme 3).

Scheme 3

Interestingly, these two-component reactions proceeded rapidly at room temperature in 1,4-dioxane and the desired triazoles were obtained in high yields in short reaction times and the results are summarized in Table 3.

Since the reaction mixture is heterogeneous in 1,4-dioxane, the catalyst could be easily separated by simple filtration. The recovered catalyst was further washed with dioxane, dried at 120 °C under reduced pressure and reused in four successive runs with only a minimal decrease in activity. For example, the coupling of benzyl azide with phenyl acetylene in the presence of triethyl amine and 10 mol% of Cu-TPA in 1,4-dioxane gave 92%, 87%, 85% and 80% yields over four cycles.

In summary, we have developed a novel and efficient protocol for the for the preparation of 1,2,3-triazoles by means of three–component reaction between alkyl bromide, sodium azide and alkyne using copper exchanged heteropoly acid (Cu-TPA) as a heterogeneous catalyst. This method offers significant advantages such as high

conversions, short reaction times, and ease of recovery and reusability of the catalyst, which makes it a useful and attractive strategy for the preparation of a wide range of triazoles in a single–step operation.

EXPERIMENTAL

General procedure for three–component reaction: A mixture of sodium azide (95 mg, 1.47 mmol), benzyl bromide (0.17 mL, 1.47 mmol), phenyl acetylene (100 mg, 0.98 mmol), triethyl amine (0.27 mL, 1.96 mmol) and Cu-TPA (10 mol%) in dimethylformamide (5 mL) was heated to 90 °C for appropriate time (Table 1). After completion, as indicated by TLC, the reaction mixture was diluted with water and extracted with ethyl acetate (3×30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, concentrated *in vacuo* and purified by column chromatography to afford pure triazole.

Two–component reaction: A mixture of benzyl azide (199 mg, 1.47 mmol), phenyl acetylene (100 mg, 0.98 mmol), triethyl amine (0.27 mL, 1.96 mmol) and CuTPA (10 mol%) in 1,4–dioxane (5 mL) was stirred at room temperature for the appropriate time. After completion of the reaction as indicated by the TLC, the reaction mixture was filtered to recover the catalyst and washed with dioxane. The filtrate was concentrated *in vacuo* and then diluted with water. The aqueous layer was extracted with ethyl acetate (3×30 mL). The combined organic layers were dried over anhydrous sodium sulfate and concentrated *in vacuo* and then purified by column chromatography on silica gel to afford pure triazole.

1–Benzyl–4–phenyl–1*H*–[1,2,3]triazole (3a):

Solid, **m.p.** 68–70 °C.

IR (neat): ν_{max} 2923, 2853,1457, 1181, 1074, 763, 726, 691 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.76 (dd, 2H, J = 7.8, 1.5 Hz), 7.59 (s, 1H), 7.40–7.25 (m, 8H), 5.56 (s, 2H).

LC–MS: *m/z* (%) 236.0 $[M+H]^+$, 258.0 $[M+Na]^+$.

(1–Benzyl–1*H*–[1,2,3]triazol–4–yl)–methanol (3b):

Solid, **m.p.** 75–77 °C.

IR (neat): ν_{max} 3266 (br), 3139, 2925, 2853, 1455, 1222, 1130, 1061, 1014, 841, 719, 689 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.49–7.21 (m, 6H), 5.50 (s, 2H), 4.71 (s, 2H), 2.91–2.75 (br s, 1H).

LC–MS: *m/z* (%) 212.0 $[M+Na]^+$.

1–Benzyl–4–(naphthalene–2–yloxymethyl)–1*H*–[1,2,3]triazole (3c):

Solid, **m.p.** 156–158 °C.

IR (neat): ν_{max} 3427, 3143, 2920, 2854, 1626, 1599, 1456, 1390, 1257, 1217, 1047, 822, 725, 695 cm^{-1}.

^{1}H NMR (300 MHz, DMSO–d_6): δ 7.81–7.67 (m, 3H), 7.43–7.08 (m, 10H), 5.55 (s, 2H), 5.25 (s, 2H).

LC–MS: *m/z* (%) 316.2 $[M+H]^+$, 338.1 $[M+Na]^+$.

1–Benzyl–4–octyl–1*H*–[1,2,3]triazole (3d):

Solid, **m.p.** 64–66 °C.

IR (neat): ν_{max} 3111, 3063, 2956, 2922, 2851, 1461, 1211, 1052, 699 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41–7.31(m, 3H), 7.28–7.21 (m, 2H), 7.10 (s, 1H), 5.47 (s, 2H), 2.65 (t, 2H, *J* = 7.5 Hz), 1.68–1.57 (m, 2H), 1.43–1.18 (m, 10H), 0.87 (t, 3H, *J* = 7.5 Hz).

LC–MS: *m/z* (%) 272.3 $[M+H]^+$, 294.1 $[M+Na]^+$.

1–Benzyl–4–(4–methoxy–phenyl)–1*H*–[1,2,3]triazole (3e):

Solid, **m.p.** 138–140 °C.

IR (neat): ν_{max} 3424, 3134, 2924, 2853, 1611, 1499, 1456, 1248, 1024, 831, 793, 718 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.67 (d, 2H, *J* = 6.8 Hz,), 7.49 (s, 1H), 7.40–7.27 (m, 5H), 6.87 (d, 2H, *J* = 6.8 Hz), 5.54 (s, 2H), 3.81 (s, 3H).

LC–MS: *m/z* (%) 266.1 $[M+H]^+$, 288.1 $[M+Na]^+$.

1–Phenethyl–4–phenyl–1*H*–[1,2,3]triazole (3f):

Solid, **m.p.** 136–138 °C.

IR (neat): ν_{max} 3081, 3028, 2924, 2854, 1455, 1221, 1081, 844, 763, 693 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (dd, 2H, *J* = 8.3, 1.5 Hz,), 7.39–7.22 (m, 7H), 7.09 (dd, 2H, *J* = 8.1,1.5Hz), 4.60 (t, 2H, *J* = 7.3 Hz), 3.24 (t, 2H, *J* = 7.1 Hz).

LC–MS: *m/z* (%) 272.1 $[M+Na]^+$.

4–(Naphthalene–2–yloxymethyl)1–phenethyl–1*H*–[1,2,3]triazole (3g):

Solid, **m.p.** 118–120 °C.

IR (neat): ν_{max} 3424, 3064, 2921, 2858, 1627, 1598, 1458, 1254, 1215, 1182, 1017, 837, 809, 736, 698 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73–7.67 (m, 3H), 7.42–7.36 (m, 1H), 7.32–7.26 (m, 1H), 7.25 (d, 1H, *J* = 2.6 Hz), 7.19–7.13 (m, 4H), 7.09 (dd, 1H, *J* = 8.8, 2.6 Hz), 7.03–6.99 (m, 2H), 5.28 (s, 2H), 4.55 (t, 2H, *J* = 7.3 Hz), 3.19 (t, 2H, *J* = 7.1 Hz).

LC–MS: *m/z* (%) 330.1 $[M+H]^+$, 352.1 $[M+Na]^+$.

4–Benzyloxymethyl–1–phenethyl–1*H*–[1,2,3]triazole (3h):

Solid, **m.p.** 52–54 °C.

IR (neat): ν_{max} 3447, 3121, 3069, 2946, 2856, 1455, 1214, 1094, 733, 697 cm^{-1}.

^{1}H NMR (**300 MHz, $CDCl_3$):** δ 7.38–7.17 (m, 9H), 7.14–7.03 (m, 2H), 4.68–4.50 (m, 6H), 3.20 (t, 2H, *J* = 7.1 Hz).

LC–MS: *m/z* (%) 294.1 $[M+H]^+$, 316.1 $[M+Na]^+$.

2–(1–Phenethyl–1*H*–[1,2,3]triazol–4–yl)–ethanol (3i):

Liquid, **IR (neat):** ν_{max} 3380 (brs), 3141, 3029, 2929, 1454, 1218, 1056, 748, 700 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.29–7.18 (m, 3H), 7.09–7.03 (m, 3H), 4.53 (t, 2H, *J* = 7.1 Hz), 3.85 (t, 2H, *J* = 5.6 Hz), 3.18 (t, 2H, *J* = 7.1 Hz), 2.84 (t, 2H, *J* = 5.6 Hz).

LC–MS: *m/z* (%) 240.4 $[M+Na]^+$.

1–Pentyl–4–phenyl–1*H*–[1,2,3]triazole (3j):

Solid, **m.p.** 55–57 °C.

IR (neat): ν_{max} 3445, 3118, 2924, 2857, 1461, 1214, 1076, 838, 760, 694 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.92–7.64 (m, 3H), 7.49–7.25 (m, 3H), 4.38 (t, 2H, *J* = 7.1 Hz), 2.03–1.89 (m, 2H), 1.46–1.21 (m, 4H), 0.92 (t, 3H, *J* = 7.1 Hz).

ESI–MS: *m/z* (%) 216.1 $[M+H]^+$.

2–(1–Pentyl–1*H*–[1,2,3]triazol–4–yl)–ethanol (3k):

Liquid, **IR (neat):** ν_{max} 3332 (br s), 2957, 2926, 2856, 1464, 1239, 1058, 829, 760 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (d, 1H, *J* = 8.3 Hz), 4.33–4.22 (m, 2H), 3.92–3.83 (m, 2H), 2.91–2.82 (m, 2H), 1.98–1.80 (m, 2H), 1.71−1.50 (br s, 1H), 1.44–1.15 (m, 4H), 0.89 (t, 3H, *J* = 6.8 Hz).

ESI–MS: *m/z* (%): 184.1 $[M+H]^+$.

1,3,5–tris[(1–phenethyl–1*H*–1,2,3–triazol–4–yl)methoxy]benzene (4):

Solid, **m.p.**133–135 °C.

IR (neat): ν_{max} 3417, 3089, 3026, 2925, 2853, 1598, 1459, 1381, 1163, 1053, 817, 748, 701 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.64 (s, 3H), 7.25–7.05 (m, 15H), 6.19 (s, 3H), 5.07 (s, 6H), 4.57 (t, 6H, *J* = 7.2 Hz), 3.18 (t, 6H, *J* = 7.2 Hz).

ESI–MS: *m/z* (%) 682.2 $[M+H]^+$, 704.2 $[M+Na]^+$.

REFRENCES

1. (a) Wamhoff, H. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R.; Rees, C. W. Eds.; Pergamon: Oxford, **1984**; Vol. 5, 669. (b) Im, C.; Maiti, S. N.; Micetich, R. G.; Daneshtalab, M.; Atchison, K.; Phillips, O. A. *J. Antibiot*. **1994**, *47*, 1030–1040. (c) Velazquez, S.; Alvarez, R.; Perez, C.; Gago, F.; De, C.; Balzarini, J.; Camaraza, M. *J. Antivir*. *Chem*. *Chemother*. **1998**, *9*, 481–489.
2. (a) Fan, W. Q.; Katritzky, A. R. *In Comprehensive Heterocyclic Chemistry II*; Katritzky, A. R., Rees, C. W., Scriven, E. F. V., Eds.; Elsevier Science: Oxford, **1996**, *4*, 1–126. (b) Genin, M. J.; Allwine, D. A.; Anderson, D. J.; Barbachyn, M. R.; Emmert, D. E.; Garmon, S. A.; Graber, D. R.; Grega, K. C.; Hester, J. B.; Hutchinson, D. K.; Morris, J.; Reischer, R. J.; Ford, C. W.; Zurenko, G. E.; Hamel, J. C.; Schaadt, R. D.; Stapert, D.; Yagi, B. H. *J. Med. Chem*. **2000**, *43*, 953–970.
3. Gouault, N.; Cupif, J. F.; Sauleau, A.; David, M. *Tetrahedron Lett*. **2000**, *41*, 7293–7297.
4. (a) Huisgen, R. *Angew. Chem., Int. Ed.* **1963**, *2*, 565–598. (b) Huisgen R. in *1,3–Dipolar Cycloaddition Chemistry* (Ed.: Padwa, A.), Wiley, New York, **1984**, 1–176. (c) Padwa A. in *Comprehensive Organic Synthesis*, Vol.4 (Ed.: B. M. Trost), Pergamon, Oxford, **1991**, 1069–1109.
5. (a) Kolb, H. C.; Finn, M. G.; Sharpless, K. B. *Angew*. *Chem. Int. Ed.* **2001**, *40*, 2004–2021. (b) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem. Int. Ed*. **2002**, *41*, 2596–2599. (c) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057–3064.
6. (a) Kolb, H. C.; Sharpless, K. B. *Drug Discovery Today* **2003**, *8*, 1128–1137. (b) Bock, V. D.; Hiemstra, H.; van Maarseveen, J. H. *Eur. J . Org. Chem*. **2006**, 51–68.
7. (a) Moorhouse, A. D.; Santos, A. M.; Gunaratnam, M.; Moore, M.; Neidle, S.; Moses, J. E. *J. Am. Chem. Soc.* **2006**, *128*, 15972–15973. (b) Lee, L. V.; Mitchell, M. L.; Huang, S. J.; Fokin, V. V.; Sharpless, K. B.; Wong, C. H. *J. Am. Chem. Soc.* **2003**, *125*, 9588–9589.
8. (a) Wu, P.; Feldman, A. K.; Nugent, A. K.; Hawker, C. J.; Scheel, A.; Voit, B.; Pyun, J.; Frechet, J. M. J.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem. Int. Ed*. **2004**, *43*, 3928–3932. (b) Wu, P.; Malkoch, M.; Hunt, J. N.; Vestberg, R.; Kaltgrad,

E.; Finn, M. G.; Fokin, V. V.; Sharpless, K. B.; Hawker, C. J. *Chem. Commun.* **2005**, 5775–5777. (c) Rozkiewicz, D. I.; Janczewski, D.; Verboom, W.; Ravoo, B. J.; Reinhoudt, D. N. *Angew. Chem. Int. Ed.* **2006**, *45*, 5292–5296.

9. Wang, Q.; Chan, T. R.; Hilgraf, R.; Fokin, V. V.; Sharpless, K. B.; Finn, M. G. *J. Am. Chem. Soc.* **2003**, *125*, 3192–3193.
10. (a) Speers, A. E.; Adam, G. C.; Cravatt, B. F. *J. Am. Chem. Soc.* **2003**, *125*, 4686–4687. (b) Speers, A. E.; Cravatt, B. F. *Chem. Biol.* **2004**, *11*, 535–546; (c) Burley, G. A.; Gierlich, J.; Mofid, M. R.; Nir, H.; Tal, S.; Eichen, Y.; Carell, T. *J. Am. Chem. Soc*. **2006**, *128*, 1398–1399.
11. (a) Clark, J. H. *Acc. Chem. Res*. **2002**, *35*, 791−797. (b) Okuhara, T.; Mizuno, N.; Misono, M. *Applied Catalysis A*: *General*, **2001**, *222*, 63−77. (c) Kozhevnikov, I. V. *Chem. Rev*. **1998**, *98*,171−198.

CHAPTER–III

Section - C

INTRODUCTION

β−Keto esters are multi coupling reagents having both electrophilic carbonyl and nucleophilic carbon, which makes them useful intermediates for the synthesis of complex molecules.[1] This type of compounds are versatile building blocks in the total synthesis of a variety of natural products such as thiolactomycin, trichodiene, polyoxamic acid, chokol, prostaglandin $PGF_{2\alpha}$, syncarpic acid, diplodialide, podophyllotoxin.[2] They are also important intermediates for the synthesis of various biologically active compounds such as 3,4-dihydropyrimidinones, 4-alkyl or arylcoumarins, 1,4-dihydropyridines and many others.[1]

Figure 1

The ready availability and facile decomposition of α-diazocarbonyl compounds under thermal, photochemical, acid, base and transition metal catalysis conditions make them useful intermediates in organic synthesis.[3,4] The simple and direct method for the synthesis of β−ketoesters involves the acid catalyzed C–H insertion of ethyl diazoacetate into aldehydes.[1,3] These C–H insertion reactions are chemoselective, which allow new carbon–carbon bond formation under mild conditions.

Acid catalysts such as boron trifluoride etherate, tin(II) chloride, titanium(IV) chloride, niobium(V) chloride, triethyloxonium tetrafluoroborate and zinc(II) chloride have been reported for this conversion.[5] However, most of these catalysts are expensive, hygroscopic and difficult to recycle which limit their use in large scale synthesis and

also the yields reported are far from satisfactory especially with aromatic aldehydes. Thus, no attempt has been made to recover the catalyst thereby making the process cost effective and environmentally benign. Furthermore, the introduction of new methods involving simple, selective and recyclable catalysts for C–H insertion continues to be a challenging endeavor in organic synthesis.

In recent years, the use of solid acids as heterogeneous catalysts has received considerable interest in different areas of organic synthesis.[6] The heterogeneous solid acids are advantageous rather than conventional homogeneous acid catalysts due to their easy reusability and they can be easily recovered by simple filtration from the reaction mixture, making the process economically viable. Among various heterogeneous catalysts heteropoly acids are most attractive because of their flexibility in modifying the acid strength, ease of handling, environmental compatibility, non-toxicity, experimental simplicity and unique properties such as well−defined structure, Bronsted acidity, possibility to modify their acid–base and redox properties by changing their chemical composition (substituted HPAs), ability to accept and release electrons, high proton mobility etc.[7] The silver salts of heteropoly acids have been studied in different organic transformations under heterogeneous conditions.[8]

PRESENT WORK

We envisioned that the silver salt of 12-tungstophosphoric acid could be an efficient catalyst for the preparation of β-ketoesters from aldehydes and ethyl diazoacetate via C–H insertion. Our first experiment was commenced with the treatment of benzaldehyde (**1**) with ethyl diazoacetate (**2**) in the presence of 5 mol% Ag-TPA in CH_2Cl_2 afforded ethyl 3-oxo-3-phenylpropanoate (**3**) in 94% yield (Scheme 1).

Scheme 1

Catalytic studies of various silver salts:

The effects of various Ag(I) salts were screened for the coupling of benzaldehyde with ethyl diazoacetate and the results are presented in Table 1, where the Ag-TPA is the best for the formation of β−ketoester as a recyclable catalyst. In the absence of catalyst, no C–H insertion was observed between aldehyde and ethyl diazoacetate. Furthermore, unmodified heteropoly acid (TPA) was also found to be ineffective for this conversion. As solvent, CH_2Cl_2 gave the best results.

The remarkable catalytic activity of Ag-TPA provided the incentive for further study of reactions with other aromatic aldehydes such as *p*-fluoro, *p*-chloro, *p*-hydroxy, 4-hydroxy-3-methoxy, 3,4-dimethoxy, *p*-isopropyl, *p*-methyl, *p*-methoxy and *p*-nitrobenzaldehydes. These aromatic aldehydes reacted efficiently with ethyl diazoacetate under similar conditions to give the corresponding β-ketoesters as the products of C–H insertion (entries b−j, Table 2a).

Table 2a: Ag-TPA−catalyzed preparation of β-ketoesters *via* C−H insertion with aromatic aldehydes.

The heteroaromatic aldehydes like Pyridine-2-carboxaldehyde also participated well in this reaction (entries k, Table 2b). This method also worked well with highly acid sensitive substrate such as furfural (entry l, Table 2b) which is known to polymerize under most of the reported conditions. Aliphatic aldehydes such as cyclohexane carboxaldehyde and 3-phenylpropanal also afforded the respective

β−ketoesters in excellent yields (entries m and n, Table 2b). In all cases, the reactions proceeded well at room temperature. Both aromatic and aliphatic aldehydes underwent smooth coupling with ethyl diazoacetate to yield the β−ketoesters in good yields.

Table 2b: Ag-TPA−catalyzed preparation of β-ketoesters *via* C−H insertion with hetero aromatic and aliphatic aldehydes

The reaction probably proceeds through the activation of the aldehyde by complexation with Ag(I) followed by nucleophilic addition of ethyl diazoacetate on the C=O group and subsequent 1,2-hydride shift with concomitant loss of N_2 resulting in the formation of β-ketoester (Figure 2).

Figure 2: A plausible mechanism for the formation of β-ketoesters.

This method is clean and free from side products such as glycidic esters. Other side products like diethyl maleate and / or fumarate arising from carbene dimerization were not detected under these conditions. The scope and generality of this method is illustrated in Table 2 and 3.

Reusability of the catalyst:

Since the reaction mixture is heterogeneous, the catalyst could be easily separated by simple filtration. The recovered catalyst was further washed with ether, dried at 60 °C under reduced pressure and reused in three to five successive runs with a gradual decrease in catalytic activity. For example, benzaldehyde and ethyl diazoacetate in the presence of 5 mol% of Ag-TPA in CH_2Cl_2 gave good reusability over five cycles are presented in Table 3.

Table 3: Reusability studies of Ag-TPA

An efficient protocol has developed for the preparation of β−ketoesters from aldehydes and ethyl diazoacetate *via* C–H insertion using silver exchanged heteropoly acid (Ag-TPA) as a heterogeneous catalyst. This method offers significant advantages such as high conversions, mild conditions, ease of recovery and reusability of the catalyst, which makes it a useful and attractive strategy for the preparation of β−ketoesters. The use of heterogeneous catalyst makes this method quite simple, more convenient and environmentally friendly.

EXPERIMENTAL

Catalyst preparation:

The silver salt of the $H_3PW_{12}O_{40}$ was prepared according to the procedure reported in literature.[9] In a typical procedure, Ag-TPA was obtained as a precipitate by adding an aqueous solution of silver nitrate to an aqueous solution of 12-tugstophosphoric acid. The excess water was removed on water bath and the resultant salt was dried at 120 °C for 12 h in an oven and finally calcinated at 300 °C for 2h.

General procedure:

A mixture of aldehyde (1.0 mol), ethyl diazoacetate (1.2 mol) and Ag-TPA (5 mol%) in CH_2Cl_2 (10 mL) was stirred at room temperature for the appropriate time (Table 2 and 3). After completion of the reaction, as indicated by TLC, the reaction mixture was extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were dried over Na_2SO_4, concentrated under vacuum and purified by column chromatography on silica gel (Merck, 100–200 mesh) using ethyl acetate: hexane (1:9) as eluant to afforded pure β-ketoester.

Ethyl 3−oxo−3−phenylpropanoate (3a):

Pale yellow liquid, **IR (neat):** ν_{max} 2982, 2925, 2853, 1740, 1687, 1324, 1267, 1202, 1030, 756, 690 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.96−7.91 (m, 2H), 7.50−7.35 (m, 3H), 4.20 (q, 2H, *J* = 6.7 Hz), 3.92 (s, 2H), 1.26 (t, 3H, *J* = 6.7 Hz) (with 7:3 keto−enol ratio).
LC−MS: *m/z* (%) 193 (25) $[M+H]^+$, 215 (100) $[M+Na]^+$.

Ethyl 3−(4−fluorophenyl)−3−oxopropanoate (3b):

Brown oil, **IR (neat):** ν_{max} 3548, 3076, 2985, 1740, 1688, 1600, 1509, 1206, 1032, 845, 768 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.98−7.95 (m, 2H), 7.16−7.11 (m, 2H), 4.18 (q, 2H, *J* = 7.4 Hz), 3.89 (s, 2H), 1.26 (t, 3H, *J* = 7.4 Hz) (with 7:3 keto−enol ratio).

EI−MS: *m/z* (%) 210 (10) $[M]^+$, 166 (5), 124 (100).

Ethyl 3−(4−chlorophenyl)−3−oxopropanoate (3c):

Brown oil, **IR (neat):** ν_{max} 3076, 2985, 1750, 1715, 1590, 1206, 1032, 810 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.88 (d, 2H, *J* = 8.3 Hz), 7.45 (d, 2H, *J* = 8.3 Hz), 4.19 (q, 2H, *J* = 6.7 Hz), 3.89 (s, 2H), 1.27 (t, 3H, *J* = 6.7 Hz) (with 55:45 keto−enol ratio).

Ethyl 3−(4−hydroxyphenyl)−3−oxopropanoate (3d):

Pale yellow liquid, **IR (neat):** ν_{max} 3351, 2928, 1732, 1671, 1601, 1324, 1281, 1212, 1166, 843 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.78 (d, 2H, *J* = 8.6 Hz), 7.57−7.45 (br s, 1H), 6.81 (d, 2H, *J* = 8.6 Hz), 4.20 (q, 2H, *J* = 7.1 Hz), 3.90 (s, 2H), 1.27 (t, 3H, *J* = 7.1 Hz) (only keto form).

LC−MS: *m/z* (%) 231 (100) $[M+Na]^+$.

3−(4−Hydroxy−3−methoxy−phenyl)−3−oxo−propionic acid ethyl ester (3e):

Pale yellow liquid, **IR (neat):** ν_{max} 3404, 2932, 1734, 1670, 1591, 1516, 1460, 1426, 1270, 1188, 1027, 877, 789, 630, 579 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.59−7.40 (m, 2H), 6.91 (d, 1H, *J* = 8.3 Hz), 6.05 (br s, 1H), 4.18 (q, 2H, *J* = 7.5 Hz), 3.96 (s, 3H), 3.86 (s, 2H), 1.26 (t, 3H, *J* = 7.5 Hz), (with 95:5 keto−enol ratio).

EI−MS: m/z (%) 239 (20) $[M+H]^+$, 152 (100).

Ethyl 3−(3,4−dimethoxyphenyl)−3−oxopropanoate (3f):

Pale yellow liquid, **IR (neat):** ν_{max} 2978, 2937, 2842, 1737, 1674, 1590, 1515, 1461, 1419, 1268, 1148, 1023, 808, 765 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.50 (s, 1H), 6.88−6.78 (m, 2H), 4.19 (q, 2H, *J* = 7.5 Hz), 3.95−3.93 (m, 6H), 3.88 (s, 2H), 1.26 (t, 3H, *J* = 6.7 Hz) (only keto form).

EI−MS: *m/z* (%) 252 (25) $[M]^+$, 165 (100).

Ethyl 3−(4−isopropylphenyl)−3−oxopropanoate (3g):

Pale yellow liquid, **IR (neat):** ν_{max} 2963, 2929, 1740, 1684, 1608, 1263, 1191, 1095, 1026, 800 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.85 (d, 2H, *J* = 8.0 Hz), 7.29 (d, 2H, *J* = 8.8 Hz), 4.19 (q, 2H, *J* = 7.3 Hz), 3.89 (s, 2H), 3.05−2.83 (m, 1H), 1.27 (t, 3H, *J* = 7.3 Hz) (with 85:15 keto−enol ratio).

EI−MS: *m/z* (%) 234 (30) $[M]^+$, 147 (100).

Ethyl 3−oxo−3−p−tolylpropanoate (3h):

Pale yellow liquid, **IR (neat):** ν_{max} 2982, 2930, 1741, 1683, 1609, 1324, 1269, 1190, 1148, 1033, 807, 570 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.82 (d, 2H, *J* = 8.3 Hz), 7.25 (d, 2H, *J* = 8.3 Hz), 4.19 (q, 2H, *J* = 7.5 Hz), 3.89 (s, 2H), 2.43 (s, 3H), 1.27 (t, 3H, *J* = 7.5 Hz) (with 9:1 keto−enol ratio).

LC−MS: *m/z* (%) 229 (100) $[M+Na]^+$.

Ethyl 3−(4−methoxyphenyl)−3−oxopropanoate (3i):

Pale yellow liquid, **IR (neat):** ν_{max} 2980, 2934, 2845, 1738, 1676, 1600, 1511, 1262, 1172, 1026, 842 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.90 (d, 2H, *J* = 8.3 Hz), 6.91 (d, 2H, *J* = 9.0 Hz), 4.19 (q, 2H, *J* = 7.5 Hz), 3.89−3.86 (m, 5H), 1.26 (t, 3H, *J* = 7.5 Hz) (with 9:1 keto−enol ratio).

EI−MS: *m/z* (%) 222 (20) $[M]^+$, 135 (100).

Ethyl 3−(4−nitrophenyl)−3−oxopropanoate (3j):

Pale brown liquid, **IR (neat):** ν_{max} 3315, 2982, 2927, 1735, 1710, 1590, 1530, 1217, 806, 705 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 8.27 (d, 2H, *J* = 9.0 Hz), 7.93 (d, 2H, *J* = 9.0 Hz), 4.29 (q, 2H, *J* = 7.5 Hz), 3.97 (s, 2H), 1.36 (t, 3H, *J* = 7.5 Hz) (with 45:55 keto−enol ratio).

Ethyl 3−(furan−2−yl)−3−oxopropanoate (3l):

Pale yellow liquid, **IR (neat):** ν_{max} 3447, 3132, 2926, 1854, 1738, 1677, 1568, 1465, 1395, 1153, 1021, 762 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.58 (s, 1H), 7.24 (d, 1H, *J* = 5.2 Hz), 6.56 (dd, 1H, *J* = 3.0, 1.5 Hz), 4.19 (q, 2H, *J* = 7.5 Hz), 3.79 (s, 2H), 1.27 (t, 3H, *J* = 7.5 Hz) (with 9:1 keto−enol ratio).

LC−MS: m/z (%) 205 (100) $[M+Na]^+$.

Ethyl 3−cyclohexyl−3−oxopropanoate (3m):

Colorless liquid, **IR (neat):** ν_{max} 1730, 1700, 1646, 1450, 1312, 1248, 1186, 1008, 1031 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 4.22 (q, 2H, *J* = 7.3 Hz), 3.45 (s, 2H), 2.75−2.67 (m, 1H), 1.92−1.74 (m, 4H), 1.65−1.13 (m, 6H), 1.00 (t, 3H, *J* = 7.3 Hz) (only keto form).

LC−MS: *m/z* (%) 198 $[M]^+$.

Ethyl 3−oxo−5−phenylpentanoate (3n):

Pale yellow liquid, **IR (neat):** ν_{max} 3445, 3062, 3027, 2930, 1740, 1738, 1646, 1604, 1496, 1452, 1367, 1312, 1248, 1186, 1076, 1031, 748, 699 cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ 7.11−7.28 (m, 5H), 4.15 (q, 2H, *J* = 7.3 Hz), 3.35 (s, 2H), 2.85−3.05 (m, 4H), 1.27 (t, 3H, *J* = 7.3 Hz) (with 95:5 keto−enol ratio).

LC−MS: *m/z* (%) 221 $[M+H]^+$, 243 $[M+Na]^+$.

REFRENCES

1. Benetti, S.; Romagnoli, R. *Chem. Rev.* **1995**, *95*, 1065−1114.
2. (a) Hoffmann, R. W.; Helbig, W.; Ladner, W. *Tetrahedron Lett.* **1982**, *23*, 3479−3482. (b) Wang, C. L. J.; Salvino, J. M. *Tetrahedron Lett.* **1984**, *25*, 5243−5246. (c) Gilbert, J. C.; Kelly, T. A. *Tetrahedron Lett.* **1989**, *30*, 4193−4196. (d) Emmer, G. *Tetrahedron* **1992**, *48*, 7165−7172. (e) Ishida, T.; Wada, K. *Chem. Commun.* **1975**, 209−210. (f) Urban, E.; Knuehl, G.; Helmchen, G. *Tetrahedron* **1995**, *51*, 13031−13038. (g) Magriotis, P. A.; Johnson, F. *J. Org. Chem.* **1984**, *49*, 1460−1461. (h) Ward, R. S. *Synthesis* **1992**, 719−730.
3. Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, John Wiley and Sons, New York, **1998**. p. 551.
4. Davis, H. M. L.; Hansen, T. *J. Am. Chem. Soc.* **1997**, *119*, 9075−9076.
5. (a) Benetti, S.; Romagnoli, R. *Chem. Rev.* **1995**, *95*, 1065−1114. (b) Fernandez, V. H.; Herrera, L. F. J.; Perez, G. C. *Carbohydr. Res.* **1983**, *124*, 333−337.(c) Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258−3260. (d) Dhavale, D.D.; Patil, P. N.; Mali, R. S.*J. Chem. Res. (S)* **1994,** 152−153. (e) Yadav, J. S.; Reddy, B. V. S.; Eshwaraiah, B.; Reddy, P. N. *Tetrahedron* **2005,** *61*, 875−878.(f) Pellicci, R.; Natalini, B.; Cecchetti, S.; Fringuelli, R. *J. Chem. Soc. Perkin Trans. 1* **1985,** 493. (g) Phukan, P.; Mohan, J. M.; Sudalai, A. *J. Chem. Soc. Perkin Trans. 1* **1999,** 3685−3689. (h) Balaji, B. S.; Chanda, B. M. *Tetrahedron* **1998,** *54*, 13237−13252. (i) Bandgar, B. P.; Pandit, S. S.; Sadaverte, V. S. *Green Chem.* **2001,** 247−249. (j) Dudley, M. E.; Morshed, M. M.; Brennan, C. L.; Islam, M. S.; Ahmad, M. M.; Branstette, R. A. B.; Hossain, M. M. *J. Org. Chem*. **2004,** *69*, 7599−7608.
6. (a) Liao, M.; Wang, J. *Tetrahedron Lett.* **2006,** *47*, 8859−8861. (b) Clark, J. H. *Accounts Chem. Res.* **2002,** *35*, 791−797.
7. (a) Kozhevnikov, I. V. *Chem. Rev.* **1998**, *98*, 171−198. (b) Okuhara, T.; Mizuno, N.; Misono, M. *Appl. Catal. A: Gen.* **2001,** *222*, 63−77.
8. (a) Misono, M.; Ono, I.; Koyano, G.; Aoshima, A.; *Pure Appl. Chem.* **2000,** *72*, 1305−1311. (c) Yadav, J. S.; Reddy, B. V. S.; Praveenkumar, S.; Nagaiah, K.; Lingaiah, N.; Saiprasad, P. S. *Synthesis* **2004**, 901–904.

9. (a) Yadav, J. S.; Reddy, B. V. S.; Sridhar, P.; Reddy, J. S. S.; Nagaiah, K.; Lingaiah, N.; Saiprasad, P. S. *Eur. J. Org. Chem.* **2004**, 552–557. (b) Lingaiah, N.; Babu, N. S.; Reddy, K. M.; Saiprasad, P. S.; Suryanarayana, I. *Chem. Commun.* **2007**, 278−279.

LIST OF PUBLICATIONS

1. The stereoselective total synthesis of Cryptophycin-24 (arenastatin A) via Prins cyclization
   J. S. Yadav, **K. V. Purnima**, B. V. Subba Reddy, K. Nagaiah and A. K. Ghamdi.
   (*manuscript under preparation*)

2. Stereoselective Total Synthesis of Leiocarpin A and (+)- -galantinic acid starting from D-mannitol
   K. Nagaiah, D. Sreenu, **K. V. Purnima**, R. Srinvasa Rao, J. S. Yadav.
   Synthesis **2009***, 8,* 1386-1392.

3. Cu-exchanged phosphotungstic acid: An efficient and reusable heteropoly acid for the cyclopropanation of alkenes via C-H insertion
   J. S. Yadav, B. V. Subba Reddy, **K. V. Purnima**, K. Nagaiah, N. Lingaiah.
   Journal of Molecular Catalysis A: Chemical, 285, 1-2, **2008***,* 36-40*.*

4. The silver salt of 12-tungstophosphoric acid: A mild and selective catalyst for the synthesis of β–ketoesters via C-H insertion
   J. S. Yadav, B. V. Subba Reddy, **K. V. Purnima**, S. Jhansi, K. Nagaiah, N. Lingaiah. *Catalysis Communications,* **2008**, *9*, 2361-2364.

5. The Copper Salt of 12-Tungstophosphoric Acid: An Efficient and Reusable Heteropoly Acid for the Click Chemistry.
   J. S. Yadav, B. V. Subba Reddy, **K. V. Purnima**, D. Sreenu, K. Nagaiah, and N. Lingaiah.
   (*manuscript under preparation*)

6. Phosphomolybdic acid (PMA) Catalysed Highly Efficient and Rapid Synthesis of the β-Enaminones
   K. Nagaiah, **K.V. Purnima**, D. Sreenu, S. Jhansi, R. Srinivasa Rao and J. S. Yadav
   (*accepted in synthetic communication*)

7. $FeCl_3$-catalyzed functionalization of monoterpenes *via* hydroalkylation of unactivated alkenes
   J.S. Yadav, B.V. Subba Reddy, G. Narasimhulu, **K.V. Purnima**.
   Tetrahedron Lett. **2009**, *50*, 5783-5785.

8. First example of $FeCl_3$-catalyzed alkylation of indoles with pinenes
   J.S. Yadav, B.V. Subba Reddy, G. Narasimhulu, N. Sivasankar Reddy, P. Narayana Reddy, **K.V. Purnima**, P. Naresh, B. Jagadeesh.
   Tetrahedron Lett. **2010**, *51*, 244-247.

SYNOPSIS

Title of the thesis:	Stereoselective Total Syntheses of Macrocyclic Depsipeptide Cryptophycin−24, (−) -Galantinic acid and Development of Heterogeneous Catalysed Synthetic Methodologies
Name of the student:	Venkata Purnima Kamaraju (07CHPH04)
Research supervisor:	Dr. J. S. Yadav
Co–supervisor:	Prof. M. Periasamy

The thesis entitled **"Stereoselective Total Syntheses of Macrocyclic Depsipeptide Cryptophycin−24, (−) -Galantinic acid and Development of Heterogeneous Catalysed Synthetic Methodologies"** consists of three chapters.

Chapter–I : Stereoselective total synthesis of cryptophycin−24 *via* Prins cyclization.

Chapter–II : Stereoselective synthesis of (−)-galantinic acid from D-mannitol.

Chapter–III : Divided into three sections.

Section A: The copper salt of 12-tungstophosphoric acid: An efficient and reusable heteropoly acid cyclopropanation of alkenes via C−H insertion.

Section B: The copper salt of 12-tungstophosphoric acid: An efficient and reusable heteropoly acid for the Click Chemistry.

Section C: The silver salt of 12-tungstophosphoric acid: A mild and selective catalyst for the synthesis of β-ketoesters via carbene insertion.

CHAPTER–I

Stereoselective total synthesis of cryptophycin−24 via Prins cyclization:

Cryptophycins were isolated by Schwartz and co-workers from *Nostoc* sp. strains ATCC 53789. Although, the Schwartz group has established the structure no details of the absolute stereochemistry were demonstrated. Subsequently, a variety of cytotoxins were isolated by Moore et al. from a crude lipophilic extract of *Nostoc* sp. GSV 224 with their absolute stereochemistry. Structurally, cryptophycins are cyclic depsipeptides and are remarkably potent against tumor cell lines.

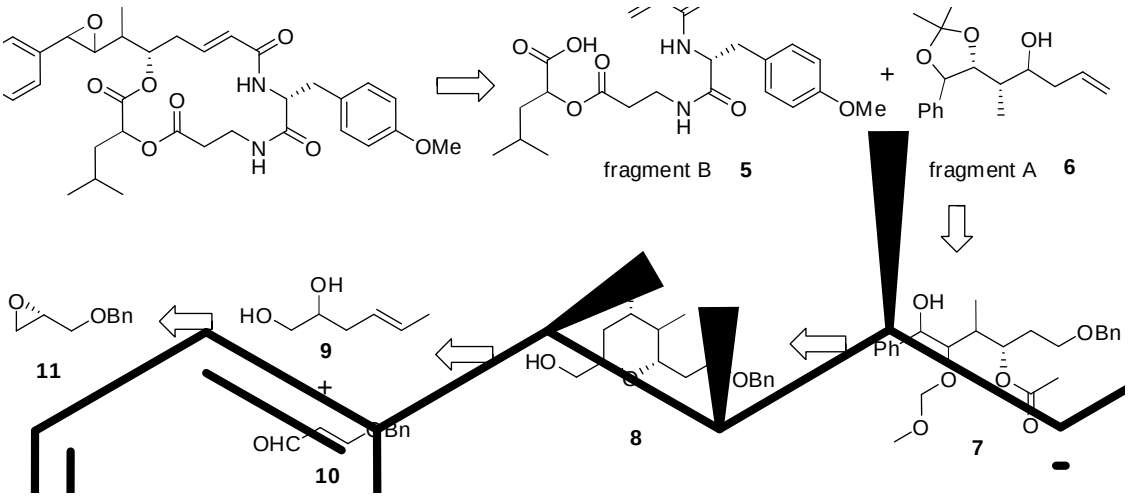
Cryptophycin A (**1**) and B (**2**) exhibit cytotoxic IC_{50} values of 5 and 7 pg/mL, respectively against KB cells. In 1994, arenastatin A (**3**) (renamed as cryptophycin−24), another member of the cryptophycin family, was isolated by Kobayashi et al. from the Okinawa marine sponge *Dysidea arenaria*. It also exhibits cytotoxicity with IC_{50} value of 5 pg/mL against KB cells. Moore et al. have found that the synthetically derived cryptophycin 8 (**4**) was more active *in vivo* than (**1**) (Figure 1).

Figure 1

Cryptophycin A (**1**) was found to be very active against a fungus called as *Cryptococcus*, which causes immunodeficiencies. The significant clinical potentials of cryptophycins and their low natural abundance have made them as attractive synthetic targets. Consequently, there have been some reports on the total synthesis of cryptophycins following multi-step synthetic sequences. However, many of these syntheses employ asymmetric dihydroxylation as a key step to generate *syn*-diols. In view of their fascinating structures and biological activity, we were interested in the synthesis of cryptophycins using Prins cyclization as a key step for the synthesis of non-peptidic part.

In recent days, Prins cyclization has become a powerful synthetic tool for the construction of multi-substituted tetrahydropyran systems and has been utilized in the synthesis of several natural products. Our group has made a significant effort to explore the utility of Prins cyclization in the synthesis of various polyketide intermediates and applied it to the total synthesis of some natural products. As a part of our ongoing program on the total synthesis of biologically active natural products, herein, we report the total synthesis of cryptophycin−24.

In our retrosynthetic analysis (Scheme 1), we envisioned that cryptophycin−24 could be divided into two parts, a homoallyl alcohol with four stereogenic centers (Fragment A) and a peptidic subunit (Fragment B). It was proposed to obtain the *anti*-1,3-diol from 2,4,5,6-tetrasubstituted tetrahydropyran **8** which in turn could be obtained *via* the Prins cyclization of a homoallylic alcohol **9** with an aldehyde **10**.



Scheme 1: Retrosynthetic analysis of cryptophycin−24

Accordingly, the synthesis of cryptophycin fragment A began with a homoallylic alcohol **9** which was prepared from (*S*)-benzyl glycidyl ether **11**. The Prins cyclization of **9** with aldehyde **10** in presence of TFA in CH_2Cl_2 followed by hydrolysis of the resulting trifluoroacetate with K_2CO_3 in methanol gave the 4-hydroxytetrahydropyran **8** in 65% yield (Scheme 2). The stereochemistry was assumed to be in anticipated line with previous results. However, it was later proved after elaborating compound **8** to the target fragment which in all respects was identical with the reported one.

Chemoselective tosylation of primary alcohol **8** with 1.1 equiv. of tosyl chloride in the presence of TEA in CH_2Cl_2 gave the corresponding tosylate **12** in 82% yield. MOM protection of the secondary alcohol **12** with methoxymethyl chloride provided the corresponding MOM ether **13** in 76% yield.

Scheme 2

Treatment of tosylate **13** with NaI in refluxing acetone gave the respective iodide **14** in 86% yield, which on exposure to potassium *t*-butoxide in THF and a subsequent rearrangement on silica gel gave the key intermediate **15** in 55% yield. Ozonolysis of the alkene **15** afforded the corresponding aldehyde **16**, which on treatment with phenylmagnesium bromide in the presence of magnesium bromide diethyl etherate in CH_2Cl_2 at –78 °C produced exclusively *syn*- alcohol **7**, in 72% overall yield (Scheme 3).

The MOM group in **7** was deprotected using *p*-TSA in methanol to give the corresponding diol in 65% yield, which was in turn protected as acetonide with 1,2-dimethoxypropane in the presence of catalytic amount of PPTS to afford compound **17** in 92% yield. The acetate **17** was hydrolyzed with K_2CO_3 in methanol to yield alcohol, which was subsequently debenzylated with 5% Pd/C under H_2 atmosphere in methanol to furnish the diol **18** in 82% yield.

Oxidation of primary hydroxyl group in **18** using TEMPO and BAIB in CH_2Cl_2 followed by Wittig olefination of the resulting aldehyde with an excess C-1 ylide generated *in situ* by the reaction of ICH_3PPh_3 with *t*-BuOK gave the fragment A **6** in

76% yield. The data of a target fragment A of cryptophycin-24 was identical in all respects to the data reported in literature.

Scheme 3

Preparation of Depsipeptide Subunit:

The preparation of depsipeptide subunit was started with (*D*)-*N*-Boc-tyrosine methyl ester **19**. Methylation of the hydroxy group of commercially available (*D*)-*N*-Boc-tyrosine methyl ester with DMS and potassium carbonate afforded compound **20** in 96% yield. The removal of *N*-Boc protecting group in **20** was achieved with TFA in CH_2Cl_2 at room temperature in 3 h providing free amine, which underwent subsequent amide formation with acryloyl chloride in presence of DIPEA in CH_2Cl_2 furnishing the compound **21** in 82% yield.

The methyl ester in **21** was hydrolyzed with $LiOH.H_2O$ in 4 h affording the acid **22** in 90% yield (Scheme 4). The acid was coupled with β-alanine methyl ester, which was prepared from β-alanine **23** using $SOCl_2$ in refluxing methanol to yield β-alanine methyl ester hydrochloride **24** in 90% yield. The coupling of **24** and acid **22** was

achieved with EDCI and HOAt in CH_2Cl_2 in presence of DIPEA as base to give amide compound **25** in 92% yield. The methyl ester of compound **25** was hydrolyzed with $LiOH.H_2O$ in 4 h to afford acid **26** in 87% yield.

Scheme 4

L-Leucic acid *t*-butyl ester **29** was prepared from L-leucic acid **27** by treatment with acetyl chloride to convert the free -OH to -OAc. This crude acetate was converted to *t*-butyl ester with *t*-BuOH, DCC and DMAP to afford the compound **28** in 81% yield. The acetyl group was hydrolyzed with K_2CO_3 in methanol at room temperature to provide the L-leucic acid *t*-butyl ester **29** in 90% yield. The L-leucic acid *t*-butyl ester **29** and acid **26** were coupled with DCC and DMAP in CH_2Cl_2 for 8 h to furnish the desire depsipeptide **30** in 82% yield (Scheme 5).

Scheme 5

The *t*-butyl ester of **30** was hydrolyzed with TFA in CH_2Cl_2 to afford the acid **5** which was used in the next reaction without further purification and characterization. The acid **5** was coupled with alcohol **6** in Yamaguchi conditions with 2,4,6-trichloro benzoyl chloride in presence of DIPEA and DMAP in THF for 18 h to afford the compound **31** in 80% overall yield. This diene **31** was subjected to RCM using 10 mol% Grubbs' second generation catalyst in refluxing CH_2Cl_2 for 2 h to yield RCM product **32** in 75% yield. The cyclized product **32** was treated with TFA in CH_2Cl_2 for 4 h to afford the diol compound **33** in 80% yield (Scheme 6).

The *syn*-diols in **33** were converted to epoxide in three sequential steps in 65% yield. At first, diol was treated with trimethoxy orthoformate in presence of PPTS in CH_2Cl_2 for 1 h, followed by acetyl bromide in CH_2Cl_2 producing the anticipated bromohydrin formate in 2 h, which was taken on to the last step without purification. The formation of epoxide was achieved with powdered $KHCO_3$ in a mixture of DME/ethanol/methanol (6:4:1) at 40 °C for 6 h. The data of target molecule of cryptophycin-24 (arenastatin A) was identical in all respects to the reported data.

Scheme 6

CHAPTER–II

Stereoselective synthesis of the (−)-galantinic acid from D−mannitol:

Galantinic acid (**35**) is a constituent of the peptide antibiotic galantin−I, which was isolated from a culture broth of *Bacillus pulvifaciens.* The originally proposed pyranoid structure **34** of (羊)-galantinic acid was later revised to **35** by Sakai and Ohfune. Galantinic acid, which is an unusual amino acid, has been an attractive target for synthetic chemists because of its unique structure with dense functionalisation and also excellent antibacterial activity.

Figure 2

A retrosynthetic analysis for galantinic acid based on chiron approach with diastereoselective allylic addition as the prominent strategy is pictorially presented in Scheme 7. We envisioned that the synthesis of galantinic acid could be achieved by employing stereoselective allylation as a key strategy to make this route more feasible and simple. The homoallylic alcohol **36a** can be obtained from **37** by converting terminal olefin to aldehyde followed by stereoselective allylation. Compound **37** could be achieved from homoallylic alcohol **38a** *via* S_N2 substitution of benzyl amine followed by protections. The homoallylic alcohol **38a** was prepared from (*R*)-2,3-*O*-isopropylidineglyceraldehyde **39** which was obtained from commercially available D−mannitol **40**. In the present chapter we describe the total synthesis of (−)-galantinic acid (**35**).

Scheme 7: Retrosynthetic analysis of galantinic acid (**35**)

The foremost step was the conversion of D-mannitol **40** into 1,2,5,6-di-*O*-isopropylidine-D-mannitol **41** using 2,2-dimethoxy propane and cat. *p*-TSA in dry DMSO for 8 h as shown in Scheme 8. The treatment of diacetonide D-mannitol **41** with $NaIO_4$, and sat. $NaHCO_3$ in CH_2Cl_2 for 8 h afforded the (*R*)-2,3-*O*-isopropylidine glyceraldehyde **39** in quantitative yield.

Scheme 8

The next endeavor was the stereoselective allyl addition to the aldehyde **39**. Accordingly**,** the compound **39** was treated with allyl bromide, in presence of activated zinc dust and saturated NH_4Cl for 4h, which gave the mixture of diastereomers **38a** and **38b** in the ratio of the 95:5 (*anti* : *syn*) in 92% yield (Scheme 8). The diastereomers were separated by column chromatography.

Scheme 9

The alcohol of **38a** was protected using benzyl bromide and NaH in dry THF at 0 °C to room temperature for 4 h to afford **42** in 90% yield. Compound **42** was treated with 2N HCl in THF for 3 h to afford diol **43** in 90% yield (Scheme 9). The diol **43** was subjected to selective protection of primary alcohol using benzyl bromide in the presence of dibutyltin oxide in benzene under reflux to produce the compound **44** in 88% yield.

Scheme 10

The free OH group in **44** was mesylated with $MeSO_2Cl$ in presence DIPEA in anhydrous CH_2Cl_2 for 3 h to afford the corresponding mesyl ester **45** in 82% yield. The mesyl ester **45** was subsequently heated with benzylamine (excess) at 120 °C under solvent free condition for 12 h to afford the desired amino compound **46** in 85% yield. The S_N2 substitution was a smooth affair, even though the mesylate group is sterically flanked by benzylic groups. The free NH proton in **46** was carbomated with CBZ−chloride in aq. ethanol for 3 h to afford the corresponding carbamate derivative **37** in 90% yield. Then the double bond in **37** was dihydroxylated with osmium tetroxide to give a diol that was cleaved with sodium periodate to give the aldehyde in a pure form in one pot operation (Scheme 10).

Scheme 11

We proceeded to the next chelation−controlled diastereoselective allylation without any purification and analytical characterization of the aldehyde. Thus, the aldehyde was treated with allyl(tributyl)stannane in the presence of magnesium bromide in CH_2Cl_2 at 0 °C to give the corresponding homoallylic alcohol as a mixture of isomers **36a** and **36b** in 72% overall yield. The desired major 1,3-*anti*-addition product

36a was easily separated by column chromatography from the undesired isomer (Scheme 11).

Scheme 12

The homoallylic alcohol **36a** was treated with a catalytic amount of osmium tetroxide to give the 1,2-diol, which was oxidatively cleaved with $NaIO_4$ in THF–H_2O (5:1) to afford the aldehyde (Scheme 16). The aldehyde was further oxidized to an acid **47** with $NaClO_2$ and $NaH_2PO_4.2H_2O$ in *t*-BuOH at room temperature, in 85% yield. Debenzylation and CBZ deprotection in **47** was achieved with 10% Pd/C in methanol at room temperature under atmospheric hydrogen pressure. After 8 h stirring, the target molecule **35** was obtained in 86% yield (Scheme 12).

CHAPTER–III

Development of new synthetic methodologies is an important subject in organic chemistry. Synthesis involves expensive reagents and catalysts, which are not easily available. To replace all such reagents and catalysts, different improved processes have been discovered to carry out the reactions efficiently and conveniently with readily available inexpensive materials. In recent years, the use of solid acids as heterogeneous catalysts has received considerable interest in different areas of organic synthesis. The heteropoly acids are more advantageous as they are reusale and easily seperable from reaction mixture by simple filtration. In this chapter we described the Cu and Ag exchanged tungstophosphoric acid catalysed synthetic methodologies.

The Cu exchanged 12-tungstophosphoric acid is used as an efficient and reusable catalyst for cyclopropanation of alkens via C−H insertion and for Click chemistry, which is summerised in Section A and Section B respectively. The Silver exchanged tungtophosphoric acid is used for the preparation of β–ketoesters via carbene insertion, which is summerised in Section C.

Section A: The Copper exchanged 12−tungstophosphoric acid for cyclopropanation of alkenes via C-H insertion

Smooth cyclopropanation of alkenes with ethyl diazoacetate using a catalytic amount of Cu-exchanged phosphotungstic acid (Cu-TPA) has been summerised in this section. The reaction conditions are mild and afforded cyclopropanecarboxylates in high yields with moderate selectivity. The catalyst is recycled and reused for three to four subsequent runs with a minimal decrease of activity.

Scheme 13

In a model experiment, styrene (**48**) was treated with ethyl diazoacetate (**49**) in the presence of 5 mol% of Cu-TPA in CH_2Cl_2. The reaction was completed in 2.5 h at room temperature and the product, ethyl 2-phenyl-1-cyclopropanecarboxylate was isolated as a mixture of **50a** and **50b** in 90% yield (Scheme 13). However, the product was obtained as a mixture of *trans*− **50a** and *cis*− **50b** isomers, favoring *trans*−diastereomer **50a**. The diastereomers *cis*− and *trans*− could be easily separated by column chromatography.

The effects of various copper(II) salts were screened in the cyclopropanation of styrene with ethyl diazoacetate. The best results were obtained using Cu-TPA as the catalyst with best *trans*-selectivity. Both electron rich and electron deficient styrene derivatives gave cyclopropane carboxylates in high yields (Table 1). In all cases, the reaction proceeds smoothly at room temperature with high *trans*-selectivity. α-and β-substituted styrenes gave the corresponding products in good yields without selectivity.

In addition, treatment of cyclohexene (**51**) with ethyl diazoacetate (**49**) gave ethyl bicyclo [4.1.0] heptanes-7-carboxylate as a mixture of *endo*− **52a** and *exo*− **52b** isomers, favoring *endo*− **52a** isomer in 95% yield (Scheme 14). Similarly, cyclooctene, indene and dihydronaphthalene worked well for this cyclopropanation (Table 2).

Scheme 14

Section B: The Copper exchanged 12-tungstophosphoric acid for Click chemistry

In this section we describe the preparation of triazoles via three component and two component reactions. Three-component coupling of alkyl bromide, sodium azide and alkyne has been achieved by means of Click Chemistry using a catalytic amount of copper-exchanged tungstophosphoric acid (Cu-TPA) in the presence of triethyl amine in DMF to afford substituted triazoles in good yields with high selectivity. In a preliminary experiment, benzyl bromide (**53**) was treated with sodium azide and phenyl acetylene (**54**) in the presence of triethyl amine and 10 mol% of Cu-TPA in DMF. The reaction went to completion in 8.0 h and the desired product, 1-benzyl-4-phenyl-1*H*-1,2,3-triazole (**55**) was obtained in 85% yield (Scheme 15).

Scheme 15

Similarly, other alkynes such as propargyl alcohol, (prop-2-ynyloxy) naphthalene, 1-decyne, *p*-methoxy-phenylacetylene, (prop-2-ynyloxy)benzene and homopropargyl alcohol also reacted effectively with halides and sodium azide under identical conditions to produce 1,2,3-triazoles in good yields (Table 3). Encouraged by the results obtained with benzyl bromide, we turned our attention to various alkyl bromides. Interestingly, (2-bromoethyl)benzene and 1-bromopentane also participated well in this reaction. The effects of various copper(II) salts such as Cu-TPA , $Cu(acac)_2$, $Cu(OTf)_2$, $Cu(OAc)_2$ and $CuSO_4$ were screened in the reaction of benzyl bromide, sodium azide and phenyl acetylene. Of these copper salts, Cu-TPA was found to give the best conversion. The two-component coupling of alkyl azide **56** with alkyne **57** proceeds rapidly at room temperature to furnish 1,2,3-triazoles **58** in excellent yields (Scheme 16). The catalyst can be recovered and reused for three to four subsequent runs with a minimal decrease of activity.

Scheme 16

This is a novel and efficient protocol for the preparation of 1,2,3-triazoles by means of three–component reaction between alkyl bromide, sodium azide and alkyne using copper exchanged heteropoly acid (Cu-TPA) as a heterogeneous catalyst. This method offers significant advantages such as high conversions, short reaction times, and ease of recovery and reusability of the catalyst, which makes it a useful and attractive strategy for the preparation of a wide range of triazoles in a single–step operation.

Section C: The Silver exchanged 12-tungstophosphoric acid for the synthesis of β-ketoesters via C−H insertion

This section contains the silver salt of tungstophosphoric acid used as an efficient catalyst for the preparation of β−ketoesters from aldehydes and ethyl diazoacetate via C–H insertion. Our first experiment was commenced with the treatment of benzaldehyde (**59**) with ethyl diazoacetate (**49**) in the presence of 5 mol% Ag-TPA in CH_2Cl_2 afforded ethyl 3−oxo−3−phenylpropanoate (**60**) in 94% yield (Scheme 17).

Scheme 17

The effects of various Ag(I) salts were screened for the coupling of benzaldehyde with ethyl diazoacetate, where the Ag-TPA is the best for the formation of β−ketoester as a recyclable catalyst. The remarkable catalytic activity of Ag-TPA provided the incentive for further study of reactions with other aromatic aldehydes such as *p*-fluoro, *p*-chloro, *p*-hydroxy, 4-hydroxy-3-methoxy, 3,4-dimethoxy, *p*-isopropyl, *p*-methyl, *p*-methoxy and *p*-nitrobenzaldehydes (Table 4). These aromatic aldehydes reacted efficiently with ethyl diazoacetate under similar conditions to give the corresponding β-ketoesters as the products of C–H insertion.

The heteroaromatic aldehydes such as Pyridine-2-carboxaldehyde and Furan-2-carboxaldehydes also participated well in this reaction. Aliphatic aldehydes such as cyclohexane carboxaldehyde and 3-phenylpropanal also afforded the respective β−ketoesters in excellent yields. This method also worked well with highly acid sensitive substrate such as furfural, which is known to polymerize under most of the reported conditions. In all cases, the reactions proceeded well at room temperature. Both aromatic and aliphatic aldehydes underwent smooth coupling with ethyl diazoacetate to yield the β−ketoesters in high yields.

The research work described in this thesis has been included in the following publications:

1. The stereoselective total synthesis of cryptophycin−24 (arenastatin A) *via* Prins cyclization
   J. S. Yadav,* **K. V. Purnima**, B. V. Subba Reddy, K. Nagaiah and A. K. Ghamdi.
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4. The silver salt of 12−tungstophosphoric acid: A mild and selective catalyst for the synthesis of *β*–ketoesters *via* C−H insertion.
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   Catalysis Commun. **2008**, *9*, 2361−2364.

5. The Copper Salt of 12−Tungstophosphoric Acid: An Efficient and Reusable Heteropoly Acid for the Click Chemistry.
   J. S. Yadav,* B. V. Subba Reddy, **K. V. Purnima**, D. Sreenu, K. Nagaiah and N. Lingaiah.
   (*manuscript under preparation*)