Synthesis of Natural Product-Inspired Macrocyclic Architectures and Hybrid Latrunculins

A Thesis
Submitted for the Degree of
DOCTOR OF PHILOSOPHY
in Chemistry

by

Madhu Aeluri

Dr. Reddy's Institute of life Sciences
University of Hyderabad Campus
Gachibowli, Hyderabad 500046, India

June 2014

DEDICATED

TO

MY BELOVED

PARENTS

Table of contents

DECLARATION

I, hereby, declare that the matter embodied in the thesis is the result of investigation carried out by me at the Dr. Reddy's Institute of Life Sciences, University of Hyderabad Campus, Hyderabad, India, under the supervision of **Professor Prabhat Arya**.

In keeping with the general practice of reporting scientific observations, due acknowledgements have been made wherever the work described is based on the findings of other investigators. Any omission, which might have occurred by oversight or error, is regretted.

Dr. Reddy's Institute of Life Sciences
University of Hyderabad
June 2014

Madhu Aeluri

CERTIFICATE

This is to certify that the thesis entitled ***"Synthesis of Natural Product-Inspired Macrocyclic Architectures and Hybrid Latrunculins"*** being submitted by ***Mr. Madhu Aeluri*** to University of Hyderabad for the award of ***Doctor of Philosophy in Chemistry*** has been carried out by him under my supervision and the same has not been submitted elsewhere for a degree. I am satisfied that the thesis has reached to the standard of fulfilling the requirements of the regulations relating to the nature of the degree.

Professor Prabhat Arya
(Research Supervisor)
Head, Department of Organic and Medicinal Chemistry
Dr. Reddy's Institute of life Sciences (DRILS)
University of Hyderabad Campus
Gachibowli, Hyderabad 500 046
Andhra Pradesh, India
Tel.: +91 40 66571500
Fax: +91 40 66571581
E-mail: prabhata@drils.org
Web site: www.prabhatarya.org

Acknowledgements

I would like to express special appreciation and thanks to my advisor, Professor Dr. PRABHAT ARYA, Head, Department of Organic and Medicinal Chemistry, Dr. Reddy's Institute of Life Sciences (DRILS) and you have been a tremendous mentor for me. I would like to thank you for encouraging my research, and, for allowing me to grow as a research scientist. Your advice on both research as well as on my academic career has been priceless. I would like to thank Director, and, other faculty members of DRILS. I would also like to thank DRILS analytical staff and administrative staff for their excellent support.

I am truly thankful to my doctoral committee members, Dr. G.V.M. Sharma (CSIR-IICT, Hyderabad) and Professor Manojit Pal (DRILS), for their critical evaluation and valuable suggestions. I also thank CSIR, India for the fellowship support.

I would like to express my special thanks to my M.Sc. teacher Dr. Sarbani Pal, M.N.R.P.G. College, Hyderabad, India, for her constant support and suggestions, and, tremendously encouraged me in my research. Also, I would like to thank other M.Sc. faculty members, Professors P. S. N. Reddy, P.N. Gupta, Jayasree, Mrs. Kavitha, and Mrs. Jyothi for their encouragement and support.

I thank all my DRILS colleagues, Srinivas Chamakuri, Ravikumar Jimmidi, Shiva Krishna Reddy, Bhanudas Dasari, Narender Reddy, Prasad Bagineni, Ratnam, Raju Adepu, Srinivas Jogula, Saidulu Konda, Mahender Katravath, Jagan Gaddam, Naveen Kumar, Ramesh Reddy, Devendram, Ramu, Rajnikanth and Dr. Alinakhi for their support.

I would like to thank my former colleagues Dr. Naveen Reddy, Dr. Upender Reddy, Dr. Balakrishna and Mohan Rao for their support at the initial stage of my research career.

I would like to thank my B.Sc. faculty, Mr. Ravinder reddy (Chemistry), Mr. Bikshapathy (Physics), Mr. Maruthi Kumar (Maths), Mrs. Sujatha, and Mr. Raffi (Hindi) for their encouragement and support.

I would like to thank my M.Sc. friends Vikas, Srikanth, Samba, Ramesh T., Ramesh, S., Santhosh, Naveen, Shankar and my dearest friends Ramu and Anil (rao garu) for sharing troubles and happiness in my life.

I would like to thank my B. Sc. Friends Amaravathi, Swapna, Navaneetha, Lavanya, Vijaya Sree, Rajeshwari and Krishna for their valuable discussions in chemistry.

I would like acknowledge all my school teachers Mr. Rajaramulu (Head Master, ZPHS, Choller), Mr. Shekar reddy, Mrs. Chandrakala , Mr. Balreddy, Mr. Satyam , Mr. Ramesh , Mr. Srinivas, Mr. Nagi reddy, Mr. Venkatesham, and Mr. Ashok.

I must thank the most important people in my life, my family members. I am nothing without them. Words are not enough to express my thanks to my Parents. My father Venkatesham and mother Janamma have sacrificed everything for the sake of happiness in my life. Their blessings and care always gave me a new zeal and enthusiasm to do something more with perfection. At this juncture, today, I dedicate my thesis to my Parents.

My wife Mamatha is part of my life to take off all my tensions and to share happiness. My sister Jothi and brother-in-law Dr. Damoder are my best mentors and the biggest pillars of support. My little thanks go to my son-in-laws Sai Krishna (Bobby) and Sai Praneeth (Bunny), who have been a source of relief while I am away from the work. I would like to thank my grandparents, Narsaiah and Laxmamma, my brother Vijay, father-in-laws Laxmipathy and Chiranjeevulu, mother-in-laws Kavitha and Padma, brother-in-laws Sravan and Naveen, and sister-in-laws Suma and Pavani for sharing my tensions and happiness.

I would like to thank the University of Hyderabad for the Ph.D. registration and Dr. Reddy's Institute of Life Sciences for providing the entire infrastructure to conduct my research.

Dr. Reddy's Institute of Life Sciences **Madhu Aeluri**

June 2014

Synopsis

This thesis entitled**, "Synthesis of Natural product-Inspired Macrocyclic Architectures and Hybrid Latrunculins"** contains five chapters

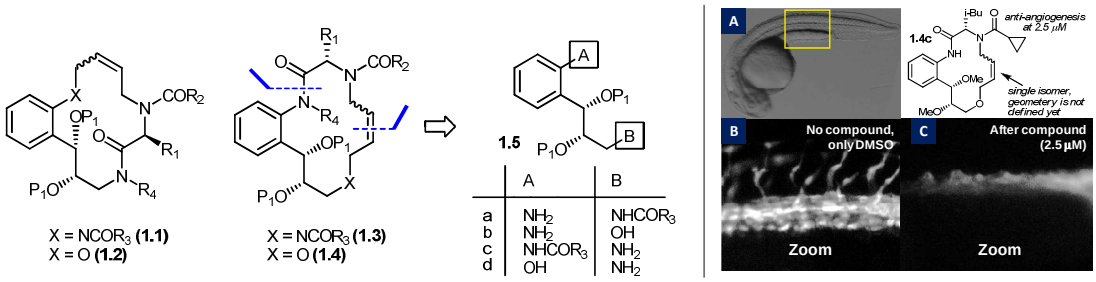
Chapter 1: Introduction to the Importance of Macrocycles

This chapter deals with literature survey on the importance of macrocycles in drug discovery arena and breifly discuss about few success stories of natrual product as well as synthetic macrocycles.

Chapter 2: Synthesis of Natural Product-Inspired, 14-Membered Ring Derived Macrocyclic Toolbox

(*Org. Lett.*, **2013**, *15*, 436-439)

Due to the growing demand in accessing small molecules to search for modulators of Protein-Protein Interactions (PPI) and the selective dissectors of signaling pathways, we are seeing a rejuvenating interest in natural products. In general, macrocyclic compounds can offer several advantages, such as, (i) ability to map a large surface area,



Scheme 1: Designed natural product-inspired 14-membered macrocycles and zebrafish based anti-angiogenesis assay

(ii) numerous binding interactions, (iii) pre-organization, and (iv) an enhanced cell-permeation properties. Some of these features are highly attractive to search for compounds with high selectivity and affinity to protein targets, as modulators of protein-protein interactions and pathways, in general. However, a high complexity of macrocycles in most bioactive natural products hampers their synthetic modification(s)

and pharmacokinetic optimization. Thus, synthetic macrocycles having sufficient complexity is gaining a serious attention in the drug discovery arena in recent years. This has led to the discovery of many synthetic macrocyclic small molecules as modulators with appropriate pharmacokinetic properties for challenging new targets related to PPI**.**

With this objective, we were interested in developing a modular synthesis method to access natural product-inspired 14-membered ring derived macrocyclic toolbox (**Scheme 1**). Natural product inspired macrocycles are more close to natural products in terms of their 3D shapes and dense display of their chiral functinal groups. In our modular design strategy, we had an option to incorporate the amino acid functionality either through the aromatic amine or from the aliphatic side chain (see, macrocyclic targets, **1.1-1.4**). Further, variation in the side chain, i.e. R_2-R_4 on the macrocyclic skeleton can also be achieved through selective alkylation and amidation, respectively. We successfully developed the synthesis methods leading to access 14-membered macrocycles, and also, tested them in a zebrafish based assay to search for anti-angiogenesis agents and the inhibitors of an early embryo development. This was achieved in collaboration with Satish Kitambi team at the Karolinska Institute in Sweden. This study identified some novel small molecules as anti-angiogenesis agents and the inhibitors of early embryonic development.

A few key references:

(1) Driggers, E. M.; Hale, S. P.; Lee, J.; Terrett, N. K. *Nat. Rev. Drug Discov*. **2008**, *7*, 608.

(2) Arkin, M. R.; Wells, J. A. *Nat. Rev. Drug Discov.* **2004**, *3*, 301.

(3) Wells, J. A.; McClendon, C. L. *Nature* **2007**, *450*, 1001.

(4) Scott, J. D.; Pawson, T. *Science* **2009**, *326*, 1220.

(5) Pawson, T.; Warner, N. *Oncogene* **2007**, *26*, 1268.

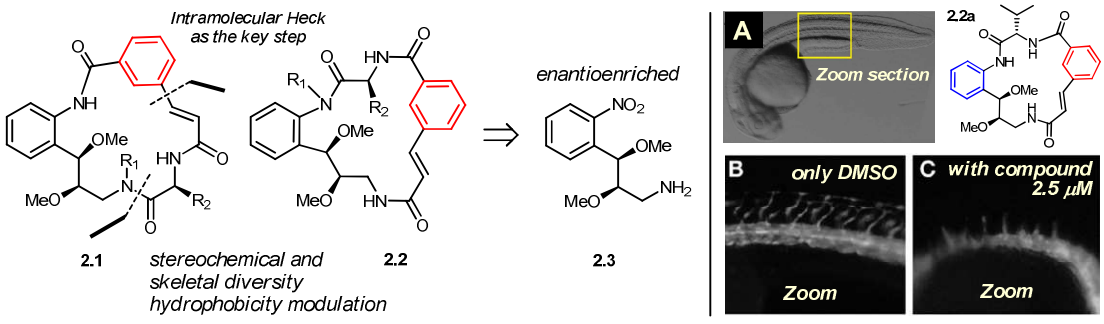
(6) Schreiber, S. L. *Proc. Natl. Acad. Sci. USA* **2011**, *108*, 6699.

(7) Dandapani, S.; Marcaurelle, L. A. *Nat. Chem. Biol*. **2010**, *6*, 861.

Chapter 3: Synthesis of Natural Product-Inspired, 17-Membered Ring Derived Macrocyclic Toolbox via an Intramolecular Heck Reaction

(*Eur. J. Org. Chem.*, **2013**, 3955-3958)

More than 40 years ago Mizoroki[1] and Heck[2] independently discovered the Pd(0)-catalyzed vinylation of aryl halides. This reaction is now known as the Heck reaction and it is broadly defined as the Pd(0)-mediated coupling of an aryl or vinyl halide or triflate with an alkene. The reaction is very attractive from the the synthetic point of view because of mild reaction conditions, high chemo-selectivity and low toxicity and cost. Although the synthetic potential of this transformation was unexplored for a number of years, the application of this powerful reaction in natural product synthesis has flourished recently[3]. There are many number of reactions are known for the macrocyclization but Heck reaction was not much evolved as the macrocyclization strategy. There are only few examples in the literature utilizing Heck reaction as the macrocyclization step. Here are the some literature examples for the synthesis of macrocycles using intra-molecular Heck reaction as the macrocyclization strategy[4]. Even though the Heck reaction was utilized as the macrocyclization strategy for the synthesis of cyclic peptides[4a,4d] and in the natural product synthesis[4b,c], this reaction is not much explored in the generation macrocyclic-based chemical toolbox. By considering this, we are interested in exploring the use of the intramolecular Heck reaction as the macrocyclization strategy in the generation of macrocyclic library of compounds.



Scheme 2: Designed natural product-inspired 17-membered macrocycles and zebrafish based anti-angiogenesis assay

In our study, we decided to develop a modular method to obtain a diverse to 17-membered functionalized macrocyclic compounds because there are several examples of bioactive natural products that have functionalized 17-membered rings. Shown in **Scheme 2** are our two proposed macrocyclic targets (**2.1** and **2.2**). The macrocyclic targets, **2.1** and **2.2** are highly attractive because of the presence of a functionalized 17-membered ring skeleton. The possibility of using both enantiomers further allows us to explore the stereochemical diversity on a similar macrocyclic ring. The incorporation of an amino acid moiety as a part of the macrocyclic ring provides an opportunity to bring various non-polar to polar groups as the chiral side chain. Further, in our present design targets, each macrocyclic ring has two diversity points that could easily be explored in generating the structurally related analogs as the library members. We successfully used an intramolecular Heck reaction to access 17-membered macrocycles, and, further, tested our chemical toolbox in a zebrafish based assays to search for anti-angiogenesis agents and the inhibitors of an early embryo development and identified some novel small molecules as anti-angiogenesis agents.

A few key references:

(1) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Japan* **1971**, *44*, 581.

(2) Heck, R.; Nolley Jr, J. *J. Org. Chem.* **1972**, *37*, 2320.

(3) (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009(b) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945(c) Le Bras, J.; Muzart, J. *Chem. Rev*. **2011**, *111*, 1170.

(4) (a) Akaji, K.; Teruya, K.; Akaji, M.; Aimoto, S. *Tetrahedron* **2001**, *57*, 2293. (b) Dieckmann, M.; Rudolph, S.; Dreisigacker, S.; Menche, D. *J. Org. Chem.* **2012**, *77*, 10782. (c) Groh, M.; Meidlinger, D.; Bringmann, G.; Speicher, A. *Org. Lett.* **2012**, *14*, 4548. (d) Reddy, P. R.; Balraju, V.; Madhavan, G. R.; Banerji, B.; Iqbal, J. *Tetrhedron Lett.* **2003**, *44*, 353.

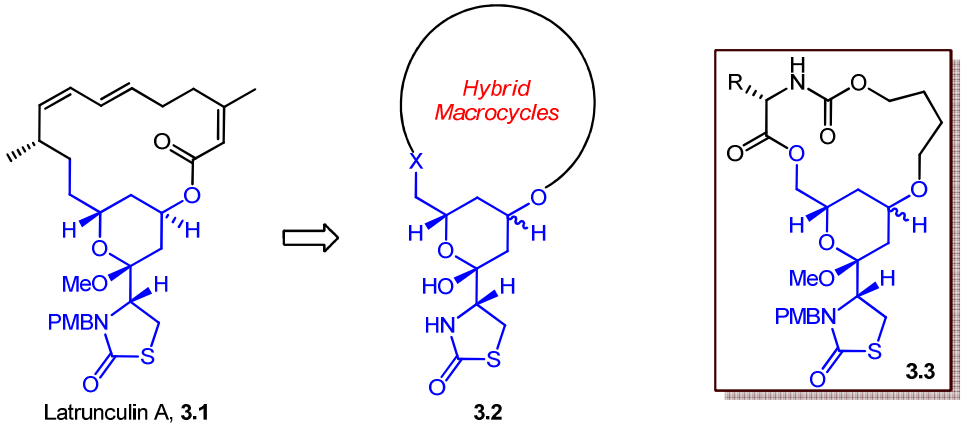
Chapter 4: Literature Work on Latrunculins

This chapter covers the isolation, biological importance and literature synthesis of latrunculin family of bioactive marine natural products.

Chapter 5: Latrunculin-Derived Hybrid Natural Products

(*Manuscript under preparation*)

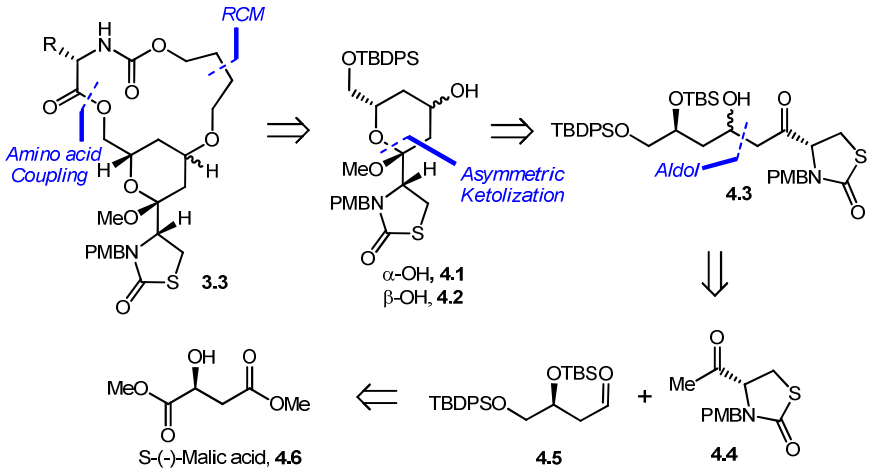
As an extension to our work in the area of building the macrocyclic diversity, we plan to develop novel chemical approaches that are focused on the bioactive natural product, Latrunculin A. Latrunculins are the marine natural products known to disrupt microfilament organization by binding specifically to the cytoskeleton protein called actin. Latrunculin A and B, two lead compounds of this family serving as the biological probes. These natural products are isolated from red sea sponge *Negombata Magnifica* (formerly known as *Latrunculia Magnifica*) in 1980 by Kashman et al. The structure of latrunculin A and B were assigned based on an extensive spectroscopic studies and the single crystal X-ray of methyl glycoside derivative of the latrunculin A.



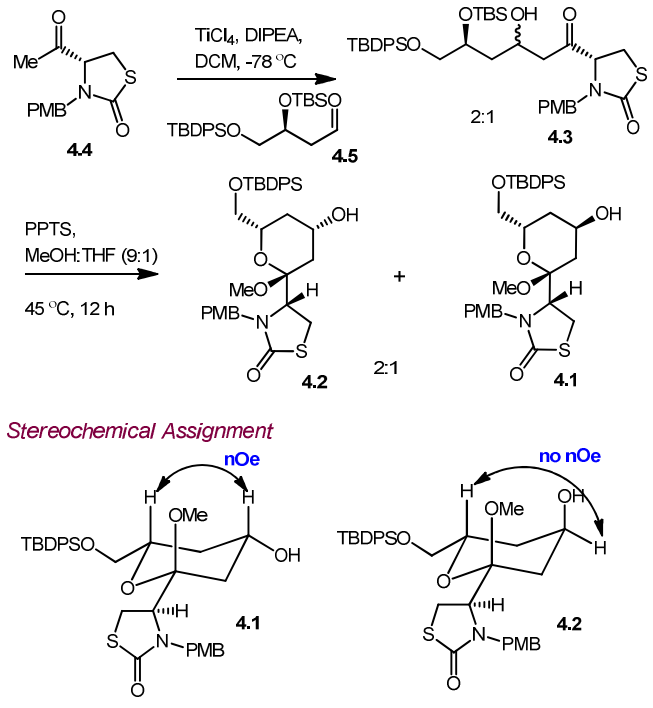
Scheme 3: The design of latrunculin derived hybrid macrocycles

These are the first marine natural products containing macrocyclic ring skeleton (latrunculin A is 16-membered and B is 14-membered macrolide) as well as with hte rare thiazolidinone ring. Moreover, it is interesting to see that it share the similar carbocyclic skeleton with epothilone B, which is already an approved drug for the treatment of breast cancer. Later, it was found to be latrunculins disrupting microfilament organization by forming 1:1 complex with the protein actin without

showing any effect on microtubule organization in mouse neuroblastoma and fibroblast cells.

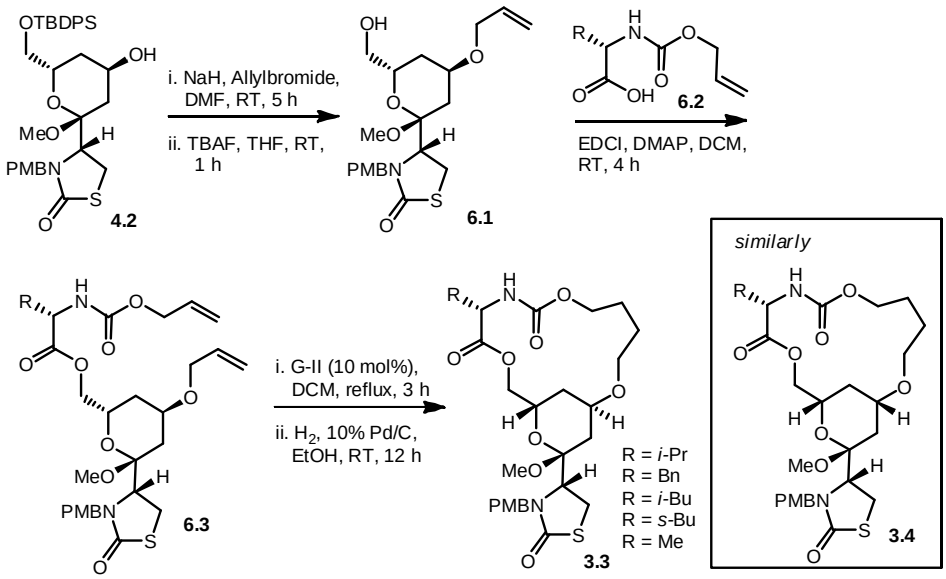


Scheme 4: Retrosynthetic analysis of latrunculin derived hybrid macrocycles



Scheme 5: Synthesis of key fragments **4.1** and **4.2**

Our plan is to develop a novel methodology to obtain a key pyran fragment of latrunculin A in sufficient scale quantity and to utilize this fragment in the generation of latrunculin derived hybrid macrocyclic library (**Scheme 3**). The retrosynthetic analysis of our designed latrunculin derived hybrid macrocycles is shown in **Scheme 4**. The aldol reaction between the fragment methyl ketone **4.4** and aldehyde **4.5,** which was obtained from *S*-malic acid in four steps, yielded two isomers (α and β) of pyran fragments **4.1** and **4.2** (**Scheme 5**). These two fragments were further utilized to the synthesis of hybrid macrocycles (**Scheme 6**). Currently, the biological evaluation of these compounds is ongoing in several research laboratories in a search of functional small molecules.



Scheme 6: Synthesis of latrunculin-derived, hybrid macrocycles, **3.3** and **3.4**

A few key references:

(1) Kashman, Y.; Groweiss, A.; Shmueli, U. *Tetrahedron Lett.* 1980, *21*, 3629–3632.

(2) Spector, I.; Shochet, N. R.; Kashman, Y.; Groweiss, A. *Science* 1983, *219*, 493–495.

(3) Coué, M.; Brenner, S. L.; Spector, I.; Korn, E. D. *FEBS Lett.* 1987, *213*, 316–318.

ABBREVIATIONS

Ac	:	acetyl
ACN	:	acetonitrile
Ac_2O	:	acetic anhydride
AcOH	:	acetic acid
aq.	:	aqueous
Ar	:	aryl
$BF_3 \cdot OEt_2$	:	borontrifluoride-etherate complex
$BH_3 \cdot DMS$	:	borane dimethylsulfide complex
BnBr	:	benzyl bromide
Boc	:	*t*-butoxycarbonyl
Boc_2O	:	di-*tert*-butyldicarbonate
Cbz	:	benzyloxy carbonyl
CSA	:	camphor sulphonic acid
DCM	:	dichloromethane
DIPEA or $_iPr_2NEt$	:	*N*, *N*'-diisopropylethylamine
DIBAL-H	:	diisobutyl aluminium hydride
DMS	:	dimethyl sulphide
DMSO	:	dimethyl sulfoxide
MeMgBr	:	methylmagnesium bromide
Et_3N	:	triethylamine
Et_2O	:	diethyl ether
EtOAc	:	ethyl acetate
EtOH	:	ethanol
Fmoc	:	fluornyloxy carbonyl chloride
G-II	:	grubb's 2nd generation catalyst
GI_{50}	:	growth inhibition of 50%
h	:	hour(s)
H_2O_2	:	hydrogen peroxide
HOBT	:	hydroxy benzotriazole
Hz	:	hertz
I_2	:	molecular iodine
IBX	:	iodoxybenzoic acid

IC_{50}	:	half maximal inhibitory concentration
IR	:	Infrared
KBr	:	potassium bromide
K_2CO_3	:	potassium carbonate
K*O*t*Bu*	:	potassium *tert*-butoxide
LAH or $LiAlH_4$	:	lithium aluminiumhydride
LiOH	:	lithium hydroxide
Me	:	methyl
MeOH	:	methanol
MOMCl	:	methoxymethylchloride
$NaBH_4$	:	sodium borohydride
NaH	:	sodium hydride
$NaHCO_3$	:	sodium bicarbonate
$NaIO_4$	:	sodium periodate
NaOH	:	sodium hydroxide
NH_4Cl	:	ammonium chloride
NMM	:	*N*-methyl morpholine
NMO	:	4-methyl morpholine-*N*-oxide
NMR	:	nuclear magnetic resonance
OsO_4	:	osmium tetraoxide
Ph	:	phenyl
PTSA or *p*-TsOH	:	*para*-toluenesulfonic acid
PPTS	:	pyridinium p-toluene sulfphonate
RT (or) rt	:	room temperature
TBAF	:	tetra-*n*-butylammonium fluoride
TBDMS	:	*tert*-butyldimethylsilyl
TBDPS	:	*tert*-butyldiphenylsilyl
TEA or Et_3N	:	triethylamine
TFA	:	trifuoroacetic acid
THF	:	tetrahydrofuran
$TiCl_4$	:	titanium tetrachloride
TPP	:	triphenylphosphine
TsCl	:	*para*-toluenesulfonyl chloride
UV	:	ultra violet

General Information

^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on Varian 400 MHz NMR spectrometer at the frequency indicated. Where indicated, the NMR peak assignments were made using COSY experiments. All chemical shifts are quoted on the δ-scale and were referenced to the residual solvent as an internal standard. Combinations of the following abbreviations are used to describe NMR spectra: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet. Mass spectra and LCMS were recorded using electron impact, chemical ionisation or electrospray ionisation techniques, on Agilent-6430 mass spectrometer. High-performance liquid chromatography was carried out on Agilent-1200 instrument using X-BRIDGE C-18 150×4.6mm 5µ column. Thin layer chromatography (TLC) was carried out on aluminium sheets coated with silica gel $60F_{254}$ (Merck, 1.05554) and the spots were visualized with UV light at 254 nm or alternatively by staining with aqueous basic potassium permanganate or ceric ammonium molybdate. Flash column chromatography was performed using silica gel (Merck, 60A, 230-400 Mesh). Commercially available reagents were used as supplied and some of them were distilled before use. All reactions were performed in oven dried glassware. DMF, DCM, MeOH and THF were dried immediately prior to use according to standard procedures: Dimethylformamide, Dichloromethane was distilled under N_2 from CaH_2, Methanol was distilled under N_2 over Mg and Tetrahydrofuran was distilled under N_2 over Na. All solvents were removed by evaporation under reduced pressure.

Chapter 1: Introduction to Importance of Macrocycles

1.1. Introduction:

In recent years, an interest in accessing macrocyclic architectures has grown significantly due to their role as the chemical modulators in a wide variety of protein-protein interaction-based signaling pathways.[1] Shown in Figure 1 are some selected examples of bioactive natural products having a large ring skeleton and their participation in several disease-related signaling pathways. Macrocyclic natural products have evolved to fulfil numerous biochemical functions, and, their profound pharmacological properties have led to their development as drugs.[2] A macrocycle provides diverse functionality and stereochemical complexity in a conformationally pre-organized ring structure. This can result in a high affinity and selectivity for protein targets, while preserving sufficient bioavailability to reach intracellular locations.[1a] Despite these valuable characteristics, and, the proven success of more than 100 marketed macrocycle drugs derived from natural products, this structural class has been poorly explored within drug discovery.[1a]

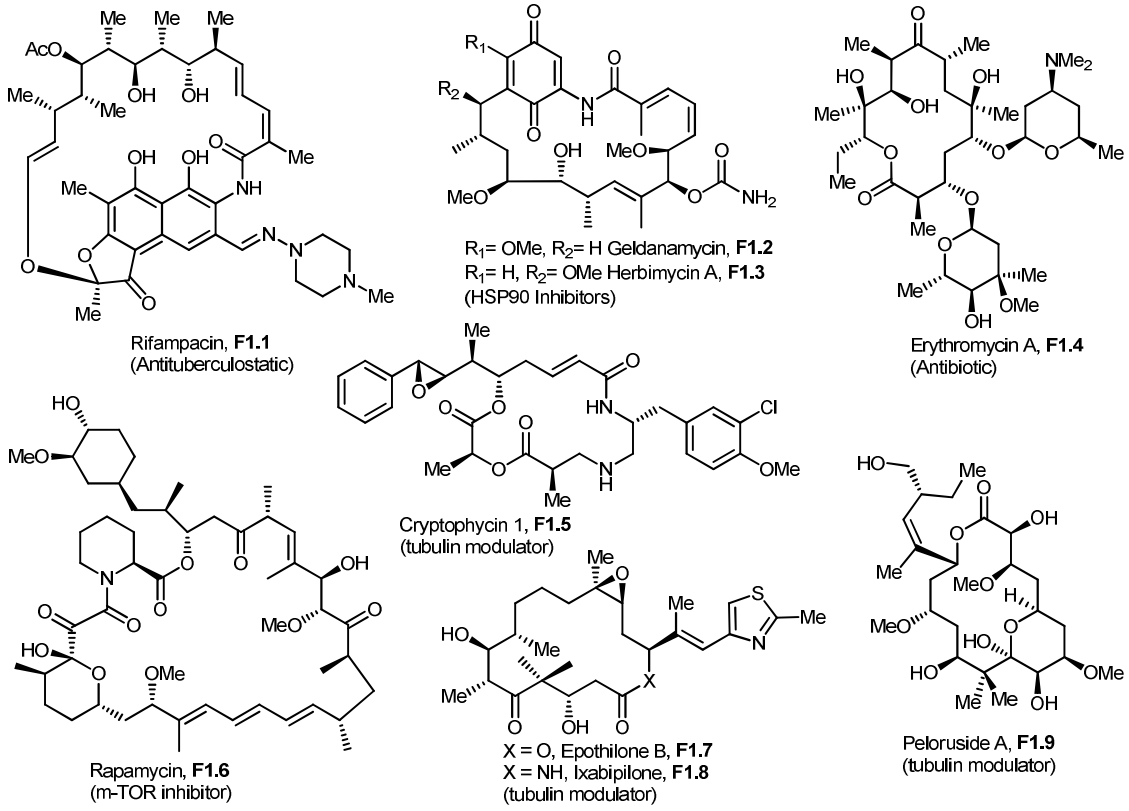


Figure 1: Examples of bioactive macrocyclic natural products

This is mainly due to our inability to develop efficient synthesis methods to access these compounds and their structural related analogues in a time efficient manner.[1a] Another reason is that these compounds also do not follow the classical Lipinski's rules[3] that are commonly and religiously applied in the traditional drug discovery arena. However, there are several research groups that are investigating the potential of synthetic macrocycles in drug discovery, and, have shown that such compounds can provide a high target affinity and selectivity in structures having acceptable drug-like properties. Several synthetic macrocycles, unrelated to natural products, are now under an active preclinical and clinical development.[1]

1.2. Key technologies:

Success in discovering, developing, and, marketing safe and efficacious pharmaceutical products has been characterized over the last three decades by a highly polarized focus in two major categories of drugs.[4] At one extreme, we have small molecules that represent a synergy of synthetic and medicinal chemistry, driven by an understanding of interactions of such molecules with receptors or enzymes. These compounds are usually readily synthesized and have characteristics bounded by the Lipinski 'Rule of 5' guidelines.[3] These molecules work by providing sufficient functionality in a concise package to bind to lipophilic pockets and polar functionality in small, concise binding sites, such as those found in an enzyme active site. In many cases, they replicate the interaction of the target protein molecule with its endogenous ligand or substrate. However, there is a growing realization that such targets represent only a fraction of all disease relevant drug opportunities, and, that to find novel drugs for important medical needs, it is necessary for the scientist community to discover molecules to disrupt Protein–Protein Interactions (PPIs).[4a,5] These recognition events between proteins depend on many weak binding interactions spread over an extended surface area often exceeding 700Å^2.[6] It has become apparent that 'Rule of 5' compliant molecules are generally unable to make sufficient interactions to disrupt PPIs. The pharmaceutical industry has responded to this challenge by developing biological drugs, frequently, derived from proteins or peptides to gain a sufficient potency by interacting over a large surface area. Antibodies or soluble receptors constitute a large part of this drug space, but increasingly, there are several new semi-synthetic biological molecules such as,

AdnectinsTM, avimers, and aptamers, discovered and manufactured by biochemical means.[4b] While providing high levels of potency, exquisite selectivity, and in many cases, long half-lives *in vivo*, molecule size significantly restricts membrane permeability. Thus, there remains a need for compounds that on one hand possessing sufficient size and functionality to interact with protein surfaces, and, yet still maintain small molecule-like properties such as cell penetration and oral bioavailability.[4b] Amongst the range of pharmacologically active compounds, macrocycles offer the potential to sit in the 'middle space' between small molecules and biologicals, and, furthermore, are precedented by natural products.[4b] (see, Figure 2)

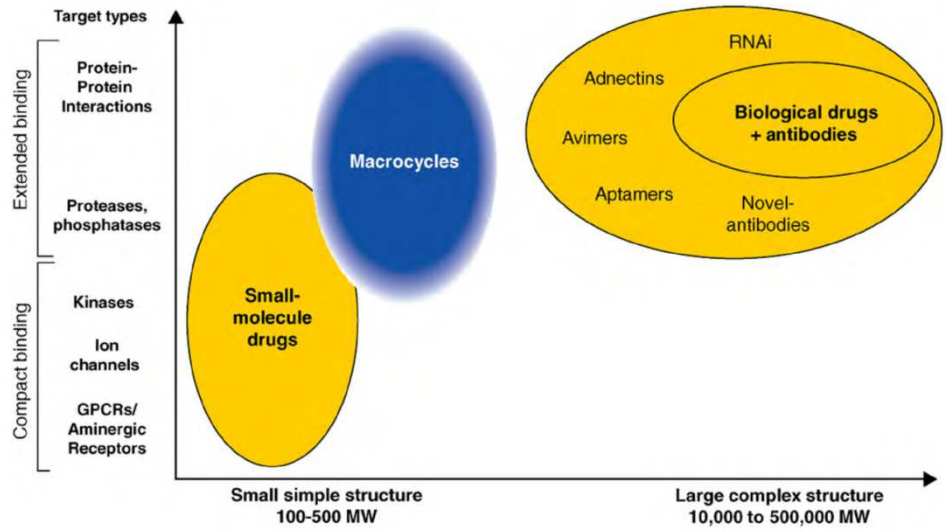


Figure 2:

In this chapter, I am going to discuss some success stories of macrocyclic natural products as well as the synthetic macrocycles.

1.3. Macrocyclic Natural Products:

In this section, I am going to discuss about two case studies of natural products, cryptophycins and geldanamycins.

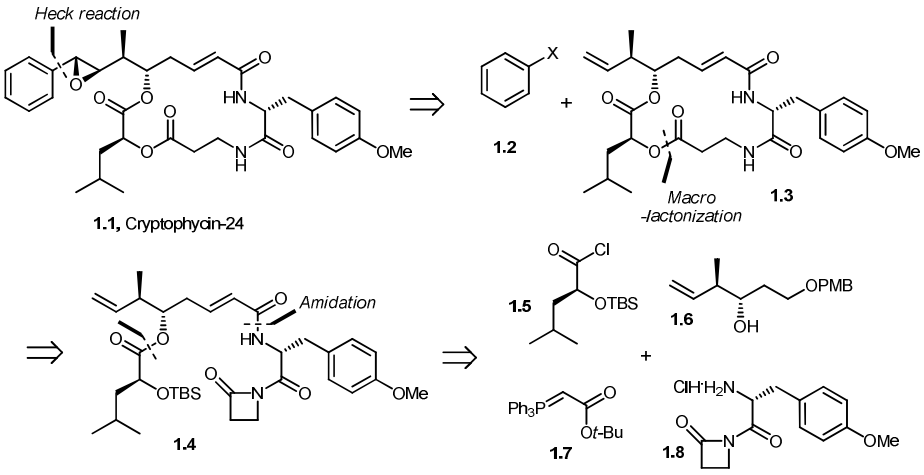
1.3.1. Cryptophycins:

Cryptophycins (**F1.5,** Figure 1) are isolated from the terrestrial *cyanobacterium*, a *Nostoc species*,[7] shows strong destabilizing properties by blocking the hydrolysis of

GTP.[8] They are not the substrate of P-glycoprotein (Pgp) that favors the specific antitumor activity against multiple cancers.[9] At lower concentrations, cryptophycins are shown to interrupt the microtubule dynamic instability. They have two forms of binding sites, a high affinity binding site, and, a few low-affinity binding sites[10] It interferes with the vinblastine-binding site on tubulin in a non-competitive manner.[11] There are many groups who successfully achieved the total synthesis of cryptophycins.[12] Herein, we outline the efforts by the Georg team at the University of Kansas to develop the synthesis of cryptophycins.[13]

Retrosynthesis:

As shown in the retrosynthesis plan, the researchers achieved the crytophycin macrolactone core by a novel macrolactonization approach that utilizes a reactive acyl-β-lactam intermediate (**1.4**) which incorporates the β-amino acid moiety (Scheme 1).[13]

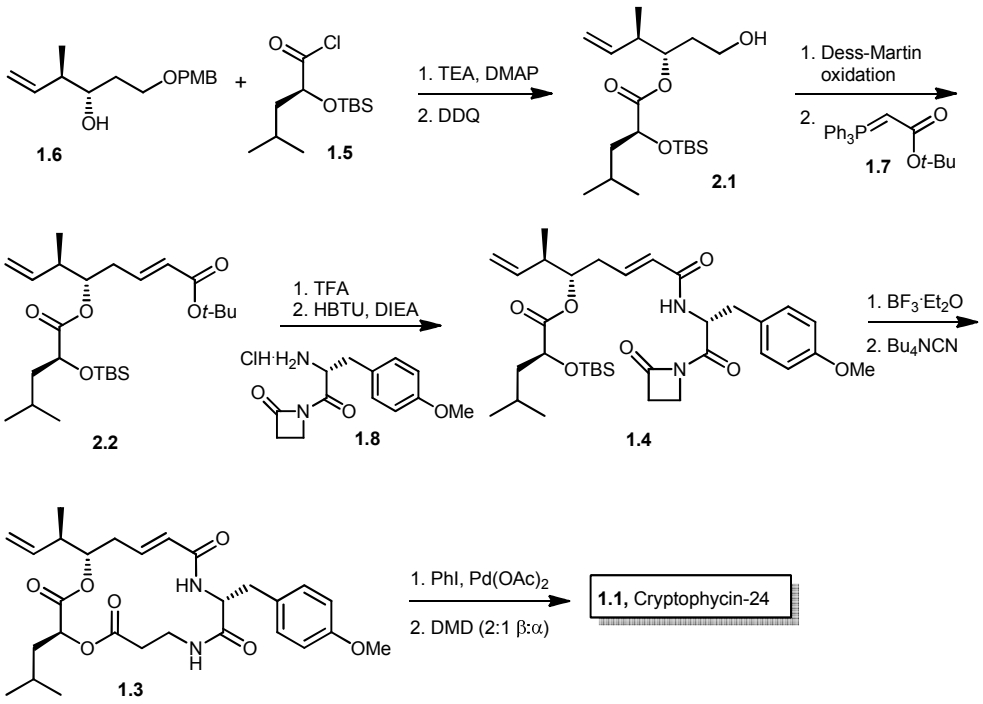


Scheme 1: The retrosynthetic analysis of cryptophycin-24

Synthesis:

The total synthesis of cryptophycin is shown in Scheme 2.[13] The alcohol **1.6** was coupled with the acid chloride **1.5** followed by the PMB removal to obtain an ester **2.1**. Oxidation of primary alcohol of ester **2.1** to aldehyde using Dess-Martin conditions followed by Wittig olefination with **1.7** resulted in compound **2.2**. The *ter*-butyl ester **2.2** was hydrolyzed using TFA condition then coupled with the acyl-β-lactam containing amino compound **1.8** to yield the macrocyclic precursor **1.4**. The TBS group in compound **1.4** was removed with $BF_3 \cdot Et_2O$ followed by

macrolactonization using Bu_4NCN resulted in the macrocyclic compound **1.3**. The Heck reaction with iodo benzene followed by the epoxidation yielded the required cryptophycin as a 2:1 (β:α) epoxide mixture.[13]



Scheme 2: Total synthesis of cryptophycin-24

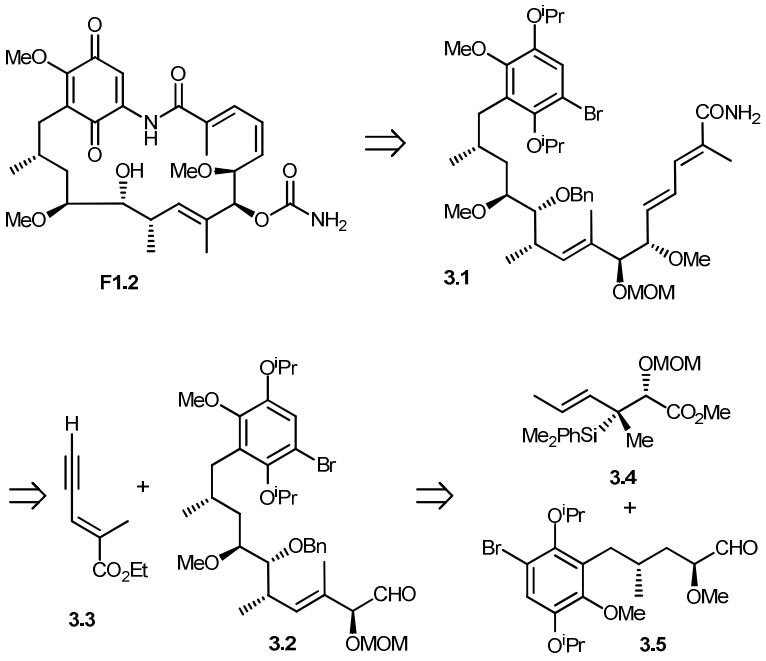
1.3.2. Geldanamycin:

Benzoquinoid anasamycins, such as geldanamycin (**F1.2**) and herbimycin A (**F1.3**), are two antibiotics that exhibit the anti-tumor effects**.** Geldanamycin was isolated by workers at Upjohn from *Streptomyces hygroscopicus* var. *geldanus* var. *nova* in 1970.[14] Studies have also shown that the Hsp90 client proteins can be destabilized when geldanamycin binds to the ATP-binding site of Hsp90, and, it inhibits the chaperone activity of the protein. Geldanamycin competitively binds to the N-terminal ATP binding site of HSP90 and this then prevents the ATP binding and disrupts the ATP-dependent conformational cyclization.[15]

The total synthesis of geldanamycin was carried-out, initially, by Andrus and co-workers,[16] and, later, by other researchers.[17] Recently, Panek team reported an enantioselective synthesis that was achieved in 20 linear steps, with an overall 2% yield.

Retrosynthesis:

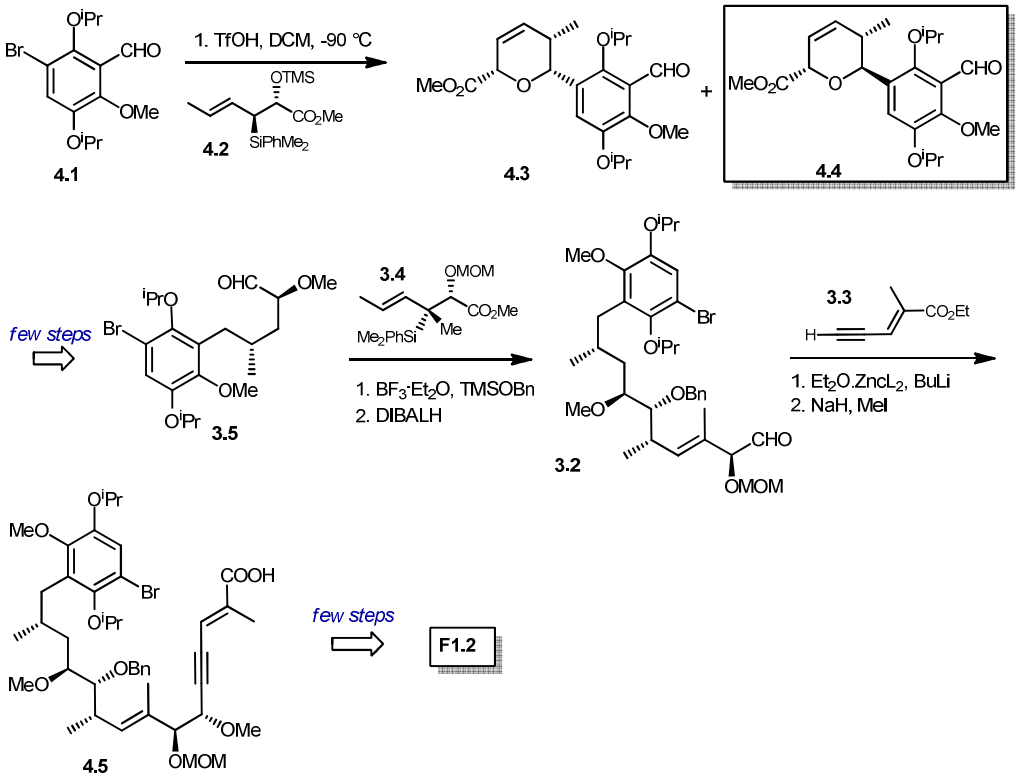
The synthesis of 19-membered macrocycle was achieved from an acylic amide **3.1** (Scheme 3) through an intramolecular aryl amidation reaction. The (*E*,*Z*)-diene was installed by the reduction of an enyne from alkynylation of precursors **3.2** and **3.3.** These were generated from easily accessible aldehyde **3.5** and a chiral silane reagent **3.4**. Organosilane **3.4** has unique features as it establishes the C10-C11 *syn* stereochemistry while simultaneously creating the C8 -C9 (*E*)-trisubstituted olefin.



Scheme 3: Retrosynthetic analysis of geldanamycin (**F1.2**)

Synthesis:

The synthesis is also highlighted by (i) a regio- and stereo-selective hydroboration reaction and a $Sc(OTf)_3/Et_3SiH$-mediated pyran ring-opening approach, (ii) an enantioselective crotylation to simultaneously install the C8–C9 (*E*)- trisubstituted olefin and the C10 and C11 stereocenters, and, (iii) a chelation controlled asymmetric metallated acetylide addition followed by an intramolecular copper (I)-mediated aryl amidation reaction to obtain the 19-membered macrolactam (Scheme 4).[17]



Scheme 4: Total synthesis of geldanamycin (**F1.2**)

1.4. Synthetic Macrocycles:

There are several success stories for the synthetic macrocyclic modulators of protein-protein interactions, and, in this section, we are going to discuss macrocyclic inhibitors of IRAP and anti-malarial macrocyclic compounds.

1.4.1. Macrocyclic Inhibitors of Insulin Regulated Amino Peptidase:

Angiotensin IV (**F3.1**),[18] a hexapeptide was proved to play an important role in improving memory and learning, and this was demonstrated by a large number of animal studies over the past two decades.[19] Ang IV binds with high affinity to insulin-regulated amino peptidase (IRAP), an enzyme localized in areas of brain, associated with memory and learning.[20] In recent years, IRAP evolved as a new drug target for the treatment of memory dysfunction.[21] There are many groups who are working on SAR studies on the Ang IV to make it more efficient by designing their stable peptides.[22]

The Design of Macrocyclic Inhibitors of IRAP:

Hallberg and co-workers conducted the SAR studies on Ang IV, and, reported that macrocyclization (11 and 13 membered rings) using disulfide bond followed by structural optimization leads to the macrocycle **F3.2** having K_i value 5.1 nM.[21,23] The disulfide is chemically and metabolically labile, and, due to these reasons, it was replaced by carbon-carbon bonds, which can be easily synthesized using ring closing metathesis. This strategy resulted in the macrocycles **F3.3** (K_i = 4.1 nM) and **F3.4.**[24]

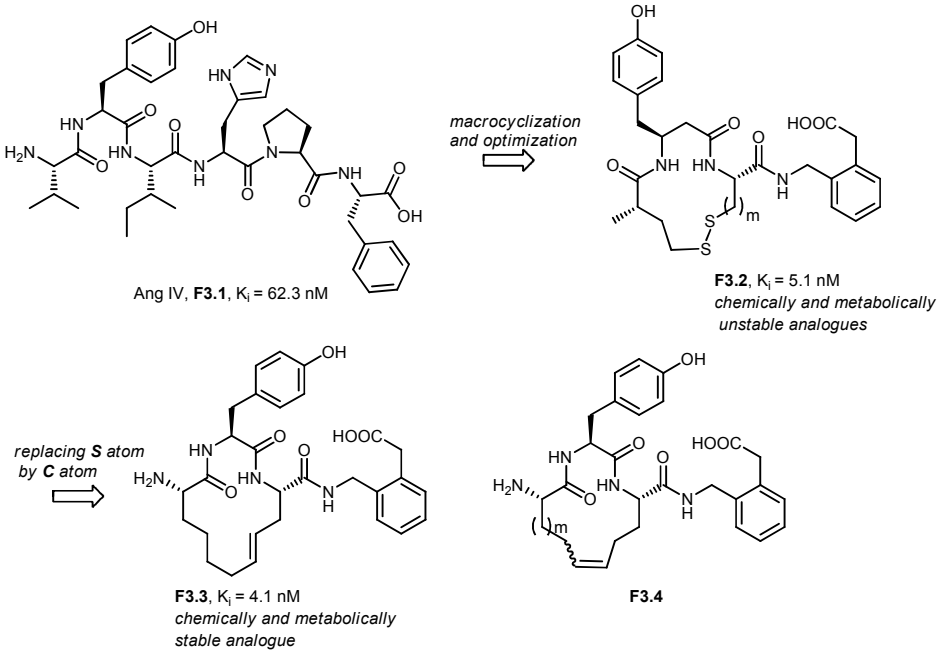
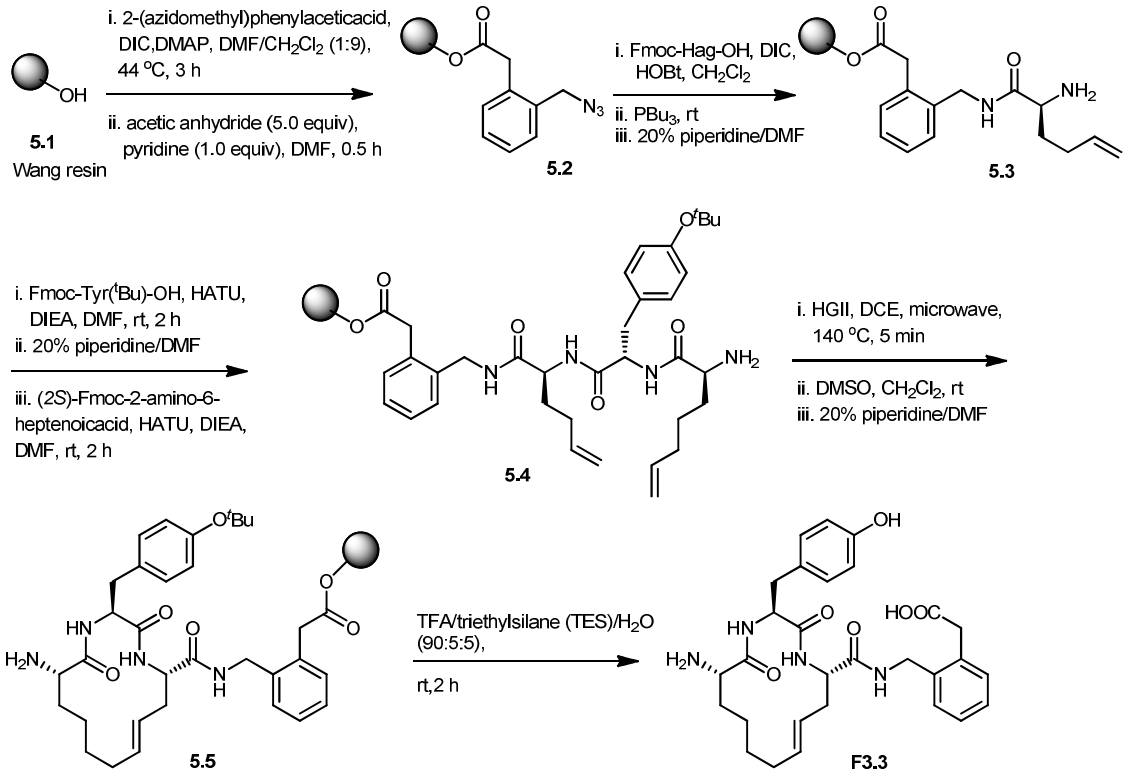


Figure 3: The design of macrocyclic inhibitors of IRAP

Synthesis:

The synthetic strategy for the macrocycle **F3.3** using Wang resin is shown in Scheme 5. The phenyl acetic acid derivative was coupled to the Wang resin (**5.1**) to give compound **5.2** which was then subsequent coupled with an activated Fmoc protected homoallyl glycine (Hag) using DIC and HOBt in the presence of tributyl phosphine. This was then followed by removal of Fmoc protecting group with piperidine to obtain the primary amine **5.3**. The remaining two amino acid couplings were carried-out in a similar manner to obtain a bisallyl compound **5.4**. This was subjected to ring closing metathesis using Hoyeda-Grubbs' II generation catalyst at 140 $^{\circ}$C, and, this yielded the macrocyclic product as well as the migration of the double bond. Following the cleavage of the resin with TFA/TES condition, gave the macrocycle **F3.3.**[24]



Scheme 5: Synthesis of macrocycle **F3.3**

1.4.2. Anti-Malarial Macrocyclic Compounds:

Diversity-oriented synthesis (DOS) enables chemists to synthesize a library of small molecules having diverse stereochemistries and skeletons.[5b,25] Heidebrecht et. al., screened 8000 membered Broad Institute of Harvard and MIT small molecule library that was generated using a DOS approach, and, this was then tested in growth inhibition assay[26] (72 h, DAPI) with multidrug resistant Dd2 *P. falciparum* parasites at 5 μM concentration. This study resulted in the 590 small molecule having greater than 90% inhibition.[27] Further, experiments at four different concentrations yielded 26 compounds having greater than 50% inhibition at 280 nM.[27] Out of these 26 compounds, 20 compounds were derived from the ring closing metathesis and identified that compound **F4.1** (Figure 4) was the most active compound from this library.[27]

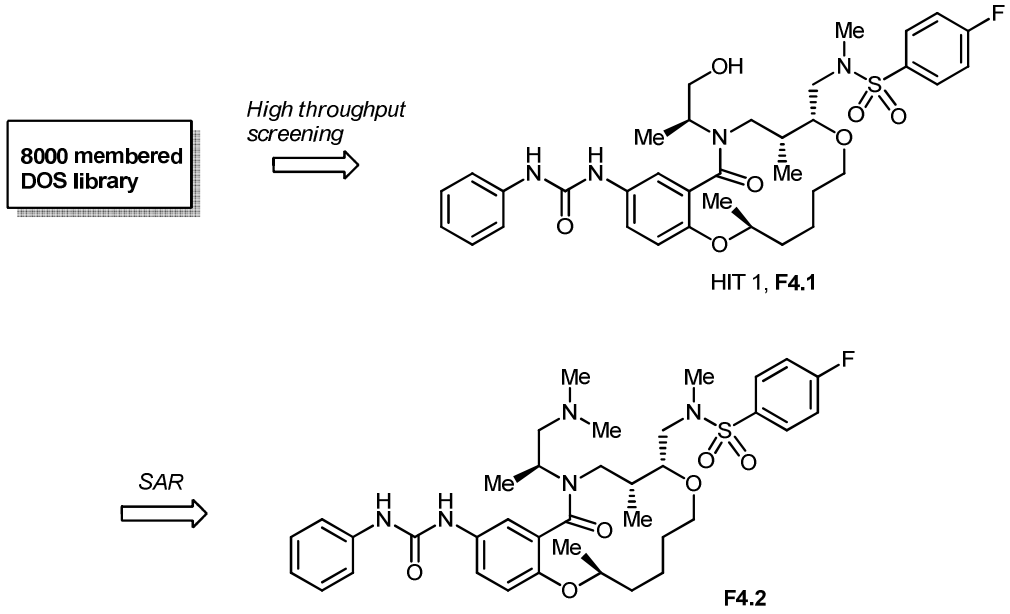


Figure 4:

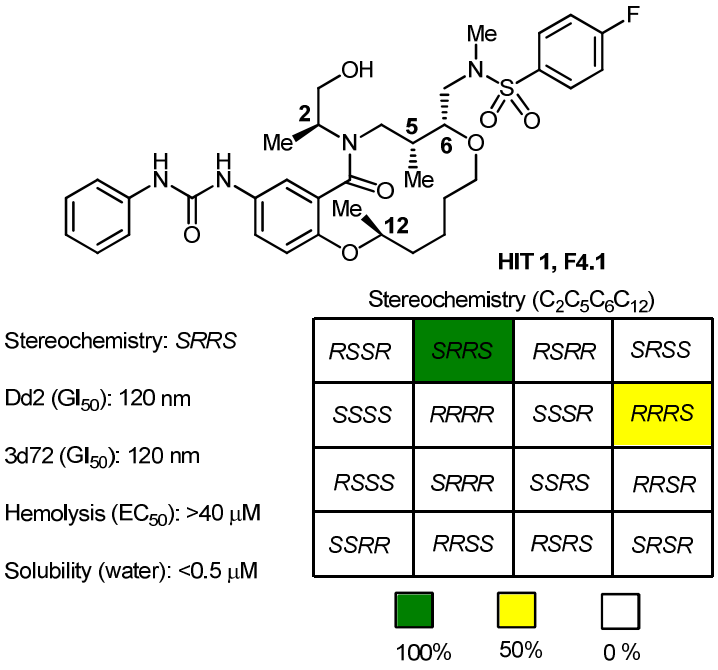


Figure 5: Stereochemical SAR studies on HIT 1

Stereochemical SAR Studies:

The most active hit (compound **F4.1**, Figure 5) was independently synthesized and iteratively titrated in a 12-point assay to confirm the potency (GI_{50}) of 120 nM against Dd2 intraerythrocytic parasites. This lead has a similar potency in a drug-sensitive 3d7 parasite strain and does not cause hemolysis of erythrocytes at upto 40 μM concentration; unfortunately, it is largely insoluble in aqueous solution (<0.5 μM

in water). Stereochemical SAR studies was conducted on the all possible 16 stereo-isomers of hit 1(**F4.1**), resulted in the interesting biological activity observation. The activity is predominantly located in two stereoisomeric compounds that are epimeric outside the macrocyclic ring (C2, Figure 5).

The stereochemical SAR studies revealed that the stereochemistry at C2, C5, C6 and C12 are important for the activity. Now, there are three diverse sites in the hit **F4.1**, as shown in Figure 6. The replacement of urea phenyl ring at R_3 resulted in the decreased activity. Replacing *p*-fluoro sulphonyl group at R_2 with any other substituent diminished the activity of hit compound. The hydroxyl group at third diversity site by dimethyl amine group increased the potency as well as the solubility of the compound. This resulted in the most active and potent compound **F4.2**.

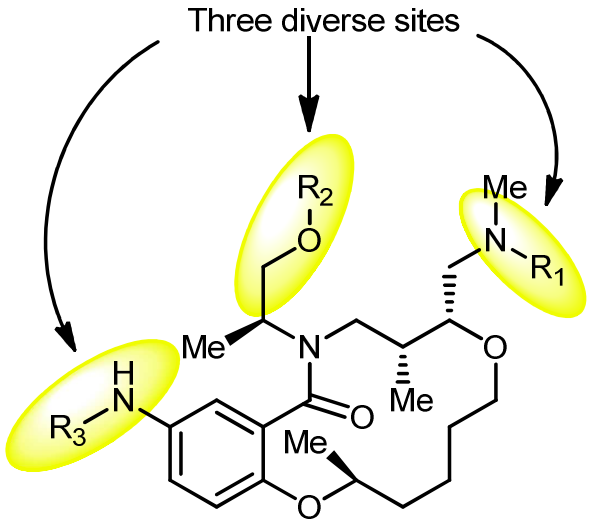
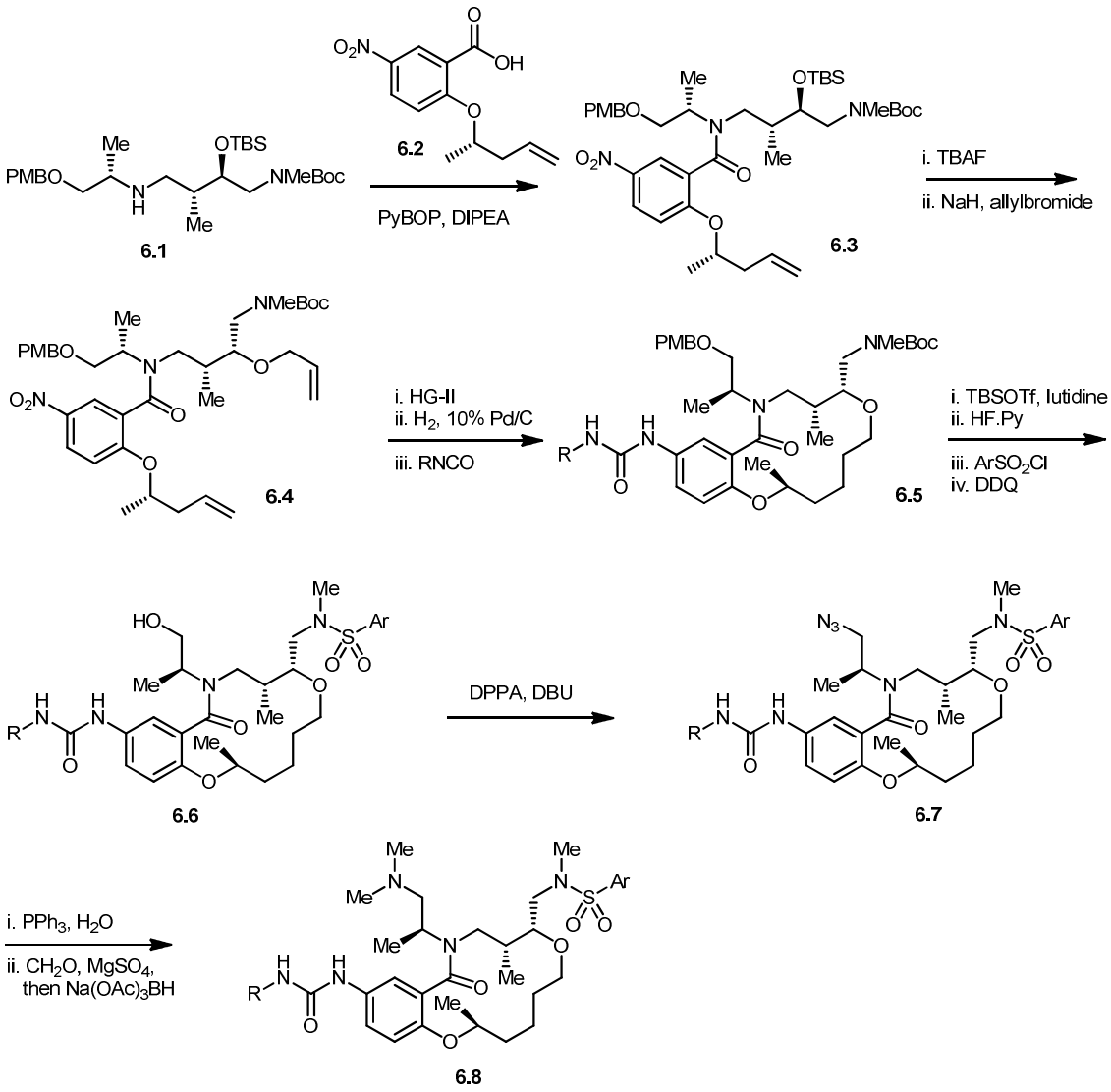


Figure 6: Diversity sites in the compound **F4.1**

Synthesis of Macrocyclic Library:

The synthesis of RCM library of compounds using DOS approach is shown in Scheme 6.[28] Secondary amine **6.1** was coupled with the benzoic acid derivative **6.2** using PyBOP coupling reagent to give an ester **6.3**. Removal of TBS group with TBAF followed by the allylation of secondary hydroxyl group with NaH and allyl bromide gave the bis-allyl product **6.4**. This compound was subjected to ring closing metathesis using Hoyeda-Grubbs second generation catalyst, followed by the reduction of the olefin with 10%Pd/C and further reaction with isocyanate gave the macrocycle **6.5**. The Boc protecting group was removed using TBSOTf then HF·Py

condition, then treating with aromatic sulphonyl chloride followed by removal of PMB group with DDQ reagent yielded the compound **6.6**. Primary alcohol was converted to azide using Mitsunobu conditions to give azide **6.7**. Reduction of azide to primary amine using Staudinger reaction followed by imino reduction with formaldehyde under $Na(OAc)_3BH$ condition gave the active macrocyclic compounds **6.8**.[28]



Scheme 6: Synthesis of macrocyclic library

1.5. References:

(1) (a) Driggers, E. M.; Hale, S. P.; Lee, J.; Terrett, N. K. *Nat. Rev.* **2008**, *7*, 608. (b) Marsault, E.; Peterson, M. L. *J. Med. Chem.* **2011**, *54*, 1961. (c) Dockendorff, C.; Nagiec, M. M.; Weiwer, M.; Buhrlage, S.; Ting, A.; Nag, P. P.; Germain, A.;

Kim, H. J.; Youngsaye, W.; Scherer, C.; Bennion, M.; Xue, L.; Stanton, B. Z.; Lewis, T. A.; Macpherson, L.; Palmer, M.; Foley, M. A.; Perez, J. R.; Schreiber, S. L. *ACS Med. Chem. Lett.* **2012**, *3*, 808.

(2) (a) Nicolaou, K.; Roschangar, F.; Vourloumis, D. *Angew. Chem. Int. Ed.* **1998**, *37*, 2014. (b) Schreiber, S. L. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 6699.

(3) (a) Lipinski, C. A. *Drug Discov. Today: Technologies* **2004**, *1*, 337. (b) Lipinski, C. A.; Lombardo, F.; Dominy, B. W.; Feeney, P. J. *Adv. Drug Deliver. Rev.* **2001**, *46*, 3.

(4) (a) Mallinson, J.; Collins, I. *Future Med. Chem.* **2012**, *4*, 1409. (b) Terrett, N. K. *Drug Discov. Today: Technologies* **2010**, *7*, e97.

(5) (a) Wells, J. A.; McClendon, C. L. *Nature* **2007**, *450*, 1001. (b) Schreiber, S. L. *Science* **2000**, *287*, 1964.

(6) Robinson, J. A. *ChemBioChem* **2009**, *10*, 971.

(7) Hamel, E. *Med. Res. Rev.* **1996**, *16*, 207.

(8) Smith, C. D.; Zhang, X. *J. Biol. Chem.* **1996**, *271*, 6192.

(9) Smith, C. D.; Zhang, X.; Mooberry, S. L.; Patterson, G. M.; Moore, R. E. *Cancer Res.* **1994**, *54*, 3779.

(10) (a) Panda, D.; Singh, J. P.; Wilson, L. *J. Biol. Chem.* **1997**, *272*, 7681. (b) Panda, D.; DeLuca, K.; Williams, D.; Jordan, M. A.; Wilson, L. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 9313.

(11) (a) Bai, R.; Schwartz, R. E.; Kepler, J. A.; Pettit, G. R.; Hamel, E. *Cancer research* **1996**, *56*, 4398. (b) Gupta, S.; Bhattacharyya, B. *Mol. Cell. Biochem.* **2003**, *253*, 41.

(12) (a) Barrow, R. A.; Hemscheidt, T.; Liang, J.; Paik, S.; Moore, R. E.; Tius, M. A. *J. Am. Chem. Soc.* **1995**, *117*, 2479. (b) Golakoti, T.; Ogino, J.; Heltzel, C. E.; Le Husebo, T.; Jensen, C. M.; Larsen, L. K.; Patterson, G. M. L.; Moore, R. E.; Mooberry, S. L. *J. Am. Chem. Soc.* **1995**, *117*, 12030. (c) White, J. D.; Hong, J.; Robarge, L. A. *J. Org. Chem.* **1999**, *64*, 6206. (d) McCubbin, J. A.; Maddess, M. L.; Lautens, M. *Org. Lett.* **2006**, *8*, 2993.

(13) (a) Eggen, M. J.; Nair, S. K.; Georg, G. I. *Org. Lett.* **2001**, *3*, 1813. (b) Buck, S. B.; Huff, J. K.; Himes, R. H.; Georg, G. I. *J. Med. Chem.* **2004**, *47*, 3697.

(14) (a) DeBoer, C.; Meulman, P. A.; Wnuk, R. J.; Peterson, D. H. *J. Antibiot.* **1970**, *23*, 442. (b) Sasaki, K.; Rinehart, K. L., Jr.; Slomp, G.; Grostic, M. F.; Olson, E. C. *J. Am. Chem. Soc.* **1970**, *92*, 7591.

(15) (a) Prodromou, C.; Roe, S. M.; Piper, P. W.; Pearl, L. H. *Nat. Struct. Biol.* **1997**, *4*, 477. (b) Stebbins, C. E.; Russo, A. A.; Schneider, C.; Rosen, N.; Hartl, F. U.; Pavletich, N. P. *Cell* **1997**, *89*, 239.

(16) Andrus, M. B.; Meredith, E. L.; Hicken, E. J.; Simmons, B. L.; Glancey, R. R.; Ma, W. *J. Org. Chem.* **2003**, *68*, 8162.

(17) Qin, H. L.; Panek, J. S. *Org. Lett.* **2008**, *10*, 2477.

(18) (a) Albiston, A. L.; McDowall, S. G.; Matsacos, D.; Sim, P.; Clune, E.; Mustafa, T.; Lee, J.; Mendelsohn, F. A.; Simpson, R. J.; Connolly, L. M. *J. Biol. Chem.* **2001**, *276*, 48623. (b) Braszko, J.; Kupryszewski, G.; Witczuk, B.; Wiśniewski, K. *Neuroscience* **1988**, *27*, 777. (c) Braszko, J. J. *Eur. Neuropsychopharm.* **2009**, *19*, 85. (d) Braszko, J. J.; Własienko, J.; Koziołkiewicz, W.; Janecka, A.; Wiśniewski, K. *Brain Res.* **1991**, *542*, 49.

(19) Wright, J. W.; Harding, J. W. *Drug Develop. Res.* **2009**, *70*, 472.

(20) (a) Moeller, I.; Paxinos, G.; Mendelsohn, F. A.; Aldred, G. P.; Casley, D.; Chai, S. Y. *Brain Res.* **1996**, *712*, 307. (b) Chai, S. Y.; Bastias, M. A.; Clune, E. F.; Matsacos, D. J.; Mustafa, T.; Lee, J. H.; McDowall, S. G.; Mendelsohn, F. A.; Albiston, A. L.; Paxinos, G. *J. Chem. Neuroanat.* **2000**, *20*, 339. (c) Fernando, R. N.; Larm, J.; Albiston, A. L.; Chai, S. Y. *J. Comp. Neurol.* **2005**, *487*, 372.

(21) Andersson, H.; Demaegdt, H.; Vauquelin, G.; Lindeberg, G.; Karlén, A.; Hallberg, M. *Bioorg. Med. Chem.* **2008**, *16*, 6924.

(22) (a) Krishnan, R.; Hanesworth, J. M.; Wright, J. W.; Harding, J. W. *Peptides* **1999**, *20*, 915. (b) Sardinia, M.; Hanesworth, J.; Krebs, L.; Harding, J. *Peptides* **1993**, *14*, 949. (c) Sardinia, M.; Hanesworth, J.; Krishnan, F.; Harding, J. *Peptides* **1994**, *15*, 1399.

(23) (a) Andersson, H.; Demaegdt, H.; Vauquelin, G.; Lindeberg, G.; Karlén, A.; Hallberg, M.; Erdélyi, M.; Hallberg, A. *J. Med. Chem.* **2010**, *53*, 8059. (b) Axén, A.; Andersson, H.; Lindeberg, G.; Rönnholm, H.; Kortesmaa, J.; Demaegdt, H.; Vauquelin, G.; Karlén, A.; Hallberg, M. *J. Pept. Sci.* **2007**, *13*, 434. (c) Axén, A.; Lindeberg, G.; Demaegdt, H.; Vauquelin, G.; Karlén, A.; Hallberg, M. *J. Pept. Sci.* **2006**, *12*, 705.

(24) Andersson, H.; Demaegdt, H.; Johnsson, A.; Vauquelin, G.; Lindeberg, G.; Hallberg, M.; Erdélyi, M.; Karlén, A.; Hallberg, A. *J. Med. Chem.* **2011**, *54*, 3779.

(25) (a) Burke, M. D.; Schreiber, S. L. *Angew. Chem. Int. Ed.* **2004**, *43*, 46. (b) Nielsen, T. E.; Schreiber, S. L. *Angew. Chem. Int. Ed.* **2008**, *47*, 48.

(26) Baniecki, M. L.; Wirth, D. F.; Clardy, J. *Antimicrob. Agents Ch.* **2007**, *51*, 716.

(27) Heidebrecht Jr, R. W.; Mulrooney, C.; Austin, C. P.; Barker Jr, R. H.; Beaudoin, J. A.; Cheng, K. C.-C.; Comer, E.; Dandapani, S.; Dick, J.; Duvall, J. R. *ACS Med. Chem. Lett.* **2011**, *3*, 112.

(28) Marcaurelle, L. A.; Comer, E.; Dandapani, S.; Duvall, J. R.; Gerard, B.; Kesavan, S.; Lee IV, M. D.; Liu, H.; Lowe, J. T.; Marie, J.-C. *J. Am. Chem. Soc.* **2010**, *132*, 16962.

Chapter 2: Synthesis of Natural Product-Inspired, 14-Membered Ring Derived Macrocyclic Toolbox

2.1. Introduction:

The need to assemble a small molecule toolbox with compounds that are more natural-product-like, to search for modulators of protein-protein interactions[1] and the dissectors of pathways[2] has grown in recent years. In particular, interest in the macrocyclic natural products is rising because they provide the diverse functionality and stereochemical complexity in a conformationally pre-organized ring structure.[3] These features might be useful for a high affinity and selectivity for protein targets, while preserving sufficient bioavailability to approach intracellular targets. Despite these valuable characteristics and the proven success of several marketed macrocycle drugs derived from natural products, this structural class has been poorly explored within drug discovery.[1b] Certainly, this testifies the need to develop practical and modular synthesis methods that allow us building a small molecule toolbox with a diverse set of macrocyclic compounds to explore their biological functions.[4]

2.2. Working Hypothesis:

With this objective, we were interested in developing a modular synthesis method to access different types of 14-membered ring macrocyclic compounds because there are several examples of the presence of this ring in a wide variety of bioactive natural products, such as, radicicol (**F1.1**),[5] pochonin (**F1.2**),[6] hypothemycin (**F1.3**),[7] aigialomycin (**F1.4**) and other related compounds (Figure 1).

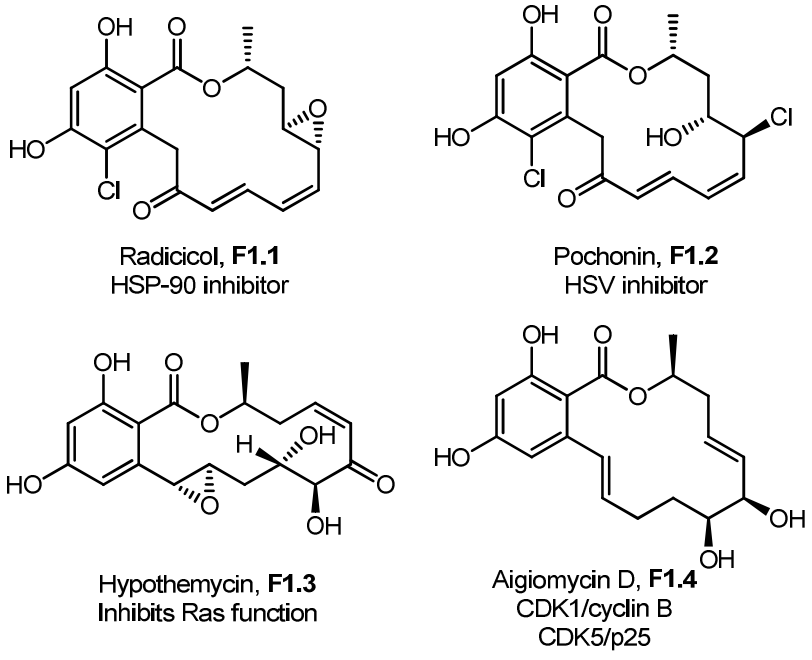
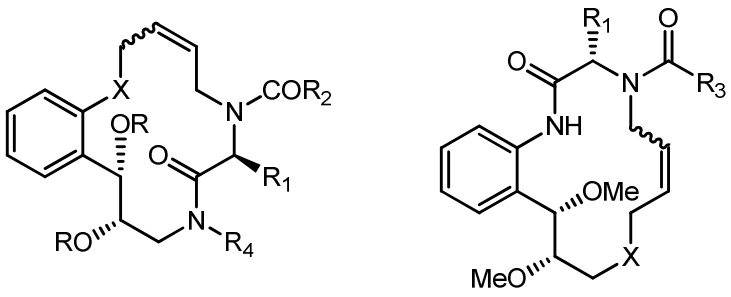


Figure 1: Examples of 14-membered macrocyclic natural products

Our designed 14-membered macrocycles (**F2.1**-**F2.4**) are shown in Figure 2. In our approach, we were interested in developing a method that is simple, practical in nature, and, in our design strategy, we can introduce the skeletal diversity and modulate various functional groups, i.e. through D- or L- amino acids and Sharpless chemistry.[8] The proposed natural product-inspired compounds are more close to bioactive natural products in terms of 3D shapes and the dense display of chiral functional groups. One of the major advantages is that they are easy to explore the stereochemical and skeletal diversity, the chemical space around the scaffold, and, are easy to synthesize on a gram scale in a reasonable time period.[4c,4i,9]



X = $NCOR_3$ **(F2.1)**
X = O **(F2.2)**

X = $NCOR_3$ **(F2.3)**
X = O **(F2.4)**

Figure 2: 14-Membered ring derived macrocycles

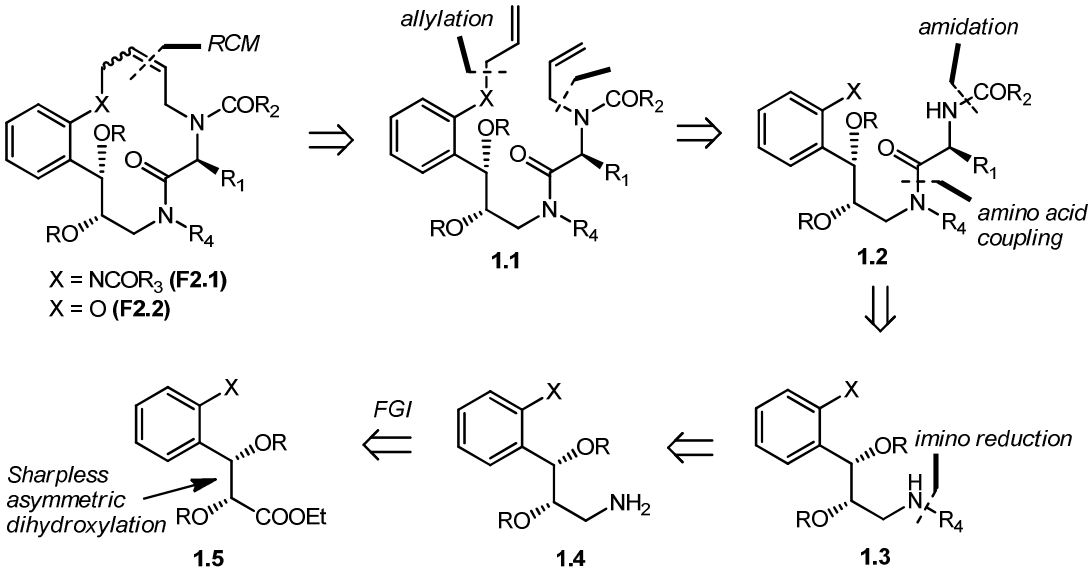
In our modular design strategy, we had the option to bring the amino acid functionality either through the aromatic amine or from the aliphatic side chain (see, macrocyclic targets, **F2.1**-**2.4**). Further, variation in the side chain, i.e. R_2-R_4 on the macrocyclic skeleton can also be acheived through selective alkylation and amidation, respectively.

2.3. Results and Discussion:

2.3.1. Retrosynthesis of Macrocycles F2.1&F2.2:

The retrosynthetic analysis of macrocycles **F2.1**&**F2.2** is shown in Scheme 1. Macrocyclization would be done by ring closing metathesis (RCM) of bis-allylated compound **1.1**, which could be obtained from bis-allylation of amide **1.2** with allyl bromide. Compound **1.2** could be obtained from coupling of amino acid building blocks with secondary amine **1.3**, which then would be obtained from imino-reduction of primary amine **1.4** with isobutaraldehyde. Primary amine **1.4** could be

derived from enantiopure dihydroxyl derivative **1.5**, which could be obtained from Sharpless asymmetric dihydroxylation of the corresponding cinnamate derivative.

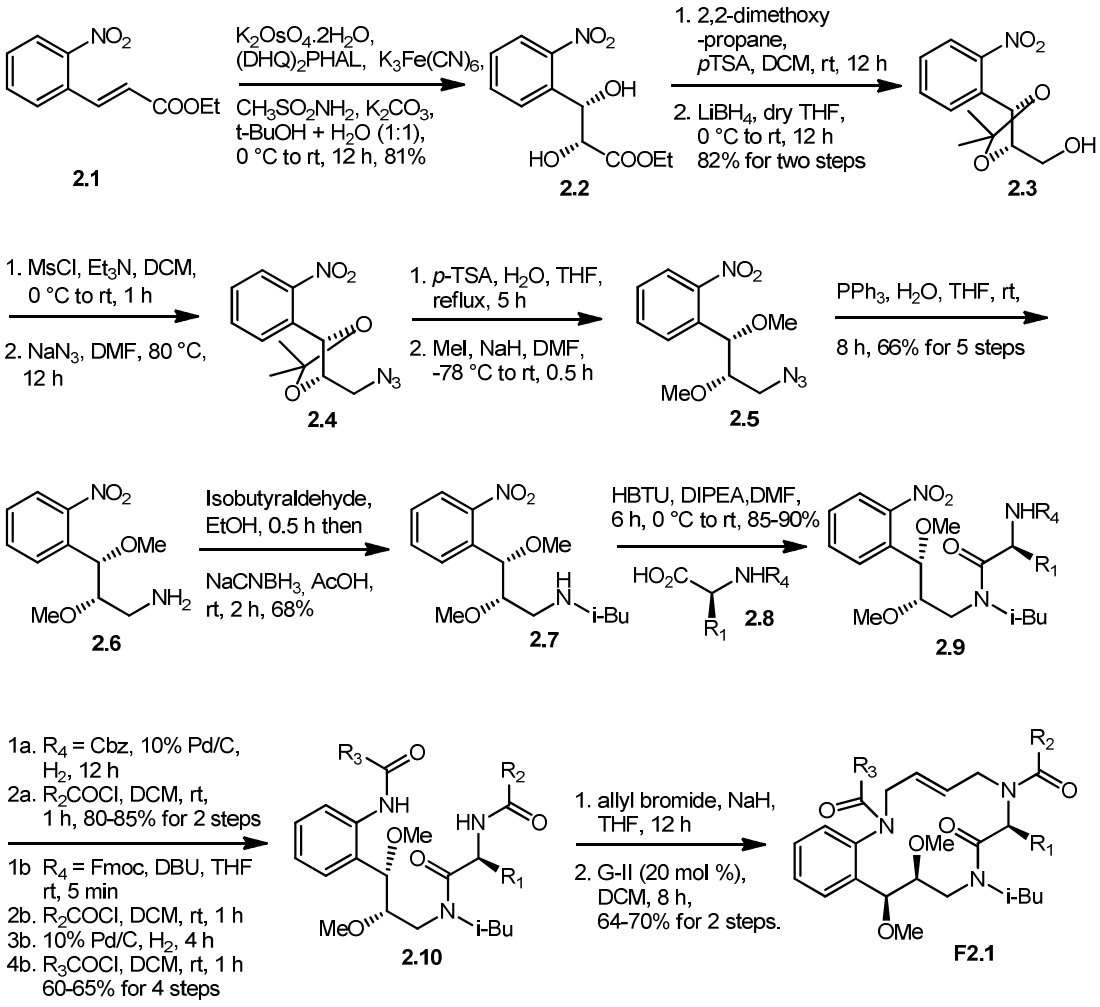


Scheme 1: Retrosynthesis of macrocycles **F2.1** & **F2.2**

2.3.2. Synthesis of Macrocycle F2.1:

As shown in Scheme 2, 2-nitrocinnnamate **2.1** was subjected to a Sharpless asymmetric dihydroxylation reaction, giving an enantiopure dihydroxyl derivative **2.2**. Following the acetonide protection of the diol, the carboxylester was then reduced with lithium borohydride to give primary alcohol **2.3**. Primary amine **2.6** was then obtained from **2.3** in four steps, (i) the conversion of alcohol to azide **2.4** by mesylation with methane sulfonyl chloride then treating with sodium azide, (ii) the deprotection of acetonide, (iii) 1,2-diol methylation with methyl iodide to give compound **2.5**, and finally, (iv) the reduction of azide by Staudinger reaction. The primary amine **2.6** was converted to secondary amine **2.7** by imino-reduction with isobutyraldehyde, which was then coupled with different *N*-protected amino acids (**2.8**) under HBTU conditions to obtain compounds **2.9**. With compounds having *N*Cbz as the protecting groups, the nitro reduction and *N*Cbz removal were performed in a single step with 10% Pd/C under hydrogen condition to obtain diamines, which were then converted to bisamides **2.10** on reaction with different acid chlorides. Compounds having *N*Fmoc were converted into **2.10** in four steps, (i) the removal of *N*Fmoc with DBU, (ii) amidation with different acid chlorides, (iii) reduction of nitro to amine with 10% Pd/C, and (iv) amidation with different acid

chlorides. Macrocyclic compounds, **F2.1** were obtained from the corresponding bisamides in two steps, i.e. bisallylation with allylbromide and NaH condition followed by ring-closing metathesis[10] using Grubbs 2nd generation catalyst (G-II). In this series, eight macrocyclic compounds were synthesized, and in all cases, the *trans* olefin geometry was obtained, as determined by NMR.



Scheme 2: Synthesis of macrocycle **F2.1**

2.3.3. Derivatives of Macrocycle F2.1

We synthesized 8 macrocyclic derivaties of **F2.1** by changing the R_1, R_2 and R_3 groups, as shown in Figure 3.

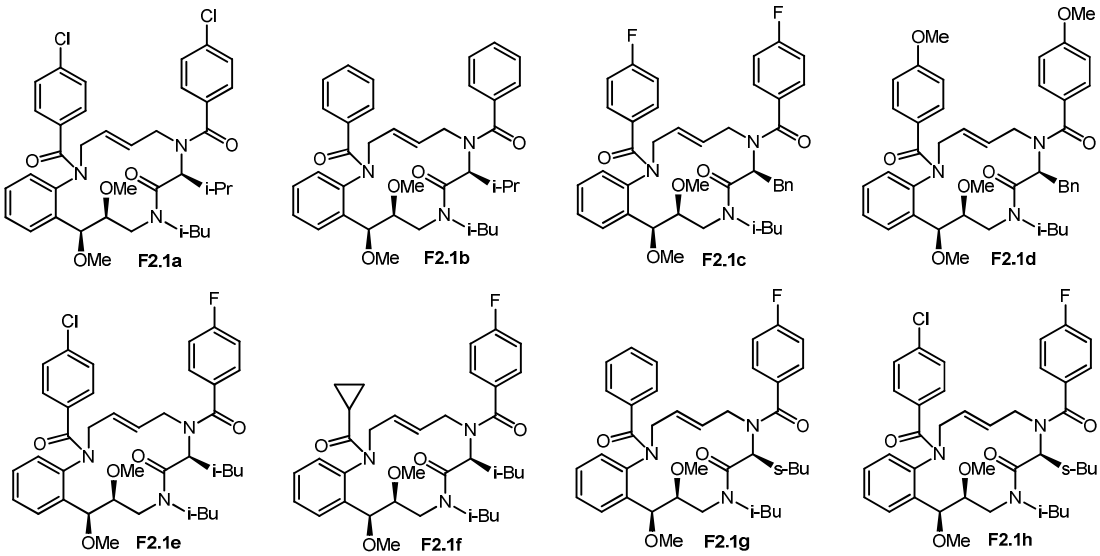
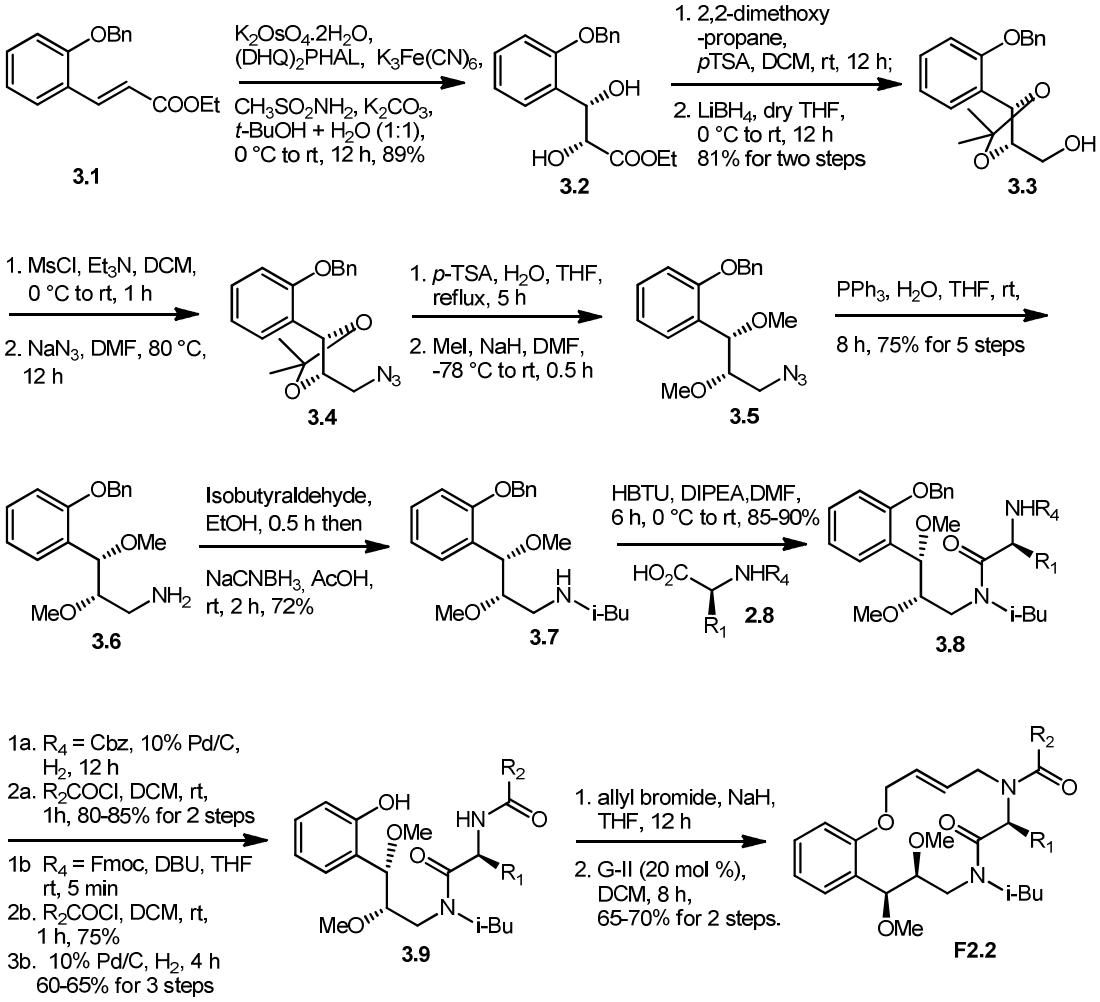


Figure 3: Derivatives of macrocycle **F2.1**

2.3.4. Synthesis of Macrocycle F2.2:



Scheme 3: Synthesis of macrocycle **F2.2**

In a similar manner, using 2-benzyloxy ethylcinnamate **3.1** as the starting material, we completed the synthesis of 8 macrocyclic compounds **F2.2**. As before, the *trans* olefin geometry was obtained following the "stitching technology". In one case (**F2.2a**), we could further obtain the X-ray to confirm the macrocyclic skeleton, and, *trans* geometry of olefin.

2.3.5. Derivatives of Macrocycle F2.2:

We synthesized eight macrocyclic derivaties of **F2.2** by changing the R_1 and R_2 groups, as shown in Figure 4.

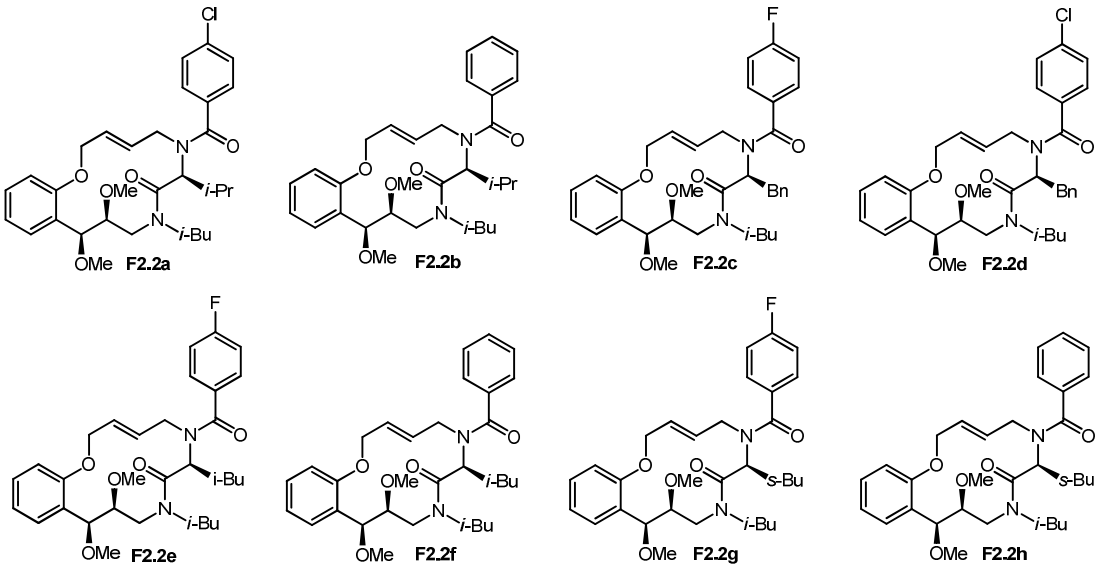
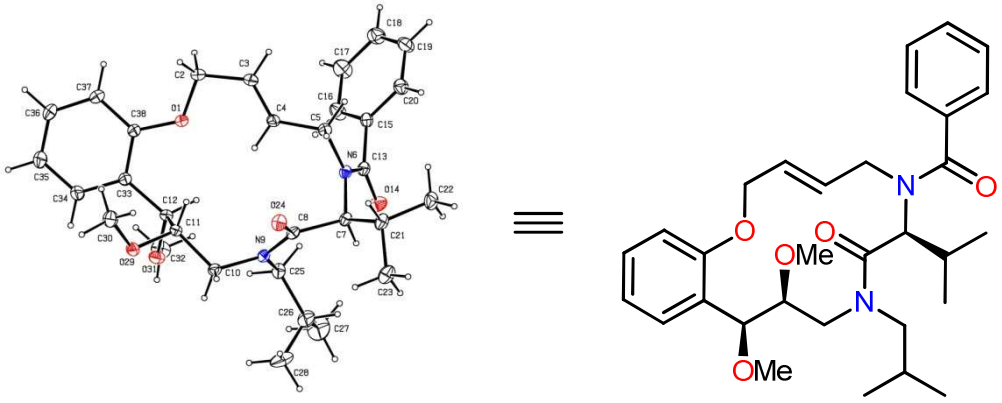


Figure 4: Derivatives of macrocycle **F2.2**

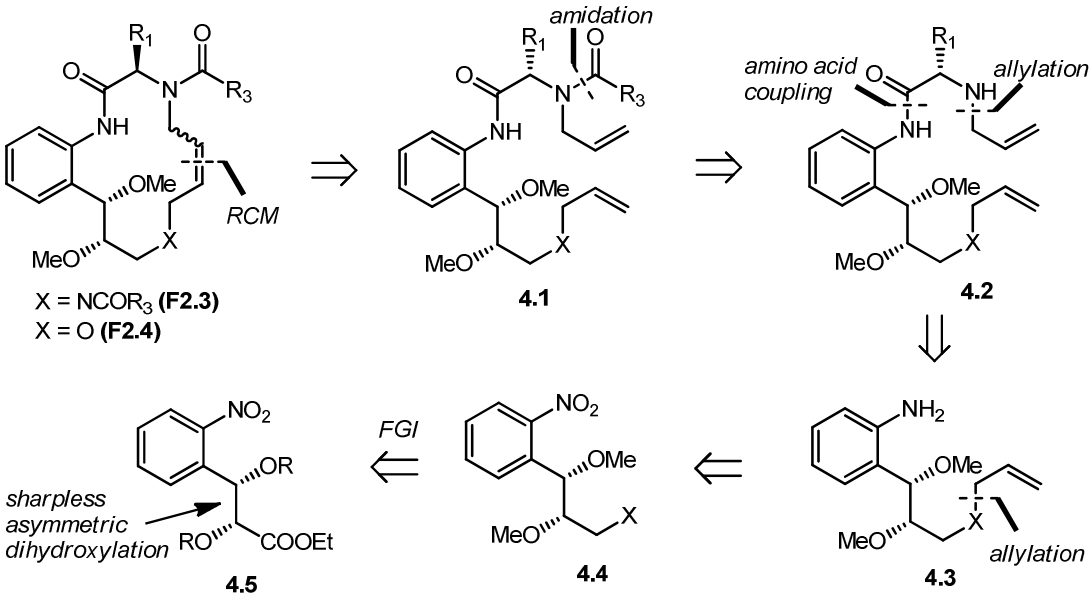
2.3.6. The X-ray Crystal structure of Macrocycle F2.2a:



Crystal data for **F2.2a**: $C_{31}H_{42}N_2O_5$, M = 522.67, colorless block, 0.21 × 0.18 × 0.09 mm^3, orthorhombic, space group $P2_12_12_1$ (No. 19), a = 8.8039(10), b = 15.7940(17), c = 22.015(2) Å, V = 3061.1(6) $Å^3$, Z = 4, D_c = 1.134 g/cm^3, F_{000} = 1128, CCD Area Detector, MoKα radiation, λ = 0.71073 Å, T = 294(2)K, $2\theta_{max}$ = 50.0°, 29693 reflections collected, 3064 unique (R_{int} = 0.0238). Final *GooF* = 1.035, *R1* = 0.0355, *wR2* = 0.1007, *R* indices based on 2818 reflections with I>2σ(I) (refinement on F^2), 349 parameters, 0 restraints, μ = 0.076 mm^{-1}.

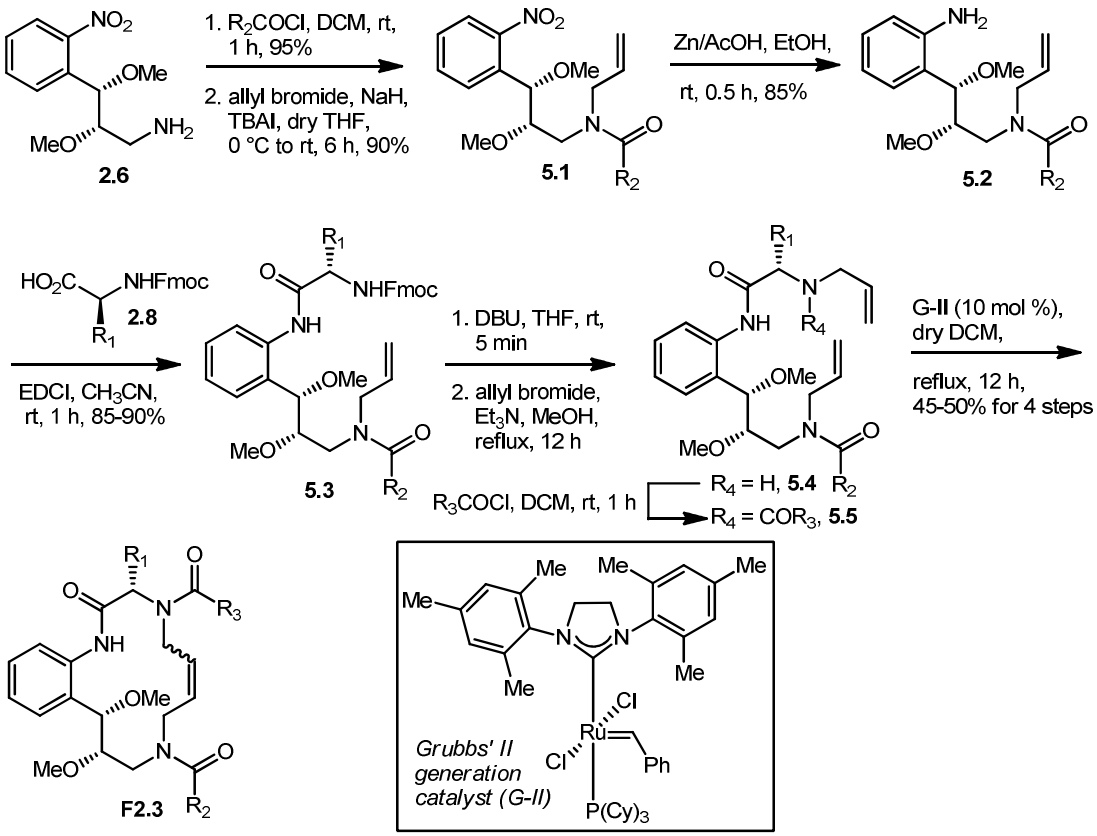
2.3.7. Retrosynthesis of Macrocycles F2.3 & F2.4:

The retrosynthetic analysis of macrocycles **F2.3** & **F2.4** is shown in Scheme 4. Macrocyclization would be done by ring closing metathesis of bis-allyl compound **4.1**, which would be obtained from amidation of seconadary amine **4.2**. This could be obtained from coupling of amino acid building blocks with aromatic primary amine **4.3**. Compound **4.3** could be obtained from allylation of **4.4**, followed by reduction of nitro group. Compound **4.4** could be obtained from enantiopure dihydroxyl derivative **4.5**, which would be obtained from Sharpless asymmetric dihydroxylation of the corresponding cinnamate derivative.



Scheme 4: Retrosynthesis of macrocycles **F2.3** & **F2.4**

2.3.8. Synthesis of Macrocycle F2.3:



Scheme 5: Synthesis of macrocycle **F2.3**

In another series, macrocycles **F2.3** (Scheme 5) were obtained from the key intermediate primary amine **2.6** in 8 steps as follows. Primary amine **2.6** was converted to an amide with benzoyl chloride then allylation on amide -*N*H gave the compound **5.1**. Reduction of an aromatic nitro gave the aromatic amine **5.2**. This was then coupled with *N*-protected amino acids (**2.8**) using EDC▪HCl and then subjected to *N*Fmoc removal to obtain **5.3**. Mono-allylation of **5.4** with allyl bromide followed by an amidation gives the key bisallyl product **5.5**, which was needed for the stitching technology. Four macrocyclic compounds **F2.3** were obtained using the ring-closing technology (Grubbs 2nd gen. catalyst, G-II). In this series, although we obtained a single isomer (determined by HPLC-MS), the olefin geometry remains to be determined.

2.3.9. Derivatives of Macrocycle F2.3:

We synthesized four macrocyclic derivaties of **F2.3** by changing the R_1 and R_2 groups, as shown in Figure 5.

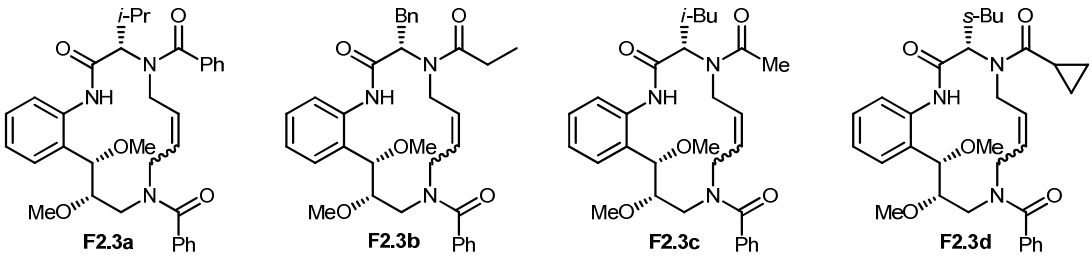
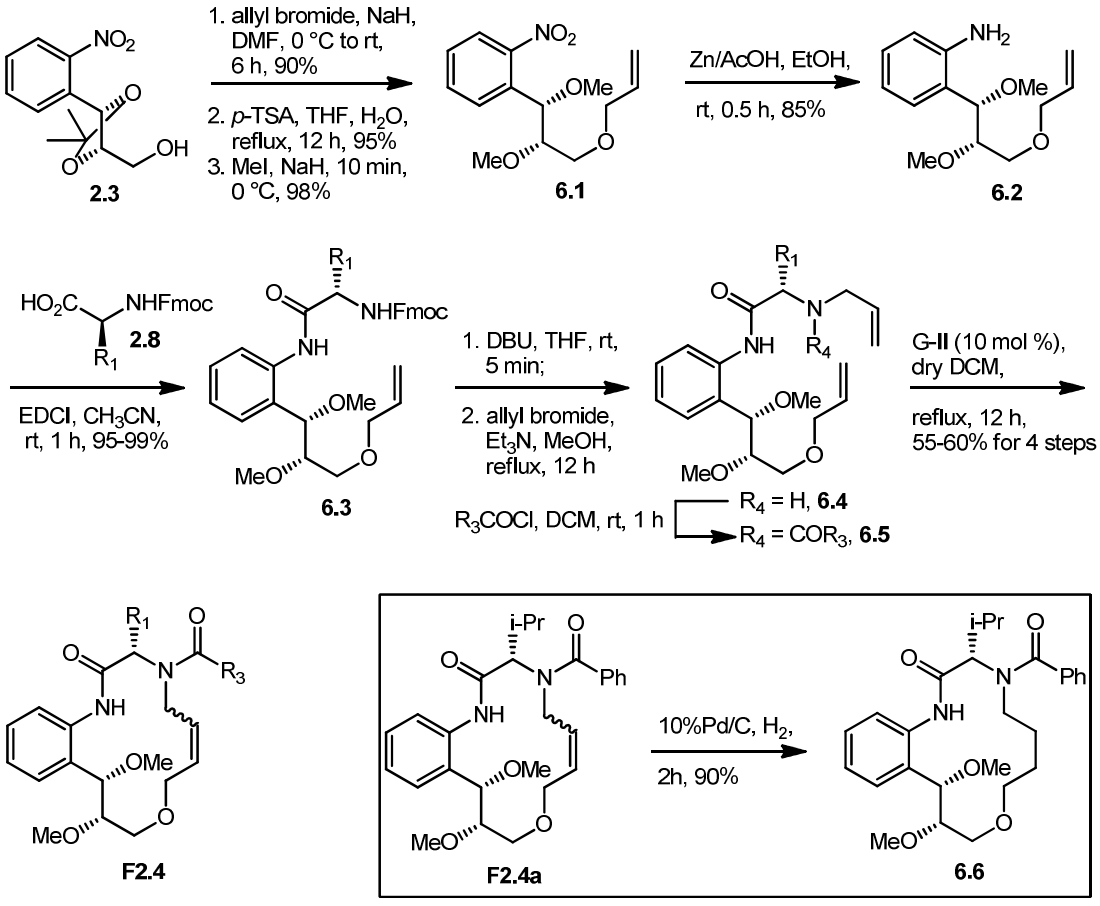


Figure 5: Derivatives of macrocycle **F2.3**

2.3.10. Synthesis of Macrocycle F2.4:



Scheme 6: Synthesis of macrocycle **F2.4**

On similar lines, 4 macrocycle compounds **F2.4** were obtained the primary alcohol **2.3** , This was subjected to allylation then deprotection of acetonide with *p*-TSA

followed by the diol methylation with MeI and NaH condition to give compound **6.1**. Reduction of aromatic nitro with Zn/AcOH gave the primary amine **6.2**. Coupling of N-Fmoc amino acid **2.8** with **6.2** yielded the compound **6.3**. Bis-allyl compound **6.5** was obtained from **6.3** in three steps, (i) removal of Fmoc group with DBU, (ii) allylation with allyl bromide to give **6.4** and, (iii) amidation with different acid chlorides. This bis allylated compound was subjected to ring closing metathesis using Grubbs 2nd generation catalyst gave the macrocycle compounds **F2.4**. Though we obtained single isomer (determined by the HPLC-MS), we could not assaign the geometry of the olefin, because the NMR spectra was complex due to the rotamers. And in one case, we could obtain the single X-ray crystal structure of the reduced double bond macrocyclic product **6.6** to further confirm our assignments.

2.3.11. Derivatives of Macrocycle F2.4:

We synthesized 4 macrocyclic derivaties of **F2.4** by changing the R_1, R_2 and R_3 groups, as shown in Figure 6.

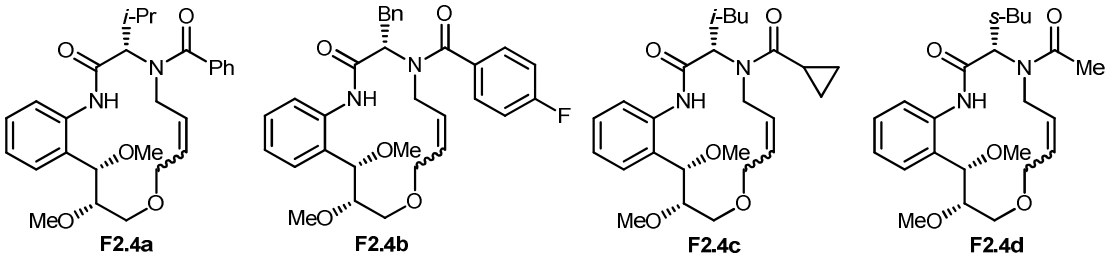
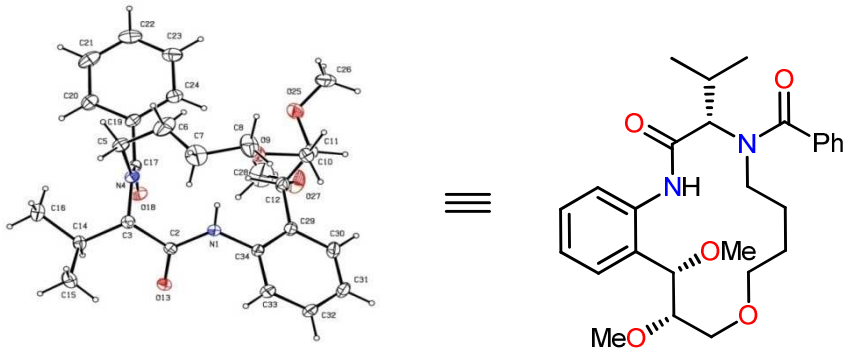


Figure 6: Derivatives of macrocycle **F2.4**

2.3.12. The X-ray Crystal Structure of Macrocycle 6.6:



Crystal data for **6.6**: $C_{27}H_{36}N_2O_5$, M = 468.58, colorless needle, 0.18 × 0.09 × 0.07 mm^3, monoclinic, space group $P2_1$ (No. 4), a = 7.9392(8), b = 19.1700(19), c =

8.6598(9) Å, β = 103.597(2)°, V = 1281.0(2) Å^3, Z = 2, D_c = 1.215 g/cm^3, F_{000} = 504, CCD Area Detector, MoKα radiation, λ = 0.71073 Å, T = 294(2)K, $2\theta_{max}$ = 50.0°, 12398 reflections collected, 2341 unique (R_{int} = 0.0225). Final *GooF* = 1.027, *R1* = 0.0473, *wR2* = 0.1357, *R* indices based on 2166 reflections with I>2σ(I) (refinement on F^2), 315 parameters, 1 restraint, μ = 0.083 mm^{-1}.

2.4. Biological Evaluation:

2.4.1. Zebrafish Assay related to angiogenesis and an early embryonic development:

Small molecule toolbox from this study (total 85 compounds) was subjected to search for compounds affecting epiboly during an early embryonic development,[11] angiogenesis,[12] neurogenesis[13] in zebrafish embryo-based assays.[13-14] These assays are well-documented in the literature and this study was carried out in collaboration

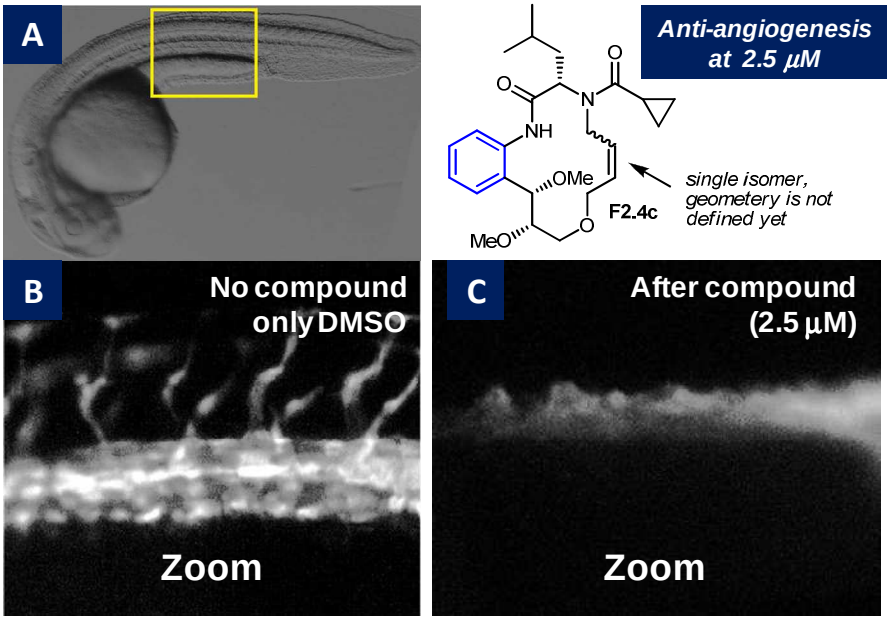


Figure 7: (**A**) Wild-type zebrafish embryo at 30 hpf of development, region zoomed in panels **B** and **C** is shown by a yellow box, (**B**) zoom section of wild-type or vehicle treated embryo, and (**C**) zoom section after treatment with compound **F2.4c**.

with Satish Kitambi team at the Karolinska Institute, Sweden.[11f,12b,15] Embryos were obtained by natural mating and staged according to the literature procedure.[16] Zebrafish embryos of stages older than 24 hours post fertilization (hpf) were treated

with 0.03% PTU (*N*-phenylthiourea) when needed to inhibit pigment formation. Wild type AB line, and transgenic lines Tg (fli:EGFP, islet1:GFP) were used to assess the effects on epiboly, angiogenesis and neurogenesis respectively. Zebrafish embryos for small molecule screening experiments were collected via pair-wise matings, cleaned and incubated in PTU treated E3 water at 28.3 ^{o}C. One to four cell stage embryos were then distributed into 96 well clear bottom plate (Corning). The compound exposure was done in 96 well plate (Corning) and three embryos were taken in each well containing 200 µl of (0.5 to 15 µM) compound in PTU treated egg water. The 96 well plates were incubated at 28.3 ^{o}C and the embryos were allowed to grow until 10 hpf or 30 hpf to assess the effect on epiboly, angiogenesis/neurogenesis respectively. Phenotypes were scored using a Zeiss Axiovert 200 inverted microscope equipped with a cooled CCD camera. Photographs were processed and assembled using Photoshop software (see **Figure 1**).

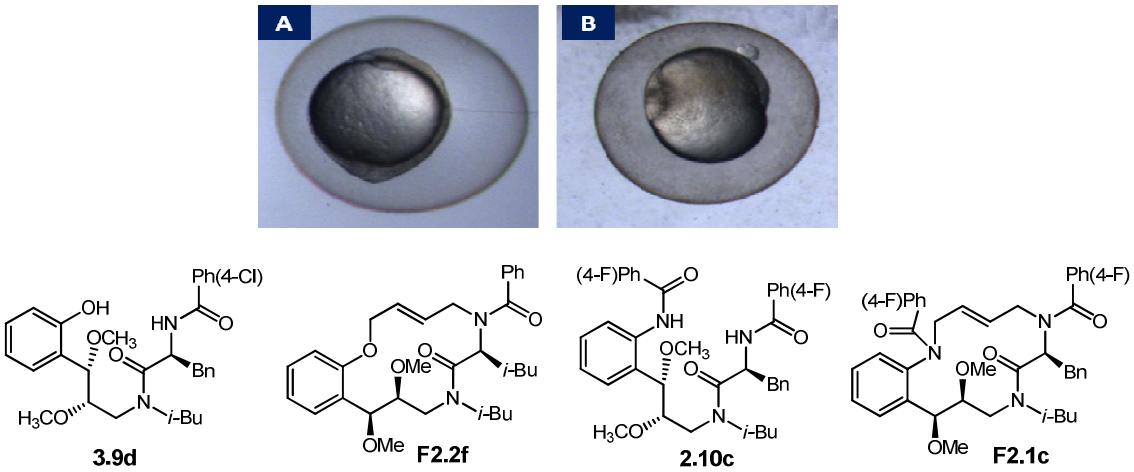


Figure 8: Zebrafish early embryonic development Assay. (A) DMSO exposed embryos at 10 hpf of development, (B) small molecule exposed embryos causing a delay in epiboly.

It was interesting to observe that among all the compounds tested from this collection, we identified a novel small molecule (**F2.4c,** Figure 7) that specifically inhibited the trunk angiogenesis (see **B** and **C** in Figure 7) at 2.5 µM without affecting either epiboly or neurogenesis. Embryos exposed to 2.5 µM of this small molecule (**F2.4c**) displayed the normal epiboly movement and neurogenesis and an overall embryonic development was also not affected. The embryos showed a

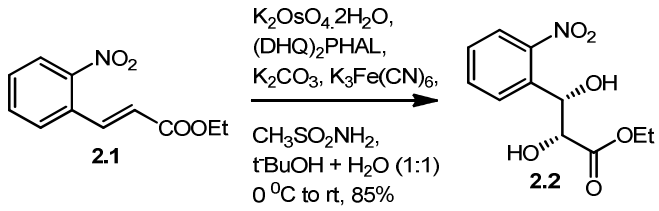
complete lack of migration of early endothelial cells (i.e. tip and stalk cells) to form an early inter-segmental vessel of the trunk.

In another parallel study, we identified four active compounds (**3.9d**, **2.10c, F2.1c** and **F2.2f**) that inhibited the epiboly cell movements during an early embryonic development. The delay in epiboly was clearly seen in embryos exposed to 5.0 μM of the small molecules; however these embryos did complete epiboly and developed normally without any visible effects on angiogenesis and neurogenesis. At higher concentrations, such as 10.0 μM, epiboly did not begin leading to lethality of the embryo. The mechanism underlying the inhibition of angiogenesis and epiboly will be investiageted further using both zebrafish and other cell based assays.

2.5. Conclusion:

In conclusion, we reported a practical and modular approach to allow us accessing a diverse set of 14-membered ring macrocyclic compounds. The ease of the synthesis and the reported modular methodology are the two attractive features in assembling a macrocyclic, small molecule toolbox to explore its value. The presence of two contiguous stereogenic hydroxyl group derivatives and an amino acid moiety in the macrocyclic ring architecture allow accessing this unique set of compounds. With the goal of going beyond the conventional chemical space in the drug discovery arena where most compounds are rich in sp2 character, the present method provides a good entry to access a diverse set of 14-membered macrocyclic compounds with variation in the display of different functional groups. Furthermore, to explore their biological effects, we utilized zebrafish embryonic screening assays. These rapid assay procedures allowed us to quickly identify the effects of small molecules on various biological processes. The effects produced by these novel molecules provided a platform for using chemical biology approaches to understand the basic biological processes such as epiboly and angiogenesis. Extensive validation procedures need to be developed to characterize the effect produced and to elucidate the mechanism of action. Further, work is needed to understand the deep impact of these functional small molecules both in the context of developing a new class of inhibitors of angiogenesis as well as the inhibitors of an early embryonic development.

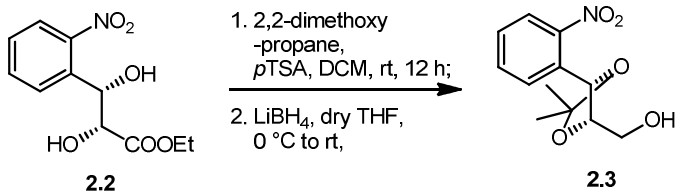
2.6. Experimental Procedure:



(2R,3S)-ethyl 2,3-dihydroxy-3-(2-nitrophenyl)propanoate (2.2):

To a stirred mixture of $K_3Fe(CN)_6$ (44 g, 133 mmol), K_2CO_3 (18.7 g, 135.3 mmol), $(DHQ)_2PHAL$ (520 mg, 0.67 mmol), K_2OsO_4 (60 mg, 0.18 mmol), methane sulfonamide (4.29 g, 45.19 mmol) in *t*-BuOH (300 mL) and water (300 mL), a solution of **2.1** (10 g, 45.20 mmol) in *t*-BuOH (100 mL) was added at a time at 0 °C and allowed to stir for 12 h at room temperature. After completion of the reaction, reaction mixture was quenched by the addition of solid sodium sulfite and extracted with ethyl acetate (3 X 300 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography (3:7 ethyl acetate/hexanes) to give the compound **2.2** (9.1 g, 81% yield) as white solid.

Molecular Formula: $C_{11}H_{13}NO_6$; R_f : 0.3 (3:7 ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.01 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.68 (t, J = 8.0 Hz, 1H), 7.47 (t, J = 8.0 Hz, 1H), 5.71 (dd, J_1 = 6.8 Hz, J_2 = 2.0 Hz, 1H), 4.52 (dd, J_1 = 5.6 Hz, J_2 = 2.4 Hz, 2H), 4.32 (q, J = 7.2 Hz, 2H), 3.29 (d, J = 6.8 Hz, 1H), 3.02 (d, J = 5.6Hz, 1H), 1.31 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.5, 147.4, 135.9, 133.3, 129.4, 128.6, 124.4, 73.3, 69.6, 62.4, 14.0; LRMS: (ES+) m/z = 256.3 (M+1)



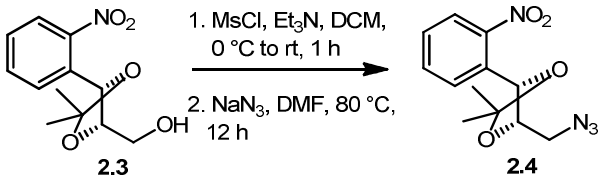
((4S,5S)-2,2-dimethyl-5-(2-nitrophenyl)-1,3-dioxolan-4-yl)methanol (2.3):

To a solution of the compound **2.2** (8.5 g, 33.34mmol) in dry dichloromethane (200 mL), 2,2-dimethoxy propane (8.16 mL, 66.68 mmol) and *p*-TSA (50 mg) were added. The reaction mixture was stirred at room temperature for 12 h under nitrogen atmosphere. After completion of the reaction, reaction mixture was quenched with

sodium bicarbonate solution, and extracted with dichloromethane (3 X 100 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography (1:9 ethyl acetate/hexanes) to give the acetonide protected ester (8.8 g, 86% yield) as yellow liquid.

To a solution of acetonide protected ester (8.5 g, 27.51mmol) in dry THF (150 mL), at 0 °C, $LiBH_4$ (1.2 g, 55.02 mmol) was added, and reaction mixture was allowed to stir for 24 h at room temperature. After completion of the reaction, reaction mixture was quenched by the addition of ice cold water, and extracted with ethyl acetate (3 X 100 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography (3:7 ethyl acetate/hexanes) to give the compound **2.3** (6.6 g, 94.8% yield) as yellow liquid.

Molecular Formula: $C_{12}H_{15}NO_5$; R_f : 0.3 (3:7 ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.85 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.65 (t, *J* = 8.0 Hz, 1H), 7.45 (t, *J* = 8.0 Hz, 1H), 5.40 (d, *J* = 8.4 Hz, 1H), 4.00 (m, 1H), 3.90 (dd, J_1 = 12.0 Hz, J_2 = 3.2 Hz, 1H), 3.81 (dd, J_1 = 12.0 Hz, J_2 = 5.2 Hz, 1H), 1.58 (s, 3H), 1.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 149.2, 133.3, 132.9, 129.2, 128.9, 124.2, 109.7, 84.4, 74.2, 61.6, 27.1, 26.9; LRMS: (ES+) m/z = 254.2 (M+1)



2.3 **2.4**

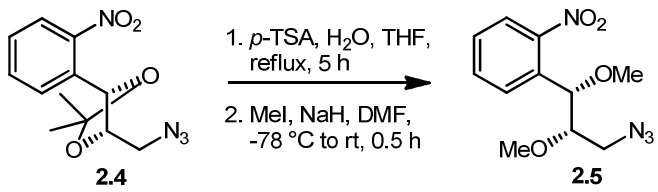
(4S,5S)-4-(azidomethyl)-2,2-dimethyl-5-(2-nitrophenyl)-1,3-dioxolane (2.4):

To a solution of **2.3** (6 g, 23.71mmol) in dry dichloromethane (150 mL), at 0 °C, Et_3N (9.98 mL, 71.13 mmol) and methane sulfonyl chloride were added, and reaction mixture was allowed to stir for 1 h at room temperature. After completion of the reaction, reaction mixture was quenched by the addition of sodium bicarbonate solution, and extracted with dichloromethane (3 X 100 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude liquid (7.5 g).

To a solution of above crude in dry DMF, NaN_3 (2.9 g, 45.2 mmol) was added, and reaction mixture was heated at 80 °C for 10 h. After completion of the reaction,

reaction mixture was quenched by the addition of sodium bicarbonate solution, and extracted with dichloromethane (3 X 100 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude liquid, which was purified by column chromatography (1:4 ethyl acetate/hexanes) to give the compound **2.4** (5.3 g, 80.3% yield) as yellow liquid.

Molecular Formula: $C_{12}H_{14}N_4O_4$; R_f : 0.3 (1:9 ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.89 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.67 (t, *J* = 8.0 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 5.42 (d, *J* = 8.0 Hz, 1H), 4.05 (m, 1H), 3.65 (dd, J_1 = 13.2 Hz, J_2 = 3.2 Hz, 1H), 3.52 (dd, J_1 = 13.2 Hz, J_2 = 6.0 Hz, 1H), 1.60 (s, 3H), 1.54 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 149.2, 133.4, 132.6, 129.2, 129.1, 124.3, 110.3, 82.9, 74.8, 51.3, 29.6, 27.0, 26.9; LRMS: (ES+) m/z = 279.3 (M+1)



1-((1S,2S)-3-azido-1,2-dimethoxypropyl)-2-nitrobenzene (2.5):

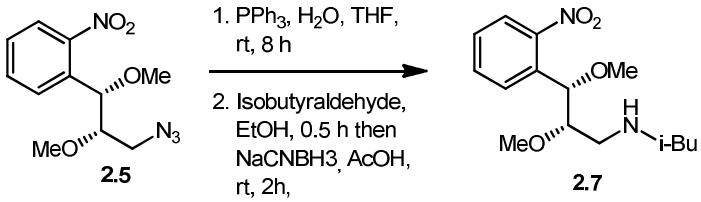
To a solution of **2.4** (5.3 g, 19.06 mmol) in THF (150 mL), PTSA (9.83 g, 57.19 mmol) and water 10 mL were added, and reaction mixture was allowed to reflux for 12 h. After completion of the reaction, reaction mixture was quenched by the addition of sodium bicarbonate solution, and extracted with ethyl acetate (3 X 100 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography (3:7 ethyl acetate/hexanes) to give the diol azide (4.5 g, 99% yield) as yellow liquid.

Molecular Formula: $C_9H_{10}N_4O_4$; R_f : 0.3 (3:7 ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.97(m, 1H), 7.75(m, 1H), 7.64(m, 1H), 7.51(m, 1H), 5.25(m, 1H), 4.0(m, 1H), 2.90-3.56 (m, 1H) ; ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 147.5, 136.5, 133.6, 128.8, 128.7, 124.7, 73.0, 69.1, 54.3; LRMS: (ES+) m/z = 239.1 (M+1)

To a -78 °C solution of NaH (2.72 g, 113.35 mmol) and MeI (11.7 mL, 188.9 mmol) in DMF (150 mL) was added a solution of diol azide (4.5 g, 18.89mmol) in DMF.

The solution was stirred for 5 min, allowed to warm to room temperature. The solution was stirred for 1 h and then quenched by drop wise addition of NH_4Cl solution (20 mL), and extracted with ethyl acetate (3 X 100 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography (3:7 ethyl acetate/hexanes) to give the compound **2.5** (4.5 g, 89.5% yield) as yellow liquid.

Molecular Formula: $C_{11}H_{14}N_4O_4$; R_f : 0.3 (1:4 ethyl acetate/hexane); ^1H NMR ($CDCl_3$, 400 MHz): 7.97 (d, *J* = 8.18 Hz, 1H), 7.78 (d, *J* = 7.85 Hz, 1H), 7.67 (t, *J* = 7.59 Hz, 1H), 7.49 (t, *J* = 7.74 Hz, 1H), 5.01 (d, *J* = 3.14 Hz, 1H), 3.68 (td, *J* = 7.76, 3.97 Hz, 1H), 3.39 (dd, *J* = 12.60, 7.61 Hz, 1H), 3.35-3.27 (m, 4H), 3.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 149.2, 133.6, 133.0, 129.4, 128.6, 124.5, 82.5, 77.9, 60.0, 57.8, 51.6; LRMS: (ES+) m/z = 267.3 (M+1)



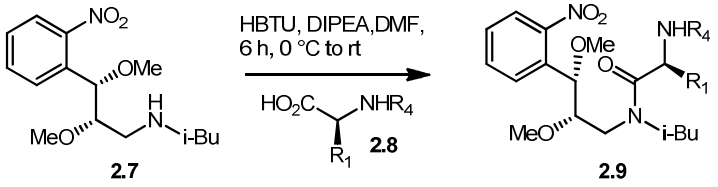
(2S,3S)-N-isobutyl-2,3-dimethoxy-3-(2-nitrophenyl)propan-1-amine (2.7):

To a solution of the compound **2.5** (4.5 g, 16.90 mmol) in THF (50 mL), TPP (8.85 g, 33.38 mmol) and water (3 mL, 169 mmol) were added and stirred for 24 h. After completion of the reaction, reaction mixture was concentrated to leave a residue, which was purified by column chromatography (4:1 ethyl acetate/hexanes) to give the compound **2.6** (3.8 g, 93.6% yield) as light yellow oil. Molecular Formula: $C_{11}H_{16}N_2O_4$; R_f (solvent system): 0.3 (ethyl acetate/hexane)

To a suspension of compound **2.6** (3.0 g, 12.48 mmol) in EtOH (30 mL), isobutyraldehyde (1.24 mL, 12.48 mmol) was added and stirred for 30 min. A mixture of $NaCNBH_3$ (1.18 g, 18.72 mmol) and acetic acid (50 µL) in ethanol (5 mL) were added to the reaction mixture at 0 °C allowed to stir for 1 h. After completion of the reaction, reaction mixture was quenched with sodium bicarbonate solution (5 mL), and extracted with ethyl acetate (3 X 20 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography

(3:7 ethyl acetate/hexanes) to give the compound **2.7** (2.5 g, 67.8% yield) as light yellow oil.

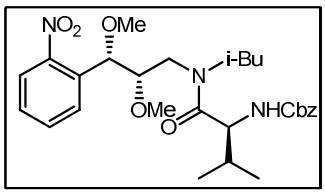
Molecular Formula: $C_{15}H_{24}N_2O_4$; R_f : 0.2 (3:7 ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.89 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 5.09 (d, *J* = 4.0 Hz, 1H), 3.61 (m, 1H), 3.30 (s, 3H), 3.28 (s, 3H), 2.66 (dd, J_1 = 12.0Hz, J_2 = 3.6 Hz, 1H), 2.54 (dd, J_1 = 12.0Hz, J_2 = 8.0 Hz, 1H), 2.36 (dd, J_1 = 6.8 Hz, J_2 = 2.4 Hz, 2H), 1.71 (m, 1H), 0.89 (s, 3H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 149.4, 134.3, 132.5, 129.2, 128.1, 124.1, 82.8, 78.4, 59.6, 57.9, 57.7, 49.9, 28.1, 20.5, 20.4; LRMS: (ES+) m/z = 297.4 (M+1)



Compound 2.9:

To a suspension of compound **2.7** (1 mmol) in DMF (10 mL), **2.8** (1.5 mmol), HBTU (1.5 mmol) and DIPEA (2 mmol) were added at 0 °C and allowed to stirred for 6 h. After completion of the reaction, reaction mixture was quenched with sodium bicarbonate solution (10 mL), and extracted with ethyl acetate (3 X 20 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography to give the pure compound **2.9.**

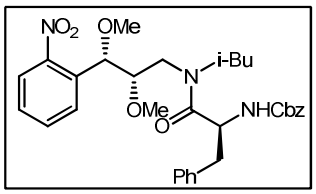
Benzyl (S)-1-(((2S,3S)-2,3-dimethoxy-3-(2-nitrophenyl) propyl) (isobutyl)amino)-3-methyl-1 oxobutan-2-ylcarbamate (2.9a):



Molecular Formula: $C_{28}H_{39}N_3O_7$; R_f : 0.4 (1:4 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-88.9% (yellow liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.00 (m, 1H), 7.83 (m, 1H), 7.68 (m, 1H), 7.54-7.24 (m, 6H), 5.56 (m, 1H), 5.23-4.83 (m, 3H), 4.52 (m, 1H), 3.98-3.70

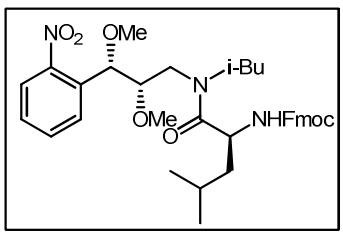
(m, 2H), 3.12 (m, 9H), 2.08-1.88 (m, 2H), 1.03-0.79 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.1, 156.3, 149.3, 149.2, 136.5, 136.5, 134.1, 133.1, 133.0, 129.4, 129.2, 128.8, 128.6, 128.5, 128.5, 128.3, 128.1, 127.9, 127.8, 127.8, 124.6, 124.4, 82.9, 81.5, 78.3, 66.6, 66.6, 60.4, 60.1, 57.6, 56.4, 55.8, 55.5, 54.1, 53.4, 48.5, 47.9, 31.4, 31.4, 28.1, 26.5, 20.1, 20.1, 19.9, 19.9, 19.8, 19.5, 16.9 ; LRMS: (ES+) m/z = 530.1 (M+1)

Benzyl (S)-1-(((2S,3S)-2,3-dimethoxy-3-(2-nitrophenyl) propyl) (isobutyl)amino)-1-oxo-3-phenylpropan-2-ylcarbamate (2.9b):



Molecular Formula: $C_{32}H_{39}N_3O_7$; R_f : 0.5 (1:4 ethyl acetate/hexanes) ; Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-86.0% (yellow liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.98 (d, *J* = 8.06 Hz,1H), 7.86-7.72 (m, 1H), 7.67 (t, *J* = 7.58 Hz, 1H), 7.48 (m, 1H), 7.38-7.10 (m, 10H), 5.59 (d, *J* = 9.31 Hz, 1H), 5.16-4.74 (m, 4H), 3.84 (d, *J* = 6.79 Hz, 1H), 3.38-2.83 (m, 12H), 1.96-1.74 (m, 1H), 0.88-0.70 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.3, 172.0, 155.6, 155.5, 149.4, 149.0, 136.6, 136.5, 136.5, 136.4, 134.3, 133.5, 133.1, 133.0, 129.6, 129.3, 129.3, 129.1, 128.6, 128.4, 128.4, 128.3, 127.9, 127.8, 127.8, 126.7, 124.6, 124.4, 82.7, 81.0, 78.1, 66.6, 66.5, 60.3, 60.0, 57.8, 57.6, 56.4, 54.6, 52.1, 51.9, 48.8, 48.4, 39.6, 39.5, 28.4, 26.7, 20.2, 20.1, 19.9, 19.7; LRMS: (ES+) m/z = 578.3 (M+1)

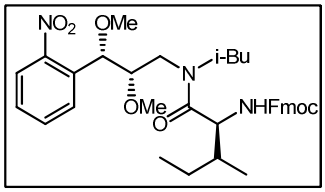
(9H-fluoren-9-yl)methyl(S)-1-(((2S,3S)-2,3-dimethoxy-3-(2-nitro-phenyl)propyl)(isobutyl) amino)-4-methyl-1-oxopentan-2-yl carbamate (2.9c):



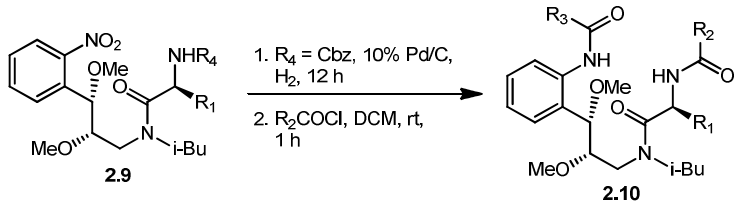
Molecular Formula: $C_{29}H_{41}N_3O_7$; R_f: 0.4 (1:4 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-85.0% (yellow

liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.95 (t, *J* = 7.00 Hz, 1H), 7.79 (m, 3H), 7.71-7.55 (m, 3H), 7.46 (t, *J* = 7.33 Hz, 1H), 7.38 (t, *J* = 7.31 Hz, 2H), 7.28 (dd, *J* = 12.51, 5.22 Hz, 2H), 5.65 (d, *J* = 9.04 Hz, 1H), 5.19-4.83 (m, 1H), 4.76 (s, 1H), 4.43-4.16 (m, 3H), 4.01-3.83 (m, 1H), 3.68-3.43 (m, 1H), 3.39-3.05 (m, 8H), 2.02 (m, 1H), 1.67-1.50 (m, 1H), 1.36 (m, 1H), 1.06-0.78 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 173.6, 173.2, 156.1, 149.1, 143.8, 141.2, 141.2, 134.3, 133.1, 132.9, 129.4, 128.5, 128.5, 127.5, 126.9, 125.2, 124.6, 124.4, 119.8, 119.8, 82.5, 81.1, 78.2, 66.9, 60.3, 60.2, 57.7, 56.4, 53.9, 49.6, 49.3, 48.3, 47.1, 47.1, 47.0, 42.4, 28.4, 26.6, 24.6, 24.5, 23.6, 23.5, 21.4, 21.63, 20.2, 20.1, 19.9, 19.7; LRMS: (ES+) m/z = 632.1 (M+1)

(9H-fluoren-9-yl)methyl(2S,3R)-1-(((2S,3S)-2,3-dimethoxy-3-(2-nitrophenyl)propyl) (isobutyl)amino)-3-methyl-1-oxopentan-2-ylcarbamate (2.9d):



Molecular Formula: $C_{29}H_{41}N_3O_7$; R_f: 0.2 (1:9 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-85.5% (yellow liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.96 (d, *J* = 8.14 Hz, 1H), 7.79 (m, 3H), 7.71-7.55 (m, 3H), 7.53-7.23 (m, 5H), 5.64 (d, *J* = 9.35 Hz, 1H), 4.92 (d, *J* = 2.56 Hz, 1H), 4.63-4.13 (m, 4H), 3.88 (t, *J* = 7.55 Hz, 2H), 3.42-2.99 (m, 8H), 1.98 (d, *J* = 6.49 Hz, 1H), 1.86-1.47 (m, 3H), 1.02-0.75 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.2, 156.2, 149.2, 144.0, 143.8, 143.8, 141.2, 141.2, 134.1, 133.1, 133.0, 132.9, 129.4, 129.4, 128.5, 128.5, 128.4, 127.5, 127.0, 1216.9, 125.1, 125.1, 124.5, 124.4, 124.4, 119.9, 119.9, 119.8, 82.8, 82.7, 81.5, 66.9, 66.8, 60.3, 60.1, 57.8, 57.6, 56.5, 55.1, 48.1, 47.9, 47.1, 47.1, 38.3, 29.6, 28.1, 23.6, 20.1, 19.5, 15.9, 11.3; LRMS: (ES+) m/z = 632.1 (M+1)

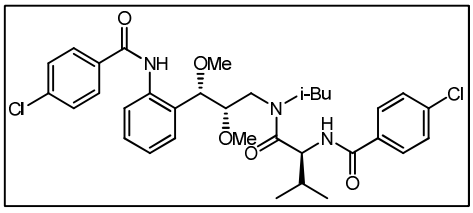


Compound 2.10:

To a suspension of compound **2.9** (1 mmol) in ethyl acetate (10 mL), 10% Pd/C (0.2 mmol) was added and stirred the reaction mixture for 12 h under hydrogen atmosphere. After completion of the reaction, reaction mixture was passed through celite and concentrated to leave crude oil, which was subjected to the next reaction without any purification.

To a suspension of above compound (0.2 mmol) in DCM (10 mL), acid chloride (0.5 mmol) was added at 0 °C and allowed to stir for 10 min. After completion of the reaction, reaction mixture was quenched with sodium bicarbonate solution (5 mL), concentrated, and extracted with ethyl acetate (3 X 20 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography to give pure compound **2.10.**

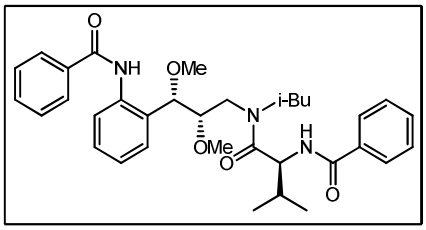
4-chloro-N-(2-((1S,2S)-3-((S)-2-(4-chlorobenzamido)-N-isobutyl-3-methylbutan amido)-1,2-dimethoxypropyl)phenyl)benzamide (2.10a):



Molecular Formula: $C_{34}H_{41}Cl_2N_3O_5$; R_f : 0.5 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-85.4% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 10.05 (s, 1H), 8.51 (d, *J* = 8.06 Hz, 1H), 7.98-7.91 (m, 2H), 7.81-7.61 (m, 2H), 7.52-6.76 (m, 10H), 5.05 (m, 1H), 4.37 (m, 1H), 3.92-2.87 (m, 12H), 2.22-1.96 (m, 2H), 1.08-0.82 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.3, 172.1, 165.9, 165.7, 163.7, 137.7, 137.6, 137.4, 133.5, 133.3, 132.3, 132.1, 129.4, 129.2, 128.9, 128.7, 128.6, 128.6, 128.5, 128.4, 128.4, 128.3, 126.0, 123.9, 121.9, 85.9, 84.6, 83.9, 60.6, 60.2,57.2, 57.0, 56.8, 54.6,

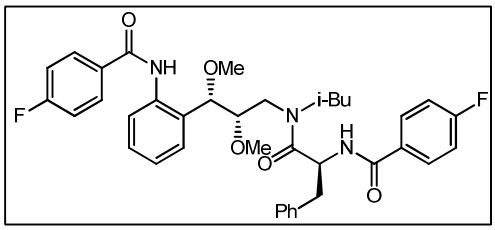
54.5, 53.8, 49.7, 49.1, 31.7, 31.6, 28.1, 26.6, 20.2, 20.1, 20.0, 19.9, 19.5, 19.4, 17.7, 17.2; LRMS: (ES+) m/z = 642.3 (M+1)

N-(2-((1S,2S)-3-((S)-2-benzamido-N-isobutyl-3-methylbutanamido)-1,2-dimethoxy propyl)phenyl)benzamide (2.10b):



Molecular Formula: $C_{34}H_{43}N_3O_5$; R_f : 0.3(3:7 ethyl acetate/ hexanes); Yield-88.6% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 10.07 (s, 1H), 8.54 (d, *J* = 8.24 Hz, 1H), 8.02 (t, *J* = 7.95 Hz, 2H), 7.78 (m, 2H), 7.44 (m, 7H), 7.22-6.79 (m, 2H), 5.07 (d, *J* = 3.12 Hz, 1H), 4.40 (m, 1H), 3.91-2.91 (m, 11H), 2.11 (s, 2H), 1.08-0.82 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.5, 172.3, 167.1, 166.8, 164.9, 137.7, 135.2, 134.9, 134.0, 133.9, 131.7, 131.6, 131.5, 131.5, 129.5, 129.2, 129.0, 128.9, 128.6, 127.2, 127.1, 127.0, 126.9, 126.1, 123.8, 122.1, 85.9, 84.9, 84.0, 60.8, 60.3, 57.3, 57.1, 56.9, 54.7, 54.4, 53.8, 49.9, 49.1, 32.0, 31.9, 28.3, 26.7, 20.3, 20.1, 20.0, 19.7, 19.6, 17.7, 17.4; LRMS: (ES+) m/z = 574.3 (M+1)

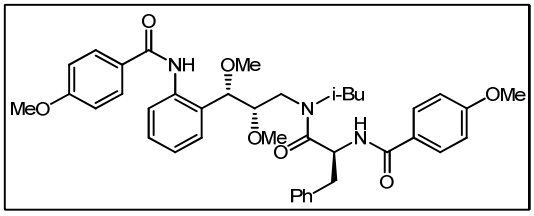
4-fluoro-N-(2-((1S,2S)-3-((S)-2-(4-fluorobenzamido)-N-isobutyl-3-phenylpropan amido)-1,2-dimethoxypropyl)phenyl)benzamide (2.10c):



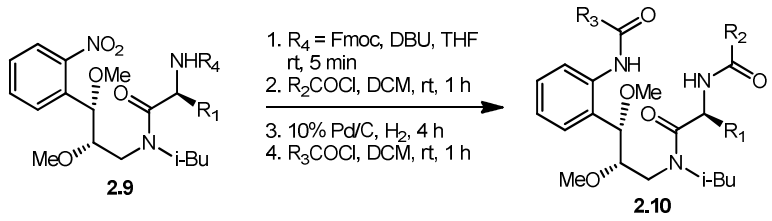
Molecular Formula: $C_{38}H_{41}F_2N_3O_5$; R_f : 0.5 (3:7 ethyl acetate/hexanes); Yield-85.4% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.94 (s, 1H), 8.42 (m, 1H), 8.10-7.90 (m, 2H), 7.69 (m, 2H), 7.46-6.69 (m, 14H), 5.44-5.25 (m, 1H), 4.43-4.23 (m, 1H), 3.86-2.95 (m, 14H), 1.98-1.76 (m, 1H), 0.97-0.72 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.6, 165.9, 165.6, 165.5, 164.2, 163.7, 163.4, 137.4, 136.4, 136.3, 131.3, 131.3, 130.9, 130.8, 129.6, 129.6, 129.5, 129.4, 129.4, 129.4, 129.3, 129.3, 129.1, 129.1, 128.9, 128.9, 128.5, 128.4, 126.9, 126.8, 126.1, 124.7, 123.8,

121.8, 1215.6, 115.5, 115.4, 115.4, 115.3, 115.2, 115.1, 114.9, 85.3, 83.9, 83.3, 60.6, 59.8, 57.2, 56.9, 56.8, 54.9, 50.8, 49.9, 49.3, 38.7, 29.5, 28.5, 26.7, 20.1, 20.0, 19.7; LRMS: (ES+) m/z = 658.1 (M+1)

N-((S)-1-(((2S,3S)-2,3-dimethoxy-3-(2-(4-methoxybenzamido)phenyl)propyl)(isobutyl) amino)-1-oxo-3-phenyl propan-2-yl)-4-methoxybenzamide (2.10d):



Molecular Formula: $C_{40}H_{47}N_3O_7$; R_f: 0.5 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-78.5% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.95 (s, 1H), 8.39 (m, 1H), 8.11-7.63 (m, 5H), 7.43-6.82 (m, 14H), 5.34 (d, *J* = 7.08 Hz, 1H), 4.45-4.25 (m, 1H), 3.92-2.98 (m, 20H), 1.95-1.71 (m, 1H), 0.82 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.8, 166.3, 16.1, 165.0, 164.5, 163.5, 162.4, 162.3, 162.2, 137.8, 137.3, 136.5, 136.4, 132.1, 129.6, 129.5, 129.3, 129.3, 129.2, 129.1, 129.0, 129.0, 128.9, 128.8, 128.8, 128.6, 128.5, 127.5, 127.1, 126.9, 126.8, 126.1, 125.9, 125.8, 124.4, 123.5, 121.9, 113.8, 113.7, 113.6, 85.3, 84.1, 83.2, 60.8, 59.9, 57.3, 56.9, 56.9, 55.4, 55.3, 54.7, 50.8, 50.5, 49.8, 49.4, 39.1, 39.0, 29.6, 28.7, 26.7, 20.1, 20.1, 20.0, 19.7; LRMS: (ES+) m/z = 682.4 (M+1)



Compound 2.10:

To a suspension of compound **2.9** (1 mmol) in THF (10 mL), DBU (1.5 mmol) was added and stirred the reaction mixture for 5 min. After completion of the reaction, reaction mixture concentrated and which was subjected to the next reaction without any purification.

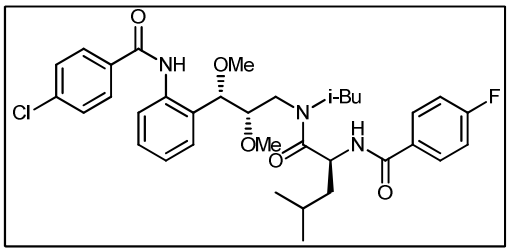
To a suspension of above compound (0.3 mmol) in DCM (10 mL), acid chloride (0.45 mmol) was added at 0 °C and allowed to stir for 10 min. After completion of

the reaction, reaction mixture was quenched with sodium bicarbonate solution (5 mL), and extracted with ethyl acetate (3 X 20 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography to give pure nitro amide.

To a suspension of above compound (1 mmol) in ethyl acetate (10 mL), 10% Pd/C (0.2 mmol) was added and stirred the reaction mixture for 12 h under hydrogen atmosphere. After completion of the reaction, reaction mixture was passed through celite and concentrated to leave 200 mg crude oil, which was subjected to the next reaction without any purification.

To a suspension of above compound (0.5 mmol) in DCM (10 mL), acid chloride (1 mmol) was added at 0 °C and allowed to stir for 10 min. After completion of the reaction, reaction mixture was quenched with sodium bicarbonate solution (5 mL), concentrated, and extracted with ethyl acetate (3 X 20 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography to give pure compound **2.10.**

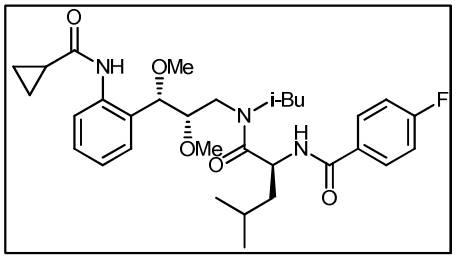
4-chloro-N-(2-((1S,2S)-3-((S)-2-(4-fluorobenzamido)-N-isobutyl-4-methylpentan amido)-1,2-dimethoxypropyl)phenyl)benzamide (2.10e):



Molecular Formula: $C_{35}H_{43}ClFN_3O_5$; R_f : 0.5 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-86.3% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 10.04 (s 1H), 8.42 (m, 1H), 8.04-7.69 (m, 4H), 7.53-6.88 (m, 9H), 5.29-5.11 (m, 1H), 4.57-4.25 (m, 1H), 4.02-3.09 (m, 11H), 2.15-1.92 (m, 1H), 1.84-1.65 (m, 1H), 1.41 (m, 1H), 1.11-0.81 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 173.5, 173.4, 165.8, 163.8, 137.5, 133.7, 129.5, 129.4, 129.4, 129.4, 129.3, 129.0, 128.8, 128.8, 128.6, 128.5, 126.1, 123.9, 121.8, 115.6, 115.5, 115.4, 115.3, 85.6, 84.5, 83.4, 60.7, 60.4, 57.3, 57.1, 57.0, 49.5, 49.4,

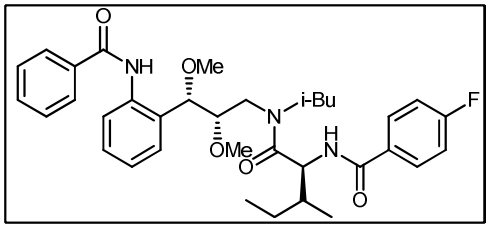
48.3, 47.9, 42.6, 28.6, 26.7, 24.9, 24.7, 23.5, 21.5, 21.5, 20.3, 19.9, 19.8 ; LRMS: (ES+) m/z = 640.1 (M+1)

N-((S)-1-(((2S,3S)-3-(2-(cyclopropanecarboxamido)phenyl)-2,3-dimethoxypropyl) (isobutyl)amino)-4-methyl-1-oxopentan-2-yl)-4-fluorobenzamide (2.10f):



Molecular Formula: $C_{32}H_{44}FN_3O_5$; R_f (solvent system): 0.5 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-60.0% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.29 (s, 1H), 8.09 (m, 1H), 7.82 (m, 2H), 7.50 (d, *J* = 8.43 Hz, 1H), 7.39-7.23 (m, 2H), 7.22-6.93 (m, 4H), 5.29-5.14 (m, 1H), 4.41 (m, 1H), 4.08-3.77 (m, 1H), 3.69 (m, 1H), 3.59-3.40 (m, 2H), 3.37-3.18 (m, 6H), 2.00 (m, 1H), 1.88-1.66 (m, 2H), 1.64-1.35 (m, 3H), 0.95 (m, 17H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 178.2, 173.6, 173.5, 166.3, 166.0, 165.8, 163.5, 136.6, 130.0, 129.9, 129.7, 129.7, 129.6, 129.5, 129.4, 129.3, 128.7, 128.6, 128.4, 124.7, 115.5, 115.4, 115.3, 115.2, 84.4, 83.2, 60.8, 60.4, 57.4, 57.1, 57.0, 54.3, 49.9, 49.7, 48.4, 47.9, 42.6, 41.8, 29.56, 28.5, 26.7, 24.9, 24.7, 23.5, 23.4, 21.5, 21.5, 20.2, 20.1, 19.8, 19.7, 12.5, 8.6, 7.6, 7.5 ; LRMS: (ES+) m/z = 570.1 (M+1)

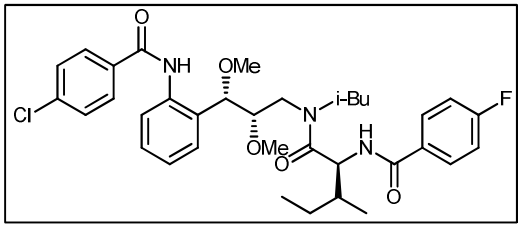
N-((2S,3R)-1-(((2S,3S)-3-(2-benzamidophenyl)-2,3-dimethoxypropyl)(isobutyl) amino)-3-methyl-1-oxopentan-2-yl)-4-fluorobenzamide (2.10g):



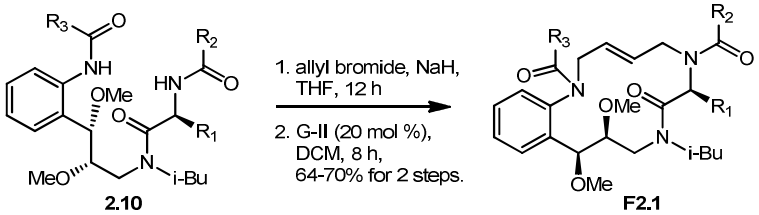
Molecular Formula: $C_{35}H_{44}FN_3O_5$; R_f : 0.5 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-86.3% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 10.06 (s, 1H), 8.42 (m, 1H), 8.06-

6.76 (m, 14H), 5.13-4.93 (m, 1H), 4.40 (m, 1H), 3.93-3.08 (m, 11H), 2.12-1.96 (m, 1H), 1.95-1.78 (m, 1H), 1.69-1.49 (m, 1H), 1.23-1.09 (m, 1H), 1.04-0.80 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.4, 172.3, 166.0, 165.9, 165.6, 164.8, 163.5, 137.6, 135.1, 134.9, 131.4, 131.4, 129.4, 129.3, 129.2, 129.2, 129.0, 128.9, 128.5, 128.5, 127.2, 127.0, 126.0, 123.8, 122.0, 115.6, 115.4, 86.0, 84.8, 83.9, 60.6, 60.2, 57.2, 57.0, 56.9, 54.8, 53.7, 53.5, 49.8, 49.1, 38.4, 38.2, 28.1, 26.6, 24.2, 23.9, 20.2, 20.0, 19.5, 16.0, 11.2, 11.1; LRMS: (ES+) m/z = 606.1 (M+1)

4-chloro-N-(2-((1S,2S)-3-((2S,3R)-2-(4-fluorobenzamido)-N-isobutyl-3-methylpentanamido) -1,2-dimethoxypropyl)phenyl)benzamide (2.10h):



Molecular Formula: $C_{35}H_{43}ClFN_3O_5$; R_f : 0.5 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-86.3% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 10.05 (s, 1H), 8.50 (d, *J* = 8.19 Hz, 1H), 8.04-7.90 (m, 2H), 7.88-7.67 (m, 2H), 7.51-7.30 (m, 3H), 7.22-6.78 (m, 4H), 5.12-4.90 (m, 1H), 4.37 (m, 1H), 3.89-3.05 (m, 10H), 2.11-1.96 (m, 1H), 1.93-1.81 (m, 1H), 1.64-1.51 (m, 1H), 1.25 (m, 1H), 1.05-0.82 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.6, 172.5, 166.0, 165.7, 163.8, 137.8, 137.7, 137.5, 1133.7, 133.4, 130.2, 129.5, 129.4, 129.3, 129.3, 129.3, 129.1, 129.0, 128.8, 128.8, 128.7, 128.7, 128.6, 126.1, 124.0, 122.0, 115.7, 115.5, 86.0, 84.9, 839, 60.7, 60.3, 57.3, 57.1, 57.0, 54.9, 53.8, 53.5, 49.2, 38.4, 38.3, 28.3, 26.7, 24.4, 24.0, 20.3, 20.1, 19.6, 16.1, 15.8, 11.3, 11.2; LRMS: (ES+) m/z = 640.1 (M+1)



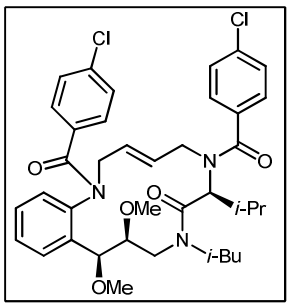
Macrocycle F2.1:

To a suspension of compound **2.10** (0.2 mmol) in dry THF (10 mL), allyl bromide (2 mmol), NaH (1 mmol) and TBAI (0.02 mmol) were added at 0 °C and allowed to stirred at room temperature for 10 h. After completion of the reaction, reaction

mixture was quenched with ammonium chloride solution (2 mL), concentrated, and extracted with ethyl acetate (3 X 20 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography (3:7 ethyl acetate/hexanes) to give the pure bisallyl product.

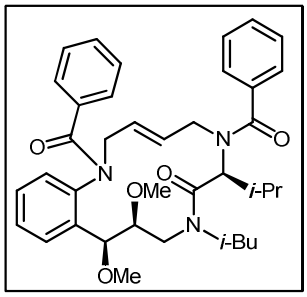
To above bisallyl compound (0.1 mmol) was taken in dry dichloromethane (50 mL) under nitrogen atmosphere and Grubb's 2nd generation catalyst (0.02 mmol) was added and reaction mixture was heated to 40 °C for 24 h. After completion of the reaction, reaction mixture was concentrated and subjected to column chromatography to give pure product **F2.1**.

((7S,11S,12S,E)-9-isobutyl-7-isopropyl-11,12-dimethoxy-8-oxo-7,8,9,10,11,12-hexahydro benzo[j][1,4,9]triazacyclotetradecine-1,6(2H,5H)-diyl)bis((4-chlorophenyl)methanone) (F2.1a):



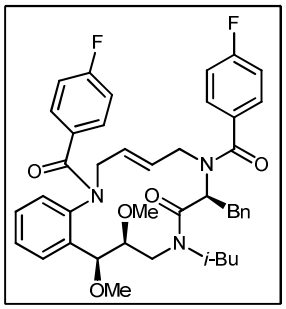
Molecular Formula: $C_{38}H_{45}Cl_2N_3O_5$; R_f : 0.3 (2:5 ethyl acetate/hexanes); Solvent system for column purification (2:5 to 1:2 ethyl acetate/hexanes); Yield-60% (colourless semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.57 (d, *J* = 7.64 Hz, 1H), 7.51 (d, *J* = 8.30 Hz, 2H), 7.40-7.24 (m, 7H), 7.14 (d, *J* = 8.46 Hz, 2H), 7.06 (d, *J* = 7.59 Hz, 1H), 5.68 (bd, *J* = 16.0, 1H), 5.46 (d, *J* = 10.8, 1H), 5.33 (bd, *J* = 16.0, 1H), 4.94 (m, 1H), 4.39 (s, 1H), 4.20-4.01 (m, 3H), 3.86 (d, *J* = 18.25 Hz, 1H), 3.61-3.51 (m, 1H), 3.40 (dd, *J* = 13.24, 9.46 Hz, 1H), 3.23 (d, *J* = 9.13 Hz, 1H), 3.13 (s, 3H), 2.84 (dd, *J* = 14.58, 7.98 Hz, 1H), 2.78 (s, 3H), 2.50 (dd, *J* = 6.55, 3.92 Hz, 1H), 2.23-2.11 (m, 1H), 1.08 (dd, *J* = 6.21, 5.01 Hz, 6H), 1.00 (dd, *J* = 13.27, 6.59 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.1, 170.3, 168.8, 142.8, 136.5, 135.2, 134.8, 134.6, 133.5, 130.7, 130.2, 128.9, 128.6, 128.3, 127.9, 127.8, 126.9, 126.5, 77.3, 59.0, 57.0, 55.9, 55.0, 54.6, 46.0, 44.8, 29.6, 29.1, 28.2, 20.2, 20.0, 19.8, 17.9; LRMS: (ES+) m/z = 694.0 (M+1)

((7S,11S,12S,E)-9-isobutyl-7-isopropyl-11,12-dimethoxy-8-oxo-7,8,9,10,11,12-hexahydro benzo[j][1,4,9]triazacyclotetradecine-1,6(2H,5H)-diyl)bis((4-chlorophenyl)methanone) (F2.1b):



Molecular Formula:$C_{38}H_{47}N_3O_5$; R_f : 0.3 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-68.5% (colourless semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.52 (m, 3H), 7.39-7.22 (m, 9H), 7.15 (t, *J* = 7.53 Hz, 2H), 7.06 (d, *J* = 7.44 Hz, 1H), 5.75 (d, *J* = 16.66 Hz, 1H), 5.48 (d, *J* = 10.63 Hz, 1H), 5.35 (d, *J* = 15.34 Hz, 1H), 4.94 (d, *J* = 15.05 Hz, 1H), 4.47 (s, 1H), 4.19-4.10 (m, 1H), 4.08-3.96 (m, 2H), 3.93 (s, 1H), 3.52 (dd, *J* = 16.14, 3.89 Hz, 1H), 3.39 (dd, *J* = 12.82, 9.63 Hz, 1H), 3.33-3.26 (m, 1H), 3.12 (s, 3H), 2.91 (dd, *J* = 14.51, 7.53 Hz, 1H), 2.75 (s, 3H), 2.58-2.47 (m, 1H), 2.17 (m, 1H), 1.09 (dd, *J* = 6.31, 4.03 Hz, 6H), 1.03 (d, *J* = 6.82 Hz, 3H), 0.99 (d, *J* = 6.41 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 173.0, 170.4, 143.3, 136.3, 135.5, 134.9, 130.6, 130.3, 129.2, 128.8, 128.7, 128.7, 128.1, 127.7, 127.5, 126.8, 126.6, 126.2, 79.4, 59.1, 57.0, 55.8, 54.9, 54.2, 46.0, 45.0, 29.6, 29.0, 28.1, 20.3, 20.0, 17.9; LRMS: (ES+) m/z = 626.4 (M+1)

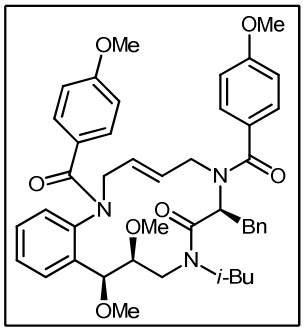
((7S,11S,12S,E)-7-benzyl-9-isobutyl-11,12-dimethoxy-8-oxo-7,8,9,10,11,12-hexahydro benzo[j][1,4,9]triazacyclotetradecine-1,6(2H,5H)-diyl)bis((4-fluorophenyl)methanone) (F2.1c):



Molecular Formula: $C_{42}H_{45}F_2N_3O_5$; R_f : 0.25 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-80%

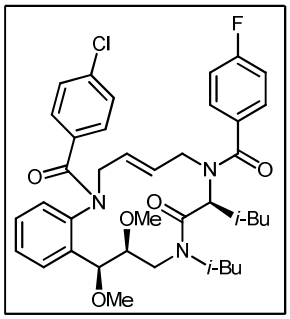
(colourless semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.56 (d, *J* = 7.67 Hz, 1H), 7.37-7.23 (m, 10H), 7.08 (m, 3H), 6.94 (t, *J* = 8.61 Hz, 2H), 6.82 (t, *J* = 8.49 Hz, 1H), 6.18 (t, *J* = 7.82 Hz, 1H), 5.70 (d, *J* = 16.0 Hz, 1H), 5.34 (d, *J* = 15.93 Hz, 1H), 4.94 (d, *J* = 16.32 Hz, 1H), 4.39 (d, *J* = 1.08 Hz, 1H), 4.22 (dd, *J* = 18.28, 1.91 Hz, 1H), 4.14 (dd, *J* = 14.64, 7.77 Hz, 1H), 4.02 (d, *J* = 12.17 Hz, 1H), 3.76 (d, *J* = 18.32 Hz, 1H), 3.54 (d, *J* = 3.74 Hz, 1H), 3.34 (dd, *J* = 13.17, 9.58 Hz, 1H), 3.28-3.10 (m, 7H), 2.85 (dd, *J* = 14.69, 6.86 Hz, 1H), 2.74 (s, 3H), 1.92 (dd, *J* = 9.78, 3.80 Hz, 1H), 0.97 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.1, 170.0, 168.8, 164.8, 164.2, 162.3, 161.8, 143.0, 136.5, 134.8, 131.9, 131.9, 131.4, 131.3, 131.3, 131.2, 130.8, 129.7, 129.6, 128.9, 128.7, 128.5, 128.4, 128.3, 128.3, 127.8, 126.9, 126.8, 126.6, 115.1, 114.9, 114.9, 114.7, 79.6, 77.2, 59.0, 55.9, 55.2, 54.7, 51.9, 45.8, 44.8, 36.4, 29.6, 28.8, 20.3, 19.6; LRMS: (ES+) m/z = 710.1 (M+1)

((7S,11S,12S,E)-7-benzyl-9-isobutyl-11,12-dimethoxy-8-oxo-7,8,9,10,11,12-hexahydro benzo[j][1,4,9]triazacyclotetradecine-1,6-(2H,5H)-diyl)bis((4-methoxyphenyl)methanone) (F2.1d):



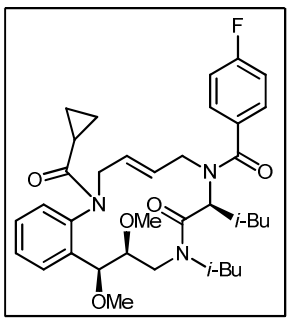
Molecular Formula: $C_{44}H_{51}N_3O_7$; R_f: 0.2 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-78.9% (colourless semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.57 (d, *J* = 7.31 Hz, 1H), 7.43-7.20 (m, 12H), 7.08 (m, 3H), 6.75 (d, *J* = 8.18 Hz, 2H), 6.64 (d, *J* = 8.08 Hz, 2H), 6.14 (t, *J* = 7.6 Hz , 1H), 5.75 (d, *J* = 15.93 Hz, 1H), 5.38 (d, *J* = 15.2 Hz, 1H), 4.90 (d, *J* = 16.0 Hz, 1H), 4.45 (s, 1H), 4.07 (m, 4H), 3.94-3.82 (m, 2H), 3.73 (m, 7H), 3.60-3.46 (m, 1H), 3.39-3.08 (m, 8H), 2.79 (s, 4H), 1.98-1.82 (m, 2H), 0.94 (d, *J* = 6.58 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.6, 170.1, 161.1, 160.2, 136.8, 130.9, 130.9, 130.7, 129.7, 128.8, 128.7, 128.3, 128.2, 128.1, 127.5, 127.4, 126.9, 126.6, 113.2, 112.9, 79.5, 77.2, 59.1, 55.2, 55.1, 55.0, 54.8, 52.2, 45.5, 45.1, 36.4, 29.6, 29.6, 28.6, 20.2, 19.5; LRMS: (ES+) m/z = 734.3 (M+1)

(7S,11S,12S,Z)-1-(4-chlorobenzoyl)-6-(4-fluorobenzoyl)-7,9-diisobutyl-11,12-dimethoxy-1,2,6,7,9,10,11,12-octahydrobenzo[j][1,4,9]triazacyclotetradecin-8(5H)-one (F2.1e):



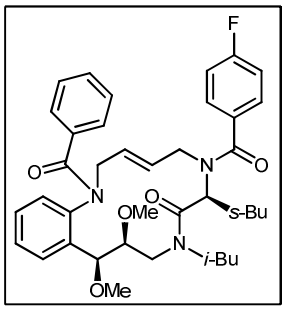
Molecular Formula:$C_{39}H_{47}ClFN_3O_5$; R_f : 0.35 (3:7 ethyl acetate/hexane); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-63.5%(colourless semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.55 (m, 3H), 7.30 (m, 5H), 7.14 (d, *J* = 8.49 Hz, 2H), 7.05 (dd, *J* = 11.83, 5.28 Hz, 3H), 5.90 (m, 1H), 5.70 (d, *J* = 15.6 Hz, 1H), 5.35 (d, *J* = 16.0 Hz, 1H), 4.90 (d, *J* = 15.6 Hz, 1H), 4.40 (s, 1H), 4.23-4.06 (m, 2H), 4.02 (d, *J* = 12.33 Hz, 1H), 3.90 (s, 1H), 3.60-3.49 (m, 1H), 3.37 (d, *J* = 13.19 Hz, 1H), 3.23 (d, *J* = 9.18 Hz, 1H), 3.13 (s, 3H), 2.91 (m, 1H), 2.78 (s, 3H), 2.18-2.01 (m, 1H), 1.90 (s, 1H), 1.65-1.48 (m, 2H), 1.13-0.97 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.0, 170.8, 168.9, 164.4, 161.9, 142.9, 136.6, 134.9, 130.8, 130.3, 128.9, 128.8, 128.7, 128.0, 127.8, 127.0, 126.5, 115.3, 115.1, 79.5, 59.0, 56.0, 55.1, 54.7, 49.1, 45.7, 44.6, 39.4, 31.8, 29.6, 28.8, 24.6, 23.5, 22.5, 20.5, 19.7, 14.0; LRMS: (ES+) m/z = 692.3 (M+1)

(7S,11S,12S,E)-1-(4-chlorobenzoyl)-6-(4-fluorobenzoyl)-7,9-diisobutyl -11,12-dimethoxy-1,2,6,7,9,10,11,12-octahydro benzo[j][1,4,9]triazacyclotetradecin-8(5H)-one (F2.1f):



Molecular Formula:$C_{36}H_{48}FN_3O_5$; R_f : 0.4 (1:3 ethyl acetate/hexanes); Solvent system for column purification (1:3 to 3:7 ethyl acetate/hexanes);Yield-58.5% (colourless semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.72 (d, *J* = 7.87 Hz, 1H), 7.51 (dd, *J* = 8.17, 5.54 Hz, 2H), 7.40 (m, 3H), 7.11 (dd, *J* = 10.31, 6.24 Hz, 3H), 5.95-5.86 (m, 1H), 5.50 (d, *J* = 16.4 Hz, 1H), 5.25 (d, *J* = 16.0 Hz, 1H), 4.70 (d, *J* = 14.8 Hz, 1H), 4.60 (s, 1H), 4.06 (m, 3H), 3.89-3.79 (m, 1H), 3.42 (s, 1H), 3.39-3.04 (m, 11H), 2.97-2.88 (m, 1H), 2.17-2.06 (m, 1H), 1.93-1.80 (m, 1H), 1.64-1.47 (m, 2H), 1.13-0.90 (m, 14H), 0.63 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 174.4, 172.1, 170.9, 143.1, 135.9, 130.9, 129.1, 128.9, 128.2, 128.2, 127.9, 127.1, 126.6, 115.3, 115.6, 79.1, 59.1, 56.8, 54.9, 52.9, 49.1, 45.4, 44.6, 39.3, 29.6, 28.7, 24.6, 23.5, 22.6, 20.5, 19.7, 12.8, 9.1, 8.7; LRMS: (ES+) m/z = 622.2 (M+1)

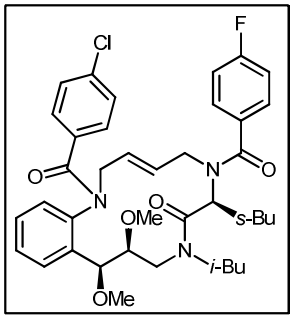
(7S,11S,12S,E)-1-benzoyl-7-sec-butyl-6-(4-fluorobenzoyl)-9-isobutyl-11,12-dimethoxy-1,2,6,7,9,10,11,12-octahydrobenzo[j][1,4,9] triazacyclotetradecin-8(5H)-one (F2.1g):



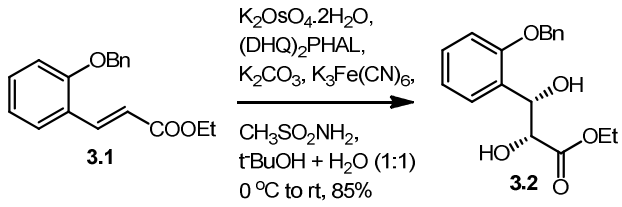
Molecular Formula: $C_{39}H_{48}FN_3O_5$; R_f :0.4 (1:3 ethyl acetate/hexanes); Solvent system for column purification (1:3 to 3:7 ethyl acetate/hexanes); Yield-65.6% (colourless semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.57 (m, 4H), 7.36-7.23 (m, 7H), 7.16 (d, *J* = 7.38 Hz, 3H), 7.10 (s, 2H), 7.04 (s, 2H), 5.75 (d, *J* = 15.6 Hz, 1H), 5.50 (d, *J* = 10.8 Hz, 1H), 5.35 (d, *J* = 15.6 Hz, 1H), 5.95 (d, *J* = 16.0 Hz, 1H), 4.42 (s, 1H), 4.25-4.14 (m, 1H), 4.05 (s, 2H), 3.94-3.82 (m, 1H), 3.61-3.50 (m, 1H), 3.45-3.35 (m, 1H), 3.29-3.21 (m, 1H), 3.13 (s, 3H), 2.93-2.81 (m, 1H), 2.69 (s, 3H), 2.37-2.24 (m, 2H), 1.81-1.63 (m, 1H), 1.59-1.46 (m, 1H), 1.13-1.05 (m, 6H), 1.01-0.91 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.3, 170.5, 170.0, 143.1, 135.3, 135.0, 132.4, 132.4, 130.6, 130.3, 128.9, 128.8, 128.7, 128.7, 128.6, 127.7, 127.6, 126.8, 126.7, 115.3, 115.1, 79.6, 59.0, 55.9, 55.8, 55.1, 54.5, 46.2, 44.9, 34.2, 31.8,

31., 29.6, 29.6, 29.3, 29.1, 23.9, 22.6, 20.3, 20.1, 16.0, 14.0, 11.0; LRMS: (ES+) m/z = 658.1 (M+1)

(7S,11S,12S,E)-7-sec-butyl-1-(4-chlorobenzoyl)-6-(4-fluorobenzoyl)-9-isobutyl-11,12-dimethoxy-1,2,6,7,9,10,11,12-octahydrobenzo[j][1,4,9]triazacyclotetradecin-8(5H)-one (F2.1h):



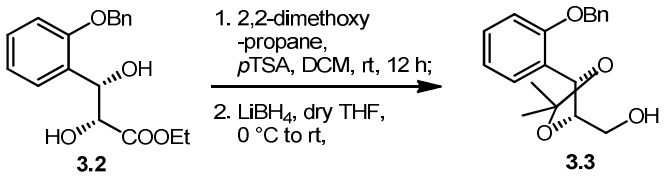
Molecular Formula:$C_{39}H_{47}ClFN_3O_5$; R_f : 0.25 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-71.2% (colourless semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.56 (dd, *J* = 8.14, 5.18 Hz, 3H), 7.39-7.23 (m, 5H), 7.14 (d, *J* = 8.46 Hz, 2H), 7.05 (t, *J* = 8.27 Hz, 3H), 5.70 (d, *J* = 16.0 Hz, 1H), 5.53 (d, *J* = 10.75 Hz, 1H), 5.35(d, *J* = 16.0 Hz, 1H), 4.95(d, *J* = 16.0 Hz, 1H), 4.40 (s, 1H), 4.25-4.15 (m, 1H), 4.06 (s, 2H), 3.93-3.82 (m, 1H), 3.61-3.51 (m, 1H), 3.45-3.35 (m, 1H), 3.26 (s, 1H), 3.14 (s, 3H), 2.89-2.80 (m, 1H), 2.78 (s, 3H), 2.37-2.24 (m, 1H), 2.24-2.11 (m, 1H), 1.58-1.47 (m, 1H), 1.26 (s, 3H), 1.13-1.05 (m, 7H), 1.01-0.91 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.2, 170.5, 168.8, 164.3, 161.8, 142.9, 136.6, 134.9, 133.6, 132.4, 132.4, 130.8, 130.3, 128.9, 128.6, 128.6, 128.0, 127.8, 126.9, 126.5, 115.3, 115.1, 79.5, 59.0, 56.0, 55.8, 55.1, 54.7, 46.2, 44.9, 34.2, 29.2, 23.9, 20.3, 20.1, 16.0, 15.9, 11.0; LRMS: (ES+) m/z = 692.3 (M+1)



(2R,3S)-ethyl 3-(2-(benzyloxy)phenyl)-2,3-dihydroxypropanoate (3.2):

Experimental procedure as per Ref. compound **2.2**

Molecular Formula: $C_{18}H_{20}O_5$; R_f (solvent system): 0.25 (3:7 ethyl acetate/hexanes); Yield-89.3% (colourless liquid); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.25-7.50 (m,, 7H), 7.03 (t, *J* = 7.50 Hz, 1H), 6.96 (d, *J* = 8.24 Hz, 1H), 5.44 (dd, *J* = 8.0, 2.0 Hz 1H), 5.18-5.06 (m, 2H), 4.51 (dd, *J* = 5.59, 2.32 Hz, 1H), 4.24 (m, 2H), 3.09 (d, *J* = 5.81 Hz, 1H), 2.94 (d, *J* = 8.12 Hz, 1H), 1.28-1.18 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 173.0, 155.0, 136.7, 128.8, 128.5, 128.5, 127.9, 127.2, 127.0, 121.0, 111.4, 73.2, 70.3, 69.9, 61.9, 14.0 ; LRMS: (ES+) m/z = 317.3 (M+1)

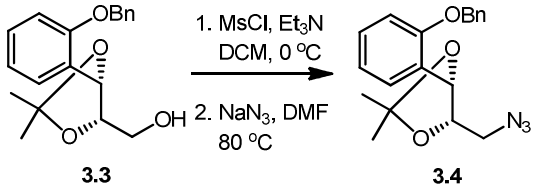


3.2 3.3

((4S,5S)-5-(2-(benzyloxy)phenyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanol (3.3):

Experimental procedure as per Ref. compound **2.3**

Molecular Formula: $C_{19}H_{22}O_4$; R_f : 0.3 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-90.8% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.58 (d, *J* = 7.60 Hz, 1H), 7.47-7.30 (m, 5H), 7.29-7.22 (m, 1H), 7.03 (t, *J* = 7.50 Hz, 1H), 6.95 (d, *J* = 8.23 Hz, 1H), 5.31 (d, *J* = 8.34 Hz, 1H), 5.12 (d, *J* = 11.52 Hz, 1H), 5.05 (d, *J* = 11.52 Hz, 1H), 3.88 (m, 1H), 3.78 (m, 1H), 3.67 (m, 1H), 1.56 (s, 3H), 1.52 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 155.7, 136.3, 128.9, 128.7, 128.2, 127.5, 127.0, m126.7, 121.4, 111.8, 108.9, 83.6, 73.7, 70.5, 61.8, 27.2, 27.0; LRMS: (ES+) m/z = 315.4 (M+1)

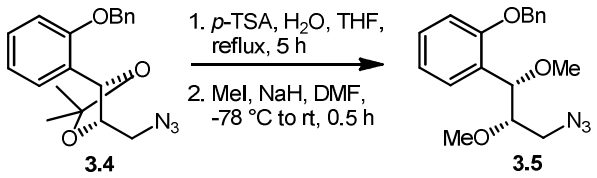


3.3 3.4

(4S,5S)-4-(azidomethyl)-5-(2-(benzyloxy)phenyl)-2,2-dimethyl-1,3-dioxolane (3.4):

Experimental procedure as per Ref. compound **2.4**

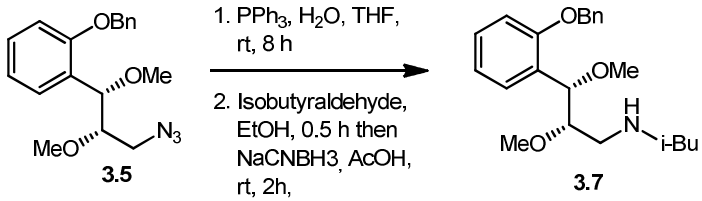
Molecular Formula: $C_{19}H_{21}N_3O_3$; R_f : 0.3 (1:9 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-86.5%



1-((1S,2S)-3-azido-1,2-dimethoxypropyl)-2-(benzyloxy)benzene (3.5):

Experimental procedure as per Ref. compound **3.5**

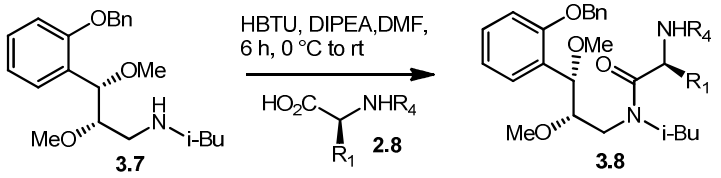
Molecular Formula: $C_{18}H_{21}N_3O_3$; R_f : 0.35 (1:4 ethyl acetate/hexanes); Solvent system for column purification (1:4 ethyl acetate/hexanes); Yield-99.8% (brown liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.35 (m, 7H), 7.02 (t, *J* = 7.42 Hz, 1H), 6.97 (d, *J* = 8.21 Hz, 1H), 5.11 (q, *J* = 11.86 Hz, 2H), 4.77 (d, *J* = 4.64 Hz, 1H), 3.57 (m, 1H), 3.37 (dd, *J* = 12.74, 7.77 Hz, 1H), 3.30 (s, 3H), 3.25 (d, *J* = 6.20 Hz, 3H), 3.16 (dd, *J* = 12.73, 4.23 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 156.2, 136.8, 128.8, 128.6, 127.9, 127.9, 127.1, 126.6, 121.1, 111.8, 83.1, 77.7, 70.1, 60.0, 57.3, 51.7; LRMS: (ES+) m/z = 328.4 (M+1)



(2S,3S)-3-(2-(benzyloxy)phenyl)-N-isobutyl-2,3-dimethoxypropan-1-amine (3.7):

Experimental procedure as per Ref. compound **2.7**

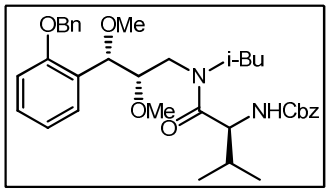
Molecular Formula: $C_{22}H_{31}NO_3$; R_f : 0.3 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-71.7% (brown liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.36 (m, 6H), 7.24 (t, *J* = 8.32 Hz, 1H), 7.00 (t, *J* = 7.46 Hz, 1H), 6.94 (d, *J* = 8.22 Hz, 1H), 5.14-5.03 (m, 2H), 4.79 (d, *J* = 5.45 Hz, 1H), 3.64-3.55 (m, 1H), 3.37 (s, 3H), 3.25 (d, *J* = 11.63 Hz, 3H), 2.69 (dd, *J* = 12.33, 8.37 Hz, 1H), 2.50 (dd, *J* = 12.39, 3.99 Hz, 1H), 2.30 (m, 2H), 1.65 (m, 1H), 0.85 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 156.2, 136.7, 128.2, 128.2, 127.8, 127.6, 127.4, 126.9, 120.7, 11.4, 83.1, 78.5, 69.8, 59.7, 57.7, 56.8, 50.2, 27.9, 20.3, 20.3; LRMS: (ES+) m/z = 358.5 (M+1)



Compound 3.8:

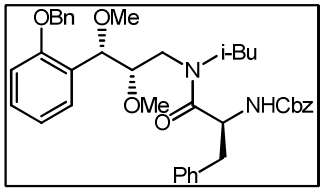
Experimental procedure as per Ref. compound **2.8**

Benzyl (S)-1-(((2S,3S)-3-(2-(benzyloxy)phenyl)-2,3-dimethoxypropyl)(isobutyl) amino)-3-methyl-1-oxobutan-2-ylcarbamate (3.8a):



MolecularFormula: $C_{35}H_{46}N_2O_6$; R_f : 0.75 (3:7 ethyl acetate/ hexanes); Solvent system for column purification (1:4 to 1:3 ethyl acetate/hexanes); Yield: 95.6% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.60-7.19 (m, 12H), 7.15-6.92 (m, 2H), 5.15-5.03 (m, 4H), 4.70 (m, 4H), 4.55-4.35 (m, 1H), 3.80-3.60 (m, 1H), 3.45-3.05 (m, 7H), 1.85-1.70 (m, 2H), 1.02-0.75 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.0, 171.6, 156.3, 156.2, 156.1, 136.9, 136.5, 128.8, 128.7, 128.6, 128.5, 128.4, 128.1, 128.0, 127.9, 127.9, 129, 127.8, 127.7, 127.7, 127.4, 127.3, 127.3, 126.9, 126.7, 121.3, 121.1, 121.0, 111.8, 111.8, 111.5, 83.9, 83.2, 82.4, 78.3, 70.2, 69.9, 66.6, 66.5, 60.5, 57.6, 57.3, 57.1, 57.0, 56.5, 55.7, 55.4, 53.9, 48.5, 48.3, 31.6, 31.4, 27.8, 26.4, 20.2, 20.1, 19.9, 19.8, 19.7, 19.4, 18.0, 16.8; LRMS: (ES+) m/z = 591.4 (M+1)

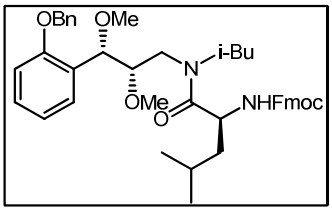
Benzyl (S)-1-(((2S,3S)-3-(2-(benzyloxy)phenyl)-2,3-dimethoxypropyl)(isobutyl) amino)-1-oxo-3-phenylpropan-2-ylcarbamate (3.8b):



Molecular Formula: $C_{39}H_{46}N_2O_6$; R_f : 0.35 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield: 88.9% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.29 (m, 16H), 7.06-6.90 (m,

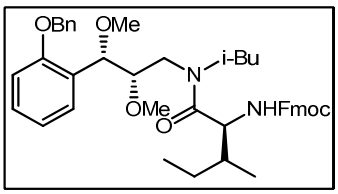
3H), 5.54-5.36 (m, 1H), 5.21-4.63 (m, 6H), 3.84-3.67 (m, 1H), 3.33-2.73 (m, 11H), 1.90-1.71 (m, 1H), 0.87-0.60 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.1, 171.6, 156.4, 156.1, 155.5, 155.4, 136.9, 136.8, 136.5, 136.4, 129.3, 128.8, 128.6, 128.6, 128.5, 128.4, 128.4, 128.1, 128.0, 127.9, 127.8, 127.8, 127.7, 127.4, 127.3, 126.9, 126.6, 121.3, 121.0, 111.8, 111.6, 83.7, 82.1, 78.1, 77.7, 70.2, 70.0, 66.5, 66.5, 60.6, 60.4, 57.2, 57.0, 56.3, 54.7, 52.1, 51.9, 49.0, 39.8, 39.6, 28.0, 26.6, 20.2, 20.1, 20.0, 19.6 ; LRMS: (ES+) m/z = 638.7 (M+1)

(9H-fluoren-9-yl)methyl(S)-1-(((2S,3S)-3-(2-(benzyloxy)phenyl)-2,3-dimethoxypropyl) (isobutyl)amino)-4-methyl-1-oxopentan-2-ylcarbamate (3.8c):

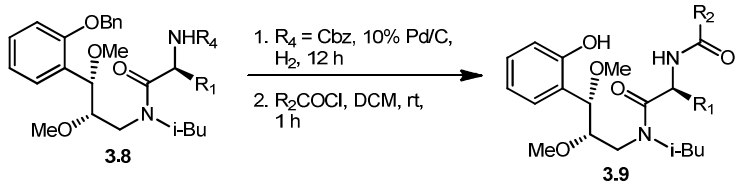


Molecular Formula: $C_{43}H_{52}N_2O_6$; R_f : 0.75 (3:7 ethyl acetate/hexanes); Solvent system for column purification (1:4 ethyl acetate/hexanes); Yield: 91.5% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.75 (d, *J* = 7.50 Hz, 2H), 7.58 (d, *J* = 7.37 Hz, 2H), 7.51-7.19 (m, 11H), 7.09-6.90 (m, 2H), 5.54 (m, 1H), 5.19-5.02 (m, 2H), 4.74 (m, 2H), 4.42-4.14 (m, 3H), 3.88-3.71 (m, 1H), 3.38 (m, 1H), 3.29-3.01 (m, 7H), 2.01-1.75 (m, 1H), 1.50 (m, 1H), 1.37-1.23 (m, 1H), 1.04-0.73 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 173.3, 172.6, 156.1, 156.0, 143.9, 143.8, 143.8, 141.2, 141.2, 136.9, 136.9, 128.6, 128.5, 128.5, 127.9, 127.9, 127.7, 127.6, 127.5, 127.4, 127.3, 127.2, 126.9, 125.2, 125.1, 125.1, 121.1, 121.1, 119.9, 119.8, 111.9, 111.6, 83.4, 82.1, 78.2, 70.2, 69.9, 66.7, 60.8, 57.3, 57.1, 56.5, 49.3, 49.1, 47.2, 47.1, 43.2, 42.8, 28.2, 26.5, 24.6, 24.4, 23.5, 21.4, 20.1, 19.8, 19.6; LRMS: (ES+) m/z = 693.5 (M+1)

(9H-fluoren-9-yl)methyl(2S,3R)-1-(((2S,3S)-3-(2-(benzyloxy) phenyl)-2,3-dimethoxypropyl) (isobutyl)amino)-3-methyl-1-oxo pentan-2-ylCarbamate (3.8d):



Molecular Formula: $C_{43}H_{52}N_2O_6$; R_f : 0.30 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield: 85.3% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.75 (d, *J* = 7.49 Hz, 2H), 7.58 (d, *J* = 7.30 Hz, 2H), 7.54-7.20 (m, 11H), 7.04 (t, *J* = 7.34 Hz, 1H), 6.94 (d, *J* = 8.20 Hz, 1H), 5.50 (d, *J* = 9.00 Hz, 1H), 5.09 (dd, *J* = 11.61, 8.19 Hz, 2H), 4.77-4.68 (m, 1H), 4.60-4.14 (m, 4H), 3.84 (t, *J* = 10.30 Hz, 2H), 3.47-2.99 (m, 8H), 1.90 (d, *J* = 7.22 Hz, 1H), 1.78-1.64 (m, 1H), 1.55-1.42 (m, 1H), 0.98-0.73 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.2, 171.7, 156.3, 156.2, 156.1, 144.0, 143.9, 143.9, 143.8, 141.2, 136.9, 128.7, 128.6, 128.5, 128.1, 127.9, 127.9, 127.7, 127.6, 127.6, 127.4, 127.3, 127.0, 126.9, 125.2, 125.1, 125.1, 121.3, 121.1, 119.9, 119.9, 111.8, 111.6, 83.9, 82.4, 78.3, 75.4, 70.2, 70.0, 66.7, 60.5, 57.2, 56.6, 55.5, 55.1, 48.6, 47.2, 47.1, 38.5, 38.3, 27.8, 26.4, 23.5, 23.4, 20.2, 20.1, 19.9, 19.5, 15.8, 11.4 ; LRMS: (ES+) m/z = 693.5 (M+1)



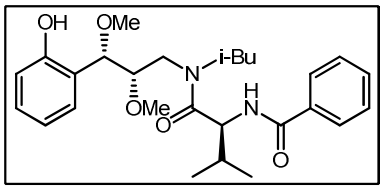
Compound 3.9:

To a suspension of compound **3.8** (1 mmol) in ethyl acetate (10 mL), 10% Pd/C (0.2 mmol) was added and stirred the reaction mixture for 12 h under hydrogen atmosphere. After completion of the reaction, reaction mixture was passed through celite and concentrated to leave 200 mg crude oil, which was subjected to the next reaction without any purification.

To a suspension of above compound (0.3 mmol) in DCM (10 mL), acid chloride (0.4 mmol) was added at 0 °C and allowed to stir for 10 min. After completion of the reaction, reaction mixture was quenched with sodium bicarbonate solution (5 mL), concentrated, and extracted with ethyl acetate (3 X 20 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and

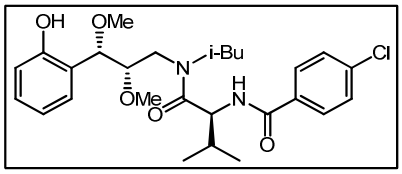
concentrated to leave a crude oil, which was purified by column chromatography to give pure compound **3.9**.

N-((S)-1-(((2S,3S)-3-(2-hydroxyphenyl)-2,3-dimethoxypropyl)(isobutyl)amino)-3-methyl-1-oxobutan-2-yl)benzamide (3.9a):



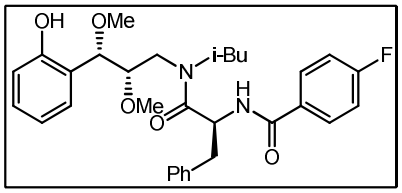
Molecular Formula: $C_{27}H_{38}N_2O_5$; R_f : 0.35 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 ethyl acetate/hexanes); Yield: 82.3% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.93 (m, 3H), 7.62-6.74 (m, 9H), 5.07 (m, 1H), 4.47-4.25 (m, 1H), 3.98-3.15 (m, 11H), 2.18-1.93 (m, 2H), 1.15-0.78 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.4, 172.1, 167.4, 166.8, 155.8, 155.3, 134.0, 134.0, 131.7, 131.6, 129.9, 129.5, 129.5, 129.4, 129.1, 128.5, 128.5, 128.2, 127.0, 122.9, 122.0, 120.1, 119.7, 117.5, 116.9, 85.1, 84.7, 83.6, 60.7, 60.4, 57.5, 57.5, 56.8, 54.6, 54.2, 53.8, 49.6, 49.0, 32.1, 32.0, 28.1, 26.7, 20.2, 20.1, 20.0, 20.0, 19.8, 19.4, 17.4, 17.3; LRMS: (ES+) m/z = 471.3 (M+1)

4-chloro-N-((S)-1-(((2S,3S)-3-(2-hydroxyphenyl)-2,3-dimethoxypropyl)(isobutyl) amino)-3-methyl-1-oxobutan-2-yl)benzamide (3.9b):



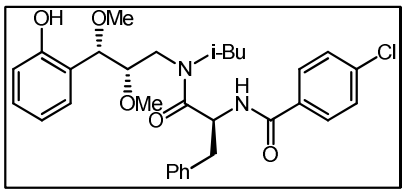
Molecular Formula: $C_{28}H_{40}N_2O_5$; R_f : 0.2 (1:4 ethyl acetate/hexanes); Solvent system for column purification (1:3 ethyl acetate/hexanes); Yield: 62.9% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.76 (m, 3H), 7.49-6.77 (m, 8H), 5.13-4.95 (m, 1H), 4.35 (m, 1H), 3.93-3.12 (m, 11H), 2.18-1.91 (m, 2H), 1.10-0.80 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.2, 172.0, 166.3, 165.8, 155.7, 155.2, 137.8, 132.4, 129.5, 129.5, 129.3, 129.1, 129.0, 128.8, 128.7, 128.7, 128.6, 128.6, 128.5, 128.4, 122.7, 122.0, 120.1, 119.8, 117.4, 117.0, 116.9, 85.0, 84.8, 83.7, 60.6, 60.4, 57.5, 56.8, 54.5, 54.3, 53.9, 49.5, 49.0, 32.0, 32.0, 28.0, 26.6, 20.2, 20.1, 20.0, 19.8, 19.4, 17.3, 17.2 ; LRMS: (ES+) m/z = 505.3 (M+1)

4-fluoro-N-((S)-1-(((2S,3S)-3-(2-hydroxyphenyl)-2,3-dimethoxypropyl)(isobutyl) amino)-1-oxo-3-phenylpropan-2-yl)benzamide (3.9c):

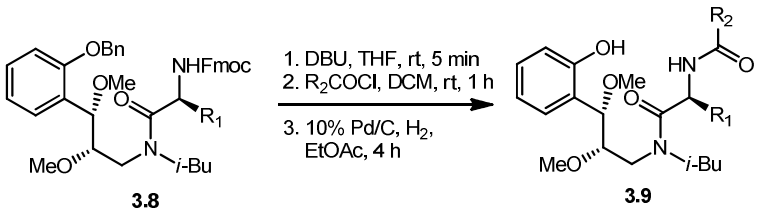


Molecular Formula: $C_{31}H_{37}FN_2O_5$; R_f : 0.3 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 ethyl acetate/hexanes); Yield: 85.7% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.74 (m, 2H), 7.34-6.75 (m, 14H), 5.35 (d, *J* = 7.67 Hz, 1H), 4.29 (dd, *J* = 13.53, 3.08 Hz, 1H), 3.95-3.68 (m, 2H), 3.58-2.95 (m, 13H), 1.84 (m, 2H), 0.92-0.70 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.3, 172.1, 165.9, 165.4, 155.8, 155.2, 136.2, 136.2, 129.6, 129.5, 129.4, 129.3, 129.3, 128.6, 128.5, 127.0, 126.9, 122.1, 120.1, 119.7, 117.4, 117.0, 115.6, 115.6, 115.4, 115.4, 84.6, 84.4, 83.3, 60.7, 60.1, 57.5, 57.4, 56.7, 54.9, 50.9, 50.6, 49.7, 49.2, 39.4, 39.3, 28.4, 26.8, 20.2, 20.1, 20.0, 19.6; LRMS: (ES+) m/z = 537.3 (M+1)

4-chloro-N-((S)-1-(((2S,3S)-3-(2-hydroxyphenyl)-2,3-dimethoxypropyl)(isobutyl) amino)-1-oxo-3-phenylpropan-2-yl)benzamide (3.9d):



Molecular Formula: $C_{31}H_{37}ClN_2O_5$; R_f : 0.4 (3:7 ethyl acetate/hexanes); Solvent system for column purification (1:3 ethyl acetate/hexanes); Yield: 83.6% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.67 (m, 3H), 7.50-6.74 (m, 14H), 5.35 (d, *J* = 7.34 Hz, 1H), 4.29 (m, 1H), 3.97-3.65 (m, 2H), 3.58-2.95 (m, 13H), 1.95-1.72 (m, 1H), 0.93-0.68 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.3, 172.2, 172.1, 165.9, 165.5, 155.8, 155.2, 137.9, 137.9, 136.1, 132.1, 132.1, 131.3, 129.6, 129.9, 129.5, 129.3, 129.3, 129.2, 128.7, 128.7, 128.6, 128.6, 128.5, 128.5, 128.5, 128.4, 127.1, 126.9, 122.5, 122.0, 120.2, 119.7, 117.4, 117.0, 84.6, 84.3, 83.3, 60.7, 60.1, 57.5, 57.4, 56.7, 54.9, 51.0, 50.6, 49.7, 49.2, 39.2, 28.4, 26.8, 20.2, 20.1, 20.0, 19.6; LRMS: (ES+) m/z = 553.3 (M+1)



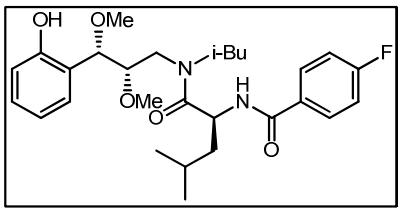
Compound 3.9:

To a suspension of compound **3.8** (1 mmol) in THF (10 mL), DBU (1.5 mmol) was added and stirred the reaction mixture for 5 min. After completion of the reaction, reaction mixture concentrated and which was subjected to the next reaction without any purification.

To a suspension of above compound (0.3 mmol) in DCM (10 mL), acid chloride (0.45 mmol) was added at 0 °C and allowed to stir for 10 min. After completion of the reaction mixture was quenched with sodium bicarbonate solution (5 mL), concentrated, and extracted with ethyl acetate (3 X 20 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography to give pure compound.

To a suspension of above compound (1 mmol) in ethyl acetate (10 mL), 10% Pd/C (0.2 mol) was added and stirred the reaction mixture for 12 h under hydrogen atmosphere. After completion of the reaction, reaction mixture was passed through celite and concentrated to leave 200 mg crude oil, which was purified by the column chromatography to give **3.9.**

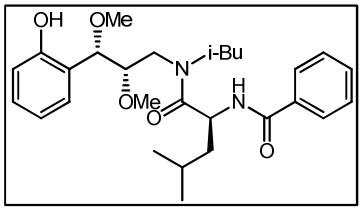
4-fluoro-N-((S)-1-(((2S,3S)-3-(2-hydroxyphenyl)-2,3-dimethoxypropyl)(isobutyl) amino)-4-methyl-1-oxopentan-2-yl)benzamide (3.9e):



Molecular Formula: $C_{28}H_{39}FN_2O_5$; R_f : 0.3 (1:4 ethyl acetate/hexanes); Solvent system for column purification (1:3 ethyl acetate/hexanes); Yield: 65.7% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.92 (m, 3H), 7.48-6.74 (m, 10H), 5.22 (m, 1H), 4.37 (m, 1H), 3.79 (m, 2H), 3.64-3.19 (m, 11H), 2.05 (m, 1H), 1.84-1.69 (m, 2H), 1.53-1.36 (m, 1H), 1.20-1.10 (m, 1H), 0.93 (m, 12H); ^{13}C NMR ($CDCl_3$,

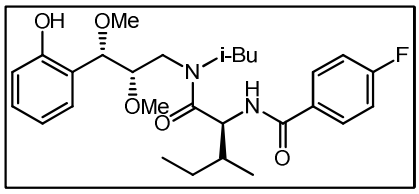
100 MHz): δ ppm 173.8, 173.6, 166.4, 165.9, 155.8, 155.3, 132.6, 132.5, 129.7, 129.6, 129.5, 129.5, 129.5, 129.2, 128.8, 122.4, 122.0, 120.1, 119.7, 117.3, 116.9, 1156.6, 115.5, 115.5, 115.3, 115.3, 115.3, 84.6, 84.3, 83.1, 60.6, 60.6, 57.4, 57.0, 54.2, 49.5, 47.9, 42.6, 42.2, 29.6, 29.6, 28.5, 26.7, 24.9, 24.7, 23.5, 23.5, 21.5, 21.5, 20.1, 20.1, 19.8, 19.7 ; LRMS: (ES+) m/z = 501.1 (M-1)

N-((S)-1-(((2S,3S)-3-(2-hydroxyphenyl)-2,3-dimethoxypropyl)(isobutyl)amino)-4-methyl-1-oxopentan-2-yl)benzamide (3.9f):



Molecular Formula: $C_{28}H_{40}N_2O_5$; R_f : 0.25 (1:4 ethyl acetate/hexanes); Solvent system for column purification (1:3 ethyl acetate/hexanes); Yield: 75.6% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.81 (m, 2H), 7.44 (m4H), 7.18 (m 1H), 7.04-6.75 (m, 4H), 5.29-5.18 (m, 1H), 4.37 (m, 1H), 3.97-3.20 (m, 11H), 2.13-1.87 (m, 2H), 1.83-1.66 (m, 2H), 1.43 (m, 1H), 0.94 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 173.4, 173.3, 167.2, 166.8, 155.8, 155.3, 134.0, 133.8, 131.6, 131.6, 129.5, 129.4, 129.2, 128.8, 128.5, 127.0, 127.0, 122.5, 122.1, 120.1, 119.7, 117.3, 116.9, 84.7, 84.6, 83.2, 60.6, 57.4, 56.9, 49.4, 47.7, 42.9, 42.7, 29.6, 28.5, 26.7, 24.8, 24.7, 23.5, 23.5, 21.6, 21.6, 20.1, 20.1, 19.9, 19.7; LRMS: (ES+) m/z = 485.3 (M+1)

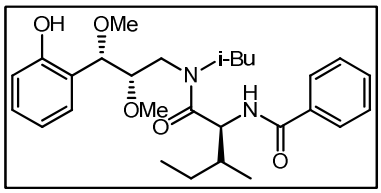
4-fluoro-N-((2S,3R)-1-(((2S,3S)-3-(2-hydroxyphenyl)-2,3-dimethoxypropyl) (isobutyl)amino) -3-methyl-1-oxopentan-2-yl)benzamide (3.9g):



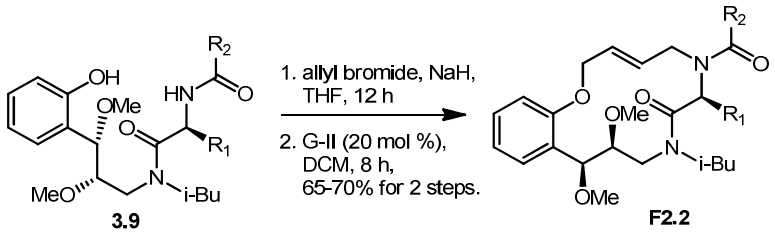
Molecular Formula: $C_{28}H_{39}FN_2O_5$; R_f : 0.2 (1:4 ethyl acetate/hexanes); Yield: 77.1% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.83 (m, 2H), 7.31-6.74 (m, 7H), 5.06 (m, 1H), 4.33 (m, 1H), 3.93-3.56 (m, 2H), 3.51-3.17 (m, 8H), 2.10-1.79 (m, 2H), 1.58 (m, 1H), 1.18 (m, 1H), 1.06-0.79 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.6, 172.2, 167.2, 166.7, 155.8, 155.3, 132.6, 132.5, 129.7, 129.6, 129.5,

129.5, 129.5, 129.2, 128.8, 122.4, 122.0, 120.1, 119.7, 117.3, 116.9, 1156.6, 115.5, 115.5, 115.3, 115.3, 115.3, 85.0, 83.6, 60.3, 56.9, 54.7, 53.4, 49.1, 38.6, 38.6, 29.6, 28.2, 26.7, 24.0, 20.2, 20.1, 20.0, n19.5, 16.0, 15.9, 11.3, 11.2; LRMS: (ES+) m/z = 503.3 (M+1)

N-((2S,3R)-1-(((2S,3S)-3-(2-hydroxyphenyl)-2,3-dimethoxypropyl)(isobutyl) amino)-3-methyl-1-oxopentan-2-yl)benzamide (3.9h):



Molecular Formula: $C_{28}H_{40}N_2O_5$; R_f: 0.2 (1:4 ethyl acetate/hexanes); Solvent system for column purification (1:3 ethyl acetate/hexanes); Yield: 62.9% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.81 (m, 3H), 7.56-7.36 (m, 3H), 7.25-6.73 (m, 6H), 5.10 (m, 1H), 4.33 (m, 1H), 3.93-3.58 (m, 2H), 3.51-3.19 (m, 8H), 2.10-1.78 (m, 2H), 1.70-1.53 (m, 2H), 1.23-1.12 (m, 1H), 1.07-0.79 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.6, 172.2, 167.2, 166.7, 158.8, 155.3, 134.0, 134.0, 131.7, 131.6, 129.5, 129.5, 129.4, 129.2, 128.5, 128.5, 127.1, 127.0, 122.8, 121.9, 120.1, 119.7, 117.6, 117.0, 109.9, 85.0, 83.6, 60.3, 56.9, 54.7, 53.4, 49.1, 38.6, 38.6, 29.6, 28.2, 26.7, 24.0, 20.2, 20.1, 20.0, 19.5, 16.0, 15.9, 11.3, 11.2; LRMS: (ES+) m/z = 485.3 (M+1)



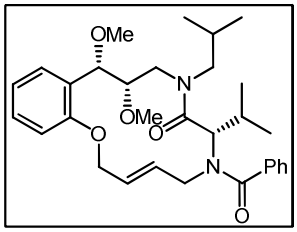
Macrocycle F2.2:

To a suspension of compound **3.9** (0.2 mmol) in dry THF, allybromide (1 mmol), NaH (2 mmol) and TBAI (0.02 mmol) were added at 0 °C and allowed to stirred at room temperature for 10 h. After completion of the reaction, reaction mixture was quenched with ammonium chloride solution, concentrated, and extracted with ethyl acetate (3 X 20 mL). Combined organic layer was washed with brine, dried over

anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography to give the compound pure bis allyl product.

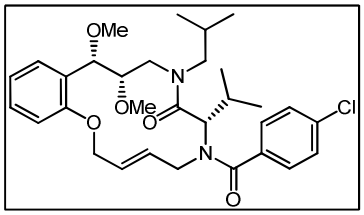
To suspension of above compound (0.069 mmol) was taken in dry dichloromethane (50 mL) under nitrogen atmosphere and Grubb's 2nd generation catalyst (0.0138 mmol) was added and reaction mixture was heated to 40 °C for 24 h. After completion of the reaction, reaction mixture was concentrated and subjected to column chromatography using to give pure compound **F2.2**.

(7S,11S,12S,E)-6-benzoyl-9-isobutyl-7-isopropyl-11,12-dimethoxy-6,7,9,10,11,12-hexahydro -2H-benzo[m][1,6,9]oxadiazacyclotetradecin -8(5H)-one (F2.2a):



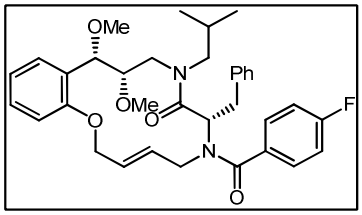
Molecular Formula: $C_{31}H_{42}N_2O_5$; R_f : 0.35 (3:7 ethyl acetate/hexanes); Solvent system for column purification (1:3 ethyl acetate/hexanes); Yield: 60.5% (colourless semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.46 (d, *J* = 6.73 Hz, 1H), 7.43-7.30 (m, 5H), 7.29-7.21 (m, 1H), 7.04 (t, *J* = 7.47 Hz, 1H), 6.79 (d, *J* = 8.08 Hz, 1H), 5.85 (ddd, *J* = 15.6 Hz, *J* = 8.8 Hz, *J* = 2.4 Hz, 1H), 5.46 (d, *J* = 10.61 Hz, 1H), 5.19 (dd, *J* = 15.65, 0.69 Hz, 1H), 4.71 (s, 1H), 4.37 (d, *J* = 0.71 Hz, 2H), 4.11 (dd, *J* = 13.01, 2.77 Hz, 1H), 4.04-3.76 (m, 4H), 3.48-3.34 (m, 4H), 3.12 (s, 3H), 2.94 (dd, *J* = 14.62, 7.43 Hz, 1H), 2.67-2.52 (m, 1H), 2.28-2.15 (m, 1H), 1.10-0.97 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): 172.2, 171.1, 155.2, 136.5, 129.2, 128.3, 128.1, 128.0, 127.8, 126.4, 124.9, 120.8, 110.7, 77.5, 65.0, 59.5, 57.2, 57.1, 54.7, 45.9, 45.7, 28.8, 27.3, 20.3, 20.0, 19.9, 17.7; LRMS: (ES+) m/z = 523.3 (M+1)

(7S,11S,12S,E)-6-(4-chlorobenzoyl)-9-isobutyl-7-isopropyl-11,12-dimethoxy-6,7,9,10,11,12-hexahydro-2H-benzo[m][1,6,9]oxadiazacyclotetradecin-8(5H)-one (F2.2b):



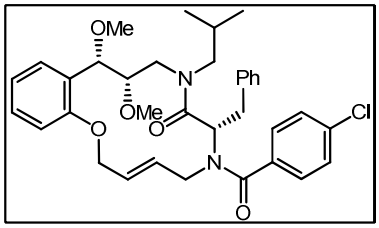
Molecular Formula: $C_{31}H_{41}ClN_2O_5$; R_f : 0.4 (3:7 ethyl acetate/hexanes); Solvent system for column purification (1:3 ethyl acetate/hexanes); Yield: 65.0% (colourless semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.46 (d, *J* = 7.38 Hz, 1H), 7.37 (d, *J* = 8.28 Hz, 2H), 7.33-7.22 (m, 3H), 7.04 (t, *J* = 7.47 Hz, 1H), 6.80 (d, *J* = 8.07 Hz, 1H), 5.80 (ddd, *J* = 16.0 Hz, *J* = 9.6 Hz, *J* = 2.4 Hz, 1H), 5.43 (d, *J* = 10.60 Hz, 1H), 5.26 (d, *J* = 15.85 Hz, 1H), 4.70 (s, 1H), 4.38 (s, 2H), 4.10 (dd, *J* = 12.97, 2.87 Hz, 1H), 4.02 (d, *J* = 16.36 Hz, 1H), 3.88 (dd, *J* = 14.60, 7.58 Hz, 1H), 3.79 (dd, *J* = 16.39, 9.00 Hz, 2H), 3.43 (dd, *J* = 12.79, 10.68 Hz, 1H), 3.37 (s, 3H), 3.12 (s, 3H), 2.93 (dd, *J* = 14.58, 7.48 Hz, 1H), 2.64-2.51 (m, 1H), 2.19 (dd, *J* = 13.59, 6.75 Hz, 1H), 1.10-0.94 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 171.2, 170.8, 155.2, 135.3, 134.9, 128.3, 128.3, 128.1, 128.0, 127.7, 126.3, 125.0, 120.8, 110.7, 64.9, 59.5, 57.3, 57.1, 54.7, 46.0, 45.7, 28.8, 27.3, 20.3, 20.0, 19.9, 17.7; LRMS: (ES+) m/z = 557.2 (M+1)

(7S,11S,12S,E)-7-benzyl-6-(4-fluorobenzoyl)-9-isobutyl-11,12-dimethoxy-6,7,9,10,11,12-hexahydro-2H-benzo[m][1,6,9]oxadiazacyclotetradecin-8(5H)-one (F2.2c):



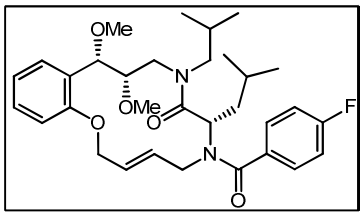
Molecular Formula: $C_{35}H_{41}FN_2O_5$; R_f : 0.4 (3:7 ethyl acetate/hexanes); Solvent system for column purification (1:3 ethyl acetate/hexanes); Yield: 79.6% (colourless semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.45 (t, *J* = 6.64 Hz, 1H), 7.36-7.22 (m, 7H), 7.08-6.94 (m, 5H), 6.80 (d, *J* = 8.00 Hz, 1H), 6.10 (t, *J* = 7.68 Hz, 1H), 5.85 (ddd, *J* = 15.6 Hz, *J* = 8.8 Hz, *J* = 2.4 Hz, 1H), 5.38-5.27 (m, 1H), 4.70 (s, 1H), 4.40 (d, *J* = 1.67 Hz, 2H), 4.21 (d, *J* = 16.41 Hz, 1H), 4.06 (dd, *J* = 12.90, 2.81 Hz, 1H), 3.91-3.71 (m, 3H), 3.43-3.32 (m, 4H), 3.27 (dd, *J* = 13.60, 7.21 Hz, 2H), 3.22-3.05 (m, 5H), 2.94 (dd, *J* = 14.62, 6.70 Hz, 1H), 2.09-1.93 (m, 1H), 0.99-0.91 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 170.9, 170.5, 155.1, 136.7, 132.1, 132.0, 129.7, 128.6, 128.6, 128.2, 128.2, 128.1, 127.7, 126.6, 126.3, 125.0, 120.8, 115.1, 114.8, 110.7, 77.6, 65.0, 56.4, 57.0, 54.8, 52.5, 45.8, 45.6, 35.7, 29.6, 28.3, 20.2, 19.4; LRMS: (ES+) m/z = 589.3 (M+1)

(7S,11S,12S,E)-7-benzyl-6-(4-chlorobenzoyl)-9-isobutyl-11,12-dimethoxy-6,7,9,10,11,12-hexahydro-2H-benzo[m][1,6,9]oxadiazacyclotetradecin-8(5H)-one (F2.2d):



Molecular Formula: $C_{35}H_{41}ClN_2O_5$; R_f : 0.4 (1:3 ethyl acetate/hexanes); Solvent system for column purification (1:3 ethyl acetate/hexanes); Yield: 75.8% (colourless semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.46 (d, *J* = 6.64 Hz, 1H), 7.36-7.22 (m, 10H), 7.04 (t, *J* = 7.42 Hz, 1H), 6.94 (d, *J* = 8.36 Hz, 2H), 6.80 (d, *J* = 7.96 Hz, 1H), 6.10 (t, *J* = 7.71 Hz, 1H), 5.85 (ddd, *J* = 15.2 Hz, *J* = 9.2 Hz, *J* = 2.4 Hz, 1H), 5.33 (d, *J* = 15.38 Hz, 1H), 4.70 (s, 1H), 4.40 (s, 2H), 4.21 (d, *J* = 16.44 Hz, 1H), 4.06 (dd, *J* = 12.98, 2.57 Hz, 1H), 3.80 (m, 3H), 3.42-3.33 (m, 4H), 3.31-3.06 (m, 7H), 2.95 (dd, *J* = 14.55, 6.62 Hz, 1H), 2.08-1.93 (m, 1H), 0.95 (dd, *J* = 6.50, 3.81 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 170.8, 170.5, 155.2, 136.7, 135.3, 134.4, 129.8, 128.3, 128.2, 128.2, 127.9, 127.69, 126.7, 126.3, 125.2, 120.9, 110.8, 77.6, 65.0, 59.5, 57.1, 54.9, 52.5, 45.8, 45.6, 35.7, 28.4, 20.2, 19.4; LRMS: (ES+) m/z = 605.3 (M+1)

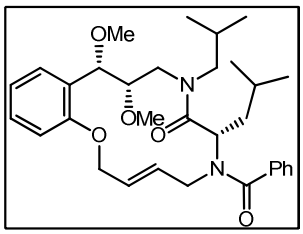
(7S,11S,12S,E)-6-(4-fluorobenzoyl)-7,9-diisobutyl-11,12-dimethoxy-6,7,9,10,11,12-hexahydro-2H-benzo[m][1,6,9]oxadiazacyclotetradecin-8(5H)-one (F2.2e):



Molecular Formula: $C_{32}H_{43}FN_2O_5$; R_f : 0.3 (1:4 ethyl acetate/hexanes); Solvent system for column purification (1:4 ethyl acetate/hexanes); Yield: 82.1% (colourless semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.46 (d, *J* = 7.26 Hz, 1H), 7.38 (dd, *J* = 8.30, 5.41 Hz, 2H), 7.26 (s, 1H), 7.07 (m, 4H), 6.80 (d, *J* = 8.08 Hz, 1H), 5.86 (d, *J* = 7.28 Hz, 1H), 5.80(ddd, *J* = 15.6 Hz, *J* = 9.2 Hz, *J* = 2.8 Hz, 1H), 5.33-5.24

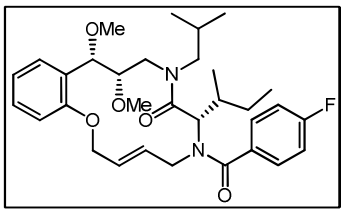
(m, 1H), 4.71 (s, 1H), 4.38 (s, 2H), 4.07 (d, *J* = 9.24 Hz, 2H), 3.95-3.73 (m, 3H), 3.37 (s, 4H), 3.12 (s, 3H), 3.02-2.94 (m, 1H), 2.17 (s, 1H), 1.75 (d, *J* = 6.81 Hz, 3H), 1.62-1.50 (m, 1H), 1.10-0.99 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 171.4, 171.0, 155.2, 132.4, 132.4, 128.9, 128.8, 128.3, 128.1, 127.7, 126.4, 125.1, 120.8, 115.3, 115.0, 110.8, 77.6, 65.0, 59.4, 57.2, 54.8, 49.7, 45.7, 45.5, 38.7, 29.6, 28.4, 24.7, 23.3, 22.8, 20.4, 19.6; LRMS: (ES+) m/z = 555.3 (M+1)

(7S,11S,12S,E)-6-benzoyl-7,9-diisobutyl-11,12-dimethoxy-6,7,9,10,11,12-hexahydro-2H benzo[m][1,6,9]oxadiazacyclotetradecin-8(5H)-one (F2.2f):



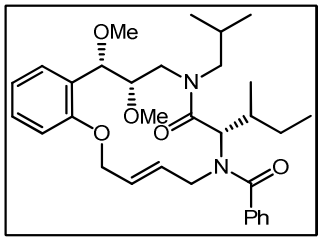
Molecular Formula: $C_{32}H_{44}N_2O_5$; R_f : 0.4 (1:3 ethyl acetate/hexanes); Solvent system for column purification (1:4 ethyl acetate/hexanes); Yield: 67.2% (colourless semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.40 (m, 7H), 7.26-7.22 (m, 1H), 7.04 (t, *J* = 7.44 Hz, 1H), 6.79 (d, *J* = 8.01 Hz, 1H), 5.94-5.78 (m, 2H), 5.23 (d, *J* = 15.70 Hz, 1H), 4.72 (s, 1H), 4.37 (s, 2H), 4.11-4.01 (m, 2H), 3.95 (dd, *J* = 14.52, 7.92 Hz, 1H), 3.86 (dd, *J* = 16.49, 8.92 Hz, 1H), 3.77 (dd, *J* = 10.28, 1.73 Hz, 1H), 3.43 (dd, *J* = 12.90, 10.50 Hz, 1H), 3.38 (s, 3H), 3.13 (s, 3H), 2.99 (dd, *J* = 14.59, 6.59 Hz, 1H), 2.22-2.09 (m, 1H), 1.84 (dd, *J* = 8.38, 5.47 Hz, 1H), 1.78-1.69 (m, 2H), 1.59 (dd, *J* = 13.09, 6.61 Hz, 2H), 1.12-0.99 (m, 13H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 171.9, 171.5, 155.3, 136.4, 129.3, 128.3, 128.1, 128.0, 127.6, 126.6, 126.5, 125.0, 120.8, 110.8, 77.6, 65.1, 59.4, 57.2, 49.6, 45.6, 45.4, 38.7, 28.3, 24.6, 23.4, 22.8, 20.5, 19.6; LRMS: (ES+) m/z = 537.4 (M+1)

(7S,11S,12S,E)-7-sec-butyl-6-(4-fluorobenzoyl)-9-isobutyl-11,12-dimethoxy-6,7,9,10,11,12-hexahydro-2H-benzo[m][1,6,9]oxadiazacyclotetradecin-8(5H)-one (F2.2g):



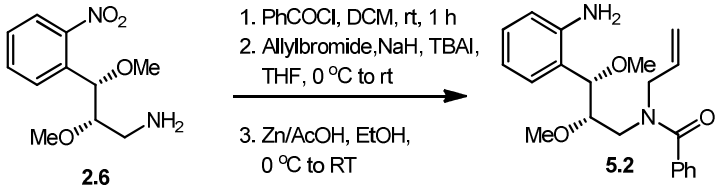
Molecular Formula: $C_{32}H_{43}FN_2O_5$; R_f : 0.3 (1:4 ethyl acetate/hexanes); Solvent system for column purification (1:4 ethyl acetate/hexanes); Yield: 67.5% (colourless semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.46 (d, *J* = 7.43 Hz, 1H), 7.35 (dd, *J* = 8.25, 5.44 Hz, 2H), 7.26 (dd, *J* = 9.00, 5.47 Hz, 1H), 7.13-7.00 (m, 3H), 6.79 (d, *J* = 8.08 Hz, 1H), 5.85 (ddd, *J* = 15.6 Hz, *J* = 9.2 Hz, *J* = 2.4 Hz, 1H), 5.48 (d, *J* = 10.71 Hz, 1H), 5.21 (d, *J* = 15.81 Hz, 1H), 4.69 (s, 1H), 4.37 (s, 2H), 4.10 (dd, *J* = 12.98, 2.82 Hz, 1H), 4.02 (d, *J* = 16.17 Hz, 1H), 3.93 (dd, *J* = 14.61, 7.44 Hz, 1H), 3.86-3.75 (m, 2H), 3.43 (dd, *J* = 12.75, 10.64 Hz, 1H), 3.37 (s, 3H), 3.12 (s, 3H), 2.92 (dd, *J* = 14.64, 7.54 Hz, 1H), 2.43-2.30 (m, 1H), 2.19 (m, 1H), 1.51-1.40 (m, 1H), 1.24-1.18 (m, 1H), 1.06 (t, *J* = 7.01 Hz, 6H), 1.00-0.92 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 171.3, 171.0, 155.2, 132.6, 132.6, 128.7, 128.6, 128.3, 128.1, 127.8, 126.3, 124.9, 120.8, 115.2, 115.0, 110.7, 77.6, 64.9, 59.5, 56.4, 56.3, 54.7, 46.1, 45.8, 33.3, 28.8, 23.8, 20.3, 19.9, 16.1, 11.1; LRMS: (ES+) m/z = 555.3 (M+1)

(7S,11S,12S,E)-7-sec-butyl-6-benzoyl-9-isobutyl-11,12-dimethoxy-6,7,9,10,11,12-hexahydro-2H-benzo[m][1,6,9]oxadiazacyclotetradecin-8(5H)-one (F2.2h):



Molecular Formula: $C_{32}H_{44}N_2O_5$; R_f: 0.3 (1:4 ethyl acetate/hexanes); Solvent system for column purification (1:4 ethyl acetate/hexanes); Yield: 68.3% (colourless semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.46 (d, *J* = 7.27 Hz, 1H), 7.43-7.30 (m, 5H), 7.25 (dd, *J* = 10.14, 2.65 Hz, 1H), 7.04 (t, *J* = 7.45 Hz, 1H), 6.79 (d, *J* = 8.03 Hz, 1H), 5.85 (ddd, *J* = 15.2 Hz, *J* = 8.8 Hz, *J* = 2.8 Hz, 1H), 5.50 (d, *J* = 10.74 Hz, 1H), 5.16 (d, *J* = 15.95 Hz, 1H), 4.70 (s, 1H), 4.35 (s, 2H), 4.11 (dd, *J* = 12.95, 2.83 Hz, 1H), 3.98 (dd, *J* = 14.41, 7.57 Hz, 2H), 3.88-3.77 (m, 2H), 3.43 (dd, *J* = 12.78, 10.53 Hz, 1H), 3.37 (s, 3H), 3.12 (s, 3H), 2.93 (dd, *J* = 14.61, 7.53 Hz, 1H), 2.44-2.32 (m, 1H), 2.27-2.13 (m, 1H), 1.55-1.44 (m, 1H), 1.25-1.18 (m, 1H), 1.07 (t, *J* = 6.49 Hz, 6H), 0.97 (dd, *J* = 6.57, 5.23 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.2, 171.1, 155.2, 136.5, 129.1, 128.3, 128.0, 128.0, 127.7, 126.4, 124.8, 120.7,

110.7, 77.5, 64.9, 59.4, 56.2, 56.2, 54.7, 46.1, 45.7, 33.3, 28.8, 23.7, 20.3, 19.9, 16.1, 11.1; LRMS: (ES+) m/z = 537.3 (M+1)



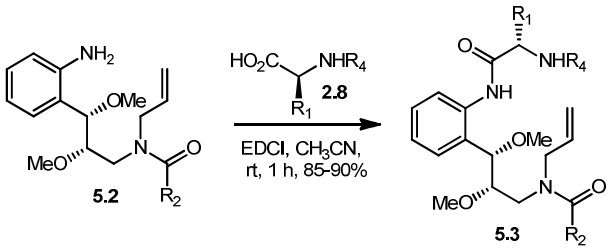
N-allyl-N-((2S,3S)-3-(2-aminophenyl)-2,3-dimethoxypropyl)benzamide (5.2):

To a suspension of **2.6** (2.0 g, 8.32 mmol) in DCM (20 mL), benzoyl chloride (1.75 g, 12.48 mmol) was added at 0 °C and allowed to stir for 5 min. After completion of the reaction, reaction mixture was quenched with sodium bicarbonate solution (15 mL), concentrated, and extracted with DCM (3 X 20 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography to give pure compound.

To suspension of above compound (1.0 g, 2.9 mmol) in dry THF, 60%NaH (348 mg, 14.5 mmol), allylbromide (1.25 mL, 14.5 mmol) and TBAI (10.7 mg, 0.029 mmol) were added at 0 °C, allowed to stir for 12 h. After completion the reaction mixture was quenched by using ammonium chloride solution (5 mL) and extracted with EtOAc (3 X 25 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was subjected next reaction without further purification.

To a suspension of above compound (1.5 g, 3.91 mmol) in EtOH (10 mL), Zn (5.07g, 78.03 mmol), AcOH (1.0 mL, 19.55 mmol) was added at 0 °C and allowed to stir the reaction mixture for 0.5 h. After completion of the reaction mixture was passed through celite and concentrated, to leave a crude oil, which was purified by column chromatography (2:3 ethyl acetate/hexane) to give the pure compound **5.2**.

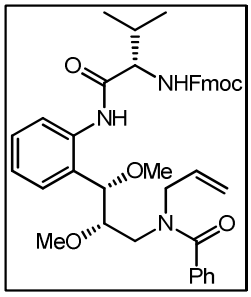
Molecular Formula: $C_{21}H_{26}N_2O_3$; R_f : 0.25 (2:3 ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): 7.28 (m, 5H), 7.13 (m, 2H), 6.83-6.47 (m, 2H), 5.93-5.56 (m, 1H), 5.11 (m, 2H), 4.42-3.75 (m, 6H), 3.66-3.13 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.2, 145.6, 136.5, 133.3, 129.5, 129.0, 128.7, 128.3, 128.1, 126.3, 125.2, 117.8, 117.2, 116.5, 85.0, 81.3, 60.2, 57.0, 57.0, 53.2, 47.7; LRMS: (ES+) m/z = 355.2 (M+1)



Compound 5.3:

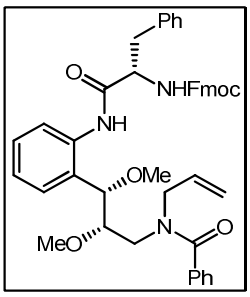
To a suspension of **5.2** (0.1 mmol) in Acetonitrile (10 mL), **2.8** (0.15 mmol), EDC·HCl (0.15 mmol) were added at room temperature and allowed to stirred for 3 h. After completion of the reaction mixture was quenched with sodium bicarbonate solution (5 mL), concentrated, and extracted with ethyl acetate (3 X 20 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography to give the pure compound **5.3.**

(9H-fluoren-9-yl)methyl(S)-1-(2-((1S,2S)-3-(N-allylbenzamido)-1,2-dimethoxypropyl) phenylamino)-3-methyl-1-oxobutan-2-ylcarbamate (5.3a):



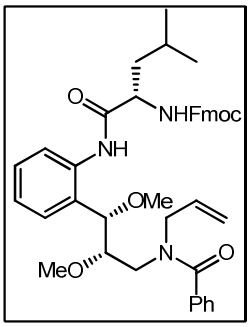
Molecular Formula: $C_{41}H_{45}N_3O_6$; R_f : 0.25 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 ethyl acetate/hexanes); Yield- 89% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.75 (s, 1H), 8.30 (d, *J* = 6.40 Hz, 1H), 7.76 (d, *J* = 7.42 Hz, 2H), 7.62 (d, *J* = 7.17 Hz, 2H), 7.47-7.24 (m, 10H), 7.14 (m, 2H), 5.87-5.50 (m, 2H), 5.25-5.03 (m, 2H),4.37 (m, 5H), 3.98 (m, 4H), 3.52-3.01 (m, 8H), 2.47-2.19 (m, 1H), 1.11-0.93 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.3, 169.4, 156.4, 143.8, 141.2, 136.1, 133.2, 129.6, 128.9, 127.7, 127.0, 127.0, 126.3, 125.2, 125.0, 124.1, 121.9, 119.9, 117.4, 85.5, 83.6, 67.0, 61.1, 60.3, 57.3, 53.5, 47.2, 30.9, 19.4, 17.4, 14.1; LRMS: (ES+) m/z = 676.4 (M+1)

(9H-fluoren-9-yl)methyl(S)-1-(2-((1S,2S)-3-(N-allylbenzamido)-1,2-dimethoxypropyl) phenylamino)-1-oxo-3-phenylpropan-2-ylcarbamate (5.3b):



Molecular Formula: $C_{45}H_{45}N_3O_6$; R_f : 0.26 (3:7 ethyl acetate/hexane); Solvent system for column purification (3:7ethyl acetate/hexanes); Yield- 80.9%(colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz) δ ppm 9.72 (s, 1H), 8.31 (d, *J* =7.49 Hz, 1H), 7.75 (d, *J* = 7.32 Hz, 2H), 7.53 (m, 2H), 7.43-7.07 (m, 17H), 5.98-5.78 (m, 1H), 5.69-5.47 (m, 1H), 5.06 (d, *J* = 11.30 Hz, 2H), 4.79-4.62 (m, 1H), 4.49 (s, 1H), 4.31 (s, 1H), 4.13 (m, 3H), 3.96 (m, 3H), 3.77-3.62 (m, 1H), 3.41-3.25 (m, 2H), 3.15 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.3, 171.1, 169.1, 169.0, 155.9, 143.7, 141.2, 136.7, 136.7, 136.1, 133.2, 129.7, 129.5, 129.0, 128.6, 128.5, 128.3, 127.7, 127.0, 126.9, 126.8, 126.3, 125.2, 125.0, 124.2, 122.0, 119.9, 117.3, 117.3, 85.8, 85.8, 83.4, 67.1, 60.3, 57.2, 56.9, 53.5, 53.5, 47.7, 47.1, 38.1; LRMS: (ES+) m/z = 724.4 (M+1)

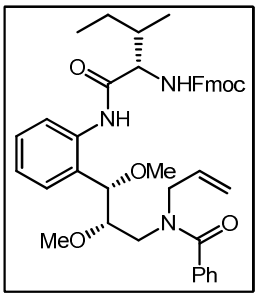
(9H-fluoren-9-yl)methyl (S)-1-(2-((1S,2S)-3-(N-allylbenzamido)-1,2-dimethoxypropyl) phenylamino)-4-methyl-1-oxopentan-2-ylcarbamate (5.3c):



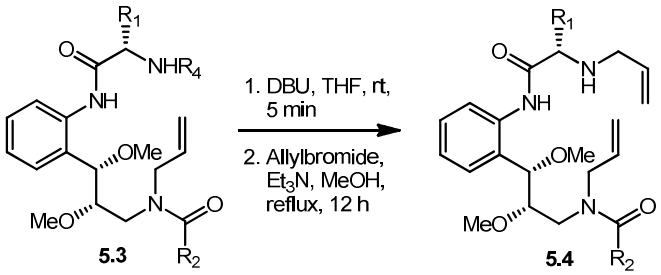
Molecular Formula: $C_{42}H_{47}N_3O_6$; R_f: 0.3 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 ethyl acetate/hexanes); Yield-85.4% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.75 (s, 1H), 8.29 (d, *J* =7.86 Hz, 1H), 7.77 (d, *J* = 7.35 Hz, 2H), 7.62 (d, *J* = 7.27 Hz, 2H), 7.47-7.26 (m, 10H), 7.19 (d, *J* = 6.91 Hz, 1H), 7.11 (d, *J* = 7.34 Hz, 1H), 5.86-5.73 (m, 1H), 5.73-5.57 (m, 1H), 5.26-5.03 (m, 2H), 4.58-4.47 (m, 1H), 4.47-4.18 (m, 4H), 4.03 (m, 3H), 3.75 (s, 1H), 3.49-3.37 (m, 1H), 3.26 (m, 6H), 1.94-1.69 (m, 4H), 1.65-1.50 (m, 1H), 0.99 (m, 6H); ^{13}C NMR

($CDCl_3$, 100 MHz): δ ppm 172.3, 170.5, 156.2, 143.8, 141.2, 136.8, 136.1, 132.2, 129.7, 129.6, 129.0, 127.1, 127.0, 127.0, 1256.3, 125.2, 125.1, 124.2, 122.1, 119.1, 117.4, 85.6, 83.5, 66.9, 60.4, 57.2, 54.6, 53.6, 47.5, 47.1, 41.9, 24.8, 23.1, 21.8; LRMS: (ES+) m/z = 690.4 (M+1)

(9H-fluoren-9-yl)methyl(2S,3R)-1-(2-((1S,2S)-3-(N-allylbenzamido)-1,2-dimethoxypropyl) phenylamino)-3-methyl-1-oxopentan-2-ylcarbamate (5.3d):



Molecular Formula: $C_{42}H_{47}N_3O_6$; R_f: 0.3 (3:7 ethyl acetate/hexanes);Solvent system for column purification (3:7 ethyl acetate/hexanes); Yield- 83.1% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.78 (s, 1H), 8.35 (d, *J* = 7.42 Hz, 1H), 7.77 (d, *J* = 7.42 Hz, 2H), 7.63 (d, *J* = 7.20 Hz, 2H), 7.47-7.27 (m, 11H), 7.18 (s, 1H), 7.11 (s, 1H), 5.85-5.56 (m, 2H), 5.25-5.02 (m, 2H), 4.60-4.44 (m, 1H), 4.30 (m, 4H), 3.98 (m, 3H), 3.87-3.72 (m, 1H), 3.55-3.36 (m, 1H), 3.27 (m, 7H), 2.19-2.06 (m, 1H), 1.91-1.73 (m, 1H), 1.67-1.47 (m, 1H), 1.26 (s, 1H), 1.10-0.86 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.3, 169.4, 156.3, 143.8, 143.8, 141.2, 136.8, 136.1, 133.2, 129.7, 129.0, 128.4, 127.7, 127.0, 127.0, 126.3, 125.2, 125.1, 124.1, 121.7, 119.9, 117.3, 85.4, 83.5, 67.0, 60.7, 60.4, 57.3, 53.5, 47.4, 47.1, 37.5, 24.5, 15.7, 11.7; LRMS: (ES+) m/z = 690.4 (M+1)



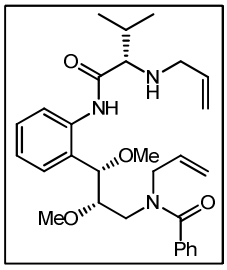
Compound 5.4:

To a suspension of compound **5.3** (0.1 mmol) in THF (10 mL), DBU (0.15 mmol) was added and stirred the reaction mixture for 5 min. After completion of the

reaction, reaction mixture concentrated and which was purified by column chromatography.

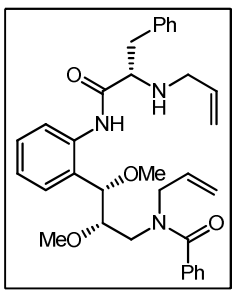
To a suspension of above compound (0.1 mmol) in MeOH (10 mL), allylbromide (0.5 mmol) and triethylamine (0.5 mmol) were added and allowed to reflux for 12 h. Concentrated the reaction mixture and purified by the column chromatography to give the pure compound **5.4.**

N-allyl-N-((2S,3S)-3-(2-((S)-2-(allylamino)-3-methylbutanamido)phenyl)-2,3-dimethoxypropyl) benzamide (5.4a):



Molecular Formula: $C_{29}H_{39}N_3O_4$; R_f : 0.25 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 ethyl acetate/hexanes); Yield- 65.8% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 10.25 (s, 1H), 8.39 (d, *J* = 8.18 Hz, 1H), 7.36 (m, 7H), 7.25-7.05 (m, 1H), 6.03-5.60 (m, 1H), 5.13 (m, 4H), 4.44-4.32 (m, 1H), 4.12-3.82 (m, 2H), 3.76-3.52 (m, 1H), 3.51-2.99 (m, 11H), 2.21 (s, 1H), 1.11-0.85 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.7, 172.1, 136.3, 133.3, 129.4, 128.8, 128.3, 126.3, 123.7, 122.0, 117.3, 116.2, 85.4, 82.6, 68.6, 62.0, 60.4, 57.1, 53.2, 59.1, 31.6, 29.6, 19.8, 18.1; LRMS: (ES+) m/z = 494.3 (M+1)

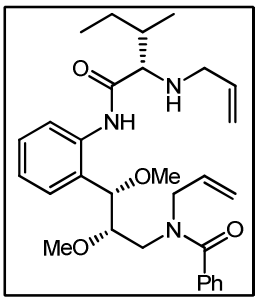
N-allyl-N-((2S,3S)-3-(2-((S)-2-(allylamino)-3-phenylpropanamido)phenyl)-2,3-dimethoxypropyl)benzamide (5.4b):



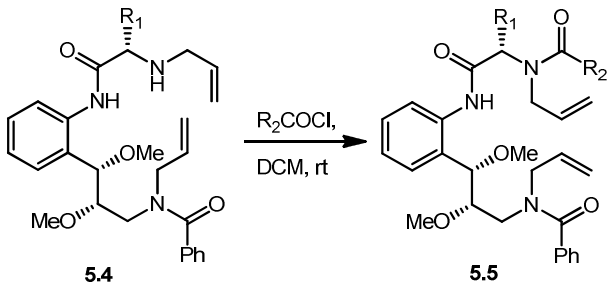
Molecular Formula: $C_{33}H_{39}N_3O_4$; R_f : 0.25 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 ethyl acetate/hexanes); Yield- 70.1% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 10.35 (s, 1H), 8.47-8.31 (m, 1H), 7.29 (m, 14H), 5.95-5.57 (m, 2H), 5.33-4.93 (m, 4H), 4.41-4.26 (m, 1H), 4.16-3.77 (m,

3H), 3.76-3.60 (m, 1H), 3.22 (m, 14H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.5, 172.2, 136.3, 133.3, 130.2, 129.5, 129.1, 128.3, 128.2, 126.7, 126.3, 123.8, 122.1, 117.2, 116.1, 85.8, 82.5, 64.2, 60.4, 57.0, 53.3, 51.0, 47.3, 39.2; LRMS: (ES+) m/z = 542.3 (M+1)

N-allyl-N-((2S,3S)-3-(2-((2S,3R)-2-(allylamino)-3-methylpentanamido)phenyl)-2,3-dimethoxypropyl)benzamide (5.4d):



Molecular Formula: $C_{30}H_{41}N_3O_4$; R_f (solvent system): 0.20 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 ethyl acetate/hexanes); Yield- 68.3% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 10.25 (s, 1H), 8.40 (d, *J* = 8.20 Hz, 1H), 7.37 (s, 6H), 7.24-7.17 (m, 1H), 7.15-6.87 (m, 1H), 6.04-5.59 (m, 2H), 5.14 (m, 4H), 4.48-4.30 (m, 1H), 4.11-3.80 (m, 3H), 3.77-3.56 (m, 1H), 3.24 (m, 10H), 2.00-1.86 (m, 1H), 1.31-1.15 (m, 1H), 1.03 (d, *J* = 6.92 Hz, 3H), 0.92 (d, *J* = 6.84 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.6, 172.1, 136.3, 133.3, 129.5, 129.4, 129.4, 128.8, 128.3, 126.3, 123.4, 122.0, 117.3, 116.3, 85.4, 82.6, 77.4, 67.8, 60.4, 57.1, 53.3, 51.9, 47.1, 38.5, 25.2, 16.1; LRMS: (ES+) m/z = 508.3 (M+1)

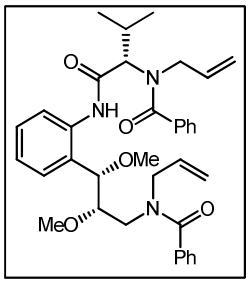


Compound 5.5:

To a suspension of **5.4** (0.1 mmol) in DCM (10 mL), acid chloride (0.15 mmol) was added at 0 °C and allowed to stir for 5 min. After completion of the reaction mixture was quenched with sodium bicarbonate solution (5 mL), concentrated, and extracted

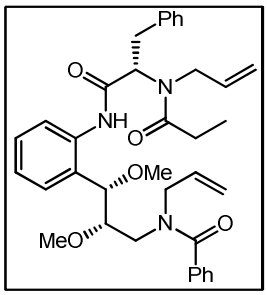
with DCM (3 X 20 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography to give pure compound **5.5**.

N-allyl-N-((S)-1-(2-((1S,2S)-3-(N-allylbenzamido)-1,2-dimethoxypropyl)phenyl amino)-3-methyl-1-oxobutan-2-yl)benzamide (5.5a):



Molecular Formula: $C_{36}H_{43}N_3O_5$, R_f : 0.40 (2:3 ethyl acetate/hexanes), Solvent system for column purification (2;3 ethyl acetate/hexanes); Yield-82.6% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.70 (s, 1H), 8.17-7.95 (m, 1H), 7.38 (m, 12H), 7.20-6.96 (m, 2H), 5.85-5.56 (m, 2H), 5.26-5.03 (m, 2H), 5.00-4.65 (m, 2H), 4.55-4.34 (m, 1H), 3.97 (m, 6H), 3.36 (m, 9H), 2.62-2.44 (m, 1H), 1.08-0.80 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 173.2, 172.2, 168.4, 136.3, 133.9, 133.2, 129.9, 129.4, 129.1, 128.3, 128.3, 126.7, 126.3, 124.4, 123.1, 117.3, 83.7, 82.6, 65.2, 62.1, 60.5, 57.1, 53.4, 47.2, 33.4, 30.1, 26.8, 19.9, 18.6, 15.8, 13.3; LRMS: (ES+) m/z = 598.4 (M+1)

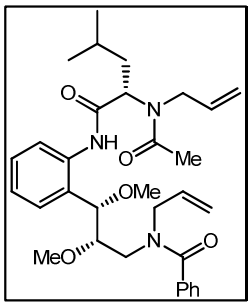
N-allyl-N-((2S,3S)-3-(2-((S)-2-(N-allylpropionamido)-3-phenylpropanamido) phenyl)-2,3-dimethoxypropyl)benzamide (5.5b):



Molecular Formula: $C_{36}H_{43}N_3O_5$, R_f : 0.45 (2:3 ethyl acetate/hexanes), Solvent system for column purification (2:3 ethyl acetate/hexanes); Yield-83.8% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.50 (s, 1H), 8.36-8.04 (m, 1H), 7.57-6.96 (m, 14H), 5.90-5.51 (m, 2H), 5.44-4.97 (m, 5H), 4.45-4.22 (m, 1H), 3.96 (s, 5H), 3.74-3.37 (m, 3H), 3.16 (m, 8H), 2.50-2.20 (m, 2H), 1.09 (t, *J* = 7.27 Hz, 3H);

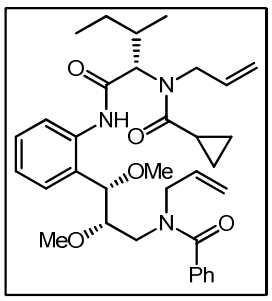
^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 174.8, 172.2, 168.6, 137.9, 136.3, 134.4, 133.2, 129.1, 128.6, 128.4, 128.3, 128.2, 126.3, 126.3, 124.0, 122.2, 117.4, 117.0, 85.0, 83.0, 77.4, 60.3, 60.3, 57.0, 48.7, 47.1, 34.6, 26.7, 9.2; LRMS: (ES+) m/z = 598.4 (M+1)

N-allyl-N-((2S,3S)-3-(2-((S)-2-(N-allylacetamido)-4-methylpentanamido)phenyl)-2,3-dimethoxypropyl)benzamide (5.5c):



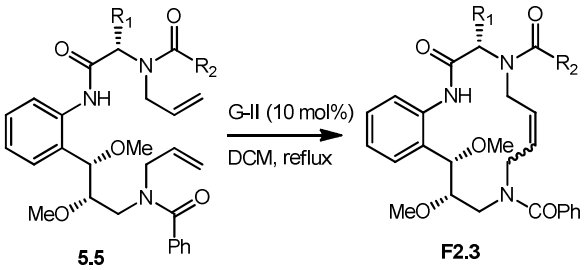
Molecular Formula: $C_{32}H_{43}N_3O_5$, R_f (solvent system): 0.35 (3:7 ethyl acetate/hexanes), Solvent system for column purification (2:3 ethyl acetate/hexanes); Yield-79.4% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.60 (s, 1H), 8.43-8.28 (m, 1H), 7.38 (s, 7H), 7.23-7.00 (m, 2H), 5.96-5.61 (m, 2H), 5.47-5.32 (m, 1H), 5.20 (m, 5H), 4.44-4.29 (m, 1H), 4.27-3.84 (m, 5H), 3.80-3.65 (m, 1H), 3.62-3.43 (m, 1H), 3.28 (m, 7H), 2.18 (s, 3H), 2.10-1.87 (m, 2H), 1.77-1.50 (m, 4H), 0.97 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.2, 172.0, 169.5, 136.2, 134.8, 133.2, 129.6, 128.7, 128.4, 126.3, 123.8, 121.6, 117.4, 116.9, 85.5, 83.3, 60.4, 57.3, 56.4, 53.3, 53.3, 48.5, 47.2, 37.3, 24.9, 24.3, 22.7, 22.0; LRMS: (ES+) m/z = 550.3 (M+1)

N-allyl-N-((2S,3S)-3-(2-((2S,3R)-2-(N-allylcyclopropanecarboxamido)-3-methylpentanamido)phenyl)-2,3-dimethoxypropyl)benzamide (5.5d):



Molecular Formula: $C_{34}H_{45}N_3O_5$, R_f : 0.40 (2:3 ethyl acetate/hexanes), Solvent system for column purification (2:3ethyl acetate/hexanes); Yield-75.2% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.50 (s, 1H), 8.15-7.96 (m, 1H), 7.53-

7.19 (m, 7H), 7.17-6.87 (m, 1H), 6.02-5.61 (m, 2H), 5.35-5.05 (m, 4H), 4.97-4.73 (m, 1H), 4.39 (s, 3H), 3.97 (s, 3H), 3.84-3.60 (m, 1H), 3.30 (m, 7H), 2.25-2.08 (m, 1H), 1.77 (m, 1H), 1.53-1.37 (m, 1H), 0.94 (m, 9H), 0.76 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 174.9, 172.2, 168.6, 136.3, 135.1, 133.3, 128.3, 126.3, 124.2, 122.9, 122.9, 117.3, 116.2, 83.6, 82.5, 62.7, 60.2, 57.0, 53.3, 47.0, 46.6, 32.9, 24.6, 15.7, 12.0, 10.7, 8.8, 8.5, 8.2; LRMS: (ES+) m/z = 576.4 (M+1)

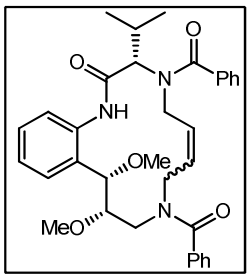


5.5 F2.3

Macrocycle F2.3:

To above bisallyl compound **5.5** (0.1 mmol) in dry dichloromethane (50 mL) under nitrogen atmosphere and Grubbs' 2nd generation catalyst (0.01 mmol) was added and reaction mixture was heated to 40 °C for 24 h. After completion of the reaction, reaction mixture was concentrated and subjected to column chromatography to give pure product **F2.3**.

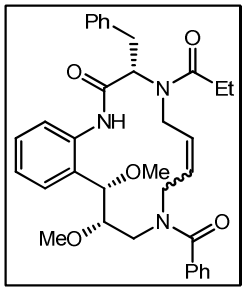
((3S,11S,12S,Z/E)-3-isopropyl-11,12-dimethoxy-2-oxo-2,3,11,12-tetrahydrobenzo [m][1,4,9] triazacyclotetradecine-4,9(1H,5H,8H,10H)-diyl)bis(phenyl methanone) (F2.3a):



Molecular Formula: $C_{34}H_{39}N_3O_5$; R_f : 0.3 (2:3 ethyl acetate/hexane); Solvent system for column purification (2:3ethyl acetate/hexanes); Yield-78%(white semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.16-8.54 (m, 1H), 8.26-6.82 (m, 18H), 6.24-5.74 (m, 1H), 5.71-4.62 (m, 2H), 4.60-3.72 (m, 7H), 3.68-2.80 (m, 11H), 2.78-2.37 (m, 2H), 1.19 (dd, *J* = 31.69, 25.73 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.6, 172.3, 167.5, 136.4, 135.4, 130.2, 129.5, 129.3, 128.7, 128.3, 127.2, 126.6, 125.0,

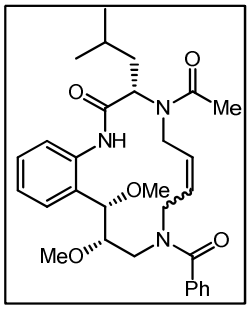
90.1, 80.5, 67.6, 60.3, 59.3, 57., 54.8, 48.7, 41.3, 29.6, 27.1, 20.0, 18.5; LRMS: (ES+) m/z = 570.3 (M+1)

(3S,11S,12S,Z/E)-9-benzoyl-3-benzyl-11,12-dimethoxy-4-propionyl-3,4,5,8,9,10,11,12-octahydrobenzo[m][1,4,9]triazacyclotetradecin-2(1H)-one (F2.3b):



Molecular Formula: $C_{34}H_{39}N_3O_5$; R_f: 0.3 (2:3 ethyl acetate/hexane); Solvent system for column purification (2:3ethyl acetate/hexanes); Yield-81%(white semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.57-8.88 (m, 1H), 8.54-7.93 (m, 1H), 7.69-6.87 (m, 14H), 6.21-5.52 (m, 2H), 4.40-3.66 (m, 4H), 3.33 (m, 11H), 2.63-2.10 (m, 3H), 0.92 (d, *J* = 6.49 Hz, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 173.9, 173.0, 172.4, 137.0, 136.9, 136.4, 135.9, 133.5, 129.5, 129.3, 129.1, 128.8, 128.4, 127.0, 126.6, 124.4, 121.5, 90.6, 81.7, 77.2, 62.7, 60.0, 56.8, 33.9, 31.8, 29.6, 25.7, 22.6, 14.0, 9.2; LRMS: (ES+) m/z = 570.3 (M+1)

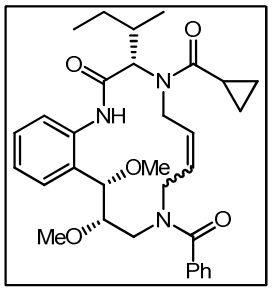
(3S,11S,12S,Z/E)-4-acetyl-9-benzoyl-3-isobutyl-11,12-dimethoxy-3,4,5,8,9,10,11,12-octahydrobenzo[m][1,4,9]triazacyclotetradecin-2(1H)-one (F2.3c):



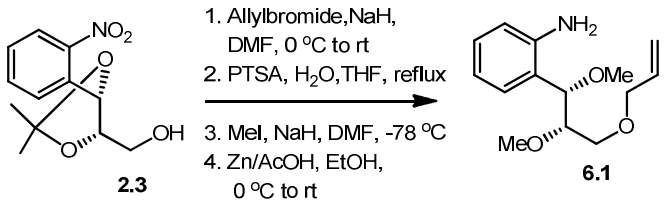
Molecular Formula: $C_{30}H_{39}N_3O_5$; R_f: 0.3 (2:3 ethyl acetate/hexanes); Solvent system for column purification (2:3ethyl acetate/hexanes); Yield-76% (white semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.60-8.98 (m, 1H), 8.66-7.97 (m, 1H), 7.64-6.73 (m, 8H), 6.32-5.33 (m, 3H), 4.39-4.17 (m, 1H), 4.15-3.77 (m, 3H), 3.72-2.98 (m,

8H), 2.33 (s, 4H), 1.99-1.84 (m, 1H), 1.84-1.67 (m, 1H), 1.69-1.46 (m, 2H), 1.11-0.90 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 173.2, 172.4, 170.8, 170.3, 169.5, 167.8, 136.5, 135.9, 133.7, 130.7, 129.8, 129.5, 129.1, 128.3, 128.0, 127.3, 126.6, 124.4, 121.7, 90.8, 81.7, 81.0, 69.4, 60.3, 60.2, 60.1, 59.0, 57.7, 56.8, 55.0, 53.7, 53.5, 49.2, 44.8, 40.5, 37.3, 36.1, 31.8, 31.7, 29.6, 29.3, 29.2, 24.6, 24.6, 23.1, 22.7, 22.1, 21.7, 14.0; LRMS: (ES+) m/z = 522.3 (M+1)

(3S,11S,12S,Z/E)-9-benzoyl-3-sec-butyl-4-(cyclopropanecarbonyl)-11,12-dimethoxy-3,4,5,8,9,10,11,12-octahydrobenzo[m][1,4,9]triazacyclotetra decin-2(1H)-one (F2.3d):



Molecular Formula: $C_{32}H_{41}N_3O_5$; R_f: 0.2 (1:1 ethyl acetate/hexanes); Solvent system for column purification (2:3ethyl acetate/hexanes); Yield-77% (white semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.43-8.84 (m, 1H), 8.27-7.91 (m, 1H), 7.51-7.24 (m, 7H), 7.23-6.75 (m, 2H), 6.20-5.62 (m, 2H), 5.17-4.50 (m, 2H), 4.47-3.73 (m, 6H), 3.50 (d, *J* = 76.44 Hz, 9H), 2.52-2.14 (m, 2H), 2.02-1.77 (m, 1H), 1.27 (d, *J* = 7.18 Hz, 4H), 1.13-0.79 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 173.6, 173.1, 172.5, 136.6, 135.8, 133.2, 130.1, 129.6, 128.3, 127.2, 126.6, 124.5, 122.8, 90.6, 81.6, 77.2, 66.4, 61.0, 42.6, 29.6, 24.5, 20.5, 16.0, 14.1, 11.7, 11.5, 8.4; LRMS: (ES+) m/z = 548.3 (M+1)



(2-((1S,2S)-3-(allyloxy)-1,2-dimethoxypropyl)aniline (6.1):

To a suspension of **2.3** (500 mg, 1.97 mmol) in dry DMF (10 mL), 60% NaH (94.8 mg, 3.95 mmol) was added at 0 °C and allowed to stir for 30 min then added allylbromide (0.35 mL, 3.95 mmol). After completion of the reaction, reaction

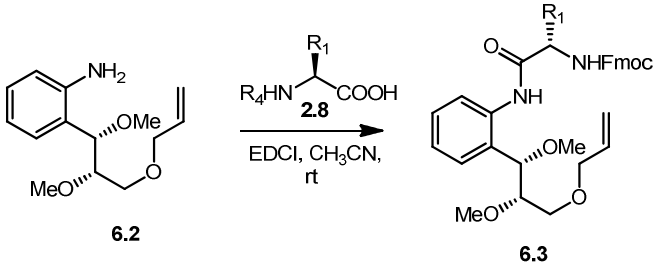
mixture was quenched with ammonium chloride solution (5 mL), and extracted with Ethyl acetate (3 X 20 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was subjected to next reaction without further purification.

To suspension of above compound (500 mg, 1.71 mmol) in THF, PTSA (880 mg, 5.12 mmol) and water 1 mL were added, allowed to reflux for 6 h. After completion of the reaction, reaction mixture was quenched with sodium bicarbonate solution (10 mL), and extracted with Ethyl acetate (3 X 20 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was subjected to next reaction without further purification.

To a suspension of nitro compound (400 mg, 1.58 mmol) in DMF (10 mL), MeI (0.9 mL, 15.8 mmol) and 60% NaH (227.5 mg, 9.48 mmol) were added at 0 °C and allowed to stir the reaction mixture for 0.5 h. After completion of the reaction, reaction mixture was quenched with ammonium chloride solution (5 mL), and extracted with Ethyl acetate (3 X 20 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was subjected to next reaction without further purification.

To a suspension of above compound (500 mg, 1.78 mmol) in EtOH (10 mL), Zn (2.3 g, 35.58 mmol), AcOH (0.5 mL, 8.9 mmol) was added at 0 °C and allowed to stir the reaction mixture for 0.5 h. After completion of the reaction, reaction mixture was passed through celite and concentrated, to leave a crude oil, which was purified by column chromatography to give the pure compound **6.1**.

Molecular Formula: $C_{14}H_{21}NO_3$; R_f (solvent system): 0.2 (1:4 ethyl acetate/hexane); Solvent system for column purification (1:4 ethyl acetate/hexanes); Yield- 65% for 4 steps LRMS: (ES+) m/z = 252.1 (M+1)

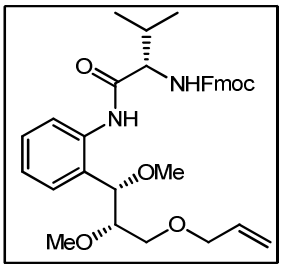


6.2 6.3

Compound 6.3:

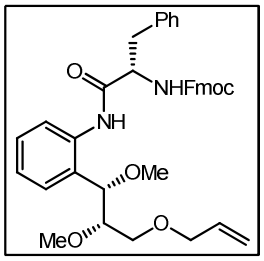
Experimental procedure as per ref. compound **5.3**

(9H-fluoren-9-yl)methyl (S)-1-(2-((1S,2S)-3-(allyloxy)-1,2-dimethoxypropyl)phenyl amino)-3-methyl-1-oxobutan-2-ylcarbamate (6.3a):



Molecular Formula: $C_{34}H_{40}N_2O_6$; R_f : 0.4 (1:4 ethyl acetate/hexanes); Solvent system for column purification (1:4 ethyl acetate/hexanes); Yield-99.5% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.22 (d, *J* = 8.05 Hz, 1H), 7.76 (d, *J* = 7.42 Hz, 2H), 7.62 (d, *J* = 7.32 Hz, 2H), 7.44-7.27 (m, 5H), 7.20 (d, *J* = 7.42 Hz, 1H), 7.09 (t, *J* = 7.47 Hz, 1H), 5.91-5.78 (m, 1H), 5.53 (d, *J* = 8.66 Hz, 1H), 5.22 (d, *J* = 17.31 Hz, 1H), 5.14 (d, *J* = 10.34 Hz, 1H), 4.47 (q, *J* = 9.25 Hz, 2H), 4.38-4.29 (m, 1H), 4.24 (t, *J* = 7.03 Hz, 1H), 4.16 (dd, *J* = 8.14, 6.09 Hz, 1H), 3.91 (d, *J* = 4.77 Hz, 2H), 3.65-3.52 (m, 2H), 3.43 (s, 3H), 3.28-3.17 (m, 4H), 2.28 (m, 1H), 1.02 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 169.2, 156.1, 143.6, 143.6, 141.0, 136.3, 134.2, 129.0, 128.4, 127.4, 127.0, 126.8, 124.9, 124.8, 123.9, 121.9, 119.7, 119.7, 116.9, 83.4, 72.1, 68.7, 66.8, 61.1, 59.1, 57.2, 30.9, 19.1, 17.5; LRMS: (ES+) m/z = 541.3 (M+1)

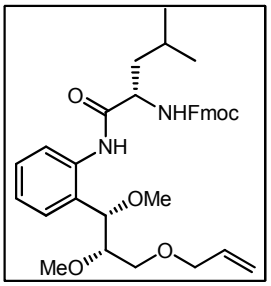
(9H-fluoren-9-yl)methyl (S)-1-(2-((1S,2S)-3-(allyloxy)-1,2-dimethoxypropyl)phenyl amino)-1-oxo-3-phenylpropan-2-ylcarbamate (6.3b):



Molecular Formula: $C_{38}H_{40}N_2O_6$; R_f : 0.25 (1:4 ethyl acetate/hexanes); Solvent system for column purification (1:4 ethyl acetate/hexanes); Yield-98.5% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.62 (s, 1H), 8.22 (d, *J* = 7.71 Hz, 1H), 7.77 (d, *J* = 7.46 Hz, 2H), 7.57 (t, *J* = 7.26 Hz, 2H), 7.46-7.13 (m, 13H), 7.09 (t, *J* = 7.40 Hz, 1H), 5.81 (m, 1H), 5.44 (d, *J* = 7.08 Hz, 1H), 5.16 (m, 2H), 4.61 (d, *J* =

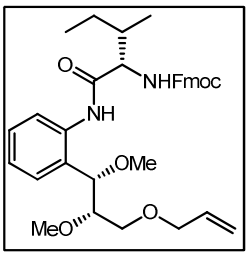
5.94 Hz, 1H), 4.55-4.44 (m, 1H), 4.39 (d, *J* = 4.53 Hz, 1H), 4.25 (m, 6.90 Hz, 2H), 3.85 (s, 2H), 3.55-3.38 (m, 2H), 3.24 (m, 5H), 3.17-3.05 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 168.9, 155.7, 143.7, 414.2, 136.5, 136.2, 134.4, 129.5, 129.3, 128.7, 128.7, 127.7, 127.0, 125.1, 125.0, 124.2, 122.1, 119.9, 11.9, 117.1, 84.3, 83.3, 72.3, 68.3, 67.1, 59.2, 57.4, 56.8, 47.1, 38.4; LRMS: (ES+) m/z = 621.3 (M+1)

(9H-fluoren-9-yl)methyl (S)-1-(2-((1S,2S)-3-(allyloxy)-1,2-dimethoxypropyl)phenyl amino)-4-methyl-1-oxopentan-2-ylcarbamate (6.3c):

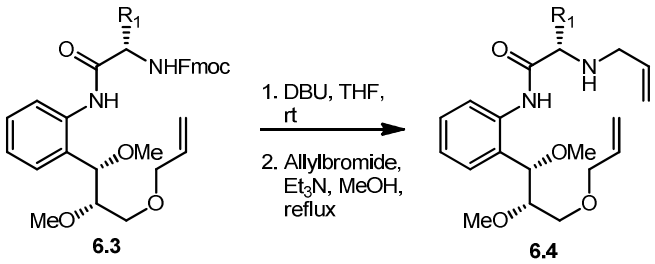


Molecular Formula: $C_{35}H_{42}N_2O_6$; R_f : 0.25 (1:4 ethyl acetate/hexanes); Solvent system for column purification (1:4 ethyl acetate/hexanes); Yield-97.8% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.66 (s, 1H), 8.21 (d, *J* = 7.90 Hz, 1H), 7.76 (d, *J* = 7.44 Hz, 2H), 7.62 (d, *J* = 7.34 Hz, 2H), 7.45-7.27 (m, 5H), 7.19 (d, *J* = 7.41 Hz, 1H), 7.09 (t, *J* = 7.45 Hz, 1H), 5.92-5.78 (m, 1H), 5.41 (d, *J* = 7.83 Hz, 1H), 5.22 (d, *J* = 17.26 Hz, 1H), 5.15 (d, *J* = 10.36 Hz, 1H), 4.55-4.41 (m, 2H), 4.34 (m, 2H), 4.23 (t, *J* = 6.90 Hz, 1H), 3.91 (s, 2H), 3.68-3.55 (m, 2H), 3.41 (d, *J* = 14.20 Hz, 3H), 3.23 (d, *J* = 11.34 Hz, 4H), 1.79 (m, 3H), 1.67-1.53 (m, 1H), 1.00 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 170.4, 156.0, 143.8, 143.8, 141.2, 136.7, 134.4, 129.2, 128.7, 127.7, 127.6, 127.1, 127.0, 125.1, 125.0, 124.1, 122.2, 119.9, 119.9, 117.1, 84.1, 84.1, 83.6, 72.3, 69.0, 66.9, 59.4, 57.4, 54.7, 47.2, 42.1, 24.8, 23.0, 22.0; LRMS: (ES+) m/z = 587.3 (M+1)

(9H-fluoren-9-yl)methyl(2S,3R)-1-(2-((1S,2S)-3-(allyloxy)-1,2-dimethoxypropyl) phenyl amino)-3-methyl-1-oxopentan-2-ylcarbamate (6.3d):



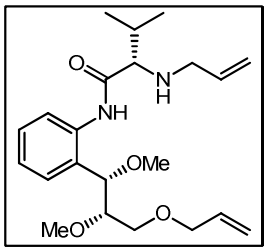
Molecular Formula: $C_{35}H_{42}N_2O_6$; R_f : 0.3 (1:4 ethyl acetate/hexanes); Solvent system for column purification (1:4 ethyl acetate/hexanes); Yield-96.9% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.60 (s, 1H), 8.24 (d, *J* = 7.96 Hz, 1H), 7.76 (d, *J* = 7.46 Hz, 2H), 7.61 (d, *J* = 7.44 Hz, 2H), 7.35 (m, 5H), 7.19 (d, *J* = 7.34 Hz, 1H), 7.09 (t, *J* = 7.47 Hz, 1H), 5.91-5.78 (m, 1H), 5.51 (d, *J* = 8.60 Hz, 1H), 5.21 (d, *J* = 17.13 Hz, 1H), 5.14 (d, *J* = 10.44 Hz, 1H), 4.47 (dd, *J* = 10.46, 6.82 Hz, 2H), 4.39-4.28 (m, 1H), 4.27-4.15 (m, 2H), 3.97-3.82 (m, 2H), 3.58 (m, 2H), 3.44 (s, 3H), 3.28-3.15 (m, 4H), 2.09-1.96 (m, 1H), 1.63-1.50 (m, 1H), 1.21 (m, 1H), 1.08-0.89 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 169.4, 156.2, 143.8, 143.8, 141.2, 136.6, 134.4, 129.2, 128.7, 127.7, 127.6, 127.1, 127.0, 125.1, 125.0, 124.1, 122.1, 119.9, 119.9, 117.1, 83.5, 72.3, 68.9, 67.0, 60.7, 59.4, 57.5, 47.2, 37.8, 24.7, 15.6, 11.6; LRMS: (ES+) m/z = 587.3 (M+1)



Compound 6.4:

Experimental procedure as per ref. compound **5.4.**

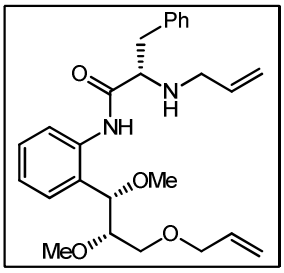
(S)-2-(allylamino)-N-(2-((1S,2S)-3-(allyloxy)-1,2-dimethoxypropyl)phenyl)-3-methylbutanamide (6.4a):



Molecular Formula: $C_{22}H_{34}N_2O_4$; R_f : 0.25(1:4 ethyl acetate/hexanes); Solvent system for column purification (1:4 ethyl acetate/hexanes); Yield-65.5% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 10.23 (s, 1H), 8.32 (d, *J* = 8.20 Hz, 1H), 7.32 (t, *J* = 7.73 Hz, 1H), 7.21 (d, *J* = 7.54 Hz, 1H), 7.07 (t, *J* = 7.48 Hz, 1H), 5.98-5.76 (m, 2H), 5.21 (dd, *J* = 17.21, 8.43 Hz, 2H), 5.12 (dd, *J* = 10.01, 1.62 Hz, 2H), 4.47 (d, *J* = 6.77 Hz, 1H), 3.91-3.79 (m, 2H), 3.73-3.66 (m, 1H), 3.54-3.46 (m, 4H),

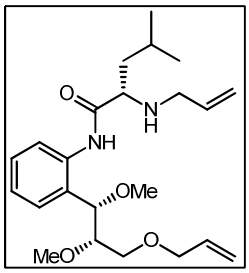
3.35 (dd, *J* = 14.02, 5.01 Hz, 1H), 3.31-3.25 (m, 3H), 3.18 (dd, *J* = 14.05, 6.83 Hz, 1H), 3.11-3.02 (m, 2H), 2.22 (m, 1H), 1.06 (d, *J* = 6.92 Hz, 3H), 0.98 (d, *J* = 6.85 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.5, 136.8, 136.1, 134.4, 129.6, 128.7, 126.8, 123.7, 122.0, 117.0, 116.5, 84.7, 82.6, 72.3, 68.9, 68.5, 59.2, 57.3, 51.9, 31.6, 19.7, 18.2; LRMS: (ES+) m/z = 391.3 (M+1)

(S)-2-(allylamino)-N-(2-((1S,2S)-3-(allyloxy)-1,2-dimethoxypropyl)phenyl)-3-phenylpropanamide (6.4b):



Molecular Formula: $C_{26}H_{34}N_2O_4$; R_f : 0.25(3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 ethyl acetate/hexanes); Yield-66.5% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 10.36 (s, 1H), 8.32 (d, *J* = 8.17 Hz, 1H), 7.39-7.15 (m, 7H), 7.07 (t, *J* = 7.37 Hz, 1H), 5.78 (m, 2H), 5.26-4.99 (m, 4H), 4.41 (d, *J* = 6.79 Hz, 1H), 3.91-3.76 (m, 2H), 3.54-3.38 (m, 6H), 3.33-3.08 (m, 6H), 3.03-2.89 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.4, 137.3, 136.7, 135.7, 134.5, 129.7, 129.2, 128.8, 128.7, 126.9, 126.9, 123.8, 122.1, 117.0, 116.3, 85.0, 82.3, 72.3, 68.9, 63.7, 59.4, 57.2, 51.1, 39.1; LRMS: (ES+) m/z = 439.2 (M+1)

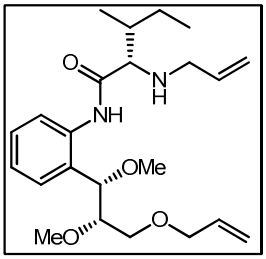
(S)-2-(allylamino)-N-(2-((1S,2S)-3-(allyloxy)-1,2-dimethoxypropyl)phenyl)-4-methylpentanamide (6.4c):



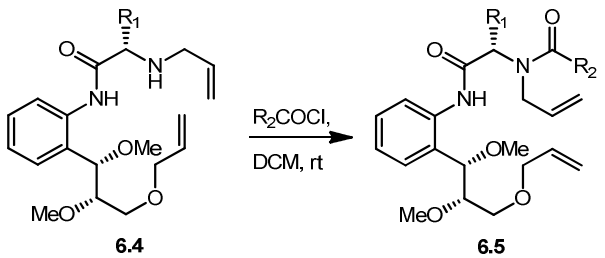
Molecular Formula: $C_{23}H_{36}N_2O_4$; R_f : 0.3(1:4 ethyl acetate/hexanes); Solvent system for column purification (1:4 ethyl acetate/hexanes); Yield-72.3% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 10.23 (s, 1H), 8.27 (d, *J* = 8.17 Hz, 1H), 7.32 (t, *J* = 7.73 Hz, 1H), 7.20 (d, *J* = 7.42 Hz, 1H), 7.07 (t, *J* = 7.43 Hz, 1H), 5.98-5.77 (m,

2H), 5.26-5.17 (m, 2H), 5.16-5.09 (m, 2H), 4.46 (d, *J* = 6.66 Hz, 1H), 3.94-3.81 (m, 2H), 3.71-3.62 (m, 1H), 3.56-3.46 (m, 4H), 3.39-3.15 (m, 6H), 3.09 (dd, *J* = 10.41, 4.63 Hz, 1H), 1.83-1.63 (m, 2H), 1.53-1.43 (m, 1H), 0.97 (t, *J* = 6.12 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 173.7, 136.9, 136.0, 134.4, 129.6, 128.7, 126.9, 123.7, 122.2, 117.1, 116.4, 84.8, 82.7, 72.3, 68.9, 61.6, 59.3, 57.3, 51.4, 43.3, 25.1, 23.1, 22.0; LRMS: (ES+) m/z = 405.3 (M+1)

(2S,3R)-2-(allylamino)-N-(2-((1S,2S)-3-(allyloxy)-1,2-dimethoxypropyl)phenyl)-3-methylpentanamide (6.4d):



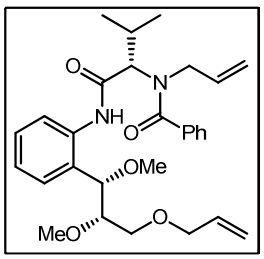
Molecular Formula: $C_{23}H_{36}N_2O_4$; R_f : 0.35 (1:4 ethyl acetate/hexanes); Solvent system for column purification (1:4 ethyl acetate/hexanes); Yield-68.5% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 10.23 (s, 1H), 8.33 (d, *J* = 8.20 Hz, 1H), 7.32 (t, *J* = 7.75 Hz,1H), 7.21 (d, *J* = 7.50 Hz, 1H), 7.07 (t, *J* = 7.75 Hz, 1H), 5.97-5.76 (m, 2H), 5.25-5.16 (m, 2H), 5.12 (dd, *J* = 10.17, 4.60 Hz, 2H), 4.47 (d, *J* = 6.82 Hz, 1H), 3.91-3.80 (m, 2H), 3.73-3.67 (m, 1H), 3.54-3.45 (m, 4H), 3.35 (dd, *J* = 14.09, 5.17 Hz, 1H), 3.29 (d, *J* = 7.66 Hz, 3H), 3.17 (dd, *J* = 14.11, 6.91 Hz, 1H), 3.13-3.04 (m, 2H), 1.98-1.87 (m, 1H), 1.64-1.50 (m, 3H), 1.25 (m, 2H), 1.02 (d, *J* = 6.92 Hz, 3H), 0.92 (t, *J* = 7.38 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.6, 136.8, 136.1, 134.4, 129.6, 128.7, 126.8, 123.7, 122.0, 117.0, 116.5, 84.7, 82.6, 72.3, 68.9, 67.9, 59.3, 57.3, 52.0, 38.5, 25.3, 16.1, 11.8; LRMS: (ES+) m/z = 405.3 (M+1)



Compound 6.5:

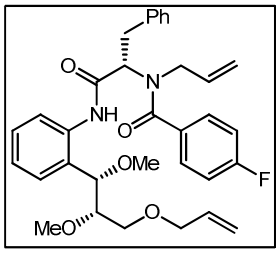
Experimental procedure as per ref. compound **5.5.**

N-allyl-N-((S)-1-(2-((1S,2S)-3-(allyloxy)-1,2-dimethoxypropyl)phenylamino)-3-methyl-1-oxobutan-2-yl)benzamide (6.5a):



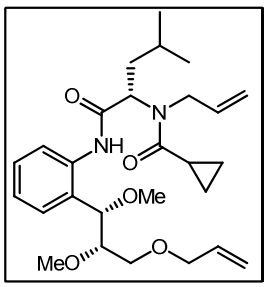
Molecular Formula: $C_{29}H_{38}N_2O_5$; R_f : 0.25 (1:4 ethyl acetate/hexanes); Solvent system for column purification (1:4 ethyl acetate/hexanes); Yield-90.5% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.65 (s, 1H), 8.07 (s, 1H), 7.52-7.22 (m, 8H), 7.13 (t, *J* = 7.46 Hz, 1H), 5.95-5.60 (m, 2H), 5.23 (m, 1H), 5.15 (d, *J* = 10.35 Hz, 1H), 4.98-4.87 (m, 1H), 4.86-4.72 (m, 1H), 4.56 (s, 2H), 3.85-4.20 (m, 5H), 3.80-3.69 (m, 1H), 3.68-3.46 (m, 4H), 3.36-3.18 (m, 6H), 2.71-2.55 (m, 1H), 1.96-1.69 (m, 1H), 1.09 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 173.3, 168.6, 136.6, 136.3, 134.5, 133.9, 129.6, 128.8, 128.4, 126.8, 124.5, 123.2, 117.7, 117.0, 83.1, 82.7, 72.3, 69.3, 65.5, 59.4, 57.4, 49.6, 26.9, 20.0, 19.0; LRMS: (ES+) m/z = 495.3 (M+1)

N-allyl-N-((S)-1-(2-((1S,2S)-3-(allyloxy)-1,2-dimethoxypropyl)phenylamino)-1-oxo-3-phenylpropan-2-yl)-4-fluorobenzamide (6.5b):



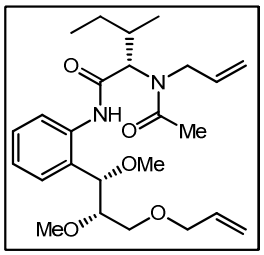
Molecular Formula: $C_{33}H_{37}FN_2O_5$; R_f : 0.4 (1:4 ethyl acetate/hexanes); Solvent system for column purification (1:4 ethyl acetate/hexanes); Yield-85.6% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.57 (s, 1H), 8.19 (s, 1H), 7.39-7.05 (m, 11H), 5.85 (m, 1H), 5.45 (m, 1H), 5.20-4.80 (m, 3H), 4.72 (s, 1H), 4.50 (s, 1H), 3.87-3.35 (m, 6H), 3.28-3.07 (m, 7H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 171.7, 168.3, 162.1, 137.8, 136.6, 134.4, 133.4, 132.2, 129.5, 129.4, 129.3, 129.2, 128.6,128.5, 126.7, 124.1, 122.7, 118.9, 117.1, 115.4, 115.1, 84.6, 82.6, 72.3, 68.2, 62.2, 58.5, 57.4, 53.0, 29.6; LRMS: (ES+) m/z = 561.3 (M+1)

N-allyl-N-((S)-1-(2-((1S,2S)-3-(allyloxy)-1,2-dimethoxypropyl)phenylamino)-4-methyl-1-oxopentan-2-yl)cyclopropanecarboxamide (6.5c):



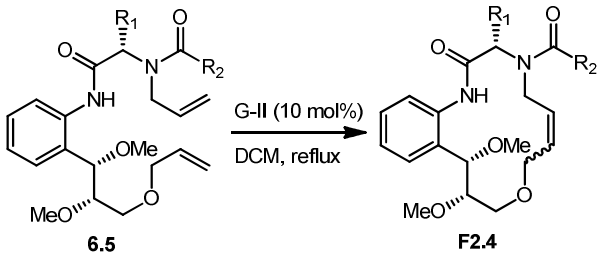
Molecular Formula: $C_{27}H_{40}N_2O_5$; R_f: 0.3 (1:4 ethyl acetate/hexanes); Solvent system for column purification (1:4 ethyl acetate/hexanes); Yield-92.3% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.45 (s, 1H), 8.18 (d, *J* = 8.17 Hz, 1H), 7.40-7.24 (m, 2H), 7.19 (d, *J* = 7.52 Hz, 1H), 7.07 (t, *J* = 7.45 Hz, 1H), 6.02-5.79 (m, 2H), 5.36-5.09 (m, 5H), 4.45 (d, *J* = 5.14 Hz, 1H), 4.40-4.28 (m, 1H), 4.10 (dd, *J* = 18.10, 5.16 Hz, 1H), 3.91 (dd, *J* = 11.34, 6.12 Hz, 2H), 3.66 (dd, *J* = 9.20, 4.65 Hz, 1H), 3.57 (dd, *J* = 10.21, 3.91 Hz, 1H), 3.45 (s, 3H), 3.26 (s, 3H), 3.17 (dd, *J* = 10.14, 5.10 Hz, 1H), 2.01-1.88 (m, 1H), 1.82-1.73 (m, 1H), 1.66-1.52 (m, 2H), 1.12-0.91 (m, 8H), 0.84-0.74 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 174.9, 169.6, 136.9, 135.3, 134.5, 128.9, 128.4, 127.1, 123.9, 122.2, 116.9, 116.4, 83.7, 83.2, 72.3, 69.1, 59.3, 57.3, 56.5, 47.2, 37.4, 24.9, 22.5, 22.5, 12.0, 8.5, 8.3; LRMS: (ES+) m/z = 473.3 (M+1)

N-allyl-N-((2S,3R)-1-(2-((1S,2S)-3-(allyloxy)-1,2-dimethoxypropyl)phenylamino)-3-methyl-1-oxopentan-2-yl)cyclopropanecarboxamide (6.5d):



Molecular Formula: $C_{25}H_{38}N_2O_5$; R_f : 0.35 (1:4 ethyl acetate/ hexanes); Solvent system for column purification (1:4 ethyl acetate/hexanes); Yield-83.5% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.41 (d, *J* = 12.94 Hz, 1H), 8.06 (d, *J* = 8.13 Hz, 1H), 7.30 (m, 1H), 7.23 (d, *J* = 7.37 Hz, 1H), 7.09 (t, *J* = 7.47 Hz, 1H), 5.83 (m, 2H), 5.17 (m, 4H), 4.83 (d, *J* = 11.01 Hz, 1H), 4.47 (d, *J* = 5.33 Hz, 1H),

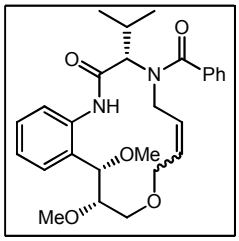
4.11 (t, *J* = 6.45 Hz, 2H), 3.92 (m, 3H), 3.69-3.62 (m, 1H), 3.59-3.51 (m, 4H), 3.28 (d, *J* = 10.68 Hz, 4H), 3.17 (dd, *J* = 10.29, 5.18 Hz, 1H), 2.30-2.25 (m, 1H), 2.21-2.08 (m, 4H), 1.42 (m, 1H), 1.13-0.98 (m, 5H), 0.93-0.87 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 171.9, 169.5, 137.0, 134.7, 134.4, 128.9, 128.4, 126.8, 123.8, 121.9, 17.0, 116.9, 83.9, 83.5, 72.2, 69.0, 59.2, 57.4, 56.3, 48.4, 37.3, 24.9, 22.7, 22.2, 22.0; LRMS: (ES+) m/z = 445.2 (M+1)



Macrocycle F2.4:

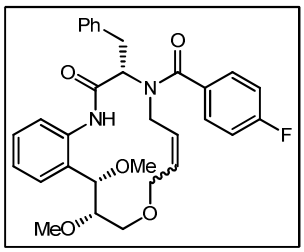
Experimental procedure as per ref. compound **F2.1.**

3S,11S,12S,Z/E)-4-benzoyl-3-isopropyl-11,12-dimethoxy-4,5,8,10,11,12-hexahydro-1H-benzo[j][1,6,9]oxadiazacyclotetradecin-2(3H)-one (F2.4a):



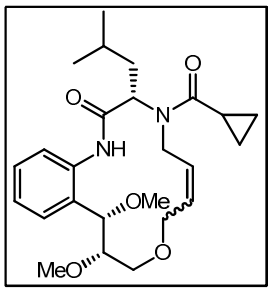
Molecular Formula: $C_{27}H_{34}N_2O_5$; R_f: 0.25 (3:7 ethyl acetate/hexane); Solvent system for column purification (3:7 ethyl acetate/hexanes); Yield-88%(white semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.49-9.23 (m, 1H), 8.99-8.71 (m, 1H), 8.14-7.95 (m, 1H), 7.70 (d, *J* = 6.49 Hz, 1H), 7.46 (s, 6H), 7.33 (d, *J* = 5.96 Hz, 2H), 7.19-6.94 (m, 2H), 5.95-5.53 (m, 1H), 5.50-4.91 (m, 1H), 4.34-3.89 (m, 5H), 3.65 (s, 4H), 3.43 (s, 7H), 2.76-2.51 (m, 1H), 1.22-0.97 (m, 6H), 0.85 (t, *J* = 6.56 Hz, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.2, 167.4, 136.3, 135.9, 135.6, 133.6, 130.3, 130.0, 129.4, 129.2, 128.7, 127.2, 124.7, 124.0, 82.5, 72.5, 67.6, 60.1, 57.6, 57.2, 41.5, 29.6, 27.3, 19.9, 18.5; LRMS: (ES+) m/z = 467.2 (M+1).

(3S,11S,12S,Z/E)-3-benzyl-4-(4-fluorobenzoyl)-11,12-dimethoxy-4,5,8,10,11,12-hexahydro-1H-benzo[j][1,6,9]oxadiazacyclotetradecin-2(3H)-one (F2.4b):



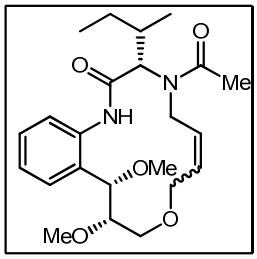
Molecular Formula: $C_{31}H_{33}FN_2O_5$; R_f : 0.25 (2:3 ethyl acetate/hexane); Solvent system for column purification (2:3 ethyl acetate/hexanes);Yield-86%(white semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.69-8.78 (m, 1H), 8.43-7.96 (m, 1H), 7.54-7.18 (m, 7H), 7.03 (d, *J* = 5.17 Hz, 6H), 6.18-5.29 (m, 2H), 5.02-4.33 (m, 1H), 4.30-3.70 (m, 4H), 3.50 (m, 11H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 171.2, 167.0, 136.9, 136.5, 135.8, 134.5, 131.3, 130.2, 129.8, 129.4, 128.7, 126.9, 124.5, 122.6, 115.8, 115.6, 82.2, 73.9, 72.9, 63.7, 60.4, 59.8, 57.1, 29.7; LRMS: (ES+) m/z = 533.2 (M+1).

(3S,11S,12S,Z/E)-4-(cyclopropanecarbonyl)-3-isobutyl-11,12-dimethoxy-4,5,8,10,11,12-hexahydro-1H-benzo[j][1,6,9]oxadiazacyclotetradecin-2(3H)-one (F2.4c):



Molecular Formula: $C_{25}H_{36}N_2O_5$; R_f : 0.3 (2:3 ethyl acetate/hexane); Solvent system for column purification (2:3 ethyl acetate/hexanes); Yield-85%(white semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.29 (d, *J* = 11.56 Hz, 4H), 5.87 (d, *J* = 5.25 Hz, 1H), 4.16 (s, 5H), 3.58 (s, 5H), 3.30 (s, 6H), 1.91 (dd, *J* = 13.50, 6.51 Hz, 3H), 1.66-1.47 (m, 1H), 1.26 (s, 2H), 1.08-0.86 (m, 15H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 174.0, 169.7, 136.0, 131.9, 129.8, 128.8, 128.8, 124.2, 123.2, 88.8, 83.5, 71.4, 59.2, 57.0, 54.5, 37.0, 29.6, 24.7, 22.9, 22.8, 22.3, 11.7, 8.7, 8.3; LRMS: (ES+) m/z = 445.3 (M+1)

(3S,11S,12S,Z/E)-4-(cyclopropanecarbonyl)-3-(seco-butyl)-11,12-dimethoxy-4,5,8,10,11,12-hexahydro-1H-benzo[j][1,6,9]oxadiazacyclotetradecin-2(3H)-one (F2.4d):



Molecular Formula: $C_{25}H_{36}N_2O_5$; R_f : 0.3 (1:1 ethyl acetate/hexane); Solvent system for column purification (2:3 ethyl acetate/hexanes); Yield-85%(white semi solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 9.36-8.97 (m, 1H), 8.36-7.91 (m, 1H), 7.50-7.26 (m, 2H), 7.21-6.89 (m, 2H), 5.81 (s, 2H), 5.17-4.49 (m, 1H), 4.32-3.74 (m, 5H), 3.65 (s, 3H), 3.36 (d, *J* = 19.65 Hz, 6H), 2.87-2.53 (m, 1H), 2.31 (s, 4H), 1.47-1.21 (m, 4H), 1.12-0.87 (m, 8H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 173.4, 171.1, 168.8, 167.5, 135.9, 134.8, 132.2, 129.9, 129.3, 128.8, 124.4, 124.1, 122.5, 114.0, 83.0, 82.7, 73.5, 72.3, 72.0, 67.9, 60.2, 59.4, 57.6, 57.2, 53.3, 44.3, 40.6, 32.7, 32.3, 29.6, 29.6, 24.5, 24.2, 22.1, 21.9, 16.7, 16.0, 11.5, 10.7; LRMS: (ES+) m/z = 419.2 (M+1)

2.7. References:

(1) (a) Arkin, M. R.; Wells, J. A. *Nat. Rev. Drug Discov.* **2004**, *3*, 301. (b) Driggers, E. M.; Hale, S. P.; Lee, J.; Terrett, N. K. *Nat. Rev.* **2008**, *7*, 608. (c) Wells, J. A.; McClendon, C. L. *Nature* **2007**, *450*, 1001.

(2) (a) Pawson, T.; Warner, N. *Oncogene* **2007**, *26*, 1268. (b) Scott, J. D.; Pawson, T. *Science* **2009**, *326*, 1220.

(3) Schreiber, S. L. *Proc. Natl. Acad. Sci. U.S.A.* **2011**, *108*, 6699.

(4) (a) Ajay, A.; Sharma, S.; Gupt, M. P.; Bajpai, V.; Hamidullah; Kumar, B.; Kaushik, M. P.; Konwar, R.; Ampapathi, R. S.; Tripathi, R. P. *Org. Lett.* **2012**, *14*, 4306. (b) Dandapani, S.; Lowe, J. T.; Comer, E.; Marcaurelle, L. A. *J. Org. Chem.* **2011**, *76*, 8042. (c) Dandapani, S.; Marcaurelle, L. A. *Nat. Chem. Biol.* **2010**, *6*, 861. (d) Dockendorff, C.; Nagiec, M. M.; Weiwer, M.; Buhrlage, S.; Ting, A.; Nag, P. P.; Germain, A.; Kim, H. J.; Youngsaye, W.; Scherer, C.; Bennion, M.; Xue, L.; Stanton, B. Z.; Lewis, T. A.; Macpherson, L.; Palmer, M.; Foley, M. A.; Perez, J. R.; Schreiber, S. L. *ACS Med. Chem. Lett.* **2012**, *3*, 808.

(e) Marcaurelle, L. A.; Comer, E.; Dandapani, S.; Duvall, J. R.; Gerard, B.; Kesavan, S.; Lee, M. D. t.; Liu, H.; Lowe, J. T.; Marie, J. C.; Mulrooney, C. A.; Pandya, B. A.; Rowley, A.; Ryba, T. D.; Suh, B. C.; Wei, J.; Young, D. W.; Akella, L. B.; Ross, N. T.; Zhang, Y. L.; Fass, D. M.; Reis, S. A.; Zhao, W. N.; Haggarty, S. J.; Palmer, M.; Foley, M. A. *J. Am. Chem. Soc.* **2010**, *132*, 16962. (f) Moretti, J. D.; Wang, X.; Curran, D. P. *J. Am. Chem. Soc.* **2012**, *134*, 7963. (g) Peng, L. F.; Stanton, B. Z.; Maloof, N.; Wang, X.; Schreiber, S. L. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 6319. (h) Stanton, B. Z.; Peng, L. F.; Maloof, N.; Nakai, K.; Wang, X.; Duffner, J. L.; Taveras, K. M.; Hyman, J. M.; Lee, S. W.; Koehler, A. N.; Chen, J. K.; Fox, J. L.; Mandinova, A.; Schreiber, S. L. *Nat. Chem. Biol.* **2009**, *5*, 154. (i) Thomas, G. L.; Wyatt, E. E.; Spring, D. R. *Cur. Opin. Drug Discov. Dev.* **2006**, *9*, 700.

(5) Winssinger, N.; Barluenga, S. *Chem. Comm.* **2007**, 22.

(6) Moulin, E.; Barluenga, S.; Winssinger, N. *Org. Lett.* **2005**, *7*, 5637.

(7) Barluenga, S.; Jogireddy, R.; Koripelly, G. K.; Winssinger, N. *ChemBioChem* **2010**, *11*, 1692.

(8) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483.

(9) Bender, A.; Fergus, S.; Galloway, W. R.; Glansdorp, F. G.; Marsden, D. M.; Nicholson, R. L.; Spandl, R. J.; Thomas, G. L.; Wyatt, E. E.; Glen, R. C.; Spring, D. R. *Ernst Schering Research Foundation workshop* **2006**, 47.

(10) (a) Grubbs, R. H. *Angew. Chem. Int. Ed. Engl.* **2006**, *45*, 3760. (b) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446.

(11) (a) Martin, C. S.; Moriyama, A.; Zon, L. I. *Genome Med.* **2011**, *3*, 83. (b) Peterson, R. T.; Fishman, M. C. *Method. Cell Biol.* **2004**, *76*, 569. (c) Peterson, R. T.; Fishman, M. C. *Method. Cell Biol.* **2011**, *105*, 525. (d) Peterson, R. T.; Link, B. A.; Dowling, J. E.; Schreiber, S. L. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 12965. (e) Schoft, V. K.; Beauvais, A. J.; Lang, C.; Gajewski, A.; Prufert, K.; Winkler, C.; Akimenko, M. A.; Paulin-Levasseur, M.; Krohne, G. *J. Cell Sci.* **2003**, *116*, 2505. (f) Vogt, A.; Cholewinski, A.; Shen, X.; Nelson, S. G.; Lazo, J. S.; Tsang, M.; Hukriede, N. A. *Dev. Dynam.* **2009**, *238*, 656.

(12) (a) Cannon, J. E.; Upton, P. D.; Smith, J. C.; Morrell, N. W. *Brit. J. Pharmacol.* **2010**, *161*, 140. (b) Evensen, L.; Link, W.; Lorens, J. B. *Curr. Pharm. Design*

2010, *16*, 3958. (c) Serbedzija, G. N.; Flynn, E.; Willett, C. E. *Angiogenesis* **1999**, *3*, 353.

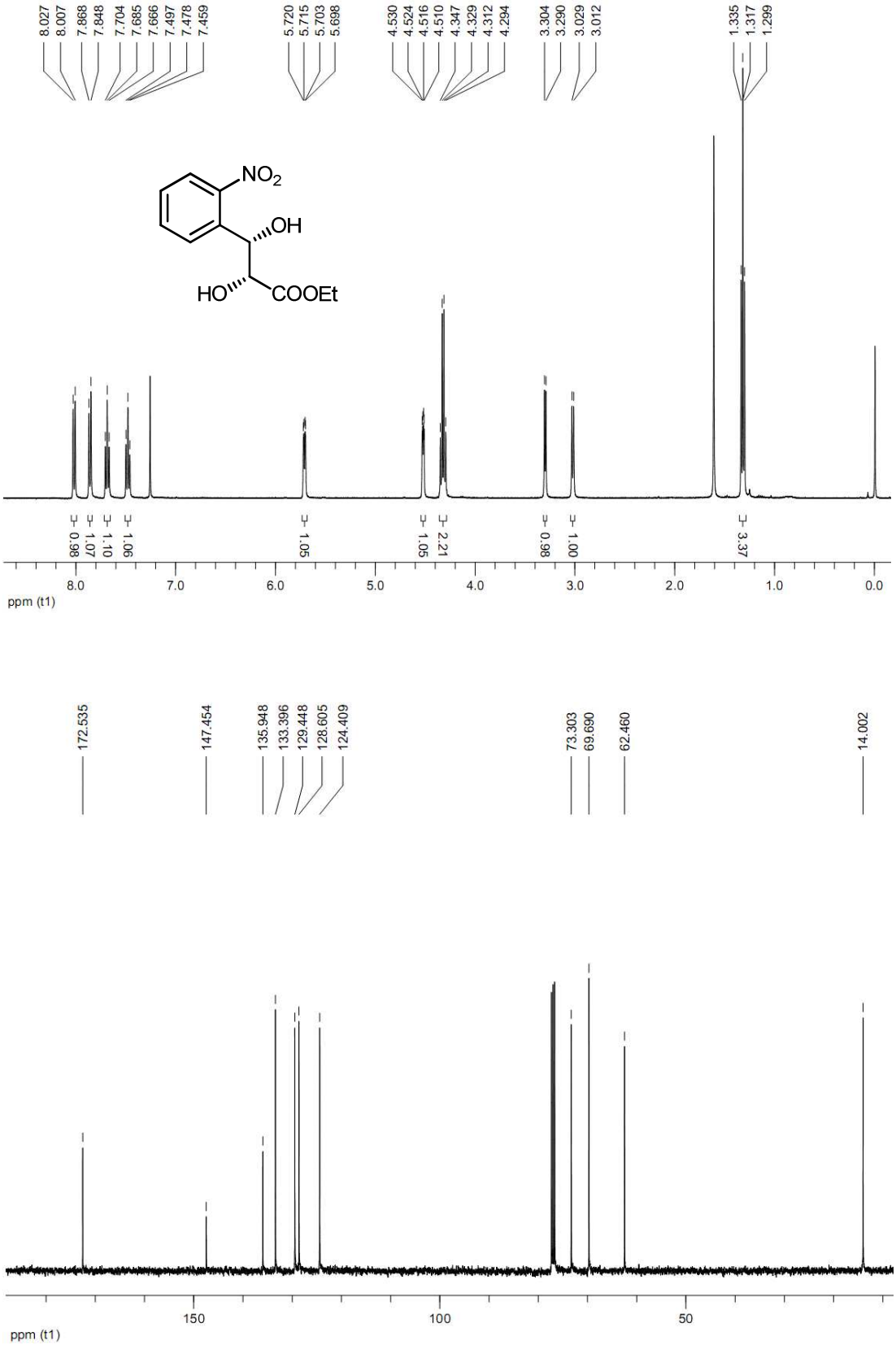
(13) Kitambi, S. S.; Malicki, J. J. *Dev. Dynam.* **2008**, *237*, 3870.

(14) (a) Kitambi, S. S.; McCulloch, K. J.; Peterson, R. T.; Malicki, J. J. *Mech. Dev.* **2009**, *126*, 464. (b) Kitambi, S. S.; Nilsson, E. S.; Sekyrova, P.; Ibarra, C.; Tekeoh, G. N.; Andang, M.; Ernfors, P.; Uhlen, P. *BMC Physiology* **2012**, *12*, 3. (c) Murphey, R. D.; Zon, L. I. *Methods* **2006**, *39*, 255.

(15) (a) Hao, J.; Ho, J. N.; Lewis, J. A.; Karim, K. A.; Daniels, R. N.; Gentry, P. R.; Hopkins, C. R.; Lindsley, C. W.; Hong, C. C. *ACS Chem. Biol.* **2010**, *5*, 245. (b) Vogt, A.; McPherson, P. A.; Shen, X.; Balachandran, R.; Zhu, G.; Raccor, B. S.; Nelson, S. G.; Tsang, M.; Day, B. W. *Chem. Biol. Drug Design* **2009**, *74*, 358. (c) Zhang, Q.; Li, Q.; Chen, Y.; Huang, X.; Yang, I. H.; Cao, L.; Wu, W. K.; Tan, H. M. *Front. Biosci.* **2012**, *4*, 2525.

(16) Kimmel, C. B.; Ballard, W. W.; Kimmel, S. R.; Ullmann, B.; Schilling, T. F. *Dev. Dynam.* **1995**, *203*, 253.

2.8. Spectra:

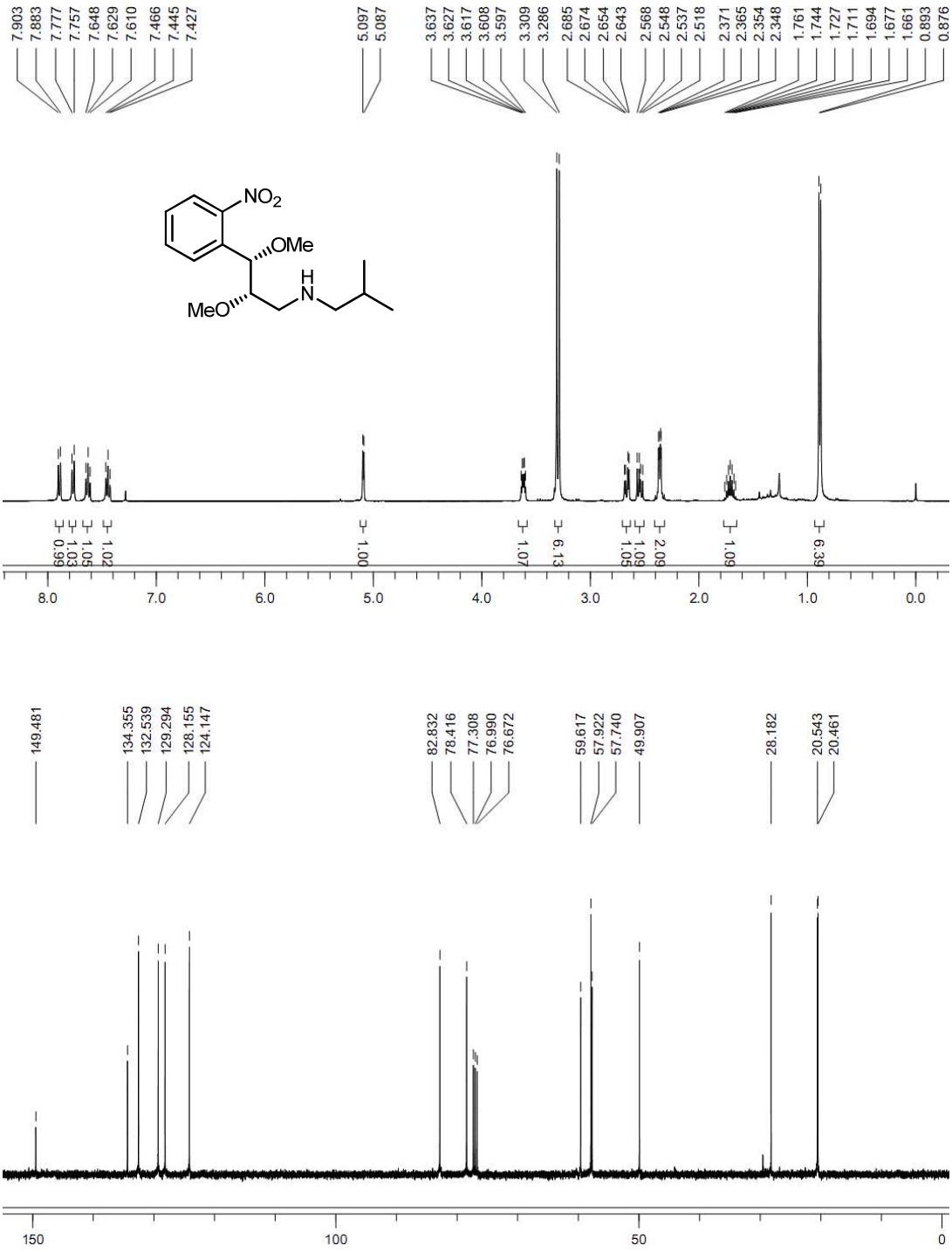


^{1}H and ^{13}C NMR of compound **2.2**

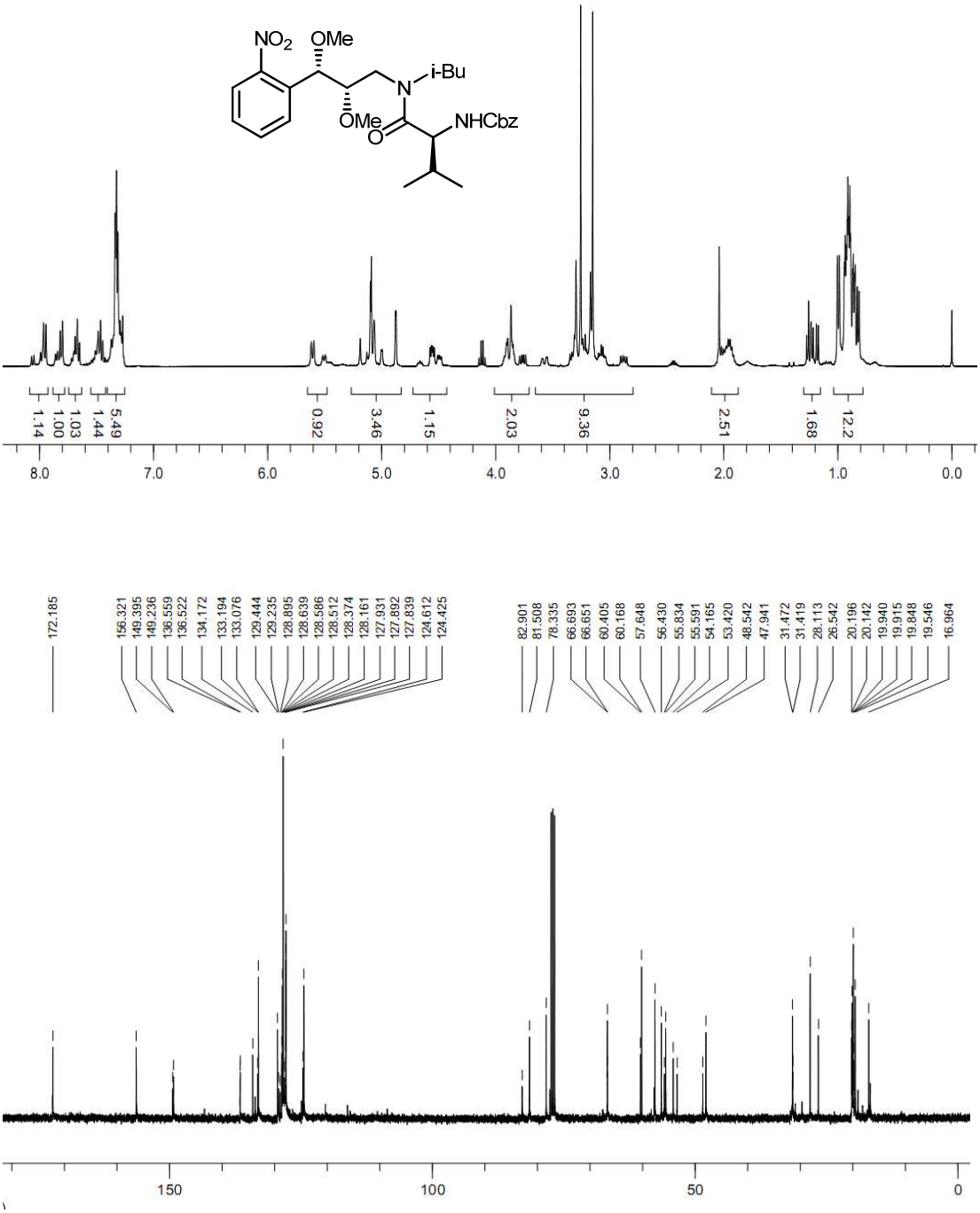
^{1}H and ^{13}C NMR of compound **2.3**

^{1}H and ^{13}C NMR of compound **2.4**

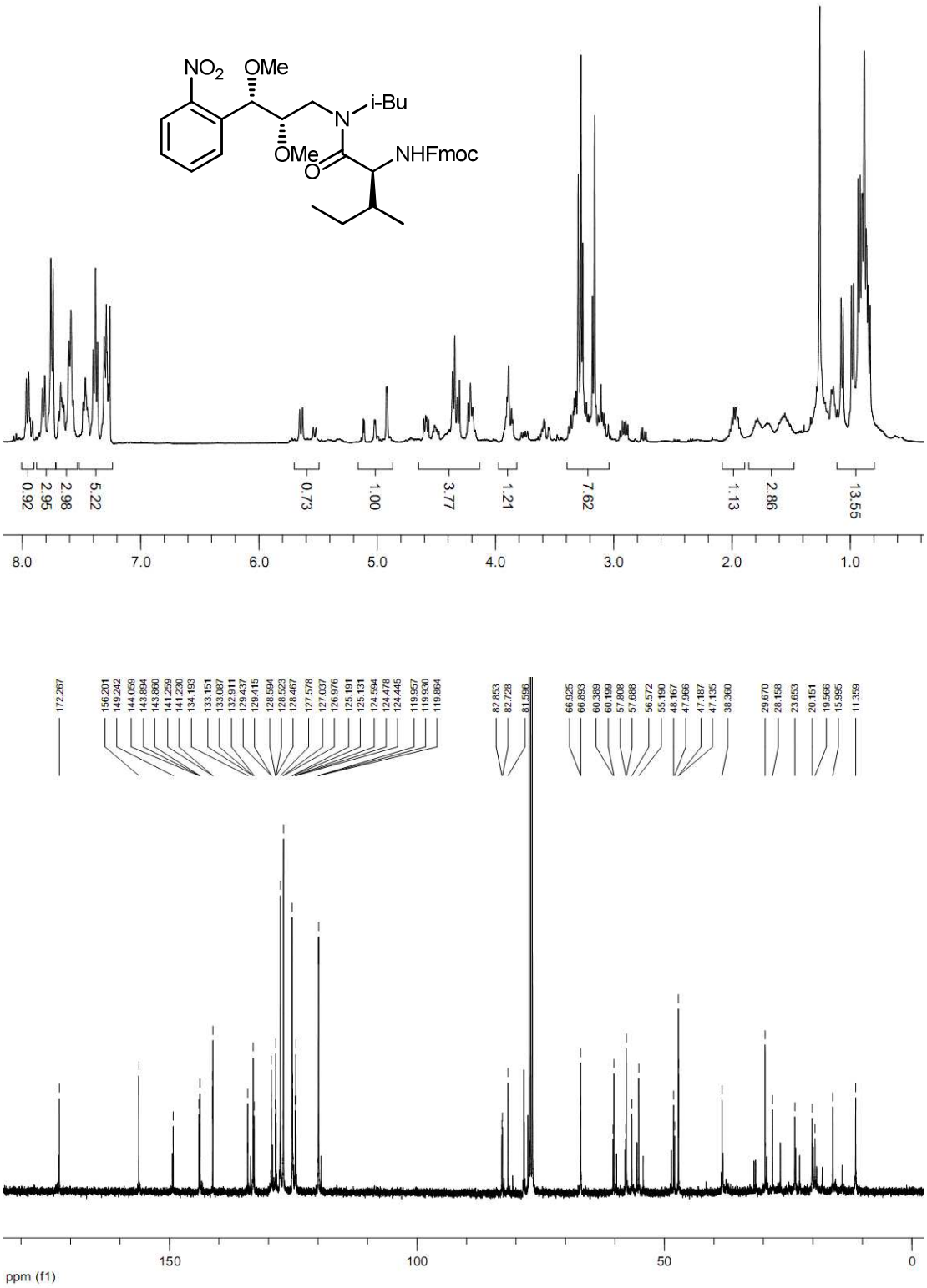
^{1}H and ^{13}C NMR of compound **2.5**



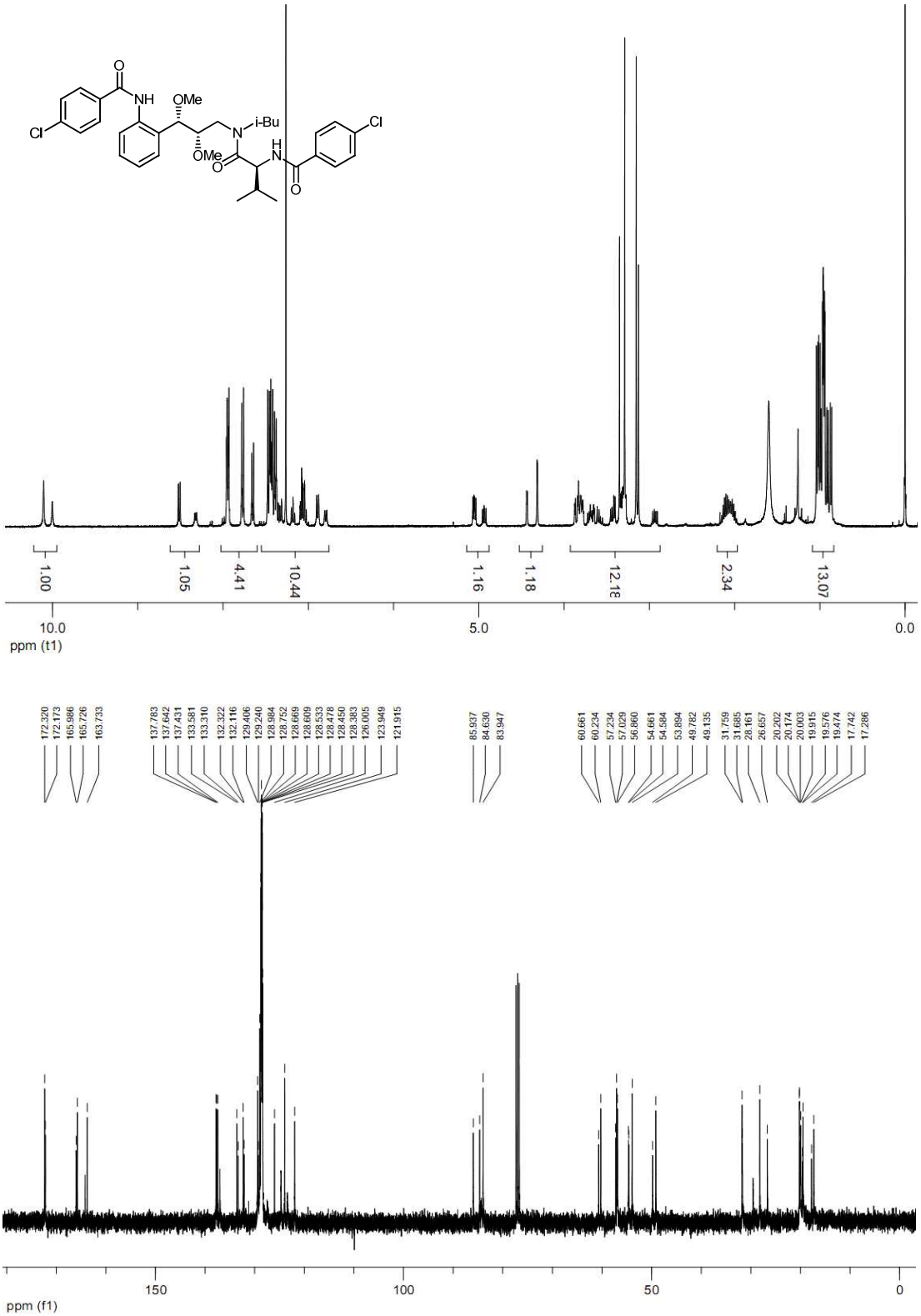
^{1}H and ^{13}C NMR of compound **2.7**



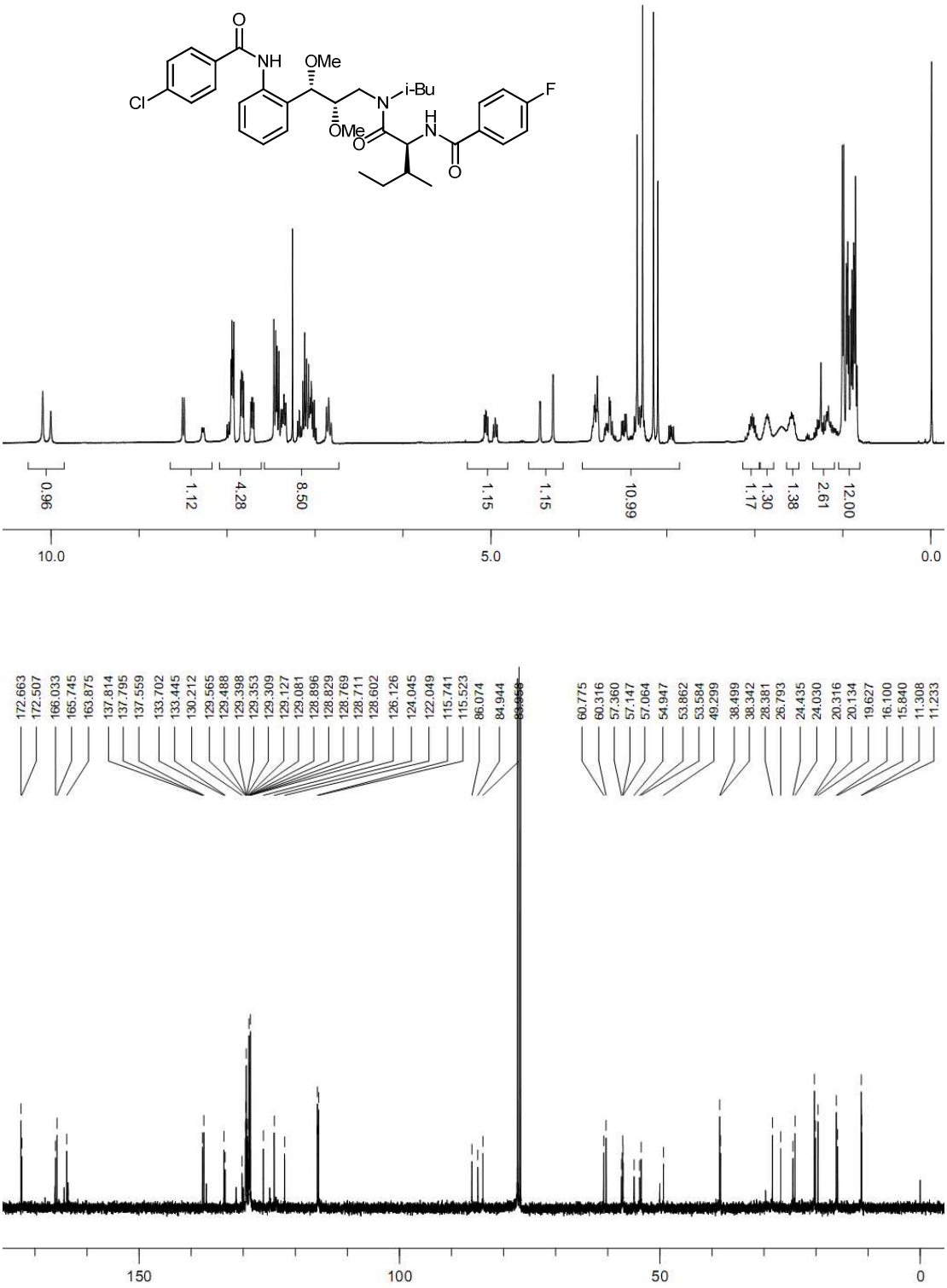
^{1}H and ^{13}C NMR of compound **2.9a**



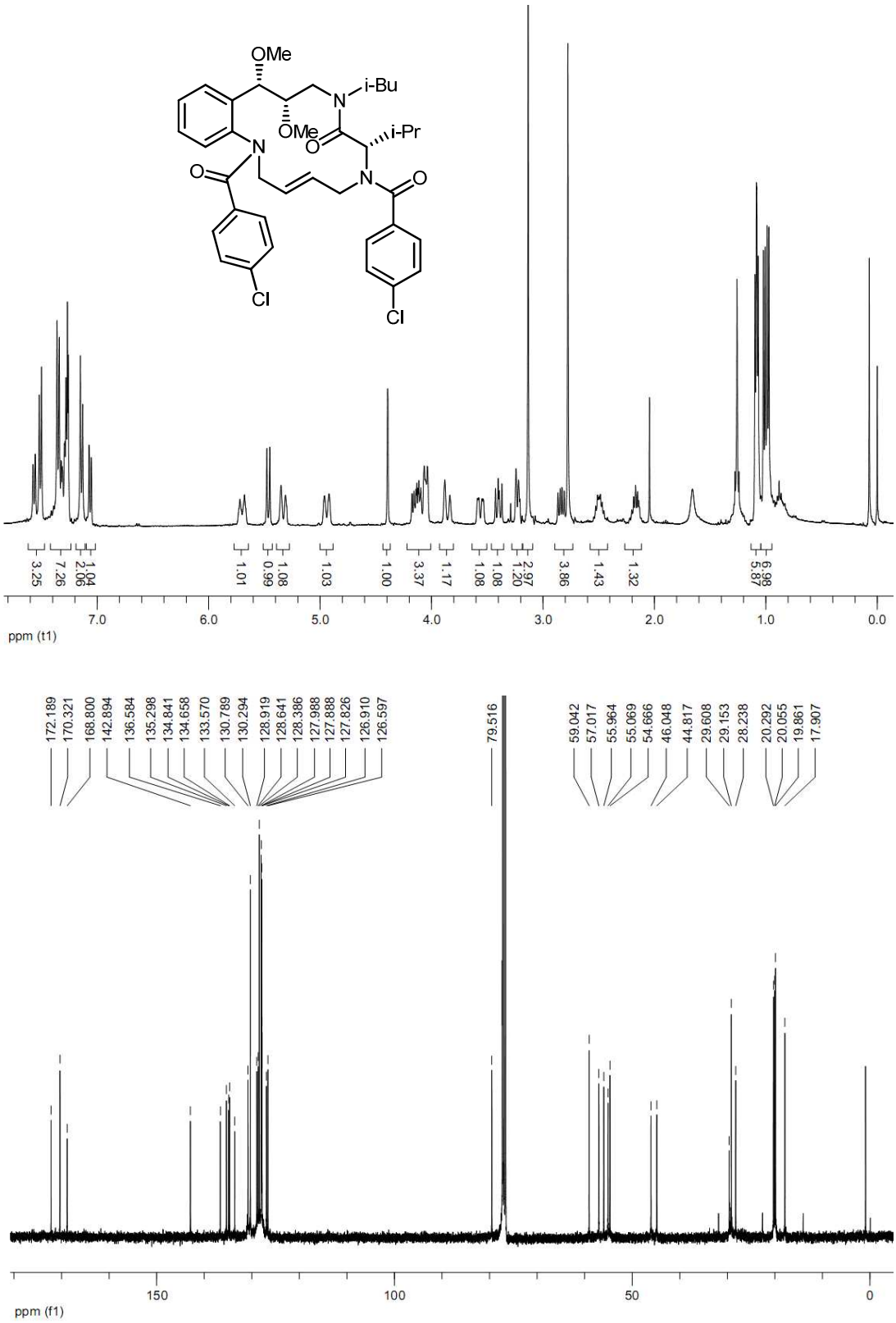
^{1}H and ^{13}C NMR of compound **2.9d**



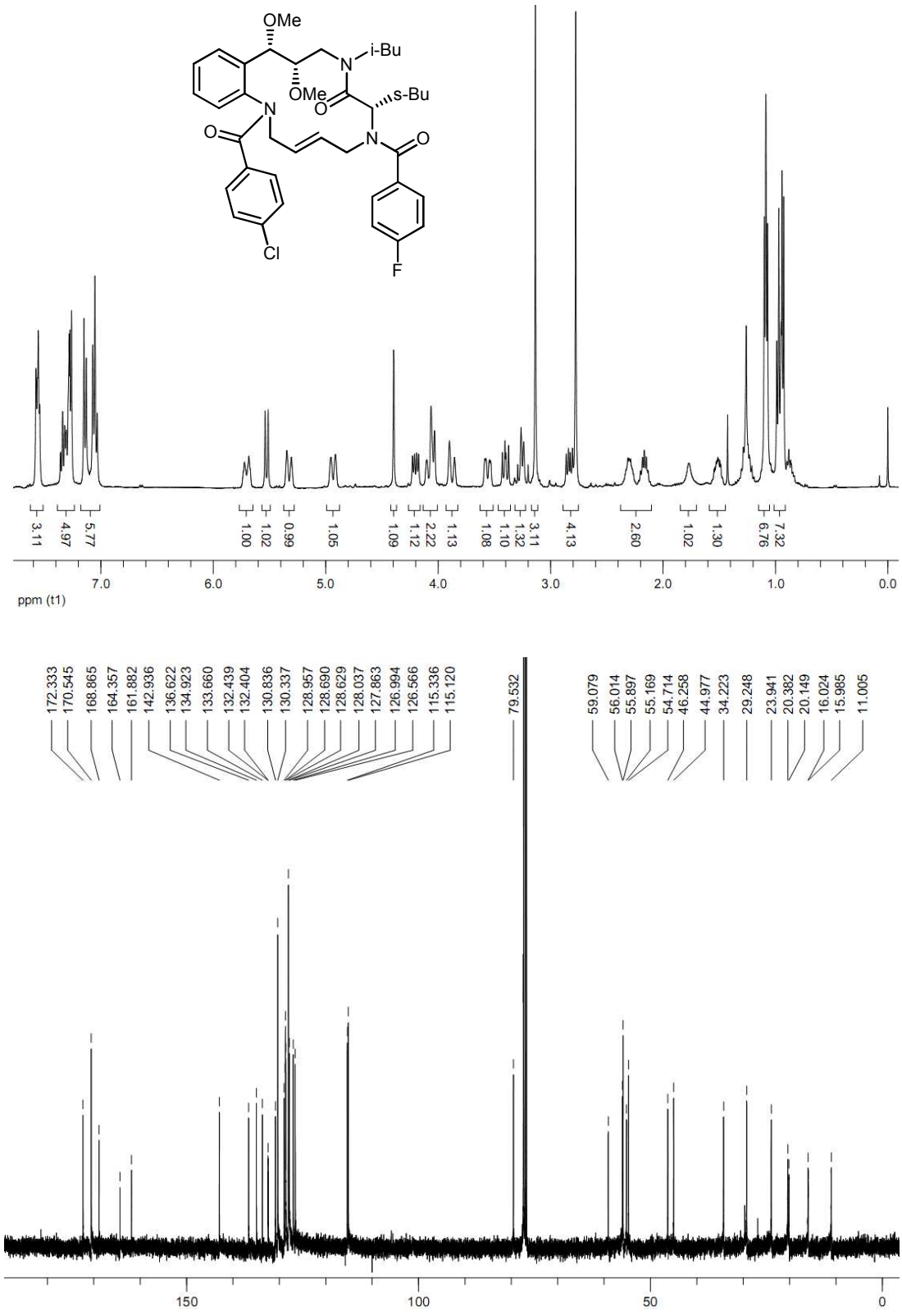
^{1}H and ^{13}C NMR of compound **2.10a**



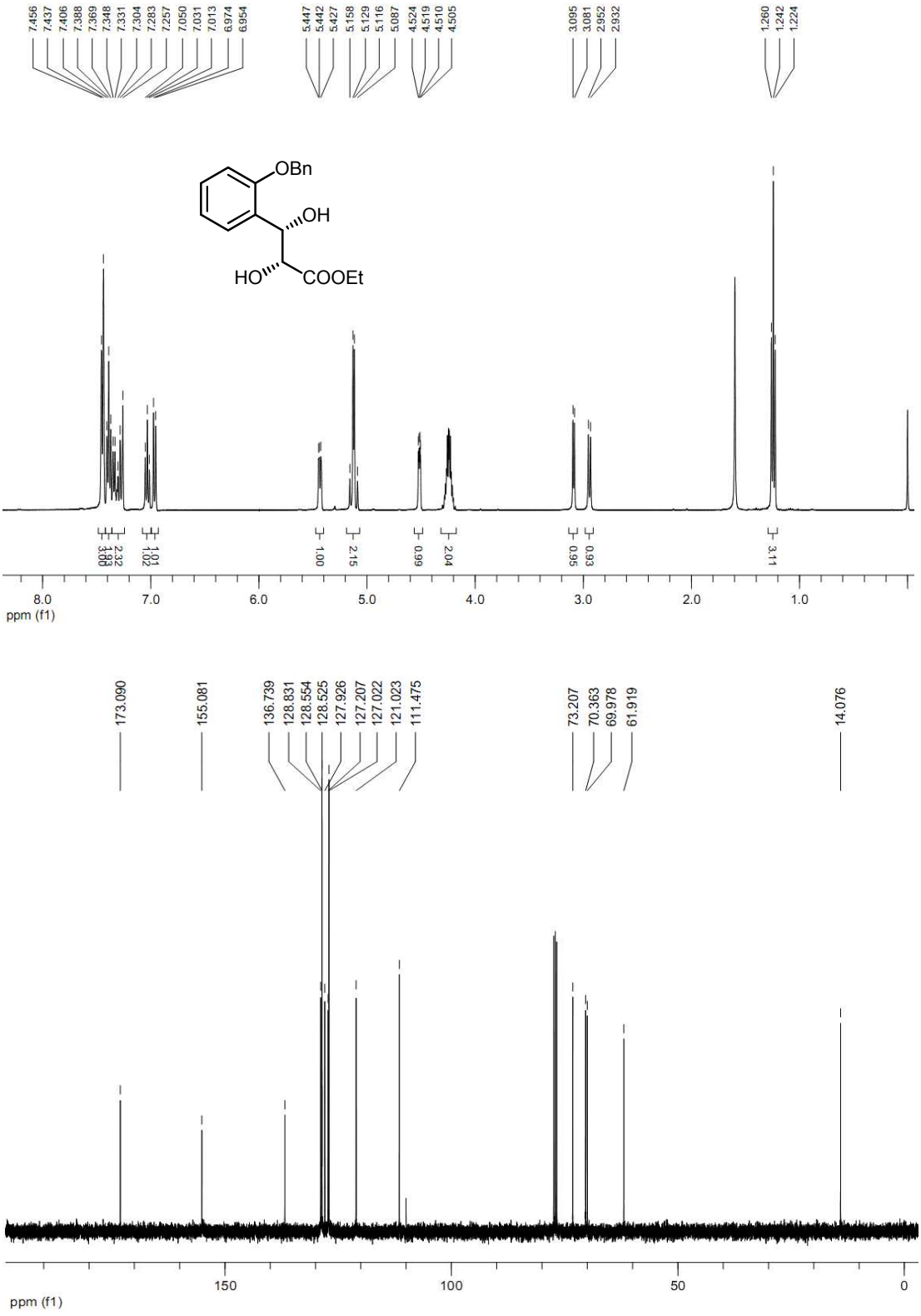
^{1}H and ^{13}C NMR of compound **2.10h**



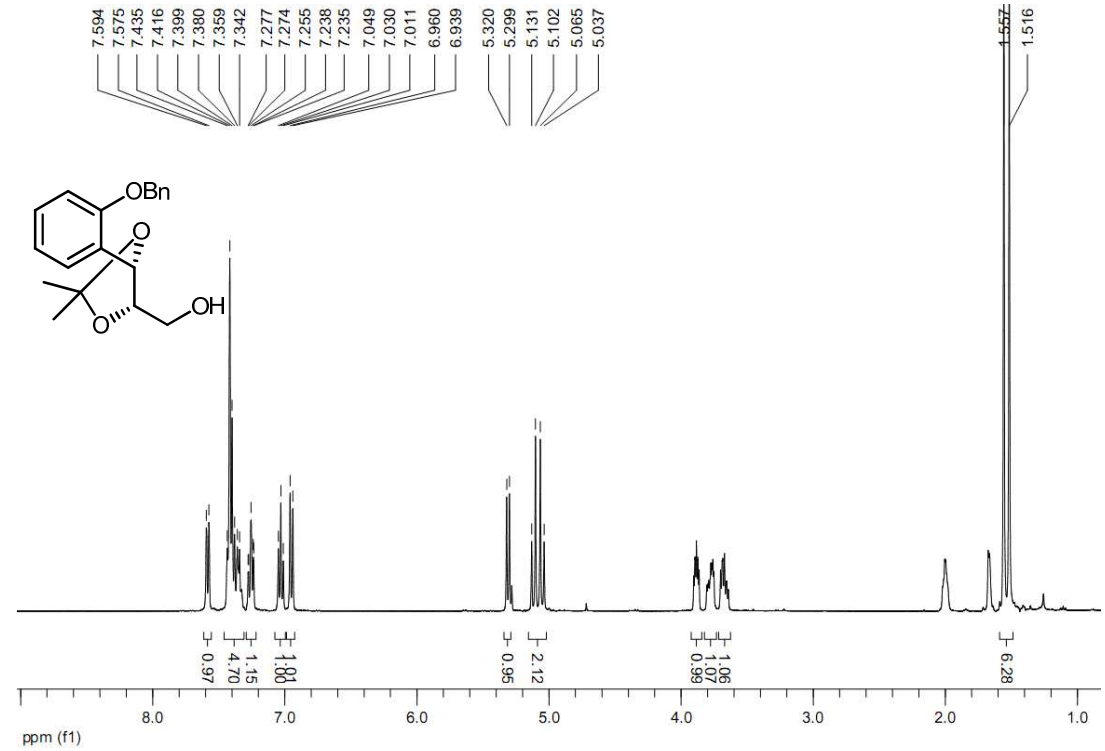
^{1}H and ^{13}C NMR of compound **F2.1a**

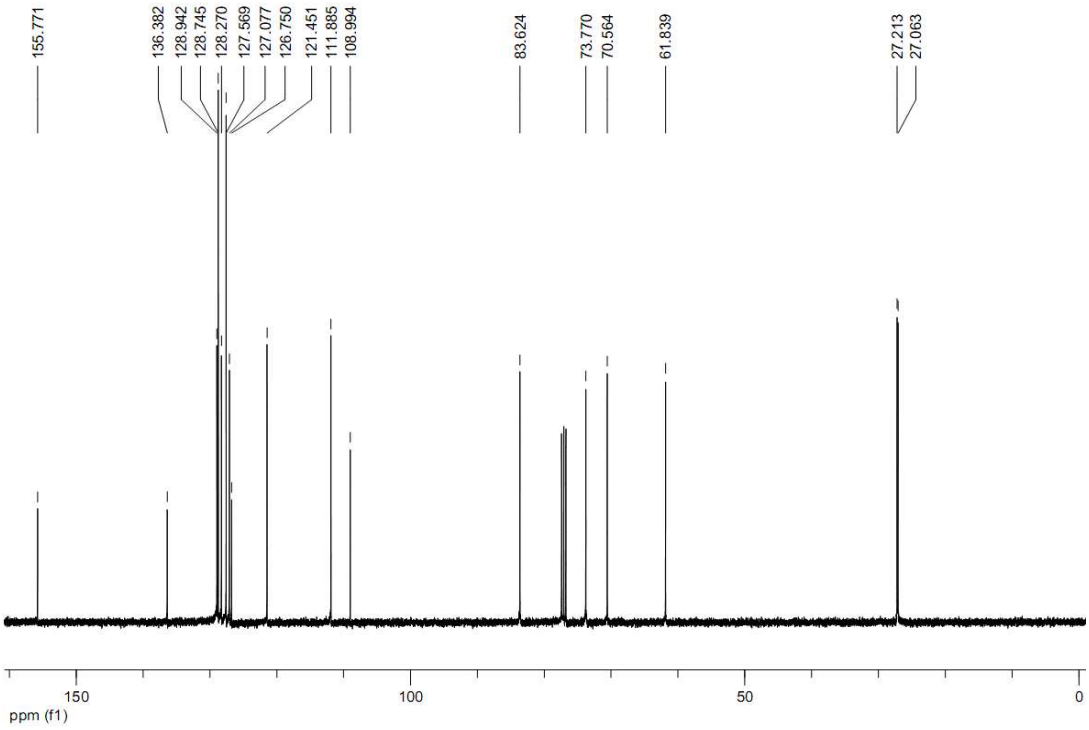


^{1}H and ^{13}C NMR of compound **F2.1h**

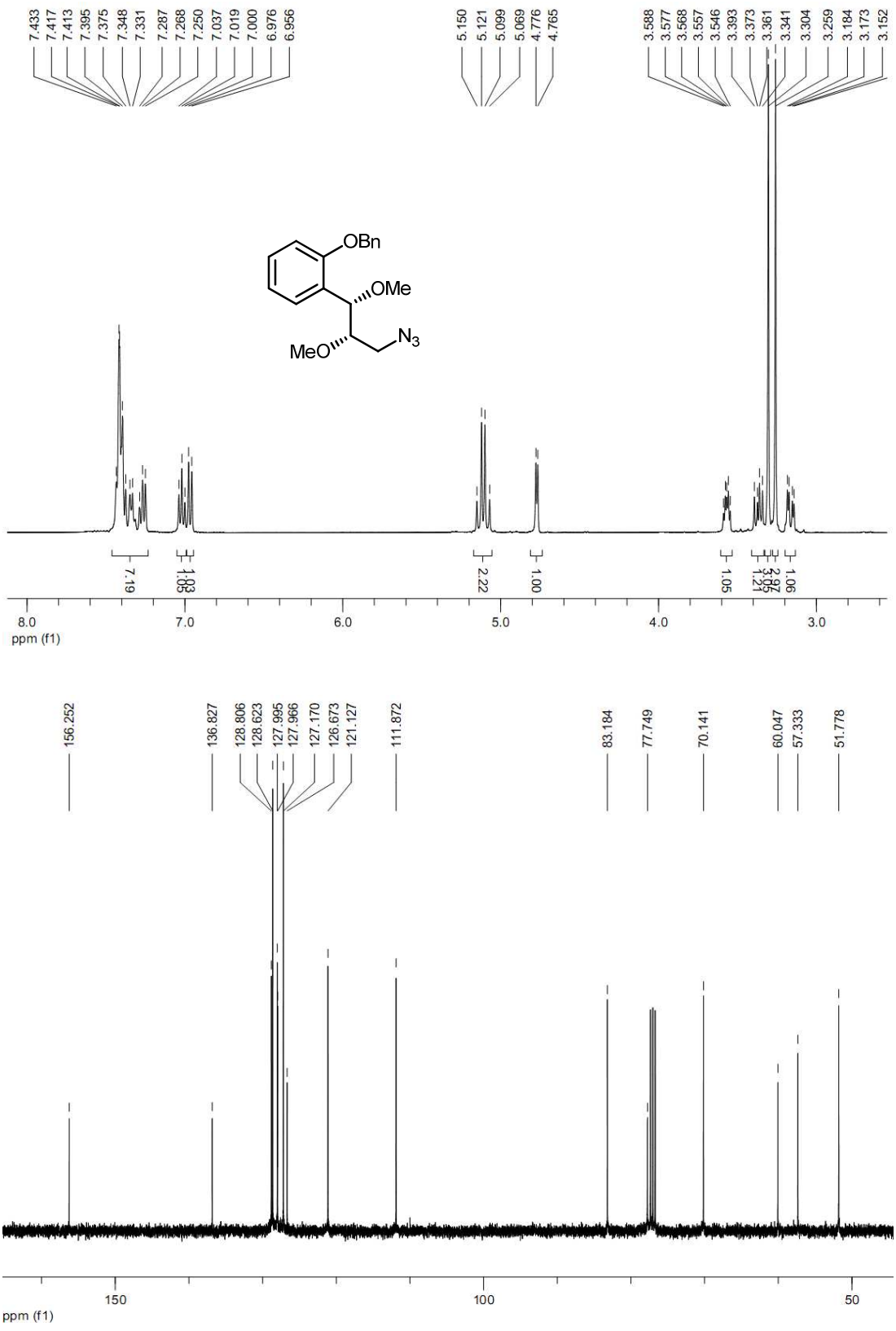


^{1}H and ^{13}C NMR of compound **3.2**

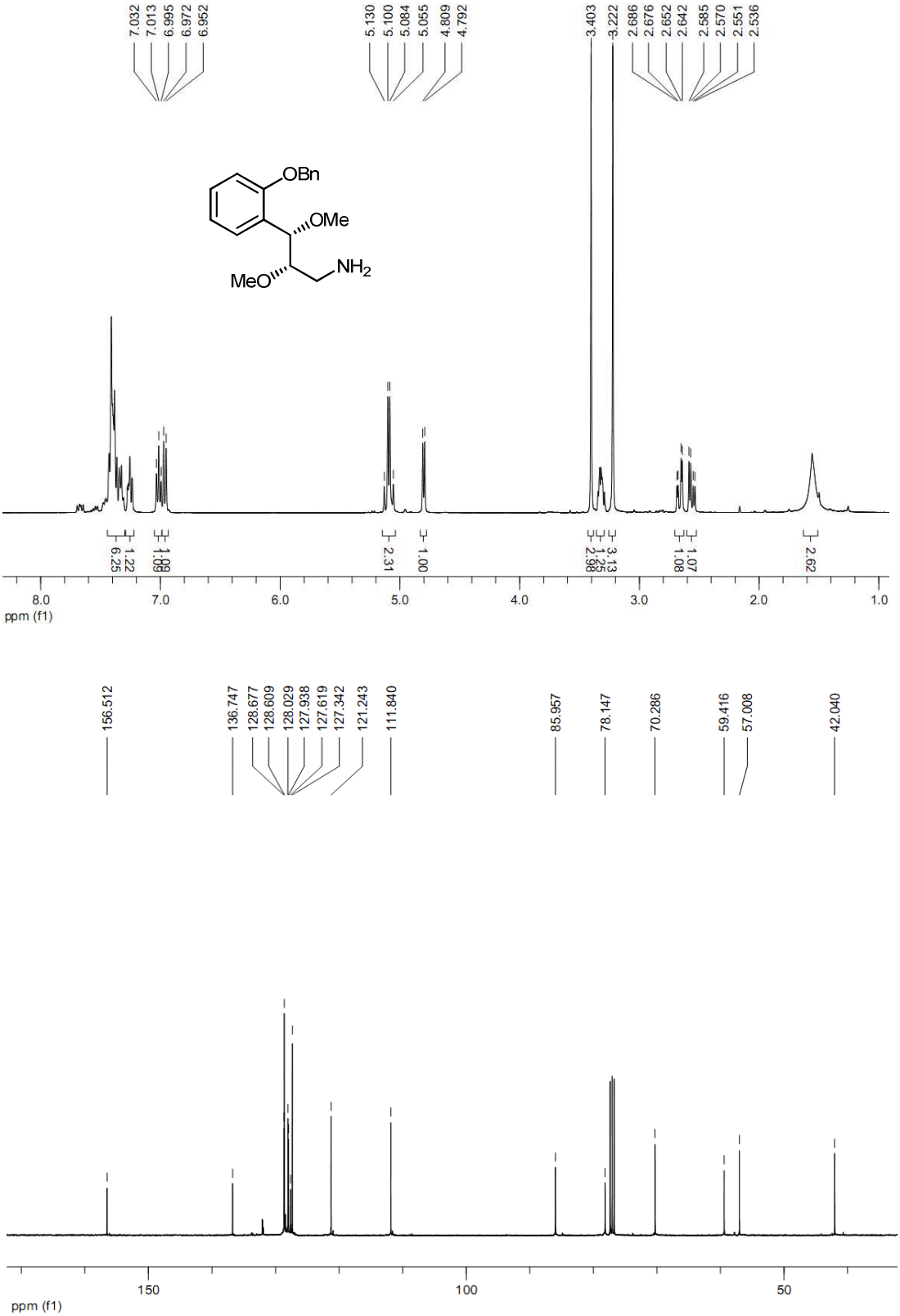




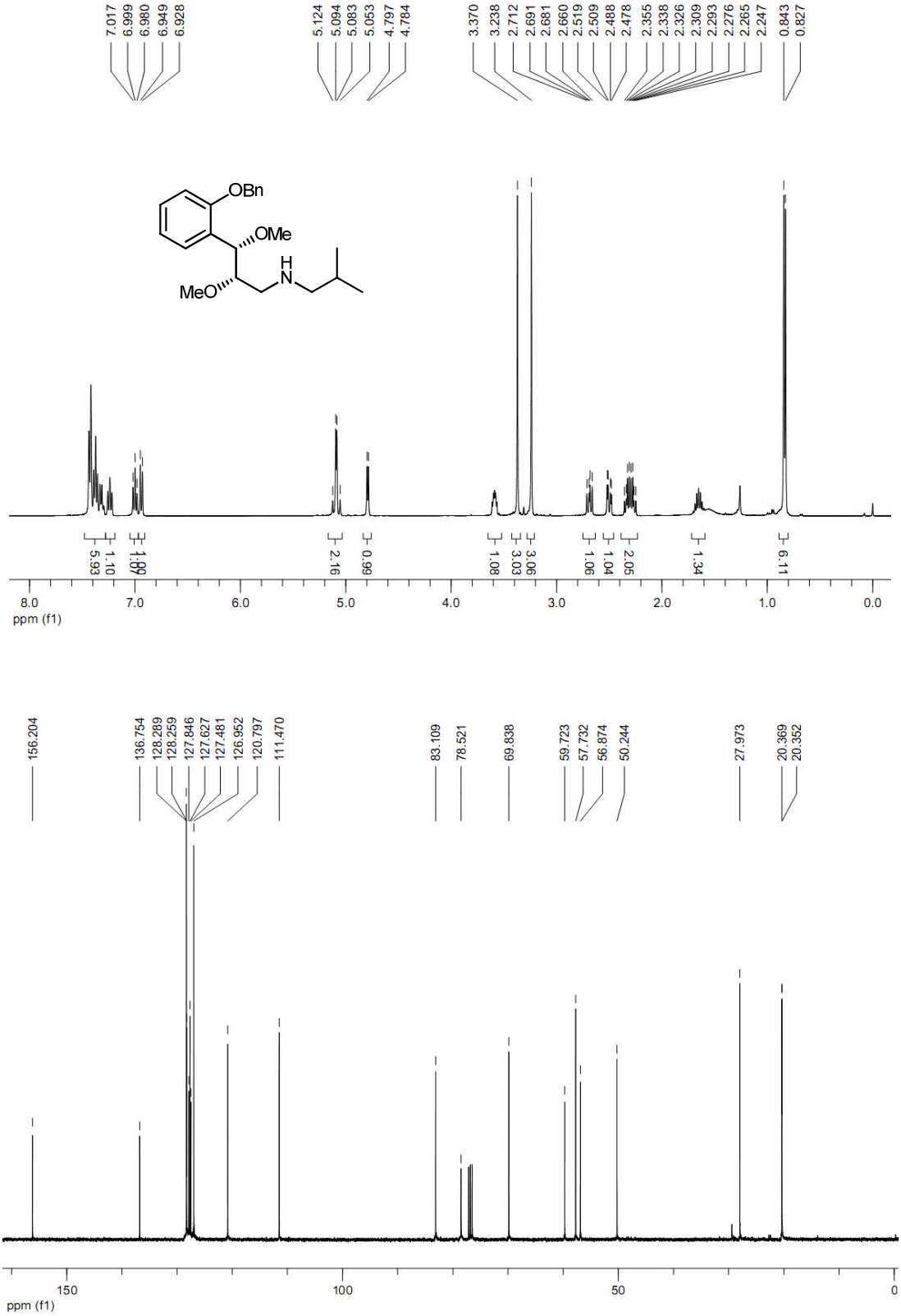
^{1}H and ^{13}C NMR of compound **3.3**



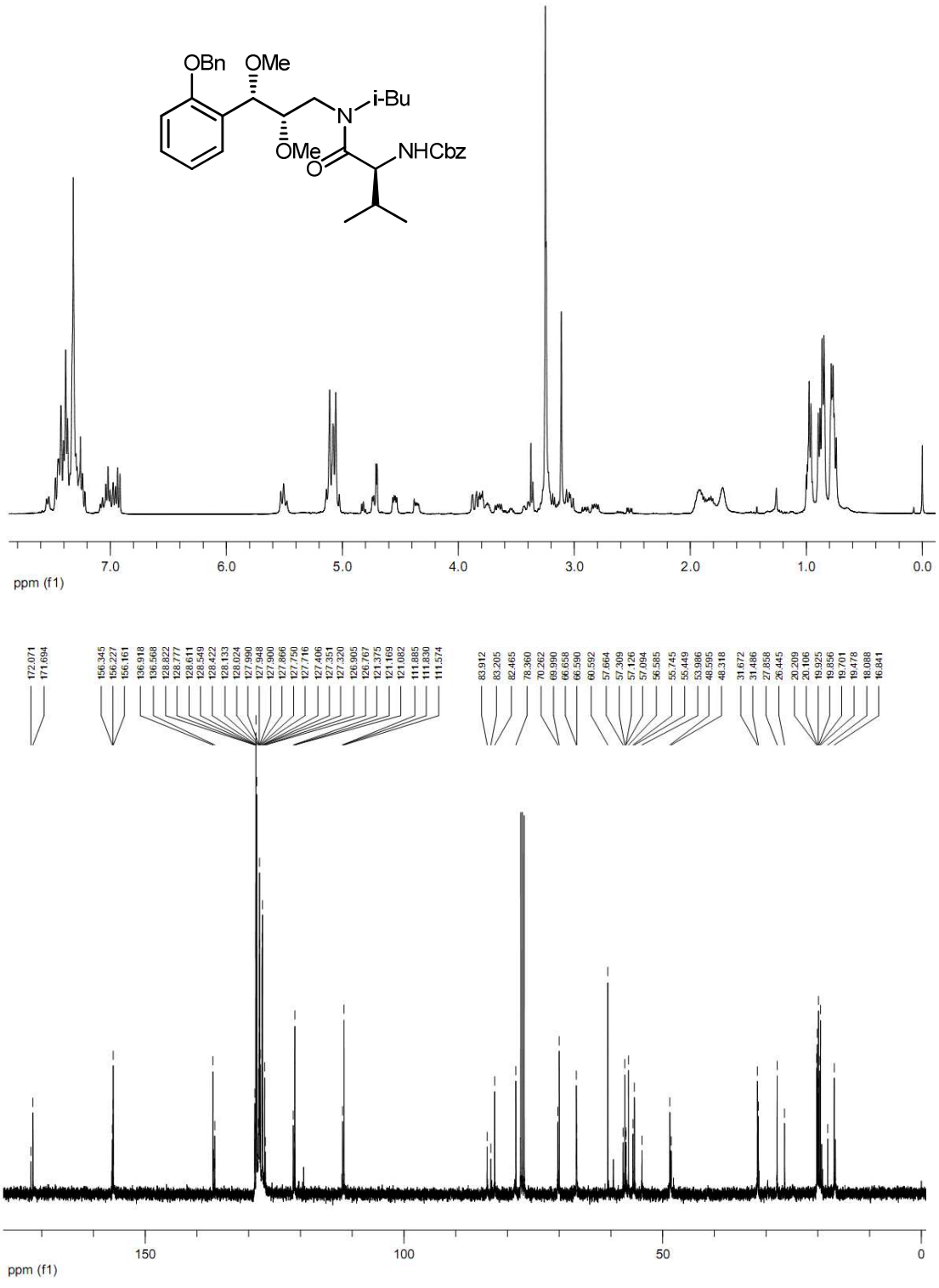
^{1}H and ^{13}C NMR of compound **3.5**



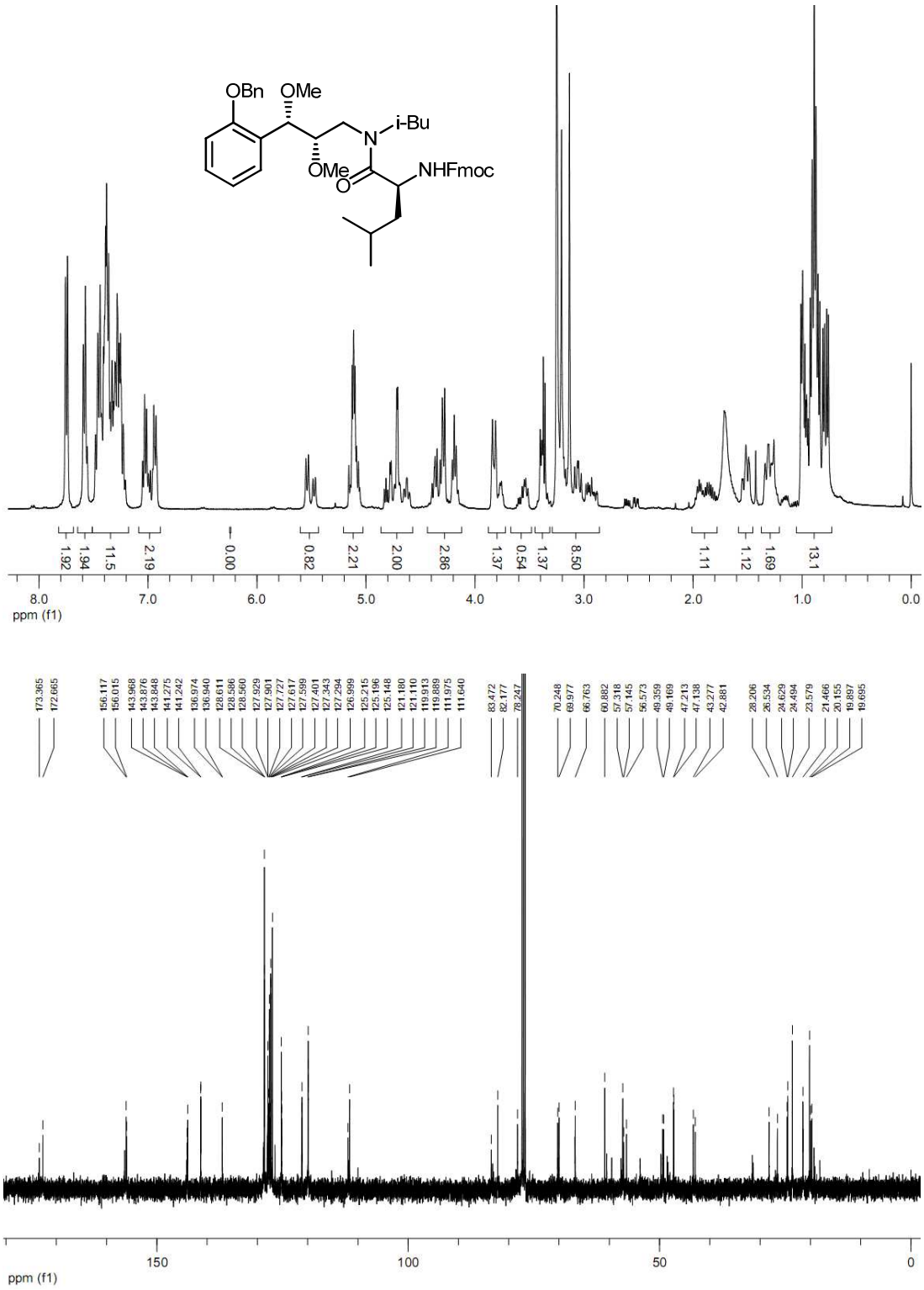
^{1}H and ^{13}C NMR of compound **3.6**



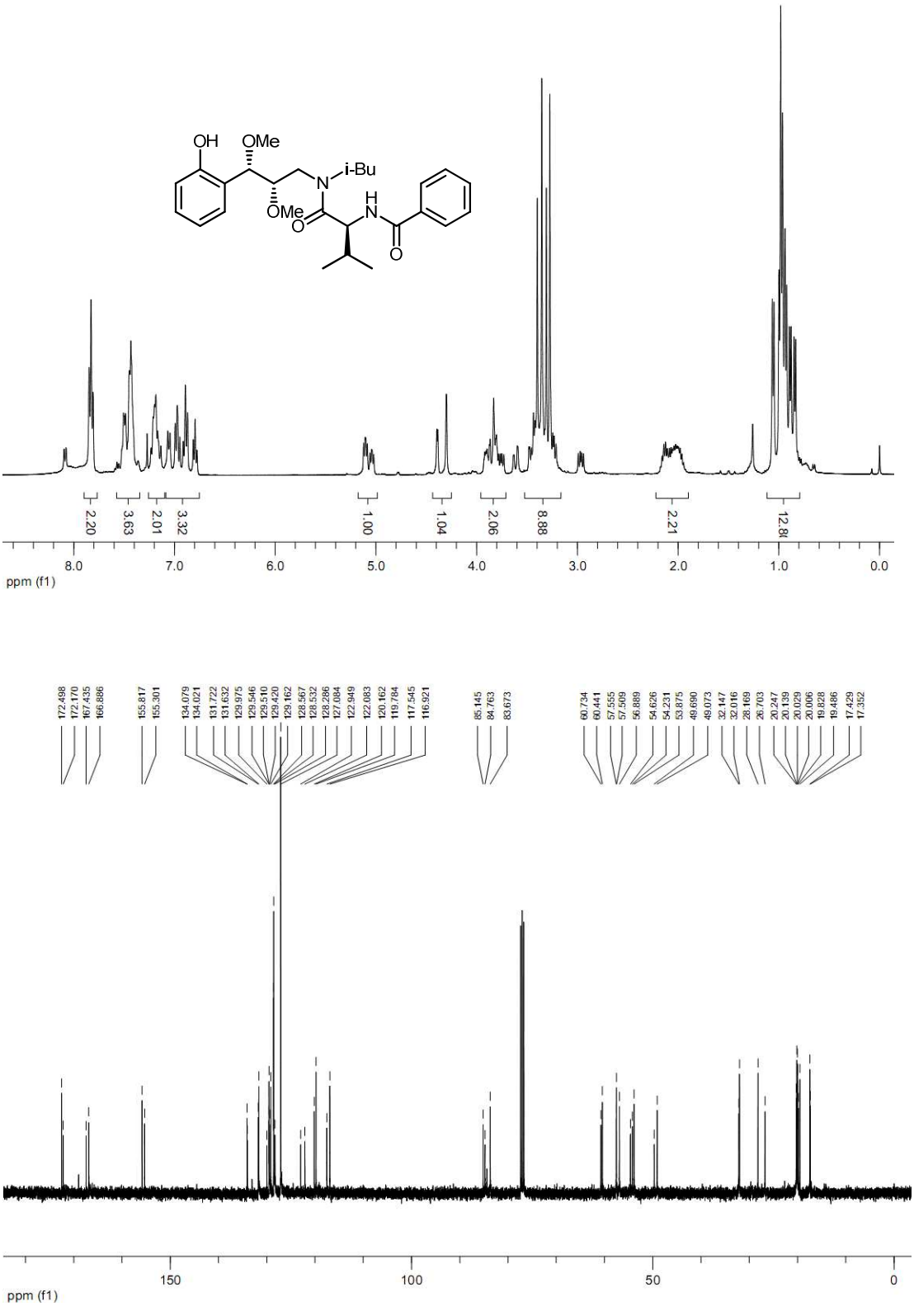
^{1}H and ^{13}C NMR of compound **3.7**



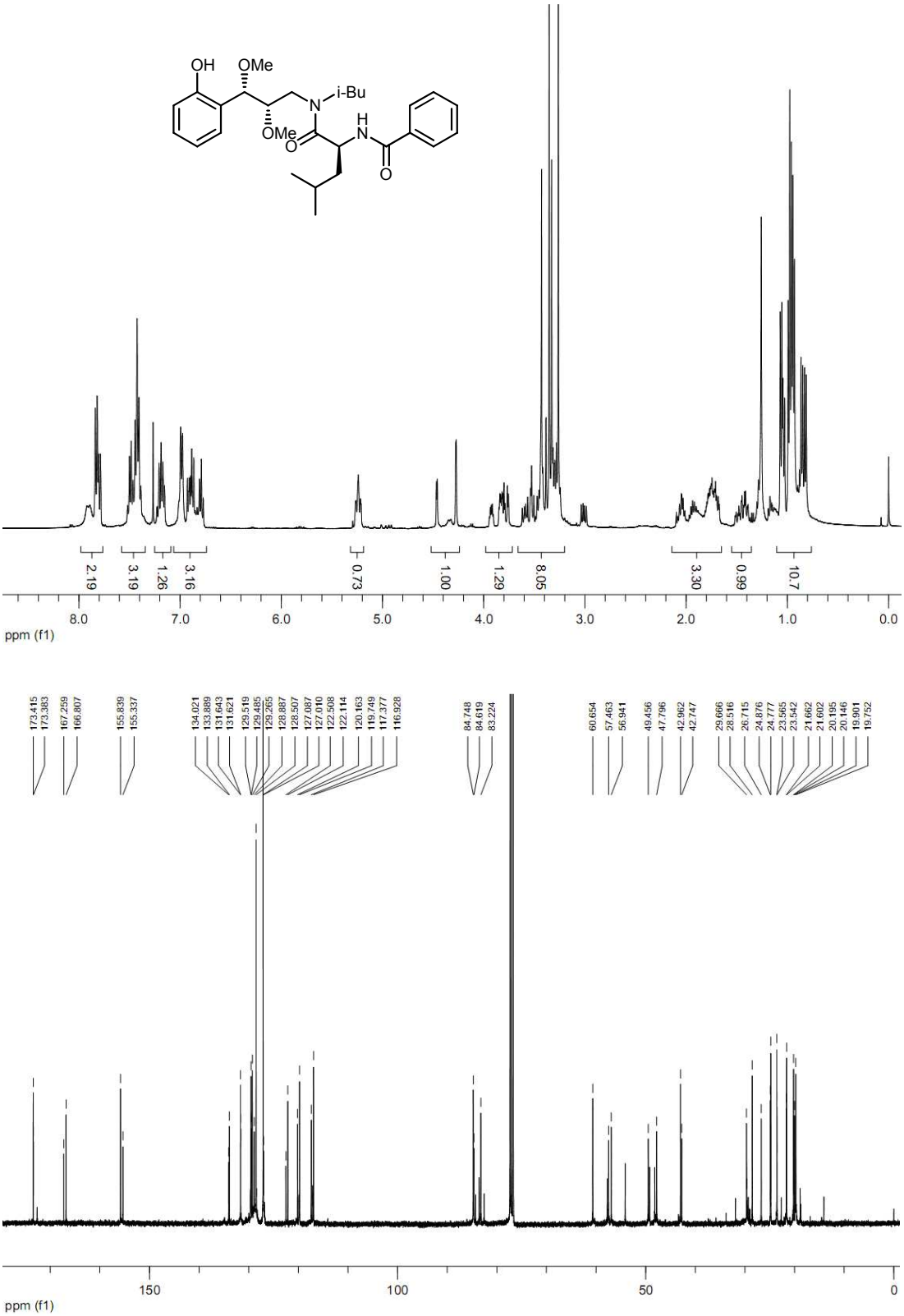
^{1}H and ^{13}C NMR of compound **3.8a**



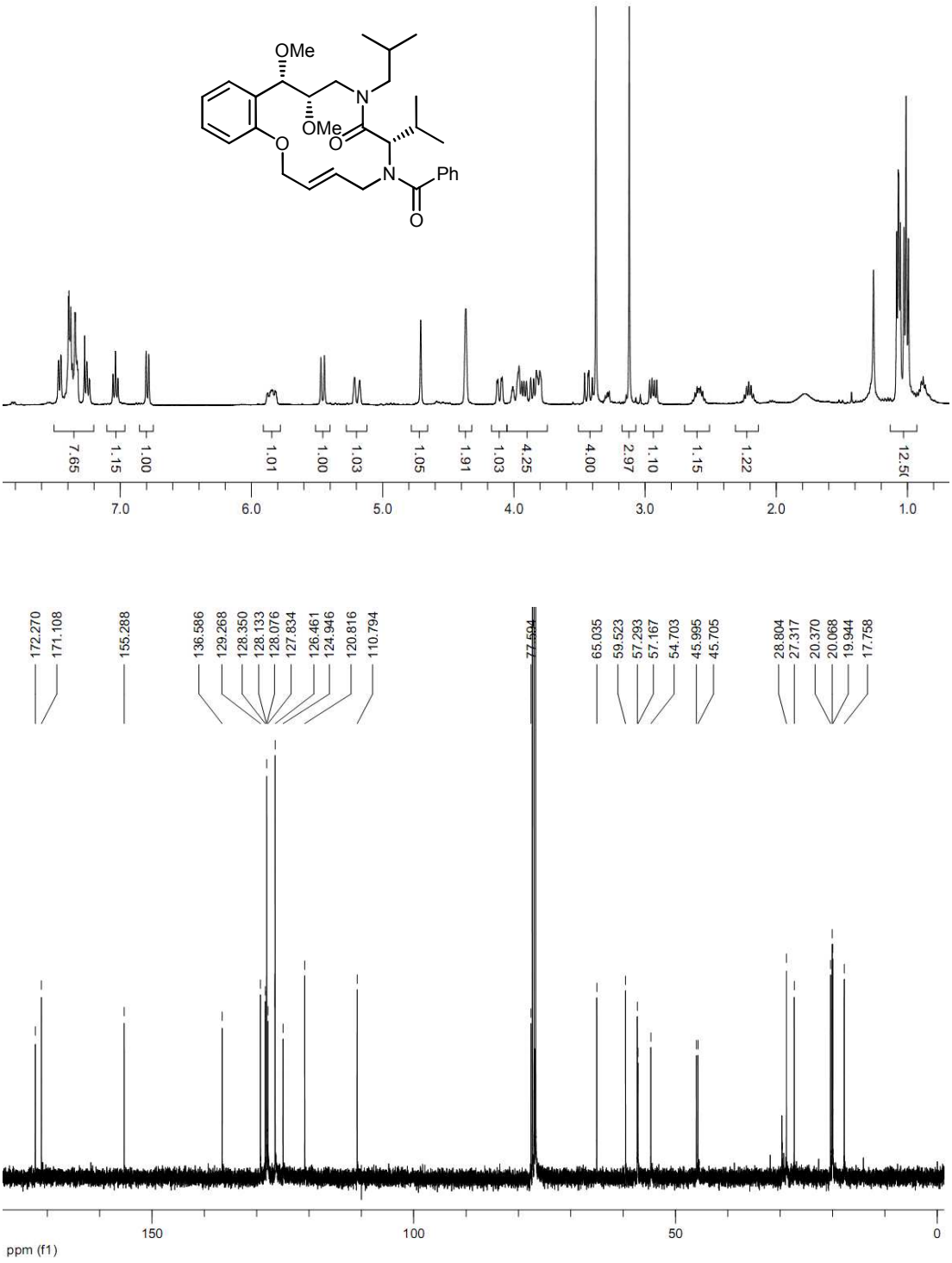
^{1}H and ^{13}C NMR of compound **3.8c**



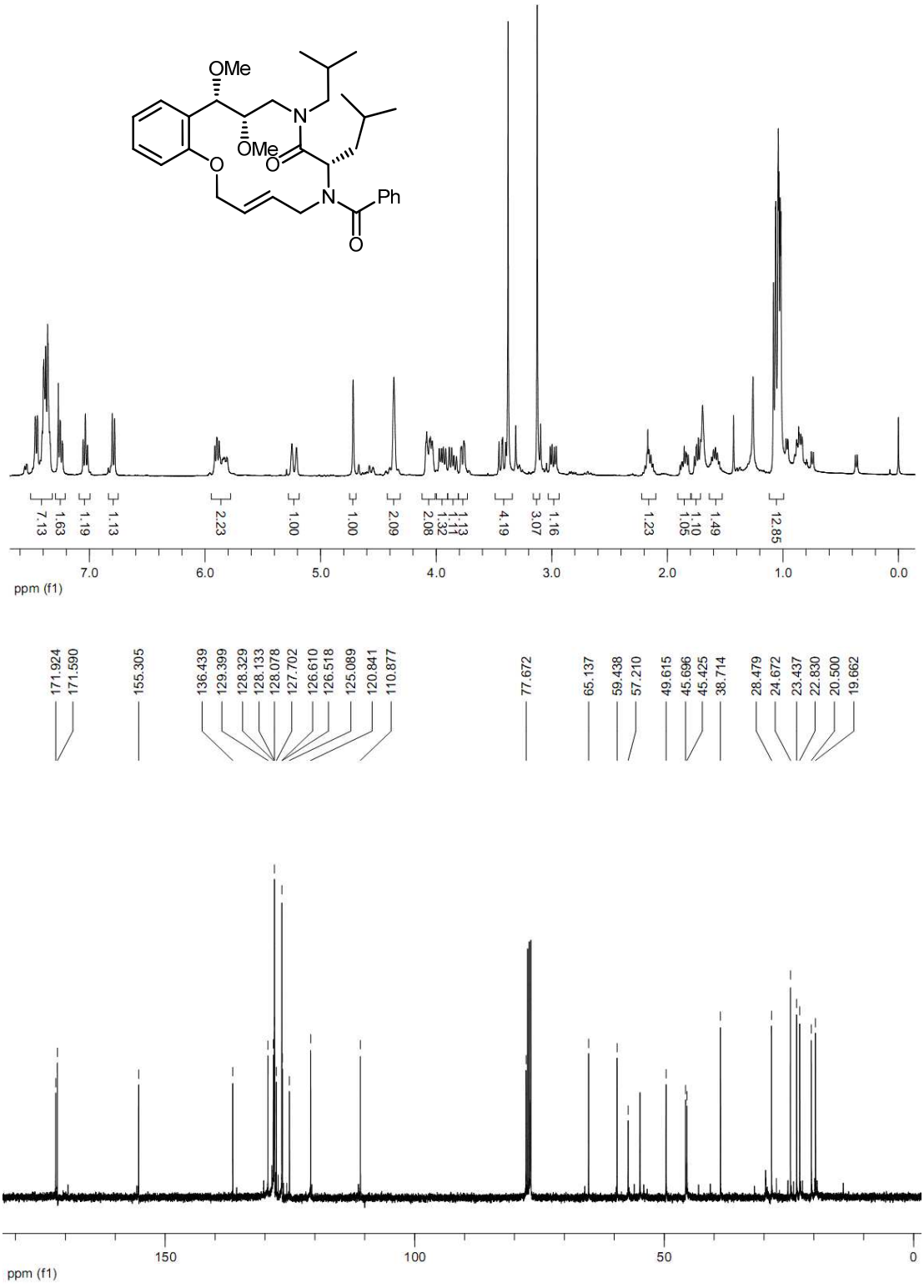
^{1}H and ^{13}C NMR of compound **3.9a**



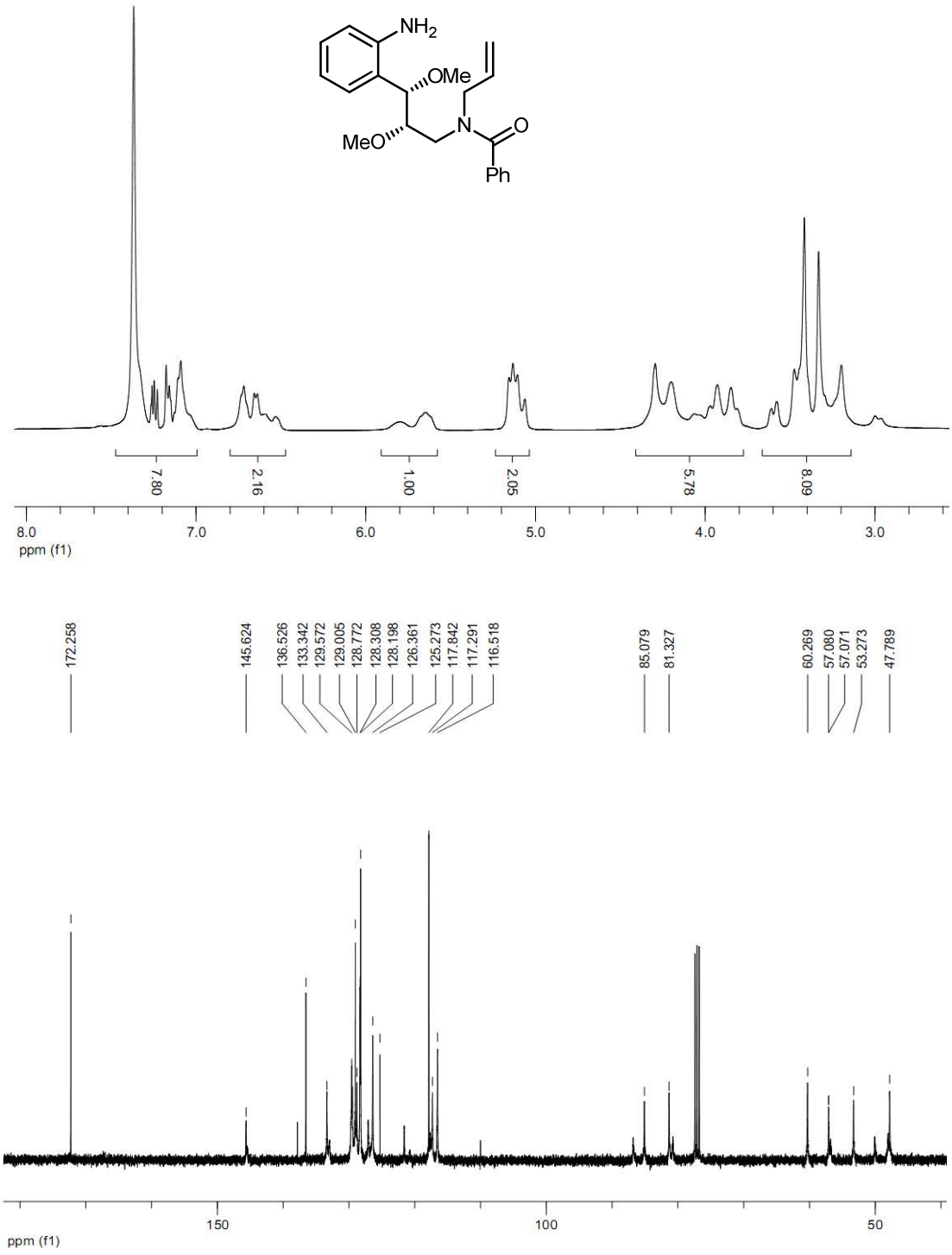
^{1}H and ^{13}C NMR of compound **3.9f**



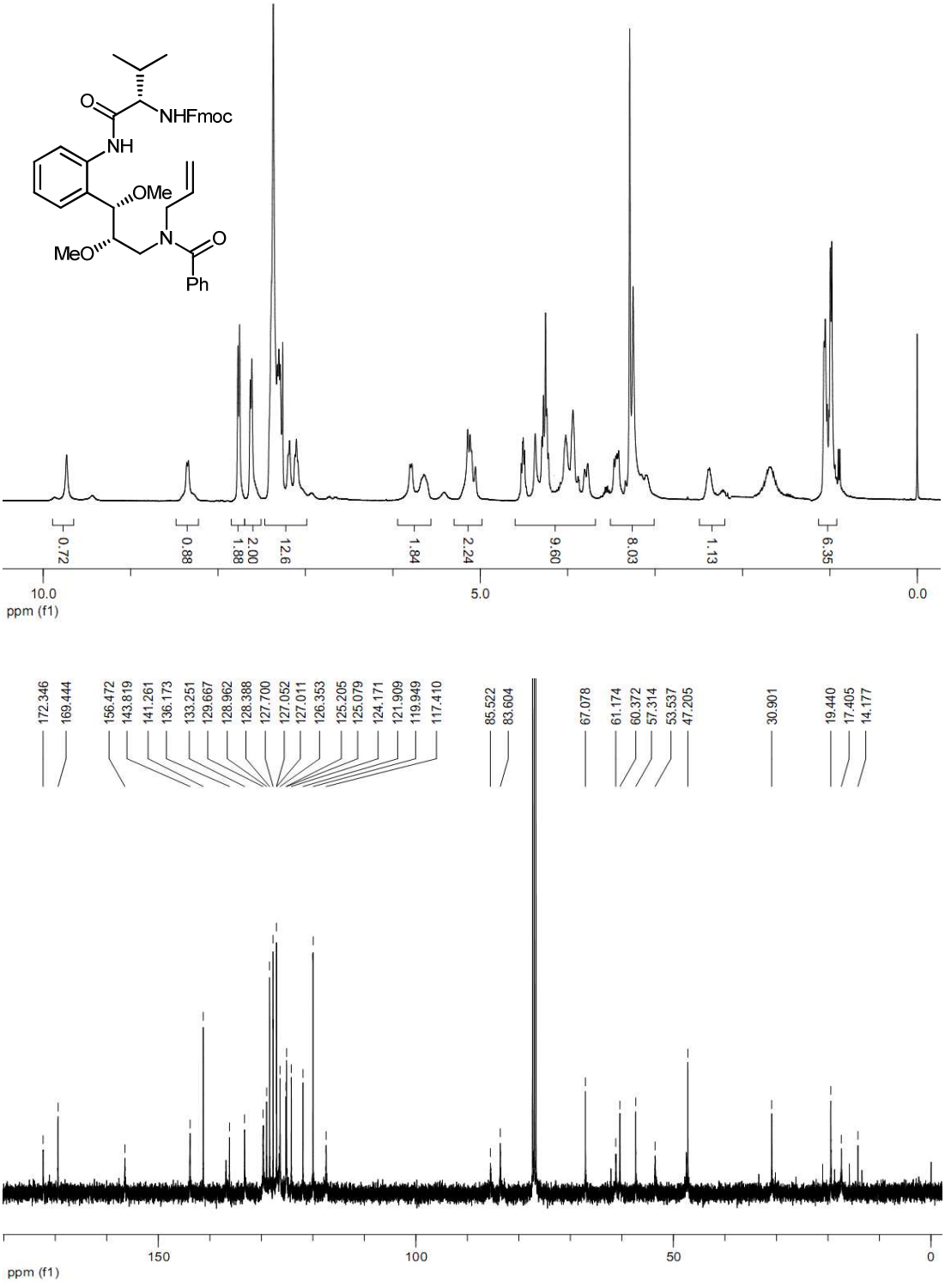
^{1}H and ^{13}C NMR of compound **F2.2a**



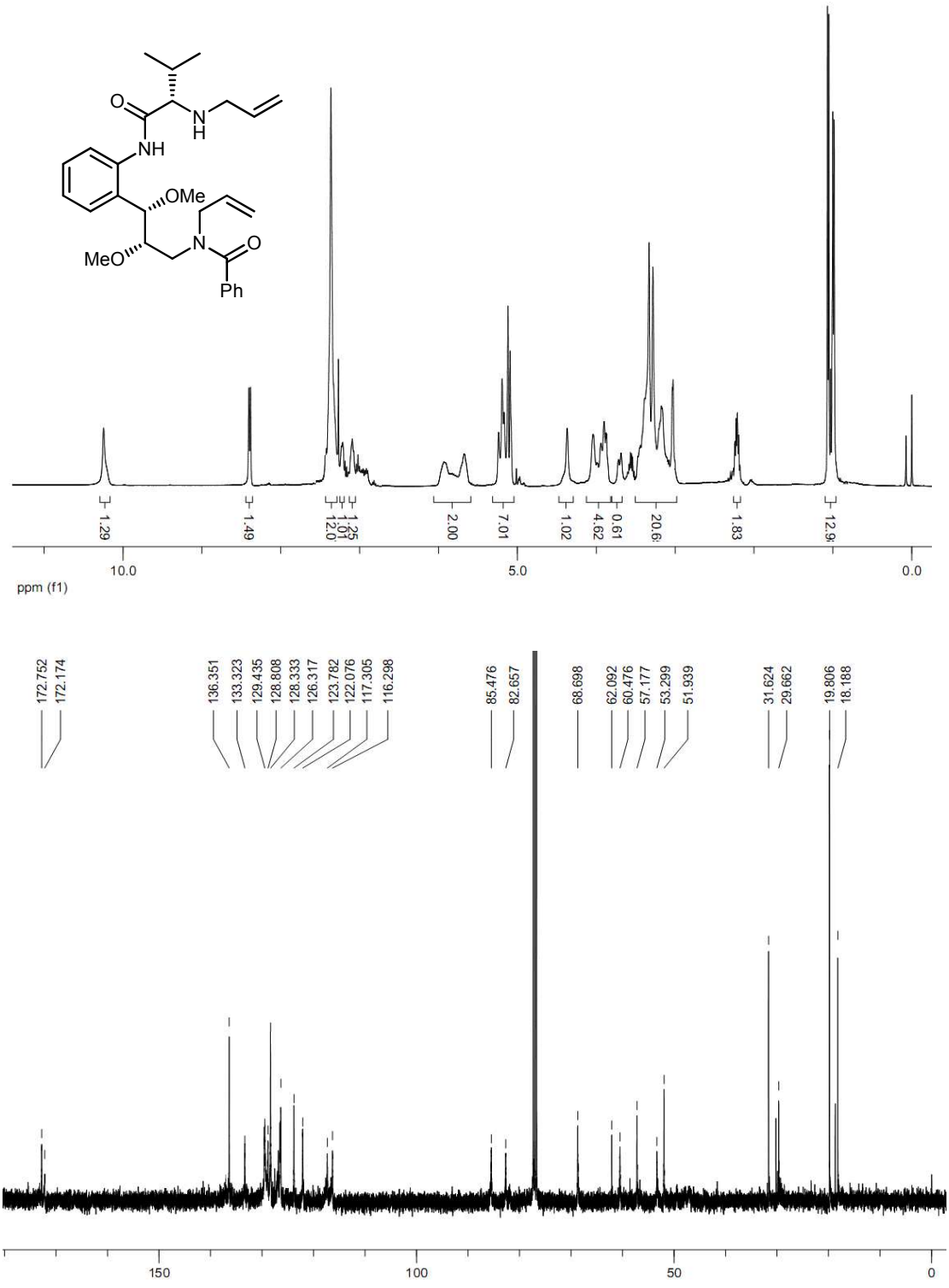
^{1}H and ^{13}C NMR of compound **F2.2f**



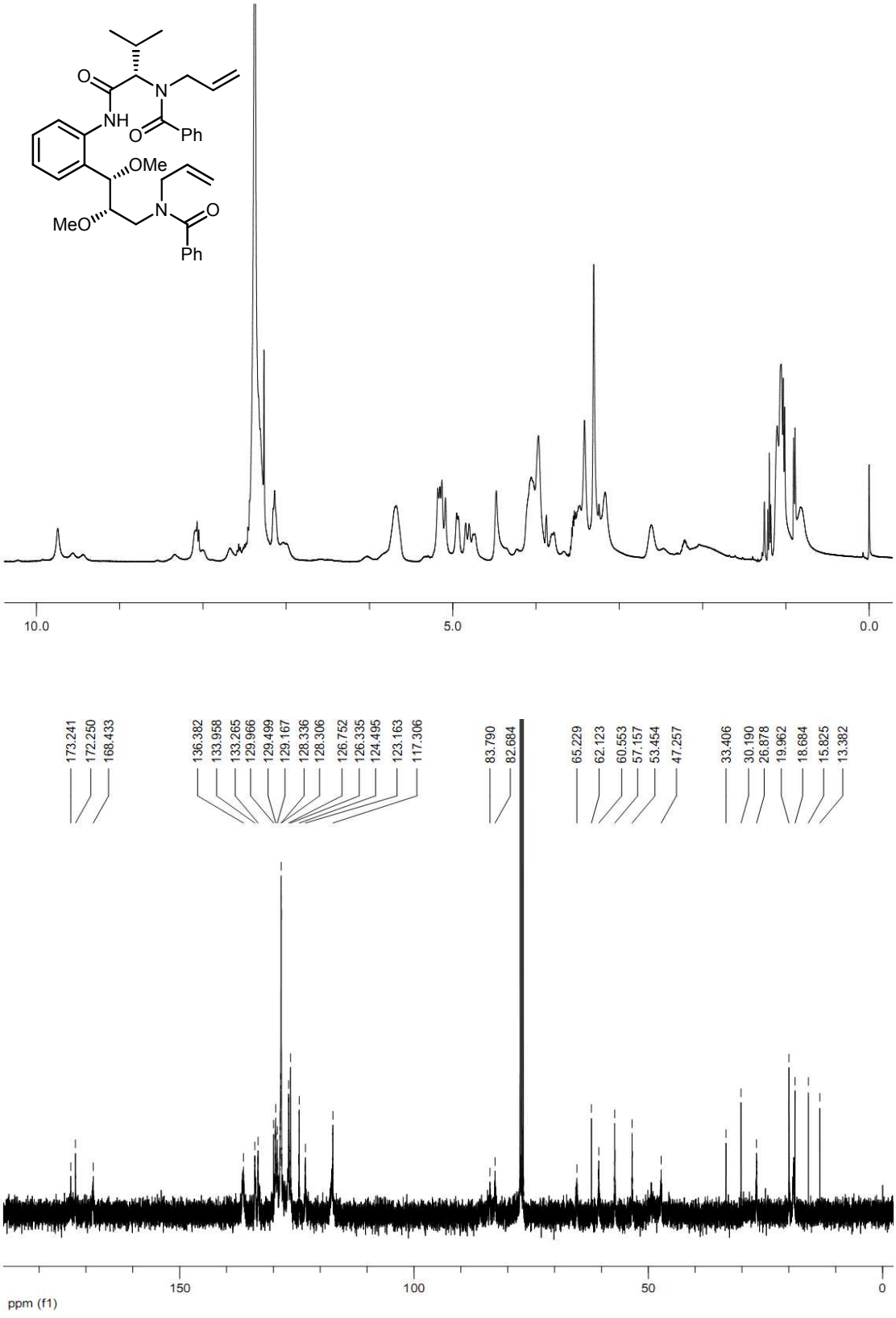
^{1}H and ^{13}C NMR of compound **5.2**



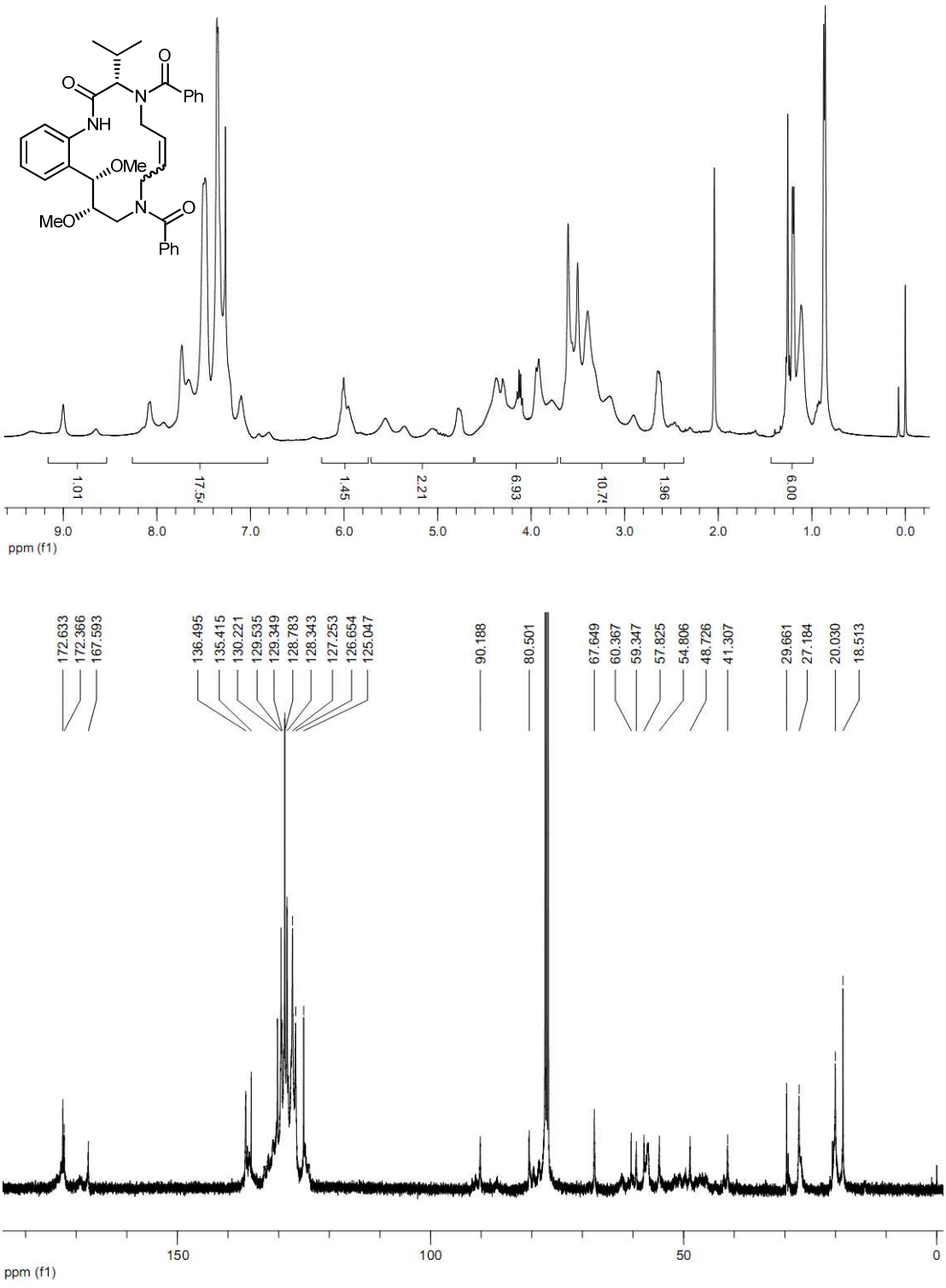
^{1}H and ^{13}C NMR of compound **5.3a**



^{1}H and ^{13}C NMR of compound **5.4a**



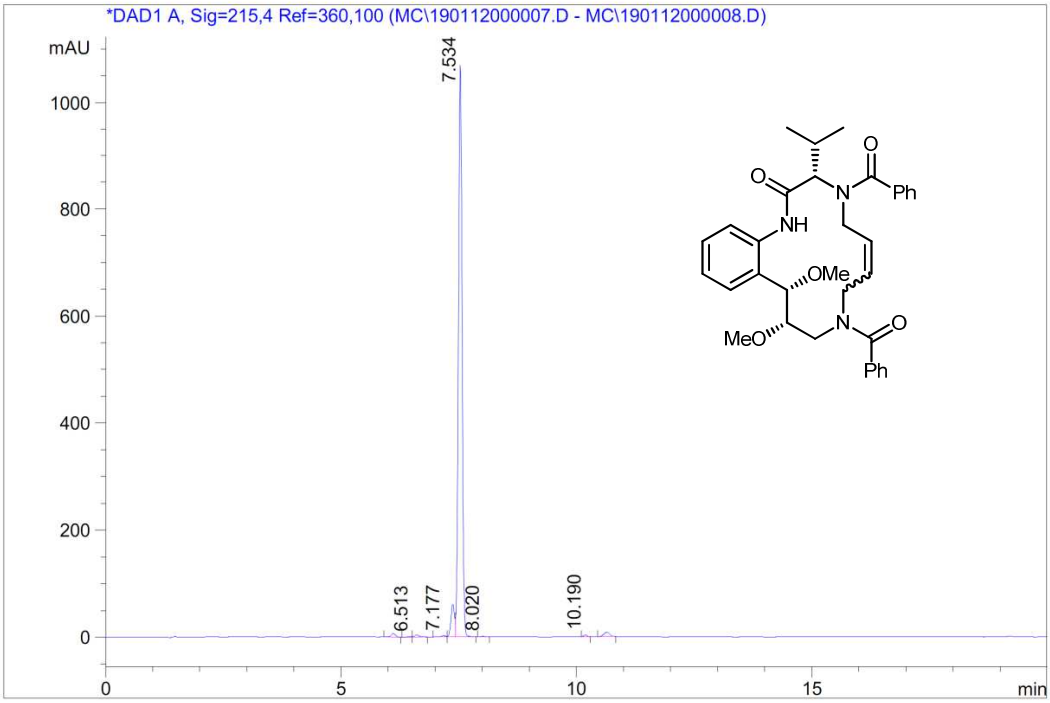
^{1}H and ^{13}C NMR of compound **5.5a**



^{1}H and ^{13}C NMR of compound **F2.3a**

HPLC ANALYSIS REPORT

		Seq Line	: 0
Injection Date	: Thu, 19. Jan. 2012	Location	: Vial 43
Sample Name	: ILS/AMD/C62/173	Inj. No.	: 0
Acq Operator	: RADHA	Inj. Vol.	: 10 µl
Acq. Method	: D:\CHEM32\1\METHODS\C-18 A50B50.M		
Analysis Method	: D:\CHEM32\1\METHODS\C-18 A50B50.M		
Method Info	: Column: X Bridge C18 150*4.6mm 5µm		
	Mobile phase: A) 0.1% HCOOH in water ,B) ACN		
	(GRADIENT) T/%B:0/50,2/50,10/98,15/95,18/50,20/50		
	Flow :1.0 ml/min Diluent:ACN Column Temp:23°C		

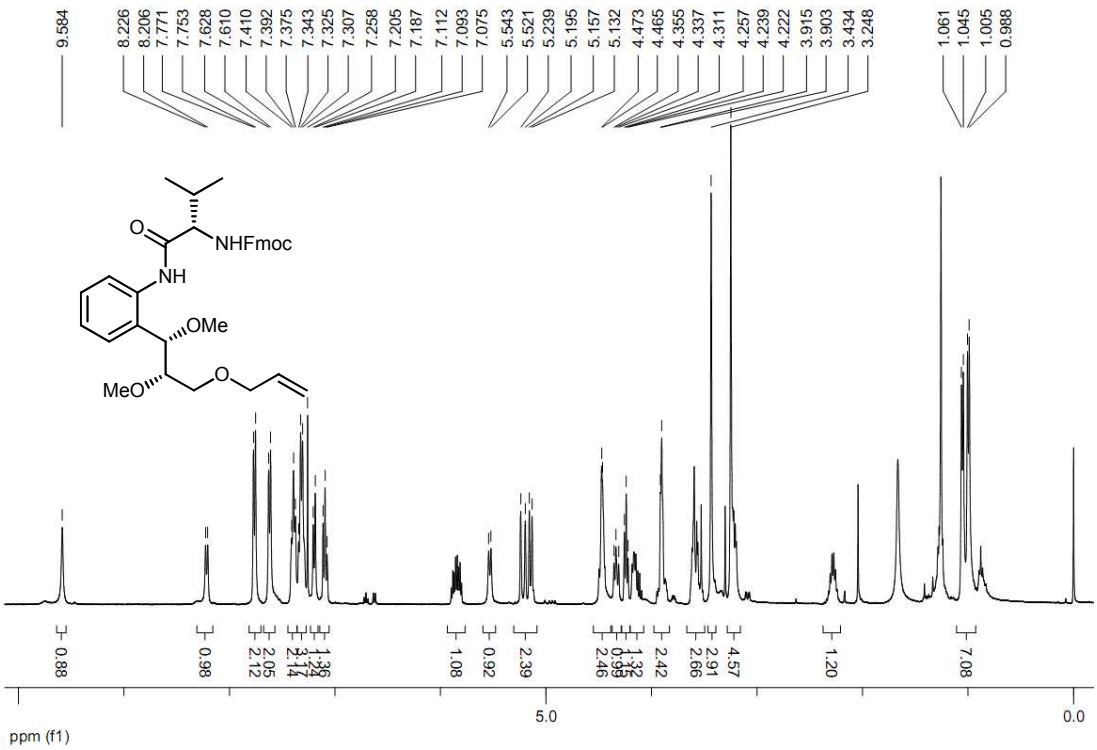


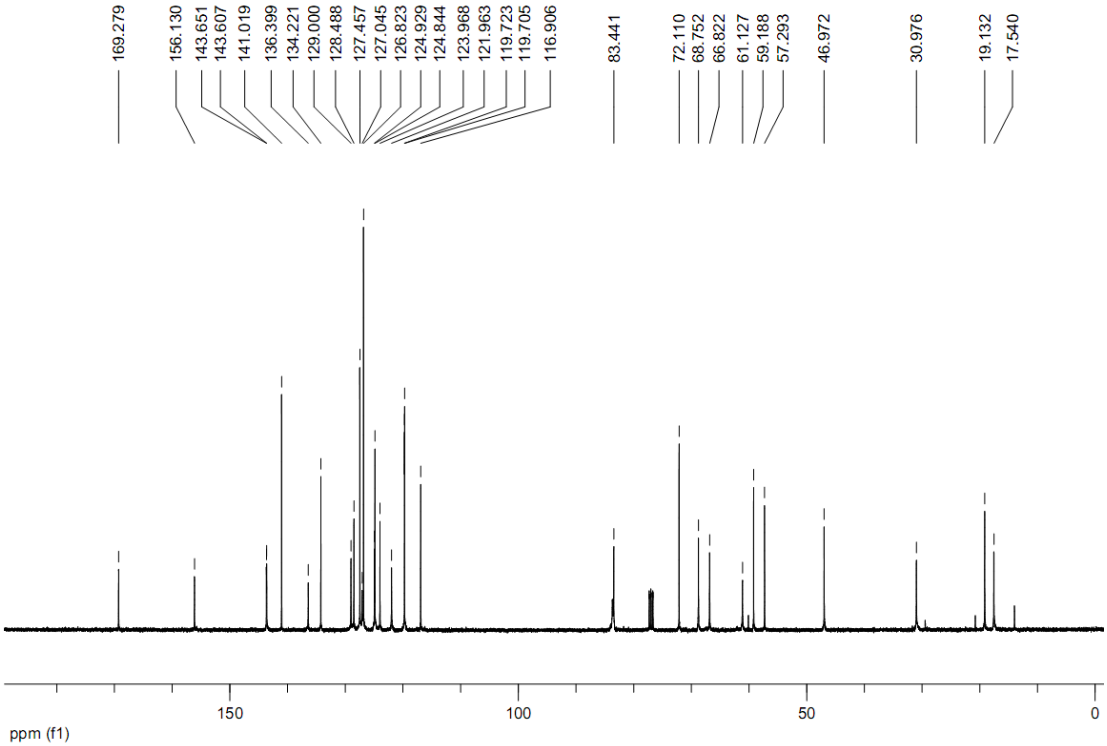
==========

Signal 1: DAD1 A, Sig=215,4 Ref=360,100

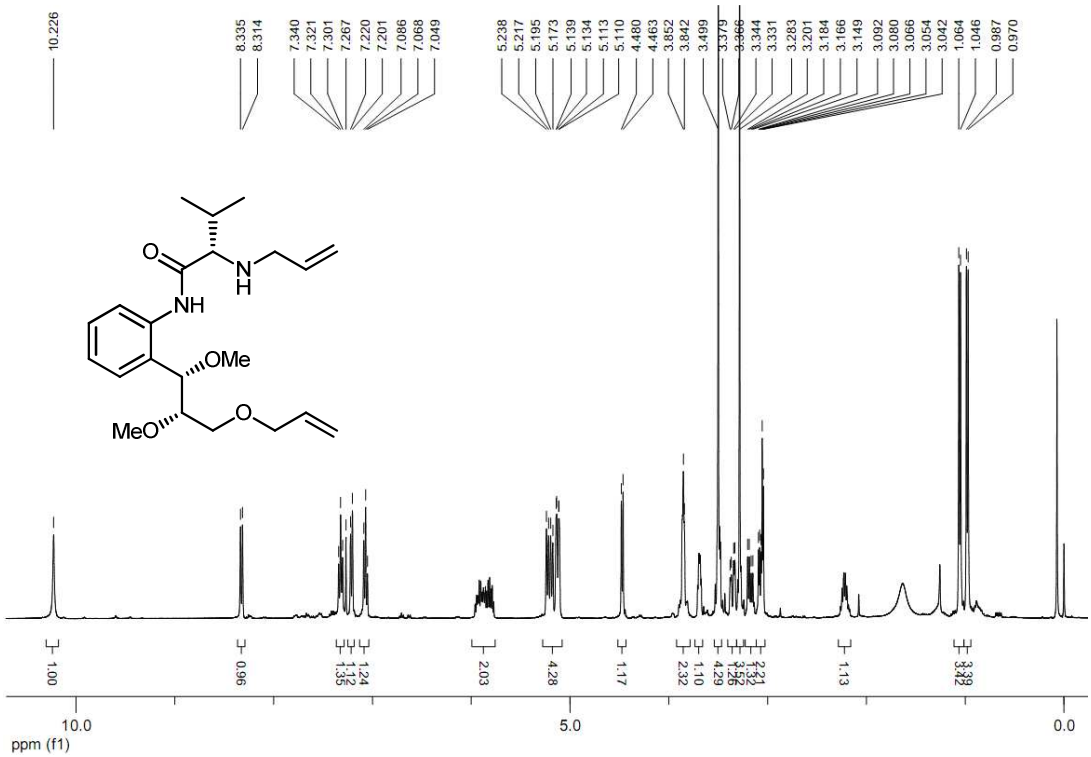
Peak #	RT [min]	Width [min]	Area	Area %	Name
1	6.113	0.109	44.436	0.715	
2	6.513	0.095	5.582	0.090	
3	6.608	0.115	30.006	0.483	
4	7.177	0.115	16.360	0.263	
5	7.375	0.087	318.266	5.120	
6	7.534	0.089	5715.140	91.947	
7	8.020	0.110	4.575	0.074	
8	10.190	0.073	13.885	0.223	
9	10.644	0.144	67.435	1.085	

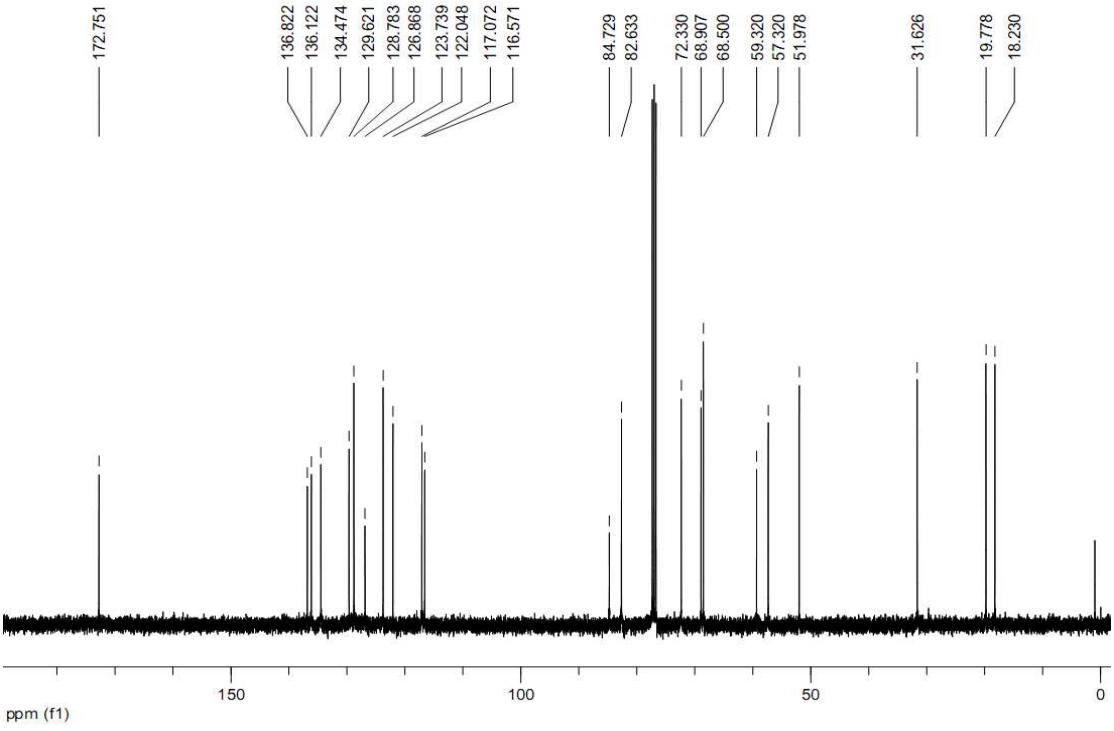
HPLC-MS of compound **F2.3a**



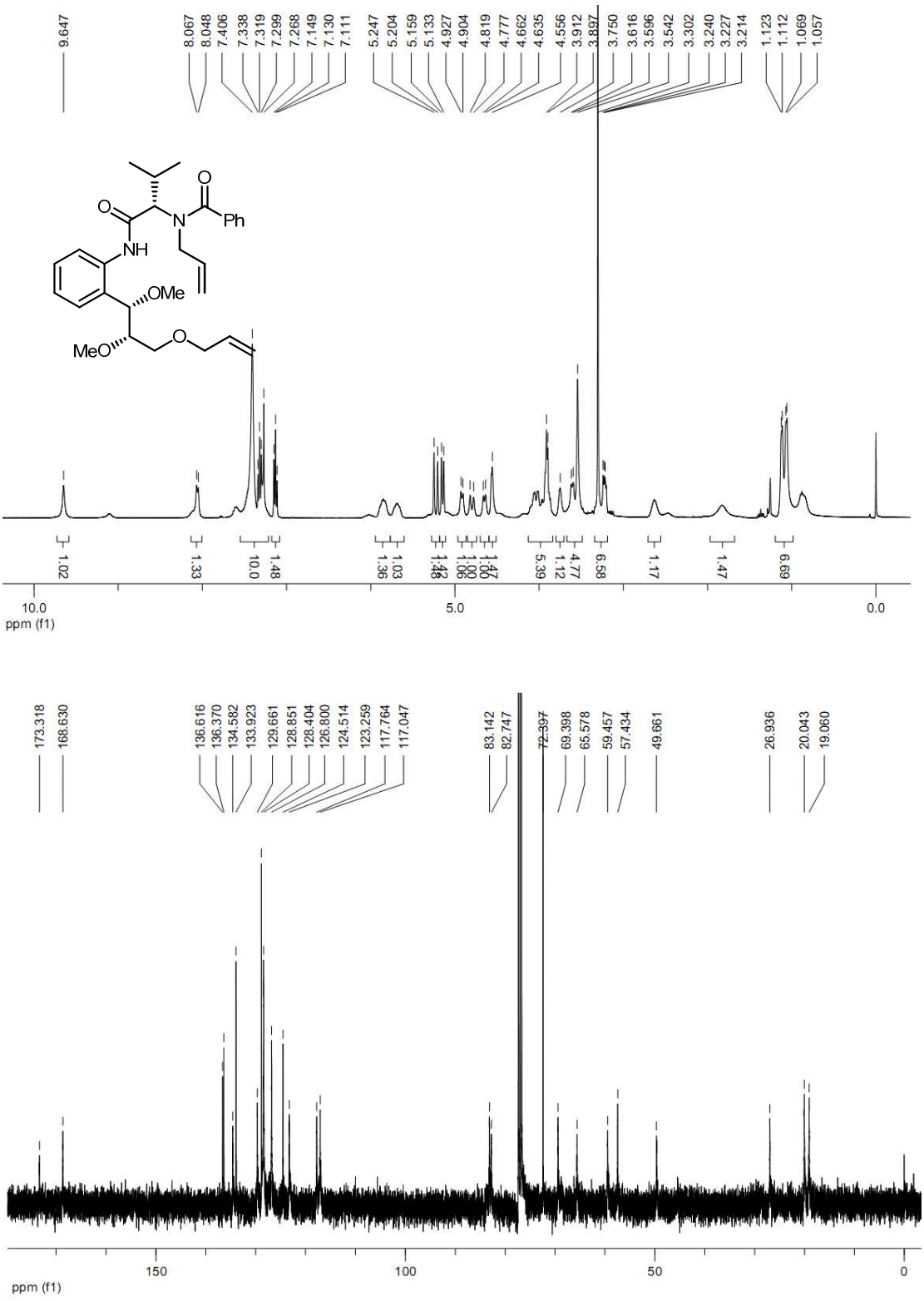


^{1}H and ^{13}C NMR of compound **6.3a**

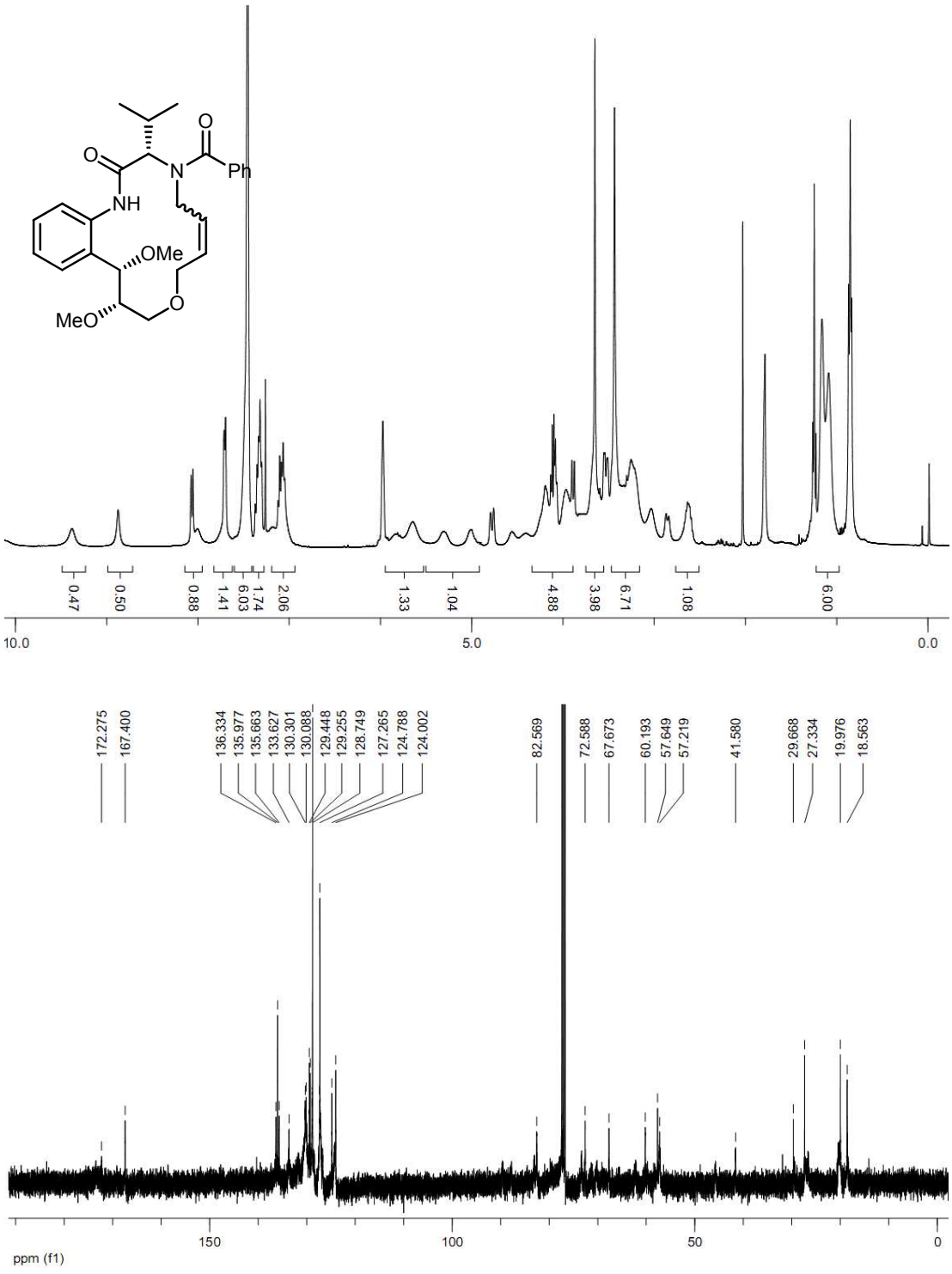




^{1}H and ^{13}C NMR of compound **6.4a**



^{1}H and ^{13}C NMR of compound **6.5a**



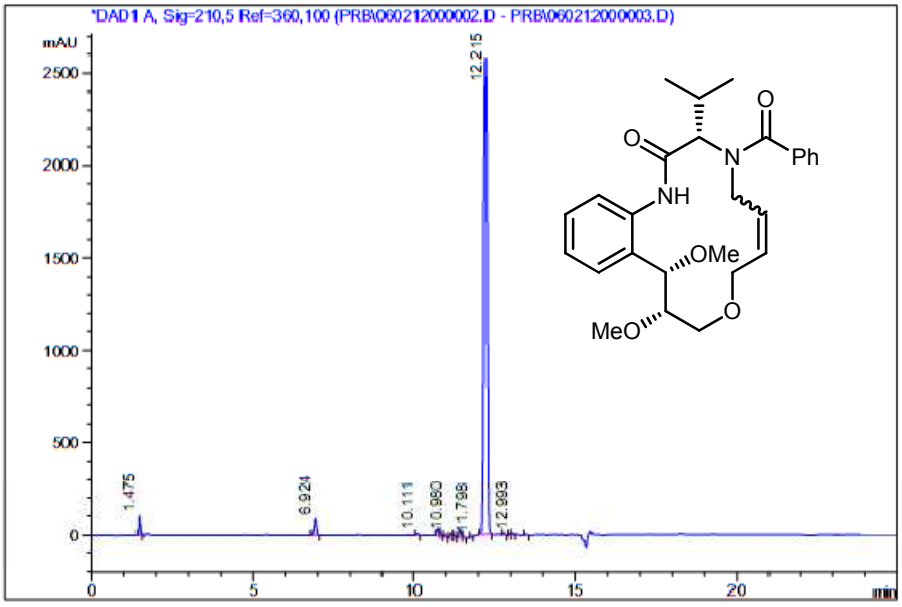
^{1}H and ^{13}C NMR of compound **F2.4a**

HPLC-MS of compound **F2.4a**

HPLC ANALYSIS REPORT

		Seq Line :	0
Injection Date	: Mon, 6. Feb. 2012	Location :	Vial 41
Sample Name	: ILS-AMD-C62-140	Inj. No. :	0
Acq Operator	: RADHA	Inj. Vol. :	4 µl
Acq. Method	: D:\CHEM32\1\METHODS\C-18 A80B20.M		
Analysis Method	: D:\CHEM32\1\METHODS\C-18 A80B20.M		
Method Info	: Column : X-BRIDGE C-18 150*4.6mm 5µ		

Mobile phase: A) 0.1% HCOOH in water ,B) ACN (Gradient)
T%B:0/20,2/20,15/95,20/95,22/20,25/20
Flow:1.0ml/min Diluent: ACN ColumnTemp :23°c



Signal 1: DAD1 A, Sig=210,5 Ref=360,100

Peak #	RT [min]	Width [min]	Area	Area %	Name
1	1.475	0.050	294.801	1.618	
2	6.924	0.078	402.203	2.207	
3	10.111	0.067	31.493	0.173	
4	10.747	0.077	186.607	1.024	
5	10.804	0.052	47.036	0.258	
6	10.980	0.069	55.480	0.304	
7	11.158	0.074	92.211	0.506	
8	11.248	0.066	60.069	0.330	
9	11.422	0.078	215.126	1.180	
10	11.527	0.063	34.059	0.187	
11	11.798	0.059	11.052	0.061	
12	12.215	0.108	16685.914	91.557	
13	12.793	0.076	47.342	0.260	
14	12.993	0.050	7.507	0.041	
15	13.064	0.089	37.032	0.203	
16	13.454	0.078	16.680	0.092	

*** End of Report ***

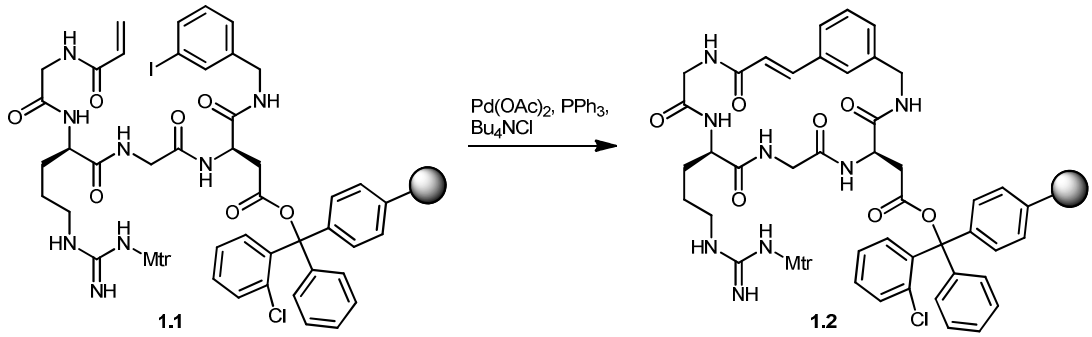
Chapter 3: Synthesis of Natural Product-Inspired, 17-Membered Ring Derived Macrocyclic Toolbox via an Intramolecular Heck Reaction

3.1. Introduction:

More than 40 years ago, Mizoroki[1] and Heck[2] independently discovered the Pd(0)-catalyzed vinylation of aryl halides. This reaction is now known as the Heck reaction, is now broadly defined as the Pd(0)-mediated coupling of an aryl or vinyl halide or triflate with an alkene. This reaction is very attractive from the synthetic point of view because of mild reaction conditions, high chemoselectivity, and, low toxicity and cost. Although the synthetic potential of this transformation was unexplored for a number of years, the application of this powerful reaction in natural product synthesis has flourished recently.[3] There are many number of reactions are known for the macrocyclization but Heck reaction was not much evolved as the macrocyclization strategy. There are only few examples in the literature that utilizes Heck reaction as the macrocyclization as the key step. Here are the some literature examples for the synthesis of macrocycles using an intra-molecular Heck reaction as the key macrocyclization strategy. [4]

3.1.1. Synthesis of Cyclic RGD Peptides:

Akaji *et. al.*, synthesized cyclic RGD peptides on solid support using an intra-molecular Heck reaction as a macrocyclization strategy.[4c] Solid support chemical synthesis[5] is one of the ways to generate chemical libraries in combinatorial chemistry, and, in order to generate library of compounds that requires to increase the number of carbon-carbon bond forming reactions. The Heck reaction is one of such reaction very useful in solid phase synthesis because of its milder reaction conditions.



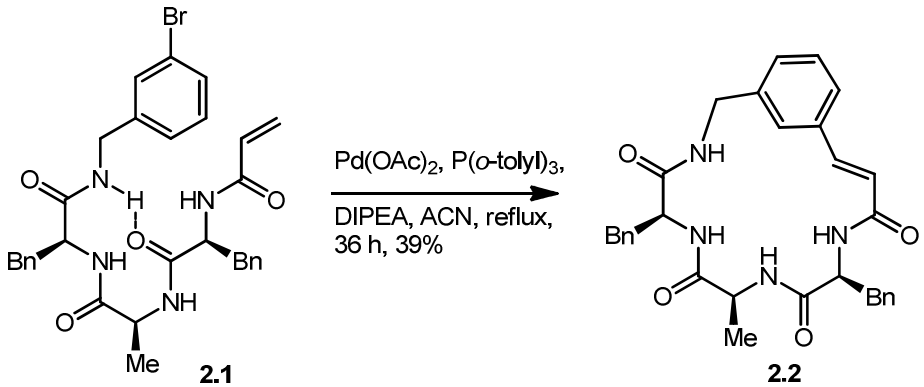
Scheme 1: Synthesis of cyclic RGD peptide via Heck macrocyclization strategy

The RGD sequence is a common recognition motif for the integrin family of receptors, which are involved in cell-cell and cell-matrix adhesion.[6] Glycoprotein

IIb/IIIa (GPIIb/IIIa), a member of the integrin family, is expressed on the surface of activated platelets which binds to fibrinogen to cause platelet aggregation. Thus, the solid phase preparation of cyclic RGD derivatives with affinities for GPIIb/IIIa could be an effective approach for the discovery of drug candidates, which could further prevent the formation of platelet-rich clots.[7] The macrocyclic precursor **1.1** on solid support (obtained from the coupling of Arg, Gly and Asp building blocks), was subjected to intramolecular Heck macrocyclization conditions, $Pd(OAc)_2$, PPh_3, Bu_4NCl, in $DMF/H_2O/Et_3N$) and this yielded the cyclic RGD peptide **1.2** (Scheme 1).

3.1.2. Synthesis of Small Cyclic Peptides:

Cyclic peptides are having many advantages over acyclic peptides. It is well accepted that acyclic peptides shows poor bioavailability and easily undergo proteolytic degradation, whereas cyclic peptides shows resistant to proteolytic degradation, good bioavailability, and, do not suffer from the entropic disadvantages. Suitably designed mimics the bioactive conformation could increase the affinity to the target protein.[8] Iqbal and co-workers reported the synthesis cyclic peptide **2.2**[4d] having aromatic linker,[4d] for conformational and binding studies for the program on mimicry of helix-turn-helix motifs. The cyclic peptide **2.2** was obtained from the precursor **2.1** subjecting to intra-molecular Heck conditions using $Pd(OAc)_2$, P(*o*-tolyl)$_3$, DIPEA and acetonitrile under reflux (Scheme 2).

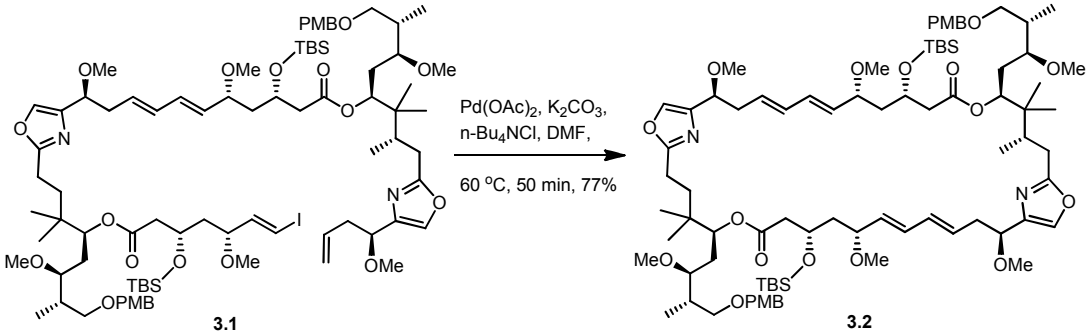


Scheme 2: Synthesis of small cyclic peptide via Heck macrocyclization strategy

3.1.3. Synthesis of the Macrocyclic Core of Rhizopodin:

The rhizopodin isolation and structural determination was reported in 1993 by the groups of Hofle and Reichenbach from myxobacteria of *Myxococcus stipitatus*.[9] This

macrolide exhibits various biological properties, including antifungal and anti-proliferative activities at a low nanomolar concentration, which arises due to specific binding to G-actin and thus hamper the polymerization to F-actin.[10] Initially the structure of rhizopodin was proposed to be 19-membered macrolide, and later, it was revised in 2008 by Menche group to a C2-symmetric dimer during studies aimed at determining its absolute configuration.[11] The unique structure of rhizopodin comprises 18 stereocenters and consists of a 38-membered macrocyclic core with two side chains terminating in labile N-vinyl formamide motifs, which are believed to be critical parts of the pharmacophore. The macrocycle itself embeds two oxazole rings and two diene systems together with an unprecedented stereo-tetrade between C16 and C21. Schubert and co-workers independently assigned the stereochemistry of rabbit actin bound rhizopodin through X-ray crystal analysis,[12] and, further confirmed the structure, in the course of an analysis of the biosynthesis of rhizopodin.

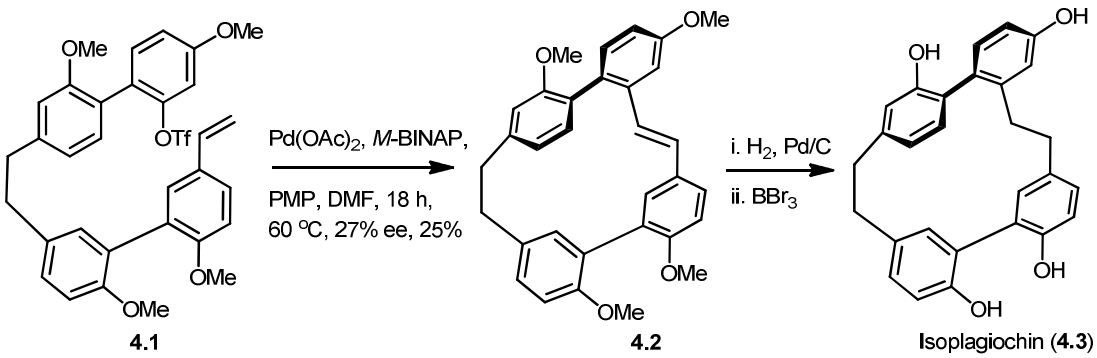


Scheme 3: Synthesis of Rhizopodin macrocyclic core via Heck macrocyclization strategy

The first total synthesis of rhizopodin was reported by Menche and co-workers[13] in 2012, where they used the Suzuki reaction as the key macrocycliztion strategy. This synthesis requires 24 steps to obtain macrocyclic core of rhizopodin, and, one year later the same group published a much shorter route to synthesize the macrocyclic core of rhizopodin.[4a] This synthesis utilized a highly advantageous intramolecular Heck reaction for the macrocylization (Scheme 3). The macrocyclic precursor **3.1** was subjected to the Heck conditions, $Pd(OAc)_2$, K_2CO_3, Bu_4NCl in DMF at 60 ^oC and this resulted in the macrocyclic core **3.2** of rhizopodin in a very good yield.

3.1.4. Enantioselective Synthesis of Bis(bibenzylic) Natural Products:

Speicher and co-workers utilized the atroposelective, Heck reaction as a macocylization strategy, to the synthesis of bis(bibenzylic) natural products[4b] e.g. isoplagiochins.[14] Macrocyclization in this kind of natural products is very challenging because of efficiency, not surprisingly, depending on ring strain, substitution pattern, and concomitant dimerization. The major reactions employed as the macrocyclization strategy for synthesis of bis(bibenzylic) natural products are Wittig,[15] McMurry[16] and Suzuki-Miyaura coupling.[17] Speicher and co-workers for the first time used atroposelective Heck reaction to the synthesis of bis(bibenzylic) natural product using chiral BINAP as a ligand.[4b] The macrocyclic precursor **4.1** under $Pd(OAc)_2$, *M*-BINAP, PMP in DMF at 60 ^oC provided the enantiopure cyclic bis(bibenzylic) product **4.2** in 27% ee (Scheme 4). Compound **4.2** was converted to natural product isoplagiochin (**4.3**) in two steps, i.e. reduction of double bond with Pd/C under hydrogen atmosphere followed by deprotection of methyl groups with BBr_3 condition.



Scheme 4: Synthesis of Bis(bibenzylic) Natural Products via Heck macrocyclization strategy

3.2. Research Objective:

Even though the Heck reaction was utilized as the macrocyclization strategy for the synthesis of cyclic peptides,[4c,d] and, in other natural product synthesis,[4a,b] this reaction is not much explored in the generation macrocyclic library. By considering this, we were interested in exploring the use of an intramolecular Heck reaction as the macrocyclization strategy in the generation of macrocyclic library of compounds.

In our study, we decided to develop a modular method to obtain a diverse to 17-membered functionalized macrocyclic compounds because there are several

examples of bioactive natural products that have functionalized 17-membered rings. Some of the representative examples with the assigned biological functions are shown in Figure 1 and these are metacridamide A & B (**F1.1** and **F1.2**),[18] OF4949 (I-IV) (**F1.4- F1.6**)[19, 20] and K13 (**F1.2**).[19a,21,22]

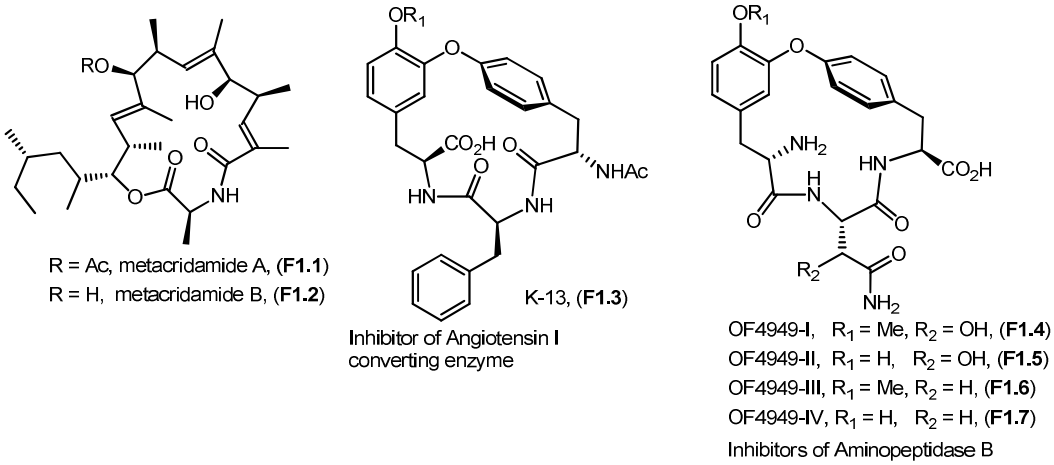


Figure 1: Examples of 17-membered macrocyclic natural products

Shown in Figure 2 are our two proposed macrocyclic targets (**F2.1** and **F2.2**). The macrocyclic targets, **F2.1** and **F2.2** are highly attractive because of the presence of a functionalized 17-membered ring skeleton. The possibility of using both enantiomers further allows us to explore the stereochemical diversity on a similar macrocyclic ring. The incorporation of an amino acid moiety as a part of the macrocyclic ring provides an opportunity to bring various non-polar to polar groups as the chiral side chain. Further, in our present design targets, each macrocyclic ring has two diversity points that could easily be explored in generating the structurally related analogues as the library members.

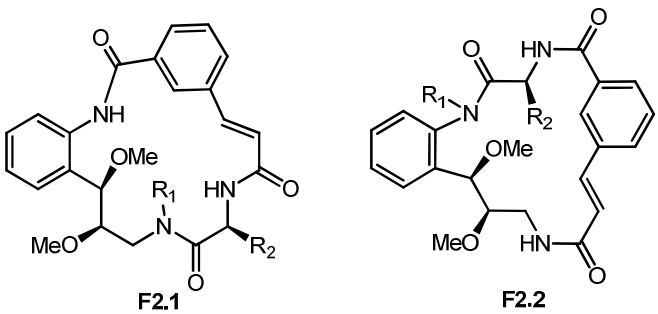
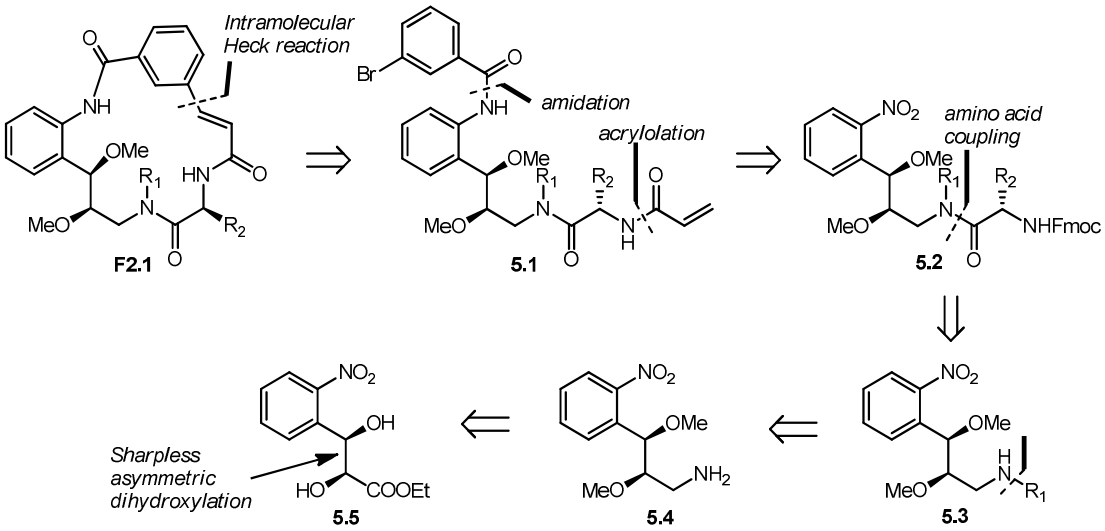


Figure 2: 17-Membered macrocyclic targets

3.3. Synthesis Plan and Execution

3.3.1. Retrosynthesis of Macrocycle F2.1:

The retrosynthetic analysis of macrocycle **F2.1** is shown in Scheme 5. The macrocyclic compound **F2.1** can be obtained from the macrocyclic precursor **5.1** by using an intramolecular Heck reaction. Compound **5.1** can be synthesized from an amidation of aromatic amine and acrylolation of aliphatic primary amine, which can be obtained from compound **5.2**. This could be synthesized from coupling of amino acid with secondary amine **5.3**, which would be obtained from aliphatic primary amine **5.4** on imino-reduction. The primary amine **5.4** could be obtained from the enantiopure dihydroxyl derivative **5.5**.

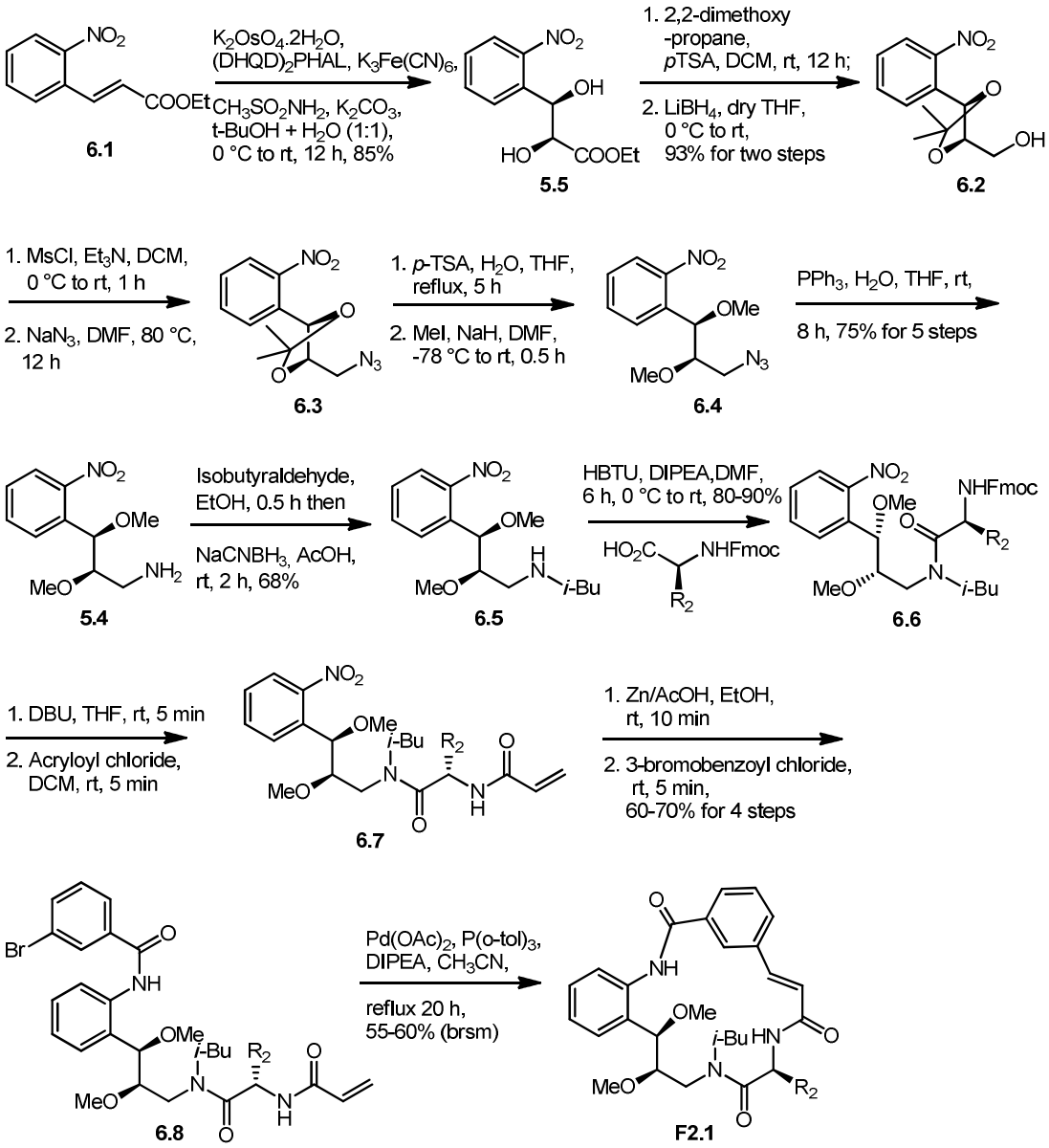


Scheme 5: Retrosynthesis of macrocycle **F2.1**

3.3.2. Synthesis of Macrocycle F2.1:

As shown in Scheme 6, ethyl-2-nitro-cinnamate (**6.1**) was subjected to Sharpless asymmetric dihydroxylation reaction,[23] giving an enantiopure dihydroxyl derivative **5.5**. Following the acetonide protection of diol, the carboxylester was then reduced with lithium borohydride to give primary alcohol **6.2**. Azide **6.3** was then obtained from **6.2** in three steps as follows: (i) mesylation of primary alcohol with methanesulfonyl chloride, (ii) treatment with sodium azide, and (ii) the deprotection of acetonide with *p*-TSA. It was further subjected to di-methylation with methyl iodide gives the compound **6.4** and reduction of azide by Staudinger reaction[24] condition (PPh_3, H_2O in THF) to obtain the primary amine, **5.4**.

The primary amine **5.4** was subjected to reductive alkylation with isobutaraldehyde and $NaCNBH_3$ conditions to obtain the secondary amine **6.5**. This was then coupled with *N*-Fmoc protected amino acid by using HBTU to obtain compounds **6.6**. *N*-Fmoc removal with DBU, followed by acryloylation gave the compound **6.7**. Aromatic nitro compound was reduced to aromatic primary amine using Zn/AcOH condition, which was then coupled with 3-bromobenzoyl chloride to give the macrocyclic precursor **6.8.** Finally, macrocyclic compounds **F2.1** were obtained from **6.8** via an intramolecular Heck reaction[4d] in the presence of $Pd(OAc)_2$, P(*o*-tol)$_3$, DIPEA in acetonitrile in good yields. The geometry of the double bond was confirmed with the coupling constant in ^{1}H NMR.



Scheme 6: Synthesis of macrocycle **F2.1**

3.3.3. Derivatives of Macrocycle F2.1:

We have synthesized five derivatives of macrocycle **F2.1**, by replacing R_2 group

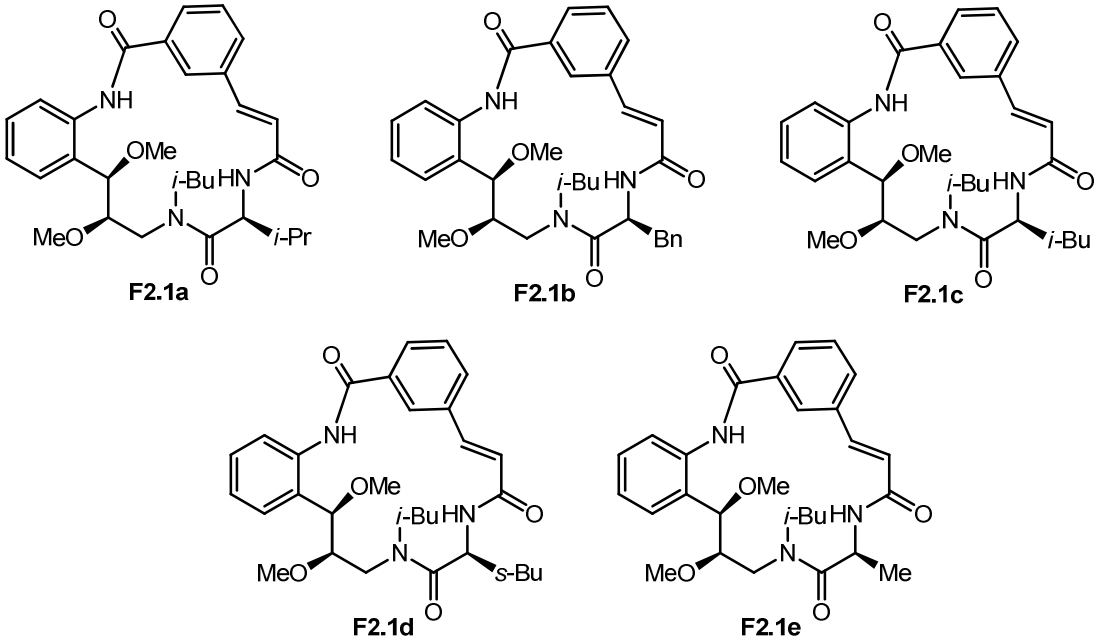
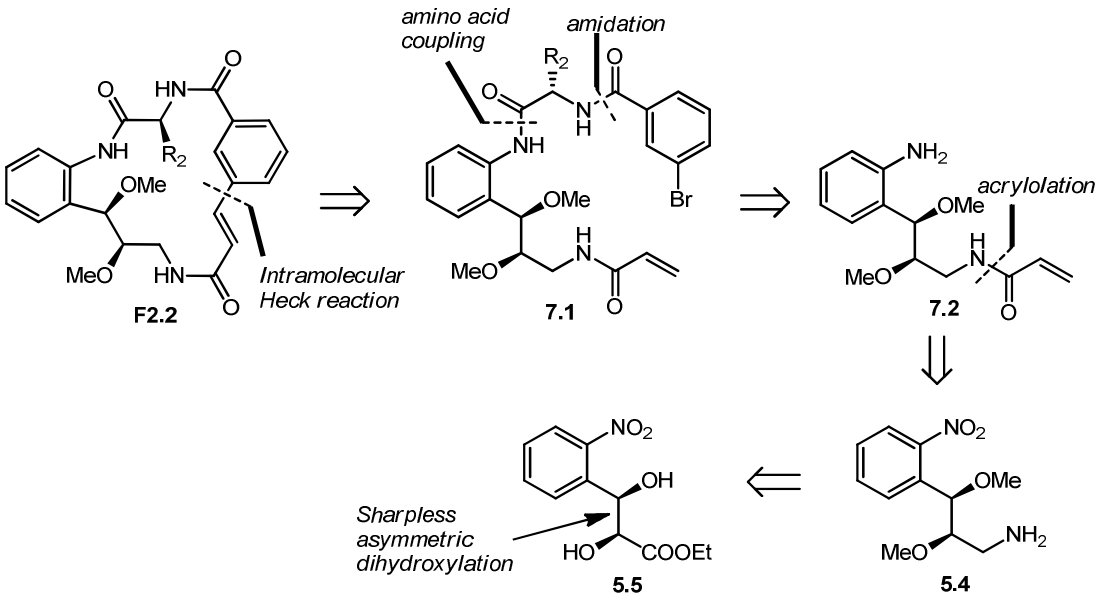


Figure 3: Derivatives of macrocycle **F2.1**

3.3.4. Retrosynthesis of Macrocycle F2.2:

The retrosynthetic analysis of macrocycle **F2.2** is shown in Scheme 7. The macrocyclization can be carried-out by an intramolecular Heck reaction of precursor **7.1**, which can then be obtained from the amino acid building block coupling of an

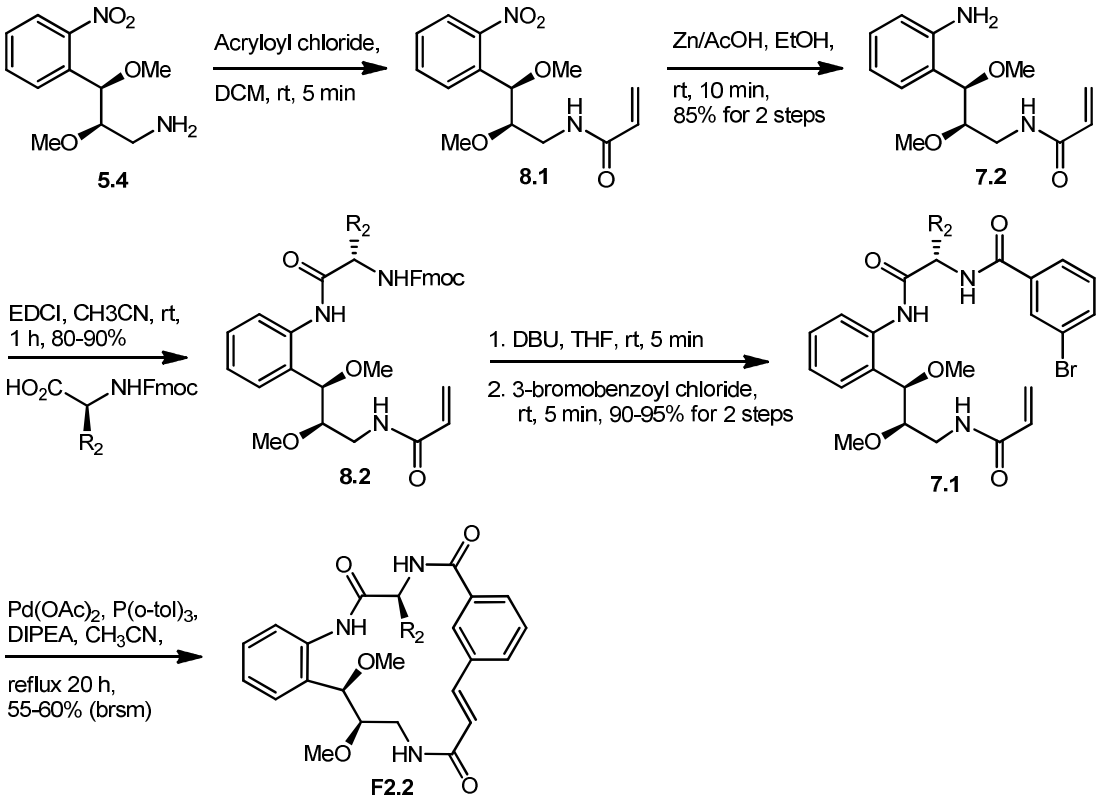


Scheme 7: Retrosynthesis of macrocycles **F2.2**

aromatic amine **7.2**. The aromatic amine could be obtained from acrylolation of primary amine followed by reduction of aromatic nitro group of compound **5.4** and this could be obtained from enantiopure dihydroxyl derivative **5.5.**

3.3.5. Synthesis of Macrocycle F2.2:

Our plan is to obtain macrocyclic compounds, **F2.2** from the key intermediate **5.4** is shown in Scheme 8. Primary amine **5.4** was converted to amide with acryloyl chloride to give compound **8.1** which then upon reduction of aromatic nitro group gave the aromatic amine **7.2**. This was coupled with *N*-Fmoc protected amino acids by using EDC▪HCl coupling reagent in acetonitrile solvent to give the coupled product **8.2**. Fmoc removed with DBU then coupling with 3-bromobenzoyl chloride gave **7.1**. Finally, this was then subjected to an intramolecular Heck reaction in the presence of $Pd(OAc)_2$, P(*o*-tol)$_3$, DIPEA in acetonitrile to obtain macrocycle **F2.2** in good yields.



Scheme 8: Synthesis of macrocycle **F2.2**

3.3.6. Derivatives of Macrocycle F2.2:

We have synthesized five derivatives of macrocycle **F2.2**, by replacing R_2 group.

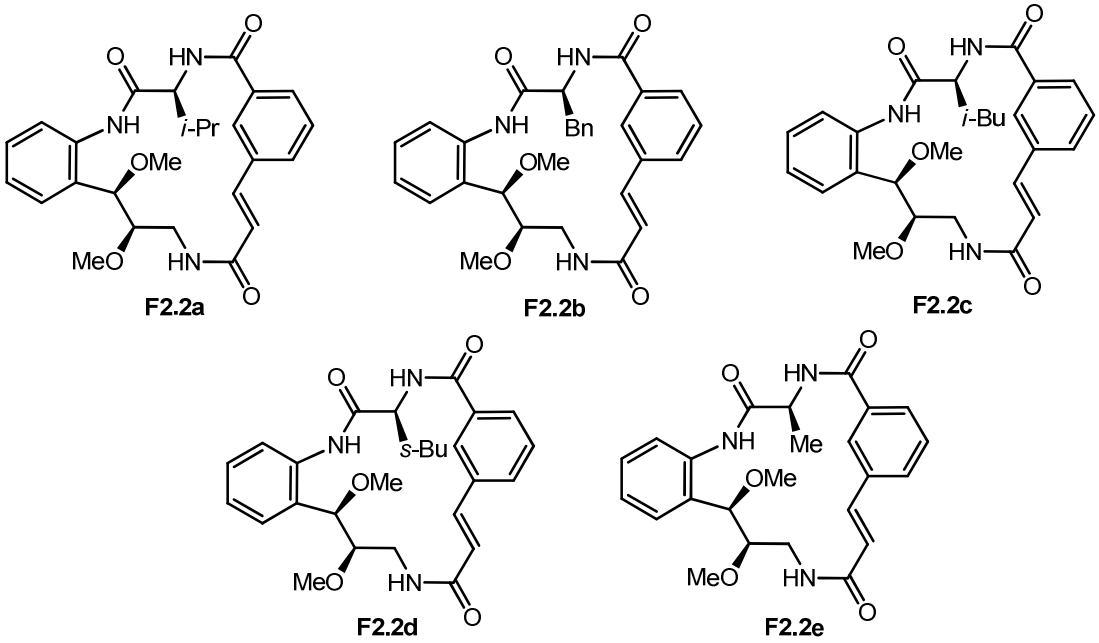


Figure 4: Derivatives of macrocycle **F2.2**

3.4. Biological Evaluation:

3.4.1. Zebrafish Assay related to angiogenesis and an early embryonic development:

The next plan was to subject our macrocyclic small molecule toolbox collection and several intermediates (45 compounds in total) to various zebrafish screens to evaluate the biological effect of these small molecules. These screens were related to search for compounds affecting epiboly during early embryonic development,[25,26,27] angiogenesis, [28] and neurogenesis[29] in zebrafish embryo-based assays.[30] All the three assays are well-documented in the literature.[27,28b,31] Zebrafish embryos for small molecule screening experiments were collected via pair wise matings, cleaned and incubated in PTU treated E3 water at 28.3 ^{o}C. The compound exposure was performed in 96 well plate and three embryos were taken in each well containing 200 µl of (0.5 to 15µM) compound in PTU treated egg water. The 96 well plates were incubated at 28.3 ^{o}C and the embryos were allowed to grow until 10 hpf or 30 hpf to assess the effect on epiboly, angiogenesis and neurogenesis respectively. Figure 1

shows the effect of a novel macrocyclic small molecule (**F2.2a**) on angiogenesis and on effect on other two screens was observed.

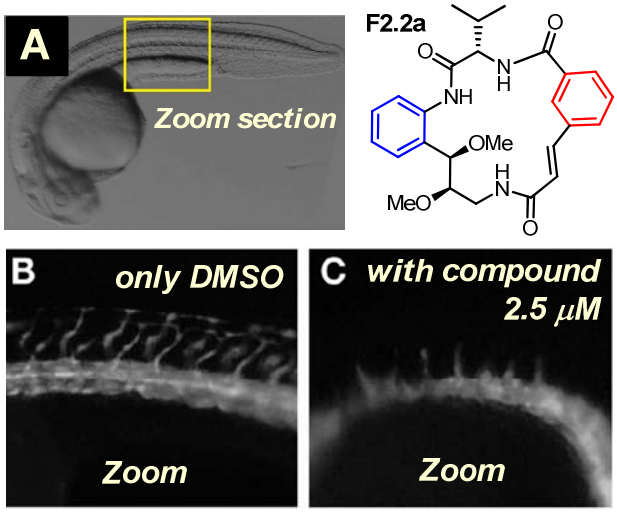
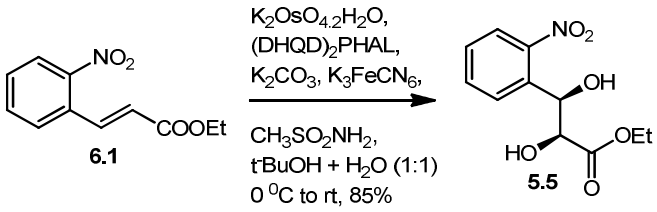


Figure 5: Wild-type zebrafish embryo at 30 hpf of development, region zoomed in panels **B**, **C** and **D** is shown by a yellow box, (**A**) zoom section of wild-type or vehicle treated embryo, and (**B** and **C**) zoom sections after treatment with a small molecule**.** A macrocyclic compound, **F2.2a**, showed the complete inhibition at 2.5 μM.

3.5. Conclusion:

In conclusion, we developed a modular method that allowed us building a small molecule toolbox having two different types of 17-membered macocyclic compounds. An intramolecular Heck reaction is the key step in our approach. When tested to search for functional small molecules as anti-angiogenesis agents in a zebrafish assay, we discovered a potent compound (**F2.2a**) as an inhibitor at 2.5 μM. Further, biological studies are needed to understand the mode action of this active compound, and, these will be reported when become available.

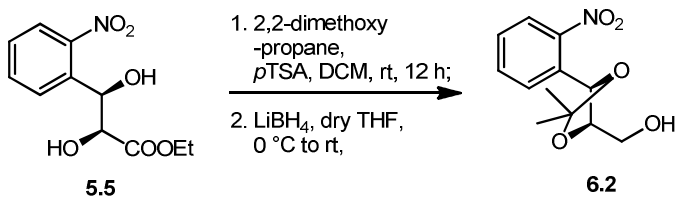
3.6. Experimental Procedure:



(2S,3R)-ethyl 2,3-dihydroxy-3-(2-nitrophenyl)propanoate (5.5):

To a stirred mixture of $K_3Fe(CN)_6$ (44 g, 133 mmol), K_2CO_3 (18.7 g, 135.3 mmol), $(DHQD)_2PHAL$ (520 mg, 0.67 mmol), K_2OsO_4 (60 mg, 0.18 mmol), methane sulfonamide (4.29 g, 45.19 mmol) in *t*-BuOH (300 mL) and water (300 mL), a solution of **6.1** (10 g, 45.20 mmol) in *t*-BuOH (100 mL) was added at a time at 0 °C and allowed to stir for 12 h at room temperature. After completion of the reaction, reaction mixture was quenched by the addition of solid sodium sulfite and extracted with ethyl acetate (3 X 300 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography (3:7 ethyl acetate/hexanes) to give the compound **5.5** (9.1 g, 81% yield) as white solid.

Molecular Formula: $C_{11}H_{13}NO_6$; R_f : 0.3 (3:7 ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.01 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.68 (t, *J* = 8.0 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 5.71 (dd, J_1 = 6.8 Hz, J_2 = 2.0 Hz, 1H), 4.52 (dd, J_1 = 5.6 Hz, J_2 = 2.4 Hz, 2H), 4.32 (q, *J* = 7.2 Hz, 2H), 3.29 (d, *J* = 6.8 Hz, 1H), 3.02 (d, *J* = 5.6Hz, 1H), 1.31 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.5, 147.4, 135.9, 133.3, 129.4, 128.6, 124.4, 73.3, 69.6, 62.4, 14.0; LRMS: (ES+) m/z = 256.3 (M+1)



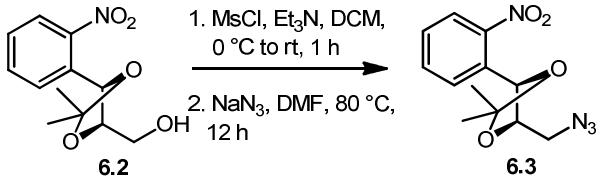
((4R,5R)-2,2-dimethyl-5-(2-nitrophenyl)-1,3-dioxolan-4-yl)methanol (6.2):

To a solution of the compound **5.5** (8.5 g, 33.34mmol) in dry dichloromethane (200 mL), 2,2-dimethoxy propane (8.16 mL, 66.68 mmol) and *p*-TSA (50 mg) were

added. The reaction mixture was stirred at room temperature for 12 h under nitrogen atmosphere. After completion of the reaction, reaction mixture was quenched with sodium bicarbonate solution, and extracted with dichloromethane (3 X 100 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography (1:9 ethyl acetate/hexanes) to give the acetonide protected ester (8.8 g, 86% yield) as yellow liquid.

To a solution of acetonide protected ester (8.5 g, 27.51mmol) in dry THF (150 mL), at 0 °C, $LiBH_4$ (1.2 g, 55.02 mmol) was added, and reaction mixture was allowed to stir for 24 h at room temperature. After completion of the reaction, reaction mixture was quenched by the addition of ice cold water, and extracted with ethyl acetate (3 X 100 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography (3:7 ethyl acetate/hexanes) to give the compound **6.2** (6.6 g, 94.8% yield) as yellow liquid.

Molecular Formula: $C_{12}H_{15}NO_5$; R_f : 0.3 (3:7 ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.85 (d, J = 8.0 Hz, 1H), 7.81 (d, J = 8.0 Hz, 1H), 7.65 (t, J = 8.0 Hz, 1H), 7.45 (t, J = 8.0 Hz, 1H), 5.40 (d, J = 8.4 Hz, 1H), 4.00 (m, 1H), 3.90 (dd, J_1 = 12.0 Hz, J_2 = 3.2 Hz, 1H), 3.81 (dd, J_1 = 12.0 Hz, J_2 = 5.2 Hz, 1H), 1.58 (s, 3H), 1.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 149.2, 133.3, 132.9, 129.2, 128.9, 124.2, 109.7, 84.4, 74.2, 61.6, 27.1, 26.9; LRMS: (ES+) m/z = 254.2 (M+1)



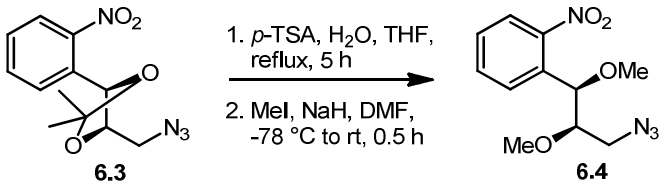
(4R,5R)-4-(azidomethyl)-2,2-dimethyl-5-(2-nitrophenyl)-1,3-dioxolane (6.3):

To a solution of **6.2** (6 g, 23.71mmol) in dry dichloromethane (150 mL), at 0 °C, Et_3N (9.98 mL, 71.13 mmol) and methane sulfonyl chloride were added, and reaction mixture was allowed to stir for 1 h at room temperature. After completion of the reaction, reaction mixture was quenched by the addition of sodium bicarbonate solution, and extracted with dichloromethane (3 X 100 mL). Combined organic layer

was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude liquid (7.5 g).

To a solution of above crude in dry DMF, NaN_3 (2.9 g, 45.2 mmol) was added, and reaction mixture was heated at 80 °C for 10 h. After completion of the reaction, reaction mixture was quenched by the addition of sodium bicarbonate solution, and extracted with dichloromethane (3 X 100 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude liquid, which was purified by column chromatography (1:4 ethyl acetate/hexanes) to give the compound **6.3** (5.3 g, 80.3% yield) as yellow liquid.

Molecular Formula: $C_{12}H_{14}N_4O_4$; R_f : 0.3 (1:9 ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.89 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.67 (t, *J* = 8.0 Hz, 1H), 7.47 (t, *J* = 8.0 Hz, 1H), 5.42 (d, *J* = 8.0 Hz, 1H), 4.05 (m, 1H), 3.65 (dd, J_1 = 13.2 Hz, J_2 = 3.2 Hz, 1H), 3.52 (dd, J_1 = 13.2 Hz, J_2 = 6.0 Hz, 1H), 1.60 (s, 3H), 1.54 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 149.2, 133.4, 132.6, 129.2, 129.1, 124.3, 110.3, 82.9, 74.8, 51.3, 29.6, 27.0, 26.9; LRMS: (ES+) m/z = 279.3 (M+1)



6.3 **6.4**

1-((1R,2R)-3-azido-1,2-dimethoxypropyl)-2-nitrobenzene (6.4):

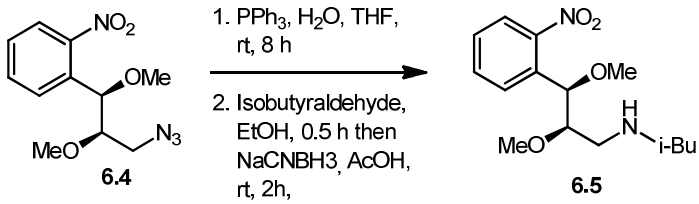
To a solution of **6.3** (5.3 g, 19.06 mmol) in THF (150 mL), PTSA (9.83 g, 57.19 mmol) and water 10 mL were added, and reaction mixture was allowed to reflux for 12 h. After completion of the reaction, reaction mixture was quenched by the addition of sodium bicarbonate solution, and extracted with ethyl acetate (3 X 100 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography (3:7 ethyl acetate/hexanes) to give the diol azide (4.5 g, 99% yield) as yellow liquid.

Molecular Formula: $C_9H_{10}N_4O_4$; R_f : 0.3 (3:7 ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.97(m, 1H), 7.75(m, 1H), 7.64(m, 1H), 7.51(m, 1H), 5.25(m, 1H), 4.0(m, 1H), 2.90-3.56 (m, 1H) ; ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm

147.5, 136.5, 133.6, 128.8, 128.7, 124.7, 73.0, 69.1, 54.3; LRMS: (ES+) m/z = 239.1 (M+1)

To a -78 °C solution of NaH (2.72 g, 113.35 mmol) and MeI (11.7 mL, 188.9 mmol) in DMF (150 mL) was added a solution of diol azide (4.5 g, 18.89mmol) in DMF. The solution was stirred for 5 min, allowed to warm to room temperature. The solution was stirred for 1 h and then quenched by drop wise addition of NH_4Cl solution (20 mL), and extracted with ethyl acetate (3 X 100 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography (3:7 ethyl acetate/hexanes) to give the compound **6.4** (4.5 g, 89.5% yield) as yellow liquid.

Molecular Formula: $C_{11}H_{14}N_4O_4$; R_f : 0.3 (1:4 ethyl acetate/hexane); ^1H NMR ($CDCl_3$, 400 MHz): 7.97 (d, *J* = 8.18 Hz, 1H), 7.78 (d, *J* = 7.85 Hz, 1H), 7.67 (t, *J* = 7.59 Hz, 1H), 7.49 (t, *J* = 7.74 Hz, 1H), 5.01 (d, *J* = 3.14 Hz, 1H), 3.68 (td, *J* = 7.76, 3.97 Hz, 1H), 3.39 (dd, *J* = 12.60, 7.61 Hz, 1H), 3.35-3.27 (m, 4H), 3.24 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 149.2, 133.6, 133.0, 129.4, 128.6, 124.5, 82.5, 77.9, 60.0, 57.8, 51.6; LRMS: (ES+) m/z = 267.3 (M+1)



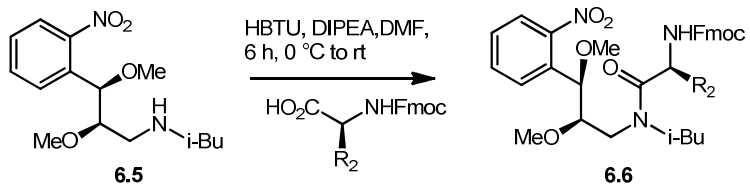
(2R,3R)-N-isobutyl-2,3-dimethoxy-3-(2-nitrophenyl)propan-1-amine (6.5):

To a solution of the compound **6.4** (4.5 g, 16.90 mmol) in THF (50 mL), TPP (8.85 g, 33.38 mmol) and water (3 mL, 169 mmol) were added and stirred for 24 h. After completion of the reaction, reaction mixture was concentrated to leave a residue, which was purified by column chromatography (4:1 ethyl acetate/hexanes) to give the compound **5.4** (3.8 g, 93.6% yield) as light yellow oil. Molecular Formula: $C_{11}H_{16}N_2O_4$; R_f (solvent system): 0.3 (ethyl acetate/hexane)

To a suspension of compound **5.4** (3.0 g, 12.48 mmol) in EtOH (30 mL), isobutyraldehyde (1.24 mL, 12.48 mmol) was added and stirred for 30 min. A mixture of $NaCNBH_3$ (1.18 g, 18.72 mmol) and acetic acid (50 µL) in ethanol (5

mL) were added to the reaction mixture at 0 °C allowed to stir for 1 h. After completion of the reaction, reaction mixture was quenched with sodium bicarbonate solution (5 mL), and extracted with ethyl acetate (3 X 20 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography (3:7 ethyl acetate/hexanes) to give the compound **6.5** (2.5 g, 67.8% yield) as light yellow oil.

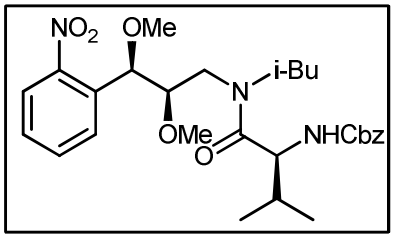
Molecular Formula: $C_{15}H_{24}N_2O_4$; R_f : 0.2 (3:7 ethyl acetate/hexane); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.89 (d, *J* = 8.0 Hz, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.44 (t, *J* = 8.0 Hz, 1H), 5.09 (d, *J* = 4.0 Hz, 1H), 3.61 (m, 1H), 3.30 (s, 3H), 3.28 (s, 3H), 2.66 (dd, J_1 = 12.0Hz, J_2 = 3.6 Hz, 1H), 2.54 (dd, J_1 = 12.0Hz, J_2 = 8.0 Hz, 1H), 2.36 (dd, J_1 = 6.8 Hz, J_2 = 2.4 Hz, 2H), 1.71 (m, 1H), 0.89 (s, 3H), 0.87 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 149.4, 134.3, 132.5, 129.2, 128.1, 124.1, 82.8, 78.4, 59.6, 57.9, 57.7, 49.9, 28.1, 20.5, 20.4; LRMS: (ES+) m/z = 297.4 (M+1)



Compound 6.6:

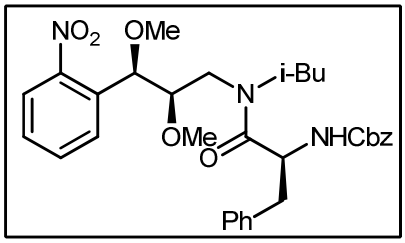
To a suspension of compound **6.5** (1 mmol) in DMF (10 mL), *N*-Fmoc amino acid (1.5 mmol), HBTU (1.5 mmol) and DIPEA (2 mmol) were added at 0 °C and allowed to stirred for 6 h. After completion of the reaction, reaction mixture was quenched with sodium bicarbonate solution (10 mL), and extracted with ethyl acetate (3 X 20 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography to give the pure compound **6.6.**

(9H-fluoren-9-yl)methyl (S)-1-(((2R,3R)-2,3-dimethoxy-3-(2-nitrophenyl)propyl) (isobutyl) amino)-3-methyl-1-oxobutan-2-ylcarbamate (6.6a):



Molecular Formula: $C_{28}H_{39}N_3O_7$; R_f : 0.4 (1:4 ethyl acetate/hexanes); Solvent system for column purification (1:4 ethylacetate/hexanes);Yield:88.9%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.99 (t, *J* = 9.0 Hz, 1H), 7.8 (dd, *J* = 7.1, 4.7 Hz, 1H), 7.75 (dd, *J* = 7.2, 3.1 Hz, 2H), 7.70-7.55 (m, 3H), 7.47 (t, *J* = 7.7 Hz, 1H), 7.43-7.34 (m, 2H), 7.34-7.24 (m, 2H), 5.53 (d, *J* = 9.5 Hz, 1H), 4.99-4.88 (m, 1H), 4.75-4.49 (m, 1H), 4.44-4.16 (m, 3H), 3.83-3.50 (m, 3H), 3.37-3.19 (m, 5H), 3.07 (m, 3H), 2.17-1.97 (m, 2H), 1.04-0.84 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.7, 172.6, 156.1, 156.0, 149.0, 148.8, 143.8, 143.8, 141.2, 134.2, 134.0, 133.1, 127.7, 127.4, 127.4, 127.1, 126.9, 126.8, 125.2, 124.5, 124.3, 120.0, 119.7, 109.9, 80.4, 80.3, 78.3, 78.1, 66.9, 59.8, 57.7, 55.7, 47.0, 31.7, 31.4, 28.5, 26.8, 20.1, 20.0 ; LRMS: (ES+) m/z = 530.1 (M+1)

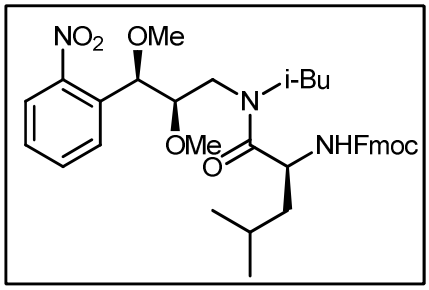
(9H-fluoren-9-yl)methyl (S)-1-(((2R,3R)-2,3-dimethoxy-3-(2-nitrophenyl)propyl) (isobutyl) amino)-1-oxo-3-phenylpropan-2-ylcarbamate (6.6b):



Molecular Formula: $C_{32}H_{39}N_3O_7$; R_f : 0.5 (1:4 ethyl acetate/hexanes) ; Solvent system for column purification (1:4 ethylacetate/hexanes); Yield:86.0%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 8.00 (m, 1H), 7.79-7.70 (m, 3H), 7.66 (t, *J* = 7.3 Hz, 1H), 7.58 (d, *J* = 7.4 Hz, 1H), 7.49 (m, 2H), 7.38 (m, 2H), 7.33-7.11 (m, 8H), 5.58 (d, *J* = 9.1 Hz, 1H), 4.91 (dd, *J* = 10.5, 1.9 Hz, 1H), 4.39-4.27 (m, 2H), 4.19 (m, 1H), 3.47-3.08 (m, 8H), 3.07 (s, 2H), 3.03-2.89 (m, 2H), 2.80 (s, 1H), 2.00-1.85 (m, 1H), 0.87-0.75 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.4, 172.2, 155.5, 155.3, 149.0, 149.0, 143.8, 143.7, 143.7, 141.2, 141.2, 141.2, 136.7, 136.5, 134.3, 134.0, 130.0, 129.6, 129.1, 128.7, 128.6, 128.2, 128.1, 127.8, 127.3, 127.3, 127.2, 126.7, 125.4,

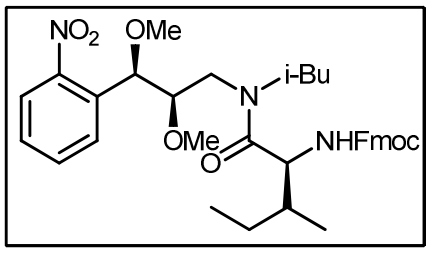
124.9, 120.0, 119.7, 80.7, 80.5, 78.5, 66.8, 66.8, 60.2, 60.0, 52.3, 47.2, 47.1, 28.7, 28.6, 26.9, 20.3, 20.1, 19.9; LRMS: (ES+) m/z = 578.3 (M+1)

(9H-fluoren-9-yl)methyl (S)-1-(((2R,3R)-2,3-dimethoxy-3-(2-nitrophenyl)propyl) (isobutyl) amino)-1-oxo-3-phenylpropan-2-ylcarbamate (6.6c):



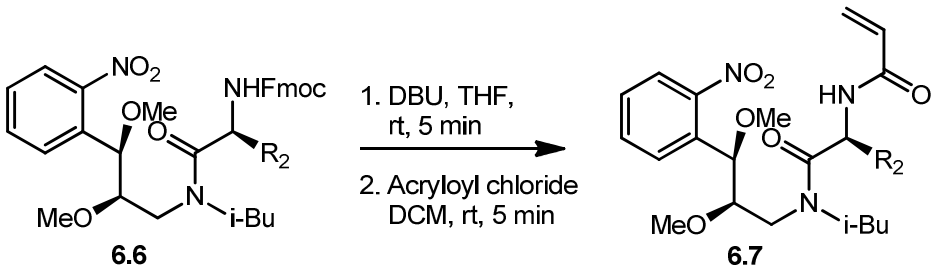
Molecular Formula: $C_{29}H_{41}N_3O_7$; R_f: 0.4 (1:4 ethyl acetate/hexanes); Solvent system for column purification (1:4 ethylacetate/hexanes); Yield:85.0%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.95 (t, *J* = 7.00 Hz, 1H), 7.79 (m, 3H), 7.71-7.55 (m, 3H), 7.46 (t, *J* = 7.3 Hz, 1H), 7.38 (t, *J* = 7.3 Hz, 2H), 7.28 (dd, *J* = 12.5, 5.2 Hz, 2H), 5.65 (d, *J* = 9.0 Hz, 1H), 5.19-4.83 (m, 1H), 4.76 (s, 1H), 4.43-4.16 (m, 3H), 4.01-3.83 (m, 1H), 3.68-3.43 (m, 1H), 3.39-3.05 (m, 8H), 2.02 (m, 1H), 1.67-1.50 (m, 1H), 1.36 (m, 1H), 1.06-0.78 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 173.6, 173.2, 156.1, 149.1, 143.8, 141.2, 141.2, 134.3, 133.1, 132.9, 129.4, 128.5, 128.5, 127.5, 126.9, 125.2, 124.6, 124.4, 119.8, 119.8, 82.5, 81.1, 78.2, 66.9, 60.3, 60.2, 57.7, 56.4, 53.9, 49.6, 49.3, 48.3, 47.1, 47.1, 47.0, 42.4, 28.4, 26.6, 24.6, 24.5, 23.6, 23.5, 21.4, 21.63, 20.2, 20.1, 19.9, 19.7; LRMS: (ES+) m/z = 632.1 (M+1)

(9H-fluoren-9-yl)methyl (2S,3S)-1-(((2R,3R)-2,3-dimethoxy-3-(2-nitrophenyl) propyl)(iso butyl)amino)-3-methyl-1-oxopentan-2-ylcarbamate (6.6d):



Molecular Formula: $C_{29}H_{41}N_3O_7$; R_f: 0.2 (1:9 ethyl acetate/hexanes); Solvent system for column purification (1:4 ethylacetate/hexanes); Yield:85.5%; ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.96 (d, *J* = 8.1 Hz, 1H), 7.79 (m, 3H), 7.71-7.55 (m, 3H), 7.53-7.23 (m, 5H), 5.64 (d, *J* = 9.3 Hz, 1H), 4.92 (d, *J* = 2.5 Hz, 1H), 4.63-4.13 (m, 4H),

3.88 (t, *J* = 7.5 Hz, 2H), 3.42-2.99 (m, 8H), 1.98 (d, *J* = 6.4 Hz, 1H), 1.86-1.47 (m, 3H), 1.02-0.75 (m, 12H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.2, 156.2, 149.2, 144.0, 143.8, 143.8, 141.2, 141.2, 134.1, 133.1, 133.0, 132.9, 129.4, 129.4, 128.5, 128.5, 128.4, 127.5, 127.0, 1216.9, 125.1, 125.1, 124.5, 124.4, 124.4, 119.9, 119.9, 119.8, 82.8, 82.7, 81.5, 66.9, 66.8, 60.3, 60.1, 57.8, 57.6, 56.5, 55.1, 48.1, 47.9, 47.1, 47.1, 38.3, 29.6, 28.1, 23.6, 20.1, 19.5, 15.9, 11.3; LRMS: (ES+) m/z = 632.1 (M+1)



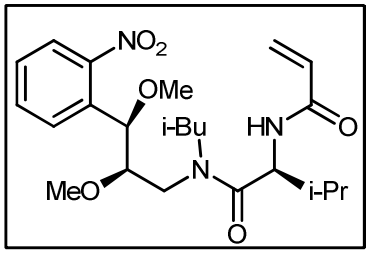
6.6 **6.7**

Compound 6.7:

To a suspension of compound **6.6** (0.7 mmol) in THF (10 mL), DBU (0.9 mmol) was added and stirred the reaction mixture for 5 min. After completion of the reaction, reaction mixture concentrated and which was subjected to the next reaction without any purification.

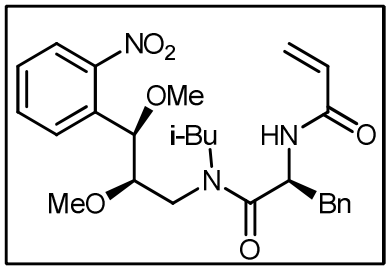
To a suspension of above compound (0.5 mmol) in DCM (10 mL), acrylol chloride (0.8 mmol) was added at 0 °C and allowed to stir for 10 min. After completion of the reaction, reaction mixture was quenched with sodium bicarbonate solution (5 mL), and extracted with ethyl acetate (3 X 20 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography to give pure compound **6.7**.

(S)-2-acrylamido-N-((2R,3R)-2,3-dimethoxy-3-(2-nitrophenyl)propyl)-N-isobutyl-3-methylbutanamide (6.7a):



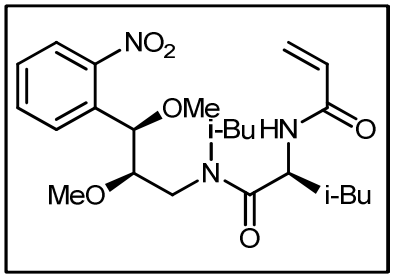
Molecular Formula: $C_{23}H_{35}N_3O_6$; R_f : 0.2 (3:7 ethyl acetate/hexanes); Solvent system for column purification (2:3 ethylacetate/hexanes); Yield:78%; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.00 (m, 1H), 7.89-7.79 (m, 1H), 7.69 (m, 1H), 7.48 (m, 1H), 6.60 (m, 1H), 6.33-6.06 (m, 2H), 5.63 (m, 1H), 5.08-4.88 (m, 2H), 3.83-3.69 (m, 2H), 3.68-3.38 (m, 2H), 3.33-3.23 (m, 4H), 3.08 (m, 3H), 2.21-1.98 (m, 2H), 1.08-0.79 (m, 12H); ^{13}C NMR (100 MHz, CDCl3) δ ppm 172.8, 172.7, 165.1, 165.0, 149.0, 134.0, 133.9, 133.1, 133.1, 133.0, 133.0, 132.7, 130.6, 129.7, 129.5, 128.7, 128.5, 128.3, 126.5, 126.4, 124.8, 124.6, 124.4, 124.2, 83.1, 82.9, 80.6, 80.4, 78.3, 78.0, 60.4, 59.7, 57.5, 53.9, 53.6, 49.6, 48.0, 31.8, 31.7, 31.4, 31.3, 28.6, 28.5, 26.6, 26.6, 20.0, 19.9, 19.9, 19.7, 19.6, 19.5, 17.6, 17.4; LRMS: (ES+) m/z = 450.3 (M+1)

N-((S)-1-(((2R,3R)-2,3-dimethoxy-3-(2-nitrophenyl)propyl)(isobutyl)amino)-1-oxo-3-phenylpropan-2-yl)acrylamide (6.7b):



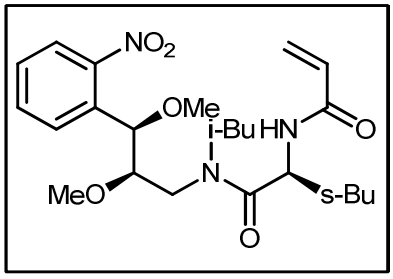
Molecular Formula: $C_{27}H_{35}N_3O_6$; R_f : 0.2 (3:7 ethyl acetate/hexanes); Solvent system for column purification (2:3 ethylacetate/hexanes); Yield:75% (yellow liquid); 1H ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.01 (m, 1H), 7.87-7.74 (m, 1H), 7.73-7.61 (m, 1H), 7.54-7.41 (m, 1H), 7.35-7.11 (m, 6H), 6.75-6.50 (m, 1H), 6.31-5.99 (m, 2H), 5.69-5.55 (m, 1H), 5.25 (d, *J* = 8.8 Hz, 1H), 4.89 (m, 1H), 3.93-3.70 (m, 1H), 3.51-2.67 (m, 13H), 1.99-1.82 (m, 1H), 0.88-0.68 (m, 6H); ^{13}C NMR (100 MHz, CDCl3) δ ppm 172.4, 172.2, 164.5, 164.4, 149.0, 148.6, 136.6, 136.4, 134.3, 134.1, 129.4, 128.6, 128.3, 126.7, 124.8, 124.6, 124.3, 82.4, 80.9, 80.6, 78.4, 78.1, 60.1, 57.7, 57.6, 56.6, 56.6, 54.8, 50.6, 50.5, 50.0, 49.2, 39.8, 39.1, 28.6, 26.9, 20.0, 19.8, 19.7, 19.6; LRMS: (ES+) m/z = 497.9 (M+1)

(S)-2-acrylamido-N-((2R,3R)-2,3-dimethoxy-3-(2-nitrophenyl)propyl)-N-isobutyl-4-methylpentanamide (6.7c):



Molecular Formula: $C_{24}H_{37}N_3O_6$; R_f : 0.3 (1:1 ethyl acetate/hexane); Solvent system for column purification (1:1 ethylacetate/hexanes); Yield:78% (yellow liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.99 (m, 1H), 7.84 (t, *J* = 8.0 Hz, 1H), 7.67 (m, 1H), 7.48 (m, 1H), 6.77 (dd, *J* = 4.0, 3.5 Hz, 1H), 6.33-6.05 (m, 2H), 5.60 (ddd, *J* = 9.2, 6.9, 1.8 Hz, 1H), 5.35-5.06 (m, 1H), 5.00-4.83 (m, 1H), 3.87-3.71 (m, 2H), 3.70-3.46 (m, 2H), 3.40-3.23 (m, 4H), 3.11 (d, *J* = 5.1 Hz, 3H), 2.80-2.59 (m, 1H), 2.16-1.94 (m, 2H), 1.82-1.56 (m, 2H), 1.54-1.32 (m, 1H), 1.08-0.82 (m, 12H); ^{13}C NMR (100 MHz, CDCl3) δ ppm 173.7, 173.7, 165.0, 164.9, 164.8, 149.0, 134.1, 133.8, 133.1, 132.9, 132.9, 131.0, 130.6, 129.8, 129.6, 128.5, 128.4, ^{13}C NMR (100 MHz, CDCl3) δ ppm 126.5, 126.0, 124.7, 124.3, 81.6, 80.2, 60.3, 59.8, 57.6, 57.4, 56.6, 53.9, 48.6, 48.1, 47.7, 47.3, 43.5, 42.6, 42.5, 28.6, 28.6, 26.8, 24.7, 24.6, 24.6, 23.5, 23.5, 23.4, 21.6, 21.5, 20.2, 20.2, 20.1, 19.9, 19.9, 14.1; LRMS: (ES+) m/z = 463.9 (M+1)

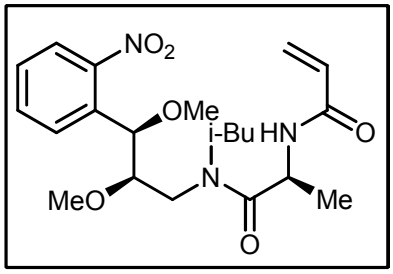
(2S,3S)-2-acrylamido-N-((2R,3R)-2,3-dimethoxy-3-(2-nitrophenyl)propyl)-N-isobutyl-3-methylpentanamide (6.7d):



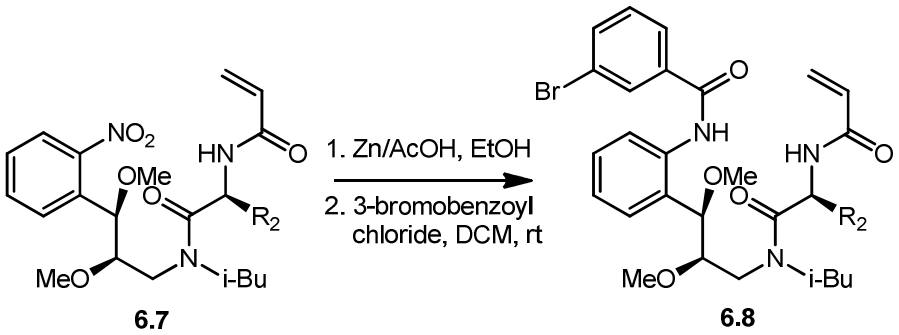
Molecular Formula: $C_{24}H_{37}N_3O_6$; R_f : 0.3 (1:1 ethyl acetate/hexanes); Solvent system for column purification (1:1 ethylacetate/hexanes); Yield:75% (yellow liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.00 (s, 1H), 7.84 (m, 1H), 7.68 (m, 1H), 7.48 (q, *J* = 7.7 Hz, 1H), 6.47 (s, 1H), 6.32-6.03 (m, 2H), 5.70-5.53 (m, 1H), 5.10-4.85 (m, 2H), 3.89-3.57 (m, 3H), 3.50 (td, *J* = 20.77, 8.20 Hz, 1H), 3.25 (dd, *J* = 17.7, 7.2 Hz, 3H), 3.08 (dd, *J* = 6.4, 4.5 Hz, 3H), 2.04 (dd, *J* = 6.9, 2.1 Hz, 1H), 1.88 (m, 1H),

1.70-1.48 (m, 1H), 1.27-1.06 (m, 1H), 0.93 (m, 12H); ^{13}C NMR (100 MHz, CDCl3) δ ppm 172.9, 172.8, 164.9, 164.8, 149.1, 148.8, 134.2, 134.1, 133.3, 133.0, 130.9, 130.5, 129.8, 129.7, 128.6, 128.4, 126.7, 126.2, 124.7, 124.4, 82.5, 82.5, 80.8, 78.5, 78.0, 78.0, 60.4, 59.9, 57.7, 57.5, 56.3, 54.5, 53.3, 53.1, 49.4, 48.4, 38.6,, 38.0, 28.6, 26.8, 24.2, 24.1, 20.2, 20.1, 19.7, 15.9, 15.9, 11.3, 11.1; LRMS: (ES+) m/z = 463.9 (M+1)

N-((S)-1-(((2R,3R)-2,3-dimethoxy-3-(2-nitrophenyl)propyl)(isobutyl)amino)-1-oxopropan-2-yl)acrylamide (6.7e):



Molecular Formula: $C_{21}H_{31}N_3O_6$; R_f : 0.2 (3:7 ethyl acetate/hexanes); Solvent system for column purification (2:3 ethylacetate/hexanes); Yield:80% (yellow liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 8.01 (m, 1H), 7.87-7.79 (m, 1H), 7.74-7.64 (m, 1H), 7.54-7.44 (m, 1H), 6.85 (dd, m, 1H), 6.27 (m, 1H), 6.13 (m, 1H), 5.62 (ddd, *J* = 9.9, 5.9, 1.1 Hz, 1H), 5.24-4.98 (m, 1H), 4.87 (dd, *J* = 6.9, 1.8 Hz, 1H), 3.87-3.62 (m, 3H), 3.60-3.47 (m, 1H), 3.38-3.22 (m, 4H), 3.12 (s, 2H), 3.02 (d, *J* = 4.5 Hz, 1H), 2.03 (m, 1H), 1.41 (m, 3H), 1.01-0.83 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 173.7, 173.5, 164.4, 164.3, 148.8, 134.2, 133.9, 133.3, 133.1, 130.9, 130.6, 129.9, 129.7, 128.7, 128.4, 126.5, 126.1, 124.7, 124.4, 82.1, 79.9, 78.4, 77.9, 60.9, 59.8, 57.6, 57.5, 56.3, 53.6, 49.5, 47.5, 45.4, 45.1, 28.2, 26.7, 20.1, 20.0, 19.8, 19.6, 19.1, 19.1; LRMS: (ES+) m/z = 421.9 (M+1)



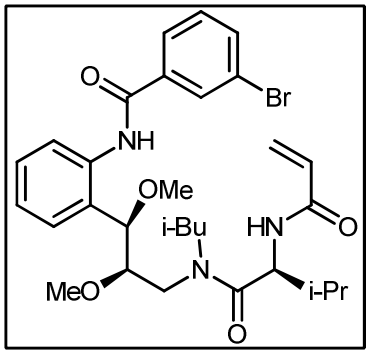
6.7 **6.8**

Compound 6.8:

To a suspension of **6.7** (0.5 mmol) in EtOH (10 mL), Zn (8.5 mmol), AcOH (2.1 mmol) was added at 0 °C and allowed to stir the reaction mixture for 0.5 h. After completion of the reaction mixture was passed through celite and concentrated, to leave a crude oil, which was purified by column chromatography to give the pure compound.

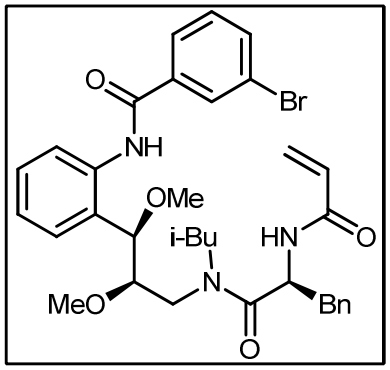
To a suspension of above compound (0.5 mmol) in DCM (10 mL), 3-bromo benzoyl chloride (0.45 mmol) was added at 0 °C and allowed to stir for 10 min. After completion of the reaction, reaction mixture was quenched with sodium bicarbonate solution (5 mL), and extracted with ethyl acetate (3 X 20 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography to give pure compound **6.8**.

N-(2-((1R,2R)-3-((S)-2-acrylamido-N-isobutyl-3-methylbutanamido)-1,2-dimethoxypropyl) phenyl)-3-bromobenzamide (6.8a):



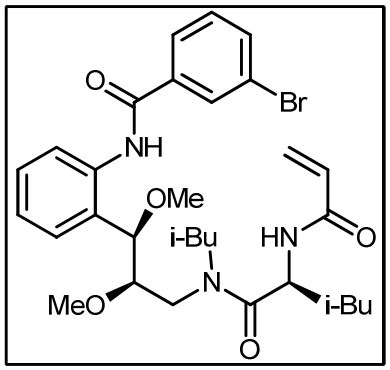
Molecular Formula: $C_{30}H_{40}BrN_3O_5$; R_f : 0.2 (3:7 ethyl acetate/ hexanes); Solvent system for column purification (2:3 ethylacetate/hexanes); Yield:85% (white solid); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.13 (s, 1H), 8.44 (d, *J* = 8.1 Hz, 1H), 8.18 (d, *J* = 13.4 Hz, 1H), 7.90 (d, *J* = 7.9 Hz, 1H), 7.67 (d, *J* = 7.1 Hz, 1H), 7.38 (dt, *J* = 7.8, 5.1 Hz, 2H), 7.25 (d, *J* = 13.3 Hz, 1H), 7.09 (dd, *J* = 7.9, 4.3 Hz, 1H), 6.60-6.40 (m, 1H), 6.35-6.06 (m, 2H), 5.65 (dd, *J* = 7.1, 3.8 Hz, 1H), 5.02-4.83 (m, 1H), 4.25 (d, *J* = 1.8 Hz, 1H), 3.88-3.60 (m, 2H), 3.56-3.43 (m, 1H), 3.39-3.16 (m, 7H), 2.18-1.89 (m, 2H), 1.09-0.74 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm 174.1, 172.9, 172.8, 165.0, 163.3, 137.3, 137.2, 137.2, 134.6, 134.2, 130.6, 130.5, 130.5, 130.4, 130.0, 129.2, 126.4, 125.7, 125.5, 122.8, 122.8, 122.7, 85.2, 85.0, 82.8, 82.5, 59.9, 56.9, 56.9, 56.8, 53.8, 53.4, 32.0, 31.8, 28.7, 28.5, 26.9, 26.7, 20.3, 20.1, 19.9, 19.7, 19.7, 19.5, 17.8, 17.5; LRMS: (ES+) m/z = 602.2 (M+1)

N-(2-((1R,2R)-3-((S)-2-acrylamido-N-isobutyl-3-phenylpropanamido)-1,2-dimethoxypropyl)phenyl)-3-bromobenzamide (6.8b):



Molecular Formula: $C_{34}H_{40}BrN_3O_5$; R_f : 0.3 (3:7 ethyl acetate /hexanes); Solvent system for column purification (3:7 ethylacetate/hexanes); Yield:80% (white solid); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.98 (s, 1H), 8.53-8.20 (m, 1H), 8.19-8.10 (m, 1H), 7.99-7.86 (m, 1H), 7.68-7.58 (m, 1H), 7.50-7.01 (m, 9H), 6.71-6.34 (m, 1H), 6.33-5.98 (m, 2H), 5.63 (m, 1H), 5.36-5.16 (m, 1H), 4.39-4.17 (m, 1H), 3.90-3.58 (m, 1H), 3.55-2.84 (m, 12H), 1.72 (dd, *J* = 13.4, 6.6 Hz, 1H), 0.91-0.68 (m, 6H); ^{13}C NMR (100 MHz, CDCl3) δ ppm 172.5, 172.3, 164.5, 164.3, 163.3, 137.4, 137.3, 136.9, 136.2, 134.4, 134.3, 130.5, 130.5, 130.4, 130.3, 130.2, 130.1, 129.4, 129.3, 129.2, 129.0, 128.6, 127.0, 126.8, 126.3, 125.8, 125.7, 124.1, 122.7, 122.2, 85.3, 83.2, 60.3, 60.2, 57.2, 56.9, 56.8, 54.3, 50.7, 50.2, 49.6, 49.2, 39.9, 39.3, 28.6, 26.9, 20.2, 20.1, 20.0, 19.7; LRMS: (ES+) m/z = 652.1 (M+1)

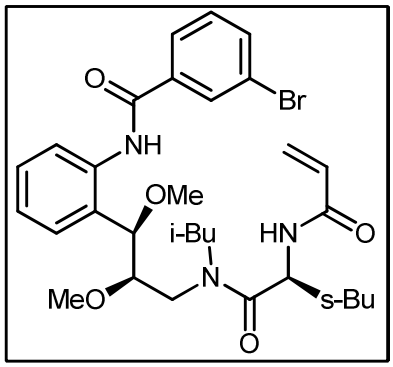
N-(2-((1R,2R)-3-((S)-2-acrylamido-N-isobutyl-4-methylpentanamido)-1,2-dimethoxypropyl)phenyl)-3-bromobenzamide (6.8c):



Molecular Formula: $C_{31}H_{42}BrN_3O_5$; R_f : 0.3 (3:7 ethyl acetate/ hexanes); Solvent system for column purification (2:3 ethylacetate/hexanes); Yield:86% (white solid);

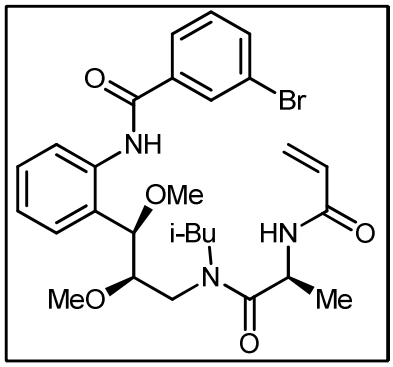
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.13 (s, 1H), 8.45 (d, *J* = 8.14 Hz, 1H), 8.25-8.09 (m, 1H), 8.04-7.86 (m, 1H), 7.66 (d, *J* = 8.4 Hz, 2H), 7.57-7.30 (m, 3H), 7.10 (d, *J* = 4.1 Hz, 1H), 6.70-6.43 (m, 1H), 6.21 (m, 2H), 5.63 (s, 1H), 5.24-5.00 (m, 1H), 3.74 (m, 5H), 3.35-3.00 (m, 8H), 2.11-1.89 (m, 1H), 1.70 (s, 2H), 1.08-0.69 (m, 12H); ^{13}C NMR (100 MHz, CDCl3) δ ppm 174.0, 173.8, 165.0, 164.9, 163.3, 137.3, 137.2, 137.0, 134.5, 134.4, 130.7, 130.7, 130.4, 130.4, 130.2, 129.4, 129.0, 129.0, 126.9, 126.5, 125.7, 124.2, 122.8, 122.3, 85.3, 82.9, 60.0, 57.2, 57.0, 56.9, 53.3, 49.0, 47.7, 47.2, 43.2, 42.6, 28.7, 26.8, 24.7, 24.6, 23.5, 23.4, 23.3, 21.6, 21.3, 20.2, 20.2, 19.9, 19.9; LRMS: (ES+) m/z = 617.9 (M+1)

N-(2-((1R,2R)-3-((2S,3S)-2-acrylamido-N-isobutyl-3-methylpentanamido)-1,2-dimethoxy propyl)phenyl)-3-bromobenzamide (6.8d):

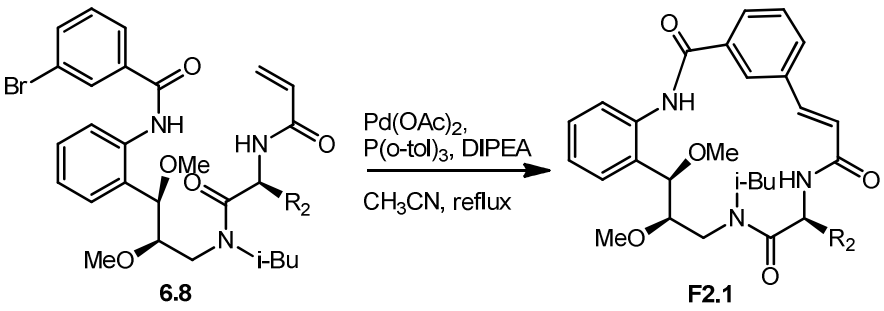


Molecular Formula: $C_{31}H_{42}BrN_3O_5$; R_f : 0.2 (3:7 ethyl acetate/ hexanes); Solvent system for column purification (2:3 ethylacetate/hexanes); Yield:84% (white solid); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.99 (s, 1H), 8.45 (d, *J* = 8.1 Hz, 1H), 8.23-8.10 (m, 1H), 7.94 (m, 1H), 7.66 (t, *J* = 6.8 Hz, 1H), 7.47-7.32 (m, 2H), 7.22 (d, *J* = 7.5 Hz, 1H), 7.15-7.00 (m, 1H), 6.40 (d, *J* = 9.0 Hz, 1H), 6.33-6.04 (m, 2H), 5.71-5.55 (m, 1H), 4.95 (m, 1H), 4.37 (s, 1H), 3.91-3.63 (m, 2H), 3.53 (dd, *J* = 13.3, 6.2 Hz, 1H), 3.45-3.14 (m, 7H), 2.11-1.77 (m, 2H), 1.70-1.35 (m, 1H), 1.09-0.75 (m, 12H); ^{13}C NMR (100 MHz, CDCl3) δ ppm 172.9, 172.9, 164.8, 163.3, 137.3, 137.2, 136.9, 134.4, 134.4, 130.7, 130.5, 130.4, 130.3, 130.2, 129.3, 129.0, 126.9, 126.6, 126.4, 125.8, 125.6, 124.1, 122.8, 122.7, 122.3, 85.2, 82.8, 60.3, 59.9, 57.2, 56.9, 53.8, 53.3, 53.0, 48.8, 48.5, 38.5, 38.4, 28.7, 26.8, 24.2, 23.9, 20.2, 20.2, 20.0, 19.6, 15.8, 15.8, 11.3, 11.1; LRMS: (ES+) m/z = 617.9 (M+1)

N-(2-((1R,2R)-3-((S)-2-acrylamido-N-isobutylpropanamido)-1,2-dimethoxypropyl)phenyl)-3-bromobenzamide (6.8e):



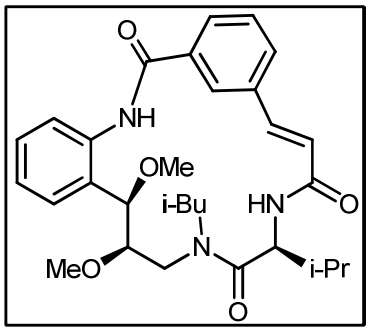
Molecular Formula: $C_{28}H_{36}BrN_3O_5$; R_f : 0.2 (3:7 ethyl acetate/hexanes); Solvent system for column purification (2:3 ethylacetate/hexanes); Yield:85% (white solid); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.03 (s, 1H), 8.41 (m, 1H), 8.16 (s, 1H), 7.89 (m, 1H), 7.67 (m, 1H), 7.51-7.33 (m, 2H), 7.25-7.05 (m, 2H), 6.75-6.54 (m, 1H), 6.27 (m, 1H), 6.11 (m, 1H), 5.63 (dd, *J* = 10.2, 1.3 Hz, 1H), 5.17-4.93 (m, 1H), 4.32 (m, 1H), 3.90-3.46 (m, 3H), 3.39-3.19 (m, 7H), 2.02 (m, 1H), 1.47-1.29 (m, 3H), 1.03-0.79 (m, 6H); ^{13}C NMR (100 MHz, CDCl3) δ ppm 173.5, 164.4, 163.3, 137.3, 137.2, 134.4, 130.7, 130.4, 130.4, 130.2, 129.4, 129.0, 126.8, 126.4, 125.7, 124.2, 122.8, 122.3, 85.2, 85.1, 82.7, 60.0, 57.0, 56.5, 53.0, 48.2, 45.0, 28.3, 26.7, 20.1, 19.6, 19.1; LRMS: (ES+) m/z = 573.8 (M+1)



To a solution of **6.8** (0.077 mmol) in acetonitrile (120mL) was added palladium acetate (0.0154 mmol) and tri-(o-tolyl)phosphine (0.0154 mmol), followed by diisopropyl ethylamine (0.155 mmol).The reaction mixture was refluxed for 36 h and then diluted with dichloromethane. It was filtered through Celite and the filtrate was concentrated in vacuo. The residue was then dissolved in dichloromethane. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered

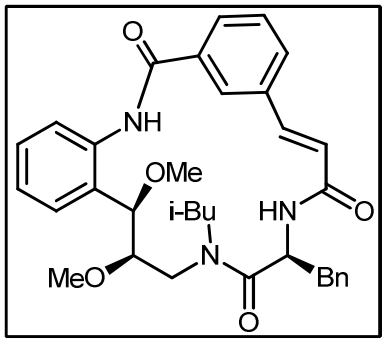
and concentrated to leave a crude oil, which was purified by column chromatography to give pure compound **F2.1**.

Compound (F2.1a):



Molecular Formula: $C_{30}H_{39}N_3O_5$; R_f : 0.3 (2:1 ethyl acetate/hexanes); Solvent system for column purification (2:1 ethylacetate/hexanes); Yield:53% (semi solid); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.40-10.34 (m, 1H), 8.86-8.80 (m, 1H), 8.46 (s, 1H), 8.19-8.11 (m, 1H), 7.73 (d, *J* = 15.6 Hz, 1H), 7.54 (d, *J* = 6.4 Hz, 2H), 7.46-7.40 (m, 1H), 7.19-7.10 (m, 3H), 6.21-6.13 (m, 1H), 4.96-4.89 (m, 1H), 4.19 (s, 1H), 4.08-4.00 (m, 1H), 3.81-3.74 (m, 1H), 3.32 (s, 3H), 3.29 (s, 3H), 2.56-2.48 (m, 1H), 2.09 (s, 3H), 1.06 (d, *J* = 6.7 Hz, 3H), 0.98 (dd, *J* = 11.7, 6.7 Hz, 7H), 0.91 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, CDCl3) δ ppm 171.4, 166.8, 164.0, 141.5, 137.8, 135.6, 135.1, 133.0, 129.8, 129.7, 129.6, 124.7, 123.8, 122.3, 120.5, 118.8, 86.2, 82.2, 61.4, 57.2, 51.9, 50.7, 29.6, 26.4, 22.4, 20.2, 19.7, 16.5, 11.8; LRMS: (ES+) m/z = 522.3 (M+1)

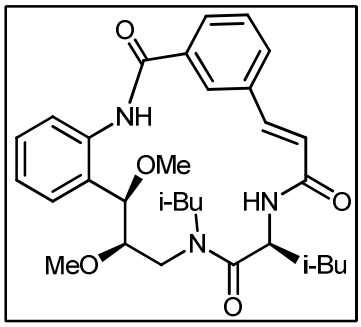
Compound (F2.1b):



Molecular Formula: $C_{34}H_{39}N_3O_6$; R_f : 0.2 (1:1 ethyl acetate/hexanes); Solvent system for column purification (1:1 ethylacetate/hexanes); Yield:55% (semi solid); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.35 (s, 1H), 8.82 (d, *J* = 8.3 Hz, 1H), 8.36 (s, 1H), 8.13

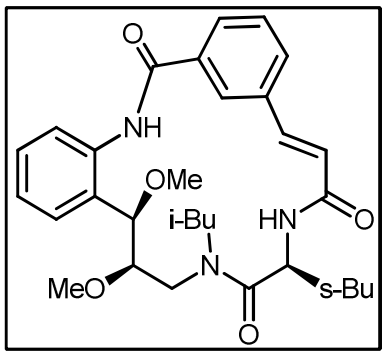
(d, *J* = 7.7 Hz, 1H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.46-7.37 (m, 3H),2.14 (s, 1H), 7.25-7.10 (m, 7H), 7.26 (s, 1H), 6.88 (d, *J* = 15.4 Hz, 1H), 6.16-6.04 (m, 1H), 5.28-5.18 (m, 1H), 4.39-4.28 (m, 1H), 4.19 (s, 1H), 3.98 (s, 1H), 3.79 (dd, *J* = 10.9, 2.0 Hz, 1H), 3.37 (s, 3H), 3.28 (s, 3H), 3.17 (m, 3H), 2.82 (dd, *J* = 14.0, 9.5 Hz, 1H), 2.61 (dd, *J* = 13.5, 7.2 Hz, 1H), 0.98 (m, 6H); ^{13}C NMR (100 MHz, CDCl3) δ ppm 171.5, 166.1, 163.9, 140.7, 137.7, 135.9, 135.6, 135.0, 132.8, 129.7, 129.7, 129.6, 129.4, 129.0, 128.7, 127.2, 124.5, 123.8, 122.1, 120.6, 118.8, 86.1, 82.2, 61.3, 57.6, 54.6, 52.0, 50.2, 41.1, 26.6, 20.4, 19.9; LRMS: (ES+) m/z = 569.9 (M+1)

Compound (F2.1c):



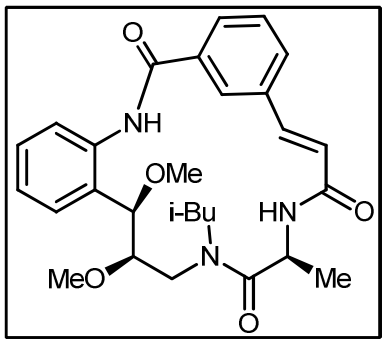
Molecular Formula: $C_{31}H_{41}N_3O_6$; R_f : 0.3 (7:3 ethyl acetate /hexanes); Solvent system for column purification (7:3 ethylacetate/hexanes); Yield:58% (semi solid); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.43 (s, 1H), 8.87 (d, *J* = 8.5 Hz, 1H), 8.52 (s, 1H), 8.20-8.14 (m, 1H), 7.74 (d, *J* = 15.4 Hz, 1H), 7.55 (d, *J* = 6.4 Hz, 2H), 7.43 (s, 1H), 7.15 (dd, *J* = 10.7, 7.9 Hz, 3H), 5.98-5.89 (m, 1H), 5.09-4.99 (m, 1H), 4.18 (s, 2H), 4.06-3.97 (m, 1H), 3.82-3.75 (m, 1H), 3.30 (s, 6H), 2.58-2.49 (m, 1H), 2.17-1.98 (m, 2H), 1.93-1.80 (m, 1H), 0.98 (t, *J* = 7.2 Hz, 6H), 0.92-0.87 (m, 6H); ^{13}C NMR (100 MHz, CDCl3) δ ppm 172.6, 166.4, 163.9, 141.6, 137.8, 135.4, 135.0, 133.1, 129.9, 129.7, 129.7, 129.7, 124.7, 123.7, 122.0, 120.5, 118.5, 86.0, 81.9, 61.3, 57.5, 51.5, 51.1, 49.8, 43.4, 29.6, 26.5, 24.3, 23.4, 20.4, 20.3, 19.7; LRMS: (ES+) m/z = 535.9 (M+1)

Compound (F2.1d):



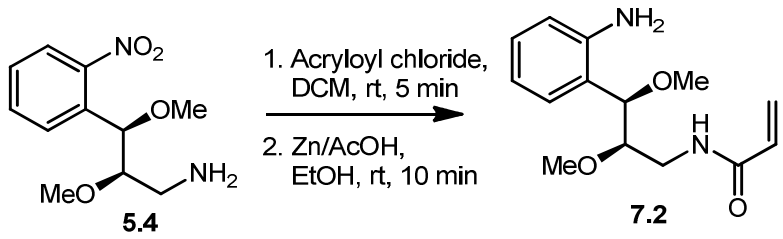
Molecular Formula: $C_{31}H_{41}N_3O_6$; R_f : 0.3 (7:3 ethyl acetate /hexanes); Solvent system for column purification (7:3 ethylacetate/hexanes); Yield:55% (semi solid); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.38 (s, 1H), 8.83 (d, *J* = 8.2 Hz, 1H), 8.47 (s, 1H), 8.15 (dd, *J* = 6.3, 2.1 Hz, 1H), 7.75 (d, *J* = 15.4 Hz, 1H), 7.58-7.51 (m, 2H), 7.46-7.39 (m, 1H), 7.19-7.09 (m, 3H), 6.03 (d, *J* = 11.1 Hz, 1H), 4.93 (dd, *J* = 11.0, 2.7 Hz, 1H), 4.25-4.16 (m, 2H), 4.04 (dd, *J* = 13.3, 7.5 Hz, 1H), 3.80-3.74 (m, 1H), 3.31 (d, *J* = 6.7 Hz, 3H), 3.31-3.25 (m, 4H), 2.52 (dd, *J* = 13.5, 7.58 Hz, 1H), 2.13 (dd, *J* = 12.2, 5.3 Hz, 1H), 1.78 (ddd, *J* = 9.6, 6.6, 3.1 Hz, 1H), 1.58 (ddd, *J* = 13.2, 7.6, 2.6 Hz, 1H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.95-0.88 (m, 6H); ^{13}C NMR (100 MHz, CDCl3) δ ppm 171.4, 166.8, 164.0, 141.5, 137.8, 135.6, 135.1, 133.0, 129.8, 129.7, 129.6, 124.7, 123.8, 122.3, 120.5, 118.8, 86.2, 82.2, 61.4, 57.2, 51.9, 50.7, 38.6, 29.6, 26.4, 22.4, 20.2, 19.7, 16.5, 11.8; LRMS: (ES+) m/z = 535.9 (M+1)

Compound (F2.1e):



Molecular Formula: $C_{28}H_{35}N_3O_5$; R_f : 0.3 (ethyl acetate); Solvent system for column purification (9:1 ethylacetate/hexanes); Yield:50% (semi solid); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.38 (s,1H), 8.84 (d, *J* = 8.1 Hz, 1H), 8.49 (s, 1H), 8.20-8.10 (m, 1H), 7.74 (d, *J* = 15.4 Hz, 1H), 7.54 (d, *J* = 6.1 Hz, 2H), 7.42 (dd, *J* = 10.9, 4.1 Hz,

1H), 7.20-7.08 (m, 3H), 6.05 (d, *J* = 10.1 Hz, 1H), 5.28-5.18 (m, 1H), 5.09 (d, *J* = 3.4 Hz, 1H), 4.22-4.15 (m, 2H), 3.78 (dd, *J* = 10.9, 1.9 Hz, 1H), 3.31 (s, 3H), 3.28 (s, 3H), 2.53 (dd, *J* = 13.4, 7.1 Hz, 1H), 1.68 (s, 1H), 1.47 (d, *J* = 6.90 Hz, 3H), 0.99 (d, *J* = 6.6 Hz, 3H), 0.90 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, CDCl3) δ ppm 172.9, 165.8, 163.9, 137.8, 135.4, 135.1, 133.2, 129.8, 129.7, 124.7, 123.7, 122.1, 120.5, 118.6, 86.0, 82.1, 61.5, 51.6, 51.0, 50.2, 48.1, 26.4, 23.0, 20.2, 19.7; LRMS: (ES+) m/z = 493.2 (M+1)



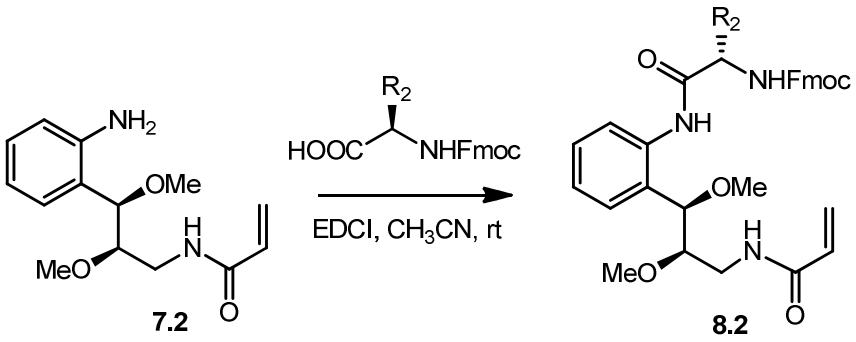
N-((2R,3R)-3-(2-aminophenyl)-2,3-dimethoxypropyl)acrylamide (7.2):

To a suspension of **5.4** (2.0 g, 8.32 mmol) in DCM (20 mL), Acrylol chloride (1.75 g, 12.48 mmol) was added at 0 °C and allowed to stir for 5 min. After completion of the reaction, reaction mixture was quenched with sodium bicarbonate solution (15 mL), concentrated, and extracted with DCM (3 X 20 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was subjected to next reaction without purification.

To suspension of above (1.5 g, 3.91 mmol) in EtOH (10 mL), Zn (5.07g, 78.03 mmol), AcOH (1.0 mL, 19.55 mmol) was added at 0 °C and allowed to stir the reaction mixture for 0.5 h. After completion of the reaction mixture was passed through celite and concentrated, to leave a crude oil, which was purified by column chromatography (1:1 ethylacetate/hexanes) to give the pure compound **7.2**.

Molecular Formula: $C_{14}H_{20}N_2O_3$; R_f : 0.3 (1:1 ethyl acetate/hexane); Yield:95% (yellow liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.09 (m, 1H), 6.99 (dd, *J* = 11.2, 4.5 Hz, 1H), 6.70 (dd, *J* = 9.1, 5.6 Hz, 1H), 6.61 (d, *J* = 7.9 Hz, 1H), 6.15 (dd, *J* = 17.0, 1.3 Hz, 1H), 5.94 (dd, *J* = 17.0, 10.2 Hz, 1H), 5.87-5.72 (m, 1H), 5.55 (dd, *J* = 10.2, 1.2 Hz, 1H), 4.30-4.17 (m, 2H), 3.87-3.78 (m, 1H), 3.47 (s, 3H), 3.3-3.1 (m,

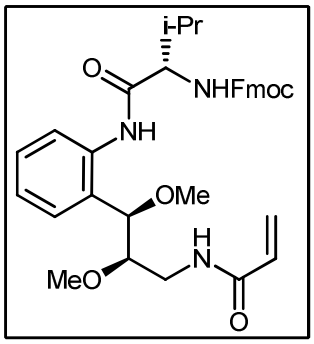
5H); ^{13}C NMR (100 MHz, CDCl3) δ ppm 165.4, 145.6, 130.7, 130.5, 130.1, 130.0, 129.6, 120.9, 116.9, 86.4, 80.6, 58.5, 57.5, 39.4; LRMS: (ES+) m/z = 265.2 (M+1)



Compound 8.2:

To a suspension of **7.2** (0.75 mmol) in Acetonitrile (10 mL), *N*-Fmoc amino acid (1.54 mmol), EDC·HCl (2.27 mmol) were added at room temperature and allowed to stirred for 3 h. After completion of the reaction mixture was quenched with sodium bicarbonate solution (5 mL), concentrated, and extracted with ethyl acetate (3 X 20 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography to give the pure compound **8.2**.

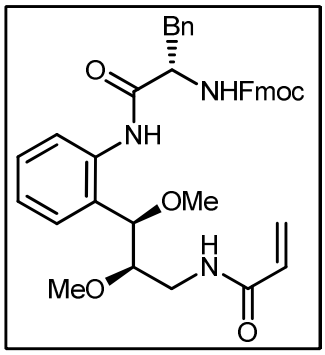
(9H-fluoren-9-yl)methyl (S)-1-(2-((1R,2R)-3-acrylamido-1,2-dimethoxypropyl) phenyl amino)-3-methyl-1-oxobutan-2-ylcarbamate (8.2a):



Molecular Formula: $C_{34}H_{39}N_3O_6$; R_f : 0.3 (1:1 ethyl acetate/hexane); Solvent system for column purification (1:1 ethylacetate/hexanes); Yield:83% (colourless liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.44 (s, 1H), 8.16 (d, *J* = 8.0 Hz, 1H), 7.77 (d, *J* = 7.3 Hz, 2H), 7.62 (d, *J* = 7.3 Hz, 2H), 7.45-7.28 (m, 5H), 7.15 (dd, *J* = 14.5, 6.8 Hz, 2H), 6.23 (dd, *J* = 16.9, 1.2 Hz, 1H), 6.08-5.96 (m, 1H), 5.96-5.84 (m, 1H), 5.60 (dd,

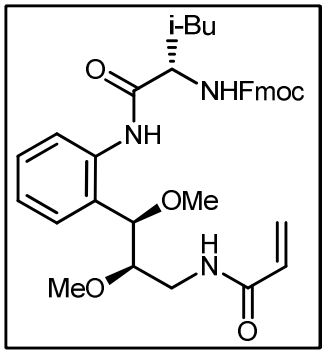
J = 10.2, 1.3 Hz, 1H), 5.48 (d, *J* = 8.3 Hz, 1H), 4.53 (s, 1H), 4.38-4.28 (m, 2H), 4.25 (t, *J* = 6.9 Hz, 1H), 4.20-4.13 (m, 1H), 3.66-3.52 (m, 2H), 3.42-3.33 (m, 1H), 3.29 (s, 3H), 3.24 (s, 3H), 2.39-2.25 (m, 1H), 1.05 (d, *J* = 6.4 Hz, 3H), 0.99 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, CDCl3) δ ppm 169.6, 165.7, 156.4, 143.7, 141.2, 136.5, 130.6, 129.0, 127.8, 127.6, 127.1, 126.9, 125.2, 125.1, 124.8, 123.0, 120.1, 119.9, 85.2, 82.4, 82.2, 67.0, 61.2, 59.3, 57.4, 47.1, 39.5, 30.9, 19.4, 17.6; LRMS: (ES+) m/z = 586.1 (M+1)

(9H-fluoren-9-yl)methyl (S)-1-(2-((1R,2R)-3-acrylamido-1,2-dimethoxypropyl) phenyl amino)-1-oxo-3-phenylpropan-2-ylcarbamate (8.2b):



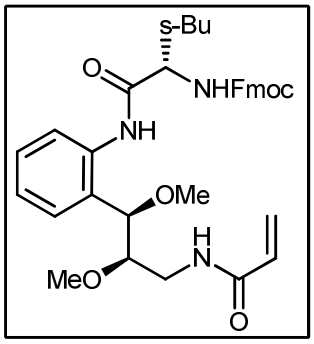
Molecular Formula: $C_{38}H_{39}N_3O_6$; R_f : 0.4 (1:1 ethyl acetate/hexane); Yield:85% (colourless liquid); Solvent system for column purification (1:1 ethylacetate/hexanes); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.37 (s, 1H), 8.09 (d, *J* = 7.6 Hz, 1H), 7.75 (d, *J* = 7.5 Hz, 2H), 7.54 (t, *J* = 6.57 Hz, 2H), 7.39 (t, *J* = 7.4 Hz, 2H), 7.35-7.19 (m, 9H), 7.12 (td, *J* = 14.5, 7.3 Hz, 2H), 6.18 (d, *J* = 16.9 Hz, 1H), 5.96 (dd, *J* = 16.8, 10.0 Hz, 2H), 5.57 (t, *J* = 11.7 Hz, 2H), 4.62-4.45 (m, 2H), 4.22 (td, *J* = 13.4, 6.9 Hz, 2H), 4.11 (q, *J* = 7.2 Hz, 2H), 3.44 (dd, *J* = 13.7, 8.0 Hz, 2H), 3.34-2.94 (m, 10H); ^{13}C NMR (100 MHz, CDCl3) δ ppm 171.1, 169.0, 165.6, 155.8, 143.6, 141.2, 141.2, 136.5, 136.1, 130.6, 129.4, 128.8, 128.7, 127.8, 127.1, 127.0, 127.0, 126.4, 125.1, 124.9, 124.8, 123.1, 120.0, 84.2, 82.0, 67.1, 60.4, 59.0, 57.1, 47.0, 39.2, 38.4; LRMS: (ES+) m/z = 633.9 (M+1)

(9H-fluoren-9-yl)methyl (S)-1-(2-((1R,2R)-3-acrylamido-1,2-dimethoxypropyl) phenyl amino)-4-methyl-1-oxopentan-2-ylcarbamate (8.2c):



Molecular Formula: $C_{35}H_{41}N_3O_6$; R_f : 0.4 (7:3 ethyl acetate/hexane); Solvent system for column purification (3:2 ethylacetate/hexanes); Yield:88.9% (colourless liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.43 (s, 1H), 8.12 (d, *J* = 7.7 Hz, 1H), 7.76 (d, *J* = 7.4 Hz, 2H), 7.61 (d, *J* = 7.3 Hz, 2H), 7.46-7.27 (m, 5H), 7.14 (dd, *J* = 15.4, 6.9 Hz, 2H), 6.21 (dd, *J* = 16.9, 0.9 Hz, 1H), 6.01 (s, 2H), 5.58 (dd, *J* = 10.2, 1.2 Hz, 1H), 5.51-5.41 (m, 1H), 4.53 (d, *J* = 2.4 Hz, 1H), 4.39-4.28 (m, 3H), 4.24 (d, *J* = 6.8 Hz, 1H), 3.66-3.54 (m, 2H), 3.25 (d, *J* = 12.6 Hz, 7H), 1.81 (dd, *J* = 13.1, 4.7 Hz, 2H), 1.61 (s, 1H), 0.99 (d, *J* = 6.3 Hz, 6H); ^{13}C NMR (100 MHz, CDCl3) δ ppm 170.5, 165.6, 156.1, 143.7, 141.2, 136.5, 130.6, 129.1, 128.9, 127.7, 127.1, 127.0, 126.5, 125.1, 124.9, 124.6, 123.1, 120.0, 109.9, 85.5, 82.1, 67.0, 59.1, 57.4, 54.5, 47.1, 41.7, 39.6, 24.8, 23.0, 21.9, 14.1; LRMS: (ES+) m/z = 600.0 (M+1)

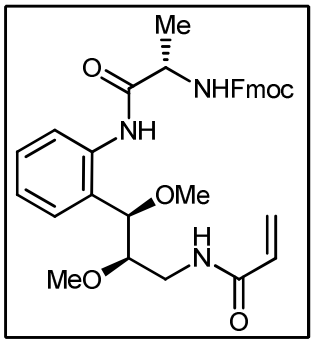
(9H-fluoren-9-yl)methyl (2S,3R)-1-(2-((1R,2R)-3-acrylamido-1,2-dimethoxypropyl)phenyl amino)-3-methyl-1-oxopentan-2-ylcarbamate (8.2d):



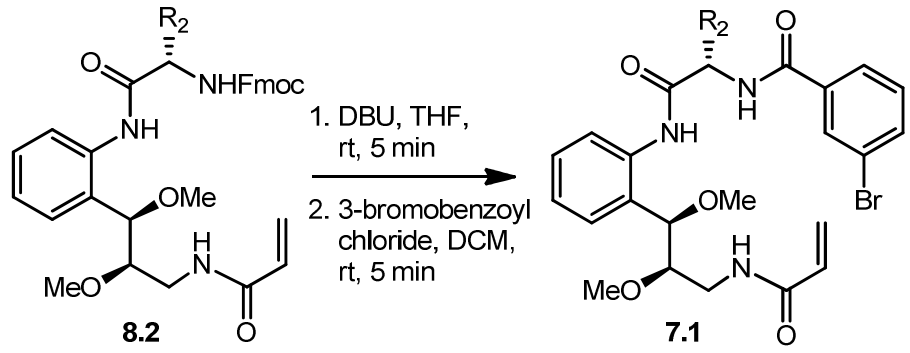
Molecular Formula: $C_{35}H_{41}N_3O_6$; R_f : 0.4 (7:3 ethyl acetate/hexane); Solvent system for column purification (3:2 ethylacetate/hexanes); Yield:86% (colourless liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.44 (s, 1H), 8.15 (d, *J* = 7.9 Hz, 1H), 7.77 (d, *J* = 7.5 Hz, 2H), 7.61 (d, *J* = 7.3 Hz, 2H), 7.45-7.28 (m, 5H), 7.15 (dd, *J* = 14.3, 7.1 Hz, 2H), 6.22 (dd, *J* = 16.9, 1.1 Hz, 1H), 6.11-5.96 (m, 1H), 5.96-5.84 (m, 1H), 5.59 (dd, *J* = 10.2, 1.3 Hz, 1H), 5.46 (d, *J* = 8.4 Hz, 1H), 4.53 (d, *J* = 2.6 Hz, 1H), 4.43-4.27

(m, 2H), 4.21 (m, 2H), 3.66-3.50 (m, 2H), 3.25 (d, *J* = 17.6 Hz, 7H), 2.05 (d, *J* = 2.7 Hz, 1H), 1.65-1.50 (m, 1H), 1.23-1.13 (m, 1H), 1.07-0.92 (m, 6H); ^{13}C NMR (100 MHz, CDCl3) δ ppm 169.6, 165.6, 156.3, 143.7, 141.2, 136.5, 130.7, 130.5, 129.0, 128.8, 127.9, 127.6, 127.1, 127.0, 125.2, 125.0, 124.8, 123.1, 123.0, 120.1, 119.9, 85.4, 82.3, 82.1, 67.0, 60.8, 60.7, 59.2, 57.4, 47.1, 39.5, 37.3, 24.5, 15.8, 15.7, 11.4; LRMS: (ES+) m/z = 600.0 (M+1)

(9H-fluoren-9-yl)methyl (S)-1-(2-((1R,2R)-3-acrylamido-1,2-dimethoxypropyl) phenyl amino)-1-oxopropan-2-ylcarbamate (8.2e):



Molecular Formula: $C_{32}H_{35}N_3O_6$; R_f : 0.3 (7:3 ethyl acetate/hexane); Solvent system for column purification (7:3 ethylacetate/hexanes); Yield:80% (colourless liquid); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.45 (s, 1H), 8.13 (d, *J* = 8.2 Hz, 1H), 7.76 (d, *J* = 7.4 Hz, 2H), 7.62 (d, *J* = 7.1 Hz, 2H), 7.44-7.27 (m, 5H), 7.21-7.08 (m, 2H), 6.23 (dd, *J* = 16.9, 1.2 Hz, 1H), 6.12-5.88 (m, 2H), 5.70 (d, *J* = 4.6 Hz, 1H), 5.60 (d, *J* = 10.3 Hz, 1H), 4.53-4.44 (m, 1H), 4.44-4.28 (m, 3H), 4.23 (t, *J* = 6.9 Hz, 1H), 3.56 (m, 2H), 3.40-3.14 (m, 7H), 1.51 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, CDCl3) δ ppm 170.4, 165.7, 155.8, 143.7, 141.2, 136.5, 130.5, 129.0, 127.7, 127.1, 125.0, 124.7, 123.0, 120.0, 119.9, 85.3, 82.2, 67.0, 59.3, 57.3, 51.5, 47.1, 39.7, 18.9; LRMS: (ES+) m/z = 558.2 (M+1)

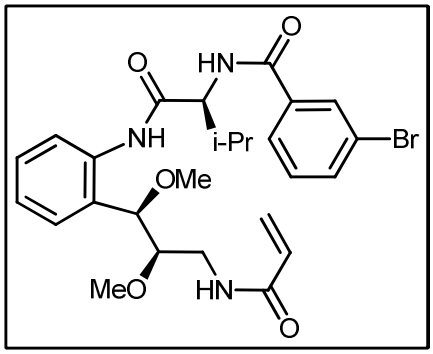


Compound 7.1:

To a suspension of compound **8.2** (0.6 mmol) in THF (10 mL), DBU (0.9 mmol) was added and stirred the reaction mixture for 5 min. After completion of the reaction, reaction mixture concentrated and which was subjected to the next reaction without any purification.

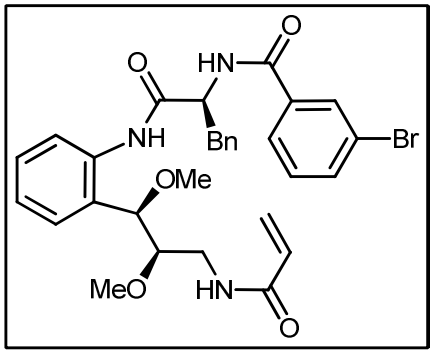
To a suspension of above compound (0.5 mmol) in DCM (10 mL), 3-bromo benzoyl chloride (0.45 mmol) was added at 0 °C and allowed to stir for 10 min. After completion of the reaction, reaction mixture was quenched with sodium bicarbonate solution (5 mL), and extracted with ethyl acetate (3 X 20 mL). Combined organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography to give pure compound **7.1**.

N-((S)-1-(2-((1R,2R)-3-acrylamido-1,2-dimethoxypropyl)phenylamino)-3-methyl-1-oxobutan-2-yl)-3-bromobenzamide (7.1a):



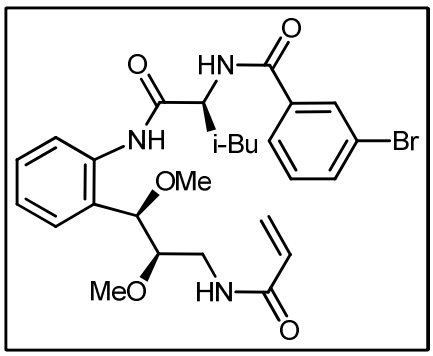
Molecular Formula: $C_{26}H_{32}BrN_3O_5$; R_f : 0.2 (1:1 ethyl acetate/hexane); Solvent system for column purification (3:2 ethylacetate/hexanes); Yield:75.2% (white solid); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.52 (s, 1H), 8.15 (t, *J* = 6.7 Hz, 1H), 8.01 (s, 1H), 7.77 (d, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 2H), 7.19-7.08 (m, 2H), 6.96 (d, *J* = 8.5 Hz, 1H), 6.2 (dd, *J* = 16.9, 1.3 Hz, 1H), 6.10 (dd, *J* = 16.9, 10.2 Hz, 1H), 6.01 (d, *J* = 6.1 Hz, 1H), 5.64 (dd, *J* = 10.2, 1.3 Hz, 1H), 4.65 (dd, *J* = 8.6, 5.9 Hz, 1H), 4.34 (d, *J* = 3.0 Hz, 1H), 3.65-3.56 (m, 2H), 3.33-3.26 (m, 1H), 3.23 (d, *J* = 4.3 Hz, 6H), 2.40 (dd, *J* = 13.0, 6.6 Hz, 1H), 1.08 (d, *J* = 6.7 Hz, 3H), 1.04 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, CDCl3) δ ppm 169.3, 165.9, 136.4, 136.1, 130.6, 130.5, 130.4, 130.3, 129.9, 127.2, 125.7, 125.4, 123.0, 122.7, 122.7, 109.9, 85.3, 82.7, 59.5, 57.4, 39.7, 31.3, 19.5, 17.7; LRMS: (ES+) m/z = 547.8 (M+1)

N-((S)-1-(2-((1R,2R)-3-acrylamido-1,2-dimethoxypropyl)phenylamino)-1-oxo-3-phenylpropan-2-yl)-3-bromobenzamide (7.1b):



Molecular Formula: $C_{30}H_{32}BrN_3O_5$; R_f : 0.3 (4:1 ethyl acetate/hexane); Solvent system for column purification (4:1 ethylacetate/hexanes); Yield:76% (white solid); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.41 (s, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 7.95 (s, 1H), 7.64 (dd, *J* = 16.7, 7.6 Hz, 2H), 7.36-7.21 (m, 7H), 7.10 (td, *J* = 5.9, 4.0 Hz, 3H), 6.26-6.18 (m, 1H), 6.03 (dd, *J* = 16.9, 10.2 Hz, 1H), 5.85 (s, 1H), 5.61 (d, *J* = 10.2 Hz, 1H), 5.03 (dd, *J* = 14.1, 6.6 Hz, 1H), 4.08 (t, *J* = 5.4 Hz, 1H), 3.48-3.40 (m, 2H), 3.36 (dd, *J* = 13.6, 5.6 Hz, 1H), 3.27 (dd, *J* = 13.7, 6.8 Hz, 1H), 3.16-3.10 (m, 4H), 3.02 (s, 3H); ^{13}C NMR (100 MHz, CDCl3) δ ppm 168.8, 165.6, 165.4, 136.4, 136.0, 135.8, 134.7, 130.5, 130.1, 129.5, 128.8, 128.8, 128.8, 127.1, 126.7, 125.5, 124.9, 123.1, 122.7, 84.2, 82.4, 59.4, 57.1, 55.4, 39.6, 37.9; LRMS: (ES+) m/z = 595.8 (M+1)

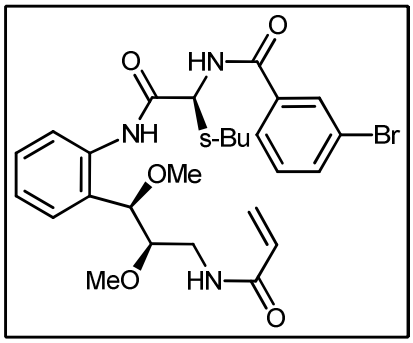
N-((S)-1-(2-((1R,2R)-3-acrylamido-1,2-dimethoxypropyl)phenylamino)-4-methyl-1-oxopentan-2-yl)-3-bromobenzamide (7.1c):



Molecular Formula: $C_{27}H_{34}BrN_3O_5$; R_f : 0.2 (7:3 ethyl acetate/hexane); Solvent system for column purification (7:3 ethylacetate/hexanes); Yield:78% (white solid); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.49 (s, 1H), 8.16-7.97 (m, 2H), 7.80 (d, *J* = 7.6

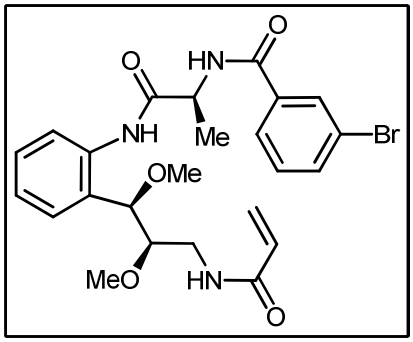
Hz, 1H), 7.72-7.58 (m, 1H), 7.41-7.27 (m, 3H), 7.24-7.08 (m, 2H), 6.42-6.01 (m, 3H), 5.69-5.59 (m, 1H), 4.83 (d, *J* = 5.7 Hz, 1H), 4.33 (s, 1H), 3.60 (s, 2H), 3.33-3.15 (m, 7H), 2.00-1.85 (m, 1H), 1.85-1.71 (m, 2H), 1.01 (s, 6H); ^{13}C NMR (100 MHz, CDCl3) δ ppm 170.5, 165.8, 136.3, 135.7, 134.7, 134.5, 130.5, 130.4, 130.1, 129.9, 127.6, 125.9, 125.7, 123.4, 123.3, 122.6, 85.2, 82.4, 59.4, 57.4, 53.2, 53.0, 41.3, 40.0, 25.0, 23.0, 22.0; LRMS: (ES+) m/z = 561.8 (M+1)

N-((2S,3S)-1-(2-((1R,2R)-3-acrylamido-1,2-dimethoxypropyl)phenylamino)-3-methyl-1-oxopentan-2-yl)-3-bromobenzamide (7.1d):

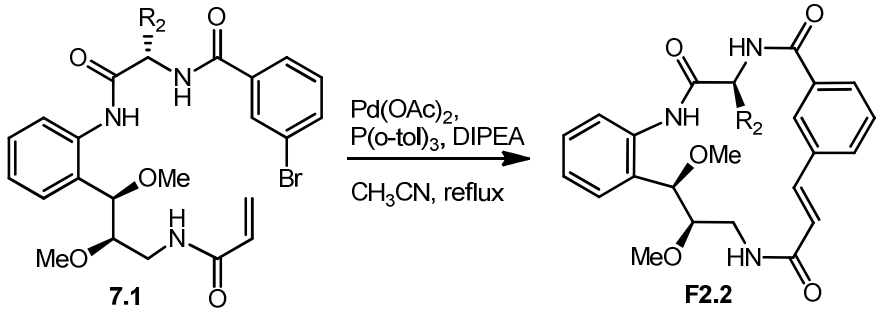


Molecular Formula: $C_{27}H_{34}BrN_3O_5$; R_f : 0.2 (7:3 ethyl acetate/hexane); Solvent system for column purification (7:3 ethylacetate/hexanes); Yield:75% (white solid); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.49 (d, *J* = 7.4 Hz, 1H), 8.13 (d, *J* = 8.1 Hz, 1H), 8.00 (d, *J* = 1.6 Hz, 1H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.35-7.27 (m, 2H), 7.13 (td, *J* = 14.7, 6.8 Hz, 2H), 6.97 (d, *J* = 8.5 Hz, 1H), 6.25 (dd, *J* = 16.9, 1.3 Hz, 1H), 6.15-6.05 (m, 1H), 6.04-5.97 (m, 1H), 5.63 (dd, *J* = 10.1, 1.3 Hz, 1H), 4.66 (dd, *J* = 8.2, 6.1 Hz, 1H), 4.33 (d, *J* = 3.2 Hz, 1H), 3.68-3.54 (m, 2H), 3.31-3.20 (m, 8H), 2.20-2.10 (m, 1H), 1.62 (m, 1H), 1.30 (d, *J* = 9.1 Hz, 1H), 1.06 (dd, *J* = 6.5, 3.0 Hz, 3H), 0.96 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, CDCl3) δ ppm 169.3, 165.7, 165.7, 136.3, 136.1, 134.6, 130.5, 130.4, 130.1, 129.1, 128.9, 127.1, 126.7, 125.6, 124.8, 123.0, 122.7,, 85.4, 82.5, 59.4, 59.1, 57.4, 39.7, 37.5, 29.6, 24.8, 15.8, 11.5; LRMS: (ES+) m/z = 561.8 (M+1)

N-((S)-1-(2-((1R,2R)-3-acrylamido-1,2-dimethoxypropyl)phenylamino)-1-oxopropan-2-yl)-3-bromobenzamide (7.1e):

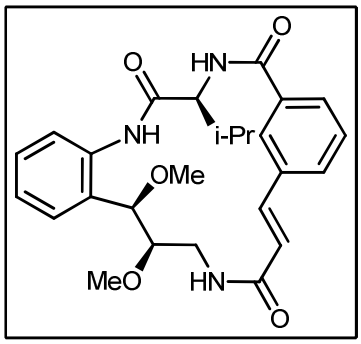


Molecular Formula: $C_{24}H_{28}BrN_3O_5$; R_f : 0.2 (4:1 ethyl acetate/hexane); Solvent system for column purification (9:1 ethylacetate/hexanes); Yield:80% (white solid); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.47 (s, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 8.04 (s, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.65 (d, *J* = 7.9 Hz, 1H), 7.38-7.29 (m, 2H), 7.25-7.20 (m, 1H), 7.20-7.11 (m, 2H), 6.26 (dd, *J* = 16.9, 1.1 Hz, 1H), 6.08 (dd, *J* = 16.9, 10.2 Hz, 1H), 5.94 (s, 1H), 5.65 (dd, *J* = 10.2, 1.1 Hz, 1H), 4.81 (dd, *J* = 8.8, 5.3 Hz, 1H), 4.32 (d, *J* = 3.0 Hz, 1H), 3.57 (td, *J* = 11.4, 4.6 Hz, 2H), 3.27-3.21 (m, 6H), 1.59 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, CDCl3) δ ppm 170.3, 165.7, 165.4, 136.4, 135.9, 134.7, 130.5, 130.4, 130.4, 130.1, 129.0, 129.0, 126.8, 125.7, 124.9, 123.2, 122.7, 85.3, 85.3, 82.5, 59.6, 57.4, 50.2, 40.1, 18.6; LRMS: (ES+) m/z = 518.2 (M+1)



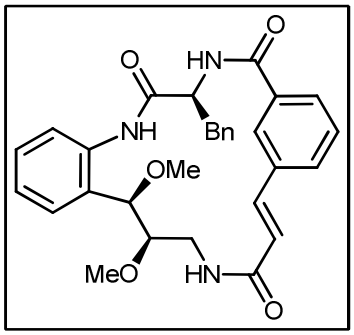
To a solution of **7.1** (70 mg, 0.084 mmol) in acetonitrile (120mL) was added palladium acetate (0.016 mmol) and tri-(o-tolyl)phosphine (2.8 mg, 0.016 mmol), followed by diisopropyl ethylamine (0.155 mmol).The reaction mixture was refluxed for 36 h and then diluted with dichloromethane. It was filtered through Celite and the filtrate was concentrated in vacuo. The residue was then dissolved in dichloromethane. The organic layer was washed with brine, dried over anhydrous sodium sulfate, filtered and concentrated to leave a crude oil, which was purified by column chromatography to give pure compound **F2.2.**

Compound (F2.2a):



Molecular Formula: $C_{26}H_{31}N_3O_5$; R_f : 0.4 (ethyl acetate); Solvent system for column purification (9:1 ethylacetate/hexanes); Yield:55%, brsm (semi solid); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.25 (s, 1H), 8.62 (d, *J* = 8.4 Hz, 1H), 8.20 (s, 1H), 8.02 (d, *J* = 7.7 Hz, 1H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 7.41-7.31 (m, 2H), 7.13-7.06 (m, 3H), 7.03 (d, *J* = 12.7 Hz, 1H), 6.29 (d, *J* = 9.3 Hz, 1H), 6.11 (d, *J* = 12.8 Hz, 1H), 6.07-6.00 (m, 1H), 4.97 (dd, *J* = 9.3, 3.26 Hz, 1H), 4.57 (s, 1H), 4.03-3.92 (m, 1H), 3.29 (s, 3H), 3.23 (d, *J* = 3.4 Hz, 1H), 2.95 (s, 3H), 2.83 (d, *J* = 3.4 Hz, 1H), 0.99 (d, *J* = 6.9 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, CDCl3) δ ppm 168.9, 167.1, 165.6, 136.5, 135.9, 135.1, 134.9, 132.0, 129.5, 129.5, 129.0, 129.0, 129.0, 126.8, 125.6, 124.1, 121.3, 89.2, 83.6, 58.7, 57.8, 39.9, 29.6, 29.3, 19.5, 16.3; LRMS: (ES-) m/z = 464.0 (M-1)

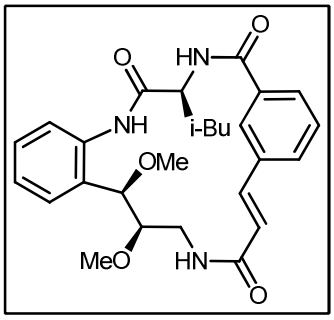
Compound (F2.2b):



Molecular Formula: $C_{30}H_{31}N_3O_5$; R_f : 0.3 (ethyl acetate); Solvent system for column purification (9:1 ethylacetate/hexanes); Yield:60%, brsm (semi solid); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.08 (s, 1H), 8.61 (d, *J* = 8.0 Hz, 1H), 8.01 (d, *J* = 7.7 Hz, 1H), 7.86 (s, 1H), 7.56 (t, *J* = 7.7 Hz, 1H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.38-7.32 (m, 1H), 7.24-7.14 (m, 5H), 7.06 (m, 2H), 7.00 (d, *J* = 12.4 Hz, 1H), 6.35 (d, *J* = 9.1 Hz, 1H), 6.03 (d, *J* = 12.7 Hz, 1H), 5.93-5.85 (m, 1H), 5.40-5.32 (m, 1H), 4.41 (s, 1H), 3.88 (dd, *J* = 14.8, 8.2 Hz, 1H), 3.74 (dd, *J* = 13.7, 4.0 Hz, 1H), 3.14 (d, *J* = 3.4 Hz,

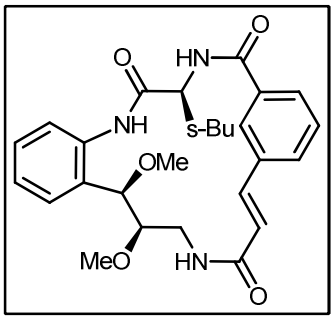
1H), 3.11-2.96 (m, 3H), 2.89 (s, 3H), 2.61 (s, 3H); ^{13}C NMR (100 MHz, CDCl3) δ ppm 168.3, 166.3, 165.5, 136.3, 136.0, 135.9, 135.1, 134.8, 131.8, 129.7, 129.5, 129.3, 128.9, 128.9, 128.8, 127.5, 127.2, 126.8, 125.3, 124.1, 121.3, 87.9, 83.5, 57.6, 56.3, 53.6, 39.8, 36.8, 29.6; LRMS: (ES-) m/z = 512.1 (M-1)

Compound (F2.2c):



Molecular Formula: $C_{27}H_{33}N_3O_5$; R_f : 0.4 (ethyl acetate); Solvent system for column purification (9:1 ethylacetate/hexanes); Yield:59%, brsm (semi solid); ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.24 (s,1H), 8.58 (d, *J* = 8.2 Hz, 1H), 8.22 (s, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.55 (t, *J* = 7.7 Hz, 1H), 7.44 (d, *J* = 7.7 Hz, 1H), 7.37-7.30 (m, 1H), 7.08 (t, *J* = 6.1 Hz, 2H), 6.99 (d, *J* = 12.8 Hz, 1H), 6.18-6.01 (m, 3H), 5.07-4.99 (m, 1H), 4.54 (s, 1H), 3.97 (ddd, *J* = 14.7, 8.1, 1.1 Hz, 1H), 3.29 (s, 3H), 3.24 (s, 1H), 3.22-3.14 (m, 1H), 2.96 (s, 3H), 2.12 (ddd, *J* = 13.2, 8.4, 3.7 Hz, 1H), 1.70-1.52 (m, 2H), 1.00 (d, *J* = 6.4 Hz, 3H), 0.96 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (100 MHz, CDCl3) δ ppm 169.9, 167.2, 165.8, 136.7, 135.8, 135.1, 134.9, 132.0, 129.4, 129.0, 128.8, 127.2, 126.7, 125.9, 124.0, 121.3, 88.2, 83.6, 60.4, 58.0, 52.8, 41.3, 39.9, 25.0, 23.2, 21.4; LRMS: (ES-) m/z = 478.1 (M-1)

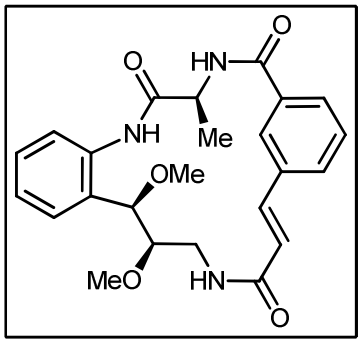
Compound (F2.2d):



Molecular Formula: $C_{27}H_{33}N_3O_5$; R_f : 0.5 (ethyl acetate); Solvent system for column purification (9:1 ethylacetate/hexanes); Yield:55%, brsm (semi solid); ^{1}H NMR (400

MHz, $CDCl_3$) δ ppm 10.25 (s, 1H), 8.62 (d, *J* = 8.3 Hz, 1H), 8.18 (s, 1H), 8.00 (d, *J* = 7.6 Hz, 1H), 7.55 (t, *J* = 7.7 Hz, 1H), 7.44 (d, *J* = 7.7 Hz, 1H), 7.38-7.30 (m, 2H), 7.08 (t, *J* = 3.3 Hz, 2H), 7.01 (d, *J* = 12.7 Hz, 1H), 6.25 (d, *J* = 9.4 Hz, 1H), 6.09 (d, *J* = 12.8 Hz, 1H), 6.05-5.99 (m, 1H), 4.99 (dd, *J* = 9.4, 3.1 Hz, 1H), 4.55 (s, 1H), 3.96 (dd, *J* = 11.9, 10.8 Hz, 1H), 3.29 (s, 3H), 3.21 (d, *J* = 3.3 Hz, 1H), 3.12 (s, 1H), 2.94 (d, *J* = 4.7 Hz, 3H), 2.51 (d, *J* = 3.4 Hz, 1H), 1.52-1.43 (m, 1H), 1.08-1.05 (m, 1H), 0.95 (m, 6H); ^{13}C NMR (100 MHz, CDCl3) δ ppm 168.9, 167.2, 165.6, 136.5, 135.9, 135.0, 135.0, 132.0, 129.5, 129.5, 129.0, 126.8, 125.6, 124.0, 121.2, 88.4, 83.7, 58.9, 57.9, 57.3, 39.9, 36.2, 29.6, 23.9, 16.0, 12.1; LRMS: (ES-) m/z = 478.1 (M-1)

Compound (F2.2e):



Molecular Formula: $C_{24}H_{27}N_3O_5$; R_f : 0.2 (9:1 ethyl acetate/hexane); Solvent system for column purification (ethylacetate);Yield:58%, brsm; ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 10.30-10.20 (m, 1H), 8.57-8.49 (m, 1H), 8.21 (s, 1H), 8.10 (s, 1H), 8.00-7.95 (m, 1H), 7.84-7.79 (m, 1H), 7.55 (s, 2H), 7.45 (s, 1H), 7.31 (s, 2H), 7.09 (s, 2H), 6.96 (d, *J* = 12.8 Hz, 1H), 6.41-6.32 (m, 1H), 6.09 (d, *J* = 12.8 Hz, 1H), 6.08 (m, 1H)5.10-4.99 (m, 1H), 4.56 (s, 1H), 4.02-3.93 (m, 1H), 2.61-2.57 (m, 1H), 3.51 (s, 1H), 3.37 (d, *J* = 9.7 Hz, 3H), 3.32-3.21 (m, 6H), 2.97 (s, 3H), 1.55 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, CDCl3) δ ppm 169.9, 167.2, 165.8, 136.7, 135.8, 135.1, 134.9, 132.0, 129.4, 129.0, 128.8, 127.2, 126.7, 125.9, 124.0, 121.3, 88.2, 83.6, 60.4, 58.0, 52.8, 41.3, 39.9, 25.0; LRMS: (ES-) m/z = 436.3 (M-1)

3.7. References:

(1) Mizoroki, T.; Mori, K.; Ozaki, A. *Bull. Chem. Soc. Japan* **1971**, *44*, 581.

(2) Heck, R.; Nolley Jr, J. *J. Org. Chem.* **1972**, *37*, 2320.

(3) (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009. (b) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945. (c) Le Bras, J.; Muzart, J. *Chem. Rev.* **2011**, *111*, 1170.

(4) (a) Dieckmann, M.; Rudolph, S.; Dreisigacker, S.; Menche, D. *J. Org. Chem.* **2012**, *77*, 10782. (b) Groh, M.; Meidlinger, D.; Bringmann, G.; Speicher, A. *Org. Lett.* **2012**, *14*, 4548. (c) Akaji, K.; Teruya, K.; Akaji, M.; Aimoto, S. *Tetrahedron* **2001**, *57*, 2293. (d) Reddy, P. R.; Balraju, V.; Madhavan, G. R.; Banerji, B.; Iqbal, J. *Tetrahedron Lett.* **2003**, *44*, 353.

(5) Lorsbach, B. A.; Kurth, M. J. *Chem. Rev.* **1999**, *99*, 1549.

(6) Ruoslahti, E.; Pierschbacher, M. *Science* **1987**, *238*, 491.

(7) Harada, T.; Katada, J.; Tachiki, A.; Asari, T.; Iijima, K.; Uno, I.; Ojima, I.; Hayashi, Y. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 209.

(8) Driggers, E. M.; Hale, S. P.; Lee, J.; Terrett, N. K. *Nat. Rev.* **2008**, *7*, 608.

(9) Sasse, F.; Steinmetz, H.; Höfle, G.; Reichenbach, H. *J. Antibiotics* **1993**, *46*, 741.

(10) Gronewold, T. M.; Sasse, F.; Lünsdorf, H.; Reichenbach, H. *Cell Tissue Res.* **1999**, *295*, 121.

(11) Horstmann, N.; Menche, D. *Chem. Comm.* **2008**, 5173.

(12) Jansen, R.; Steinmetz, H.; Sasse, F.; Schubert, W.-D.; Hagelüken, G.; Albrecht, S. C.; Müller, R. *Tetrahedron Lett.* **2008**, *49*, 5796.

(13) Dieckmann, M.; Kretschmer, M.; Li, P.; Rudolph, S.; Herkommer, D.; Menche, D. *Angew. Chem. Int. Ed.***2012**, *51*, 5667.

(14) Isoplagiochins, C. *Chem. Lett.* **1996**, *9*, 741.

(15) Eicher, T.; Fey, S.; Puhl, W.; Büchel, E.; Speicher, A. *Eur. J. Org. Chem.* **1998**, *1998*, 877.

(16) Speicher, A.; Kolz, J.; Sambanje, R. P. *Synthesis* **2002**, 2503.

(17) Esumi, T.; Wada, M.; Mizushima, E.; Sato, N.; Kodama, M.; Asakawa, Y.; Fukuyama, Y. *Tetrahedron Lett.* **2004**, *45*, 6941.

(18) Krasnoff, S. B.; Englich, U.; Miller, P. G.; Shuler, M. L.; Glahn, R. P.; Donzelli, B. G.; Gibson, D. M. *J. Nat. Prod.* **2012**, *75*, 175.

(19) (a) Ciasullo, L.; Casapullo, A.; Cutignano, A.; Bifulco, G.; Debitus, C.; Hooper, J.; Gomez-Paloma, L.; Riccio, R. *J. Nat. Prod.* **2002**, *65*, 407. (b) Janetka, J. W.; Satyshur, K. A.; Rich, D. H. *Acta Crystallogr. C* **1996**, *52 (Pt 12)*, 3112.

(20) (a) Sano, S.; Ikai, K.; Katayama, K.; Takesako, K.; Nakamura, T.; Obayashi, A.; Ezure, Y.; Enomoto, H. *J. Antibiotics* **1986**, *39*, 1685. (b) Sano, S.; Ikai, K.; Kuroda, H.; Nakamura, T.; Obayashi, A.; Ezure, Y.; Enomoto, H. *J. Antibiotics* **1986**, *39*, 1674.

(21) Bovenschen, H. J.; Otero, M. E.; Langewouters, A. M.; van Vlijmen-Willems, I. M.; van Rens, D. W.; Seyger, M. M.; van de Kerkhof, P. C. *Brit. J. Dermotol.* **2007**, *156*, 263.

(22) Kase, H.; Kaneko, M.; Yamada, K. *J. Antibiotics* **1987**, *40*, 450.

(23) (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483. (b) Arya, P.; Durieux, P.; Chen, Z.-X.; Joseph, R.; Leek, D. M. *J. Comb. Chem.* **2004**, *6*, 54.

(24) Staudinger, H.; Meyer, J. *Helv. Chim. Acta* **1919**, *2*, 635.

(25) (a) Peterson, R. T.; Fishman, M. C.*Metod. Cell Biol.* **2011**, *105*, 525. (b) Peterson, R. T.; Link, B. A.; Dowling, J. E.; Schreiber, S. L. *Proc. Natl. Acad. Sci. U.S.A.* **2000**, *97*, 12965. (c) Peterson, R. T.; Fishman, M. C. *Method. Cell Biol.* **2004**, *76*, 569.

(26) (a) Schoft, V. K.; Beauvais, A. J.; Lang, C.; Gajewski, A.; Prufert, K.; Winkler, C.; Akimenko, M. A.; Paulin-Levasseur, M.; Krohne, G. *J. Cell Sci.* **2003**, *116*, 2505. (b) Martin, C. S.; Moriyama, A.; Zon, L. I. *Genome Med.* **2011**, *3*, 83.

(27) Vogt, A.; Cholewinski, A.; Shen, X.; Nelson, S. G.; Lazo, J. S.; Tsang, M.; Hukriede, N. A. *Dev. Dynam.* **2009**, *238*, 656.

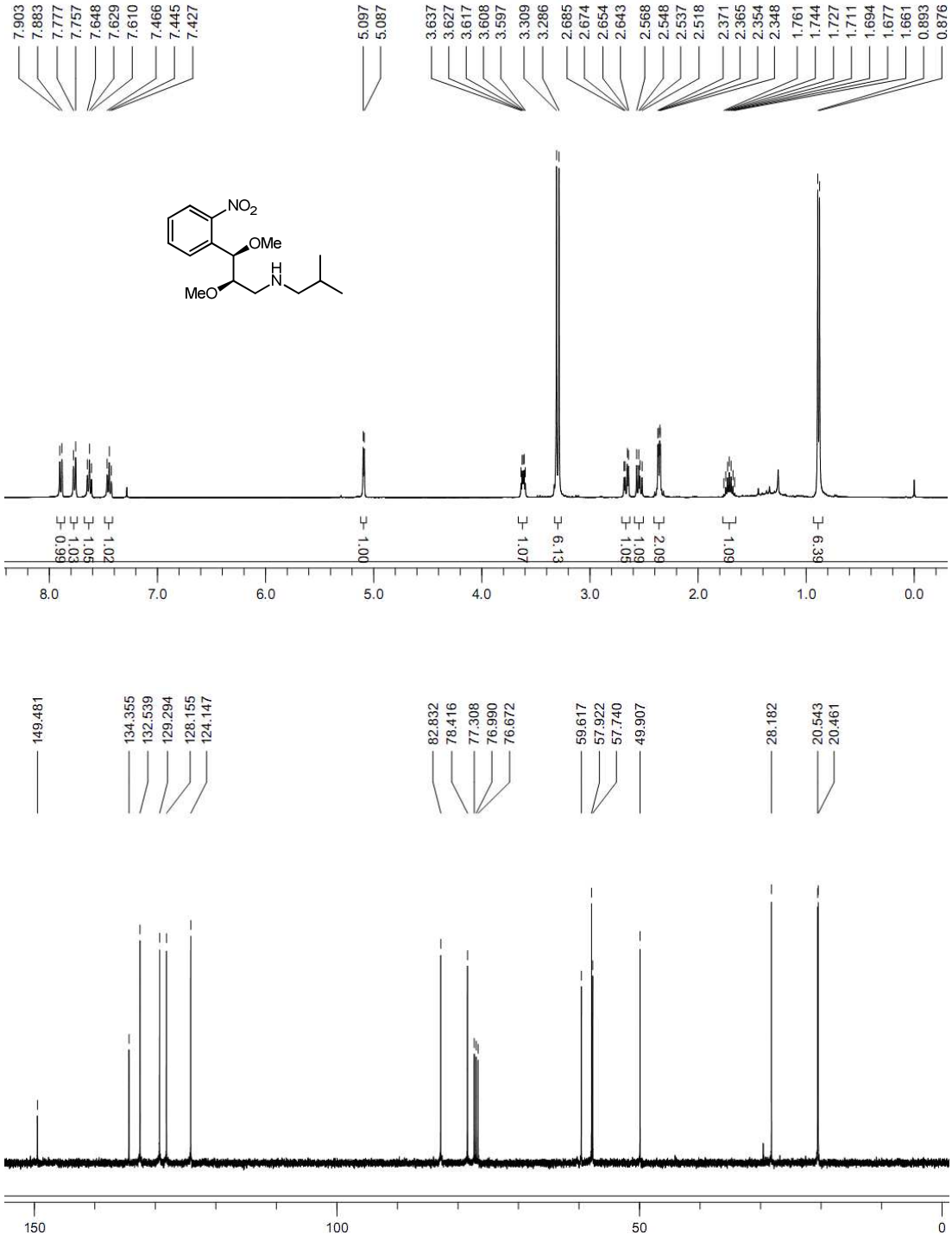
(28) (a) Cannon, J. E.; Upton, P. D.; Smith, J. C.; Morrell, N. W. *Brit. J. Pharmacol.* **2010**, *161*, 140. (b) Evensen, L.; Link, W.; Lorens, J. B. *Curr. Pharm. Design* **2010**, *16*, 3958(c) Serbedzija, G. N.; Flynn, E.; Willett, C. E. *Angiogenesis* **1999**, *3*, 353.

(29) Kitambi, S. S.; Malicki, J. J. *Dev. Dynam.* **2008**, *237*, 3870.

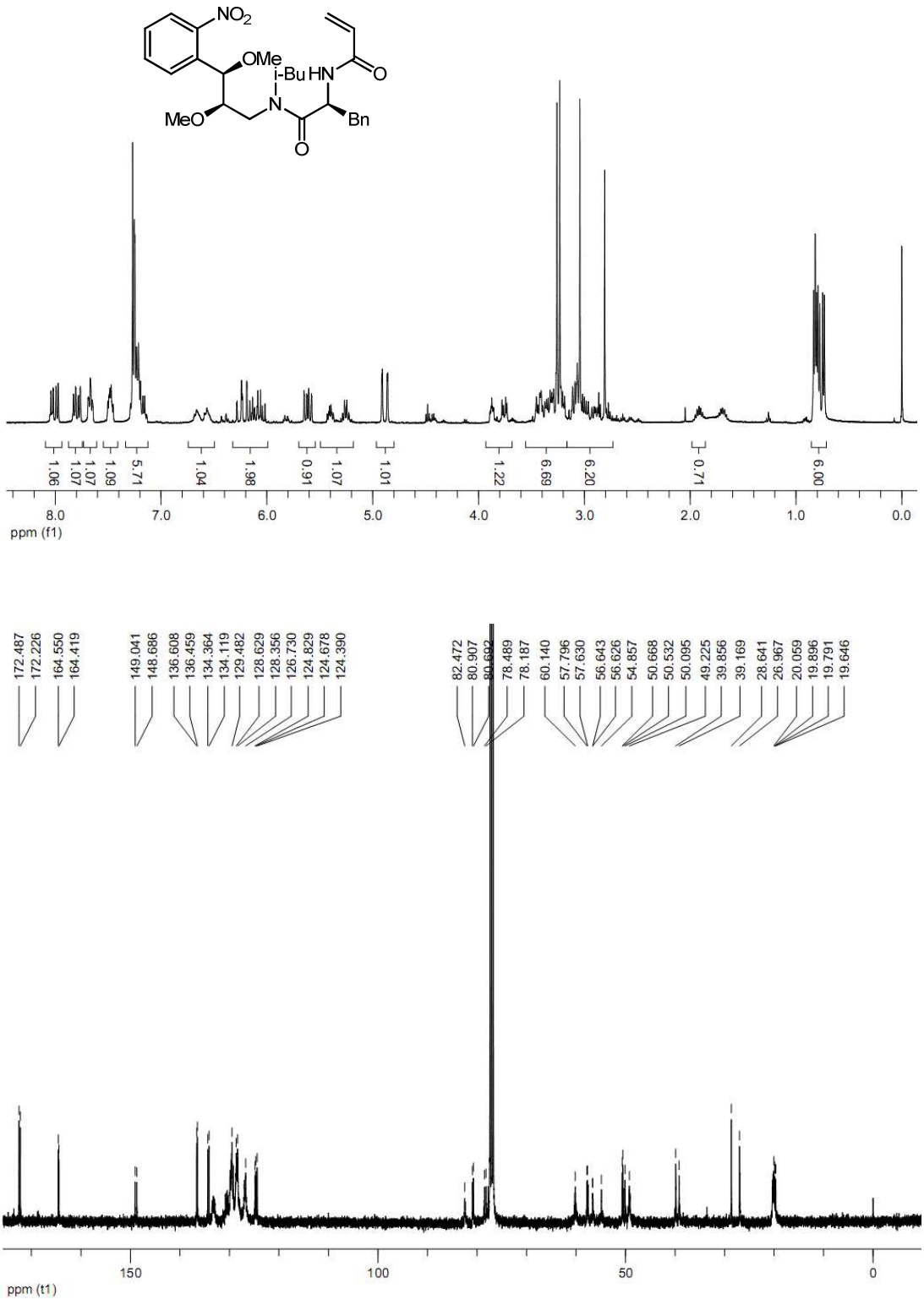
(30) (a) Kitambi, S. S.; Nilsson, E. S.; Sekyrova, P.; Ibarra, C.; Tekeoh, G. N.; Andang, M.; Ernfors, P.; Uhlen, P. *BMC Physiology* **2012**, *12*, 3. (b) Kitambi, S. S.; McCulloch, K. J.; Peterson, R. T.; Malicki, J. J. *Mech. Dev.* **2009**, *126*, 464. (c) Murphey, R. D.; Zon, L. I. *Methods* **2006**, *39*, 255.

(31) (a) Zhang, Q.; Li, Q.; Chen, Y.; Huang, X.; Yang, I. H.; Cao, L.; Wu, W. K.; Tan, H. M. *Front. Biosci.* **2012**, *4*, 2525. (b) Hao, J.; Ho, J. N.; Lewis, J. A.; Karim, K. A.; Daniels, R. N.; Gentry, P. R.; Hopkins, C. R.; Lindsley, C. W.; Hong, C. C. *ACS Chem. Biol.* **2010**, *5*, 245. (c) Vogt, A.; McPherson, P. A.; Shen, X.; Balachandran, R.; Zhu, G.; Raccor, B. S.; Nelson, S. G.; Tsang, M.; Day, B. W. *Chem. Biol. Drug Design* **2009**, *74*, 358.

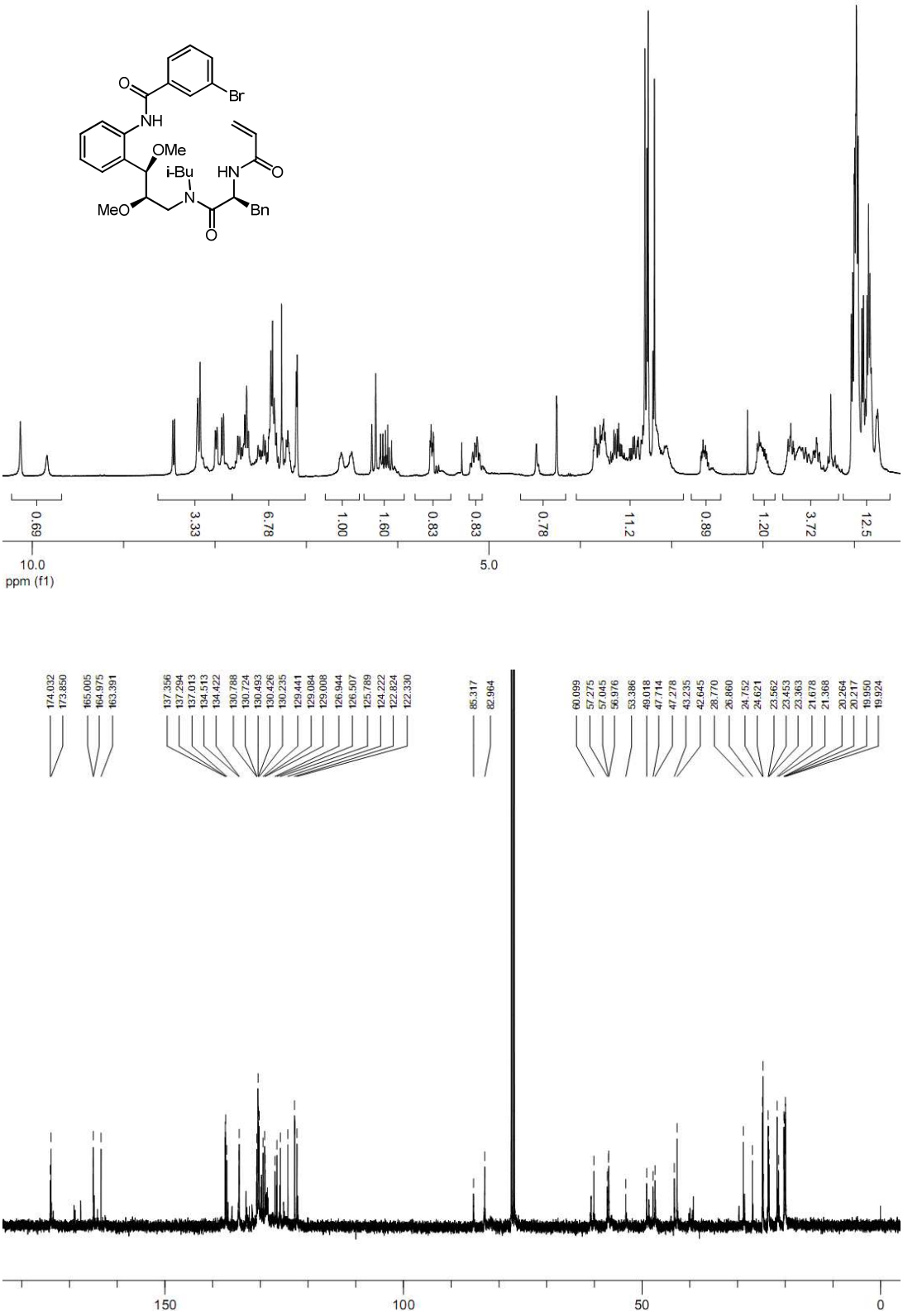
3.8. Spectra:



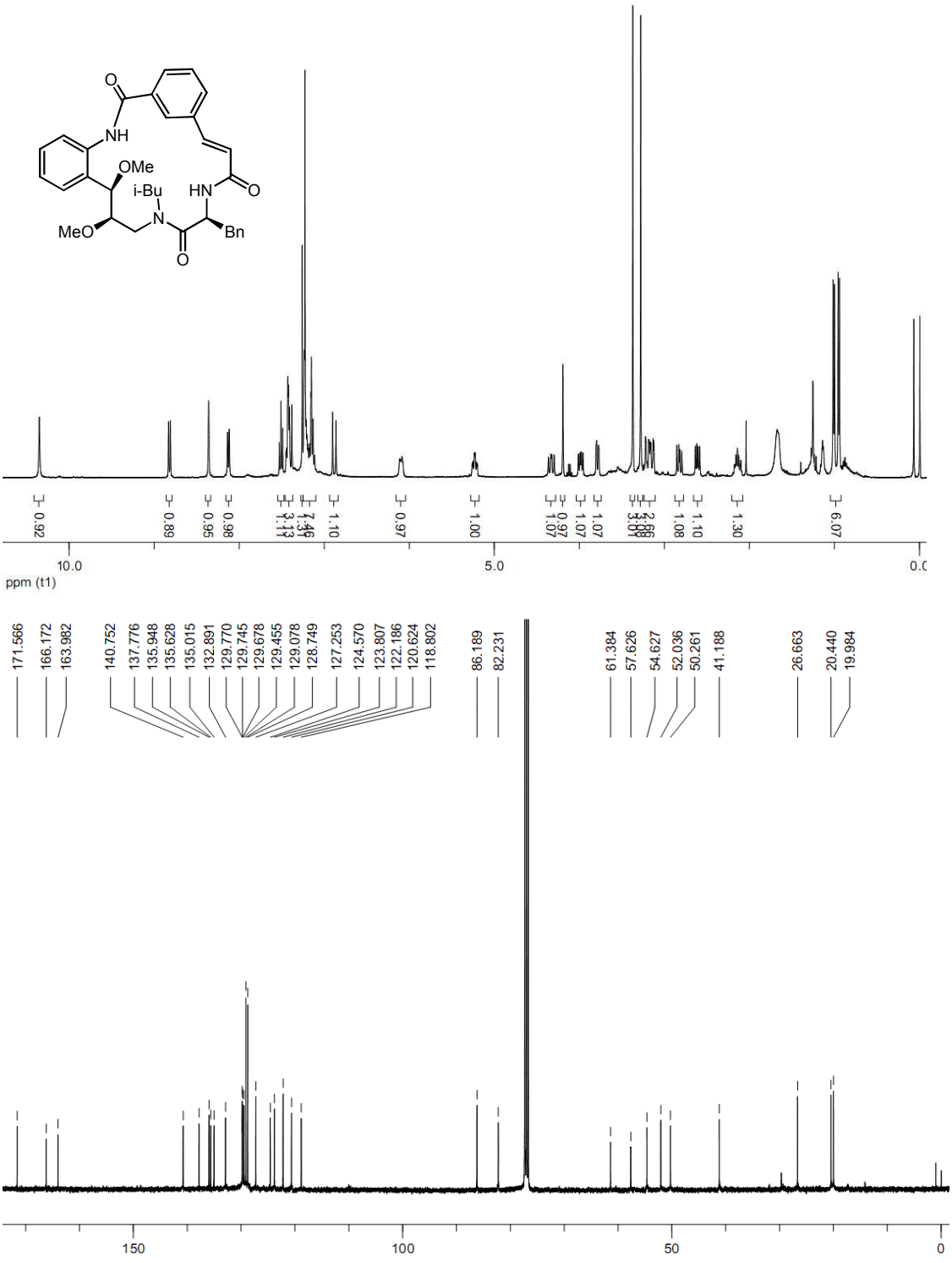
^{1}H and ^{13}C NMR of Compound **6.5**



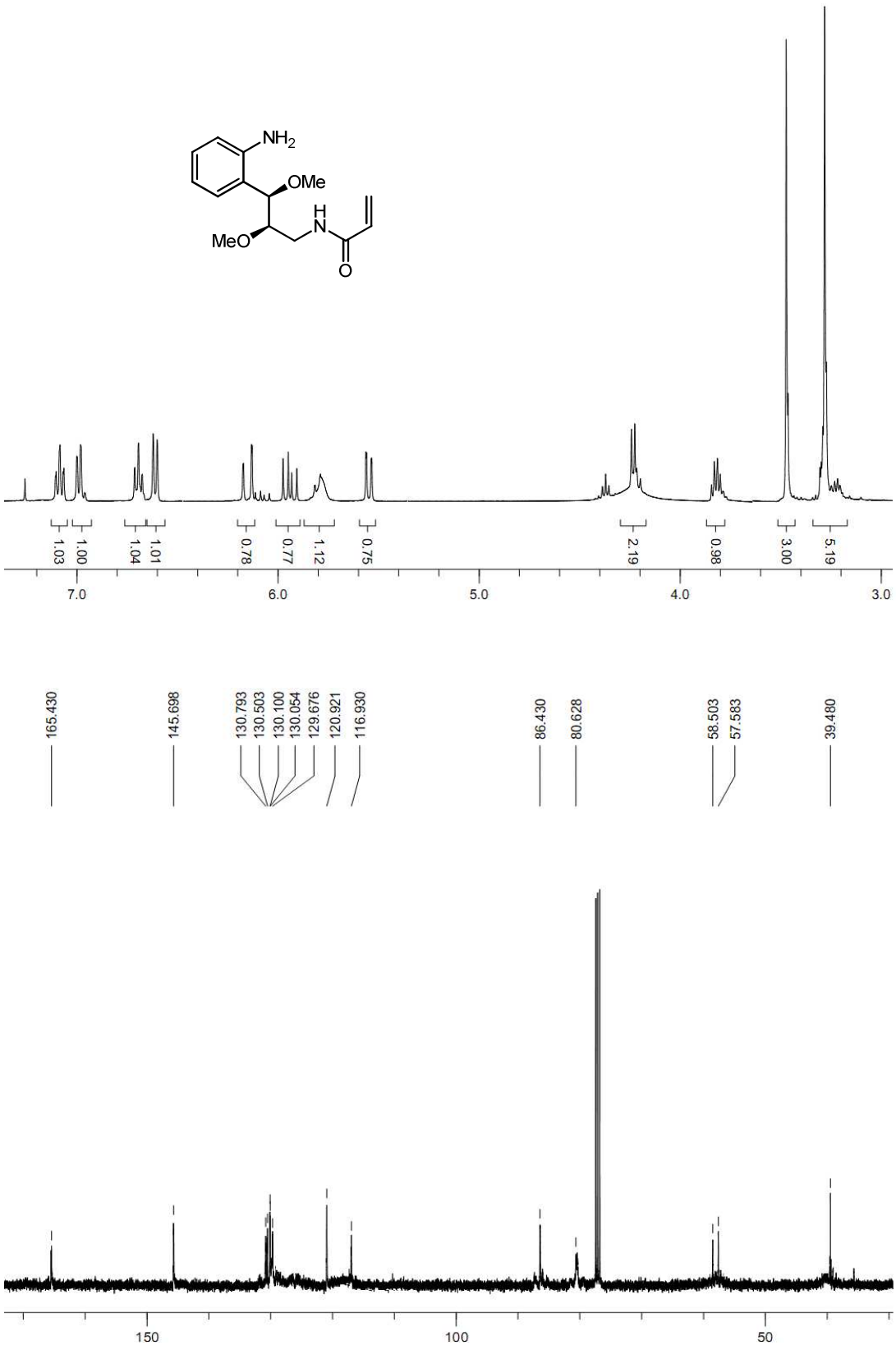
^{1}H and ^{13}C NMR of Compound **6.7b**



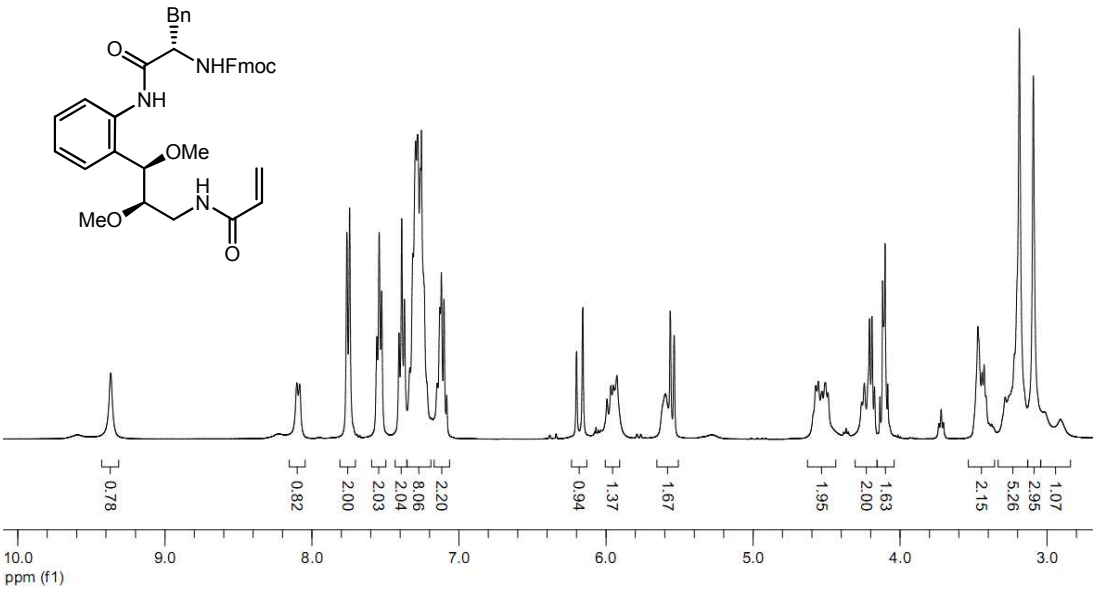
^{1}H and ^{13}C NMR of Compound **6.8b**

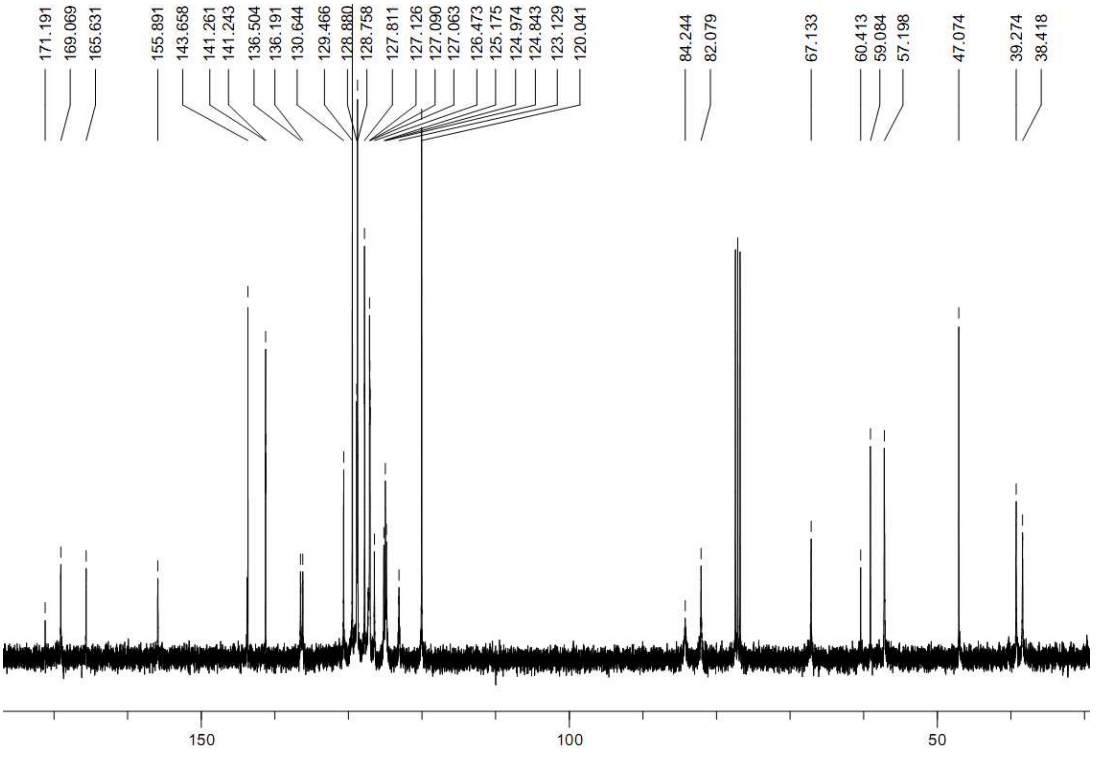


^{1}H and ^{13}C NMR of Compound **F2.1b**

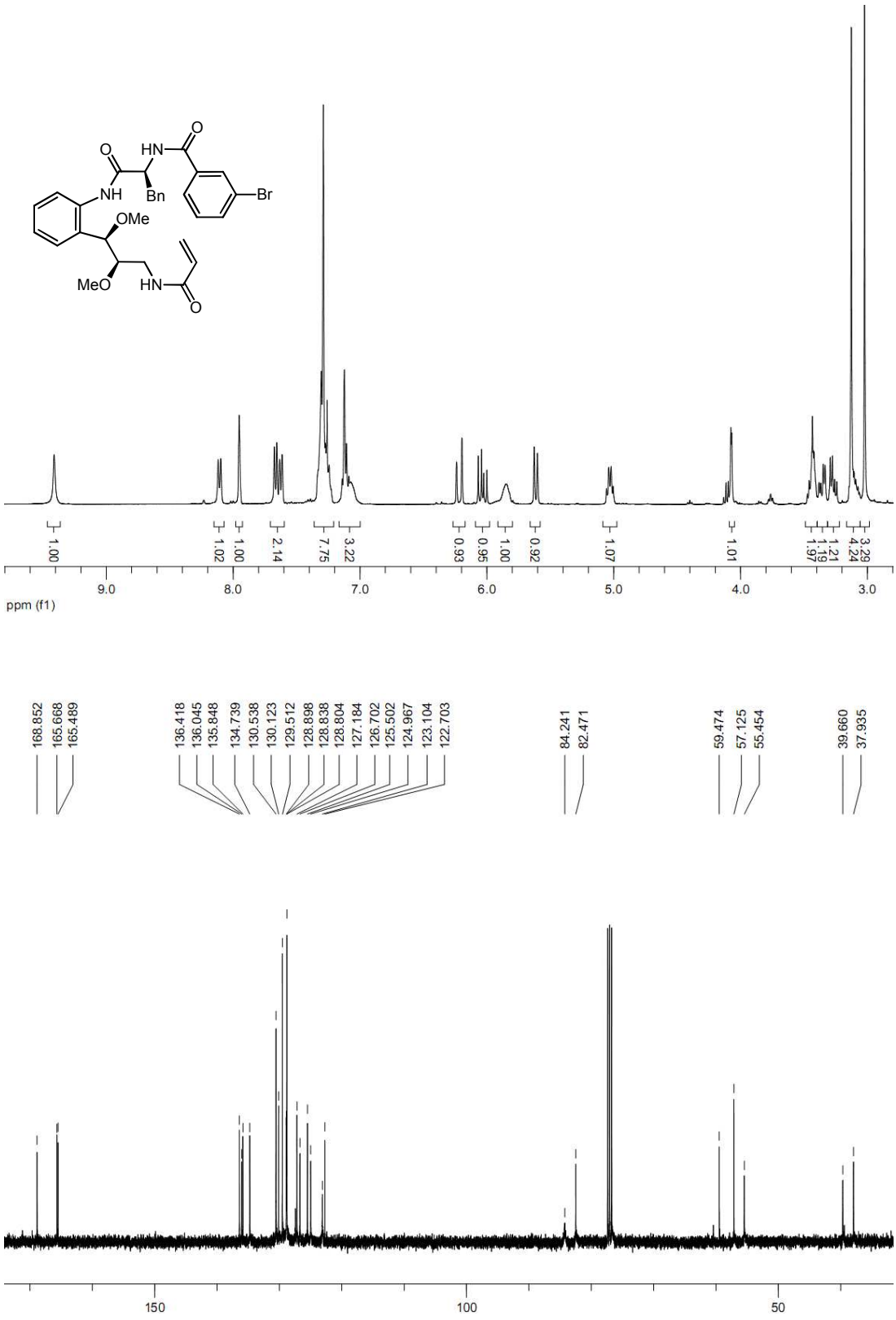


^{1}H and ^{13}C NMR of Compound **7.2**

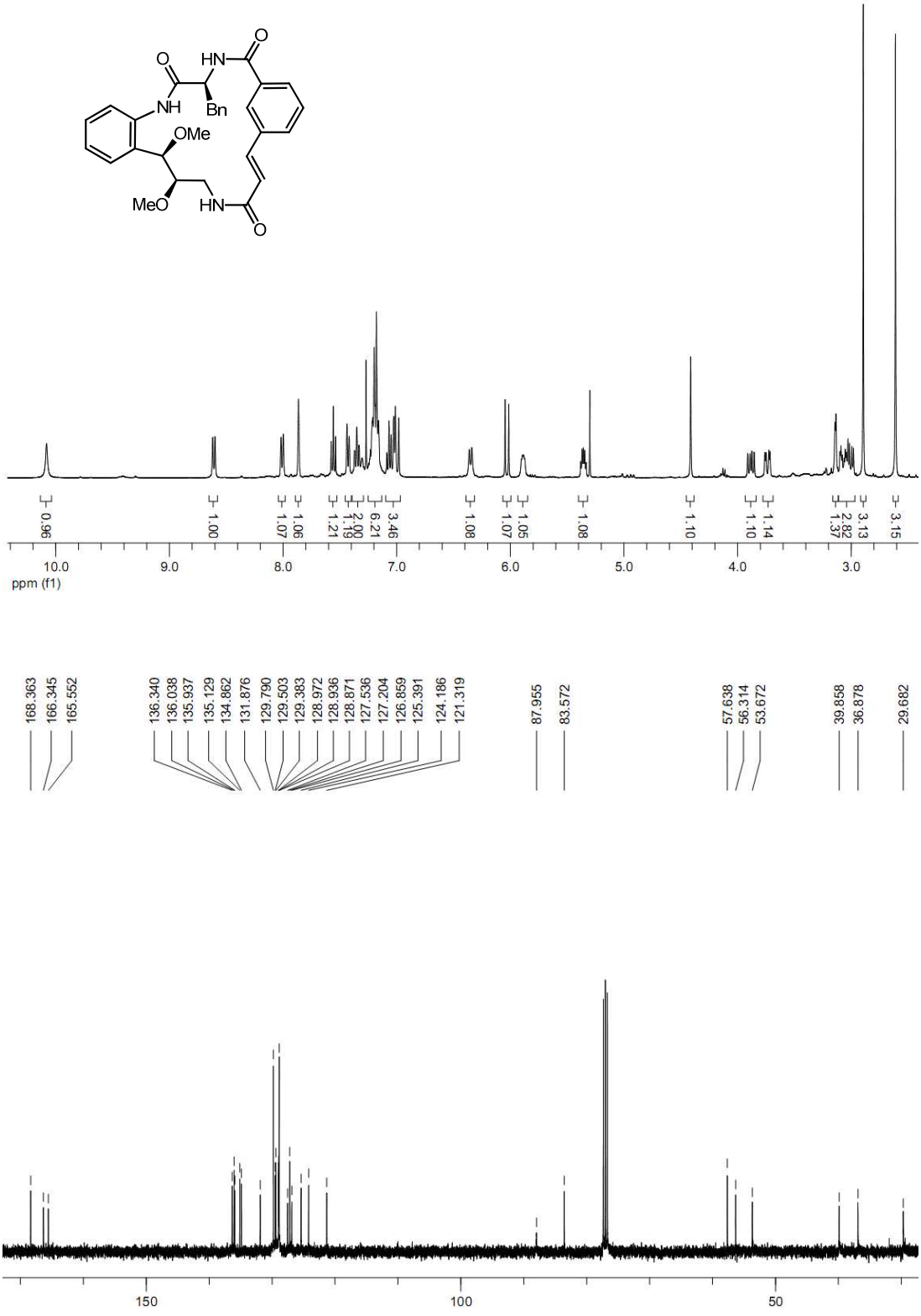




^{1}H and ^{13}C NMR of Compound **8.2b**



^{1}H and ^{13}C NMR of Compound **7.1b**



^{1}H and ^{13}C NMR of Compound **F2.2b**

Chapter 4: Literature Work on Latrunculins

4.1. Isolation and Biology of Latrunculins:

In 1975, Kashman et al. isolated a novel marine toxin from the red sea sponge *Negombata Magnifica* (formerly known as *Latrunculia Magnifica*) which was found to be toxic for fish.[1] Later, it was found that this toxin contains two closely related isomers, contaminated with glycerides.[2] The three pure toxins were separated named as latrunculin A, B and C. Extensive spectroscopic analysis and the X-ray crystal structure of the latrunculin A

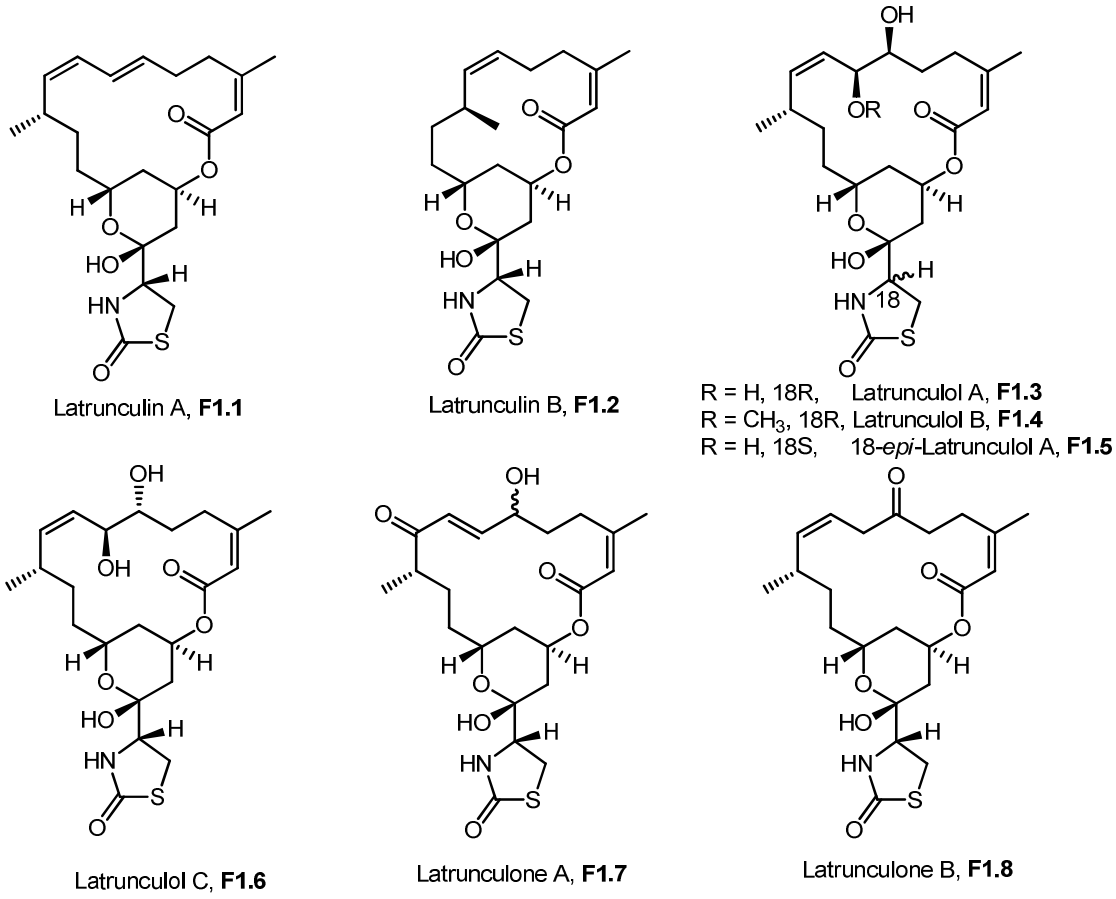


Figure1: Latrunculin family of compounds

derivative confirmed the structure of latrunculin A (**F1.1**) and B (**F1.2**) as 16 and 14-membered macrolides and latrunculin C (structure was not shown) is a stereo-isomer of latrunculin A. Latrunculins are the first marine natural products having 14 and 16-membered macrocyclic skeleton, as well as, the first natural products containing the rare thiazolidinone ring.[2] Spector et al. identified that submicromolar concentration of latrunculin A and B causes the morphological change in the mouse neuroblastoma (N1E-115) and fibroblast (3T3) cells.[3] Further studies with specific antibodies for actin and microtubules revealed that

latrunculins inducing a significant change in the microfilament dynamics without affecting the microtubules organisation, and, also identified that, the effect of latrunculins on cell morphology and actin disruption is reversible. Before identification of latrunculins, there is only class of molecules known to disrupt cellular process by specifically binding to microfilament organization are cytochalasins, [4] moreover, latrunculins are showing their effect concentration 1/10 to 1/100 of the cytochalasins. The rate of polymerization of pure actin was altered by cytochalasins, where as latrunculins did not show such effect, suggesting that site of action of these two molecules are different.

Compound **F1.1** was found to affect the polymerization of pure actin *in vitro* in a manner consistent with the formation of a nonpolymerizable 1:1 molar complex between **F1.1** and G-actin[5] with a dissociation constant for the reaction of about 0.2 pM.[6] These effects are very different from those of filament capping agents such as cytochalasins.[7] *In vivo*, they alter cell shape, disrupt microfilament organization, and, inhibit the microfilament-mediated processes of fertilization, and, an early development.

Mutation studies on actin are one of the best ways to determine the importance of actin dynamics and to know the binding site of actin regulatory proteins and drugs. Ayscough et al. conducted mutation studies to know binding site of **F1.1** on actin by taking the congenic collection of 23 mutant actins generated by charged-to-alanine mutagenesis scan of ACT1, the single, yeast conventional scan.[8] This collection was previously use to map binding site of phalloidin,[9] yeast fimbrin[10] and other interacting proteins[11] on actin. Halo assay was used to study at the sensitivity of latrunculin A towards all the strains. The affect of **F1.1** on each mutant allele was compared with wild type actin and this study identified that **F1.1** showing different effect on each allele. In a total collection of mutants, there are four strains which are resistant to **F1.1**. Act1-119, partially resistant and act1-112 (K213A, E214A, K215A), act1-113 (R210A, D211A) and act1-117 (R183A, D184A) exhibiting complete resistant to the **F1.1**. When they look at the mutations carried out in these alleles, all these mutations are clustered around the neucleotide binding cleft. These results suggests that these residues could be forming a direct hydrogen bond or salt bridge with the neucleotide, or form a salt bridge and bring other residues which themselves interact with neucleotide. Drubin and co-

workers[9] purified D157E actin and measured the rate of ATP exchange in the presence and absence of **F1.1**. This study concluded that the rate of ATP exchange was faster for D157E actin (t1/2 = 36 seconds) when compared to wild-type yeast actin (t1/2 = 100 seconds). Treating wild-type yeast actin with 10 µM of **F1.1** caused complete inhibition of ATP exchange but had no effect on the ATP exchange rate of D157E actin. For comparison, they performed the similar experiment on purified G158A actin (t1/2=250 seconds), and found that ATP exchange was inhibited completely by 10 µM of **F1.1**. These mutation experiments suggested that D157E mutation disrupting the binding site of latrunculin A, and, this is also supported by an observation that D157 lays in close proximity to other residues whose mutation result in **F1.1** resistance.

4.2. X-ray crystal structure of Latrunculin A with G-actin:

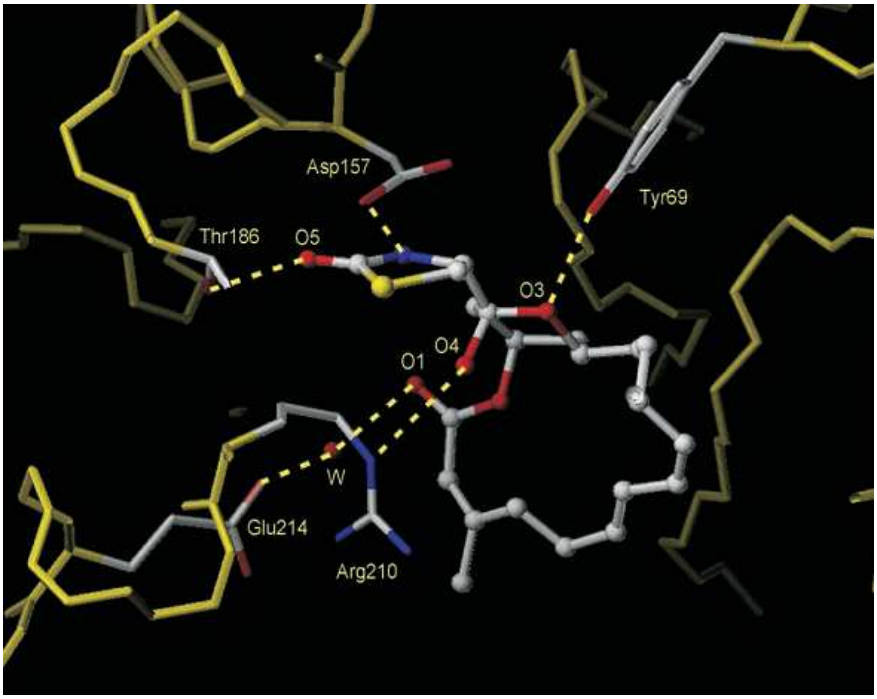


Figure 2: X-ray crystal structure of latrunculin A bound with G-actin (ref. 12)

The co-crystal structure of latrunculin A (**F1.1)** with actin protein was obtained by McLaughins and co-workers in 2000.[12] Actin not known to be crystallizes in the absence of its binding proteins. There are three known examples of such binding proteins; (i) profilin known to increase the rate of nucleotide exchange, so it is unsuitable, (ii) deoxyribosenuclease1 binds to the latrunculin binding domain, which was observed from the yeast genetics studies, and (iii) gelosin domain 1

binds with actin by leaving all other domains free.[13] Therefore **F1.1** was crystallized with the actin in the presence of its binding protein gelosin domain 1. Refinement of the X-ray crystal structure of latrunculin with actin showed that binding site was located between the subdomains II and IV, which was just above to the nucleotide binding site. All the polar atoms forming a hydrogen bonding with actin either directly or through the salt bridge, except, one of the lactone oxygen. The rare thiazolidinone ring nicely fit into the deep pocket, latrunculin forming hydrogen bonds with Tyr69 in subdomain II, Thr186 and Arg210 in subdomain IV as well as Asp157 in subdomain III. This model revealed that latrunculin could be preventing the nucleotide exchange by forming a bridge between subdomains II and IV.

4.3. Literature Synthesis of Latrunculins:

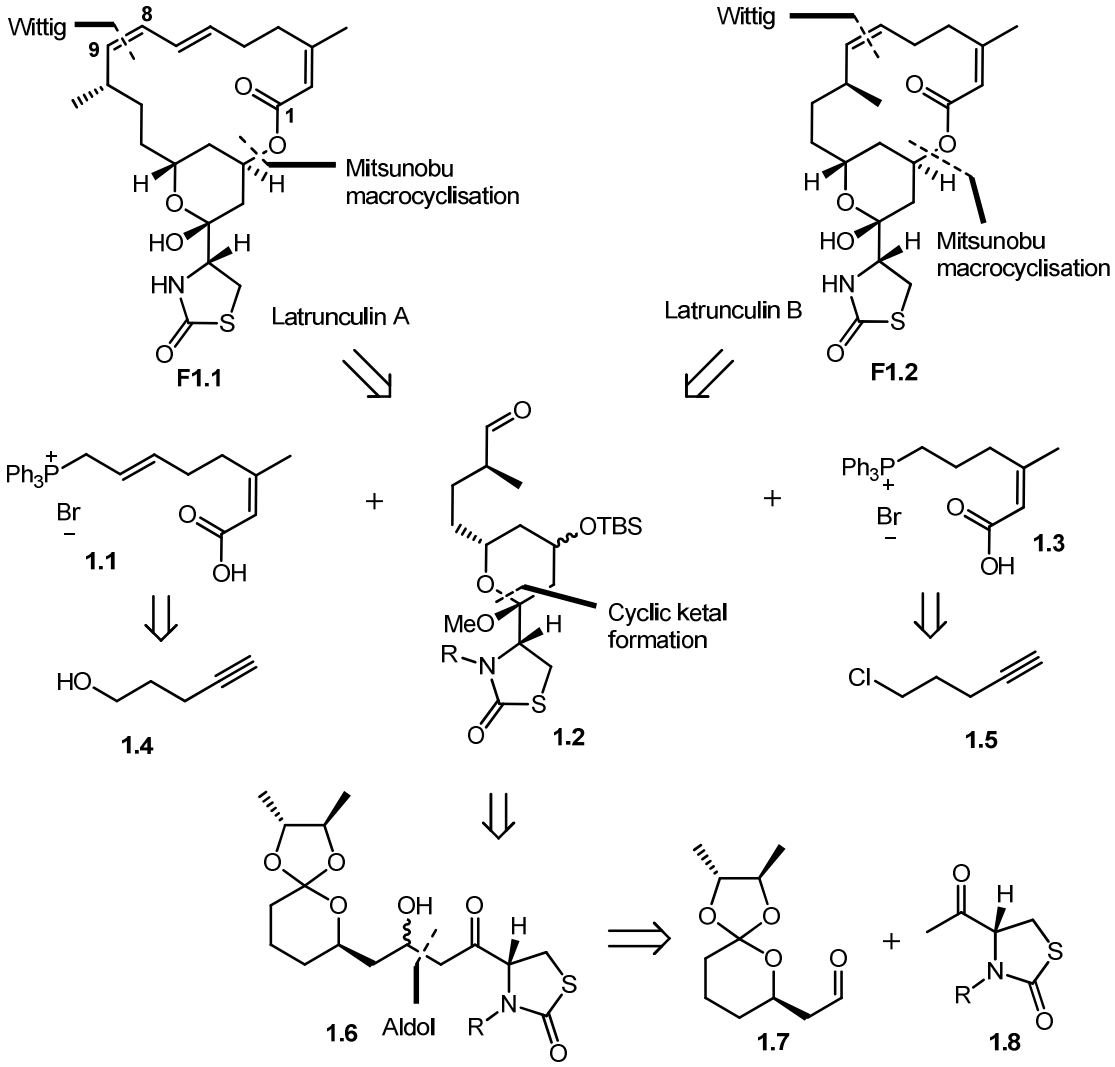
There are three major groups working on the synthesis of latrunculin family of compounds. Amos B. Smith III from university of Pennsylvania, James D. White from Oregon state university and Alois Furstner from Max-Planck Institute, Germany.

4.3.1 Smith III Approach:

The first total synthesis of latrunculin B (**F1.2**) was reported by his group in 1986[14] and latrunculin A in 1990[15] followed by 18-*epi*-latrunculol A in 2013.[16]

Retrosynthesis of Latrunculin A and B:

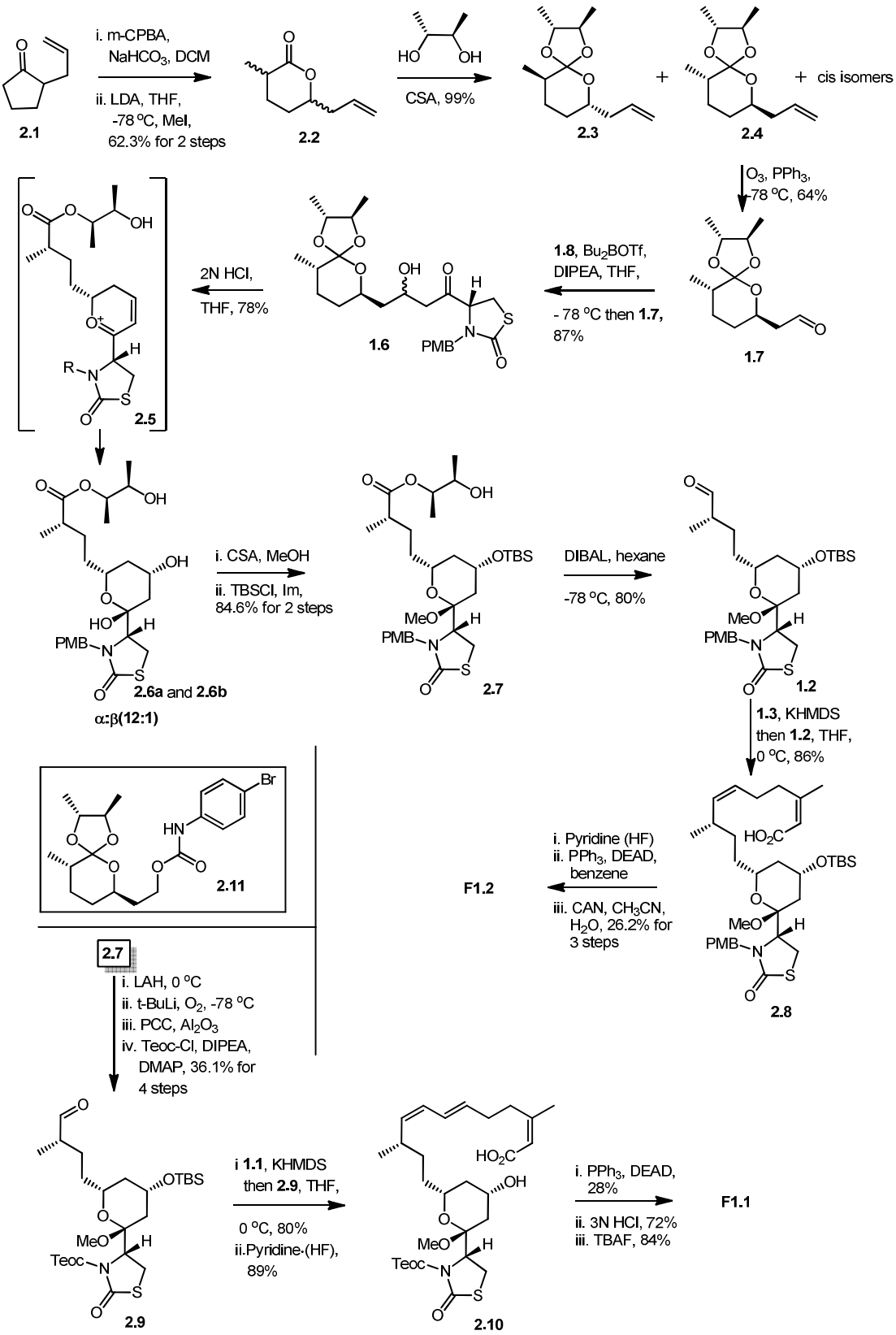
The retrosynthetic analysis of **F1.1** and **F1.2** was shown in **Scheme 2.**[15] The key steps involved in the synthesis are macrolactonization using Mitsunobu reaction and synthesis of a *cis* olefin between C8 and C9 using wittig olefination of the two fragments tetrahydropyaran (**1.2**) and the Wittig reagent (**1.1/1.3)**. The fragment **1.2** could be obtained from an aldol reaction between the methyl ketone **1.8** and aldehyde **1.7**. Wittig reagents **1.1** could be obtained from alkyne **1.4** and **1.3** from **1.5**.



Scheme 1: Retrosynthetic analysis of latrunculin A and B (Amos B. Smith III and co-workers)

Synthesis of Latrunculin A and B:

The synthesis of aldehyde **1.7** started with 2-allylcyclopentanone **2.1**, upon Baeyer-Villiger oxidation to give lactone followed by methylation of in α-postion with LDA and MeI, furnished (±)-**2.2** as a mixture of 1:1 diastereomers.[15] The resolution and equilibration of lactone **2.2** with (+)-(*R*,*R*)-2,3-butanediol resulted in the 6:1 mixture of trans:cis isomers. The absolute stereochemistry of **2.4** was assigned based on the single X-ray



Scheme 2: Synthesis of latrunculin A and B (Smith III and co-workers)

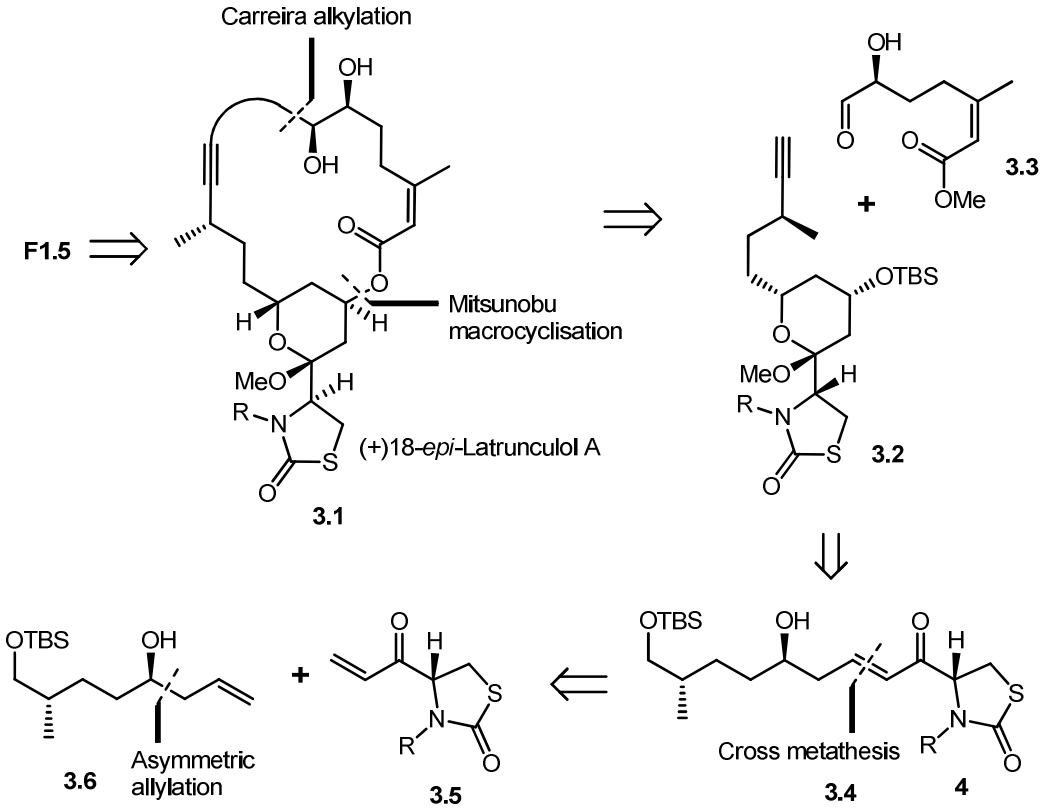
crystal structure[15] of its *p*-bromophenyl carbamate derivative **2.11.** Ozonolysis of alkene **2.4** furnished the aldehyde **1.7** for the aldol reaction. The methyl ketone **1.8**

was obtained from L-cystein hydrochloride. The aldol reaction between **1.8** and **1.7** under Bu_2BOTf and DIPEA condition resulted in the 4:1 (α:β) inseparable epimeric mixture of the aldol product.[15] Hemiacetalization under 2N HCl in THF (1:5) condition gave 12:1 mixture of separable mixture of α (**2.6a**) and β (**2.6b**) via formation of oxonium ion **2.5**. Methyl acetal formation under CSA/MeOH condition and protection of secondary alcohol with TBS followed by reduction of ester with DIBAL resulted in the aldehyde **1.2**. Compound **F1.2** was obtained from **1.2** in four steps; first the dianion generated from the **1.3** was coupled with the aldehyde **1.2** to give *cis* wittig product **2.8** and then deprotection with TBS.

In the case of **F1.1** removal of PMB group in the final step, leads to decomposition of the product, because of the sensitive diene moiety. To overcome this circumstance the PMB protecting group was replaced with Teoc in the early stage of the synthesis. Methyl acetal **2.7** was subjected to LAH reduction, *t*-BuLi, O_2 condition to remove PMB protection then Moffatt oxidation of primary alcohol to aldehyde followed by protection of carbamate NH with Teoc to give aldehyde **2.9**. Witting coupling of dianion derived from **1.1** with **2.9** gives the cis olefin followed by the deprotection of TBS group gives compound **2.10**,[15] which was then subjected to the Mitsunobu macrocylization followed by the deprotection of Teoc and methyl acetal resulted in **F1.1**.

Retrosynthesis of (+)-18-*epi*-Latrunculol A:

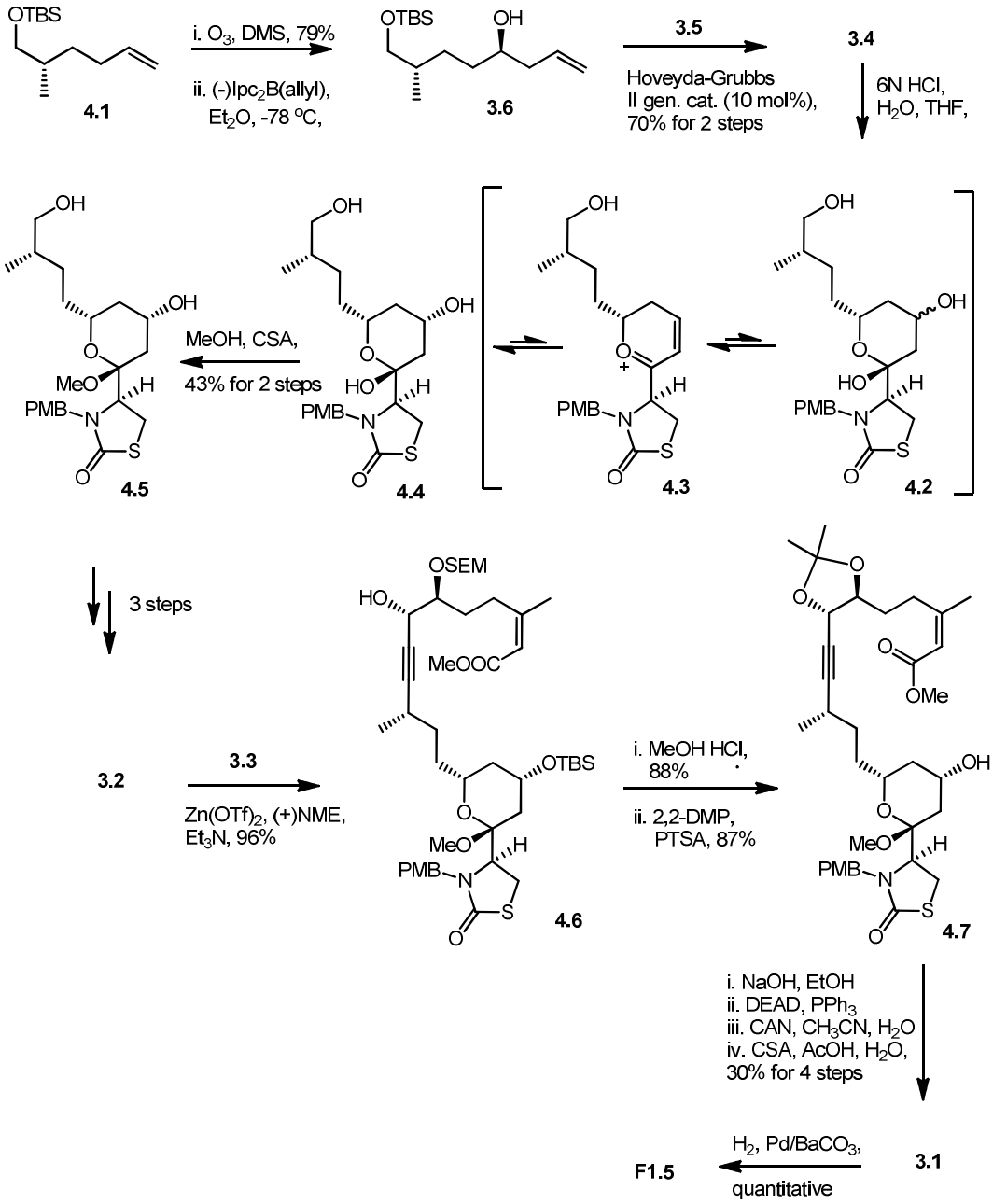
The (+)-18-*epi*-latrunculol A (**F1.5**) differ from the latrunculin A by the replacement of an *E*-olefin with 1,2-diol and the stereocenter at the 18 position in thiazolidinone ring by *S*-configuration. Retrosynthetic analysis of **F1.5** was shown in **Scheme 3.**[16] Macrocyclization strategy for this molecule is similar to latrunculin A, but the construction the double bond was carried out by partial reduction of alkyne from the compound **3.1**. Macrocyclic precursor **3.1** could be obtained from Carreira alkynylation of terminal alkyne **3.2** and aldehyde **3.3**. Alkyne **3.2** would be obtained from α,β-unstaurated carbony compound **3.4**, which could be obtained from cross coupling between vinylkeone **3.5** drived from the *S*-cysteine and homoallylic alcohol **3.6**.



Scheme 3: Retrosynthetic analysis of (+)-18-*epi*-latrunculol A (Amos B. Smith III and co-workers)

Synthesis of (+)-18-*epi*-Latrunculol A:

The homoallylic alcohol **3.6** was obtained from the olefin **4.1** in two steps, ozonolysis followed by the Brown asymmetric allylation. Cross metathesis between **3.6** and vinyl ketone **3.5** resulted in the α,β-unstaurated carbonyl compound **3.4**,[16] which was subjected to acid catalyzed hemiacetalization with 6N HCl. This gives the hemiacetal **4.4** as a single diasteromer, which could be obtained via intermediates **4.2** and oxonium ion **4.3**. Methanolysis of **4.4** in the presence of CSA yielded methyl acetal **4.5**. Terminal alkyne **3.2** was obtained from the **4.5** in three steps, which was subjected to the carreira alkynylation with aldehyde **3.3** derived from the *S*-malic acid to give propargyl alcohol **4.6** as a single diastereomer. Semihydrogenation experiments on **4.6** with either Lindlar or P-2 nickel catalysts met with failures, this could be reasoned by a possible steric hinderence. To look at the steric interaction they conducted MM2 modeling studies, and further observed that



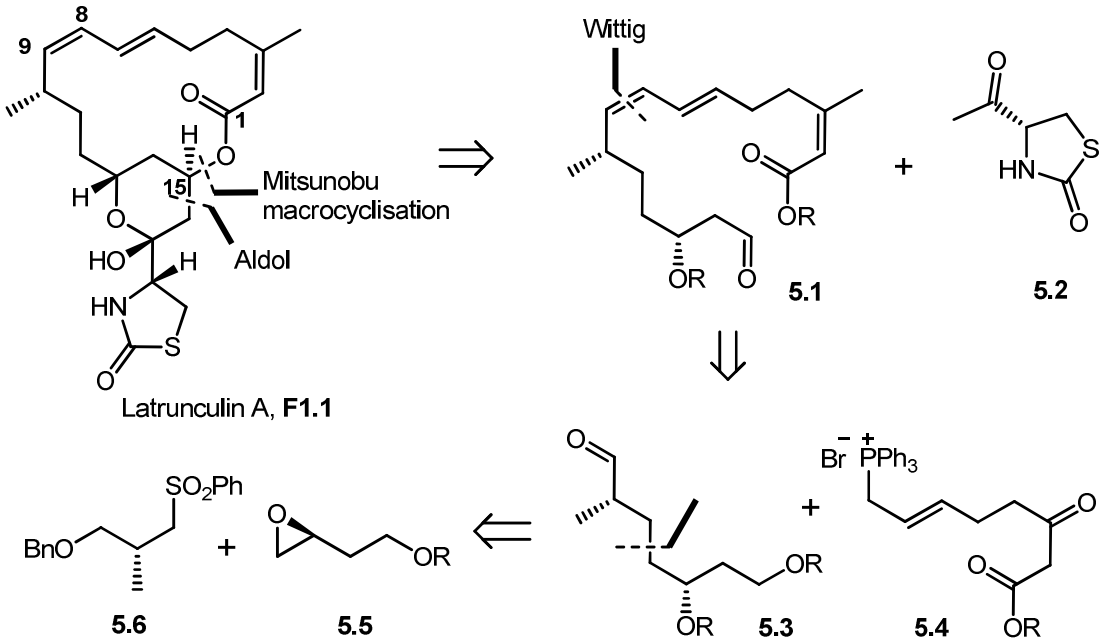
Scheme 4: Synthesis of (+)-18-*epi*-latrunculol A (Smith III and co-workers)

ester group in **4.6** was pre-organized for mitsunobu macrocyclization.[16] Next, they deprotected the SEM group and protected 1,2-diol with 2,2-dimethoxy propane to give **4.7**. Hydrolysis of ester sodium hydroxide then Mitsunobu macrocyclization followed by deprotection of the PMB group and methyl acetal yielded **F1.5** precursor **3.1**. Subjecting **3.1** for semihydrogenation by using Lindlar catalyst smoothly furnished the **F1.5**.

4.3.2. White Approach:

The total synthesis of **F1.1** was accomplished by White and co-workers in 1990.[17] In this synthesis, the researchers designed a novel strategy to synthesize *E,Z*-diene via one pot three component reaction. This strategy enables the synthesis of major part of the macrocyclic core.

Retrosynthesis of Latrunculin A:



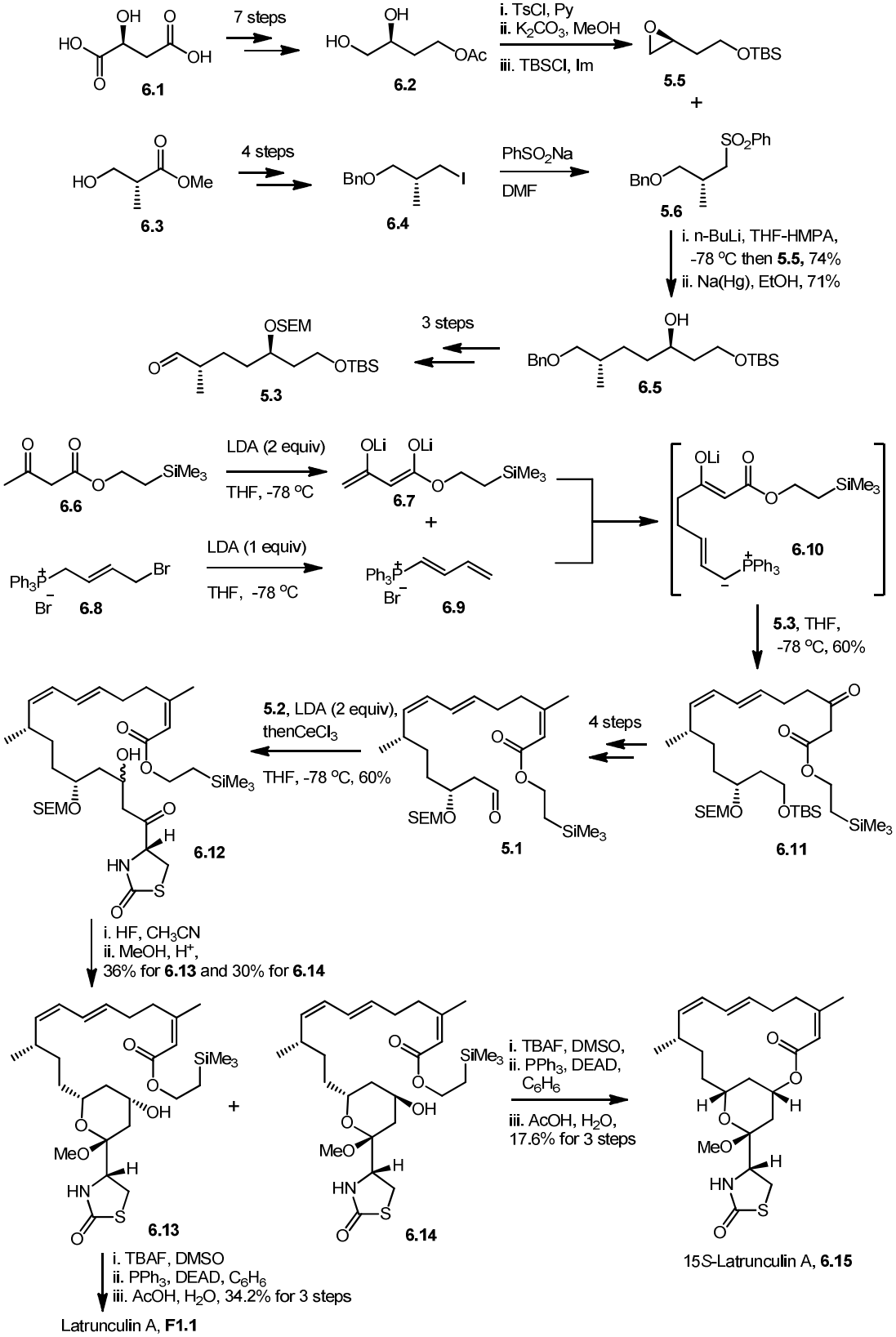
Scheme 5: Retrosynthetic analysis of latrunculin A (James D. White and co-workers)

The retrosynthetic analysis is shown in **Scheme 5**. The macrocyclization would be carried out by Mitsunobu reaction and C-15 hydroxyl group would obtained by the aldol reaction between aldehyde **5.1** and methyl ketone **5.2**. Aldehyde **5.1** could be obtained from Wittig reagent **5.4** and aldehyde **5.3**, which could be obtained from epoxide **5.5** and sulfone **5.6**.

Synthesis of Latrunculin A:

The epoxide **5.5** was obtained from 1,2-diol **6.2** (synthesized from S-malic acid **6.1** in 7 steps) in three steps, tosylation of primary alcohol then treating with K_2CO_3 in methanol to give epoxide and free primary hydroxyl followed by the protecting

with TBS.[17] The sulfone **5.6** was obtained by treating the phenyl sulfone with alkyl iodo compound **6.4**, which was synthesized from corresponding ester **6.3** in four steps. Coupling of sulfone **5.6** with epoxide **5.5** under n-BuLi condition then reductive cleavage of the sulfone gives the secondary alcohol **6.5**. Aldehyde **5.3** was obtained from **6.5** in three steps. The dianion **6.7**[17] was generated from β-ketoester **6.6** by treating with LDA coupled with the dienylphosphonium reagent **6.9** generated from the **6.8** by treating with LDA gives the intermediate **6.10**, addition of aldehyde **5.3** to the same pot furnished the cis wittig product **6.11**. The aldehye **5.1** was obtained from the **6.11** in four steps. The enolate was generated from methyl ketone **5.2** by using two equivalents of LDA and $CeCl_3$ then added to the aldehyde **5.1** furnished the aldol product **6.12** as a 1:1 diastereomeric mixture in a good yield.[17] This reaction has an advantage over the Smith synthesis[15] because, in case of Smith synthesis it was protected with PMB, which would, became problematic to remove in the final stage because of sensitive diene moiety where as this synthesis, no protection group was used for carbamate NH in **5.2**, thus, it also avoids protection and deprotection steps . The removal of SEM protection and methonolysis of **6.12** gives the two separable diastereomers of methyl acetal **6.13** (α-OH) and **6.14** (β-OH). **F1.1** was obtained from **6.13** in three steps, first hydrolysis of ester with TBAF then Mitsunobu macrocyclization followed by acid hydrolysis of methy acetal. 15-epi-latrunculin A was obtained from **6.14** following the similar steps.[17]

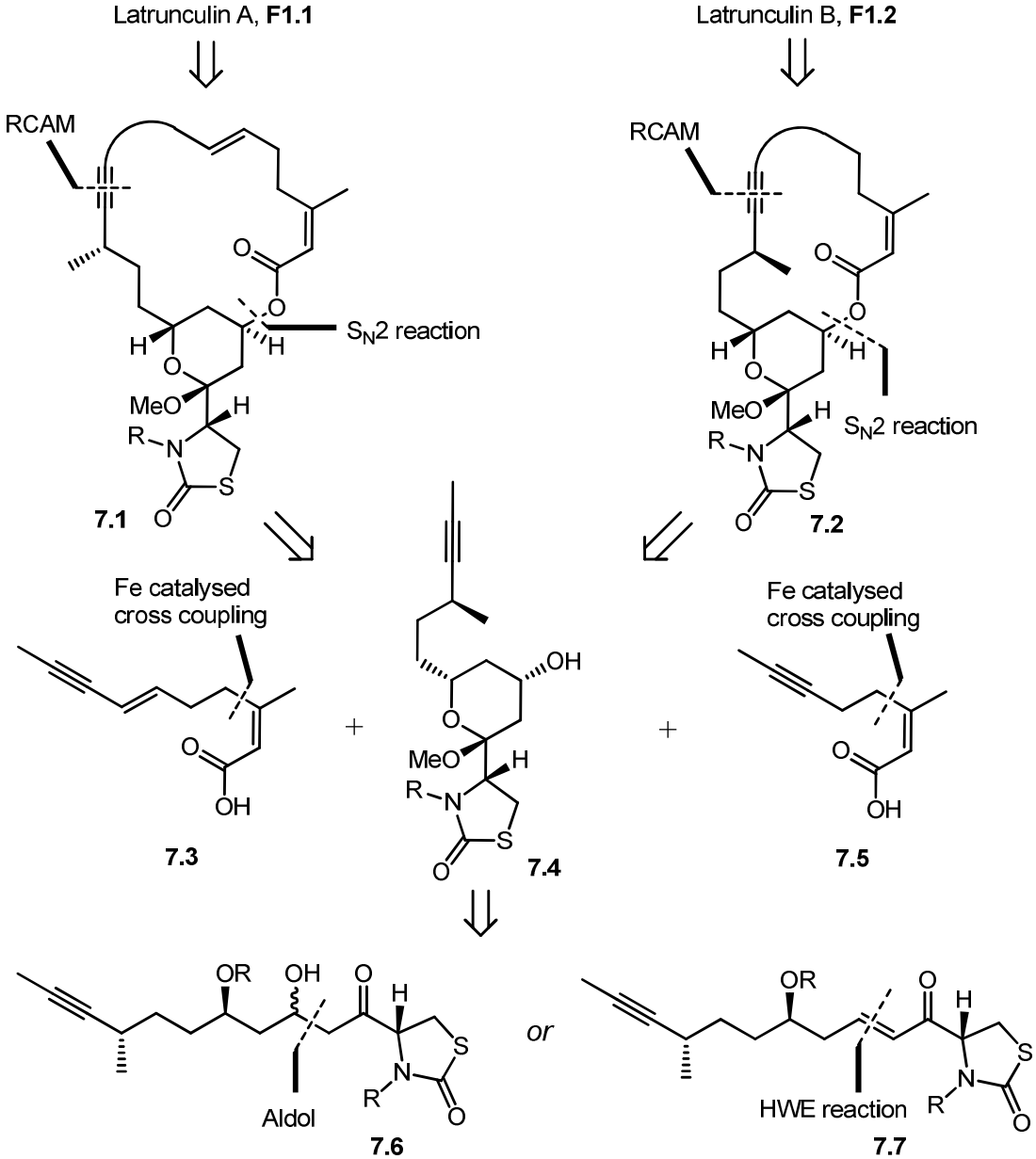


Scheme 6: Synthesis of latrunculin A (White and co-workers)

4.3.3. Fuerstner Approach:

In 2003, Fuerstner and co-workers reported the total synthesis of **F1.2**[18] followed by the **F1.1** in 2005.[19] In this synthesis, the team used ring closing alkyne metathesis (RCAM) as key strategy for macrocyclization,[20] which could be further reduced to a *cis* olefin by Lindlar catalyst.

Retrosynthesis of Latrunculin A and B:



Scheme 7: Retrosynthetic analysis of latrunculin A&B (Furstner and co-workers)

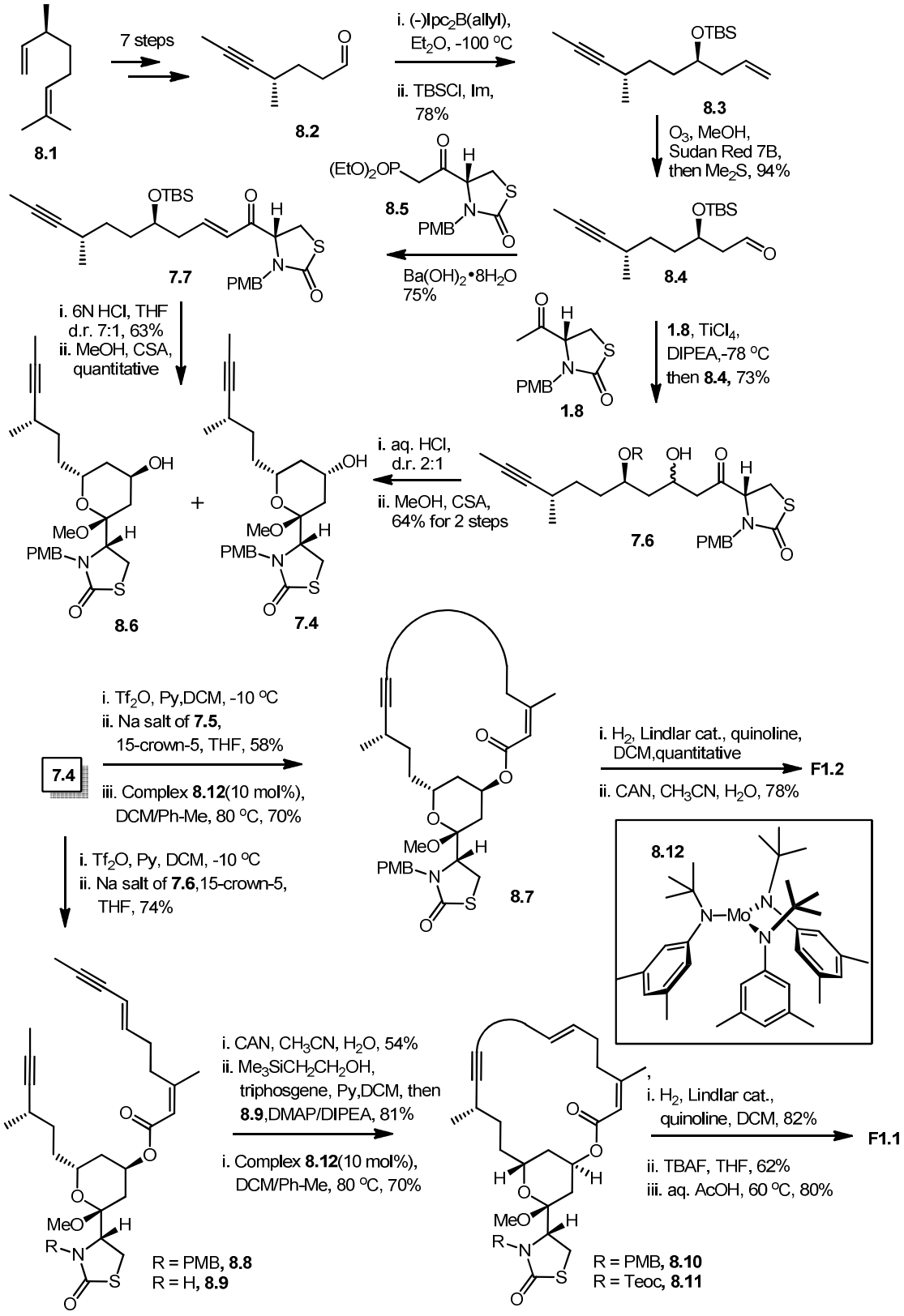
The retrosynthetic analysis of **F1.1** is shown in **Scheme 7**.[19] Latrunculin A and B precursors **7.1** and **7.2** would be obtained by alkyne metathesis, which could be obtained from coupling of a common intermediate **7.4** with **7.3** for latrunculin A

and **7.5** for latrunculin B. The alkyne **7.4** could be obtained from the aldol product **7.6** or α,β-unsaturated carbonyl compound **7.7** obtained from Wittig reaction.

Synthesis of Latrunculin A and B:

In this synthesis C(10) methyl group stereochemistry was brought from the *S*-citronellene **8.1**, aldehyde **8.2** was obtained from **8.1** in seven steps.[19] Brown asymmetric allylation of **8.2** followed by protection of secondary alcohol with TBS gave the compound **8.3**. This was subjected to ozonolysis to give aldehyde **8.4**. The methy acetals **8.6** and **7.4** were obtained from **8.4** in two ways. (i) Wittig reaction[19] of aldehyde **8.4** with Wittig reagent **8.5** in presence of activated $Ba(OH)_2 \cdot 8H_2O$ to give α,β-unsaturated carbonyl compound **7.7,** which was subjected to acid catalyzed cyclization followed by methanolysis gave the methyl acetals **8.6** and **7.4** in 1:7 ratio. (ii) The aldol reaction of titanium enolate generated from methyl ketone in the presence of $TiCl_4$ and DIPEA with aldehyde **8.4** gave the aldol product **7.6**, which was subjected acid catalyzed cyclization followed by methanolysis gave the methyl acetals **8.6** and **7.4** in 1:2 ratio.[19] Latrunculin B was obtained from **7.4** in five steps,[19] (i) triflation of sendary alcohol with Tf_2O, (ii) SN^2 displacement of OTf with sodium salt of **7.5** in presence of 15-crown-5, (iii) ring closing alkyne metathesis by using Mo catalyst **8.12** to give **8.7**, (iv) semihydrogenation of alkyne to alkene in the presence of Lindlar catalyst, and (v) removal PMB group and hydrolysis of methyl acetal with CAN in acetonitrile and water.

It was already known from Smith III total synthesis of **F1.1**,[15] the final step of PMB removal leads to decomposition of product due to sensitive diene moiety. The similar thing was happening in the case with enyne **8.10**, and this resulted in the decomposition of the product. Now, the change in the protecting group was needed, so they decided to exchange the protecting group in the RCAM precursor **8.8**. PMB group was replaced with the Teoc group in two steps, deprotection PMB with CAN



Scheme 8: Synthesis of latrunculin A and B (Fuerstner and co-workers)

followed by Teoc protection using trimethylsilylethanol and triphosgene. This was subjected to RCAM by using Mo catalyst[20] to gives the compound **8.11**. **F1.1** was obtained from **8.11** in the three steps, semihydrogenation of alkyne to alkene in the

presence of Lindlar catalyst and removal Teoc group by TBAF followed by hydrolysis of methyl acetal with acetic acid.

From the X-ray crystal structure of **F1.1** with actin protein,[12] it was anticipated that pyran and cystein moiety were important for the biological property as they involved in the hydrogen bonding network with the actin. Furstner *et al.* conducted the SAR studies to know the importance of macrocyclic skeleton,[21] sulfur atom and C(16) chiral center. To test this, they synthesized different analogues (**F3.1-F3.12**) of latrunculin A and B shown in Figure3. In case of **F3.1** to **F3.6** methyl group at C(4) position was chapped out and in **F3.5** and **F3.6** sulfur atom replaced with oxygen. **F3.9** to **F3.11** are the open chain analogues of latrunculin A and B and also in case of **F3.9** thaizolidinone ring replaced with hydroxy thiazole group. The compound **F3.12** is the only macrocyclic core of **F1.2**. This small library of compounds was evaluated to determine their acting binding properties by

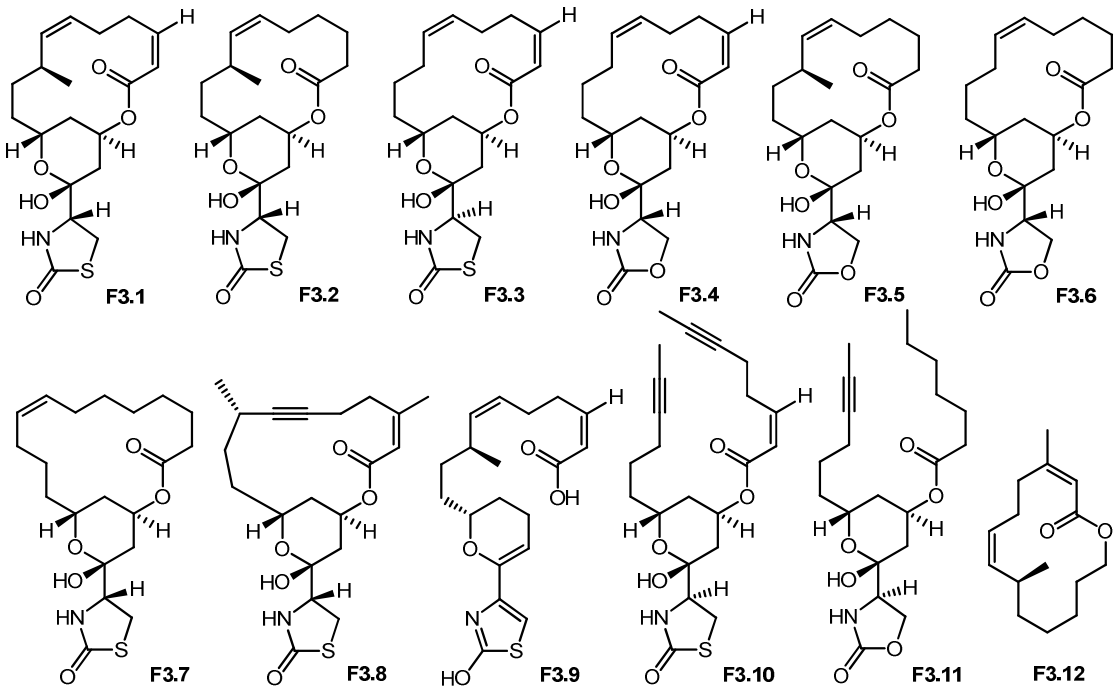


Figure 3: Latrunculin A and B analogs

using NIH3T3 fibroblast cell line and identified that the entire compound showing microfilament disrupting effect at 10 μM concentration except two compounds, one is open chain precursor **F3.9** and another is only macrolactone core **F3.12**. One

of the **F1.2** analog **F3.3** was found to be more potent compared to its parent compound **F1.2** and the potency of this molecule almost equals to the **F1.1**.

4.4. References:

(1) Neeman, I.; Fishelson, L.; Kashman, Y. *Mar.Biol.* **1975**, *30*, 293.

(2) Kashman, Y.; Groweiss, A.; Shmueli, U. *Tetrahedron Lett.* **1980**, *21*, 3629.

(3) Spector, I.; Shochet, N. R.; Kashman, Y.; Groweiss, A. *Science* **1983**, *219*, 493.

(4) Flanagan, M. D.; Lin, S. *J. Biol. Chem.* **1980**, *255*, 835.

(5) Spector, I.; Shochet, N. R.; Blasberger, D.; Kashman, Y. *Cell Motil. Cytoskel.* **1989**, *13*, 127.

(6) Coué, M.; Brenner, S. L.; Spector, I.; Korn, E. D. *FEBS Lett.* **1987**, *213*, 316.

(7) Brenner, S.; Korn, E. *J. Biol. Chem.* **1979**, *254*, 9982.

(8) (a) Ayscough, K. R.; Stryker, J.; Pokala, N.; Sanders, M.; Crews, P.; Drubin, D. G. *J. Cell Biol.* **1997**, *137*, 399. (b) Belmont, L. D.; Patterson, G.; Drubin, D. G. *J. Cell Sci.* **1999**, *112*, 1325.

(9) Drubin, D. G.; Jones, H. D.; Wertman, K. F. *Mol. Biol. Cell* **1993**, *4*, 1277.

(10) Holtzman, D. A.; Wertman, K. F.; Drubin, D. G. *J. Cell Biol.* **1994**, *126*, 423.

(11) Amberg, D. C.; Basart, E.; Botstein, D. *Nat. Struct. Biol.* **1995**, *2*, 28.

(12) Morton, W. M.; Ayscough, K. R.; McLaughlin, P. J. *Nat. Cell Biol.* **2000**, *2*, 376.

(13) McLaughlin, P.; Gooch, J.; Mannherz, H.-G.; Weeds, A. *Nature*, **1993**, *364*, 685.

(14) Zibuck, R.; Liverton, N. J.; Smith, A. B. *J. Am. Che. Soc.* **1986**, *108*, 2451.

(15) Smith III, A. B.; Noda, I.; Remiszewski, S. W.; Liverton, N. J.; Zibuck, R. *J. Org. Chem.* **1990**, *55*, 3977.

(16) Williams, B. D.; Smith III, A. B. *Org. Lett.* **2013**, *15*, 4584.

(17) (a) White, J. D.; Kawasaki, M. *J. Am. Chem. Soc.* **1990**, *112*, 4991(b) White, J. D.; Kawasaki, M. *J. Org. Chem.* **1992**, *57*, 5292.

(18) Fürstner, A.; De Souza, D.; Parra-Rapado, L.; Jensen, J. T. *Angew. Chem. Int. Ed.* **2003**, *115*, 5516.

(19) Fürstner, A.; Turet, L. *Angew. Chem. Int. Ed.* **2005**, *117*, 3528.

(20) Fürstner, A.; Guth, O.; Rumbo, A.; Seidel, G. *J. Am. Chem. Soc.* **1999**, *121*, 11108.

(21) (a) Fürstner, A.; Kirk, D.; Fenster, M. D.; Aïssa, C.; De Souza, D.; Müller, O. *Proc. Natl. Acad. Sci. U.S.A.* **2005**, *102*, 8103. (b) Fürstner, A.; Kirk, D.; Fenster, M. D.; Aïssa, C.; De Souza, D.; Nevado, C.; Tuttle, T.; Thiel, W.; Müller, O. *Chem. Eur. J.* **2007**, *13*, 135.

Chapter 5: Latrunculin-Derived Hybrid Natural Products

5.1. Hybrid Natural Products:

The concept of hybrid natural products is not quite new, even nature also synthesize hybrid molecules.[1] For example, indole alkaloid, vincristine (**F1.2**)[2] has completely changed the fate of young children afflicted with lymphatic leukemia. Previously, this disease was fatal, but vincristine is now used in the treatment with a success rate of over 60%. The compound is a dimeric indole alkaloid consisting of vindoline[3] an alkaloid of the *Aspidosperma* subgroup and catharanthine,[4] a member of the *Iboga* subgroup of indole alkaloids. It is of special interest that both monomeric alkaloids do not express any pronounced or useful biological activity. Another interesting example of natural hybrids is the antimicrobial antibiotic thiomarinol (**F1.3**),[5] which was isolated from a culture broth of the marine bacterium *Alteromonas rava sp. nov.* SANK 73390 and shown to be a hybrid of the pseudomonic acid C[6] analogue and holothin. Importantly, the antimicrobial spectrum of **F1.3** shows characteristics of both parent compounds: it is active against Gram-positive and Gram-negative bacteria (e.g. multiresistant *Staphylococcus aurea* strains), and, its effects are more pronounced than those of either parent compound.

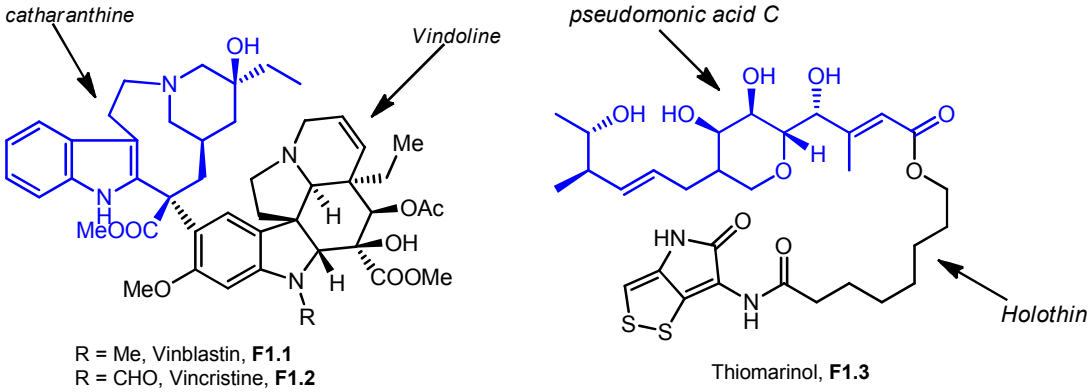


Figure 1: Naturally occurring hybrid natural products

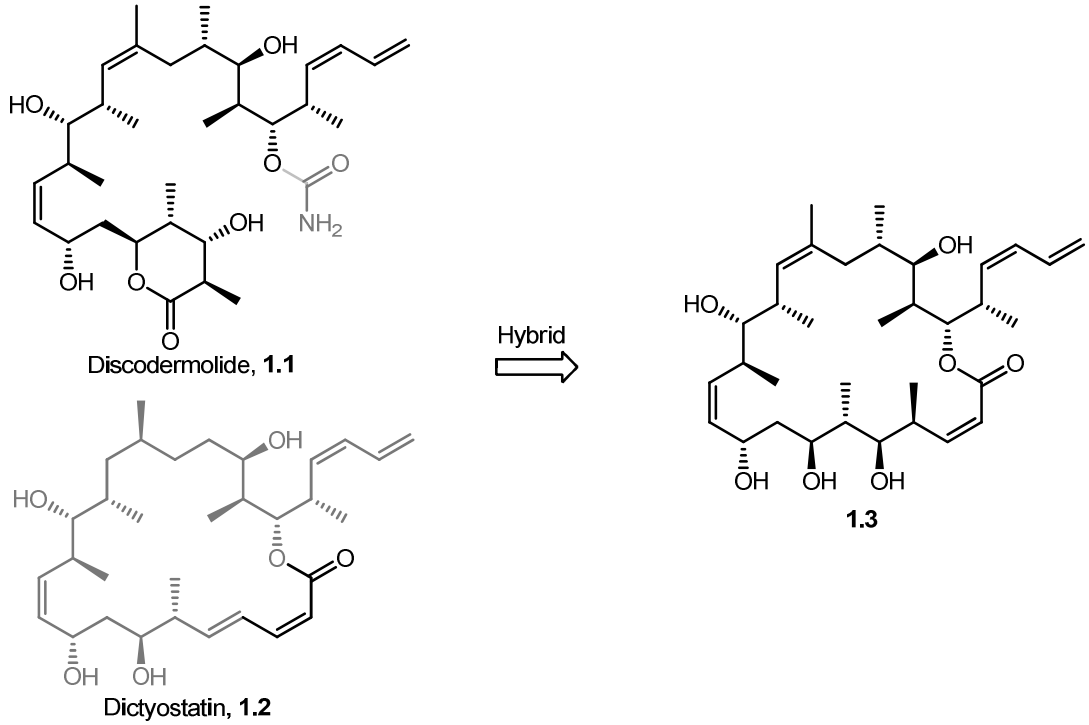
Artificial natural product hybrids have not yet been used as drugs, as this idea is quite new, but several novel compounds of this type developed in the last few years show promising biological activity, and, some of them are discussed below.

5.1.1. Discodermolide and Dictyostatin Hybrid:

Discodermolide (**1.1**, Scheme 1), isolated from the deep-sea sponge *Discodermia dissoluta*, shows potent antiproliferative activity against a wide range of human cancer cell lines, and, it also inhibits the growth of drug-resistant solid tumors.[7] It

shares a similar microtubule-stabilizing mechanism to that of taxol, while having a greater tubulin binding affinity, and, has progressed into clinical development as a novel anticancer agent.

Dictyostatin (**1.2**, Scheme 1) is also known for antiproliferative activity against a wide range of human cancer cell lines, and, emerged as a new microtubule stabilizing agent.[8] There are structural similarities existing between **1.1** and **1.2**, especially, in terms of their stereochemical functionality.[8b] Inspiration from Curran and co-workers studies on the conformational constrains of discodermolide, Paterson and co-workers designed the hybrid of **1.1** and **1.2**. The designed 22-membered hybrid macrolide **1.3,**[9] incorporating the full C2–C24 linear sequence of discodermolide and the (Z)-enoate of dictyostatin. The cell growth inhibitory activity of hybrid macrocycle **1.3** was evaluated *in vitro* against three cancer cell lines: MDA-MB-231(breast), A549 (non-small cell lung) and HT29 (colon). Interestingly, hybrid **1.3** displayed significant antiproliferative activity against these human carcinoma cells, with a cytotoxicity around one-tenth that of discodermolide. [9]

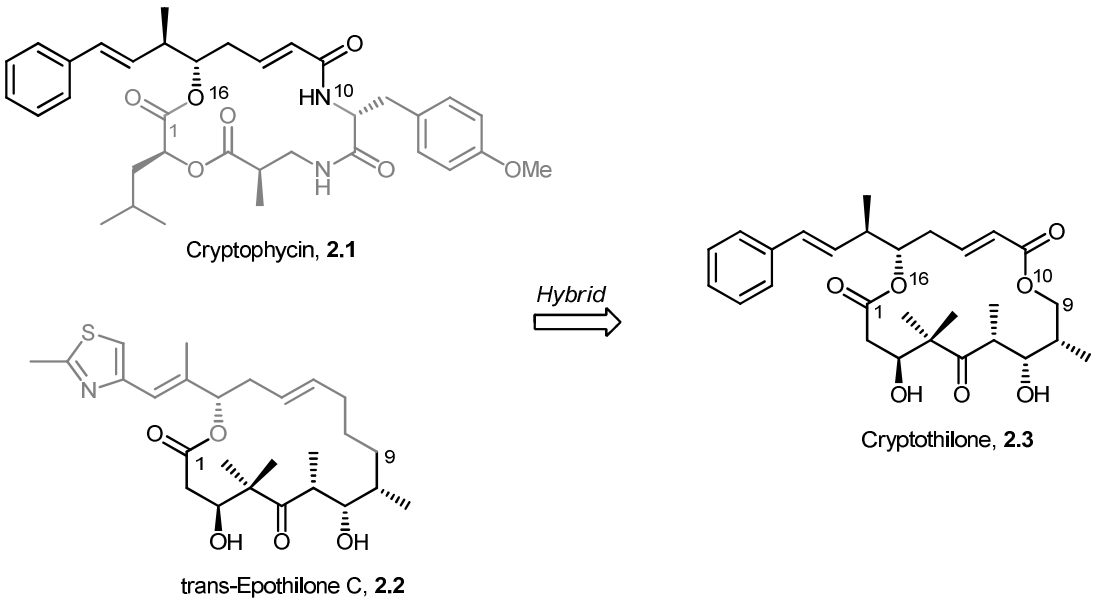


Scheme 1: Discodermolide/dictyostatin hybrid macrocycle

5.1.2. Cryptophycin and Epothilone Hybrid:

Cryptophycins and epothilones are cytotoxic natural products of widely different origin, the one emanating from a bluegreen alga,[10] and, the other from the soil bacterium.[11] Interestingly, both found to possess tubulin binding properties that inhibit cell proliferation at mitosis.[12]

Cryptophycins are believed to bind to the ends of microtubules and, like vinblastine and certain other antimitotic agents. They disrupt the polymerization process by which α,β-tubulin heterodimers condense into aggregates.[13] Epothilones, on the other hand, are known to bind to an interior region of the microtubule at a site close to that which complexes taxol.[14] This site is believed to be located on the β-tubulin subunit in a location adjacent to the neighbouring protofilament. The epothilones and taxol coordinate to microtubules in a manner that reduces the rate of α/β-tubulin dissociation by serving as a bracketing device.



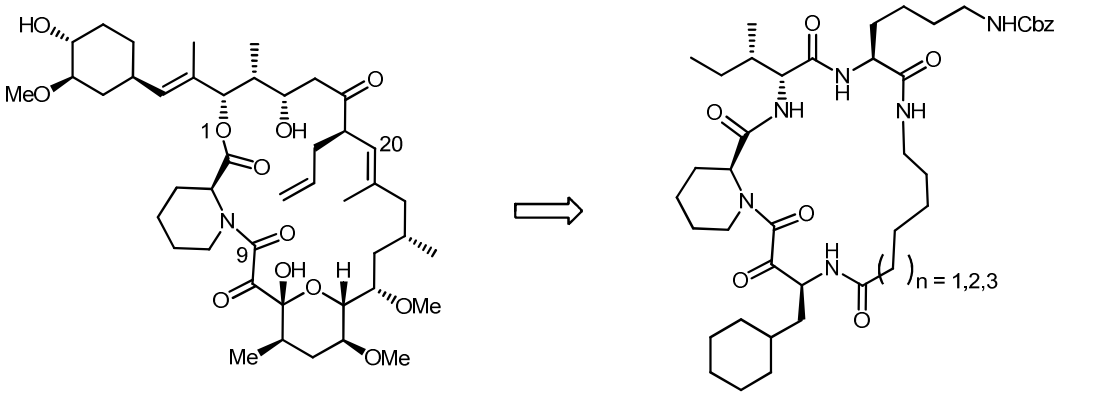
Scheme 2: Cryptophycin/trans-epothilone hybrid macrocycles

Common features in both structures are (i) a 16-membered ring, (ii) an aryl substituent attached to a conjugated double bond (which is epoxidized in some cryptophycins), (iii) a methyl substituent at or in close proximity to the conjugated double bond, (iv) (*S*) configuration at the oxygen substituent to which the lactone carbonyl is attached, and, (v) an alkene (which is epoxidized in epothilones A and B) separated from the acyloxy carbon by one methylene unit. On the other hand, there is

one region of the macrocycle perimeter that is different in these two structures. The C8-C11 segment of epothilones is relatively flexible, whereas, the cryptophycin sector that would superimpose on this set of four atoms is quite rigid due to the two amide linkages. Hydrogen bonding in this peptidic section of the cryptophycin perimeter imposes conformation that is not matched in epothilones.[15]

White and co-workers designed cryptophycin (**2.1**) and *trans*-Epothilone (**2.2**) hybrid by combining the upper half of cryptophycin and a lower half common to most epothilones, and named as cryptothilone (**2.3**)[15] (Scheme 2). Unfortunately, this hybrid macrocycle **2.3** did not show any effect on polymerization or depolymerization of tubulin up to 40 μM.[15]

5.1.3. FK506 Derived Hybrid Macrocycles:



FK-506, **3.1**

FK-506 hybrid macrocycles, n = 1, **3.2**
n = 2, **3.3**
n = 3, **3.4**

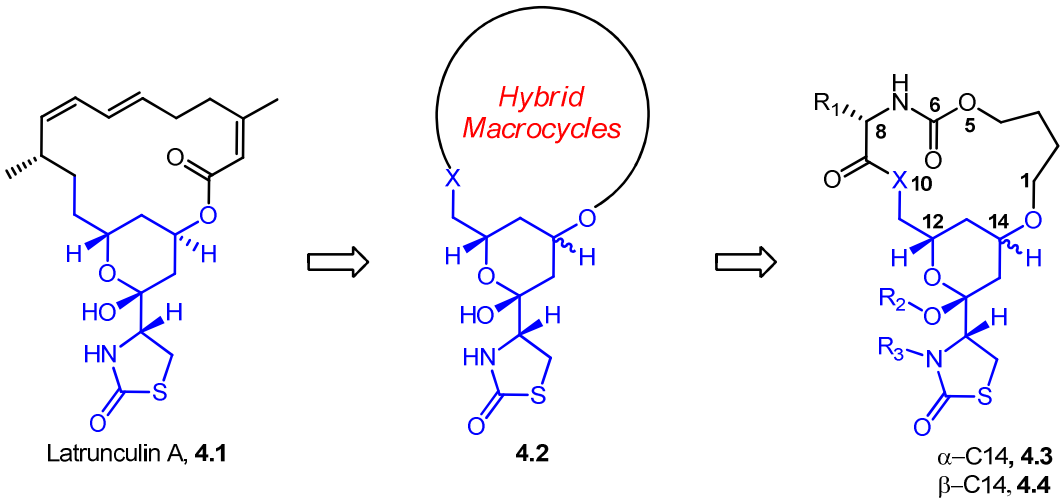
Scheme 3: FK-506 derived hybrid macrocycles

A possible explanation for the biological activity of some natural products is the assumption that the molecule mimics an endogenous peptide substance and thus exerts its action by binding to the corresponding receptor. This has long been proposed for the alkaloid morphine, which mimics the encephalin peptides. There is now some evidence that the natural macrocycle, FK506 (**3.1**),[16] which shows high immunosuppressive and anticancer activity, uses the nonpeptide structural elements in binding to its intracellular FKBP12 receptor. To gain some insight into the binding of this compound and rapamycin, another potent immunosuppressor, to immunophilin receptors, several cyclic FK506 hybrids **3.2**–**3.4** were synthesized,[16] in

which, parts of the compound was replaced by a peptide moiety (Scheme 3). This approach is different from the well-known design of peptidomimetics in which an active peptide is mimicked by, for example, an *N*-heterocycle to avoid enzymatic cleavage by peptidases. For the synthesis of the hybrids **3.2-3.4**, tethers of variable lengths were introduced through a macrocyclization protocol. Interestingly, the X-ray crystallographic studies of the complex of the receptor with hybrid **3.3** show a nearly identical overall protein topology to that observed in the FKBP12–FK506 complex. However, as expected, the affinities of the hybrids **3.2-3.4** for the receptor were considerably lower than that of FK506 (**3.1**).

5.2. Designing of Latrunculin Derived Hybrid Macrocycles:

As an extension to our work in the area of building the macrocyclic diversity,[17] we have planned to develop novel chemical approaches that are focused on the key fragments of bioactive natural product, latrunculin A (**4.1**). Latrunculins are the marine natural products known to disrupt microfilament organization, binding specifically to the cytoskeleton protein called actin by forming 1:1 complex[18] without affecting the microtubule dynamics.[19] Latrunculin A and B, two lead compounds of this family serving as a biological probe. These are isolated from red sea sponge *Negombata Magnifica* in 1980 by Kashman *et al.*, the structures of latrunculin A and B were



Scheme 4: Designof latrunculin-derived hybrid macrocycles

assigned based on extensive spectroscopic studies and the single crystal X-ray of methyl glycoside derivative of the latrunculin A.[20] These are the first marine natural

products containing macrocyclic ring skeleton (latrunculin A is 16 and B is 14-membered macrolide) as well as the rare thiazolidinone ring.[20] One of the common features observed in all latrunculin family of compounds is the pyran ring containing thaizolidinone. The X-ray crystal structure between the actin monomer and latrunculin A[21] revealed that the interactions made by pyran ring containing thiazolidinone substitution with actin are very crucial for the biological activity.

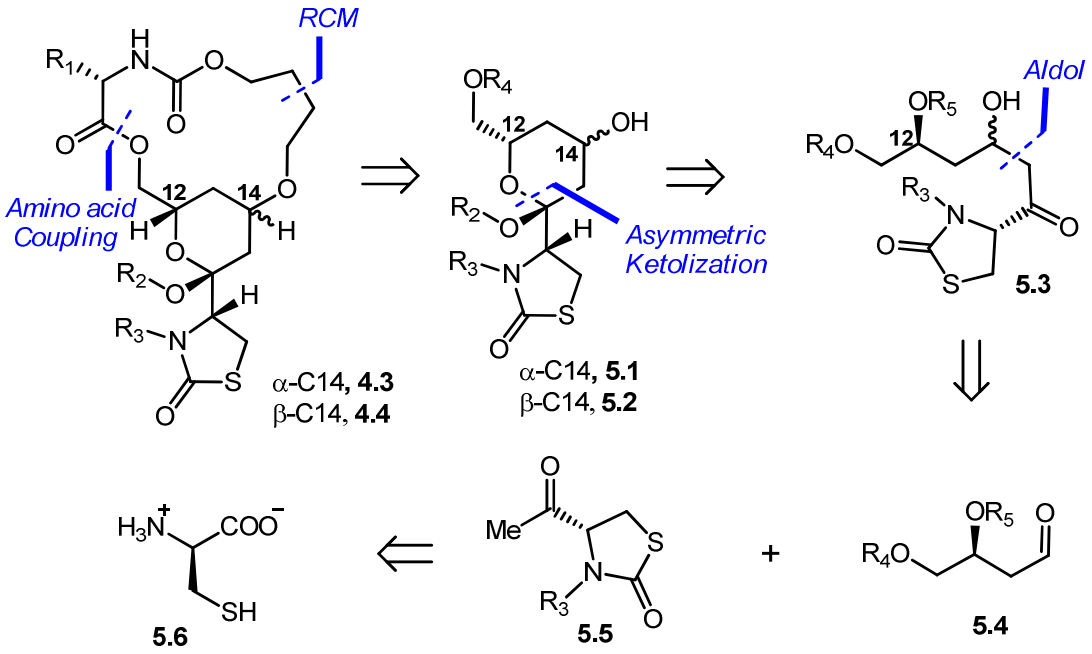
5.3. Working Hypothesis:

With this objective, we are interested in developing a novel methodology to obtain a key synthon (pyran fragment) of latrunculin A (**4.1**) on grams quantity in a reasonable time, and, then utilize this fragment in the generation of latrunculin derived hybrid macrocyclic library (**4.2**). We have designed two 15-membered macrocyclic targets **4.3** and **4.4** as shown in Scheme 1. The difference between two macrocycles is the stereochemistry at C4 position of pyran ring. We can introduce the skeletal diversity through coupling of different amino acids (D/L), either from primary alcohol or from secondary alcohol side chain and the stereochemical diversity by changing C14 hydroxyl group stereochemistry. Further, variation in the side chain (R_2 and R_3) could be obtained through the selective alkylation.

5.4. Results and Discussion:

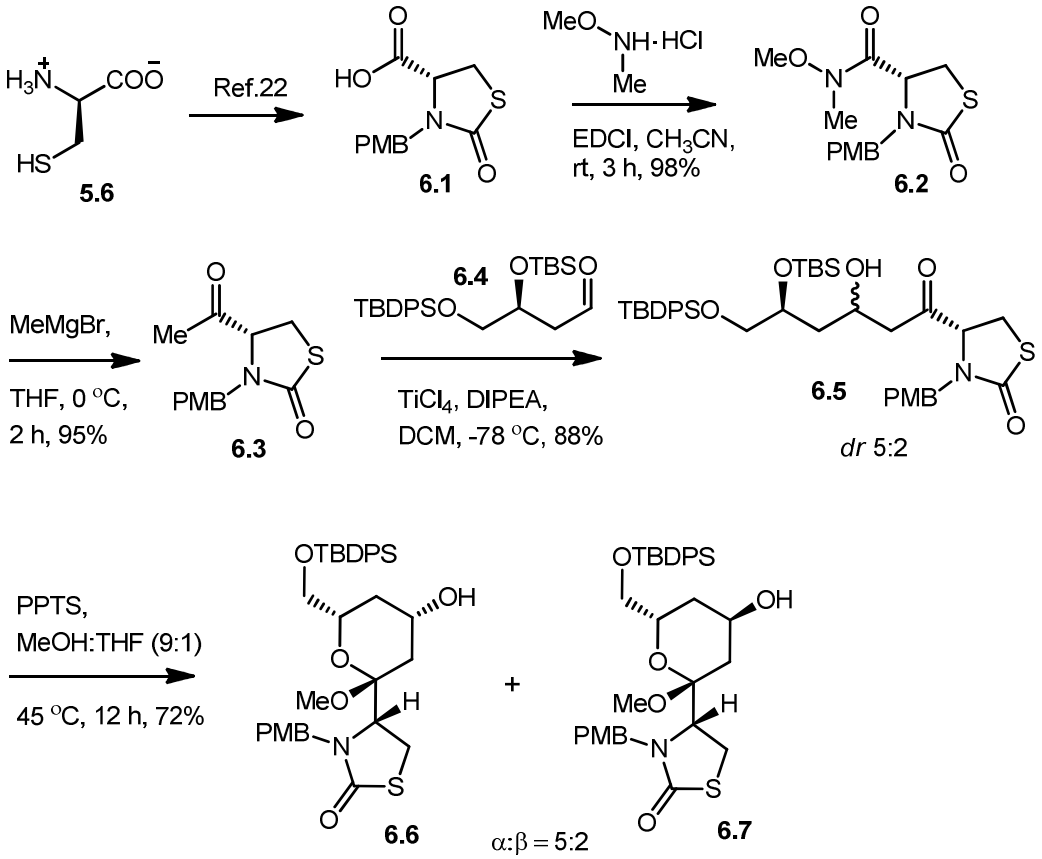
5.4.1. Retrosynthetic analysis:

Retrosynthetic analysis of latrunculin hybrid macrocycles **4.3** & **4.4** is shown in Scheme 1. Macrocycles **4.3** & **4.4** could be obtained from the coupling of pyran fragments (**5.1** & **5.2**) and alloc amino acids followed by ring closing metathesis and the reduction of a double bond. These pyran fragments (**5.1** & **5.2**) could be obtained from asymmetric ketolization of aldol product **5.3**, which would be obtained from the aldol reaction between thiazolidinone methyl ketone **5.5** and the aldehyde **5.4**. The thiazolidinone fragment **5.5** could be obtained from L-cystein (**5.6**) by simple functional group modifications.



Scheme 5: Retrosynthetic analysis of latrunculin derived hybrid macrocycles

5.4.2. Synthesis of Macrocycles 4.3 & 4.4:



Scheme 6: Synthesis of key pyran fragments

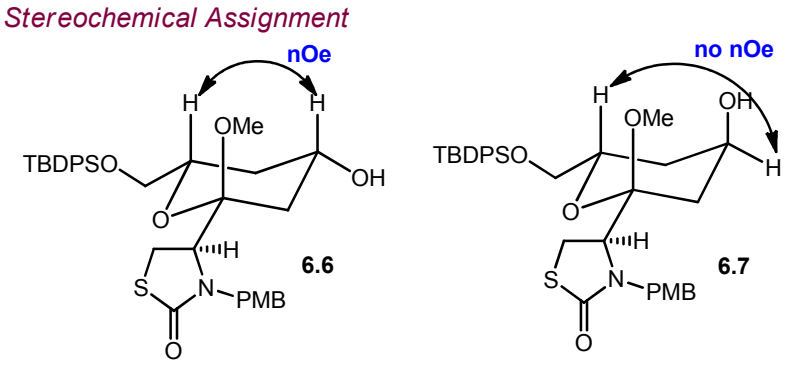
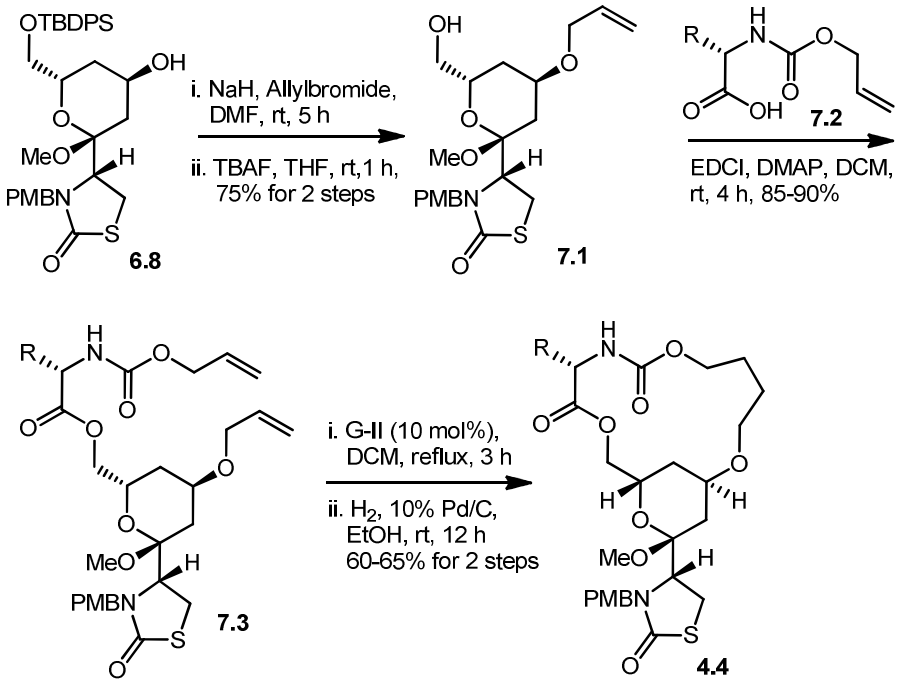


Figure 2: Stereochemical assignment



Scheme 7: Synthesis of latrunculin hybrid macrocycle **4.4**

The synthesis of pyran fragments **6.6** & **6.7** is shown in Scheme 3. The thiazolidinone acid **6.1** was obtained from L-cystein in two steps following the reported protocol.[22] Coupling of hydroxylamine hydrochloride with acid **6.1** using EDCI reagent gave the Weinreb amide **6.2**, followed by treating the compound **6.2** with methyl magnesium bromide, yielded the methyl ketone **6.3** in a very good yield.[23] Titanium tetrachloride mediated aldol reaction[24] between the aldehyde **6.4,** which was obtained from *S*-malic acid in four steps[25] and methyl ketone **6.3** gave β-hydroxy ketone **6.5** as inseparable 5:2 (from ^{1}H NMR) diastereomeric mixture in 88% yield. Removal of the TBS group followed by asymmetric ketolization of the aldol product **6.5** in the presence of pyridinium *p*-toluene sulphonate (PPTS) and

methanol condition smoothly furnished the separable mixture of methylacetal fragments **6.6** (50% yield) and **6.7** (20% yield). The stereochemical assignments of the major and minor products were carried out based on nOe experiments (Figure 2).

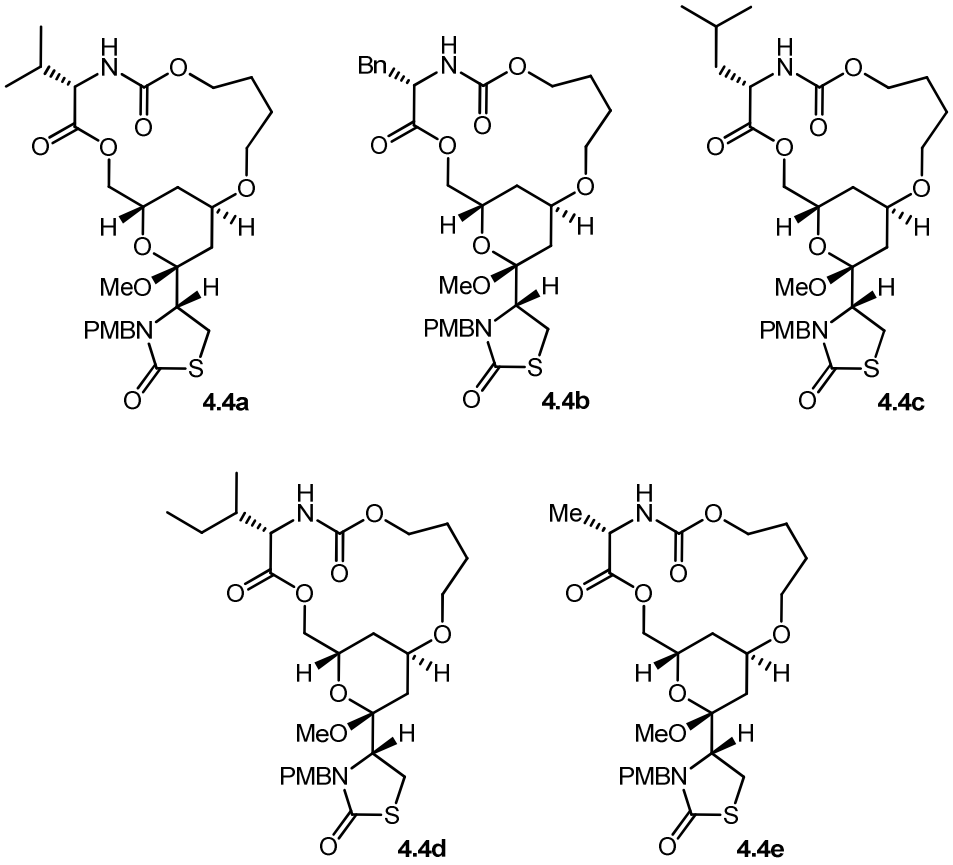
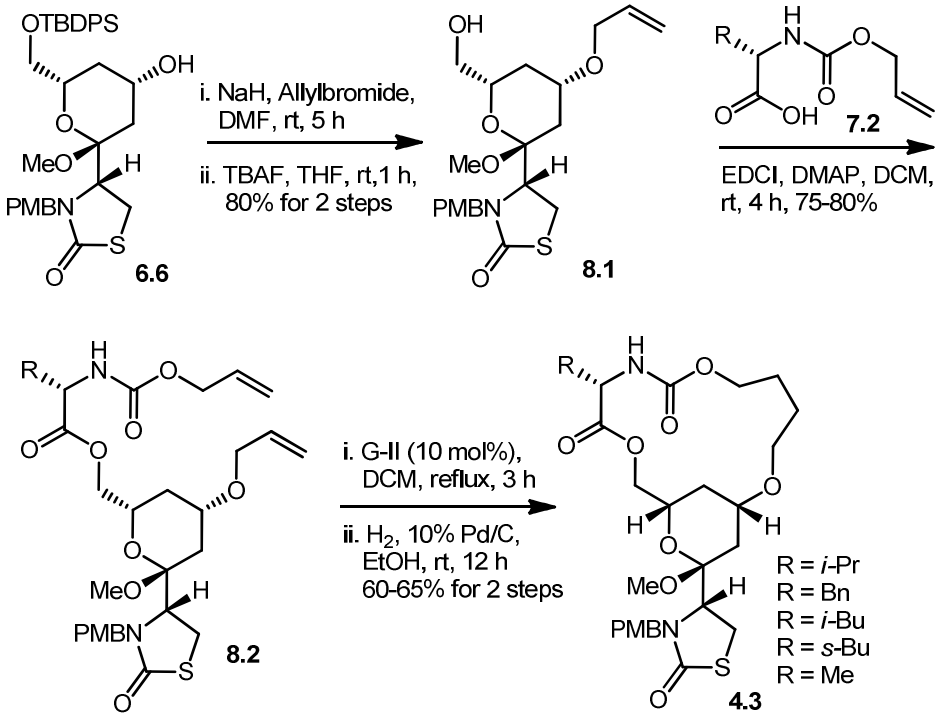


Figure 3: Derivatives of macrocycle **4.4**

Allylation of secondary hydroxyl group of pyran fragment **6.7,** with allyl bromide and NaH condition followed by removal of TBDPS group with tetrabutylammonium fluoride gave the primary alcohol **7.1** in 75% yields (Scheme 4). Coupling of alloc amino acid **7.2** with primary alcohol **7.1** in the presence of EDCI and DMAP condition gave the bisallyl compound **7.3**, which was then subjected to ring closing metathesis[26] using Grubbs' II generation catalyst[27] (10 mol %) followed by hydrogenation of olefin with 10% Pd/C in the presence of hydrogen gas gave the macrocycle **4.4** in very good yields. In a similar manner, we have synthesized the macrocycle **4.3** starting from the pyran fragment **6.6** (Scheme 8). In both cases, we have synthesized five macrocyclic derivatives by replacing different R group.



Scheme 8: Synthesis of macrocycle **4.3**

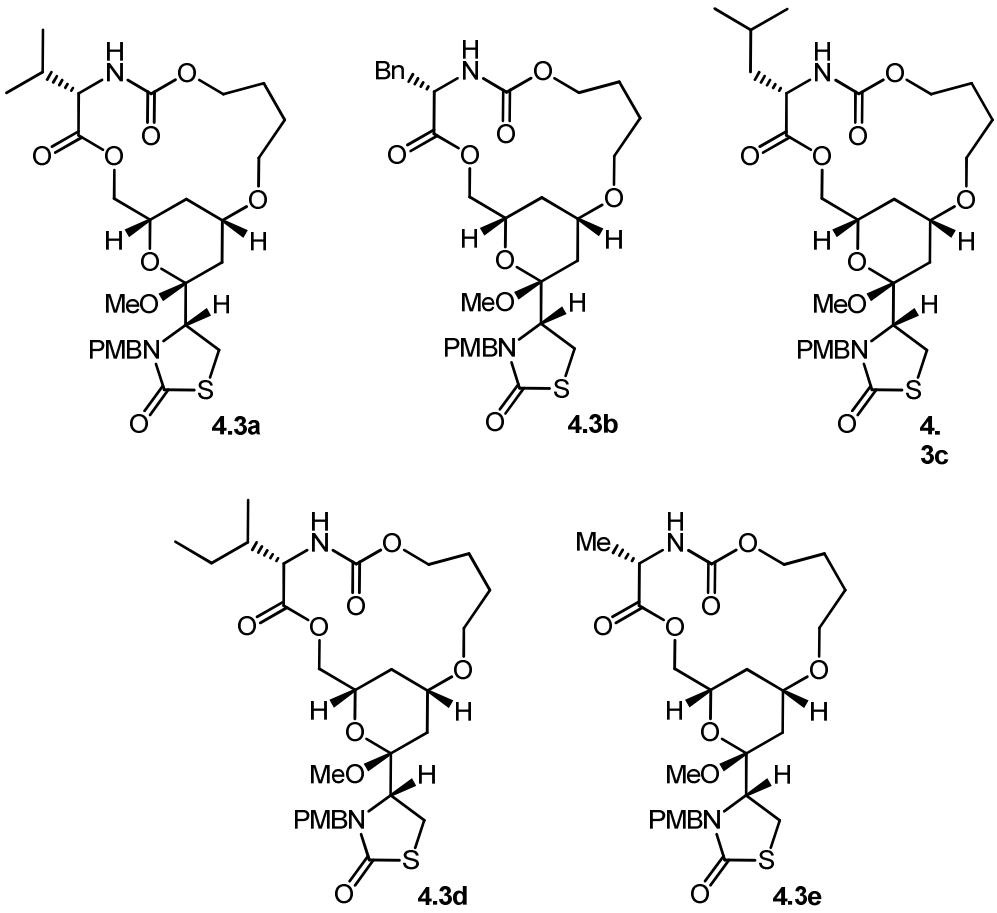
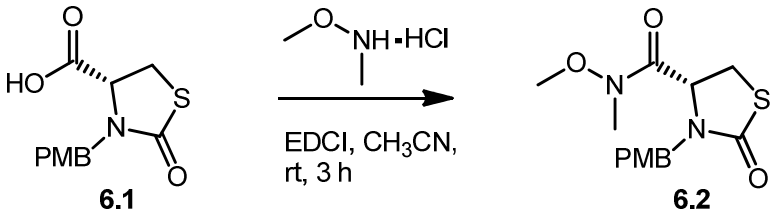


Figure 4: Derivatives of macrocycle **4.3**

5.5. Conclusion:

In conclusion, we developed a novel and efficient methodology to synthesize a key synthon, i.e., pyran fragment (**6.6** & **6.7**) of latrunculin A in gram quantities. The amino acid moiety and C14 hydroxyl group allow us to accessing a unique set of latrunculin hybrid macrocyclic architectures. Biological activities of these molecules are now under exploration in various cell signaling based assays.

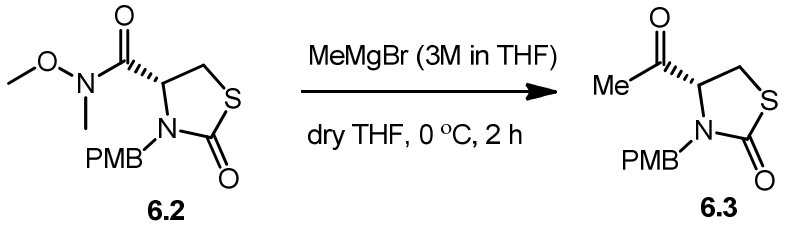
5.6. Experimental Procedure:



(R)-N-methoxy-3-(4-methoxybenzyl)-N-methyl-2-oxothiazolidine-4-carboxamide (6.2):

To a stirred solution of thiazolidinone acid **6.1** (1.50 g, 5.61 mmol) in acetonitrile (20 mL), N,O-dimethylhydroxylamine hydrochloride (0.47 g, 6.73 mmol) and EDCI (1.60 g, 8.45 mmol) was added at room temperature and stirred for 3 h. The reaction mixture was diluted with ethyl acetate (50 mL) and washed with water followed by brine. Solvent was concentrated to leave crude yellow oil, which was purified by the flash coloumn chromatography (1:1 ethyl acetate/hexanes) to give the weinreb amide **6.2** (1.68 g, 98%yield) as a yellow solid.

Molecular Formula: $C_{14}H_{18}N_2O_4S$; R_f : 0.3 (1:1 ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.16 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.12 (d, *J* = 14.6 Hz, 1H), 4.42 (dd, *J* = 8.8, 4.8 Hz, 1H), 3.84 (d, *J* = 14.6 Hz, 1H), 3.79 (s, 3H), 3.48 (dd, *J* = 11.2, 8.8 Hz, 1H), 3.40 (s, 3H), 3.21 (s, 3H), 3.15 (dd, *J* = 11.4, 4.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.2, 169.1, 159.3, 130.0, 127.5, 61.2, 57.4, 55.3, 46.9, 32.5, 28.0; LRMS: (ES+) m/z = 311.0 (M+1)

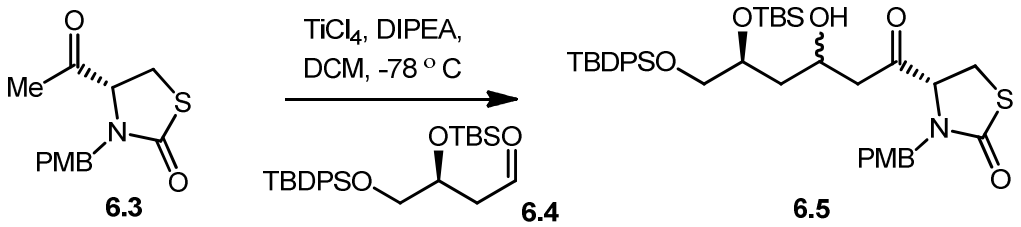


6.2 6.3

(R)-4-acetyl-3-(4-methoxybenzyl)thiazolidin-2-one (6.3):

To a stirred solution of weinreb amide **6.2** (1 g, 3.23 mmol) in THF (10 mL), MeMgBr (3M in THF, 9.70 mL) was added drop wise at 0 oC and stirred for 2 h. The reaction mixture was quenched with addition of saturated ammonium chloride solution and extracted with ethyl acetate (25 mL) for three times. Organic layers were combined and washed with brine, dried over anhydrous sodium sulphate. Solvent was concentrated to leave crude yellow oil, which was purified by the flash coloumn chromatography (2:5 ethyl acetate/hexanes) to give the ketone **6.3** (0.79 g, 95%) as a white solid.

Molecular Formula: $C_{13}H_{15}NO_3S$; R_f : 0.5 (1:1 ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.14 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 5.02 (d, *J* = 14.6 Hz, 1H), 4.10 (dd, *J* = 9.6, 4.0 Hz, 1H), 3.91 (d, *J* = 14.6 Hz, 1H), 3.80 (s, 3H), 3.51 (dd, *J* = 11.4, 9.2 Hz, 1H), 3.12 (dd, *J* = 11.4, 3.9 Hz, 1H), 2.14 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 204.3, 171.6, 159.3, 129.8, 127.2, 114.2, 65.3, 55.2, 47.3, 27.6, 26.2; LRMS: (ES+) m/z = 265.9 (M+1)



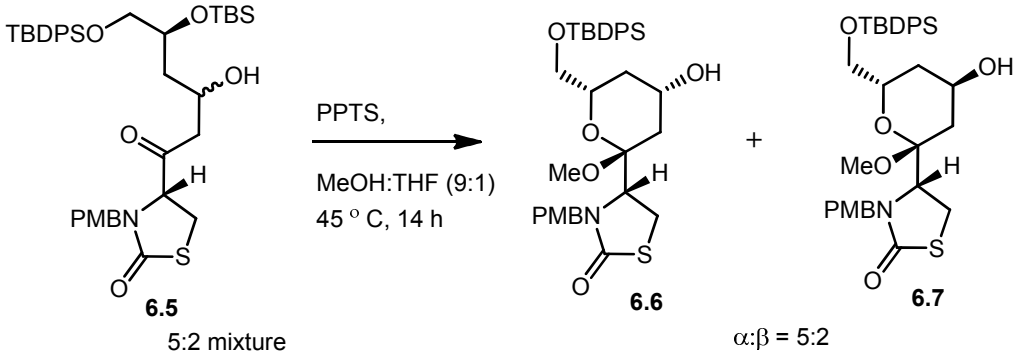
6.3 6.4 6.5

Compound 6.5:

To a stirred solution of ketone **6.3** (0.30 g, 1.13 mmol) in dichloromethane (5 mL), $TiCl_4$ (0.23 mL, 1.24 mmol) was added at -78 °C. The resulting brown suspension was stirred for 10 min before adding a solution of DIPEA (0.33 mL, 1.9 mmol). The mixture was stirred at -78 °C for 1 h followed by at 0 °C for 2 h. The resulting red coloured solution was cooled to -78 °C before adding a solution of aldehyde **6.4** (0.77 g, 1.69 mmol) in DCM (5 mL) and stirred for 3 h at the same temperature. The

reaction was quenched with saturated ammonium chloride solution at that temperature and cooling bath was removed. After reaching the room temperature reaction mixture was filtered through a celite pad and separated the two layers. Washed the aqueous layer twice with dichloromethane (25 mL) and combined the organic layers washed with brine, dried over anhydrous sodium sulphate. Solvent was concentrated to leave crude yellow colour oil, which was purified by flash column chromatography (1:3 ethyl acetate/hexanes) to give 5:2 mixture of aldol product **6.5** (0.71 g, 88% yield) as a brown liquid.

Molecular Formula: $C_{39}H_{55}NO_6SSi_2$; R_f : 0.3 (1:3 ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.66 (t, *J* = 5.97 Hz, 4H), 7.53-7.32 (m, 6H), 7.19-7.08 (m, 2H), 5.07 (m, 1H), 6.94-6.75 (m, 2H), 4.35 (d, *J* = 3.72 Hz, 1H), 4.21 (m, 1H), 4.03-3.74 (m, 5H), 3.69-3.55 (m, 2H), 3.53-3.38 (m, 2H), 3.31-3.15 (m, 1H), 2.73-2.57 (m, 1H), 2.42 (m, 1H), 1.89 (m, 1H), 1.82-1.63 (m, 1H), 1.05 (s, 9H), 0.86-0.77 (m, 9H), 0.02 (s, 3H), -0.10 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): 205.6, 205.6, 171.8, 159.3, 159.3, 135.5, 135.5, 133.0, 132.9, 130.1, 129.8, 129.8, 127.8, 127.7, 127.7, 127.6, 127.4, 114.1, 114.0, 72.2, 67.6, 66.5, 65.2, 55.2, 55.2, 47.1, 46.5, 41.0, 27.2, 26.8, 25.7, 19.1, 17.8, -4.3, -5.0; LRMS: (ES+) m/z = 722.6 (M+1)



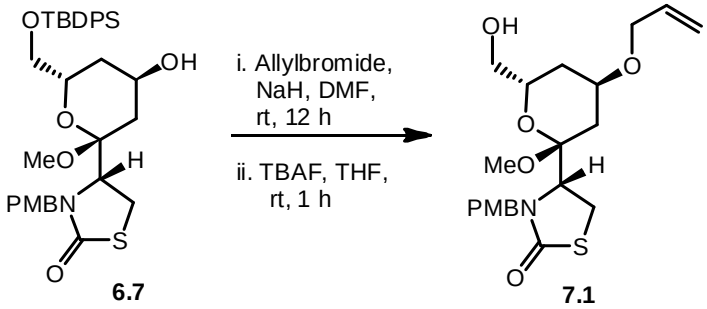
Compounds 6.6 & 6.7:

To a solution of aldol product **6.5** (3.0 g, 4.15 mmol) in MeOH:THF (9:1), pyridinium p-toluene sulphonate (1.56 g, 6.23 mmol) was added and the mixture was heated at 45 o C for 14 h. Reaction mixture was quenched with the addition of triethylamine (2 mL) and stirred for 10 minutes. Solvent was concentrated under vacuo then diluted with ethylacetate (50 mL) and washed with sodium bicarbonate followed by brine, and dried over anhydrous sodium sulphate. Solvent was concentrated to leave crude yellow oil, which was purified by the flash coloumn

chromatography (1:24 ethyl acetate/hexanes) to give the α-OH compound **6.6** (1.35 g, 50.4% yield), and β-OH compound **6.7** (0.55 g, 21.3% yield).

Compound 6.6: Molecular Formula: $C_{34}H_{43}NO_6SSi$; R_f : 0.2 (3:7 ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.46-7.36 (m, 7H), 7.68 (dd, *J* = 10.0, 3.8 Hz, 4H), 7.25 (d, *J* = 8.6 Hz,, 2H), 6.77 (d, *J* = 8.6 Hz, 2H), 5.08 (d, *J* = 14.2 Hz, 1H), 4.36 (d, *J* = 14.2 Hz, 1H), 4.09 (dt, *J* = 11.2, 5.4 Hz, 1H), 3.88 (dd, *J* = 8.4, 3.2 Hz, 1H), 3.77 (s, 3H), 3.72-3.65 (m, 2H), 3.28-3.19 (m, 2H), 3.08 (s, 3H), 2.23 (dd, *J* = 12.6, 3.6 Hz, 1H), 1.97-1.88 (m, 1H), 1.59-1.50 (t, *J* = 11.6,, 1H), 1.45-1.32 (m, 1H), 1.09 (s, 10H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.8, 159.0, 135.6, 135.6, 135.5, 135.5, 133.1, 133.1, 130.3, 129.8, 128.6, 128.5, 127.8, 127.7, 127.6, 114.1, 113.9, 103.3, 71.2, 66.5, 64.5, 58.6, 55.2, 47.4, 47.0, 36.8, 36.2, 26.9, 25.2, 22.7, 19.2 ; LRMS: (ES+) m/z = 644.5 (M+23), 590.3 (M-OMe)

Compound 6.7: Molecular Formula: $C_{34}H_{43}NO_6SSi$; R_f : 0.2 (3:7 ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.67 (dd, *J* = 10.8, 4.41 Hz, 4H), 7.48-7.33 (m, 6H), 7.25 (d, *J* = 8.5 Hz, 2H), 6.76 (d, *J* = 8.5 Hz, 2H), 5.06 (d, *J* = 14.2 Hz, 1H), 3.34-3.21 (m, 2H), 3.87-3.74 (m, 6H), 4.08-3.97 (m, 1H), 4.20 (s, 1H), 4.36 (d, *J* = 14.2 Hz, 1H), 3.70 (d, *J* = 8.8 Hz, 1H), 3.20 (d, *J* = 11.6 Hz, 3H), 2.14-1.99 (m, 2H), 1.89 (dd, *J* = 14.4, 3.54 Hz, 1H), 1.67 (dd, *J* = 11.2, 2.4 Hz, 3H), 1.08 (s, 9H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.6, 159.0, 139.2, 135.6, 135.5, 133.1, 133.0, 130.3, 129.8, 128.5, 127.8, 127.7, 113.9, 103.7, 67.3, 66.6, 63.8, 58.6, 55.2, 47.7, 47.1, 33.3, 26.8, 25.1, 22.6, 19.2; LRMS: (ES+) m/z = 644.5 (M+23), 590.3 (M-OMe)



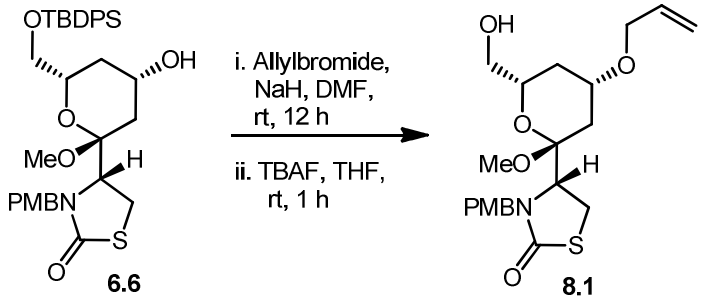
(R)-4-((2R,4R,6S)-4-(allyloxy)-6-(hydroxymethyl)-2-methoxytetrahydro-2H-pyran-2-yl)-3-(4-methoxybenzyl)thiazolidin-2-one (7.1):

To a stirred solution of glycoside **6.7** (0.1 g, 0.16 mmol) in dry DMF, 60% NaH (0.019 g, 0.80 mmol) and allyl bromide (0.07 mL, 0.80 mmol) were added at 0 o C.

The reaction mixture was stirred at room temperature for 12 h and then quenched with addition of saturated ammonium chloride solution. The reaction mixture was extracted with ethyl acetate (10 mL) for three times and combined the organic layers, dried over anhydrous sodium sulphate. Solvent was concentrated to leave crude yellow colour oil, which was subjected to next reaction without purification

To above allylated product in THF, TBAF (1M in THF, 0.25 mL) was added at room temperature and stirred for 1 h. The reaction mixture was quenched with addition of ice cold water and extracted with ethylacetate (10 mL) for three times. Organic layers were combined and washed with brine, dried over anhydrous sodium sulphate. Solvent was concentrated to leave crude yellow oil, which was purified by the flash coloumn chromatography (2:5 ethyl acetate/hexanes) to give the primary alcohol **7.1** (0.05 g, 75% yield) as a colourless liquid.

Molecular Formula: $C_{21}H_{29}NO_6S$; R_f : 0.2 (2:3 ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.18 (d, *J* = 8.4 Hz, 2H), 6.80 (d, *J* = 8.4 Hz, 2H), 5.96-5.80 (m, 1H), 5.24 (d, *J* = 17.2 Hz, 1H), 5.13 (d, *J* = 10.4 Hz, 1H), 5.05 (d, *J* = 14.5 Hz, 1H), 4.24 (d, *J* = 14.4 Hz, 1H), 4.14-4.05 (m, 1H), 4.05-3.89 (m, 2H), 3.89-3.79 (m, 2H), 3.76 (d, *J* = 2.8 Hz, 3H), 3.73-3.62 (m, 2H), 3.32-3.20 (m, 2H), 3.09 (d, *J* = 10.2 Hz, 3H), 2.24 (m, 1H), 2.07 (d, *J* = 14.6 Hz, 1H), 1.84-1.70 (m, 2H), 1.41 (t, *J* = 12.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 173.1, 159.0, 135.0, 129.5, 128.5, 116.8, 114.0, 101.7, 69.3, 69.0, 66.9, 65.8, 59.2, 55.2, 47.5, 47.3, 30.0, 29.8, 25.3; LRMS: (ES+) m/z = 424.3 (M+1)

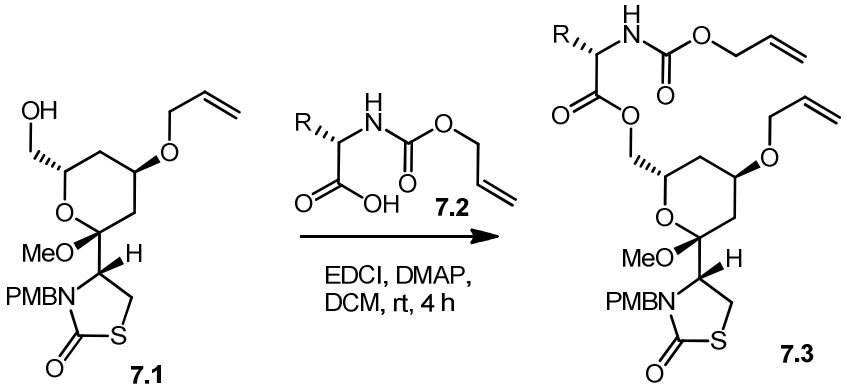


(R)-4-((2R,4S,6S)-4-(allyloxy)-6-(hydroxymethyl)-2-methoxytetrahydro-2H-pyran-2-yl)-3-(4-methoxybenzyl)thiazolidin-2-one (8.1):

Experimental procedure as per ref. compound **7.1**

Molecular Formula: $C_{21}H_{29}NO_6S$; R_f : 0.2 (2:3 ethyl acetate/hexanes); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.18 (d, *J* = 8.5 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 5.89 (ddd, *J* = 15.9, 10.6, 5.2 Hz, 1H), 5.29 (d, *J* = 3.0 Hz, 1H), 5.20 (ddd, *J* = 11.6, 8.7,

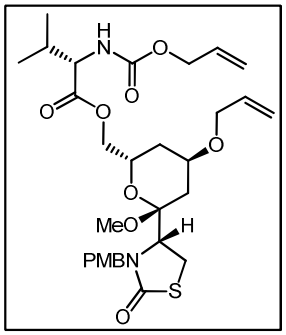
1.3 Hz, 2H), 5.12 (d, *J* = 14.5 Hz, 1H), 4.21-4.15 (m, 1H), 4.06-3.97 (m, 2H), 3.86 (dd, *J* = 9.4, 2.7 Hz, 1H), 3.83-3.76 (m, 5H), 3.72 (d, *J* = 10.8 Hz, 2H), 3.27 (dq, *J* = 11.6, 4.5 Hz, 2H), 3.07 (d, *J* = 6.0 Hz, 3H), 2.31-2.23 (m, 1H), 2.02-1.95 (m, 1H), 1.53 (dd, *J* = 12.6, 11.2 Hz, 1H), 1.26 (dd, *J* = 10.7, 7.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.5, 158.8, 134.5, 129.2, 128.2, 128.1, 116.7, 113.9, 102.9, 70.7, 70.6, 68.7, 65.7, 58.6, 55.0, 47.3, 47.0, 33.7, 32.9, 24.9; LRMS: (ES+) m/z = 424.3 (M+1)



Compound 7.3:

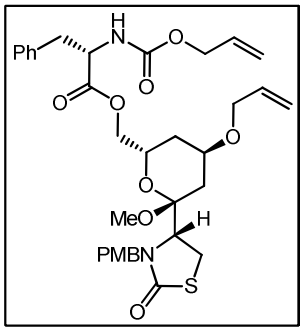
To a stirred solution of primary alcohol **7.1** (0.12 mmol) in DCM (5 mL), Alloc Amino acid **7.2** (0.23mmol), EDCI (0.23 mmol) and DMAP (0.35 mmol) were added. The mixture was stirred at room temperature for 4 h and then quenched with addition of saturated sodium bicarbonate solution. Aqueous layer was washed twice with dichloromethane (10 mL) and combined the organic layers washed with brine solution, dried over anhydrous sodium sulphate. Solvent was concentrated to leave crude solid, which was purified by the flash coloumn chromatography to give the bisallyl product **7.3**.

(S)-((2S,4R,6R)-4-(allyloxy)-6-methoxy-6-((R)-3-(4-methoxybenzyl)-2-oxothia zolidin-4-yl)tetrahydro-2H-pyran-2-yl)methyl 2-(((allyloxy)carbonyl)amino)-3-methylbutanoate (7.3a):



Molecular Formula: $C_{30}H_{42}N_2O_9S$; R_f : 0.5 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 ethyl acetate/hexanes); Yield-85.5% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.21 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 5.90 (m, 2H), 5.34-5.14 (m, 5H), 5.07 (d, *J* = 14.3 Hz, 1H), 4.52 (m, 2H), 4.29 (m, 5H), 4.04 (dd, *J* = 13.0, 5.6 Hz, 1H), 3.98 (dd, *J* = 13.0, 5.4 Hz, 1H), 3.90 (bs, 1H), 3.85 (dd, *J* = 8.4, 3.2 Hz, 1H), 3.80 (m, 3H), 3.33-3.22 (m, 2H), 3.13 (m, 3H), 2.24-2.07 (m, 3H), 1.88-1.76 (m, 2H), 1.56-1.39 (m, 2H), 0.98 (d, *J* = 6.82 Hz, 3H), 0.89 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 173.0, 172.0, 159.0, 155.9, 134.9, 132.4, 130.0, 129.7, 128.6, 117.9, 117.0, 114.0, 113.9, 102.2, 69.4, 68.9, 67.4, 65.9, 64.2, 59.1, 59.0, 55.2, 47.5, 31.1, 30.1, 29.8, 25.4, 19.0, 17.5; LRMS: (ES+) m/z = 629.1 (M+23), 575.1 (M-OMe)

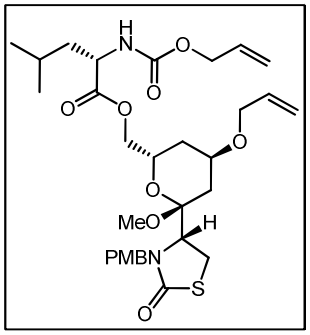
(S)-((2S,4R,6R)-4-(allyloxy)-6-methoxy-6-((R)-3-(4-methoxybenzyl)-2-oxothia zolidin-4-yl)tetrahydro-2H-pyran-2-yl)methyl 2-(((allyloxy)carbonyl)amino)-3-phenylpropanoate (7.3b):



Molecular Formula: $C_{34}H_{42}N_2O_9S$; R_f : 0.5 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 ethyl acetate/hexanes); Yield-90% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.24 (m, 5H), 7.11 (d, *J* = 7.2 Hz, 2H),

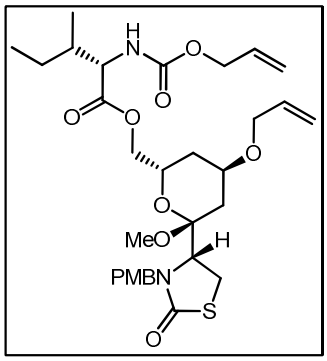
6.84 (d, *J* = 8.4 Hz, 2H), 5.97-5.78 (m, 2H), 5.34-5.10 (m, 5H), 5.05 (d, *J* = 14.4 Hz, 1H), 4.64 (d, *J* = 7.6 Hz, 1H), 4.35-4.50 (m, 2H), 4.32-4.18 (m, 4H), 4.08 (dd, *J* = 14.2, 5.6 Hz, 1H), 3.92 (*J* = 14.2, 5.6 Hz, 1H),, 3.89-3.73 (m, 5H), 3.32-3.21 (m, 2H), 3.17-2.99 (m, 5H), 2.08 (dd, *J* = 17.6, 8.4 Hz, 2H), 1.78 (dd, *J* = 14.8, 3.9 Hz, 1H), 1.70 (d, *J* = 13.8 Hz, 1H), 1.29 (t, *J* = 12.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.9, 171.6, 159.0, 155.3, 135.4, 134.9, 132.3, 129.8, 129.1, 128.7, 128.6, 127.2, 117.9, 117.0, 114.0, 102.1, 69.4, 68.9, 67.4, 65.8, 64.1, 59.1, 55.2, 47.5, 38.2, 29.9, 29.7, 25.6, 25.3; LRMS: (ES+) m/z = 677.0 (M+23), 623.0 (M-OMe)

(S)-((2S,4R,6R)-4-(allyloxy)-6-methoxy-6-((R)-3-(4-methoxybenzyl)-2-oxothia zolidin-4-yl)tetrahydro-2H-pyran-2-yl)methyl 2-(((allyloxy)carbonyl)amino)-4-methylpentanoate (7.3c):



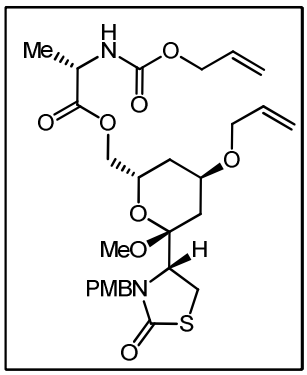
Molecular Formula: $C_{31}H_{44}N_2O_9S$; R_f : 0.5 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 ethyl acetate/hexanes); Yield-89.5% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.19 (d, *J* = 8.4 Hz, 2H), 6.83 (d, *J* = 8.4 Hz, 2H), 5.96-5.78 (m, 2H), 5.31-5.09 (m, 5H), 5.00 (d, *J* = 14.4 Hz, 1H), 4.57-4.43 (m, 2H), 4.38 (dt, *J* = 9.1, 4.8 Hz, 1H), 4.33-4.19 (m, 4H), 4.08-3.92 (m, 3H), 3.89 (bs, 1H), 3.82 (dd, *J* = 8.4, 3.1 Hz, 1H), 3.79-3.75 (m, 4H), 3.29-3.22 (m, 2H), 3.11 (d, *J* = 9.2 Hz, 3H), 2.09 (d, *J* = 14.3 Hz, 2H), 1.85-1.75 (m, 2H), 1.73-1.64 (m, 1H), 1.63-1.55 (m, 1H), 1.50 (m, 2H), 0.87 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.9, 172.8, 158.9, 155.6, 134.8, 132.3, 129.7, 128.4, 117.7, 116.8, 113.9, 113.8, 102.0, 69.3, 68.8, 67.3, 65.7, 64.1, 58.9, 55.0, 52.3, 47.4, 47.0, 41.5, 29.9, 29.7, 25.2, 24.5, 22.8, 21.4; LRMS: (ES+) m/z = 643.1(M+23), 589.1 (M-OMe)

(2S,3R)-((2S,4R,6R)-4-(allyloxy)-6-methoxy-6-((R)-3-(4-methoxybenzyl)-2-oxothia zolidin-4-yl)tetrahydro-2H-pyran-2-yl)methyl 2-(((allyloxy)carbonyl)amino)-3-methylpentanoate (7.3d):

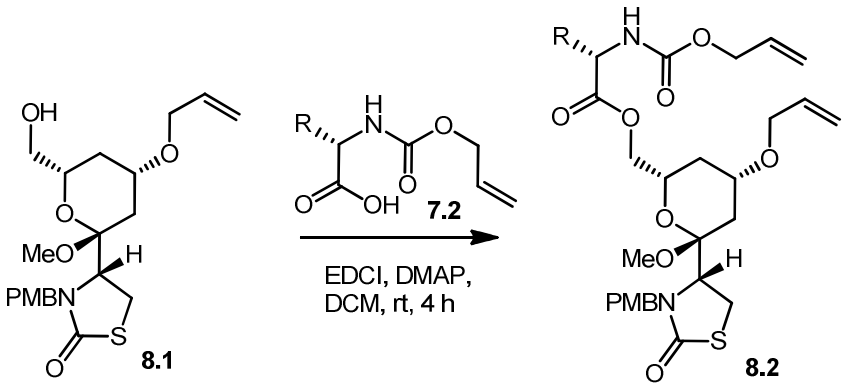


Molecular Formula: $C_{31}H_{44}N_2O_9S$; R_f : 0.5 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 ethyl acetate/hexanes); Yield-83.9% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.18 (d, *J* = 8.4 Hz, 2H),6.83 (d, *J* = 8.4 Hz, 2H), 5.97-5.77 (m, 2H), 5.23 (m, 5H), 5.04 (d, *J* = 14.4 Hz, 1H), 4.58-4.42 (m, 2H), 4.38-4.19 (m, 5H), 4.08 (dd, *J* = 14.2, 5.6 Hz, 1H), 3.93 (*J* = 14.2, 5.6 Hz, 1H),3.89 (bs, 1H), 3.82 (dd, *J* = 8.2, 3.2 Hz, 1H), 3.78 (s, 3H), 3.33-3.21 (m, 2H), 3.13 (s, 3H), 2.10 (d, *J* = 16.0 Hz, 1H), 1.93-1.74 (m, 3H), 1.54-1.34 (m, 2H), 1.21-1.09 (m, 1H), 0.89 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 174.3, 173.4, 160.4, 157.2, 136.3, 133.9, 131.1, 130.0, 119.3, 118.4, 115.4, 103.6, 70.8, 70.3, 68.8, 67.2, 65.6, 60.5, 59.8, 56.6, 49.0, 48.8, 39.2, 31.5, 31.2, 26.8, 26.3, 16.9, 13.0; LRMS: (ES+) m/z = 643.1(M+23), 589.1 (M-OMe)

(S)-((2S,4R,6R)-4-(allyloxy)-6-methoxy-6-((R)-3-(4-methoxybenzyl)-2-oxothia zolidin-4-yl)tetrahydro-2H-pyran-2-yl)methyl 2-(((allyloxy)carbonyl)amino) propanoate (7.3e):



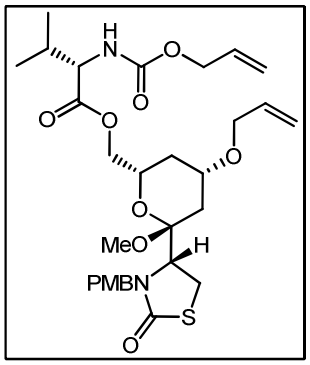
Molecular Formula: $C_{28}H_{38}N_2O_9S$; R_f : 0.2 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-86% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.21 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 5.91 (m, 2H), 5.35-5.15 (m, 5H), 5.08 (d, *J* = 14.4 Hz, 1H), 4.55 (dd, *J* = 10.0, 6.0 Hz, 2H), 4.46-4.33 (m, 2H), 4.33-4.21 (m, 3H), 4.09 (dd, *J* = 14.2, 5.6 Hz, 1H), 3.95 (*J* = 14.2, 5.6 Hz, 1H), 3.91 (s, 1H), 3.86-3.77 (m, 4H), 3.33-3.22 (m, 2H), 3.14 (s, 3H), 2.12 (d, *J* = 16.7 Hz, 1H), 1.88-1.77 (m, 2H), 1.53-1.46 (m, 1H), 1.43 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.9, 172.8, 159.1, 155.3, 134.9, 132.4, 129.8, 128.6, 117.9, 117.0, 114.0, 102.1, 69.4, 68.9, 67.5, 65.8, 64.2, 58.9, 55.2, 49.6, 47.5, 47.1, 30.0, 29.8, 29.6, 25.4, 18.6; LRMS: (ES+) m/z = 601.0 (M+23), 547.0 (M-OMe)



Compound 8.2:

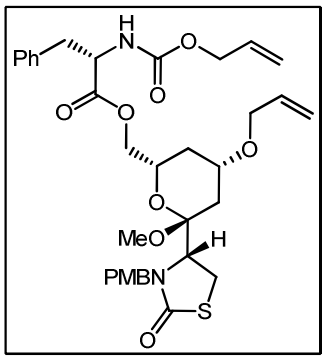
Experimental procedure as per ref. compound **7.3**.

(S)-((2S,4S,6R)-4-(allyloxy)-6-methoxy-6-((R)-3-(4-methoxybenzyl)-2-oxothia zolidin-4-yl)tetrahydro-2H-pyran-2-yl)methyl 2-(((allyloxy)carbonyl)amino)-3-methylbutanoate (8.2a):



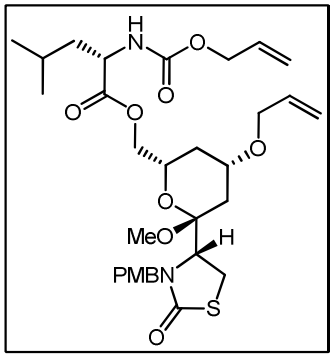
Molecular Formula: $C_{30}H_{42}N_2O_9S$; R_f : 0.5 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 ethyl acetate/hexanes); Yield-84.5% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.22 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 5.91 (m, 2H), 5.37-5.16 (m, 6H), 5.10 (d, *J* = 14.4 Hz, 1H), 4.54 (t, *J* = 5.61 Hz, 2H), 4.38-4.18 (m, 5H), 4.10-3.97 (m, 3H), 3.95-3.77 (m, 7H), 3.27 (m, 2H), 3.10 (s, 3H), 2.31 (dd, *J* = 13.0, 3.8 Hz, 1H), 2.19 (m, 2H), 2.04 (dd, *J* = 12.7, 2.4 Hz, 1H), 1.58 (dd, *J* = 12.4, 11.2 Hz, 1H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.92 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.5, 172.0, 159.0, 155.9, 134.6, 132.4, 129.7, 128.5, 117.9, 117.0, 113.9, 103.5, 70.6, 69.0, 68.1, 65.8, 59.0, 58.7, 55.1, 47.5, 33.6, 33.2, 31.0, 29.6, 25.2, 19.0, 17.4; LRMS: (ES+) m/z = 629.0 (M+23), 575.0 (M-OMe)

(S)-((2S,4S,6R)-4-(allyloxy)-6-methoxy-6-((R)-3-(4-methoxybenzyl)-2-oxothia zolidin-4-yl)tetrahydro-2H-pyran-2-yl)methyl 2-(((allyloxy)carbonyl)amino)-3-phenylpropanoate (8.2b):



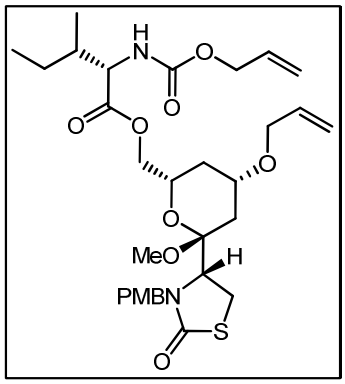
Molecular Formula: $C_{34}H_{42}N_2O_9S$; R_f : 0.5 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-80% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.34-7.18 (m, 5H), 7.18-7.09 (d, *J* = 6.4 Hz, 2H), 6.87 (d, *J* = 12.73, 8.4 Hz, 2H), 6.00-5.77 (m, 2H), 5.35-5.13 (m, 5H), 5.10 (d, *J* = 14.4, 1H), 4.73-4.61 (m, 1H), 4.57-4.46 (m, 2H), 4.25 (m, 3H), 4.06-3.99 (m, 2H), 3.90-3.75 (m, 6H), 3.33-3.19 (m, 2H), 3.17-3.02 (m, 4H), 2.28 (dd, *J* = 12.8, 3.6 Hz, 1H), 2.01-1.92 (d, *J* = 12.4 Hz, 1H), 1.55 (t, *J* = 12.4 Hz, 1H), 1.27 (t, *J* = 8.4 Hz, 1H) ; ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.5, 171.6, 159.0, 155.4, 135.4, 134.7, 132.4, 130.0, 129.8, 129.0, 128.7, 128.5, 128.3, 127.3, 117.9, 116.9, 114.0, 103.5, 70.6, 69.0, 68.0, 67.2, 65.8, 58.7, 55.2, 47.6, 47.1, 38.1, 33.7, 33.2, 25.2; LRMS: (ES+) m/z = 677.0 (M+23), 623.0 (M-OMe)

(S)-((2S,4S,6R)-4-(allyloxy)-6-methoxy-6-((R)-3-(4-methoxybenzyl)-2-oxothia zolidin-4-yl)tetrahydro-2H-pyran-2-yl)methyl 2-(((allyloxy)carbonyl)amino)-4-methylpentanoate (8.2c):



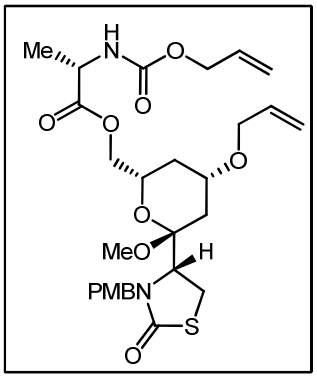
Molecular Formula: $C_{31}H_{44}N_2O_9S$; R_f : 0.5 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 ethyl acetate/hexanes); Yield-88.6% (white solid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.16 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 5.88 (m, 2H), 5.27 (d, *J* = 17.2 Hz, 2H), 5.18 (t, *J* = 9.8 Hz, 2H), 5.09 (d, *J* = 14.2, 1H), 4.51 (d, *J* = 4.11 Hz, 2H), 4.37 (m, 1H), 4.32-4.16 (m, 3H), 4.07-3.95 (m, 2H), 3.91-3.73 (m, 6H), 3.31-3.17 (m, 2H), 3.08 (s, 3H), 2.27 (dd, *J* = 12.6, 3.6 Hz, 1H), 2.06-1.97 (d, *J* = 12.8, 1H), 1.74-1.43 (m, 4H), 1.30 (m, 1H), 0.90 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 173.0, 172.5, 159.0, 155.7, 134.7, 132.4, 129.8, 128.5, 128.3, 117.9, 117.0, 114.1, 114.0, 103., 70.7, 69.0, 68.1, 67.1, 65.8, 58.7, 55.2, 52.4, 47.5, 47.0, 41.5, 33.7, 33.2, 29.6, 25.1, 24.7, 22.9, 21.5; LRMS: (ES+) m/z = 643.0 (M+23), 589.1 (M-OMe)

(2S,3R)-((2S,4S,6R)-4-(allyloxy)-6-methoxy-6-((R)-3-(4-methoxybenzyl)-2-oxothia zolidin-4-yl)tetrahydro-2H-pyran-2-yl)methyl 2-(((allyloxy)carbonyl)amino)-3-methylpentanoate (8.2d):



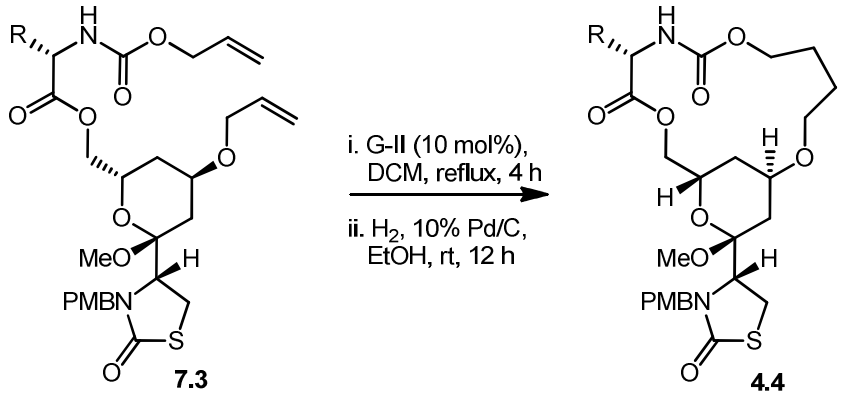
Molecular Formula: $C_{31}H_{44}N_2O_9S$; R_f : 0.5 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-80% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 1H NMR (400 MHz, *Solvent*) δ ppm 7.21 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.90 (m, 2H), 5.34-5.16 (m, 5H), 5.09 (d, *J* = 14.4 Hz, 1H), 4.59-4.46 (m, 2H), 4.39-4.17 (m, 4H), 4.03 (bs, 2H), 3.93-3.76 (m, 6H),3.26 (td, *J* = 11.62, 6.62 Hz, 2H), 3.10 (s, 3H), 2.30 (dd, *J* = 12.6, 3.8 Hz, 1H), 2.08-1.99 (m, 1H), 1.80 (d, *J* = 15.8 Hz, 1H), 1.55 (t, *J* = 11.8 Hz, 1H), 1.47-1.38 (m, 1H), 1.27 (m, 2H), 1.12 (m, 1H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.5, 172.0, 159.0, 155.8, 134.7, 132.4, 129.7, 128.6, 128.3, 117.9, 117.0, 114.1, 114.0, 103.5, 70.6, 69.0, 68.1, 67.1, 65.8, 58.8, 58.4, 55.2, 47.6, 47.0, 37.7, 33.7, 33.3, 30.0, 25.2, 24.9, 15.6, 11.5; LRMS: (ES+) m/z = 643.0 (M+23), 589.1 (M-OMe)

(S)-((2S,4S,6R)-4-(allyloxy)-6-methoxy-6-((R)-3-(4-methoxybenzyl)-2-oxothiazolidin-4-yl)tetrahydro-2H-pyran-2-yl)methyl 2-(((allyloxy)carbonyl)amino) propanoate (8.2e):



Molecular Formula: $C_{28}H_{38}N_2O_9S$; R_f : 0.2 (3:7 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-81.2% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.21 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 5.99-5.82 (m, 2H), 5.37-5.16 (m, 5H), 5.12 (d, *J* = 14.4 Hz, 1H), 4.61-4.51 (m, 2H), 4.46-4.31 (m, 2H), 4.32-4.25 (m, 1H), 4.25-4.18 (m, 1H), 4.06-3.99 (m, 2H), 3.94-3.77 (m, 6H), 3.33-3.20 (m, 2H), 3.10 (s, 3H), 2.30 (dd, *J* = 12.7, 3.2 Hz, 1H), 2.07-1.99 (m, 1H), 1.57 (dd, *J* = 12.7, 11.1 Hz, 1H), 1.42 (d, *J* = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.8, 172.5, 159.1, 155.4, 134.6, 132.4, 129.8, 128.5, 128.4, 117.9, 117.0, 114.1, 114.0, 103.5, 70.6, 69.0, 68.1, 67.2,

65.8, 58.6, 55.2, 49.6, 47.5, 47.0, 33.7, 33.2, 25.2, 18.5; LRMS: (ES+) m/z = 601.0 (M+23), 547.0 (M-OMe)

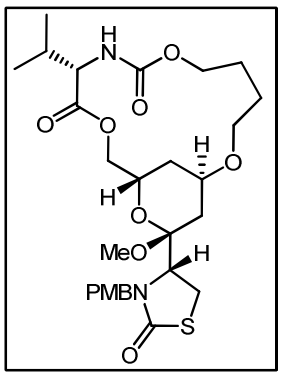


Compound 4.4:

To bisallyl compound **7.3** (0.05 mmol) was taken in dry dichloromethane (50 mL) under nitrogen atmosphere and Grubb's 2nd generation catalyst (0.005 mmol) was added and reaction mixture was refluxed for 4 h. After completion of the reaction, reaction mixture was concentrated and subjected to further reaction without purification.

To above macrocyclic compound in ethanol, 10% Pd/C (5 mg) was added and reaction mixture was stirred under hydrogen atmosphere for 12 h. The reaction mixture was passed through celite pad and concentrated then subjected to column chromatography to give pure product **4.4.**

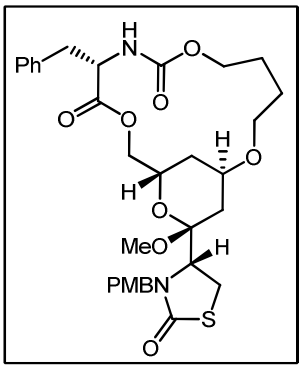
(1R,10S,14S,16R)-10-isopropyl-16-methoxy-16-((R)-3-(4-methoxybenzyl)-2-oxothi azolidin-4-yl)-2,7,12,15-tetraoxa-9-azabicyclo[12.3.1]octadecane-8,11-dione (4.4a):



Molecular Formula: $C_{28}H_{40}N_2O_9S$; R_f : 0.3 (1:1 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-63.2%

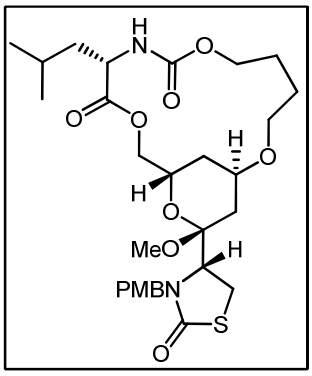
(colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.18 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 5.03 (d, *J* = 14.4 Hz, 1H), 4.89 (dd, *J* = 15.2, 8.0 Hz, 1H), 4.77 (t, *J* = 8.0 Hz 1H), 4.68 (dd, *J* = 14.0, 3.2 Hz, 1H), 4.17 (m, 4H), 3.82 (m, 10H), 3.52-3.39 (m, 1H), 3.36-3.07 (m, 7H), 2.38-2.25 (m, 1H), 2.18 (m, 2H), 2.01 (m, 3H), 1.91-1.78 (m, 3H), 1.35 (m, 2H), 1.04 (d, *J* = 6.8 Hz, 3H), 0.95 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 173.2, 170.8, 159.1, 156.6, 129.8, 129.7, 128.4, 114.0, 102.4, 71.7, 70.6, 65.8, 65.5, 63.8, 60.0, 59.0, 55.2, 47.9, 47.5, 32.7, 31.9, 30.9, 29.6, 28.0, 25.9, 25.3, 22.6, 19.3, 17.7; LRMS: (ES+) m/z = 603.1(M+23), 549.1 (M-OMe)

(1R,10S,14S,16R)-10-benzyl-16-methoxy-16-((R)-3-(4-methoxybenzyl)-2-oxothiazolidin-4-yl)-2,7,12,15-tetraoxa-9-azabicyclo[12.3.1]octadecane-8,11-dione (4.4b):



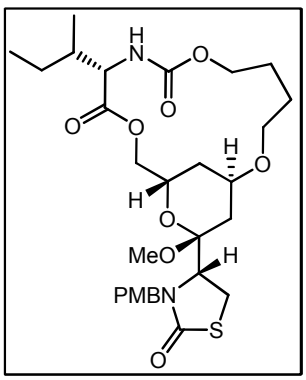
Molecular Formula: $C_{32}H_{40}N_2O_9S$; R_f : 0.4 (2:3 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-60.5% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.43-7.28 (m, 3H), 7.19 (d, *J* = 8.2 Hz, 4H), 6.89 (d, *J* = 8.4 Hz, 2H), 5.05 (d, *J* = 14.4 Hz, 1H), 4.82 (d, *J* = 8.4 Hz, 1H), 4.53 (m, 2H), 4.22-4.07 (m, 2H), 3.88-3.79 (m, 6H), 3.77 (m, 2H), 3.71 (m, 1H), 3.33-3.07 (m, 7H), 3.40 (m, 1H), 2.95-2.75 (m, 1H), 2.04 (m, 5H), 1.80 (m, 2H), 1.46 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 173.0, 170.8, 159.0, 156.0, 135.7, 135.7, 129.7, 128.9, 128.8, 128.3, 127.2, 114.0, 102.3, 71.5, 70.3, 67.0, 66.1, 65.1, 63.6, 58.9, 55.1, 53.3, 52.7, 51.9, 47.7, 47.4, 38.2, 36.6, 29.5, 25.5, 25.2; LRMS: (ES+) m/z = 651.2 (M+23), 597.1 (M-OMe)

(1R,10S,14S,16R)-10-isobutyl-16-methoxy-16-((R)-3-(4-methoxybenzyl)-2-oxothia zolidin-4-yl)-2,7,12,15-tetraoxa-9-azabicyclo[12.3.1]octadecane-8,11-dione (4.4c):



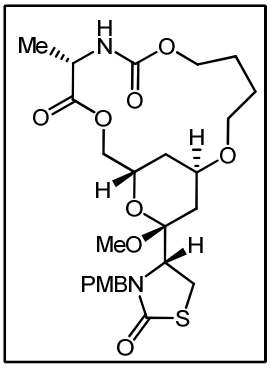
Molecular Formula: $C_{29}H_{42}N_2O_9S$; R_f : 0.4 (2:3 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-61.5% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.18 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 5.05 (d, *J* = 14.4 Hz, 1H), 4.85 (d, *J* = 8.4 Hz, 1H), 4.72 (t, *J* = 8.4 Hz, 1H), 4.60 (dd, *J* = 10.0, 2.8 Hz, 1H), 4.44-4.28 (m, 2H), 4.23-4.09 (m, 3H), 3.88-3.66 (m, 9H), 3.52-3.39 (m, 1H), 3.35-3.18 (m, 3H), 3.14 (s, 3H), 2.16 (m, 1H), 2.02 (dd, *J* = 13.2, 9.6 Hz, 2H), 1.93-1.80 (m, 2H), 1.77-1.70 (m, 2H), 1.54 (t, *J* = 6.0 Hz, 1H), 0.95 (t, *J* = 6.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 173.1, 171.7, 159.1, 156.3, 129.8, 128.4, 114.1, 102.4, 71.6, 70.4, 66.0, 65.4, 63.8, 59.0, 55.2, 53.4, 53.0, 47.9, 47.4, 39.8, 32.7, 32.6, 29.6, 27.8, 25.3, 24.7, 22.9, 21.3; LRMS: (ES+) m/z = 617.1(M+23), 563.1 (M-OMe)

(1R,10S,14S,16R)-10-((R)-sec-butyl)-16-methoxy-16-((R)-3-(4-methoxybenzyl)-2-oxothiazolidin-4-yl)-2,7,12,15-tetraoxa-9-azabicyclo[12.3.1]octadecane-8,11-dione (4.4d):

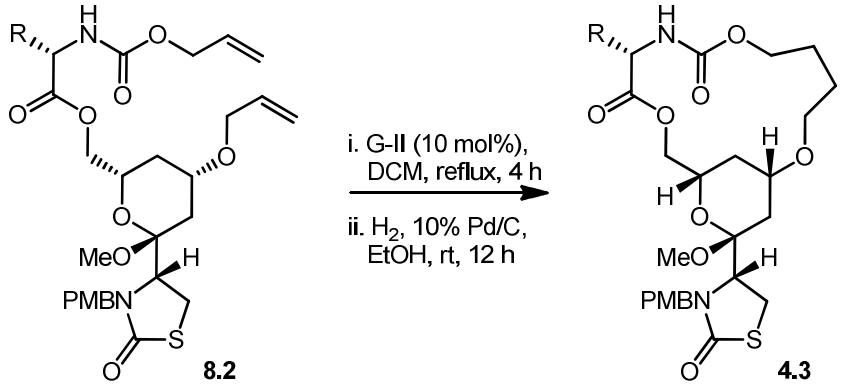


Molecular Formula: $C_{29}H_{42}N_2O_9S$; R_f : 0.4 (2:3 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-60% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.18 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.4 Hz, 2H), 5.05 (d, *J* = 14.4 Hz, 1H), 4.87 (d, *J* = 9.2 Hz, 1H), 4.75 (t, *J* = 8.4 Hz, 1H), 4.65 (dd, *J* = 8.8, 3.6 Hz, 1H), 4.32-4.07 (m, 4H), 3.82 (s, 8H), 3.54-3.40 (m, 1H), 3.21 (m, 6H), 2.20-2.11 (m, 1H), 2.08-1.97 (m, 3H), 1.94-1.80 (m, 4H), 1.63-1.47 (m, 3H), 1.01 (d, *J* = 6.85 Hz, 3H), 0.93 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 173.1, 170.9, 159.1, 156.6, 129.8, 128.4, 114.0, 102.4, 71.7, 70.6, 65.8, 65.5, 63.8, 59.3, 59.0, 55.2, 53.4, 47.9, 47.5, 36.1, 32.8, 32.6, 29.6, 25.9, 25.3, 25.0, 14.1, 11.5; LRMS: (ES+) m/z = 617.1(M+23), 563.1 (M-OMe)

(1R,10S,14S,16R)-16-methoxy-16-((R)-3-(4-methoxybenzyl)-2-oxothiazolidin-4-yl)-10-methyl-2,7,12,15-tetraoxa-9-azabicyclo[12.3.1]octadecane-8,11-dione (4.4e):



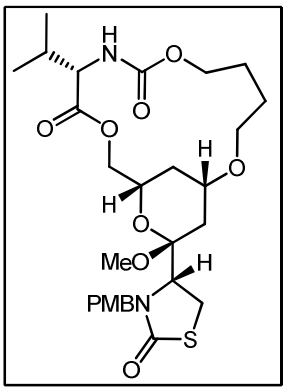
Molecular Formula: $C_{26}H_{36}N_2O_9S$; R_f : 0.3 (1:1 ethyl acetate/hexanes); Solvent system for column purification (2:3 to 1:1 ethyl acetate/hexanes); Yield-65.9% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.17 (d, *J* = 8.4 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.06 (d, *J* = 14.4 Hz, 1H), 4.95 (d, *J* = 8.0 Hz, 1H), 4.78-4.63 (m, 1H), 4.50 (dd, *J* = 10.0, 2.4 Hz, 1H), 4.39-4.36 (m, 1H), 4.25-4.10 (m, 3H), 3.92-3.70 (m, 9H), 3.52-3.36 (m, 1H), 3.35-3.08 (m, 6H), 2.16 (d, *J* = 12.2 Hz, 1H), 2.09-1.97 (m, 3H), 1.91-1.78 (m, 3H), 1.70-1.55 (m, 2H), 1.45 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 173.2, 169.3, 15.9.1, 156.1, 129.8, 129.7, 129.7, 128.4, 114.1, 102.4, 71.6, 70.5, 66.1, 65.2, 63.8, 59.0, 55.2, 50.0, 47.8, 47.4, 31.9, 29.6, 27.7, 25.9, 25.3, 22.6; LRMS: (ES+) m/z = 575.0(M+23), 521.0 (M-OMe)



Compound 4.3:

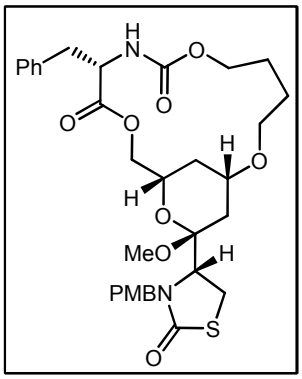
Experimental procedure as per ref. compound **4.4**.

(1S,10S,14S,16R)-10-isopropyl-16-methoxy-16-((R)-3-(4-methoxybenzyl)-2-oxothi azolidin-4-yl)-2,7,12,15-tetraoxa-9-azabicyclo[12.3.1]octadecane-8,11-dione (4.3a):



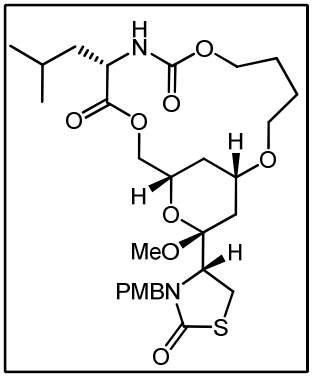
Molecular Formula: $C_{28}H_{40}N_2O_9S$; R_f : 0.3 (1:1 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-67.5% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.17 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4 Hz, 2H), 5.13 (d, *J* = 14.4 Hz, 2H), 4.70 (t, *J* = 9.6 Hz, 1H), 4.55 (dd, *J* = 10.0, 4.0 Hz, 1H), 4.24-4.11 (m, 2H), 4.07 (t, *J* = 8.4 Hz, 1H), 3.91-3.65 (m, 9H), 3.57-3.45 (m, 1H), 3.33-3.18 (m, 2H), 3.09 (s, 3H), 2.21-2.14 (m, 2H), 2.12-2.01 (m, 2H), 1.87-1.76 (m, 2H), 1.70-1.60 (m, 5H), 1.03 (m, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.7, 171.7, 159.0, 156.8, 129.7, 128.4, 128.3, 114.0, 103.7, 71.9, 67.1, 66.9, 64.9, 60.8, 58.4, 55.2, 47.6, 47.1, 34.5, 34.4, 31.8, 29.6, 26.6, 25.1, 19.2, 18.4, 14.0; LRMS: (ES+) m/z = 603.1(M+23), 549.0 (M-OMe)

(1S,10S,14S,16R)-10-benzyl-16-methoxy-16-((R)-3-(4-methoxybenzyl)-2-oxothia zolidin-4-yl)-2,7,12,15-tetraoxa-9-azabicyclo[12.3.1]octadecane-8,11-dione (4.3b):



Molecular Formula: $C_{32}H_{40}N_2O_9S$; R_f : 0.4 (2:3 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-61.8% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.37-7.11 (m, 8H), 6.87 (d, *J* = 8.47 Hz, 2H), 5.15 (d, *J* = 8.4 Hz, 1H), 5.09 (d, *J* = 14.4 Hz, 1H), 4.60-4.45 (m, 2H), 4.16-4.05 (m, 2H), 3.89-3.65 (m, 7H), 3.57-3.43 (m, 1H), 3.32-2.97 (m, 7H), 2.21-2.02 (m, 4H), 1.90-1.75 (m, 1H), 1.59 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.7, 171.3, 159.1, 156.4, 135.7, 129.9, 129.0, 128.8, 128.4, 127.2, 114.1, 114.0, 103.8, 71.9, 67.6, 66.9, 65.3, 63.4, 60.4, 58.5, 55.8, 55.2, 47.6, 47.1, 36.8, 34.5, 29.6, 25.2, 24.9; LRMS: (ES+) m/z = 651.0 (M+23), 597.0 (M-OMe)

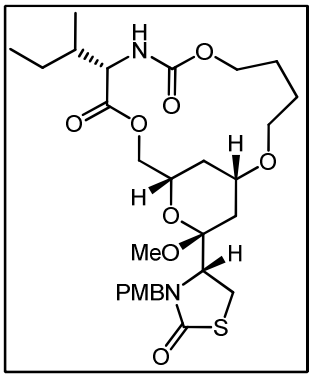
(1S,10S,14S,16R)-10-isobutyl-16-methoxy-16-((R)-3-(4-methoxybenzyl)-2-oxothia zolidin-4-yl)-2,7,12,15-tetraoxa-9-azabicyclo[12.3.1]octadecane-8,11-dione (4.3c):



Molecular Formula: $C_{29}H_{42}N_2O_9S$; R_f : 0.4 (2:3 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-60.3% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.18 (d, *J* = 8.4 Hz, 2H),

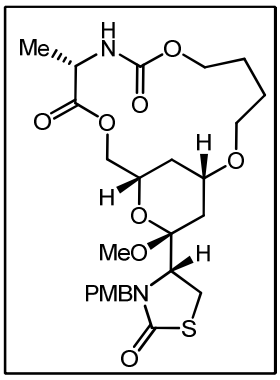
6.87 (d, *J* = 8.4 Hz, 2H), 5.14 (d, *J* = 14.4 Hz, 1H), 5.03 (d, *J* = 8.0 Hz, 1H), 4.66 (t, *J* = 8.8 Hz, 1H), 4.52 (dd, *J* = 10.0 Hz, *J* = 4.0 Hz, 1H), 4.36-4.27 (m, 1H), 4.17 (d, *J* = 14.4 Hz, 2H), 3.84 (m, 8H), 3.75-3.68 (m, 1H), 3.58-3.49 (m, 1H), 3.33-3.20 (m, 2H), 3.10 (s, 3H), 2.44-2.29 (m, 1H), 2.23-2.14 (m, 2H), 1.86-1.77 (m, 1H), 1.62 (m, 7H), 0.93 (d, *J* = 6.4 Hz, 3H), 0.85 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.7, 172.3, 159.0, 156.5, 129.7, 128.4, 114.0, 103.7, 71.8, 67.2, 66.9, 65.1, 63.2, 58.5, 55.2, 53.4, 47.6, 47.1, 39.8, 34.6, 34.4, 29.6, 26.5, 25.5, 25.1, 24.7, 22.6, 21.6; LRMS: (ES+) m/z = 617.1(M+23), 563.0 (M-OMe)

(1S,10S,14S,16R)-10-((R)-sec-butyl)-16-methoxy-16-((R)-3-(4-methoxybenzyl)-2-oxothiazolidin-4-yl)-2,7,12,15-tetraoxa-9-azabicyclo[12.3.1]octadecane-8,11-dione (4.3d):



Molecular Formula: $C_{29}H_{42}N_2O_9S$; R_f : 0.4 (2:3 ethyl acetate/hexanes); Solvent system for column purification (3:7 to 2:3 ethyl acetate/hexanes); Yield-65% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.17 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 5.12 (d, *J* = 14.2 Hz, 2H), 4.66 (t, *J* = 9.6 Hz, 1H), 4.51 (dd, *J* = 10.0, 4.0 Hz, 1H), 4.23-4.07 (m, 3H), 3.88-3.62 (m, 9H), 3.56-3.43 (m, 1H), 3.31-3.17 (m, 2H), 3.08 (s, 3H), 2.25-2.15 (m, 2H), 2.05 (d, *J* = 10.4 Hz, 1H), 1.88-1.74 (m, 2H), 1.70-1.48 (m, 6H), 0.97 (t, *J* = 6.4 Hz, 3H), 0.93-0.86 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.7, 171.8, 159.1, 156.8, 129.8, 128.4, 114.0, 103.8, 71.9, 67.1, 67.0, 65.0, 63.1, 59.6, 58.5, 55.2, 47.6, 47.1, 36.0, 34.5, 34.4, 29.6, 26.6, 25.2, 24.9, 15.6, 10.9; LRMS: (ES+) m/z = 617.1(M+23), 563.0 (M-OMe)

(1S,10S,14S,16R)-16-methoxy-16-((R)-3-(4-methoxybenzyl)-2-oxothiazolidin-4-yl)-10-methyl-2,7,12,15-tetraoxa-9-azabicyclo[12.3.1]octadecane-8,11-dione (4.3e):



Molecular Formula: $C_{26}H_{36}N_2O_9S$; R_f : 0.3 (1:1 ethyl acetate/hexanes); Solvent system for column purification (2:3 to 1:1 ethyl acetate/hexanes); Yield-63.8% (colourless liquid); ^{1}H NMR ($CDCl_3$, 400 MHz): δ ppm 7.16 (d, *J* = 8.41 Hz, 2H), 6.85 (d, *J* = 8.63 Hz, 2H), 5.15 (d, *J* = 8.0 Hz, 1H), 5.11 (d, *J* = 14.4 Hz, 1H), 4.59 (t, *J* = 11.2 Hz, 1H), 4.50 (dd, *J* = 10.4, 4.4 Hz, 1H), 4.36-4.24 (m, 1H), 4.20-4.04 (m, 2H), 3.91-3.66 (m, 8H), 3.57-3.43 (m, 1H), 3.23 (m, 2H), 3.08 (s, 3H), 2.16 (dd, *J* = 11.9, 3.4 Hz, 2H), 2.06 (d, *J* = 11.2 Hz, 1H), 1.87-1.77 (m, 1H), 1.74-1.52 (m, 5H), 1.42 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ ppm 172.7, 172.3, 159.1, 156.4, 129.8, 128.4, 128.3, 114.1, 114.0, 103.8, 71.9, 67.4, 66.9, 65.3, 63.3, 58.5, 55.2, 50.4, 47.6, 47.1, 34.8, 34.4, 31.9, 29.6, 26.6, 25.2, 24.9, 22.6, 16.8; LRMS: (ES+) m/z = 575.0 (M+23), 521.0 (M-OMe)

5.7. References:

(1) Tietze, L. F.; Bell, H. P.; Chandrasekhar, S. *Angew. Chem. Int. Ed.* **2003**, *42*, 3996.

(2) Kuboyama, T.; Yokoshima, S.; Tokuyama, H.; Fukuyama, T. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 11966.

(3) Kato, D.; Sasaki, Y.; Boger, D. L. *J. Am. Chem. Soc.* **2010**, *132*, 3685.

(4) Raucher, S.; Bray, B. L. *J. Org. Chem.* **1985**, *50*, 3236.

(5) Shiozawa, H.; Kagasaki, T.; Kinoshita, T.; Haruyama, H.; Domon, H.; Utsui, Y.; Kodama, K.; Takahashi, S. *J. Antibiotics* **1993**, *46*, 1834.

(6) Sutherland, R.; Boon, R.; Griffin, K.; Masters, P.; Slocombe, B.; White, A. *Antimicrob. Agents Ch.*. **1985**, *27*, 495.

(7) (a) Gunasekera, S. P.; Gunasekera, M.; Longley, R. E.; Schulte, G. K. *J. Org. Chem.* **1990**, *55*, 4912. (b) Mita, A.; Lockhart, A.; Chen, T.; Bochinski, K.;

Curtright, J.; Cooper, W.; Hammond, L.; Rothenberg, M.; Rowinsky, E.; Sharma, S. *J. Clin. Oncol.* **2004**, *22*, 2025.

(8) (a) Pettit, G. R.; Cichacz, Z. A.; Gao, F.; Boyd, M. R.; Schmidt, J. M. *J. Chem. Soc., Chem. Comm.* **1994**, 1111. (b) Shin, Y.; Fournier, J. H.; Fukui, Y.; Brückner, A. M.; Curran, D. P. *Angew. Chem. Int. Ed.***2004**, *43*, 4634. (c) Madiraju, C.; Edler, M. C.; Hamel, E.; Raccor, B. S.; Balachandran, R.; Zhu, G.; Giuliano, K. A.; Vogt, A.; Shin, Y.; Fournier, J.-H.; Fukui, Y.; Brückner, A. M.; Curran, D. P.; Day, B. W. *Biochemistry* **2005**, *44*, 15053.

(9) Paterson, I.; Gardner, N. M. *Chem. Comm.* **2007**, 49.

(10) Smith, C. D.; Zhang, X.; Mooberry, S. L.; Patterson, G. M.; Moore, R. E. *Cancer Res.* **1994**, *54*, 3779.

(11) Höfle, G.; Bedorf, N.; Steinmetz, H.; Schomburg, D.; Gerth, K.; Reichenbach, H. *Angew. Chem. Int. Ed.* **1996**, *35*, 1567.

(12) Bollag, D. M.; McQueney, P. A.; Zhu, J.; Hensens, O.; Koupal, L.; Liesch, J.; Goetz, M.; Lazarides, E.; Woods, C. M. *Cancer Res.* **1995**, *55*, 2325.

(13) Hamel, E. *Med. Res. Rev.* **1996**, *16*, 207.

(14) Nicolaou, K.; Roschangar, F.; Vourloumis, D. *Angew. Chem. Int. Ed.***1998**, *37*, 2014.

(15) White, J. D.; Smits, H.; Hamel, E. *Org. Lett.* **2006**, *8*, 3947.

(16) Ikeda, Y.; Schultz, L. W.; Clardy, J.; Schreiber, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 4143.

(17) (a) Aeluri, M.; Gaddam, J.; Trinath, D. V.; Chandrasekar, G.; Kitambi, S. S.; Arya, P. *Eur. J. Org. Chem.* **2013**, *2013*, 3955. (b) Aeluri, M.; Pramanik, C.; Chetia, L.; Mallurwar, N. K.; Balasubramanian, S.; Chandrasekar, G.; Kitambi, S. S.; Arya, P. *Org. Lett.* **2013**, *15*, 436.

(18) (a) Schatten, G.; Schatten, H.; Spector, I.; Cline, C.; Paweletz, N.; Simerly, C.; Petzelt, C. *Exp. Cell Res.* **1986**, *166*, 191. (b) Spector, I.; Shochet, N. R.; Blasberger, D.; Kashman, Y. *Cell Motil. Cytoskel.* **1989**, *13*, 127.

(19) Spector, I.; Shochet, N. R.; Kashman, Y.; Groweiss, A. *Science* **1983**, *219*, 493.

(20) Kashman, Y.; Groweiss, A.; Shmueli, U. *Tetrahedron Lett.* **1980**, *21*, 3629.

(21) Morton, W. M.; Ayscough, K. R.; McLaughlin, P. J. *Nat. Cell Biol.* **2000**, *2*, 376.

(22) Williams, B. D.; Smith III, A. B. *Org. Lett.* **2013**, *15*, 4584.

(23) (a) White, J. D.; Kawasaki, M. *J. Am. Chem. Soc.* **1990**, *112*, 4991. (b) Zibuck, R.; Liverton, N. J.; Smith, A. B. *J. Am. Chem. Soc.* **1986**, *108*, 2451.

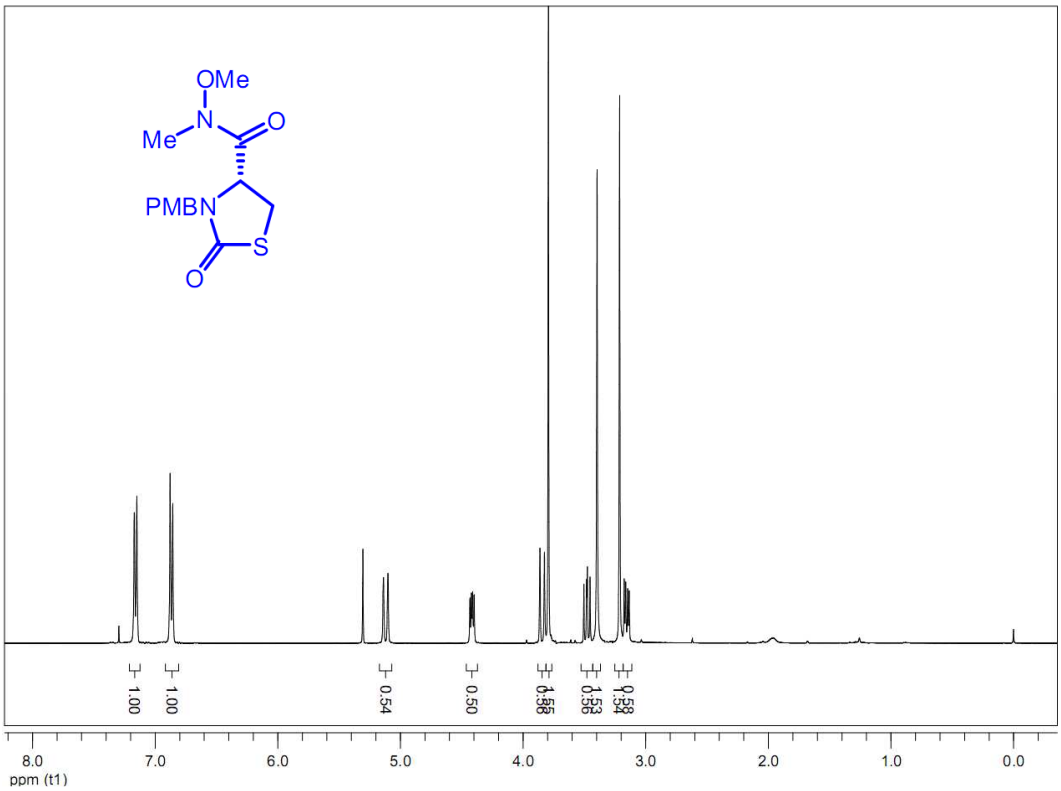
(24) (a) Fürstner, A.; De Souza, D.; Parra-Rapado, L.; Jensen, J. T. *Angew. Chem. Int. Ed.* **2003**, *115*, 5516. (b) Fürstner, A.; Turet, L. *Angew. Chem. Int. Ed.* **2005**, *117*, 3528. (c) Fürstner, A.; Kirk, D.; Fenster, M. D.; Aïssa, C.; De Souza, D.; Nevado, C.; Tuttle, T.; Thiel, W.; Müller, O. *Chem. Eur. J.* **2007**, *13*, 135.

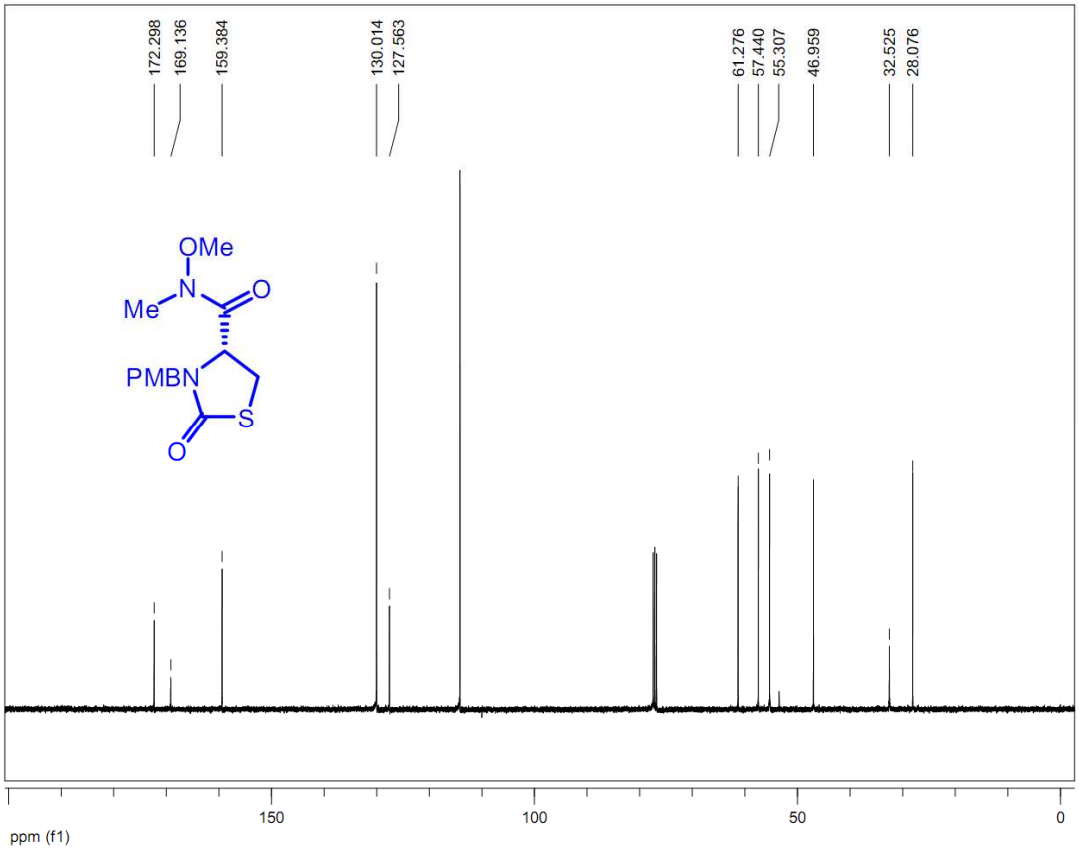
(25) (a) Aponick, A.; Li, C.-Y.; Palmes, J. A. *Org. Lett.* **2008**, *11*, 121. (b) Patron, A. P.; Richter, P. K.; Tomaszewski, M. J.; Miller, R. A.; Nicolaou, K. C. *Chem. Comm.* **1994**, 1147.

(26) Maier, M. E. *Angew. Chem. Int. Ed.***2000**, *39*, 2073.

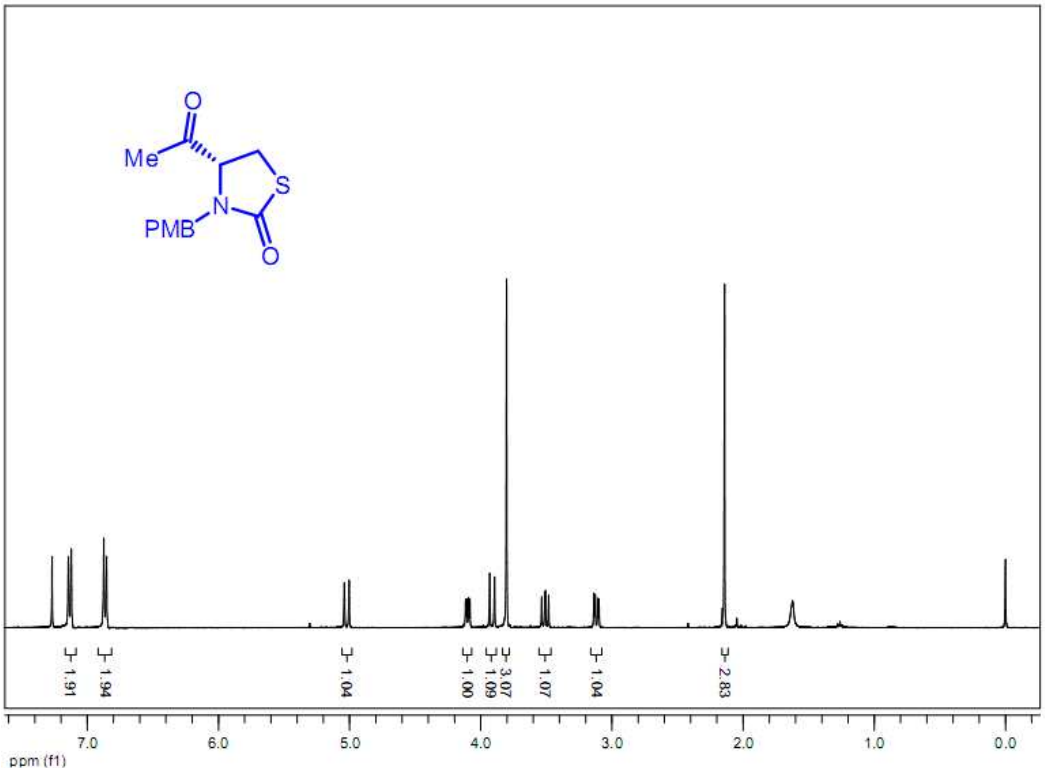
(27) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446.

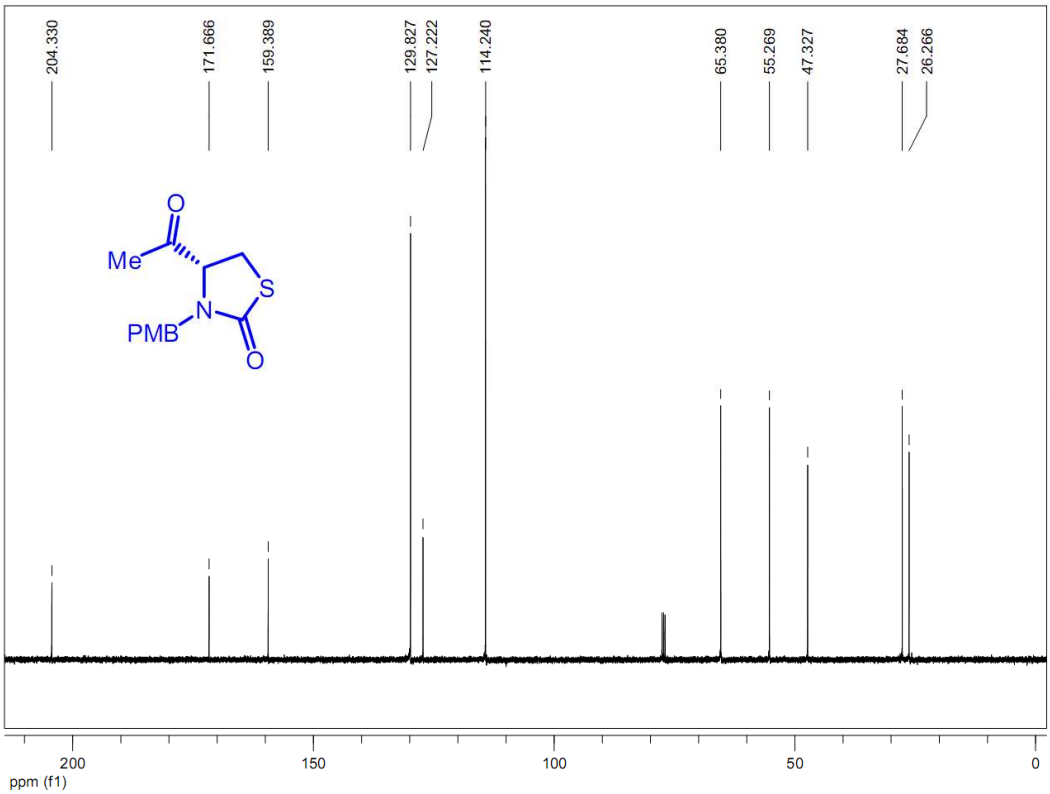
5.8. Spectra:



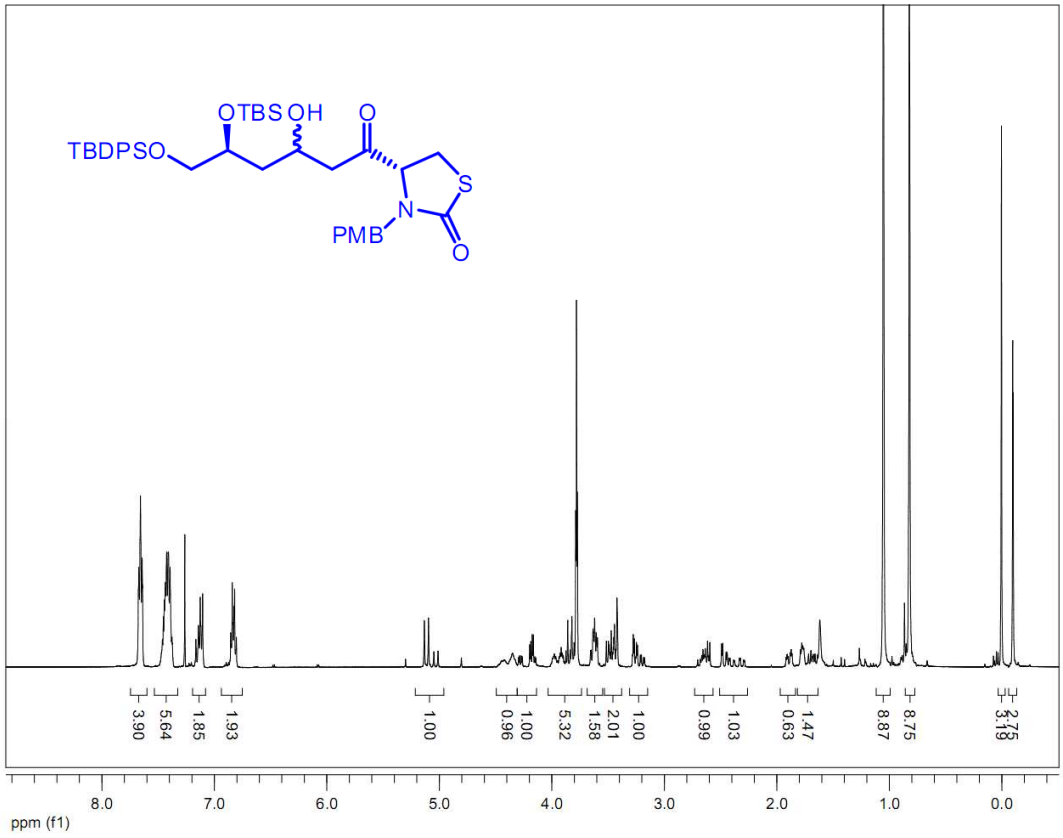


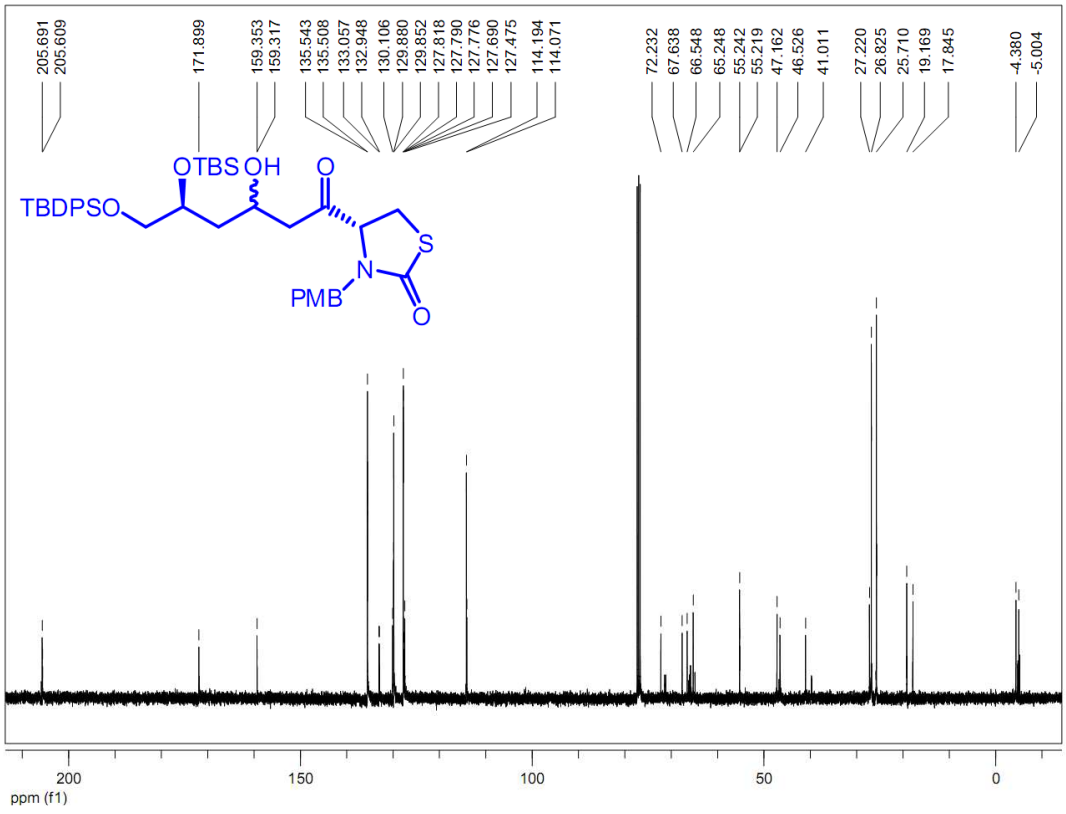
^{1}H and ^{13}C spectra of compound **6.2**



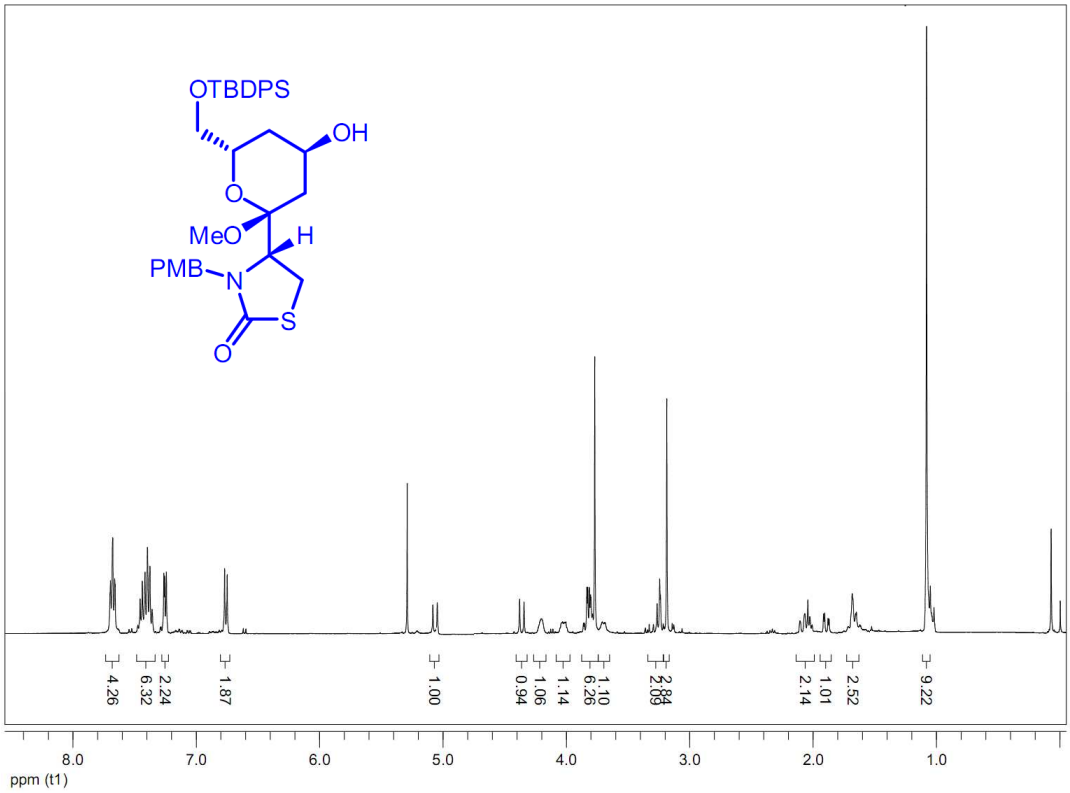


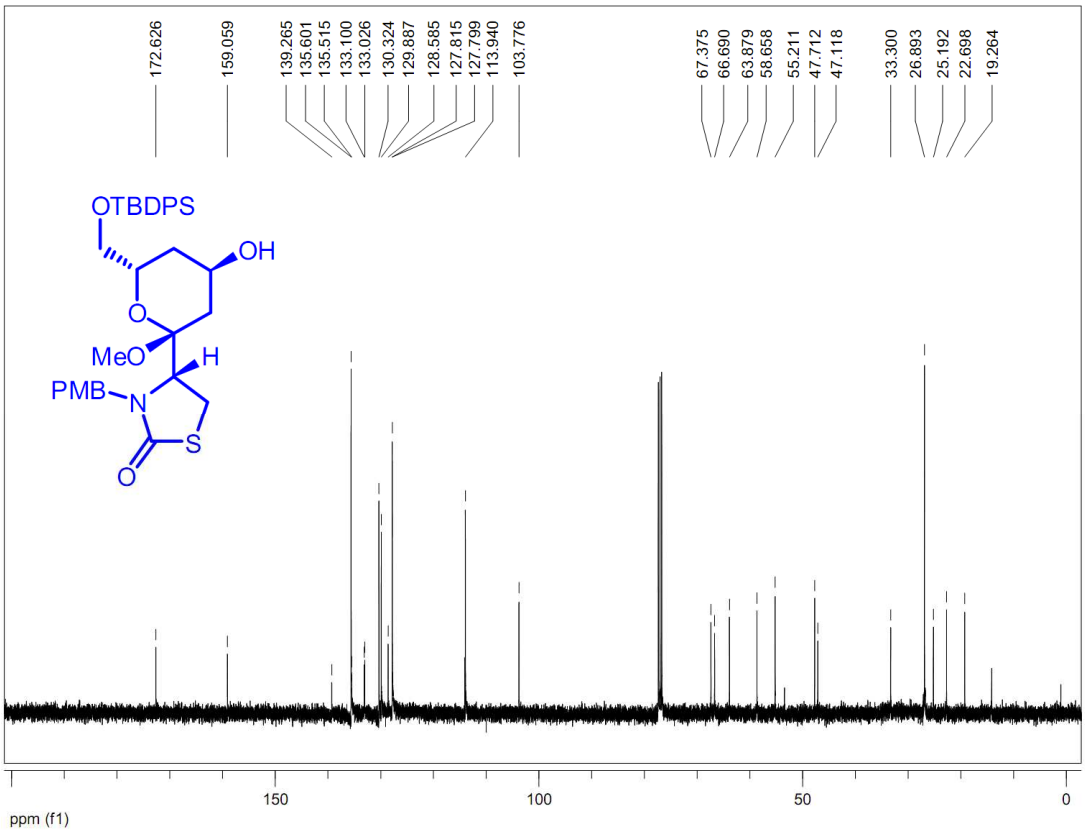
^{1}H and ^{13}C spectra of compound **6.3**



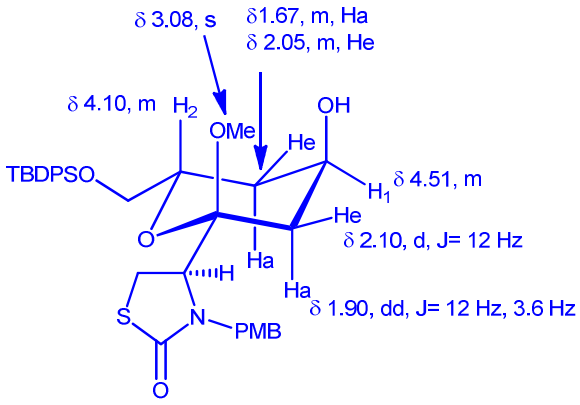


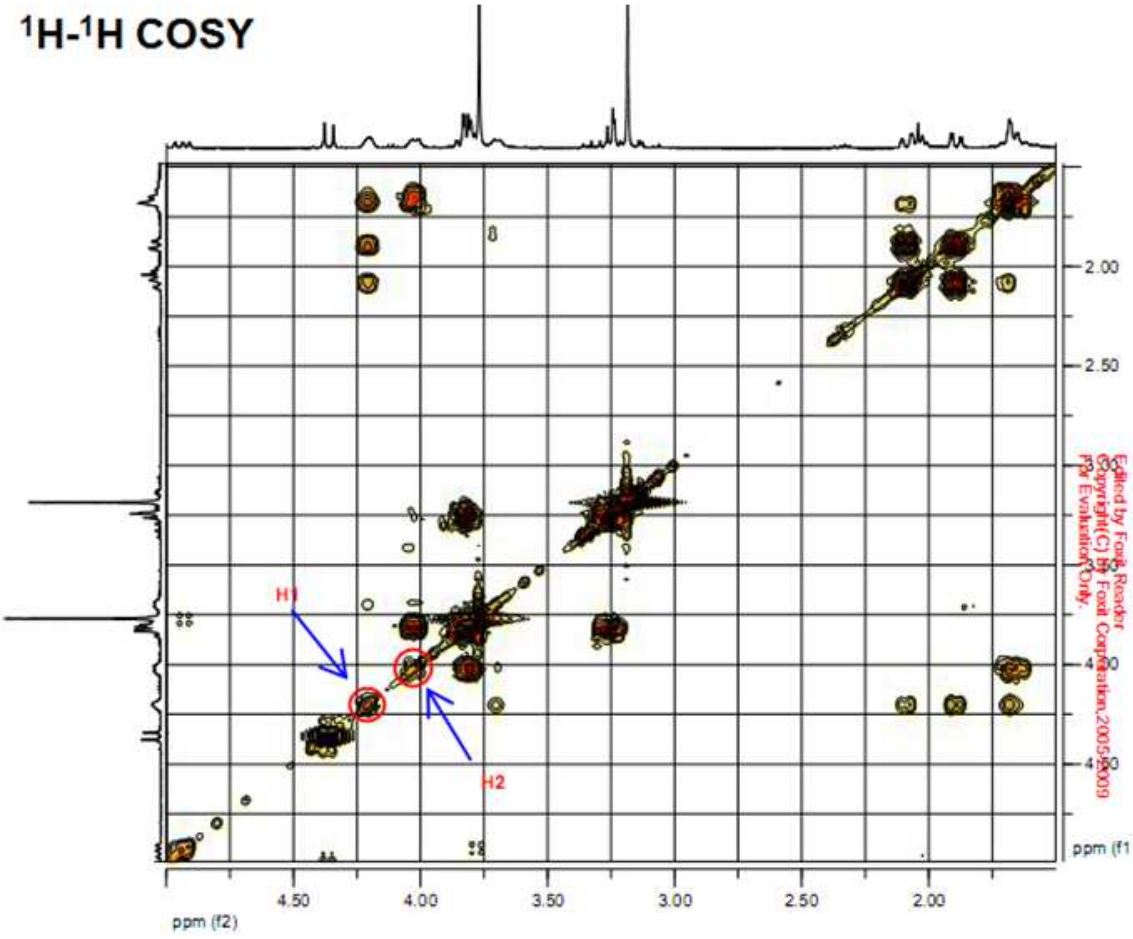
^{1}H and ^{13}C spectra of compound **6.5**



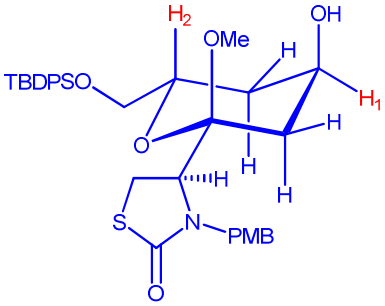


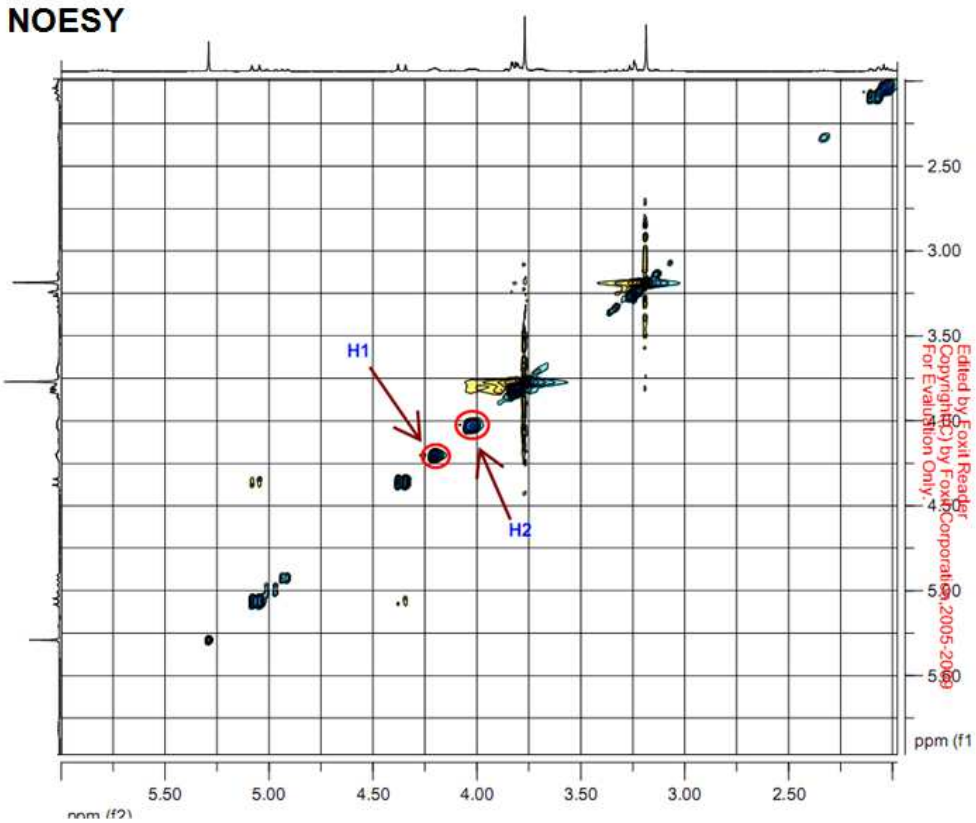
^{1}H and ^{13}C spectra of compound **6.7**



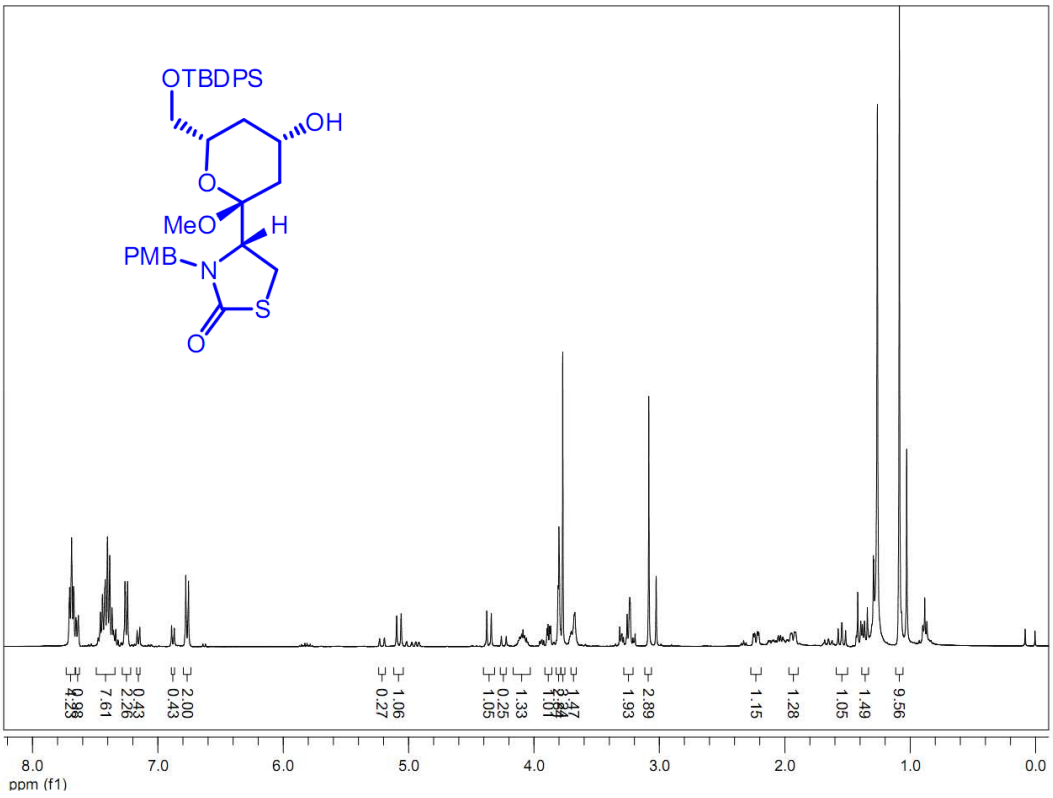


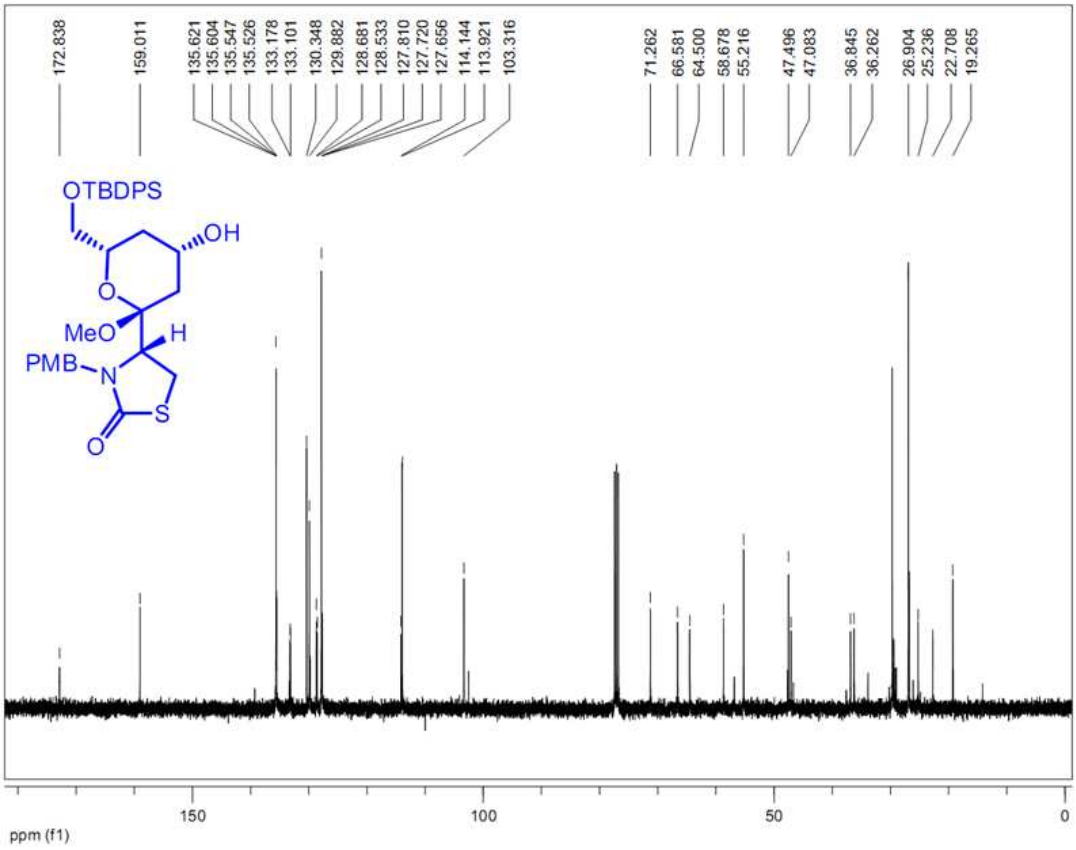
^{1}H-^{1}H COSY spectrum of compound **6.7**



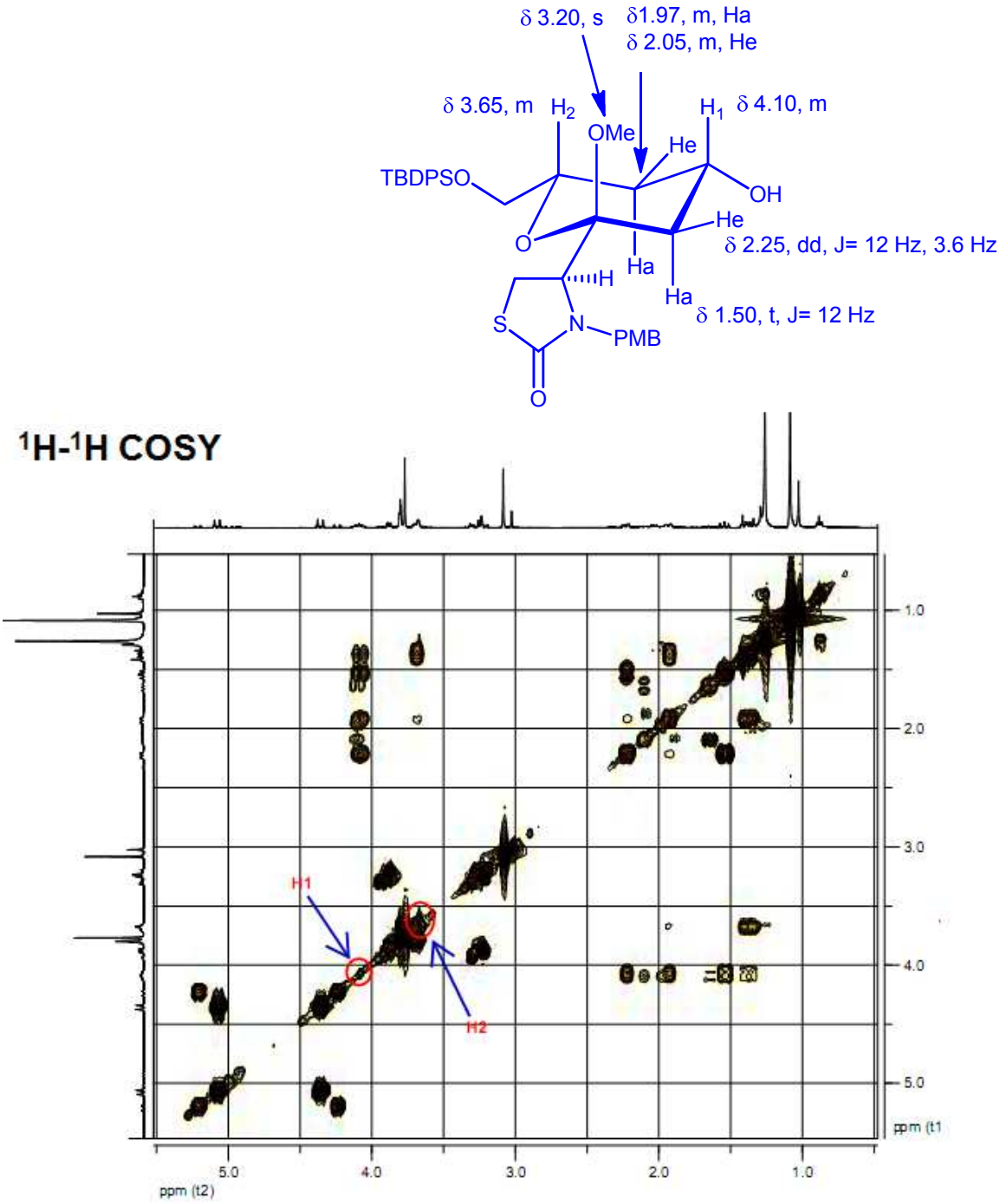


NOESY spectrum of compound **6.7**

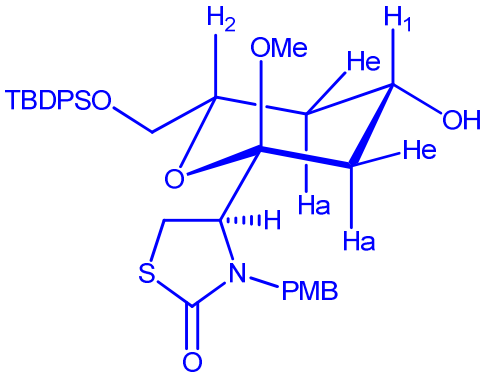


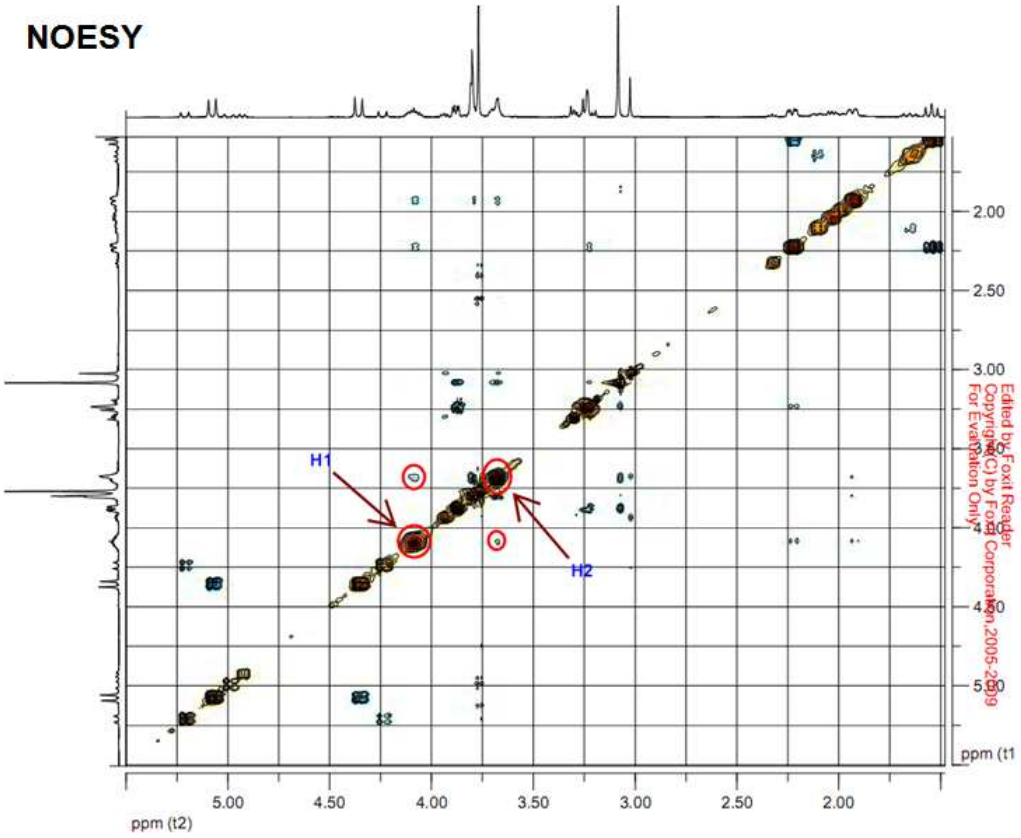


^{1}H and ^{13}C spectra of compound **6.6**

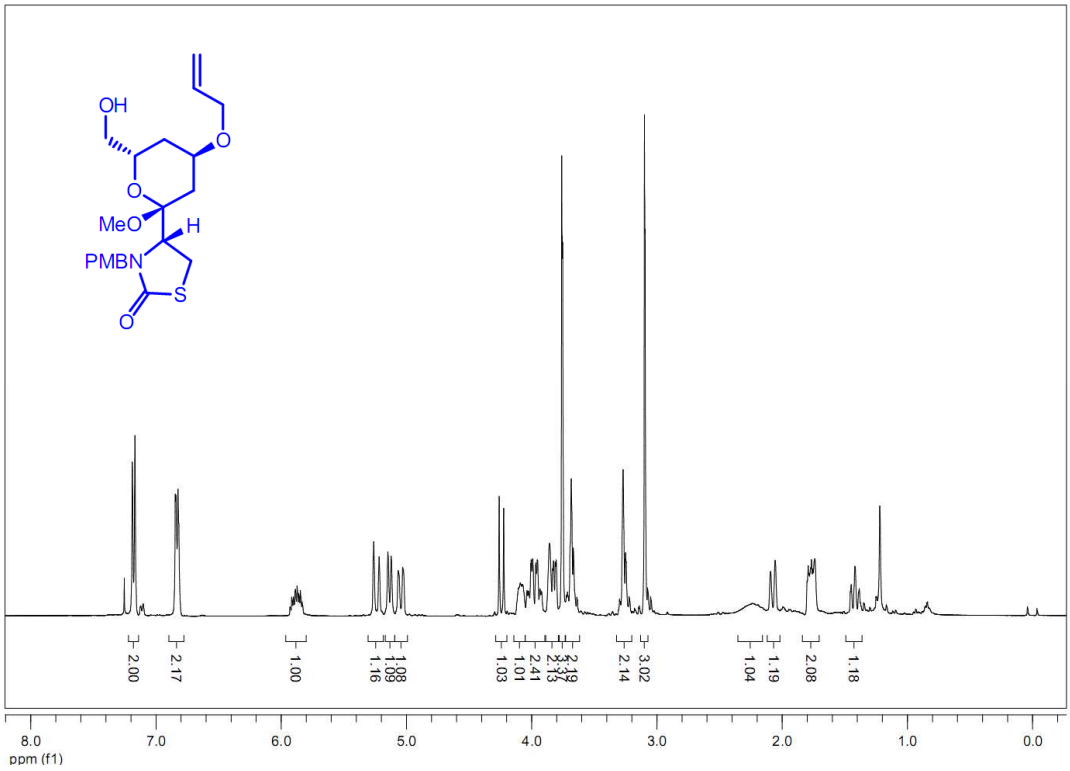


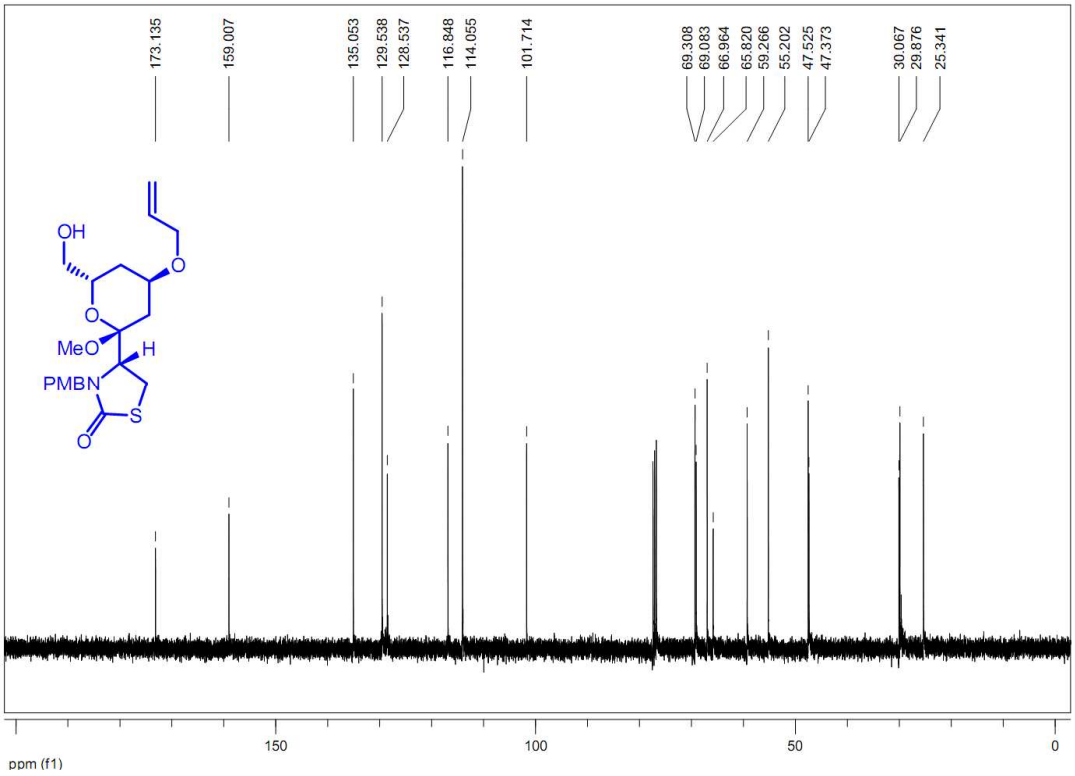
^{1}H-^{1}H COSY spectrum of compound **6.6**



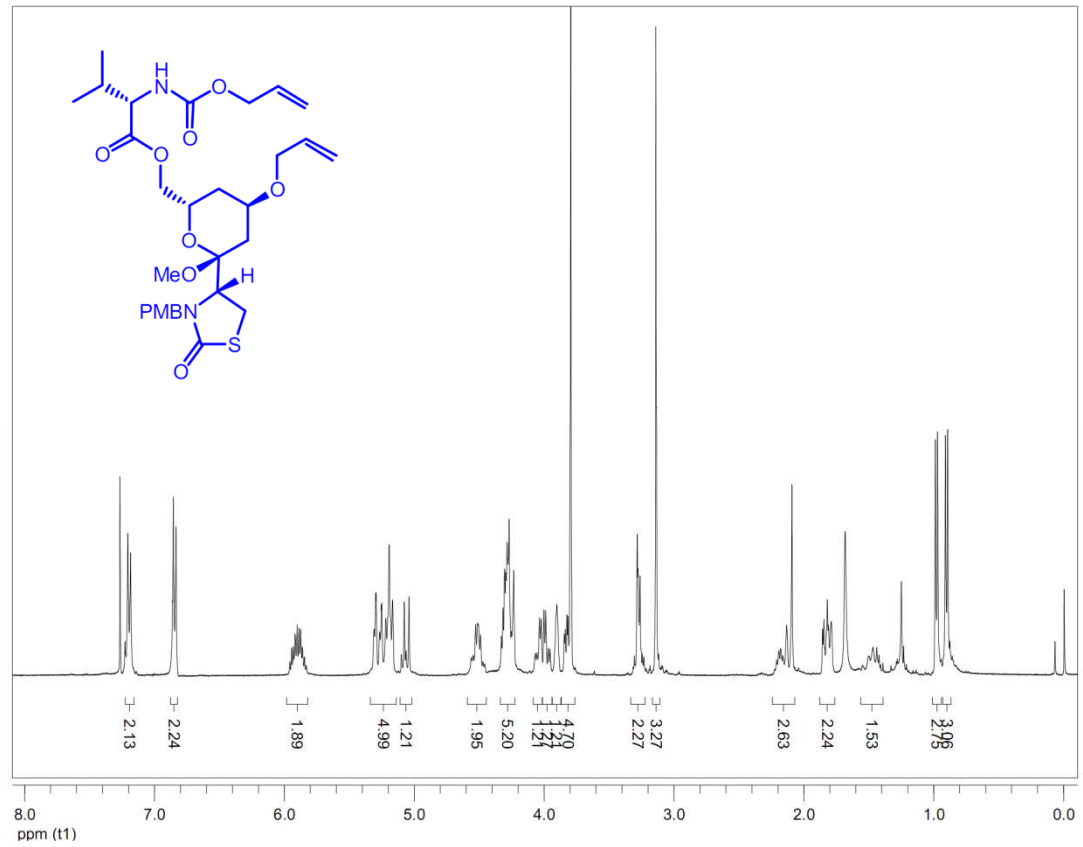


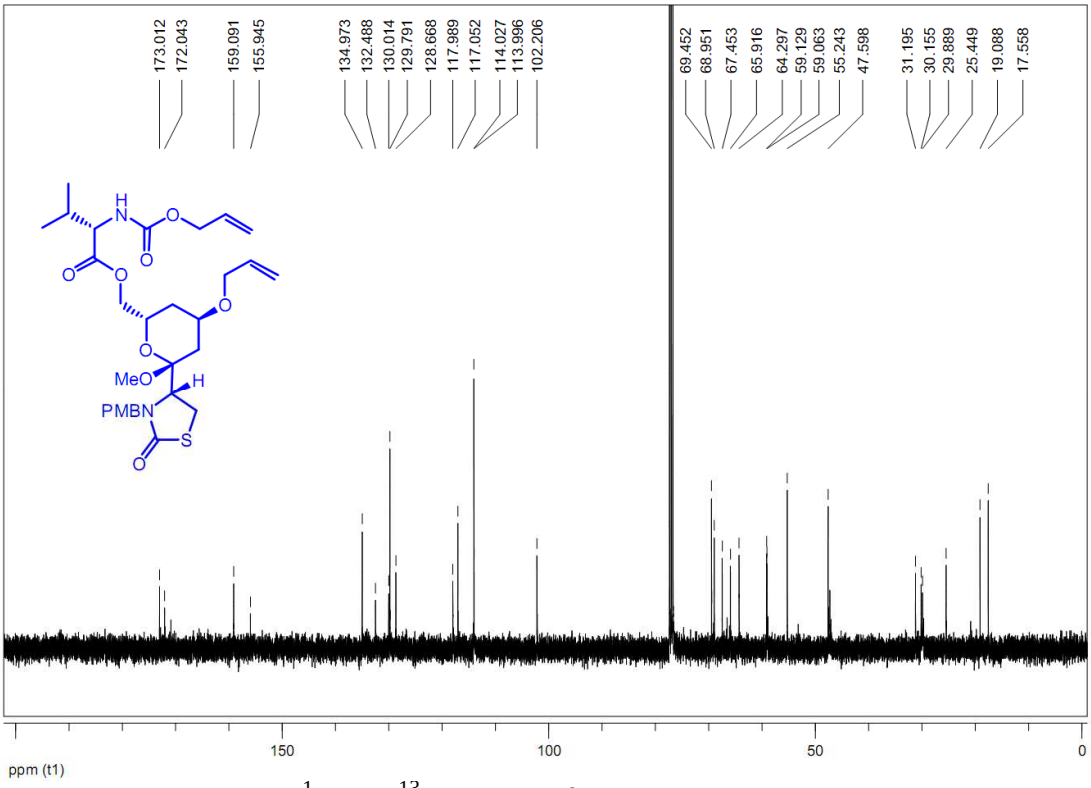
NOESY spectrum of compound **6.6**



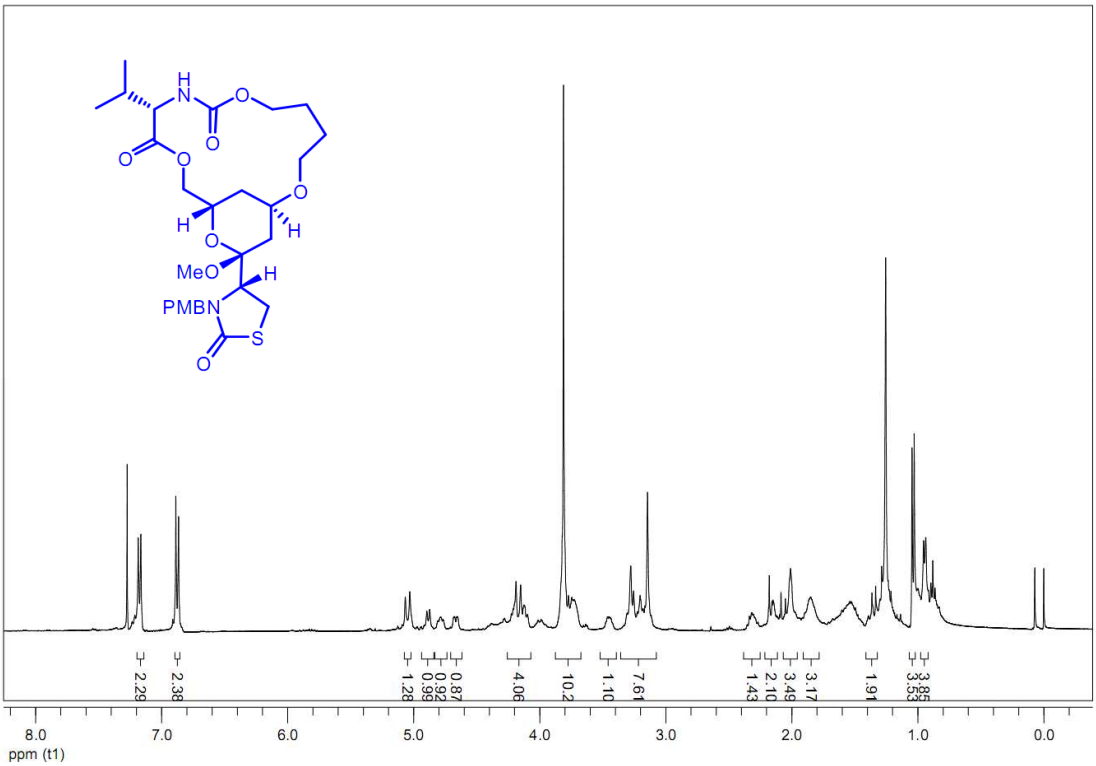


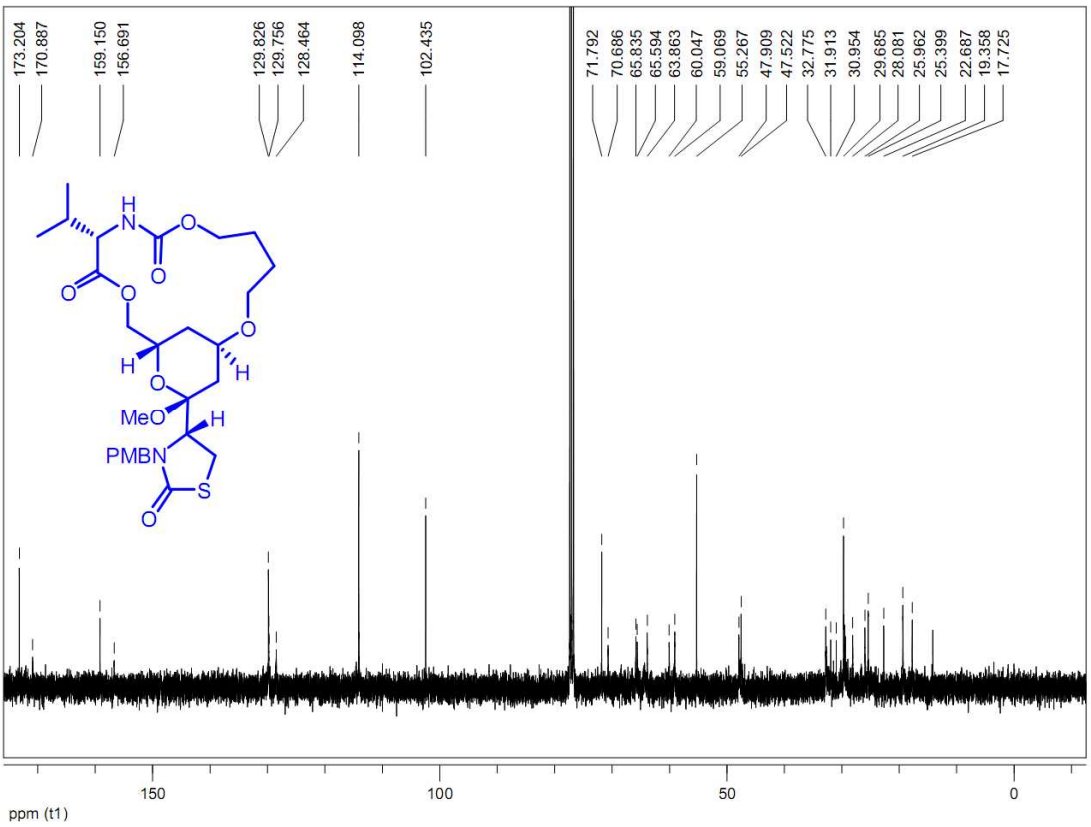
^{1}H and ^{13}C spectra of compound **7.1**



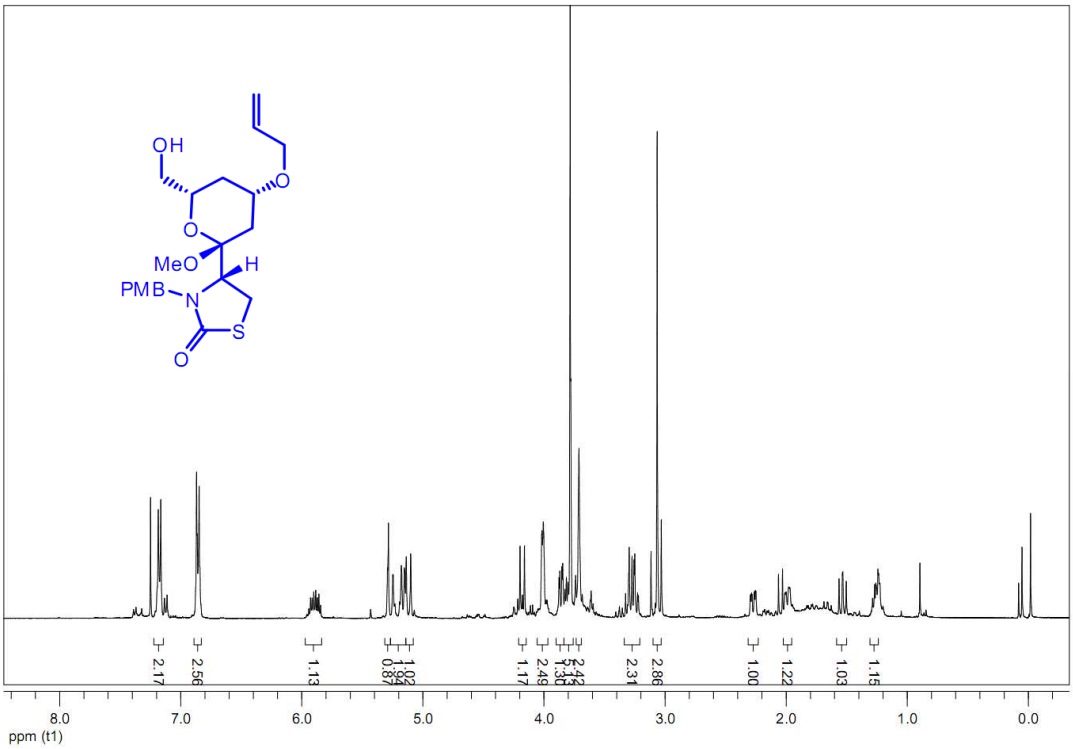


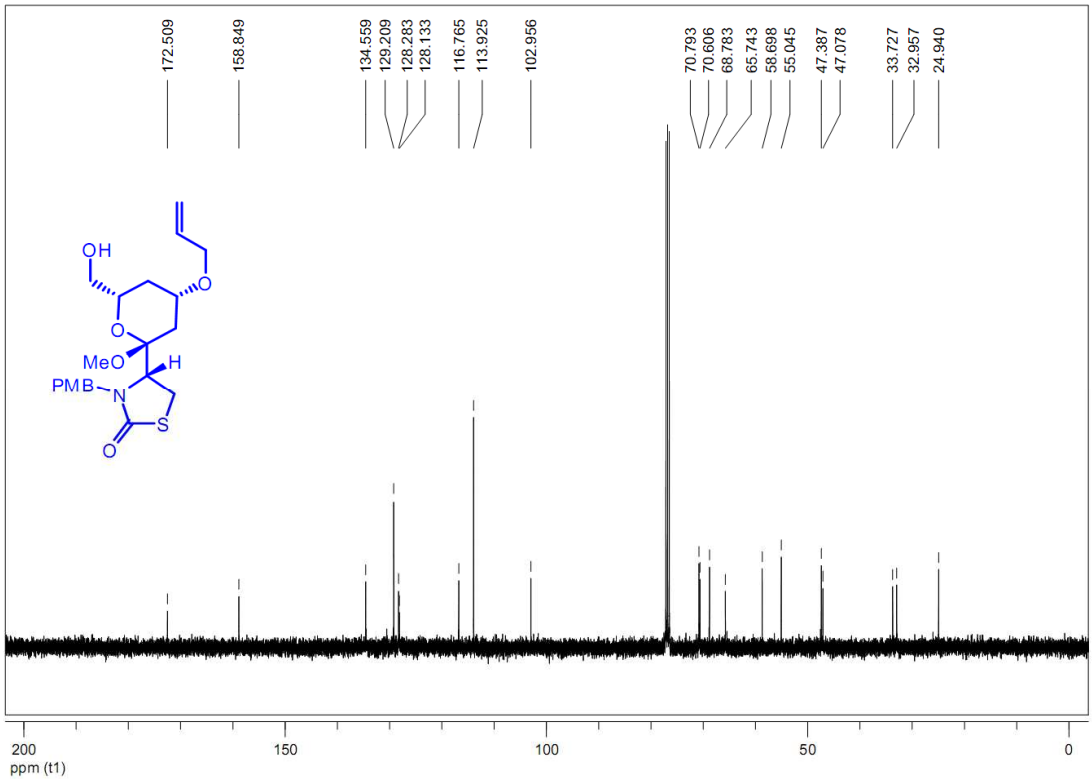
^{1}H and ^{13}C spectra of compound **7.3a**



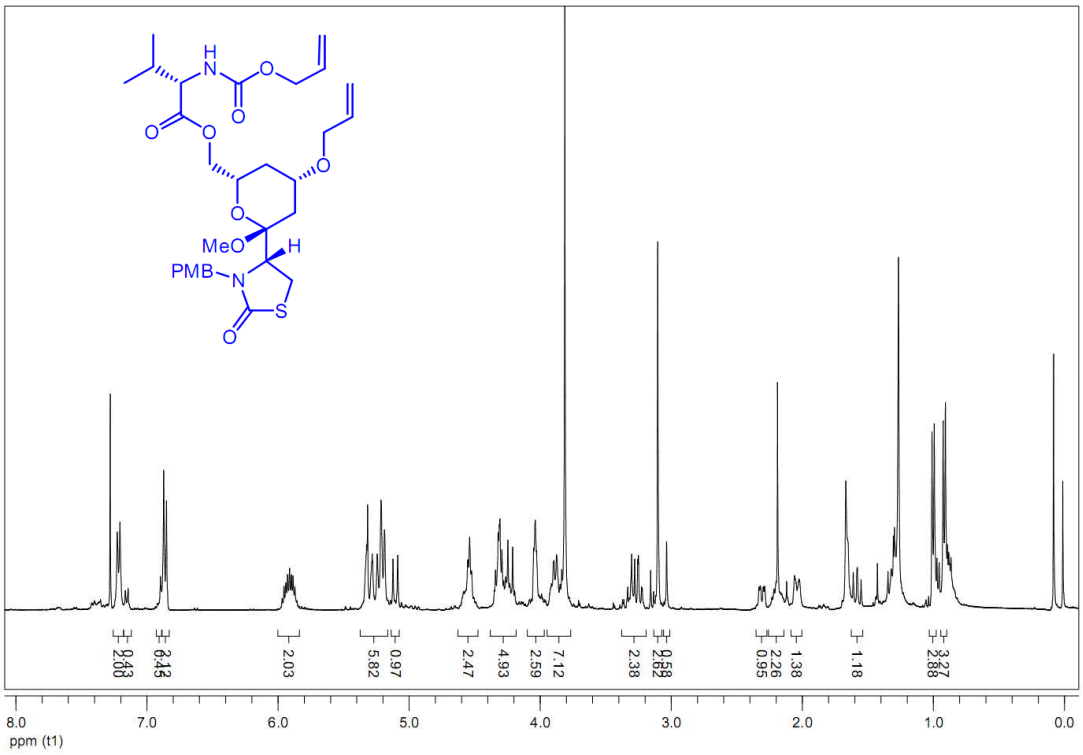


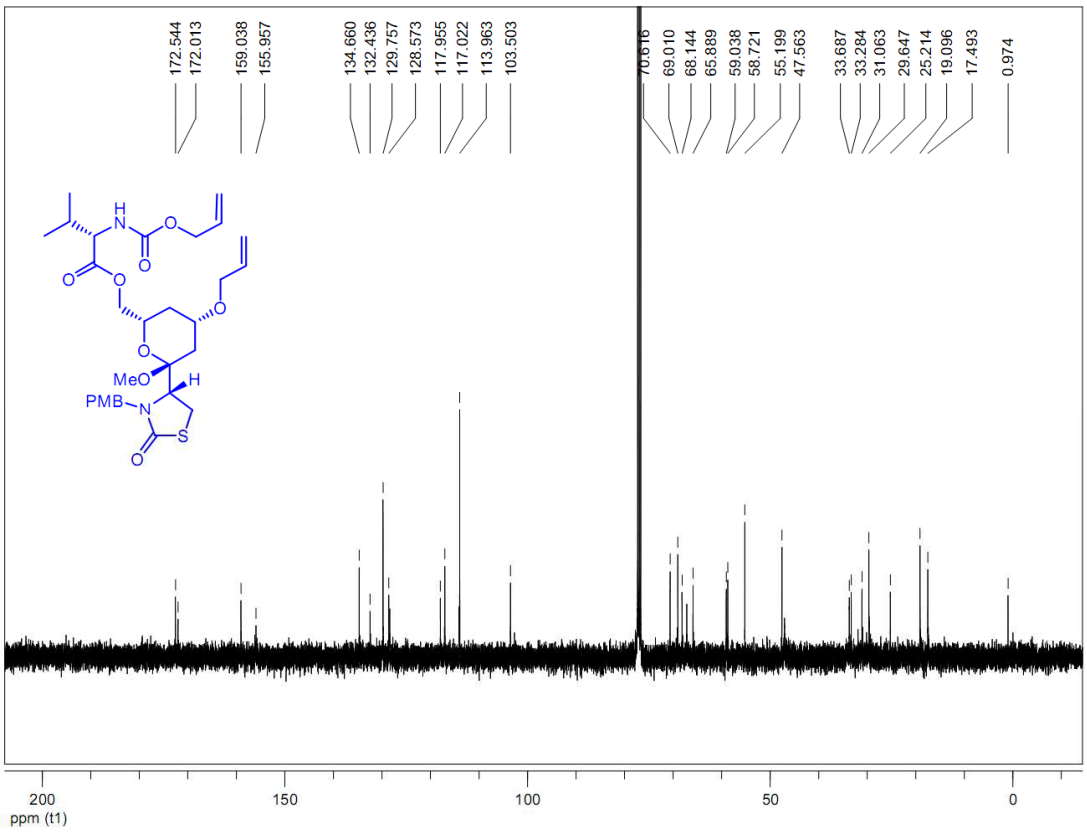
^{1}H and ^{13}C spectra of compound **4.4a**



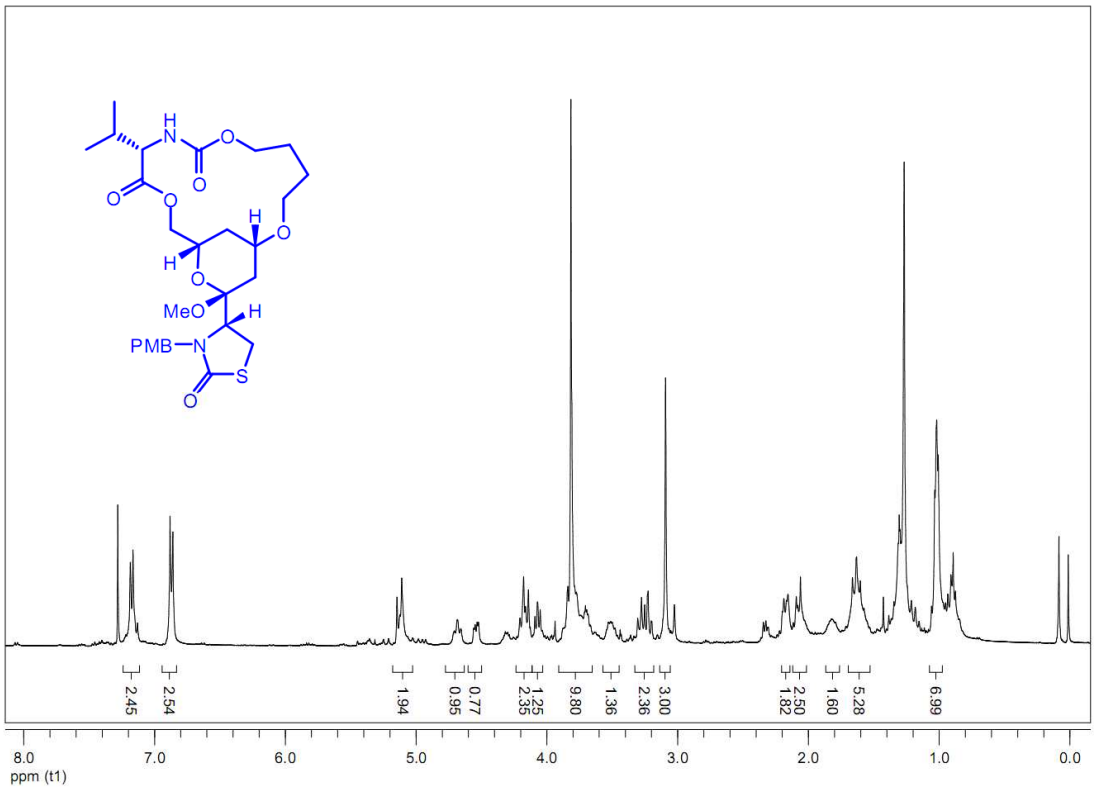


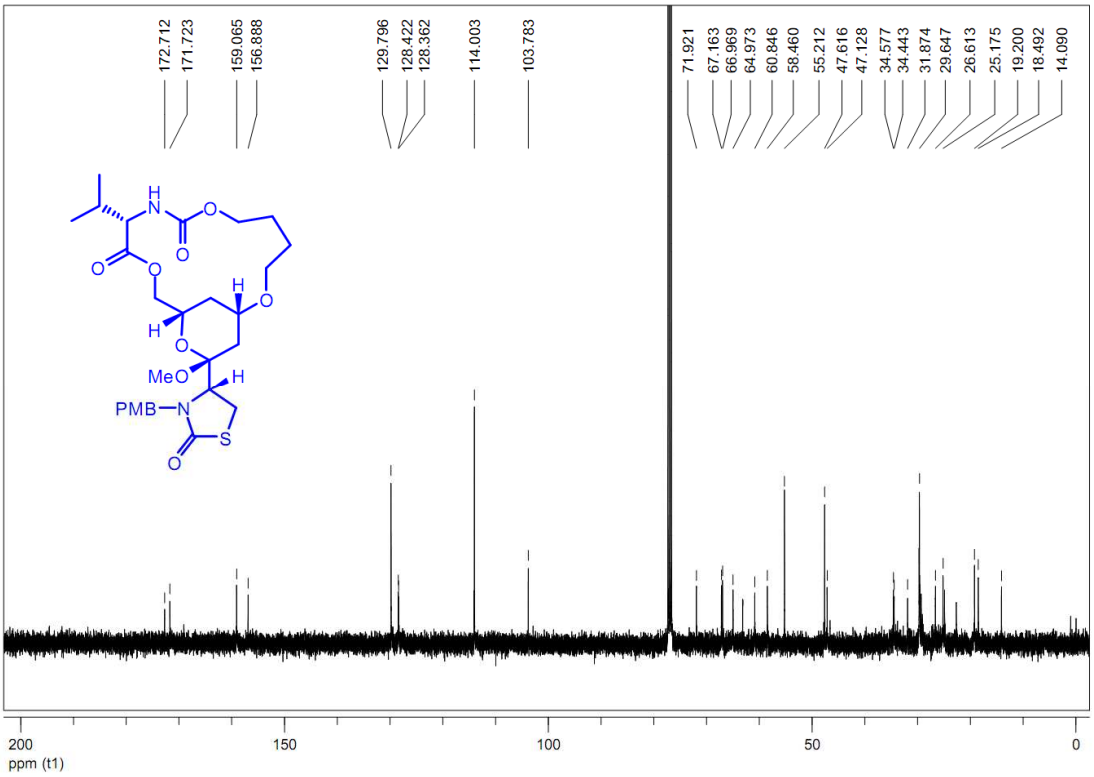
^{1}H and ^{13}C spectra of compound **8.1**





^{1}H and ^{13}C spectra of compound **8.2a**





^{1}H and ^{13}C spectra of compound **4.3a**

List of Publications:

Publications from the PhD Program

1. Small Molecule Modulators of Protein-Protein Interactions: Selected Case Studies. Aeluri, M.; Chamakuri, S.; Dasari, B.; Guduru, S. K. R.; Jimmidi, R.; Jogula, S.; Arya, P. *Chem. Rev*. **2014,** *114,* 4640-4694 *(for a theme topic: Chemical Biology of Protein-Protein Interactions; Guest Editor: Prabhat Arya)*

2. 14-Membered Macrocyclic Ring Derived Toolbox: Identification of Small Molecule Inhibitor of Angiogenesis and Early Embryonic Development. Aeluri, M.; Pramanik, C.; Lakshindra Chetia, L.; Mallurwar, N. K.; Balasubramanian, S.; Chandrasekar, G.; Kitambi, S. S.; Arya, P. *Org. Lett.* **2013**, *15,* 436−439.

3. 17-Membered Macrocyclic Ring Derived Toolbox: Identification of Small Molecule Inhibitor of Angiogenesis. Aeluri, M.; Gaddam, J.; Trinath, D. V. K. S.; Chandrasekar, G.; Kitambi, S. S.; Arya, P. *Eur. J. Org. Chem.* **2013**, 3955-3958.

4. Synthesis of Latrunculin-derived Hybrid Macrocycles. Aeluri, M.; Arya, P. **2014,** *(Manuscript under preparation)*

5. Building a Natural Product-inspired, Small Molecule Toolbox for Protein-Protein Interactions. Aeluri, M.; Chamakuri, S.; Dasari, B.; Guduru, S. R. K.; Jimmidi, R.; Jogula, S.; Arya, P. *Acc. Chem. Res*. **2014**, *submitted.*

6. Chemical Biology of Actin Modulators. Aeluri, M.; Arya, P. *Chem. Eur. J.* **2014,** *(Manuscript under preparation, Invited review article)*

Other Publications

7. Synthesis of indole based novel small molecules and their *in vitro* anti-proliferative effects on various cancer cell lines. Dulla, B.; Sailaja, E., Reddy CH,

U.; Aeluri, M.; Kalle, A.M.; Bhavani, S.; Rambabu, D.; Basaveswara Rao, M.V.; Pal, M. *Tet. Lett.* **2013**, *55*, 921-926.

8. A greener synthesis of 1,8-dioxo-octahydroxanthene derivatives under ultrasound. Mulakayala, N.; Kumar, P. G.; Rambabu, D.; Aeluri, M.; Rao, M. V. B.; Pal, M. *Tet. Lett.* **2012**, *53*, 6923-6926.

9. Catalysis by molecular iodine: A rapid synthesis of 1,8-dioxo-octahydroxanthenes and their evaluation as potential anticancer agents. **.** Mulakayala, N.; Murthy, P. V. N. S.; Rambabu, D.; Aeluri, M.; Adepu, R.; Krishna, G. R.; Reddy, C. M.; Prasad, K. R. S.; Chaitanya, M.; Kumar, C. S.; Rao, M. V. B.; Pal, M. *Bioorg. Med. Chem. Lett*. **2012**, *22*, 2186-2191.

Conferences Attended:

2013 Attended and presented an oral talk at the IX-JNOST international conference, IISER, Bhopal, India

2013 Participated in two days international symposium "Catalyst-2013-Chemistry Conclave", Dr. Reddy's Laboratories, Hyderabad

2009 Participated in one day course on "Seminar on Chemistry Chem Covergence", conducted by Loyola College of Academy, Hyderabad, India

2009 Participated in one day seminar held on 3rd February, at MNR P.G College, Hyderabad on "New Perspectives in The Frontier of Drug Discovery"

2008 Attended a two-day seminar on Spectroscopy, conducted by R.B.V.R.R. Women's College, Hyderabad, 20th-21st August

2008 Participated in one day seminar on "Green Chemistry in Drug Synthesis", conducted by MNR P.G. College, Hyderabad, 29th January