Synthesis of Small Cyclic Peptides Constrained with Novel Linkers using Palladium-catalyzed Reactions

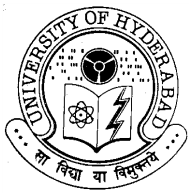
A Thesis

Submitted for the Degree of

DOCTOR OF PHILOSOPHY

By

VADLA BALRAJU



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Statement

I hereby declare that the matter embodied in this thesis is the result of investigations carried out by me in the Discovery Research, Dr. Reddy's Research Laboratories Ltd., Hyderabad, under the supervision of **Professor Javed Iqbal** and **Professor M. Periasamy**.

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the findings of other investigators.

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Certificate

Certified that the work embodied in this thesis entitled "**Synthesis of Small Cyclic Peptides Constrained with Novel Linkers using Palladium-Catalyzed Reactions"** has been carried out by Mr. **Vadla Balraju** under our supervision and the same has not been submitted elsewhere for a Degree.

PROFESSOR JAVED IQBAL
(Supervisor)

PROFESSOR M. PERIASAMY
(Co-supervisor)

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Vadla Balraju

Abbreviations

[α]	specific rotation [expressed without units; the actual units, deg.mL/g.dm, are understood]
AIBN	2,2'-azobisisobutyronitrile
Ala	Alanine
aq.	aqueous
Ar	aryl
BDMP	5-(1H-benzotriazol-1-yl)-3,4-dihydro-1-methyl 2H-pyrrolium hexachloroantimonate N-oxide
BINAP	2,2'-Bis(diphenylphosphino)-1,1'-binaphthyl
Boc	tertiary butyloxy carbonyl
BOP	(1H-benzotriazol-1-yloxy) tris(dimethylamino)-phosphonium hexafluorophosphate
BOP-Cl	N,N'-bis(2-oxo-3-oxzolidinyl)phosphinic chloride
br	broad (spectral)
Bu	butyl
cat.	catalytic
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DMF	N, N-Dimethyl formamide
EDC	1-Ethyl-3-(3'-(dimethylamino) propyl)carbodiimide
dr	diastereomeric ratio
EI	electron impact (in mass spectrometry)
equiv.	equivalent
er	enantiomeric ratio
ESMS	Electrospray Mass spectrometry
Et	ethyl

HATU	N-[(dimethylamino)-1H-1,2,3-triazolo[4,5-b]pyridin-1-ylmethylene)-N-methylmethanaminium hexafluorophosphate N-oxide
HAPyU	1-(1-pyrrolidinyl-1H-1,2,3-triazolo[4,5-b]pyridin-1-ylmethylene)pyrrolidinium hexafluorophosphate N-oxide
HBPipU	O-(1H-benzotriazol-1-yl)-N,N,N',N'-bis(pentamethylene)uronium hexafluorophosphate
HPLC	high-performance liquid chromatography
HOBt	1-Hydroxybenzotriazole hydrate
i	iso
Ile	Isoleucine
J	coupling constant (in NMR spectroscopy)
Leu	Leucine
Lit.	literature
m	multiplet (spectral)
Me	methyl
mp	melting point
n	primary
o	ortho
ORTEP	oak ridge thermal ellipsoid plot
Ph	phenyl
Phe	Phenyl alanine
PyBOP	(1H-benzotriazol-1-yloxy)tripyrrolidinophosphnium hexafluorophosphate
PyBroP	bromotripyrrolidino phosphonium hexafluorophosphate
Pr	propyl

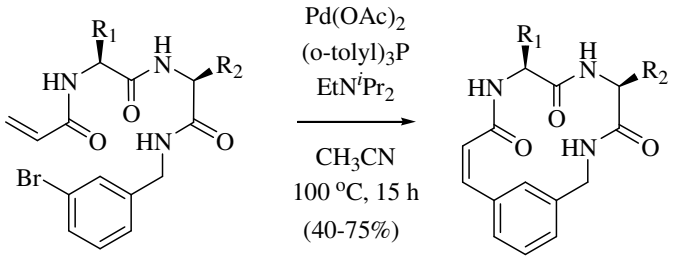
q	quartet (spectral)
rac	racemic
ROESY	Rotating frame Overhauser Effect Spectroscopy
rt	room temperature
s	singlet (spectral)
t	triplet (spectral)
t	tertiary
TBTU	N-[(1H-benzotriazol-1-yl)-(dimethylamino)methylene]-Nmethylmethanaminium Tetrafluorborate N-oxide
TFA	Trifluoroacetic acid
THF	tetrahydrofuran
TFFH	tetramethylfluoromamidinium hexafluorophosphate
Val	Valine
X	halide

Abstract

This thesis entitled **"Synthesis of Small Cyclic Peptides Constrained with Novel Linkers using Palladium-Catalyzed Reactions"** comprises six chapters. Chapter 1 describes a brief literature survey on cyclization strategies for the synthesis of cyclic peptides. Chapter 2 onwards, each chapter is subdivided into four sections namely **Introduction**, **Results and Discussion**, **Conclusions** and **Experimental Section** along with **References**.

The first chapter describes general introduction on known cyclization strategies in the literature toward the synthesis of cyclic peptides. The cyclization strategies are broadly divided into two parts: 1. non-metal-mediated reactions and 2. metal-mediated reactions. In the last quarter of the 20^{th} century, palladium-catalyzed carbon-carbon or carbon-heteroatom bond forming reactions evolved as powerful tools in the synthesis. In this thesis we focused on the most commonly applied palladium-catalyzed reactions, namely, the Heck, Sonogashira, Suzuki, Trost enyne-cycloisomerization and the Buchwald-Hartwig reactions to the synthesis of cyclic peptides constrained with novel linkers.

The second chapter describes the synthesis of cyclic peptides constrained with 1,3-disubstituted phenyl linkers. We have demonstrated that small peptides (di- and tri-), having a 3-bromobenzylamine group at the C-terminus and an acryloyl group at the N-terminus undergo an efficient intramolecular Heck reaction to afford the corresponding cyclic peptides in good yields. Six 14-Membered macrocyclic peptides **2a-f** were prepared from their corresponding acyclic precursors **1a-f** using $Pd(OAc)_2$ catalyzed intramolecular Heck reaction (Scheme 1).



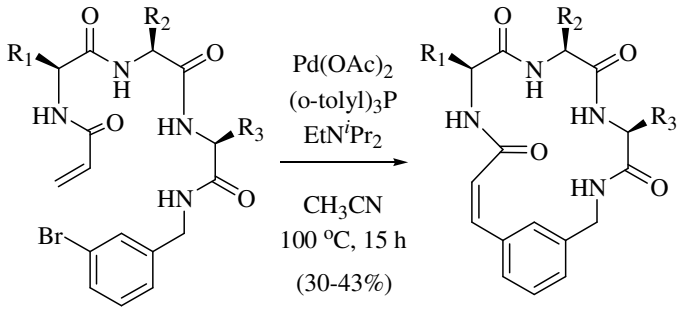
1 **2**

1a	$R_1 = CH_2Ph$	$R_2 = CH_3$	**2a**
1b	$R_1 = CH_3$	$R_2 = CH_2Ph$	**2b**
1c	$R_1 = CH_2Ph$	$R_2 = CH_2CH(CH_3)_2$	**2c**
1d	$R_1 = CH_2CH(CH_3)_2$	$R_2 = CH_3$	**2d**
1e	$R_1 = CH_2Ph$ (D-Phe)	$R_2 = CH_3$	**2e**
1f	$R_1 = CH_2Ph$	$R_2 = (CH_3)_2$	**2f**

Scheme 1

We also carried out the intramolecular Heck reaction in the synthesis of 17-membered cyclic peptide compounds **4a-d** from their corresponding acyclic peptides **3a-d** (Scheme 2).

We have also studied the further functionalization of the resulting double bond of the cyclic peptides **2**. We have carried out the reduction of double bond in **2c** with 10% Pd-C under H_2 atmosphere to synthesize cyclic peptide **5** constrained with 3(3-aminomethylphenyl) propionic acid linker. The same cyclic peptide **5** was also synthesized using Bu_3SnH-AIBN mediated free-radical macrocyclization of **1c** (Scheme 3).



3 **4**

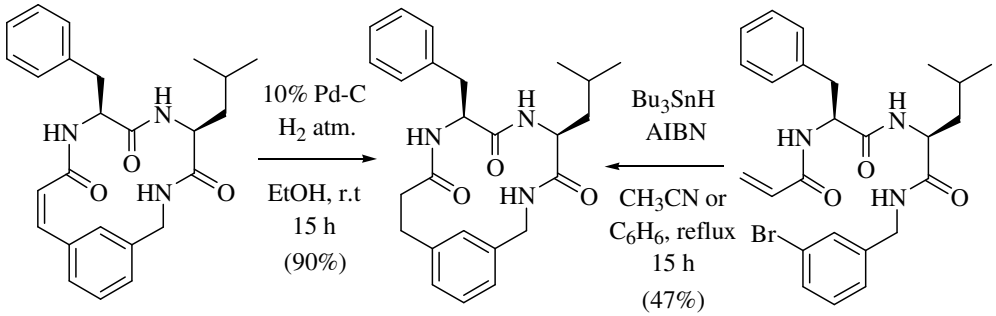
3a $R_1 = CH(CH_3)_2$ $R_2 = CH_2CH(CH_3)_2$ $R_3 = CH_3$ **4a**

3b $R_1 = CH_2Ph$ $R_2 = CH_2CH(CH_3)_2$ $R_3 = CH_3$ **4b**

3c $R_1 = CH_2Ph$ $R_2 = CH_3$ $R_3 = CH_2CH(CH_3)_2$ **4c**

3d $R_1 = CH_2Ph$ $R_2 = CH(CH_3)CH_2CH_3$ $R_3 = CH_3$ **4d**

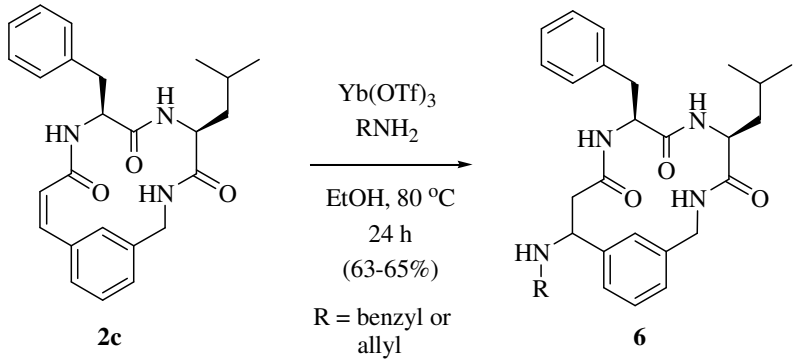
Scheme 2



2c **5** **1c**

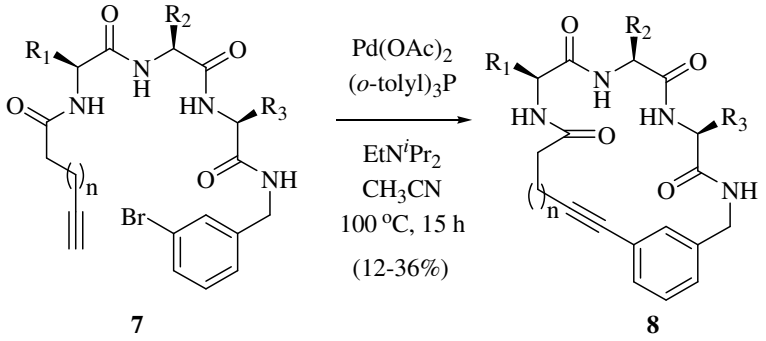
Scheme 3

We also demonstrated the scope of Michael additions on cyclic peptides **2** using different nucleophiles (Scheme 4).



Scheme 4

Synthesis of cyclic peptides constrained with n(3-aminomethylphenyl)alkynoic acid linkers using an intramolecular Sonogashira coupling has been discussed in the third chapter. The acyclic peptides **7a-d** are prepared following standard solution chemistry. Acyclic peptides **7a-d** under the copper-free Sonogashira coupling conditions involving a bulky electron-rich phosphine ligand [$Pd(OAc)_2$, (o-tolyl)$_3$P and EtN^iPr_2] in acetonitrile at 100 °C, resulted in formation of the desired cyclic peptides **8a-d** in 12-36% yields (Scheme 5).



7a n = 1, $R_1 = CH_2Ph$, $R_2 = CH_2CH(CH_3)_2$, $R_3 = CH_3$ **8a**

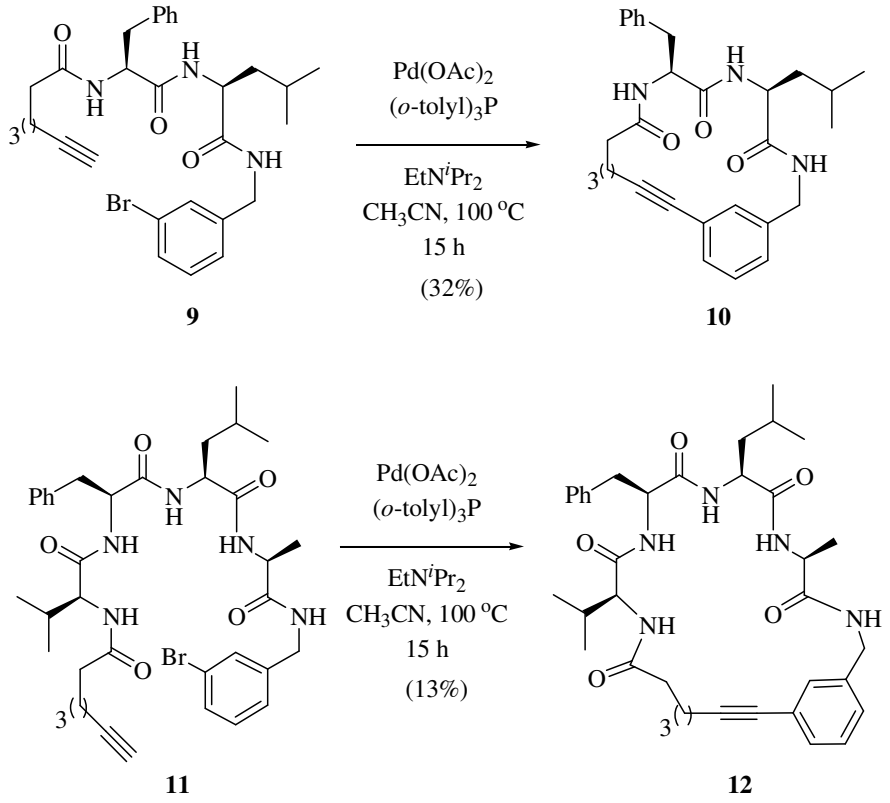
7b n = 2, $R_1 = CH_2Ph$, $R_2 = CH_2CH(CH_3)_2$, $R_3 = CH_3$ **8b**

7c n = 3, $R_1 = CH_2Ph$, $R_2 = CH_2CH(CH_3)_2$, $R_3 = CH_3$ **8c**

7d n = 3, $R_1 = CH_2Ph$, $R_2 = CH(CH_3)_2$, $R_3 = CH_3$ **8d**

Scheme 5

We also described the copper-free Sonogashira coupling reaction in the synthesis of different sized cyclic peptides constrained with n(3-aminomethylphenyl)alkynoic acid linkers. Compounds **9** and **11** furnished cyclic compounds **10** and **12**, respectively in good yields (Scheme 6).



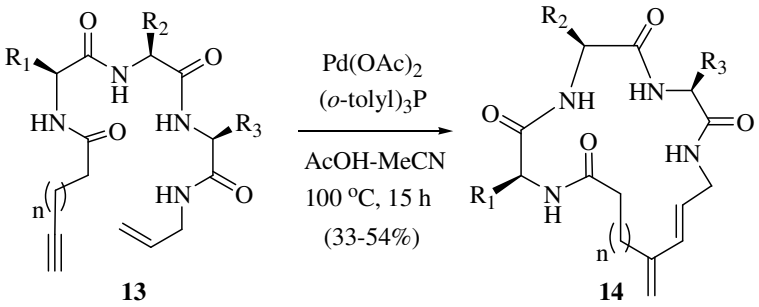
9 **10**

11 **12**

Scheme 6

Fourth chapter describes the palladium-catalyzed enyne cycloisomerization of linear peptides to generate small cyclic peptides embedded with a conjugated 1,3-diene. The utility of these resulting macrocyclic dienes is demonstrated by carrying out [4+2] cycloadditions with dienophiles to generate constrained cyclic peptides with cyclic linkers.

The tripeptides **13a-e** underwent cycloisomerization under $Pd(OAc)_2$, (*o*-tolyl)$_3$P, AcOH-MeCN conditions to furnish the desired macrocycles **14a-e** in good yields (Scheme 7). The *E*-stereochemistry of the endocyclic double bond and *s*-transoid form of the 1,3-diene were established using NMR data (1-D and 2-D).



13 **14**

13a $R_1 = CH_2Ph$, $R_2 = CH_2CH(CH_3)_2$, $R_3 = CH_3$, n = 1 **14a**

13b $R_1 = CH_2Ph$, $R_2 = CH_2CH(CH_3)_2$, $R_3 = CH_3$, n = 2 **14b**

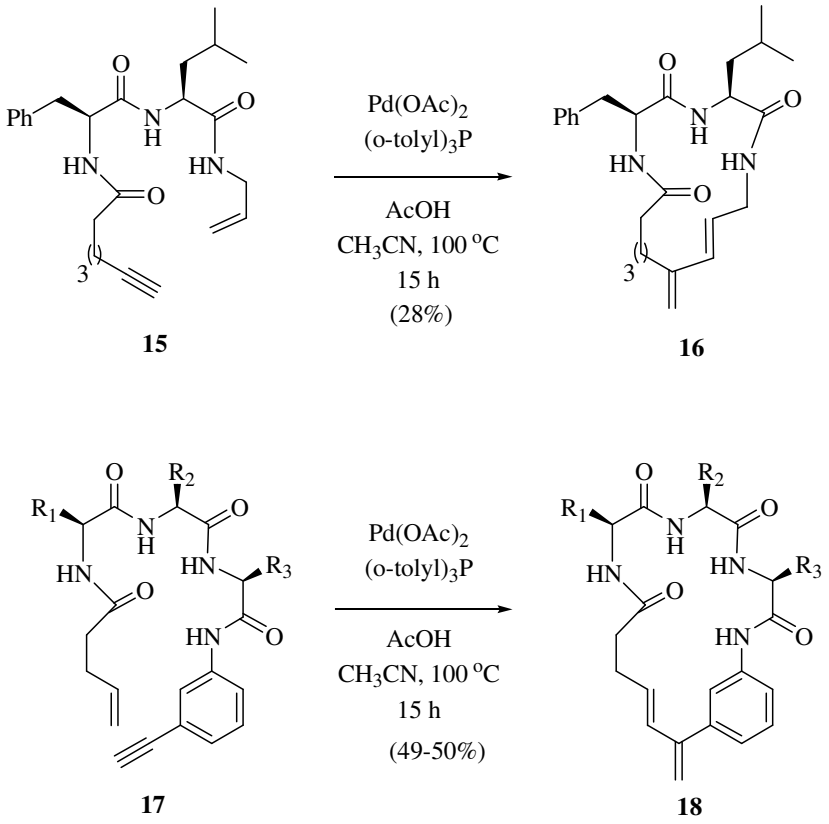
13c $R_1 = CH_2Ph$, $R_2 = CH_2CH(CH_3)_2$, $R_3 = CH_3$, n = 3 **14c**

13d $R_1 = CH_2Ph$, $R_2 = CH(CH_3)_2$, $R_3 = CH_3$, n = 1 **14d**

13e $R_1 = CH(CH_3)CH_2CH_3$, $R_2 = CH(CH_3)_2$, $R_3 = CH_2Ph$ n = 1 **14e**

Scheme 7

The macrocyclization using Enyne-cycloisomerization on compounds **15** and **17** produced the cyclic peptides **16** and **18** in good yields, respectively. Here, we observed that the size of the peptide and the rigid aryl acetylene linker has no effect on cycloisomerization as well as on the geometry of the endocyclic double bond of the resulting cyclic peptides (Scheme 8).

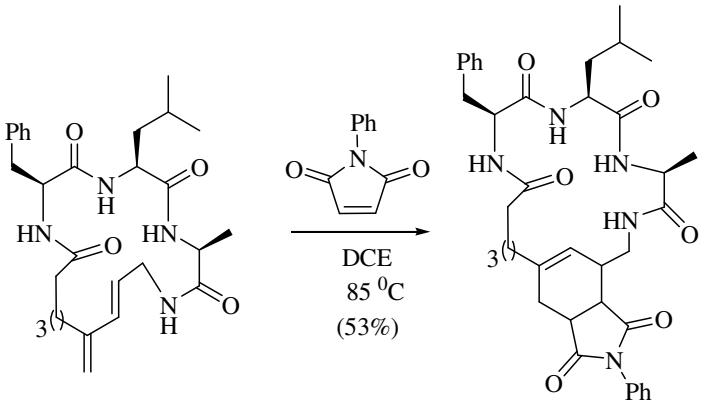


17a $R_1 = CH_2Ph$, $R_2 = CH_2CH_2CH_2$, $R_3 = CH_3$ **18a**

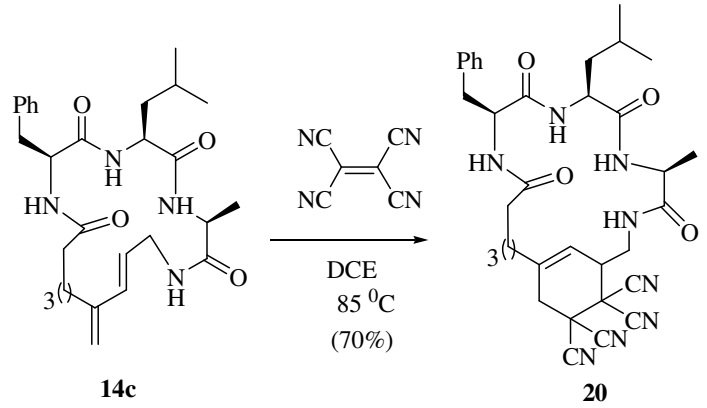
17b $R_1 = CH_2Ph$, $R_2 = CH_2CH(CH_3)_2$, $R_3 = CH_3$ **18b**

Scheme 8

The cyclic peptidomimetics formed during the Enyne-cycloisomerization possess conjugated 1,3-diene moiety, a functional group with several synthetic applications. We have tried the Diels-Alder reaction on these compounds that is one of the straight forward synthetic applications of 1,3-dienes. Diels-Alder reaction of **14c** with the reactive dienophiles N-phenyl maleimide and tetracyanoethylene gave adducts **19** and **20** in good yields, respectively (Scheme 9).



14c **19**

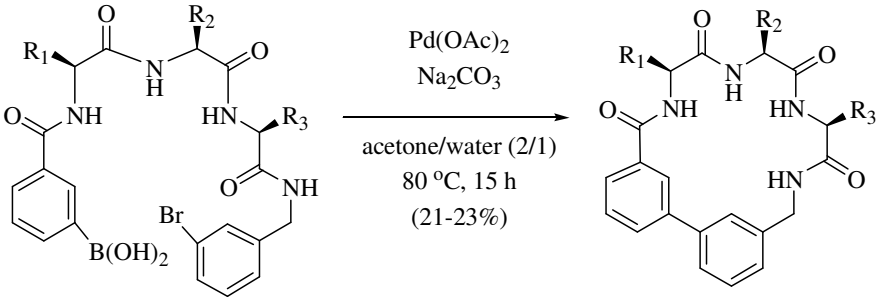


14c **20**

Scheme 9

Fifth chapter describes the synthesis of biaryl-bridged cyclic peptides towards constrained mimics of Vancomycin (glycopeptidic antibiotic) using intramolecular Suzuki coupling as the final ring-closing reaction.

The macrocyclic peptidomimetics **22** were synthesized from their corresponding acyclic peptides **21** using intramolecular Suzuki coupling (Scheme 10).



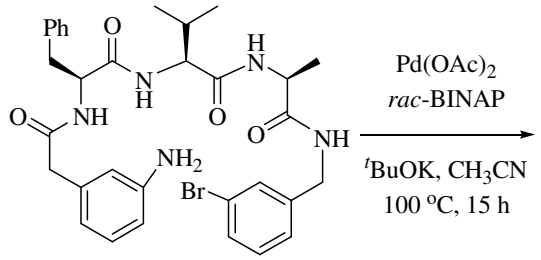
21 **22**

21a $R_1 = CH_2Ph$, $R_2 = CH_2CH(CH_3)_2$, $R_3 = CH_3$ **22a**

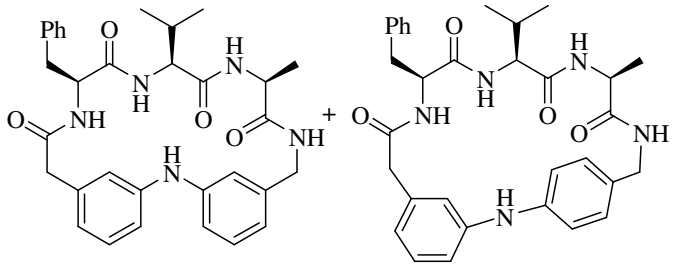
21b $R_1 = CH(CH_3)CH_2CH_3$, $R_2 = CH_2Ph$, $R_3 = CH_3$ **22b**

Scheme 10

Sixth chapter explains the synthesis of cyclic peptides constrained with diarylamine linkers (as diarylamine mimetic of the glycopeptide's antibiotic teicoplanin FG ring biaryl ether system) using palladium-catalyzed intramolecular Buchwald-Hartwig C-N coupling.



23b

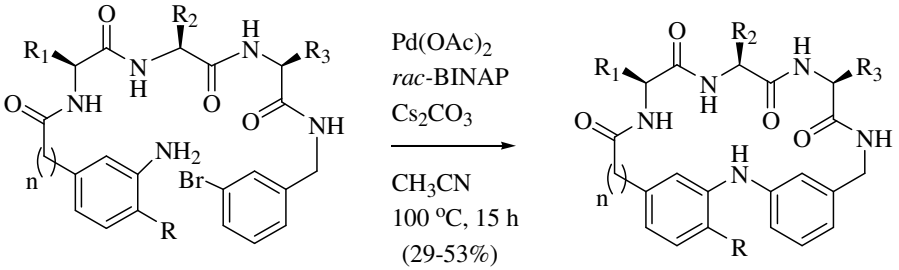


24b (14 %) **25b** (40 %)

Scheme 11

The Buchwald-Hartwig C-N coupling of **23b**, with $Pd(OAc)_2$, *rac*-BINAP catalytic system and ^{t}BuOK as base in acetonitrile at 100 ^{o}C, produced two regioisomeric cyclic peptides **24b** and **25b** in the ratio of 1:3 in 54% overall yield (Scheme 11).

However, acyclic peptides **23a-g** were subjected to Buchwald-Hartwig reaction using Cs_2CO_3 as base to furnish cyclic peptides **24a-g** in good yields (Scheme 12).



23 **24**

23a R = H, $R_1 = CH_2Ph$, $R_2 = CH(CH_3)_2$, $R_3 = CH_3$, n = 0 **24a**

23b R = H, $R_1 = CH_2Ph$, $R_2 = CH(CH_3)_2$, $R_3 = CH_3$, n = 1 **24b**

23c R = H, $R_1 = CH(CH_3)_2$, $R_2 = CH(CH_3)_2$, $R_3 = CH_3$, n = 2 **24c**

23d R = H, $R_1 = CH_2Ph$, $R_2 = CH_3$, $R_3 = CH_2CH(CH_3)_2$, n = 0 **24d**

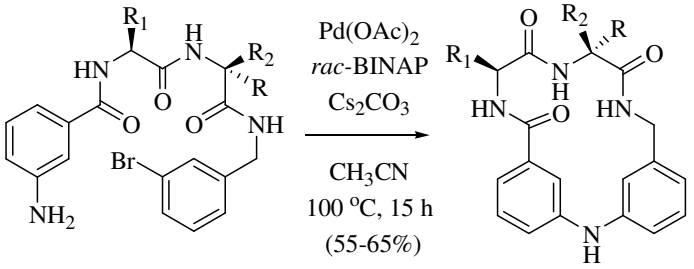
23e R = H, $R_1 = CH_2Ph$, $R_2 = CH(CH_3)CH_2CH_3$, $R_3 = CH_3$, n = 0 **24e**

23f R = H, $R_1 = CH(CH_3)_2$, $R_2 = CH_2CH(CH_3)_2$, $R_3 = CH_3$, n = 0 **24f**

23g R = CH_3, $R_1 = CH_2Ph$, $R_2 = CH_3$, $R_3 = CH_2CH(CH_3)_2$, n = 0 **24g**

Scheme 12

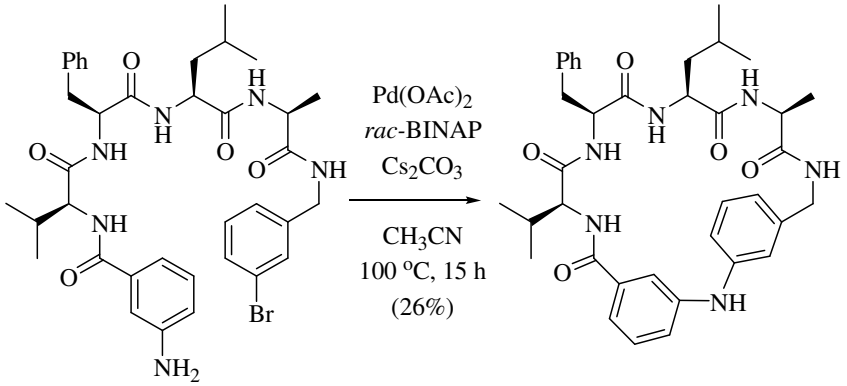
We further substantiated our Buchwald-Hartwig C-N coupling reaction for the synthesis of different sized cyclic peptides constrained with diarylamine linker. Acyclic compounds **26a-b** and **28** were subjected to Buchwald-Hartwig reaction to afford cyclic peptides **27a-b** and **29**, respectively in good yields (Scheme 13).



26 **27**

26a $R_1 = CH_2Ph$, $R_2 = CH_3$, R = H **27a**

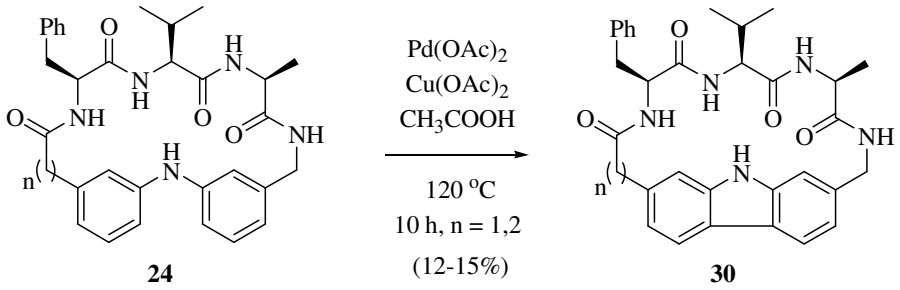
26b $R_1 = CH_2Ph$, $R_2 = CH_3$, $R = CH_3$ **27b**



28 **29**

Scheme 13

We attempted the $C(sp^2)$-$C(sp^2)$ bond-forming reaction on diarylamine constrained cyclic peptides to incorporate carbazole constraint in to the macrocyclic peptides. Compounds **24** with $Pd(OAc)_2$ in acetic acid gave carbazole contained cyclic peptides **30** (Scheme 14).



24 **30**

Scheme 14

We have demonstrated the utility of palladium-catalyzed carbon-carbon or carbon-nitrogen bond forming reactions during the macrocyclization of linear peptides to furnish constrained small cyclic peptides with novel linkers. The resulting macrocycles with different linker moieties have been used for further functionalization of linker moiety to incorporate a variety of linkers as constraints in the cyclic peptides.

Note: Scheme numbers and compound numbers given in this abstract are different from those given in the Chapters. Also, different set of numbers for Schemes, Tables, compounds, Figures and references etc. are given in different Chapters.

To

The Lord Sri Venkateshwara Swamy

Tirumala- Tirupati

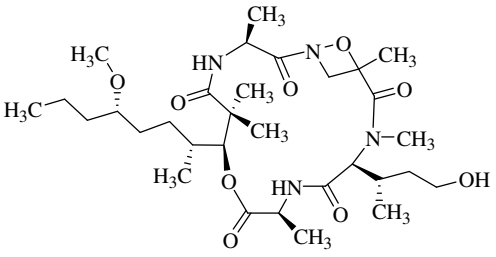
Chapter 1

Synthesis of Cyclic Peptides Constrained with Different Linkers using Various Cyclization Strategies-A Literature Survey

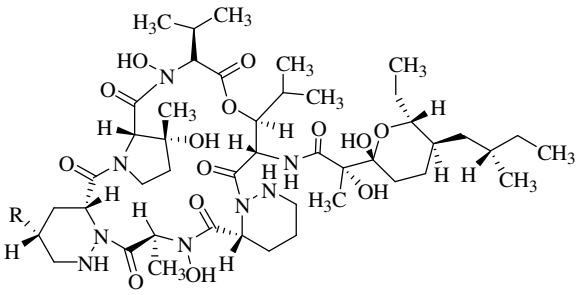
1.1 Introduction

Cyclic peptides are currently attracting the attention of chemists and biochemists alike. Naturally occurring cyclic peptides, such as the recently discovered cyclic peptides **1** - **9** (Figure 1), exhibit a wide range of biological activities. Cyclic peptides generally exhibit improved biological properties when compared to their linear counterparts. The absence of ionizable C- and N-termini in cyclic peptides confer greater resistance to *in vivo* enzymatic degradation, and provide for enhanced membrane permeability, thereby resulting in improved bioavailability of the cyclic peptides. Cyclization also considerably reduces the conformational flexibility of the peptide backbone, which consequently enhances their receptor selectivities and binding affinities by reducing unfavorable entropic effects. In addition, the constrained geometries of cyclic peptides are conducive to conformational investigations, and for computer-aided molecular modeling and/or peptide ligand design.

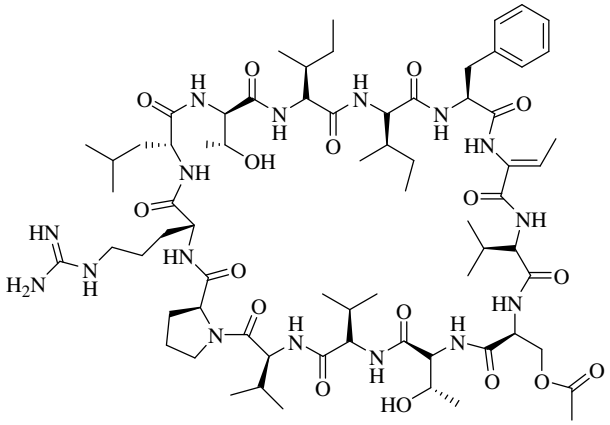
The naturally occurring cyclic peptides also attract the attention of synthetic chemists not only because of the unique and promising properties and biological significance of the cyclopeptides, but also because of the extra level of synthetic complexity of such endeavors. Chemical synthesis of these cyclic peptides is also useful for structure proof and for providing ample quantities of samples that might not be easily available in large scale from natural sources or through fermentation methods. In addition, macrocyclization of peptide-based pharmaceuticals is one of the most commonly used and effective modification approaches to enhance selectivity, activity, and bioavailability to develop more promising lead compounds from peptide structures.



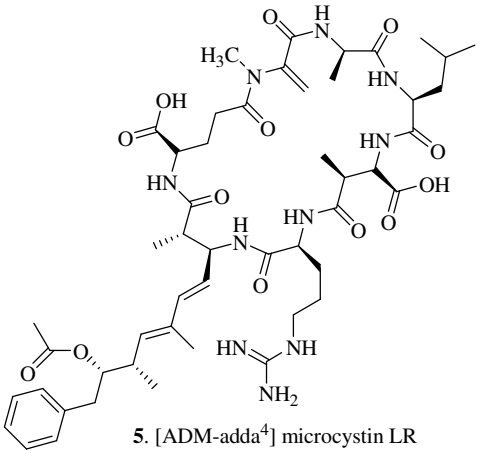
1. Halipeptin A
Isolated from the marine sponge *Haliclona sp*
Potent anti-inflammatory activity[1]



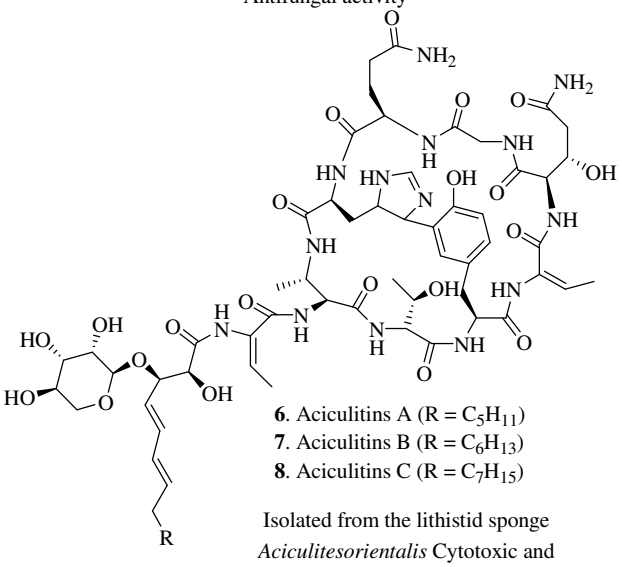
2. Polyoxypeptin A (R = OH)
3. Polyoxypeptin B (R = H)
Isolated from the culture broth of *Streptomyces* sp
Potent apoptosis-inducing activity[2]



4. Tolybyssidins A
Isolated from the culture medium of mass cultured cyanobacterium *Tolypothirx byssoidea*
Antifungal activity[3]

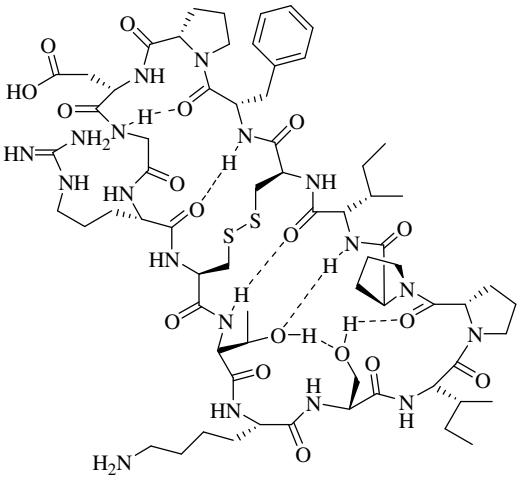


5. [ADM-adda[4]] microcystin LR
Produced by *Nostoc* sp. strain 152
Cytotoxic activity[4]



6. Aciculitins A (R = C_5H_{11})
7. Aciculitins B (R = C_6H_{13})
8. Aciculitins C (R = C_7H_{15})

Isolated from the lithistid sponge *Aciculitesorientalis* Cytotoxic and antifungal activity[5]



9. SFTI-1
Isolated from sunflower seeds
Very potent proteinase inhibitory activity[6]

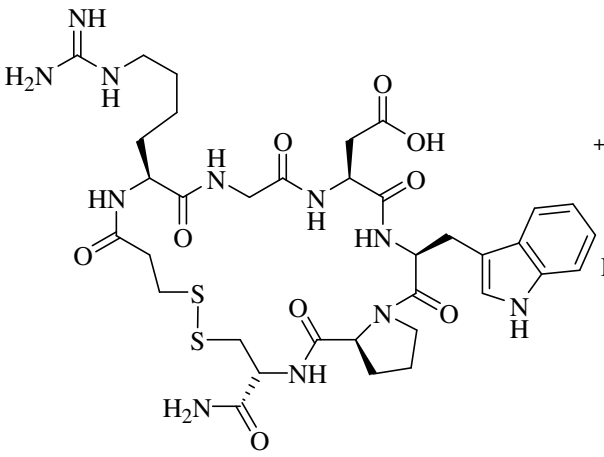
Figure 1: Structures and activities of naturally occurring cyclic peptides

Although the pharmaceutical industry has not been over enthusiastic in its development of peptides as drugs,[7] there are islands of success quoted for cyclic peptides, e.g. octreotide (Novartis), antitumor agent, integrilin, a cyclic heptapeptide Gp IIb/IIIa inhibitor (Cor Pharmaceuticals) and the naturally occurring cyclosporin A, an immunosuppressant (Figure 2). The cost of synthesizing cyclic peptides is often prohibitive, as the sophisticated reagents required are not cheap commodities. However, optimized yields of cyclization, the use of cheaper reagents and advantageous chromatographic separations have been raised[8] as criteria capable of pushing the balance in favor of the synthesis of cyclosporin A, as compared with its isolation from microbiological preparations.

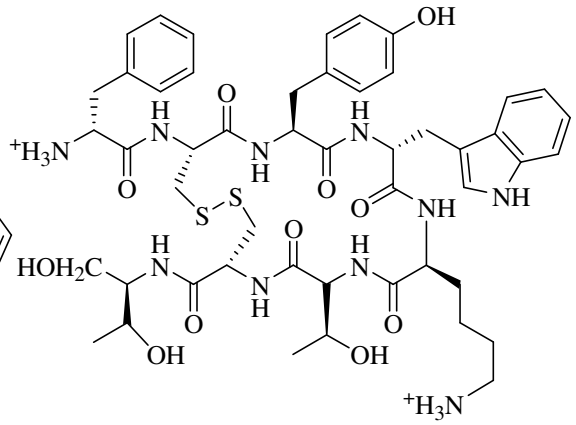
During the past decades, many effective methods for peptide cyclization have been developed to synthesize conformationally constrained peptide-based drugs.[12,13] In this chapter, we discuss briefly about the strategies for the peptide cyclizations, documented in the literature. Recently developed general methods for peptide cyclization are classified into nonmetal-mediated and metal-mediated cyclization strategies.

1.1.1 Synthesis of cyclic peptides using nonmetal-mediated reactions

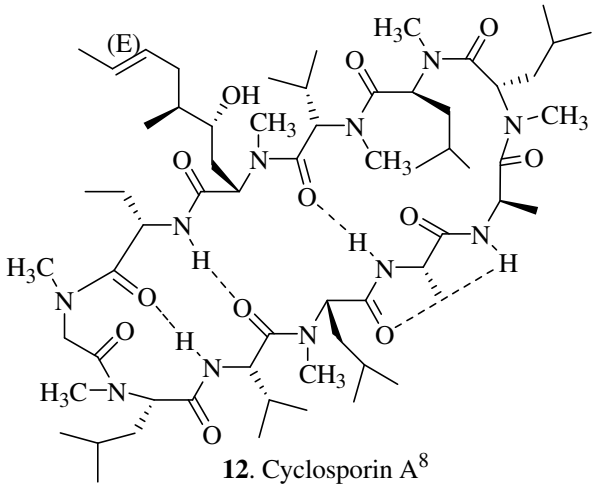
This is the most commonly used method for the synthesis of cyclic peptides. Also, many naturally occurring cyclopeptides are cyclized in this way. Therefore, great efforts have been made for the development of efficient peptide macrocyclization methods promoted by non-metal coupling reagents.



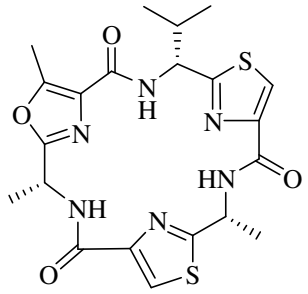
10. Integrilin
(Gp IIb/IIIa inhibitor)
[Cor Pharmaceuticals]



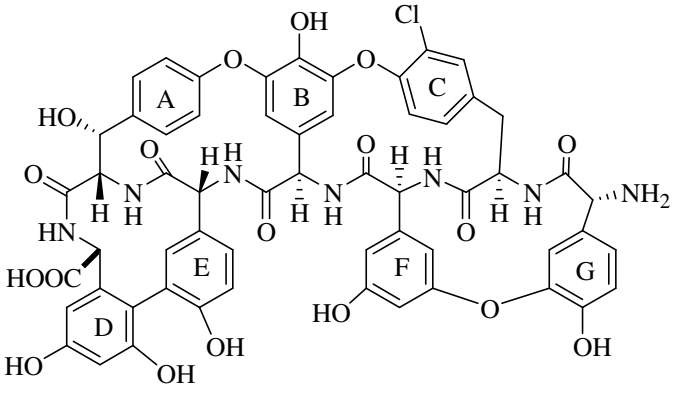
11. Octreotide analogue
(antitumer agent)
[Novartis]



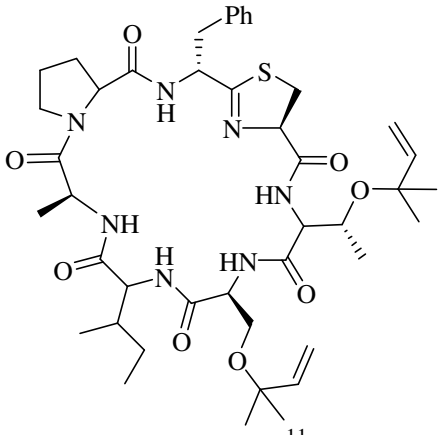
12. Cyclosporin A[8]
(Calceneurin inhibitors)



13. Dendroamide A[9]
(Multiple Drug Resistant)



14. Teicoplanin glycone[10]
(antitumour compound)



15. Trunkamide[11]
(A cytotoxic metabolite
from *Lissoclinum* sp.)

Figure 2: Selected bioactive cyclic peptides synthesized by macrocyclization strategies

1.1.1.1 Macrolactamization strategy in solution

The most commonly used cyclization strategy for the synthesis of cyclic peptides is solution phase macrolactamization using suitable peptide coupling reagents. The widely used and relatively more efficient coupling reagents that can promote rapid peptide cyclization with low racemization and high yield are shown in Figure 3.

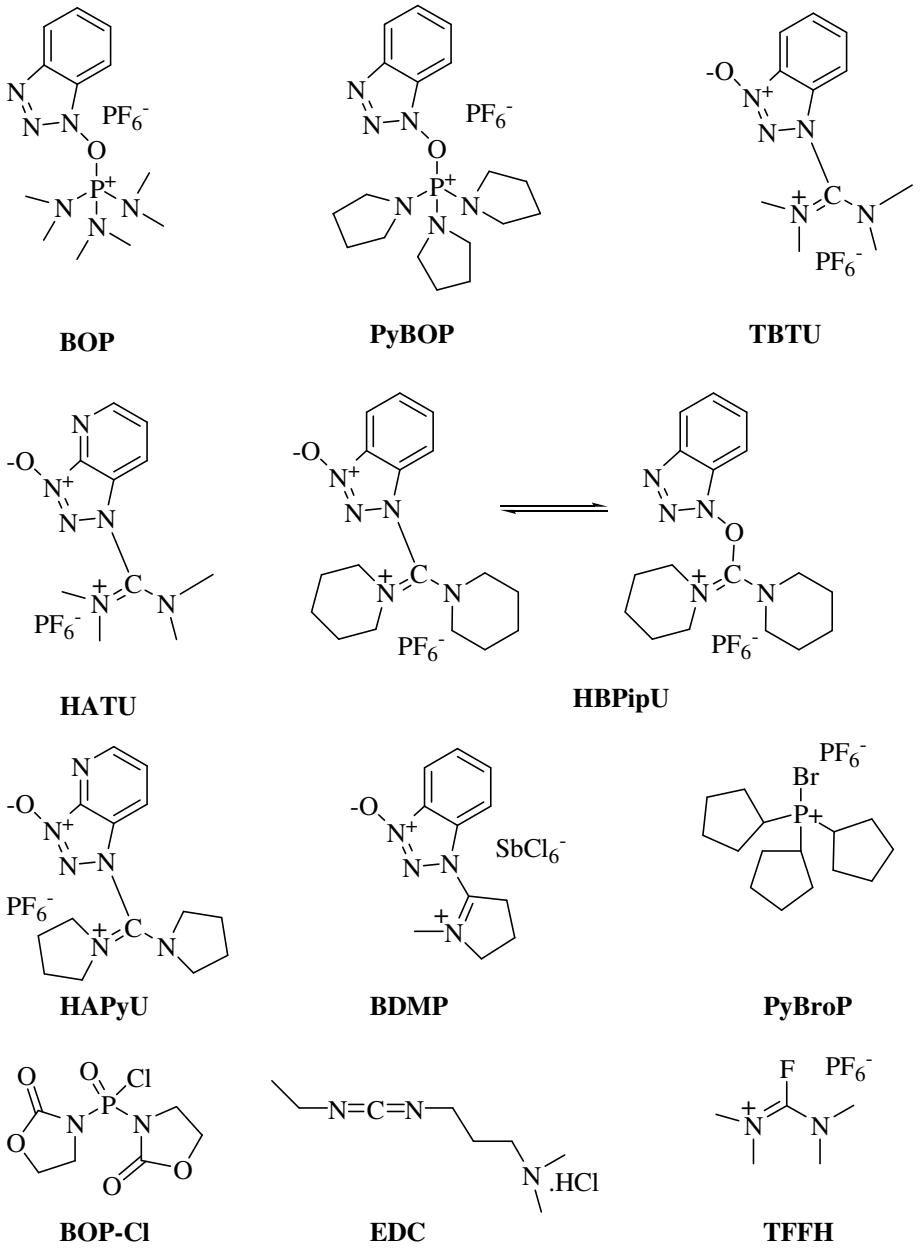
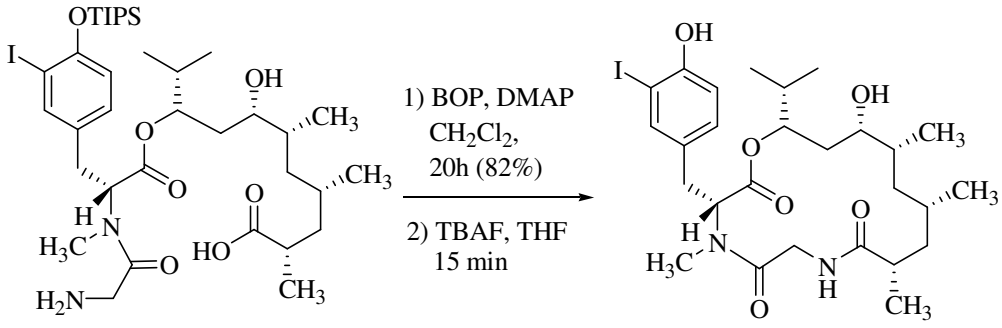


Figure 3: Commonly used and highly efficient peptide coupling reagents

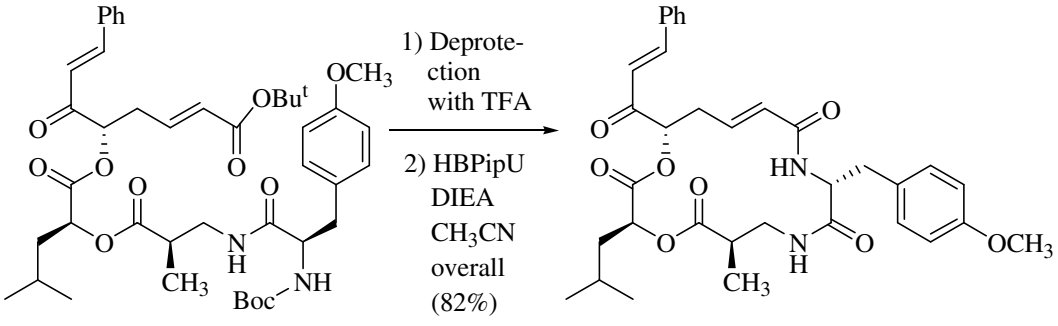
During the synthesis of antitumor depsipeptide (-)-Doliculide **17** (Scheme 1), Ghosh *et al.* accomplished the final macrocyclization using coupling reagent BOP in 82% high yield after 20 h reaction.[14] HOBt-derived phosphonium-type reagent BOP activates the carboxylic group of the linear precursor **16** that results in the selective formation of amide bond without the protection of hydroxyl group.



16 **17**

Scheme 1

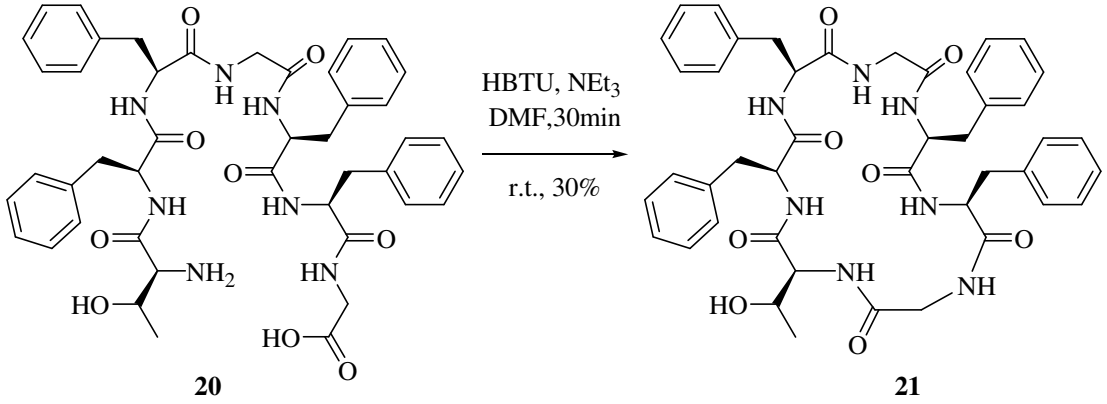
Rej *et al*. reported that the cyclization of the linear depsipeptide **18** was completed within 30 min using uronium salt HBPipU. The cyclic compound **19** was isolated in 82% overall high yield[15-17] (Scheme 2).



18 **19**

Scheme 2

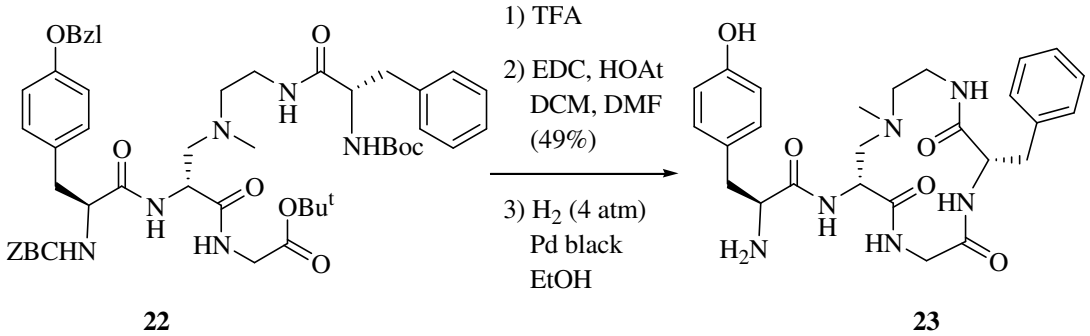
Baraguey *et al*. also adopted uronium/aminium salt HBTU as a coupling reagent for the macrolactamization of the linear heptapeptide **20** to naturally occurring cyclopeptide Mahafacyclin B **21** (Scheme 3) that was isolated from *Jatropha mahafalensis*, and exhibited antimalarial activity.[18]



20 **21**

Scheme 3

During the synthesis of a methylamine-bridged enkephalin analog (MABE) **23** (Scheme 4), Goodman's group selected EDC as a coupling reagent, with HOAt as an additive, to construct the cyclic backbone from the linear peptidomimetic **22**.[19] The

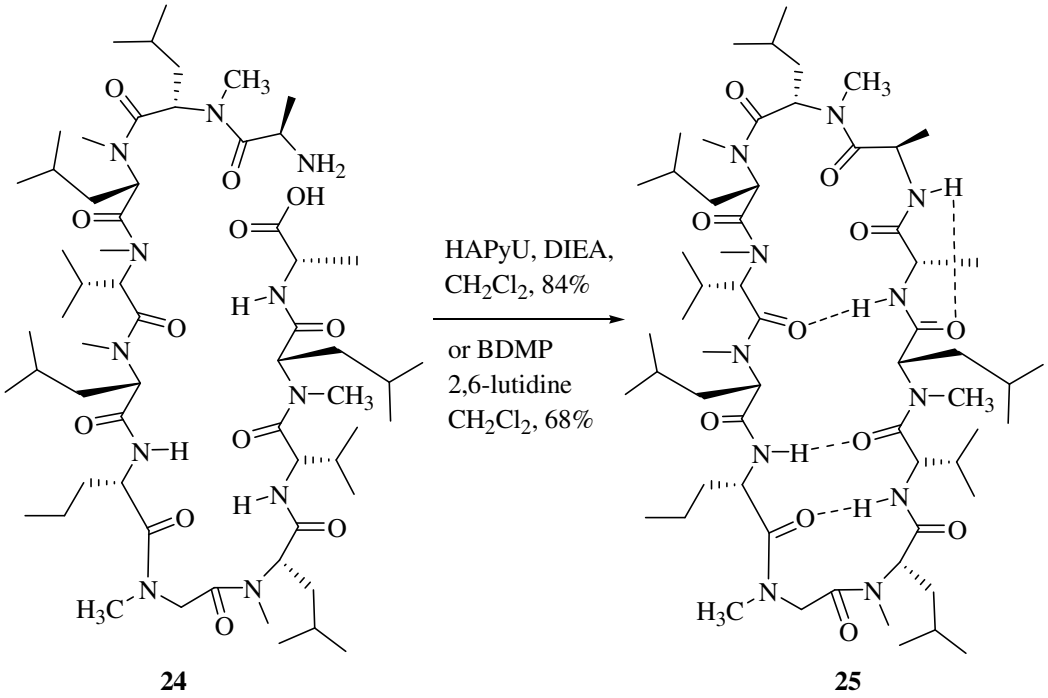


22 **23**

Scheme 4

combined use of EDC with HOAt can not only enhance reactivity and effectively suppress the racemization of the *C*-terminal amino acid residue during coupling, but also can suppress side reactions caused by the carbodiimide-type coupling reagent, such as EDC, DIC and DCC.

HOAt-derived uronium/aminium-type reagents, such as HATU and HAPyU, proved to be more efficient than the corresponding HOBt-derived analogs in some specific cases. For example, Li *et al*. accomplished the macrocyclization of the undecapeptide **24** using reagent HAPyU in 84% high yield to give the immuno suppressive cyclopeptide Cyclosporin O **25** (Scheme 5).[20]



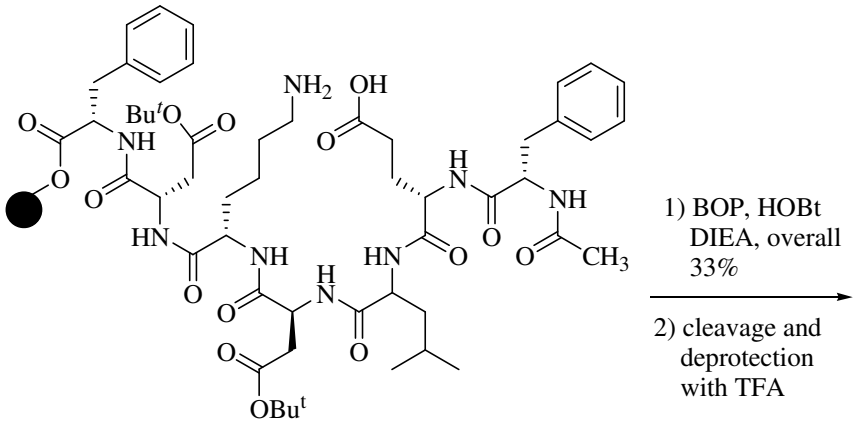
24 **25**

Scheme 5

1.1.1.2 Macrolactamization strategy on solid-phase

As for the synthesis of cyclic peptides on solid-phase, more factors need to be considered, such as the selection of resin, orthogonal protection and deprotection/ cleavage strategy, and patterns of loading onto resin.

During the synthesis of the inhibitor of mammalian ribonucleotide reductase (mRR) **27**, Liehr and co-workers linked the *C*-terminal amino acid Fmoc-Phe-OH to Tentagel resin, followed by solid-phase peptide synthesis and selective deprotection to give the linear peptide **26**, that underwent on-resin cyclization and cleavage to afford



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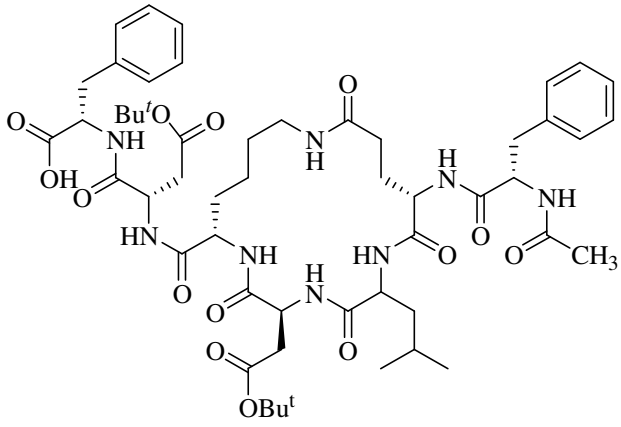
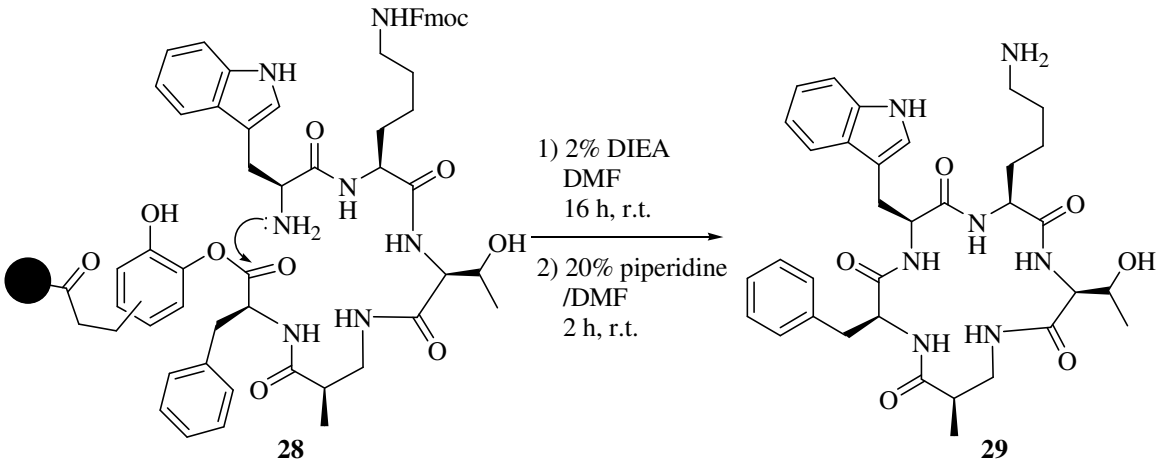


27

Scheme 6

the lactam-bridged peptide **27** (Scheme 6).[21] This kind of cyclization method has been widely used, by anchoring the side chains of aspartic and glutamic acids, lysine, serine, and tyrosine[22] or the carboxyl group of *C*-terminal amino acid residue[23] onto resin, followed by on-resin backbone or side chain macrocyclization and cleavage/deprotection to give the desired cyclopeptides.

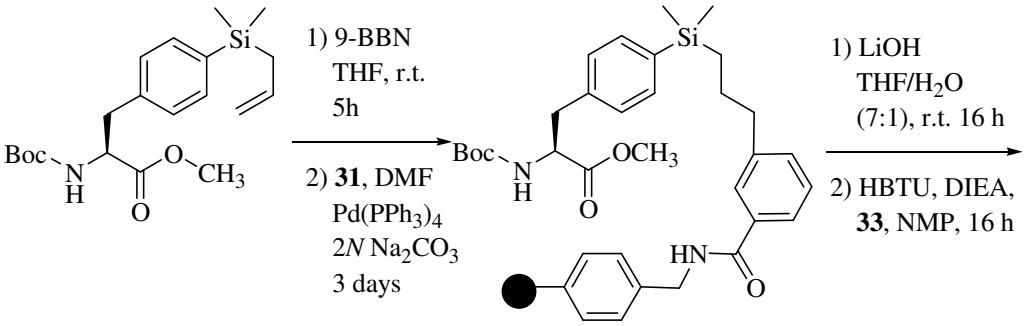
Recently, Bourne and co-workers developed a new safety-catch linker which is stable during assembly of the linear peptide and explained the resin cleavage by macro cyclization of **28** to form **29** (Scheme 7).[24]



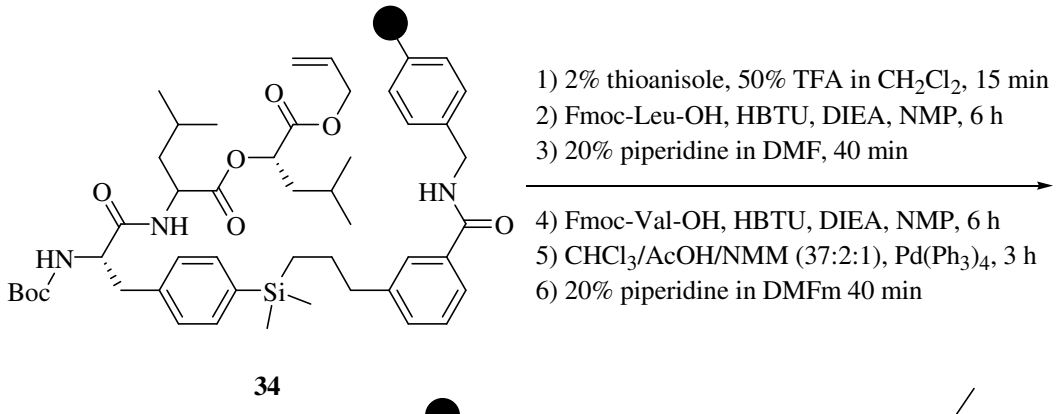
28 **29**

Scheme 7

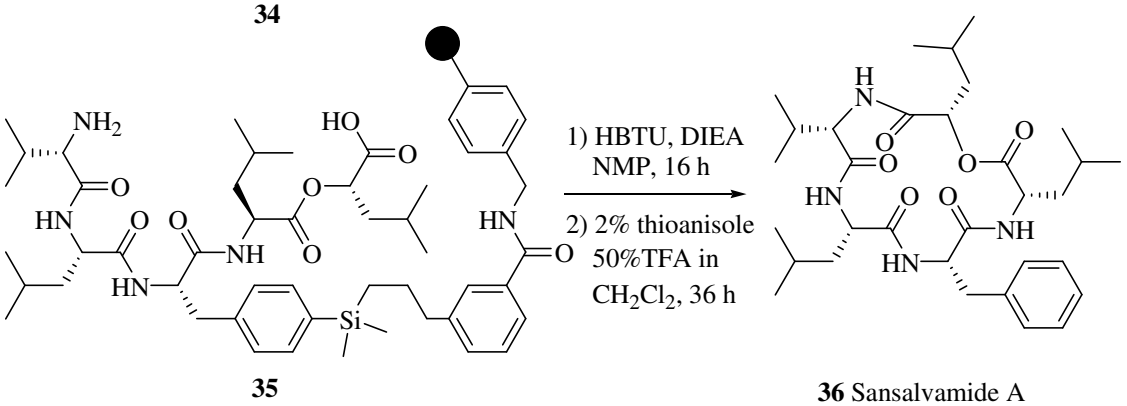
Recently, Lee and Silverman reported their arylsilane based "traceless linker" strategy for on-resin head-to-tail macrocyclization.[25,26] This strategy can be regarded as a variant of the conventional side-chain anchoring method. Specifically, the side-chain of phenylalanine is anchored onto the solid support *via* a traceless linker. Using this strategy, they accomplished the solid-phase synthesis of the cytotoxic depsipeptide sansalvamide A **36** in an overall yield of 67% with >95% purity from the polymer-bound



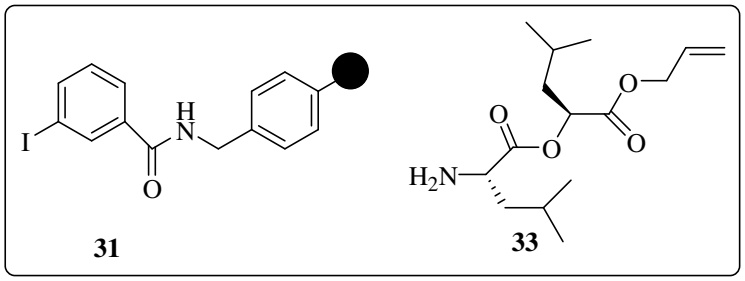
30 **32**



34



35 **36** Sansalvamide A



31 **33**

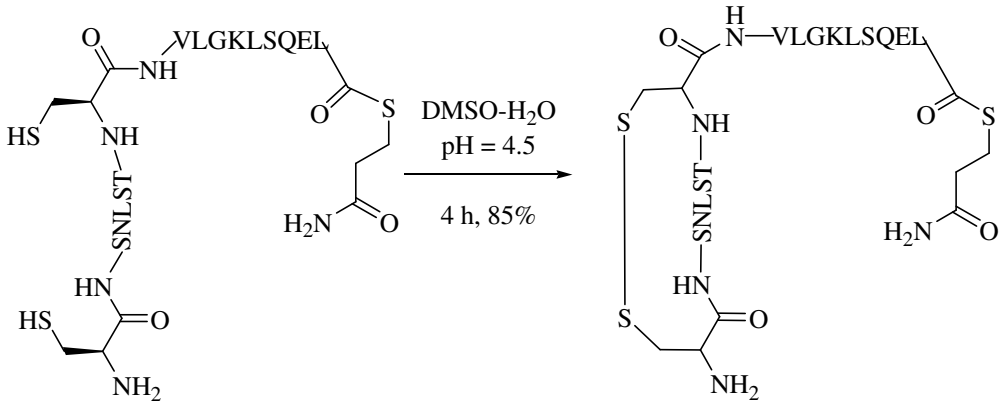
Scheme 8

phenylalanine building block **32**, which was obtained by hydroboration of the allyl substituent of **30**, followed by the Suzuki coupling of the generated borane complex with 3-iodobenzamidomethylpolystyrene **31**. After the deprotection of the methyl ester group by hydrolysis using LiOH, the resin-bound tripeptide **34** was prepared by coupling with depsipeptide ester **33** using HBTU, followed by traditional protective group manipulation and solid-phase peptide synthesis using Fmoc chemistry to give the resin supported peptide **35**. After on-resin head-to-tail cyclization, the final cyclodepsipeptide **36** was released from the resin by treating with TFA to cleave the C-Si bond (Scheme 8). This traceless linker strategy provides a general approach to the solid-phase synthesis of cyclopeptides and cyclic depsipeptides that contain phenylalanine or other hydrophobic side chains.

1.1.1.3 Disulfide cyclization strategy

Disulfide bridges are key structural features of many peptides and proteins, including hormones, enzymes, growth factors, toxins, and immunoglobulins. These intramolecular disulfides play fundamental roles in the folding and stabilization of the bioactive conformations, as well as promoting entropic destabilization of the denatured state.[27,28] The disulfide induced loops and turns in peptides and proteins are functionally important for their biological activities and specificities, and therefore these structures are highly interesting from a pharmaceutical point of view, and as targets for peptidomimetics.

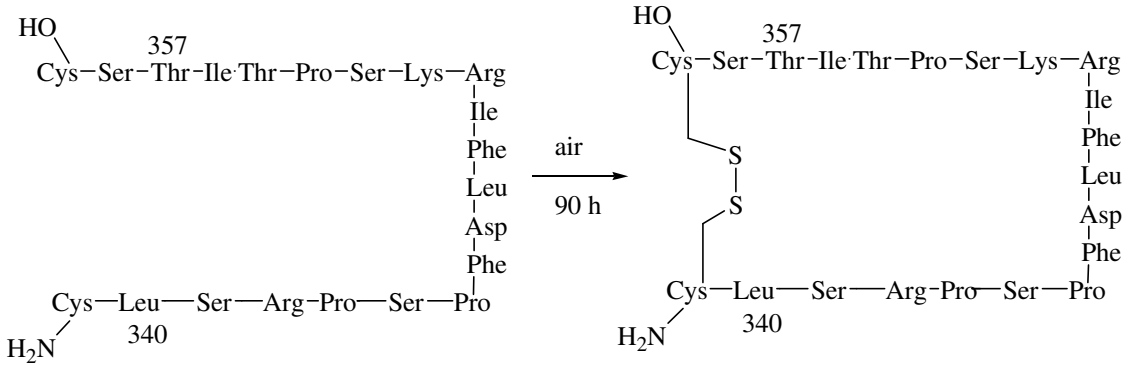
Tam's group reported very useful and efficient cyclization strategy for the synthesis of disulfide contained cyclic peptides using aqueous buffered solutions at pH ranging from 4 to 7.5 (Scheme 9).[29]



37 **38**

Scheme 9

Recently, Spivey and co-workers used an air oxidation for the synthesis of disulfide-constrained cyclic peptide **40**, containing residues Leu340-Thr357 of native



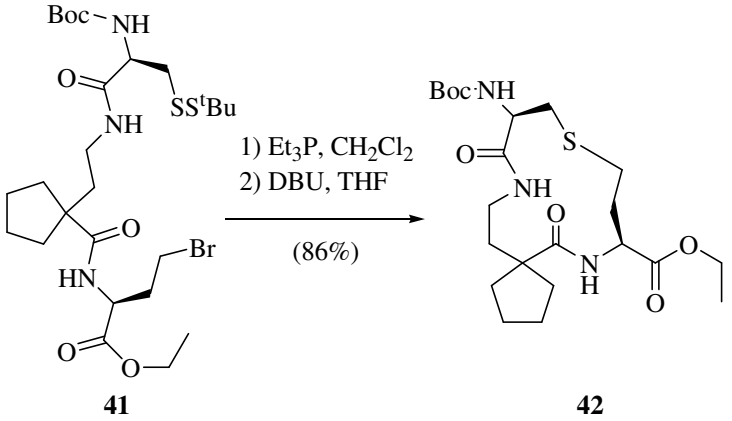
39 **40**

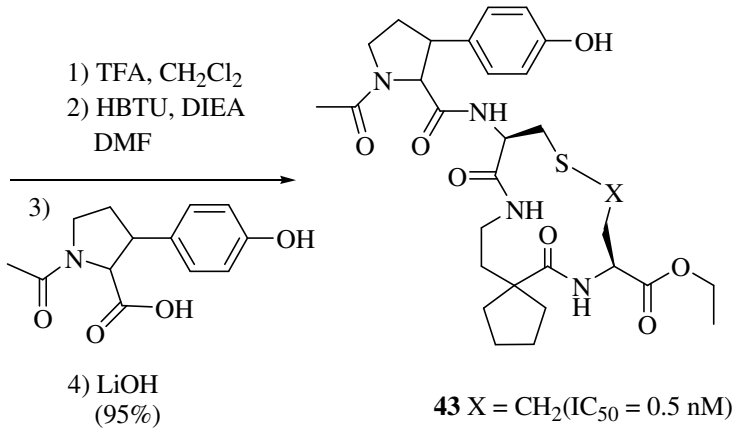
Scheme 10

hIgE that inhibits hIgE-triggered 5-hydroxytryptamine secretion in a genetically engineered rat basophilic leukemia cell line transfected with the extracellular domain (α-chain) of human FcεRI with an IC_{50} of ~12 μM (Scheme 10).[30]

1.1.1.4 An intramolecular thioetherification strategy

The thioether linkage has been widely employed as a metabolically stable surrogate to replace native disulfide bridge of bioactive cyclopeptide. Commonly used

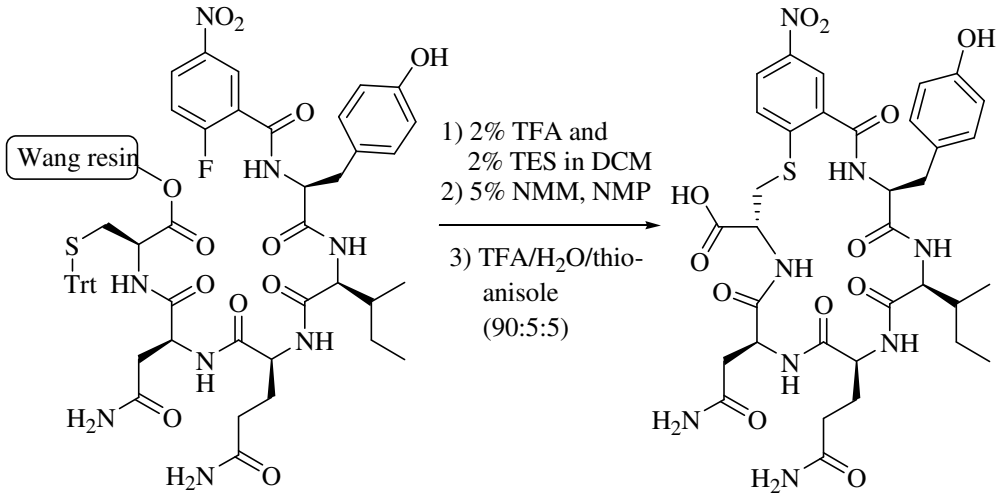




Scheme 11

strategy for the synthesis of thioether-linked cyclic peptides and peptidomimetics is *via* S_N^2 displacement reactions involving haloalkyl electrophiles, such as β-haloalanine, γ-halo-α-amino butyric acid, and haloacetic acid.[31-35] Fotouhi *et al.* developed a potent disulfide bridged inhibitor of the VLA-4/VCAM interactions, **44**, with an IC_{50} of 0.1 nM, shown in Scheme 11.[36,37] To enhance the metabolic stability of this disulfide bridged cyclopeptide, they further designed and synthesized its redox stable thioether analogs, such as compound **43** (IC_{50} of 0.5 nM). The construction of the thioether bridge was realized by S_N^2 reaction of γ-bromo homoalanine with deprotected cysteine under basic conditions in 86% yield to give compound **42**. This intermediate was condensed with a specific proline derivative, followed by deprotection to afford the thioether cyclopeptide inhibitor **43** (Scheme 11).[37]

In the synthesis of tocinoic acid analogs, Fotsch and coworkers employed on-resin macrocyclization *via* an intramolecular S_NAr reaction to give the thioether bridged cyclic



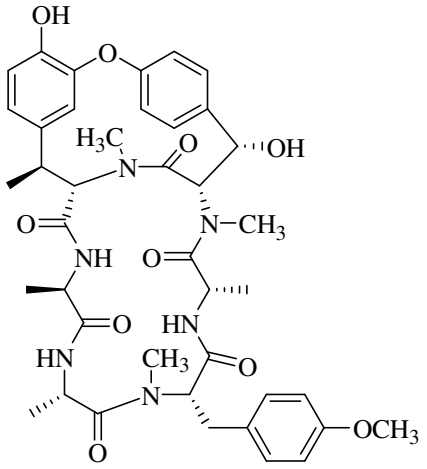
45 **46**

Scheme 12

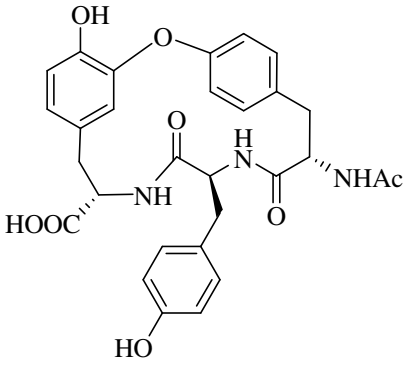
peptidomimetic **46** (Scheme 12).[38] After the deprotection of the side chain of the *C*-terminal cysteine in the Wang resin anchored linear peptide **45**, the *N*-terminal 2-fluoro-5-nitrobenzoate functionality was attacked by the nucleophilic SH group of the cysteine side chain, followed by cleavage to give the cyclic peptidomimetic **46** in >90% purity.

1.1.1.5 An intramolecular etherification strategy

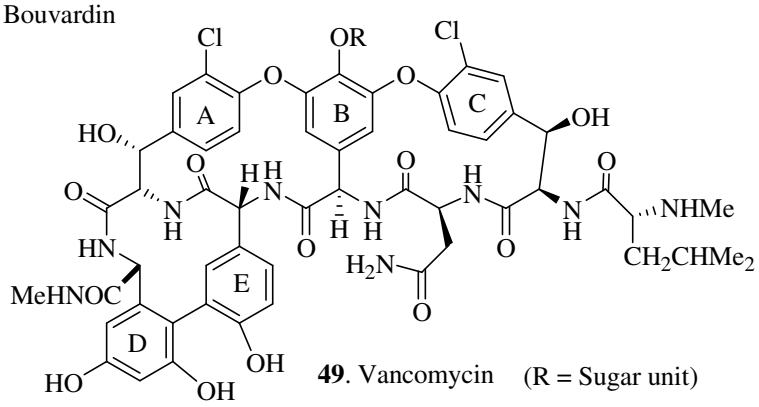
The bisaryl ether bonds exist in a variety of naturally occurring cyclic peptides and peptidomimetics, such as the antitumor antibiotics bouvardin **47**,[39] the angiotensin I



47. Bouvardin



48. K-13

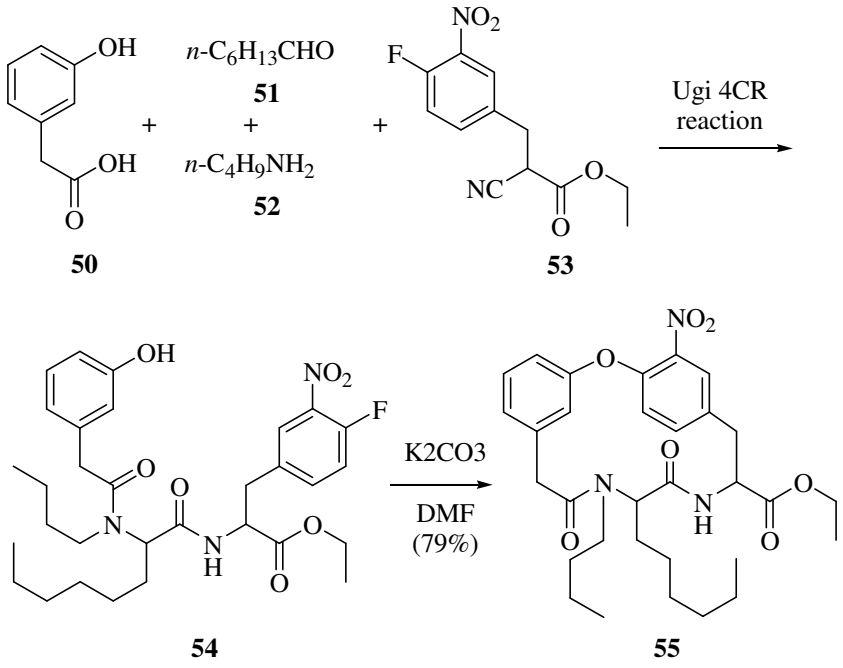


49. Vancomycin (R = Sugar unit)

Figure 4: Biologically active cyclic peptides

converting enzyme inhibitor K-13 **48**,[40] and the glycopeptide antibiotics vancomycin **49**, which is a highly effective and widely used clinical agent for combating severe bacterial infections caused by drug resistant pathogens (Figure 4).[41, 42] Because of the tremendous biological importance of these natural products, great efforts have been made to develop highly efficient approaches to synthesis of these ether-bond-containing cyclic peptides and peptidomimetics.

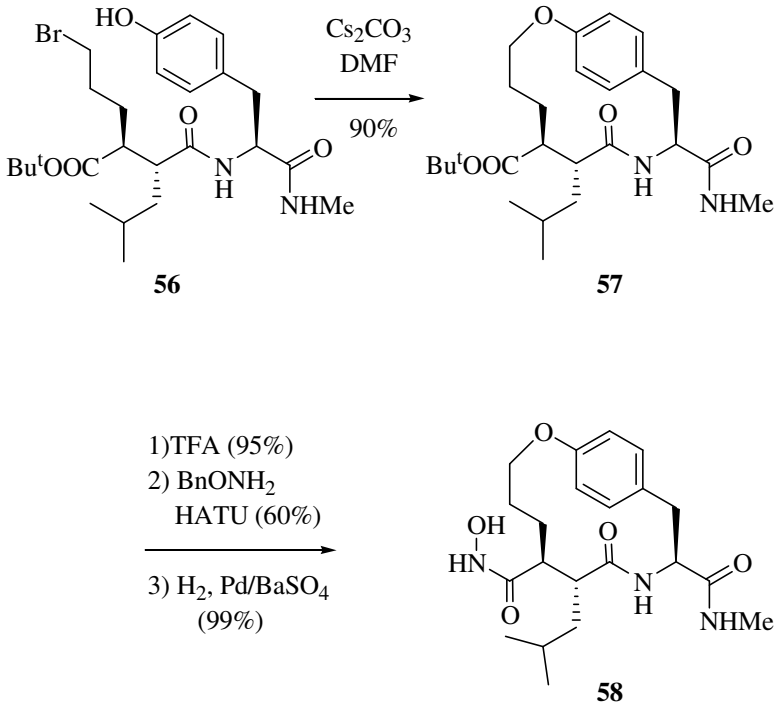
Recently, Zhu group developed an efficient method for the synthesis of ether-bond-containing cyclic peptidomimetics by pair wise use of Ugi four-component (Ugi 4CR) reaction and S_NAr-based cycloetherification.[43] As shown in scheme 13 the linear peptide precursor **54** was obtained from the ω-(3'-hydroxyphenyl) alkane carboxylic acid **50**, aldehyde **51**, the amine **52**, and the isonitrile **53** *via* the Ugi reaction. The linear precursor **54** underwent cyclization by an intramolecular etherification to give the desired



Scheme 13

bisaryl ether containing macrocycle **55** in a good yield (Scheme 13). This strategy provides a step-efficient method for the high throughput synthesis of bioactive cyclic peptidomimetics containing diaryl ether motif.

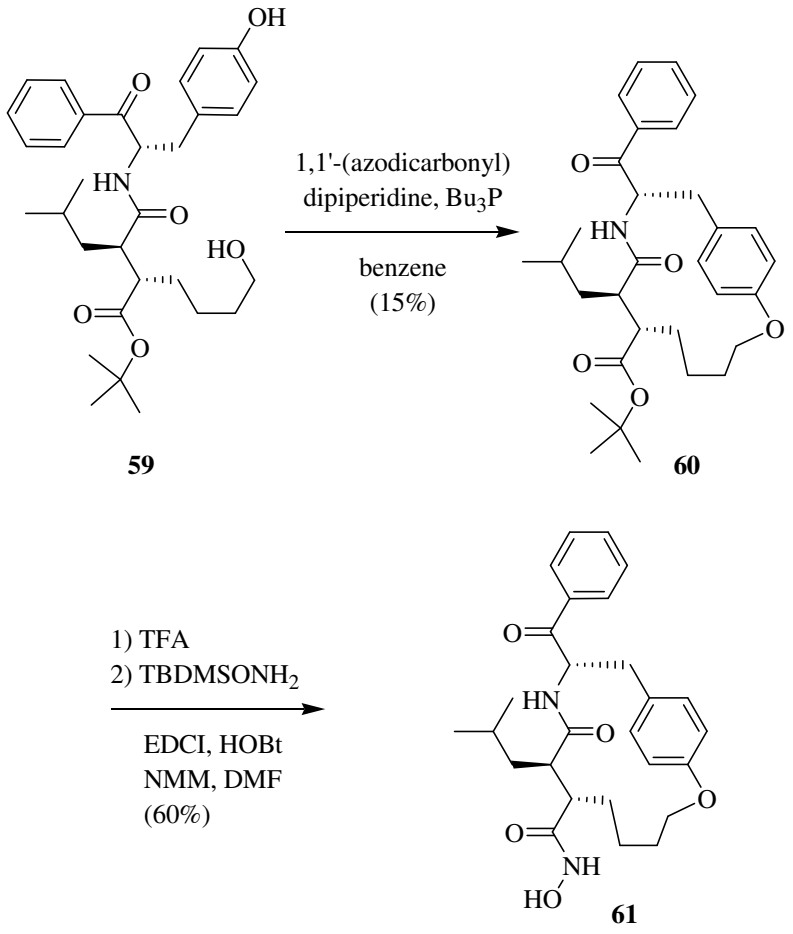
Xue *et al.* successfully synthesized the cyclic ether **58**, a potent inhibitor of matrix metalloproteinases (MMPs) (Scheme 14). The key step of the synthesis was the intramolecular S_N^2 reaction of compound **56** driven by Cs_2CO_3, the resulting macrocycle **57** was subsequently modified to give the peptidomimetic **58**. The latter agent found to have strong inhibitory activities to MMP-1, MMP-3, and MMP–9.[44]



Scheme 14

Recently, Steinman and Sheppard have exploited the application of Mitsunobu cyclization in the synthesis of cyclic peptidomimetics containing aryl-alkyl ether

bonds.[45,46] For instance, in the synthesis of the MMP inhibitory agent **61**, Sheppard and co-workers adopted this strategy to build the macrocycle **60** from the linear peptide **59** (Scheme 15).

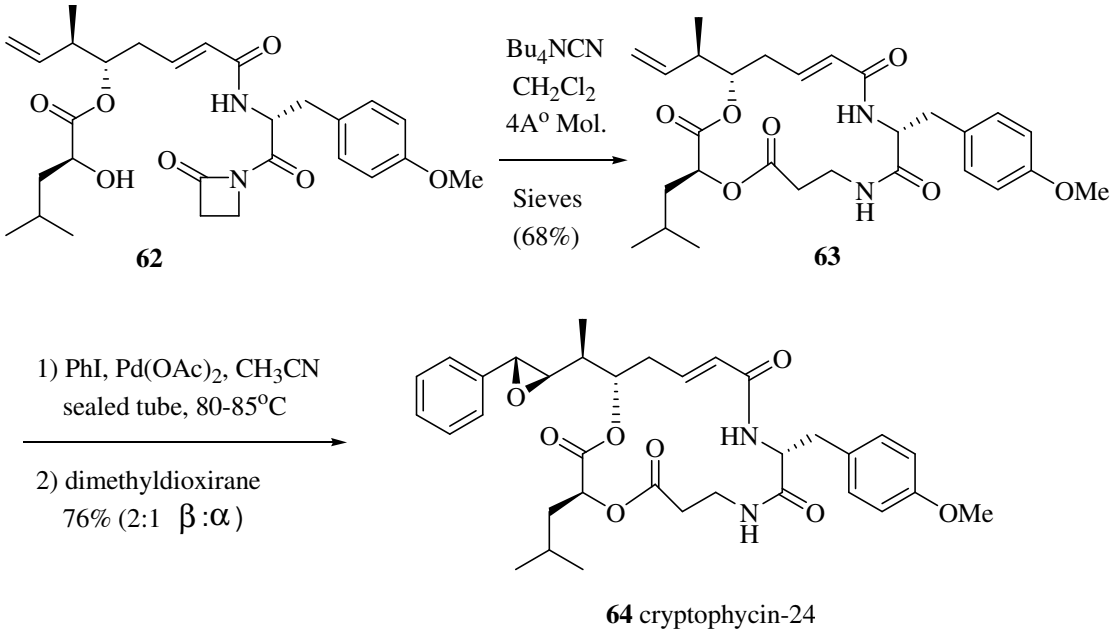


Scheme 15

1.1.1.6 Synthesis of cyclic depsipeptides via β-lactam-based macrolactonization

β-Lactam-based macrocyclization is another useful strategy for the synthesis of macrocyclodepsipeptides. β- Lactams have been used as acylating agents in both inter- and intramolecular reactions with oxygen, nitrogen and carbon nucleophiles, and applied

to the synthesis of many alkaloid natural products.[47] In the total synthesis of Cryptophycin-24 **64**, Eggen *et al.* reported this method to construct the macrocycle **63** from linear peptide **62** as shown in Scheme 16.[48]



Scheme 16

1.1.2 Synthesis of cyclic peptides using metal-mediated reactions

Small cyclic peptides (less than 6 residues in size) are recognized as important targets for their interesting biological activities and stability towards proteolytic enzymes. However, efficient and general synthetic methods for small cyclic peptides have not been developed using general peptide synthesis protocols. Recently several innovative methods for the synthesis of small cyclic peptides and peptidomimetics have been reported.[49] Metal-catalyzed ring closure is a useful tool for the synthesis of small cyclic peptide mimics. Cyclization of sidechain-to-sidechain or sidechain-to-backbone peptides

have been possible in a highly efficient manner and this method could be utilized to replace labile disulfide bridges in peptide structures or incorporate a conformationally restricted element by installing intramolecular loop of cyclic peptides.

1.1.2.1 Ruthenium-catalyzed Ring-Closing Metathesis

A recent method for the preparation of olefin-linked macrocycles, the ring-closing metathesis reaction (RCM), is a promising approach toward the synthesis of novel cyclic peptides. The structures of some commonly used catalysts **A-D** in RCM reactions are shown in Figure 5.[50-54]

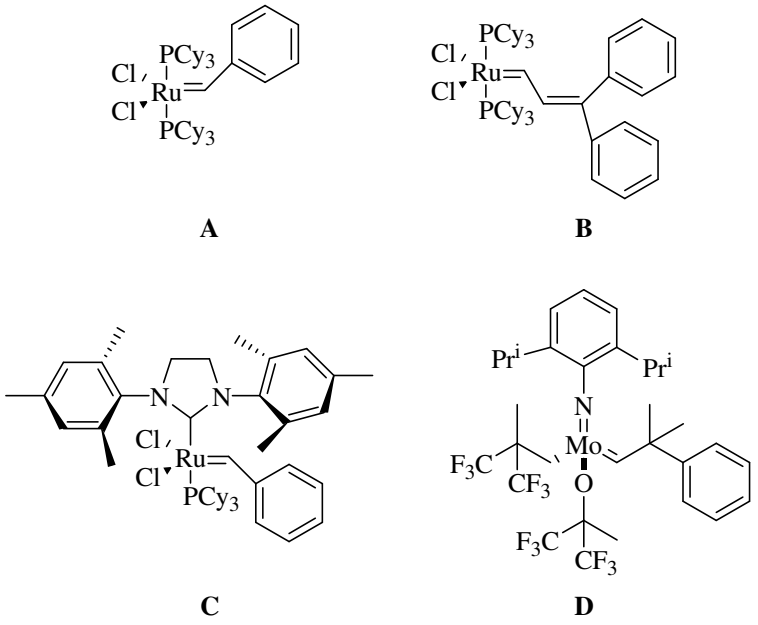
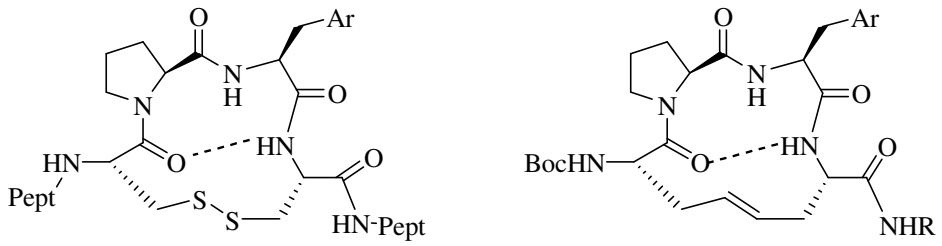


Figure 5: Commonly used catalysts in ring closing metathesis

Cyclizations of peptides, in general, results in an increased stability toward proteases, also in cystine peptides the disulfide bonds are sensitive to reduction. The metabolic stability of these compounds can dramatically be increased by replacing the

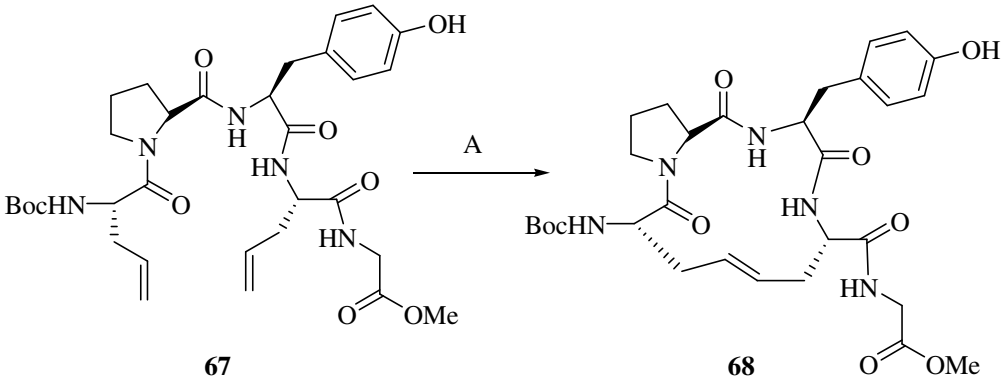
critical disulfide bond by a noncleavable C-C bond.[55] The ring-closing approach can directly be used for the synthesis of cyclic peptides, such as **66**, a carba analogue of the glutaredoxin active site **65** (Figure 6).[56]



65 **66**

Figure 6: Carba analogue of the glutaredoxin active site

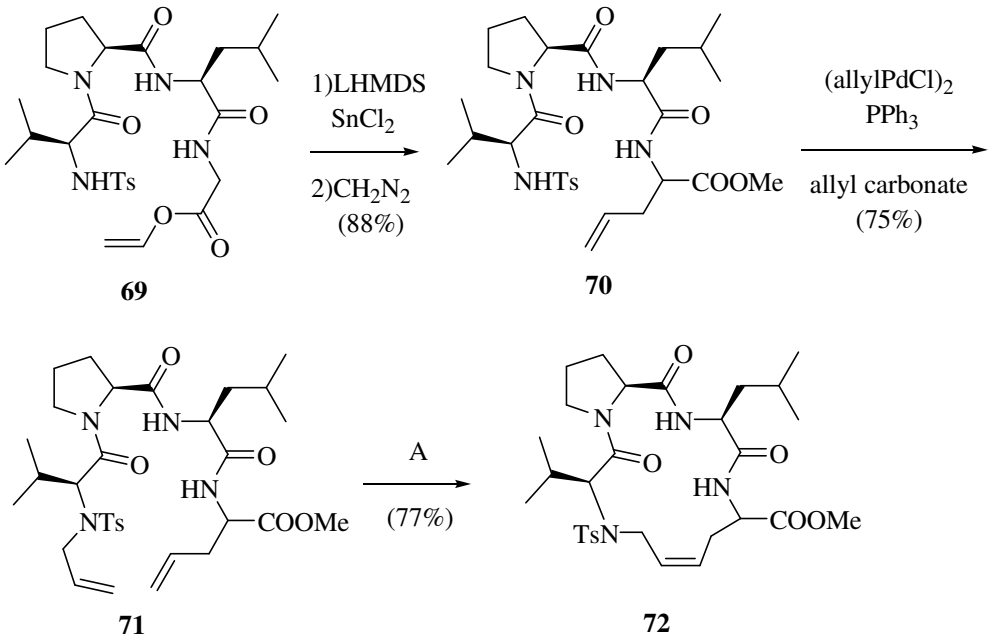
Grubbs *et al.* exposed **67** to the ruthenium catalyst **A** under standard macro cyclization conditions (0.004 M, CH_2Cl_2, 40 °C) for the formation of the macrocycle **68** in 70% yield (Scheme 17).[56]



67 **68**

Scheme 17

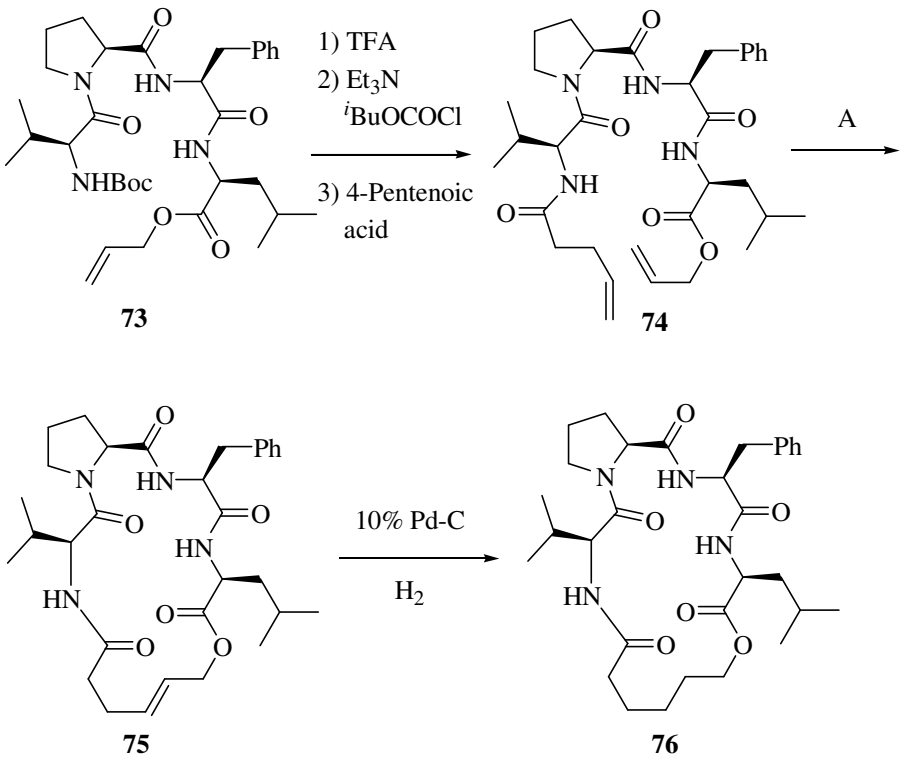
Kazmaier *et al.* used the RCM strategy for the synthesis of carba analogue of the glutaredoxin active site **65,** starting from the tetrapeptide ester **69.** Upon Claisen rearrangement, **69** gave the allylated tetra peptide **70.**[57] *N*-Allylation provided the substrate **71** which on subsequent ring-closing metathesis resulted in the formation of the cyclic peptide **72** (15-membered ring) in high yield (Scheme 18).[58]



69 **70** **71** **72**

Scheme 18

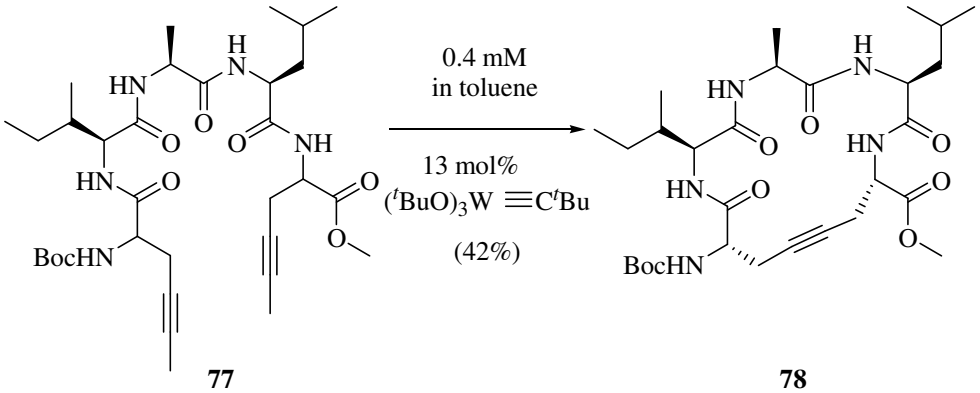
Javed Iqbal *et al.* used the RCM strategy for the development carba analogue of the small cyclic peptides as type VIβ-turn protease inhibitors. Starting from the tetra peptide allyl ester **73**, this converted to **74** on reaction with pentenoic acid. The peptide **2** afforded the corresponding cyclic peptide **75** as a mixture of *E*/*Z* isomers (5:1) in good yield (70%) when subjected to RCM using Grubbs **A** catalyst. Cyclic peptide **75** reduced to **76** by hydrogenation (Scheme 19).[59]



Scheme 19

1.1.2.2 Tungsten-catalyzed Ring-Closing Alkyne Metathesis

Liskamp *et al.* performed ring-closing alkyne metathesis of **77** in the presence of the tungsten-alkylidyne complex $(^tBuO)_3W{\equiv}C^tBu$ as a catalyst in toluene at 80 °C to

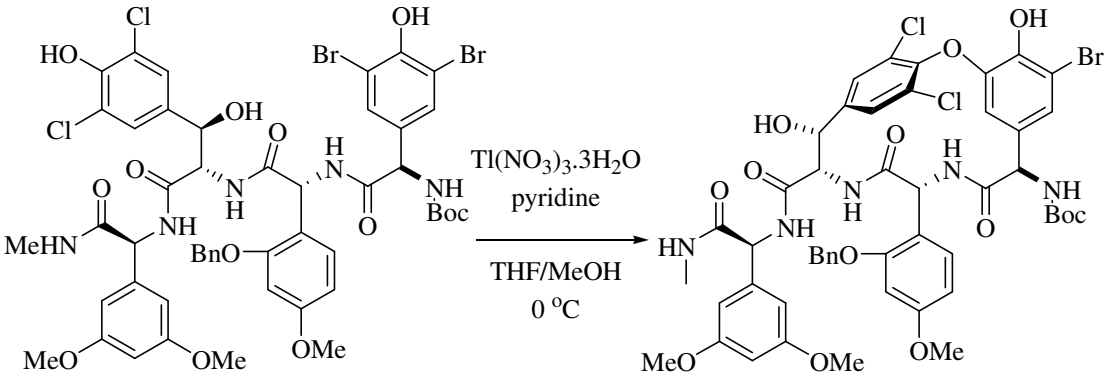


Scheme 20

obtain alkyne bridged cyclic peptide **78**, in the synthesis of the alkyne-bridged mimics of the peptide antibiotic nisin Z (Scheme 20).[60]

1.1.2.3 Thallium-catalyzed reactions

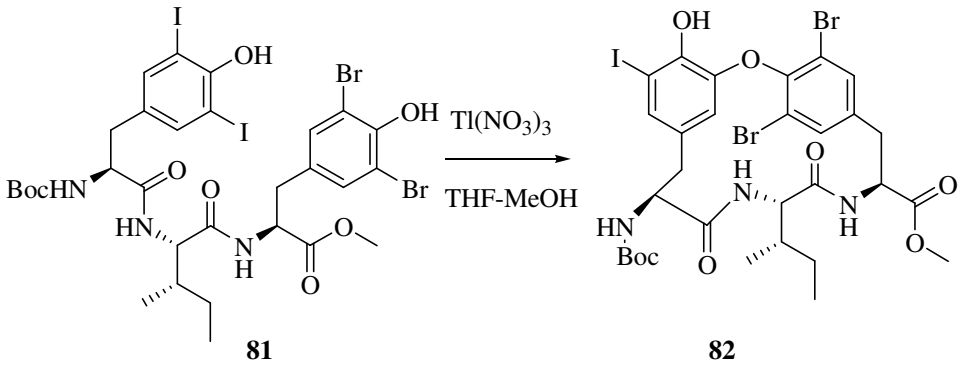
Evans *et al.* successfully synthesized the cyclic ether **80**, as a tripeptide unit of the vancomycin related antibiotics (Scheme 21). The key step of the synthesis was the thallium trinitrate (TTN)-mediated oxidative macrocyclization of **79**.[61]



79 **80**

Scheme 21

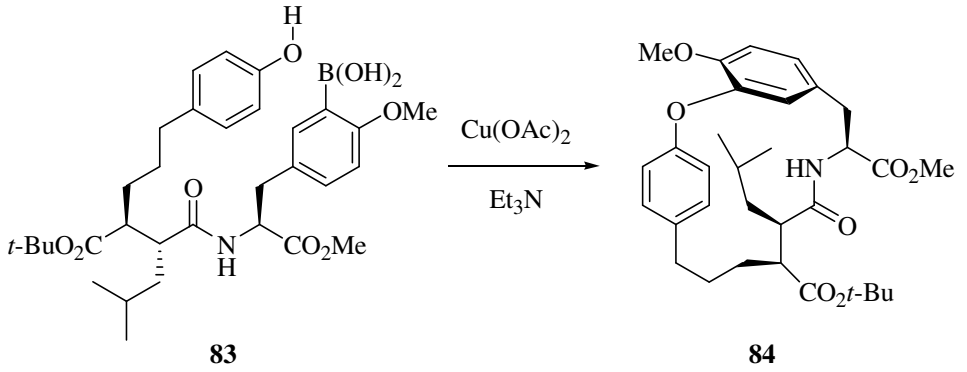
Nakamura *et al*. are also used thallium trinitrate (TTN)-mediated oxidative macrocyclization for the synthesis of isodityrosine-class bioactive molecules. They synthesized cyclic tripetide **82** constrained with biraryl ether linker from its acyclic peptide **81** using this oxidative macrocyclization strategy (Scheme 22).[62]



Scheme 22

1.1.2.4 Copper-catalyzed reactions

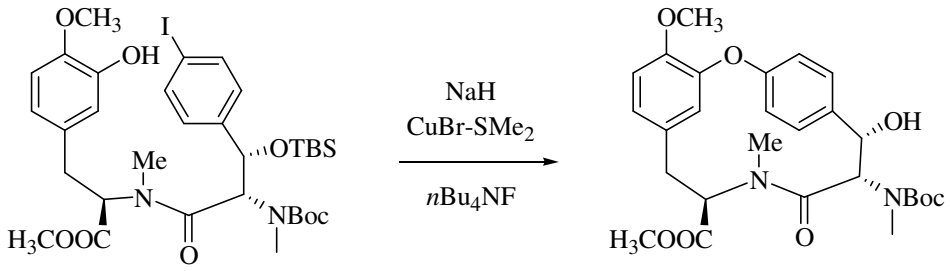
Recently, Decicco and Evans have developed the copper acetate mediated macro cyclization methodology for the synthesis of diphenyl ether contained cyclic peptide **84**, a matrix metalloproteinase inhibitor (scheme 23).[63]



Scheme 23

Boger *et al*. detailed the success of copper-mediated Ullmann macrocyclization methodology to the preparation of the highly functionalized and more sensitive 13-hydroxy-N-methylcycloisodityrosine compound **86** and its incorporation into the first

total syntheses of potent antitumor antibiotics bouvardin and *o*-methylbouvardin (Scheme 24).[64]

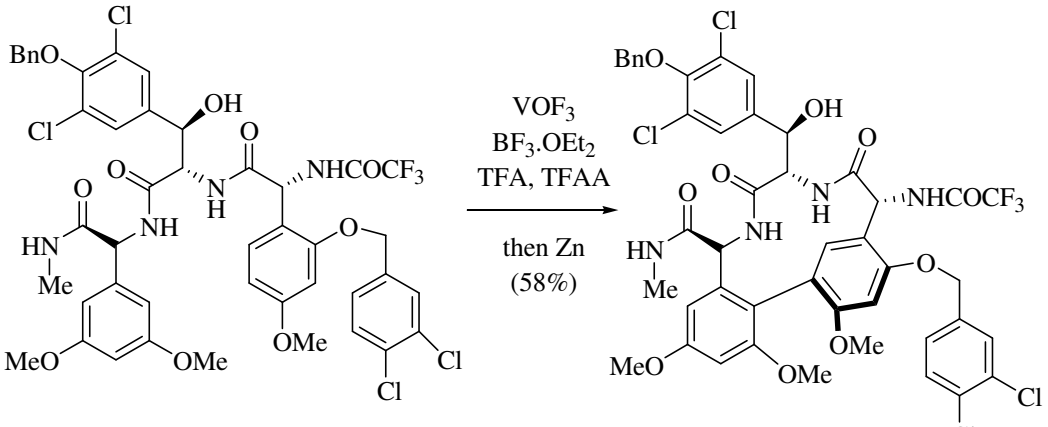


85 **86**

Scheme 24

1.1.2.5 Vanadium-mediated reactions

Evans group developed a vanadium-based approach to the biaryl ring system of vancomycin (Scheme 25).[65]

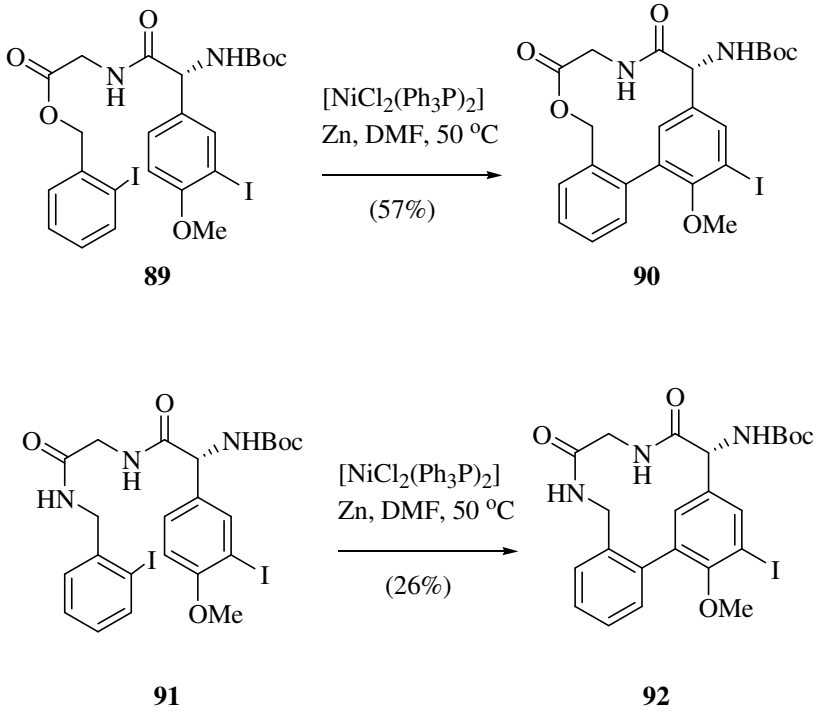


87 **88**

Scheme 25

1.1.2.6 Nickel-mediated reactions

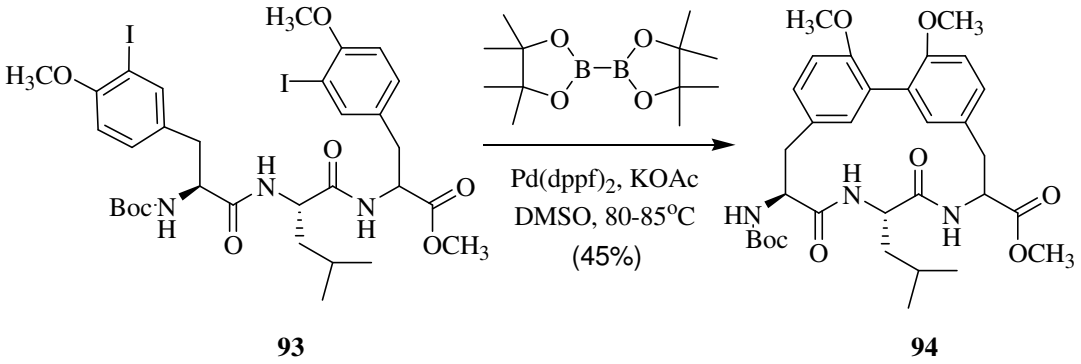
Nicolaou *et al.* employed the nickel-mediated coupling of aryl iodides to form biaryl systems in an intramolecular fashion to construct model system of the AB ring system of the glycopeptide antibiotics (mimic of vancomycin) (Scheme 26).[66]



Scheme 26

1.1.2.7 Palladium-catalyzed reactions

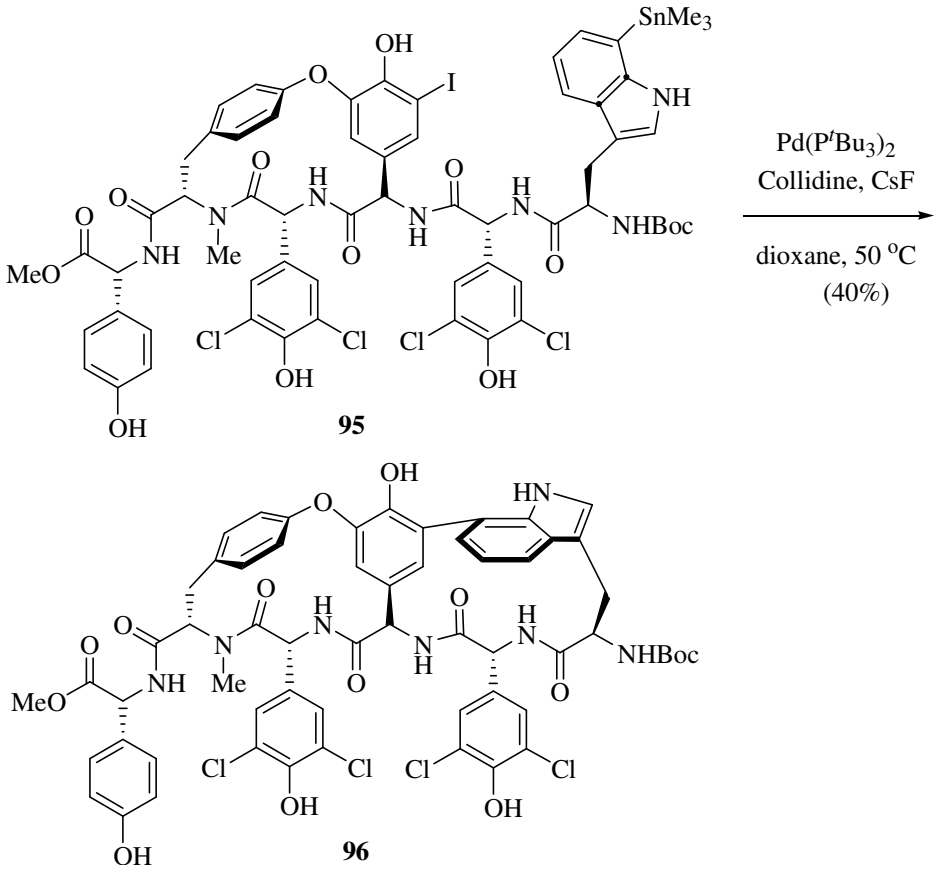
Recently, Zhu and Carbonnelle developed a novel palladium catalyzed-diboron ester mediated cyclization reaction of linear diaryl halides.[67] Using this strategy, they synthesized a biophenomycin-like model compound **94** in a 45% yield from the linear peptide **93** (Scheme 27). The reaction involves Miyura arylboronic ester formation, followed by intramolecular Suzuki reaction, using the catalyst $Pd(dppf)_2Cl_2$.



93 **94**

Scheme 27

Hoveyda and co-workers used palladium-catalyzed cross-coupling to construct biaryl system during the synthesis of anti-HIV agent chloropeptin I (Scheme 28).[68]



95 **96**

Scheme 28

The synthetic strategies outlined above reveal that a lot of research went into identifying the new and better methods for the cyclization to furnish desired biologically active cyclic peptides. As the side chains are generally considered to be the main mediators for receptor interaction,[69] cyclization is preferably accomplished between the C- and N-termini. Whereas the synthesis of linear peptides generally proceeds well, head-to-tail cyclization is often troublesome, especially for small peptides of less than seven residues in length.[70] The primary reason for ineffective cyclization originates from a sequence-related inefficiency to bring the termini together for head-to-tail cyclization. Since peptide bonds contain strong π-character and preferentially adopt a *trans* conformation, linear peptides prefer more extended conformations. This places the terminal carboxylic acid and amine functional groups in remote positions that are unfavorable for cyclization. Incorporation of turn-inducing elements such as Gly, Pro, or D-amino acids are known to enhance cyclization yields.[71] For linear peptides of 4-6 residues that do not contain amino acids that stabilize turn structures, slow cyclizations lead to side reactions such as cyclodimerization and epimerization.[72] At this point one question arises, is it possible to synthesize cyclic peptides without turn inducer and with minimum side reactions? Our answer is: Yes, it is. Of course several groups represented various methods to synthesize cyclic peptides without turn-inducer. Here, we are interested in the development of palladium-catalyzed reactions as cyclization strategies for the synthesis of cyclic peptides from the corresponding linear peptides having appropriate functional groups on C- and N-termini to introduce various unnatural amino acids as covalent constraints. Different palladium-catalyzed reactions have been used to incorporate various covalent constraints in the cyclic peptides.

The increasing number of synthetic transformations facilitated by transition metal catalysts shows no sign of abating. Of all the organometallic compounds known, those derived from palladium have become the most important catalysts for an eclectic array of synthetic manipulations in basic feedstocks, to fine chemicals through to more elaborate, often complicated, natural products or π-conjugated materials. Since mid nineties, the general synthetic applications of palladium have expanded significantly. It has matured into an area which is a mainstay in the synthetic chemists' armoury, providing a myriad of versatile transformations, in ways that facilitate exquisite control in the conversion of simple starting materials into targets of varying complexity. Selectivity is a key facet in palladium-mediated synthesis, for example, in the chemo-, regio- and stereo-selective processes that often result, allowing one to access some of the most intricate synthetic targets, not available by traditional methods. Now-a-days there is no synthetic journal without the report of the application of a palladium-mediated process. The reactions discovered by Kumada and Corriu; Heck; Hiyama; Negishi; Suzuki and Miyaura; Kosugi, Migita and Stille; Sonogashira, Trost and others, have inspired us to apply this state-of-the-art technology to the synthesis of cyclic peptides. We have also inspired by the recent, well known, contributions of Buchwald and Hartwig's group[73] in the development of C–N and C–O bond formation to synthesize aniline and aryl ether derivatives, respectively.

Generally, palladium has achieved a prominent role in catalysis and synthesis due to its electronegativity (2.2), which facilitates the formation of relatively strong Pd–H and Pd–C bonds, but also gives rise to polarized Pd–X bonds. It also allows easy access to 0 and +II oxidative states, where palladium-centered reactions such as oxidative addition,

transmetallation and reductive elimination processes, occur with dynamic changes in geometry on palladium. However, one must not forget that +I, +III and +IV oxidation states are also possible, yet these are rarely mentioned, and that Pd(VI) (formally) has been proposed,[74] albeit disputed by theoretical studies.[75] Pd(II)/(IV) catalytic cycles have been proposed by scientists over the years, but have generally proved contentious. Although disproved in the majority of cases, particularly in reactions employing palladacycles[76] such catalytic cycles are not ill-conceived, particularly given the fact that many Pd(IV) complexes are known,[77] and following the recent discovery by Sanford that such species are important in C–H activation/oxidation and C–C bond forming processes.[78] Reliability, good catalytic activity, diverse substrate scope, and more importantly, the ability to perform reactions under standard laboratory conditions (non-glove box), will certainly bring about the broad application of the palladium-mediated reactions, and provide near atom-efficient organic transformations. One important practical consideration is that ligands and palladium catalysts are mostly commercially available (and inexpensive), or at the very least can be readily prepared in one to two steps. Contributions to this thesis for the synthesis of cyclic peptides (di-, tri- and tetra-) and application of highly active and selective palladium catalysts for macrocyclization of peptides are made by us in this organometallic chemistry field. The specific topics included are: aryl bromide coupling to acryloyl group, the intramolecular Heck arylation of electron-rich olefins; Copper-free Sonogashira coupling, for intramolecular aryl alkynylation, reactions mediated by $Pd(OAc)_2$ catalyst. Studies on aryl alkynylation versus alkyne homocoupling in copper co-catalyzed Sonogashira reaction are also described. Trost enyne-cycloisomerization reaction for the synthesis of 1,3-diene

embedded cyclic peptides. These peptides further functionalized with Diels-Alder reaction to obtain bi-cyclic bridged cyclic peptides. Ligand-free intramolecular Suzuki coupling of aryl bromide to aryl boronic acids for the synthesis of biaryl bridged cyclic peptides. The Buchwald–Hartwig protocol for the intramolecular amination of aryl bromides using $Pd(OAc)_2$/BINAP catalytic system for the synthesis of cyclic peptides constrained with biarylamine linker. Synthesis of carbazole contained cyclic peptides using $Pd(OAc)_2$ catalyzed aryl C-H activation. Overall, we use the palladium-catalyzed reactions for the synthesis of cyclic peptides. Our general approach for various palladium-catalyzed reactions for the synthesis of cyclic peptides is represented in Figure 6.

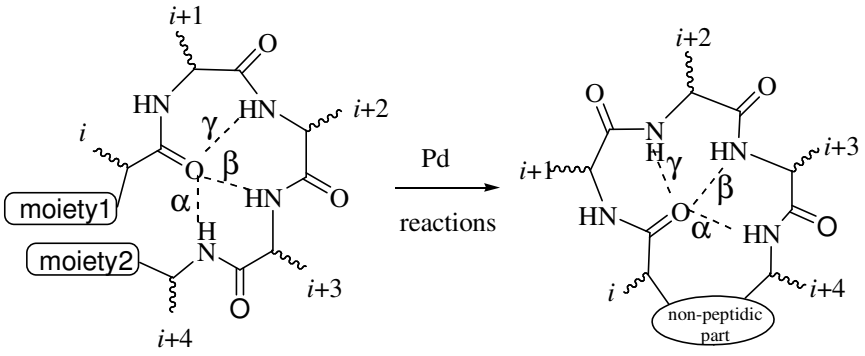


Figure 6: Synthesis of cyclic peptides

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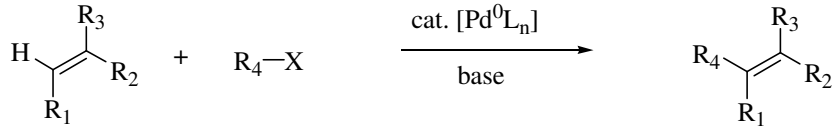
Chapter 2

Synthesis of Small Cyclic Peptides Constrained with 1,3-Disubstituted Phenyl Linkers using the Heck Reaction

2.1 Introduction

The Heck reaction can be broadly defined as the palladium-catalyzed coupling of alkenyl or aryl (sp^2) halides or triflates with alkenes (Figure 1) to yield products which formally result from the substitution of a hydrogen atom in the alkene coupling partner. The first examples of this reaction were reported independently by Mizoroki [1] and, in an improved form, by Heck.[2] However, it would be more than a decade before the broader applicability of this transformation began to be investigated by the wider synthetic organic community. The development of catalytic asymmetric Heck reactions in the late 1980s led to a further resurgence of interest in this field.[3] The Heck reaction now stands as a remarkably robust and efficient method for carbon-carbon bond formation, particularly in the generation of tertiary and quaternary stereocenters and intramolecular ring for- mation, and remains a flourishing area of research.

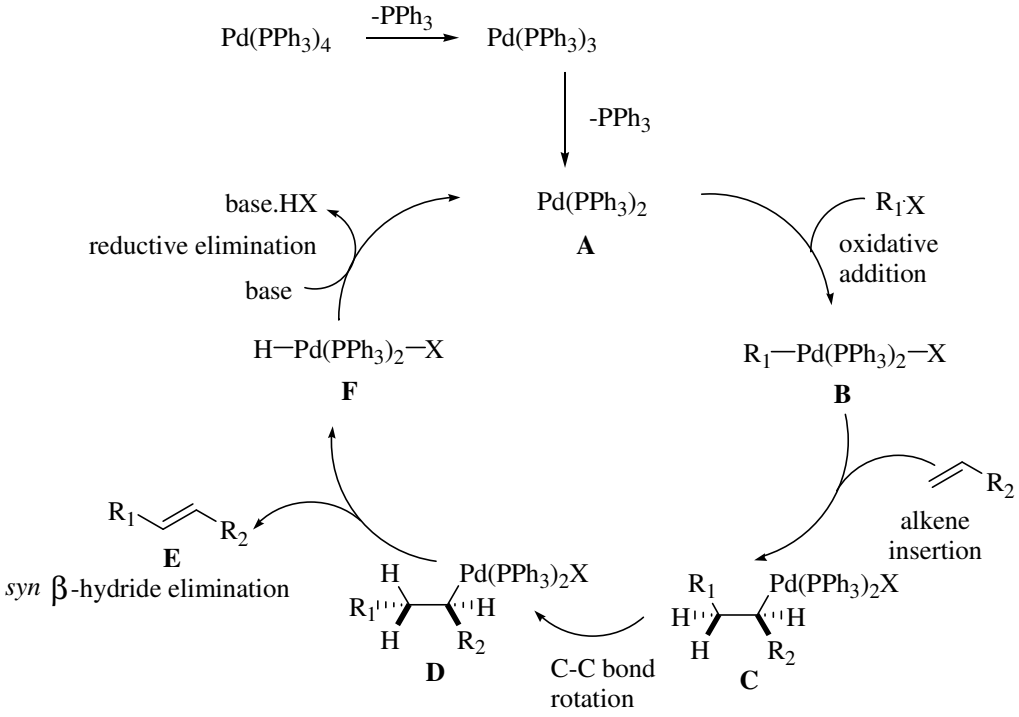


R_4 = aryl, benzyl, vinyl
X = Cl, Br, I, OTf

Figure 1: The Heck reaction

The presumed catalytic cycle for the Heck reaction is summarized in Scheme 1. A coordinatively unsaturated 14-electron palladium (0) complex **A** is the catalytically active species. Once formed, bis(triphenylphosphine)palladium(0) **A** initiates the first step in catalytic cycle by taking part in an oxidative addition reaction with an alkenyl

halide or an aryl halide (R_1X) to give the 16-electron complex **B**. Although intermediate **B** possesses an available coordination site which could be occupied by an olefin, it is



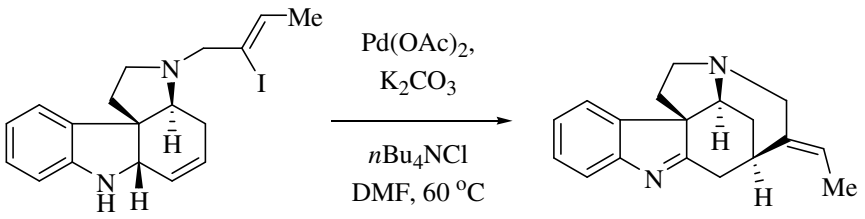
Scheme 1

possible that loss of a neutral donor phosphine ligand from the intermediate **B** precedes the olefin coordination step. In any event, olefin complexation is followed by an insertion of the olefin into the σ-alkenyl or σ-aryl C-Pd bond, generating intermediate **C** via a four-center transition state. It is important that the crucial olefin insertion step occurs as a *syn* addition and that the organic ligand from the palladium complex becomes bonded to the less hindered carbon of the olefin, in other words, the regiochemistry of the olefin insertion is determined primarily by steric effects.

From intermediate **C**, the next step in the catalytic cycle involves a simple bond rotation to give **D**. This event is essential because it establishes the necessary *syn* relationship between a β-hydrogen and the palladium atom. The β-hydride elimination can take place to give the coupling product **E** and the hydridopalldium complex **F** with a β-hydrogen and the transition metal in a common plane. Finally, a base-assisted reductive elimination of HX from the intermediate **F** regenerates the palladium(0) catalyst, thus permitting a subsequent turn through the cycle. It is important to note that R_1 in complex **B** must not contain any sp^3- bonded hydrogen atoms at the β-position, otherwise a premature β-hydride elimination can compete with the desired coupling reaction.

Several research groups have utilized the Heck reaction in the synthesis of a variety of organic molecules. These molecules range from intermediates to final compounds in the syntheses of natural products, biologically active compounds or, synthetic targets. In many cases, the Heck reaction was used in the final step for the synthesis of target molecules.

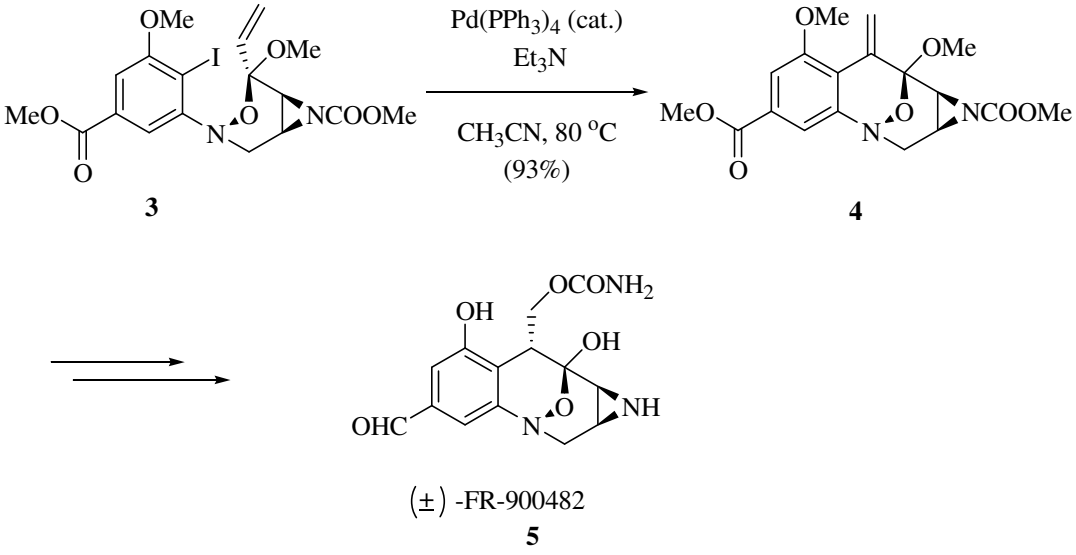
Rawal and co-workers have cleverly used palladium-mediated intramolecular Heck reaction for the stereocontrolled synthesis of *Strychnos* alkaloid (±)-dehydro-tubifoline **2** from compound **1,** using 5 mol% of $Pd(OAc)_2$ and potassium carbonate, tetrabutyl ammonium chloride in DMF at 60 ^oC (Scheme 2).[4]



1 (±)-dehydrotubifoline **2**

Scheme 2

The Danishefsky group accomplished the assembly of tetracyclic compound **5** using again an intramolecular Heck arylation as a key step towards the synthesis of the multifunctional FR-900482 molecule, which exhibit potent antitumor property (Scheme 3).[5] This intramolecular reaction proceeded very efficiently and the success of this cyclization reaction is important in view of the potentially sensitive functionality contained within compound **3**.

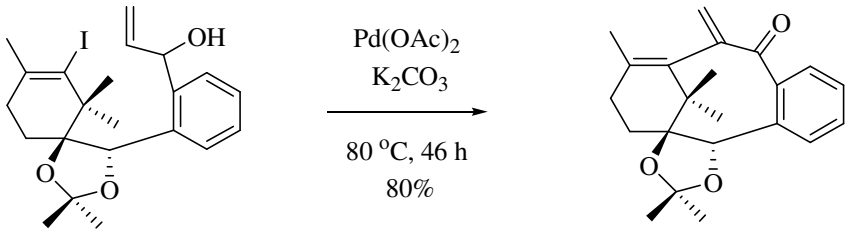


3 **4**

(±)-FR-900482 **5**

Scheme 3

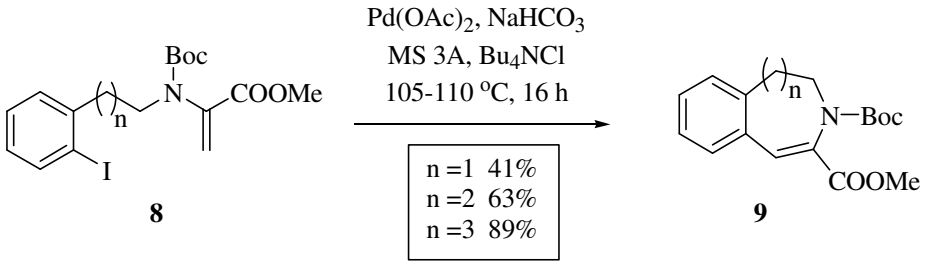
In the third example of an intramolecular Heck reaction, Masters and Danishefsky synthesized a highly functionalized C-aryl taxol analog as depicted in Scheme 4.[6]



6 **7**

Scheme 4

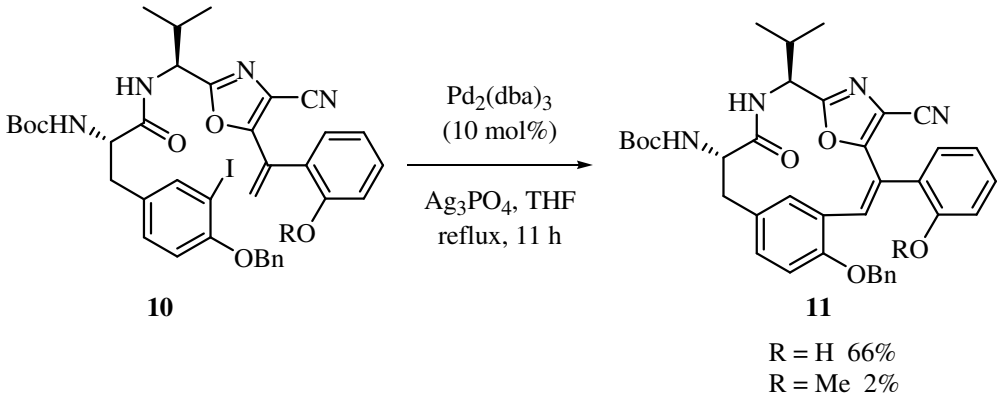
The Heck reaction has also been used in synthesizing useful synthetic molecules. Tozer *et al.* reported that, where the *endo* mode is favored for electronic reasons the reaction can lead to the formation of larger macrocycles. The reaction eases as the size of the newly forming macrocycle increases, generally a behavior not common in the cyclization chemistry (Scheme 5).[7]



8 **9**

Scheme 5

Peptidic and peptidomimetic chemistry have also benefited greatly from this efficient Pd-catalyzed C-C bond forming reaction. The Heck reaction played a vital role in the synthesis of macrocycle **11** from acyclic precursor **10** (Scheme 6).[8]

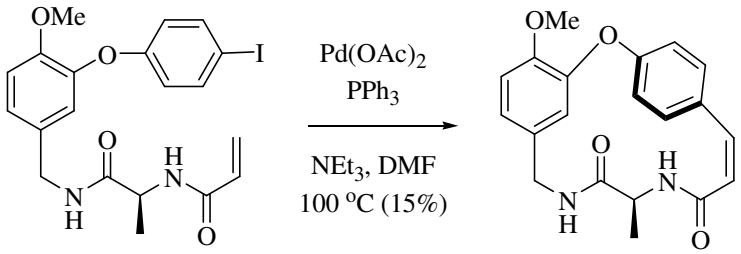


10 **11**

R = H 66%
R = Me 2%

Scheme 6

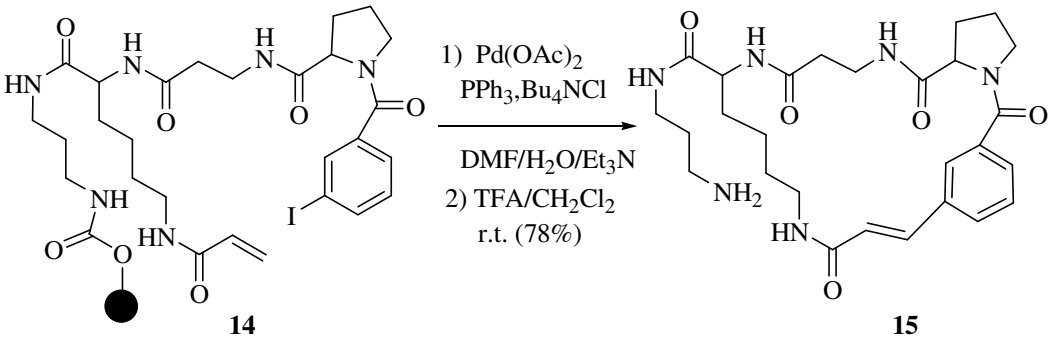
Nicolaou and co-workers have synthesized vancomycin-type bisaryl ether macrocycle **13** using ring closure method involving the Heck reaction, albeit in low yield (Scheme 7).[9]



12 **13**

Scheme 7

Solid Phase Organic Synthesis has also not been deprived of this wonderful reaction. Hauske and co-workers have reported, first time, a novel synthetic protocol for the rapid and efficient generation of macrocyclic peptide on solid support using the Heck reaction conditions (Scheme 8).[10] The reaction was optimized in a more liophilic medium.



14 **15**

Scheme 8

Rational drug design based on protein targeting requires the understanding of the bound conformation of bioactive peptides.[11] Generally, acyclic peptides are difficult to develop as drugs and this limitation has necessitated the use of small cyclic peptides as potent therapeutic agents in recent years. In addition to circumventing the problems of poor bioavailabity and proteolytic degradation, cyclic peptides do not suffer from significant entropic disadvantages and if suitably designed can mimic the 'bioactive conformation' which enhances the affinity of such structures to the target. Small cyclic peptides[12] based on protein turn motifs[13] are attractive mimics of the 'bioactive conformations' because numerous peptides elicit biological responses via such a conformation. The β-turn peptidomimetics have potential applications in medicinal

chemistry.[13] In an ongoing program in our group on the mimicry of helix-turn-helix motifs,[14] we required the synthesis of small cyclic peptides I, particularly 14-membered rings[15] (Figure 2), having an aromatic ring linker,[16] for conformational and binding studies. This chapter describes our studies which demonstrate that intramolecular Heck reactions can be used in the cyclization step leading to an efficient synthesis of cyclic peptides. These cyclisations are accompanied by a concomitant formation of cinnamoyl groups having amino methyl functionality at the 3-position of the aromatic ring.

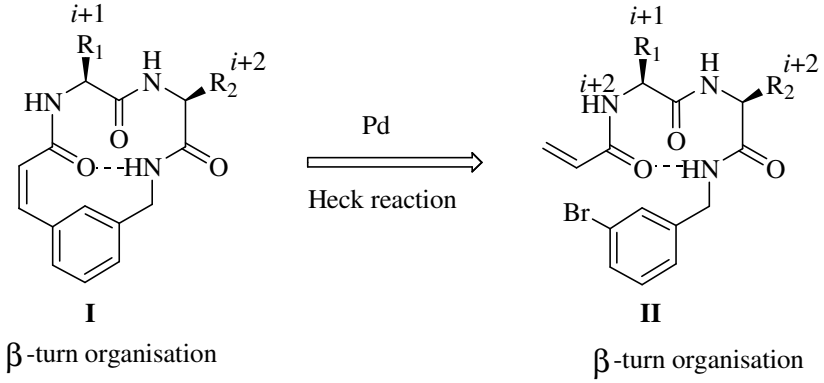
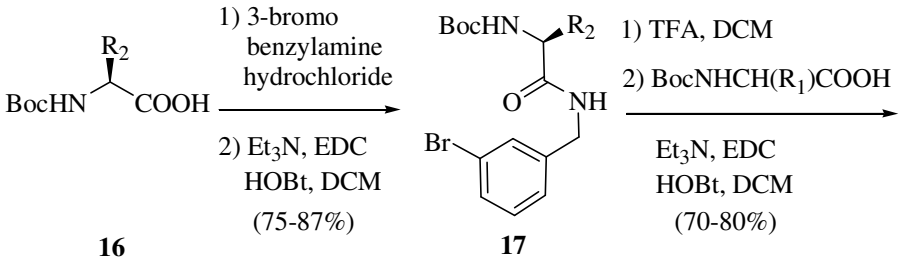


Figure 2: The Heck reaction

2.2 Results and Discussion

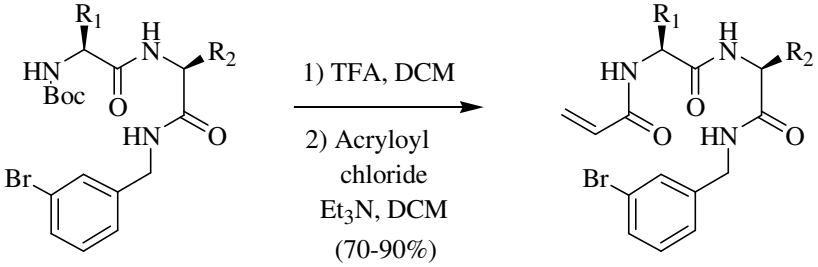
2.2.1 Synthesis of 14-membered cyclic peptides constrained with *cis*-3-[3-aminophenyl] prop-2-enoic acid linker using the Heck reaction

We have designed the acyclic precursors **19** for the intramolecular Heck reaction. Scheme 9 represents the preparation of the starting materials **19**. Thus, *N*-Boc-Ala-OH **16a** was coupled with 3-bromobenzylamine following a standard solution chemistry[17]



16 **17**

17a $R_2 = CH_3$
17b $R_2 = CH_2Ph$
17c $R_2 = CH_2CH(CH_3)_2$
17d $R_2 = (CH_3)_2$



18 **19**

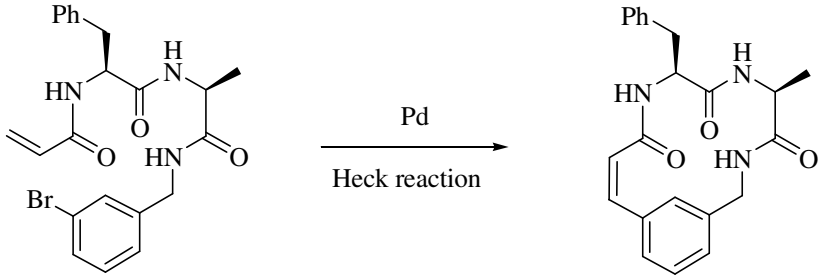
18a $R_1 = CH_2Ph$, $R_2 = CH_3$
18b $R_1 = CH_3$, $R_2 = CH_2Ph$
18c $R_1 = CH_2Ph$, $R_2 = CH_2CH(CH_3)_2$
18d $R_1 = CH_2CH(CH_3)_2$, $R_2 = CH_3$
18e $R_1 = CH_2Ph(D)$, $R_2 = CH_3$
18f $R_1 = CH_2Ph$, $R_2 = (CH_3)_2$

19a $R_1 = CH_2Ph$, $R_2 = CH_3$
19b $R_1 = CH_3$, $R_2 = CH_2Ph$
19c $R_1 = CH_2Ph$, $R_2 = CH_2CH(CH_3)_2$
19d $R_1 = CH_2CH(CH_3)_2$, $R_2 = CH_3$
19e $R_1 = CH_2Ph(D)$, $R_2 = CH_3$
19f $R_1 = CH_2Ph$, $R_2 = (CH_3)_2$

Scheme 9

using HOBt and EDC as coupling reagents and triethyl amine as base, in dichloro-methane to synthesize compound **17a** in excellent yield. Reaction was started at 0 ^{o}C and allowed to run at room temperature for 15 h. Deprotection of **17a**, followed by coupling with N-Boc-Phe-OH, using standard solution-phase technique gave peptide **18a** in very good yield. Compound **18a** on deprotection followed by an acylation with acryloyl chloride gave the desired precursor **19a** in an overall satisfactory yield.

The preliminary experiments were carried out to optimize the most efficient protocol for the intramolecular cyclization of **19a** to form cyclic peptide **20a** using the Heck reaction (Scheme 10).



19a **20a**

Scheme 10

Optimization results are summarized in Table 1. Initially, the Heck reactions (entries 1,2) were carried out in acetonitrile using different palladium catalysts at 80 ^{o}C. However, these conditions did not work well. The Heck macrocyclization of **19a** to form cyclic compound **20a** did not proceed in polar solvents (entries 3-7). When the Heck reaction of **19a** was carried out in acetonitrile with 20 mol % $Pd(OAc)_2$/40 mol % (*o*-tolyl)$_3$P as the catalytic system in the presence of N-ethyldiisopropyl amine as a base at 100 ^{o}C, product **20a** was obtained, albeit in low yield (12%) (entry 8). The structure of

the newly formed compound **20a** was determined by ^{1}HNMR and Mass spectral data. The hydrogens at double bond resonate as a doublet at δ 6.00 with J = 12.6 Hz and δ 6.60 with J = 12.3 Hz. The coupling constants of J = 12.6 and 12.3 Hz confirm that double bond has (*Z*)-configuration.

Table 1

Entry	Solvent	Base	Catalyst/Ligand/Condition	Yield of **20a**	Ref. No.
1.	CH_3CN	Et_3N	$(Ph_3P)_4Pd(0)$/80 ^oC	--	5
2.	CH_3CN	K_2CO_3	$Pd(OAc)_2/PPh_3$/80 ^oC	--	18
3.	DMF	K_2CO_3	$Pd(Oac)_2$/*n*-Bu_4NCl/60 ^oC	--	4
4.	DMF	K_2CO_3	$PdCl_2(PPh_3)_2$/ *n*-Bu_4NCl /120 ^oC	--	19
5.	DMF	NaOAc	$Pd(OAc)_2$/P(o-tolyl)$_3$/ 130^oC	--	20
6.	DMF H_2O	Et_3N	$Pd(OAc)_2/PPh_3$/ *n*-Bu_4NCl /60 ^oC	--	10
7.	DMF H_2O	EtN(i-Pr)$_2$	$Pd(OAc)_2$/P(o-tolyl)$_3$/ 105^oC	--	21
8.	CH_3CN	EtN(i-Pr)$_2$	$Pd(OAc)_2$/P(o-tolyl)$_3$/ 100^oC	12%	22

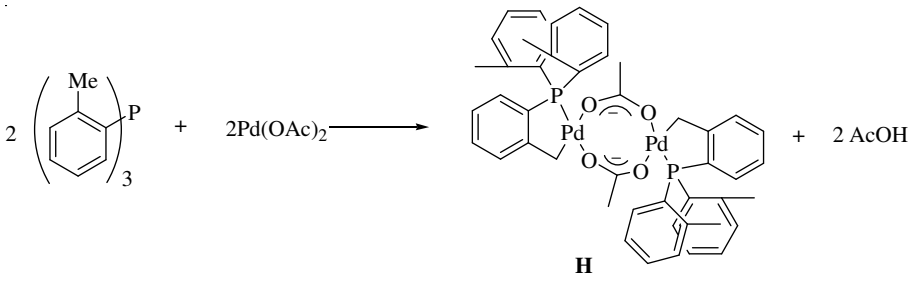
We then, focused on optimizing the reaction conditions to improve overall reaction yield. We varied the reaction mixture concentration, reaction temperature, mol % of catalyst and reaction time. Among all these four variants, reaction concentration, in

other words, reaction dilution played a significant role. The results of the experiments with different dilutions are summarized in Table 2. The effect of temperature amount of catalyst and reaction time turned out to be insignificant.

Table 2

Entry	Solution concentration	Yield of **20a**	Reaction Time
1.	1 x 10^{-1}M	12%	6 h
2.	1 x 10^{-2}M	29%	10 h
3.	1 x 10^{-3}M	45%	15 h
4.	1 x 10^{-4}M	45%	18 h

Compound **19a** has poor solubility in acetonitrile[23] at lower temperatures (<60 ^{o}C). The solubility was increased, when the reaction mixture heated above 80 ^{o}C. Use of bulky amine, Hunig's base, turned out to be more efficient in scavenging PdH, which formed during β-hydride elimination. Key to the Heck reaction success with $Pd(OAc)_2$ (30 mol%) and (*o*-tolyl)$_3$P (60 mol%) at above 100 ^{o}C, can be explained on the basis of the Pd-complex formed in the reaction mixture. Hermann explained that the metal

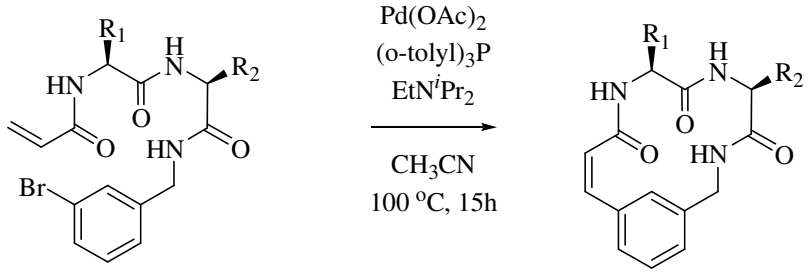


H

Figure 3: Hermann complex formed from $Pd(OAc)_2$/(*o*-tolyl)$_3$P

complex formed by the combination of $Pd(OAc)_2$ and $(o\text{-tolyl})_3P$ is not only active but also its catalytic life is longer. This is explained by formation of the palladacycle **H**, called the Hermann complex, which is stable to air and moisture and commercially available (Figure 3).[24] This catalyst is not active at low temperature, and active above 100 ^oC.

Under these conditions **20a-f** were obtained in 40-75% yields. However, formation of byproducts could not be prevented, as was apparent from most of the reactions. Acyclic peptides **19a-d** having different amino acids at i+1 and i+2 positions,



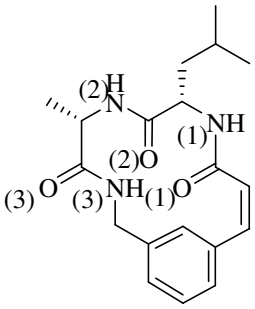
19 **20**

19a	$R_1 = CH_2Ph$	$R_2 = CH_3$	**20a** (45%)
19b	$R_1 = CH_3$	$R_2 = CH_2Ph$	**20b** (43%)
19c	$R_1 = CH_2Ph$	$R_2 = CH_2CH(CH_3)_2$	**20c** (50%)
19d	$R_1 = CH_2CH(CH_3)_2$	$R_2 = CH_3$	**20d** (40%)
19e	$R_1 = CH_2Ph$ (D-Phe)	$R_2 = CH_3$	**20e** (75%)
19f	$R_1 = CH_2Ph$	$R_2 = (CH_3)_2$	**20f** (63%)

Scheme 11

were subjected to intramolecular Heck reaction following the procedure described in entry 8 in Table 1, to prepare 14-membered cyclic peptide **20a-d** in 40-50 % yields. The scope of the reaction was also studied by using unnatural amino acids. Cyclic peptide **20e** was synthesized using D-Phenylalanine at i+1 position in 75% yield and cyclic peptide **20f** was prepared using aminoisobutyric acid at i+2 position in 63% yield (scheme 11).

Single crystals of compound **20d** (Figure 4) were obtained by dissolving the compound in toluene, methanol and DMF solvent mixture at room temperature. The compound **20d** crystallizes in Orthorhombic crystal system (space group $P2_12_12_1$) with unit cell parameters a = 8.781(5) Å, b = 9.191(5) Å, c = 22.373(13) Å, V = 1805.6(17) $Å^3$ and Z = 4. The intensity data was collected on a Rigaku Mercury CCD detector with graphite monochromated Mo-Kα radiation. The crystal structure was solved by direct methods (SIR 92) and refined by full-matrix least squares to a final R-value of 0.072 with 2365 unique reflections. In the crystal structure of the compound **20d** the N1 is showing hydrogen bonding with O1 of the adjacent molecule which is at –X+2, 1/2+Y, 1/2-Z and N2 and N3 are showing a bidentate hydrogen bonding with O3 of the adjacent molecule which is at –X+1, 1/2+Y, 1/2+Z. This cyclic peptide is also stabilized by three weak intramolecular hydrogen bonds. The molecule is arranged in a zig-zag chain along the direction of an axis. The ORTEP and Packing of compound **20d** are shown in Figure 5 and Figure 6, respectively.



20d

Figure 4: Cyclic compound **20d**

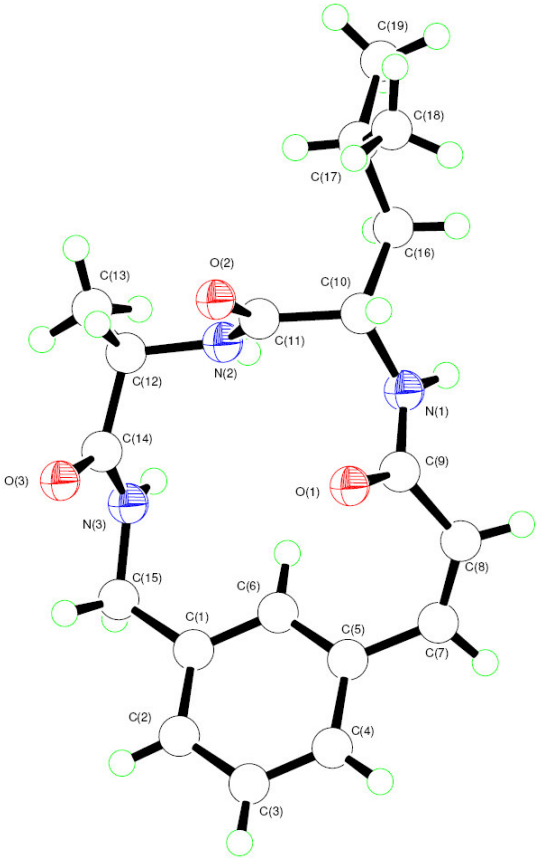


Figure 5: ORTEP diagram of the cyclic compound **20d**

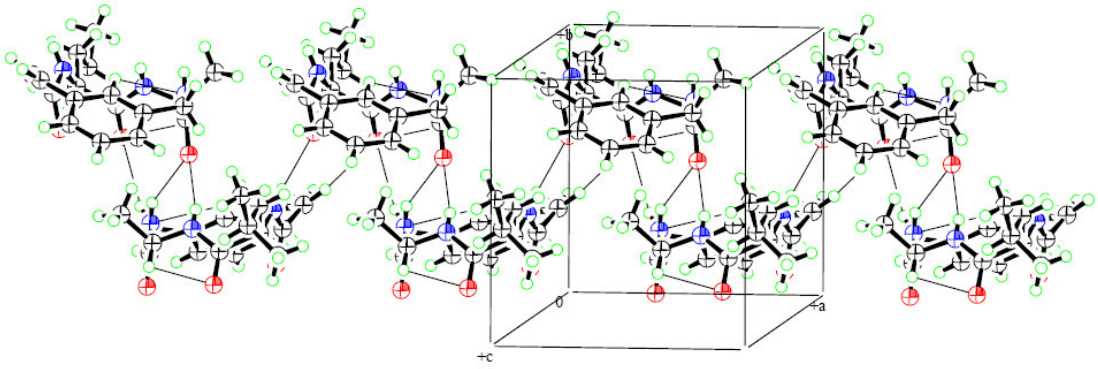
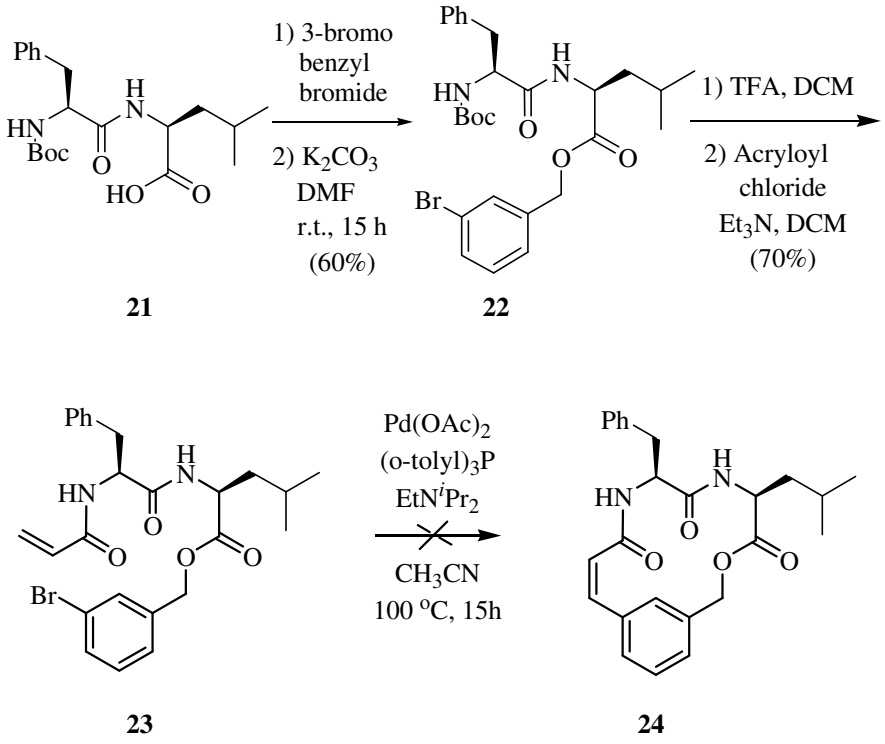


Figure 6: Crystal packing of the cyclic compound **20d**

Table 3: X-ray data and structure refinement for cyclic compound 20d

Empirical formula	$C_{19}H_{25}N_3O_3$
Formula weight	343.42
Temperature	293(2) K
Wavelength	0.71070 Å
Crystal system	Orthorhombic
Space group	$P2_12_12_1$ (#19)
Unit cell dimensions	a = 8.781(5) Å
	b = 9.191(5) Å
	c = 22.373(13) Å
Volume	1805.6(17) $Å^3$
Z	4
Calculated density	1.263 g/cm^3
Absorption coefficient	0.86 cm^{-1}
F(000)	736.00
Crystal size	0.50 X 0.20 X 0.20 mm
θ Range for data collection	1.51 to 27.00°
Reflections collected/unique	21151 / 2365 [R(int) = 0.051]
Completeness to θ = 27.47	99 %
Refinement method	full-matrix least-square on F
Data / parameters	1152 / 261
Goodness-of-fit on F	1.117
Final *R* indices [I> 2σ (I)]	R_1 =0.072, wR_2 = 0.120
R indices (all data)	R_1 = 0.108, wR_2 = 0.120
Largest diff. Peak and hole	0.33 $eÅ^{-3}$ and -0.32 $eÅ^{-3}$

We also studied the scope of the intramolecular Heck reaction on compound **23** (Scheme 12). The N-Boc-dipeptide **21** esterified with 3-bromobenzyl bromide using fused potassium carbonate in dimethyl formamide to afford peptide **22** in 60% yield. Boc deprotection of **22** followed by acylation with acryloyl chloride gave the desired precursor compound **23** in 70% yield. We observed that the Heck macrocyclization of **23** to form 14-membered depsipeptide **24** did not occur under similar Heck reaction conditions.



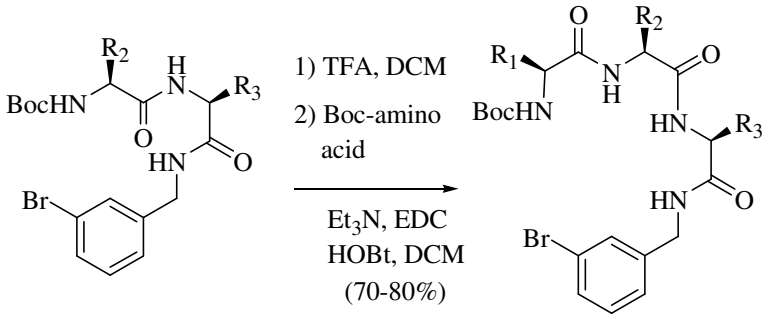
Scheme 12

Based on these experimental results, we proposed that compounds **19a-f** are pre-organized structures through intramolecular H-bonding (γ/β-turn) of the benzylic NH with *i* amino acid carbonyl or acryloyl carbonyl oxygen, that is not possible in the case

of the corresponding oxygen analogue **23**. Therefore, compound **23** did not cyclize to the corresponding compound **24**.

2.2.2 Synthesis of 17-membered cyclic peptides constrained with *cis*-3-[3-aminophenyl] prop-2-enoic acid linker using the Heck reaction

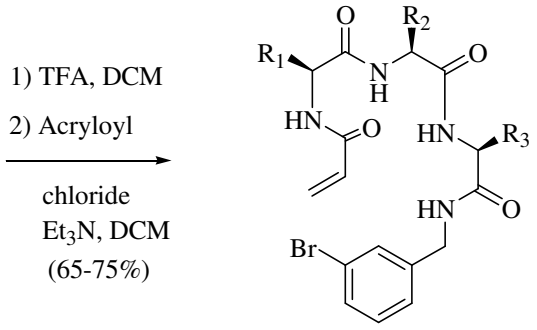
Further, we wanted to expand the scope of the methodology, developed for synthesizing 14-membered macrocyclic peptidomimetics. As a logical step forward, we



18 **25**

18g R_2= CH_3
R_3 = $CH_2CH(CH_3)_2$
18h R_2= $CH(CH_3)CH_2CH_3$
R_3 = CH_3

25a R_1 = $CH(CH_3)_2$, R_2 = $CH_2CH(CH_3)_2$, R_3 = CH_3
25b R_1 = CH_2Ph, R_2 = $CH_2CH(CH_3)_2$, R_3 = CH_3
25c R_1 = $CH(CH_3)_2$, R_2 = $CH_2CH(CH_3)_2$, R_3 = CH_3
25d R_1 = CH_2Ph, R_2 = $CH(CH_3)CH_2CH_3$, R_3 = CH_3

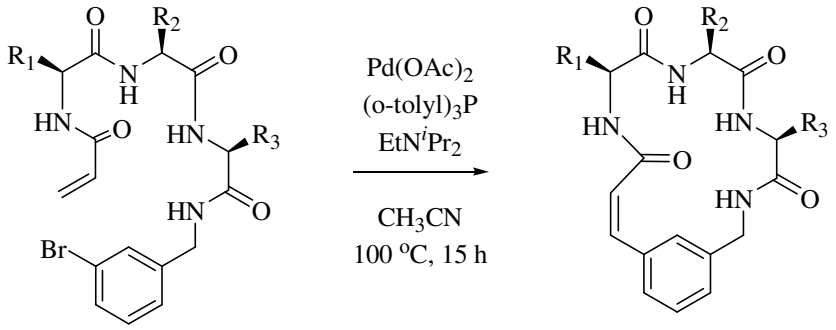


26

Scheme 13

decided to synthesize 17-membered cyclic peptidomimetics containing a tripeptide unit. All the acyclic peptide derivatives **26** were synthesized by following standard solution-phase peptide coupling and procedures summarized in Scheme 13. The Boc deprotection of **18**, followed by coupling with respective Boc-amino acid yielded compounds **25** in good yields (70-80%). Upon subsequent deprotection and treatment with acryloyl chloride using triethylamine as a base in dichloromethane, **25** gave precursors **26** for the Heck macrocyclization.

All acyclic compounds **26a-d** cyclized on intramolecular Heck reaction to desired 17-membered cyclic peptidomimetics in moderate yields (Scheme 14). The cyclic peptidomimetic compounds **26a-d** were well characterized by analytical data. It is also important to note that the geometry of the newly formed double bond in these cyclic compounds was assigned as *Z* based on the coupling constants of the hydrogens at double bond, those resonate as a doublet at δ 6.21 with J = 12.6 Hz and δ 6.80 with J = 12.3 Hz.



26 **27**

26a R_1 = -$CH(CH_3)_2$ R_2 = -$CH_2CH(CH_3)_2$ R_3 = -CH_3 **27a** (43%)

26b R_1 = -CH_2Ph R_2 = -$CH_2CH(CH_3)_2$ R_3 = -CH_3 **27b** (33%)

26c R_1 = -CH_2Ph R_2 = -CH_3 R_3 = -$CH_2CH(CH_3)_2$ **27c** (36%)

26d R_1 = -CH_2Ph R_2 = -$CH(CH_3)CH_2CH_3$ R_3 = -CH_3 **27d** (30%)

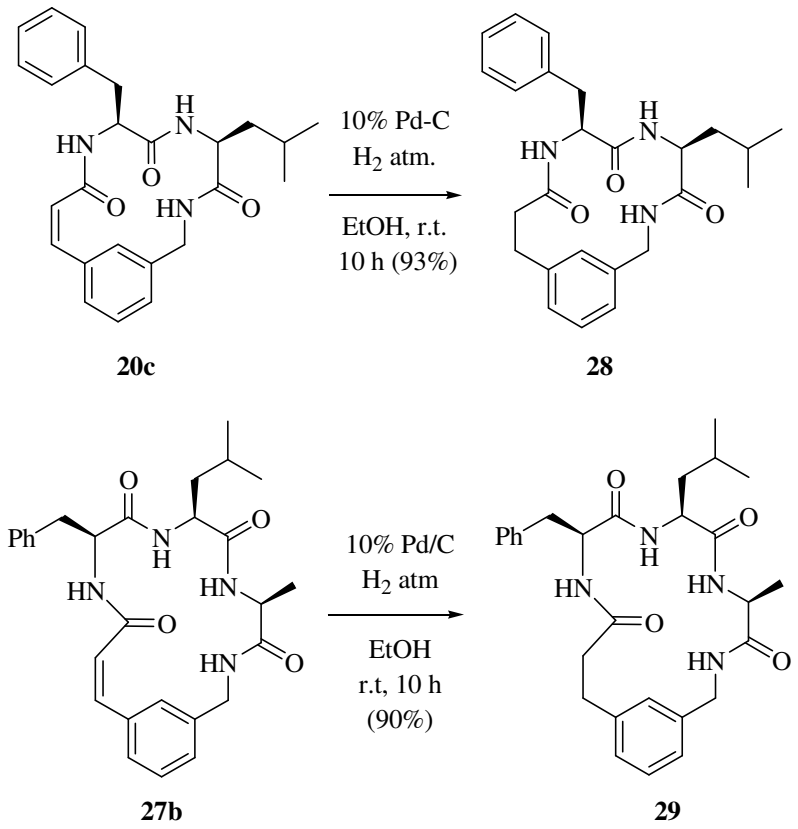
Scheme 14

2.2.3 Synthesis of 14- & 17-membered cyclic peptides constrained with 3-[3-aminophenyl]propanoic acid linker

We reasoned that saturation of the Z-double bond in our cyclic molecules would bring in more flexibility. This reduction of ring strain in the molecule may have some role in bioactivity studies in the future. Therefore, we attempted a few reactions to saturate the double bond.

(i) Pd/C mediated reaction under H_2 atmosphere

The hydrogenation of the *Z*-double bond in cyclic peptidomimetics **20c** and **27b** with 10% Pd-C in ethanol under hydrogen gas pressure (20psi) provided cyclic compounds **28** and **29**, respectively (Scheme 15).



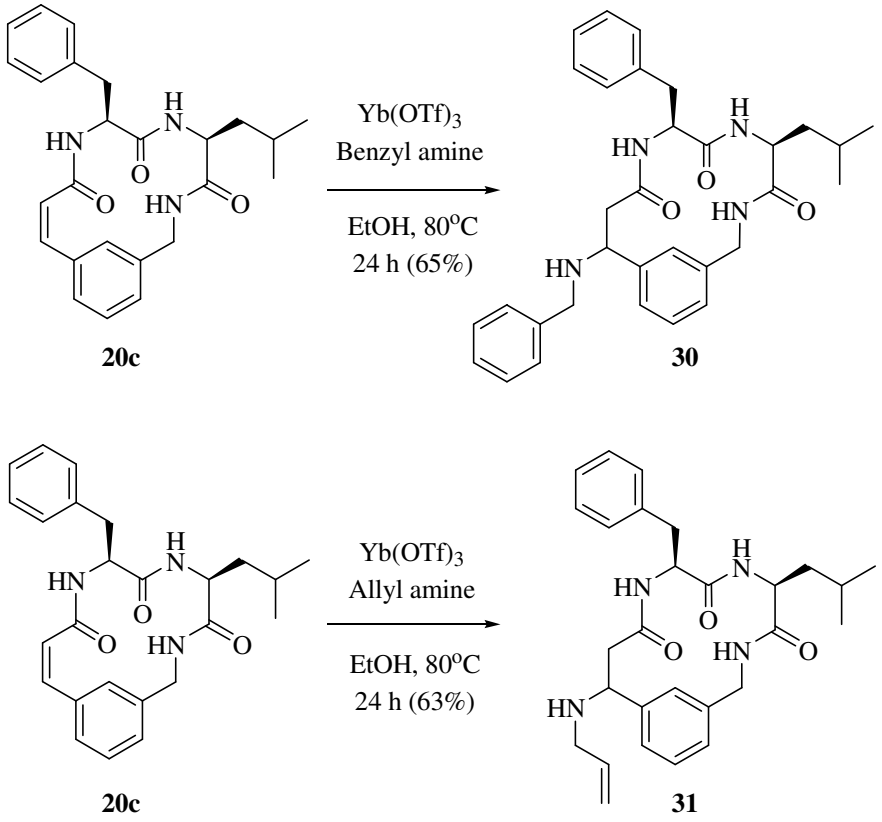
20c **28**

27b **29**

Scheme 15

(ii) The Michael additions on cyclic peptidomimetics

The $Yb(OTf)_3$ mediated Michael addition reaction in ethanol with benzylamine and allylamine on cyclic peptide **20c**, furnished the cyclic peptidomimetics **30** and **31** respectively in good yields (Scheme 16). We also observed that only one diastereoisomer is formed in these reactions.

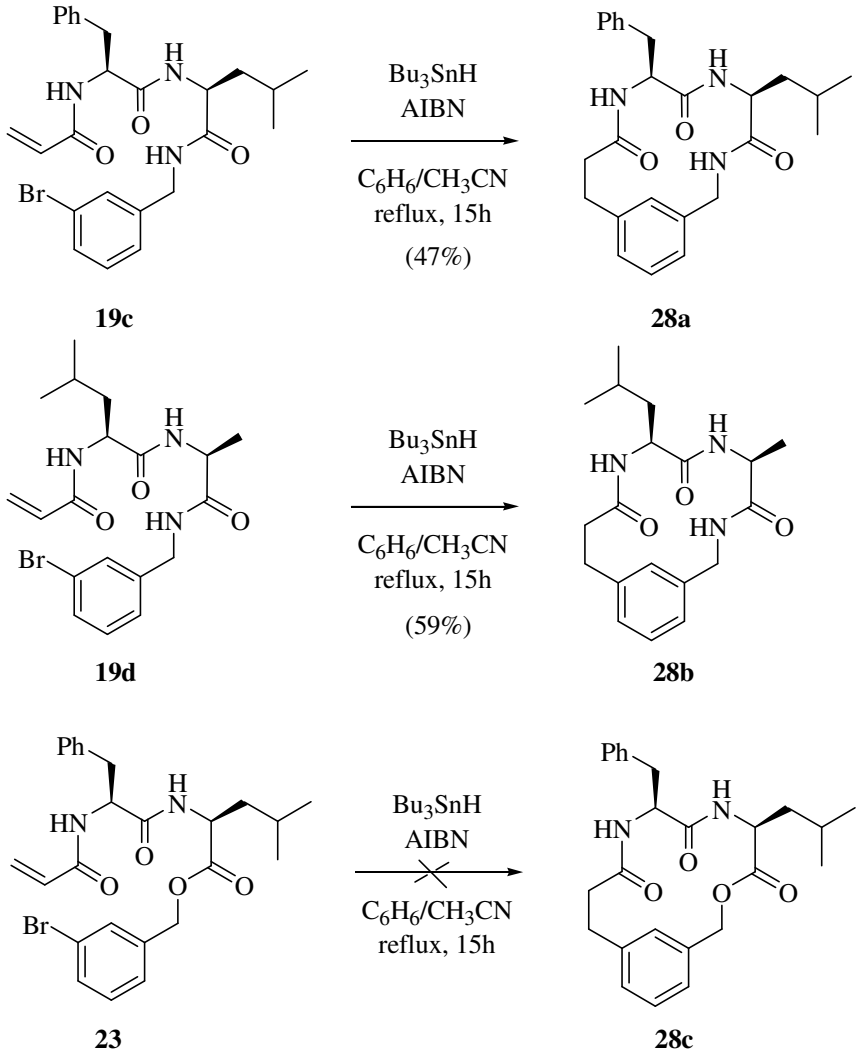


Scheme 16

(iii) Bu_3SnH/AIBN mediated free-radical Michael additions for single-step synthesis of saturated 14 and 17-membered cyclic peptidomimetics

The radical carbon-carbon bond forming reactions have gained much importance in organic synthesis. We were interested in the synthesis of cyclic peptide **28** directly

from acyclic peptides **19c** in a single-step. We applied an intramolecular Bu_3SnH/AIBN mediated free radical reaction for the macrocyclization of **19c.** To our delight, compound **19c** underwent smooth cyclization to furnish the cyclic peptide **28a** in 47% yield. The spectral data of **31a** is matched with the compound **28** which was obtained by reduction



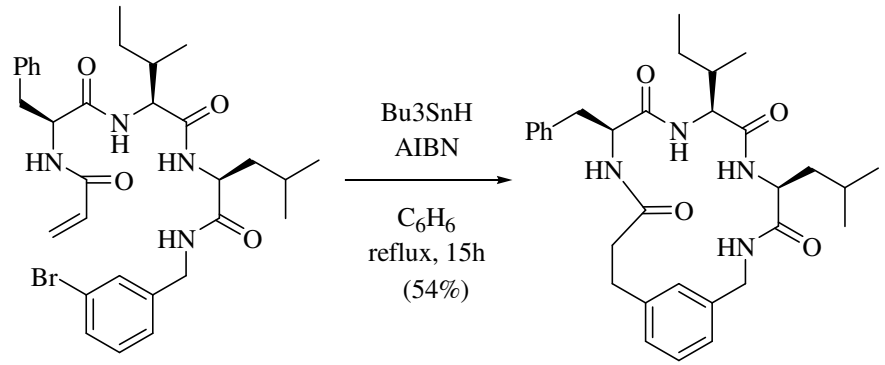
Scheme 17

of **20c**. Subsequently, we subjected compounds **19d** and **23** to an intramolecular free radical macrocyclization. Compound **19d** underwent cyclization to afford cyclic peptido-

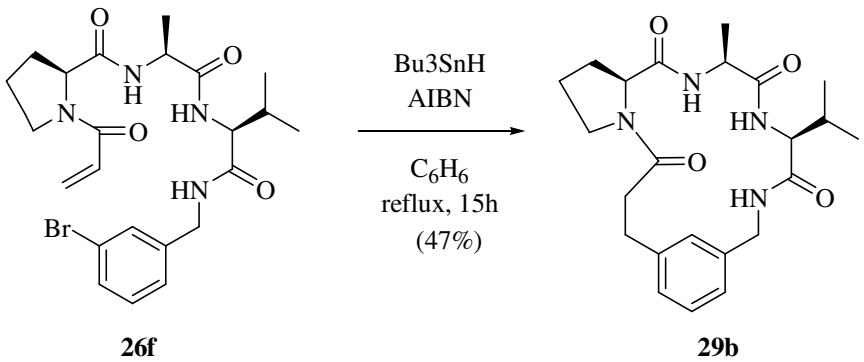
mimetic **28b**. However, in the case of acyclic peptide **23**, the Bu_3SnH-AIBN mediated free radical cycliczation failed to give the corresponding cyclic peptide **28c** despite many attempts (Scheme 17).

These experimental results, further supporting our proposal that compounds **19c** and **19d** are pre-organized structures through intramolecular H-bonding (γ/β-turn) of the benzylic NH with *i* amino acid or acryloyl carbonyl oxygen, which is not possible in the case of the corresponding oxygen analogue **23**.

Encouraged by the success with the dipeptide-cyclization, we explored the versatility of this intramolecular free radical Michael addition reaction in tripeptide-cyclization i.e. in the synthesis of 17-membered cyclic peptides. For the preparation of



26e **29a**



26f **29b**

Scheme 18

macrocycles **29a** and **29b**, the corresponding acyclic compounds **26e** and **26f** were prepared using standard peptide protocol, starting from the respective Boc protected amino acid and detailed procedures are described in the experimental section. The acyclic compounds **26e** and **26f** were subjected to the Bu_3SnH-AIBN mediated intramolecular free radical reaction in dry benzene resulting in smooth cyclization to furnish the corresponding cyclic peptides **29a** and **29b**, respectively (Scheme 18).

2.3 Conclusions

We have developed an efficient protocol for the synthesis of cyclic peptides constrained with the 3-(3-aminomethylphenyl)prop-2-enoic acid linker using the intramolecular Heck reaction. The double bond in the above linker was functionlized using $Yb(OTf)_3$ mediated Michael addition reactions with various nucleophilic amines. The saturation of double bond was carried out using 10% Pd-C under H_2 atmosphere. We have also developed a protocol for the synthesis of cyclic peptides constrained with the 3-(3-aminomethylphenyl)propionic acid linker using a Bu_3SnH-AIBN mediated intramolecular free radical Michael addition reaction in one step from the acyclic precursor. We also proposed that these macrocyclizations are controlled by the presence of an intramolecular H-bond (γ/β-turn) in the acyclic precursors as well as in cyclic peptides. These cyclic peptides may be useful probes in understanding the role of constrained structures in the search for bioactive conformations in larger proteins.

2.4 Experimental Section

2.4.0 Materials and Methods

Acetonitrile, dichloromethane and all other solvents were purified by standard procedures. All the amino acids were purchased from Loba Chemie, India limited and used as such. Column chromatography was performed on 100-200 mesh Laboratory Reagent silica gel. TLC was performed on 25 TLC aluminium sheets, 20x20 cm silica gel 60_{254}, were irradiated with a UV lamp or polymolybdic acid solution. Melting points were determined on Buchi melting point B-540 apparatus. Infra-red spectra were recorded on Perkin-Elmer FT-IR 1600 spectrophotometer using either a neat sample or a solution in $CHCl_3/CH_2Cl_2$ and solids were examined as KBr pellets and the values are reported in ν_{max} (cm^{-1}). Proton nuclear magnetic resonance (^{1}HNMR) spectra were recorded on a varian Gemini 400MHz and 200MHz spectrophotometers in $CDCl_3$ and DMSO-d_6 . Chemical shifts are given relative to TMS in ppm (δ). Multiplicity is indicated by following abbreviations: singlet (s); broad singlet (bs); doublet (d); triplet (t); quarted (q); doublet of doublet (dd); doublet of triplet (dt). Mass spectra were recorded on HP-5989A mass spectrometer. Palladium acetate, tri-o-tolyl phoshine and Hunig's base were purchased from Lancaster and were used as such.

2.4.1 General procedure for peptide coupling:

(a) A stirred solution of the TFA salt of C-protected peptide in CH_2Cl_2 (5 mL/mmol) at 0 ^oC (ice-bath) under N_2 was treated successively with Et_3N (5 equiv.), HOBt (1.2 equiv.), a solution of the Boc-protected amino acid (1 equiv.) in CH_2Cl_2 (2.5

mL/mmol), and EDC (1.2 equiv.). The mixture was allowed to warm to r.t., and stirring was continued for 15 h. The mixture was diluted with CH_2Cl_2 and washed with 10% aq. citric acid, aq. saturated $NaHCO_3$, H_2O and NaCl solution. The organic phase was dried (Na_2SO_4), evaporated, and the residue was purified using flash column chromatography to get the pure material.

(b) To a stirred solution of TFA salt of C-protected peptide in CH_2Cl_2 (3 mL/mmol) and DMF (2 mL/mmol) at 0 ^oC (ice-bath) under N_2 was added successively Et_3N (5 equiv.), HOBt (1.2 equiv.), a solution of the Boc-protected amino acid (1 equiv.) in CH_2Cl_2 (2.5 mL/mmol), and EDC (1.2 equiv.). The mixture was allowed to warm to r.t., and stirring was continued for 15 h. The residue obtained after the removal of all volatiles was dried under vacuum for 1 h and then stirred in MeOH for 20 min. The white precipitate was collected by filtration and thoroughly washed successively with MeOH/H_2O 1:1 mixture and MeOH. The solid product was dried under high vacuum for several hours.

(c) Under anhydrous conditions, isobutychloroformate (1.1 equiv.) was added to a solution of N-protected amino acid (1 equiv) and Et_3N (1.1 equiv.) in CH_2Cl_2 (5 mL/mmol) at 0 ^oC and the mixture was stirred at this temperature for 10 min. A pre-cooled solution of the methyl ester amino acid hydrochloride (1.1 equiv.) and Et_3N (1.1 equiv) in CH_2Cl_2 (5 mL/mmol) was then added and the reaction mixture was allowed to warm to rt and stirred overnight. The reaction mixture was then poured into CH_2Cl_2 (100 ml/1 g substrate). The organic solution was washed with NH_4Cl (aq), $NaHCO_3$ (aq), water, and then brine, dried over Na_2SO_4. The crude compound obtained after the

removal of solvent was purified by column chromatography to give the desired coupled peptide.

2.4.2 General procedure for ester hydrolysis

A solution of LiOH (1.5 equiv.) in water (1.5M solution) was added dropwise to a solution of methyl ester protected peptide (1 equiv) in MeOH (3 mL/mmol) and the reaction mixture stirred at rt until the reaction was complete as judged by TLC (typically 2 h). Reaction mixture was concentrated under reduced pressure to half of its volume and diluted with water (50 mL/1 g substance). The aqueous layer was washed with CH_2Cl_2 (50 mL/1 g substance) and acidified with 1N HCl at 0-5 °C to pH~2, then extracted with CH_2Cl_2. The combined extract was washed with brine, dried over Na_2SO_4, and the solvent was evaporated to give the desired free carboxylic acid.

2.4.3 General procedure for Boc deprotection

CF_3COOH (1.5 mL/mmol) was added to an ice-cold solution of the Boc-protected peptide in CH_2Cl_2 (5 mL/mmol). The reaction mixture was allowed to warm to r.t. and stirring was continued for 2 h. The mixture was evaporated and the residue dried under high vaccum. The salts with CF_3COOH were used without further purification and characterization.

2.4.4 General procedure for N-acryloylation

Under ice cooling acryloyl chloride (1.1 equiv.) was added to a solution of N-deprotected peptide (1 equiv) and Et_3N (2 equiv.) in CH_2Cl_2 (5 ml/mmol). The reaction

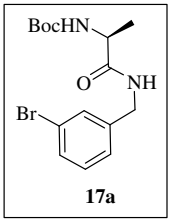
mixture allowed to warm to r.t. and stirred for 2 h. The reaction mixture poured into CH_2Cl_2 (100 mL/1 g substance) and organic solution washed with $NaHCO_3$(aq), water, and then brine, dried over Na_2SO_4, filtered, and the solvent was evaporated, and the crude compound was purified by column chromatography to give the desired acryolyl peptide.

2.4.5 General Procedure for macrocyclization using the Heck reaction

30 mol% $Pd(OAc)_2$, 60 mol% $(o\text{-tolyl})_3P$ were added to warm HPLC grade acetonitrile (1.5×10^{-3}M) and solution refluxed at 100 ^oC (oil bath temp.) for 30 min. Then acylic peptide was added in single portion and the reaction continued for 15 min at the same temperature. Finally N-ethyldiisopropylamine (5 equiv.) was added. After15 h., the reaction mixture was filtered through a pad of Celite and washed with hot acetonitrile (100 ml). The filtrate was concentrated and the product was isolated by flash column chromatography on (230-400) silica gel using CH_2Cl_2/MeOH as eluent.

2.4.6 General Procedure for free radical-mediated cyclization

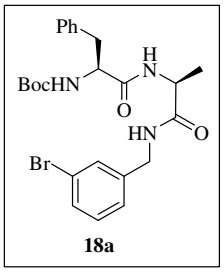
To a refluxing solution of acyclic peptide (1 equiv.) and 2,2'-azobis isobutyronitrile (cat.) in dry benzene (100 mL/0.1mmol) and was added Bu_3SnH (1.2 equiv.) very slowly in such a rate that 0.5 mL/h. The reaction mixture refluxed for 15 h. The solvent was evaporated, and the crude compound was purified by column chromatography to give the desired cyclic peptide.



17a

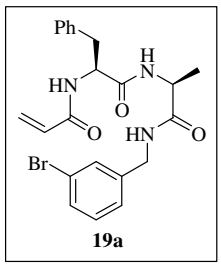
Compound 17a: Compound was prepared by following general procedure **2.4.1a** (yield 87%), mp 86-88 °C; $[\alpha]_D^{25}$ = -21.80 (*c* 1, $CHCl_3$); IR (KBr) 3309, 2978, 2931, 1658, 1525, 1367 cm^{-1}; ^1H NMR (400 MHz,

DMSO-*d6*): δ 7.42-7.36 (m, 2H), 7.20-7.15 (m, 2H), 6.68 (bs, 1H), 4.97 (bs, 1H), 4.40-4.36 (m, 2H), 4.18 (t, *J* = 6.7 Hz, 1H), 1.42 (s, 9H), 1.38 (d, *J* = 4.0 Hz, 3H); ESMS *m/z* calcd for $C_{15}H_{21}BrN_2O_3$ 357, found 359 (M+2), 357 (M).



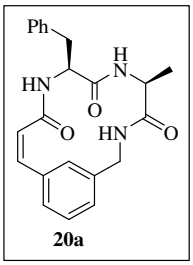
18a

Compound 18a: Compound was prepared by following general procedure **2.4.1a** as white solid (yield 75%), mp 104–105 °C; $[\alpha]_D^{25}$ = -6.2, (*c* 1, CH_3OH); IR (KBr) 3290, 1644, 1527 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.39-7.37 (m, 2H), 7.36-7.26 (m, 3H), 7.24-7.15 (m, 4H), 6.74 (brs, 1H), 6.31 (d, *J* = 7.5 Hz, 1H), 4.90 (brs, 1H), 4.50-4.27 (m, 4H), 3.09-2.99 (m, 2H), 1.35 (s, 9H), 1.34 (d, *J* = 7.2 Hz, 3H); ESMS *m/z* calcd for $C_{24}H_{30}BrN_3O_4$ 504, found 506 (M+2), 504 (M).



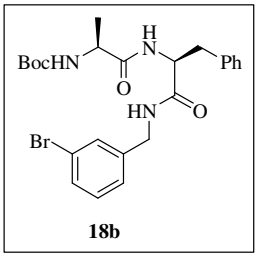
19a

Compound 19a: Compound was prepared by following general procedure **2.4.4** as a white solid (yield 85%), mp 300–302 °C, $[\alpha]_D^{25}$ = +12.1 (*c* 1, DMSO); IR (KBr) 3273, 1626, 1536 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.32-8.27 (m, 3H), 7.43-7.42 (m, 2H), 7.41-7.13 (m, 7H), 6.25 (dd, J_1 = 10.2 Hz, J_2 = 17.2 Hz, 1H), 5.99 (dd, J_1 = 2.1 Hz, J_2 = 17.2 Hz, 1H), 5.53 (dd, J_1 = 2.1 Hz, J_2 = 10.2 Hz, 1H), 4.67-4.61 (m, 1H), 4.33-4.24 (m, 3H), 3.06 (dd, J_1 = 4.3 Hz, J_2 = 14.0 Hz, 1H), 2.77 (dd, J_1 = 10.0 Hz, J_2 = 13.7 Hz, 1H), 1.26 (d, *J* = 7.0 Hz, 3H) **(Spectrum No. 1)**. ^{13}C NMR (50 MHz, DMSO-*d6*): δ 172.2, 171.0, 164.4, 142.2, 137.9, 131.4, 130.4, 129.7, 129.5, 129.1(2C), 127.9(2C), 126.2, 126.0, 125.5, 121.6, 53.8, 48.4, 41.4, 37.5, 18.1 **(Spectrum No. 2)**. ESMS *m/z* calcd for $C_{22}H_{24}BrN_3O_3$ 458, found 460 (M+2), 458 (M).



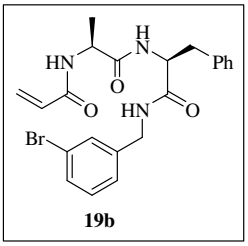
20a

Compound 20a: Compound was prepared using general procedure **2.4.5** as white solid (yield 45%), mp 300–302 °C; $[\alpha]_D^{25}$ = -183.2, (*c* 0.5, DMSO); IR (KBr) 3290, 2925, 1650, 1544 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.27 (d, *J* = 7.5 Hz, 1H), 8.20 (d, *J* = 8.3 Hz, 1H), 7.94 (dd, J_1 = 4.8 Hz, J_2 = 6.7 Hz, 1H), 7.31-7.20 (m, 7H), 7.11 (t, *J* = 9.0 Hz, 2H), 6.60 (d, *J* = 12.6 Hz, 1H), 6.00 (d, *J* = 12.4 Hz, 1H), 4.59 (dd, J_1 = 7.2 Hz, J_2 = 16.1 Hz, 1H), 4.33-4.22 (m, 2H), 3.93 (dd, J_1 = 4.3 Hz, J_2 = 16.1 Hz, 1H), 3.02-2.91 (m, 2H), 1.18 (d, *J* = 7.0 Hz, 3H) **(Spectrum No. 3)**. ^{13}C NMR (50 MHz, DMSO-*d6*): δ 171.3, 170.9, 167.1, 138.7, 137.4, 135.3, 135.0, 129.0(2C), 128.2(2C), 128.1, 128.0, 126.9, 126.5, 124.4, 124.2, 56.3, 48.2, 41.2, 36.6, 15.8 **(Spectrum No. 4)**. ESMS *m/z* calcd for $C_{22}H_{23}N_3O_3$ 377, found 378 (M+1).



18b

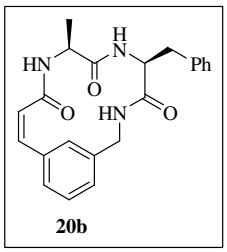
Compound 18b: Compound was prepared by following general procedure **2.4.1a** as white solid (yield 60%), mp 140–142 °C; $[\alpha]_D^{25}$ = -29.6 (*c* 0.5, CH_3OH); IR (KBr) 3290, 1647 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36–7.07 (m, 9H), 6.80 (bs, 1H), 6.55–6.50 (m, 1H), 4.78–4.68 (m, 2H), 4.37–4.24 (m, 2H), 4.02–3.99 (m, 1H), 3.15–3.00 (m, 2H), 1.35–1.23 (m, 12H); CIMS *m/z* calcd for $C_{24}H_{30}BrN_3O_4$ 504, found 506 (M+2), 504 (M).



19b

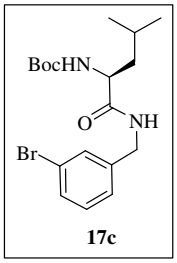
Compound 19b: Compound **19b** was prepared by following general procedure **2.4.4** as a white solid (yield, 88%), mp 240–242 °C; $[\alpha]_D^{25}$ = -49.6 (*c* 0.5, DMSO); IR (KBr) 3276, 1644, 1547 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$+DMSO-*d6*) δ 7.94 (t, *J* = 5.6 Hz, 1H), 7.86 (d, *J* = 6.4 Hz, 1H), 7.53 (d, *J* = 8.3 Hz, 1H), 7.36-7.34 (m, 2H), 7.24-7.15 (m, 7H),

6.26-6.15 (m, 2H), 5.59 (dd, J_1 = 2.9 Hz, J_2 = 8.9 Hz, 1H), 4.66-4.60 (m, 1H), 4.40-4.24 (m, 3H), 3.12-3.00 (m, 2H), 1.28 (d, J = 7.2 Hz, 3H); ^{13}C NMR (50 MHz, DMSO-*d6*): δ 172.0, 170.8, 164.4, 142.0, 137.6, 131.4, 130.3, 129.8, 129.5, 129.1(2C), 128.0(2C), 126.2, 126.1, 125.5, 121.5, 54.1, 48.3, 41.5, 37.3, 17.9; ESMS *m/z* calcd for $C_{22}H_{24}BrN_3O_3$ 458, found 460 (M+2), 458 (M).



20b

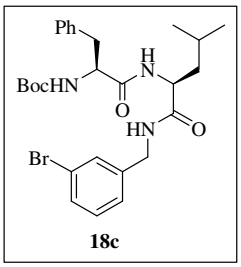
Compound 20b: Compound was prepared using general procedure **2.4.5** as white solid (yield 43%), mp 326 – 328 °C; $[\alpha]_D^{25}$ = -145.2, (*c* 0.25, DMSO); IR (KBr) 3278, 1653, 1616, 1544 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d6*): δ 8.61 (d, J = 7.8 Hz, 1H), 8.55 (d, J = 7.6 Hz, 1H), 7.91 (dd, J_1 = 4.6 Hz, J_2 = 7.2 Hz, 1H), 7.29-7.20 (m, 7H), 7.19-7.11 (m, 2H), 6.57 (d, J = 12.6 Hz, 1H), 6.02 (d, J = 12.4 Hz, 1H), 4.56 (dd, J_1 = 7.5 Hz, J_2 = 16.1 Hz, 1H), 4.49 (q, J = 7.5 Hz, 1H), 4.38 (quint, J = 7.2 Hz, 1H), 3.99 (dd, J_1 = 4.3 Hz, J_2 = 16.1 Hz, 1H), 3.07 (dd, J_1 = 7.0 Hz, J_2 = 14.0 Hz, 1H), 2.87 (dd, J_1 = 8.1 Hz, J_2 = 13.7 Hz, 1H), 1.11 (d, J = 7.0 Hz, 3H); ^{13}C NMR (50 MHz, DMSO-*d6*): δ 171.2, 170.0, 167.1, 138.7, 137.4, 135.3, 135.0, 128.8(2C), 128.2(2C), 128.1, 127.9, 126.9, 126.5, 124.4, 124.2, 56.3, 48.2, 41.1, 36.6, 15.8; ESMS *m/z* calcd for $C_{22}H_{23}N_3O_3$ 377, found 378 (M+1).



17c

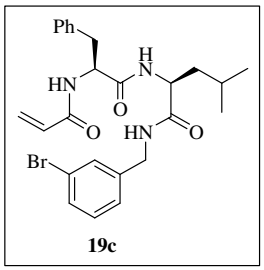
Compound 17c: Compound was prepared by following general procedure **2.4.1a** (yield 87%)**,** m.p. 82-84 °C, $[\alpha]_D^{25}$ = -21.70 *(c* 1, $CHCl_3$); IR (KBr) 3300, 2958, 1657, 1528 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d6*): δ 7.39-7.37 (m, 2H), 7.19-7.14 (m, 2H), 6.70 (bs, 1H), 4.91 (d, J = 7.5 Hz, 1H), 4.39 (bs, 2H), 4.12-4.11 (m, 1H), 1.74-1.63 (m, 2H),

1.52-1.41 (m, 1H), 1.39 (s, 9H), 0.94 (dd, J_1 = 10.2 Hz, J_2 = 16.4 Hz, 6H); ESMS *m/z* calcd for $C_{18}H_{27}BrN_2O_3$ 399, found 401 (M+2).



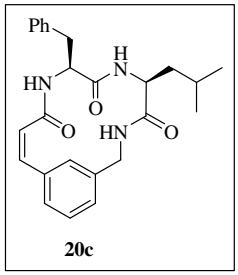
18c

Compound 18c: Compound was prepared by following general procedure **2.4.1a** (yield 75%), mp 163-164 ^{o}C; $[\alpha]_D^{25}$ = -22.50 (*c* 1, $CHCl_3$); IR (KBr) 3322, 3296, 2965, 1689, 1646, 1530 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d6*): δ 8.36 (t, *J* = 5.9 Hz, 1H), 7.95 (d, *J* = 8.1 Hz, 1H), 7.43-7.41 (m, 2H), 7.29-7.16 (m, 7H), 6.91 (d, *J* = 8.3 Hz, 1H), 4.37-4.16 (m, 4H), 2.96 (dd, J_1 = 4.6 Hz, J_2 = 14.0 Hz, 1H), 2.75 (dd, J_1 = 10.2 Hz, J_2 = 13.4 Hz, 1H), 1.63-1.44 (m, 3H), 1.29 (s, 9H), 0.89 (d, *J* = 6.4 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 3H); ESMS *m/z* calcd for $C_{27}H_{36}BrN_3O_3$ 546, found 548 (M+2), 546 (M)



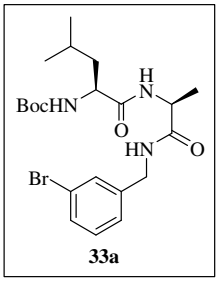
19c

Compound 19c: Compound was prepared by following general procedure **2.4.4** as a white solid (yield 75%), mp 190-192 °C; $[\alpha]_D^{25}$ = -4.0 (*c* 0.5, DMSO); IR (KBr) 3275, 2953, 1643, 1542 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d6*): δ 8.36 (t, *J* = 5.9 Hz, 1H), 8.30 (d, *J* = 8.3 Hz, 1H), 8.17 (d, *J* = 8.1 Hz, 1H), 7.42-7.41 (m, 2H), 7.29-7.13 (m, 7H), 6.26 (dd, J_1 = 10.2 Hz, J_2 = 17.2 Hz, 1H), 6.00 (dd, J_1 = 1.1 Hz, J_2 = 16.2 Hz, 1H), 5.53 (dd, J_1 = 2.1 Hz, J_2 = 10.2 Hz, 1H), 4.67-4.62 (m, 1H), 4.34-4.20 (m, 3H), 3.04 (dd, J_1 = 4.3 Hz, J_2 = 13.7 Hz, 1H), 2.78 (dd, J_1 = 9.9 Hz, J_2 = 14.0 Hz, 1H), 1.60-1.51 (m, 3H), 0.89 (d, *J* = 6.4 Hz, 3H), 0.83 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (50 MHz, DMSO-*d6*): δ 171.9, 171.1, 164.5, 142.3, 137.8, 131.4, 130.4, 129.7, 129.5, 129.1(2C), 128.0(2C), 126.2, 126.1, 125.5, 121.6, 53.9, 51.3, 41.4, 40.9, 37.4, 24.2, 22.9, 21.7; ESMS *m/z* calcd for $C_{25}H_{30}BrN_3O_3$ 500, found 502 (M+2), 500 (M).



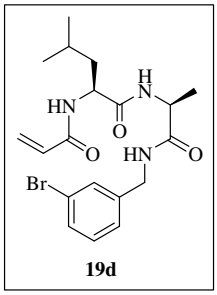
20c

Compound 20c: Compound was prepared using general procedure **2.4.5** as white solid (yield 50%), mp 270- 272 °C; $[\alpha]_D^{25}$ = -145.2 (*c* 0.5, DMSO); IR (KBr) 3292, 2954, 1651 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.25-8.21 (m, 2H), 8.10 (d, *J* = 8.8 Hz, 1H), 7.31-7.17 (m, 7H), 7.10 (t, *J* = 7.8 Hz, 2H), 6.60 (d, *J* = 12.6 Hz, 1H), 6.00 (d, *J* = 12.3 Hz, 1H), 4.52 (dd, J_1 = 6.4 Hz, J_2 = 16.1 Hz, 1H), 4.34-4.23 (m, 2H), 3.98 (dd, J_1 = 5.4 Hz, J_2 = 16.4 Hz, 1H), 3.02-2.91 (m, 2H), 1.59-1.50 (m, 2H), 1.44-1.34 (m, 1H), 0.87 (d, *J* = 6.7 Hz, 3H), 0.82 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (50 MHz, DMSO-*d6*): δ 171.4, 171.1, 167.0, 138.7, 137.4, 135.4, 135.2, 128.9(2C), 128.2(2C), 128.1, 127.9, 126.8, 126.5, 124.3, 124.1, 56.6, 51.3, 41.2, 38.9, 36.5, 24.2, 22.8, 22.1; ESMS *m/z* calcd for $C_{25}H_{29}N_3O_3$ 419, found 420 (M+1).



33a

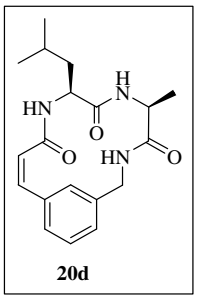
Compound 18d: Compound was prepared by following general procedure **2.4.1a** (yield 80%), mp 143-144 °C; $[\alpha]_D^{25}$ = -20.80 *(c* 0.5, MeOH); IR (KBr) 3348, 3298, 2959, 2869, 1686, 1648, 1519 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.38 (t, *J* = 5.6 Hz, 1H), 7.86 (d, *J* = 7.5 Hz, 1H), 7.43-7.41 (m, 2H), 7.29-7.22 (m, 2H), 6.90 (d, *J* = 8.1 Hz, 1H), 4.32-4.26 (m, 3H), 3.93 (q, *J* = 6.7 Hz, 1H), 1.62-1.58 (m, 1H), 1.43-1.39 (m, 2H), 1.36 (s, 9H), 1.23 (d, *J* = 7.0 Hz, 3H), 0.86 (dd, J_1 = 6.6 Hz, J_2 = 13.4 Hz, 6H); ESMS *m/z* calcd for $C_{21}H_{32}BrN_3O_4$ 470, found 472 (M+2), 470 (M).



19d

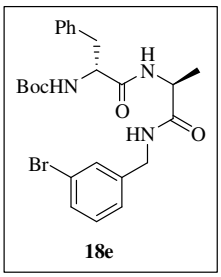
Compound 19d: Compound was prepared by following general procedure **2.4.4** as a white solid (yield 73%), mp 214- 216 °C; $[\alpha]_D^{25}$ = -62.8 (*c* 0.5, CH_3OH); IR (KBr) 3270, 2956, 1639, 1615 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.32 (t, *J* = 5.9 Hz, 1H), 8.20 (d, *J* =

8.1 Hz, 1H), 8.13 (d, J = 7.2 Hz, 1H), 7.43-7.41 (m, 2H), 7.28-7.22 (m, 2H), 7.32 (dd, J_1 = 10.0 Hz, J_2 = 16.9 Hz, 1H), 6.06 (dd, J_1 = 2.4 Hz, J_2 = 17.1 Hz, 1H), 5.58 (dd, J_1 = 2.1 Hz, J_2 = 10.2 Hz, 1H), 4.40 (q, J = 7.5 Hz, 1H), 4.30-4.22 (m, 3H), 1.62-1.58 (m, 1H), 1.56-1.45 (m, 2H), 1.18 (d, J = 7.2 Hz, 3H), 0.87 (d, J = 6.4 Hz, 3H), 0.82 (d, J = 6.9 Hz, 3H); ^{13}C NMR (50 MHz, DMSO-*d6*): δ 172.2, 171.7, 164.4, 142.2, 131.5, 130.3, 129.7, 129.5, 126.0, 125.4, 121.6, 50.9, 48.2, 41.3, 40.7, 24.1, 23.0, 21.5, 17.9; CIMS *m/z* calcd for $C_{19}H_{26}BrN_3O_3$ 424, found 426 (M+2).



20d

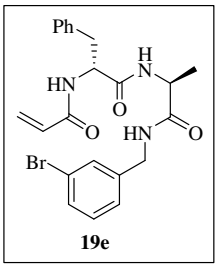
Compound 20d: Compound **20d** was prepared using general procedure **2.4.5** as white solid (yield 40%), mp 297 – 299 °C; $[\alpha]_D^{25}$ = -263.0 (*c* 0.5, DMSO); IR (KBr) 3270, 2956, 1691, 1656 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d6*): δ 8.09-8.06 (m, 2H), 7.99-7.96 (m, 1H), 7.28-7.24 (m, 1H), 7.19 (s, 1H), 7.11 (t, J = 7.5 Hz, 2H), 6.61 (d, J = 12.6 Hz, 1H), 6.11 (d, J = 12.3 Hz, 1H), 4.59 (dd, J_1 = 7.2 Hz, J_2 = 16.1 Hz, 1H), 4.39-4.32 (m, 1H), 4.15-4.10 (m, 1H), 3.94 (dd, J_1 = 4.6 Hz, J_2 = 16.1 Hz, 1H), 1.69-1.44 (m, 3H), 1.21 (d, J = 7.0 Hz, 3H), 0.91 (d, J = 6.4 Hz, 3H), 0.85 (d, J = 6.4 Hz, 3H); ^{13}C NMR (50 MHz, DMSO-*d6*): δ 171.8, 171.5, 167.0, 138.7, 135.4, 135.0, 128.0, 127.9, 126.7, 124.6, 124.1, 53.3, 47.9, 41.2, 40.3, 24.3, 22.6, 21.7, 16.0; CIMS *m/z* calcd for $C_{19}H_{25}N_3O_3$ 343, found 344 (M+1).



18e

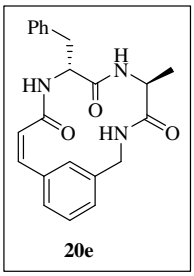
Compound 18e: Compound was prepared by following general procedure **2.4.1a** as a white solid (yield 75%), mp 80–82 °C; $[\alpha]_D^{25}$ = -11.5 (*c* 1, $CHCl_3$); IR (KBr) 3315, 2977, 1649, 1536 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.35 (m, 2H), 7.32-7.21 (m, 3H), 7.20-

7.09 (m, 5H), 6.05 (brs, 1H), 5.01 (brs, 1H), 4.48-4.29 (m, 3H), 4.14 (q, *J* = 7.0 Hz, 1H), 3.06-2.99 (m, 2H), 1.35 (s, 9H), 1.21 (d, *J* = 7.0 Hz, 3H); ESMS *m/z* calcd for $C_{24}H_{30}BrN_3O_4$ 504, found 506 (M+2), 504 (M).



19e

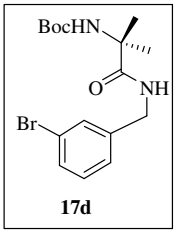
Compound 19e: Compound **19e** was prepared by following general procedure **2.4.4** as a white solid (yield 75%), mp 224-226 °C, $[\alpha]_D^{25}$ = -15.0 (*c* 0.5, DMSO); IR (KBr) 3276, 1640, 1542 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.42 (d, *J* = 7.5 Hz, 1H), 8.38-8.35 (m, 2H), 7.42-7.39 (m, 2H), 7.28-7.17 (m, 7H), 6.27 (dd, J_1 = 10.2 Hz, J_2 = 16.9 Hz, 1H), 5.98 (dd, J_1 = 2.1 Hz, J_2 = 17.2 Hz, 1H), 5.53 (dd, J_1 = 2.1 Hz, J_2 = 10.2 Hz, 1H), 4.60-4.54 (m, 1H), 4.27-4.22 (m, 3H), 2.97 (dd, J_1 = 6.2 Hz, J_2 = 13.7 Hz, 1H), 2.84 (dd, J_1 = 9.0 Hz, J_2 = 13.4 Hz, 1H), 1.14 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (50 MHz, DMSO-*d6*): δ 172.1, 170.1, 164.7, 142.1, 137.5, 131.1, 130.4, 129.7, 129.5, 129.2(2C), 128.0(2C), 126.3, 126.0, 125.6, 121.6, 54.6, 48.2, 41.4, 37.4, 17.8; ESMS *m/z* calcd for $C_{22}H_{24}BrN_3O_3$ 458, found 460 (M+2), 458 (M).



20e

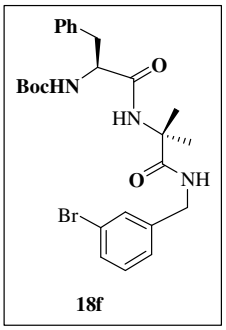
Compound 20e: Compound **20e** was prepared using general procedure **2.4.5** as white solid (yield 75%), mp 230 – 232 °C; $[\alpha]_D^{25}$ = +48.4 (*c* 0.5, DMSO) IR (KBr) 3274, 1651, 1613, 1526 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.80 (d, *J* = 8.3 Hz, 1H), 8.55 (d, *J* = 7.5 Hz, 1H), 7.61 (d, *J* = 5.6 Hz, 1H), 7.28-7.11 (m, 9H), 6.57 (d, *J* = 12.6 Hz, 1H), 5.96 (d, *J* = 12.6 Hz, 1H), 4.60-4.54 (m, 1H), 4.42 (dd, J_1 = 7.4 Hz, J_2 = 16.4 Hz, 1H), 4.28-4.17 (m, 2H), 2.96-2.85 (m, 2H), 1.17 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (50 MHz, DMSO-*d6*): δ 171.9, 171.6, 167.6, 138.5, 137.8, 135.5, 133.9, 129.1(2C), 128.5,

128.1(3C), 127.1, 126.9, 126.4, 124.1, 54.2, 48.8, 41.3, 35.9, 15.6; ESMS *m/z* calcd for $C_{22}H_{23}N_3O_3$ 377, found 378 (M+1).



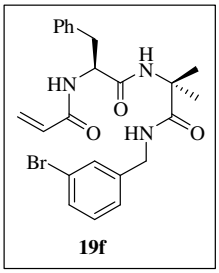
17d

Compound 17d: Compound was prepared by following general procedure **2.4.1a** (yield 68%) mp 102-104 °C; IR (KBr) 3315, 2980, 1686, 1652, 1528 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.11 (t, J = 5.6 Hz, 1H), 7.43 (s, 1H), 7.38 (d, J = 7.5 Hz, 1H), 7.27-7.20 (m, 3H), 4.24 (d, J = 6.2 Hz, 2H), 1.37 (brs, 6H), 1.32 (s, 9H); ES-MS *m/z* calcd for $C_{16}H_{23}N_2O_3Br$ 371, found 373 (M+2), 371 (M).



18f

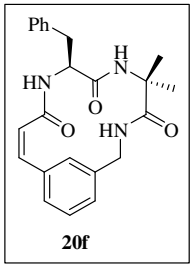
Compound 18f: Compound was prepared by following general procedure **2.4.1a** as a white solid (yield 87%), mp 127-129 °C; $[\alpha]_D^{25}$ = +9.4 (*c* 1, DMSO); IR (KBr) 3539, 3349, 2978, 1690, 1647, 1506 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.04 (s, 1H), 7.94 (t, J = 5.9 Hz, 1H), 7.43 (s, 1H), 7.41-7.38 (m, 1H), 7.29-7.17 (m, 6H), 7.02 (d, J = 6.7 Hz, 1H), 4.31-4.09 (m, 3H), 2.92 (dd, J_1 = 5.9 Hz, J_2 = 13.7 Hz, 1H), 2.77 (dd, J_1 = 9.1 Hz, J_2 = 13.4 Hz, 1H), 1.40 (s, 3H), 1.32 (s, 3H), 1.25 (s, 9H); ESMS *m/z* calcd for $C_{25}H_{32}N_3O_4Br$ 518, found 535 ($M+NH_3$), 520 (M+2), 518 (M).



19f

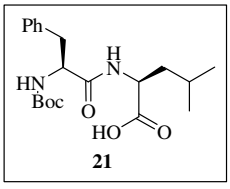
Compound 19f: Compound was prepared by following general procedure **2.4.4** as a white solid (yield 72%), mp 182–184 °C; $[\alpha]_D^{25}$ = +11.8 (*c* 0.5, CH_3OH); IR (KBr) 3288, 3062, 2927, 1652, 1544 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.36 (s, 1H), 7.36-7.10 (m, 8H), 7.04 (t, J = 5.9 Hz, 1H), 6.70 (d, J = 6.7 Hz, 1H), 6.35 (s, 1H), 6.10 (dd, J_1 = 1.9 Hz, J_2 = 16.2 Hz, 1H), 6.02 (dd, J_1 = 9.9 Hz, J_2 = 16.9 Hz, 1H), 5.57 (dd, J_1 = 1.9 Hz, J_2 = 9.9 Hz, 1H), 4.49 (q, J = 6.7 Hz, 1H), 4.36-4.25 (m, 2H), 3.08-3.01 (m, 2H), 1.43 (s,

3H), 1.32 (s, 3H) **(Spectrum No. 5)**. ^{13}C NMR (50 MHz, DMSO-*d6*): δ 173.9, 170.7, 164.8, 142.4, 137.4, 130.9, 130.1, 129.4, 129.1(2C), 127.9(2C), 126.2, 125.7, 125.5, 121.4, 56.0, 54.7, 41.7, 37.0, 28.1, 26.0, 24.2 **(Spectrum No, 6)**. ESMS *m/z* calcd for $C_{23}H_{26}BrN_3O_3$ 472, found 474 (M+2), 472 (M).



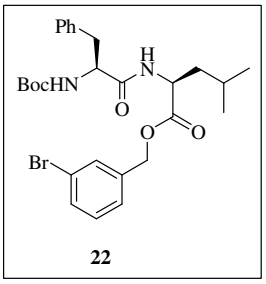
20f

Compound 20f: Compound **20f** was prepared using general procedure **2.4.5** as white solid (yield 63%), mp 190–192 °C; $[\alpha]_D^{25}$ = +8.2 (*c* 0.5, DMSO); IR (KBr) 3276, 2924, 1650, 1538 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d6*+$CDCl_3$): δ 8.62 (d, *J* = 8.1 Hz, 1H), 8.52 (s, 1H), 7.32-7.20 (m, 7H), 7.19-7.09 (m, 2H), 6.95 (dd, J_1 = 2.7 Hz, J_2 = 6.2 Hz, 1H), 6.62 (d, *J* = 12.3 Hz, 1H), 6.00 (d, *J* = 12.1 Hz, 1H), 4.66-4.58 (m, 2H), 3.92 (dd, J_1 = 2.4 Hz, J_2 = 15.8 Hz, 1H), 2.85 (d, *J* = 7.5 Hz, 2H), 1.26 (s, 3H), 1.24 (s, 3H) **(Spectrum No. 7)**. ^{13}C NMR (50 MHz, DMSO-*d6*): δ 173.3, 171.5, 167.6, 138.1, 137.5, 135.4, 134.1, 129.2 (3C), 127.9 (3C), 127.2, 126.2, 125.5, 125.2, 55.9, 54.2, 42.3, 36.6, 26.7, 22.7 **(Spectrum No. 8)**. ESMS *m/z* calcd for $C_{23}H_{25}N_3O_3$ 391, found 392 (M+1).



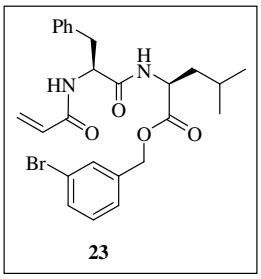
21

Compound 21: Compound **21** was prepared by following general procedure **2.4.2** from its ester analog (yield 83%), m.p.138–140 °C; $[\alpha]_D^{25}$ = -12.3, (c 1, MeOH); IR (KBr) 3331, 2956, 1729, 1673 cm^{-1}; ^{1}H NMR (200 MHz, CD_3OD): δ 7.24 (s, 5H), 4.48–4.41 (m, 1H), 4.35–4.28 (m, 1H), 3.17–2.72 (m, 2H), 1.75–1.62 (m, 3H), 1.34 (s, 9H), 0.96–0.90 (m, 6H); CIMS *m/z* calcd for $C_{20}H_{30}N_2O_5$ 378, found 379 (M^++1).



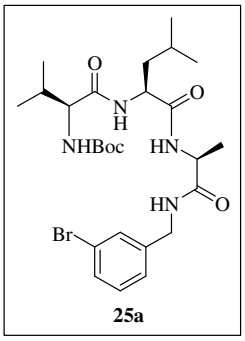
22

Compound 22: 3-bromobenzylbromide (0.79 g, 3.17mmol) in DMF (15 mL) was added to a solution of Boc-L-Phe-L-Ala (1 g, 2.64mmol) and K_2CO_3 (0.72 g, 5.28mmol) in DMF (15ml/mmol) at 0 °C. The reaction mixture allowed to warm to rt and stirred for overnight. The reaction mixture poured into EtOAc and water (100 mL and 50 mL) and organic layer collected. Aqueous extracted with EtOAc. The combined extracts washed with water, brine and dried over Na_2SO_4, and filtered, the solvent was evaporated, and the crude compound was purified by column chromatography to give the desired peptide **22** as gum (yield 60%), $[\alpha]_D^{25}$ = -11.2 (*c* 1, $CHCl_3$); IR (Neat): 3312, 2960, 1745, 1643 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$): δ 7.47–7.45 (m, 2H), 7.35–7.18 (m, 7H), 6.25 (d, J = 8.1 Hz, 1H), 5.07 (dd, $J_1 = J_2$ = 12.6 Hz, 2H), 4.97 (bs, 1H), 4.62–4.56 (m, 1H), 4.36–4.31 (m, 1H), 3.05 (d, J = 6.7Hz, 2H), 1.61–1.42 (m, 3H), 1.40 (s, 9H), 0.88 (dd, $J_1 = J_2$ = 6.6 Hz, 6H); CIMS *m/z* calcd for $C_{27}H_{35}BrN_2O_5$ 547, found 549 (M +2).



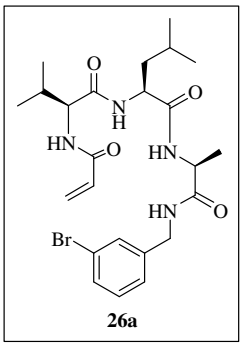
23

Compound 23: Compound **23** was prepared by following general procedure **2.4.4** as a white solid (yield 70%)**,** mp 120-122 °C; $[\alpha]_D^{25}$ = -25.0 (*c* 0.5, $CHCl_3$); IR (KBr): 3283, 2957, 1748, 1653, 1627 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.49–7.45 (m, 2H), 7.28–7.19 (m, 7H), 6.30–6.24 (m, 3H), 6.08 (dd, $J_1 = J_2$ = 10.4 Hz, 1H), 5.65 (d, J = 10.2 Hz, 1H), 5.09 (dd, $J_1 = J_2$ = 12.5 Hz, 2H), 4.79–4.74 (m, 1H), 4.56–4.51 (m, 1H), 3.16–3.02 (m, 2H), 1.58–1.43 (m, 3H), 0.86 (d, J = 6.1 Hz, 6H); CIMS *m/z* calcd for $C_{25}H_{29}BrN_2O_4$ 501, found 503 (M +2), 501 (M).



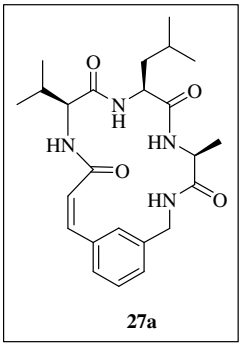
25a

Compound 25a: Compound was prepared as a white solid using general procedure **2.4.1b** (yield 90%), mp 203-204 °C; $[\alpha]_D^{25}$ = -21.7 (*c* 1, DMSO); IR (KBr) 3283, 2961, 1641, 1548 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.33 (t, *J* = 5.6 Hz, 1H), 7.99 (d, *J* = 7.0 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.43-7.41 (m, 2H), 7.28-7.21 (m, 2H), 6.74 (d, *J* = 8.6 Hz, 1H), 4.37-4.21 (m, 4H), 3.75 (t, *J* = 8.1 Hz, 1H), 1.94-1.89 (m, 1H), 1.65-1.58 (m, 3H), 1.43 (s, 9H), 1.22 (d, *J* = 7.2 Hz, 3H), 0.87-0.79 (m, 12H); ESMS *m/z* calcd for $C_{26}H_{41}N_4O_5Br$ 569, found 571 (M+2), 569 (M).



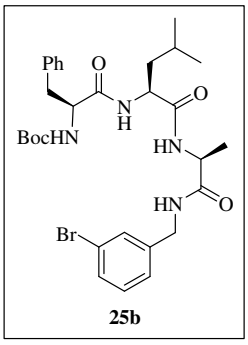
26a

Compound 26a : Compound **26a** was prepared by following general procedure **2.4.4** as a white solid (yield 81%)**,** mp 180-182 °C; $[\alpha]_D^{25}$ = -29.4 (*c* 1, DMSO); IR (KBr) 3286, 2960, 1637, 1545 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.33 (t, *J* = 5.9 Hz, 1H), 8.09 (d, *J* = 7.6 Hz, 1H), 8.02 (d, *J* = 7.8 Hz, 1H), 7.79 (d, *J* = 7.2 Hz, 1H), 7.43 (brs, 2H), 7.28-7.22 (m, 2H), 6.43 (dd, J_1 = 10.2 Hz, J_2 = 16.9 Hz, 1H), 6.08 (dd, J_1 = 2.1 Hz, J_2 = 16.9 Hz, 1H), 5.58 (dd, J_1 = 2.4 Hz, J_2 = 10.2 Hz, 1H), 4.32-4.21 (m, 5H), 2.01-1.96 (m, 1H), 1.61-1.55 (m, 1H), 1.46 (t, *J* = 7.5 Hz, 2H), 1.22 (d, *J* = 7.0 Hz, 3H), 0.87-0.81 (m, 12H) **(Spectrum No. 9)**. ^{13}C NMR (50 MHz, DMSO-*d6*): δ 172.1, 171.5, 170.9, 164.6, 142.2, 131.6, 130.4, 129.7, 129.5, 126.0, 125.4, 121.6, 57.8, 50.9, 48.3, 41.3, 40.3, 30.5, 24.1, 23.0, 21.5, 19.2, 18.1, 18.0 **(Spectrum No. 10)**. ES-MS *m/z* calcd for $C_{24}H_{35}N_4O_5Br$ 523, found 525 (M+2), 523 (M).



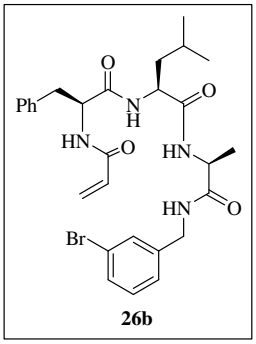
27a

Compound 27a: Compound **27a** was prepared using general procedure **2.4.5** as a white solid (yield 43%), mp 172-174 °C; $[\alpha]_D^{25}$ = -27.6 (*c* 0.5, DMSO); IR (KBr) 3288, 2960, 1657, 1530 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.31 (d, *J* = 7.0 Hz, 2H), 7.95 (d, *J* = 8.1 Hz, 1H), 7.88 (d, *J* = 7.2 Hz, 1H), 7.60 (s, 1H), 7.31-7.19 (m, 2H), 7.09 (t, *J* = 9.1 Hz, 1H), 6.81 (d, *J* = 12.4 Hz, 1H), 6.19 (d, *J* = 12.6 Hz, 1H), 4.45 (dd, J_1 = 6.4 Hz, J_2 = 15.8 Hz, 1H), 4.21-4.17 (m, 1H), 4.06-3.98 (m, 2H), 3.92 (q, *J* = 5.1 Hz, 1H), 2.23-2.18 (m, 1H), 1.66-1.44 (m, 3H), 1.22 (d, *J* = 7.0 Hz, 3H), 0.96-0.83 (m, 12H) **(Spectrum No. 11)**. ^{13}C NMR (50 MHz, DMSO-*d6*): δ 171.8, 171.0, 170.8, 165.7, 138.6, 138.4, 135.9, 127.5, 127.4, 126.6, 126.0, 123.6, 59.1, 52.4, 49.3, 42.1, 40.8, 29.1, 24.3, 23.1, 21.5, 19.3, 17.3, 16.2; **(Spectrum No. 12)**. ESMS *m/z* calcd for $C_{24}H_{34}N_4O_5$ 442, found 443 (M+1).



25b

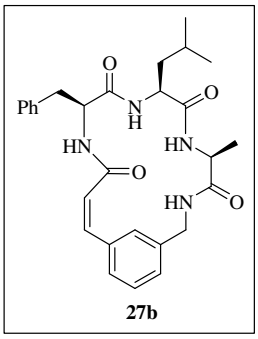
Compound 25b: Compound was prepared by following general procedure **2.4.1b** (yield 86%), mp 214-216 °C; $[\alpha]_D^{25}$ = -7.00 *(c* 0.5, DMSO); IR (KBr), 3286, 3064, 2956, 1692, 1638, 1541 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.39-8.32 (m, 1H), 8.06 (d, *J* = 7.0 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.45-7.41 (m, 2H), 7.36-7.15 (m, 7H), 6.91 (d, *J* = 8.6 Hz, 1H), 4.38-4.14 (m, 5H), 2.98 (dd, J_1 = 3.8 Hz, J_2 = 13.7 Hz, 1H), 2.72 (dd, J_1 = 10.5 Hz, J_2 = 13.7 Hz, 1H), 1.68-1.58 (m, 1H), 1.52-1.45 (m, 2H), 1.30 (s, 9H), 1.23 (d, *J* = 4.0 Hz, 3H), 1.47 (dd, J_1 = 6.7 Hz, J_2 = 12.4 Hz, 6H); ESMS *m/z* calcd for $C_{30}H_{41}BrN_4O_5$ 617, found 619 (M+2), 617 (M).



26b

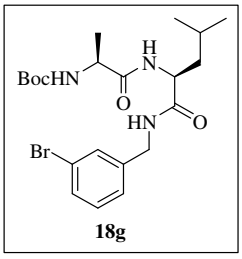
Compound 26b: Compound **26b** was prepared by following general procedure **2.4.4** as a white solid (yield 81%)**,** mp 210-212

°C; $[\alpha]_D^{25}$ = -4.3 (*c* 1, DMSO); IR (KBr) 3279, 3064, 2956, 1638, 1545; ^{1}H NMR (400 MHz, DMSO-*d6*): δ 8.34 (t, *J* = 5.9 Hz, 1H), 8.30 (d, *J* = 8.3 Hz, 1H), 8.11 (d, *J* = 8.1 Hz, 1H), 7.98 (d, *J* = 7.2 Hz, 1H), 7.43-7.40 (m, 2H), 7.28-7.15 (m, 7H), 6.25 (dd, J_1 = 10.2 Hz, J_2 = 16.9 Hz, 1H), 6.00 (dd, J_1 = 1.1 Hz, J_2 = 16.9 Hz, 1H), 5.54 (dd, J_1 = 2.1 Hz, J_2 = 10.2 Hz, 1H), 4.65-4.59 (m, 1H), 4.33-4.24 (m, 4H), 3.04 (dd, J_1 = 3.3 Hz, J_2 = 14.0 Hz, 1H), 2.76 (dd, J_1 = 10.0 Hz, J_2 = 13.7 Hz, 1H), 1.60-1.55 (m, 1H), 1.49-1.45 (m, 2H), 1.24 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 6.4 Hz, 3H), 0.83 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (50 MHz, DMSO-*d6*): δ 172.2, 171.5, 171.2, 164.5, 142.2, 137.9, 131.4, 130.4, 129.7, 129.5, 129.1(2C), 127.9(2C), 126.2, 126.0, 125.5, 121.6, 53.9, 51.1, 48.3, 41.4, 40.6, 37.4, 24.1, 23.1, 21.6, 18.0; ESMS *m/z* calcd for $C_{28}H_{35}N_4O_5Br$ 571, found 573 (M+2), 571 (M).



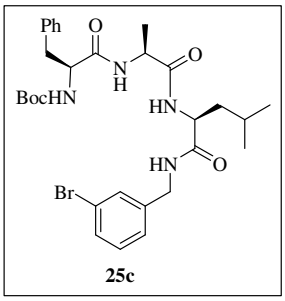
27b

Compound 27b: Compound **27b** was prepared using general procedure **2.4.5** as a white solid (yield 33%), mp 286-288 °C; $[\alpha]_D^{25}$ = -21.0 (*c* 0.1, DMSO); IR (KBr) 3306, 3062, 2957, 1656, 1529 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d6*): δ 8.35 (d, *J* = 7.0 Hz, 1H), 8.30 (t, *J* = 5.9 Hz, 1H), 8.20 (d, *J* = 7.5 Hz, 1H), 8.13 (d, *J* = 7.8 Hz, 1H), 7.67 (s, 1H), 7.32-7.18 (m, 6H), 7.11 (d, *J* = 7.5 Hz, 1H), 7.06 (d, *J* = 7.5 Hz, 1H), 6.72 (d, *J* = 12.6 Hz, 1H), 5.91 (d, *J* = 12.6 Hz, 1H), 4.50 (dd, J_1 = 7.0 Hz, J_2 = 16.1 Hz, 1H), 4.19-4.10 (m, 3H), 4.02 (dd, J_1 = 5.1 Hz, J_2 = 16.1 Hz, 1H), 3.18 (dd, J_1 = 4.0 Hz, J_2 = 13.9 Hz, 1H), 2.90 (dd, J_1 = 10.7 Hz, J_2 = 13.4 Hz, 1H), 1.69-1.62 (m, 1H), 1.57-1.39 (m, 2H), 1.23 (d, *J* = 6.7 Hz, 3H), 0.95-0.83 (m, 6H); ESMS *m/z* calcd for $C_{28}H_{34}N_4O_5$ 490, found 491 (M+1).



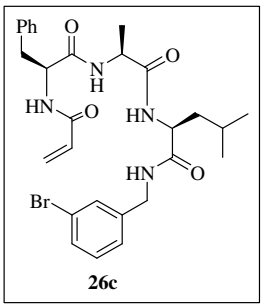
18g

Compound 18g: Compound was prepared as a white solid by following procedure **2.4.1b** (yield 85%), mp 166-168 °C; $[\alpha]_D^{25}$ = -16.4 (*c* 1, DMSO); IR (KBr) 3280, 2959, 1646, 1522 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.42 (brs, 1H), 7.80 (d, *J* = 8.3 Hz, 1H), 7.42-7.40 (m, 2H), 7.28-7.21 (m, 2H), 6.94 (d, *J* = 6.7 Hz, 1H), 4.34-4.22 (m, 3H), 3.97-3.93 (m, 1H), 1.62-1.56 (m, 1H), 1.54-1.46 (m, 2H), 1.35 (s, 9H), 1.16 (d, *J* = 7.8 Hz, 3H), 0.88 (d, *J* = 6.4 Hz, 3H), 0.83 (d, *J* = 6.2 Hz, 3H); ESMS *m/z* calcd for $C_{21}H_{32}N_3O_4Br$ 470, found 472 (M+2), 470 (M).



25c

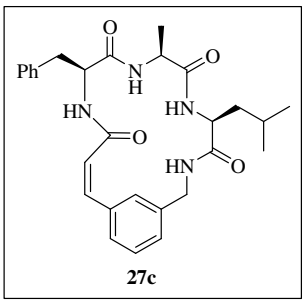
Compound 25c: Compound was prepared as a white solid by following the general procedure **2.4.1b** (yield 90%), mp 159-160 °C; $[\alpha]_D^{25}$ = -12.7 (*c* 1, DMSO); IR (KBr) 3290, 2958, 1642, 1547 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.43 (t, *J* = 5.4 Hz, 1H), 7.97 (t, *J* = 6.4 Hz, 2H), 7.42 (brs, 2H), 7.41-7.17 (m, 7H), 6.91 (d, *J* = 8.3 Hz, 1H), 4.35-4.14 (m, 5H), 2.97 (dd, J_1 = 3.2 Hz, J_2 = 14.0 Hz, 1H), 2.71 (t, *J* = 10.7 Hz, 1H), 1.61-1.55 (m, 1H), 1.48 (t, *J* = 7.5 Hz, 2H), 1.29 (s, 9H), 1.22 (d, *J* = 6.7 Hz, 3H), 0.88 (d, *J* = 6.7 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 3H); ESMS *m/z* calcd for $C_{30}H_{41}N_4O_5Br$ 617, found 619 (M+2), 617 (M).



26c

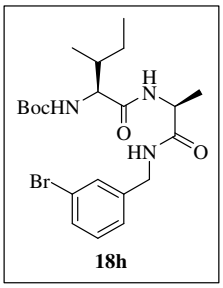
Compound 26c : Compound **26c** was prepared by following general procedure **2.4.4** as a white solid (yield 82%)**,** mp 233-235 °C; $[\alpha]_D^{25}$ = -10.2 (*c* 1, DMSO); IR (KBr) 3278, 3083, 2956, 1638, 1542 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.43 (brs, 1H), 8.32 (d, *J* = 8.0 Hz, 1H), 8.25 (d, *J* = 7.0 Hz, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.42-7.40 (m, 2H), 7.28-7.17 (m, 7H), 6.25 (dd, J_1 = 10.2 Hz, J_2 = 16.9

Hz, 1H), 6.00 (d, *J* = 16.9 Hz, 1H), 5.54 (d, *J* = 10.2 Hz, 1H), 4.62 (brs, 1H), 4.32-4.22 (m, 4H), 3.04 (dd, J_1 = 2.2 Hz, J_2 = 14.0 Hz, 1H), 2.77 (t, *J* = 10.5 Hz, 1H), 1.62-1.48 (m, 3H), 1.23 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 6.2 Hz, 3H), 0.84 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (50 MHz, DMSO-*d6*): δ 172.1, 171.9, 171.2, 164.5, 142.3, 137.9, 131.4, 130.4, 129.7, 129.5, 129.1(2C), 128.0(2C), 126.2, 126.0, 125.5, 121.6, 54.0, 51.2, 48.4, 41.4, 40.8, 37.5, 24.2, 24.9, 21.7, 17.9; ESMS *m/z* calcd for $C_{28}H_{35}N_4O_5Br$ 571, found 573 (M+2), 571 (M).



27c

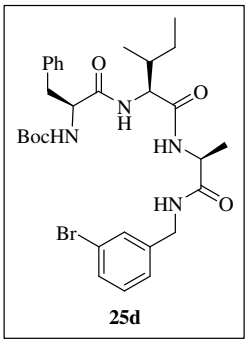
Compound 27c : Compound **27c** was prepared using general procedure **2.4.5** as white solid (yield 36%); mp 290-292 °C; $[\alpha]_D^{25}$ = -0.2 (*c* 1, DMSO); IR (KBr) 3298, 3062, 2956, 1654, 1522 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d6*): δ 8.62 (d, *J* = 4.3 Hz, 1H), 8.60 (d, *J* = 7.0 Hz, 1H), 8.36 (d, *J* = 6.7 Hz, 1H), 8.24 (d, *J* = 6.7 Hz, 1H), 7.60 (s, 1H), 7.38-7.18 (m, 7H), 7.06 (d, *J* = 7.8 Hz, 1H), 6.70 (d, *J* = 12.6 Hz, 1H), 5.93 (d, *J* = 12.6 Hz, 1H), 4.46 (dd, J_1 = 6.9 Hz, J_2 = 16.0 Hz, 1H), 4.32-4.24 (m, 1H), 4.15-4.06 (m, 2H), 3.99-3.93 (m, 1H), 3.18 (dd, J_1 = 4.6 Hz, J_2 = 14.0 Hz, 1H), 2.97-2.93 (m, 1H), 1.72-1.49 (m, 3H), 1.37 (d, *J* = 7.2 Hz, 3H), 0.92 (d, *J* = 5.9 Hz, 3H), 0.88 (d, *J* = 5.1 Hz, 3H); ESMS *m/z* calcd for $C_{28}H_{34}N_4O_5$ 490, found 491 (M+1).



18h

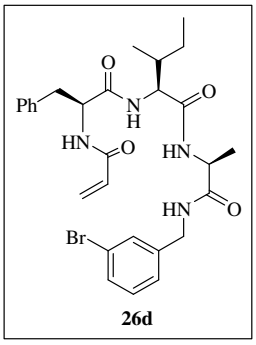
Compound 18h: Compound was prepared as a white solid by following procedure **2.4.1b** (yield 84%), mp 170-172 °C; $[\alpha]_D^{25}$ = -7.1 (*c* 1, DMSO); IR (KBr) 3337, 3299, 2967, 1684, 1648 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d6*): *δ* 8.42 (t, *J* = 5.1 Hz, 1H), 7.92 (d, *J* = 7.0 Hz, 1H), 7.43-7.40 (m, 2H), 7.28-7.21 (m, 2H), 6.73 (d, *J* = 8.3

Hz, 1H), 4.34-4.22 (m, 3H), 3.82-3.80 (m, 1H), 1.71-1.69 (m, 1H), 1.36 (s, 9H), 1.36-1.23 (m, 1H), 1.23 (d, *J* = 7.0 Hz, 3H), 1.09-1.07 (m, 1H), 0.81-0.78 (m, 6H); ESMS *m/z* calcd for $C_{21}H_{32}N_3O_4Br$ 470, found 472 (M+2), 470 (M).



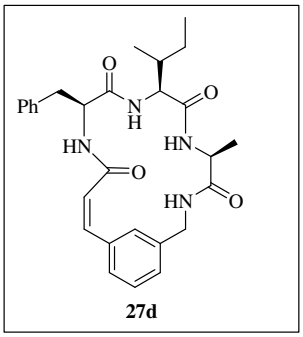
25d

Compound 25d: Compound was prepared as a white solid by following the general procedure **2.4.1b** (yield 85%), mp 166-168 °C; $[\alpha]_D^{25}$ = -9.3 (*c* 1, DMSO); IR (KBr) 3299, 2963, 1648, 1547 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.37 (t, *J* = 5.6 Hz, 1H), 8.13 (d, *J* = 7.0 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.43-7.40 (m, 2H), 7.28-7.16 (m, 7H), 6.97 (d, *J* = 8.3 Hz, 1H), 4.33-4.15 (m, 5H), 2.96 (dd, J_1 = 4.0 Hz, J_2 = 14.0 Hz, 1H), 2.72 (dd, J_1 = 10.5 Hz, J_2 = 13.7 Hz, 1H), 1.76-1.70 (m, 1H), 1.49-1.41 (m, 1H), 1.32 (s, 9H), 1.23 (d, *J* = 7.0 Hz, 3H), 1.15-1.05 (m, 1H), 0.83-0.78 (m, 6H); ESMS *m/z* calcd for $C_{30}H_{41}N_4O_5Br$ 617, found 619 (M+2), 617 (M).



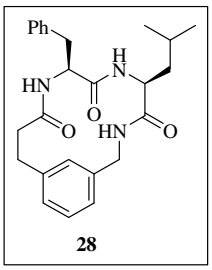
26d

Compound 26d : Compound **26d** was prepared by following general procedure **2.4.4** as a white solid (yield 75%)**,** mp 210-212 °C; $[\alpha]_D^{25}$ = -4.3 (*c* 1, DMSO); IR (KBr) 3277, 3064, 3080, 2962, 1636, 1547 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.36 (t, *J* = 5.9 Hz, 1H), 8.30 (d, *J* = 8.3 Hz, 1H), 8.05 (d, *J* = 7.0 Hz, 1H), 7.95 (d, *J* = 8.6 Hz, 1H), 7.43-7.40 (m, 2H), 7.30-7.14 (m, 7H), 6.25 (dd, J_1 = 10.2 Hz, J_2 = 17.0 Hz, 1H), 6.00 (dd, J_1 = 1.2 Hz, J_2 = 16.0 Hz, 1H), 5.54 (dd, J_1 = 1.2 Hz, J_2 = 10.2 Hz, 1H), 4.70-4.65 (m, 1H), 4.33-4.20 (m, 4H), 3.06 (dd, J_1 = 4.8 Hz, J_2 = 15.8 Hz, 1H), 2.76 (dd, J_1 = 10.2 Hz, J_2 = 14.0 Hz, 1H), 1.75-1.73 (m, 1H), 1.46-1.40 (m, 1H), 1.24 (d, *J* = 7.0 Hz, 3H), 1.10-1.03 (m, 1H), 0.81 (t, *J* = 6.4 Hz, 6H); ESMS *m/z* calcd for $C_{28}H_{35}N_4O_5Br$ 571, found 573 (M+2), 571 (M).



27d

Compound 27d: Compound **27d** was prepared using general procedure **2.4.5** as white solid (yield 30%), mp 250-252 °C; $[\alpha]_D^{25}$ = -40.4 (*c* 0.5, DMSO); IR (KBr) 3302, 3062, 2964, 2929, 1654, 1524 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.66 (d, *J* = 7.2 Hz, 1H), 8.65 (d, *J* = 7.5 Hz, 1H), 8.48 (d, *J* = 7.0 Hz, 1H), 8.33 (d, *J* = 7.8 Hz, 1H), 7.52 (s, 1H), 7.37-7.15 (m, 7H), 7.01 (d, *J* = 7.5 Hz, 1H), 6.78 (d, *J* = 12.4 Hz, 1H), 5.94 (d, *J* = 12.4 Hz, 1H), 4.52 (dd, J_1 = 7.0 Hz, J_2 = 16.4 Hz, 1H), 4.28-4.17 (m, 3H), 3.98-3.92 (m, 1H), 3.24 (dd, J_1 = 3.5 Hz, J_2 = 14.2 Hz, 1H), 2.90-2.81 (m, 1H), 1.98-1.85 (m, 1H), 1.50-1.44 (m, 1H), 1.33-1.19 (m, 3H), 1.11-1.06 (m, 1H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.87-0.86 (m, 3H); ESMS *m/z* calcd for $C_{28}H_{34}N_4O_5$ 490, found 491 (M+1).

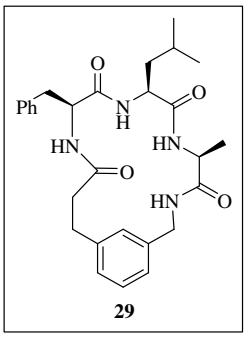


28

Compound 28:

To a solution of cyclic peptidomimetic **20c** (75 mg) in ethanol was added 10% Pd-C (75mg). The reaction mixture was stirred at room temperature under hydrongen atmosphere for 6 h. Pd-C filtered off on celite bed. Solvent evaporated and the residue washed with diethyl ether to obtained white solid product **28** in quantitative yield (yield 99%), mp 305-306 °C; $[\alpha]_D^{25}$ = -103.0 (*c* 0.1, DMSO); IR (KBr): 3297, 2926, 1650 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*+$CDCl_3$): δ 8.45 (t, *J* = 5.9 Hz, 1H), 8.02 (d, *J* = 8.3 Hz,1H), 7.82 (d, *J* = 8.6 Hz, 1H), 7.29-7.12 (m, 6H), 7.02-6.99 (m, 2H), 6.86 (s,1H), 4.43-4.34 (m, 2H), 4.17 (q, *J* = 7.5 Hz, 1H), 4.00 (dd, J_1 = 5.4 Hz, J_2 = 15.3 Hz, 1H), 3.10-3.04 (m,1H), 2.95-2.83 (m, 2H), 2.66-2.60 (m, 1H), 2.36-2.33 (m, 2H), 1.56-1.49 (m, 2H), 1.35(spt, *J*

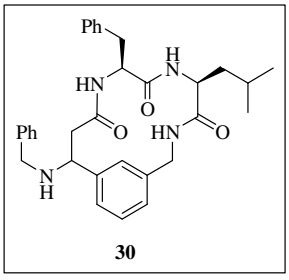
= 7.7 Hz, 1H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.86 (d, *J* = 6.7 Hz, 3H); CIMS *m/z* calcd for $C_{25}H_{31}N_3O_3$ 421, found 422 (M+1).



29

Compound 29

To a solution of cyclic peptidomimetic **26c** (100 mg) in ethanol was added 10% Pd-C (100 mg). The reaction mixture was stirred at room temperature under hydrongen atmosphere for 6 h. Pd-C filtered off on celite bed. Solvent evaporated and the residue washed with diethyl ether to obtained as white solid product **29** in quantitative yield (yield 99%), mp 252-254 °C; $[\alpha]_D^{25}$ = -35.4 (*c* 0.5 DMSO); IR (KBr) 3320, 3062, 2927, 1655, 1532 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.22 (t, *J* = 6.7 Hz, 2H), 8.05 (t, *J* = 5.4 Hz, 2H), 7.29-7.12 (m, 7H), 7.01 (t, *J* = 5.6 Hz, 2H), 4.40-4.29 (m, 2H), 4.10 (dd, J_1 = 5.4 Hz, J_2 = 14.8 Hz, 1H), 4.02-3.94 (m, 2H), 3.04 (dd, J_1 = 4.6 Hz, J_2 = 13.7 Hz, 1H), 2.95-2.92 (m, 1H), 2.83 (dd, J_1 = 9.9 Hz, J_2 = 13.7 Hz, 1H), 2.74-2.71 (m, 1H), 2.55-2.50 (m, 1H), 2.34-2.28 (m, 1H), 1.66-1.62 (m, 1H), 1.50-1.47 (m, 2H), 1.31 (d, *J* = 7.2 Hz, 3H), 0.89 (d, *J* = 6.2 Hz, 3H), 0.84 (d, *J* = 5.9 Hz, 3H) **(Spectrum No. 13)**. ESMS *m/z* calcd for $C_{28}H_{36}N_4O_5$ 492, found 493 (M+1).



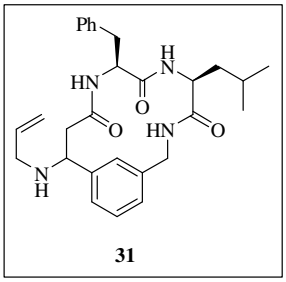
30

Compound 30:

A solution of cyclic peptide VBR-JI-100 (0.05g, 0.119 mmol), benzylamine (0.0195 mL, 0.179 mmol) and Ytterbium (III) trifluoromethane sulfornate hydrate (7.4 mg, 0.1 mmol)

in absolute ethanol (0.5 mL) was refluxed for 3 d. Ethanol evaporated under vacuo and crude subjected to column chromatography on 100-200mesh silica gel in 2/98 MeOH/CH_2Cl_2 system to yield the miachel addition product

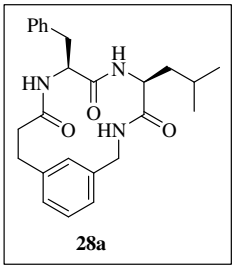
30 as a white solid (yield 65%), mp 248–250 °C, $[\alpha]_D^{25}$ = -73.0 (*c* 0.1, DMSO); IR (KBr) 3256, 2925, 1657 cm^{-1}; ^1H NMR (400MHz, DMSO-*d6*+$CDCl_3$): δ 8.17 (d, *J* = 8.3 Hz, 1H), 7.97 (d, *J* = 8.3 Hz, 1H), 7.92–7.89 (m, 1H), 7.36–7.06 (m, 14H), 4.64 (dd, $J_1 = J_2 =$ 7.4 Hz, 1H), 4.37-4.35 (m, 1H), 4.05–3.89 (m, 3H), 3.58–3.33 (m, 2H), 2.94 (d, *J* = 7.8 Hz, 2H), 2.67–2.63 (m, 1H), 2.36–2.30 (m, 1H), 1.66–1.63 (m, 2H), 1.40–1.25 (m, 2H), 0.88 (d, *J* = 6.4 Hz, 3H), 0.82 (d, *J* = 6.4 Hz, 3H) **(Spectrum No. 14)**. CIMS *m/z* calcd for $C_{32}H_{38}N_4O_3$ 526, found 527 (M+1).



31

Compound 31:

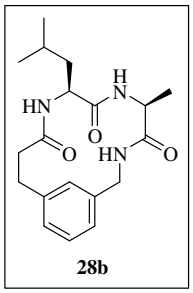
A solution of cyclic peptide VBR-JI-100 (0.05g, 0.119 mmol), allylamine (0.014mL, 0.178mmol) and Ytterbium (III) trifluoro methanesulfonate hydrate (0.015g, 10 mol%) in absolute ethanol (0.5mL) was refluxed for 3 days. Ethanol evaporated under vacuo and crude subjected to column chromatography on 100-200mesh silica gel in 2/98 MeOH/CH_2Cl_2 system to yield the miachel addition product **31** as a white solid (yield 63%), mp 216 – 218 °C, $[\alpha]_D^{25}$ = -30.0 (*c* 0.06, CH_3OH); IR (KBr) 3292 , 2957 , 1652 cm^{-1}; ^1H NMR (400MHz, DMSO-*d6*): δ 8.25 (d, *J* = 8.3 Hz, 1H), 8.12 (bs, 1H), 7.94 (bs, 1H), 7.29–7.08 (m, 9H), 5.89–5.79 (m, 1H), 5.16–5.06 (m, 2H), 4.61–4.56 (m, 1H), 4.27 (dd, $J_1 = J_2 =$ 8.0 Hz, 1H), 4.02-3.96 (m, 2H), 3.86–3.83 (m, 1H), 3.32–2.92 (m, 2H), 2.89 (d, *J* = 5.6 Hz, 2H), 2.66–2.62 (m, 1H), 2.49–2.21 (m, 1H), 1.62–1.58 (m, 2H), 1.39–1.19 (m, 2H), 0.85 (d, *J* = 6.7 Hz, 3H), 0.80 (d, *J* = 6.7 Hz, 3H) **(Spectrum 15)**; CIMS *m/z* calcd for $C_{28}H_{36}N_4O_3$ 476, found 477 (M+1).



28a

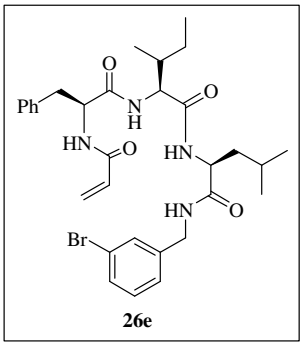
Compound 28a : Compound **28a** was prepared by following general procedure **2.4.6** as a white solid (yield 47%), mp 305-306 °C; $[\alpha]_D^{25}$ =

-103.0 (*c* 0.1, DMSO); IR (KBr) 3297, 2926, 1650 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*+$CDCl_3$): δ 8.45 (t, *J* = 5.9 Hz, 1H), 8.02 (d, *J* = 8.3 Hz, 1H), 7.82 (d, *J* = 8.6 Hz, 1H), 7.29-7.12 (m, 6H), 7.02-6.99 (m, 2H), 6.86 (s, 1H), 4.43-4.34 (m, 2H), 4.17 (q, *J* = 7.5 Hz, 1H), 4.00 (dd, J_1 = 5.4 Hz, J_2 = 15.3 Hz, 1H), 3.10-3.04 (m, 1H), 2.95-2.83 (m, 2H), 2.66-2.60 (m, 1H), 2.36-2.33 (m, 2H), 1.56-1.49 (m, 2H), 1.35 (spt, *J* = 7.7 Hz, 1H), 0.89 (d, *J* = 6.71 Hz, 3H), 0.86 (d, *J* = 6.71 Hz, 3H) **(Spectrum No. 16)**. ^{13}C NMR (50 MHz, DMSO-*d6*): δ 171.5, 171.3, 171.1, 141.8, 139.5, 137.4, 129.1, 128.8 (2C), 128.2 (2C), 127.7, 127.2, 126.4, 124.9, 124.2, 56.1, 52.1, 41.5, 36.7, 35.1, 29.1, 24.3, 22.5, 22.2 **(Spectrum No. 17)**. CIMS *m/z* calcd for $C_{25}H_{31}N_3O_3$ 421, found 422 (M+1).



28b

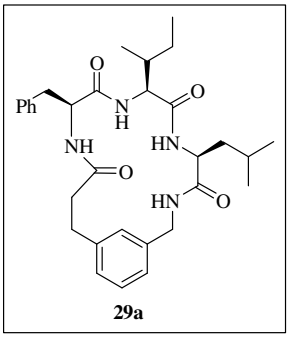
Compound 28b : Compound **28b** was prepared by following general procedure **2.4.6** (yield 59%), mp 287-288 °C; $[\alpha]_D^{25}$ = -113.0 (*c* 0.1 ,DMSO); IR (KBr) 3298, 2957, 1647 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.30 (t, *J* = 5.4 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.68 (d, *J* = 8.3 Hz, 1H), 7.14 (dd, J_1 = 7.5 Hz, J_2 = 14.8 Hz, 1H), 7.02 (d, *J* = 7.2 Hz, 2H), 6.89 (s, 1H), 4.46 (dd, J_1 = 7.0 Hz, J_2 = 15.6 Hz, 1H), 4.27-4.16 (m, 2H), 3.93 (dd, J_1 = 4.8 Hz, J_2 = 15.3 Hz, 1H), 3.16-3.09 (m, 1H), 2.68-2.62 (m, 1H), 2.46-2.35 (m, 2H), 1.61-1.39 (m, 3H), 1.16 (d, *J* = 6.7 Hz, 3H), 0.89 (d, *J* = 6.7 Hz, 3H), 0.83 (d, *J* = 6.7 Hz, 3H); CIMS *m/z* calcd for $C_{19}H_{27}N_3O_3$ 526, found 345 (M+1).



26e

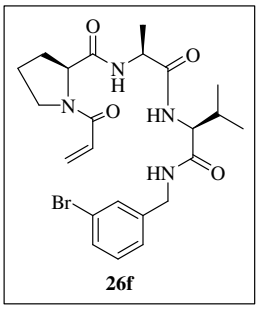
Compound 26e: Compound **26e** was prepared by following general procedure **2.4.4** as a white solid (yield 62%), mp 210-212 °C; $[\alpha]_D^{25}$ = -11.2 (*c* 0.25, DMSO); IR (KBr): 3281, 2959,

1737, 1633 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6* + $CDCl_3$): δ 8.48-8.38 (m, 1H), 8.30-8.23 (m, 1H), 8.13-7.97 (m, 2H), 7.42-7.37 (m, 2H), 7.27-7.14 (m, 7H), 6.30-6.21 (m, 1H), 6.05-5.98 (m, 1H), 5.57-5.52 (m, 1H), 4.76-.4.65 (m, 1H), 4.36-4.15 (m, 4H), 3.08-2.91 (m, 2H), 1.95-1.79 (m, 1H), 1.65-1.42 (m, 4H), 1.16-1.00 (m, 1H), 0.94-0.69 (m, 12H); CIMS *m/z* calcd for $C_{31}H_{41}BrN_4O_4$ 613, found 615 (M+2), 613 (M).



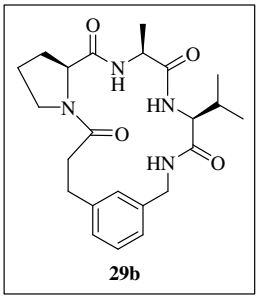
29a

Compound 29a : Compound **29a** was prepared by following general procedure **2.4.6** as a solid (yield 54%), mp 259-261 °C; $[\alpha]_D^{25}$ = -32.8 (*c* 0.25, DMSO); IR (KBr) 3290, 2928, 1639 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.53-8.44 (m, 1H), 8.07 (d, *J* = 8.3 Hz, 1H), 7.98 (d, *J* = 8.1 Hz, 1H), 7.75-7.73 (m, 1H), 7.29-6.98 (m, 9H), 4.71-3.66 (m, 7H), 2.97-2.49 (m, 3H), 2.38- 2.20 (m, 1H), 1.69-1.32 (m, 5H), 1.09-0.91 (m, 1H), 0.89-0.78 (m, 12H); CIMS *m/z* calcd for $C_{31}H_{42}N_4O_4$ 534, found 535 (M+1).



26f

Compound 26f: Compound **26f** was prepared by following general procedure **2.4.4** as a white solid (yield 55%)**,** mp 205 – 206 °C, $[\alpha]_D^{25}$ = -67.0, (*c* 0.5, $CHCl_3$); IR (KBr) 3282, 1269, 1690, 1636 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.51–8.40 (m, 1H), 8.13 (t, *J* = 7.0 Hz, 1H), 7.80–7.75 (m, 1H), 7.44 – 7.40 (m, 2H), 7.28–7.22 (m, 2H), 6.64–6.25 (m, 1H), 6.14–6.06 (m, 1H), 5.70–5.58 (m, 1H), 4.55–4.11 (m, 5H), 3.65–3.40 (m, 2H), 2.10–1.65 (m, 5H), 1.28–1.20 (m, 3H), 0.89–0.79 (m, 6H). CIMS *m/z* calcd for $C_{23}H_{31}BrN_4O_4$ 507, found 509 (M+2), 507 (M).



29b

Compound 29b: Compound **29b** was prepared by following general procedure **2.4.6** as a solid (yield 47%), mp 132-134 °C;

$[\alpha]_D^{25}$ = - 42.0 (*c* 0.1, DMSO); IR (KBr) 3308, 2964, 1650 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.58-8.53 (m, 1H), 8.33 (d, *J* = 7.5 Hz, 1H), 7.91 (d, *J* = 9.1 Hz, 1H), 7.35-7.00 (m, 4H), 4.70-4.59 (m, 1H), 4.39-3.63 (m, 4H), 3.43-3.32 (m, 2H), 2.81-2.66 (m, 1H), 2.63-2.54 (m, 2H), 2.35-2.29 (m, 1H), 2.15-1.58 (m, 4H), 1.33-1.23 (m, 3H), 0.99-0.79 (m, 7H); CIMS *m/z* calcd for $C_{23}H_{32}N_4O_4$ 428, found 429 (M+1).

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Chapter 3

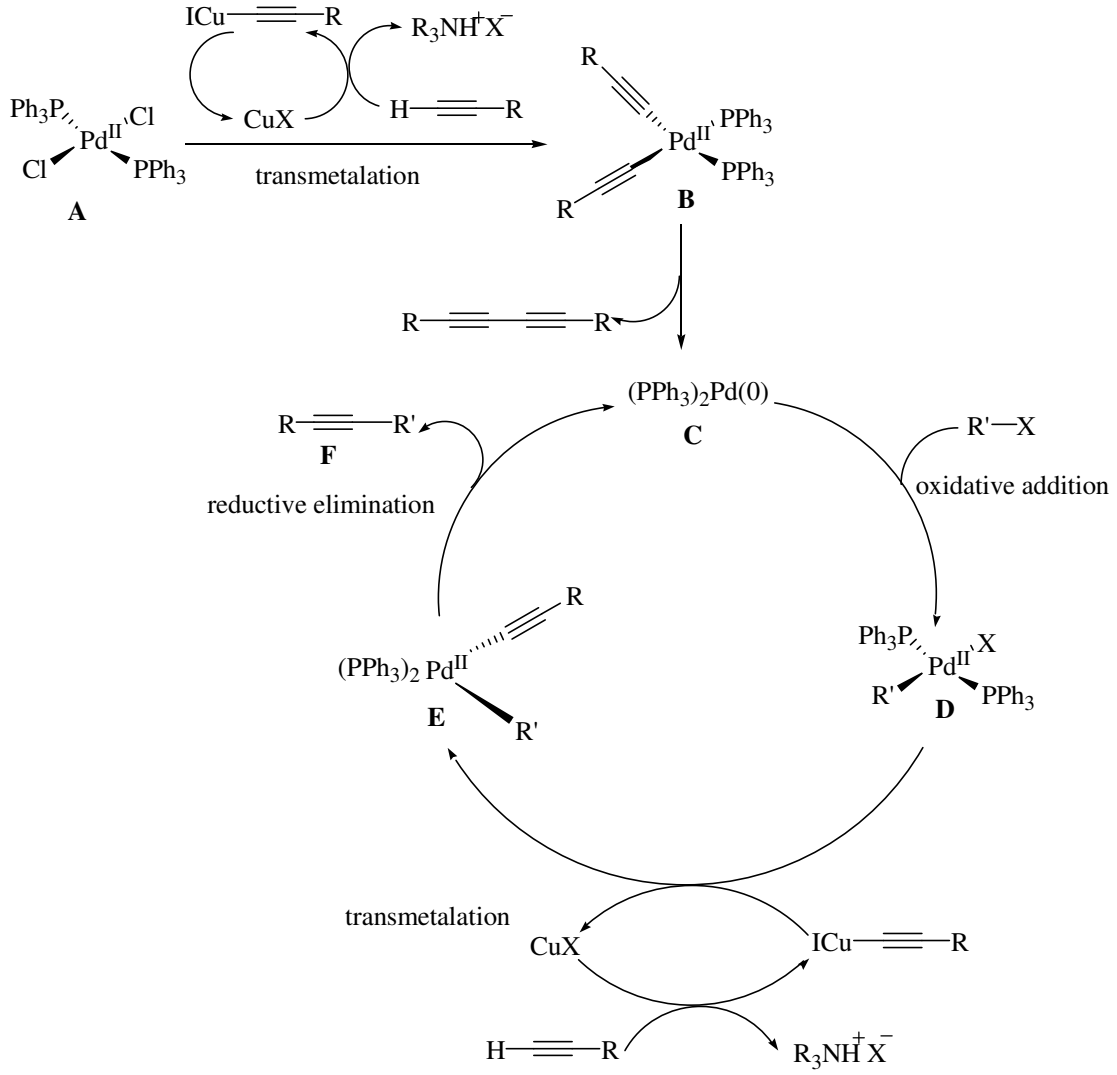
Synthesis of Small Cyclic Peptides Constrained with n(3-Aminomethylphenyl)alkynoic Acid Linkers using the Sonogashira Coupling Reaction

3.1 Introduction

Palladium-catalyzed coupling of terminal alkynes with vinyl or aryl halides was first reported independently and simultaneously by the groups of Cassar[1] and Heck[2] in 1975. A few months later, Sonogashira and co-workers demonstrated that, in many cases, this cross-coupling reaction could be accelerated by the addition of cocatalytic Cu(I) salts to the reaction mixture.[3,4] This protocol has become known as the Sonogashira reaction and can be viewed both as an alkyne version of the Heck reaction and an application of palladium catalysis to the venerable Stephens-Castro reaction. The coupling of vinyl or aryl halides with stoichiometric amounts of copper(I) acetylides is known as Stephens-Castro reaction.[5] The Sonogashira reaction provides a valuable method for the synthesis of conjugated acetylenic systems, which are used in a diverse array of important applications from natural products and pharmaceuticals to designed molecules of interest in biotechnology and nanotechnology. Interestingly, the utility of the "copper-free" Sonogashira protocol, i.e., the original Cassar-Heck version of this reaction, has subsequently been "rediscovered" independently by a number of other researchers in recent years.[6] In recognition of the valuable contribution of Sonogashira *et al*. the Pd^0/Cu^I-catalyzed coupling of sp-sp^2-hybridized carbon atoms is often referred to as the Sonogashira coupling reaction.

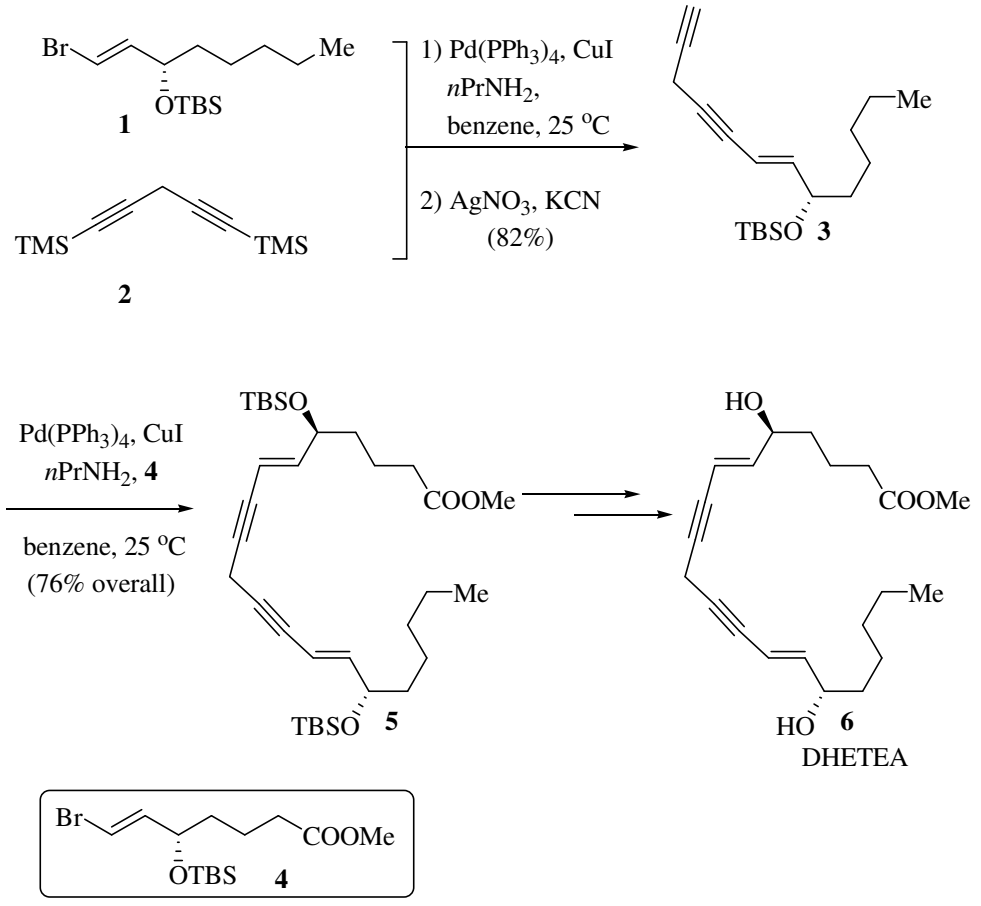
The presumed catalytic cycle for the Sonogashira coupling is shown in Scheme 1.[3,7] Bis(triphenylphosphine)palladium(0) (**C**), the putative active catalyst, could conceivably be formed in situ through sequential copper(I) iodide-catalyzed bis-alkynylation and reductive elimination reactions (see A→B→C, Scheme 1). Once

formed, the highly coordinative unsaturated 14-electron palladium(0) complex **C** participates in an oxidative addition reaction with the aryl or vinyl halide to give the 16-electron palladium(II) complex **D**. A copper(I) catalyzed alkynylation of **D** then furnishes an aryl or vinyl alkynyl palladium(II) complex **E**. Finally, a terminating reductive elimination step reveals the coupling product **F** and regenerates the active palladium(0) catalyst **C**.



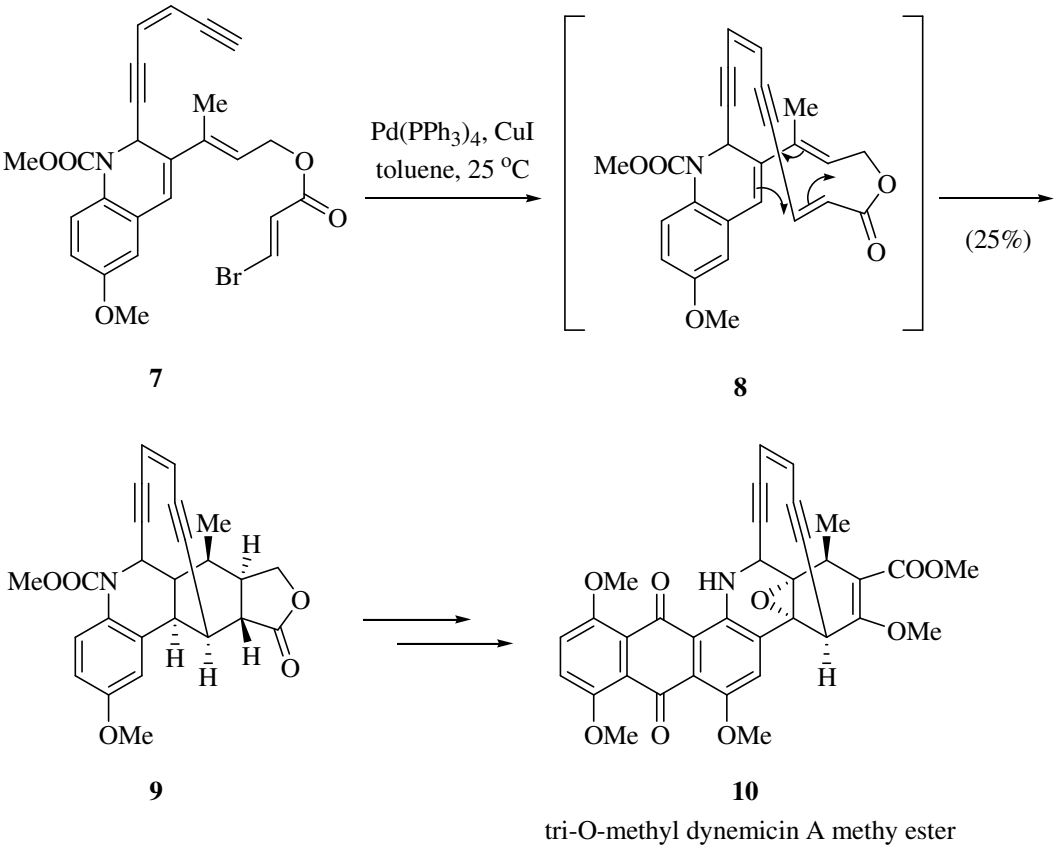
Scheme 1

An early application of the Sonogashira reaction in organic synthesis can be found in the generalized synthetic route to the biologically significant lipoxins and related eicosanoids pioneered by the Nicolaou group in the early 1980s. They have used Sonogashira coupling for the stereospecific synthesis of (5S,15S)-dihydroxy-6,13-trans-8,11-cis-eicosatetraenoic acid (DHETEA) **6**,[8] an important metabolite of arachidonic acid (Scheme 2).



Scheme 2

Schreiber and co-workers used intramolecular Sonogashira reaction in their captivating and highly inventive approach to the core molecular framework of dynemicin A. They have synthesized tri-o-methyl dynemicin A methyl ester **10** (Scheme 3).[9]

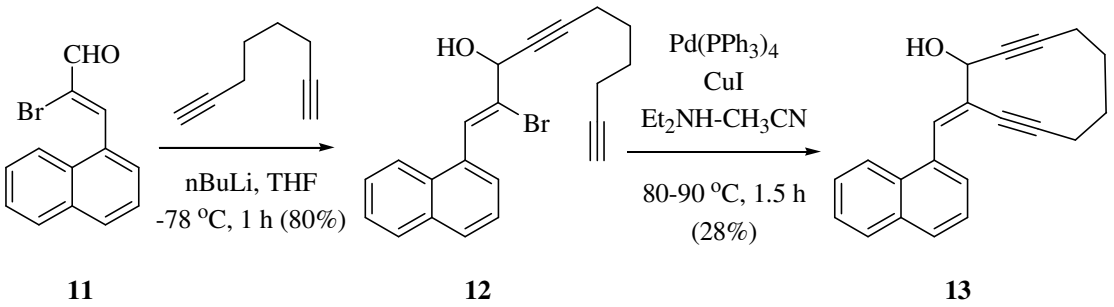


7 **8** **9** **10**

tri-O-methyl dynemicin A methy ester

Scheme 3

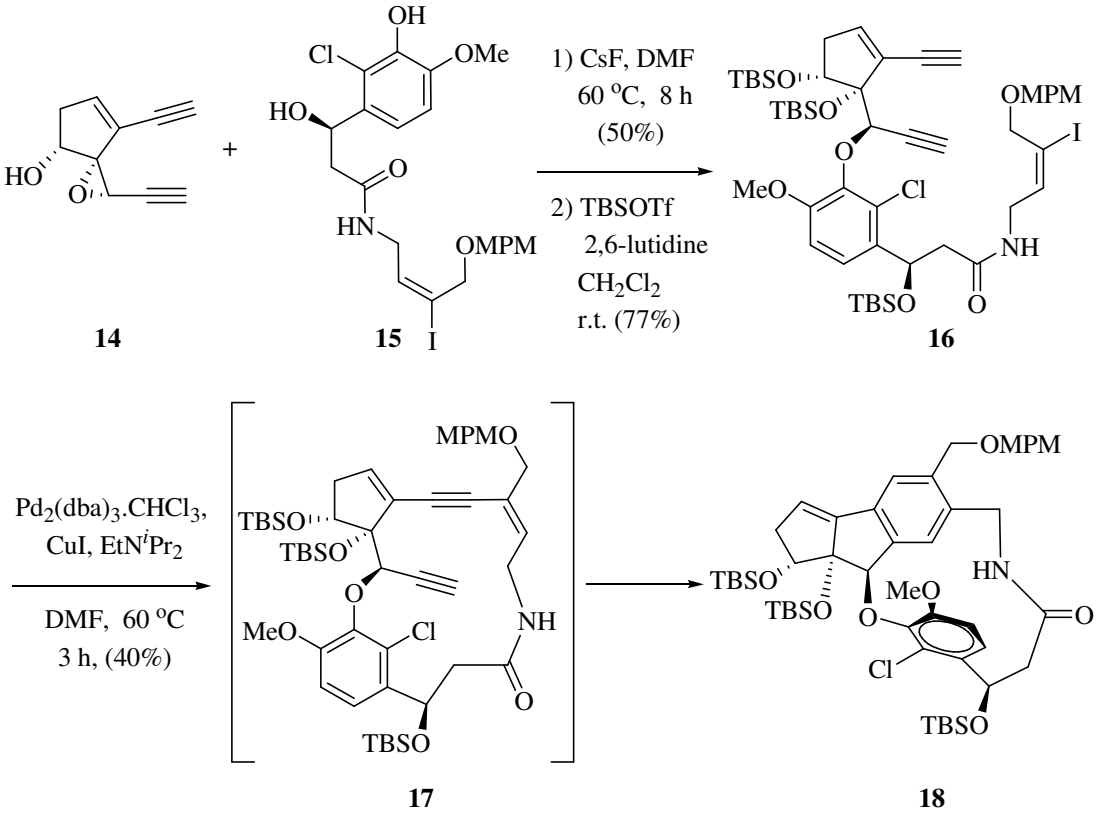
Dai and Wu have synthesized cyclodeca-1,5-diyne **13** skeleton via intramolecular Sonogashira coupling in mostly diethylamine or diethylamine-THF or acetonitrile solvent (Scheme 4).[10]



11 **12** **13**

Scheme 4

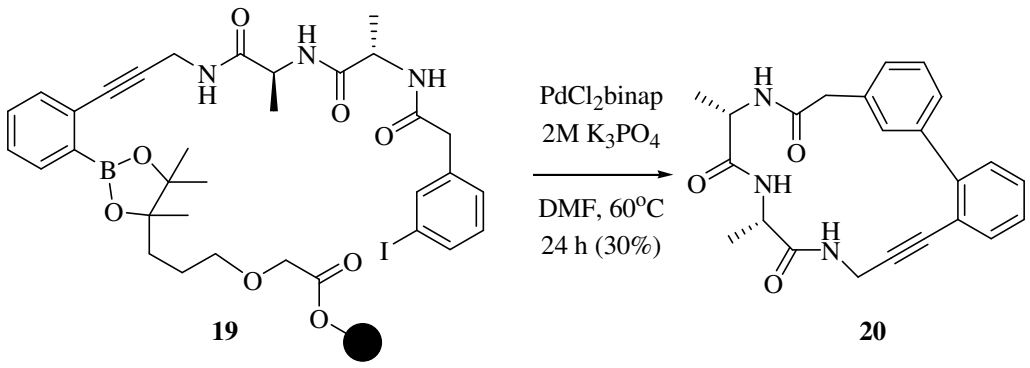
Recently, Hirama and co-workers have used an intramolecular Sonogashira coupling towards the synthesis of Maduropeptin chormophore **18**. Maduropeptin exhibits potent antibacterial and antitumor activities (Scheme 5).[11]



14 **15** **16** **17** **18**

Scheme 5

Burgess *et al*. synthesized biphenylalkyne-bridged cyclic peptides **20** as part of their work on solid-phase synthesis of β-turn analogues to mimic or disrupt protein-protein interactions (scheme 6).[12]

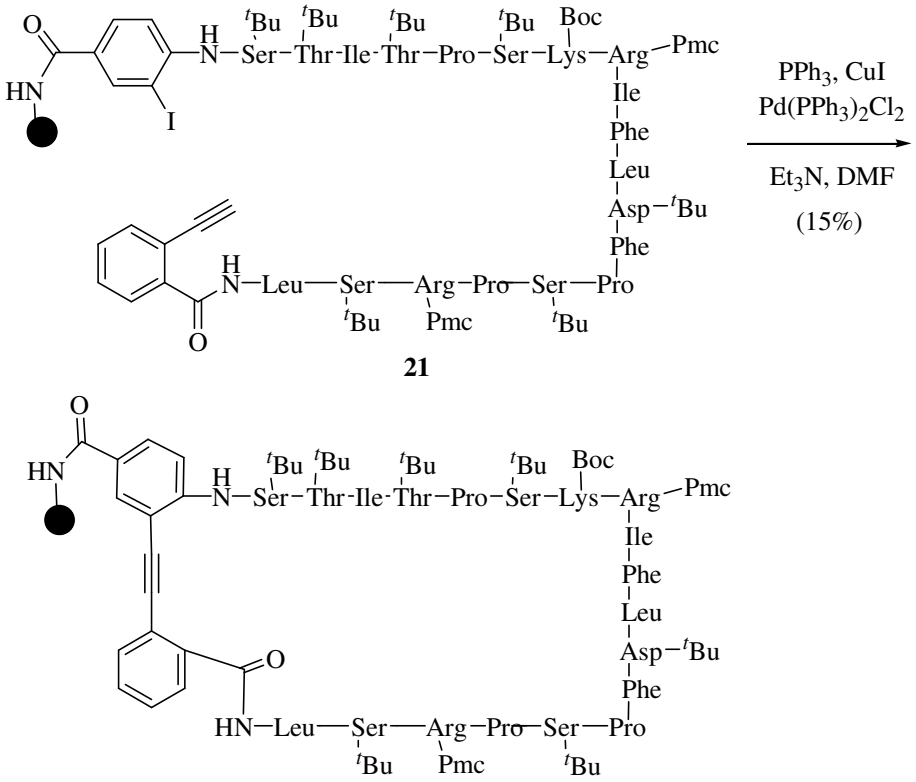


19 **20**

Scheme 6

Recently, Spivey and co-workers used an intramolecular Sonogashira coupling in the macrocylization step towards the solid-phase synthesis of an A-B loop mimetic of the Cε3 domain of human IgE, **22** (Scheme 7).[13]

In connection with our project on peptidomimetics,[14] we were interested in developing novel and efficient methods for macrocyclizations to furnish cyclic peptides with various linkers (or constraints). Conformationally restricted mimetics of peptide ligands often exhibit enhanced specificity, affinity, and oral activity against a given receptor.[15] Moreover, incorporation of covalent constraints into bioactive peptides is an important design consideration to reduce the unfavorable entropy loss upon receptor-binding.[16] In addition, covalent constraints also play a decisive role in controlling the three-dimensional structure of a molecule that is essential for biological activity. We



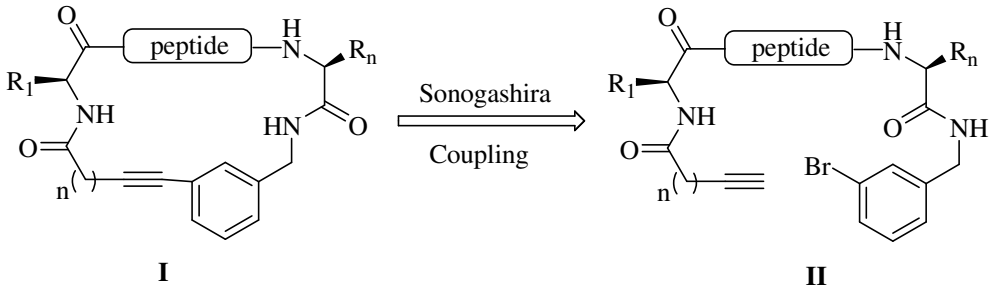
21

22

Scheme 7

envisaged the introduction of a rigid linker with an aryl alkynyl moiety in macrocycle **I** from the corresponding precursor **II** through sp-sp^2 bond formation using a Pd-catalyzed intramolecular Sonogashira coupling reaction (Figure 1). Additionally, the Sonogashira coupling reaction displays a broad functional group tolerance.[3,4,17-21] Since a triple bond can be selectively reduced to either the *E*- or *Z*-isomer,[22-24] the Sonogashira coupling reaction enables the stereocontrol of the newly formed cyclic system. Further, partial or complete reduction of the triple bond gradually releases the ring strain of the cyclic peptide. Such conformationally relaxed structures can be used to probe the conformation-bioactivity relationships.

This chapter describes the scope and limitations for the macrocyclization of di, tri and tetra peptide containing acyclic molecules to form the cyclic peptides under the Sonogashira coupling reaction conditions.



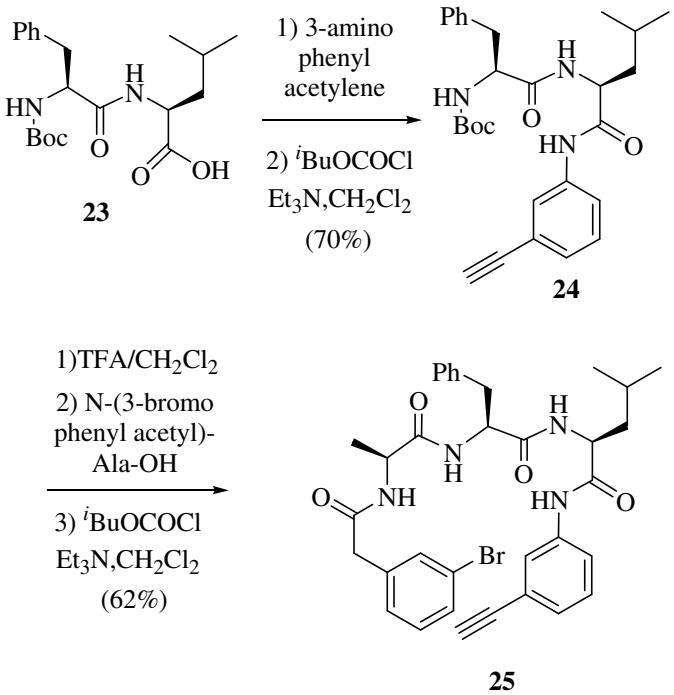
I **II**

Figure 1: The Sonogashira coupling

3.2 Results and Discussion

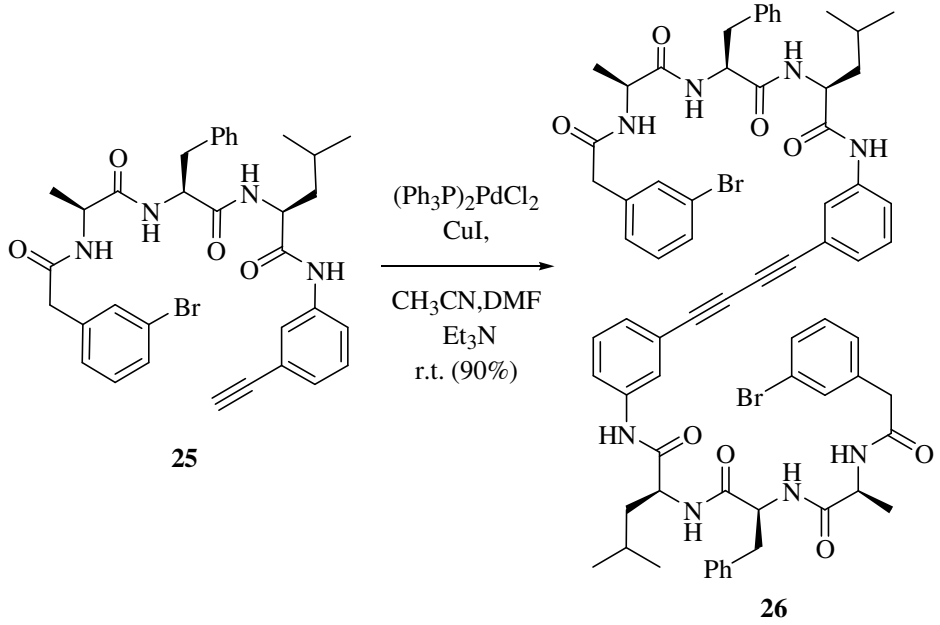
3.2.1 Synthesis of cyclic peptides constrained with diphenylacetylene

Initially, we were interested in the synthesis of cyclic peptides constrained with a diphenylacetylene linker (Spivey *et al.*[13] showed that diphenylacetylene moiety mimics the disulfide bridge of the Cε3 domain of Human IgE) using Sonogashira coupling reaction. The synthesis of precursor **25** for the intramolecular Sonogashira coupling reaction is summarized in Scheme 8. The N-Boc-Phe-Leu-OH **23** was reacted with 3-aminophenylacetylene to give compound **24** by standard solution-phase peptide coupling. The Boc deprotection on **24**, followed by coupling with N-(3-bromophenyl acetyl)-Ala-OH furnished the acyclic peptide **25** in 56% yield. The structure of **25** was confirmed by spectral data.



Scheme 8

The Sonogashira coupling of **25** was carried out at room temperature in CH_3CN/DMF solvent system with $(Ph_3P)_2PdCl_2$/CuI as the catalytic system in the presence of triethylamine.[25] Overnight stirring (15 h) formed a solid that was filtered off and washed with diethyl ether. The ^1H NMR spectrum of the solid showed the absence of acetylenic proton at δ 2.68 (s, 1H), and ESMS showed 1289 (M+1, 100%) as base peak and this data confirmed the formation of dimer **26** as the sole product as shown in Scheme 9. The formation of compound **26** can be explained by a Glaser-type oxidative dimerization of the alkyne which is one of the side reactions commonly encountered in Sonogashira reactions.[26]

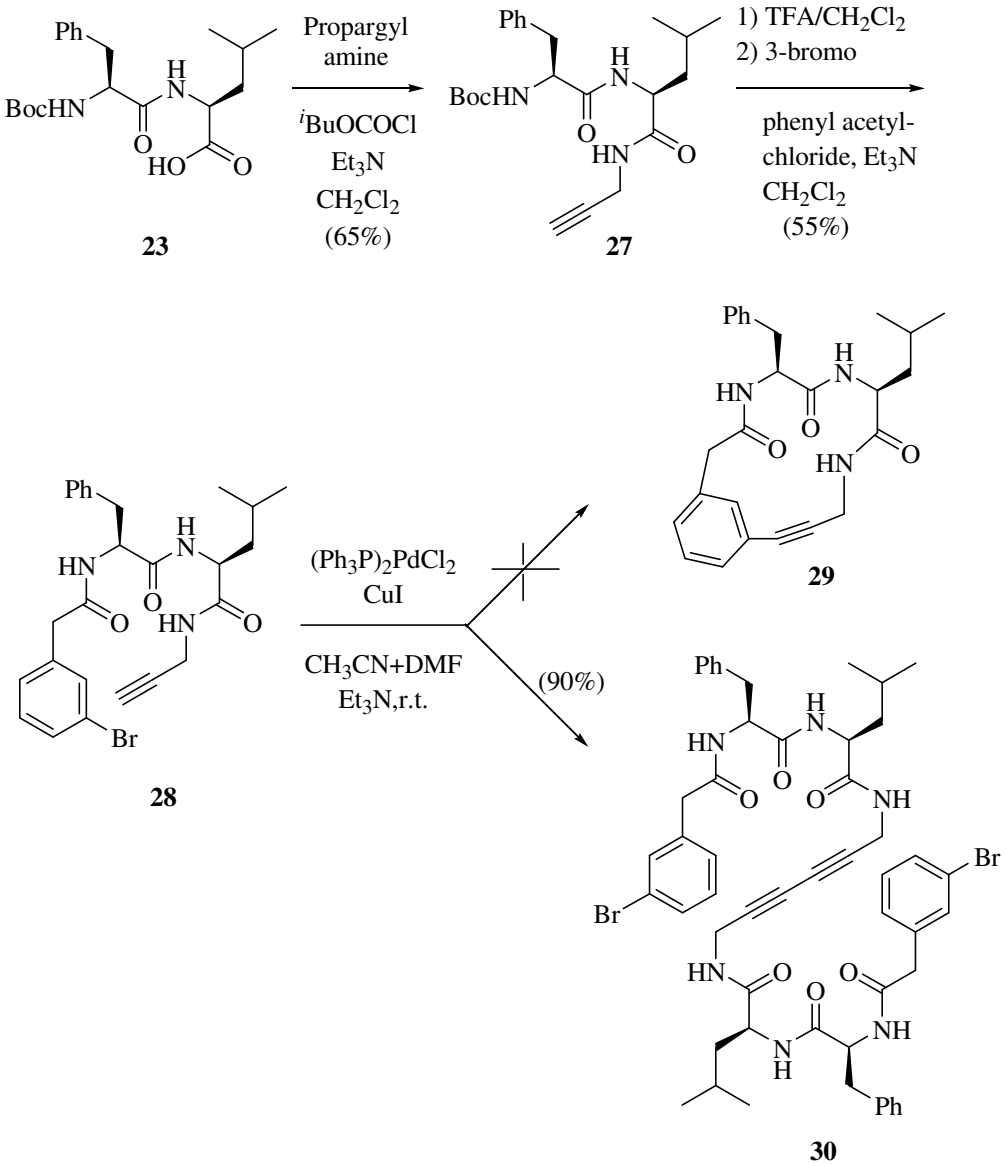


Scheme 9

We wanted to bring more flexibility in the molecule and therefore decided to design our next acyclic precursor accordingly.

3.2.2 Synthesis of cyclic peptides constrained with phenyl alkyne linkers

Rigid aromatic groups on both termini of the acyclic precursor could be responsible for the reactive ends not getting close enough for the macrocyclization. Therefore, we decided to replace one with a flexible group and start exploring with a dipeptide chain. We chose an alkyne without the phenyl at the *C*-terminus that would

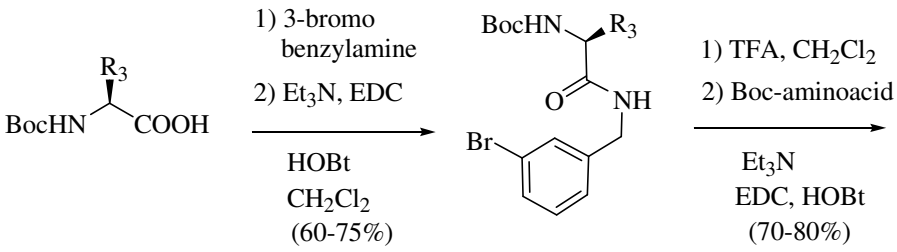


Scheme 10

generate phenyl-alkyne containing cyclic peptides similar to the Kevin Burgess's work.[13] We designed the acyclic precursor **28** having 3-bromophenyl acetyl on *N*-terminus and propargyl amine on *C*-terminus (Scheme 10). The N-Boc-Phe-Leu-OH **23** was treated with propargylamine using standard solution-phase peptide coupling to give compound **27**. Boc deprotection of **27**, followed by acylation with 3-bromophenyl acetyl chloride furnished the acyclic peptide **28** in 66% yield. We then turned our attention to the key Sonogashira reaction and accordingly, cyclization of **28** was performed with $(Ph_3P)_2PdCl_2$ /CuI, Et_3N in DMF/CH_3CN at room temperature and once again, dimer **30** formed exclusively.

3.2.3 Synthesis of (19-21)-membered cyclic peptides constrained with 3-aminophenyl alkynoic acid linkers

We wanted to incorporate enhanced flexibility in the design of our next acyclic precursor. A multi-pronged approach was chosen to execute this strategy. We increased the number of amino acids to three from two; increased flexibility and length around the propargyl end at the *N*-terminus and brought in additional flexibility around the bromo phenyl end at the *C*-terminus. Scheme 11 depicts the preparation of the acyclic precursors **35** starting from the corresponding N-Boc protected amino acids **31**. The N-Boc protected amino acids **31** were treated with 3-bromobenzylamine using standard solution phase peptide coupling protocol to furnish the corresponding amides **32**. Boc deprotection of **32**, followed by coupling with corresponding Boc-amino acids afforded compounds **33** in good yields. Compounds **33** on Boc deptrotection and coupling with aminoacids gave acyclic compound **34**, which on subsequent deprotection and coupling

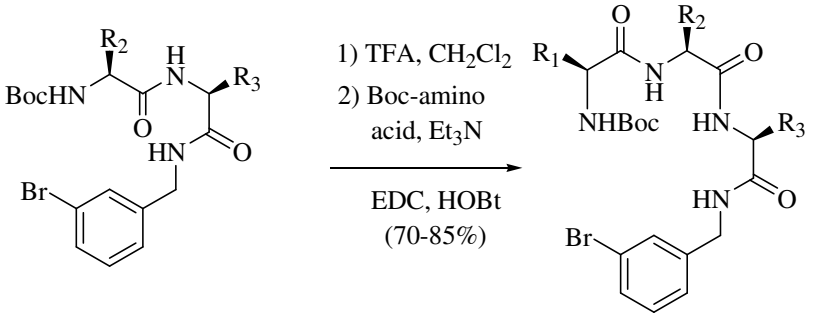


31

31a $R_3 = CH_3$
31b $R_3 = CH_2CH(CH_3)_2$

32

32a $R_3 = CH_3$
32b $R_3 = CH_2CH(CH_3)_2$

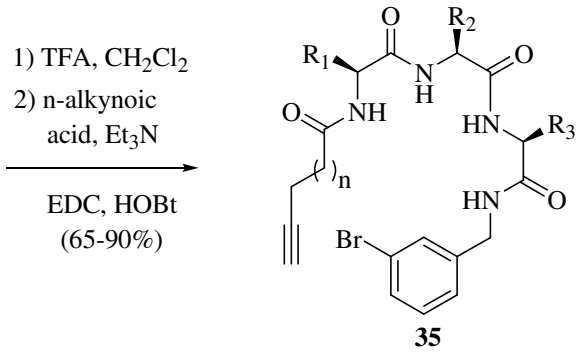


33

33a $R_2 = CH_2CH(CH_3)_2$, $R_3 = CH_3$
33b $R_2 = CH(CH_3)_2$, $R_3 = CH_3$
33c $R_2 = CH_2Ph$, $R_3 = CH_2CH(CH_3)_2$

34

34a $R_1 = CH_2Ph$, $R_2 = CH_2CH(CH_3)_2$
$R_3 = CH_3$
34b $R_1 = CH_2Ph$, $R_2 = CH(CH_3)_2$
$R_3 = CH_3$



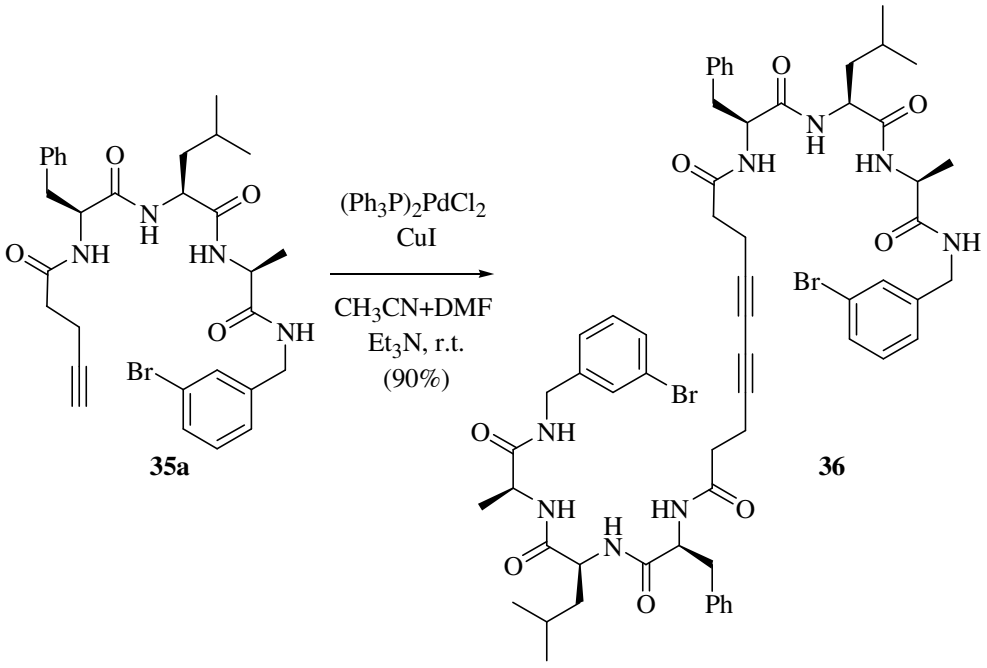
35

35a $R_1 = CH_2Ph$, $R_2 = CH_2CH(CH_3)_2$, $R_3 = CH_3$, n =1
35b $R_1 = CH_2Ph$, $R_2 = CH_2CH(CH_3)_2$, $R_3 = CH_3$, n =2
35c $R_1 = CH_2Ph$, $R_2 = CH_2CH(CH_3)_2$, $R_3 = CH_3$, n =3
35d $R_1 = CH_2Ph$, $R_2 = CH(CH_3)_2$, $R_3 = CH_3$, n = 3

Scheme 11

with respective n-alkynoic acids under standard solution phase peptide conditions gave the precursors **35** for the Sonogashira cyclization.

Compound **35a,** again disappointed us, when subjected to the copper co-catalyzed Sonogashira reaction resulting in the formation of dimer **36** as the sole product (Scheme 12).

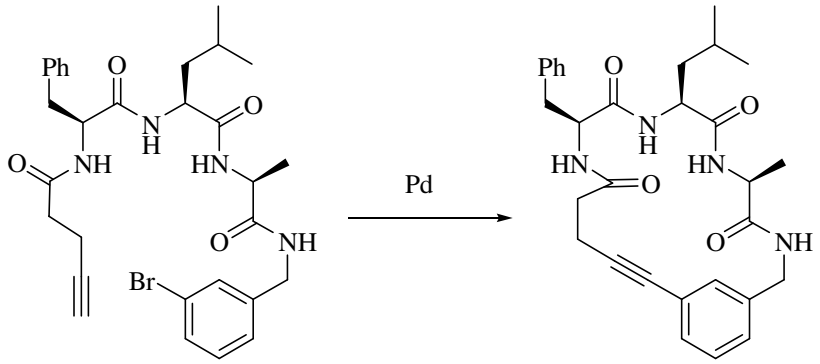


Scheme 12

We, then concentrated on the optimization of the Sonogashira reaction conditions. Careful examination of the published procedures reveals several difficulties that can affect the efficiency and practicability of the Sonogashira coupling: (i) The reactivity of the coupling of aryl bromides is often rather low, and therefore harsher conditions have to be used; alternatively, more reactive aryl iodides are employed that are more expensive and difficult to prepare. (ii) In some cases, acceptable yields are only obtained after

cumbersome purification of the reactants and with strict exclusion of oxygen,[27] diminishing the practical value of the method. (iii) Under the conditions of the Sonogashira coupling, the oxidative homocoupling (Glaser coupling) of the alkyne to the corresponding symmetrical diyne is also catalyzed if oxygen is not excluded completely. The Sonogashira reaction is generally cocatalyzed by Cu(I), and an amine as a base. An important side reaction encountered with the presence of a Cu(I) co-catalyst is the Glaser-type oxidative dimerization of the alkyne.[26] The formation of **36** can be explained by the Glaser-type oxidative dimerization of terminal alkyne moiety in **35a**.

To solve these problems, preliminary experiments were carried out in order to optimize the most efficient protocol for the intramolecular cyclization of peptides **35** to form cyclic peptides **37** (Figure 2) and conditions are summerized in Table 1.



35a **37a**

Figure 2: The Sonogashira reactions

When the Sonogashira reaction of **35a** was carried out at room temperature in neat dry Et_3N with $Pd(PPh_3)_4$ and CuI, no reaction occurred with recovery of starting material **35a** (entry 1). The same reaction at 80 ^oC gave black residue due to decomposition of **35a** (entry 2).[25b] The Sonogashira reaction in the presence of solvent

such as DMF with $(Ph_3P)_2PdCl_2$ /CuI, PPh_3, Et_3N[13] at room temperature gave an oxidative coupling byproduct in 90% yield, resulting from the dimerization of the terminal alkyne moiety in **35a** (entry 3). The same byproduct also formed when the reaction was carried out with *N*-ethyldiisopropylamine base at 60 ^oC (entry 4).[10] The cyclization of **35a** was also carried out in CH_3CN/EtN^iPr_2 solvent system with $Pd(PPh_3)_4$, CuI at 60 ^oC for 10 h, no reaction occurred with the lose of precursor (entry 5)[11]. Therefore, the standard reaction protocol for the Sonogashira coupling (Pd catalyst, cocatalyst Cu(I), base or solvent) failed for the cyclization of **35a**.

At this stage we realized that using CuI as co-catalyst could be the reason to form dimeric product. Generally, Cu salts mediate homocoupling of terminal alkynes when the copper acetylide is exposed to oxidative agents or air. The use of other cocatalysts such as zinc, tin, boron, aluminium, Ag_2O, and AgOTf have been developed to address this issue,[28] but additional steps are needed to make these reagents.

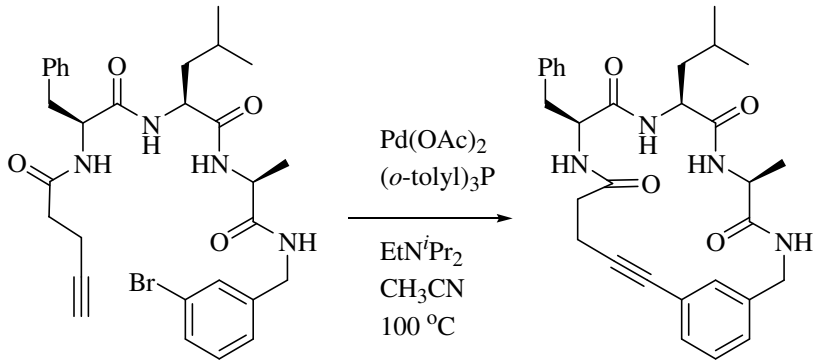
One of the complications with the Sonogashira coupling is that the reaction needs degassed solvents, and have to be carried out under an intert atmosphere. This is particularly inconvenient when the reactions are carried out in high dilution conditions that favor intramolecular reactions. Therefore, development of a conveneient copper-free Sonogashira coupling reaction seemed to be an important objective for the successful syntheses of cyclic peptide. Significant progress has been made in the Sonogashira reaction to give diminished homocoupling.[29] Many of the reactions were carried out without copper salts,[30] that provides the opportunity to develop the Sonogashira reaction under aerobic conditions, because the copper-mediated oxidative homocoupling of acetylene is prevented.

Table1. Optimization of the Sonogashira reaction[a] for macrocycliczation

Entry	Precursor	Conc, M	solvent	Base	Catalyst system And condition	Product (Yield)
1	**35a**	$1x10^{-2}$	Et_3N	Et_3N	$Pd(PPh_3)_4$, CuI r.t	--
2	**35a**	$1x10^{-2}$	Et_3N	Et_3N	$Pd(PPh_3)_4$, CuI 80 ^oC	Decom.
3	**35a**	$1.5x10^{-3}$	DMF	Et_3N	$(Ph_3P)_2PdCl_2$ CuI, PPh_3, r.t	Dimer **36**(90%)
4	**35a**	$1.5x10^{-2}$	DMF	EtN^iPr_2	$Pd(OAc)_2$,CuI, PPh_3, 60 ^oC	Dimer
5	**35a**	$1.5x10^{-3}$	CH_3CN	EtN^iPr_2	$Pd(PPh_3)_4$, CuI, 60 ^oC	--
6	**35a**	$1.5x10^{-3}$	CH_3CN	EtN^iPr_2	$Pd(OAc)_2$, CuI P(*o*-tolyl)$_3$, 100 ^oC	Trace
7	**35a**	$1.5x10^{-3}$	CH_3CN	EtN^iPr_2	$Pd(OAc)_2$ (*o*-tolyl)$_3$P, 100 ^oC	**37a** (12%)

a. Reaction time 15 h, 30 mol% $Pd(OAc)_2$ as catalyst, 60 mol % ligand, 2 equiv of base used.

To realize this goal, we screened a variety of coupling conditions and were pleased to find that the coupling reaction proceeded using $Pd(OAc)_2$, (*o*-tolyl)$_3$P, *N*-ethyldiisopropylamine in acetonitrile solvent in the macrocyclization of **35a** to form cyclic peptide **37a** (Scheme 13). We then studied the effect of various reaction parameters (palladium catalyst, base, ligand and temperature) on the macrocyclization of **35a**. We found out that among the catalysts tested [$Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, and $Pd(OAc)_2$], the $Pd(OAc)_2$ proved to be the most efficient. Among the bases used [triethylamine, pyridine, pyrrolidine and *N*-ethyldiisopropylamine], *N*-ethyldiisopropyl amine was the best choice. The tri(*o*-tolyl) phosphine turned out to be the choice among



35a **37a**

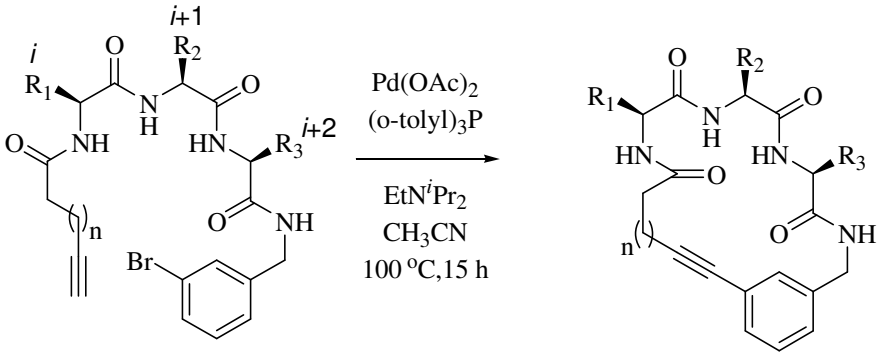
Scheme 13

the ligands tried [PPh_3, P(*o*-tolyl)$_3$ and BINAP]. From the range of temperatures evaluated [25, 60, 80, 100 ^oC], 100 ^oC gave the best result. Longer reaction times (15→30 h), increasing the amount of catalyst (30 → 50 mol%), running the reaction at a higher dilution (10^{-3} to 10^{-4}) were not successful for increasing the yields of this Sonogashira macrocyclization reaction. To summarize, the best results were obtained

when the reactions were carried out with 30 mol % $Pd(OAc)_2$, 60 mol % $(o\text{-tolyl})_3P$, N-ethyldiisopropylamine (3-5 equiv) in acetonitrile (~10^{-3}M) at 100 °C on overnight stirring (15 h) (entry 7 in Table 1).

The structure of **37a** was confirmed based on ^{1}HNMR which showed the absence of acetylenic proton at δ 2.68 (s, 1H) and 4-pentynoyl four protons are now diastereotopic protons coming separately at δ 2.80-2.70 (m, 1H), 2.68-2.60 (m, 1H), 2.40-2.33 (m, 1H), 2.22-2.14 (m, 1H), whereas in acyclic precursor **35a** all four protons showing multiplet at δ 2.25-2.19 (m, 4H), and ESMS m/z 517 (M+1, 100%) a base peak further confirms the structure of cyclic peptide **37a**.

To examine the scope of this copper-free Sonogashira coupling reaction, different acyclic precursors **35** were subjected to this macrocyclization reaction, and good results were obtained (Scheme 14). The copper-free Sonogashira coupling of **35a** gave macro-



35 **37**

35a n = 1, R_1 = -CH_2Ph, R_2 = -$CH_2CH(CH_3)_2$, R_3 = -CH_3 **37a** (12%)

35b n = 2, R_1 = -CH_2Ph, R_2 = -$CH_2CH(CH_3)_2$, R_3 = -CH_3 **37b** (23%)

35c n = 3, R_1 = -CH_2Ph, R_2 = -$CH_2CH(CH_3)_2$, R_3 = -CH_3 **37c** (35%)

35d n = 3, R_1 = -CH_2Ph, R_2 = -$CH(CH_3)_2$, R_3 = -CH_3 **37d** (36%)

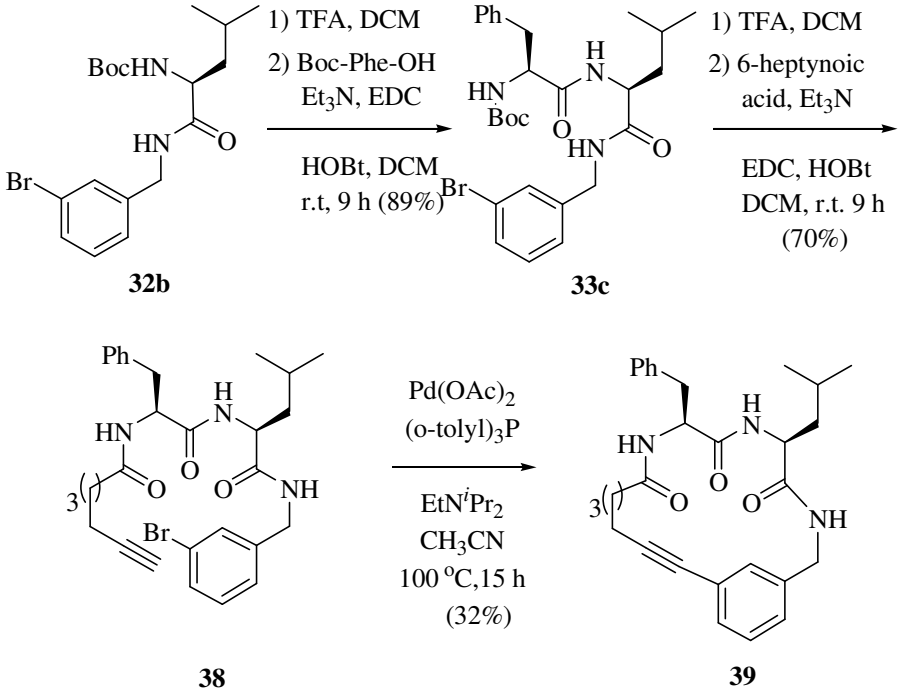
Scheme 14

cyclic peptide **37a** in 12% yield. It is noteworthy that the same coupling reaction was tried with copper cocatalyzed Sonogoshira reaction ($Pd(OAc)_2$, CuI, (o-tolyl)$_3$P, EtN^iPr_2), and only trace amounts of the desired product **37a** was obtained (entry 6 in Table 1).

We then focused our research to improve yields in the cyclization of peptides, and studied the scope of this copper-free intramolecular Sonogshira reaction in the synthesis of 20- and 21-membered macrocylic peptides. The acyclic precursors **35b** and **36c** underwent smooth cyclization to furnish the cyclic peptides **37b** in 23% yield and **37c** in 35% yield, respectively. The spectral data that confirm the structures of **37b** and **37c** are summarized in experimental section. It is interesting to observe that increasing the chain length between the alkyne and the amide bond resulted in a higher isolated yield of the cyclic peptide. Thus, the peptide **35c** having 6-heptynoic acid moiety on *N*-terminus afforded compound **37c** in better yields (35% isolated yield) than to the 12% isolated yield of the cyclic peptide **37a** from the macrocyclization of **35a** which is having 4-Pentynoic acid moiety on *N*-terminus. However, acyclic peptides **25** and **28** did not yield cyclic compounds under newly optimized Sonogashira reaction conditions. We further extended the scope of this reaction to other acyclic peptide precursors by varying the amino acids. The change at the *i* +1 amino acid residue from L-Leucine to L-Valine (**35d)** gave desired cyclization in 36% yield to furnish cyclic peptide **37d**. All the cyclic peptides were purified on silica gel column chromatography on 230-400 mesh silica gel using 2% methanol in dichloromethane solvent system (Scheme 14).

3.2.4 Synthesis of 18- & 24-membered cyclic peptides constrained with 3-amino phenyl alkynoic acid linkers

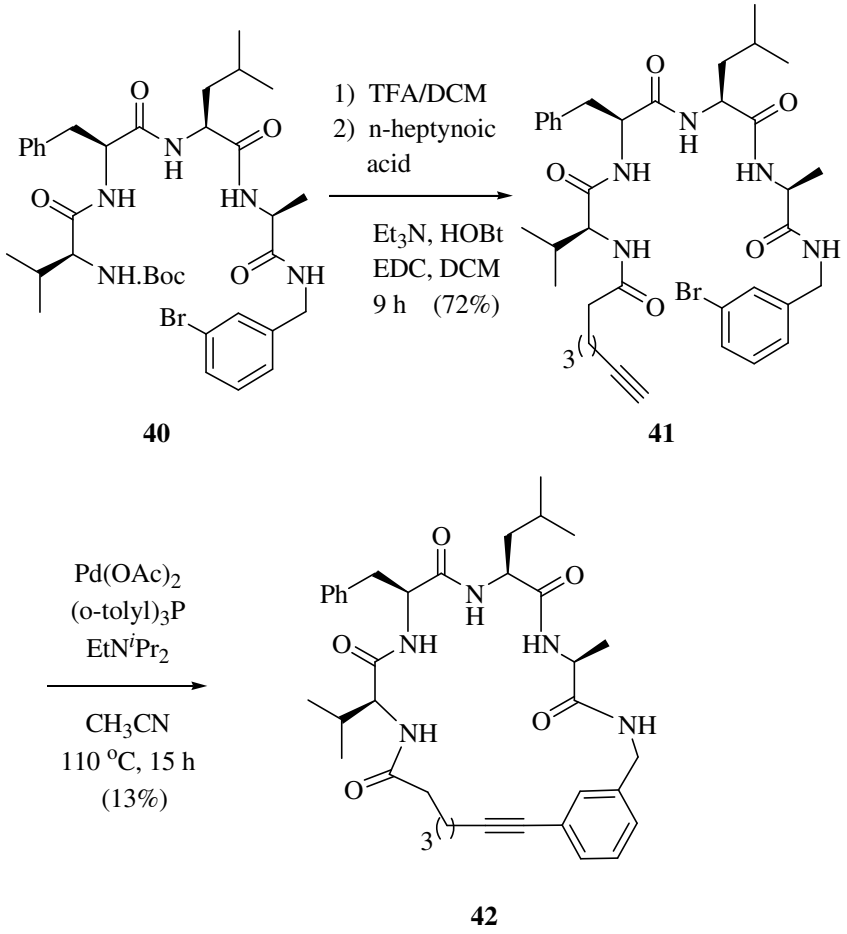
In an effort to further expand the scope of our copper-free Sonogashira reaction, we next investigated the macrocyclization of acyclic precursors of different sizes. Towards this study, the Boc deprotection of **32b** followed by coupling with N-Boc-Phe-OH gave compound **33c**. The Boc deprotection of **33c**, followed by coupling with readily available 6-heptynoic acid gave desired acyclic precursor **38** in 70% yield. This acyclic dipeptide **38** underwent smooth cylization via copper-free Sonogashira reaction to furnish 18-membered macrocyclic peptidomimetic **39** in 32% yield (Scheme 15).



32b **33c** **38** **39**

Scheme 15

However, the tetra-peptide derivative **41** gave the corresponding 24-membered macrocyclic peptide **42** in poor yield. The acyclic tetrapeptide derivative **41** was obtained from **40** (Scheme 16).



40 **41** **42**

Scheme 16

These preliminary studies indicated that the yields of the cyclization of the acyclic peptides precursors under the copper-free Sonogashira conditions are dependent upon both the number of amino acid residues and the chain length of the incorporated n-alkynoic acids.

3.3 Conclusions

We have demonstrated that copper-free Sonogashira coupling conditions can be used for the macrocyclization of di-, tri-, and tetra peptide containing molecules to produce cyclic peptides with phenyl acetylene linkers leading to useful peptidomimetics. Incorporation of a triple bond opens an avenue to a diversity of subsequent compounds accessible by, for example, click chemistry, selective reduction, oxidation, etc. We have showed the optimum length of the acyclic peptide precursor for the successful cyclization. We found that the reaction proceed when there is enough flexibility for the reactive ends to get close enough to react and the hard enough reaction conditions required to make the reaction go, especially, considering the inferior reactivity of aryl bromides. We also developed the Sonogashira coupling reaction conditions that work well under normal laboratory conditions and of course, dilution of the reaction medium also optimized for the successful cyclization. These cyclic peptides may prove to be useful in understanding the utility of constrained structures in the search for novel lead molecules in a particular therapeutic area.

3.4 Experimental Section

3.4.1 General procedure for peptide coupling.

(a) To a stirred solution of the TFA salt of C-protected peptide in CH_2Cl_2 (5 mL/mmol) at 0 ^oC (ice-bath) under N_2 was added successively Et_3N (5 equiv.), HOBt (1.2 equiv.), a solution of the Boc-protected amino acid (1 equiv.) in CH_2Cl_2 (2.5 mL/mmol), and EDC (1.2 equiv.). The mixture was allowed to warm to r.t., and stirring was continued for 15 h. The mixture was diluted with CH_2Cl_2 and washed with 10% aq. citric acid, aq. saturated $NaHCO_3$, H_2O and NaCl solution. The organic phase was dried (Na_2SO_4), evaporated, and the residue was purified using flash column chromatography to get the pure material.

(b) A stirred solution of TFA salt of C-protected peptide in CH_2Cl_2 (3 mL/mmol) and DMF (2 mL/mmol) at 0 ^oC (ice-bath) under N_2 was treated successively with Et_3N (5 equiv.), HOBt (1.2 equiv.), a solution of the Boc-protected amino acid (1 equiv.) in CH_2Cl_2 (2.5 mL/mmol), and EDC (1.2 equiv.). The mixture was allowed to warm to r.t., and stirring was continued for 15 h. The residue obtained after the removal of all volatiles was dried under vacuum for 1 h and then stirred in MeOH for 20 min. The white precipitate was collected by filtration and thoroughly washed successively with MeOH/H_2O 1:1 mixture and MeOH. The solid product was dried under high vacuum for several hours.

(c) Under anhydrous conditions, isobutychloroformate (1.1 equiv) was added to a solution of N-protected amino acid (1 equiv) and Et_3N (1.1 equiv) in CH_2Cl_2 (5 mL/mmol) at 0 ^oC and the mixture was stirred at this temperature for 10 min. A pre-

cooled solution of the methyl ester amino acid hydrochloride (1.1 equiv) and Et_3N (1.1 equiv) in CH_2Cl_2 (5 mL/mmol) was then added and the reaction mixture was allowed to warm to rt and stirred overnight. The reaction mixture was then poured into CH_2Cl_2 (100 ml/1 g substrate). The organic solution was washed with NH_4Cl (aq), $NaHCO_3$ (aq), water, and then brine, dried over Na_2SO_4. The crude compound obtained after the removal of solvent was purified by column chromatography to give the desired coupled peptide.

3.4.2 General procedure for Boc deprotection

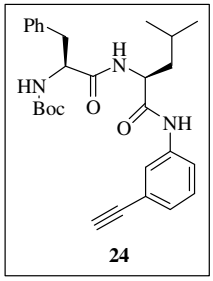
CF_3COOH (1.5 mL/mmol) was added to an ice-cold solution of the Boc-protected peptide in CH_2Cl_2 (5 mL/mmol). The reaction mixture was allowed to warm to r.t. and stirring was continued for 2 h. The mixture was evaporated and the residue dried under high vaccum. The salts with CF_3COOH were used without further purification and characterization.

3.4.3 General Procedure for macrocyclization

30 mol% $Pd(OAc)_2$, 60 mol% $(o\text{-tolyl})_3P$ were added to warm HPLC grade acetonitrile ($1.5x10^{-3}$M) and solution refluxed at 110 ^oC for 30 min. Then acylic peptide was added in single portion and the reaction continued for 15 min at the same temperature. Finally N-ethyldiisopropylamine (5equiv.) was added. After15 h., the reaction mixture was filtered through a pad of Celite and washed with hot acetonitrile (100 ml). The filtrate was concentrated and the product was isolated by flash column chromatography on (230-400) silica gel using CH_2Cl_2/MeOH as eluent.

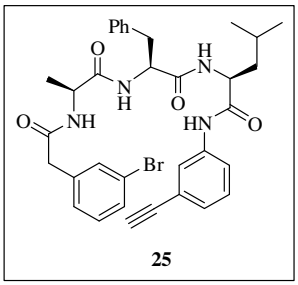
3.4.4 General Procedure for Copper co-catalyzed Sonogashira reaction

30 mol% $(Ph_3P)_2PdCl_2$, 40 mol% CuI were added to warm dry solvent (1.5×10^{-3} M). Then acylic peptide was added in single portion and finally base (5equiv.) was added. Reaction performed at ambient temperatures. After15 h, the reaction mixture was worked up and further purified by flash column chromatography on (230-400) silica gel using CH_2Cl_2/MeOH as eluent.



24

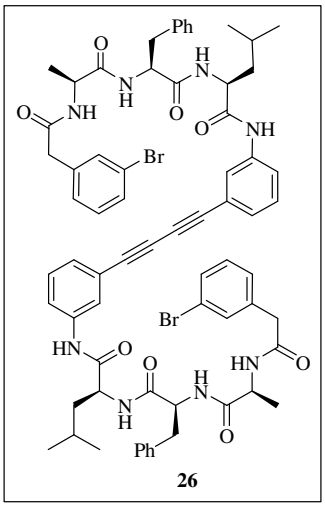
Compound 24: Compound was prepared by following procedure **3.4.1c** (yield 70%), mp 148-150 ^oC; $[\alpha]_D^{25}$ = -27.8 *(c* 0.5, $CHCl_3$); IR (KBr), 3295, 3065, 2959, 1688, 1645, 1548 cm^{-1}; ^1H NMR (400MHz, DMSO-*d6*): δ 8.49 (s, 1H), 7.69 (d, *J* = 7.4 Hz, 1H), 7.26-7.16 (m, 9H), 6.29 (d, *J* = 8.0 Hz, 1H), 4.94 (bs, 1H), 4.56-4.51 (m, 1H), 3.13 (dd, J_1 = 6.6 Hz, J_2 = 14.1 Hz, 1H), 3.05 (dd, J_1 = 7.1 Hz, J_2 = 15.8 Hz, 1H), 3.04 (s, 1H), 1.84-1.80 (m, 1H), 1.61-1.47 (m, 2H), 1.39 (s, 9H), 0.91 (d, *J* = 4.4 Hz, 6H); CIMS *m/z* calcd for $C_{28}H_{35}N_3O_4$ 477, found 478 (M+1).



25

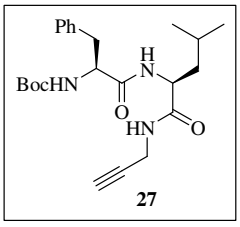
Compound 25: Compound was synthesized by following general procedure **3.4.1c** (yield 62%), mp 135-137 ^oC; $[\alpha]_D^{25}$ = -31.0 *(c* 0.5, DMSO); IR (KBr), 3283, 3084, 2957, 1636, 1542 cm^{-1}; ^1H NMR (400MHz, DMSO-*d6*): δ 9.99 (s, 1H), 8.27 (d, *J* = 7.3 Hz, 1H), 8.07 (d, *J* = 7.8 Hz, 1H), 7.99 (d, *J* = 8.0 Hz, 1H), 7.80 (s, 1H), 7.57 (d, *J* = 8.3 Hz, 1H), 7.56 (s, 1H), 7.45-7.39 (m, 1H), 7.33 (t, *J* = 7.8 Hz, 1H), 7.26-7.18 (m, 8H), 4.52-4.49 (m, 1H), 4.48-4.40 (m, 1H), 4.24 (quint, *J* = 7.1 Hz, 1H), 4.16 (s, 1H), 3.44 (q, *J* = 14.4 Hz, 2H), 3.03 (dd, J_1 = 4.9 Hz, J_2 = 13.9 Hz,

1H), 2.82 (dd, J_1 = 8.8 Hz, J_2 = 13.9 Hz, 1H), 1.61-1.50 (m, 3H), 1.15 (d, J = 6.8 Hz, 3H), 0.90 (d, J = 6.3 Hz, 3H), 0.87 (d, J = 6.3 Hz, 3H); ESMS *m/z* calcd for $C_{34}H_{37}BrN_4O_4$ 645, found 647 (M+2), 645 (M).



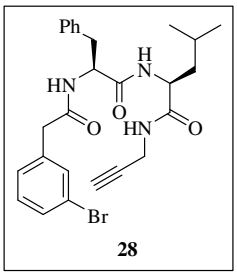
26

Compound 26: Compound was prepared as a solid by following general procedure **3.4.4** in the reaction solid formed that was filtered dried (yield 90%), mp 235-237 ^oC; $[\alpha]_D^{25}$ = -23.0 *(c* 0.5, DMSO); IR (KBr), 3265, 3064, 2956, 1640, 1538 cm^{-1}; ^1H NMR (400MHz, DMSO-*d6*): δ 10.07 (s, 2H), 8.28 (d, J = 7.2 Hz, 2H), 8.10 (d, J = 8.9 Hz, 2H), 8.00 (d, J = 7.8 Hz, 2H), 7.91 (s, 2H), 7.64 (d, J = 8.1 Hz, 2H), 7.55-7.13 (m, 22H), 4.51 (q, J = 8.1 Hz, 2H), 4.42 (q, J = 8.1 Hz, 2H), 4.22 (quint, J = 7.0 Hz, 2H), 3.45 (q, J = 14.2 Hz, 4H), 3.03 (dd, J_1 = 4.8 Hz, J_2 = 14.0 Hz, 2H), 2.83 (dd, J_1 = 8.9 Hz, J_2 = 13.7 Hz, 2H), 1.62-1.52 (m, 6H), 1.15 (d, J = 7.0 Hz, 6H), 0.91 (d, J = 6.2 Hz, 6H), 0.87 (d, J = 6.2 Hz, 6H). ESMS *m/z* calcd for $C_{68}H_{72}Br_2N_8O_8$ 1288, found 1306 ($M+NH_4$), 1289 (M+1).



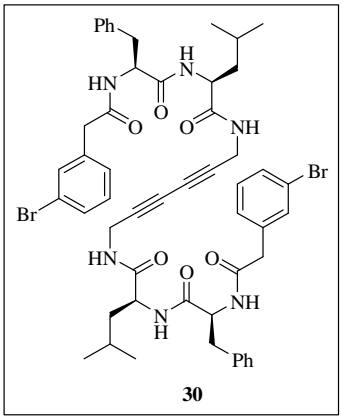
27

Compound 27: Compound was prepared by following general procedure **3.4.1c** (yield 65%), mp 138-140 ^oC; $[\alpha]_D^{25}$ = -20.8 *(c* 0.5, $CHCl_3$); IR (KBr), 3296, 2960, 1694, 1642, 1527 cm^{-1}; ^1H NMR (400MHz, DMSO-*d6*): δ 7.33-7.21 (m, 5H), 6.59 (t, J = 5.1 Hz, 1H), 6.32 (d, J = 8.3 Hz, 1H), 5.02 (d, J = 6.7 Hz, 1H), 4.47-4.31 (m, 2H), 3.99-3.89 (m, 2H), 3.11-3.01 (m, 2H), 2.19-2.16 (m, 1H), 1.71-1.67 (m, 1H), 1.58-1.44 (m, 2H), 1.42 (s, 9H), 0.94-0.89 (m, 6H); CIMS *m/z* calcd for $C_{23}H_{33}N_3O_4$ 415, found 416 (M+1).



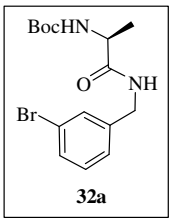
28

Compound 28: Compound was prepared as 3-bromophenyl acetyl chloride (1.2 equiv.) was added to the Boc deprotected dipeptide derivative in presence of triethyl amine base (5 equiv.) in dichloromethane at room temperature. Reaction mixture stirred at room temperature for 15 h. Reaction mixture concentrated under reduced pressure and purified by column chromatography (yield 55%), mp 164-166 ^{o}C; $[\alpha]_D^{25}$ = -2.2 *(c* 0.5, DMSO); IR (KBr), 3279, 3065, 2926, 1635, 1542 cm^{-1}; ^{1}H NMR (400MHz, DMSO-*d6*): δ 8.33-8.23 (m, 2H), 8.04 (d, *J* = 8.3 Hz, 1H), 7.39-7.34 (m, 2H), 7.24-7.07 (m, 7H), 4.57-4.51 (m, 1H), 4.31-4.26 (m, 1H), 3.85-3.78 (m, 2H), 3.48-3.37 (m, 2H), 3.09 (t, *J* = 2.4 Hz, 1H), 3.01 (dd, J_1 = 4.3 Hz, J_2 = 13.7 Hz, 1H), 2.74 (dd, J_1 = 9.6 Hz, J_2 = 13.7 Hz, 1H), 1.56-1.34 (m, 3H), 0.85 (d, *J* = 6.4 Hz, 3H), 0.81 (d, *J* = 6.4 Hz, 3H); CIMS *m/z* calcd for $C_{26}H_{30}BrN_3O_3$ 512, found 514 (M+2), 512 (M).



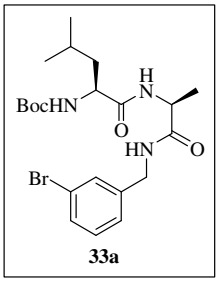
30

Compound 30: Compound was prepared as a solid by following general procedure **3.4.4** in the reaction solid formed that was filtered dried (yield 90%), mp 264-266 ^{o}C; $[\alpha]_D^{25}$ = -5.0 *(c* 0.1, DMSO); IR (KBr), 3278, 3063, 2955, 1639, 1539 cm^{-1}; ^{1}H NMR (400MHz, DMSO-*d6*): δ 8.38-8.24 (m, 4H), 8.07 (d, *J* = 8.3 Hz, 2H), 7.38-7.34 (m, 4H), 7.24-7.07 (m, 14H), 4.57-4.51 (m, 2H), 4.30-4.24 (m, 2H), 3.96 (d, *J* = 5.2 Hz, 4H), 3.39 (d, *J* = 6.7 Hz, 4H), 3.01 (dd, J_1 = 4.5 Hz, J_2 = 14.0 Hz, 2H), 2.74 (dd, J_1 = 9.9 Hz, J_2 = 14.0 Hz, 2H), 1.54-1.39 (m, 6H), 0.85 (d, *J* = 6.4 Hz, 6H), 0.80 (d, *J* = 6.4 Hz, 6H); ESMS *m/z* calcd for $C_{52}H_{58}Br_2N_6O_6$ 1022, found 1045 (M+Na).



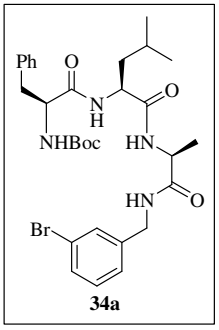
32a

Compound 32a: Compound was prepared by following general procedure **3.4.1a** (yield 87%), mp 85-87 °C; $[\alpha]_D^{25}$ = -21.80 *(c* 1.0, $CHCl_3$); IR (KBr) 3309, 2978, 2931, 1658, 1525, 1367 cm^{-1}; ^1H NMR (400MHz, DMSO-*d6*): δ 7.42-7.36 (m, 2H), 7.20-7.15 (m, 2H), 6.68 (bs, 1H), 4.97 (bs, 1H), 4.40-4.36 (m, 2H), 4.18 (t, *J* = 6.7 Hz, 1H), 1.42 (s, 9H), 1.38 (d, *J* = 4.0 Hz, 3H); ESMS *m/z* calcd for $C_{15}H_{21}BrN_2O_3$ 357, found 359 (M+2), 357 (M)



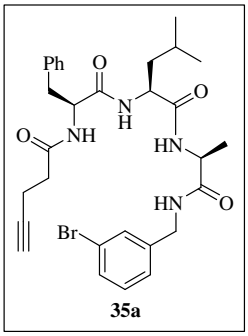
33a

Compound 33a: Compound was prepared by following general procedure **3.4.1a** (yield 80%), mp 143-144 °C; $[\alpha]_D^{25}$ = -20.80 *(c* 0.5, MeOH); IR (KBr) 3348, 3298, 2959, 2869, 1686, 1648, 1519 cm^{-1}; ^1H NMR (400MHz, DMSO-*d6*): δ 8.38 (t, *J* = 5.6 Hz, 1H), 7.86 (d, *J* = 7.5 Hz, 1H), 7.43-7.41 (m, 2H), 7.29-7.22 (m, 2H), 6.90 (d, *J* = 8.1 Hz, 1H), 4.32-4.26 (m, 3H), 3.93 (q, *J* = 6.7 Hz, 1H), 1.62-1.58 (m, 1H), 1.43-1.39 (m, 2H), 1.36 (s, 9H), 1.23 (d, *J* = 7.0 Hz, 3H), 0.86 (dd, J_1 = 6.6 Hz, J_2 = 13.4 Hz, 6H); ESMS *m/z* calcd for $C_{21}H_{32}BrN_3O_4$ 470, found 472 (M+2), 470 (M).



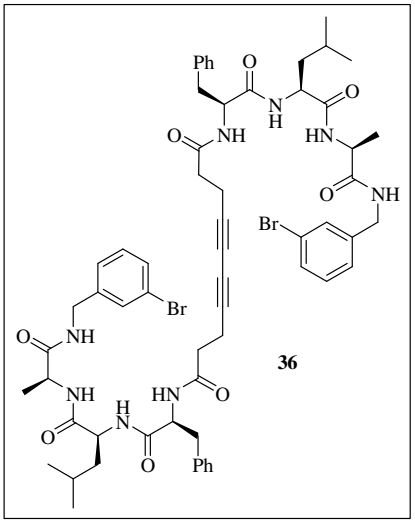
34a

Compound 34a: Compound was prepared by following general procedure **3.4.1a** (yield 86%), mp 214-215 °C; $[\alpha]_D^{25}$ = -7.0 *(c* 0.5, DMSO); IR (KBr), 3286, 3064, 2956, 1692, 1638, 1541 cm^{-1}; ^1H NMR (400MHz, DMSO-*d6*): δ 8.39-8.32 (m, 1H), 8.06 (d, *J* = 7.0 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.45-7.41 (m, 2H), 7.36-7.15 (m, 7H), 6.91 (d, *J* = 8.6 Hz, 1H), 4.38-4.14 (m, 5H), 2.98 (dd, J_1 = 3.8 Hz, J_2 = 13.7 Hz, 1H), 2.72 (dd, J_1 = 10.5 Hz, J_2 = 13.7 Hz, 1H), 1.68-1.58 (m, 1H), 1.52-1.45 (m, 2H), 1.30 (s, 9H), 1.23 (d, *J* = 4.0 Hz, 3H), 1.47 (dd, J_1 = 6.7 Hz, J_2 = 12.4 Hz, 6H); ESMS *m/z* calcd for $C_{30}H_{41}BrN_4O_5$ 617, found 619 (M+2), 617 (M).



35a

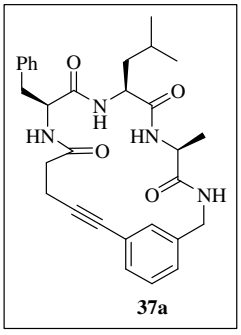
Compound 35a: Compound was prepared by following general procedure **3.4.1a** (yield 76%), mp 269-270 ^{o}C; $[\alpha]_D^{25}$ = -11.3 *(c* 1, DMSO); IR (KBr), 3289, 3068, 2925, 1635, 1546 cm^{-1}; ^{1}H NMR (400MHz, DMSO-*d6*): δ 8.33 (t, *J* = 5.6 Hz, 1H), 8.08 (d, *J* = 8.1 Hz, 1H), 7.99 (dd, J_1 = 8.1 Hz, J_2 = 13.2 Hz, 2H), 7.43-7.41 (m, 2H), 7.28-7.14 (m, 7H), 4.55-4.49 (m, 1H), 4.33-4.22 (m, 4H), 3.02 (dd, J_1 = 4.3 Hz, J_2 = 14.0 Hz, 1H), 2.74 (dd, J_1 = 9.7 Hz, J_2 = 14.0 Hz, 1H), 2.68 (s, 1H), 2.25-2.19 (m, 4H), 1.58 (sept, *J* = 6.7 Hz, 1H), 1.47 (dd, J_1 = 7.0 Hz, J_2 = 13.7 Hz, 2H), 1.24 (d, *J* = 6.7 Hz, 3H), 0.87 (d, *J* = 6.4 Hz, 3H), 0.83 (d, *J* = 6.5 Hz, 3H) **(Spectrum No. 18)**; ^{13}C NMR (100MHz, DMSO-*d6*): δ 172.1, 171.5, 171.1, 170.2, 142.2, 137.8, 130.3, 129.7, 129.5, 129.1(2C), 127.9(2C), 126.1, 125.9, 121.5, 83.5, 71.1, 53.7, 50.9, 48.3, 41.3, 40.6, 37.3, 34.0, 24.0, 23.0, 21.6, 18.0, 14.0 **(Spectrum No. 19)**; ESMS *m/z* 599 (M+2), 597 (M); HRMS calcd for $C_{30}H_{38}N_4O_4Br$ 597.2076, found 597.2058.



36

Compound 36: To a solution of HPLC acetonitrile(500 mL) and HPLC dimethyformamide (50mL) were added successively, compound 5a(200 mg, 0.33mmol), $(Ph_3P)_2PdCl_2$ (23.5 mg, 10 mol%), CuI (13 mg, 20 mol%), Et_3N (350 µL, 1.65 mmol). The reaction continued under nitrogen atmosphere for 15 h at room temperature. Solid was separated in the reaction mixture, filtered, washed with water and diethylether and dried for 6 h under high vaccum (yield 90%), mp 254-256 ^{o}C (turns

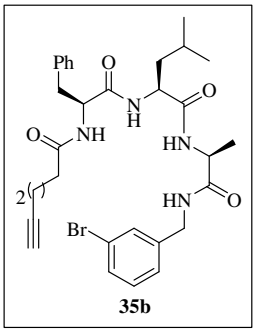
black); $[\alpha]_D^{25}$ = -14.00 *(c* 0.5, DMSO); IR (KBr), 3285, 3065, 2955, 1637, 1544 cm^{-1}; ^1H NMR (400MHz, DMSO-*d6*): δ 8.34 (bs, 2H), 8.10 (d, *J* = 8.3 Hz, 2H), 8.05 (d, *J* = 7.8 Hz, 2H), 7.96 (d, *J* = 7.0 Hz, 2H), 7.43-7.40 (m, 4H), 7.28-7.16 (m, 14H), 4.56-4.50 (m, 2H), 4.32-4.22(m, 8H), 3.03-2.98 (m, 2H), 2.77-2.71 (m, 2H), 2.34 (d, *J* = 6.7 Hz, 4H), 2.27 (d, *J* = 6.4 Hz, 4H),1.61-1.45 (m, 6H), 1.24 (d, *J* = 7.0 Hz, 6H), 0.86 (dd, J_1 = 6.4 Hz, J_2 = 15.6 Hz, 12H) **(Spectrum No. 20)**; ^{13}C NMR (50MHz, DMSO-*d6*) δ 172.1 (2C), 171.5 (2C), 171.1 (2C), 169.9 (2C), 142.2 (2C), 137.7 (2C), 130.3 (2C), 129.6 (2C), 129.5 (2C), 129.1 (4C), 127.9 (4C), 126.1 (2C), 125.9 (2C), 121.6 (2C), 77.2 (2C), 65.2 (2C), 53.7 (2C), 51.0 (2C), 48.3 (2C), 41.3 (2C), 40.7 (2C), 37.4 (2C), 33.5 (2C), 24.1 (2C), 23.0 (2C), 21.6 (2C), 18.0 (2C), 14.6 (2C) **(Spectrum No. 21)**; ESMS *m/z* calcd for $C_{60}H_{72}Br_2N_8O_8$ 1192, found 1193 (M+1).



37a

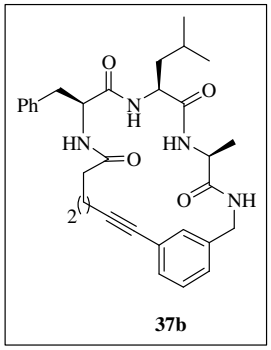
Compound 37a: Compound was prepared by following general procedure **3.4.3** (yield 12%), mp 236-237 ^oC; $[\alpha]_D^{25}$ = +3.2 *(c* 0.25, DMSO); IR (KBr), 3290, 2955, 1652, 1519 cm^{-1}; ^1H NMR (400MHz, DMSO-*d6*), δ 8.28 (d, *J* = 8.9 Hz, 1H), 8.23 (d, *J* = 4.8 Hz, 1H), 8.11 (t, *J* = 4.8 Hz, 1H), 7.50 (s, 1H), 7.28-7.13 (m, 9H), 4.53-4.35 (m, 3H), 4.06-4.00(m, 2H), 3.19 (dd, J_1 = 4.0 Hz, J_2 = 4.1 Hz, 1H), 2.80-2.70 (m, 2H), 2.68-2.60 (m, 1H), 2.40-2.33 (m, 1H), 2.22-2.14 (m, 1H), 1.60-1.55 (m, 1H), 1.48-1.40 (m, 1H), 1.34-1.29 (m, 1H), 1.27 (d, *J* = 8.6 Hz, 3H), 0.88 (d, *J* = 6.4 Hz, 3H), 0.77 (d, *J* = 6.7 Hz, 3H) **(Spectrum No. 22)**; ^{13}C NMR (50MHz, DMSO-*d6*): δ 172.1, 171.4, 170.6, 170.4, 139.7, 138.4, 130.3, 129.5, 128.9(2C), 128.1(2C), 127.7, 126.4, 126.2, 123.4, 89.4, 80.5, 54.4, 49.9, 41.9, 41.1, 40.7,

36.3, 33.6, 23.9, 23.4, 21.5, 16.4, 14.3 **(Spectrum No. 23)**; ESMS m/z 517.5 (M+1); HRMS calcd for $C_{30}H_{37}N_4O_4$ 517.2814, found 517.2802.



35b

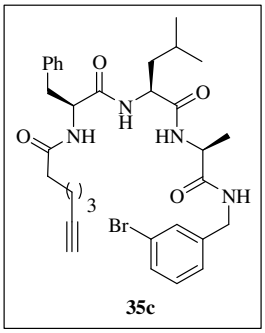
Compound 35b: Compound was prepared by following general procedure **3.4.1b** (yield 65%), mp 244-245 ^oC; $[\alpha]_D^{25}$ = -11.00 *(c* 0.5, DMSO); IR (KBr), 3279, 3065, 2956, 1634, 1542 cm^{-1}; ^1H NMR (400MHz, DMSO-*d6*), δ 8.33 (t, *J* = 6.2 Hz, 1H), 8.04 (d, *J* = 8.3 Hz, 1H), 7.98 (dd, J_1 = 4.0 Hz, J_2 = 7.0 Hz, 2H), 7.43 (s, 1H), 7.42-7.40 (m, 1H), 7.28-7.14 (m, 7H), 4.55-4.49 (m, 1H), 4.34-4.22 (m, 5H), 3.01 (dd, J_1 = 4.0 Hz, J_2 = 13.7 Hz, 1H), 2.72 (dd, J_1 = 2.4 Hz, J_2 = 5.1 Hz, 1H), 2.17-2.05 (m, 2H), 2.02-1.97 (m, 2H), 1.62-1.45 (m, 5H), 1.24 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 6.7 Hz, 3H), 0.84 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (50MHz, DMSO-*d6*): δ 172.2, 171.5(2C), 171.3, 142.2, 137.9, 130.3, 129.7, 129.5, 129.1(2C), 127.9(2C), 126.1, 126.0, 121.6, 84.1, 71.2, 53.7, 50.9, 48.3, 41.4, 40.7, 37.2, 34.0, 24.2, 24.1, 23.1, 21.6, 18.0, 17.2; ESMS *m/z* 613 (M+2), 611 (M); HRMS calcd for $C_{31}H_{40}N_4O_4Br$ 611.2232, found 611.2234.



37b

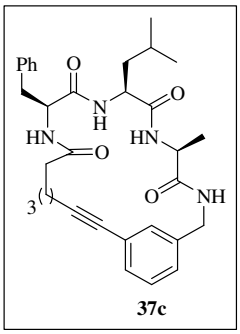
Compound 37b: Compound was prepared by following general procedure **3.4.3** (yield 23%), mp 267-268 ^oC; $[\alpha]_D^{25}$ = +49.6 *(c* 0.25, DMSO); IR (KBr), 3298, 2957, 1651, 1531 cm^{-1}; ^1H NMR (400MHz, DMSO-*d6*): δ 8.24 (dd, J_1 = 3.2 Hz, J_2 = 8.6 Hz, 1H), 8.18 (t, *J* = 5.1 Hz, 2H), 7.47 (s, 1H), 7.28-7.15 (m, 9H), 4.74 (dd, J_1 = 8.9 Hz, J_2 = 16.7 Hz, 1H), 4.42-4.30 (m, 2H), 4.14 (dd, J_1 = 5.1 Hz, J_2 = 7.0 Hz, 1H), 3.88 (dd, J_1 = 2.9 Hz, J_2 = 16.4 Hz, 1H), 3.08 (dd, J_1 = 4.3 Hz, J_2 = 14.0 Hz, 1H), 2.79 (dd, J_1 = 10.5 Hz, J_2 = 14.2 Hz, 1H), 2.42-

2.33 (m, 2H), 2.21-2.14 (m, 2H), 1.85-1.72 (m, 2H), 1.61-1.40 (m, 3H), 1.27 (d, J = 7.0 Hz, 3H), 0.92 (d, J = 6.2 Hz, 3H), 0.87 (d, J = 6.2 Hz, 3H); ^{13}C NMR (100MHz, DMSO-*d6*): δ 172.3, 171.5, 170.6, 170.1, 139.7, 138.0, 129.5, 128.8 (2C), 128.3, 128.1(2C), 127.9, 126.2, 123.4, 89.9, 81.7, 54.9, 49.8, 49.3, 42.0, 40.8, 40.1, 36.7, 34.5, 24.4, 24.0, 23.4, 21.4, 18.2, 17.0; ESMS *m/z* 531.5 (M+1); HRMS calcd for $C_{31}H_{39}N_4O_4$ 531.2971, found 531.2964.



35c

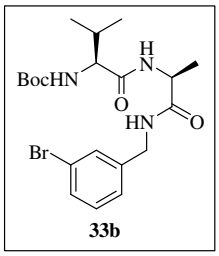
Compound 35c: Compound was prepared by following general procedure **3.4.1b** (yield 70%), mp 247-248 ^{o}C; $[\alpha]_D^{25}$ = -17.4 *(c* 0.5, DMSO); IR (KBr), 3279, 3064, 2953, 1633, 1543 cm^{-1}; ^{1}H NMR (400MHz, DMSO-*d6*), δ 8.34 (t, J = 5.9 Hz, 1H), 8.00-7.97 (m, 3H), 7.43 (s, 1H), 7.43-7.40 (m, 1H), 7.28-7.14 (m, 7H), 4.56-4.50 (m, 1H), 4.34-4.22 (m, 4H), 3.00 (dd, J_1 = 4.0 Hz, J_2 = 14.0 Hz, 1H), 2.75-2.69 (m, 2H), 2.08-2.01 (m, 4H), 1.62-1.50 (m, 1H), 1.48-1.42 (m, 4H), 1.29-1.25 (m, 2H), 1.26 (d, J = 7.8 Hz, 3H), 0.85 (dd, J_1 = 6.7 Hz, J_2 = 15.0 Hz, 6H); ^{13}C NMR (50MHz, DMSO-*d6*): δ 172.5, 171.9, 171.5, 171.4, 142.2, 137.9, 130.3, 129.7, 129.1(2C), 127.9(2C), 126.1, 125.9, 121.6, 84.2, 71.1, 53.7, 50.9, 48.3, 41.3, 40.7, 40.3, 37.2, 34.5, 27.2, 24.2, 24.1, 23.1, 21.6, 18.1, 17.4; ESMS *m/z* 627 (M+2), 625 (M); HRMS calcd for $C_{32}H_{42}N_4O_4Br$ 625.2389, found 625.2374.



37c

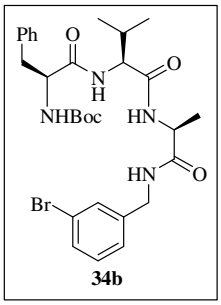
Compound 37c: Compound was prepared by following general procedure **3.4.3** (yield 35%), mp 289-290 ^{o}C; $[\alpha]_D^{25}$ = +6.8 *(c* 0.5, DMSO); IR (KBr), 3315, 2929, 1652, 1590, 1524, 1467 cm^{-1}; ^{1}H NMR (400MHz, DMSO-*d6*): δ 8.29 (m, 2H), 8.19 (t, J = 5.4 Hz, 1H), 7.28-7.14 (m, 10H), 4.50 (dd, J_1 = 7.2 Hz, J_2 = 16.1 Hz, 1H),

4.41-4.36 (m, 2H), 4.20-4.16 (m, 1H), 4.05 (dd, J_1 = 4.8 Hz, J_2 = 16.1 Hz, 1H), 3.12 (dd, J_1 = 4.6 Hz, J_2 = 14.0 Hz, 1H), 2.80 (dd, J_1 = 10.2 Hz, J_2 = 14.0 Hz, 1H), 2.38 (t, J = 7.0 Hz, 2H), 2.19-2.14 (m, 1H), 2.03-1.98 (m, 1H), 1.73-1.44 (m, 7H), 1.26 (d, J = 7.2 Hz, 3H), 0.84 (dd, J_1 = 6.2 Hz, J_2 = 14.2 Hz, 6H); ^{13}C NMR (50MHz, DMSO-*d6*): δ 172.5, 172.4, 171.6, 170.6, 139.7, 138.3, 137.9, 134.6, 129.1, 128.9(2C), 128.8, 128.1 (2C), 127.9, 126.2, 126.1, 123.5, 54.3, 50.2, 49.1, 41.8, 41.0, 35.8, 34.9, 27.9, 24.6, 23.8, 23.2, 21.6, 18.6, 16.9; ESMS *m/z* 545 (M); HRMS calcd for $C_{32}H_{41}N_4O_4$ 545.3127, found 545.3115.



33b

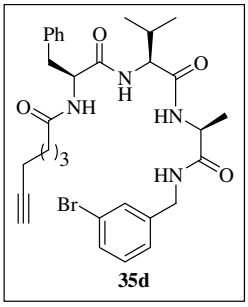
Compound 33b: Compound was prepared by following general procedure **3.4.1a** (yield 75%), mp 159-160 °C; $[\alpha]_D^{25}$ = -8.0 *(c* 0.5, DMSO); IR (KBr) 3285, 2968, 1685, 1645, 1531 cm^{-1}; ^{1}H NMR (400MHz, DMSO-*d6*): δ 8.42 (t, J = 5.4 Hz, 1H), 7.93 (d, J = 7.2 Hz, 1H), 7.43 (s, 1H), 7.42-7.40 (m, 1H), 7.28-7.22 (m, 2H), 6.68 (d, J = 8.6 Hz, 1H), 4.36-4.21 (m, 3H), 3.80 (t, J = 8.1 Hz, 1H), 1.98-1.91 (m, 1H), 1.37 (s, 9H), 1.23 (d, J = 7.0 Hz, 3H), 0.84 (d, J = 6.7 Hz, 3H), 0.79 (d, J = 6.7 Hz, 3H); ESMS *m/z* calcd for $C_{20}H_{30}BrN_3O_4$ 456, found 458 (M+2), 456 (M).



34b

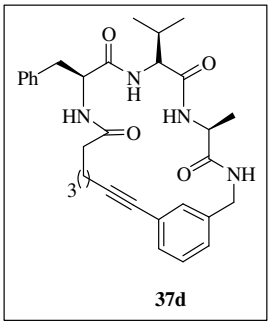
Compound 34b. Compound was prepared by following general procedure **3.4.1a** (yield 85%), mp 234-235 °C; $[\alpha]_D^{25}$ = -9.4 *(c* 0.5, DMSO); IR (KBr), 3286, 2956, 1692, 1640, 1531 cm^{-1}; ^{1}H NMR (400MHz, DMSO-*d6*): δ 8.39 (t, J = 5.6 Hz, 1H), 8.14 (d, J = 7.0 Hz, 1H), 7.66 (d, J = 8.9 Hz, 1H), 7.43 (s, 1H), 7.42-7.40 (m, 1H), 7.28-7.17 (m, 7H), 7.01 (d, J = 8.6 Hz, 1H), 4.33-4.16 (m, 5H), 2.99 (dd, J_1 = 4.0 Hz, J_2 = 14.0 Hz, 1H), 2.73 (dd, J_1 = 10.7 Hz, J_2 = 13.7 Hz, 1H), 2.02-1.94 (m, 1H), 1.29 (s, 9H),

1.23 (d, J = 7.0 Hz, 3H), 0.84 (dd, J_1 = 6.7 Hz, J_2 = 9.7 Hz, 6H); ESMS *m/z* calcd for $C_{29}H_{39}BrN_4O_5$ 603, found 605 (M+2), 603 (M).



35d

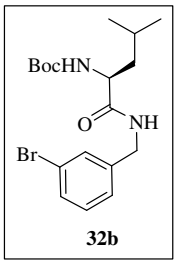
Compound 35d: Compound was prepared by following general procedure **3.4.1b.** (yield 93%), mp 250-252 ^oC; $[\alpha]_D^{25}$ = -8.6 *(c* 0.5, DMSO); IR (KBr), 3276, 3071, 2961, 1634, 1547 cm^{-1}; ^1H NMR (400MHz, DMSO-*d6*), δ 8.38 (t, J = 5.9 Hz, 1H), 8.08 (d, J = 7.2 Hz, 1H), 8.03 (d, J = 8.6 Hz, 1H), 7.76 (d, J = 8.9 Hz, 1H), 7.43 (s, 1H), 7.43-7.40 (m, 1H), 7.28-7.15 (m, 7H), 4.58-4.57 (m, 1H), 4.32-4.17 (m, 4H), 3.00 (dd, J_1 = 4.1 Hz, J_2 = 14.0 Hz, 1H), 2.72 (dd, J_1 = 10.2 Hz, J_2 = 14.0 Hz, 1H), 2.69 (s, 1H), 2.07-1.96 (m, 5H), 1.44 (quint, J = 3.1 Hz, 2H), 1.28-1.23 (m, 5H), 0.83 (dd, J_1 = 7.7 Hz, J_2 = 9.9 Hz, 6H); ^{13}C NMR (50MHz, DMSO-*d6*): δ 172.2, 171.9, 171.3, 170.3, 142.2, 138.0, 130.3, 129.7, 129.5, 129.1(2C), 127.9(2C), 126.1, 126.0, 121.6, 84.2, 71.1, 57.3, 53.6, 48.2, 41.1, 37.1, 34.5, 30.7, 27.1, 24.2, 19.1, 18.1, 17.9, 17.4; ESMS *m/z* 613 (M+2), 611(M); HRMS calcd for $C_{31}H_{40}N_4O_4Br$ 611.2232, found 611.2215.



37d

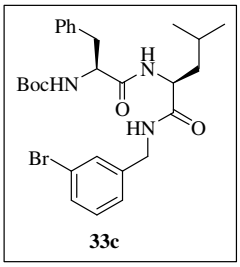
Compound 37d: Compound was prepared by following general procedure **3.4.3.** (yield 36%), mp 288-290 ^oC; $[\alpha]_D^{25}$ = +18.0 *(c* 0.25, DMSO); IR (KBr), 3281, 3061, 2926, 1648, 1538 cm^{-1}; ^1H NMR (400MHz, DMSO-*d6*): δ 8.32 (q, J = 6.8 Hz, 3H), 7.33 (s, 1H), 7.28-7.13 (m, 8H), 6.94 (d, J = 8.9 Hz, 1H), 4.60 (dd, J_1 = 8.2 Hz, J_2 = 16.4 Hz, 1H), 4.43-4.38 (m, 1H), 4.34 (dd, J_1 = 12.6 Hz, J_2 = 18.0 Hz, 1H), 4.31-4.17 (m, 1H), 3.96 (dd, J_1 = 4.3 Hz, J_2 = 16.4 Hz, 1H), 3.22 (dd, J_1 = 3.8 Hz, J_2 = 14.0 Hz, 1H), 2.79 (dd, J_1 = 11.3 Hz, J_2 = 14.2 Hz, 1H), 2.37 (t, J = 6.9 Hz, 2H), 2.20-2.15 (m, 1H), 2.04-1.93 (m, 2H), 1.75-1.52 (m, 4H), 1.24 (d, J = 7.0 Hz, 3H), 0.84 (d, J =

6.7 Hz, 3H), 0.78 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (100MHz, DMSO-*d6*): δ 172.5, 172.3, 170.4, 170.3, 139.6, 138.6, 129.0, 128.9, 128.8(3C), 128.1(2C), 127.8, 126.1, 123.5, 89.8, 80.8, 55.9, 54.3, 49.1, 41.1, 35.9, 35.0, 31.8, 28.0, 24.6, 19.2, 18.6, 17.4, 16.9; ESMS *m/z* 530 (M+1); HRMS calcd for $C_{31}H_{39}N_4O_4$ 531.2971, found 531.2954.



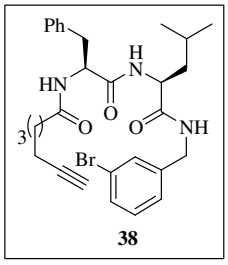
32b

Compound 32b: Compound was prepared by following general procedure **3.4.1a** (yield 87%)**,** m.p. 82-84 °C, $[\alpha]_D^{25}$ = -21.7 *(c* 1, $CHCl_3$); IR (KBr) 3300, 2958, 1657, 1528 cm^{-1}; ^{1}H NMR (400MHz, DMSO-*d6*): δ 7.39-7.37 (m, 2H), 7.19-7.14 (m, 2H), 6.70 (bs, 1H), 4.91 (d, *J* = 7.5 Hz, 1H), 4.39 (bs, 2H), 4.12-4.11 (m, 1H), 1.74-1.63 (m, 2H), 1.52-1.41 (m, 1H), 1.39 (s, 9H), 0.94 (dd, J_1 = 10.2 Hz, J_2 = 16.4 Hz, 6H); ESMS *m/z* calcd for $C_{18}H_{27}BrN_2O_3$ 399, found 401 (M+2).



33c

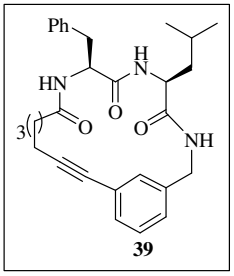
Compound 33c: Compound was prepared by following general procedure **3.4.1a** (yield 75%), mp 163-164 °C; $[\alpha]_D^{25}$ = -22.5 *(c* 1.0, $CHCl_3$); IR (KBr) 3322, 3296, 2965, 1689, 1646, 1530 cm^{-1}; ^{1}H NMR (400MHz, DMSO-*d6*): δ 8.36 (t, *J* = 5.9 Hz, 1H), 7.95 (d, *J* = 8.1 Hz, 1H), 7.43-7.41 (m, 2H), 7.29-7.16 (m, 7H), 6.91 (d, *J* = 8.3 Hz, 1H), 4.37-4.16 (m, 4H), 2.96 (dd, J_1 = 4.6 Hz, J_2 = 14.0 Hz, 1H), 2.75 (dd, J_1 = 10.2 Hz, J_2 = 13.4 Hz, 1H), 1.63-1.44 (m, 3H), 1.29 (s, 9H), 0.89 (d, *J* = 6.4 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 3H); ESMS *m/z* calcd for $C_{27}H_{36}BrN_3O_4$ 546, found 548 (M+2), 546 (M).



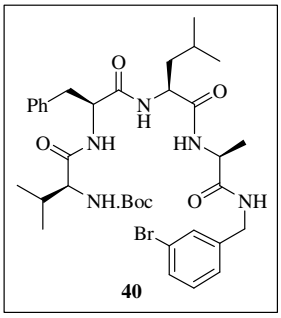
38

Compound 38: Compound was prepared by following general procedure **3.4.1b** (yield 70%), mp 167-168 °C; $[\alpha]_D^{25}$ = -18.0 *(c* 0.5, CH_3OH); IR (KBr), 3279, 3081, 2933, 1634, 1546 cm^{-1}; ^{1}H NMR (400MHz, DMSO-*d6*): δ 8.34 (t, *J* = 5.9 Hz, 1H), 8.02 (t, *J* = 9.1 Hz,

2H), 7.43-7.41 (m, 2H), 7.29-7.13 (m, 7H), 4.58-4.52 (m, 1H), 4.34-4.20 (m, 3H), 3.00 (dd, J_1 = 4.3 Hz, J_2 = 13.7 Hz, 1H), 2.74 (dd, J_1 = 9.9 Hz, J_2 = 13.7 Hz, 1H), 2.70 (t, J = 2.7 Hz, 1H), 2.07-2.01 (m, 4H), 1.60-1.41 (m, 5H), 1.29-1.21 (m, 2H), 0.89 (d, J = 6.4 Hz, 3H), 0.84 (d, J = 6.2 Hz, 3H) **(Spectrum No. 24)**; ^{13}C NMR (50MHz, DMSO-*d6*): δ 172.0(2C), 171.3, 142.3, 137.9, 130.4, 129.7, 129.5, 129.1(2C), 127.9(2C), 126.2, 126.1, 121.6, 84.3, 71.1, 53.7, 51.2, 41.4, 40.9, 37.3, 34.5, 27.2, 24.3, 24.2, 22.9, 21.6, 17.4 **(Spectrum No. 25)**; ESMS *m/z* 556.5 (M+2), 554.5 (M); HRMS calcd for $C_{29}H_{37}N_3O_3Br$ 554.2018, found 554.2023.

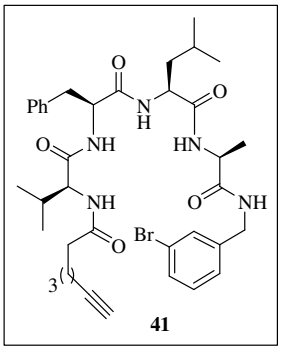


Compound 39: Compound was prepared by following general procedure **3.4.3** (yield 32%), mp 215-216 ^{o}C; $[\alpha]_D^{25}$ = +116.8 *(c* 0.25, CH_3OH); IR (KBr), 3301, 3063, 2955, 2927, 2868, 1648, 1524 cm^{-1}; ^{1}H NMR (400MHz, DMSO-*d6*): δ 8.60-8.57 (m, 1H), 7.93 (d, J = 8.9 Hz, 1H), 7.80 (d, J = 6.2 Hz, 1H), 7.56 (s, 1H), 7.27-7.17 (m, 8H), 4.78 (dd, J_1 = 8.3 Hz, J_2 = 16.8 Hz, 1H), 4.47-4.41 (m, 1H), 4.23 (q, J = 7.0 Hz, 1H), 3.83 (dd, J_1 = 3.5 Hz, J_2 = 16.1 Hz, 1H), 3.09 (dd, J_1 = 4.3 Hz, J_2 = 14.0 Hz, 1H), 2.80 (dd, J_1 = 10.7 Hz, J_2 = 14.0 Hz, 1H), 2.46-2.38 (m, 3H), 2.19-2.15 (m, 1H), 1.93-1.87 (m, 2H), 1.63-1.46 (m, 5H), 0.93 (d, J = 6.2 Hz, 3H), 0.89 (d, J = 6.4 Hz, 3H) **(Spectrum No. 26)**; ^{13}C NMR (100MHz, DMSO-*d6*): δ 172.5, 171.8, 171.0, 139.9, 138.1, 130.4, 128.9(2C), 128.4, 128.0(3C), 126.5, 126.2, 123.5, 90.1, 82.0, 54.6, 52.4, 41.3, 41.2, 37.3, 35.5, 27.0, 25.0, 24.3, 22.5, 22.4, 18.3 **(Spectrum No. 27)**; ESMS *m/z* 474.5 (M+1); HRMS calcd for $C_{29}H_{36}N_3O_3$ 474.2756, found 474.2738.



40

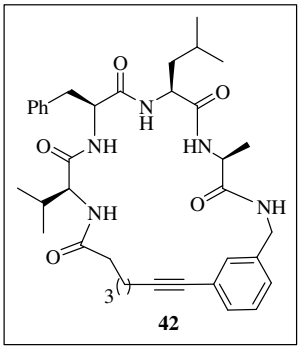
Compound 40: Compound was prepared by following general procedure **3.4.1a** (yield 90%), mp 251-252 ^{o}C; $[\alpha]_D^{25}$ = -15.6 *(c* 1.0, DMSO); IR (KBr), 3286, 3062, 2959, 1638, 1544 cm^{-1}; ^{1}H NMR (400MHz, DMSO-*d6*): δ 8.34 (t, *J* = 5.9 Hz, 1H), 8.06 (d, *J* = 7.8 Hz, 1H), 7.98 (d, *J* = 7.2 Hz, 1H), 7.86 (d, *J* = 8.3 Hz, 1H), 7.43 (s, 1H), 7.43-7.40 (m, 1H), 7.28-7.13 (m, 7H), 6.62 (d, *J* = 9.1 Hz, 1H), 4.60-4.57 (m, 1H), 4.33-4.23 (m, 4H), 3.71 (t, *J* = 7.2 Hz, 1H), 3.00 (dd, J_1 = 4.3 Hz, J_2 = 14.0 Hz, 1H), 2.77 (dd, J_1 = 9.4 Hz, J_2 = 14.0 Hz, 1H), 1.83-1.75 (m, 1H), 1.59-1.46 (m, 1H), 1.45-1.43 (m, 2H), 1.36 (s, 9H), 1.23 (d, *J* = 7.2 Hz, 3H), 0.86 (d, *J* = 6.4 Hz, 3H), 0.81 (d, *J* = 7.4 Hz, 3H), 0.70 (dd, J_1 = 7.7 Hz, J_2 = 12.1 Hz, 6H); ESMS *m/z* calcd for $C_{35}H_{50}BrN_5O_6$ 716, found 718 (M+2), 716 (M).



41

Compound 41: Compound was prepared by following general procedure **3.4.1b** (yield 72%), mp 296-297 ^{o}C; $[\alpha]_D^{25}$ = -23.4 *(c* 0.5, DMSO); IR (KBr), 3275, 3064, 2958, 1633, 1543 cm^{-1}; ^{1}H NMR (400MHz, DMSO-*d6*): δ 8.33 (t, *J* = 5.9 Hz, 1H), 7.98-7.92 (m, 3H), 7.72 (d, *J* = 8.6 Hz, 1H), 7.43 (s, 1H), 7.42-7.41 (m, 1H), 7.28-7.14 (m, 7H), 4.56-4.51 (m, 1H), 4.33-4.22 (m, 4H), 4.11 (dd, J_1 = 7.0 Hz, J_2 = 7.6 Hz, 1H), 3.99 (dd, J_1 = 4.6 Hz, J_2 = 14.2 Hz, 1H), 2.79 (dd, J_1 = 9.7 Hz, J_2 = 14.0 Hz, 1H), 2.72 (t, *J* = 2.7 Hz, 1H), 2.18-2.07 (m, 4H), 1.89 (sext, *J* = 7.0 Hz, 1H), 1.66-1.50 (m, 3H), 1.47-1.37 (m, 4H), 1.23 (d, *J* = 7.0 Hz, 3H), 0.86 (d, *J* = 6.4 Hz, 3H), 0.82 (d, *J* = 6.4 Hz, 3H), 0.82 (d, *J* = 6.6 Hz, 3H), 0.76 (d, *J* = 3.5 Hz, 3H) **(Spectrum No. 28)**; ^{13}C NMR (50MHz, DMSO-*d6*): δ 172.1, 171.9, 171.4,

171.0, 170.8, 142.0, 137.7, 130.3, 129.7, 129.5, 129.1(2C), 127.9(2C), 126.1, 125.9, 121.6, 84.3, 71.1, 57.5, 53.6, 50.9, 48.3, 41.4, 40.7, 37.1, 34.4, 30.3, 27.5, 24.4, 23.9, 23.1, 21.5, 19.1, 18.0(2C), 17.43 **(Spectrum No. 29)**; ESMS *m/z* 726 (M+2), 724 (M); HRMS calcd for $C_{37}H_{51}N_5O_5Br$ 724.3073, found 724.3048.



42

Compound 42: Compound was prepared by following general procedure **3.4.3** (yield 13%), mp 231-232 ^{o}C; $[\alpha]_D^{25}$ = -8.8 *(c* 0.25, DMSO); IR (KBr), 3311, 2960, 1644, 1526 cm^{-1}; ^{1}H NMR (400MHz, DMSO-*d6*): δ 8.07 (dd, J_1 = 5.1 Hz, J_2 = 7.2 Hz, 1H), 7.86 (d, *J* = 7.2 Hz, 2H), 7.71 (d, *J* = 7.5 Hz, 1H), 7.67 (d, *J* = 7.2 Hz, 1H), 7.24-7.17 (m, 9H), 4.50 (dd, J_1 = 7.2 Hz, J_2 = 15.6 Hz, 1H), 4.42-4.40 (m, 1H), 4.26 (t, *J* = 7.5 Hz, 1H), 4.23-4.19 (m, 1H), 4.02 (dd, J_1 = 4.8 Hz, J_2 = 15.6 Hz, 1H), 3.86 (t, *J* = 7.0 Hz, 1H), 3.16 (dd, J_1 = 4.3 Hz, J_2 = 14.2 Hz, 1H), 2.89 (dd, J_1 = 10.2 Hz, J_2 = 14.2 Hz, 1H), 2.41-2.11 (m, 4H), 1.87 (sext, *J* = 7.0 Hz, 1H), 1.66-1.40 (m, 7H), 1.25 (d, *J* = 7.0 Hz, 3H), 0.86 (d, *J* = 6.2 Hz, 3H), 0.81 (d, *J* = 6.4 Hz, 3H), 0.71 (d, *J* = 6.7 Hz, 3H), 0.67 (d, *J* = 7.0 Hz, 3H) **(Spectrum No. 30)**; ^{13}C NMR (50MHz, DMSO-*d6*): δ 173.0, 172.1, 171.4, 171.2(2C), 139.5, 137.7, 129.5, 129.0, 128.8(2C), 128.1(3C), 127.0, 126.2, 123.5, 90.1, 80.8, 59.2, 54.5, 51.6, 48.3, 41.57, 36.2, 34.5, 28.6, 27.5, 24.4, 23.9, 23.0, 21.4, 19.1, 18.4, 18.1, 17.5 **(Spectrum No. 31)**; ESMS *m/z* 644 (M+1); HRMS calcd for $C_{37}H_{50}N_5O_5$ 644.3811, found 644.3801.

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Chapter 4

Synthesis of Small Cyclic Peptides Embedded with a Conjugated 1,3-Diene System using Palladium-Catalyzed Enyne-Cycloisomerization

4.1 Introduction

The increasing need for environmentally responsible means of preparing the diverse range of chemical products demanded by society drives the quest for synthetic efficiency. Thus, in order to minimize the usage of raw materials and waste production, a chemical reaction should proceed with high levels of atom economy[1] and selectivity (chemo-, regio-, diastereo-, and enantioselectivity). For example, thermal reactions, the ene reaction involves the addition of a group possessing a π-bond (enophile) to a group possessing an allylic hydrogen (ene), with concomitant transfer of the allylic hydrogen to the enophile.[2] When performed in an intramolecular[3] fashion, the ene reaction is referred to as a cycloisomerization and can serve as an efficient method for the construction of carbocyclic frameworks (Figure 1).

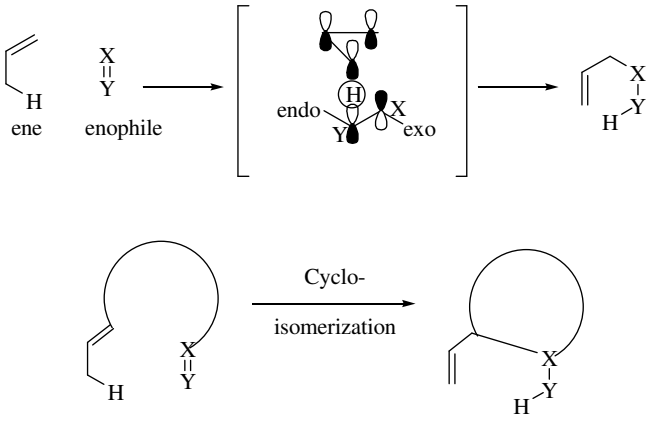


Figure 1: Cycloisomerization

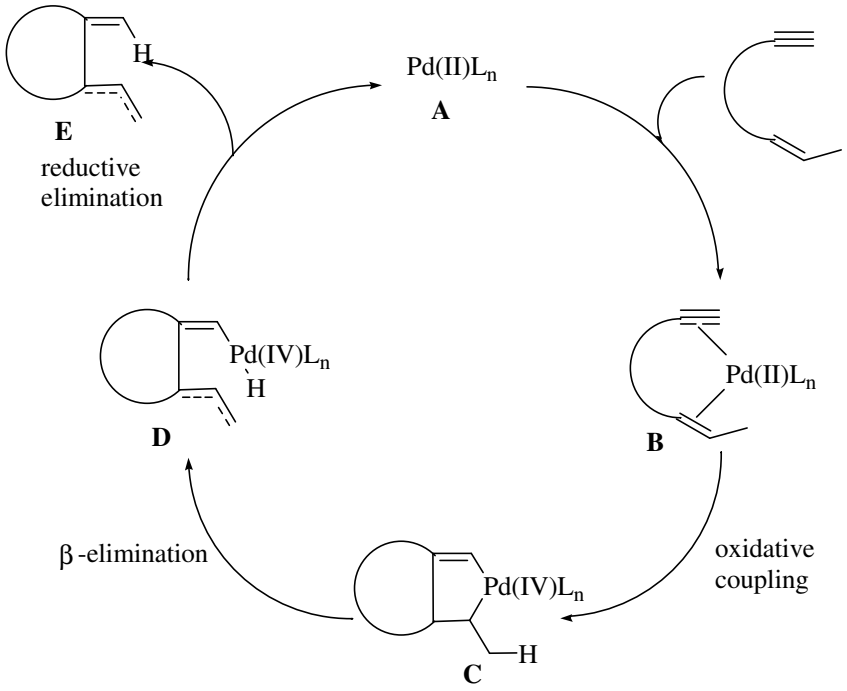
The need for high reaction temperatures and substrate activation has limited the applicability of the thermal reaction in the synthesis of complex structures. Therefore,

toward this atom economy reaction (cycloisomerization), the use of homogeneous transition metal catalysts in conjunction with ligand fields has garnered much success. The use of transition-metal catalysts[4] has provided a means for performing cycloisomerizations[5] under mild conditions with enhanced selectivity and a wider substrate scope than was previously impossible.[6] Most notably, the use of palladium for the cycloisomerization of enynes has been elegantly demonstrated by Trost[7] and has proven to be a valuable tool for the synthesis of natural products.[8] The Pd-catalyzed reaction has also provided encouraging results in enantioselective cycloisomerizations.[9,10] Although early transition metal complexes have been extensively applied to the cyclization of enynes,[11] no palladium-metal-mediated or catalyzed cycloisomerization reactions have been reported in the macrocyclic peptide synthesis. In the course of our studies toward the syntheses of cyclic peptides, we found the palladium catalyzed cycloisomerization can serve as a cyclization strategy for the synthesis of cyclic peptides from the acyclic peptides having ene and yne functionality on the respective termini.

The use of alkynes as enophiles in the intramolecular variation of the transition metal catalyzed Alder-ene process, or enyne cycloisomerization reaction has found widespread use largely owing to the development of palladium derived catalyst systems.[12] The palladium catalyzed cycloisomerization of enynes is believed to proceed *via* a Pd(II)-Pd(IV) or Pd(0)-Pd(II) cycle depending on the reaction conditions and choice of precatalyst. Using a Pd(II) precatalyst such as $Pd(OAc)_2$ in the absence of a reducing agent favors the Pd(II)-Pd(IV) cycle.[13,14] The Pd(0)-Pd(II) cycle is favored by the use of a Pd(0) precatalyst such as $Pd_2(dba)_3 \bullet CHCl_3$ in conjunction with a carboxylic acid partner.[15] The two postulated catalytic cycles are depicted below (Schemes 1 & 2).

4.1.1 The Metallacyclopentene Pathway for Palladium catalyzed Cycloisomerization

The formation of metallacyclopentenes is very general and occurs with a large variety of transition metals and unsaturated partners. The main steps of the palladium catalytic cycle are described in Scheme 1.

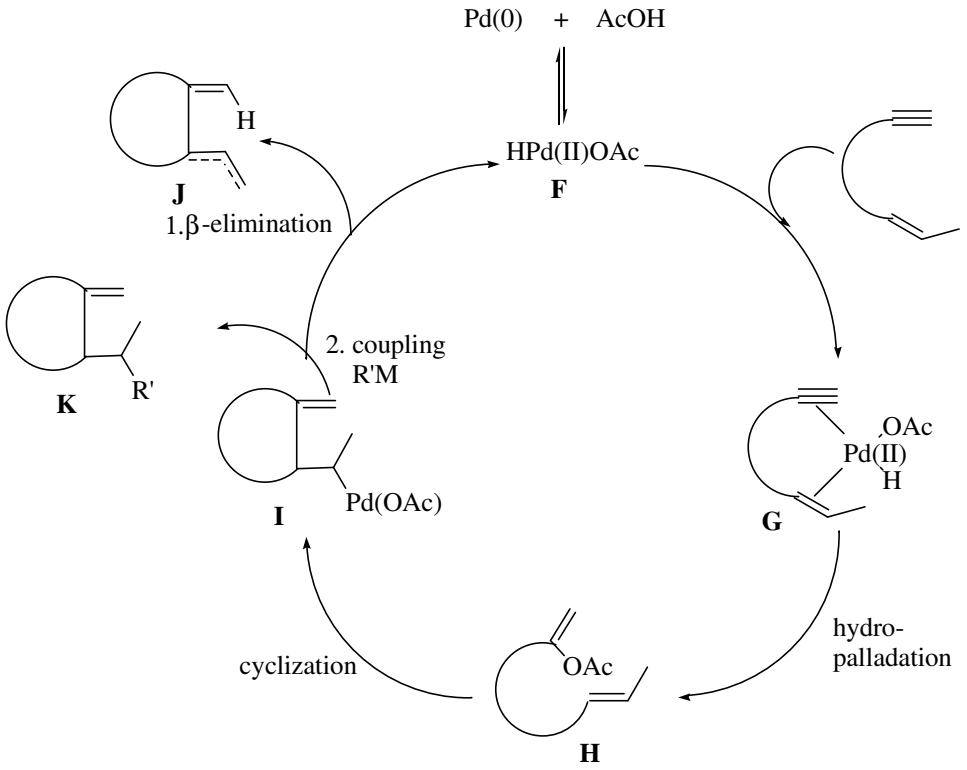


Scheme 1: Pd(II)/Pd(IV) cycloisomerization mechanism

The complexation of the enyne with the palladium(II) moiety **A** affords intermediate **B**, which on oxidative coupling leads to the metallacyclopentene **C**. The metallacyclopentene **C** undergo β-hydride elimination to form **D**. After reductive elimination, **D** furnishes either one or a mixture of 1,3- and 1,4-dienes **E**.

4.1.2 Vinylmetal Pathway/Hydrometalation for palladium catalyzed cycloisomerization

The mechanism and the factors governing the regio-, chemo-, and stereoselectivity have been fully investigated by Trost group.[16] In the presence of a carboxylic acid, a Pd(0) precatalyst generates a Pd(II) hydride **F** that is the active species during the cyclization. After the complexation of the Pd(II) to both unsaturated moieties, a hydrometalation of the alkyne provides **H**, the vinymetal that is able to carbometalate the alkene. The resulting alkylpalladium species **I** can follow two pathways: (1) a β-elimination that furnishes the 1,3- or 1,4- diene **J** and regenerates the palladium (II)



Scheme 2. Vinylmetal pathway for the Palladium Catalyzed Enyne

Cyclo isomerization Reaction

hydride **F** or (2) coupling reaction of further cyclizations leading to functionalized cycloadducts **K**. It has to be noted that in this pathway the oxidation state of the metal remains unchanged during the whole process of the cyclization (Scheme 2).

The possibility of formation of metal-hydrogen bond by simple protonation gives an idea to consider transition metal catalyzed additions to alkynes. The excellent coordinating properties of the alkyne to a transition metal suggests that an equilibrium as shown in Figure 2 may provide a very mild approach for the formation of vinylpalladium intermediates. Indeed, such an equilibrium was originally conjectured as one of the possible pathways to explain the cycloisomerization of enynes catalyzed by palladium catalyst.[17,18]

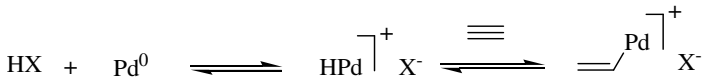
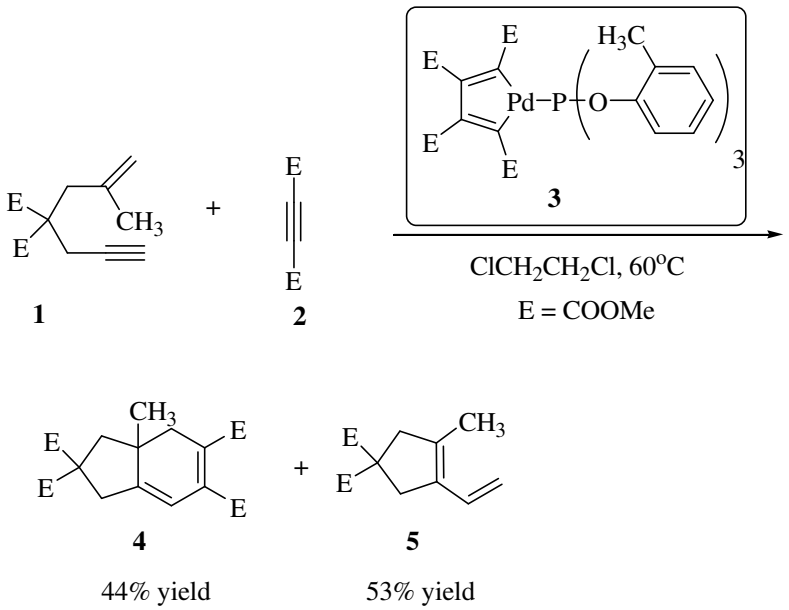


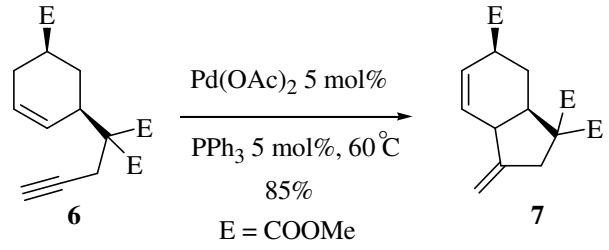
Figure 2: Vinylpalladium intermediate

In 1988, while investigating palladium-catalyzed enyne cyclizations, Trost isolated an unexpected rearrangement product (Scheme 3).[19] Enyne **1**, when treated with dimethyl acetylenedicarboxylate (DMAD, **2**), tri-*o*-tolylphosphine, and tetracarbomethoxypallada cyclopentadiene (TCPC, **3**), gives a 1:1.2 ratio of the expected [2+2+2] cycloadduct **4** and unexpected vinylcyclopentene **5** in an overall yield of 97%.

The use of palladium catalyst has greatly expanded the scope of the cycloisomerization (intramolecular Alder-ene reaction). For example, Trost *et al.* reported that under thermal conditions enyne **6** fails to cyclize at temperatures as high as 550°C, whereas treatment with a palladium(II) catalyst afforded the ene product **7** in 85% yield at only 60 °C (Scheme 4).[13]

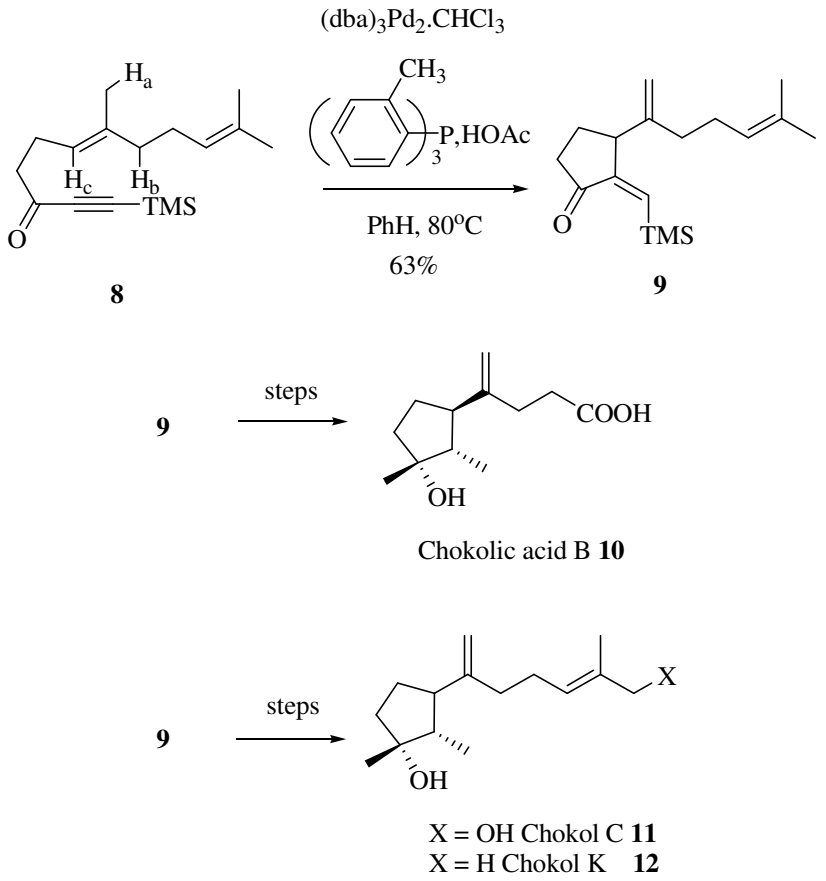


Scheme 3



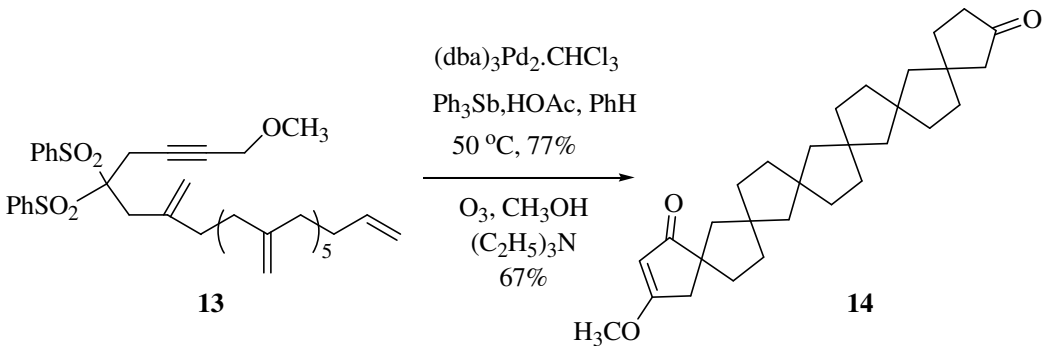
Scheme 4

Trost *et al*. observed that in case of Pd(0)/CH_3COOH catalyzed cycloisomerization, the dienyne **8** regioselectively affords 1,4-diene **9** rather than a 1,3-diene. The triene **9** serves as a pivotal intermediate to a number of members of the chokol family of antifungal agents Chokolic acid B **10**, Chokol C **11** and Chokol K **12** (Scheme 5).[20]



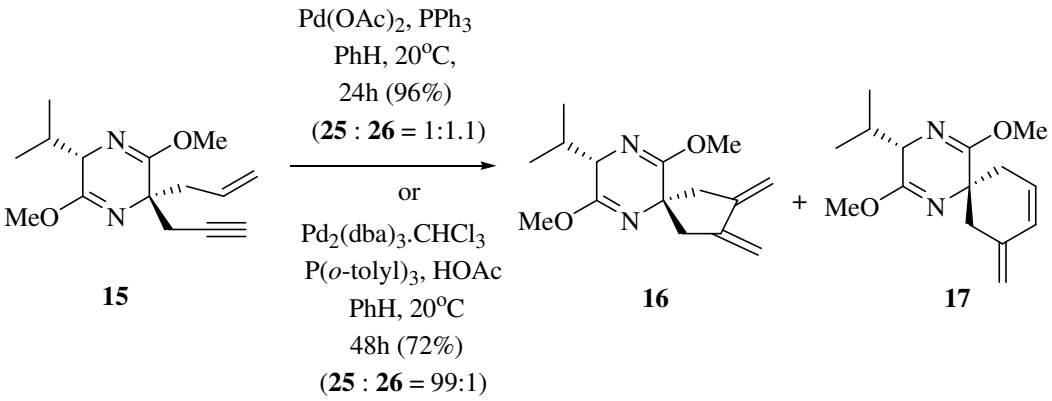
Scheme 5

Trost and Shi reported that if β-hydrogen elimination is precluded and additional π-unsaturation exists in the molecule, depending on the juxtaposition of the unsaturation, a number of polycyclic skeletons can be created, including fused, bridged, spiro, and propeller. For example, a spiro ring system **14** containing up to seven rings prepared from **13** in one step (Scheme 6).[21]



Scheme 6

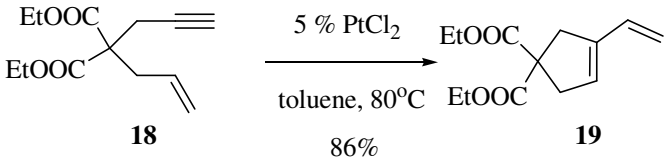
Undheim *et al.* showed that, when the enyne **15** was treated with $Pd(OAc)_2$ and PPh_3 in benzene the isomers **16** and **17** were formed almost in equimolar quantities in high yield. The reaction conditions were adapted from the protocol used by Trost *et al.* for enyne cycloisomerizations which gave exclusively 1,3-dienes such as dimethylenecyclopentanes from simple 1,6-enynes (Scheme 7).[22]



Scheme 7

Other transition metal catalysts were also used in the enyne-cycloisomerization reaction. Pioneering work of Murai has shown that platinum (II) chloride ($PtCl_2$) is a versatile catalyst for the enyne metathesis of 1,6-enynes. The cyclization occurs in very

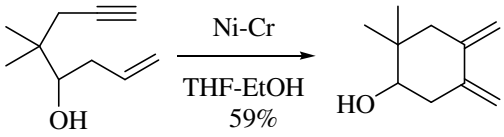
mild conditions, compatible with a lot of functional groups including vinylic and acetylenic halides, and no additional ligands are necessary (Scheme 8).[23] The reaction of 1,7-enyne to a six-membered ring is also feasible but proceeds slowly (4 days), and the 1,3-diene is isolated in moderate yield (40%).



18 **19**

Scheme 8

Trost *et al*. reported that enyne cycloisomerization may also be affected *via* nickel-chromium based catalyst systems.[24] The reactivity profile of the nickel-chromium based system provides a useful complement to the palladium derived systems. They observed high degree of chemoselectivity and the tolerance of hydroxyl functionality in the cyclization of **20** to for **21** (Scheme 9).

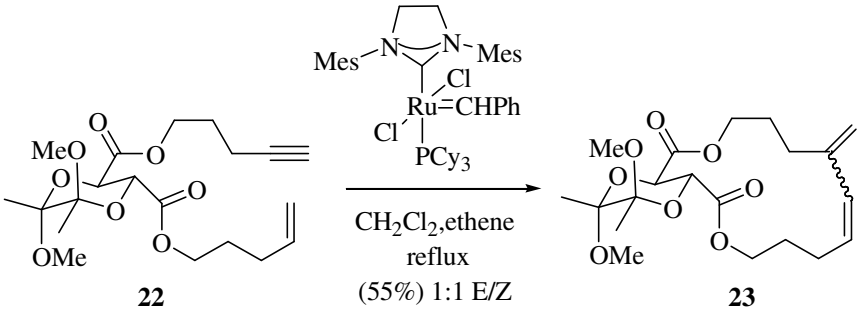


20 **21**

Scheme 9

Hansen and Lee reported that the endo cyclization mode is preferred for the formation of larger rings (size greater than 12 members) in ruthenium catalyzed ring-

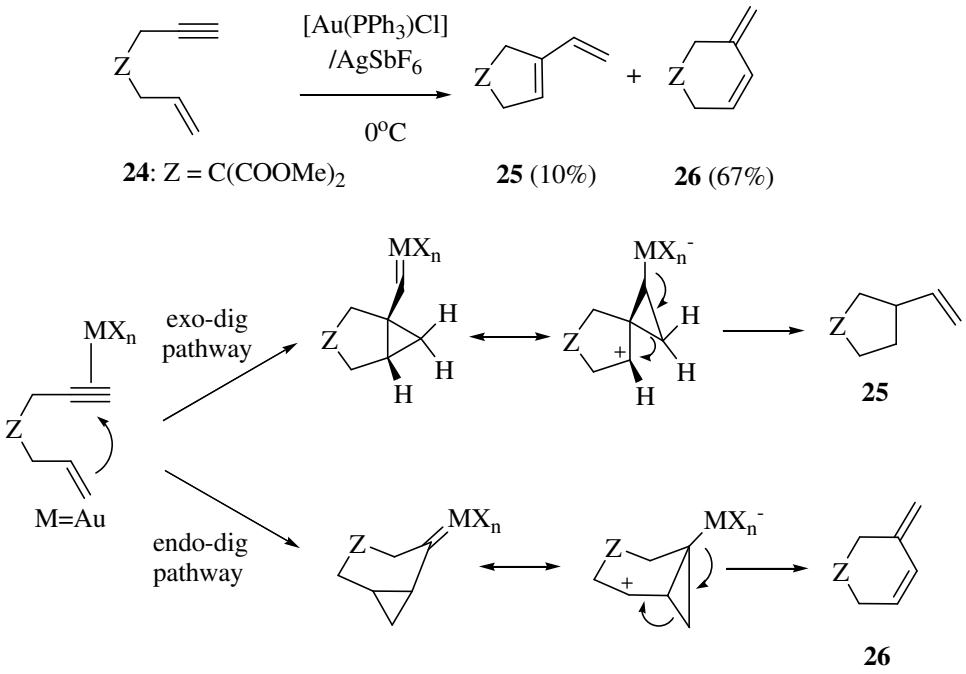
closing enyne metathesis (RCEYM). Compound **22** on RCEYM gave cyclic diene compound **23** in 55% yield as 1:1 geometrical isomers (Scheme 10).[25]



22 **23**

Scheme 10

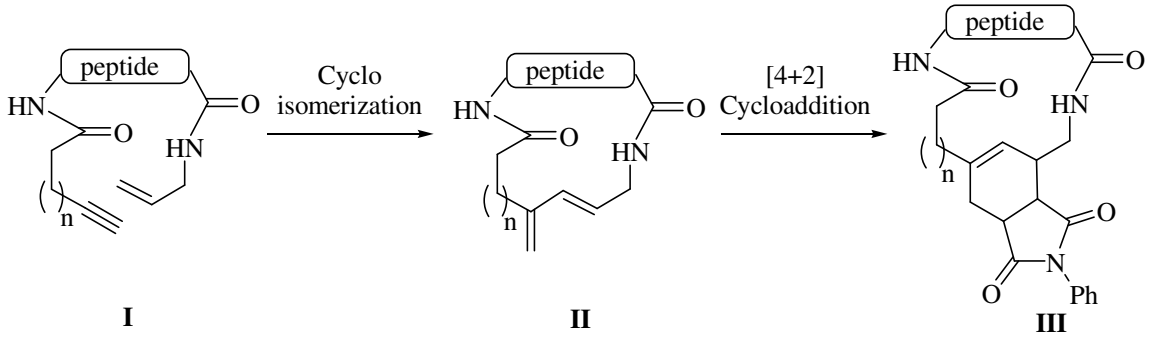
Significantly, skeletal rearrangement by an *endo-dig* pathway was observed by



Scheme 11

Echavarren and co-workers for the first time with Au(I) catalysts.[26] Thus, enyne **24** gave a 1:7 mixture of exo **25** and endo **26** rearrangement products. Mechanism for the exo- or endo-skeletal rearrangement can be explained as coordination of MX_n (M=Au) to the alkyne forms a (η^2-alkyne)metal complex, which involves to form the metal cyclopropyl carbene complexes (exo-dig) or (endo-dig) (Scheme 11).

As part of an ongoing program in our laboratory on peptidomimetics, we became interested in applying the palladium catalyzed enyne cycloisomerization to incorporate a diene moiety in a macrocyclic structure, a functionality having significant synthetic application. This chapter describes the Palladium catalyzed enyne cycloisomerization of linear peptides **I** to generate small cyclic peptides embedded with a conjugated 1,3-diene **II**. The utility of these resulting macrocyclic dienes is demonstrated by carrying out [4+2] cycloadditions with dienophiles to generate constrained cyclic peptides with cyclic linkers **III** (Figure 3).



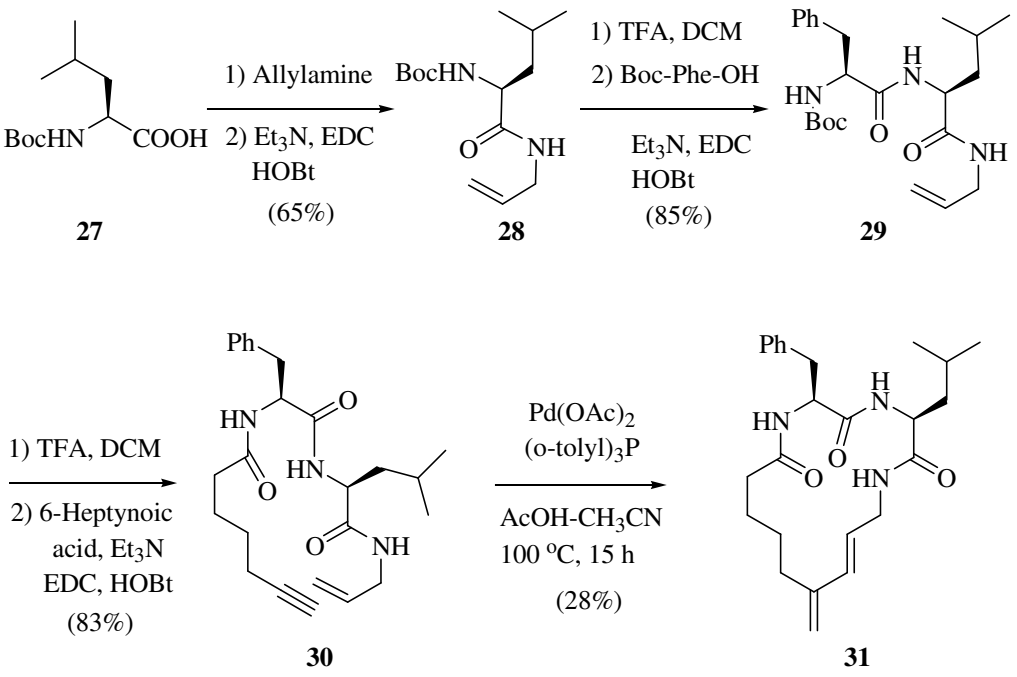
I **II** **III**

Figure 3: Enyne Cycloisomerization

4.2 Results and Discussion

4.2.1 Synthesis of 16-membered macrocyclic peptides embedded with a conjugated 1,3-diene

Our first target was macrocylce **31** (Scheme 12) containing a dipeptide and a conjugated 1,3-diene constraint. The Boc-Leu-OH **27** was treated with allylamine using standard solution phase peptide coupling to isolate peptide **28** in 65% yield. Peptide **28** on deprotection followed by coupling with Boc-Phe-OH gave dipeptide **29** in 85% yield. Finally, the Boc deprotection on **29**, followed by coupling with readily available 6-heptynoic acid gave desired acyclic precursors **30** in 83% yields. The structure of **30** was determined by NMR spectroscopy. To furnish macrocyclization the acyclic dipeptide **30** was subjected to an enyne-cycloisomerization conditions as reported by Trost *et al*.[5] The macrocyclization was successful and the cyclic product **31** was obtained in 28% yield (Scheme 12). The structure of the newly formed compound **31** was determined mainly by ^{1}HNMR spectroscopy. The two methylene hydrogens of exo double bond resonate as a doublet at δ 4.90 with J = 1.9 Hz, and the hydrogen of endo double bond which is closer to exo double bond resonate as a doublet at δ 6.07 with J = 13.8 Hz and the other hydrogen of endo double bond resonate between δ 5.58-5.52 as multiplet. The *E*-stereochemistry of the endocylic double bond and *s*-transoid form of the 1,3-diene were established using NMR data (1-D and 2-D) The coupling constant J = 13.8 Hz for hydrogen of endo double bond confirm that double bond has (*E*)-configuration and proximity of NMR signal in 1D NMR confirms the s-transoid form of the 1,3-diene.

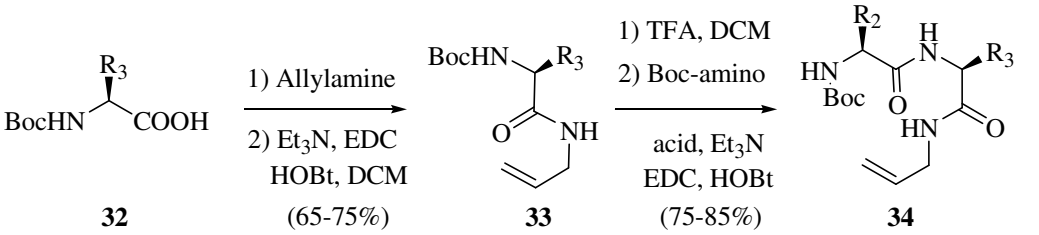


Scheme 12

4.2.2 Synthesis of (17-19)-membered macrocyclic peptides embedded with a conjugated 1,3-diene

Next, we wanted to test the versatility of the macrocyclization methodology by varying the overall size. We synthesized macrocyclic peptidomimetics **37a-e** from their respective acyclic tripeptide derivatives **36a-e** by varying the length of the linker chain and the amino acid residues at i or i+1 or i+2 positions. The synthesis of acyclic peptides **36** is described in Scheme 13. Thus, N-Boc protected amino acids **32** treated with allylamine to furnish the corresponding amides **33** using standard solution phase peptide coupling protocol. The Boc deprotection of **33**, followed by coupling with respective Boc-amino acids yielded compounds **34** in good yields. Compounds **34** on repeating Boc deptrotection and coupling with amino acids gave peptides **35**, which form precursors **36**

on subsequent deprotection and coupling with respective n-alkynoic acid under standard solution phase peptide protocol system.

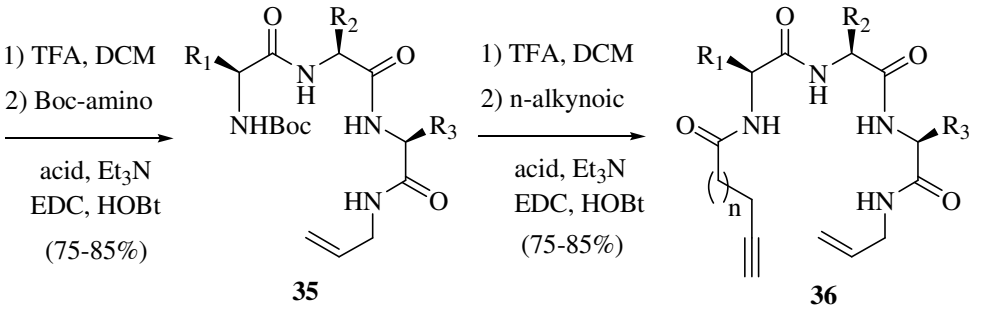


32 **33** **34**

32a $R_3 = CH_3$
32b $R_3 = CH_2Ph$

33a $R_3 = CH_3$
33b $R_3 = CH_2Ph$

34a $R_2 = CH_2CH(CH_3)_2$, $R_3 = CH_3$
34b $R_2 = CH(CH_3)_2$, $R_3 = CH_3$
34c $R_2 = CH(CH_3)_2$, $R_3 = CH_2Ph$



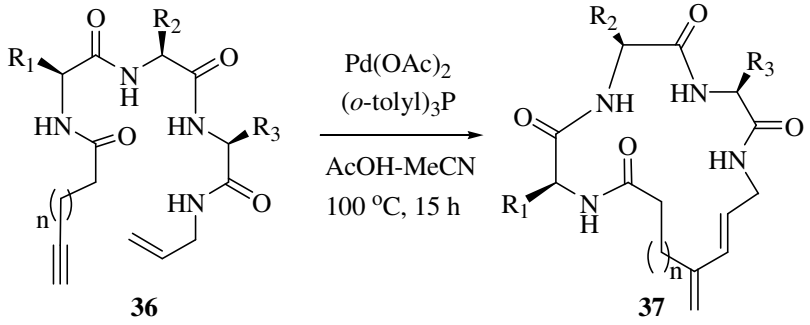
35 **36**

35a $R_1 = CH_2Ph$, $R_2 = CH_2CH(CH_3)_2$, $R_3 = CH_3$
35b $R_1 = CH_2Ph$, $R_2 = CH(CH_3)_2$, $R_3 = CH_3$
35c $R_1 = CH(CH_3)CH_2CH_3$, $R_2 = CH(CH_3)_2$, $R_3 = CH_2Ph$

Scheme 13

The tripeptide compounds **36a-c** underwent cycloisomerization in $Pd(OAc)_2$, (o-tolyl)$_3$P catalytic system in acetic acid and acetonitrile solvent system, to furnish the desired macrocycles **37a-c** in fair yields (33-54%). We had anticipated that the linker length might play a role in the *E, Z*-selectivity of the endocyclic double bond, but only *E*-

isomers were observed in all cases. This was described in the synthesis of (17-19)-membered cyclic peptides **37a-c**. We also observed in the synthesis of the cyclic peptides **37d** and **37e** that, the change in amino acids had little or no effect on the macrocylization reaction (Scheme 14).



36 **37**

36a R_1 = -CH_2Ph, R_2 = -$CH_2CH(CH_3)_2$, R_3 = -CH_3, n = 1 **37a** (33%)

36b R_1 = -CH_2Ph, R_2 = -$CH_2CH(CH_3)_2$, R_3 = -CH_3, n = 2 **37b** (45%)

36c R_1 = -CH_2Ph, R_2 = -$CH_2CH(CH_3)_2$, R_3 = -CH_3, n = 3 **37c** (54%)

36d R_1 = -CH_2Ph, R_2 = -$CH(CH_3)_2$, R_3 = -CH_3, n = 1 **37d** (40%)

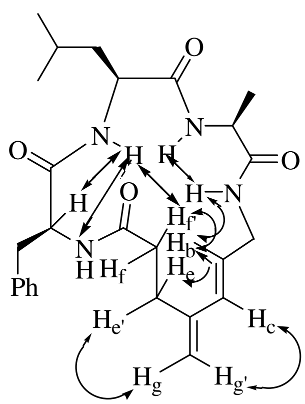
36e R_1 = -$CH(CH_3)CH_2CH_3$, R_2 = -$CH(CH_3)_2$, R_3 = -CH_2Ph n = 1 **37e** (46%)

Scheme 14

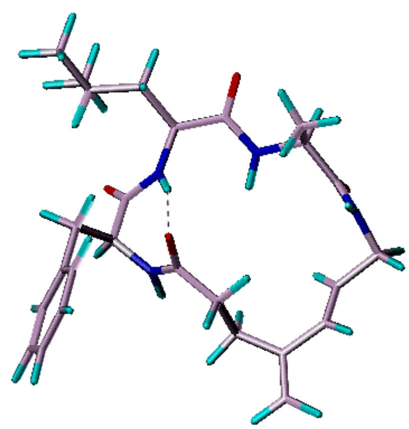
4.2.3 Conformational studies of 17-membered macrocyclic peptide embedded with a conjugated 1,3-diene

The conformational studies of **37a** demonstrating the molecule is pre-organized through γ-turn. The ^{1}H NMR investigations on cyclicpeptide **37a** has been carried out in polar solvent (DMSO-d_6). The cyclic peptide **37a** shows presence for a single rotamer. The cross peaks in the ROESY spectrum between Leu NH/Phe CαH (i+2/i+1), Leu

NH/Phe NH (i+2/i+1),Leu NH/Ala NH (i+2/i+3), Ala NH/diene NH (i+3/i+4) weak and Leu NH/diene Hf which is very weak, as well as participation of Leu NH in hydrogen bonding with CO of diene which is 7 membered (i/i+2) is confirmed by the magnitude of its temperature coefficients (Δδ/ΔT) of –3.5 ppb/c, and confirms the presence of γ-turn. And the observed dihedral angles prove it as a classical γ-turn (Figure **4**). In linear peptide **36a**, we could not find these nOes and Hydrogen bonding between Leu NH and CO of diene i.e. it was proved that there is no secondary structure in linear peptide **36a**.



37a



37A

Figure 4: (**37a**) NOEs observed structure, and (**37A**) MD simulated structure

Torsion angles (i+1) of STD γ-turn and observed γ-turn

γ-turn	φ	ψ
STD type classical γ-turn [a]	70 to 85	-60 to –70
Observed type classical γ-turn	90	-55

[a] As originally defined by Nemethy and Printz

^{1}H Chemical shifts (δ in ppm) and coupling constants (*J* in Hz) in DMSO-d_6 of cyclic peptide 37a

Protons	Phe	Leu	Ala
NH	7.76	7.83	8.07
	(d, *J* = 8.2 Hz)	(d, *J* = 8.2 Hz)	(d, *J* = 7.1 Hz)
CαH	4.39	4.14	4.00
	(ddd, *J* = 5.2, 8.2, 9.8 Hz)	(ddd, *J* = 5.2, 8.2, 9.6Hz)	(dq, *J* = 7.0, 7.1 Hz)
CβH	2.99	1.45	1.21
	(dd, *J* = 5.2, 14.1 Hz)	(m)	(d, *J* = 7.0 Hz)
Cβ'H	2.82	1.45	
	(dd, *J* = 9.8, 14.1 Hz)	(m)	
CγH		1.54	
		(m)	
CδH		0.88	
		(d, *J* = 6.1 Hz)	
Cδ'H		0.84	
		(d, *J* = 6.1 Hz)	

Others: 8.00 (t, *J* = 5.6 Hz, NH), 7.19-7.30 (m, 5H, aromatic), 6.04 (d, *J* = 16.1 Hz, Hc), 5.54 (ddd, *J* = 4.0, 8.2, 16.1 Hz, Hb), 4.92 (d, *J* = 2.5 Hz, Hg), 4.91 (d, *J* = 2.5 Hz, Hg'), 3.78 (ddd, *J* = 5.6, 8.2, 15.4 Hz, Ha), 3.60 (ddd, *J* = 4.0, 5.6, 15.4 Hz, Ha'), 2.59 (ddd, *J* = 4.3, 8.1, 13.4 Hz, He), 2.32 (ddd, *J*=4.3,8.9,16.1Hz,Hf),2.26 (ddd, *J* = 8.1, 8.3, 16.1 Hz, Hf'), 2.16 (ddd, *J* = 8.3, 8.9, 13.4 Hz, He).

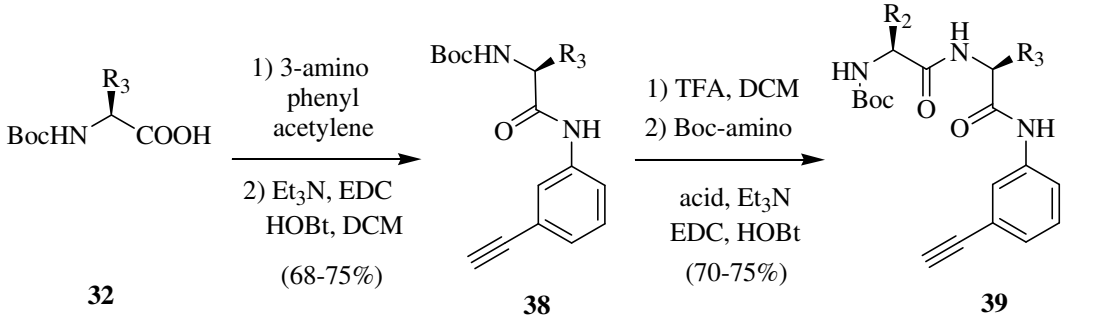
^{1}H Chemical shifts (δ in ppm) and coupling constants (*J* in Hz) in DMSO-d_6 of Linear peptide 36a

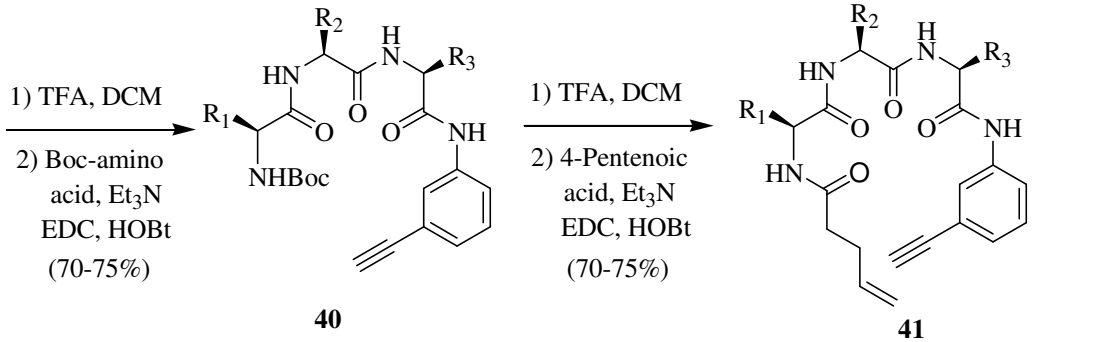
Protons	Phe	Leu	Ala
NH	8.09	8.02	7.87
	(d, *J* = 8.3 Hz)	(d, *J* = 8.1 Hz)	(d, *J* = 7.4 Hz)
CαH	4.52	4.28	4.24
	(ddd, *J* = 4.4, 8.3, 9.7 Hz)	(m)	(dq, *J* = 7.0, 7.4 Hz)
CβH	3.01	1.47	1.21
	(dd, *J* = 4.4, 14.0 Hz)	(m)	(d, *J* = 7.0 Hz)
Cβ'H	2.75	1.47	
	(dd, *J* = 9.7, 14.0 Hz)	(m)	
CγH		1.58	
		(m)	
CδH		0.88	
		(d, *J* = 6.0 Hz)	
Cδ'H		0.84	
		(d, *J* = 6.0Hz)	

Others: 7.92 (t, *J* = 5.7 Hz, 1H, NH), 7.16-7.26(m, 5H, aromatic), 5.77 (dddd, *J* = 5.0, 5.1, 10.3, 17.2 Hz, 1H, Hb), 5.12 (dd, *J* = 2.0, 17.2 Hz, 1H, Hc), 5.03 (dd, *J* = 2.0, 10.3 Hz, 1H, Hc'), 3.68 (m, 2H, Ha), 2.67 (m, 1H, Hf), 2.23 (m, 3H, He, He', Hf'), 2.23 (s, 1H, Hd) .

4.2.4 Synthesis of 19-membered macrocyclic peptides constrained with 6-(3-aminophenyl)-4,6-heptadiene linker

The linear tri peptide embedded compounds **41a** and **41b** were synthesized by switching the alkene to the *N*-terminus and alkyne moiety to the *C*-terminus. Thus, N-Boc protected amino acids **32** treated with 3-aminophenylacetylene to furnish corresponding amides **38** using standard solution phase peptide coupling protocol. The Boc deprotection on **38**, followed by coupling with respective Boc-amino acids yield compounds **39** with good efficiency. Compounds **39** on repeating Boc deptrotection and

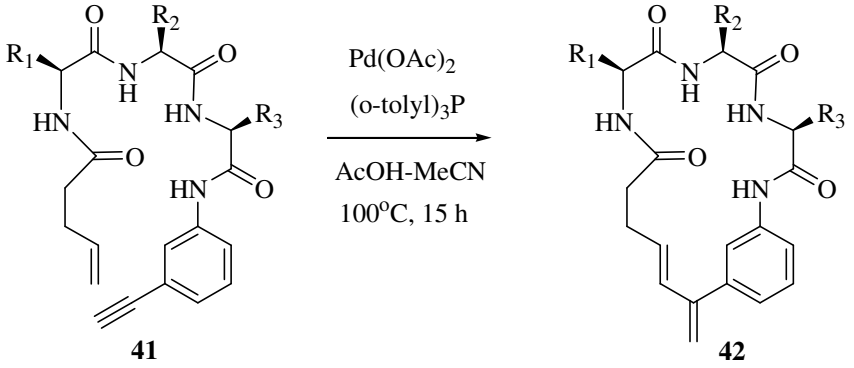




Scheme 15

coupling with aminoacids gave peptides **40**, which form precursors **41** on subsequent Boc deprotection and coupling with 6-heptynoic acid under standard solution phase peptide protocol system (Scheme 15).

The enyne cycloisomerization of compounds **41a** and **41b** gave the cyclic peptide compounds **42a** and **42b** in good yields, respectively. The structures of **42a** and **42b** were well characterized by analytical data (experimental section) and it was observed that the rigid aryl acetylene linker has no effect on the efficiency of cycloisomerization as well as on the geometry of the endocyclic double bond of the resulting cyclic peptides (Scheme 16).



41 **42**

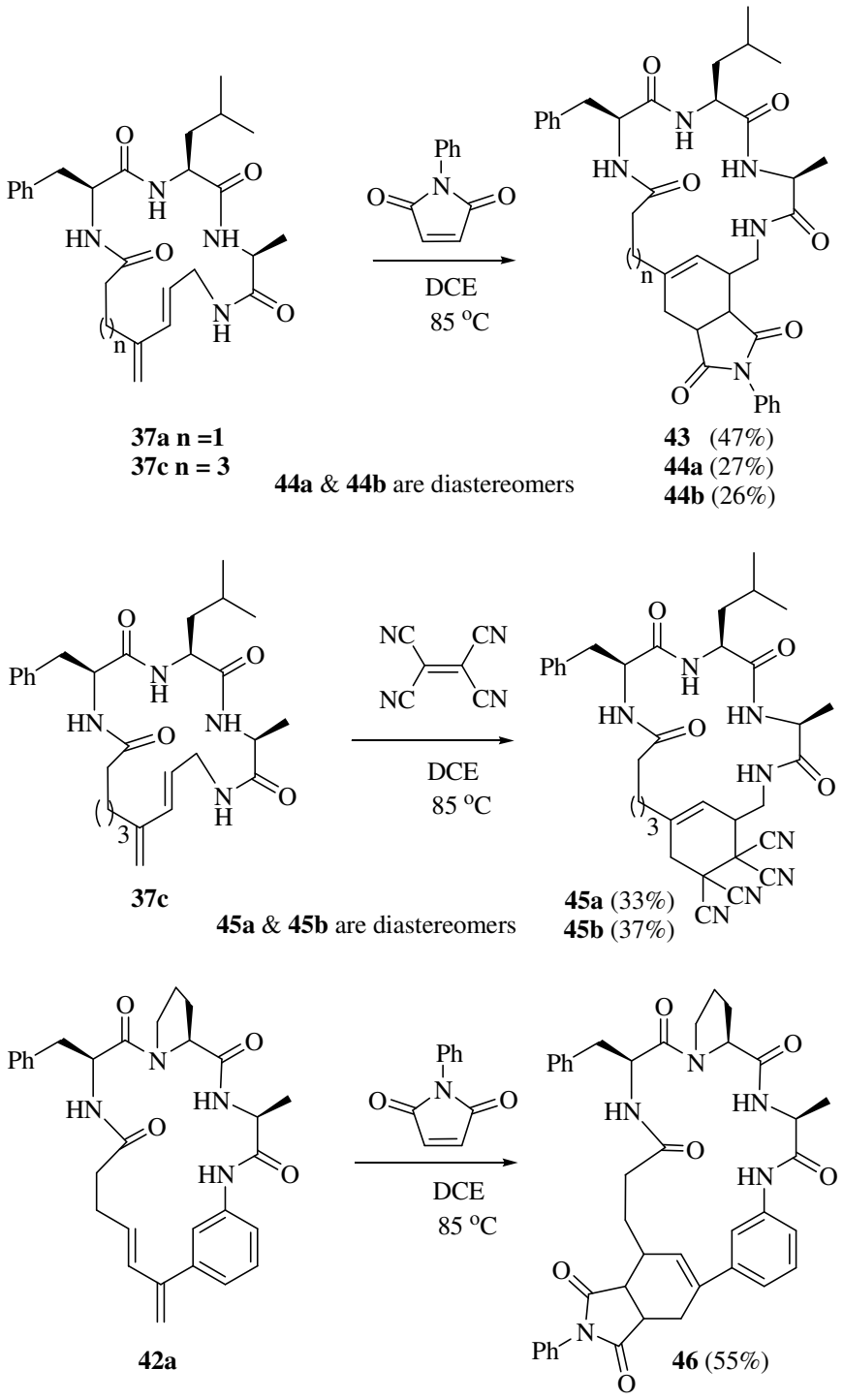
41a $R_1 = CH_2Ph$, $R_2 = CH_2CH_2CH_2$, $R_3 = CH_3$ **42a** (50%)
41b $R_1 = CH_2Ph$, $R_2 = CH_2CH(CH_3)_2$, $R_3 = CH_3$ **42b** (49%)

Scheme 16

4.2.5 Synthesis of bicyclic peptides using Diels-Alder reactions on macrocyclic peptides embedded with a conjugated 1,3-diene

The cyclic peptides formed during the cycloisomerization possess a conjugated 1,3-diene moiety, a functional group with several potential synthetic applications. We

attempted the Diels-Alder reaction on these compounds to demonstrate the synthetic utility of the conjugated diene present in these cyclic peptides. The reactive dienophile



Scheme 17

N-phenylmaleimide was refluxed with macrocyclic diene **37a** in dicholoroethane to give compound **43** in combined 47% yield as 1:1 diastereomers. Similarly, macrocyclic diene **37c** reacted with *N*-phenylmaleimide and tetracyanoethylene to produce the corresponding adducts **44** in 53% yield and **45** in 70% yields respectively, as 1:1 diastereomeric mixture. However, the cyclic peptide **42a** on Diels-Alder reaction with the reactive dienophile N-phenylmaleimide in dicholoroethane gave compound **46** in 55% yield as single isomer (Scheme 17).

4.3 Conclusions

In conclusion, we have demonstrated the utility of palladium-catalyzed enyne cycloisomerization during the macrocylization of linear peptides to furnish constrained small cyclic peptides with novel linkers. The resulting macrocycles having a 1,3-diene moiety can be used for further functionalization to generate a variety of other linkers leading to useful peptidomimetic molecules. We also demonstarted that, the Diels-Alder reaction of these cyclic dienes could be performed in several cases by reacting with dienophiles.

4.4 Experimental Section

4.4.1 General procedure for peptide coupling.

(a) To a stirred solution of the TFA salt of C-protected peptide in CH_2Cl_2 (5 mL/mmol) at 0 ^oC (ice-bath) under N_2 was added successively Et_3N (5 equiv.), HOBt (1.2 equiv.), a solution of the Boc-protected amino acid (1 equiv.) in CH_2Cl_2 (2.5 mL/mmol), and EDC (1.2 equiv.). The mixture was allowed to warm to r.t., and stirring was continued for 15 h. The mixture was diluted with CH_2Cl_2 and washed with 10% aq. citric acid, aq. saturated $NaHCO_3$, H_2O and NaCl solution. The organic phase was dried (Na_2SO_4), evaporated, and the residue was purified using flash column chromatography to get the pure material.

(b) To a stirred solution of TFA salt of C-protected peptide in CH_2Cl_2 (3 mL/mmol) and DMF (2 mL/mmol) at 0 ^oC (ice-bath) under N_2 was added successively Et_3N (5 equiv.), HOBt (1.2 equiv.), a solution of the Boc-protected amino acid (1 equiv.) in CH_2Cl_2 (2.5 mL/mmol), and EDC (1.2 equiv.). The mixture was allowed to warm to r.t., and stirring was continued for 15 h. The residue obtained after the removal of all volatiles was dried under vacuum for 1 h and then stirred in MeOH (10mL/mmol) for 20 min. The white precipitate was collected by filtration and thoroughly washed successively with 1:1 mixture of MeOH/H_2O and MeOH. The solid product was dried under high vacuum for several hours.

(c) To a stirred solution of N-Boc amino acid in CH_2Cl_2 (3 mL/mmol) at 0 ^oC (ice-bath) under N_2 was added Et_3N (1.2 equiv.) and isobutylchloroformate (1.2 eq). After stirring reaction mixture for 5 minutes, free amine compound (1 eq) in CH_2Cl_2 (3

mL/mmol) was added at the same temperature. Reaction mixture allowed to warm to room temperature and stirring was continued for 15 h. The mixture was diluted with CH_2Cl_2 and washed with 10% aq. citric acid, aq. saturated $NaHCO_3$, H_2O and NaCl solution. The organic phase was dried (Na_2SO_4), evaporated, and the residue was purified using flash column chromatography to get the pure material.

4.4.2 General procedure for Boc deprotection

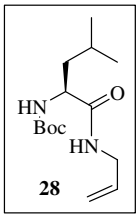
CF_3COOH (5 mL/mmol) was added to an ice-cold solution of the Boc-protected peptide in CH_2Cl_2 (10 mL/mmol). The reaction mixture was allowed to warm to r.t. and stirring was continued for 2 h. The mixture was evaporated and the residue dried under high vaccum. The salts with CF_3COOH were used without further purification and characterization.

4.4.3 General Procedure of enyne cycloisomerization for macrocyclization

30 mol% $Pd(OAc)_2$, 60 mol% $(o\text{-tolyl})_3P$ were added to warm HPLC grade acetonitrile ($1.5x10^{-3}M$) and solution refluxed at 110 ^oC for 30 min. Then glacial acetic acid (10 eq) wad added to refluxing solution. After 10 min acylic peptide was added in single portion and the reaction continued for 15 h at the same temperature. The reaction mixture was filtered through a pad of Celite and washed with hot acetonitrile (100 ml). The filtrate was concentrated and the product was isolated by flash column chromatography on (230-400) silica gel using CH_2Cl_2/MeOH as eluent.

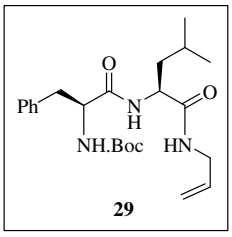
4.4.4 General Procedure for Diels-Alder Reaction

A solution of 1,3-Diene compound and dienophile in 1,2-dichloroethane was heated at 85 ^{o}C for 15-36 h. After evaporation of solvent crude compound purified by flash column chromatography on (230-400) silica gel using CH_2Cl_2/MeOH as eluent.



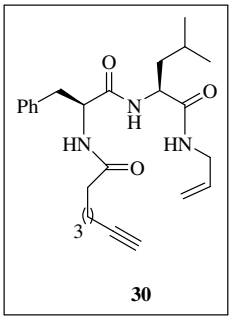
28

Compound 28: Compound was prepared by following general procedure **4.4.1c** (yield 65%), mp 85-87 ^{o}C; $[\alpha]_D^{25}$ = -39.5 *(c* 1, $CHCl_3$); IR (KBr) 3328, 2964, 1660, 1541 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$): δ 6.29 (br s, 1H), 5.87-5.77 (m, 1H), 5.20 (dd, J_1 = 1.6 Hz, J_2 = 3.2 Hz, 1H), 5.16 (dd, J_1 = 1.6 Hz, J_2 = 3.2 Hz, 1H), 4.89 (br s, 1H), 4.09 (br s, 1H), 3.87 (t, *J* = 5.6 Hz, 2H), 1.72-1.63 (m, 2H), 1.59-1.46 (m, 1H), 1.44 (s, 9H), 0.94 (d, *J* = 4.3 Hz, 3H), 0.92 (d, *J* = 4.0 Hz, 3H); CIMS *m/z* calcd for $C_{14}H_{26}N_2O_3$ 270, found 272 (M+2).



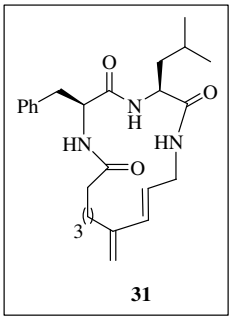
29

Compound 29: Compound was prepared by following general procedure **4.4.1b** (yield 85%), mp 159-161 ^{o}C; $[\alpha]_D^{25}$ = +0.2 *(c* 0.5, DMSO); IR (KBr) 3326, 2961, 1693, 1642 cm^{-1}; ^{1}H NMR (400MHz, DMSO-*d6*): δ 7.94 (t, *J* = 5.6 Hz, 1H), 7.85 (d, *J* = 8.3 Hz, 1H), 7.27-7.18 (m, 5H), 6.91 (t, *J* = 8.6 Hz, 1H), 5.79-5.71 (m, 1H), 5.10 (dd, J_1 = 1.6 Hz, J_2 = 17.2 Hz, 1H), 5.03 (dd, J_1 = 1.6 Hz, J_2 = 10.2 Hz, 1H), 4.35-4.29 (m, 1H), 4.19-4.14 (m, 1H), 3.68-3.65 (m, 2H), 2.95 (dd, J_1 = 4.6 Hz, J_2 = 14.0 Hz, 1H), 2.73 (dd, J_1 = 10.2 Hz, J_2 = 13.7 Hz, 1H), 1.62-1.57 (m, 1H), 1.49-1.34 (m, 2H), 1.30 (s, 9H), 0.88 (d, *J* = 6.4 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 3H); ESMS *m/z* calcd for $C_{23}H_{35}N_3O_4$ 417, found 418 (M+1).



30

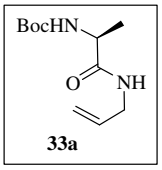
Compound 30: Compound was prepared by following general procedure **4.4.1b** (yield 83%), mp 165-166 °C; $[\alpha]_D^{25}$ = -7.0 *(c* 1, DMSO); IR (KBr), 3278, 3087, 2955, 1634, 1547 cm^{-1}; ^1H NMR (400MHz, DMSO-*d6*): δ 8.00 (d, *J* = 8.3 Hz, 1H), 7.92 (t, *J* = 8.3 Hz, 2H), 7.28-7.14 (m, 5H), 5.81-5.71 (m, 1H), 5.10 (dd, J_1 = 1.9 Hz, J_2 = 14.0 Hz, 1H), 5.03 (dd, J_1 = 1.6 Hz, J_2 = 10.8 Hz, 1H), 4.56-4.51 (m, 1H), 4.28 (q, *J* = 6.4 Hz, 1H), 3.66 (t, *J* = 5.4 Hz, 2H), 3.00 (dd, J_1 = 4.6 Hz, J_2 = 13.7 Hz, 1H), 2.76-2.70 (m, 2H), 2.08-2.01 (m, 4H), 1.60-1.41 (m, 5H), 1.29-1.22 (m, 2H), 0.88 (d, *J* = 6.4 Hz, 3H), 0.88 (d, *J* = 6.4 Hz, 3H) (**Spectrum No. 32**); ^{13}C NMR (50MHz, DMSO-*d6*): δ 171.8, 171.6, 171.1, 137.9, 135.0, 129.1 (2C), 127.9(2C), 126.1, 114.8, 84.2, 71.0, 53.7, 51.1, 41.1, 40.7, 37.2, 34.5, 27.2, 24.2, 24.1, 22.9, 21.6, 17.4 (**Spectrum No. 33**); ESMS *m/z* 426 (M+1); HRMS calcd for $C_{25}H_{36}N_3O_3$ 426.2756, found 426.2752.



31

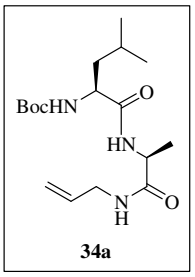
Compound 31: Compound was prepared by following general procedure **4.4.3** (yield 28%), mp 197-199 °C; $[\alpha]_D^{25}$ = -10.0 *(c* 0.1, DMSO); IR (KBr), 3300, 2955, 1651, 1539 cm^{-1}; ^1H NMR (400MHz, DMSO-*d6*): δ 7.97 (d, *J* = 7.8 Hz, 1H), 7.89 (t, *J* = 7.8 Hz, 2H), 7.29-7.17 (m, 5H), 6.07 (d, *J* = 13.8 Hz, 1H), 5.58-5.52 (m, 1H), 4.90 (d, *J* = 1.9 Hz, 2H), 4.28 (q, *J* = 6.4 Hz, 1H), 3.93-3.89 (m, 2H), 3.44-3.37 (m, 1H), 2.92-2.83 (m, 2H), 2.22-1.91 (m, 4H), 1.59-1.39 (m, 4H), 1.36-1.23 (m, 3H), 0.84 (d, *J* = 6.4 Hz, 3H), 0.78 (d, *J* = 6.4 Hz, 3H) (**Spectrum No. 34**); ^{13}C NMR (50MHz, DMSO-*d6*): δ 172.3, 171.4, 170.7, 145.7, 137.5, 132.5, 128.6 (2C),

128.1(2C), 126.8, 126.3, 115.2, 55.8, 52.3, 40.8, 37.1, 35.1, 34.8, 32.7, 28.3, 24.5, 24.3, 22.6, 21.9 (**Spectrum No. 35**); 1-D nOe NMR (400 MHz, DMSO-*d6*) (**Spectrum No. 36**); ESMS *m/z* 426 (M+1); HRMS calcd for $C_{25}H_{36}N_3O_3$ 426.2756, found 426.2758.



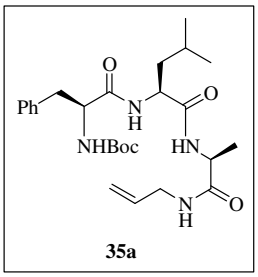
33a

Compound 33a: Compound was prepared by following general procedure **4.4.1a** (yield 66%), mp 108-110 ^oC; $[\alpha]_D^{25}$ = -37.0 *(c* 1, $CHCl_3$); IR (KBr) 3303, 2980, 1657, 1529 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$): δ 6.28 (br s, 1H), 5.87-5.78 (m, 1H), 5.16 (dddd, J_1 = 10.5 Hz, J_2 = 10.5 Hz, J_3 = 1.5 Hz, J_4 = 1.5 Hz, 2H), 4.98 (br s, 1H), 4.17-4.14 (m, 1H), 3.88 (t, *J* = 5.5 Hz, 2H), 1.44 (s, 9H), 1.37 (d, *J* = 7.0 Hz, 3H); ESMS *m/z* calcd for $C_{11}H_{20}N_2O_3$ 228, found 173 (M-C_3H_5N).



34a

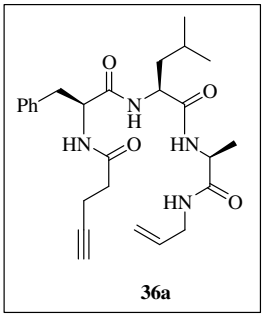
Compound 34a: Compound was prepared by following general procedure **4.4.1a** (yield 69%), mp 156-158 ^oC; $[\alpha]_D^{25}$ = -15.2 *(c* 0.5, DMSO); IR (KBr) 3290, 2954, 1674, 1634, 1536 cm^{-1}; ^1H NMR (400MHz, DMSO-*d6*): δ 6.65 (d, *J* = 7.0 Hz, 1H), 6.57 (br s, 1H), 5.86-5.76 (m, 1H), 5.15 (dddd, J_1 = 10.9 Hz, J_2 = 1.6 Hz, J_3 = 10.2 Hz, J_4 = 1.6 Hz, 2H), 4.89 (d, *J* = 7.0 Hz, 1H), 4.51-4.44 (m, 1H), 4.07 (br s, 1H), 3.90-3.81 (m, 2H), 1.70-1.60 (m, 3H), 1.44 (s, 9H), 1.39 (d, *J* = 7.0 Hz, 3H), 0.94 (dd, J_1 = 5.1 Hz, J_2 = 4.8 Hz, 6H); ESMS *m/z* calcd for $C_{17}H_{31}N_3O_4$ 341, found 342 (M+1).



35a

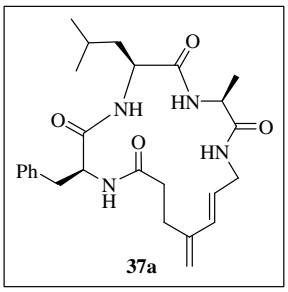
Compound 35a. Compound was prepared by following general procedure **4.4.1b** (yield 75%), mp 222-224 ^oC; $[\alpha]_D^{25}$ = -11.4 *(c* 1, DMSO); IR (KBr), 3290, 2928, 1641, 1543 cm^{-1}; ^1H NMR (400MHz, DMSO-*d6*): δ 7.97-7.89 (m, 3H), 7.25-7.15 (m, 5H), 6.90 (d, *J* = 8.3 Hz, 1H), 5.81-5.72 (m, 1H), 5.09 (dddd, J_1 = 1.6

Hz, J_2 = 15.6 Hz, J_3 = 18.3 Hz, J_4 = 8.9 Hz, 2H), 4.36-4.13 (m, 3H), 3.69-3.66 (m, 2H), 2.98-2.94 (m, 1H), 2.76-2.69 (m, 1H), 1.66-1.60 (m, 1H), 1.48-1.44 (m, 2H), 1.29 (s, 9H), 1.21 (d, J = 7.2 Hz, 3H), 0.86 (dd, J_1 = 6.7 Hz, J_2 = 6.4 Hz, 6H); ESMS *m/z* calcd for $C_{26}H_{40}N_4O_5$ 488, found 489 (M+1).



36a

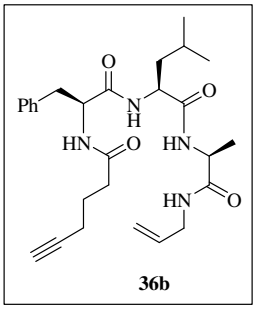
Compound 36a: Compound was prepared by following general procedure **4.4.1b** (yield 75%), mp 264-266 °C; $[\alpha]_D^{25}$ = -6.6 *(c* 0.5, DMSO); IR (KBr), 3289, 3076, 2926, 1635, 1548 cm^{-1}; ^1H NMR (400MHz, DMSO-*d6*): δ 8.08 (d, J = 8.1 Hz, 1H), 8.01 (d, J = 8.1 Hz, 1H), 7.92 (t, J = 5.6 Hz, 1H), 7.87 (d, J = 7.5 Hz, 1H), 7.26-7.15 (m, 5H), 5.82-5.72 (m, 1H), 5.13 (dd, J_1 = 1.6 Hz, J_2 = 3.5 Hz, 1H), 5.09 (dd, J_1 = 1.6 Hz, J_2 = 3.5 Hz, 1H), 4.55-4.49 (m, 1H), 4.31-4.21 (m, 2H), 3.69-3.66 (m, 2H), 3.01 (dd, J_1 = 4.3 Hz, J_2 = 14.0 Hz, 1H), 2.77-2.67 (m, 2H), 2.28-2.19 (m, 4H), 1.55 (sept, J = 6.7 Hz, 1H), 1.45-1.44 (m, 2H), 1.21 (d, J = 7.0 Hz, 3H), 0.88 (d, J = 6.7 Hz, 3H), 0.83 (d, J = 6.4 Hz, 3H) (**Spectrum No. 37**); ^{13}C NMR (50MHz, DMSO-*d6*): δ 171.8, 171.4, 171.1, 170.2, 137.8, 135.0, 129.1(2C), 127.9(2C), 126.1, 114.8, 83.5, 71.1, 53.7, 51.0, 48.2, 40.7, 40.6, 37.3, 34.0, 24.0, 23.0, 21.6, 18.3, 14.0 (**Spectrum No. 38**); ESMS *m/z* 469 (M+1); HRMS calcd for $C_{26}H_{37}N_4O_4$ 469.2814, found 469.2821.



37a

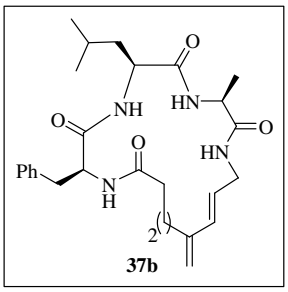
Compound 37a: Compound was prepared by following general procedure **4.4.3** (yield 30%), mp 276-278 °C; $[\alpha]_D^{25}$ = -36.7 *(c* 0.3, DMSO); IR (KBr), 3315, 2957, 1650, 1531 cm^{-1}; ^1H NMR (400MHz, DMSO-*d6*): δ 7.98 (d, J = 7.0 Hz, 1H), 7.93 (t, J = 5.5 Hz, 1H), 7.84 (d, J = 8.3 Hz, 1H), 7.55 (d, J = 8.3 Hz, 1H),

7.27-7.17 (m, 5H), 6.04 (d, *J* = 15.8 Hz, 1H), 5.61-5.54 (m, 1H), 4.91-4.90 (m, 2H), 4.51-4.45(m, 1H), 4.21-4.15 (m, 1H), 4.08-4.04 (m, 1H), 3.86-3.79 (m, 1H), 3.64-3.60 (m, 1H), 3.04-2.99 (m, 1H), 2.90-2.84 (m, 1H), 2.67-2.61 (m, 1H), 2.38-2.17 (m, 3H), 1.59-1.45 (m, 3H), 1.32 (d, *J* = 7.2 Hz, 3H), 0.89 (dd, J_1 = 6.0 Hz, J_2 = 6.0 Hz, 6H) (**Spectrum No. 39**); ^{13}C NMR (50MHz, DMSO-*d6*): δ 171.5, 171.3, 171.1, 171.0, 145.1, 137.7, 130.6, 128.9(2C), 128.8, 128.1(2C), 126.3, 115.0, 55.3, 52.2, 49.4, 40.7, 40.3, 37.3, 26.9, 24.2, 23.0, 21.7, 21.3, 16.9 (**Spectrum No. 40**); 1-D nOe NMR (400 MHz, DMSO-*d6*) (**Spectrum No. 41**); ROESY spectrum (400 MHz, DMSO-*d6*) (**Spectrum No. 42**); ESMS m/z 468 (M); HRMS calcd for $C_{26}H_{37}N_4O_4$ 469.2814, found 469.2804.

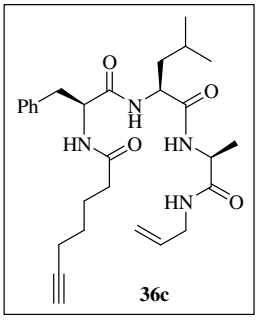


36b

Compound 36b: Compound was prepared by following general procedure **4.4.1b** (yield 73%), mp 245-247 ^{o}C; $[\alpha]_D^{25}$ = -10.6 *(c* 0.5, DMSO); IR (KBr), 3285, 3079, 2956, 1634, 1542 cm^{-1}; ^{1}H NMR (400MHz, DMSO-*d6*): δ 8.04 (d, *J* = 8.3 Hz, 1H), 7.99 (d, *J* = 8.1 Hz, 1H), 7.94-7.88 (m, 2H), 7.26-7.15 (m, 5H), 5.81-5.72 (m, 1H), 5.13 (dd, J_1 = 1.6 Hz, J_2 = 3.5 Hz, 1H), 5.09 (dd, J_1 = 1.6 Hz, J_2 = 3.5 Hz, 1H), 4.55-4.49 (m, 1H), 4.32-4.23 (m, 2H), 3.69-3.66 (m, 2H), 3.00 (dd, J_1 = 4.0 Hz, J_2 = 14.0 Hz, 1H), 2.75-2.69 (m, 2H), 2.14-1.97 (m, 4H), 1.61-1.45 (m, 5H), 1.21 (d, *J* = 7.0 Hz, 3H), 0.88 (d, *J* = 6.7 Hz, 3H), 0.84 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR (50MHz, DMSO-*d6*): δ 171.8, 171.5, 171.4, 171.3, 138.0, 135.0, 129.1(2C), 127.9(2C), 126.1, 114.8, 84.0, 71.2, 53.7, 51.0, 48.2, 40.6, 40.3, 37.2, 34.0, 24.2, 24.1, 23.1, 21.5, 18.3, 17.2; ESMS *m/z* 483 (M); HRMS calcd for $C_{27}H_{39}N_4O_4$ 483.2971, found 483.2964.

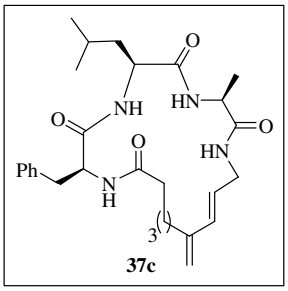


Compound 37b: Compound was prepared by following general procedure **4.4.3** (yield 45%), mp 148-150 ^{o}C; $[\alpha]_D^{25}$ = +12. *(c* 0.25, DMSO); IR (KBr), 3308, 2957, 1651, 1530 cm^{-1}; ^{1}H NMR (400MHz, DMSO-*d6*): δ 8.05 (d, *J* = 5.4 Hz, 1H), 7.92 (d, *J* = 8.3 Hz, 1H), 7.78 (dd, J_1 = 4.6 Hz, J_2 = 6.4 Hz, 1H), 7.68 (d, *J* = 7.2 Hz, 1H), 7.28-7.17 (m, 5H), 6.11 (d, *J* = 16.1 Hz, 1H), 5.77-5.72 (m, 1H), 4.90 (d, *J* = 18.3 Hz, 2H), 4.43-4.38 (m, 1H), 4.11-4.09 (m, 1H), 3.95-3.88 (m, 2H), 3.41-3.30 (m, 1H), 3.10 (dd, J_1 = 3.3 Hz, J_2 = 14.0 Hz, 1H), 2.80 (dd, J_1 = 10.2 Hz, J_2 = 15.0 Hz, 1H), 2.19-2.11 (m, 3H), 1.97-1.94 (m, 1H), 1.70-1.51 (m, 5H), 1.22 (d, *J* = 7.0 Hz, 3H), 0.89-0.85 (m, 6H); ^{13}C NMR (100MHz, DMSO-*d6*): δ 172.1, 171.6, 171.3, 171.2, 145.6, 138.0, 131.9, 128.9 (2C), 128.1(2C), 127.5, 126.3, 114.1, 54.5, 51.9, 49.9, 41.0, 40.7, 37.1, 35.2, 31.8, 24.1, 23.1, 21.7, 18.3, 16.5; ESMS *m/z* 483 (M); HRMS calcd for $C_{27}H_{39}N_4O_4$ 483.2971, found 483.2981.

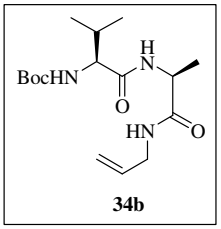


Compound 36c: Compound was prepared by following general procedure **4.4.1b** (yield 75%), mp 240-242 ^{o}C; $[\alpha]_D^{25}$ = -10.0 *(c* 0.5, DMSO); IR (KBr), 3285, 3067, 2933, 1634, 1544 cm^{-1}; ^{1}H NMR (400MHz, DMSO-*d6*): δ 8.01 (d, *J* = 2.4 Hz, 2H), 7.99-7.88 (m, 2H), 7.26-7.14 (m, 5H), 5.82-5.72 (m, 1H), 5.13 (dd, J_1 = 1.6 Hz, J_2 = 3.2 Hz, 1H); 5.04 (dd, J_1 = 1.3 Hz, J_2 = 3.2 Hz, 1H); 4.55-4.50 (m, 1H), 4.32-4.21 (m, 2H), 3.69-3.66 (m, 2H), 3.00 (dd, J_1 = 4.3 Hz, J_2 = 4.0 Hz, 1H), 2.75-2.69 (m, 2H), 2.08-2.01 (m, 4H), 1.56 (sept, *J* = 6.4 Hz, 1H), 1.46-1.41 (m, 4H), 1.28-1.22 (m, 2H), 1.21 (d, *J* = 7.0 Hz, 3H), 0.88 (d, *J* = 6.4 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (50MHz, DMSO-*d6*): δ 171.8, 17179, 171.4, 171.3, 138.0,

135.0, 129.1(2C), 127.9(2C), 126.1, 114.8, 84.2, 71.1, 53.6, 51.0, 48.1, 40.7, 40.3, 37.2, 34.5, 27.2, 24.2, 24.0, 23.1, 21.5, 18.3, 17.4; ESMS *m/z* 497 (M+1); HRMS calcd for $C_{28}H_{41}N_4O_4$ 497.3127, found 497.3138.

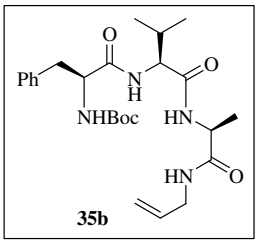


Compound 37c: Compound was prepared by following general procedure **4.4.3** (yield 54%), mp 170-172 ^{o}C; $[\alpha]_D^{25}$ = +21.6 *(c* 0.25, DMSO); IR (KBr), 3309, 2932, 1648, 1532 cm^{-1}; ^{1}H NMR (400MHz, DMSO-*d6*): δ 8.02 (d, *J* = 6.2 Hz, 1H), 7.93 (d, *J* = 4.8 Hz, 1H), 7.91 (d, *J* = 7.2 Hz, 1H), 7.55 (t, *J* = 4.8 Hz, 1H), 7.34-7.18 (m, 5H), 6.15 (d, *J* = 15.8 Hz, 1H), 5.98-5.84 (m, 1H), 4.90 (dd, J_1 = 2.1 Hz, J_2 = 13.2 Hz, 2H), 4.40-4.36 (m, 1H), 3.98-3.91 (m, 2H), 3.80-3.74 (m, 1H), 3.64-3.54 (m, 1H), 3.23 (dd, J_1 = 3.5 Hz, J_2 = 15.5 Hz, 1H), 2.74 (dd, J_1 = 10.7 Hz, J_2 = 14.2 Hz, 1H), 2.49-1.94 (m, 4H), 1.64-1.40 (m, 5H), 1.36-1.21 (m, 5H), 0.91-0.83 (m, 6H); ^{13}C NMR (50MHz, DMSO-*d6*): δ 172.6, 172.5, 171.7, 171.3, 146.7, 138.3, 132.9, 130.8(2C), 128.9 (2C), 126.2, 115.1, 54.3, 52.8, 49.4, 41.9, 40.7, 36.3, 33.9, 33.0, 27.4, 24.0, 23.4, 21.9, 21.6, 21.2, 16.3; ESMS *m/z* 497 (M+1); HRMS calcd for $C_{28}H_{41}N_4O_4$ 497.3127, found 497.3127.



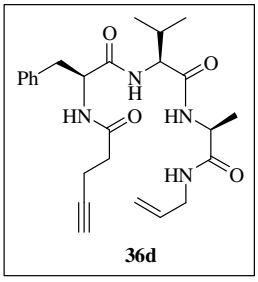
Compound 34b: Compound was prepared by following general procedure **4.4.1a** (yield 69%), mp 199-201 ^{o}C; $[\alpha]_D^{25}$ = -7.9 *(c* 1, DMSO); IR (KBr) 3315, 2977, 1676, 1638, 1525 cm^{-1}; ^{1}H NMR (400MHz, DMSO-*d6*): δ 7.99 (br s, 1H), 7.84 (d, *J* = 7.2 Hz, 1H), 6.72 (d, *J* = 8.3 Hz, 1H), 5.81-5.72 (m, 1H), 5.12 (dd, J_1 = 1.6 Hz, J_2 = 13.4 Hz, 1H), 5.03 (dd, J_1 = 1.6 Hz, J_2 = 10.2 Hz, 1H), 4.30 (quint, *J* = 7.0 Hz, 1H), 3.79 (t, *J* = 8.1 Hz, 1H), 3.69-3.64 (m, 2H), 1.97-1.93 (m, 1H), 1.38 (s, 9H), 1.20 (d, *J* = 7.0 Hz, 3H), 0.84 (d, *J* =

6.7 Hz, 3H), 0.80 (d, *J* = 6.7 Hz, 3H); ESMS *m/z* calcd for $C_{16}H_{29}N_3O_4$ 327, found 328 (M+1).



35b

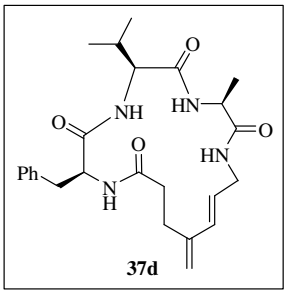
Compound 35b. Compound was prepared by following general procedure **4.4.1b** (yield 75%), mp 236-238 ^{o}C; $[\alpha]_D^{25}$ = -7.0 *(c* 1, DMSO); IR (KBr), 3296, 2965, 1638, 1545 cm^{-1}; ^{1}H NMR (400MHz, DMSO-*d6*): δ 8.06 (d, *J* = 7.2 Hz, 1H), 7.95 (t, *J* = 5.6 Hz, 1H), 7.68 (d, *J* = 8.9 Hz, 1H), 7.28-7.16 (m, 5H), 7.00 (d, *J* = 8.6 Hz, 1H), 5.81-5.72 (m, 1H), 5.10 (dd, J_1 = 1.9 Hz, J_2 = 17.2 Hz, 1H), 5.03 (dd, J_1 = 1.6 Hz, J_2 = 10.5 Hz, 1H), 4.29-4.16 (m, 3H), 3.70-3.66 (m, 2H), 2.97 (dd, J_1 = 4.3 Hz, J_2 = 14.2 Hz, 1H), 2.73 (dd, J_1 = 10.7 Hz, J_2 = 14.0 Hz, 1H), 2.00-1.95 (m, 1H), 1.29 (s, 9H), 1.21 (d, *J* = 7.2 Hz, 3H), 0.86 (d, *J* = 6.7 Hz, 3H), 0.83 (d, *J* = 7.0 Hz, 3H); ESMS *m/z* calcd for $C_{25}H_{38}N_4O_5$ 474, found 475 (M+1).



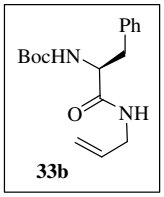
36d

Compound 36d: Compound was prepared by following general procedure **4.4.1b**. (yield 70%); mp 281-282 ^{o}C; $[\alpha]_D^{25}$ = -7.8 *(c* 1, DMSO); IR (KBr), 3281, 3076, 2966, 1634, 1547 cm^{-1}; ^{1}H NMR (400MHz, DMSO-*d6*): δ 8.12 (d, *J* = 8.3 Hz, 1H), 7.99-7.94 (m, 2H), 7.83 (d, *J* = 8.9 Hz, 1H), 7.24-7.15 (m, 5H), 5.80-5.73 (m, 1H), 5.12 (dd, J_1 = 1.6 Hz, J_2 = 15.3 Hz, 1H), 5.03 (dd, J_1 = 1.6 Hz, J_2 = 7.2 Hz, 1H), 4.60-4.57 (m, 1H), 4.29-4.26 (m, 1H), 4.19-4.15 (m, 1H), 3.69-3.66 (m, 2H), 3.01 (dd, J_1 = 4.6 Hz, J_2 = 14.2 Hz, 1H), 2.74 (dd, J_1 = 7.7 Hz, J_2 = 14.0 Hz, 1H), 2.67 (s, 1H), 2.26-2.22 (m, 4H), 1.98 (sext, *J* = 6.7 Hz, 1H), 1.22 (d, *J* = 7.2 Hz, 3H), 0.86-0.82 (m, 6H); ^{13}C NMR (50MHz, DMSO-*d6*): δ 171.7, 171.0, 170.3, 170.2, 137.8, 135.0, 129.1(2C), 127.9(2C), 126.1, 114.9, 83.5, 71.2, 57.4, 53.7, 48.1, 40.6, 37.2, 34.0, 30.6, 19.1, 18.3,

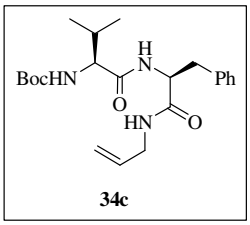
18.0, 14.0; ESMS *m/z* 455 (M+1); HRMS calcd for $C_{25}H_{35}N_4O_4$ 455.2658, found 455.2654.



Compound 37d: Compound was prepared by following general procedure **4.4.3**. (yield 40%); mp 294-296 ^oC; $[\alpha]_D^{25}$ = -85.2 *(c* 0.25, DMSO); IR (KBr), 3302, 2966, 1655, 1530 cm^{-1}; ^1H NMR (400MHz, DMSO-*d6*): δ 8.26 (d, *J* = 6.7 Hz, 1H), 8.05 (t, *J* = 5.6 Hz, 1H), 7.98 (d, *J* = 8.1 Hz, 1H), 7.56 (d, *J* = 8.9 Hz, 1H), 7.49-7.17 (m, 5H), 6.05 (d, *J* = 16.1 Hz, 1H), 5.57-5.51 (m, 1H), 4.92 (d, *J* = 6.4 Hz, 2H), 4.38-4.33 (m, 1H), 4.01 (dd, J_1 = 7.0 Hz, J_2 = 8.6 Hz, 1H), 3.95-3.78 (m, 2H), 3.54-3.50 (m, 1H), 3.02 (dd, J_1 = 4.3 Hz, J_2 = 14.0 Hz, 1H), 2.82 (dd, J_1 = 10.5 Hz, J_2 = 14.0 Hz, 1H), 2.65-2.59 (m, 1H), 2.49-2.21 (m, 2H), 2.16-2.08 (m, 1H), 2.05-1.97 (m, 1H), 1.22 (d, *J* = 7.0 Hz, 3H), 0.87-0.72 (m, 6H); ^{13}C NMR (50MHz, DMSO-*d6*): δ 171.8, 171.3, 171.0, 170.2, 145.0, 137.8, 130.8, 129.1, 128.8(2C), 128.3(2C), 126.4, 115.2, 58.4, 56.0, 49.7, 40.7, 37.3, 33.9, 31.0, 26.7, 19.2, 18.1, 16.7; ESMS *m/z* 455 (M+1); HRMS calcd for $C_{25}H_{35}N_4O_4$ 455.2658, found 455.2657.

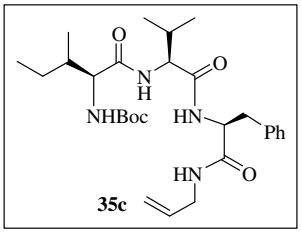


Compound 33b: Compound was prepared by following general procedure **4.4.1c** (yield 84%), mp 106-107 ^oC; $[\alpha]_D^{25}$ = -1.5 *(c* 1, $CHCl_3$); IR (KBr) 3340, 2986, 1685, 1523 cm^{-1}; ^1H NMR (400MHz, $CDCl_3$): δ 7.31-7.19 (m, 5H), 5.97 (br s, 1H), 5.74-5.64 (m, 1H), 5.10-5.01 (m, 3H), 4.33 (d, *J* = 7.2 Hz, 1H), 3.79 (t, *J* = 5.4 Hz, 2H), 3.05 (d, *J* = 7.0 Hz, 2H), 1.39 (s, 9H); CIMS *m/z* calcd for $C_{17}H_{24}N_2O_3$ 304, found 306 (M+2).



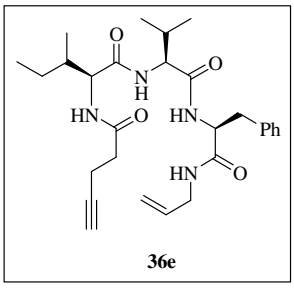
34c

Compound 34c: Compound was prepared by following general procedure **4.4.1c** (yield 60%), mp 171-172 ^{o}C; $[\alpha]_D^{25}$ = -42.8 *(c* 1, $CHCl_3$); IR (KBr) 3294, 3085, 2965, 1646, 1525 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$): δ 7.31-7.18 (m, 5H), 6.49 (br s, 1H), 6.29 (br s, 1H), 5.74-5.64 (m, 1H), 5.06 (dd, J_1 = 1.3 Hz, J_2 = 3.7 Hz, 1H), 5.03 (dd, J_1 = 8.6 Hz, J_2 = 9.9 Hz, 1H), 4.84-4.82 (m, 1H), 4.68 (q, *J* = 7.5 Hz, 1H), 3.87 (t, *J* = 5.4 Hz, 1H), 3.85-3.72 (m, 2H), 3.17 (dd, J_1 = 6.4 Hz, J_2 = 13.7 Hz, 1H), 3.05 (dd, J_1 = 7.0 Hz, J_2 = 13.7 Hz, 1H), 2.18-2.10 (m, 1H), 1.25 (s, 9H), 0.90 (d, *J* = 6.7 Hz, 3H), 0.80 (d, *J* = 6.7 Hz, 3H); CIMS *m/z* calcd for $C_{22}H_{33}N_3O_4$ 403, found 404 (M+1).



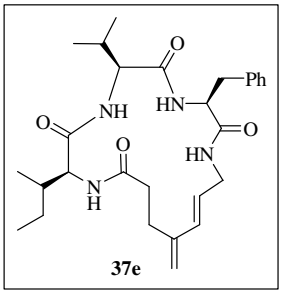
35c

Compound 35c: Compound was prepared by following general procedure **4.4.1b** (yield 80%), mp 207-208 ^{o}C; $[\alpha]_D^{25}$ = -39.0 *(c* 0.5, CH_3OH); IR (KBr), 3285, 2965, 1640, 1548 cm^{-1}; ^{1}H NMR (400MHz, DMSO-*d6*): δ 8.06-8.01 (m, 2H), 7.57 (d, *J* = 8.6 Hz, 1H), 7.25-7.15 (m, 5H), 6.85 (d, *J* = 8.9 Hz, 1H), 5.77-5.64 (m, 1H), 5.03 (dd, J_1 = 1.6 Hz, J_2 = 8.6 Hz, 1H), 5.01 (dd, J_1 = 1.7 Hz, J_2 = 13.2 Hz, 1H), 4.55-4.49 (m, 1H), 4.17 (t, *J* = 7.4 Hz, 1H), 3.80 (t, *J* = 8.1 Hz, 1H), 3.63 (t, *J* = 3.7 Hz, 2H), 2.93 (dd, J_1 = 5.9 Hz, J_2 = 13.7 Hz, 1H), 2.81 (dd, J_1 = 8.6 Hz, J_2 = 14.0 Hz, 1H), 1.93-1.88 (m, 1H), 1.74-1.66 (m, 1H), 1.42-1.41 (m, 1H), 1.41 (s, 9H), 1.09-1.02 (m, 1H), 0.85-0.74 (m, 12H); CIMS *m/z* calcd for $C_{28}H_{44}N_4O_5$ 516, found 517 (M+1).



36e

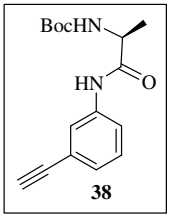
Compound 36e: Compound was prepared by following general procedure **4.4.1b**. (yield 71%); mp 271-272 ^{o}C; $[\alpha]_{D}^{25}$ = +26.2 *(c* 0.5, DMSO); IR (KBr), 3290, 1636, 1545 cm^{-1}; ^{1}H NMR (400MHz, DMSO-*d6*): δ 8.04-7.98 (m, 2H), 7.73 (d, *J* = 8.8 Hz, 1H), 7.31 (bs, 1H), 7.25-7.15 (m, 5H), 5.73-5.65 (m, 1H), 5.03 (dd, J_1 = 1.6 Hz, J_2 = 17.2 Hz, 1H), 4.99 (dd, J_1 = 1.6 Hz, J_2 = 10.2 Hz, 1H), 4.55-4.49 (m, 1H), 4.18 (t, *J* = 8.3 Hz, 1H), 4.09 (dd, J_1 = 7.2 Hz, J_2 = 8.6 Hz, 1H), 3.66-3.31 (m, 2H), 2.95 (dd, J_1 = 5.6 Hz, J_2 = 13.7 Hz, 1H), 2.82 (dd, J_1 = 8.8 Hz, J_2 = 13.7 Hz, 1H), 2.70 (s, 1H), 2.40-2.29 (m, 4H), 1.88 (sext, *J* = 6.7 Hz, 1H), 1.71-1.69 (m, 1H), 1.43-1.38 (m, 1H), 1.08-1.05 (m, 1H), 0.80-0.73 (m, 12H); ^{13}C NMR (50MHz, DMSO-*d6*) 170.9, 170.4(2C), 170.2, 137.5, 134.8, 129.0(2C), 127.9(2C), 126.1, 114.9, 83.6, 71.1, 57.8, 57.0, 53.9, 40.7, 37.6, 36.1, 34.0, 30.4, 24.3, 19.0, 18.1, 15.3, 14.2, 10.8; ESMS *m/z* 497 (M+1); HRMS calcd for $C_{28}H_{41}N_4O_4$ 497.3127, found 497.3123.



37e

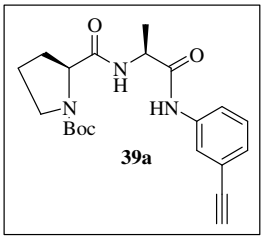
Compound 37e: Compound was prepared by following general procedure **4.4.3** (yield 46%); mp 326-328 ^{o}C; $[\alpha]_{D}^{25}$ = -92.8 *(c* 0.25, DMSO); IR (KBr), 3307, 2965, 1652, 1532 cm^{-1}; ^{1}H NMR (400MHz, DMSO-*d6*): δ 8.14-8.12 (m, 2H), 7.65 (d, *J* = 8.6 Hz, 1H), 7.51 (d, *J* = 8.6 Hz, 1H), 7.28-7.14 (m, 5H), 6.06 (d, *J* = 15.9 Hz, 1H), 5.52-5.44 (m, 1H), 4.92 (d, *J* = 7.5 Hz, 2H), 4.20 (q, *J* = 7.4 Hz, 1H), 4.04-3.98 (m, 2H), 3.78-3.71 (m, 1H), 3.49-3.45 (m, 1H), 3.03 (dd, J_1 = 7.2 Hz, J_2 = 13.4 Hz, 1H), 2.92 (dd, J_1 = 7.52 Hz, J_2 = 13.4 Hz, 1H), 2.67-2.62 (m, 1H), 2.50-2.14 (m, 3H), 1.85 (sext, *J* = 6.7 Hz, 1H), 1.71-1.67 (m, 1H), 1.48-1.42 (m, 1H), 1.19-1.11 (m, 1H), 0.86-0.81 (m, 6H), 0.79-0.67 (m, 6H); ^{13}C NMR (50MHz, DMSO-*d6*): δ 171.5, 170.8,

170.5, 169.8, 145.0, 137.8, 130.6, 128.9(2C), 128.6, 128.1(2C), 126.2, 115.0, 58.9, 58.6, 55.5, 40.9, 36.7, 36.1, 33.8, 30.8, 27.0, 24.8, 19.4, 18.0, 15.5, 10.9; ESMS *m/z* 497 (M+1); HRMS calcd for $C_{28}H_{41}N_4O_4$ 497.3127, found 497.3141.



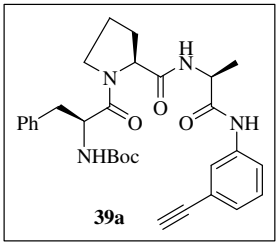
38

Compound 38: Compound was prepared by following general procedure **4.4.1a** (yield 68%), mp 106-107 ^oC; $[\alpha]_D^{25}$ = -51.0 *(c* 1, CH_3OH); IR (KBr) 3299, 2979, 1668, 1553 cm^{-1}; ^1H NMR (400MHz, DMSO-*d6*): δ 10.00 (s, 1H), 7.80 (t, *J* = 1.6 Hz, 1H), 7.57 (d, *J* = 8.3 Hz, 1H), 7.32 (t, *J* = 7.8 Hz, 1H), 7.16-7.05 (m, 2H), 4.14 (t, *J* = 2.5 Hz, 1H), 4.10 (t, *J* = 7.2 Hz, 1H), 1.38 (s, 9H), 1.26 (d, *J* = 7.0 Hz, 3H); ESMS *m/z* calcd for $C_{16}H_{20}N_2O_3$ 288, found 288 (M).



39a

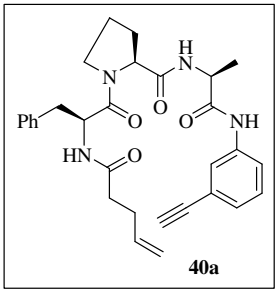
Compound 39a: Compound was prepared by following general procedure **4.4.1a** (yield 73%), mp 81-82 ^oC; $[\alpha]_D^{25}$ = -101.2 *(c* 0.5, CH_3OH); IR (KBr) 3296, 2978, 1662, 1550, 1406 cm^{-1}; ^1H NMR (400MHz, DMSO-*d6*): δ 8.97 (s, 1H), 7.80 (br s, 1H), 7.71 (br s, 1H), 7.26-7.18 (m, 2H), 6.91 (br s, 1H), 4.64 (br s, 1H), 4.30 (br s, 1H), 3.53-3.46 (m, 2H), 3.03 (s, 1H), 2.17 (br s, 2H), 1.92 (t, *J* = 6.2 Hz, 2H), 1.46-1.28 (m, 12H); ESMS *m/z* calcd for $C_{21}H_{27}N_3O_4$ 385, found 386 (M+1).



39a

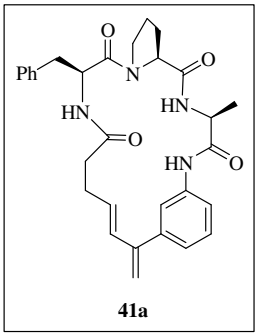
Compound 39a. Compound was prepared by following general procedure **4.4.1a** (yield 80%), mp 98-99 ^oC; $[\alpha]_D^{25}$ = -115.4 *(c* 0.5, CH_3OH); IR (KBr), 3297, 2978, 1639, 1546 cm^{-1}; ^1H NMR (400MHz, DMSO-*d6*): δ 9.89 (s, 1H), 8.13 (d, *J* = 6.7 Hz, 1H), 7.84 (s, 1H), 7.34-7.15 (m, 7H), 7.03 (d, *J* = 8.3 Hz, 1H), 4.41-4.32 (m, 3H), 4.15 (s, 1H), 3.67-3.55 (m, 2H), 2.93 (dd, J_1 = 3.7 Hz, J_2 = 14.2 Hz, 1H),

2.76 (dd, J_1 = 9.9 Hz, J_2 = 14.0 Hz, 1H), 2.11-2.05 (m, 1H), 1.95-1.88 (m, 3H), 1.36-1.22 (m, 12H); ESMS *m/z* calcd for $C_{30}H_{36}N_4O_5$ 532, found 533 (M+1).



40a

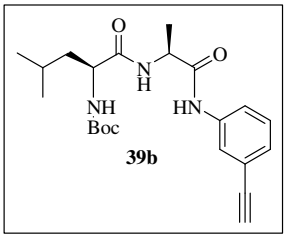
Compound 40a: Compound was prepared by following general procedure **4.4.1b** (yield 75%), mp 88-90 ^oC; $[\alpha]_D^{25}$ = -115.4 *(c* 0.5, MeOH); IR (KBr), 3290, 3077, 2928, 1633, 1549, 1448 cm^{-1}; ^1H NMR (400MHz, DMSO-*d6*): δ 9.86 (s, 1H), 8.19 (d, *J* = 6.4 Hz, 1H), 8.11 (d, *J* = 7.0 Hz, 1H), 7.83 (s, 1H), 7.61 (d, *J* = 5.10 Hz, 1H), 7.34-7.13 (m, 7H), 5.71-5.62 (m, 1H), 4.93 (d, *J* = 15.3 Hz, 1H), 4.87 (d, *J* = 8.1 Hz, 1H), 4.76-4.70 (m, 1H), 4.39-4.32 (m, 2H), 4.15 (s, 1H), 3.67-3.52 (m, 2H), 2.98 (dd, J_1 = 4.6 Hz, J_2 = 14.2 Hz, 1H), 2.78 (dd, J_1 = 5.1 Hz, J_2 = 14.1 Hz, 1H), 2.16-2.02 (m, 5H), 1.94-1.84 (m, 3H), 1.34 (d, *J* = 7.8 Hz, 3H); ^{13}C NMR (50MHz, DMSO-*d6*): δ 171.5, 171.4, 171.3, 170.3, 139.1, 137.8, 137.6, 129.3, 129.2 (2C), 128.0 (3C), 126.6, 126.2, 122.0, 119.8, 114.8, 83.3, 80.5, 59.6, 51.9, 49.9, 46.9, 36.7, 34.1, 29.1, 28.9, 24.5, 17.8; ESMS *m/z* 515 (M+1); HRMS calcd for $C_{30}H_{35}N_4O_4$ 515.2658, found 515.2673.



41a

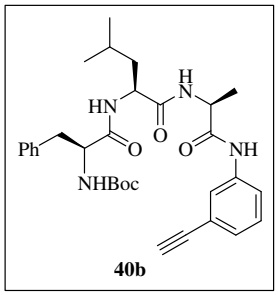
Compound 41a: Compound was prepared by following general procedure **4.4.3** (yield 50%), mp 186-187 ^oC; $[\alpha]_D^{25}$ = +7.6 *(c* 0.25, MeOH); IR (KBr), 3313, 2925, 1634, 1543, 1445 cm^{-1}; ^1H NMR (400MHz, DMSO-*d6*): δ 9.22 (s, 1H), 8.14 (d, *J* = 6.2 Hz, 1H), 7.92-7.85 (m, 2H), 7.45 (s, 1H), 7.37-7.01 (m, 7H), 6.32 (d, *J* = 15.8 Hz, 1H), 6.05-5.99 (m, 1H), 5.23 (d, *J* = 8.1 Hz, 2H), 4.58-

4.53 (m, 1H), 4.24-4.08 (m, 2H), 3.92-3.80 (m, 2H), 3.46 (dd, J_1 = 2.1 Hz, J_2 = 14.2 Hz, 1H), 3.16-3.12 (m, 1H), 2.89-2.66 (m, 2H), 2.41-1.82 (m, 6H), 1.42 (d, J = 8.3 Hz, 3H); ESMS *m/z* 515 (M+1); HRMS calcd for $C_{30}H_{35}N_4O_4$ 515.2658, found 515.2663.



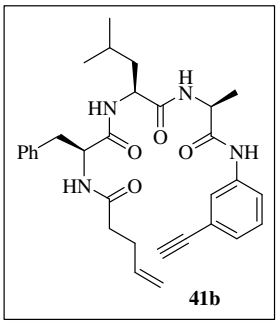
39b

Compound 39b: Compound was prepared by following general procedure **4.4.1a** (yield 74%), mp 145-146 °C; $[\alpha]_D^{25}$ = -20.7 *(c* 1, $CHCl_3$); IR (KBr), 3299, 2960, 2934, 1685, 1548 cm^{-1}; ^{1}H NMR (400MHz, DMSO-*d6*): δ 10.03 (s, 1H), 7.99 (d, J = 7.2 Hz, 1H), 7.77 (t, J = 1.9 Hz, 1H), 7.56 (d, J = 8.3 Hz, 1H), 7.32 (t, J = 7.8 Hz, 1H), 7.17-7.14 (m, 1H), 6.89 (d, J = 8.1 Hz, 1H), 4.41-4.37 (m, 1H), 4.15 (s, 1H), 3.99-3.96 (m, 1H), 1.64-1.61 (m, 1H), 1.44-1.37 (m, 2H), 1.31 (s, 9H), 1.28 (d, J = 4.9 Hz, 3H), 0.87 (t, J = 6.7 Hz, 6H); ESMS *m/z* calcd for $C_{22}H_{31}N_3O_4$ 401, found 402 (M+1).



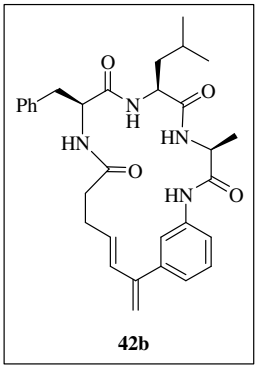
40b

Compound 40b: Compound was prepared by following general procedure **4.4.1a** (yield 64%), mp 115-116 °C; $[\alpha]_D^{25}$ = -25.8 *(c* 1, DMSO); IR (KBr), 3295, 3065, 2959, 2930, 1645, 1548 cm^{-1}; ^{1}H NMR (400MHz, DMSO-*d6*): δ 10.02 (s, 1H), 8.18 (d, J = 7.0 Hz, 1H), 7.88 (d, J = 8.3 Hz, 1H), 7.79 (s, 1H), 7.55 (d, J = 8.3 Hz, 1H), 7.34-7.15 (m, 7H), 6.91 (d, J = 8.6 Hz, 1H), 4.42-4.34 (m, 3H), 4.17 (t, J = 2.9 Hz, 1H), 2.97 (dd, J_1 = 4.0 Hz, J_2 = 13.7 Hz, 1H), 2.73 (dd, J_1 = 10.2 Hz, J_2 = 13.4 Hz, 1H), 1.68-1.64 (m, 1H), 1.57-1.42 (m, 2H), 1.29 (d, J = 8.3 Hz, 3H), 1.28 (s, 9H), 0.88 (d, J = 7.5 Hz, 3H), 0.84 (d, J = 7.8 Hz, 3H); ESMS *m/z* calcd for $C_{31}H_{40}N_4O_5$ 548, found 571 (M+Na), 549 (M+1).



41b

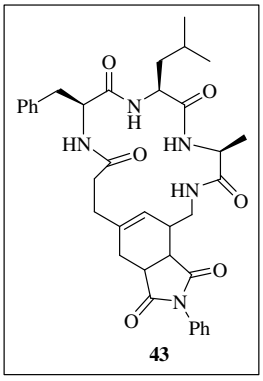
Compound 41b: Compound was prepared by following general procedure **4.4.3** (yield 68%), mp 221-222 ^{o}C; $[\alpha]_D^{25}$ = -19.8 *(c* 0.5, DMSO); IR (KBr), 3274, 3078, 2958, 1634, 1542 cm^{-1}; ^{1}H NMR (400MHz, DMSO-*d6*): δ 10.00 (s, 1H), 8.07 (d, *J* = 8.5 Hz, 1H), 8.00 (d, *J* = 6.9 Hz, 1H), 7.96 (d, *J* = 8.1 Hz, 1H), 7.78 (s, 1H), 7.54 (d, *J* = 1.1 Hz, 1H), 7.33-7.14 (m, 7H), 5.69-5.63 (m, 1H), 4.92 (dd, J_1 = 1.6 Hz, J_2 = 16.9 Hz, 1H), 4.86 (dd, J_1 = 1.9 Hz, J_2 = 10.2 Hz, 1H), 4.56-4.51 (m, 1H), 4.40-4.31 (m, 2H), 4.15 (s, 1H), 3.02 (dd, J_1 = 4.3 Hz, J_2 = 14.0 Hz, 1H), 2.74 (dd, J_1 = 9.9 Hz, J_2 = 14.0 Hz, 1H), 2.12 (t, *J* = 7.2 Hz, 4H), 1.64-1.58 (m, 1H), 1.52-1.46 (m, 2H), 1.31 (d, *J* = 7.2 Hz, 3H), 1.17-0.86 (m, 6H); ^{13}C NMR (50MHz, DMSO-*d6*): δ 171.7, 171.4, 171.3, 169.6, 139.1, 137.9, 137.5, 129.1 (3C), 127.9 (2C), 126.5, 126.1, 122.0, 121.9, 119.7, 114.7, 83.2, 80.5, 53.7, 50.9, 49.1, 40.7, 37.2, 34.2, 29.1, 24.0, 23.1, 21.5, 17.8; ESMS *m/z* 531 (M+1); HRMS calcd for $C_{31}H_{39}N_4O_4$ 531.2971, found 531.2965.



42b

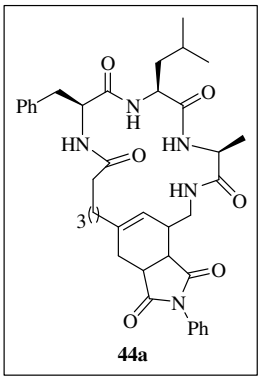
Compound 42b: Compound was prepared by following general procedure **4.4.3** (yield 40%), mp 210-212 ^{o}C; $[\alpha]_D^{25}$ = +36.0 *(c* 0.25, DMSO); IR (KBr), 3303, 3060, 2958, 1657, 1544 cm^{-1}; ^{1}H NMR (400MHz, DMSO-*d6*): δ 9.30 (s, 1H), 8.43 (d, *J* = 3.5 Hz, 1H), 7.94 (d, *J* = 5.9 Hz, 1H), 7.75 (d, *J* = 7.5 Hz, 1H), 7.59 (t, *J* = 1.9 Hz, 1H), 7.34-7.06 (m, 8H), 6.30 (d, *J* = 15.8 Hz, 1H), 5.96-5.91 (m, 1H), 5.20 (d, *J* = 10.7 Hz, 2H), 4.58-4.53 (m, 1H), 4.13-4.06 (m, 1H), 3.90-3.86 (m, 1H), 3.37 (dd, J_1 = 7.0 Hz, J_2 = 11.8 Hz, 1H), 2.70 (dd, J_1 = 10.5 Hz, J_2 = 14.0 Hz, 1H), 2.42-2.07 (m, 4H), 1.76-1.63 (m, 2H), 1.56-1.50 (m, 1H), 1.36 (d, *J* = 7.2 Hz, 3H),

0.93 (d, *J* = 8.3 Hz, 3H), 0.87 (d, *J* = 8.6 Hz, 3H); ^{13}C NMR (50MHz, DMSO-*d6*): δ 173.2, 172.1, 171.7, 170.8, 146.3, 139.7, 138.1, 137.9, 132.8, 130.6, 129.0 (2C), 128.0 (2C), 126.3, 122.2, 119.7, 118.5, 114.6, 54.4, 54.2, 50.1, 40.7, 40.3, 33.8, 27.5, 24.1, 22.6, 22.1, 21.8, 17.1; ESMS *m/z* 531 (M+1); HRMS calcd for $C_{31}H_{39}N_4O_4$ 531.2971, found 531.2963.



43

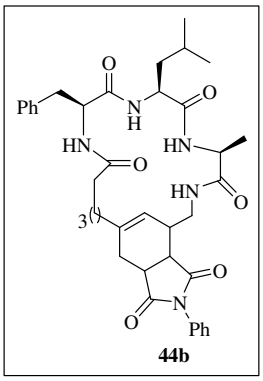
Compound 43: Compound was prepared by following general procedure **4.4.4** (yield 47%), mp 165-167 ^{o}C; $[\alpha]_D^{25}$ = -24.0 *(c* 0.25, MeOH); IR (KBr), 3339, 2956, 1707, 1652, 1538 cm^{-1}; ^{1}H NMR (400MHz, DMSO-*d6*): δ 8.78 (d, *J* = 6.7 Hz, 0.5H), 8.16 (d, *J* = 8.9 Hz, 0.5H), 8.09-8.02 (m, 2.5H), 7.76 (d, *J* = 7.5 Hz, 0.5H), 7.52-7.38 (m, 3H), 7.29-7.09 (m, 7H), 5.62 (br s, 0.5H), 5.46 (br s, 0.5H), 4.57-4.52 (m, 0.5H), 4.42-4.41 (m, 0.5H), 4.15-4.11 (m, 0.5H), 3.92-3.83 (m, 0.5H), 3.71-3.63 (m, 3H), 3.39-3.31 (m, 2H), 3.16-3.00 (m, 1H), 2.91-2.72 (m, 1H), 2.42-2.03 (m, 7H), 1.85-1.81 (m, 1H), 1.61-1.45 (m, 2H), 1.34-1.24 (m, 3H), 0.90-0.79 (m, 6H). ^{13}C NMR (50MHz, DMSO-*d6*): δ 178.9, 177.3, 172.4, 171.6, 171.1, 170.5, 139.9, 137.9, 132.4, 129.1(4C), 128.9(2C), 128.2, 128.1(2C), 127.0(2C), 126.4, 122.8, 53.6, 53.2, 49.5, 43.2, 38.0, 37.2, 34.8, 31.6, 29.9, 28.4, 24.5, 23.4, 21.6, 16.7 ; ESMS m/z 642 (M+1); HRMS calcd for $C_{36}H_{44}N_5O_6$ 642.3291, found 642.3294.



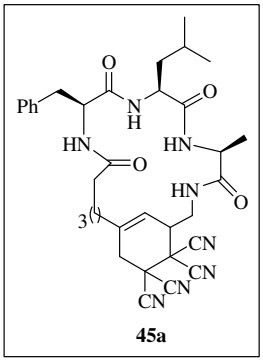
44a

Compound 44a: Compound was prepared by following general procedure **4.4.4** (yield 27%), mp 163-164 ^{o}C; $[\alpha]_D^{25}$ = -1.6 *(c* 0.25, DMSO); IR (KBr), 3359, 2927, 1706, 1656, 1530 cm^{-1}; ^{1}H NMR (400MHz, DMSO-*d6*): δ 8.28 (d, *J* = 8.3 Hz, 1H), 8.14 (d, *J* = 4.1 Hz, 1H), 7.41 (t, J = 6.2 Hz, 1H), 7.40-7.38 (m, 3H), 7.27-7.15

(m, 5H), 7.08 (dd, J_1 = 2.1 Hz, J_2 = 5.9 Hz, 2H), 6.98 (d, J = 8.6 Hz, 1H), 5.56 (br s, 1H), 4.39-4.28 (m, 2H), 3.96-3.93 (m, 1H), 3.49-3.24 (m, 5H), 3.14 (dd, J_1 = 4.0 Hz, J_2 = 14.0 Hz, 1H), 2.75 (dd, J_1 = 10.5 Hz, J_2 = 14.0 Hz, 1H), 2.40 (d, J = 13.7 Hz, 2H), 2.11-1.94 (m, 5H), 1.60-1.22 (m, 6H), 1.20 (d, J = 7.0 Hz, 3H), 0.90 (d, J = 5.9 Hz, 3H), 0.85 (d, J = 6.2 Hz, 3H) (**Spectrum No. 43**); ^{13}C NMR (50MHz, DMSO-*d6*): δ 178.9, 177.2, 172.5, 172.1, 171.2, 170.4, 138.7, 138.3, 132.2, 129.0, 128.9(2C), 128.8(2C), 128.3, 128.1(2C), 126.8(2C), 126.1, 123.9, 79.1, 54.4, 49.8, 42.3, 41.8, 40.5, 37.1, 35.9, 35.6, 35.1, 28.3, 26.5, 24.8, 23.8, 23.6, 21.5, 16.3 (**Spectrum No. 44**); ESMS m/z 670 (M+1); HRMS calcd for $C_{38}H_{48}N_5O_6$ 670.3604, found 670.3620.

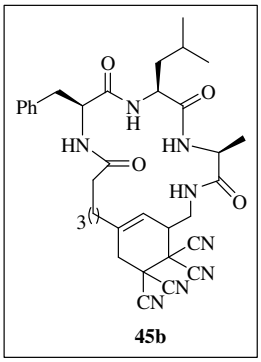


Compound 44b: Compound was prepared by following general procedure **4.4.4** (yield 26%), mp 162-163 °C; $[\alpha]_D^{25}$ = -0.4 *(c* 0.25, DMSO); IR (KBr), 3361, 2926, 1706, 1661, 1529 cm^{-1}; ^{1}H NMR (400MHz, DMSO-*d6*): δ 8.11-8.08 (m, 2H), 7.72 (dd, J_1 = 2.4 Hz, J_2 = 8.0 Hz, 1H), 7.49-7.37 (m, 3H), 7.27-7.08 (m, 7H), 5.56 (br s, 1H), 4.42-4.38 (m, 1H), 4.37-4.26 (m, 1H), 3.92-3.83 (m, 2H), 3.37 (t, J = 3.5 Hz, 1H), 3.30 (t, J = 7.4 Hz, 1H), 3.16-3.11 (m, 2H), 2.73 (dd, J_1 = 10.7 Hz, J_2 = 14.0 Hz, 1H), 2.39 (br s, 1H), 2.37 (d, J = 4.2 Hz, 1H), 2.23-2.15 (m, 2H), 1.92-1.87 (m, 3H), 1.64-1.37 (m, 6H), 1.35-1.21 (m, 2H), 1.18 (d, J = 7.0 Hz, 3H), 0.92 (d, J = 6.2 Hz, 3H), 0.88 (d, J = 6.2 Hz, 3H). ^{13}C NMR (50MHz, DMSO-*d6*): δ 178.9, 177.1, 172.1, 171.9, 171.2, 170.8, 139.3, 138.3, 132.3, 128.9 (2C), 128.8 (2C), 128.2, 128.1 (2C), 126.7 (2C), 126.2, 123.6, 79.1, 54.2, 50.2, 49.8, 42.4, 41.8, 40.5, 37.1, 36.9, 36.5, 35.1, 29.0, 25.8, 25.3, 24.0, 23.4, 21.5, 16.8; ESMS m/z 670 (M+1); HRMS calcd for $C_{38}H_{48}N_5O_6$ 670.3604, found 670.3609.



45a

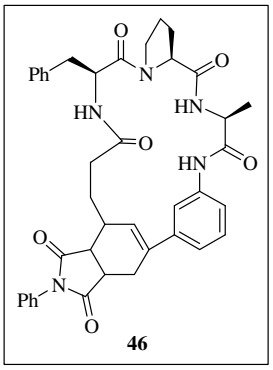
Compound 45a: Compound was prepared by following general procedure **4.4.4** (yield 37%), mp 165-166 °C; $[\alpha]_D^{25}$ = -44.0 (*c* 0.25, DMSO); IR (KBr), 3327, 2933, 1662, 1530 cm^{-1}; ^1H NMR (400MHz, DMSO-*d6*): δ 8.19-8.05 (m, 3H), 7.30-7.16 (m, 6H), 5.81 (br s, 1H), 4.41-4.36 (m, 1H), 4.28-4.23 (m, 1H), 3.91-3.87 (m, 1H), 3.64-3.57 (m, 1H), 3.42-3.38 (m, 1H), 3.32-3.22 (m, 1H), 3.15-3.06 (m, 2H), 2.77 (dd, J_1 = 10.5 Hz, J_2 = 14.0 Hz, 1H), 2.26-2.20 (m, 1H), 1.98-1.88 (m, 5H), 1.66-1.41 (m, 6H), 1.28 (d, *J* = 7.0 Hz, 3H), 0.94-0.85 (m, 6H). ^{13}C NMR (50MHz, DMSO-*d6*): δ 172.7, 172.4, 171.7, 171.1, 138.1, 133.2, 128.9(2C), 128.1(2C), 126.2, 117.3, 112.9, 111.9, 110.3, 109.6, 54.4, 50.6, 50.2, 49.9, 41.7, 41.3, 40.7, 39.8, 36.5, 34.8, 34.2, 33.6, 25.6, 25.2, 23.9, 23.3, 21.4, 16.6 ; ESMS m/z 647 (M+Na), 625 (M+1) ; HRMS calcd for $C_{34}H_{41}N_8O_4$ 625.3250, found 625.3240.



45b

Compound 45b: Compound was prepared by following general procedure **4.4.4** (yield 33%), mp 166-167 °C; $[\alpha]_D^{25}$ = +13.2 (*c* 0.25, DMSO); IR (KBr), 3324, 2932, 1661, 1522 cm^{-1}; ^1H NMR (400MHz, DMSO-*d6*): δ 8.44 (d, *J* = 4.3 Hz, 1H), 8.34 (t, *J* = 5.9 Hz, 1H), 8.24(d, *J* = 8.1 Hz, 1H), 7.35-7.17 (m, 5H), 7.11 (d, *J* = 8.1 Hz, 1H), 5.75 (br s, 1H), 4.36-4.30 (m, 2H), 3.92-3.86 (m, 1H), 3.67-3.62 (m, 1H), 3.55 (d, *J* = 8.8 Hz, 1H), 3.39-3.37 (m, 1H), 3.17-3.09 (m, 3H), 2.79 (dd, J_1 = 10.7 Hz, J_2 = 14.0 Hz, 1H), 2.17-1.88 (m, 4H), 1.64-1.31 (m, 7H), 1.23 (d, *J* = 8.9 Hz, 3H), 0.89 (d, *J* = 6.2 Hz, 3H), 0.83 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (50MHz, DMSO-*d6*): δ 173.1, 172.3, 171.8, 170.6, 138.3, 132.8, 128.9, 128.8 (2C), 128.1 (2C), 126.2, 117.3, 112.2, 111.6, 110.7, 109.1, 54.8, 49.9(2C), 41.7, 41.6, 39.7, 38.6, 36.3,

35.0, 34.5, 33.7, 25.7, 24.6, 23.9, 23.2, 21.6, 15.82 ; ESMS m/z 647 (M+Na), 625 (M+1) ; HRMS calcd for $C_{34}H_{41}N_8O_4$ 625.3250, found 625.3243.



46

Compound 46: Compound was prepared by following general procedure **4.4.4** (yield 55%), mp 212-214 ^{o}C; $[\alpha]_D^{25}$ = +129.0 (*c* 0.1, MeOH); IR (KBr), 3345, 2927, 1706, 1627 cm^{-1}; ^{1}H NMR (400MHz, DMSO-*d6*): δ 8.78 (s, 1H), 8.28-8.23 (m, 2H), 7.50-7.35 (m, 6H), 7.27 (t, *J* = 8.1 Hz, 1H), 7.19-7.13 (m, 3H), 6.95 (d, *J* = 6.8 Hz, 1H), 6.78 (t, *J* = 7.5 Hz, 2H), 6.68 (t, *J* = 7.2 Hz, 1H), 5.92 (br s, 1H), 4.68 (q, *J* = 5.1 Hz, 1H), 4.17-4.08 (m, 2H), 3.89-3.85 (m, 1H), 3.77-3.70 (m, 1H), 3.53-3.29 (m, 4H), 3.07 (d, *J* = 4.5 Hz, 1H), 2.95 (dd, J_1 = 5.9 Hz, J_2 = 14.2 Hz, 1H), 2.60 (br s, 1H), 2.46-2.33 (m, 2H), 2.25-2.11 (m, 4H), 1.96-1.84 (m, 2H), 1.47 (d, *J* = 7.2 Hz, 3H); ESMS m/z 688 (M+1) ; HRMS calcd for $C_{40}H_{42}N_5O_6$ 688.3135, found 688.3139.

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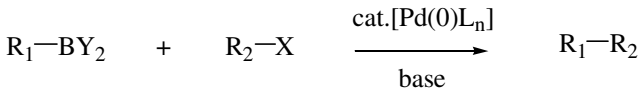
Chapter 5

Synthesis of Small Cyclic Peptides Constrained with Biphenyl Linkers Using Suzuki Coupling Reaction

5.1 Introduction

The palladium-mediated coupling of organic electrophiles, such as aryl or alkenyl halides and triflates, with organoboron compounds in the presence of a base (Figure 1),[1] is known as the Suzuki reaction.



R_1 = alkyl, alkynyl, aryl, vinyl

R_2 = alkyl, alkynyl, aryl, benyl, vinyl

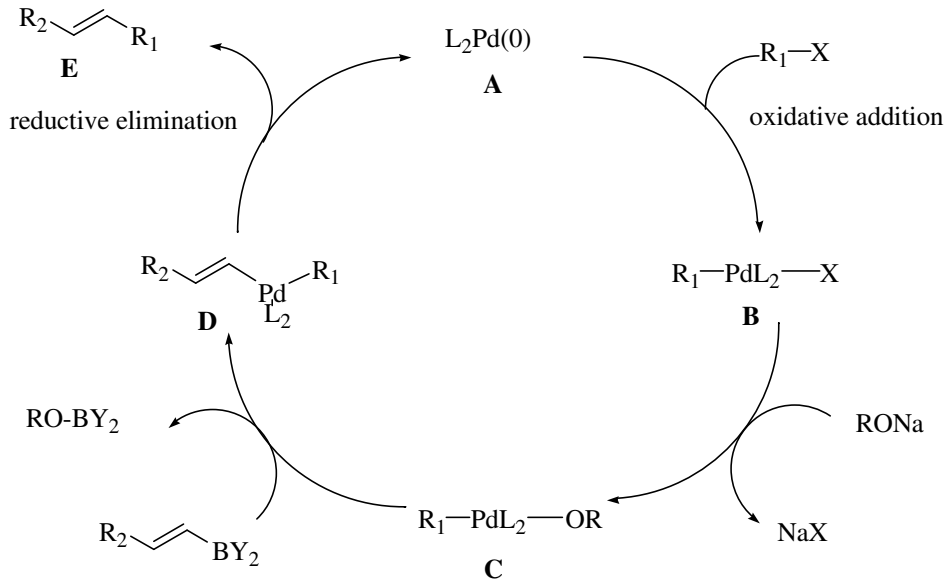
X = Br, Cl, I, $OP(=O)(OR)_2$, OTf, OTs

Figure 1: The Suzuki Reaction

The first examples of this protocol were reported by the Suzuki group[2] in 1979 although, again, the inspiration or the seeds of this development can be found in earlier work by others, the groups of Heck[3] and Negishi.[4] The ensuing quarter of a century saw remarkable developments in this field. Amongst its manifold applications, the Suzuki reaction is particularly useful as a method for the construction of conjugated dienes and higher polyene systems of high stereoisomeric purity, as well as of biaryl and related system. Furthermore, tremendous progress has been made in the development of Suzuki coupling reaction of unactivated alkyl halides, enabling $C(sp^2)$-$C(sp^3)$ and even $C(sp^3)$-$C(sp^3)$ bond-forming processes.[5,6] The ease of preparation of organoboron compounds (e.g. aryl, vinyl, alkyl) and their relative stability to air and water, combined with the

relatively mild conditions for the reaction as well as the formation of nontoxic by-products, makes the Suzuki reaction a valuable addition to the armory of the synthetic organic chemist. Indeed, it has become one of the most reliable and widely applied palladium-catalyzed cross-coupling reactions in the synthesis of natural products, where it has found a prominent role.[7] It is, again, worth mentioning that the Suzuki reaction may be considered as a variation of the Heck reaction, in which a boron-containing group replaces a hydrogen atom in the olefinic partner of the cross-coupling.

The postulated steps that constitute the Suzuki coupling process are shown in Scheme 1. After oxidative addition of the organic halide to the palladium(0) catalyst **A**,

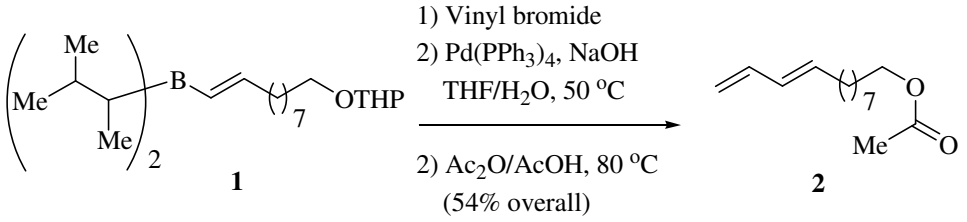


Scheme 1: Catalytic cycle for the Suzuki coupling

it is presumed that a metathetical displacement of the halide substituent in the palladium (II) complex **B** by ethoxide ion (or Hydroxide ion) takes place to give an alkoxo-palladium(II) complex **C**. The latter complex then reacts with the alkenylborane,

generating the dioorganopalladium complex **D**. Finally, reductive elimination of **D** furnishes the cross-coupling product **E** and regenerates the palladium(0) catalyst.

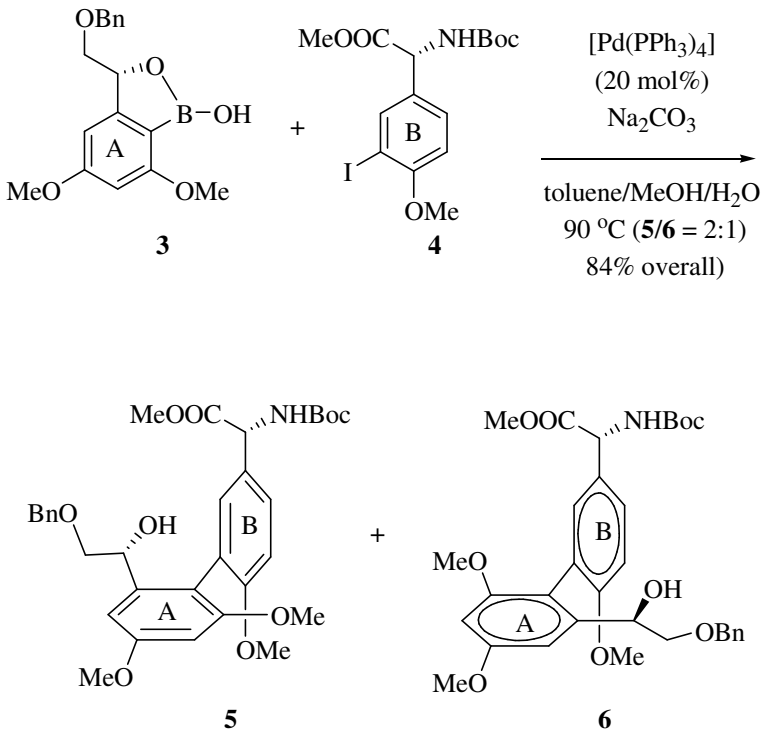
The first application of Suzuki cross-coupling reaction in natural products synthesis was reported by Rossi and co-workers in 1981, less than two years after the seminal publications by the Suzuki group[2] detailing an expedient synthesis of (*E*)-9,11-dodecadien-1-yl acetate **1**, an insect sex pheromone isolated from *Diparopsis castanea*[8] (Scheme 2).



Scheme 2

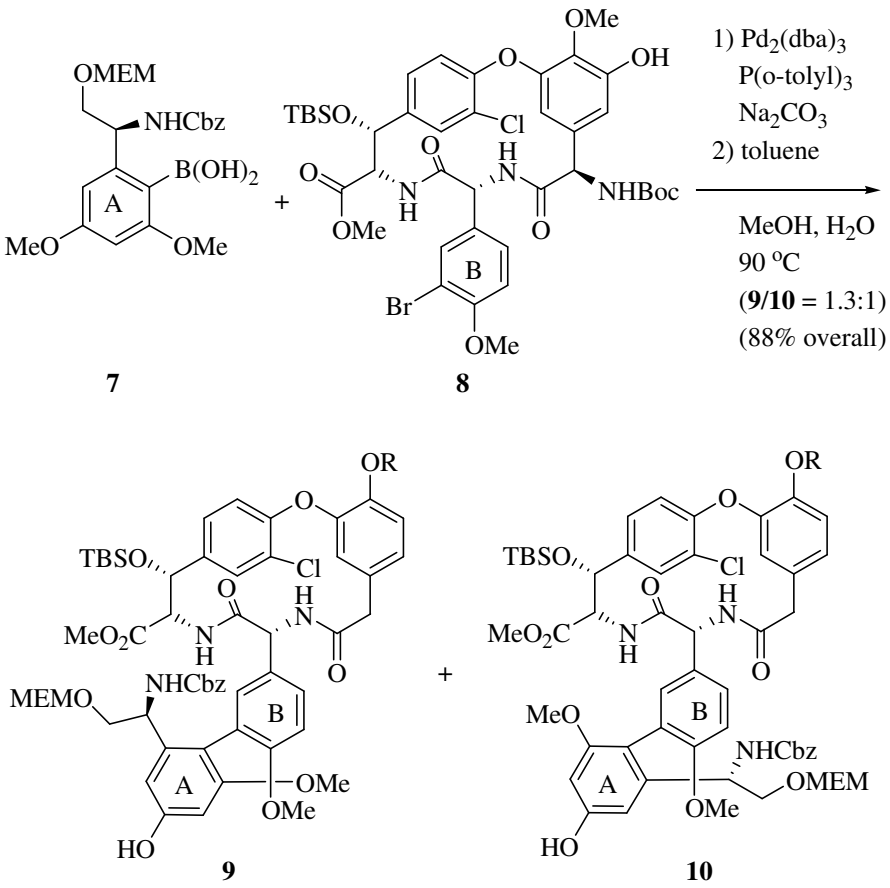
Suzuki coupling method was adopted by Nicolaou group[9] in building the crucial biarly linkage in the approaches to the total synthesis of the vancomycin aglycon. This protocol, involving the coupling of boronic acid **3** with iodide **4**, could potentially produce either or both atropisomeric products **5** and **6** (Scheme 3), and it is not easy to gauge through cursory inspection which of the two compounds would predominate in such a reaction.

Boger *et al.*[10] observed that the coupling of boronic acid **7** with bromide **8** gave a nearly stereorandom mixture of the desired product **9** and the unwanted atropisomer **10** (**9/10** ~ 1.3:1), although the overall yield for the process was excellent (88 %). Boger also explained that key to success of this reaction was the use of the catalyst system derived



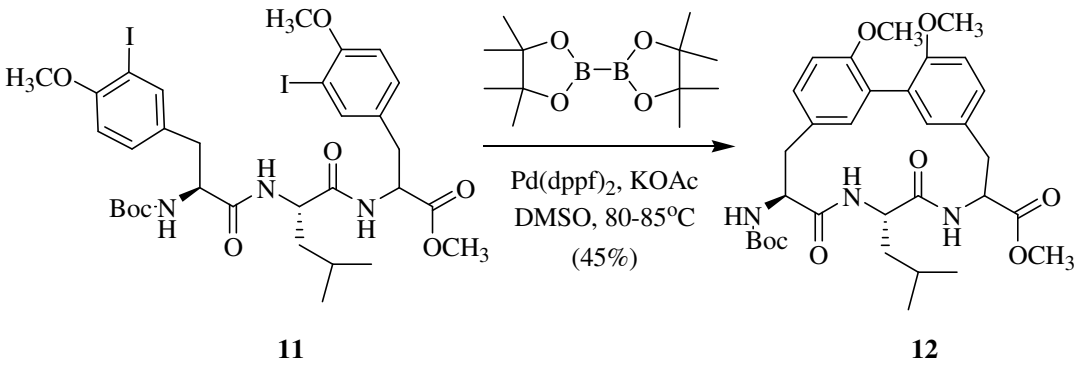
Scheme 3

from $[Pd_2(dba)_3]$ (30 mol%) and P(*o*-tolyl)$_3$ (150 mol%) (Scheme 4). At elevated reaction temperatures P(*o*-tolyl)$_3$ has often been found to be a superior ligand to the more traditional PPh_3 in such couplings. This is true particularly with organic electrophiles that prove recalcitrant towards oxidative addition to Pd^0, since the more bulky phosphine minimizes undesired quaternization of the phosphorus atom by the halide and also results in the formation of the more thermally stable 14-electron $[Pd\{P(o\text{-tolyl})_3\}_2]$ complexes.[11]



Scheme 4

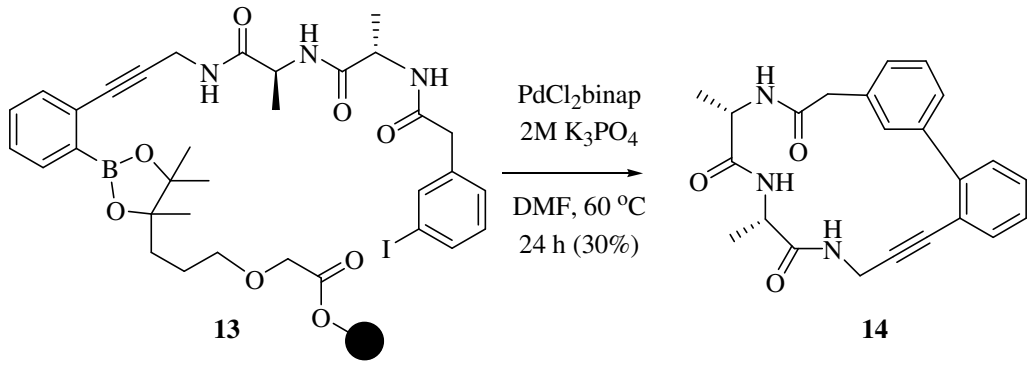
Recently, Zhu *et al.* developed a novel palladium catalyzed-diboron ester mediated cyclization reaction of linear diaryl halides.[12] Using this strategy, they synthesized a biophenomycin-like model compound **12** in a 45% yield from the linear peptide **11** (Scheme 5). The reaction involves Miyura arylboronic ester formation, followed by intramolecular Suzuki reaction, using the catalyst $Pd(dppf)_2Cl_2$.



11 **12**

Scheme 5

Burgess group synthesized biphenylalkyne-bridged cyclic peptides **14** using Suzuki reaction, as part of their work on solid-phase synthesis of β-turn analogues to mimic or disrupt protein-protein interactions (scheme 6).[13]

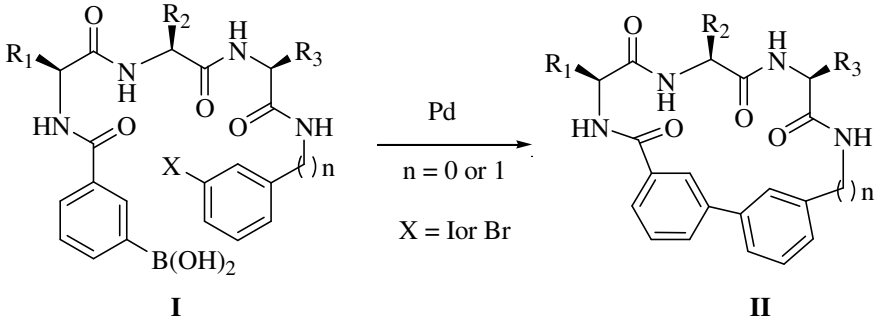


13 **14**

Scheme 6

Biaryl bridge is a unique structural feature existing in several families of naturally occurring cyclic peptidomimetics, such as Biphenomycins[14,15] and Vancomycin-type glycopeptide antibiotics.[16] Because of their prominent pharmaceutical activities, a number of research groups have made great efforts to develop efficient synthetic methodologies for ring closure *via* formation of a biaryl bond. However, we were

interested in the Suzuki coupling reaction to incorporate biaryl linker as a constraint in the cyclic peptide. Figure 2 describes our approach for the synthesis of cyclic peptides **II** from the acyclic peptide **I** using Suzuki coupling reaction.

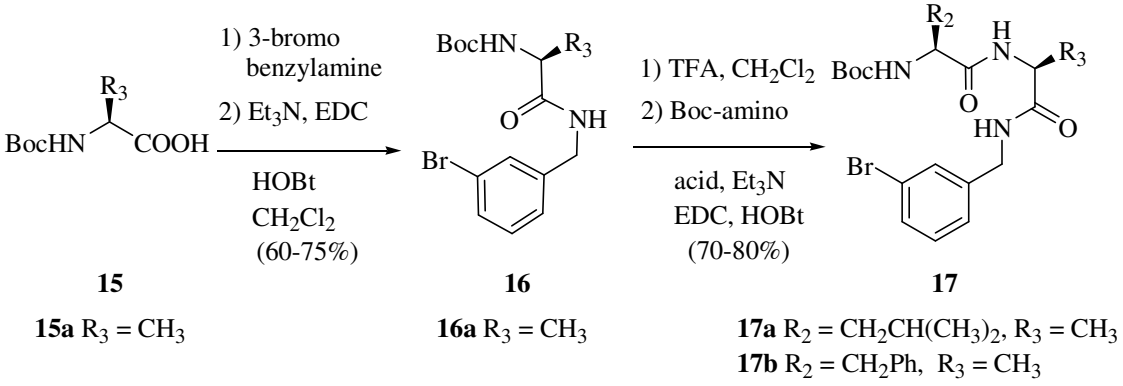


I **II**

Figure 2: Suzuki coupling

5.2.1 Synthesis of 18-membered cyclic peptides constrained with 3-(3-aminomethyl phenyl) benzoic acid linker

The Suzuki cross-coupling reaction is one of the most important methods for the selective construction of biaryl.[17] We have designed acyclic peptide compounds **19** for an intramolecular Suzuki coupling reaction. Scheme 7 describes the synthesis of precursors

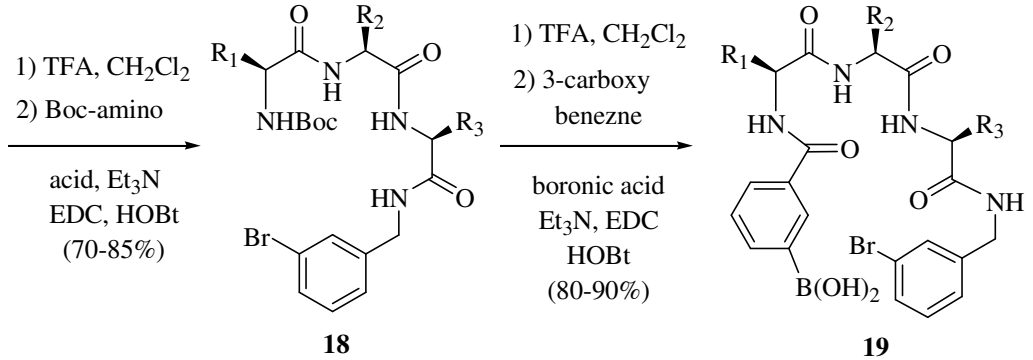


15 **16** **17**

15a $R_3 = CH_3$

16a $R_3 = CH_3$

17a $R_2 = CH_2CH(CH_3)_2$, $R_3 = CH_3$
17b $R_2 = CH_2Ph$, $R_3 = CH_3$



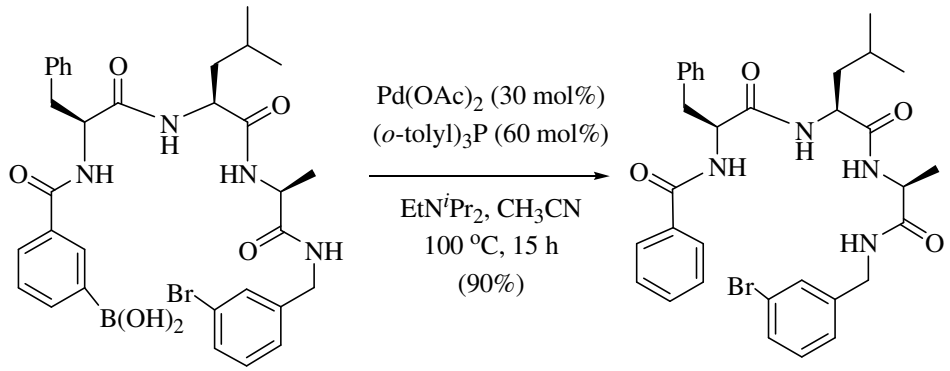
18 **19**

18a $R_1 = CH_2Ph$, $R_2 = CH_2CH(CH_3)_2$, $R_3 = CH_3$
18b $R_1 = CH(CH_3)CH_2CH_3$, $R_2 = CH_2Ph$, $R_3 = CH_3$

Scheme 7

19. The *N*-Boc-alanine **15a** was treated with 3-bromobenzylamine using standard solution chemistry[18] to give compound **16a**. Boc deprotection of **16a**, followed by coupling with *N*-Boc-leucine afforded compound **17a** in 75% yield. Compound **17a** on Boc deprotection and coupling with *N*-Boc-phenylalanine gave acyclic peptide **18a**, which on subsequent Boc deprotection and coupling with 3-carboxybenzeneboronic acids under standard solution chemistry conditions gave the precursor **19a** for the Suzuki macrocyclization.

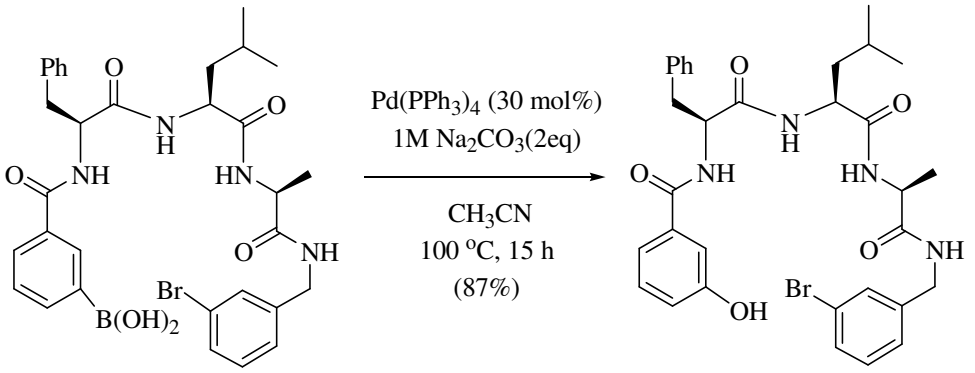
Compound **19a**, when subjected to the Suzuki coupling reaction with $Pd(OAc)_2$ and $(o\text{-tolyl})_3P$ using N-ethyldiisopropylamine as a base in acetonitrile at 100 ^oC, gave only the deboronated compound **20** in 90% yield (Scheme 8).



19a **20**

Scheme 8

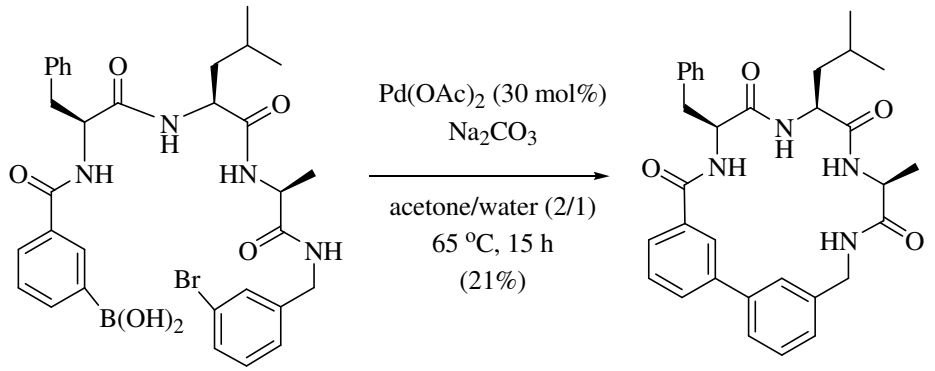
We also observed, the Suzuki coupling reaction of compound **19a** with $Pd(PPh_3)_4$ catalyst, using 1M Na_2CO_3 solution as base in acetonitrile at 100 ^oC furnished hydroxy benzoic acid compound **21** in 87% yield (Scheme 9).



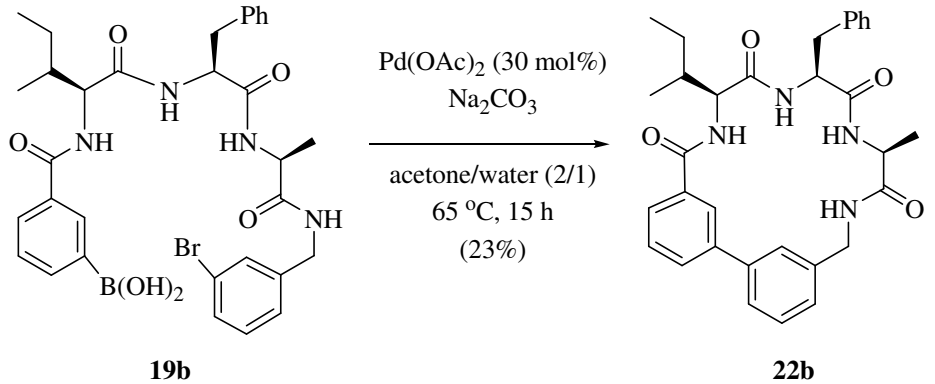
19a **21**

Scheme 9

Recently, the use of water as co-solvent for the Suzuki reaction received much



19a **22a**



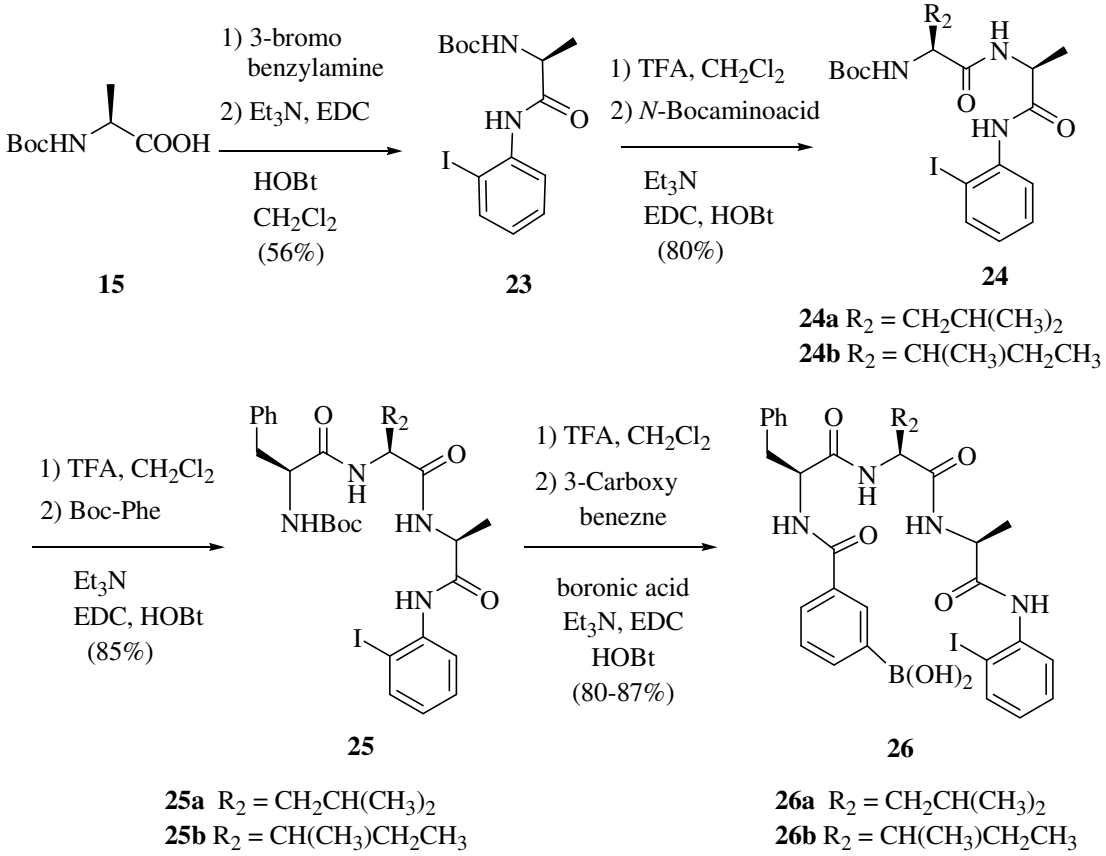
19b **22b**

Scheme 10

attention.[19] We were interested in the ligand-free Suzuki reaction and applied for the macrocyclization of **19a** and **19b** with the catalyst $Pd(OAc)_2$ (30 mol%) and base Na_2CO_3 (2 equiv.) using 2:1 acetone/water as solvent (10^{-3}M). To our delight, the reaction was successful and compounds **22a** and **22b** were isolated in 21% and 23% yields respectively (Scheme 10).

5.2.2 Synthesis of 17-membered cyclic peptides constrained with 3-(3-aminophenyl) benzoic acid linker

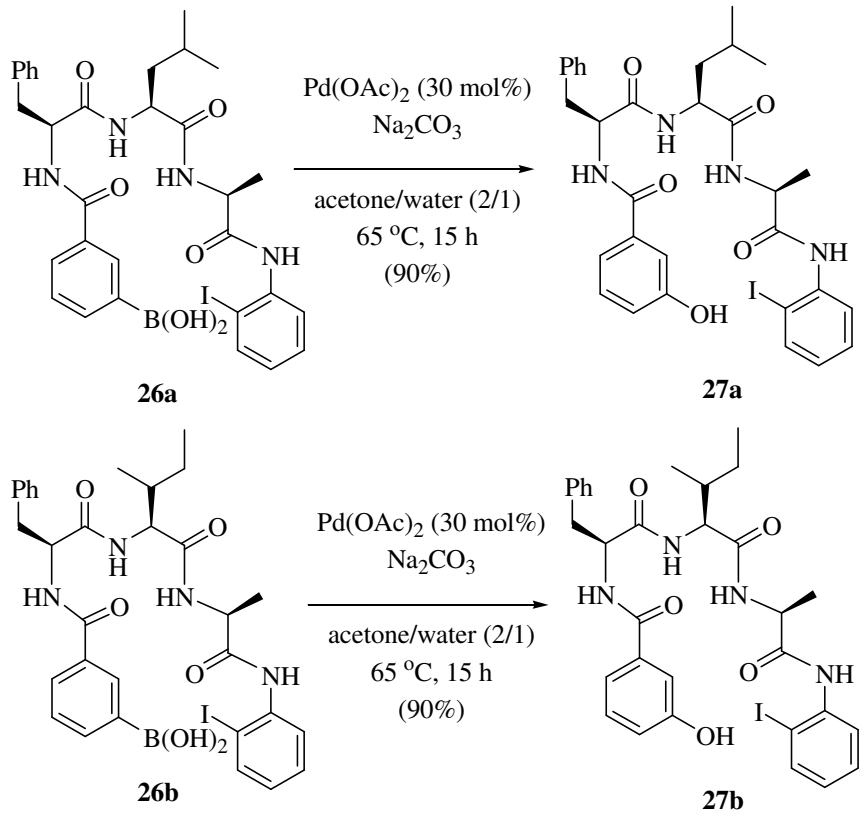
We also studied the scope of this Suzuki reaction in the macrocyclization of compounds **26**. Scheme 11 outlines the preparation of the precursors **26**. The synthesis



Scheme 11

started with the conversion of N-Boc-alanine **15** to 2-iodophenyl-N-Boc-alanine amide **23** using standard solution chemistry for coupling. Boc deprotection of **23**, followed by coupling with Boc-leucine afforded compound **24** in 80% yield. Compounds **24** on Boc deprotection and coupling with Boc-phenylalanine gave acyclic peptide **25**, which on subsequent deprotection and coupling n-carboxybenzene boronic acid under standard solution phase peptide coupling conditions gave the precursor **26** for the Suzuki coupling.

Compounds **26a** and **26b** are subjected to the Suzuki reaction using $Pd(OAc)_2$, Na_2CO_3 in 2:1 acetone/water as solvent (10^{-3}M) at 65 ^oC. However, both compounds (**26a** as well as **26b**) gave uncyclized compounds **27a** and **27b** in 90% yield (Scheme 12). Compounds **27a** and **27b** are formed due to the substitution of boron group



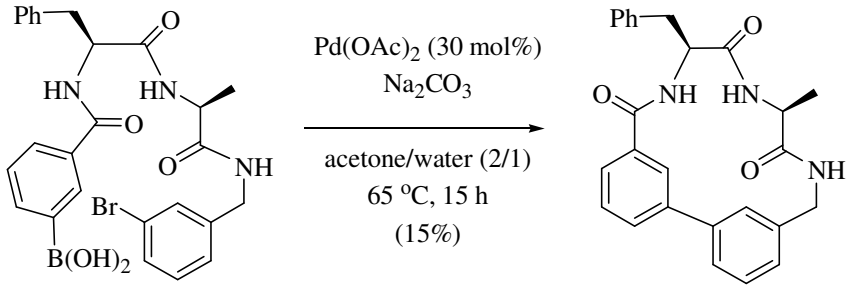
Scheme 12

with OH group. This is one of the side products commonly encountered in the aqueous-base Suzuki reaction. The structures of **27a** and **27b** were confirmed based on NMR and Mass spectral data.

Compounds **26a** and **26b** have rigid linkers on both termini and that ends are not close enough to react intramolecularly in the Suzuki coupling reaction. This might be the reason for the unsuccessful cyclization of compounds **26**.

5.2.3 Synthesis of 15-membered cyclic peptides constrained with 3-(3-aminomethyl phenyl)benzoic acid linker

We also studied the scope of the Suzuki reaction in the synthesis of cyclic dipeptides. The acyclic peptide **28** underwent smooth cyclization to form cyclic peptide **29** in 15 % yield (Scheme 13).



28 **29**

Scheme 13

5.3 Conclusions

We have demonstrated that the Suzuki coupling reaction can be used for the macrocyclization of di-, and tri- peptides to produce corresponding cyclic peptides constrained with biphenyl linkers. The biphenyl moiety present in our cyclic peptides mimics the biphenyl moiety present in a variety of naturally occurring cyclic structures such as the glycopeptide antibiotics vancomycin, teicoplanin and biphenomycins. We have also applied ligand-free Suzuki reaction using water as co-solvent for the synthesis of cyclic peptides. These biaryl bridged cyclic peptides may be useful tools in understanding the utility of constrained structures in the search for novel lead molecules.

5.4 Experimental Section

5.4.1 General procedure for the Suzuki Coupling Reaction

To a mixture solution of acetone (1L) and water (350 mL) were added acyclic precursor (500 mg), Na_2CO_3 (2.5 equiv) and palladium acetate (30 mol%) at room temperature. The resulting reaction mixture was stirred at 80 ^oC for 15 h. Cooled to room temperature and extracted with ethylacetate (3 x 500 mL), the combined extracts washed with 10% citric acid, water and finally washed with brine. Dried over anhydrous Na_2SO_4 and concentrated under reduced pressure and the residue was subsequently purified by column chromatography.

5.4.2 General procedure for peptide coupling

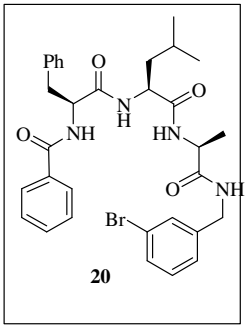
(a) To a stirred solution of the TFA salt of C-protected peptide in CH_2Cl_2 (5 mL/mmol) at 0 ^oC (ice-bath) under N_2 was added successively Et_3N (5 equiv.), HOBt (1.2 equiv.), a solution of the Boc-protected amino acid (1 equiv) in CH_2Cl_2 (2.5 mL/mmol), and EDC (1.2 equiv). The mixture was allowed to warm to r.t., and stirring was continued for 15 h. The mixture was diluted with CH_2Cl_2 and washed with 10% aq. citric acid, aq. saturated $NaHCO_3$, H_2O and saturated NaCl solution. The organic phase was dried (Na_2SO_4), evaporated, and the residue was purified using flash column chromatography to get the pure material.

(b) To a stirred solution of TFA salt of C-protected peptide in CH_2Cl_2 (3 mL/mmol) and DMF (2 mL/mmol) at 0 ^oC (ice-bath) under N_2 was added successively Et_3N (5 equiv.), HOBt (1.2 equiv.), a solution of the Boc-protected amino acid (1 equiv)

in CH_2Cl_2 (2.5 mL/mmol), and EDC (1.2 equiv). The mixture was allowed to warm to r.t., and stirring was continued for 15 h. The residue obtained after the removal of all volatiles was dried under vacuum for 1 h and then stirred in MeOH for 20 min. The white precipitate was collected by filtration and thoroughly washed successively with MeOH/H_2O 1:1 mixture and MeOH. The solid product was dried under high vacuum for several hours.

5.4.3 General procedure for Boc deprotection

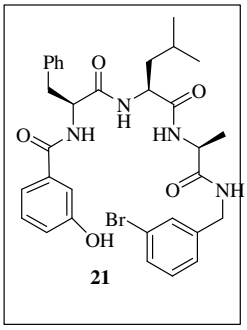
(**a**) CF_3COOH (1.5 mL/mmol) was added to an ice-cold solution of the Boc-protected peptide in CH_2Cl_2 (5 mL/mmol). The reaction mixture was allowed to warm to r.t. and stirring was continued for 2 h. The mixture was evaporated and the residue dried under high vaccum. The salts with CF_3COOH were used without further purification and characterization.



20

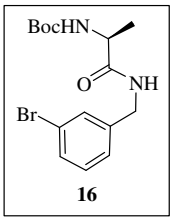
Compound 20: $Pd(OAc)_2$ (30 mg, 30mol%) and (*o*-tolyl)$_3$P (90 mg, 60 mol%) were added to the acetonitrile (1L) and heated to 100 ^oC. At this temperature acyclic compound **19a** (300 mg, 0.45 mmol) and *N*-ethyldiisopropylamine (0.39 ml, 2.25 mmol) were added simultaneously. Reaction mixture stirred at the same temperature for 15 h. Solution concentrated and purified by column chromatography. Compound **20** was obtained as a white solid (yield 90%), mp 256-258 °C; $[\alpha]_D^{25}$ = -14.0 (*c* 0.5, DMSO); IR (KBr), 3279, 3063, 2955, 2929, 1634, 1537 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.53 (d, *J* = 8.3 Hz, 1H), 8.39-8.32 (m, 1H),

8.10 (d, *J* = 8.1 Hz, 1H), 8.03 (d, *J* = 7.2 Hz, 1H), 7.75 (d, *J* = 7.0 Hz, 2H), 7.52-7.13 (m, 12H), 4.74-4.68 (m, 1H), 4.38-4.22 (m, 4H), 3.11 (dd, J_1 = 9.9 Hz, J_2 = 14.0 Hz, 1H), 2.96 (dd, J_1 = 2.9 Hz, J_2 = 13.7 Hz, 1H), 1.66-1.58 (m, 1H), 1.49 (t, *J* = 7.3 Hz, 2H), 1.24 (d, *J* = 7.0 Hz, 3H), 0.86 (d, *J* = 7.8 Hz, 3H), 0.82 (d, *J* = 7.8 Hz, 3H); ESMS *m/z* calcd for $C_{32}H_{37}N_4O_4Br$ 621, found 623 (M+2), 621 (M).



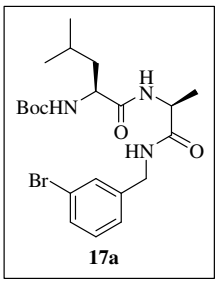
21

Compound 21: $Pd(PPh_3)_4$ (50 mg, 10mol%), acyclic compound **19a** (300 mg, 0.45 mmol) and 1M Na_2CO_3 (235 mg, 2.25 mmol) were added to the acetonitrile (1L) and heated to 100 ^oC. Reaction mixture stirred at the same temperature for 15 h. Solution concentrated and purified by column chromatography. Compound **21** was obtained as a white solid (yield 87%), mp 280-282 °C; $[\alpha]_D^{25}$ = -21.2 (*c* 0.5, DMSO); IR (KBr) 3284, 3069, 2957, 2927, 1639, 1537 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 9.60 (s, 1H), 8.40 (d, *J* = 8.0 Hz, 1H), 8.39-8.32 (m, 1H), 8.09-8.01 (m, 2H), 7.42-7.15 (m, 12H), 6.91-6.88 (m, 1H), 4.71-4.60 (m, 2H), 4.38-4.21 (m, 3H), 3.12-2.92 (m, 2H), 1.65-1.60 (m, 1H), 1.52-1.42 (m, 2H), 1.24 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 6.7 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 3H); ESMS *m/z* calcd for $C_{32}H_{37}N_4O_5Br$ 637, found 639 (M+2), 637 (M).



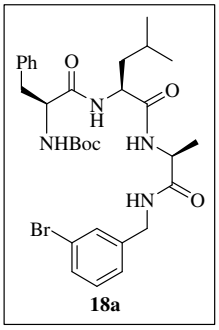
16

Compound 16: Compound was prepared by following general procedure **5.4.2a** (yield 87%), mp 85-87 °C; $[\alpha]_D^{25}$ = -21.8 (*c* 1, $CHCl_3$); IR (KBr) 3309, 2978, 2931, 1658, 1525, 1367 cm^{-1}; ^1H NMR (400MHz, DMSO-*d6*): δ 7.42-7.36 (m, 2H), 7.20-7.15 (m, 2H), 6.68 (bs, 1H), 4.97 (bs, 1H), 4.40-4.36 (m, 2H), 4.18 (t, *J* = 6.7 Hz, 1H), 1.42 (s, 9H), 1.38 (d, *J* = 4.0 Hz, 3H); ESMS *m/z* calcd for $C_{15}H_{21}N_2O_3Br$ 357, found 359 (M+2), 357 (M).



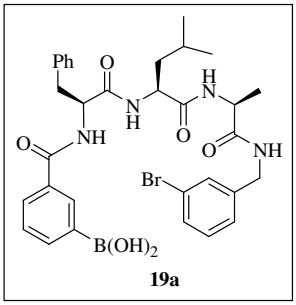
17a

Compound 17a: Compound was prepared by following general procedure **5.4.2a** (yield 80%), mp 143-144 ^{o}C; $[\alpha]_{D}^{25}$ = -20.8 *(c* 0.5, MeOH); IR (KBr) 3348, 3298, 2959, 2869, 1686, 1648, 1519 cm^{-1}; ^{1}H NMR (400MHz, DMSO-*d6*): δ 8.38 (t, *J* = 5.6 Hz, 1H), 7.86 (d, *J* = 7.5 Hz, 1H), 7.43-7.41 (m, 2H), 7.29-7.22 (m, 2H), 6.90 (d, *J* = 8.1 Hz, 1H), 4.32-4.26 (m, 3H), 3.93 (q, *J* = 6.7 Hz, 1H), 1.62-1.58 (m, 1H), 1.43-1.39 (m, 2H), 1.36 (s, 9H), 1.23 (d, *J* = 7.0 Hz, 3H), 0.86 (dd, J_1 = 6.6 Hz, J_2 = 13.4 Hz, 6H); ESMS *m/z* calcd for $C_{21}H_{32}N_3O_4Br$ 470, found 472 (M+2), 470 (M).



18a

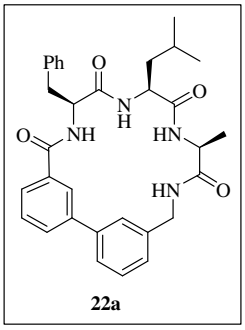
Compound 18a: Compound was prepared by following general procedure **5.4.2b** (yield 85%), mp 214-215 ^{o}C; $[\alpha]_{D}^{25}$ = -7.0 *(c* 0.5, DMSO); IR (KBr) 3286, 3064, 2956, 1692, 1638, 1541 cm^{-1}; ^{1}H NMR (400MHz, DMSO-*d6*): δ 8.39-8.32 (m, 1H), 8.06 (d, *J* = 7.0 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.45-7.41 (m, 2H), 7.36-7.15 (m, 7H), 6.91 (d, *J* = 8.6 Hz, 1H), 4.38-4.14 (m, 5H), 2.98 (dd, J_1 = 3.8 Hz, J_2 = 13.7 Hz, 1H), 2.72 (dd, J_1 = 10.5 Hz, J_2 = 13.7 Hz, 1H), 1.68-1.58 (m, 1H), 1.52-1.45 (m, 2H), 1.30 (s, 9H), 1.23 (d, *J* = 4.0 Hz, 3H), 1.47 (dd, J_1 = 6.7 Hz, J_2 = 12.4 Hz, 6H); ESMS *m/z* calcd for $C_{30}H_{41}N_4O_5Br$ 617, found 619 (M+2), 617 (M).



19a

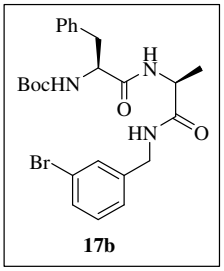
Compound 19a: Compound was obtained as a white solid by following general procedure **5.4.2b**, (yield 87%), mp 165-167 °C; $[\alpha]_{D}^{25}$ = -21.8 (*c* 0.5, DMSO); IR (KBr) 3280, 2957, 1638, 1537 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d6*): *δ* 8.42 (d, *J* = 8.3 Hz, 1H), 8.39-8.31 (m, 1H), 8.19 (s, 1H), 8.11 (s, 2H), 8.08 (d, *J* = 7.2 Hz, 1H), 8.04 (d, *J* = 7.2 Hz, 1H), 7.89 (d, *J* = 7.5 Hz, 1H), 7.77 (d, *J* =

7.8 Hz, 1H), 7.43-7.13 (m, 10H), 4.76-4.70 (m, 1H), 4.38-4.22 (m, 4H), 3.14-3.10 (m, 1H), 2.99 (dd, J_1 = 10.7 Hz, J_2 = 13.7 Hz, 1H), 1.66-1.53 (m, 1H), 1.49 (t, J = 7.2 Hz, 2H), 1.24 (d, J = 7.0 Hz, 3H), 0.87 (d, J = 6.4 Hz, 3H), 0.84 (d, J = 6.4 Hz, 3H) **(Spectrum No. 45)**; ^{13}C NMR (50 MHz, DMSO-*d6*): δ 172.3, 171.7, 171.5, 166.9, 142.3, 138.4, 136.9, 133.2, 130.4(2C), 129.7(2C), 129.6(2C), 129.2(2C), 128.9, 128.0(2C), 127.2, 126.2, 121.7, 54.8, 51.1, 48.4, 41.5, 40.8, 37.1, 24.2, 23.2, 21.7, 18.1 **(Spectrum No. 46)**; ESMS *m/z* calcd for $C_{32}H_{38}BBrN_4O_6$ 665, found 667 (M+2), 665 (M).



22a

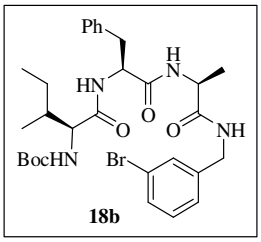
Compound 22a: Compound was obtained as a white solid by following general procedure **5.4.1**, (yield 27%), mp 210-212 °C; $[\alpha]_D^{25}$ = -7.5 (*c* 0.25, DMSO); IR (KBr) 3315, 2956, 1650, 1540 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d6*): δ 8.61 (d, J = 9.1 Hz, 1H), 8.42 (s, 1H), 8.18 (d, J = 3.2 Hz, 1H), 7.99 (s, 1H), 7.78 (d, J = 6.4 Hz, 1H), 7.65 (d, J = 9.1 Hz, 1H), 7.56 (d, J = 7.0 Hz, 1H), 7.51 (t, J = 8.1 Hz, 1H), 7.41 (t, J = 7.5 Hz, 3H), 7.30-7.18 (m, 6H), 4.93 (dd, J_1 = 8.1 Hz, J_2 = 16.6 Hz, 1H), 4.60-4.54 (m, 1H), 4.40-4.28 (m, 1H), 4.07-4.04 (m, 1H), 3.95 (dd, J_1 = 2.4 Hz, J_2 = 16.6 Hz, 1H), 3.09-2.91 (m, 2H), 1.73-1.62 (m, 2H), 1.51-1.44 (m, 1H), 1.27 (d, J = 7.0 Hz, 3H), 0.93 (d, J = 6.2 Hz, 3H), 0.91 (d, J = 6.2 Hz, 3H) **(Spectrum No. 47)**; ES-MS *m/z* calcd for $C_{32}H_{36}N_4O_4$ 540, found 541 (M+1).



17b

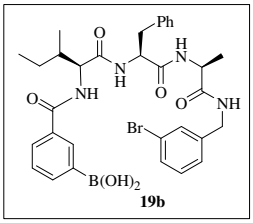
Compound 17b: Compound was prepared by following general procedure **5.4.2a** as white solid (yield 75%), mp 104–105 °C; $[\alpha]_D^{25}$ = -6.2 (*c* 1, CH_3OH); IR (KBr) 3290, 1644, 1527 cm^{-1}; ^{1}H NMR (400MHz, $CDCl_3$): δ 7.39-7.37 (m, 2H), 7.36-7.26 (m, 3H), 7.24-

7.15 (m, 4H), 6.74 (brs, 1H), 6.31 (d, *J* = 7.5 Hz, 1H), 4.90 (brs, 1H), 4.50-4.27 (m, 4H), 3.09-2.99 (m, 2H), 1.35 (s, 9H), 1.34 (d, *J* = 7.2 Hz, 3H); ESMS *m/z* calcd for $C_{24}H_{30}BrN_3O_4$ 504, found 506 (M+2), 504 (M).



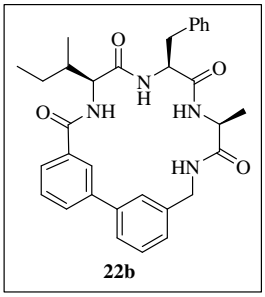
18b

Compound 18b: Compound was prepared as a white solid using procedure **5.4.2b** (yield 90%), mp 230-232 °C; $[\alpha]_D^{25}$ = -3.7 (*c* 1, DMSO); IR (KBr) 3284, 2968, 1639, 1538 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.27 (t, *J* = 5.6 Hz, 1H), 8.15 (d, *J* = 7.0 Hz, 1H), 7.87 (d, *J* = 8.1 Hz, 1H), 7.44-7.42 (m, 2H), 7.31-7.12 (m, 7H), 7.68 (d, *J* = 8.9 Hz, 1H), 4.64-4.58 (m, 2H), 4.35-4.22 (m, 3H), 3.00 (dd, J_1 = 3.5 Hz, J_2 = 7.8 Hz, 1H), 2.78 (dd, J_1 = 8.7 Hz, J_2 = 14.0 Hz, 1H), 1.57-1.51 (m, 1H), 1.37 (s, 9H), 1.37-1.34 (m, 1H), 1.24 (d, *J* = 7.0 Hz, 3H), 1.00-0.93 (m, 1H), 0.72 (t, *J* = 7.5 Hz, 3H), 0.60 (d, *J* = 6.7 Hz, 3H); ESMS *m/z* calcd for $C_{30}H_{41}N_4O_5Br$ 617, found 619 (M+2), 617 (M).



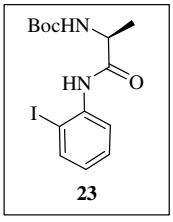
19b

Compound 19b: Compound was obtained as a white solid by following general procedure **5.4.2b**, (yield 86%), mp 224-226 °C; $[\alpha]_D^{25}$ = -3.7 (*c* 1, DMSO); IR (KBr) 3277, 2964, 1636, 1540 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.24 (d, *J* = 5.6 Hz, 2H), 8.16 (s, 1H), 8.11-8.06 (m, 2H), 7.92 (d, *J* = 6.2 Hz, 1H), 7.85 (d, *J* = 6.2 Hz, 1H), 7.45-7.41 (m, 3H), 7.31-7.07 (m, 9H), 4.62-4.57 (m, 1H), 4.33-4.17 (m, 4H), 3.04 (dd, J_1 = 4.3 Hz, J_2 = 9.40 Hz, 1H), 2.80-2.77 (m, 1H), 1.82-1.80 (m, 1H), 1.41-1.38 (m, 1H), 1.23 (d, *J* = 7.0 Hz, 3H), 1.14-1.09 (m, 1H), 0.78 (t, *J* = 7.2 Hz, 3H), 0.72 (d, *J* = 7.0 Hz, 3H); ESMS *m/z* calcd for $C_{32}H_{38}$ $BBrN_4O_6$ 665, found 684 ($M+NH_4$), 682 ($M+NH_4$-2), 667 (M+2), 665 (M).



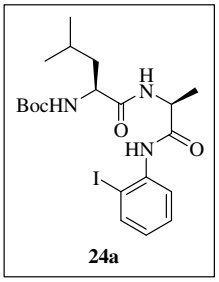
22b

Compound 22b: Compound was obtained as a white solid by following general procedure **5.4.1**, (yield 29%), mp 220-222 °C; $[\alpha]_D^{25}$ = -9.5 (*c* 0.25, DMSO); IR (KBr) 3283, 2963, 2929, 1645, 1525 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.47 (s, 2H), 8.34 (d, *J* = 3.2 Hz, 1H), 8.28 (d, *J* = 9.9 Hz, 1H), 7.99 (s, 1H), 7.92-7.87 (m, 1H), 7.77 (d, *J* = 5.9 Hz, 1H), 7.76-7.49 (m, 3H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.32-7.21 (m, 6H), 4.92 (dd, J_1 = 8.8 Hz, J_2 = 16.6 Hz, 1H), 4.65-4.59 (m, 1H), 4.35-4.25 (m, 1H), 4.11-4.01 (m, 2H), 3.36 (dd, J_1 = 2.9 Hz, J_2 = 13.4 Hz, 1H), 2.62 (dd, J_1 = 2.8 Hz, J_2 = 14.0 Hz, 1H), 1.90-1.80 (m, 1H), 1.61-1.59 (m, 1H), 1.32 (d, *J* = 7.0 Hz, 3H), 1.09-0.99 (m, 1H), 0.79-0.72 (m, 3H), 0.44 (d, *J* = 5.7 Hz, 3H); ESMS *m/z* calcd for $C_{32}H_{36}N_4O_4$ 540, found 541 (M+1).



23

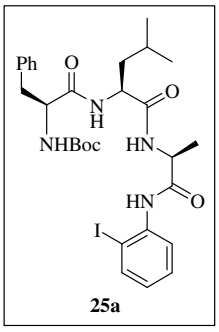
Compound 23: Compound was prepared by following general procedure **5.4.2a** (yield 55%)**,** mp 96-98 °C; $[\alpha]_D^{25}$ = -30.3 *(c* 1, $CHCl_3$); IR (KBr) 3348, 3295, 2972, 1710, 1663, 1586, 1537, 1510, 1433, 1367 cm^{-1}; ^1H NMR (400MHz, DMSO-*d6*): δ 9.17 (s, 1H), 7.86 (d, *J* = 8.1 Hz, 1H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.38 (t, *J* = 7.0 Hz, 1H), 7.21 (d, *J* = 5.9 Hz, 1H), 6.95 (t, *J* = 7.8 Hz, 1H), 4.17-4.14 (m, 1H), 1.41 (s, 9H), 1.33 (d, *J* = 6.2 Hz, 3H); ESMS *m/z* calcd for $C_{14}H_{19}N_2O_3I$ 390, found 391 (M+1).



24a

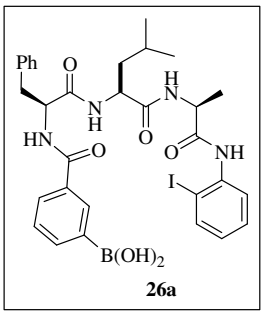
Compound 24a: Compound was prepared by following general procedure **5.4.2a** (yield 90%), mp 153-154 ^oC; $[\alpha]_D^{25}$ = -29.3 *(c* 0.5, MeOH); IR (KBr) 3348, 3298, 2959, 2870, 1712, 1658, 1519 cm^{-1}; ^1H NMR (400MHz, DMSO-*d6*): δ 9.39 (s, 1H), 7.99 (d, *J* = 7.2 Hz, 1H), 7.88 (d, *J* = 6.7 Hz, 1H), 7.47 (d, *J* = 7.1 Hz, 1H), 7.38 (t, *J* =

7.6 Hz, 1H), 6.98 (t, *J* = 7.8 Hz, 1H), 6.92 (d, *J* = 8.6 Hz, 1H), 4.51-4.48 (m, 1H), 4.02 (q, *J* = 7.8 Hz, 1H), 1.63-1.60 (m, 1H), 1.45 (t, *J* = 7.2 Hz, 2H), 1.37 (bs, 12H), 0.86 (t, *J* = 6.4 Hz, 6H); ESMS *m/z* calcd for $C_{20}H_{30}N_3O_4I$ 503, found 504 (M+1).



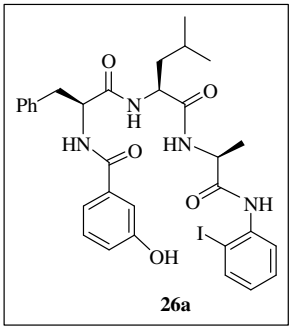
25a

Compound 25a: Compound was prepared by following general procedure **5.4.2b** (yield 94%), mp 234-235 ^oC; $[\alpha]_D^{25}$ = -21.6 *(c* 1, DMSO); IR (KBr), 3283, 2956, 1691, 1643, 1532 cm^{-1}; ^1H NMR (400MHz, DMSO-*d6*): δ 9.35 (s, 1H), 8.18 (d, *J* = 8.0 Hz, 1H), 7.89 (d, *J* = 9.7 Hz, 1H), 7.87 (d, *J* = 6.5 Hz, 1H), 7.46 (d, *J* = 6.7 Hz, 1H), 7.38 (dd, J_1 = 6.2 Hz, J_2 = 7.2 Hz, 1H), 7.36-7.16 (m, 5H), 6.99-6.89 (m, 2H), 4.50-4.40 (m, 2H), 4.18-4.17 (m, 1H), 2.97 (dd, J_1 = 3.9 Hz, J_2 = 13.7 Hz, 1H), 2.74 (dd, J_1 = 10.2 Hz, J_2 = 13.4 Hz, 1H), 1.67-1.64 (m, 1H), 1.52-1.49 (m, 2H), 1.38 (d, *J* = 7.0 Hz, 3H), 1.30 (s, 9H), 0.88 (d, *J* = 6.4 Hz, 3H), 0.85 (d, *J* = 6.4 Hz, 3H); ESMS *m/z* calcd for $C_{29}H_{39}N_4O_5I$ 650, found 651 (M+1).



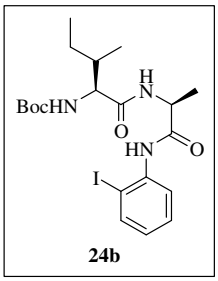
26a

Compound 26a: Compound was obtained as a white solid by following general procedure **5.4.2b**, (yield 87%), mp 190-192 °C; $[\alpha]_D^{25}$ = -21.8 (*c* 0.5, DMSO); IR (KBr) 3280, 2957, 1638, 1537 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): *δ* 9.36 (s, 1H), 8.43 (d, *J* = 8.2 Hz, 1H), 8.19-8.14 (m, 2H), 8.11 (s, 2H), 7.87 (t, *J* = 8.1 Hz, 2H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.47-7.13 (m, 9H), 6.99-6.95 (m, 1H), 4.77-4.72 (m, 1H), 4.49 (t, *J* = 7.0 Hz, 1H), 4.41 (q, *J* = 8.4 Hz, 1H), 3.13 (dd, J_1 = 4.0 Hz, J_2 = 13.97 Hz, 1H), 3.00 (dd, J_1 = 10.5 Hz, J_2 = 13.7 Hz, 1H), 1.67-1.62 (m, 1H), 1.55-1.51 (m, 2H), 1.38 (d, *J* = 7.2 Hz, 3H), 0.90 (d, *J* = 6.1 Hz, 3H), 0.85 (d, *J* = 6.4 Hz, 3H); ESMS *m/z* calcd for $C_{31}H_{36}BIN_4O_6$ 698, found 699 (M+1).



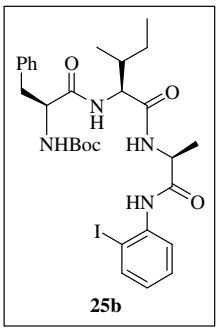
26a

Compound 27a: Compound was obtained as a white solid by following general procedure **5.4.1**, (yield 90%), mp 243-245 °C; $[\alpha]_D^{25}$ = -55.2 (*c* 0.025, DMSO); IR (KBr) 3417, 2956, 1642, 1526 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 9.60 (s, 1H), 9.36 (bs, 1H), 8.40 (d, *J* = 8.3 Hz, 1H), 8.16 (d, *J* = 7.0 Hz, 1H), 8.12 (d, *J* = 8.6 Hz, 1H), 7.87 (d, *J* = 6.7 Hz, 1H), 7.48-7.14 (m, 10H), 6.99-6.90 (m, 1H), 6.89-6.87 (m, 1H), 4.69-4.66 (m, 1H), 4.51-4.38 (m, 2H), 3.12-2.96 (m, 2H), 1.67-1.43 (m, 3H), 1.38 (d, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 6.4 Hz, 3H), 0.85 (d, *J* = 6.4 Hz, 3H); ESMS *m/z* calcd for $C_{31}H_{35}N_4O_5I$ 670, found 671 (M+1).



24b

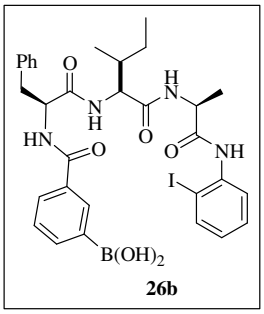
Compound 24b: Compound was prepared by following general procedure **5.4.2a** (yield 88%), mp 163-164 °C; $[\alpha]_D^{25}$ = -9.8 (*c* 1, DMSO); IR (KBr) 3282, 2967, 2932, 1690, 1646, 1524 cm^{-1}; ^1H NMR (400MHz, DMSO-*d6*): δ 9.41 (s, 1H), 8.05 (d, *J* = 7.2 Hz, 1H), 7.87 (d, *J* = 6.4 Hz, 1H), 7.53-7.36 (m, 2H), 7.01-6.99 (m, 1H), 6.77 (d, *J* = 7.6 Hz, 1H), 4.58-4.46 (m, 1H), 3.90-3.81 (m, 1H), 1.74-1.69 (m, 1H), 1.47-1.43 (m, 1H), 1.36 (d, *J* = 8.1 Hz, 3H), 1.31 (s, 9H), 1.15-1.09 (m, 1H), 0.84-0.80 (m, 6H); ESMS *m/z* calcd for $C_{20}H_{30}N_3O_4I$ 503, found 504 (M+1).



25b

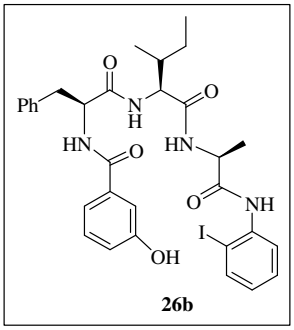
Compound 25b: Compound was prepared by following general procedure **5.4.2b** (yield 75%), mp 244-245 °C; $[\alpha]_D^{25}$ = -17.0 (*c* 1, DMSO); IR (KBr), 3284, 2965, 2927, 1690, 1644, 1529 cm^{-1}; ^1H NMR (400MHz, DMSO-*d6*): δ 9.38 (s, 1H), 8.26 (d, *J* = 7.0 Hz, 1H), 7.86 (d, *J* = 6.4 Hz, 1H), 7.73 (d, *J* = 9.1 Hz, 1H), 7.45-7.35 (m, 2H), 7.27-7.17 (m, 5H), 6.99-6.95 (m, 2H), 4.51 (quint, *J* = 7.0 Hz,

1H), 4.29 (dd, J_1 = 7.5 Hz, J_2 = 8.9 Hz, 1H), 4.21-4.16 (m, 1H), 2.77-2.71 (m, 2H), 1.76-1.74 (m, 1H), 1.48-1.45 (m, 1H), 1.37 (d, J = 7.0 Hz, 3H), 1.32 (s, 9H), 1.12-1.09 (m, 1H), 0.86-0.80 (m, 6H); ESMS *m/z* calcd for $C_{29}H_{39}N_4O_5I$ 650, found 651 (M+1).



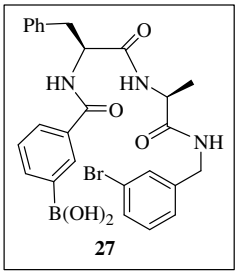
26b

Compound 26b: Compound was obtained as a white solid by following general procedure **5.4.2b**, (yield 85%), mp 210-212 °C; $[\alpha]_D^{25}$ = -24.8 (*c* 0.5, DMSO); IR (KBr) 3282, 2966, 1630, 1521 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 9.36 (s, 1H), 8.48 (d, J = 8.3 Hz, 1H), 8.23 (d, J = 9.4 Hz, 1H), 8.19 (s, 1H), 8.01 (s, 1H), 7.99-7.76 (m, 5H), 7.51-7.12 (m, 8H), 6.99-6.95 (m, 1H), 4.82-4.79 (m, 1H), 4.57-4.49 (m, 1H), 4.36-4.26 (m, 1H), 3.15-3.09 (m, 1H), 3.07-3.01 (m, 1H), 1.79-1.75 (m, 1H), 1.52-1.43 (m, 1H), 1.38 (d, J = 7.0 Hz, 3H), 1.15-1.07 (m, 1H), 0.87-0.81 (m, 6H); ES-MS *m/z* calcd for $C_{31}H_{36}BIN_4O_6$ 698, found 699 (M+1).



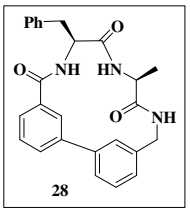
26b

Compound 27b: Compound was obtained as a white solid by following general procedure **5.4.1**, (yield 90%), mp 256-258 °C; $[\alpha]_D^{25}$ = -24.8 (*c* 0.25, DMSO); IR (KBr) 3278, 2965, 1638, 1522 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 9.61 (s, 1H), 9.39 (s, 1H), 8.44 (d, J = 8.3 Hz, 1H), 8.25 (d, J = 7.0 Hz, 1H), 7.89 (d, J = 8.9 Hz, 1H), 7.87 (d, J = 6.7 Hz, 1H), 7.48-7.14 (m, 10H), 6.97 (t, J = 8.9 Hz, 1H), 6.88 (d, J = 6.7 Hz, 1H), 4.75-4.69 (m, 1H), 4.55-4.50 (m, 1H), 4.32-4.28 (m, 1H), 3.09-2.96 (m, 2H), 1.78-1.76 (m, 1H), 1.50-1.44 (m, 1H), 1.38 (d, J = 7.2 Hz, 3H), 1.12-1.07 (m, 1H), 0.86 (d, J = 6.7 Hz, 3H), 0.82 (t, J = 7.5 Hz, 3H); ESMS *m/z* calcd for $C_{31}H_{35}N_4O_5I$ 670, found 671 (M+1).



27

Compound 28: Compound was obtained as a white solid by following general procedure **5.4.2b**, (yield 86%), mp 165-167 °C; $[\alpha]_D^{25}$ = -9.8 (*c* 1, DMSO); IR (KBr) 3296, 2928, 1640, 1530 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.45 (d, *J* = 8.3 Hz, 1H), 8.36 (t, *J* = 5.9 Hz, 1H), 8.28 (d, *J* = 7.5 Hz, 1H), 8.21 (s, 1H), 8.12 (bs, 1H), 7.90 (d, *J* = 7.2 Hz, 1H), 7.79 (d, *J* = 6.2 Hz, 1H), 7.44-7.13 (m, 11H), 4.79-4.73 (m, 1H), 4.38-4.25 (m, 3H), 3.15 (dd, J_1 = 3.8 Hz, J_2 = 13.7 Hz, 1H), 3.00 (dd, J_1 = 10.5 Hz, J_2 = 13.7 Hz, 1H), 1.29 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (50 MHz, DMSO-*d6*): δ 172.4, 171.3, 169.9, 142.3, 138.4, 136.9, 134.4, 133.3, 133.2, 130.5, 129.8, 129.7, 129.3(2C), 129.1, 128.1(2C), 127.3, 126.3, 126.1, 121.7, 54.8, 48.6, 41.5, 37.2, 18.3; ESMS *m/z* calcd for $C_{26}H_{27}BBrN_3O_5$ 552, found 554 (M+2).



28

Compound 28: Compound was obtained as a white solid by following general procedure **5.4.1**, (yield 15%), mp 184-186 °C; $[\alpha]_D^{25}$ = -104.0 (*c* 0.05, DMSO); IR (KBr) 3258, 3060, 2929, 1634, 1534 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 9.0 (bs, 1H), 8.60 (d, *J* = 9.4 Hz, 1H), 8.39 (d, *J* = 9.4 Hz, 1H), 7.96-7.88 (m, 2H), 7.75-7.10 (m, 11H), 4.83-4.77 (m, 2H), 4.71-4.55 (m, 1H), 4.10 (dd, J_1 = 4.3 Hz, J_2 = 16.6 Hz, 1H), 3.12-2.98 (m, 2H), 1.22 (d, *J* = 8.8 Hz, 3H); ^{13}C NMR (50 MHz, DMSO-*d6*): δ 172.3, 171.1, 171.0, 167.2, 142.3, 137.7, 137.0, 133.6, 133.2, 130.5, 129.8, 129.7, 129.2, 129.1(2C), 128.1(2C), 127.4, 126.3, 126.1, 121.8, 53.6, 48.5, 41.5, 37.3, 18.2; ESMS *m/z* calcd for $C_{26}H_{25}N_3O_3$ 427, found 428 (M+1).

5.5 References

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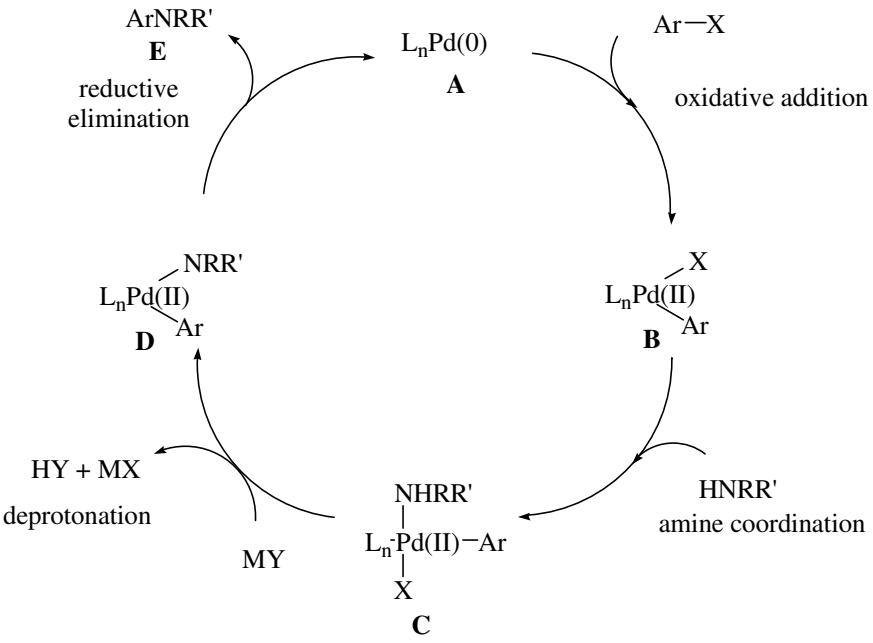
Chapter 6

Synthesis of Small Cyclic Peptides Constrained with Diarylamine Linkers using Buchwald-Hartwig C-N Coupling

6.1 Introduction

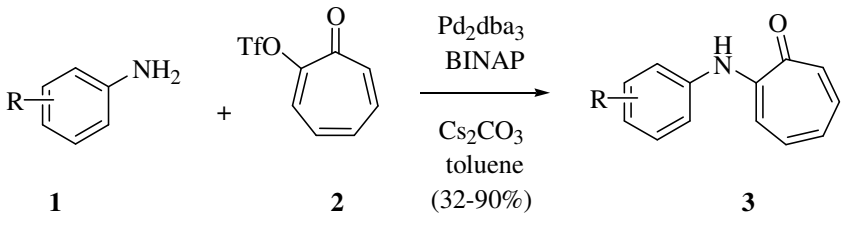
Palladium-catalyzed amination of aryl halides has become an important method for the synthesis of arylamines found in pharmaceutical,[1,2] agrochemicals,[3] photographic materials,[4] xeroxography, [5] pigments, [6] electronic materials,[7] and natural products.[8] A number of useful methods for aryl C-N bond formation have emerged over the years mainly including the Ullmann reaction[9] and the Goldberg reaction[10] using Cu reagent. However, these methods suffer from a limited substrate scope due to the requirement of relatively harsh reaction conditions and/or the presence of activating electron withdrawing groups. In the mid ninties Buchwald and Hartwig independently discovered the Pd-catalyzed amination of aryl bromides showing a wide scope.[11] This new procedure has established itself as a very important method for C-N bond formation on aromatic compounds currently available.[12]

The generally accepted Buchwald-Hartwig reaction mechanism[13] is depicted in Scheme 1. It involves a phosphine–palladium(0) complex **A** (either formed by reduction of Pd(II) or by simple ligand exchange, when a Pd(0) source is used), which undergoes oxidative addition of the aryl halide to form complex **B**. Amine coordination with **B** forms palladium(II) complex **C**. In the presence of base palladium(II) complex **C** is converted into the corresponding arylpalladium amide **D**. Reductive elimination finally yields the aryl amine **E** and regenerates the palladium(0) complex **A**, closing the catalytic cycle.



Scheme 1

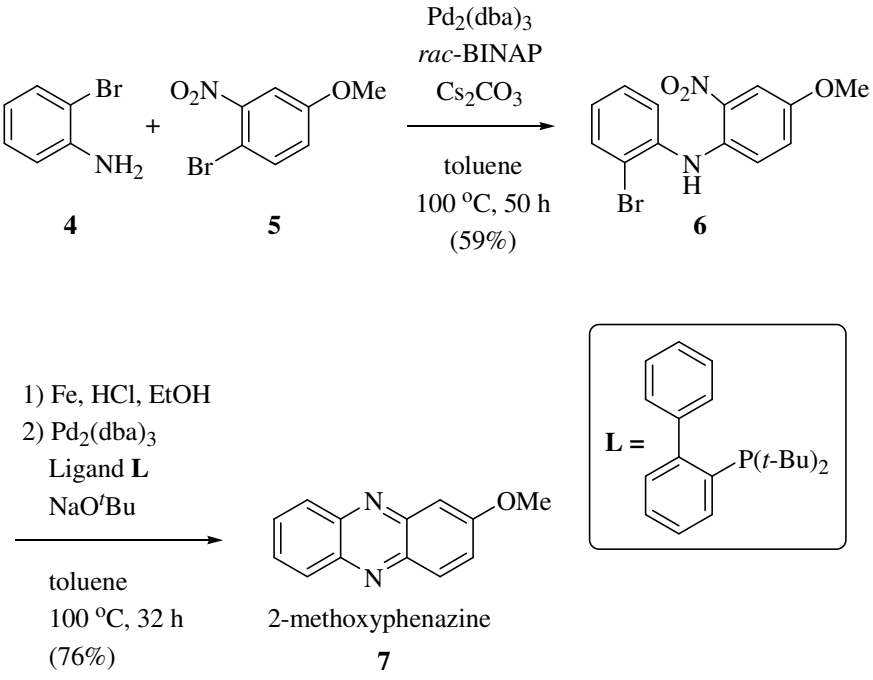
One of the very first examples of palladium-catalyzed amination reactions of vinylic substrates was in fact, the coupling between anilines **1** and 2-triflatotropona **2** (Scheme 2). Tropona derivatives are interesting compounds due to their homoaromaticity and the presence of this structural entity in biologically active natural products.[14]



1 **2** **3**

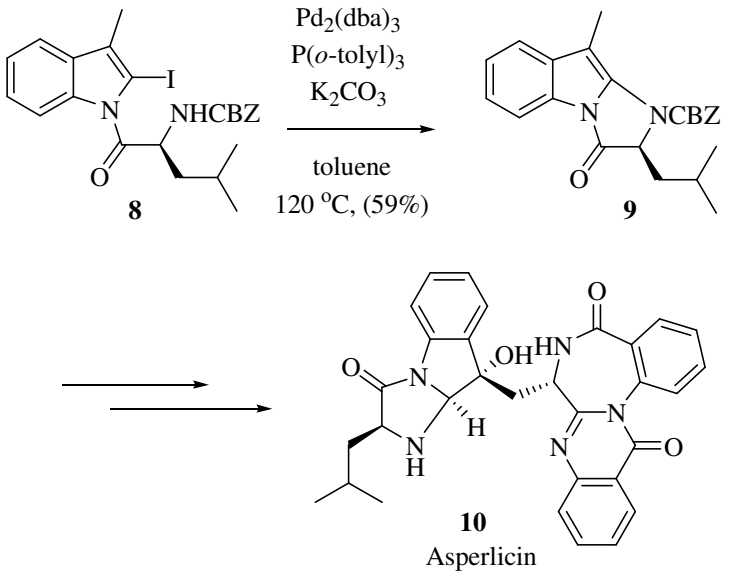
Scheme 2

Tietze *et al*. reported the synthesis of substituted diphenylamines by Buchwald-Hartwig reaction using *o*-haloaniline and nitro-substituted aryl bromides (Scheme 3). Cyclization of these diphenylamines by the intramolecular Pd(0)-catalyzed N-arylation produces phenazines. Naturally occurring phenazines have various biological activities. Majority of phenazines are produced by strains of *Pseudomonas* and *Streptomyces* species.[15]



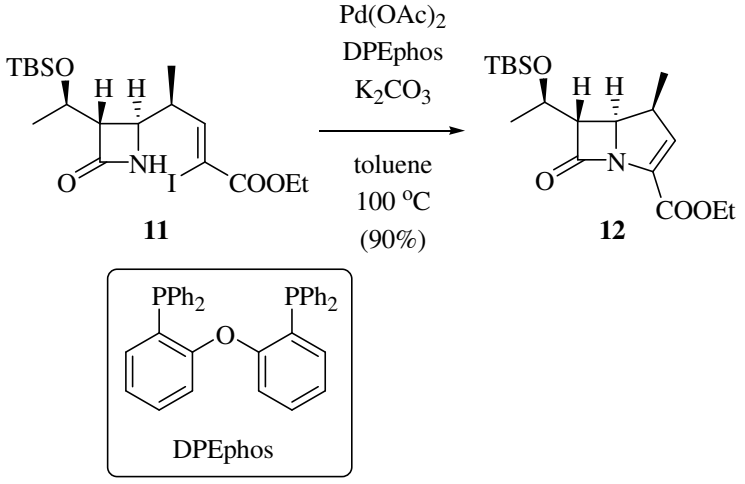
Scheme 3

Snider and co-workers used the palladium-catalyzed amide bond formation reaction developed by Buchwald to construct the crucial imidazoindolone moiety towards the total synthesis of the potent cholecystokinin antagonist asperlicin (Scheme 4).[16]



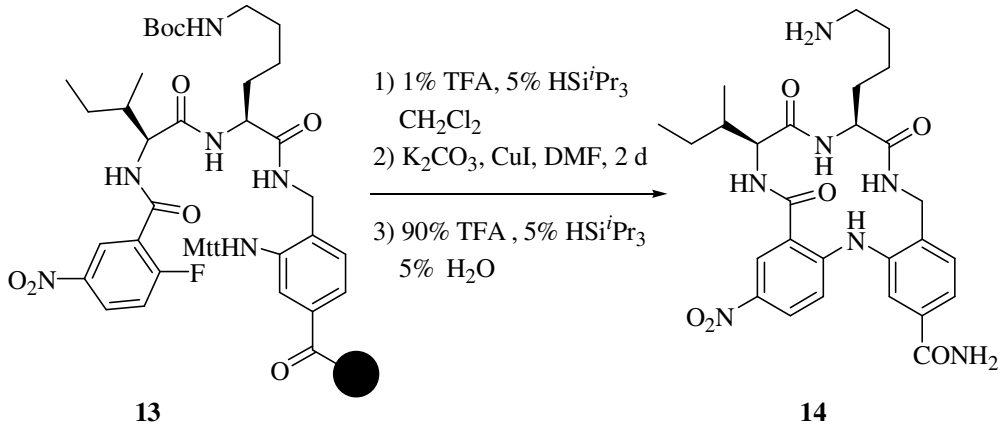
Scheme 4

Mori *et al*. used palladium-catalyzed C-N bond-forming reaction for the synthesis of carbapenem antibiotic derivative 3-alkoxycarbonyl-1β-methylcarbapenem. In this reaction, Mori emphasized that the generation of Pd(0) from $Pd(OAc)_2$ in the absence of a base and use of DPEphos as ligand are necessary to increase the yield of the product.[17]



Scheme 5

Burgess *et al*. reported the copper-mediated macrocyclization methodology for the preparation of the diarylamine bridged macrocyclic peptidomimetics of neurotrophin-3 (Scheme 6).[18] To our knowledge this is the only method known in the literature for the synthesis of cyclic peptides with diarylamine linker. Neurotrophin-3 (NT-3) is a member of the neurotrophin family and related to Nerve Growth Factor (NGF). The tyrosine kinase receptor for NGF is TrkA, and the tyrosine kinase receptor for NT-3 is termed TrkC.[19] β-Turn peptidomimetic **14** was synthesized to mimic hot spots of neurotrophin-3 and others.

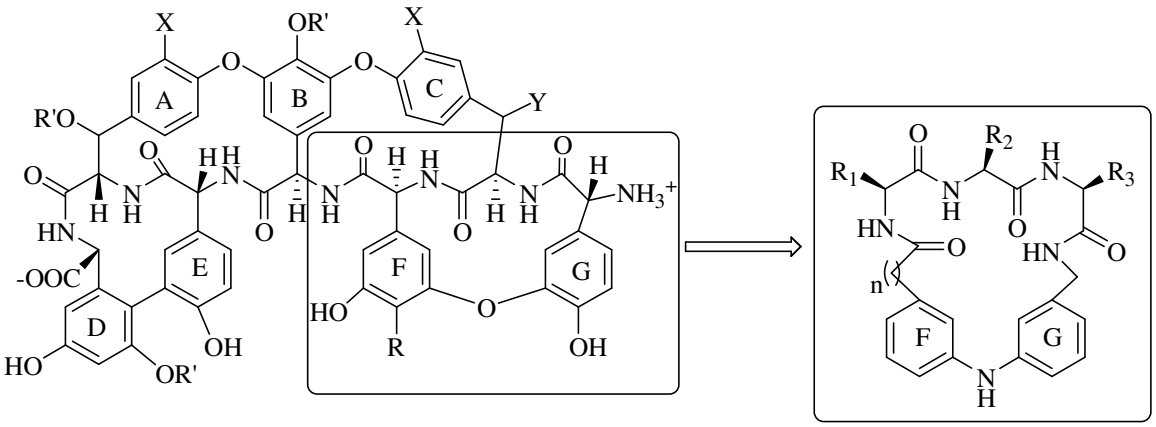


13 **14**

Scheme 6

Although, simultaneous and independent work from several research groups has led to the development of very powerful protocols for the preparation of the above diaryl heteroatom (mainly with oxygen atom) bridged cyclic peptidomimetics. Still there is a growing interest in the development of novel synthetic methodology for conformational restriction of peptides to mimic the bioactive conformation as closely as possible. As part of ongoing programe on peptidomimetics in our group, we were interested in studying

carbon-nitrogen bond forming reactions, importantly Buchwald-Hartwig coupling,[20] during the final cyclization step to synthesize biarylamine bridged macrocylicpeptides to mimic the biarylether bridged cyclic peptides and peptidomimetics, such as the glycopeptide antibiotics vancomycin, teicoplanin and ristocetin A, which are highly effective and widely used clinical agents for bacterial infections (Figure 1).[18,21]



15 Teicoplanin : X = Cl; Y = H; R = H (R' = sugar unit)

16 Ristocetin A: X = H; Y = OH; R =Me (R' = sugar unit)

Figure 1: Macrocyclic peptidomimetics inspired by the teicoplanin FG ring system.

In our present study, we described the utility of palladium-catalyzed Buchwald-Hartwig C-N coupling reaction in cyclization of linear peptides **I** to furnish the diarylamine bridged cyclic peptides **II** (Figure 2).

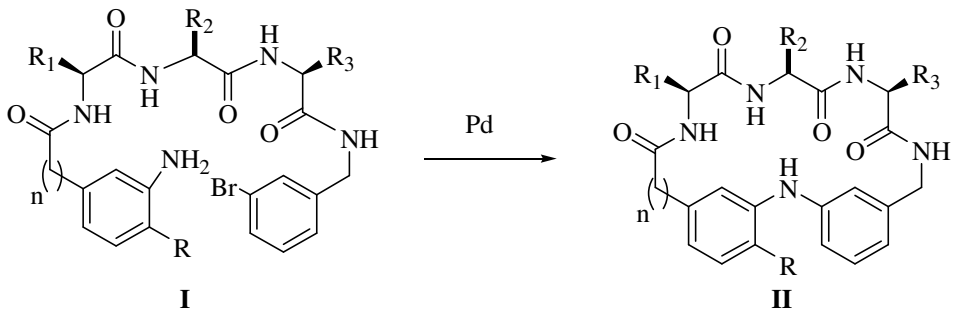


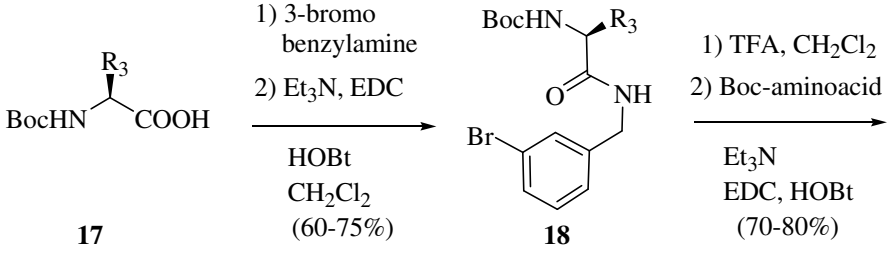
Figure 2: Buchwald-Hartwig Reaction

6.2 Results and Discussion

6.2.1 Synthesis of (19-21)-membered cyclic peptides constrained with diarylamine linkers

We have designed the acyclic precursors **22** for the Buchwald-Hartwig reaction. Scheme 7 outlines the preparation of the precursors **22**. The synthesis started with the conversion of the corresponding N-Boc protected amino acids **17** to respective 3-bromobenzyl amides **18** using solution chemistry. After the removal of the Boc group by treatment with trifluroacetic acid in dichloromethane, the corresponding TFA salt of **18** coupled with respective Boc-amino acid to obtain compounds **19** in good yields. Compounds **20** were obtained on deprotection of **19** followed by coupling with respective Boc-amino acids. Similarly, intermediate **21** was obtained from compound **20**. Next, the precursors **22** for the Buchwald-Hartwig cyclization were obtained by deprotection of **21** followed by treatment with triethylamine.

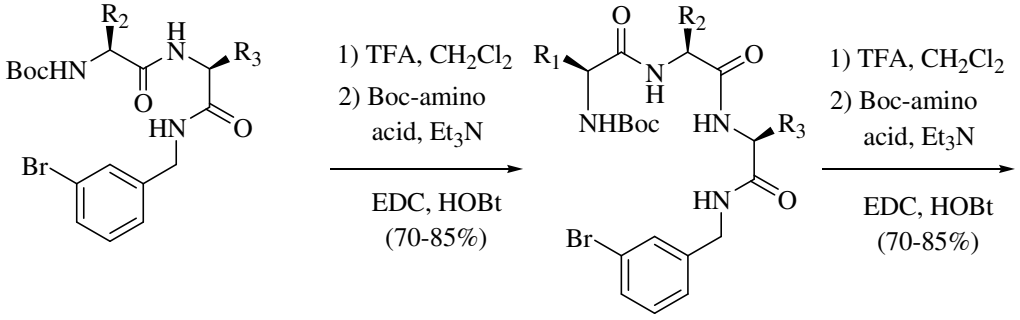
Preliminary experiments were carried out in order to optimize the most efficient protocol for the intramolecular cyclization of **22a** to form cyclic peptides **23a** using known Buchwald-Hartwig coupling conditions shown in Table 1. In the previous chapters 2 and 3, we reported that a $Pd(OAc)_2$–(*o*-tolyl)$_3$P catalyst in combination with Hunig's base (EtN^iPr_2) protocol for the intramolecular coupling of aryl bromides and alkene (the Heck reaction) or alkyne (the Sonogashira reaction) to form corresponding cyclic peptides in good yields. First, we applied this protocol for Buchwald-Hartwig reaction of **22a** to form cyclic peptide **23a** (Scheme 8). This reaction did not yield the



17 **18**

17a $R_3 = CH_3$
17b $R_3 = CH_2CH(CH_3)_2$

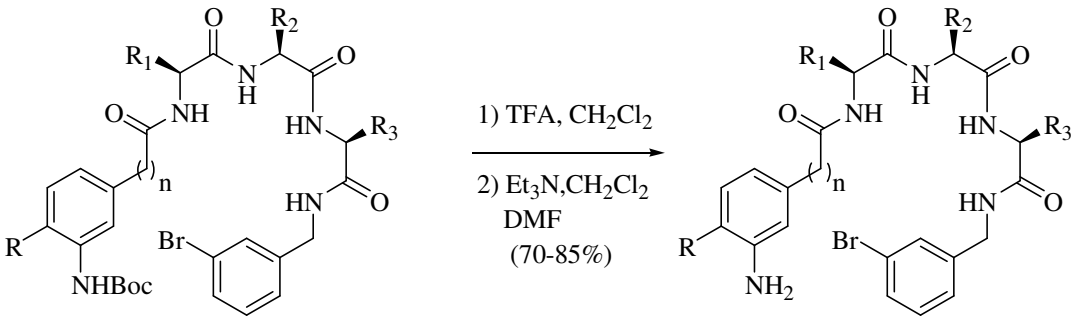
18a $R_3 = CH_3$
18b $R_3 = CH_2CH(CH_3)_2$



19 **20**

19a $R_2 = CH(CH_3)_2$, $R_3 = CH_3$
19b $R_2 = CH_3$, $R_3 = CH_2CH(CH_3)_2$
19c $R_2 = CH(CH_3)CH_2CH_3$, $R_3 = CH_3$
19d $R_2 = CH_2CH(CH_3)_2$, $R_3 = CH_3$

20a $R_1 = CH_2Ph$, $R_2 = CH(CH_3)_2$, $R_3 = CH_3$
20b $R_1 = CH_2Ph$, $R_2 = CH_3$, $R_3 = CH_2CH(CH_3)_2$
20c $R_1 = CH_2Ph$, $R_2 = CH(CH_3)CH_2CH_3$, $R_3 = CH_3$
20d $R_1 = CH(CH_3)_2$, $R_2 = CH_2CH(CH_3)_2$, $R_3 = CH_3$

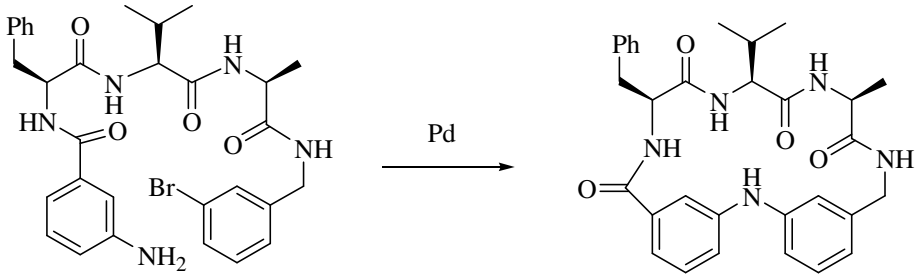


21 **22**

21a $R_1 = CH_2Ph$, $R_2 = CH(CH_3)_2$, $R_3 = CH_3$, R = H, n = 0 **22a**
21b $R_1 = CH_2Ph$, $R_2 = CH(CH_3)_2$, $R_3 = CH_3$, R = H, n = 1 **22b**
21c $R_1 = CH_2Ph$, $R_2 = CH(CH_3)_2$, $R_3 = CH_3$, R = H, n = 2 **22c**
21d $R_1 = CH_2Ph$, $R_2 = CH_3$, $R_3 = CH_2CH(CH_3)_2$, R = H, n = 0 **22d**
21e $R_1 = CH_2Ph$, $R_2 = CH(CH_3)CH_2CH_3$, $R_3 = CH_3$, R = H, n = 0 **22e**
21f $R_1 = CH(CH_3)_2Ph$, $R_2 = CH_2CH(CH_3)_2$, $R_3 = CH_3$, R = H, n = 0 **22f**
21g $R_1 = CH_2Ph$, $R_2 = CH(CH_3)_2$, $R_3 = CH_3$, R = CH_3, n = 0 **22g**

Scheme 7

product and starting material was recovered quantitatively (entry 1). We attempted the protocol using $Pd(OAc)_2$–(*o*-tolyl)$_3$P complex in the presence of sodium *tert*-butoxide, effective catalyst for the cross-coupling of aryl halides and amine.[22] Compound **22a** not cyclized to the desired cyclic peptide **23a** (entry 2). Buchwald and Wolf observed that the $Pd_2(dba)_3$ or $Pd(OAc)_2$/BINAP catalyst system is effective for the cross-coupling of a variety of primary amines with aryl bromides. They also observed that significantly better results were obtained using this catalyst than with catalysts with (*o*-tolyl)$_3$P as



22a **23a**

Scheme 8

ligands.[23] This protocol spurred us to attempt the $Pd(OAc)_2$/(±)BINAP catalyst for the intramolecular Buchwald-Hartwig reaction of **22a** using sodium *tert*-butoxide as a base in acetonitrile at 100 ^oC. To our delight, the reaction proceeded to completion in overnight (15 h). Cyclic peptide **23a** was obtained in moderate yield (entry 3) and the structure was confirmed by analytical data. We have also used the $Pd(OAc)_2$/(±)BINAP catalyzed intramolecular Buchwald-Hartwig reaction conditions on **22a** using potasium *tert*-butoxide as base in acetonitrile at 100 ^oC to form cyclic peptide **23a** in good yield (entry 4). Both racemic and nonracemic BINAP gave similar results for this Buchwald-Hartwig

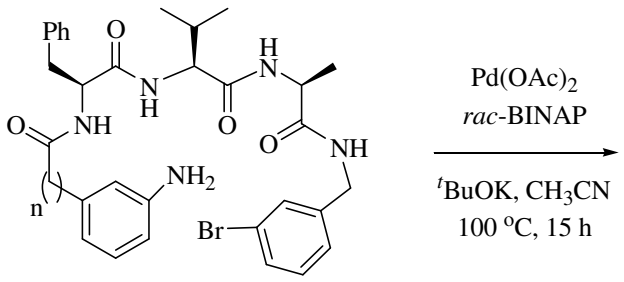
reaction of **22a** to form cyclic peptide **23a** (entry 4,5). Relatively slow reactions were observed when Cs_2CO_3 was used as a base (entry 6).

Table1. Optimization[24] of the Buchwald-Hartwig reaction[a] for macrocycliczation

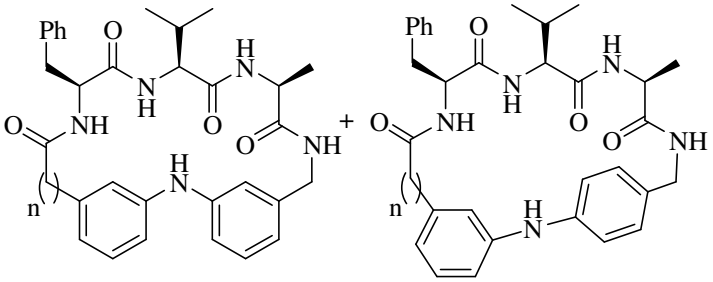
entry	precursor	concn, M	solvent	Base	Ligand	Product **23a** (yield %)
1	**22a**	$1.5x10^{-3}$	CH_3CN	$EtN(i\text{-}Pr)_2$	(o-tolyl)P	--
2	**22a**	$1.5x10^{-3}$	CH_3CN	^{t}BuONa	(o-tolyl)P	--
3	**22a**	$1.5x10^{-3}$	CH_3CN	^{t}BuONa	*rac*-BINAP	44
4	**22a**	$1.5x10^{-3}$	CH_3CN	^{t}BuOK	*rac*-BINAP	44
5	**22a**	$1.5x10^{-3}$	CH_3CN	^{t}BuOK	*(R)*-BINAP	45
6	**22a**	$1.5x10^{-3}$	CH_3CN	Cs_2CO_3	*rac*-BINAP	42

a. Reaction time 15 h, 30 mol % $Pd(OAc)_2$ as catalyst, 40 mol % ligand, 2 equiv of base (^{t}BuOK) or 3-5 equiv of base (Cs_2CO_3) used.

We, first investigated the cyclization of three substrates **22a-c** using Buchwald-Hartwig protocol with a $Pd(OAc)_2$/BINAP catalyst in combination with potasium *tert*-butoxide (2 equiv). Interestingly, all three substrates were cyclized to furnish the corresponding cyclic peptides **23a-c** in moderate yields. To our surprise, in the case of **22b**, we isolated two products **23b** and **24b** in (14 % and 40 % respectively) an overall yield 54% (Scheme 9).



22a n = 0
22b n = 1
22c n = 2



23a (45 %)
23b (14 %)
23c (56 %)

24a (00 %)
24b (40 %)
24c (02 %)

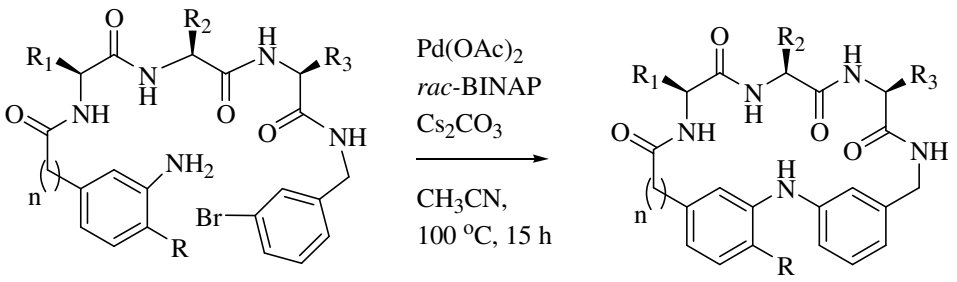
Scheme 9

The cyclic peptide **23a** was confirmed by its ^{1}H NMR and ESMS spectral data. The signal that corresponds to the amine (NH_2) at δ 5.19 as a broad singlet in the acyclic peptide **22a** disappeared and this clearly indicates reaction has proceeded and singlet at δ 8.33 confirms the diaryl amine -NH- in cyclic peptide **23a**. Electro-spray mass spectrum also confirmed the cyclic peptide **23a** formation by showing the correct molecular ion peak. ES mass spectra of both **23b** and **24b** showed the proper molecular ion peaks and in

^{1}H NMR spectrum of **23b**, a singlet at δ 7.98 represents –NH- of diarylamine moiety. Singlet at δ 8.03 in ^{1}H NMR spectrum of **24b** and pattern in the aromatic region (6.63-7.30) different from that pattern of **23b**, clearly represent **24b** was the regioisomer of **23b**. Consequently, we proposed that cyclic peptide **24b** most likely formed via a benzyne intermediate.[25] Probably, the size and/or conformation of the peptide are dictating the possible nucleophilic attack on benzyne intermediate from either side to give regioisomeric mixture of cyclic peptides.

In contrast, Buchwald-Hartwig reaction of **22b** gave only **23b** with the use of a $Pd(OAc)_2$/BINAP catalyst in combination with a mild base Cs_2CO_3. Consequently, we used this mild base and observed that, 2 equiv of Cs_2CO_3 gave a lower isolated yield in the same reaction time in comparison to the reaction with 2 equiv of ^{t}BuOK. The use of 4 equiv of cesium carbonate gave 50% of cyclic peptide **23b** in an overnight reaction at 100 ^{o}C. However, addition of cesium carbonate in two equal parts in regular interval (7 hours since 1st portion addition) was required to isolate product in good yields.

Cyclization of peptides **22a-g** were carried out using Buchwald-Hartwig reaction under standard condtions [($Pd(OAc)_2$/BINAP, Cs_2CO_3, CH_3CN, 100 ^{o}C] to synthesize corresponding cyclic peptides **23a-g**. We observed better yields in the synthesis of 21-membered cyclic peptides, for example, cyclic peptide **23c** was isolated in 53% yield. However, the 20-membered cyclic peptide **23b** (50%) isolated in little higher yields than 19-membered cyclic peptide **23a** (42%). Albeit, 19-membered cyclic peptide **23g** isolated in low yield (29%) (Scheme 10).



22 **23**

22a R = H, $R_1 = CH_2Ph$, $R_2 = CH(CH_3)_2$, $R_3 = CH_3$, n = 0 **23a** (42 %)

22b R = H, $R_1 = CH_2Ph$, $R_2 = CH(CH_3)_2$, $R_3 = CH_3$, n = 1 **23b** (50 %)

22c R = H, $R_1 = CH(CH_3)_2$, $R_2 = CH(CH_3)_2$, $R_3 = CH_3$, n = 2 **23c** (53 %)

22d R = H, $R_1 = CH_2Ph$, $R_2 = CH_3$, $R_3 = CH_2CH(CH_3)_2$, n = 0 **23d** (44 %)

22e R = H, $R_1 = CH_2Ph$, $R_2 = CH(CH_3)CH_2CH_3$, $R_3 = CH_3$, n = 0 **23e** (46 %)

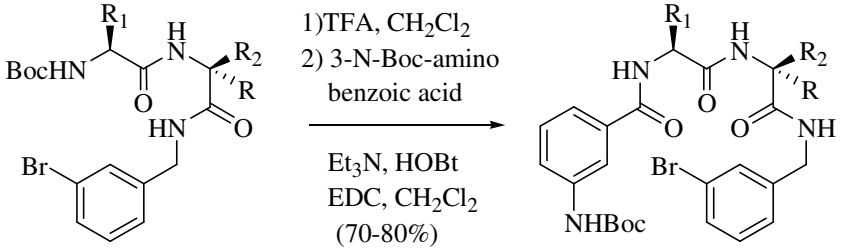
22f R = H, $R_1 = CH(CH_3)_2$, $R_2 = CH_2CH(CH_3)_2$, $R_3 = CH_3$, n = 0 **23f** (36 %)

22g $R = CH_3$, $R_1 = CH_2Ph$, $R_2 = CH_3$, $R_3 = CH_2CH(CH_3)_2$, n = 0 **23g** (29 %)

Scheme 10

6.2.2 Synthesis of 16- & 22-membered cyclic peptides constrained with diaryl amine linkers

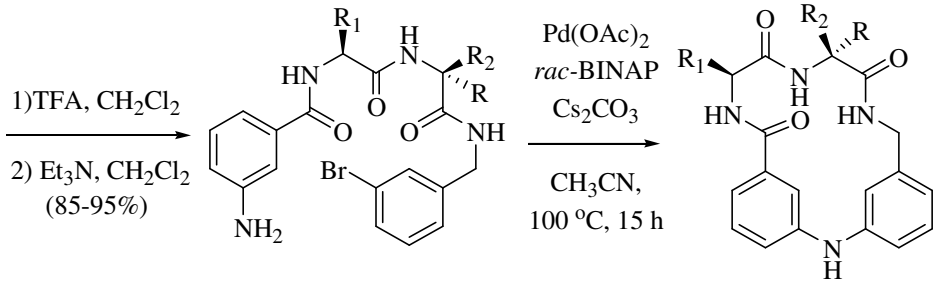
We have also employed successfully the $Pd(OAc)_2$/(±)BINAP catalyzed intramolecular Buchwald-Hartwig reaction of **26a** and **26b**, using cesium carbonate as a base in acetonitrile at 100 °C in an overnight to form cyclic dipeptide derivatives **27a, 27b** in good yields respectively (Scheme 11). Cyclic peptidomimetic **27b** was isolated in better yield (65%) than cyclic compound **27a** (55%) and these compounds were characterized by analytical data.



19 **25**

19e $R_1 = CH_2Ph$, $R_2 = CH_3$, R = H
19f $R_1 = CH_2Ph$, $R_2 = CH_3$, $R = CH_3$

25a $R_1 = CH_2Ph$, $R_2 = CH_3$, R = H
25b $R_1 = CH_2Ph$, $R_2 = CH_3$, $R = CH_3$

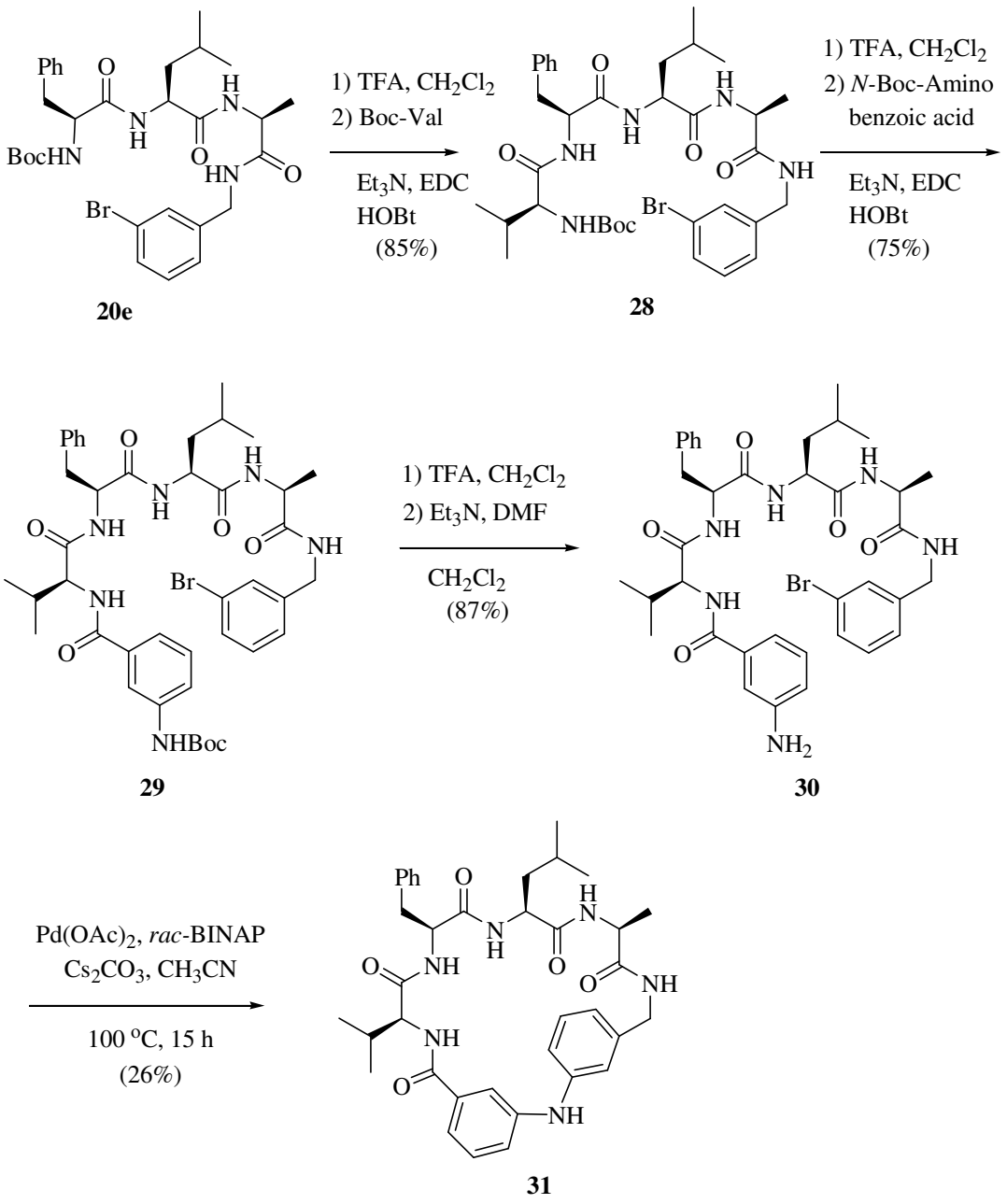


26 **27**

26a $R_1 = CH_2Ph$, $R_2 = CH_3$, R = H **27a** (55 %)
26b $R_1 = CH_2Ph$, $R_2 = CH_3$, $R = CH_3$ **27b** (65 %)

Scheme 11

We further substantiated our cyclization method using Buchwald-Hartwig conditions by synthesizing 22-membered cyclic tetrapeptide compound. However, the cyclic tetra-peptide compound **31** was isolated in poor yield (26%) from its corresponding acyclic peptide **30**. The synthesis of cyclic compound **31** is described in Scheme 12.



20e **28** **29** **30** **31**

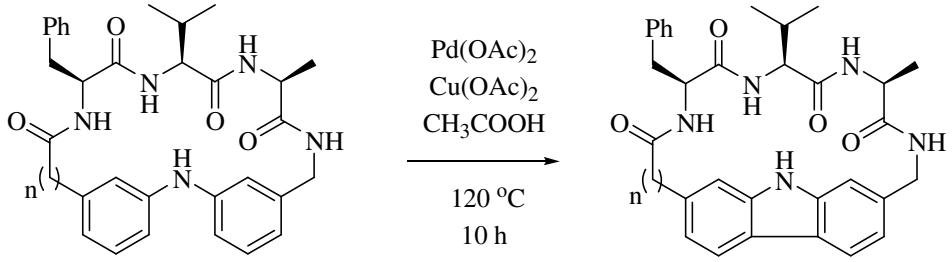
Scheme 12

6.2.3 Synthesis of carbazole contained cyclic peptides

Carbazoles are crucial building blocks in organic synthesis and the core structures of numerous biologically active compounds.[26,27] A wide range of biologically interesting

carbazole derivatives have been prepared by metal-catalyzed processes, particularly those employing palladium. For example, the palladium-catalyzed cyclization of N,N-diarylamines[28] and the heteroannulations of 1,3-dienes[29] have been extensively investigated and provide efficient approaches to the synthesis of carbazoles.

As a logical extension of our ongoing project, we attempted the C(sp2)-C(sp2) bond-forming reaction on diarylamine constrained cyclic peptide compounds **23b** and **23c**. Compounds **23b** and **23c** did furnish carbazole contained cyclic peptidomimetics **32a** and **32b**, respectively to our delight (scheme 13). The structures of **32a** and **32b** were confirmed by ^{1}H NMR and ESMS spectral data.



23b n = 1 **32a** (12 %)

23c n = 2 **32b** (15 %)

Scheme 13

6.3 Conclusions

We have demonstrated that Buchwald-Hartwig C-N coupling reaction can be used for the macrocyclization of di-, tri-, and tetra peptide derivatives to produce corresponding cyclic peptide compounds with diarylamine linkers. The diarylamine moiety present in our cyclic peptide compounds mimics the diarylether moiety present in a variety of naturally occurring cyclic structures such as the glycopeptide antibiotics vancomycin, teicoplanin and ristocetin A. We have also described the synthesis of carbazole bridged cyclic peptide compounds toward biologically important macrocyclic peptidomimetics. These cyclic compounds may also prove to be useful tools in understanding the utility of constrained structures in the search for novel lead molecules.

6.4 Experimental Section

6.4.1 General Procedure 1 for the Buchwald-Hartwig Cyclization Reaction

rac-BINAP (40 mol%) was added to HPLC grade acetonitirle (1.5 x 10^{-3}M) solvent and solution refluxed for 30 min. Allowed to room temperature and the palladium acetate (30 mol%) was added and stirred for 15 min, followed by acyclic peptide (500 mg) and finally the base Cs_2CO_3 (4 equiv.) were added. The resulting reaction mixture was stirred at 100 ^oC for 15 h. After this period of stirring, the solvent was removed under reduced pressure, and the residue was subsequently purified by column chromatography.

6.4.2 General Procedure 2 for the Buchwald-Hartwig Cyclization Reaction

rac-BINAP (40 mol%) was added to HPLC grade acetonitirle (1.5 x 10^{-3}M) solvent and solution refluxed for 30 min. Allowed to room temperature and the palladium acetate (30 mol%) was added and stirred for 15 min, followed by acyclic peptide (500 mg) and finally the base ^tBuOK (2 equiv.) were added. The resulting reaction mixture was stirred at 100 ^oC for 15 h. After this period of stirring, the solvent was removed under reduced pressure, and the residue was subsequently purified by column chromatography.

6.4.3 General procedure for peptide coupling

(a) To a stirred solution of the TFA salt of C-protected peptide in CH_2Cl_2 (5 mL/mmol) at 0^o (ice-bath) under N_2 was added successively Et_3N (5 equiv), HOBt (1.2

equiv), a solution of the Boc-protected amino acid (1 equiv.) in CH_2Cl_2 (2.5 mL/mmol), and EDC (1.2 equiv.). The mixture was allowed to warm to r.t., and stirring was continued for 15 h. The mixture was diluted with CH_2Cl_2 and washed with 10% aq. citric acid, aq. saturated $NaHCO_3$, H_2O and saturated NaCl solution. The organic phase was dried (Na_2SO_4), evaporated, and the residue was purified using flash column chromatography to get the pure material.

(b) To a stirred solution of TFA salt of C-protected peptide in CH_2Cl_2 (3 mL/mmol) and DMF (2 mL/mmol) at 0^o (ice-bath) under N_2 was added successively Et_3N (5 equiv.), HOBt (1.2 equiv.), a solution of the Boc-protected amino acid (1 equiv.) in CH_2Cl_2 (2.5 mL/mmol), and EDC (1.2 equiv.). The mixture was allowed to warm to r.t., and stirring was continued for 15 h. The residue obtained after the removal of all volatiles was dried under vacuum for 1 h and then stirred in MeOH for 20 min. The white precipitate was collected by filtration and thoroughly washed successively with MeOH/H_2O 1:1 mixture and MeOH. The solid product was dried under high vacuum for several hours.

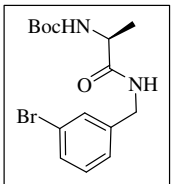
6.4.4 General procedure for Boc deprotection

(**a**) CF_3COOH (1.5 mL/mmol) was added to an ice-cold solution of the Boc-protected peptide in CH_2Cl_2 (5 mL/mmol). The reaction mixture was allowed to warm to r.t. and stirring was continued for 2 h. The mixture was evaporated and the residue dried under high vaccum. The salts with CF_3COOH were used without further purification and characterization.

(**b**) CF_3COOH (1.5 mL/mmol) was added to an ice-cold solution of the Boc-protected peptide in CH_2Cl_2 (5 mL/mmol). The reaction mixture was allowed to warm to r.t. and stirring was continued for 3 h. The mixture was evaporated and the residue dried under high vaccum. Then the residue dissolved in mixture of DCM and DMF solution and basified (p^H = 8) with Et_3N. The mixture solution was concentrated to its 1/3 volume and 1:1 Methanol and water solution added. Solid compound was obtained on stirring for 30 min at room temperature. Filtered off and dried under vaccum for 6-10 h.

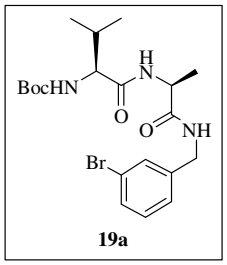
6.4.5 General procedure for the synthesis of carbazole contained cyclic peptides

To a diarylamine constrained cyclic compound in acetic acid, were added 50 mol% $Pd(OAc)_2$, $Cu(OAc)_2$ (3 equiv.) and solution refluxed for 6 h at 120 ^oC. Reaction mixture cooled to room temperature, taken into water and extrated with ethyl acetate (3x 50 ml). Combined extracts were washed with water, brine and dried over anhydrous Na_2SO_4. Solution concentrated and cruded compound was purified by flash column chromatography to obtained carbazole contained cyclic peptide.



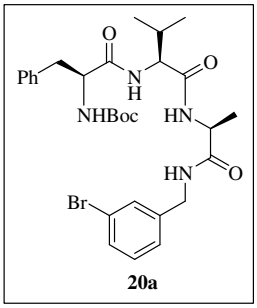
18a

Compound 18a: Compound was obtained as a white solid in the procedure **6.4.3a** (yield 83%), mp 86-88 °C; $[\alpha]_D^{25}$ = +7.6 (*c* 1, DMSO); IR (KBr) 3339, 3311, 2988, 2934, 1664, 1658, 1627 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.32 (t, *J* = 5.9 Hz, 1H), 7.43 (s, 1H), 7.43-7.40 (m, 1H), 7.28-7.24 (m, 2H), 6.95 (d, *J* = 7.0 Hz, 1H), 4.27 (d, *J* = 5.9 Hz, 2H), 4.01-3.94 (m, 1H), 1.23 (s, 9H), 1.20 (d, *J* = 7.0 Hz, 3H); ESMS *m/z* calcd for $C_{15}H_{21}BrN_2O_3$ 357, found 359 (M+2), 357 (M).



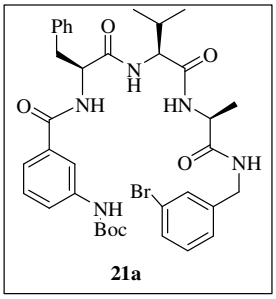
19a

Compound 19a: Compound was prepared as white solid by following procedure **6.4.3a** (yield 76%), mp 152-154 °C; $[\alpha]_D^{25}$ = -5.3 (*c* 1, DMSO); IR (KBr) 3285, 2969, 1645, 1542, 1528 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.41 (t, *J* = 5.4 Hz, 1H), 7.93 (d, *J* = 7.0 Hz, 1H), 7.43-7.40 (m, 2H), 7.28-7.22 (m, 2H), 6.68 (d, *J* = 8.6 Hz, 1H), 4.34-4.21 (m, 3H), 3.80 (t, *J* = 7.8 Hz, 1H), 1.96-1.93 (m, 1H), 1.37 (s, 9H), 1.23 (d, *J* = 7.2 Hz, 3H), 0.84 (d, *J* = 7.0 Hz, 3H), 0.79 (d, *J* = 6.7 Hz, 3H); ESMS *m/z* calcd for $C_{20}H_{30}BrN_3O_4$ 456, found 458 (M+2), 456 (M).



20a

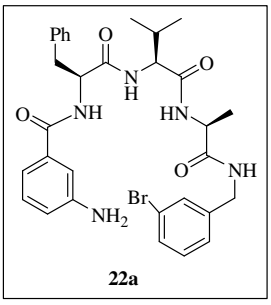
Compound 20a: Compound was prepared as a white solid using procedure **6.4.3b** (yield 96%), mp 234-236 °C; $[\alpha]_D^{25}$ = -7.9 (*c* 1, DMSO); IR (KBr) 3284, 2966, 1640, 1533 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.39 (t, *J* = 5.9 Hz, 1H), 8.15 (d, *J* = 7.0 Hz, 1H), 7.67 (d, *J* = 8.9 Hz, 1H), 7.43-7.40 (m, 2H), 7.28-7.17 (m, 7H), 7.01 (d, *J* = 8.6 Hz, 1H), 4.34-4.16 (m, 5H), 2.98 (dd, J_1 = 4.0 Hz, J_2 = 13.9 Hz, 1H), 2.73 (dd, J_1 = 10.5 Hz, J_2 = 13.7 Hz, 1H), 2.01-1.96 (m, 1H), 1.34 (s, 9H), 1.24 (d, *J* = 7.0 Hz, 3H), 0.85 (dd, J_1 = 10.5 Hz, J_2 = 17.2 Hz, 6H); ESMS *m/z* calcd for $C_{29}H_{39}BrN_4O_5$ 603, found 605 (M+2), 603 (M).



21a

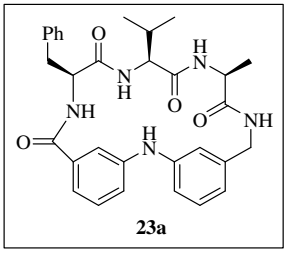
Compound 21a: Compound was synthesized as a white solid by following procedure **6.4.3b** (yield 87%), mp 220-222 °C; $[\alpha]_D^{25}$ = -19.2 (*c* 1, DMSO); IR (KBr) 3279, 2968, 1636, 1542 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 9.44 (s, 1H), 8.46 (d, *J* = 8.3 Hz, 1H), 8.38 (t, *J* = 5.6 Hz, 1H), 8.13 (d, *J* = 7.2 Hz, 1H), 7.88-7.85 (m, 2H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.43-7.13 (m, 11H), 4.75-4.69 (m, 1H), 4.33-4.20 (m,

4H), 3.11 (dd, J_1 = 3.7 Hz, J_2 = 13.7 Hz, 1H), 2.98 (dd, J_1 = 10.7 Hz, J_2 = 13.7 Hz, 1H), 2.03-1.98 (m, 1H), 1.47 (s, 9H), 1.24 (d, J = 7.0 Hz, 3H), 0.85 (t, J = 7.0 Hz, 6H); ES-MS *m/z* calcd for $C_{36}H_{44}BrN_5O_6$ 720, found 722 (M+2), 720 (M).



22a

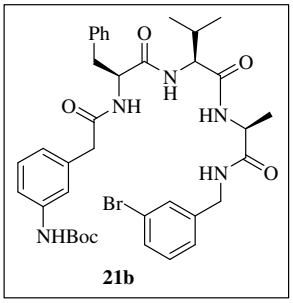
Compound 22a: Compound was prepared as a white solid by following procedure **6.4.4b** (yield 95%), mp 253-254 °C; $[\alpha]_D^{25}$= -17.2 (*c* 1, DMSO); IR (KBr) 3274, 2964, 1634, 1537 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.38 (t, J = 5.9 Hz, 1H), 8.28 (d, J = 8.3 Hz, 1H), 8.14 (d, J = 7.2 Hz, 1H), 7.83 (d, J = 8.9 Hz, 1H), 7.43-7.40 (m, 2H), 7.32-7.14 (m, 7H), 7.05 (t, J = 7.8 Hz, 1H), 6.93 (s, 1H), 6.87 (d, J = 7.5 Hz, 1H), 6.67 (dd, J_1 = 1.3 Hz, J_2 = 7.8 Hz, 1H), 5.19 (s, 2H), 4.73-4.67 (m, 1H), 4.32-4.20 (m, 4H), 3.09 (dd, J_1 = 4.0 Hz, J_2 = 14.2 Hz, 1H), 2.99 (dd, J_1 = 9.5 Hz, J_2 = 13.7 Hz, 1H), 2.02-1.97 (m, 1H), 1.24 (d, J = 7.2 Hz, 3H), 0.85 (t, J = 7.2 Hz, 6H) **(Spectrum No. 48)**; ^{13}C NMR (50 MHz, DMSO-*d6*): δ 172.4, 171.5, 170.6, 167.3, 148.7, 142.3, 138.4, 135.0, 130.5, 129.8, 129.7, 129.2(2C), 128.7, 128.2(2C), 126.3, 126.1, 121.7, 116.8, 114.6, 112.8, 57.4, 54.8, 48.4, 41.5, 36.8, 30.9, 19.3, 18.0(2C) **(Spectrum No. 49)**; ESMS *m/z* calcd for $C_{31}H_{36}BrN_5O_4$ 622, found 646 (M+1+Na), 644 (M-1+Na). HRMS calcd for $C_{31}H_{37}BrN_5O_4$ 622.2028, found 622.2048.



23a

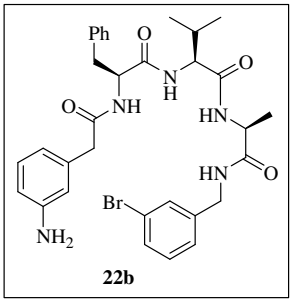
Cyclic compound 23a: Compound was synthesized as a brown solid by following the general procedure **6.4.1** (yield 42%), mp 178-180 °C; $[\alpha]_D^{25}$ = -50.8 (*c* 0.25 DMSO); IR (KBr) 3310, 2962, 1654, 1590, 1525 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.70 (d, J = 6.4 Hz, 1H), 8.33 (s, 1H), 8.27-8.20 (m, 1H), 7.54 (d, J = 8.1 Hz, 1H), 7.69 (s, 1H), 7.40-7.12 (m, 10H), 7.02 (dd, J_1 = 1.3 Hz, J_2 = 2.4 Hz,

1H), 6.77 (dd, J_1 = 2.1 Hz, J_2 = 8.1 Hz, 1H), 6.70 (d, J = 6.7 Hz, 1H), 4.75 (q, J = 6.7 Hz, 1H), 4.26-4.11 (m, 3H), 3.98 (dd, J_1 = 6.2 Hz, J_2 = 15.2 Hz, 1H), 3.09 (dd, J_1 = 7.8 Hz, J_2 = 13.4 Hz, 1H), 2.96 (dd, J_1 = 7.8 Hz, J_2 = 13.4 Hz, 1H), 2.24-2.20 (m, 1H), 1.25 (d, J = 7.2 Hz, 3H), 0.67 (d, J = 6.7 Hz, 3H) , 0.58 (d, J = 7.0 Hz, 3H) **(Spectrum No. 50)**; ^{13}C NMR (50 MHz, DMSO-*d6*): δ 172.3, 171.4, 170.5, 167.9, 143.1, 142.9, 141.1, 137.6, 134.7, 129.4(2C), 129.0, 128.8, 128.1(2C), 126.3, 126.1, 121.1, 119.6, 118.3, 117.1, 113.6, 57.5, 55.9, 48.0, 42.5, 36.4, 28.0, 19.1, 18.4, 16.7 **(Spectrum No. 51)**; ESMS *m/z* calcd for $C_{31}H_{35}N_5O_4$ 541, found 542 (M+1); HRMS calcd for $C_{31}H_{36}N_5O_4$ 542.2767, found 542.2780.



21b

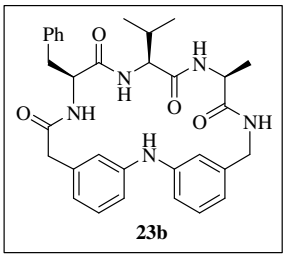
Compound 21b: Compound was obtained as a white solid in accordance to procedure **6.4.3b** (yield 82%), mp 290 °C; $[\alpha]_D^{25}$ = -7.0 (*c* 1, DMSO); IR (KBr) 3275, 2970, 1636, 1544 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d6*): δ 9.20 (s, 1H), 8.39 (t, J = 5.9 Hz, 1H), 8.18 (d, J = 7.3 Hz, 1H), 8.06 (d, J = 7.2 Hz, 1H), 7.82 (d, J = 8.7 Hz, 1H), 7.43-7.40 (m, 2H), 7.34 (s, 1H), 7.27-7.13 (m, 8H), 7.06 (t, J = 7.8 Hz, 1H), 6.69 (d, J = 7.8 Hz, 1H), 4.59-4.54 (m, 1H), 4.33-4.15 (m, 4H), 3.37-3.27 (m, 2H), 2.99 (dd, J_1 = 4.6 Hz, J_2 = 14.0 Hz, 1H), 2.76 (dd, J_1 = 9.7 Hz, J_2 = 14.0 Hz, 1H), 1.98-1.93 (m, 1H), 1.46 (s, 9H), 1.23 (d, J = 7.2 Hz, 3H), 0.79 (dd, J_1 = 7.0 Hz, J_2 = 12.9 Hz, 6H); ES-MS *m/z* calcd for $C_{37}H_{46}BrN_5O_6$ 734, found 736 (M+2), 734 (M).



22b

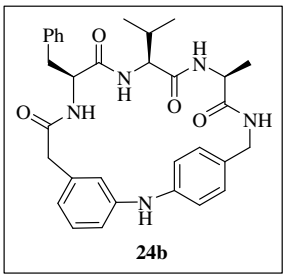
Compound 22b: Compound was prepared as a white solid by following procedure **6.4.4b** (yield 94%), mp 238-240 °C; $[\alpha]_D^{25}$ = -15.0 (*c* 1, DMSO); IR (KBr) 3274, 2962, 1635, 1547 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d6*): δ 8.38 (t, J = 5.9 Hz, 1H),

8.09-8.06 (m,2H), 7.80 (t, *J* = 8.6 Hz, 1H), 7.43-7.40 (m, 2H), 7.27-7.14 (m, 7H), 6.84 (t, *J* = 7.5 Hz, 1H), 6.39 (s, 1H), 6.36 (s, 1H), 6.24 (d, *J* = 7.5 Hz, 1H), 4.90 (brs, 2H), 4.59-4.53 (m, 1H), 4.34-4.16 (m, 4H), 3.21 (q, *J* = 5.9 Hz, 2H), 3.00 (dd, J_1 = 4.3 Hz, J_2 = 14.0 Hz, 1H), 2.77 (dd, J_1 = 9.4 Hz, J_2 = 13.7 Hz, 1H), 1.96 (sext, *J* = 6.7 Hz, 1H), 1.24 (d, *J* = 7.0 Hz, 3H), 0.83 (d, *J* = 7.0 Hz, 3H), 0.80 (d, *J* = 7.0 Hz, 3H) **(Spectrum No. 52)**; ^{13}C NMR (50 MHz, DMSO-*d6*): δ 172.2, 171.0, 170.4, 170.2, 148.3, 142.2, 137.7, 136.4, 130.3, 129.7, 129.5, 129.2(2C), 128.5, 127.9(2C), 126.1, 126.0, 121.6, 116.6, 114.8, 112.1, 57.4, 53.7, 48.3, 42.4, 41.4, 37.3, 30.7, 19.1, 18.1, 18.0 **(Spectrum No. 53)**; ESMS *m/z* calcd for $C_{32}H_{38}BrN_5O_4$ 636, found 660 (M+1+Na), 658 (M-1+Na).



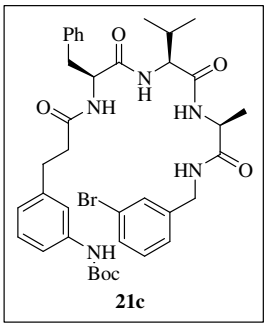
23b

Cyclic compound 23b: Compound was prepared as white solid by following the general procedure **6.4.1** & **6.4.2** (yield 50%), mp 202 °C; $[\alpha]_D^{25}$ = +6.0 (*c* 0.1, DMSO); IR (KBr) 3355, 2926, 1664, 1590, 1526 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d6*): δ 8.26 (d, *J* = 7.5 Hz, 2H), 8.12 (t, *J* = 5.9 Hz, 1H), 7.98 (s, 1H), 7.88 (d, *J* = 5.1 Hz, 1H), 7.67 (s, 1H), 7.38-7.04 (m, 8H), 6.79-6.75 (m, 2H), 6.69 (d, *J* = 7.5 Hz, 1H), 6.61 (d, *J* = 7.5 Hz, 1H), 4.50-4.45 (m, 1H), 4.33- 4.27 (m, 1H), 4.15 (dd, J_1 = 5.4 Hz, J_2 = 14.2 Hz, 1H), 3.79-3.72 (m, 2H), 3.38 (d, *J* = 12.3 Hz, 1H), 3.18 (dd, J_1 = 3.2 Hz, J_2 = 14.2 Hz, 1H), 3.08 (d, *J* = 9.9 Hz, 1H), 2.74 (dd, J_1 = 10.3 Hz, J_2 = 14.2 Hz, 1H), 1.91-1.85 (m, 1H), 1.30 (d, *J* = 7.0 Hz, 3H), 0.87-0.82 (m, 6H) **(Spectrum No. 54)**; ^{13}C NMR (50 MHz, DMSO-*d6*): δ 172.8, 171.0, 170.6, 170.5, 143.4, 143.3, 140.3, 138.2, 136.7, 129.0 (2C), 128.8, 128.7, 128.0 (2C), 126.2, 120.4, 119.4, 117.0, 115.8, 115.5, 115.3, 59.8, 54.0, 49.7, 43.0, 42.3, 37.0, 29.4, 18.9(2C), 16.0 **(Spectrum No. 55)**; ESMS *m/z* calcd for $C_{32}H_{37}N_5O_4$ 555, found 556 (M+1).



24b

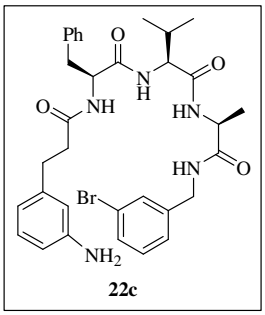
Cyclic compound 24b: Compound was obtained as a white solid in procedure **6.4.2** (yield 40%), mp 148-150 °C; $[\alpha]_D^{25}$ = -11.2 (*c* 0.25, DMSO); IR (KBr) 3312, 2965, 1653, 1591, 1531 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.32 (d, *J* = 5.1 Hz, 1H), 8.03 (s,1H), 7.88-7.80 (m, 3H), 7.30-7.10 (m, 7H), 7.00 (s, 1H), 6.95 (s, 1H), 6.78-6.63 (m, 4H), 4.48 (q, *J* = 5.1 Hz, 1H), 4.33 (dd, J_1 = 6.7 Hz, J_2 = 15.8 Hz, 1H), 4.04-3.88 (m, 3H), 3.46 (d, *J* = 14.8 Hz, 1H), 3.31 (d, *J* = 14.5 Hz, 1H), 2.95-2.90 (m, 2H), 2.06-2.01 (m, 1H), 1.08 (d, *J* = 7.0 Hz, 3H), 0.61 (d, *J* = 7.0 Hz, 3H), 0.55 (d, *J* = 7.0 Hz, 3H) **(Spectrum No. 56)**; ^{13}C NMR (50 MHz, DMSO-*d6*): δ 172.5, 172.4, 171.1, 170.5, 144.2, 143.3, 139.7, 137.0, 136.2, 129.2 (2C), 129.0, 128.2 (2C), 126.4, 121.7, 118.2, 118.0, 117.0, 116.3, 112.4, 58.2, 55.4, 49.4, 41.9, 41.7, 36.8, 28.6, 22.5, 18.9, 16.8(2C) **(Spectrum No. 57)**; ESMS *m/z* calcd for $C_{32}H_{37}N_5O_4$ 555, found 556 (M+1).



21c

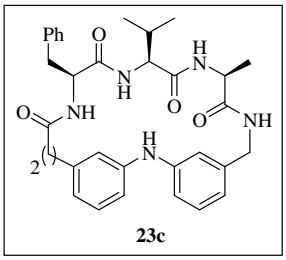
Compound 21c: Compound was prepared as a light brown solid by following procedure **6.4.3b** (yield 78%), mp 270-272 °C; $[\alpha]_D^{25}$ = -3.5 (*c* 1, DMSO); IR (KBr) 3276, 2968, 1635, 1544 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 9.19 (s, 1H), 8.38 (t, *J* = 5.9 Hz, 1H), 8.09 (dd, J_1 = 8.3 Hz, J_2 = 15.8 Hz,1H), 7.95 (s, 1H), 7.81 (d, *J* = 8.6 Hz, 1H), 7.43-7.14 (m, 11H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 4.61-4.55 (m, 1H), 4.33- 4.16 (m, 4H), 3.03 (dd, J_1 = 7.0 Hz, J_2 = 12.1 Hz, 1H), 2.74 (dd, J_1 = 11.0 Hz, J_2 = 17.7 Hz, 1H), 2.60 (t, *J* = 7.0 Hz, 2H), 2.30 (t, *J* = 6.2 Hz, 2H), 2.01-1.96 (m, 1H), 1.46 (m, 9H), 1.24 (d, *J* = 7.2 Hz, 3H), 0.84 (d, *J* =

6.7 Hz, 3H), 0.82 (d, *J* = 6.7 Hz, 3H); ESMS *m/z* calcd for $C_{38}H_{48}BrN_5O_6$ 750, found 752 (M+2), 750 (M).



22c

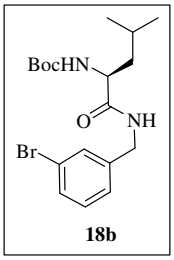
Acyclic compound 22c: Compound was prepared as a light brown solid by following procedure **6.4.4b** (yield 85%), mp 238-240 °C; $[\alpha]_D^{25}$ = +26.7 (*c* 0.5, DMSO); IR (KBr) 3274, 2964, 1634, 1546 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.39 (t, *J* = 5.9 Hz, 1H), 8.08 (d, *J* = 6.4 Hz, 1H), 7.80 (d, *J* = 8.6 Hz, 1H), 7.43-7.40 (m, 2H), 7.27-7.15 (m, 8H), 6.87 (t, *J* = 7.5 Hz, 1H), 6.38-6.36 (m, 2H), 6.28 (d, *J* = 7.8 Hz, 1H), 5.01 (brs, 2H), 4.61-4.56 (m, 1H), 4.33- 4.17 (m, 4H), 3.00 (dd, J_1 = 4.3 Hz, J_2 = 14.0 Hz, 1H), 2.74 (dd, J_1 = 10.0 Hz, J_2 = 14.0 Hz, 1H), 2.53-2.49 (m, 2H), 2.29-2.00 (m, 2H), 1.98-1.96 (m, 1H), 1.24 (d, *J* = 7.0 Hz, 3H), 0.85 (d, *J* = 6.7 Hz, 3H), 0.82 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (50 MHz, DMSO-*d6*): δ 172.2, 171.6, 171.2, 170.4, 148.1, 142.2, 141.7, 137.9, 130.3, 129.7, 129.5, 129.1 (2C), 128.7, 127.9 (2C), 126.1, 126.0, 121.6, 115.8, 113.9, 111.8, 57.4, 53.7, 48.3, 41.4, 37.2, 36.9, 31.3, 30.7, 19.1, 18.1, 17.9; ESMS *m/z* calcd for $C_{33}H_{40}BrN_5O_4$ 650, found 652 (M+2), 650 (M).



23c

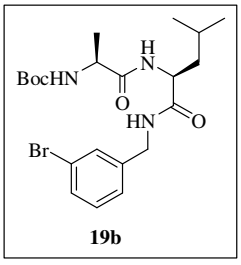
Cyclic compound 23c: Compound was prepared as a light brown solid by following procedure **6.4.1** & **6.4.2** (yield 56%), mp 233-235 °C; $[\alpha]_D^{25}$ = +17.6 (*c* 0.25, DMSO); IR (KBr) 3301, 2962, 1640, 1590, 1531 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.43 (d, *J* = 7.2 Hz, 1H), 8.31 (t, *J* = 6.9 Hz, 1H), 8.06 (s, 1H), 7.91 (d, *J* = 8.3 Hz, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.30-7.06 (m, 9H), 6.77-6.62 (m, 4H), 4.52 (q, *J* = 7.5 Hz, 1H), 4.29-4.24 (m, 2H), 4.00- 3.93 (m, 2H), 3.00 (dd, J_1 = 7.0 Hz, J_2

= 13.7 Hz, 1H), 2.85-2.78 (m, 2H), 2.70-2.59 (m, 2H), 2.42-2.36 (m, 1H), 2.11=2.06 (m, 1H), 1.21 (d, *J* = 7.2 Hz, 3H), 0.75 (d, *J* = 6.7 Hz, 3H), 0.71 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (50 MHz, DMSO-*d6*): δ 173.0, 171.8, 171.6, 170.1, 143.3, 143.1, 142.1, 140.3, 137.8, 129.1, 128.8 (2C), 128.2, 128.0 (2C), 126.1, 119.4, 119.3, 117.0, 115.5, 114.6, 113.9, 58.1, 54.6, 48.1, 42.6, 36.8, 35.8, 31.2, 28.8, 19.0, 18.3, 17.2; ESMS *m/z* calcd for $C_{33}H_{39}N_5O_6$ 569, found 570 (M+1).



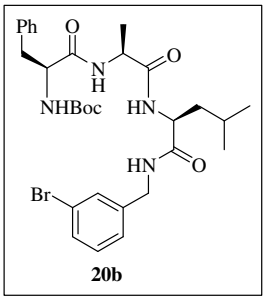
18b

Compound 18b: Compound was prepared by following general procedure **6.4.3a** (yield 75%)**,** m.p. 82-84 ^{o}C, $[\alpha]_D^{25}$ = -21.7 *(c* 1, $CHCl_3$); IR (KBr) 3300, 2958, 1657, 1528 cm^{-1}; ^{1}H NMR (DMSO-*d6*, 400MHz): δ 7.39-7.37 (m, 2H), 7.19-7.14 (m, 2H), 6.70 (bs, 1H), 4.91 (d, *J* = 7.5 Hz, 1H), 4.39 (bs, 2H), 4.12-4.11 (m, 1H), 1.74-1.63 (m, 2H), 1.52-1.41 (m, 1H), 1.39 (s, 9H), 0.94 (dd, J_1 = 10.2 Hz, J_2 = 16.4 Hz, 6H); ESMS *m/z* calcd for $C_{18}H_{27}BrN_2O_3$ 399, found 401 (M+2).



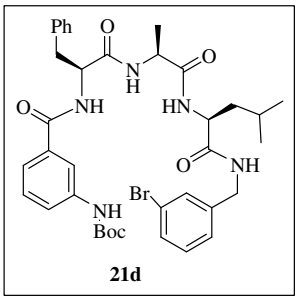
19b

Compound 19b: Compound was prepared as a white solid by following procedure **6.4.3b** (yield 85%), mp 166-168 °C; $[\alpha]_D^{25}$ = -16.4 (*c* 1, DMSO); IR (KBr) 3280, 2959, 1646, 1522 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d6*): δ 8.42 (brs, 1H), 7.80 (d, *J* = 8.3 Hz, 1H), 7.42-7.40 (m, 2H), 7.28-7.21 (m, 2H), 6.94 (d, *J* = 6.7 Hz, 1H), 4.34-4.22 (m, 2H), 3.97-3.93 (m, 1H), 3.01 (q, *J* = 7.5 Hz, 1H), 1.62-1.56 (m, 1H), 1.54-1.46 (m, 2H), 1.35 (s, 9H), 1.16 (d, *J* = 7.8 Hz, 3H), 0.88 (d, *J* = 6.4 Hz, 3H), 0.83 (d, *J* = 6.2 Hz, 3H); ESMS *m/z* calcd for $C_{21}H_{32}BrN_3O_4$ 470, found 472 (M+2), 470 (M).



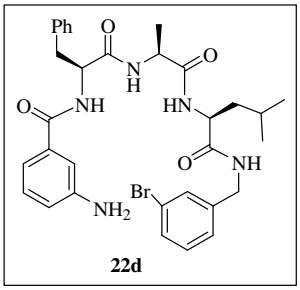
20b

Compound 20b: Compound was prepared as a white solid by following the general procedure **6.4.3b** (yield 90%), mp 158-160 °C; $[\alpha]_D^{25}$ = -12.7 (*c* 1, DMSO); IR (KBr) 3290, 2958, 1642, 1547 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.43 (t, *J* = 5.4 Hz, 1H), 7.97 (t, *J* = 6.4 Hz, 2H), 7.42 (brs, 2H), 7.41-7.17 (m, 7H), 6.91 (d, *J* = 8.3 Hz, 1H), 4.35-4.14 (m, 5H), 2.97 (dd, J_1 = 3.2 Hz, J_2 = 14.0 Hz, 1H), 2.71 (t, *J* = 10.7 Hz, 1H), 1.61-1.55 (m, 1H), 1.48 (t, *J* = 7.5 Hz, 2H), 1.29 (s, 9H), 1.22 (d, *J* = 6.7 Hz, 3H), 0.88 (d, *J* = 6.7 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 3H); ESMS *m/z* calcd for $C_{30}H_{41}BrN_4O_5$ 617, found 619 (M+2), 617 (M).



21d

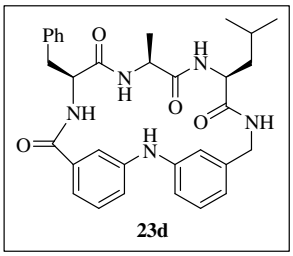
Compound 21d: Compound was prepared as a white solid by following procedure **6.4.3b** (yield 83%), mp 170-172 °C; $[\alpha]_D^{25}$ = -23.3 (*c* 1, DMSO); IR (KBr) 3285, 2959, 1637, 1538 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 9.43 (s, 1H), 8.42 (dd, J_1 = 6.2 Hz, J_2 = 9.1 Hz, 2H), 8.21 (d, *J* = 7.5 Hz, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.88 (s, 1H), 7.52 (d, *J* = 7.8 Hz, 1H), 7.42-7.14 (m, 11H), 4.69-4.64 (m, 1H), 4.35-4.25 (m, 4H), 3.08 (dd, J_1 = 5.9 Hz, J_2 = 10.2 Hz, 1H), 2.97 (dd, J_1 = 10.7 Hz, J_2 = 13.7 Hz, 1H), 1.60-1.57 (m, 1H), 1.55-1.48 (m, 2H), 1.47 (s, 9H), 1.25 (d, *J* = 7.0 Hz, 3H), 0.87 (d, *J* = 6.4 Hz, 3H), 0.83 (d, *J* = 6.4 Hz, 3H); ESMS *m/z* calcd for $C_{37}H_{46}BrN_5O_6$ 736, found 738 (M+2), 736 (M).



22d

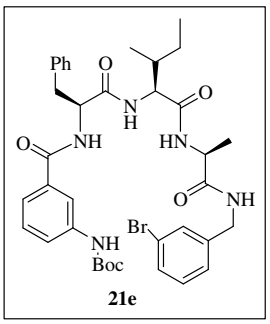
Compound 22d: Compound was prepared by following procedure **6.4.4b** as a white solid (yield 95%), mp 230-232 °C; $[\alpha]_D^{25}$ = -25.7 (*c* 1, DMSO); IR (KBr) 3284, 2956, 1638, 1539 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.43 (t, *J* = 5.9 Hz,

1H), 8.21 (d, *J* = 8.3 Hz, 1H), 8.17 (t, *J* = 7.5 Hz, 1H), 7.94 (d, *J* = 8.1 Hz, 1H), 7.42-7.40 (m, 2H), 7.32-7.13 (m, 7H), 7.04 (t, *J* = 7.8 Hz, 1H), 6.94-6.88 (m, 2H), 6.68-6.65 (m, 1H), 5.17 (s, 2H), 4.69-4.63 (m, 1H), 4.35-4.25 (m, 4H), 3.08 (dd, J_1 = 4.0 Hz, J_2 = 14.0 Hz, 1H), 2.96 (dd, J_1 = 10.5 Hz, J_2 = 13.7 Hz, 1H), 1.60-1.50 (m, 1H), 1.49-1.46 (m, 2H), 1.25 (d, *J* = 4.0 Hz, 3H), 0.88 (d, *J* = 6.4 Hz, 3H), 0.85 (d, *J* = 5.9 Hz, 3H); ^{13}C NMR (50 MHz, DMSO-*d6*): δ 172.0, 171.9, 171.3, 167.1, 148.6, 142.3, 138.3, 134.9, 130.4, 129.7, 129.5, 129.1(2C), 128.5, 128.0(2C), 126.2, 126.0, 121.6, 116.6, 114.5, 112.8, 54.7, 51.2, 48.2, 41.4, 40.8, 37.0, 24.2, 22.9, 21.7, 18.1; ESMS *m/z* calcd for $C_{32}H_{38}BrN_5O_4$ 636, found 638 (M+2), 636 (M).



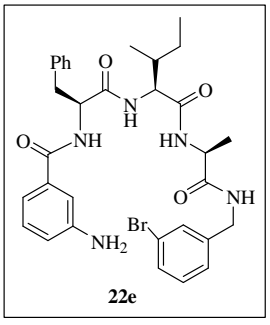
23d

Cyclic compound 23d: Compound was prepared by following general procedure **6.4.1** as a light brown coloured solid (yield 41%), mp 184-186 °C; $[\alpha]_D^{25}$ = -9.2 (*c* 0.25, DMSO); IR (KBr) 3313, 2957, 1647, 1589, 1521 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d6*): δ 8.72 (d, *J* = 6.2 Hz, 1H), 8.58 (d, *J* = 7.8 Hz, 1H), 8.33 (s, 1H), 8.04 (t, *J* = 7.4 Hz, 1H), 7.67 (s, 1H), 7.44-7.12 (m, 10H), 7.01 (dd, J_1 = 1.6 Hz, J_2 = 8.1 Hz, 1H), 6.76 (d, *J* = 8.3 Hz, 1H), 6.70 (d, *J* = 7.5 Hz, 1H), 4.45 (q, *J* = 8.3 Hz, 1H), 4.19-4.15 (m, 3H), 4.01 (dd, J_1 = 6.4 Hz, J_2 = 14.5 Hz, 1H), 3.07 (dd, J_1 = 8.3 Hz, J_2 = 13.4 Hz, 1H), 2.98 (dd, J_1 = 6.4 Hz, J_2 = 14.7 Hz, 1H), 1.71-1.54 (m, 2H), 1.39-1.24 (m, 1H), 1.60 (d, *J* = 7.5 Hz, 3H), 0.76 (d, *J* = 6.4 Hz, 6H); ^{13}C NMR (50 MHz, DMSO-*d6*): δ 171.8, 171.7, 171.4, 168.5, 143.0, 142.8, 140.8, 137.8, 134.9, 129.2(2C), 128.9, 128.8(2C), 128.1, 126.3, 120.9, 119.4, 118.2, 116.9, 113.9, 113.6, 79.1, 56.5, 50.8, 48.4, 42.4, 36.0, 23.9, 23.2, 20.7, 16.8; ESMS *m/z* calcd for $C_{32}H_{37}N_5O_4$ 555, found 556 (M+1).



21e

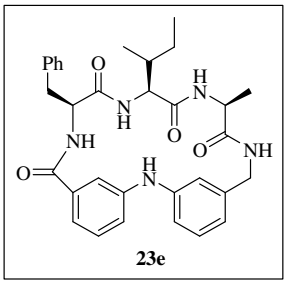
Compound 21e: Compound was prepared as a white solid by following procedure **6.4.3b** (yield 90%), mp 254-256 °C; $[\alpha]_D^{25}$ = -20.4 (*c* 1, DMSO); IR (KBr) 3279, 2969, 1636, 1542 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 9.44 (s, 1H), 8.44 (d, *J* = 8.3 Hz, 1H), 8.37 (t, *J* = 5.9 Hz, 1H), 8.11 (d, *J* = 6.2 Hz, 1H), 7.90 (d, *J* = 9.7 Hz, 1H), 7.88 (s, 1H), 7.54-7.50 (m, 1H), 7.43-7.13 (m, 11H), 4.74-4.68 (m, 1H), 4.34-4.21 (m, 4H), 3.09 (dd, J_1 = 3.8 Hz, J_2 = 13.7 Hz, 1H), 2.98 (dd, J_1 = 10.5 Hz, J_2 = 13.7 Hz, 1H), 1.79-1.72 (m, 1H), 1.44 (s, 9H), 1.24 (d, *J* = 7.0 Hz, 3H), 1.14-1.05 (m, 2H), 0.84-0.78 (m, 6H); ESMS *m/z* calcd for $C_{37}H_{46}BrN_5O_6$ 736, found 738 (M+2), 736 (M).



22e

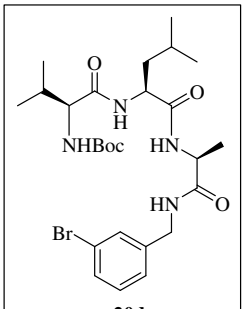
Compound 22e: Compound was prepared as a brown solid using procedure **6.4.4b** (yield 95%), mp 270-272 °C; $[\alpha]_D^{25}$ = -23.6 (*c* 1, DMSO); IR (KBr) 3273, 2962, 1634, 1538 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.37 (t, *J* = 5.6 Hz, 1H), 8.25 (d, *J* = 8.1 Hz, 1H), 8.12 (d, *J* = 7.0 Hz, 1H), 7.87 (d, *J* = 8.9 Hz, 1H), 7.43 (s, 1H), 7.42-7.40 (m, 1H), 7.31-7.13 (m, 7H), 7.05 (t, *J* = 7.8 Hz, 1H), 6.92 (s, 1H), 6.87 (d, *J* = 7.8 Hz, 1H), 6.67 (d, *J* = 6.7 Hz, 1H), 5.19 (s, 2H), 4.72-4.67 (m, 1H), 4.32-4.21 (m, 4H), 3.08 (dd, J_1 = 3.8 Hz, J_2 = 14.0 Hz, 1H), 2.98 (dd, J_1 = 9.2 Hz, J_2 = 13.3 Hz, 1H), 1.75-1.74 (m, 1H), 1.48-1.42 (m, 1H), 1.24 (d, *J* = 7.0 Hz, 3H), 1.12-1.03 (m, 1H), 0.83 (d, *J* = 7.0 Hz, 3H), 0.79 (d, *J* = 7.5 Hz, 3H); ^{13}C NMR (50 MHz, DMSO-*d6*): δ 172.2, 171.2, 170.5, 167.1, 148.6, 142.2, 138.3, 134.9, 130.3, 129.7, 129.5, 129.1(2C), 128.6, 128.0(2C), 126.1, 126.0, 121.6, 116.6, 114.4, 112.7, 56.6, 54.6,

48.3, 41.4, 37.0, 36.8, 24.2, 18.0, 15.3, 11.1; ESMS *m/z* calcd for $C_{32}H_{38}BrN_5O_4$ 636, found 638 (M+2), 636 (M).



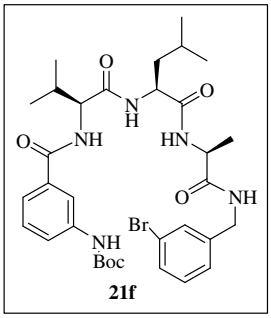
23e

Compound 23e: Compound was synthesized as a brown solid by following general procedure **6.4.1** (yield 46%), mp 288-290 °C; $[\alpha]_D^{25}$ = -47.4 (*c* 0.5, DMSO); IR (KBr) 3315, 2925, 1646, 1588, 1527 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.39 (d, *J* = 8.3 Hz, 1H), 8.28 (s, 1H), 8.21 (t, *J* = 5.9 Hz, 1H), 8.08 (d, *J* = 7.2 Hz, 1H), 7.87 (d, *J* = 6.4 Hz, 1H), 7.66 (s, 1H), 7.38-7.16 (m, 8H), 7.05-7.92 (m, 2H), 6.79-6.66 (m, 2H), 4.57-4.51 (m, 1H), 4.32-4.20 (m, 2H), 4.03 (quint, *J* = 6.7 Hz, 1H), 3.84 (t, *J* = 7.2 Hz, 1H), 3.18-2.95 (m, 2H), 1.94-1.88 (m, 1H), 1.44-1.36 (m, 2H), 1.23 (d, *J* = 7.0 Hz, 3H), 1.10-0.98 (m, 6H); ^{13}C NMR (50 MHz, DMSO-*d6*): δ 171.9, 171.1, 170.3, 167.9, 143.6, 142.8, 140.1, 138.2, 136.1, 129.3, 129.1, 128.9 (2C), 128.2(2C), 128.0, 126.3, 120.6, 120.0, 117.6, 115.3, 113.4, 58.6, 55.5, 49.1, 42.4, 36.7, 35.2, 24.6, 17.6, 15.6, 10.9; ESMS *m/z* calcd for $C_{32}H_{37}N_5O_4$ 555, found 578 (M+Na), 556 (M+1).



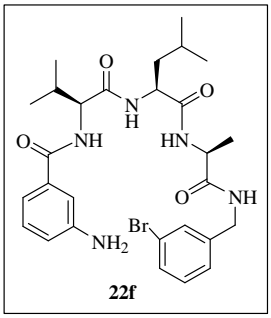
20d

Compound 20d: Compound was prepared as a white solid using general procedure **6.4.3b** (yield 90%), mp 202-204 °C; $[\alpha]_D^{25}$ = -21.7 (*c* 1, DMSO); IR (KBr) 3283, 2961, 1641, 1548 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.33 (t, *J* = 5.6 Hz, 1H), 7.99 (d, *J* = 7.0 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.43-7.41 (m, 2H), 7.28-7.21 (m, 2H), 6.74 (d, *J* = 8.6 Hz, 1H), 4.37-4.21 (m, 4H), 3.75 (t, *J* = 8.1 Hz, 1H), 1.94-1.89 (m, 1H), 1.65-1.58 (m, 3H), 1.43 (s, 9H), 1.22 (d, *J* = 7.2 Hz, 3H), 0.87-0.79 (m, 12H); ESMS *m/z* calcd for $C_{26}H_{41}BrN_4O_5$ 569, found 571 (M+2), 569 (M).



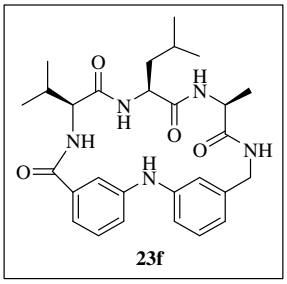
21f

Compound 21f: Compound was prepared as a white solid by following the general procedure **6.4.3b** (yield 85%), mp 172-173 °C; $[\alpha]_D^{25}$ = -11.3 (*c* 1.0 DMSO); IR (KBr) 3284, 2963, 1638, 1547 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 9.45 (s, 1H), 8.33 (t, *J* = 5.9 Hz, 1H), 8.09 (d, *J* = 8.6 Hz, 1H), 7.98 (t, *J* = 8.3 Hz, 2H), 7.92 (s, 1H), 7.57 (d, *J* = 8.1 Hz, 1H), 7.44-7.22 (m, 6H), 4.37-4.22 (m, 5H), 2.14-2.07 (m, 1H), 1.65-1.57 (m, 3H), 1.48 (s, 9H), 1.23 (d, *J* = 7.0 Hz, 3H), 0.91-0.81 (m, 12H); ESMS *m/z* calcd for $C_{33}H_{46}BrN_5O_6$ 688, found 690 (M+2), 688 (M).



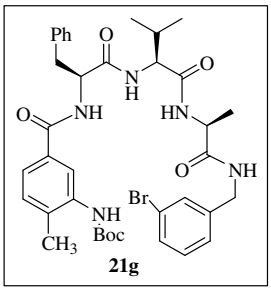
22f

Compound 22f: Compound was prepared as a white solid using procedure **6.4.4b** (yield 72%), mp 226-228 °C; $[\alpha]_D^{25}$ = -10.0 (*c* 1, DMSO); IR (KBr) 3280, 2960, 1638, 1537 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.39-8.32 (m, 1H), 7.97 (d, *J* = 8.1 Hz, 2H), 7.90 (d, *J* = 8.6 Hz, 1H), 7.43-7.40 (m, 2H), 7.29-7.22 (m, 2H), 7.08 (t, *J* = 7.8 Hz, 1H), 7.02 (s, 1H), 6.96 (d, *J* = 7.8 Hz, 1H), 6.70 (d, *J* = 6.4 Hz, 1H), 5.23 (s, 2H), 4.38-4.21 (m, 5H), 2.14-2.04 (m, 1H), 1.65-1.56 (m, 1H), 1.45 (t, *J* = 7.0 Hz, 2H), 1.22 (d, *J* = 7.0 Hz, 3H), 0.91-0.81 (m, 12H); ^{13}C NMR (50 MHz, DMSO-*d6*): δ 172.2, 171.6, 171.1, 167.3, 148.6, 142.3, 135.3, 130.3, 129.7, 129.5, 128.6, 126.0, 121.6, 116.6, 114.6, 112.8, 58.9, 50.8, 48.3, 41.4, 40.5, 30.2, 24.1, 23.0, 21.5, 19.3, 18.6, 18.0; ESMS *m/z* calcd for $C_{28}H_{38}BrN_5O_4$ 588, found 590 (M+2), 588 (M).



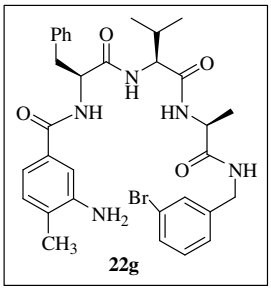
23f

Compound 23f: Compound was synthesized as a brown solid using general procedure **6.4.1** (yield 36%), mp 290-292 °C; $[\alpha]_D^{25}$ = -26.4 (*c* 0.5, DMSO); IR (KBr) 3311, 2958, 1658, 1589, 1524 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.56 (d, *J* = 6.7 Hz, 1H), 8.35 (s, 1H), 8.30 (d, *J* = 7.2 Hz, 1H), 8.23 (t, *J* = 5.6 Hz, 1H), 7.79 (s, 1H), 7.59 (d, *J* = 8.1 Hz, 1H), 7.36-7.16 (m, 4H), 7.01 (d, *J* = 6.2 Hz, 1H), 6.75 (d, *J* = 6.4 Hz, 1H), 6.72 (d, *J* = 7.5 Hz, 1H), 4.56 (dd, J_1 = 7.0 Hz, J_2 = 15.6 Hz, 1H), 4.26-4.19 (m, 2H), 3.97-3.89 (m, 2H), 2.18-2.13 (m, 1H), 1.69-1.55 (m, 3H), 1.06 (d, *J* = 7.2 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.93 (d, *J* = 6.7 Hz, 3H), 0.91-0.81 (m, 6H); ^{13}C NMR (50 MHz, DMSO-*d6*): δ 171.7, 171.1, 170.5, 167.5, 143.5, 142.7, 140.1, 134.8, 129.2, 128.9, 120.8, 118.7, 118.0, 116.8, 113.0, 112.8, 60.7, 52.2, 48.1, 41.7, 40.7, 28.9, 24.4, 23.2, 21.2, 19.2(2C), 18.4; ESMS *m/z* calcd for $C_{28}H_{37}N_5O_4$ 507, found 530 (M+Na), 508 (M+1).



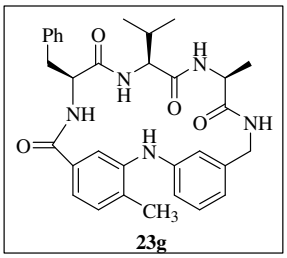
21g

Compound 21g: Compound was obtained as a white solid in the procedure **6.4.3b** (yield 85%), mp 238-240 °C; $[\alpha]_D^{25}$ = -26.9 (*c* 1, DMSO); IR (KBr) 3265, 2971, 1629, 1522 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.59 (s, 1H), 8.48 (d, *J* = 8.3 Hz, 1H), 8.38 (t, *J* = 6.2 Hz, 1H), 8.11 (d, *J* = 7.2 Hz, 1H), 7.86 (d, *J* = 8.6 Hz, 1H), 7.74 (s, 1H), 7.74-7.12 (m, 11H), 4.76-4.70 (m, 1H), 4.34-4.20 (m, 4H), 3.09 (dd, J_1 = 4.3 Hz, J_2 = 14.0 Hz, 1H), 3.00 (dd, J_1 = 10.7 Hz, J_2 = 13.7 Hz, 1H), 2.21 (s, 3H), 2.02-1.97 (m, 1H), 1.46 (s, 9H), 1.24 (d, *J* = 7.0 Hz, 3H), 0.84 (dd, J_1 = 3.0 Hz, J_2 = 6.7 Hz, 6H); ESMS *m/z* calcd for $C_{37}H_{46}BrN_5O_6$ 736, found 738 (M+2), 736 (M).



22g

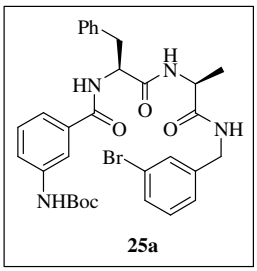
Compound 22g: Compound was prepared as a white solid using procedure **6.4.4b** (yield 88%), mp 253-254 °C; $[\alpha]_D^{25}$ = -40.8 (*c* 1, DMSO); IR (KBr) 3277, 2966, 1634, 1539 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.38 (t, *J* = 5.1 Hz, 1H), 8.21 (d, *J* = 8.1 Hz, 1H), 8.14 (d, *J* = 7.0 Hz, 1H), 7.82 (d, *J* = 9.9 Hz, 1H), 7.42-7.40 (m, 2H), 7.31-7.13 (m, 8H), 7.00 (s, 1H), 6.95 (d, *J* = 7.8 Hz, 1H), 6.88 (d, *J* = 7.5 Hz, 1H), 4.95 (s, 2H), 4.72-4.67 (m, 1H), 4.32-4.21 (m, 4H), 3.10 (dd, J_1 = 3.8 Hz, J_2 = 14.0 Hz, 1H), 2.06 (s, 3H), 2.02-1.95 (m, 1H), 1.24 (d, *J* = 7.2 Hz, 3H), 0.84 (d, *J* = 7.2 Hz, 3H) , 0.83 (d, *J* = 7.3 Hz, 3H) **(Spectrum No. 58)**; ^{13}C NMR (50 MHz, DMSO-*d6*): δ 172.2, 171.3, 170.4, 166.9, 146.4, 142.2, 138.4, 132.5, 130.3, 129.7, 129.5(2C), 129.1(2C), 128.0(2C), 126.1, 126.0, 124.6, 121.6, 114.7, 112.9, 57.3, 54.6, 48.3, 41.4, 36.7, 30.9, 19.2, 18.0, 17.9, 17.4 **(Spectrum No. 59)**; ESMS *m/z* calcd for $C_{32}H_{38}BrN_5O_4$ 636, found 660 (M+Na+2), 658 (M+Na), 638 (M+2), 636 (M).



23g

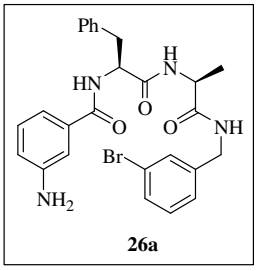
Compound 23g: Compound was prepared as a white solid using procedure **6.4.1** (yield 29%), mp 194-196 °C; $[\alpha]_D^{25}$ = -43.6 (*c* 0.25, DMSO); IR (KBr) 3309, 2954, 1645, 1530 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.57 (d, *J* = 6.7 Hz, 1H), 8.25 (d, *J* = 8.6 Hz, 1H), 8.07 (t, *J* = 6.2 Hz, 1H), 7.73 (s, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.34-7.13 (m, 10H), 6.93 (dd, J_1 = 1.3 Hz, J_2 = 8.1 Hz, 1H), 6.68 (d, *J* = 7.5 Hz, 1H), 4.77 (q, *J* = 7.0 Hz, 1H), 4.19-4.11 (m, 1H), 4.09-3.99 (m, 3H), 3.08 (dd, J_1 = 7.5 Hz, J_2 = 13.4 Hz, 1H), 2.96 (dd, J_1 = 7.8 Hz, J_2 = 13.4 Hz, 1H), 2.21 (m, 3H), 2.19-2.16 (m, 1H), 1.17 (d, *J* = 7.2 Hz, 3H), 0.68 (d, *J* = 6.7 Hz, 3H) , 0.60 (d, *J* = 7.0 Hz, 3H) **(Spectrum No. 60)**; ^{13}C NMR (50 MHz, DMSO-*d6*): δ 172.3, 171.3, 170.3,

167.5, 143.7, 140.9, 140.4, 137.5, 132.2, 130.7, 130.2, 129.3(2C), 129.0, 128.0(2C), 126.2, 119.4, 116.9, 116.4, 113.9, 79.1, 57.8, 55.6, 48.1, 42.5, 36.5, 28.1, 19.1, 18.4, 17.9, 16.8 **(Spectrum No. 61)**; ESMS *m/z* calcd for $C_{32}H_{37}N_5O_4$ 555, found 556 (M+1).



25a

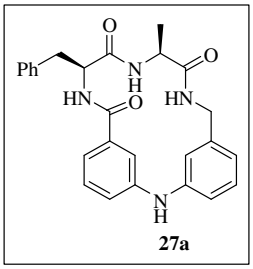
Compound 25a: Compound was prepared as a white solid using procedure **6.4.3a** (yield 75%), mp 123-124 °C; $[\alpha]_D^{25}$= -22.8 (*c* 0.5 DMSO); IR (KBr) 3301, 2977, 1638, 1546 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 7.94 (d, *J* = 7.8 Hz, 1H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.66 (s, 1H), 7.34-7.24 (m, 5H), 7.14-6.92 (m, 9H), 5.21 (q, *J* = 7.8 Hz, 1H), 4.57 (quint, *J* = 7.2 Hz, 1H), 4.33 (dd, J_1 = 6.2 Hz, J_2 = 15.3 Hz, 1H), 4.25 (dd, J_1 = 5.9 Hz, J_2 = 15.3 Hz, 1H), 3.12 (d, *J* = 7.0 Hz, 2H), 1.50 (s, 9H), 1.32 (d, *J* = 7.2 Hz, 3H); ESMS *m/z* calcd for $C_{31}H_{35}BrN_4O_5$ 623, found 642 ($M+NH_3+2$), 640 ($M+NH_3$), 625 (M+2) 623 (M, 62).



26a

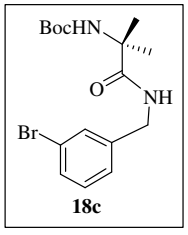
Compound 26a: Compound was prepared as a white solid using procedure **6.4.4b** (yield 95%), mp 212-214 °C; $[\alpha]_D^{25}$ = -11.8 (*c* 1, DMSO); IR (KBr) 3282, 1634, 1530 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.37 (t, *J* = 5.9 Hz, 1H), 8.22 (d, *J* = 5.6 Hz, 1H), 8.20 (d, *J* = 4.8 Hz, 1H), 7.44-7.41 (s, 2H), 7.33-7.13 (m, 7H), 7.04 (t, *J* = 7.8 Hz, 1H), 6.94 (t, *J* = 1.9 Hz, 1H), 6.89 (d, *J* = 6.7 Hz, 1H), 6.68-6.65 (m, 1H), 5.18 (s, 2H), 4.71-4.65 (m, 1H), 4.35-4.28 (m, 3H), 3.11 (dd, J_1 = 4.0 Hz, J_2 = 13.7 Hz, 1H), 2.98 (dd, J_1 = 10.5 Hz, J_2 = 14.0 Hz, 1H), 1.28 (d, *J* = 7.2 Hz, 3H) **(Spectrum No. 62)**; ^{13}C NMR (50 MHz, DMSO-*d6*): δ 172.2, 171.2, 167.0, 148.5, 142.2, 136.4, 134.9, 130.4, 129.7, 129.6, 129.1(2C), 128.5, 128.0(2C), 126.2, 126.0, 121.6, 116.6,

114.5, 112.8, 54.6, 48.4, 41.4, 37.0, 18.3 **(Spectrum No. 63)**; ESMS *m/z* calcd for $C_{26}H_{27}BrN_4O_3$ 523, found 525 (M+2), 523 (M).



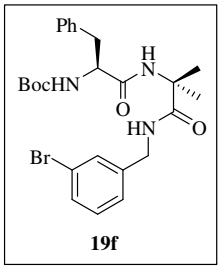
27a

Compound 27a: Compound was prepared as a white solid using procedure **6.4.1** (yield 55%), mp 312-314 °C; $[\alpha]_D^{25}$ = -61.6 (*c* 0.25, DMSO); IR (KBr) 3316, 1644, 1589, 1528 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.73 (t, *J* = 4.8 Hz, 1H), 8.37 (s, 1H), 8.30 (d, *J* = 9.1 Hz, 1H), 7.89 (d, *J* = 7.8 Hz, 1H), 7.67 (s, 1H), 7.39 (s, 1H), 7.37-7.15 (m, 7H), 6.99-6.94 (m, 2H), 6.81-6.75 (m, 2H), 4.56 (q, *J* = 7.5 Hz, 1H), 4.49 (dd, J_1 = 11.5 Hz, J_2 = 18.8 Hz, 1H), 4.29 (quint, *J* = 6.8 Hz, 1H), 3.78 (dd, J_1 = 4.8 Hz, J_2 = 14.5 Hz, 1H), 2.97 (d, *J* = 7.0 Hz, 2H), 1.17 (d, *J* = 6.7 Hz, 3H) **(Spectrum No. 64)**; ^{13}C NMR (50 MHz, DMSO-*d6*): δ 171.0, 170.9, 167.9, 143.24, 143.20, 140.6, 137.5, 136.2, 129.5, 129.1, 128.9(2C), 128.0, 128.2(2C), 126.4, 120.3, 120.0, 117.8, 114.1, 112.8, 56.9, 48.4, 42.6, 37.1, 17.8 **(Spectrum No. 65)**; ESMS *m/z* calcd for $C_{26}H_{26}N_4O_3$ 442, found 443 (M+1).



18c

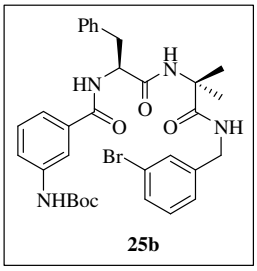
Compound 18c: Compound was prepared as a white solid by following procedure **6.4.3a** (yield 68%), mp 150-152 °C; IR (KBr) 3315, 2980, 1686, 1652, 1528 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.11 (t, *J* = 5.6 Hz, 1H), 7.43 (s, 1H), 7.38 (d, *J* = 7.5 Hz, 1H), 7.27-7.20 (m, 2H), 6.87 (bs, 1H), 4.24 (d, *J* = 6.2 Hz, 2H), 1.37 (brs, 6H), 1.32 (s, 9H); ESMS *m/z* calcd for $C_{16}H_{23}BrN_2O_3$ 371, found 373 (M+2), 371 (M).



19f

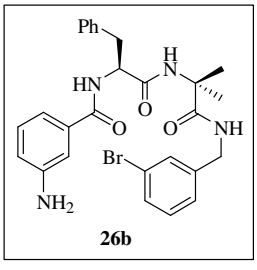
Compound 19f: Compound was prepared as a white solid using general procedure **6.4.3a** (yield 90%), mp 127-128 °C; $[\alpha]_D^{25}$ = +9.4 (*c* 1, DMSO); IR (KBr) 3539, 3349, 2978, 1690, 1647, 1506 cm^{-1};

^{1}H NMR (400 MHz, DMSO-*d6*): δ 8.04 (s, 1H), 7.94 (t, *J* = 5.9 Hz, 1H), 7.43 (s, 1H), 7.41-7.38 (m, 2H), 7.29-7.17 (m, 6H), 7.02 (d, *J* = 6.7 Hz, 1H), 4.31-4.09 (m, 3H), 2.92 (dd, J_1 = 5.9 Hz, J_2 = 13.7 Hz, 1H), 2.77 (dd, J_1 = 9.1 Hz, J_2 = 13.4 Hz, 1H), 1.40 (s, 3H), 1.32 (s, 3H), 1.25 (s, 9H); ESMS *m/z* calcd for $C_{25}H_{32}BrN_3O_4$ 518, found 535 ($M+NH_3$), 520 (M+2), 518 (M).



25b

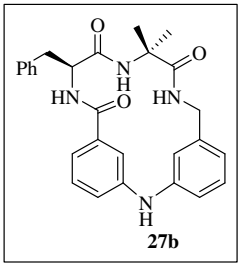
Compound 25b: Compound was prepared as a white solid using procedure **6.4.3a** (yield 78%), mp 98-100 °C; $[\alpha]_D^{25}$ = -3.2 (*c* 0.5, DMSO); IR (KBr) 3304, 2978, 1654, 1539 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d6*): δ 9.20 (s, 1H), 8.31 (d, *J* = 6.7 Hz, 1H), 8.06 (s, 1H), 7.92 (t, *J* = 5.9 Hz, 1H), 7.39-7.36 (m, 3H), 7.25-7.15 (m, 8H), 7.06 (t, *J* = 7.8 Hz, 1H), 6.69 (d, *J* = 7.5 Hz, 1H), 4.39 (q, *J* = 6.7 Hz, 1H), 4.20 (dd, J_1 = 6.2 Hz, J_2 = 15.8 Hz, 1H), 4.06 (dd, J_1 = 6.2 Hz, J_2 = 15.6 Hz, 1H), 3.36 (d, *J* = 14.0 Hz, 1H), 3.24 (d, *J* = 14.0 Hz, 1H), 2.97 (dd, J_1 = 6.2 Hz, J_2 = 13.7 Hz, 1H), 2.82 (dd, J_1 = 8.6 Hz, J_2 = 13.7 Hz, 1H), 1.32 (s, 9H), 1.28 (s, 3H), 1.25 (s, 3H); ESMS *m/z* calcd for $C_{33}H_{39}BrN_4O_5$ 651, found 653 (M+2), 651 (M).



26b

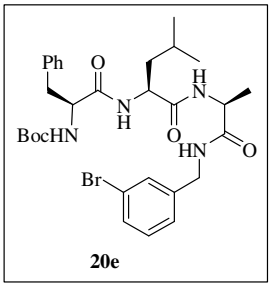
Compound 26b: Compound was prepared as a white solid using procedure **6.4.4a** (yield 90%), mp 82-84 °C; $[\alpha]_D^{25}$ = -1.4 (*c* 0.5 , DMSO); IR (KBr) 3312, 2926, 1653, 1539 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d6*): δ 8.20 (d, *J* = 6.7 Hz, 1H), 8.05 (s, 1H), 7.94 (t, *J* = 5.9 Hz, 1H), 7.40-7.37 (m, 2H), 7.27-7.16 (m, 7H), 6.83 (t, *J* = 7.8 Hz, 1H), 6.39-6.36 (m, 2H), 6.26 (d, *J* = 7.5 Hz, 1H), 4.88 (s, 2H), 4.38 (q, *J* = 4.6 Hz, 1H), 4.21 (dd, J_1 = 6.2 Hz, J_2 = 15.8 Hz, 1H), 4.09 (dd, J_1 = 6.2 Hz, J_2 = 15.8 Hz, 1H), 3.24 (d, *J* = 14.0 Hz, 1H), 3.13 (d, *J* = 14.0 Hz, 1H), 2.97 (dd, J_1 = 6.2 Hz, J_2 = 13.7

Hz, 1H), 2.82 (dd, J_1 = 8.6 Hz, J_2 = 13.7 Hz, 1H), 1.31 (s, 3H), 1.24 (s, 3H) **(Spectrum No. 66)**; ^{13}C NMR (50 MHz, DMSO-*d6*): δ 174.1, 170.9(2C), 148.3, 142.6, 137.4, 136.4, 130.2, 129.5, 129.3(2C), 128.5, 127.9(2C), 126.2, 125.8, 121.5, 116.5, 114.7, 112.0, 56.0, 54.7, 42.1, 41.6, 36.1, 25.9, 24.2 **(Spectrum No. 67)**; ESMS *m/z* calcd for $C_{27}H_{31}BrN_4O_3$ 551, found 553 (M+2), 551 (M).



27b

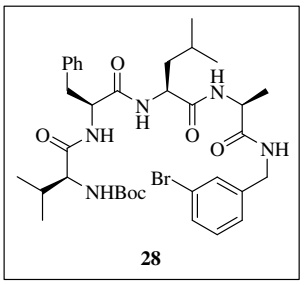
Compound 27b: Compound was prepared as a brown solid using procedure **6.4.1** (yield 65%), mp 174-176 °C; $[\alpha]_D^{25}$ = +5.2 (*c* 0.25, DMSO); IR (KBr) 3316, 2925, 1653, 1590, 1526 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d6*): δ 8.05 (d, *J* = 9.1 Hz, 2H), 7.75 (t, *J* = 5.4 Hz, 1H), 7.66 (d, *J* = 6.7 Hz, 1H), 7.27-7.07 (m, 9H), 6.75-6.63 (m, 4H), 4.47-4.37 (m, 2H), 3.95 (dd, J_1 = 5.1 Hz, J_2 = 15.6 Hz, 1H), 3.49 (d, *J* = 15.6 Hz, 1H), 3.26 (d, *J* = 18.5 Hz, 1H), 2.86-2.83 (m, 2H), 1.23 (s, 3H), 1.21 (s, 3H) **(Spectrum No. 68)**; ^{13}C NMR (50 MHz, DMSO-*d6*): δ 173.9, 170.3(2C), 143.8, 143.3, 140.1, 137.2, 135.9, 129.3(2C), 129.1, 128.8, 127.9(2C), 126.3, 120.7, 119.3, 117.6, 116.7, 114.5, 79.2, 56.2, 54.2, 43.1, 42.2, 37.6, 27.3, 23.0 **(Spectrum No. 69)**; ESMS *m/z* calcd for $C_{28}H_{30}N_4O_3$ 470, found 471 (M+1).



20e

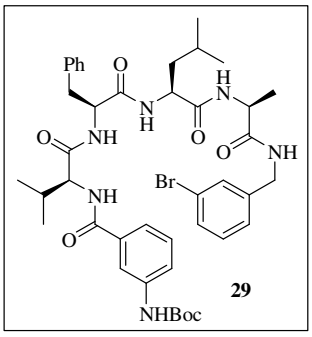
Compound 20e: Compound was prepared by following general procedure **6.4.3a** (yield 86%), mp 214-216 °C; $[\alpha]_D^{25}$ = -7.0 *(c* 0.5, DMSO); IR (KBr), 3286, 3064, 2956, 1692, 1638, 1541 cm^{-1}; ^{1}H NMR (400MHz, DMSO-*d6*): δ 8.39-8.32 (m, 1H), 8.06 (d, *J* = 7.0 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.45-7.41 (m, 2H), 7.36-7.15 (m, 7H), 6.91 (d, *J* = 8.6 Hz, 1H), 4.38-4.14 (m, 5H), 2.98 (dd, J_1 = 3.8 Hz, J_2 = 13.7 Hz, 1H), 2.72 (dd, J_1 = 10.5 Hz, J_2 = 13.7 Hz, 1H), 1.68-1.58 (m, 1H), 1.52-1.45

(m, 2H), 1.30 (s, 9H), 1.23 (d, J = 4.0 Hz, 3H), 1.47 (dd, J_1 = 6.7 Hz, J_2 = 12.3 Hz, 6H); ESMS *m/z* calcd for $C_{30}H_{41}BrN_4O_5$ 617, found 619 (M+2), 617 (M).



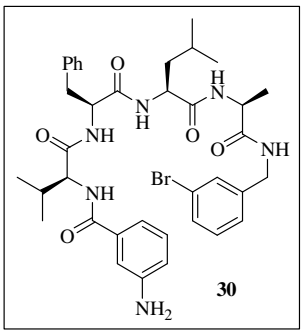
28

Compound 28: Compound was prepared by following general procedure **5.4.3b** (yield 85%), mp 251-252 ^{o}C; $[\alpha]_D^{25}$ = -15.6 (*c* 1, DMSO); IR (KBr), 3286, 3062, 2959, 1638, 1544 cm^{-1}; ^{1}H NMR (400MHz, DMSO-*d6*): δ 8.34 (t, J = 5.9 Hz, 1H), 8.06 (d, J = 7.8 Hz, 1H), 7.98 (d, J = 7.2 Hz, 1H), 7.86 (d, J = 8.3 Hz, 1H), 7.43 (s, 1H), 7.43-7.40 (m, 1H), 7.28-7.13 (m, 7H), 6.62 (d, J = 9.1 Hz, 1H), 4.60-4.57 (m, 1H), 4.33-4.23 (m, 4H), 3.71 (t, J = 7.2 Hz, 1H), 3.00 (dd, J_1 = 4.3 Hz, J_2 = 14.0 Hz, 1H), 2.77 (dd, J_1 = 9.4 Hz, J_2 = 14.0 Hz, 1H), 1.83-1.75 (m, 1H), 1.59-1.46 (m, 1H), 1.45-1.43 (m, 2H), 1.36 (s, 9H), 1.23 (d, J = 7.2 Hz, 3H), 0.86 (d, J = 6.4 Hz, 3H), 0.81 (d, J = 7.4 Hz, 3H), 0.70 (dd, J_1 = 7.7 Hz, J_2 = 12.1 Hz, 6H); ESMS *m/z* calcd for $C_{35}H_{50}BrN_5O_6$ 716, found 718 (M+2), 716 (M).



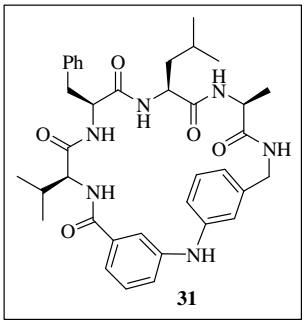
29

Compound 29: Compound was synthesized as a white solid using procedure **6.4.3b** (yield 75%), mp 304-305 °C; $[\alpha]_D^{25}$ = -12.8 (*c* 0.5, DMSO); IR (KBr) 3278, 2959, 1637, 1541 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d6*): δ 9.45 (s, 1H), 8.32 (t, J = 5.9 Hz, 1H), 8.08 (d, J = 8.3 Hz, 1H), 7.99 (t, J = 8.6 Hz, 3H), 7.93 (s, 1H), 7.57 (d, J = 7.8 Hz, 1H), 7.42-7.09 (m, 11H), 4.62-4.56 (m, 1H), 4.33-4.21 (m, 5H), 3.01 (dd, J_1 = 4.3 Hz, J_2 = 14.0 Hz, 1H), 2.78 (dd, J_1 = 10.4 Hz, J_2 = 14.0 Hz, 1H), 2.01 (sext, J = 7.0 Hz, 1H), 1.59-1.53 (m, 1H), 1.52 (s, 9H), 1.48-1.43 (m, 2H), 1.23 (d, J = 7.0 Hz, 3H), 0.88-0.78 (m, 12H); ESMS *m/z* calcd for $C_{42}H_{55}BrN_6O_7$ 835, found 837 ($M^{+\cdot}$+2, 100), 835 ($M^{+\cdot}$, 99).



30

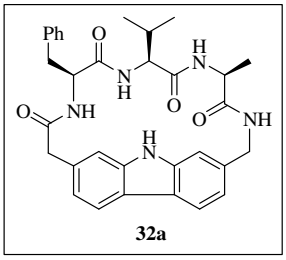
Compound 30: Compound was synthesized as a white solid using procedure **6.4.3b** (yield 87%), mp 302-303 °C; $[\alpha]_D^{25}$ = -8.6 (*c* 1, DMSO); IR (KBr) 3277, 2958, 1637, 1538 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.33 (t, *J* = 5.6 Hz, 1H), 8.07 (d, *J* = 8.3 Hz, 1H), 8.00 (dd, J_1 = 8.1 Hz, J_2 = 13.1 Hz, 2H), 7.81 (d, *J* = 8.9 Hz, 1H), 7.43-7.40 (m, 2H), 7.28-7.01 (m, 9H), 6.94 (d, *J* = 7.8 Hz, 1H), 6.70 (dd, J_1 = 1.6 Hz, J_2 = 8.0 Hz, 1H), 5.22 (s, 2H), 4.62-4.56 (m, 1H), 4.33-4.19 (m, 5H), 3.01 (dd, J_1 = 4.3 Hz, J_2 = 13.9 Hz, 1H), 2.77 (dd, J_1 = 9.7 Hz, J_2 = 14.0 Hz, 1H), 1.99 (sext, *J* = 7.2 Hz, 1H), 1.59-1.53 (m, 1H), 1.45 (t, *J* = 7.5 Hz, 2H), 1.23 (d, *J* = 7.0 Hz, 3H), 0.85-0.73 (m, 12H); ^{13}C NMR (50 MHz, DMSO-*d6*): δ 172.3, 171.6, 171.0(2C), 167.1, 148.6, 142.3, 137.7, 135.2, 130.4, 129.7, 129.6, 129.2(2C), 128.7, 128.0(2C), 126.2, 126.1, 121.7, 116.7, 114.7, 112.8, 58.9, 53.6, 51.1, 48.4, 41.5, 40.7, 37.4, 30.4, 24.1, 23.1, 21.6, 19.2, 18.6, 18.1; ESMS *m/z* calcd for $C_{37}H_{47}N_6O_5Br$ 735, found 759 (M+Na+2), 757 (M+Na), 737 (M+2), 735 (M).



31

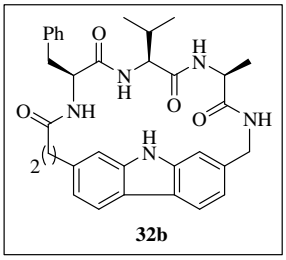
Compound 31: Compound was synthesized as a brown solid by following general procedure **6.4.1** (yield 26%), mp 258-259 °C; $[\alpha]_D^{25}$ = -56.0 (*c* 0.15, DMSO); IR (KBr) 3316, 2959, 1653, 1522 cm^{-1}; ^1H NMR (400 MHz, DMSO-*d6*): δ 8.40-8.35 (m, 1H), 8.32 (s, 1H), 8.26 (d, *J* = 7.9 Hz, 1H), 7.91 (t, *J* = 6.4 Hz, 1H), 7.81 (s, 1H), 7.54 (d, *J* = 6.7 Hz, 1H), 7.39-7.16 (m, 11H), 7.12-7.01 (m, 1H), 6.81 (t, *J* = 7.2 Hz, 1H), 4.73-4.67 (m, 1H), 4.34-4.19 (m, 2H), 3.99-3.83 (m, 3H), 3.21 (dd, J_1 = 4.0 Hz, J_2 = 14.2 Hz, 1H), 2.67 (dd, J_1 = 11.0 Hz, J_2 = 14.2 Hz, 1H), 1.86-1.80 (m, 1H), 1.55-1.40 (m, 1H), 1.30-1.22 (m, 6H), 0.85-0.66 (m,

9H), 0.51 (d, *J* = 6.7 Hz, 2H); ^{13}C NMR (50 MHz, DMSO-*d6*): δ 172.4, 171.9, 171.0, 170.7, 166.7, 143.5, 143.0, 140.7, 137.4, 135.1, 129.3, 129.1(2C), 128.6, 128.0(2C), 126.3, 121.2, 120.4, 119.1, 117.6, 114.2, 112.1, 61.2, 52.7, 52.6, 49.1, 42.8, 37.9, 29.4, 28.9, 23.9, 22.6, 21.9, 19.5, 18.9, 15.8; ESMS *m/z* calcd for $C_{37}H_{46}N_6O_5$ 654, found 655 (M+1).



32a

Cyclic compound 32a: Compound was synthesized as a white solid by following general procedure **6.4.5** (yield 12%), mp 221-222 °C; $[\alpha]_D^{25}$ = +2.0 (*c* 0.01, DMSO); IR (KBr) 3329, 2929, 1649, 1508 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-*d6*): δ 11.44 (s, 1H), 8.47-8.42 (m, 2H), 8.06 (d, *J* = 7.5 Hz, 1H), 7.91 (d, *J* = 9.1 Hz, 1H), 7.41-7.18 (m, 9H), 7.08 (d, *J* = 6.2 Hz, 1H), 6.83 (d, *J* = 6.7 Hz, 1H), 4.84 (dd, J_1 = 5.9 Hz, J_2 = 14.5 Hz, 1H), 4.70 (dd, J_1 = 4.0 Hz, J_2 = 14.2 Hz, 1H), 4.31-4.21 (m, 2H), 4.07-4.02 (m, 2H), 3.66 (t, *J* = 9.7 Hz, 1H), 2.98-2.96 (m, 2H), 2.09-2.06 (m, 1H), 1.25 (d, *J* = 6.7 Hz, 3H), 0.83 (d, *J* = 6.7 Hz, 3H), 0.78 (d, *J* = 6.4 Hz, 3H) **(Spectrum No. 70)**; ESMS *m/z* calcd for $C_{32}H_{35}N_5O_6$ 553, found 554 (M+1).



32b

Cyclic compound 32b: Compound was prepared as a white solid by following general procedure **6.4.5** (yield 15%), mp 196-197 °C; $[\alpha]_D^{25}$ = +3.0 (*c* 0.01, DMSO); IR (KBr) 3329, 2929, 1649, 1518 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-*d6*): δ 10.77 (s, 1H), 8.36 (t, *J* = 6.4 Hz, 1H), 7.40 (dd, J_1 = 7.2 Hz, J_2 = 15.0 Hz, 2H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 5.9 Hz, 1H), 7.44 (s, 1H), 7.35 (s, 1H), 7.27-7.15 (m, 5H), 6.85 (d, *J* = 7.8 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 6.18 (d, *J* = 8.0 Hz, 1H), 4.56-4.50 (m, 1H), 4.25-4.23 (m, 1H), 4.16-4.08 (m, 2H), 3.81 (dd, J_1 = 4.0 Hz, J_2 =

8.1 Hz, 1H), 2.96 (dd, J_1 =10.0 Hz, J_2 = 12.9 Hz, 2H), 2.71-2.67 (m, 2H), 2.32-2.19 (m, 2H), 1.12 (d, J = 7.0 Hz, 3H), 0.86-0.85 (m, 1H), -0.23 (d, J = 6.7 Hz, 3H), -0.56 (d, J = 7.0 Hz, 3H) **(Spectrum No. 71)**; ESMS *m/z* calcd for $C_{33}H_{37}N_5O_6$ 567, found 568 (M+1).

6.5 References

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Appendix I

Representative Spectra

Appendix II

X-Ray Crystallographic Data

Table 1. Atomic coordinates and equivalent anisotropic displacement parameters (A^2 x 10^3) for compound number **20d (Chapter 2, section 2.2.1)**. B(eq) is defined as follows:

Atom	**x**	**y**	**z**	**B_{eq}**
O(1)	0.9221(6)	0.1383(5)	0.2353(2)	5.27(10)
O(2)	0.7162(6)	0.0852(5)	0.3638(3)	5.89(12)
O(3)	0.4162(7)	0.0494(5)	0.2424(2)	5.90(12)
N(1)	0.9247(6)	0.3487(6)	0.2860(2)	4.17(11)
N(2)	0.6174(6)	0.2842(6)	0.3215(3)	4.05(11)
N(3)	0.4203(7)	0.2799(6)	0.2119(2)	4.36(11)
C(1)	0.5564(7)	0.2270(6)	0.1171(3)	4.06(11)
C(2)	0.5622(9)	0.1462(7)	0.0642(3)	5.2(2)
C(3)	0.6967(10)	0.1342(9)	0.0333(3)	5.8(2)
C(4)	0.8268(9)	0.1960(9)	0.0542(3)	5.6(2)
C(5)	0.8247(8)	0.2744(7)	0.1086(3)	4.69(13)
C(6)	0.6896(7)	0.2881(7)	0.1389(3)	4.23(12)
C(7)	0.9656(8)	0.3427(8)	0.1297(3)	4.9(1)
C(8)	1.0142(8)	0.3509(7)	0.1846(3)	4.8(1)
C(9)	0.9481(6)	0.2714(6)	0.2364(3)	3.86(11)
C(10)	0.8892(6)	0.2769(7)	0.3426(3)	3.93(11)
C(11)	0.7318(7)	0.2074(6)	0.3429(3)	3.89(11)
C(12)	0.4615(7)	0.2284(7)	0.3171(3)	4.20(12)
C(13)	0.3434(7)	0.3375(9)	0.3394(3)	5.5(2)
C(14)	0.4302(7)	0.1789(6)	0.2537(3)	3.91(11)
C(15)	0.4076(8)	0.2485(7)	0.1491(3)	4.8(1)
C(16)	0.9015(7)	0.3892(7)	0.3934(3)	4.40(12)
C(17)	0.8779(9)	0.3274(8)	0.4552(3)	5.4(2)
C(18)	1.001(1)	0.2195(12)	0.4712(4)	9.1(3)
C(19)	0.8655(12)	0.4478(11)	0.5018(3)	7.6(2)

$B_{eq} = 8/3\ \pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}(aa^*bb^*)\cos\gamma + 2U_{13}(aa^*cc^*)\cos\beta + 2U_{23}(bb^*cc^*)\cos\alpha$

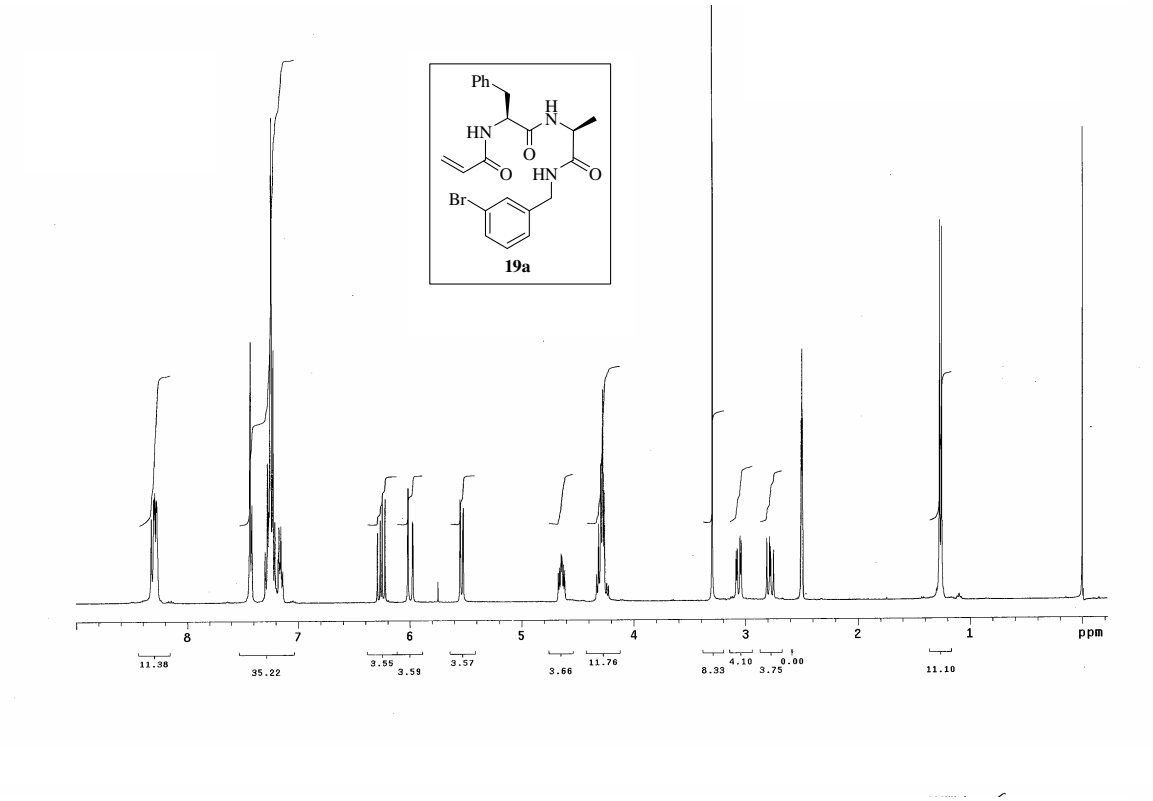
List of Publications

1. Synthesis of small cyclic peptides via intramolecular Heck reactions: P. R. Reddy, **V. Balraju**, G. R. Madhavan, B. Banerji, J. Iqbal. *Tetrahedron Lett.* **2003***, 44,* 353-356.
2. Synthesis of small cyclic peptides constrained with 3-(3-aminomethylphenyl) propionic acid linkers using free radical-mediated macrocyclization: **V. Balraju**, D. S. Reddy, M. Periasamy, J. Iqbal. *Tetrahedron Lett.* **2005***,* 46, 5207-5210.
3. Synthesis of Conformationally Constrained Cyclic Peptides Using an Intramolecular Sonogashira Coupling: **V. Balraju**, D. S. Reddy, M. Periasamy, J. Iqbal *J. Org. Chem.* **2005**, *70*, 9626–9628.
4. Synthesis of cyclic peptides using a palladium-catalyzed enyne cycloisomerization: **V. Balraju**, R. Vasu Dev, D. S. Reddy, J. Iqbal. *Tetrahedron Lett.* **2006***,* 47, 3569-3571.
5. Synthesis of Cyclic Peptides Constrained with Biarylamine Linkers Using Buchwald-Hartwig C-N Coupling: **V. Balraju**, J. Iqbal. *J. Org. Chem.* **2006,** *71*, xxx – xxx.
6. Synthesis of Biaryl-Bridged Cyclic Peptides using Ligand Free Suzuki Coupling. **V. Balraju**, J. Iqbal to be communicated.
7. Synthesis of Cyclic peptides Constrained with 3-(Aminophenyl)-2-propenoic acid linker Using the Heck Reaction and Michael Addition Reactions on Cyclic Peptides. **V. Balraju**, and J. Iqbal to be communicated.

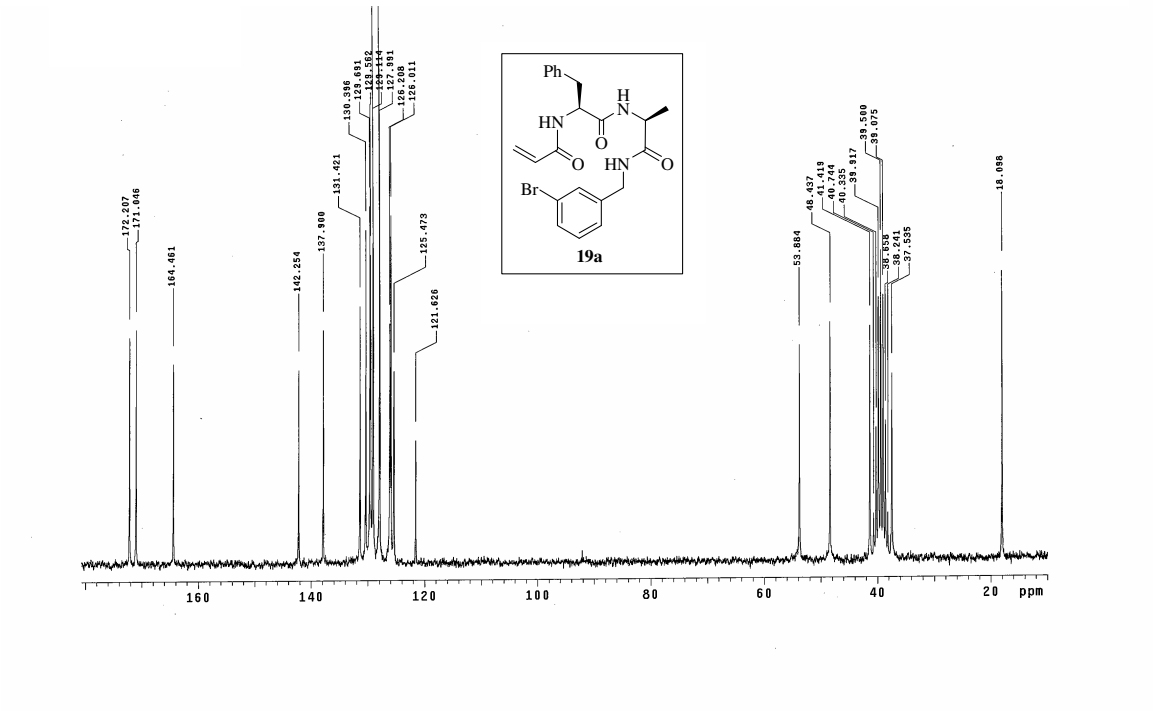
List of Posters Presented

1. Synthesis of Small Cyclic Peptides Via Intramolecular Heck reaction: **V. Balraju,** J. Iqbal, Pharmacophore **2004**, Hyderabad, A. P., India, Janurary 16-17, **2004**.
2. Palladium-Catalyzed Synthesis of Conformationally Constrained Small Cyclic Peptides via Sonogashira coupling, Heck and Enyne cycloisomerization: **V. Balraju**, M. Periasamy, J. Iqbal, 230th ACS National meeting, Washington, DC USA, Aug 28-Sept 1, **2005**.
3. Palladium-Catalyzed Synthesis of Conformationally Constrained Small Cyclic Peptides via intramolecular Buchwald-Hartwig C-N coupling: **V**. **Balraju**, M. Periasamy, J. Iqbal, 231st ACS National meeting, Atlanta, USA, March 26-30, **2006**.
4. Palladium-Catalyzed Synthesis of Conformationally Constrained Small Cyclic Peptides via Intramolecular Suzuki Coupling: **V**. **Balraju**, M. Periasamy J. Iqbal, 232nd ACS National meeting, San Francisco, CA, USA, September 10-14, **2006**.

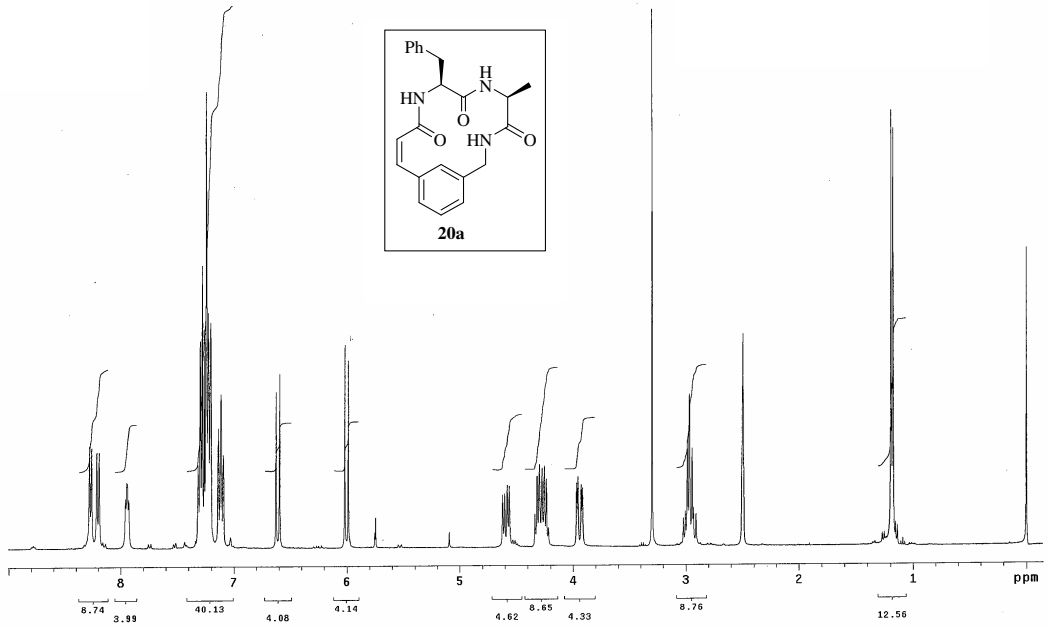
Spectrum No. 1 (Chapter 2, Section 2.4) ^{1}H NMR Spectrum (400MHz, DMSO-d$_6$)



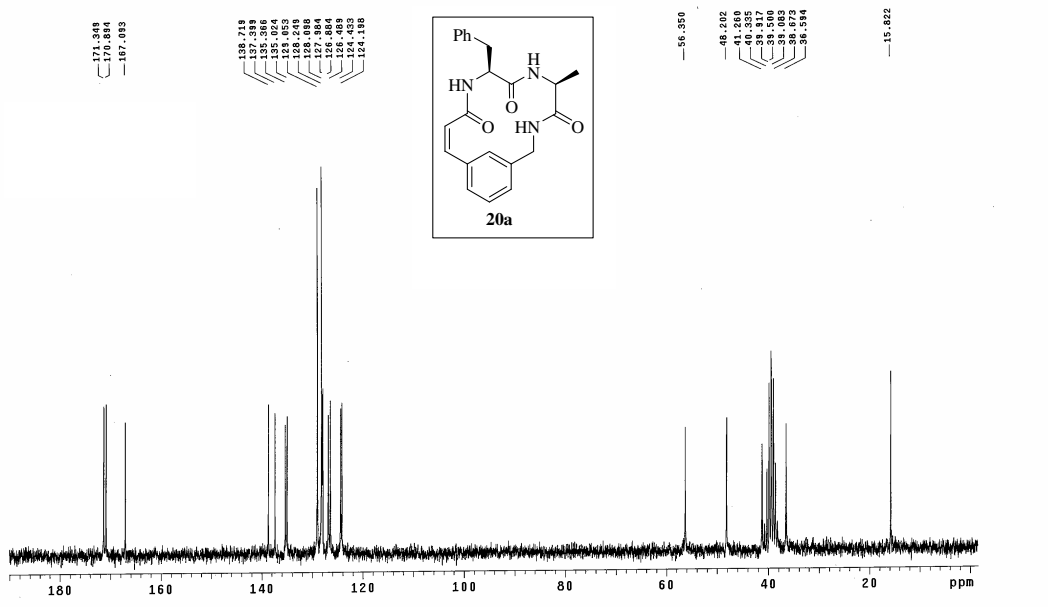
Spectrum No. 2 (Chapter 2, Section 2.4) ^{13}C NMR Spectrum (50MHz, DMSO-d$_6$)



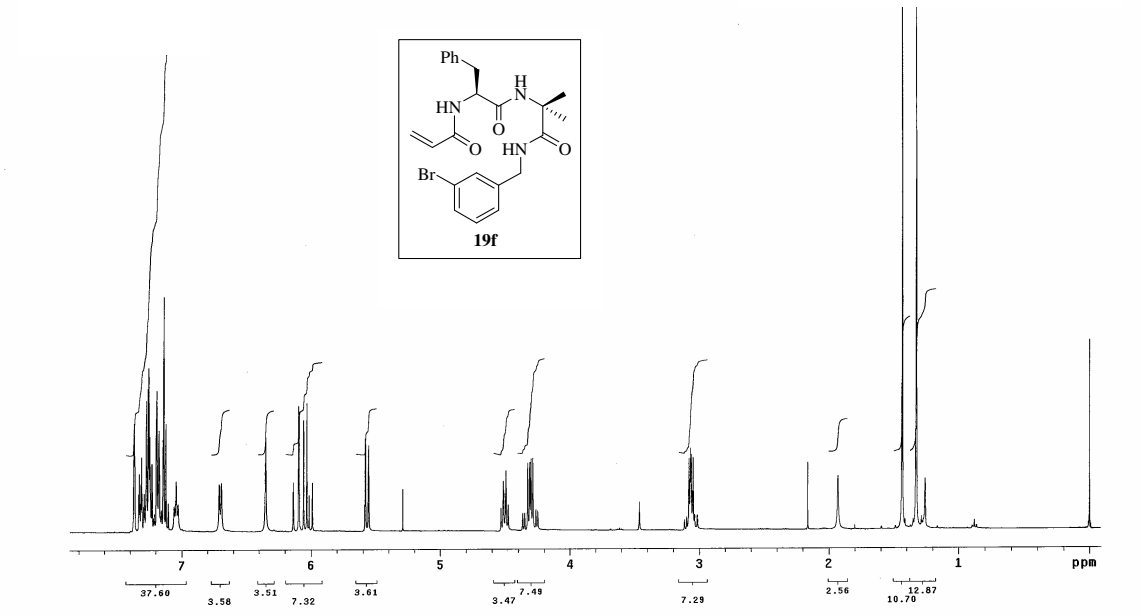
Spectrum No. 3 (Chapter 2, Section 2.4) ^{1}H NMR Spectrum (400MHz, DMSO-d$_6$)



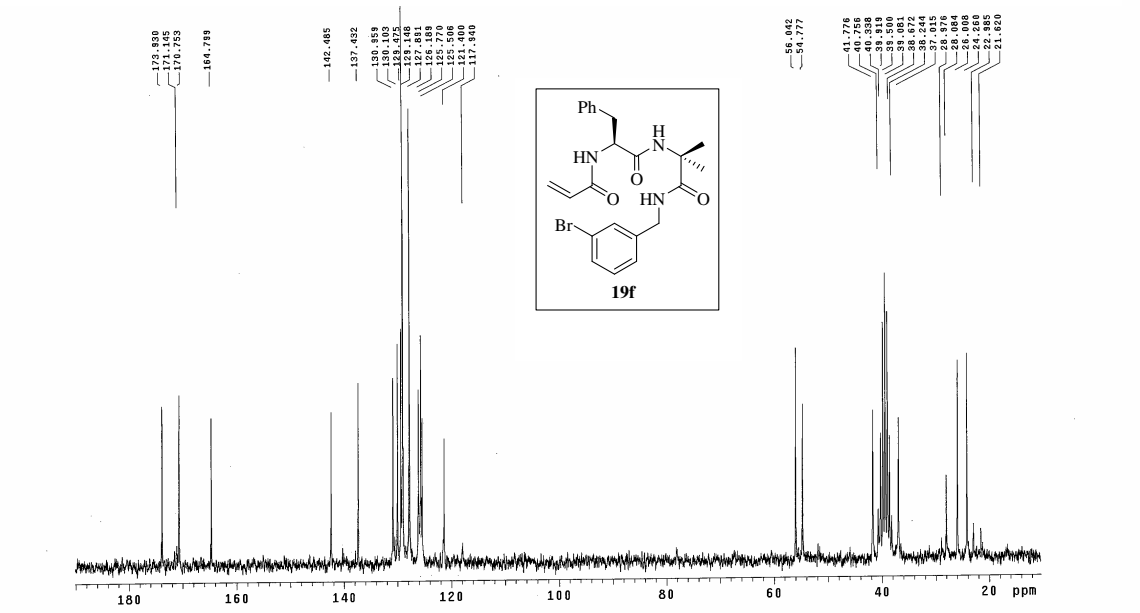
Spectrum No. 4 (Chapter 2, Section 2.4) ^{13}C NMR Spectrum (50MHz, DMSO-d$_6$)



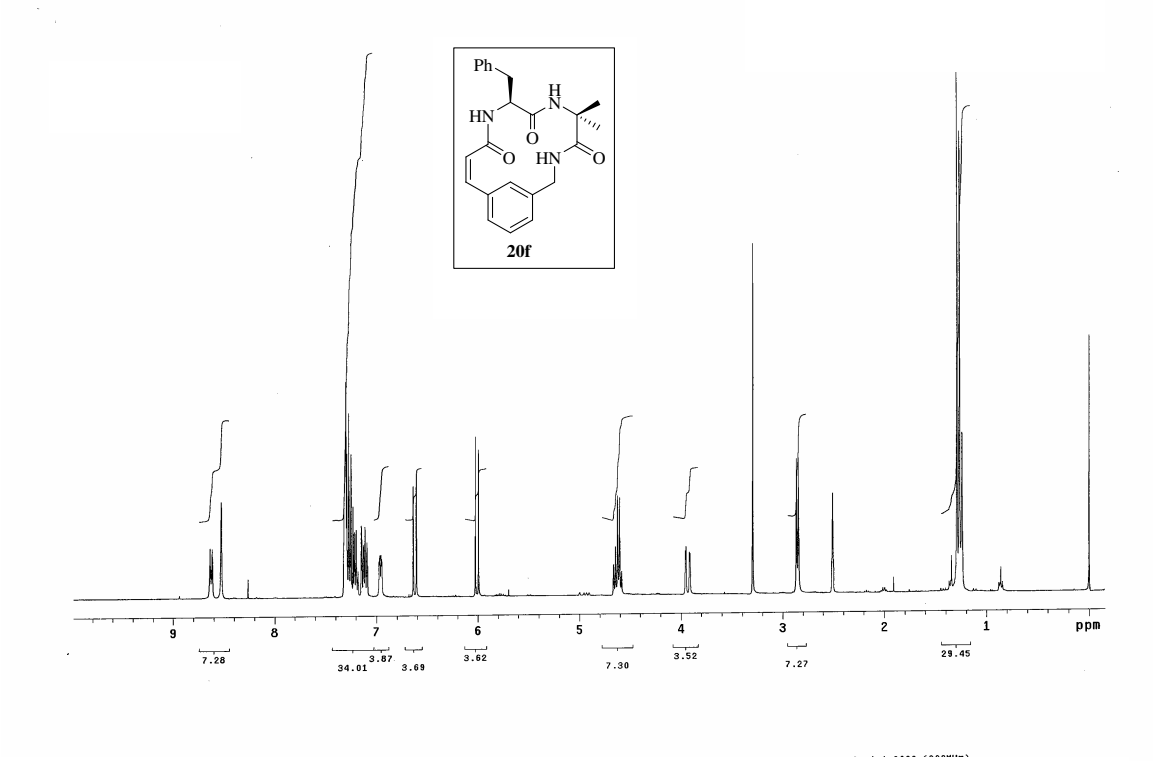
Spectrum No. 5 (Chapter 2, Section 2.4) ^{1}H NMR Spectrum (400MHz, $CDCl_3$)



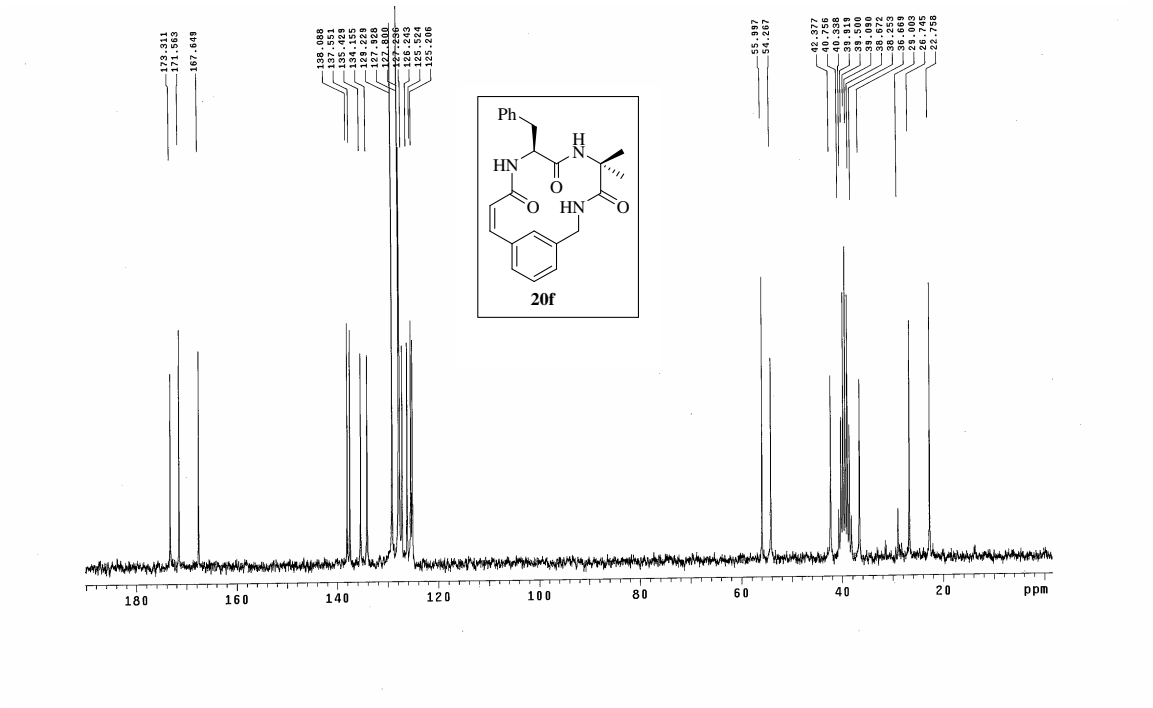
Spectrum No. 6 (Chapter 2, Section 2.4) ^{13}C NMR Spectrum (50MHz, DMSO-d_6)



Spectrum No. 7 (Chapter 2, Section 2.4) ^{1}H NMR Spectrum (400MHz, $CDCl_3$+DMSO-d_6)



Spectrum No. 8 (Chapter 2, Section 2.4) ^{13}C NMR Spectrum (50MHz, DMSO-d_6)



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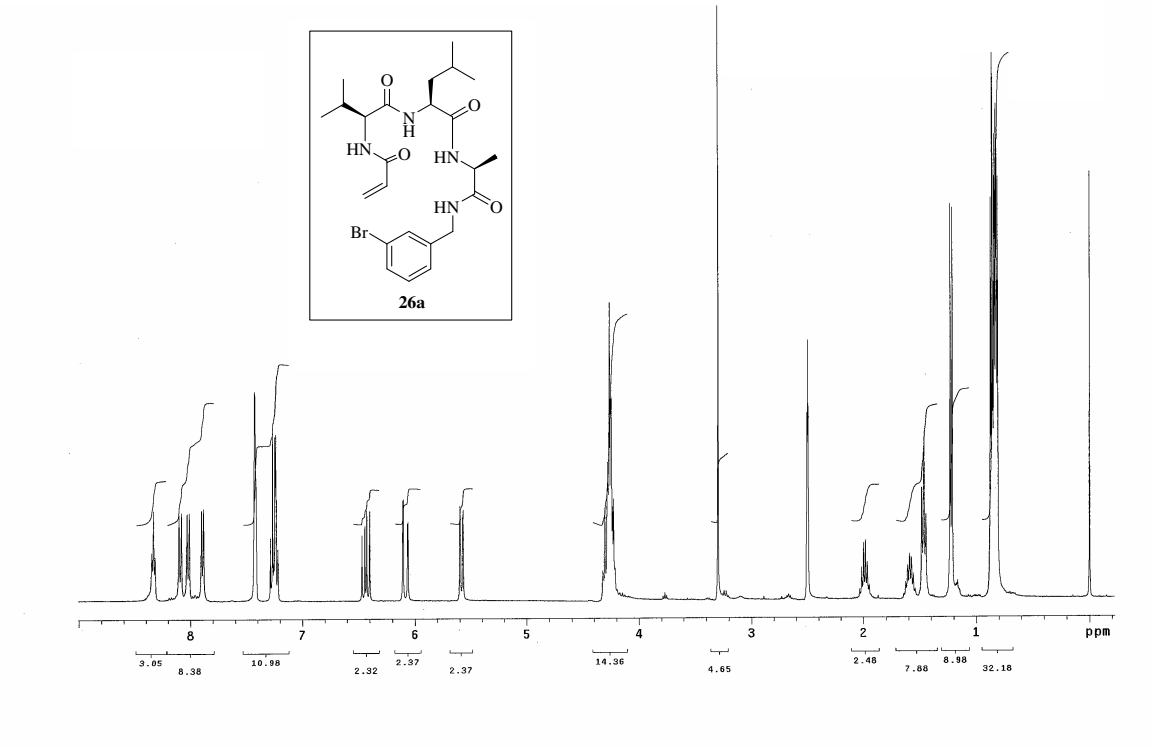
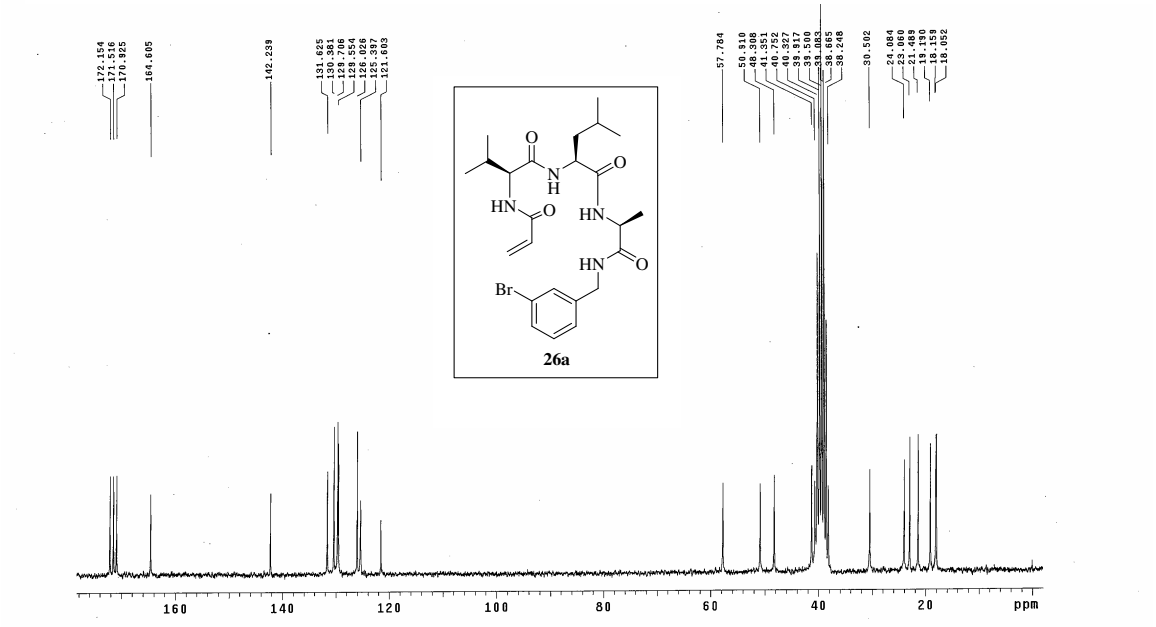
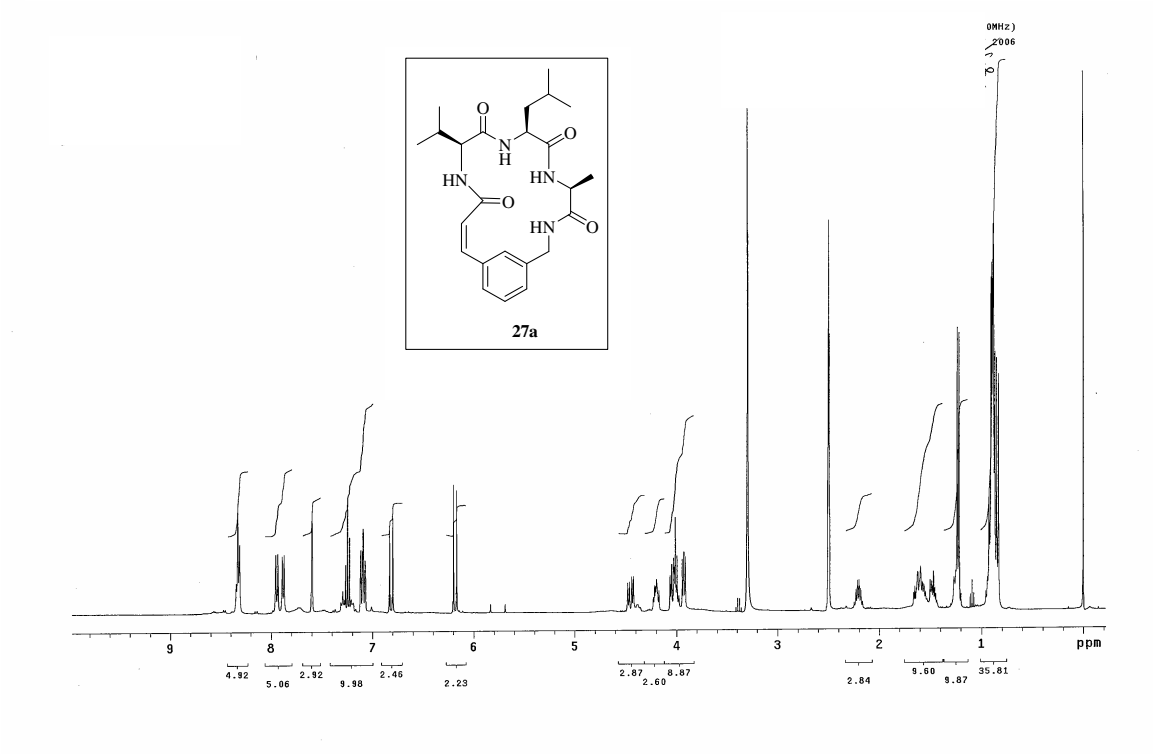


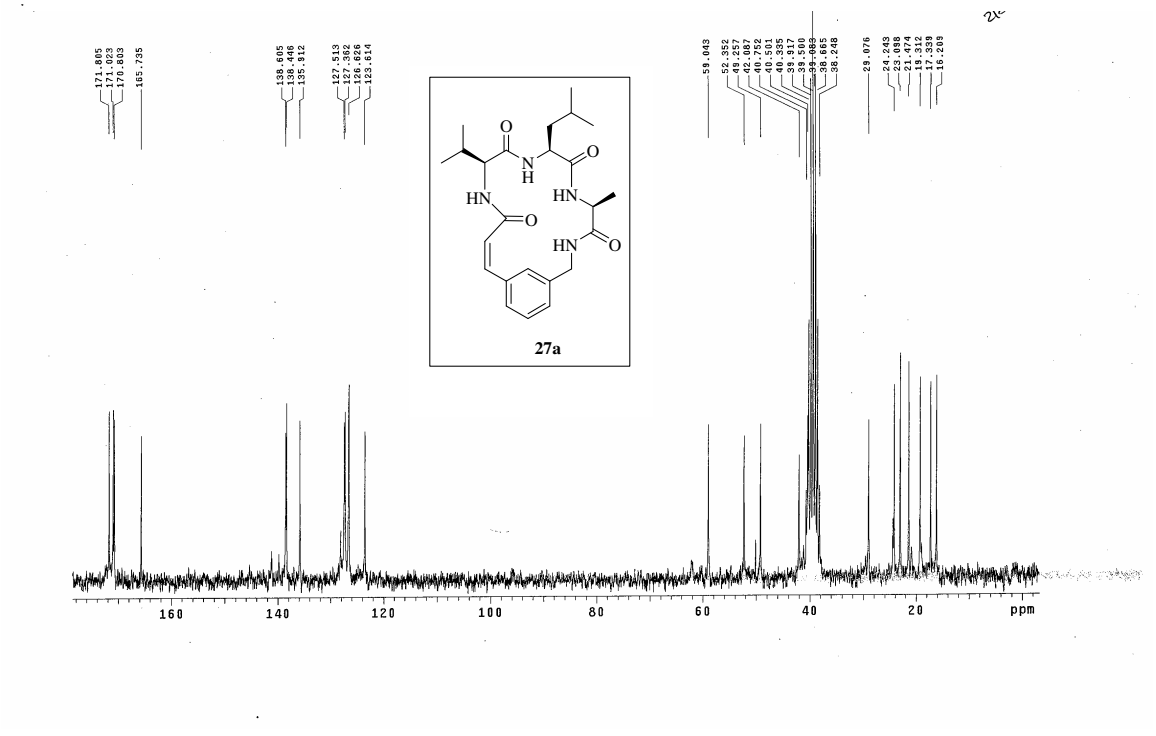
Spectrum No. 10 (Chapter 2, Section 2.4) ^{13}C NMR Spectrum (50MHz, DMSO-d$_6$)



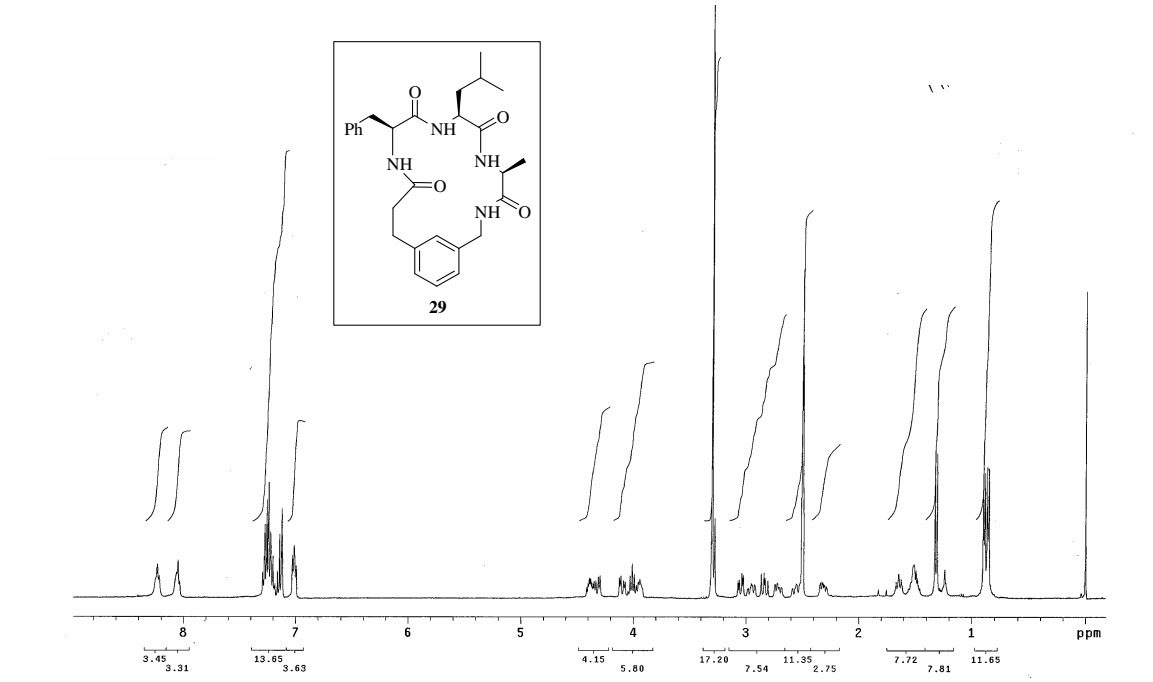
Spectrum No. 11 (Chapter 2, Section 2.4) ^{1}H NMR Spectrum (400MHz, DMSO-d$_6$)



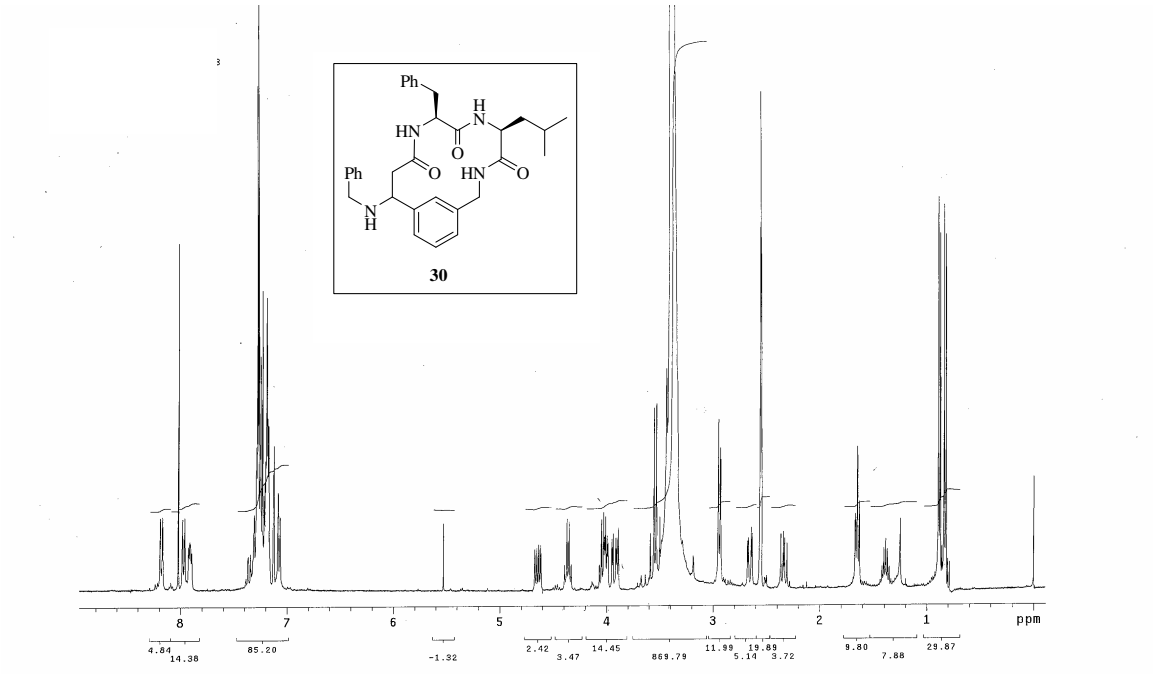
Spectrum No. 12 (Chapter 2, Section 2.4) ^{13}C NMR Spectrum (50MHz, DMSO-d$_6$)



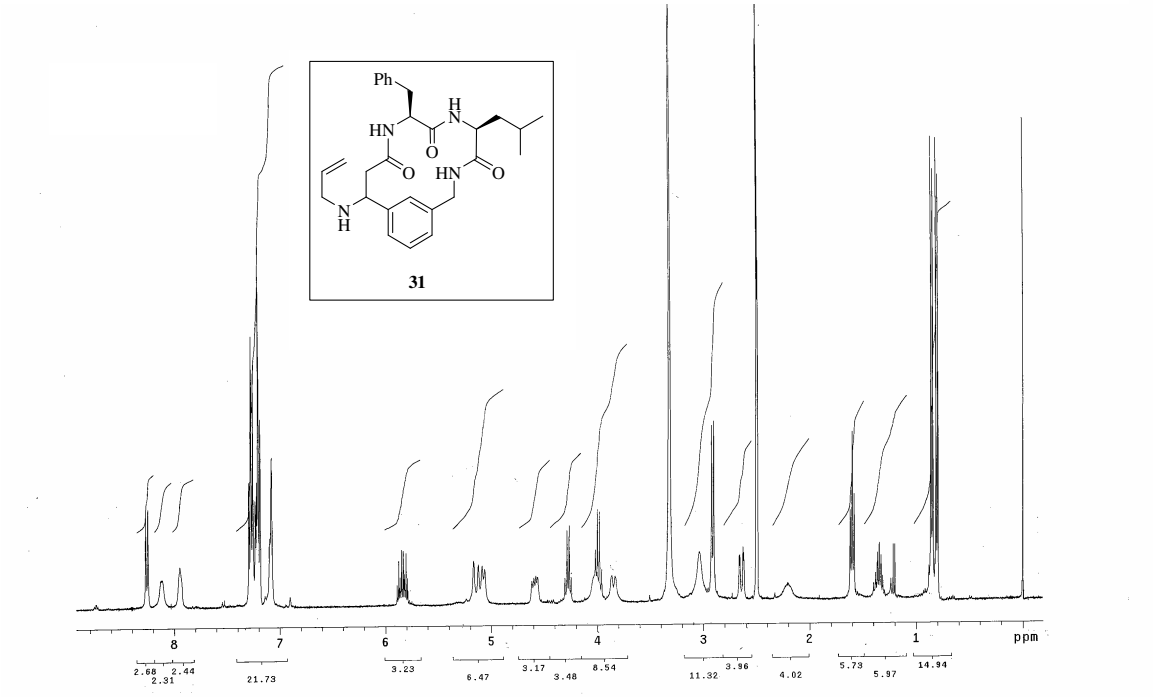
Spectrum No. 13 (Chapter 2, Section 2.4) ^{1}H NMR Spectrum (400MHz, DMSO-d$_6$)



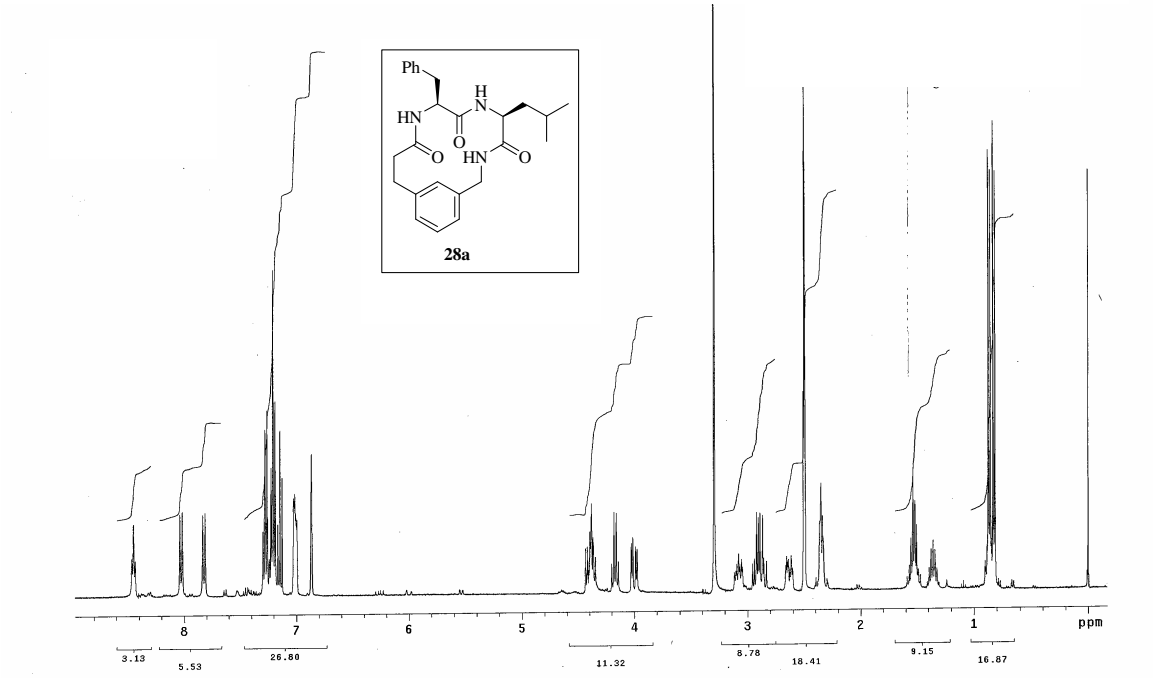
Spectrum No. 14 (Chapter 2, Section 2.4) ^{1}H NMR Spectrum (400MHz, CDCl$_3$+DMSO-d$_6$)



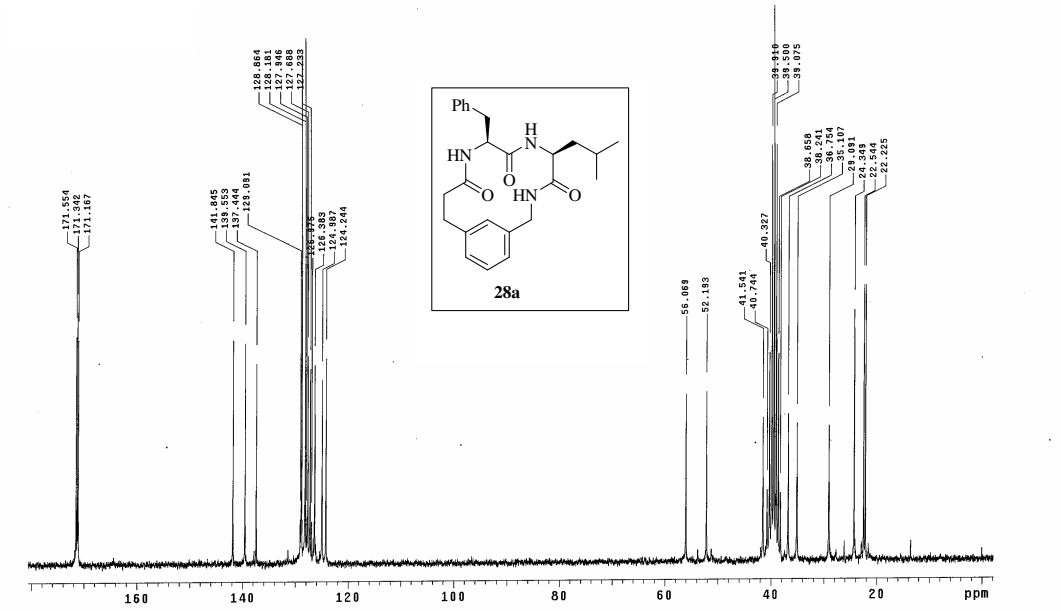
Spectrum No. 15 (Chapter 2, Section 2.4) ^{1}H NMR Spectrum (400MHz, DMSO-d$_6$)



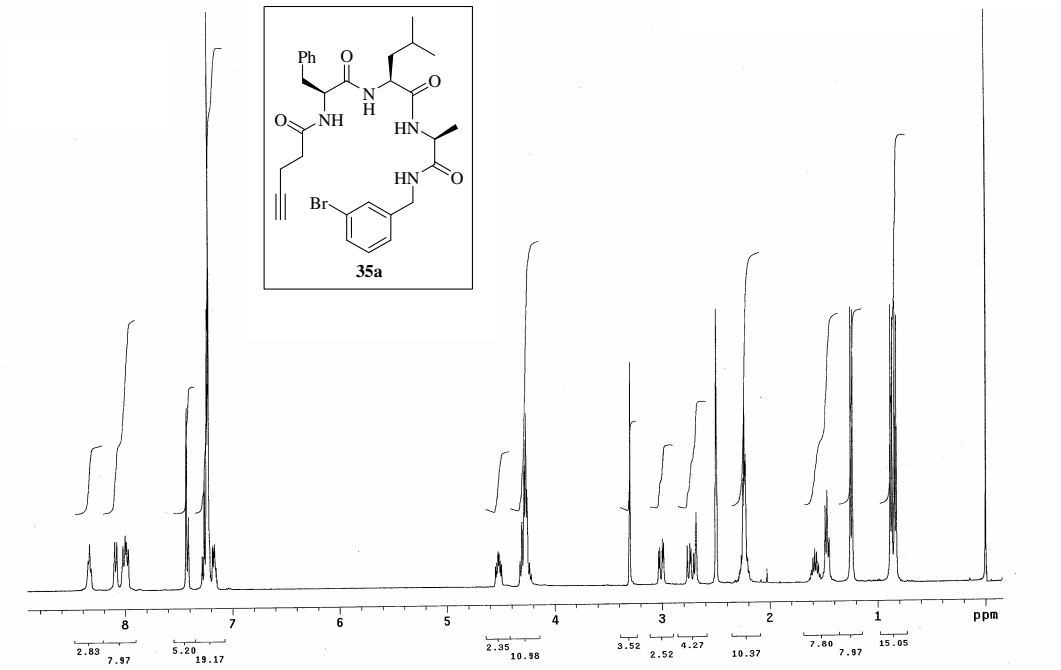
Spectrum No. 16 (Chapter 2, Section 2.4) ^{1}H NMR Spectrum (400MHz, DMSO-d$_6$)



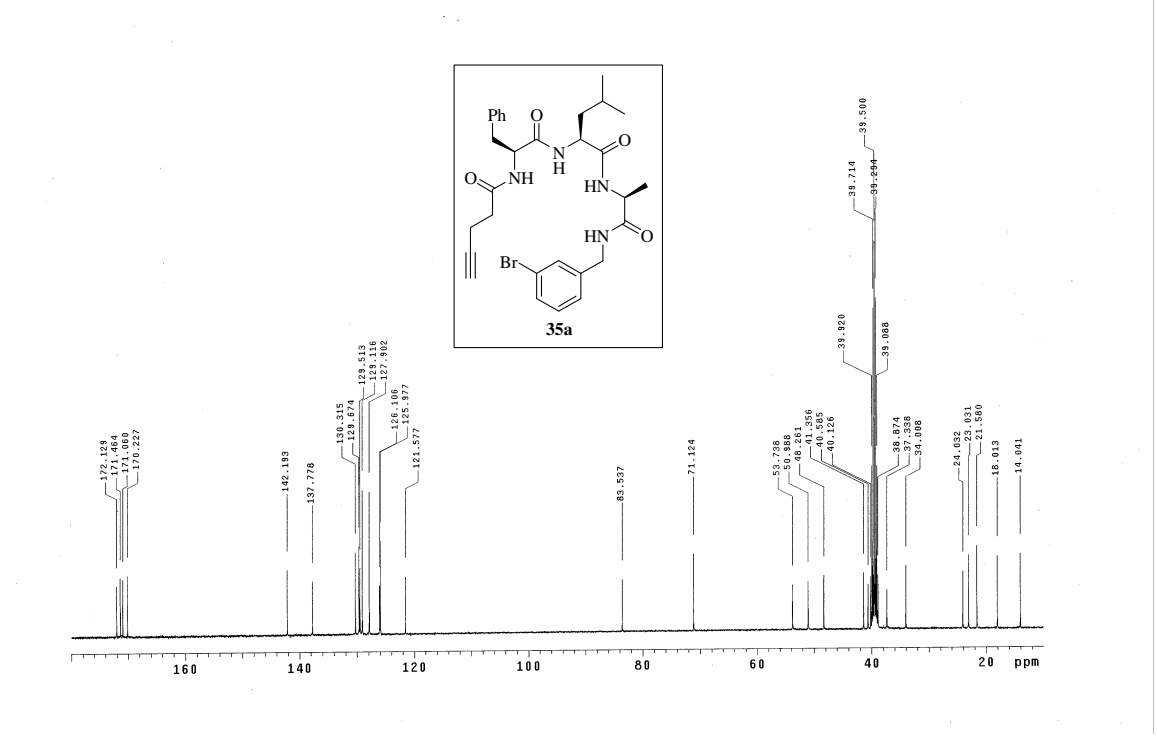
Spectrum No. 17 (Chapter 2, Section 2.4) ^{13}C NMR Spectrum (50MHz, DMSO-d$_6$)



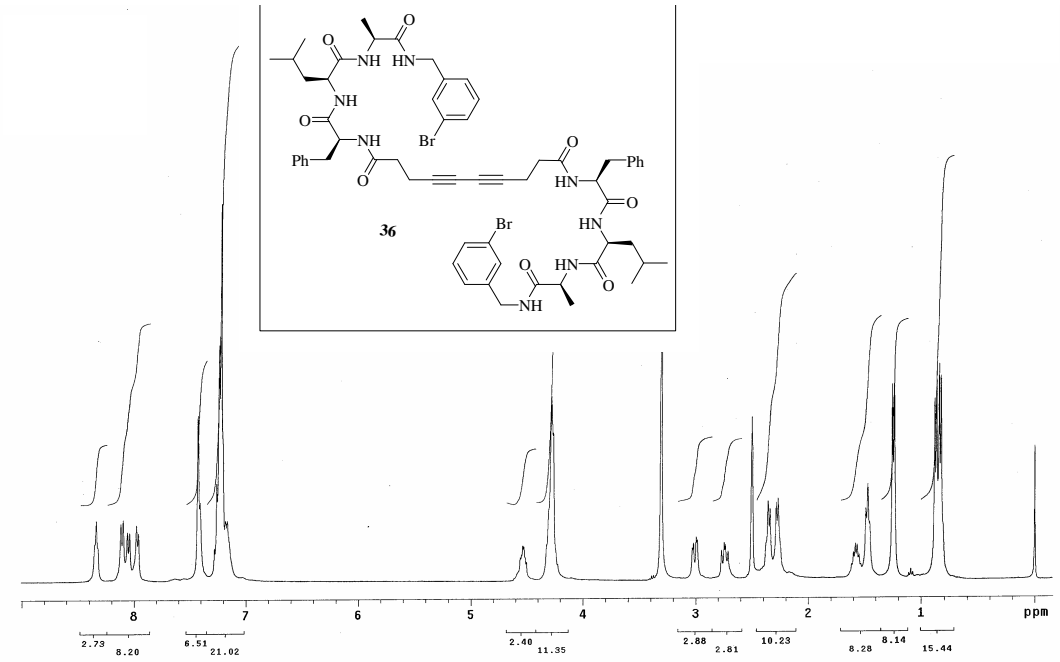
Spectrum No. 18 (Chapter 3, Section 3.4) ^{1}H NMR Spectrum (400MHz, DMSO-d$_6$)



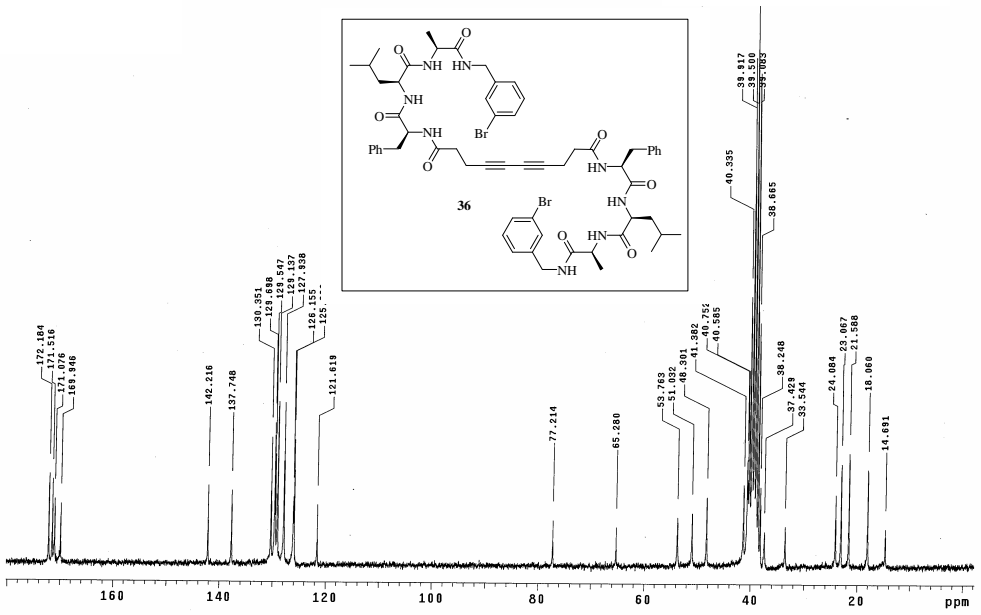
Spectrum No. 19 (Chapter 3, Section 3.4) ^{13}C NMR Spectrum (50MHz, DMSO-d$_6$)



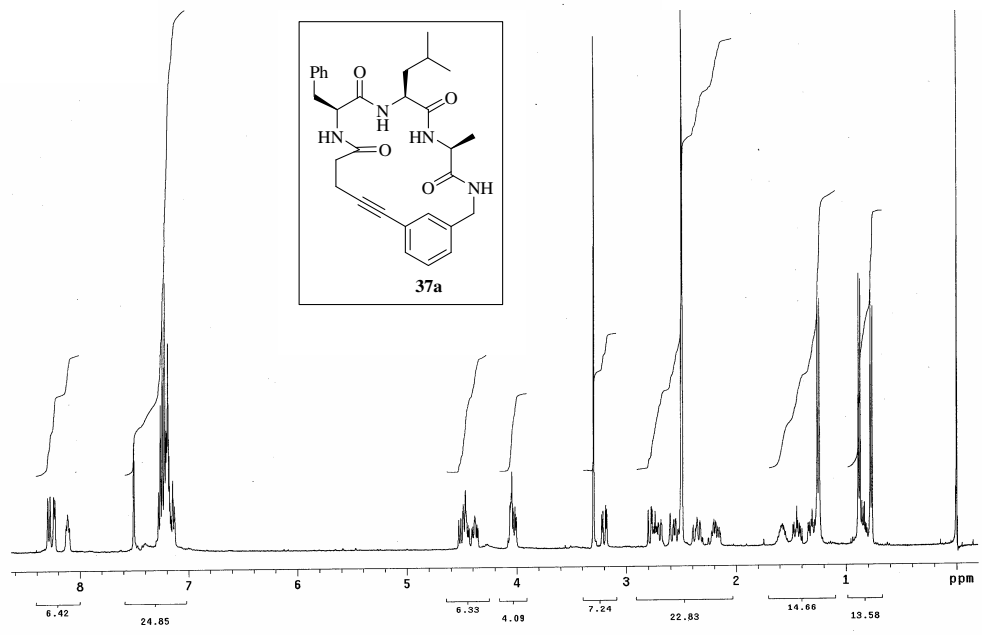
Spectrum No. 20 (Chapter 3, Section 3.4) ^{1}H NMR Spectrum (400MHz, DMSO-d$_6$)



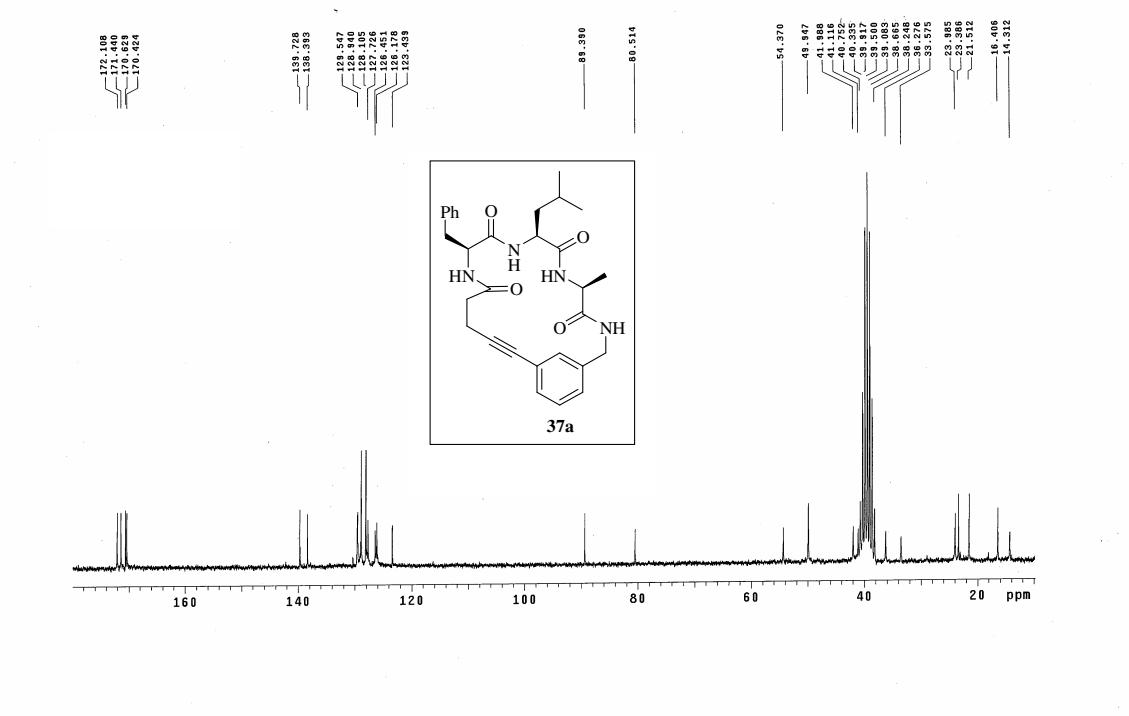
Spectrum No. 21 (Chapter 3, Section 3.4) ^{13}C NMR Spectrum (50MHz, DMSO-d$_6$)



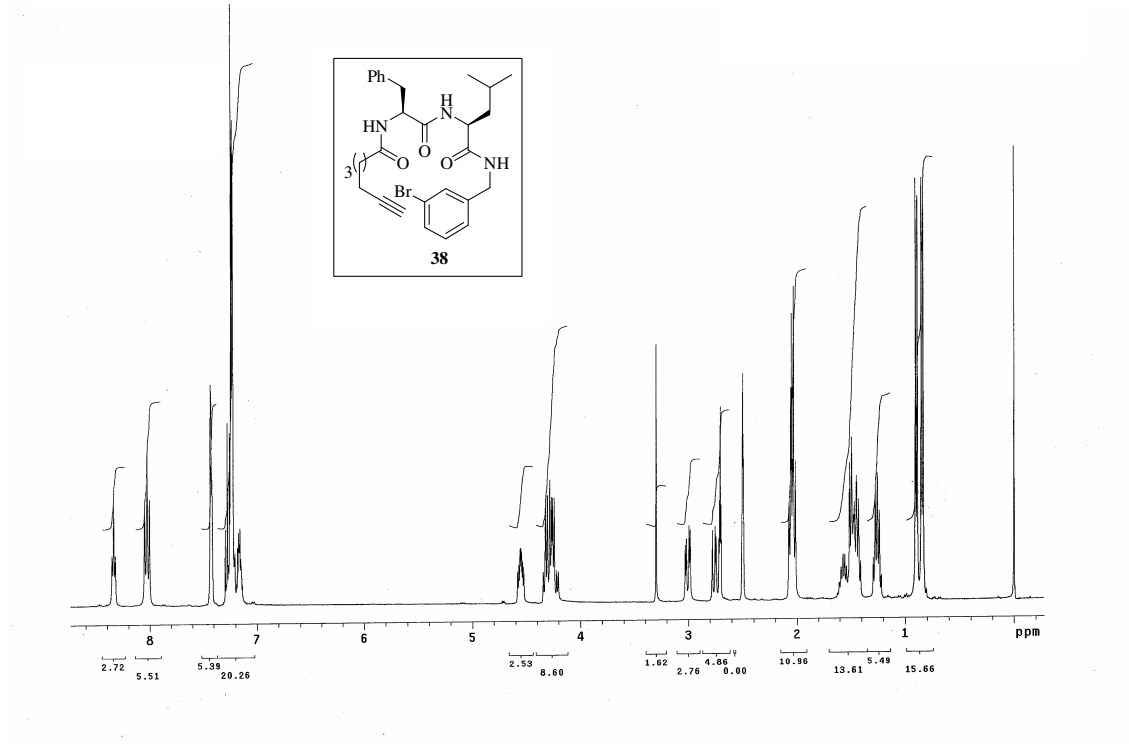
Spectrum No. 22 (Chapter 3, Section 3.4) ^{1}H NMR Spectrum (400MHz, DMSO-d$_6$)



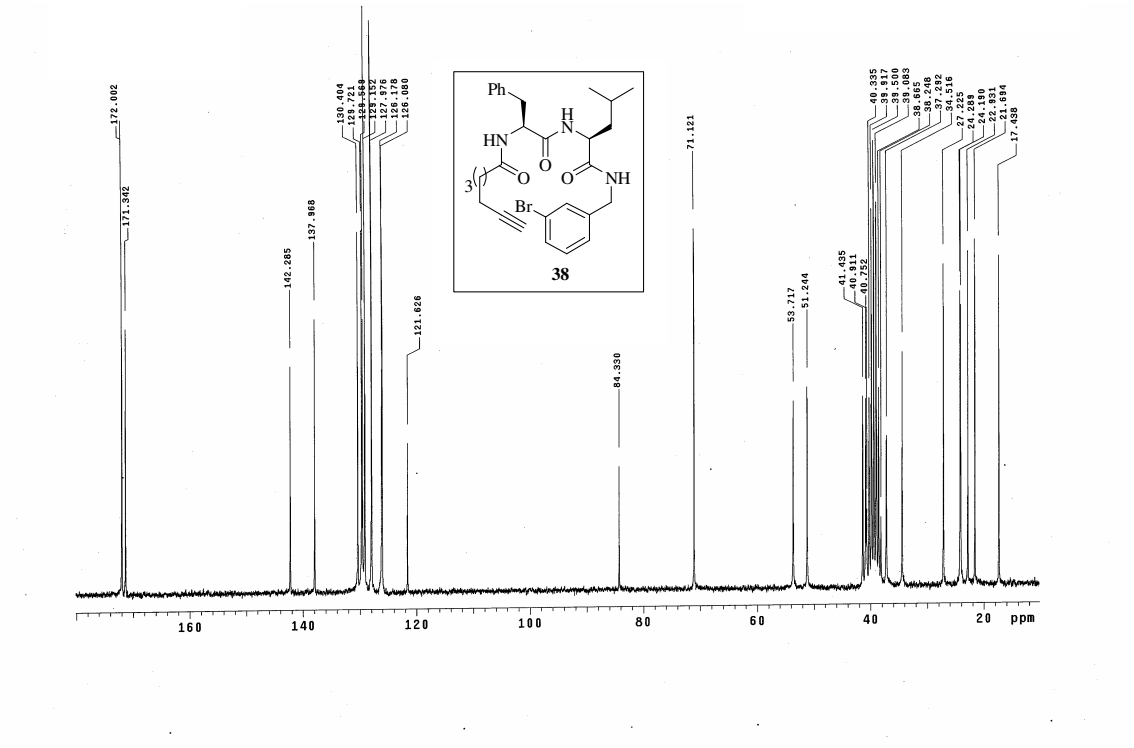
Spectrum No. 23 (Chapter 3, Section 3.4) ^{13}C NMR Spectrum (50MHz, DMSO-d$_6$)



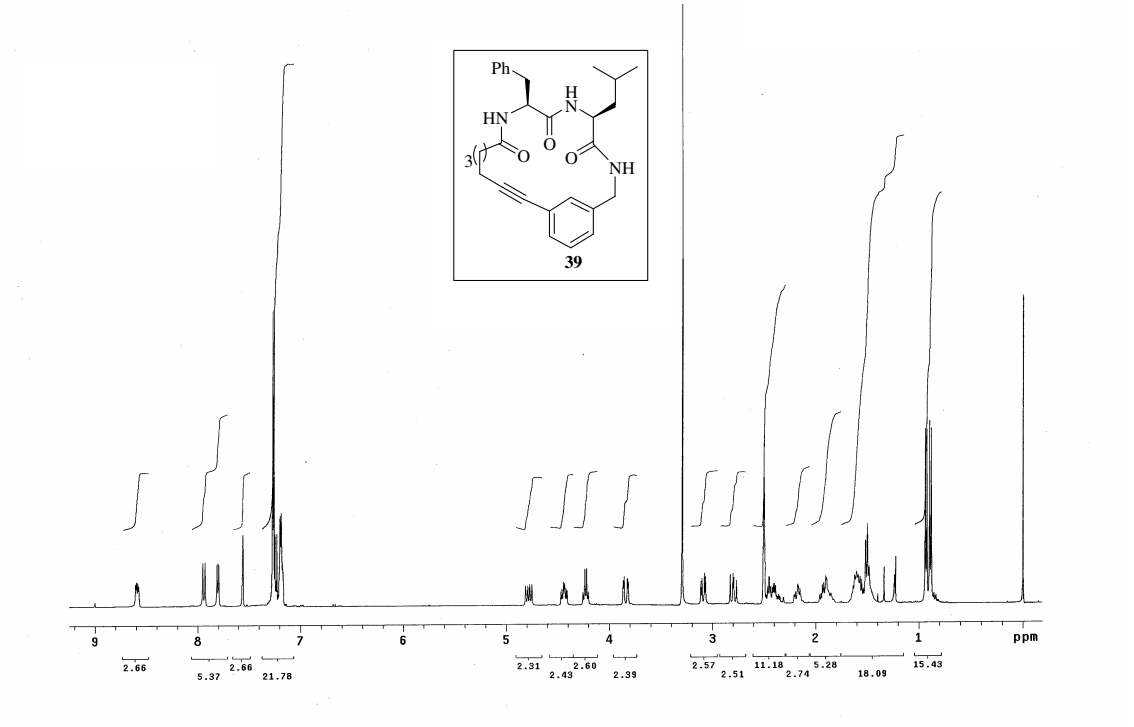
Spectrum No. 24 (Chapter 3, Section 3.4) ^{1}H NMR Spectrum (400MHz, DMSO-d$_6$)



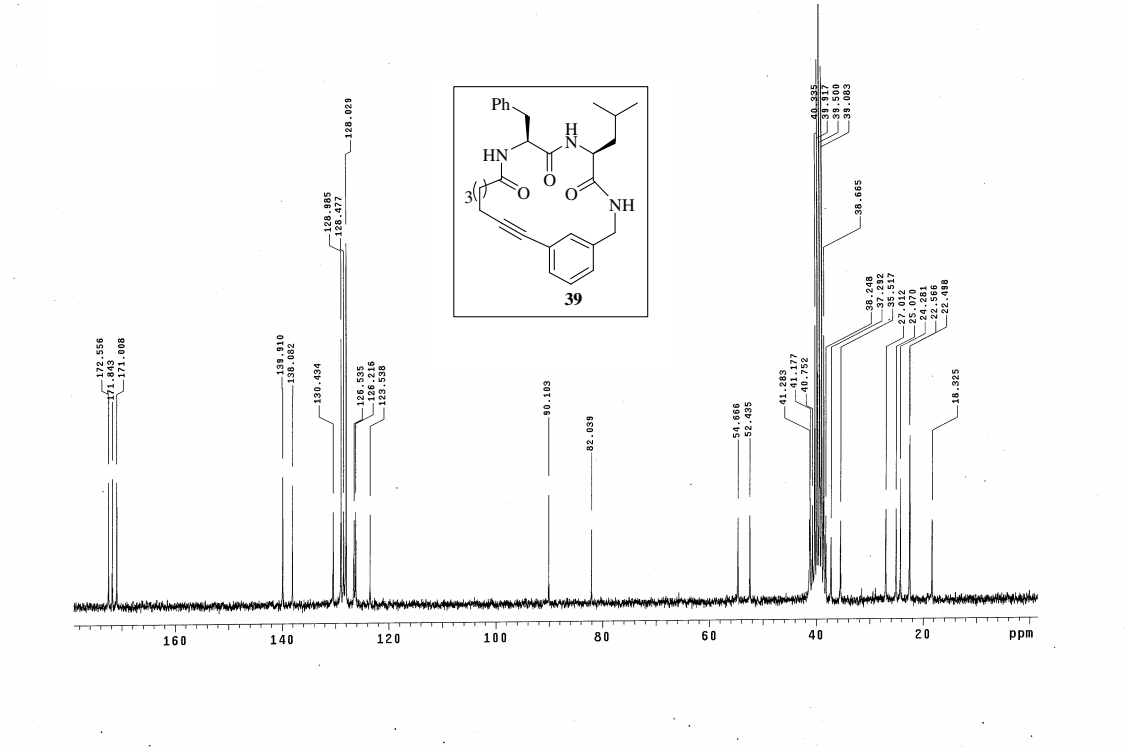
Spectrum No. 25 (Chapter 3, Section 3.4) ^{13}C NMR Spectrum (50MHz, DMSO-d$_6$)



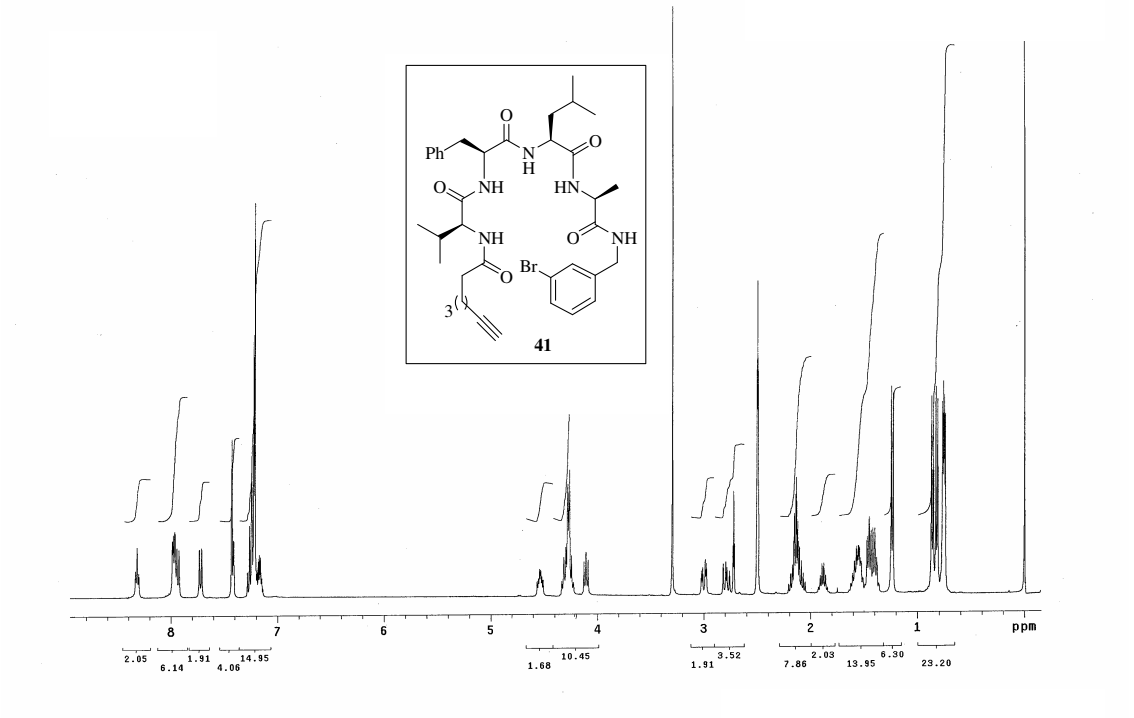
Spectrum No. 26 (Chapter 3, Section 3.4) ^{1}H NMR Spectrum (400MHz, DMSO-d$_6$)



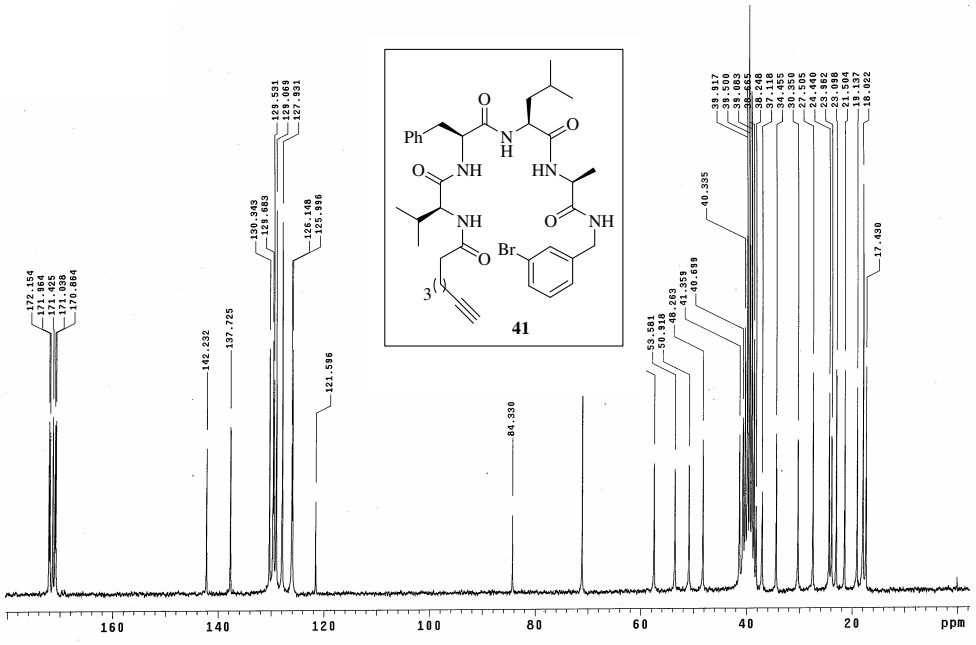
Spectrum No. 27 (Chapter 3, Section 3.4) ^{13}C NMR Spectrum (50MHz, DMSO-d$_6$)



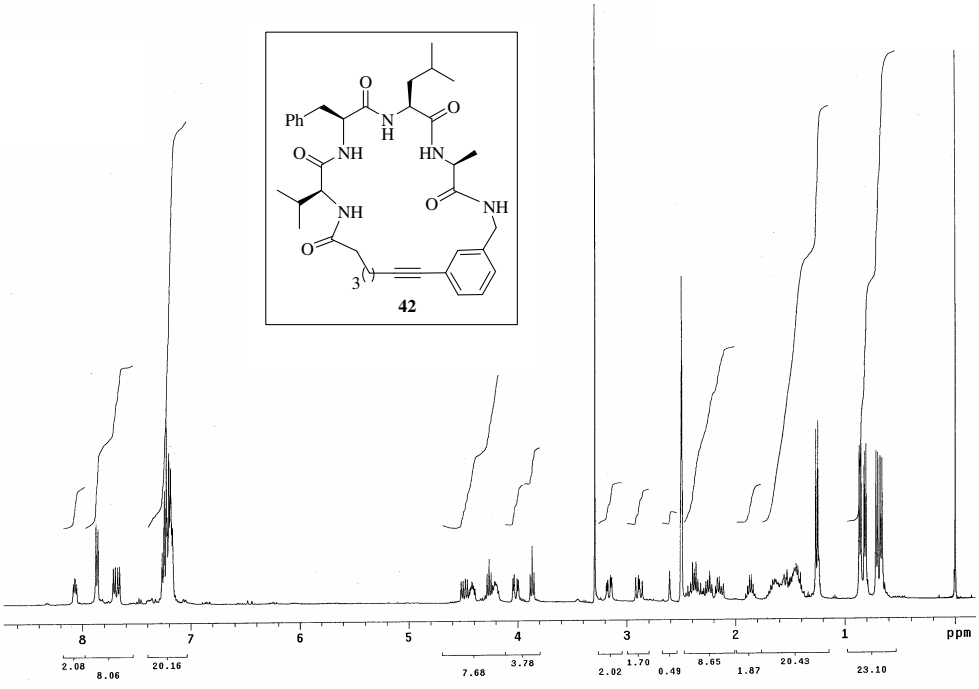
Spectrum No. 28 (Chapter 3, Section 3.4) ^{1}H NMR Spectrum (400MHz, DMSO-d$_6$)



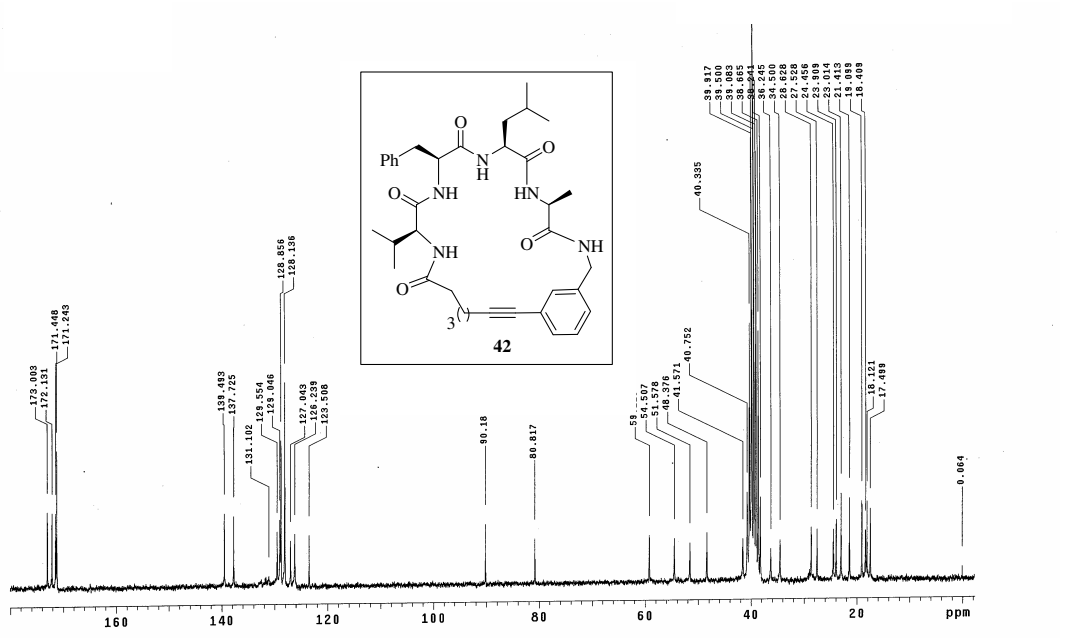
Spectrum No. 29 (Chapter 3, Section 3.4) ^{13}C NMR Spectrum (50MHz, DMSO-d$_6$)



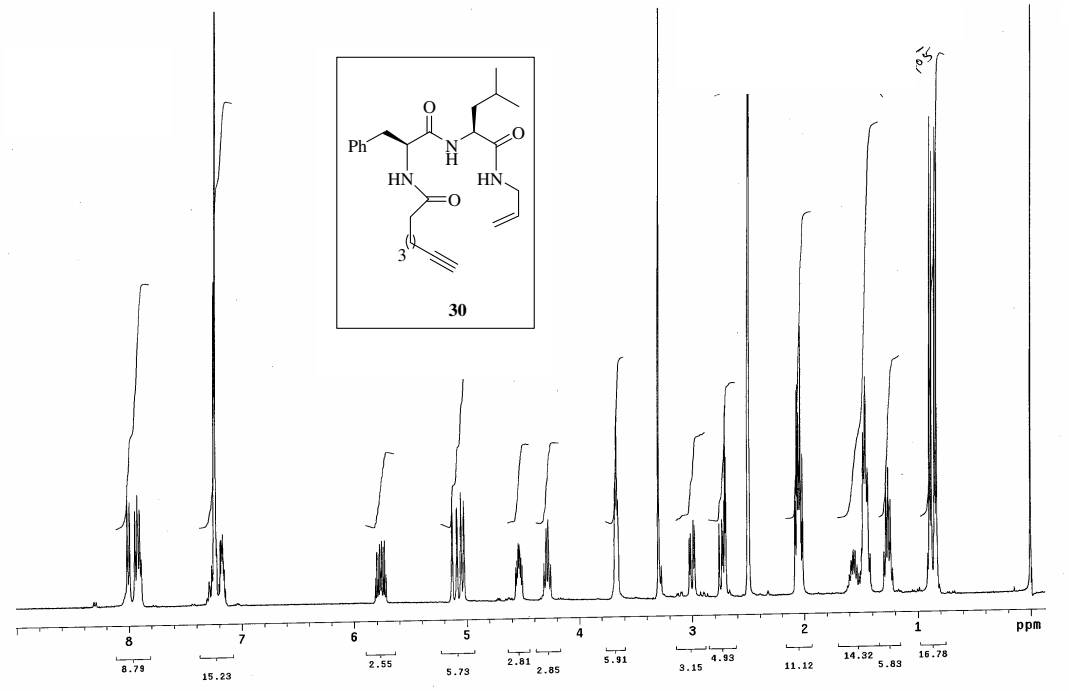
Spectrum No. 30 (Chapter 3, Section 3.4) ^{1}H NMR Spectrum (400MHz, DMSO-d$_6$)



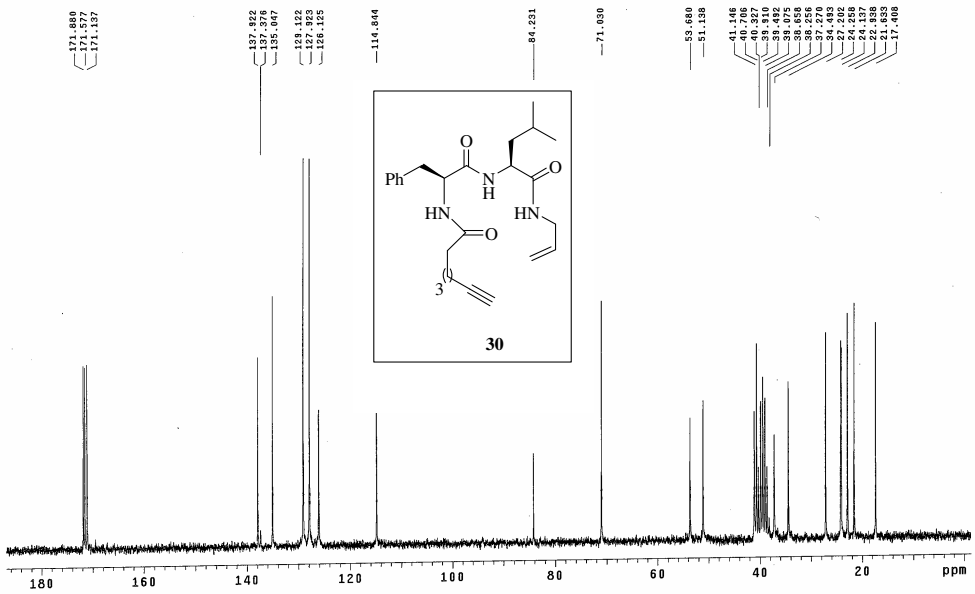
Spectrum No. 31 (Chapter 3, Section 3.4) ^{13}C NMR Spectrum (50MHz, DMSO-d$_6$)



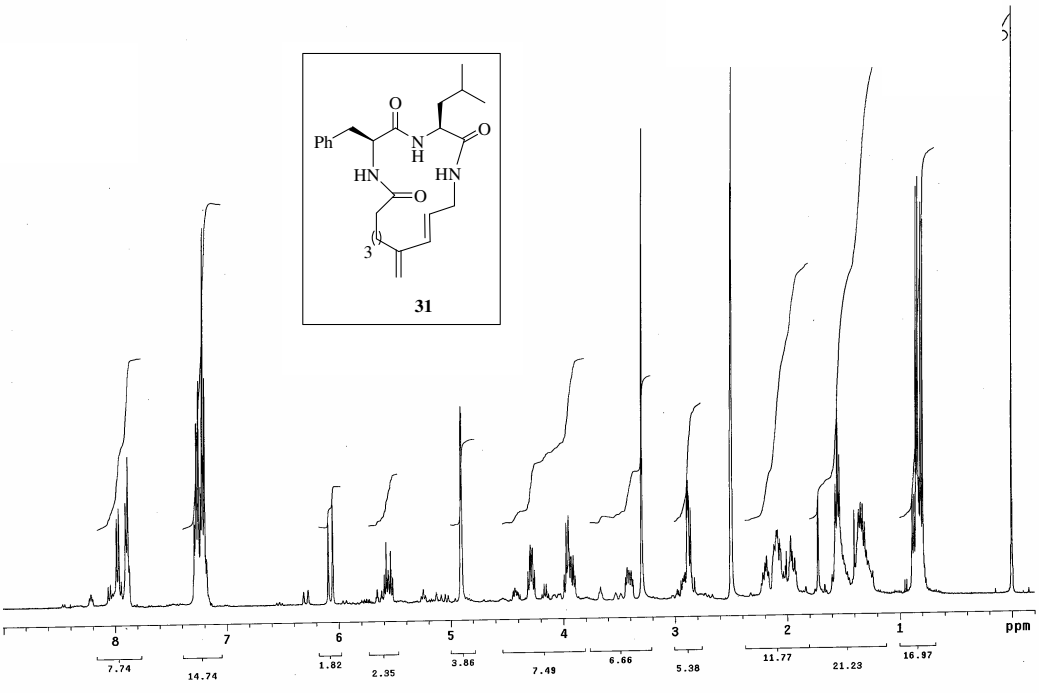
Spectrum No. 32 (Chapter 4, Section 4.4) ^{1}H NMR Spectrum (400MHz, DMSO-d$_6$)



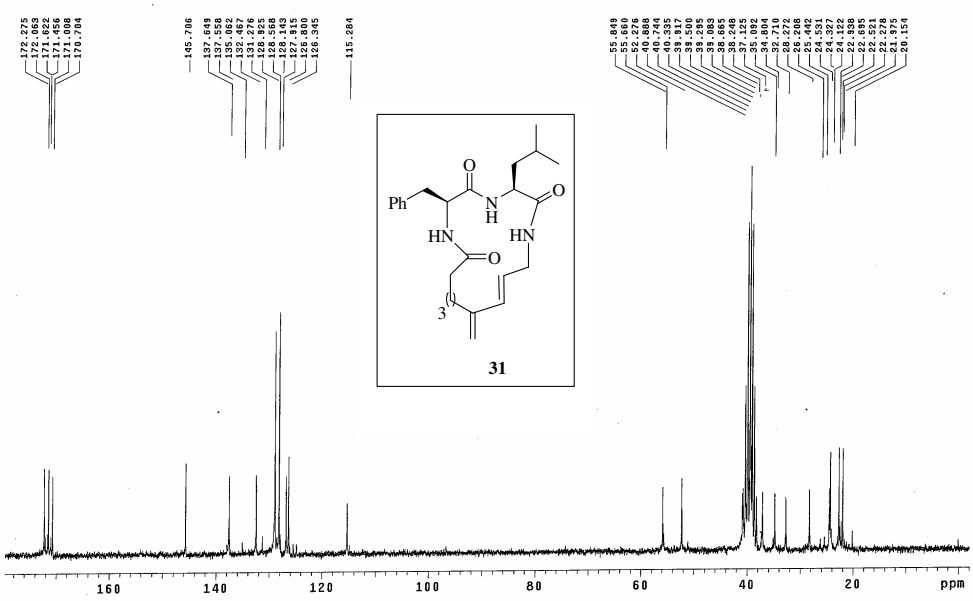
Spectrum No. 33 (Chapter 4, Section 4.4) ^{13}C NMR Spectrum (50MHz, DMSO-d$_6$)



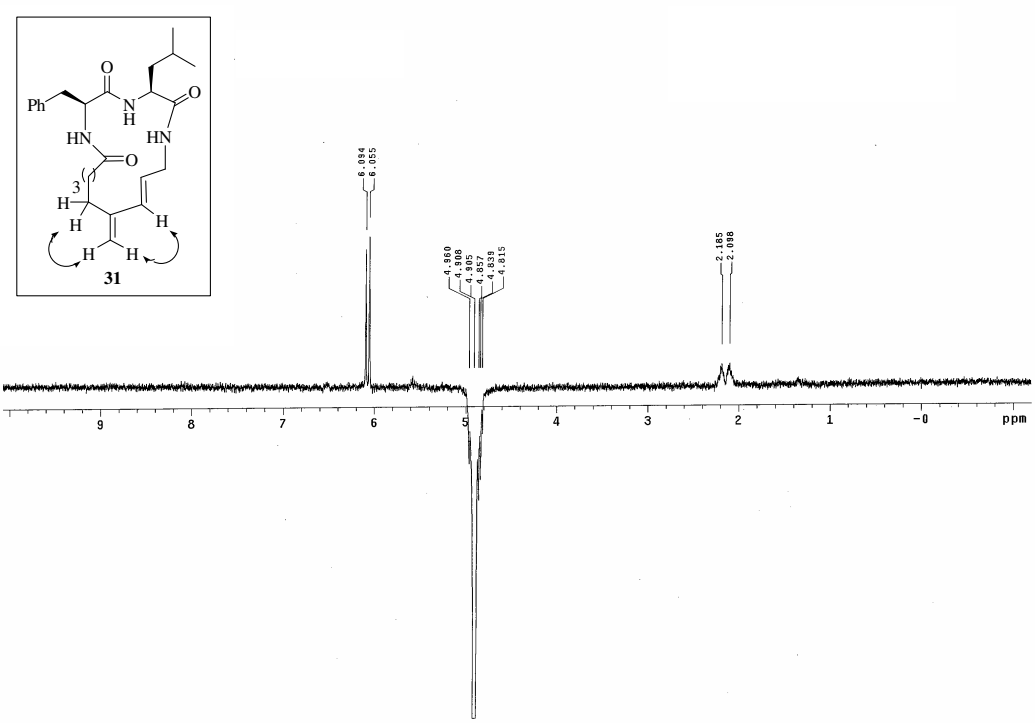
Spectrum No. 34 (Chapter 4, Section 4.4) ^{1}H NMR Spectrum (400MHz, DMSO-d$_6$)



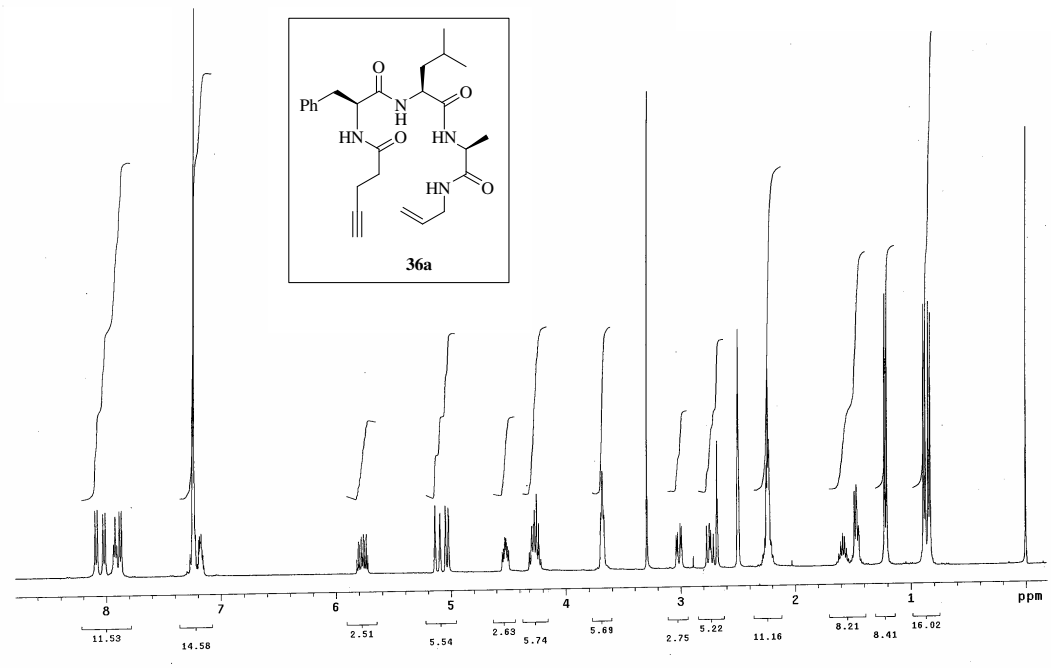
Spectrum No. 35 (Chapter 4, Section 4.4) ^{13}C NMR Spectrum (50MHz, DMSO-d$_6$)



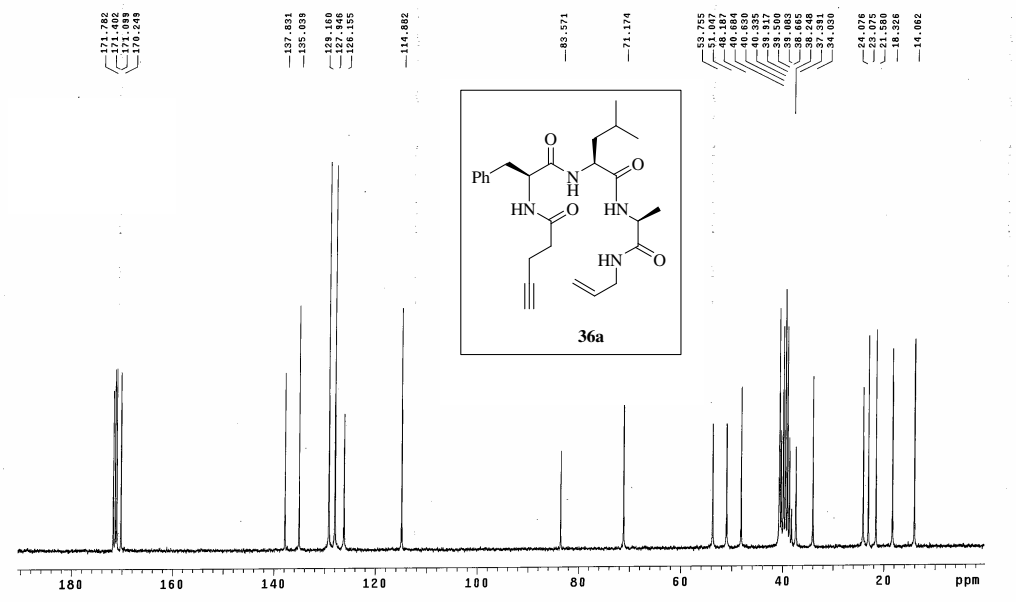
Spectrum No. 36 (Chapter 4, Section 4.4) 1D nOe Spectrum (400MHz, DMSO-d$_6$)



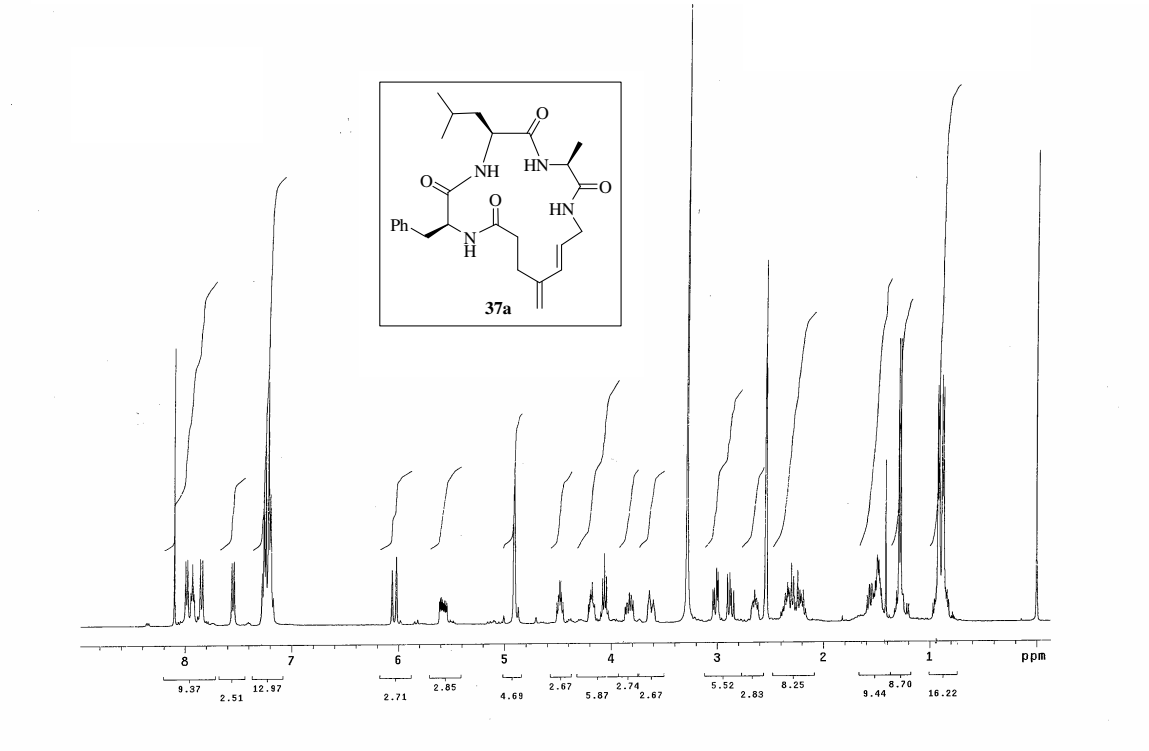
Spectrum No. 37 (Chapter 4, Section 4.4) ^{1}H NMR Spectrum (400MHz, DMSO-d$_6$)



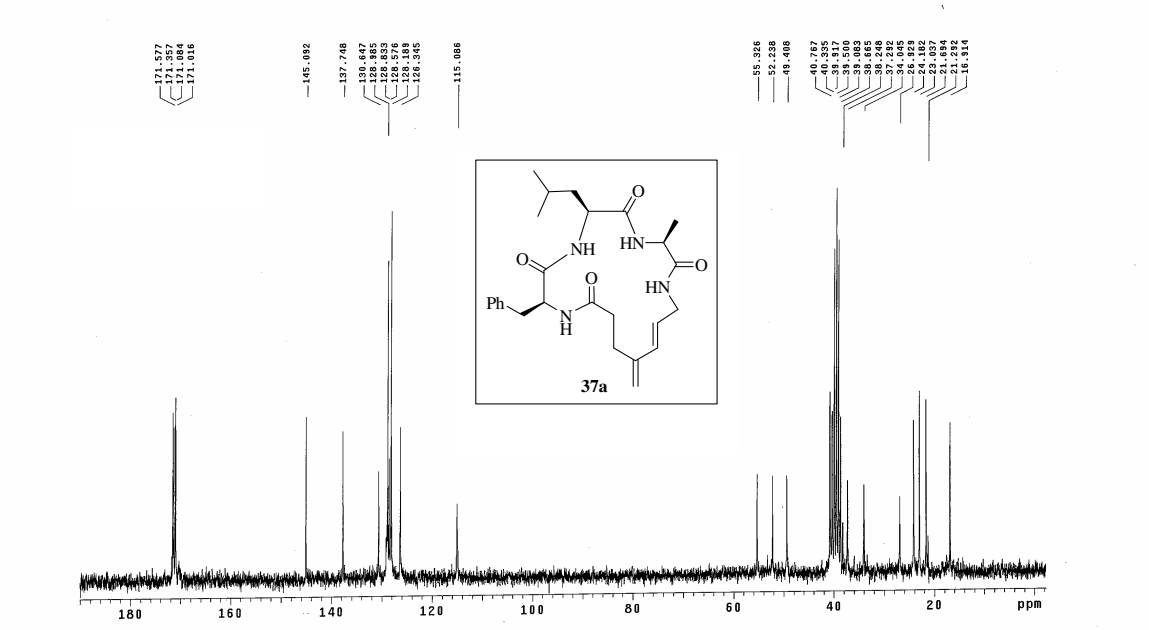
Spectrum No. 38 (Chapter 4, Section 4.4) ^{13}C NMR Spectrum (50MHz, DMSO-d$_6$)



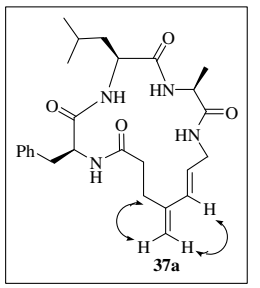
Spectrum No. 39 (Chapter 4, Section 4.4) ^{1}H NMR Spectrum (400MHz, DMSO-d$_6$)

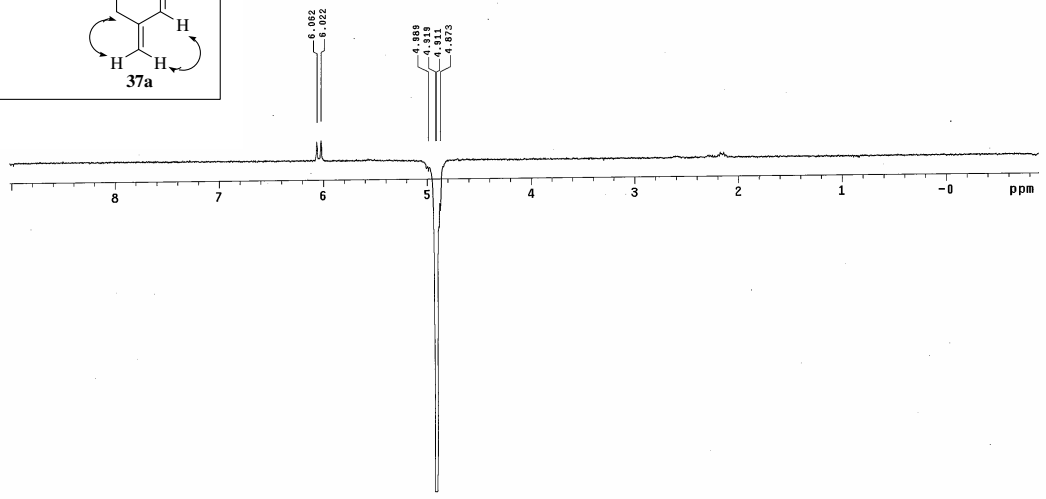


Spectrum No. 40 (Chapter 4, Section 4.4) ^{13}C NMR Spectrum (50MHz, DMSO-d$_6$)

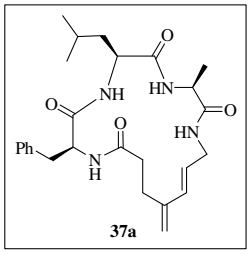


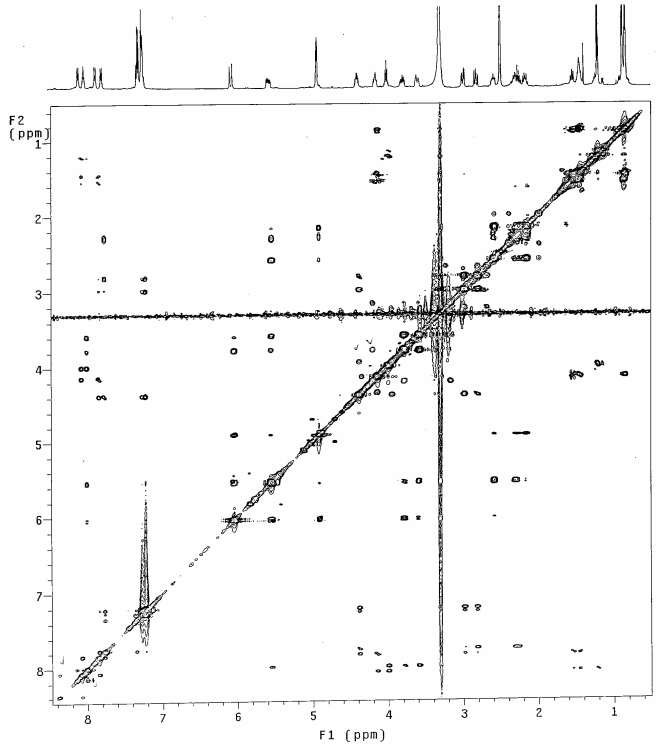
Spectrum No. 41 (Chapter 4, Section 4.4) 1D nOe Spectrum (400MHz, DMSO-d_6)



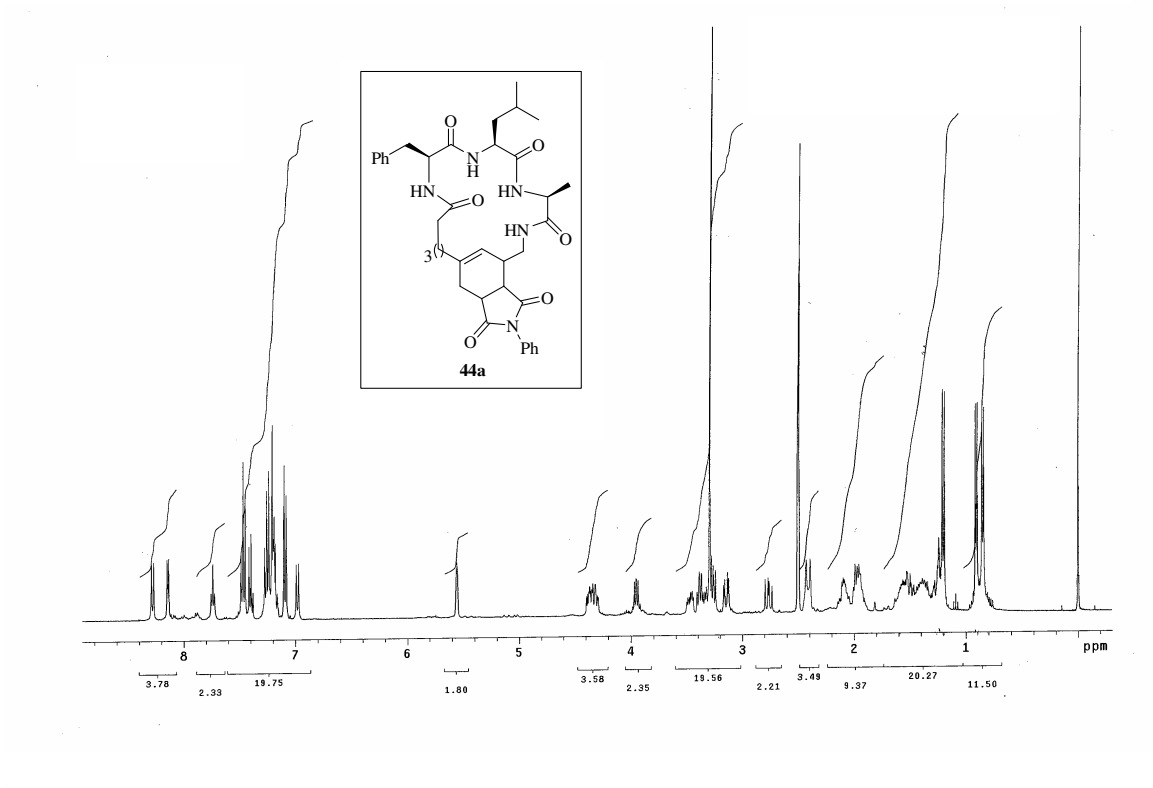


Spectrum No. 42 (Chapter 4, Section 4.4) ROESY Spectrum (400MHz, DMSO-d_6)

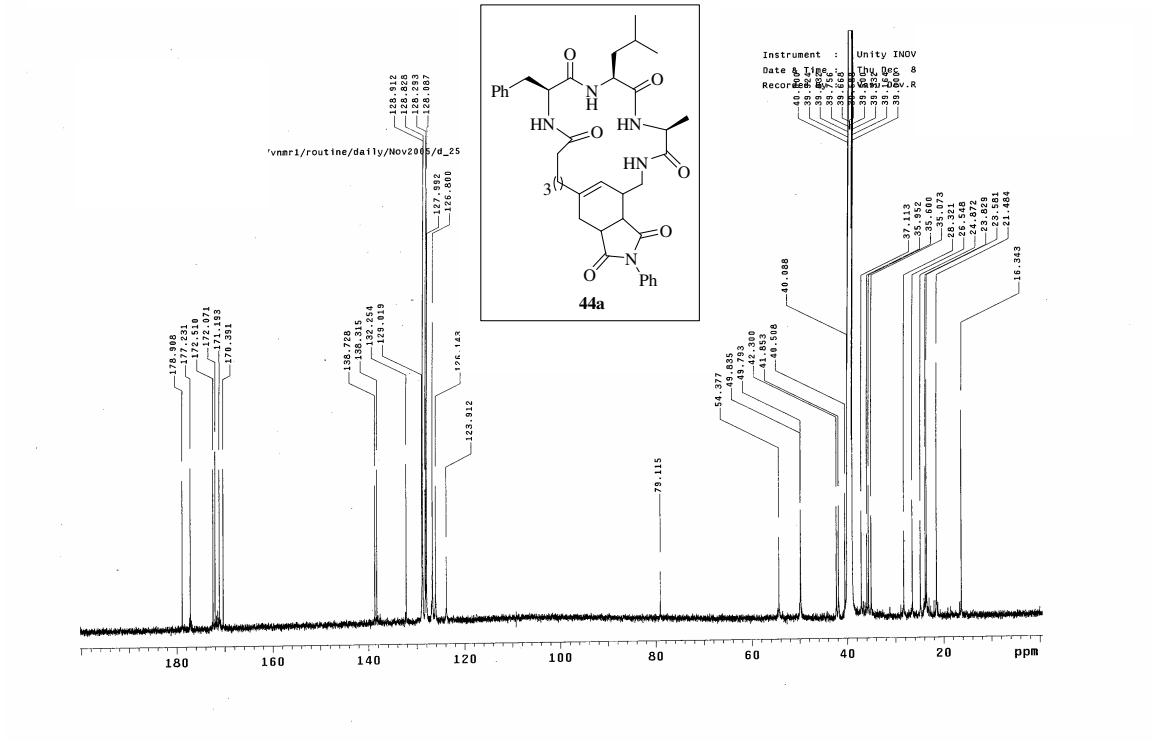




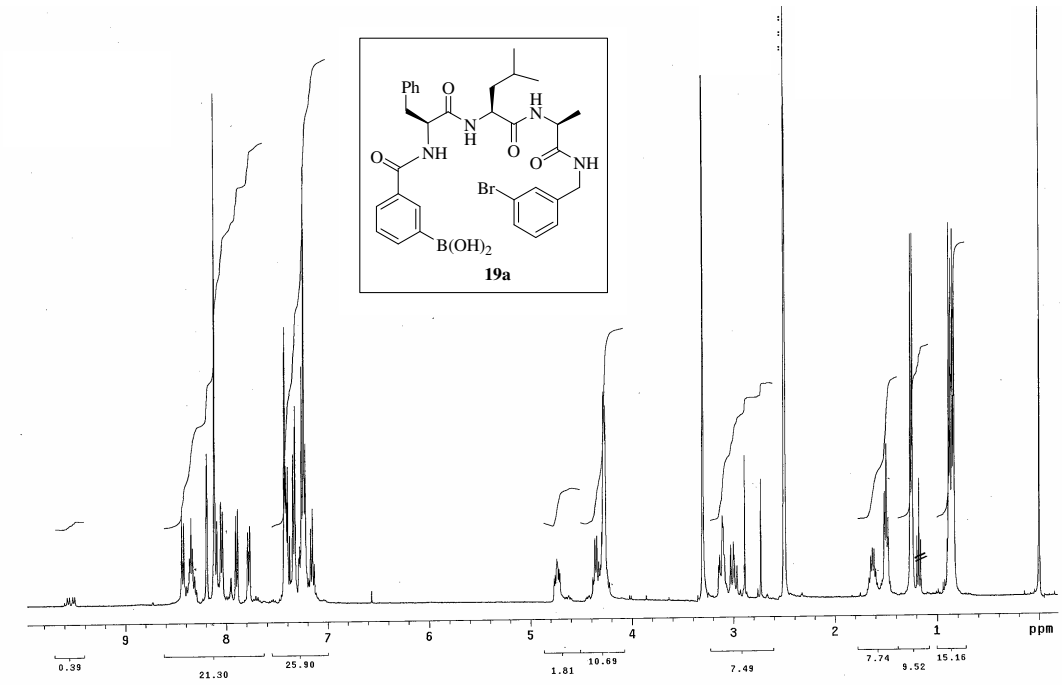
Spectrum No. 43 (Chapter 4, Section 4.4) ^{1}H NMR Spectrum (50MHz, DMSO-d$_6$)



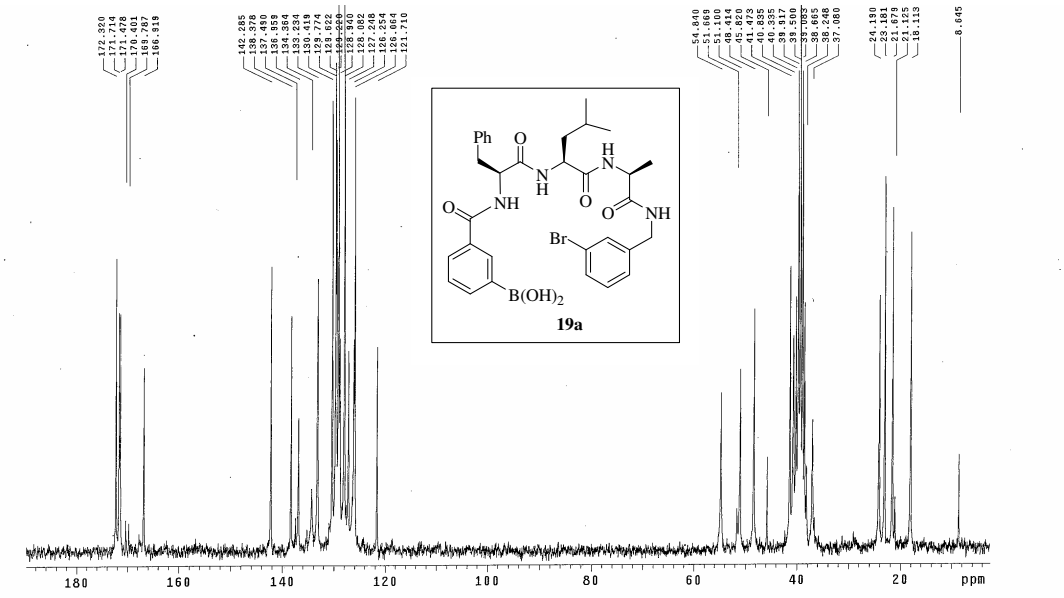
Spectrum No. 44 (Chapter 4, Section 4.4) ^{13}C NMR Spectrum (50MHz, DMSO-d$_6$)



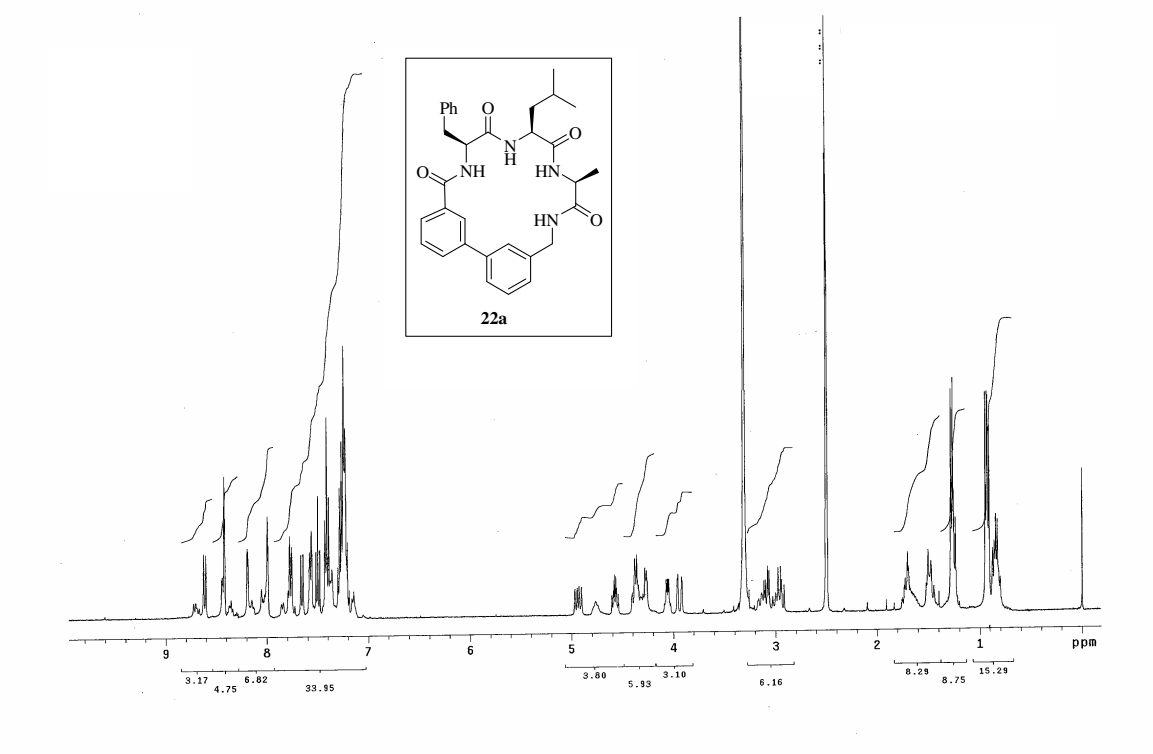
Spectrum No. 45 (Chapter 5, Section 5.4) ^{1}H NMR Spectrum (400MHz, DMSO-d$_6$)



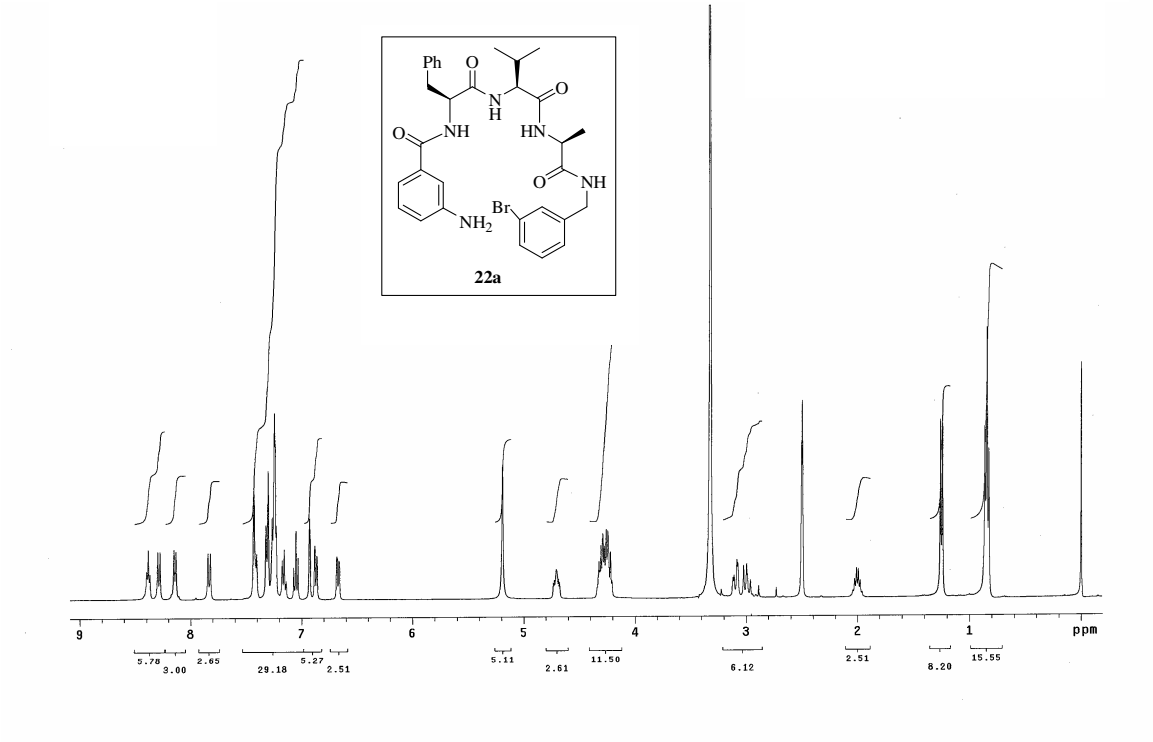
Spectrum No. 46 (Chapter 5, Section 5.4) ^{13}C NMR Spectrum (50MHz, DMSO-d$_6$)



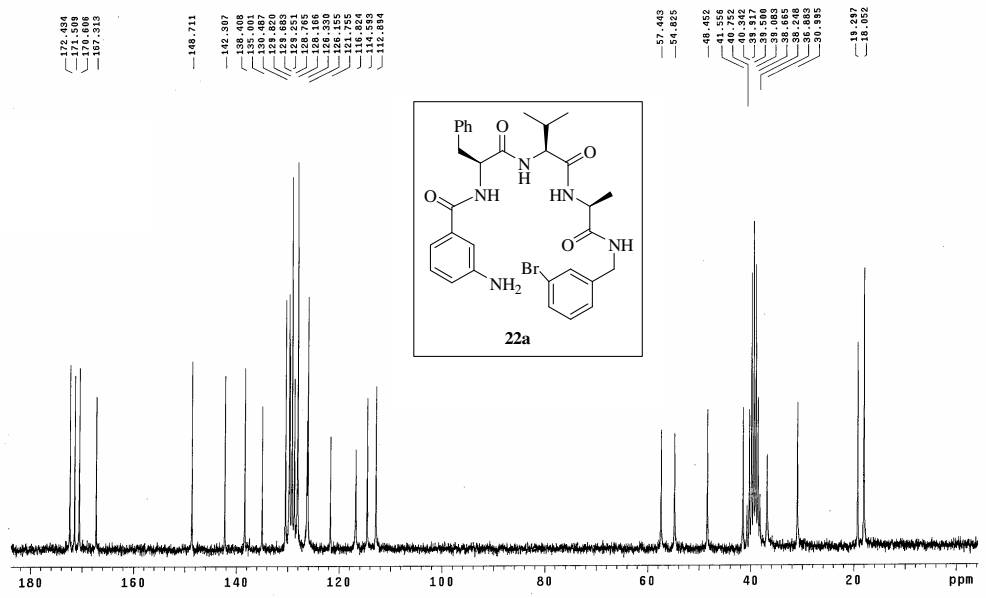
Spectrum No. 47 (Chapter 5, Section 5. 4) ^{1}H NMR Spectrum (400MHz, DMSO-d$_6$)



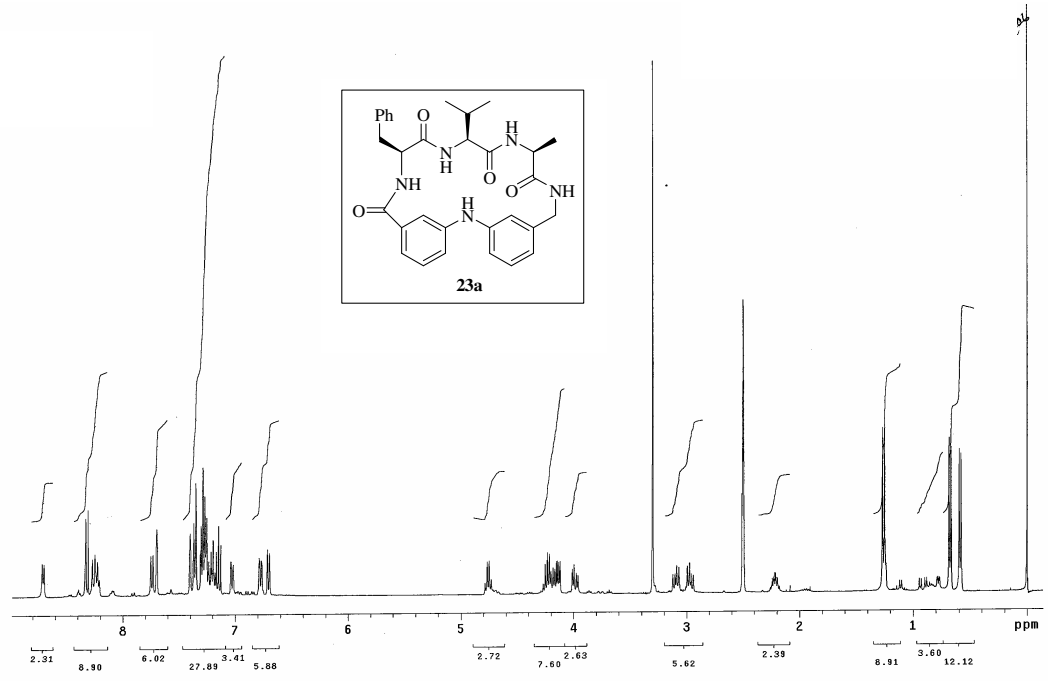
Spectrum No. 48 (Chapter 6, Section 6.4) ^{1}H NMR Spectrum (400MHz, DMSO-d$_6$)



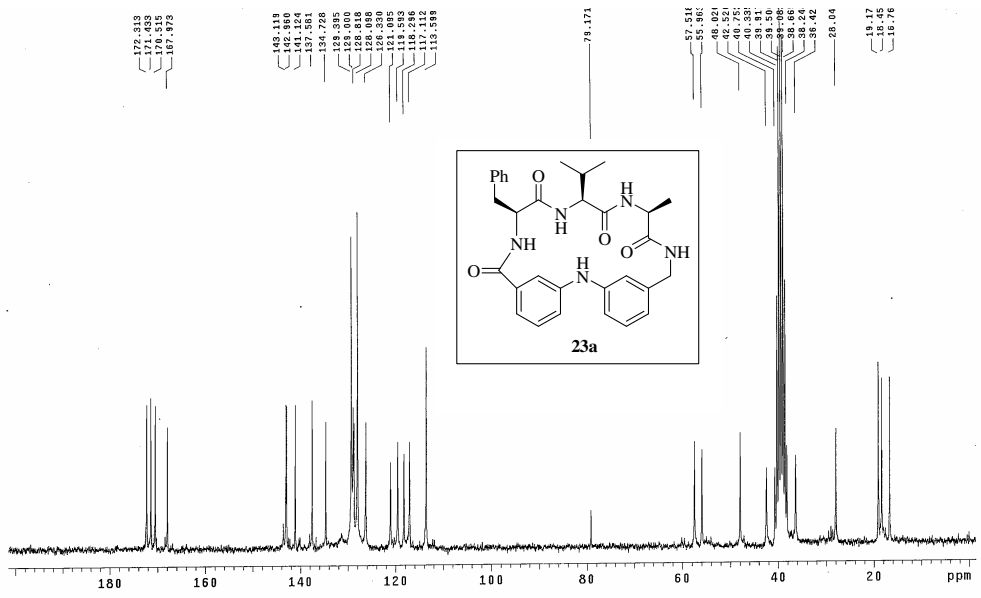
Spectrum No. 49 (Chapter 6, Section 6.4) ^{13}C NMR Spectrum (50MHz, DMSO-d$_6$)



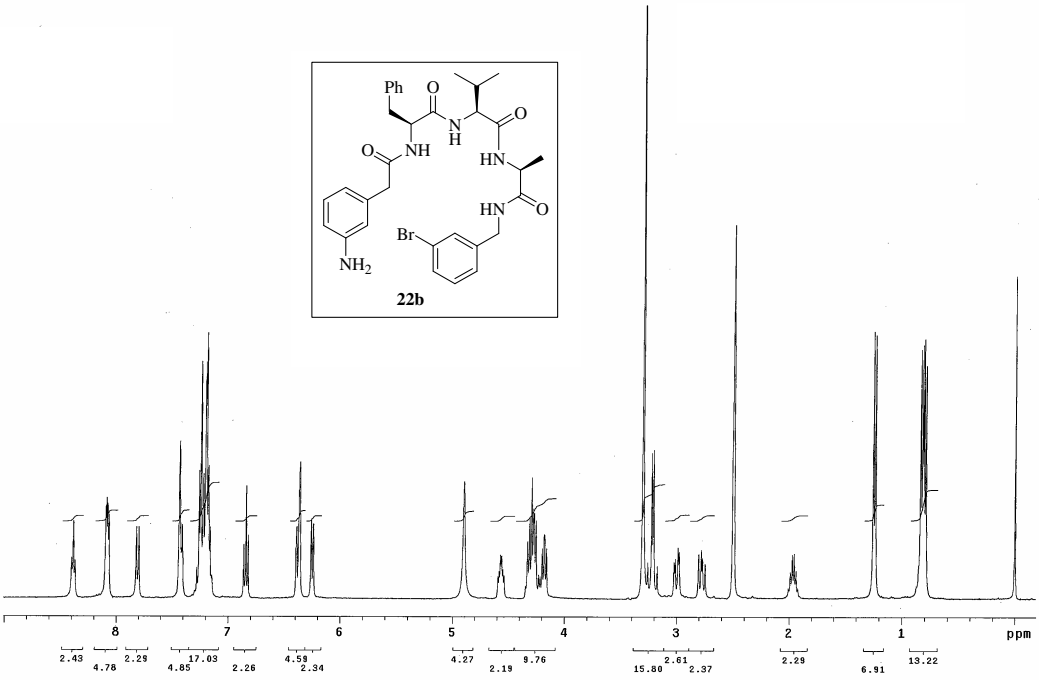
Spectrum No. 50 (Chapter 6, Section 6.4) ^{1}H NMR Spectrum (400MHz, DMSO-d$_6$)



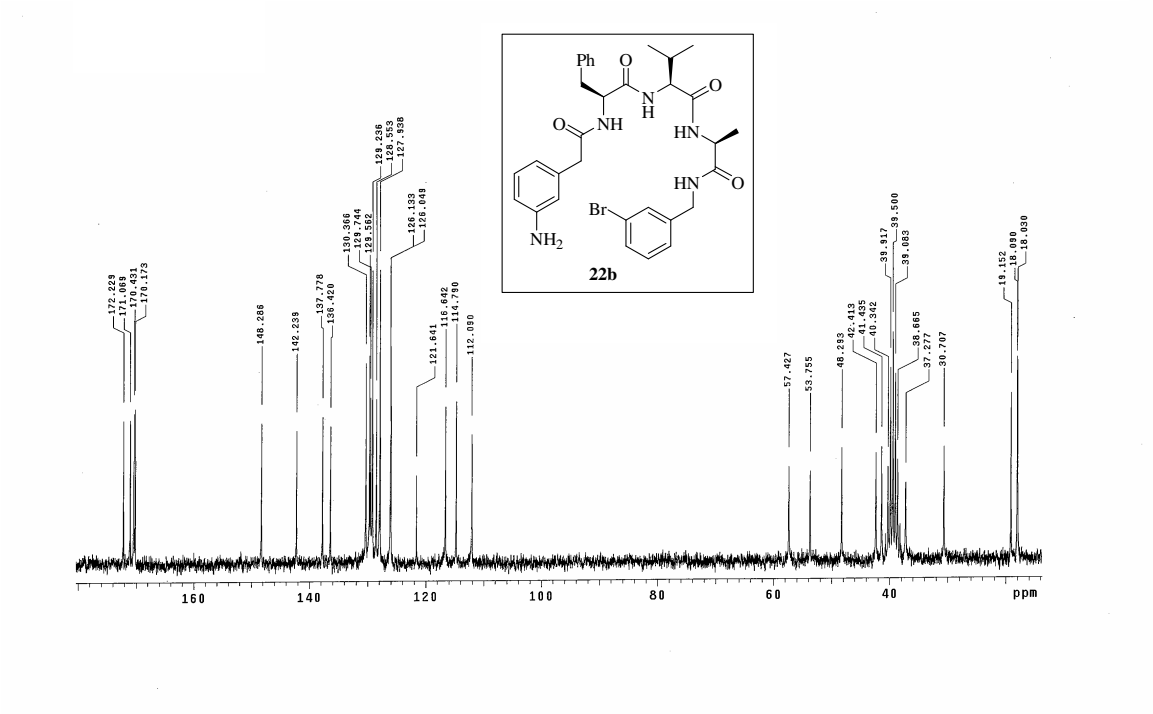
Spectrum No. 51 (Chapter 6, Section 6.4) ^{13}C NMR Spectrum (50MHz, DMSO-d$_6$)



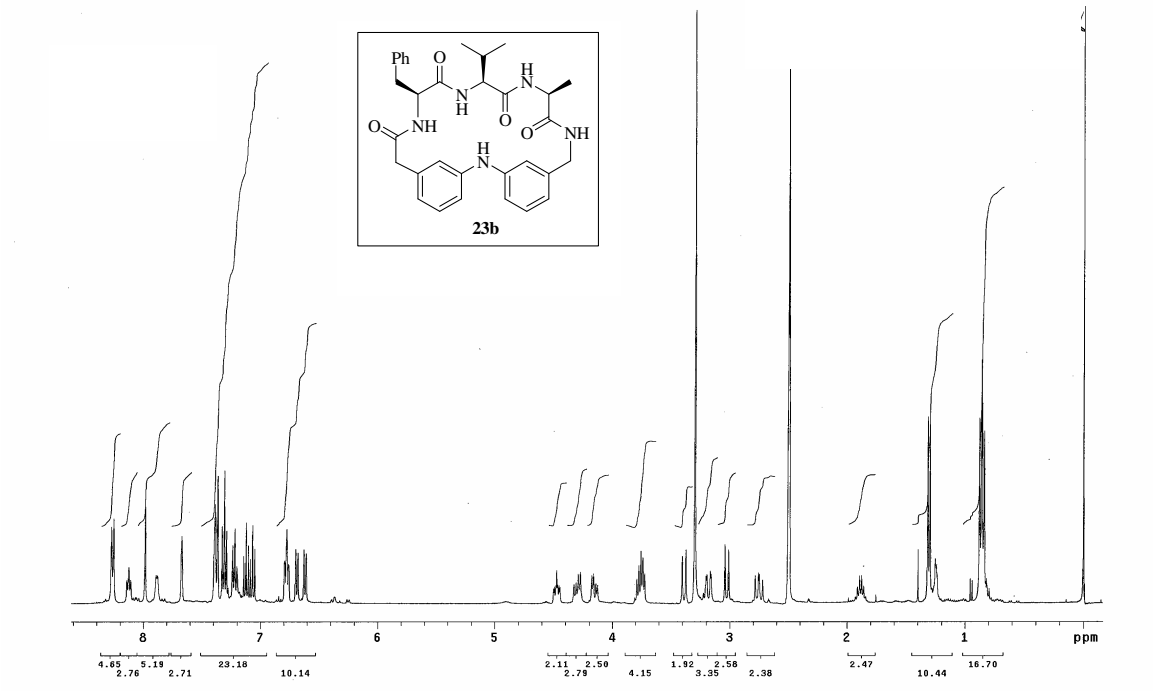
Spectrum No. 52 (Chapter 6, Section 6.4) ^{1}H NMR Spectrum (400MHz, DMSO-d$_6$)



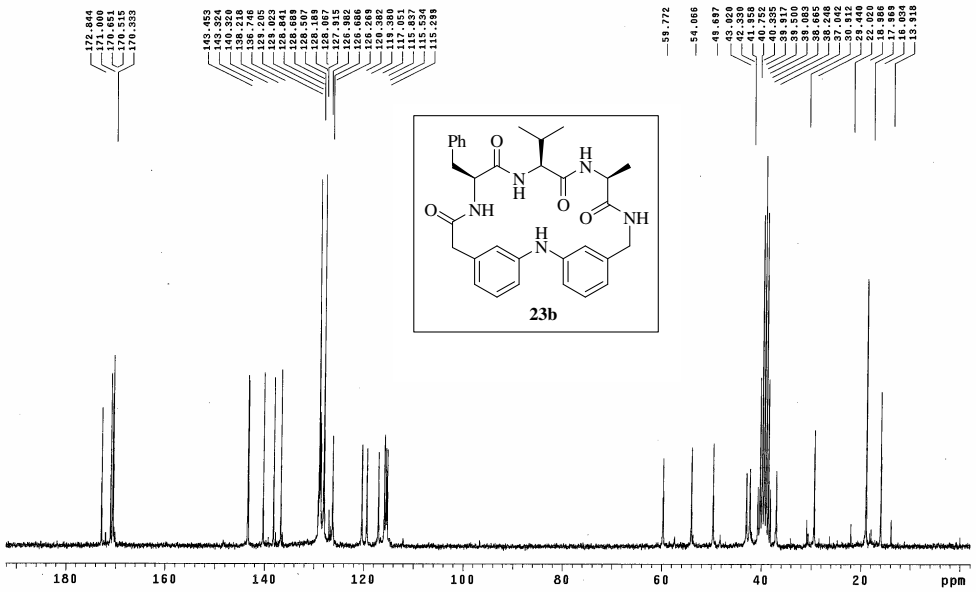
Spectrum No. 53 (Chapter 6, Section 6.4) ^{13}C NMR Spectrum (50MHz, DMSO-d$_6$)



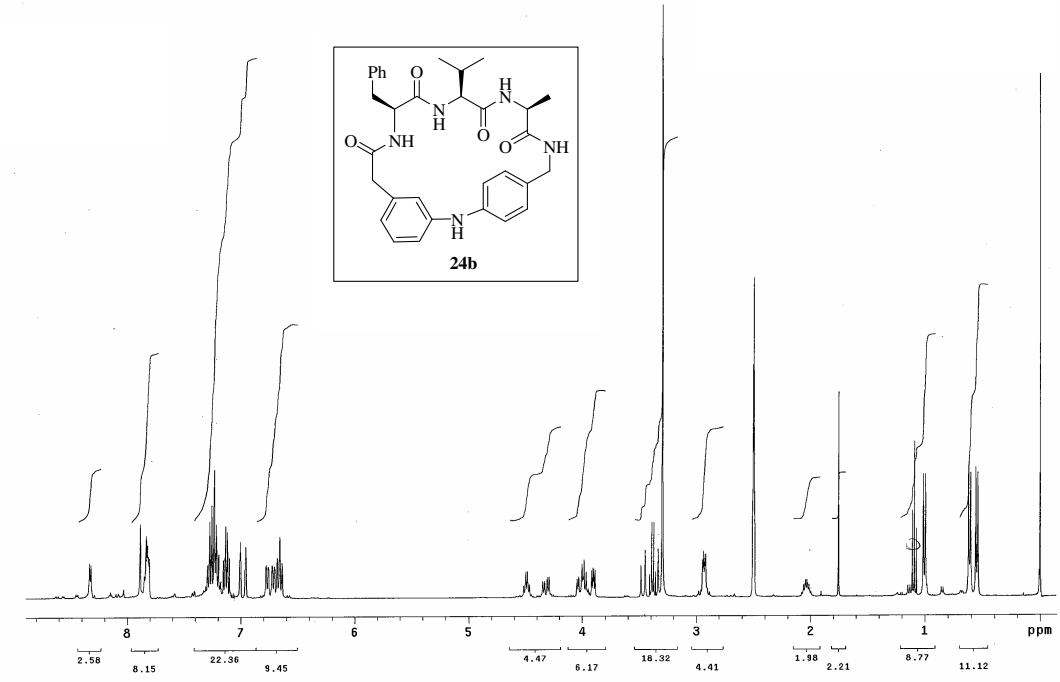
Spectrum No. 54 (Chapter 6, Section 6.4) ^{1}H NMR Spectrum (400MHz, DMSO-d$_6$)



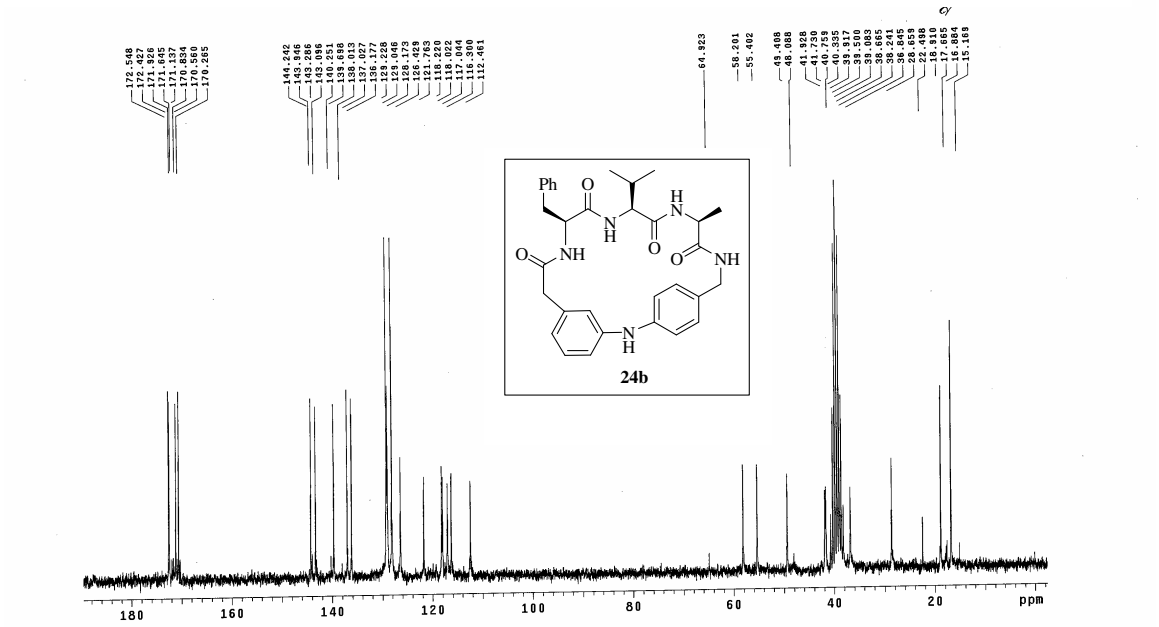
Spectrum No. 55 (Chapter 6, Section 6.4) ^{13}C NMR Spectrum (50MHz, DMSO-d$_6$)



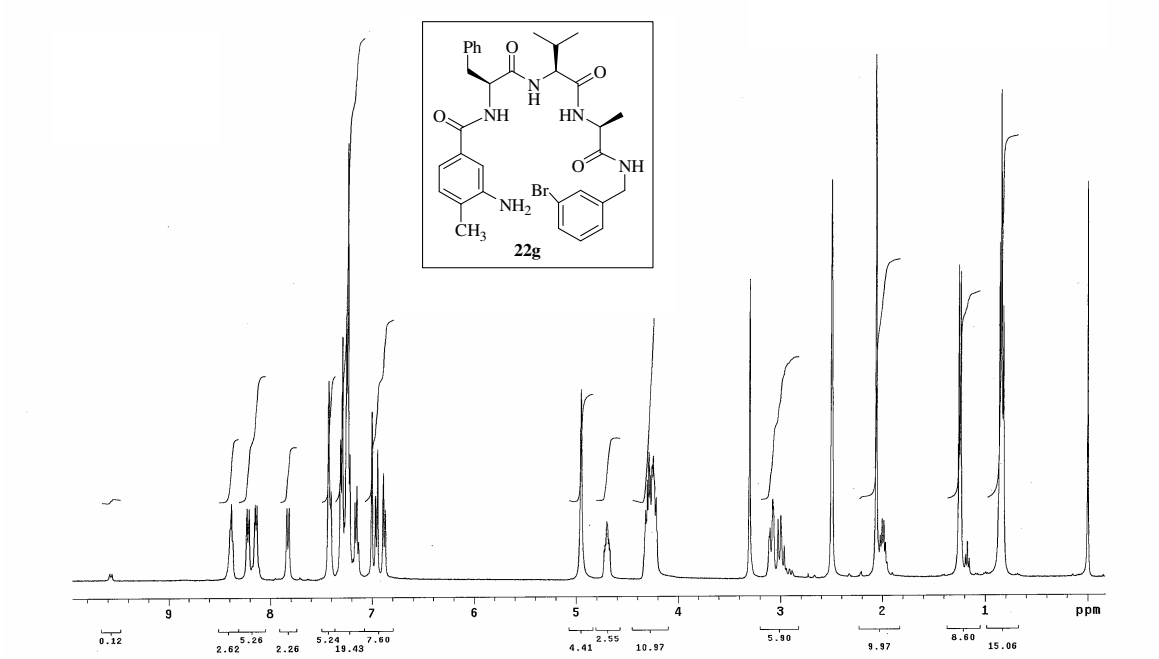
Spectrum No. 56 (Chapter 6, Section 6.4) ^{1}H NMR Spectrum (400MHz, DMSO-d$_6$)



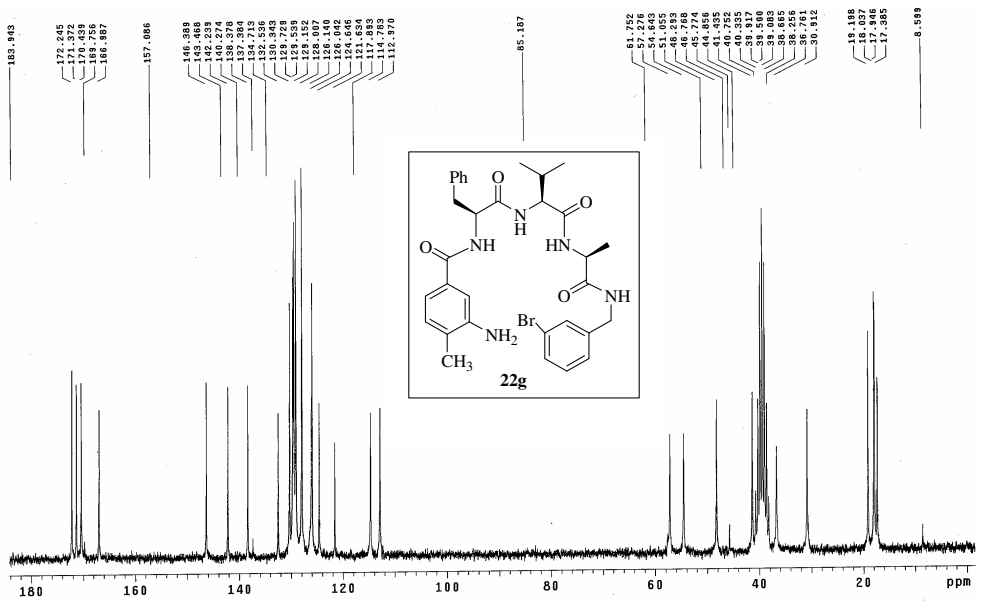
Spectrum No. 57 (Chapter 6, Section 6.4) ^{13}C NMR Spectrum (50MHz, DMSO-d$_6$)



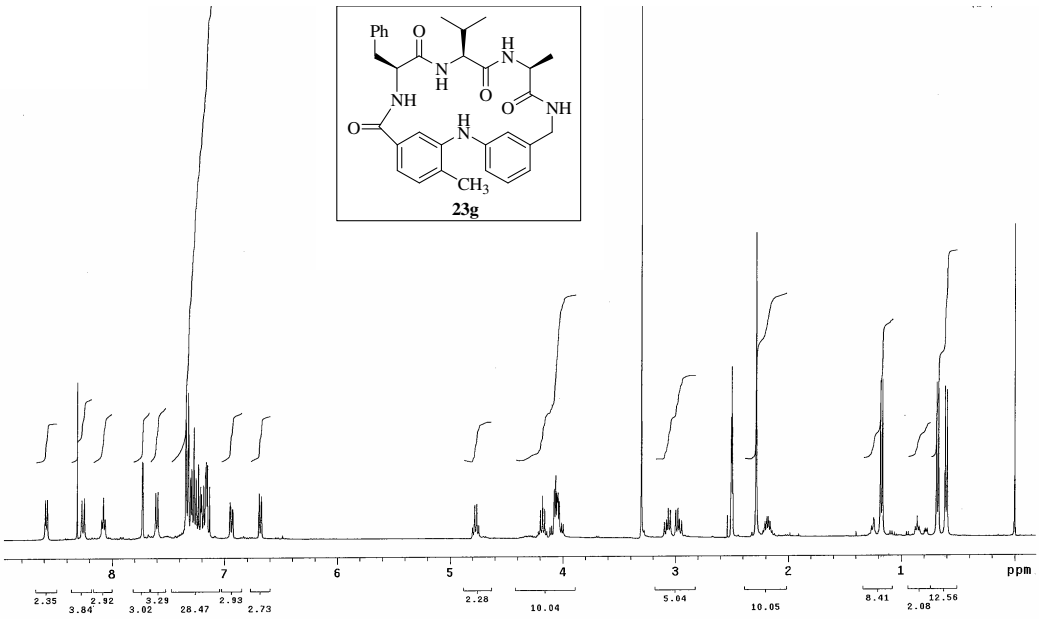
Spectrum No. 58 (Chapter 6, Section 6.4) ^{1}H NMR Spectrum (400MHz, DMSO-d$_6$)



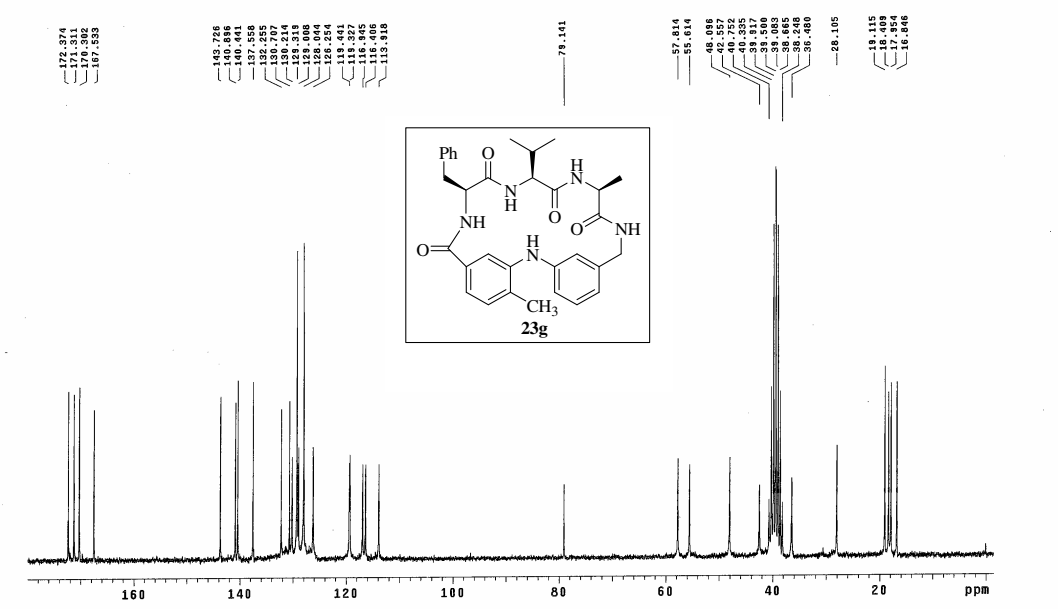
Spectrum No. 59 (Chapter 6, Section 6.4) ^{13}C NMR Spectrum (50MHz, DMSO-d$_6$)



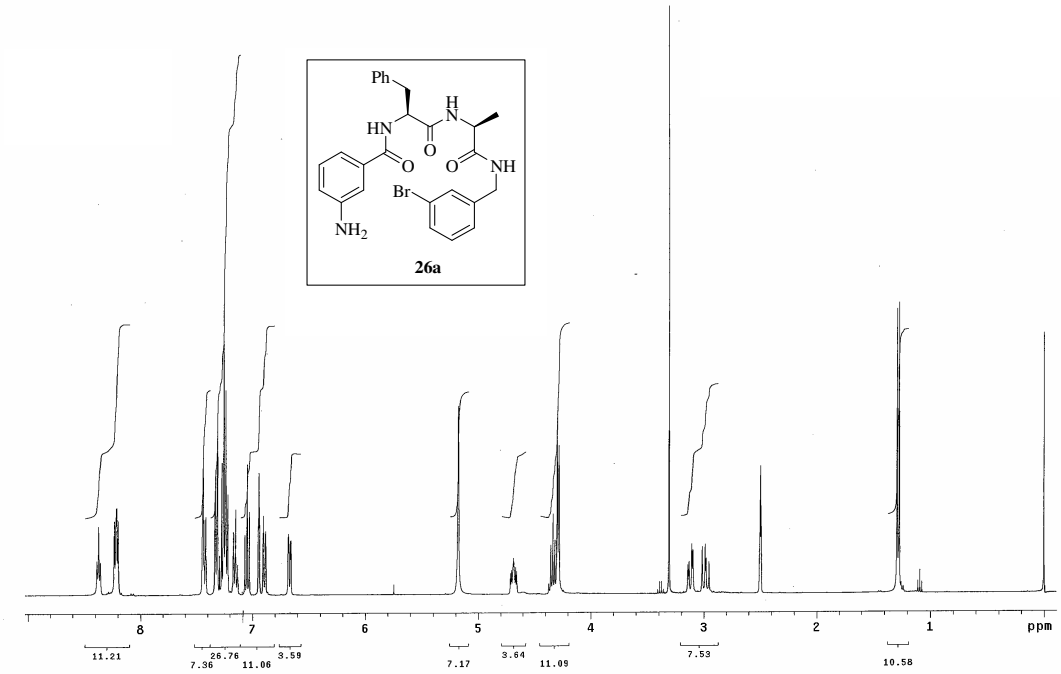
Spectrum No. 60 (Chapter 6, Section 6.4) ^{1}H NMR Spectrum (400MHz, DMSO-d$_6$)



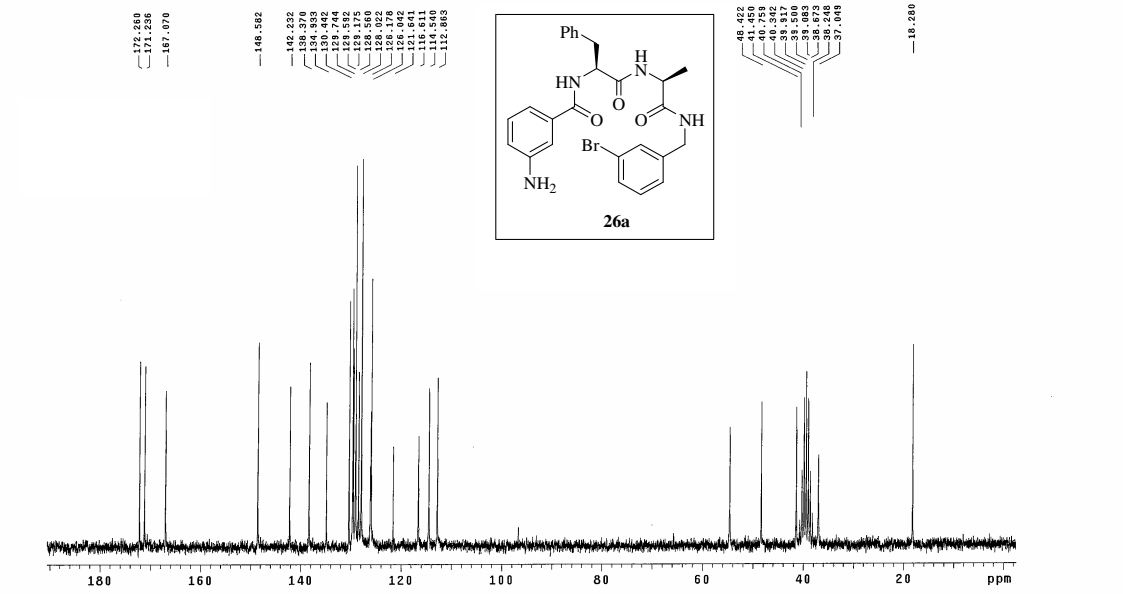
Spectrum No. 61 (Chapter 6, Section 6.4) ^{13}C NMR Spectrum (50MHz, DMSO-d$_6$)



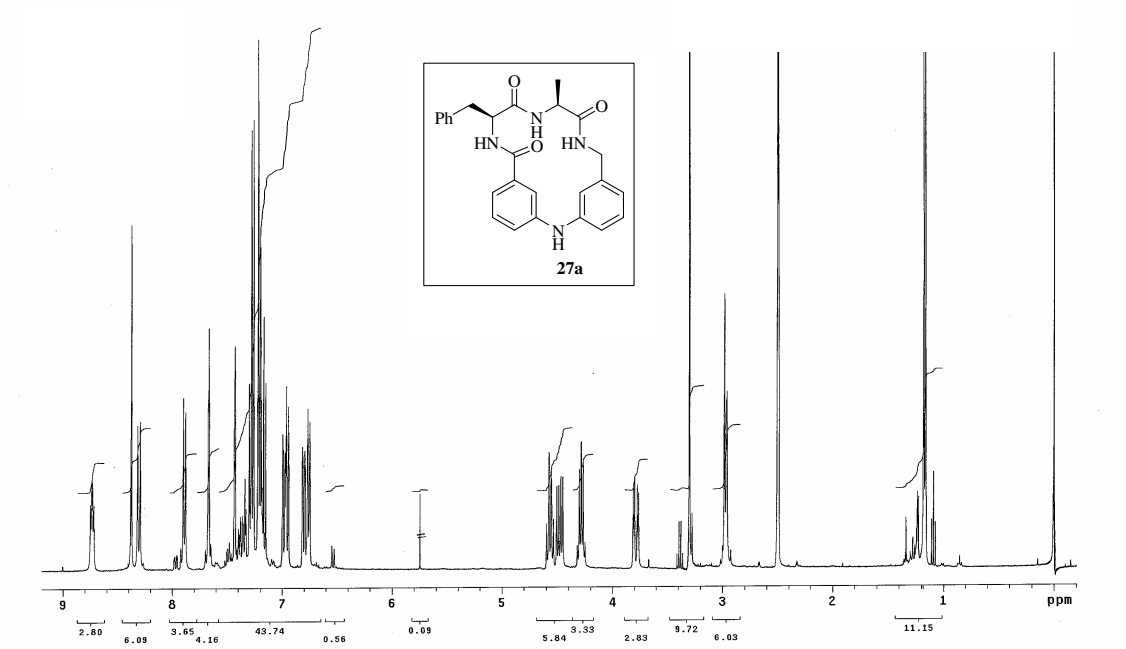
Spectrum No. 62 (Chapter 6, Section 6.4) ^{1}H NMR Spectrum (400MHz, DMSO-d$_6$)



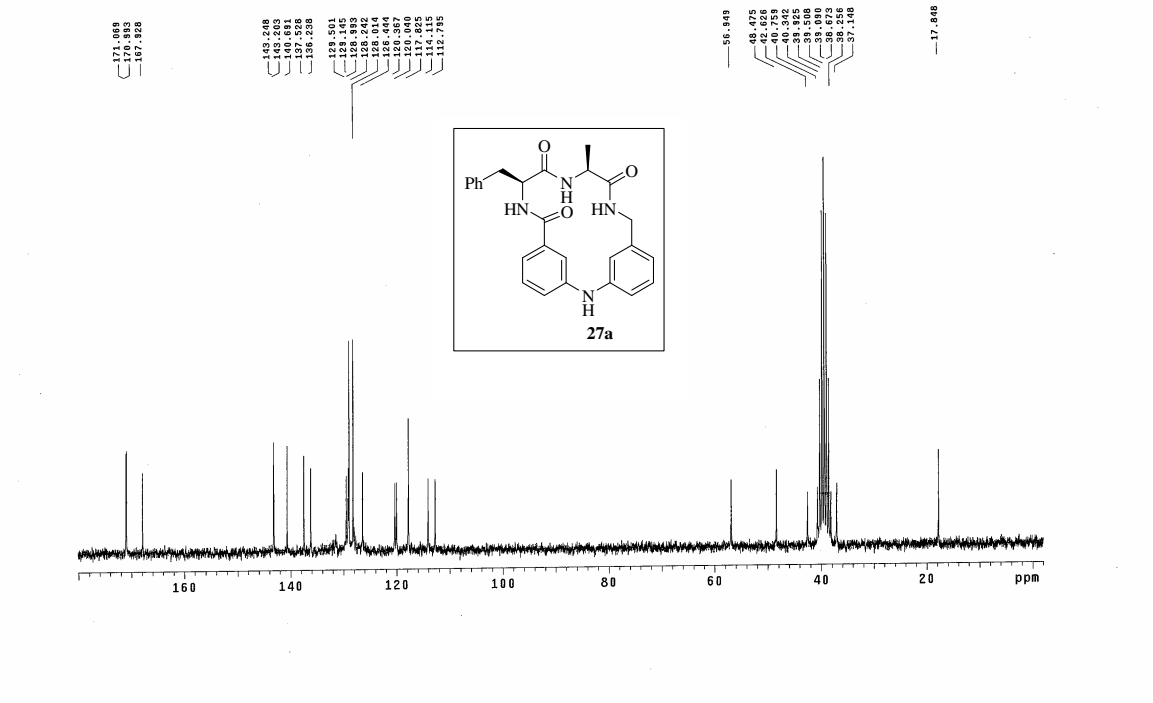
Spectrum No. 63 (Chapter 6, Section 6.4) ^{13}C NMR Spectrum (50MHz, DMSO-d$_6$)



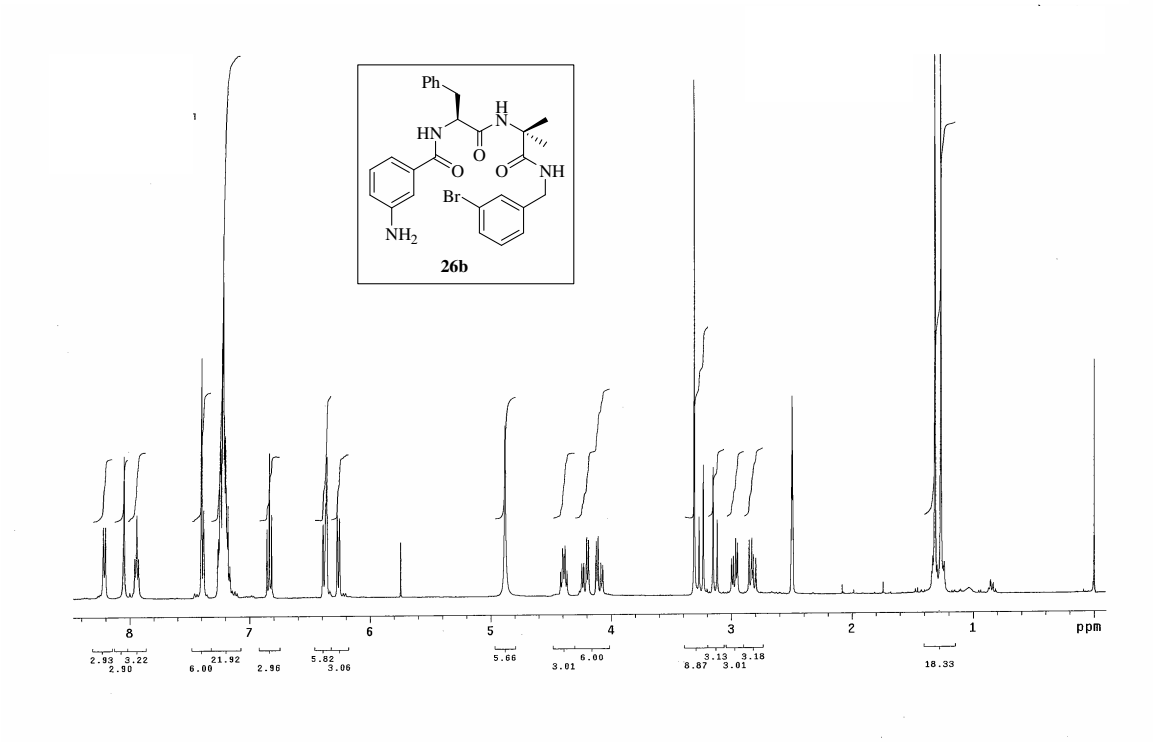
Spectrum No. 64 (Chapter 6, Section 6.4) ^{1}H NMR Spectrum (400MHz, DMSO-d$_6$)



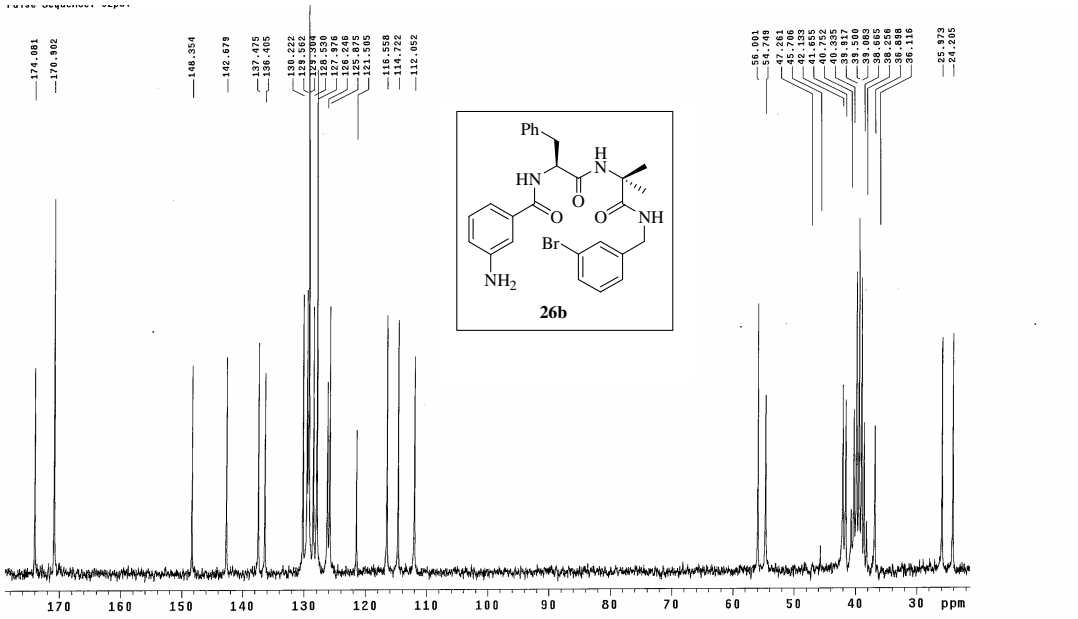
Spectrum No. 65 (Chapter 6, Section 6.4) ^{13}C NMR Spectrum (50MHz, DMSO-d$_6$)



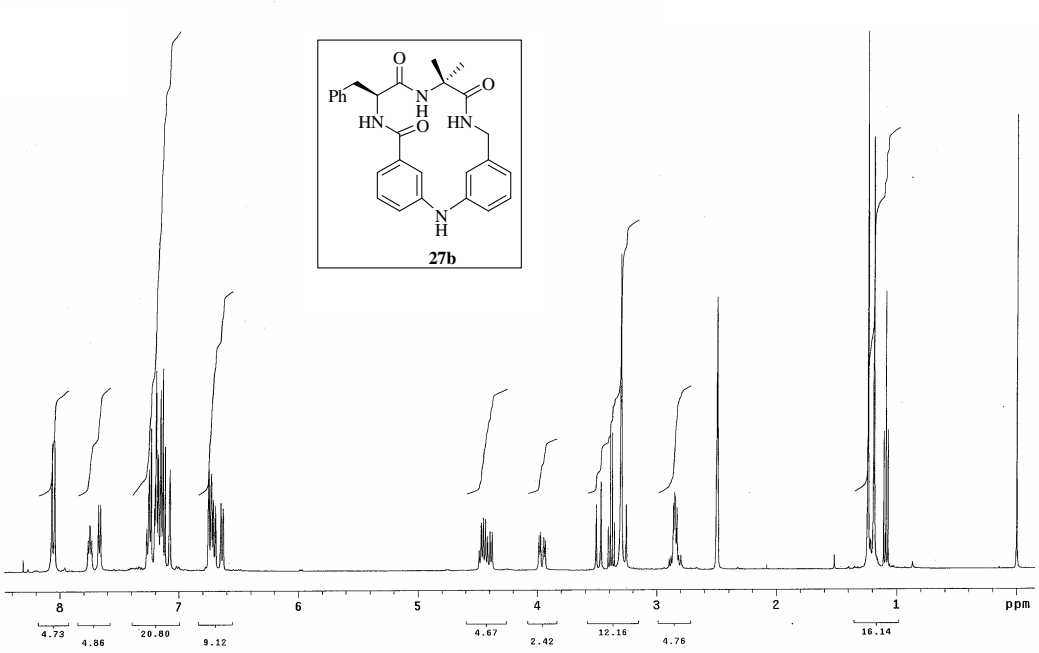
Spectrum No. 66 (Chapter 6, Section 6.4) ^{1}H NMR Spectrum (400MHz, DMSO-d$_6$)



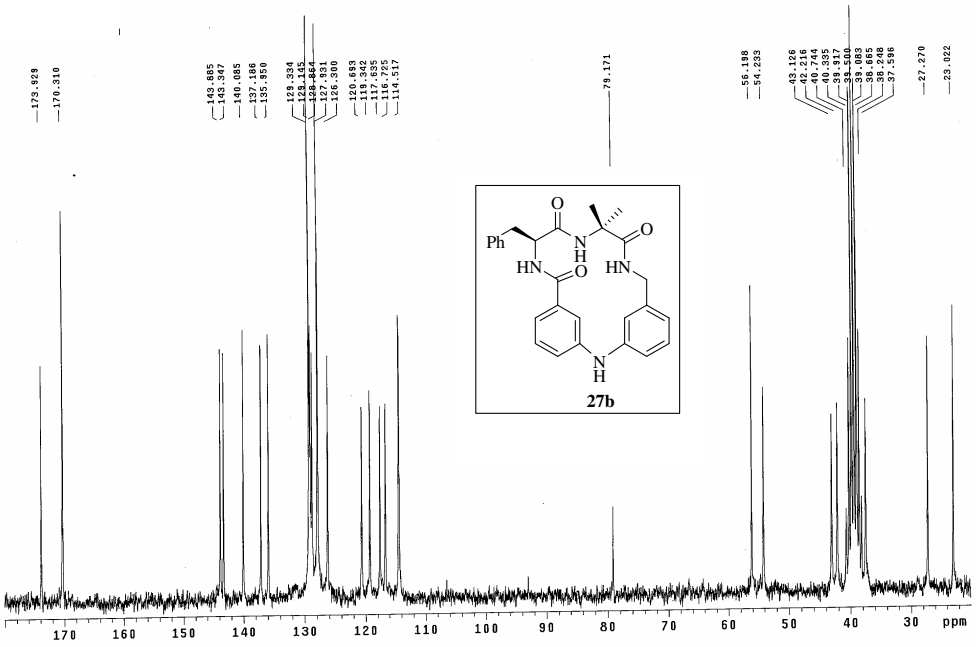
Spectrum No. 67 (Chapter 6, Section 6.4) ^{13}C NMR Spectrum (50MHz, DMSO-d$_6$)



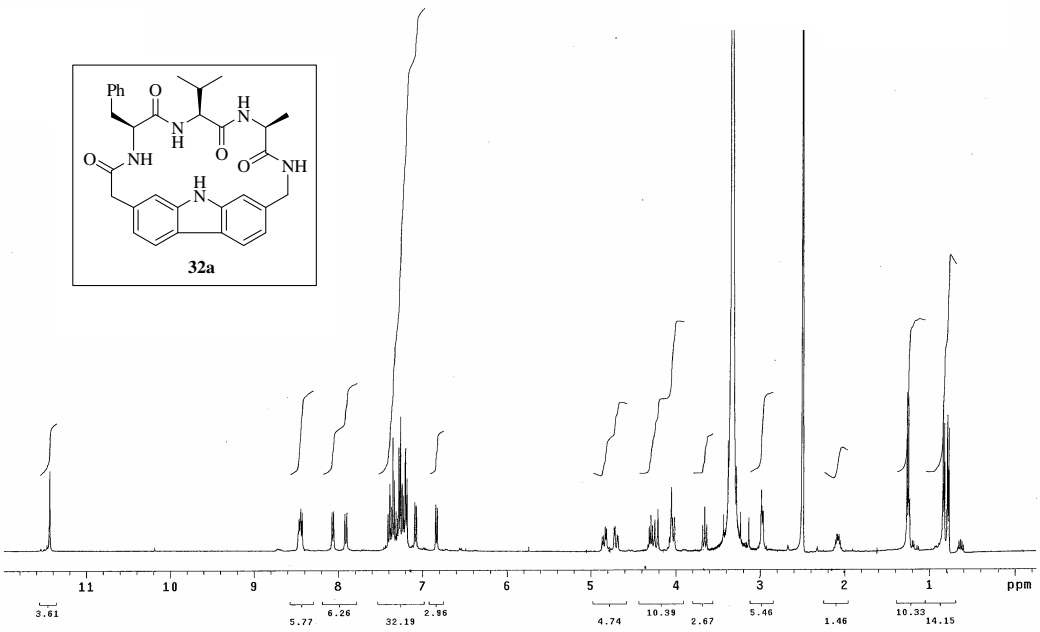
Spectrum No. 68 (Chapter 6, Section 6.4) ^{1}H NMR Spectrum (400MHz, DMSO-d$_6$)



Spectrum No. 69 (Chapter 6, Section 6.4) ^{13}C NMR Spectrum (50MHz, DMSO-d$_6$)



Spectrum No. 70 (Chapter 6, Section 6.4) ^{1}H NMR Spectrum (400MHz, DMSO-d$_6$)



Spectrum No. 71 (Chapter 6, Section 6.4) ^{1}H NMR Spectrum (400MHz, DMSO-d$_6$)