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SYNTHESIS OF DERIVATIZED OXOPIPERAZINES FROM AMINO ACIDS

Nazim Mohamed

A Thesis Submitted to the Faculty of Graduate Studies and Research
in Partial Fulfillment of the Requirements for the Degree of
Doctor of Philosophy

Department of Chemistry
McGill University
Montreal, Quebec, Canada
H3A 2K6

0-612-44518-6

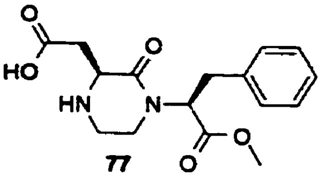
To my venerated parents for all eternity,
Rose and Hosein Mohamed.

For all my sisters and brothers,
Joy, Joan, Judy, Fareeda,
Ashaff, Buggie and Kazim.

"A work such as this is actually never complete.
One must declare it to be complete when one has done all that is
possible given the time and the circumstances."
Johann Wolfgang von Goethe, *Italian Journey* **1787**.

ABSTRACT

The efficient syntheses of substituted oxopiperazines from naturally occurring amino acids have been achieved. These may serve as conformationally constrained peptide mimics. In the first approach, N-prenylated amino acids were condensed with acid fluorides to give dipeptide analogues which upon ozonolysis, reductive work-up and hydrogenation gave cyclic dipeptides. A cyclized aspartame analogue **77** was prepared using this methodology.



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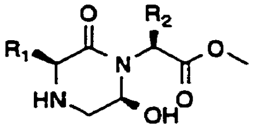
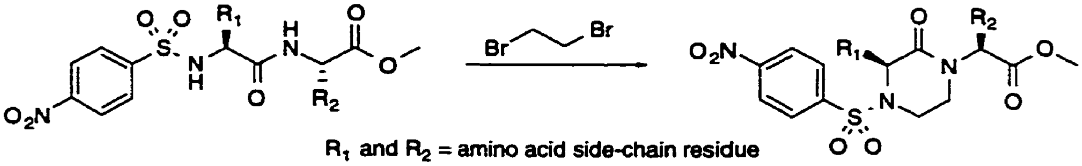
The second approach used a sequence opposite to the first approach and therefore provided oxopiperazines **92** and **93** substituted with a hydroxyl group at the C-6 position. This group may serve as a handle to further functionalize the oxopiperazine ring.



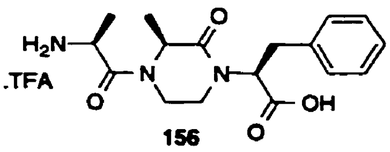
92 : $R_1 = CH_3$, $R_2 = CH_2Ph$
93 : $R_1 = CH_2Ph$, $R_2 = CH_3$

The third approach was based on the cyclization of sulfonamide dipeptides with dibromoethane as the 1,2-dielectrophile.



R_1 and R_2 = amino acid side-chain residue

Preliminary studies on solid phase have been carried out and this may open up the synthesis of a library of such constrained dipeptides. Cyclized tripeptide analogue **156** was prepared on a 2-chlorotrityl resin solid support.



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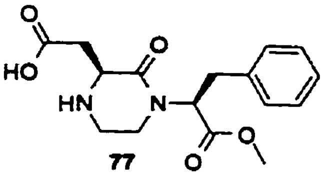
RÉSUMÉ

La synthèse efficace d'oxapipérazines substituées d'acides aminés naturels a été accomplie. Ces derniers pourraient servir comme modèles de peptides ayant des contraintes conformationelles. Dans un premier temps, les acides aminés N-prénylés ont été condensés avec des fluorures d'acides pour former leurs analogues dipeptidiques qui à la suite d'une ozonolyse, d'une réduction et d'une hydrogénation ont donné lieu à des dipeptides cycliques. Un analogue cyclique de l'aspartame **77** a été préparé selon cette méthodologie.



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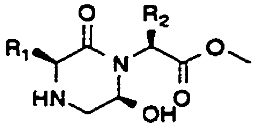
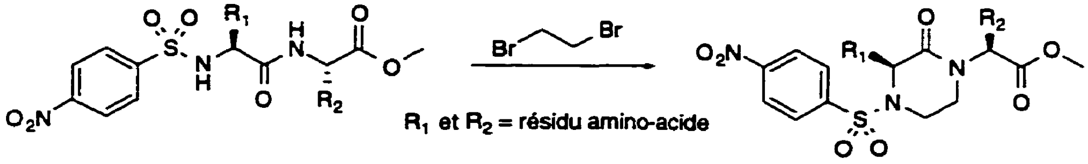
Dans un deuxième temps une approche opposée à la première nous a permis de synthétiser les oxapipérazines **92** et **93** ayant un groupement hydroxyle à la position C-6. Ce groupement pourrait servir a rajouter de nouveaux groupements fonctionnels sur le cycle de l'oxypipérazine.

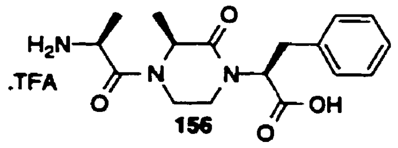


92 : $R_1 = CH_3$, $R_2 = CH_2Ph$
93 : $R_1 = CH_2Ph$, $R_2 = CH_3$

La troisième approche était fondée sur la cyclisation de sulfonamides dipeptidiques en utilisant le dibromoéthane comme 1,2-diélectrophile.



Des études préliminaires sur support solide ont été conduites et pourraient aboutir à l'élaboration d'une bibliothèque de dipeptides ayant des contraintes conformationnelles. Un tripeptide cyclique **156** a été préparé sur un support solide à base de résine de 2-chlorotrityle.



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ACKNOWLEDGEMENTS

First of all, I would like to express my deepest gratitude to have worked under the auspicious guidance of Professor George Just. His panache, succor and fecund discussions throughout my studies are greatly appreciated.

I am very grateful to McGill University, Department of Chemistry for funding in the form of teaching and research assistantships.

I would also like to thank:

Dr. Louis A. Cuccia, Dr. Jaffar A. Damavandi, Dr. Robert Hambalek, Dr. Irene Idziak, Dr. Philippe Klotz, Dr. Kristina Kutterer and all my co-workers past and present for their kind suggestions and helpful discussions.

Eric Marsault and Constantin Yannopoulos for their great friendship throughout my stay at McGill.

Dr. Ralf Schmidt, Dr. Brian Takasaki and Dr. Mirek Tomaszewski for their help on solid phase synthesis and also for the recording of all LC-MS experiments. Also, all the people at ASTRA who made my stay there pleasurable.

Dr. Françoise Sauriol for assistance and instruction in NMR experiments. Dr. Orval Mamer and Mr. Nadim Saadeh for the recording of mass spectra.

Ms. Renée Charron for her help with administrative matters.

Jean Liao for her fine work as a summer student.

Mr. Erwin Schultz for translation of the abstract.

GLOSSARY OF ABBREVIATIONS

ACE	angiotensin-converting enzyme
A-I	angiotensin I
A-II	angiotensin II
ACTH	adrenocorticotropic hormone
b.p.	boiling point
br	broad (in NMR)
Bn	benzyl group
BOC	*tert*-butyloxycarbonyl group
BOP reagent	benzotriazol-1-yloxy-tris(dimethylamino) phosphonium hexafluorophosphate
Cbz	carboxybenzyl group
CI	chemical ionization
^{13}C NMR	carbon NMR
CNS	central nervous system
COSY	correlated spectroscopy
δ	chemical shift
d	doublet (in NMR)
dd	doublet of doublets (in NMR)
ddd	doublet of doublet of doublets (in NMR)
DBU	1,8-diazobicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DCU	1,3-dicyclohexylurea
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DIC	1,3-diisopropylcarbodiimide
DIPEA	diisopropylethylamine
DMF	N,N-dimethylformamide
DMAP	4-dimethylaminopyridine

DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
DSS	3-(trimethylsilyl)-1-propanesulfonic acid, sodium salt
EDAC.HCl	1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide hydrochloride
EEDQ	3-ethoxy-1-ethyloxycarbonyl quinoline
EI	electron ionization
eq.	equivalent (usually per mol)
ES-MS (±)	Electron Spray-Mass Spectrometry in positive or negative mode
EtOAc	ethyl acetate
FAB	fast atom bombardment
Fmoc	9-fluorenylmethoxycarbonyl group
g	gram(s)
GH	growth hormone
GnRH	gonatropin releasing hormone
HATU	O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
HBTU	O-benzotriazol-1-yl-N,N,N',N'-tetramethyl-uronium hexafluorophosphate
HOBt	1-hydroxybenzotriazole hydrate
^{1}H NMR	proton NMR
hr(s).	hour(s)
Hz	hertz
HRMS	high resolution mass spectroscopy
IBCF	isobutyl chloroformate
IR	Infra Red spectrocopy
LC-MS	high pressure liquid chromatography-mass spectroscopy
$LiAlH_4$	lithium aluminum hydride
m	multiplet (in NMR)

m/e	mass to charge ration
min(s).	minute(s)
MKP	monoketopiperazine
ml	milliliter(s)
mmol	1×10^{-3} mol
m.p.	melting point
MS	mass spectroscopy
MTBD	1,3,4,6,7,8-hexahydro-1-methyl-2*H*-pyrimido[1,2-a]-pyrimidine
N	normality
NBA	nitrobenzyl alcohol
NEM	N-ethylmorpholine
NKA	neurokinin A
NKB	neurokinin B
NK-1	substance P receptor
NK-2	neurokinin A receptor
NK-3	neurokinin B receptor
NMM	N-methylmorpholine
NMR	nuclear magnetic resonance
Ph	phenyl group
ppm	parts per million
p.s.i.	pounds per square inch [14.7 p.s.i. = 1 atm]
PyBrOP	bromotris(pyrolidino)phosphonium hexafluorophosphate
q	quartet (in NMR)
RAS	renin-angiotensin system
R_f	retention factor
RP-HPLC	reverse phase-high performance liquid chromatography
R.T.	room temperature
s	singlet (in NMR)
SAR	structural-activity relationships

SP	substance P
SPPS	solid phase peptide synthesis
t	triplet (in NMR)
TEA	triethylamine
TBDMSCl	*tert*-butyldimethylsilylchloride
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMG	tetramethylguanidine
TRH	thyrotropin-releasing hormone

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CHAPTER 4: EXPERIMENTAL

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CHAPTER 1: INTRODUCTION AND LITERATURE SURVEY

1.1 Peptidomimetics: Perspective

A fascinating revelation in the field of peptidomimetics dates to a publication of Hughes *et al.* in 1975.[1] Their work demonstrated that the heterocyclic species morphine and the linear pentapeptide leucine enkephalin, elicit their biological response, analgesia, by binding to the opiate receptor despite their disparate structures. Over two decades later and much intensive efforts, this relationship still remains unclear.[2] An even more sobering thought is that the resolution of this question would not provide any generic solutions for traversing the elusive pathway of peptides to peptidomimetics. Molecular mimicry of peptides depends on two factors: firstly, the ensemble of pharmacophoric information present in the primary sequence and secondly, the three-dimensional presentation of this information. A successful peptidomimetic must meet these two criteria in order to retain significant bioactivity.

During the last 30 years, a multitude of biologically active peptides have been discovered and characterized.[3] Many of these have been found in both neuronal and in nonneuronal tissues. Representative examples include somatostatin, substance P, cholecystokinin, endorphin, enkephalin, angiotensin II and endothelin. After binding to their membrane-bound receptors, these neurotransmitters, neuromodulators, and hormones influence cell-cell communication and control a series of vital functions such as metabolism, immune defense, digestion, respiration, sensitivitiy to pain, reproduction, behaviour, and electrolyte levels. Thus, they are of enormous medical interest.

As a result of major advances in organic chemistry and in molecular biology,[4] most bioactive peptides have been prepared in larger quantities and made available for phamacological and clinical experiments. Thus, in the last few years new methods have

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[1] Hughes, J.; Smith, T.W.; Kostelitz, H. W.; Fothergill, L. A.; Morgan, B. A.; Morris, H. R., *Nature* **1975**, *258*, 577.

[2] Portoghese, P. S.; Sultana, M.; Nagase, H.; Takemori, A. E., *J. Med. Chem.* **1988**, *31*, 281.

[3] (a) Schmidt, G., *Top. Curr. Chem.* **1986**, *136*, 109. (b) Krieger, D. T., *Science* **1983**, *222*, 975. (c) Schwarz, J. H., *Principles of Neural Science* **1991**, p 213.

[4] Jung, G.; Beck-Sickinger, A. G., *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 367.

been established for the treatment and therapy of a series of diseases, and hopes have also been raised for the therapy of other illnesses in which peptides have been implicated.

Although many peptidic agents of therapeutic value are known,[5] a number of factors are responsible for the inability of peptides to serve directly as acceptable agents. For example, peptides can fall prey to the destructive action of peptidases, a characteristic that can severely limit the ability of peptides to elicit or sustain a desired physiological effect. Peptides can also exhibit poor bioavailability, poor solubility, rapid excretion through the kidneys and inappropriate physiological distribution since peptide receptors and/or isoreceptors are widely distributed in an organism.

From the pharmacological and medical viewpoint, it is frequently desirable to not only imitate the effect of the peptide at the receptor level (agonism) but also to block the receptor when required (antagonism). The same pharmocological considerations mentioned above hold for peptidal antagonists, but, in addition, their development in the absence of lead structures is more difficult. Even today it is not unequivocally clear which factors are decisive for the agonistic and antagonistic effects respectively.[6] In recent years intensive efforts have been made to develop peptidomimetics[7] that display more favourable pharmacological properties than their prototypes.

1.2 Design and Development Criteria for Peptide Mimetics

An important goal in contemporary peptide research is the modification of a peptide to a mimetic with specific physical, chemical and biological properties. In Figure 1[8], a general strategy is depicted featuring approaches to and stages in the rational design of peptidomimetics.

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[5] Hruby, V. J.; Kazmierski, W.; Kawasaki, A. M.; Matsunaga, T. O., In *Peptide Pharmaceuticals*, Ward, D. J., Ed., Elsevier, New York, **1991**, pp. 135-184.

[6] Hirschmann, R., *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 1278.

[7] (a) Veber, D. F.; Freidinger, R. M., *Trends Neurosci.* **1985**, 392. (b) DeGrado, W. F., *Adv. Protein Chem.* **1988**, *39*, 51. (c) Freidinger, R. M., *Trends Pharmacol. Sci* **1989**, 270; (d) Hruby, V. J., Al-Obeidi, F.; Kazmierski, W., *Biochem. J.* **1990**, *268*, 249.

[8] Adang, A. E. P.; Hermkens, P. H. H.; Linders, J. T. M.; Ottenheijm, H. C. J.; Van Stavern, C. J., *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 63.

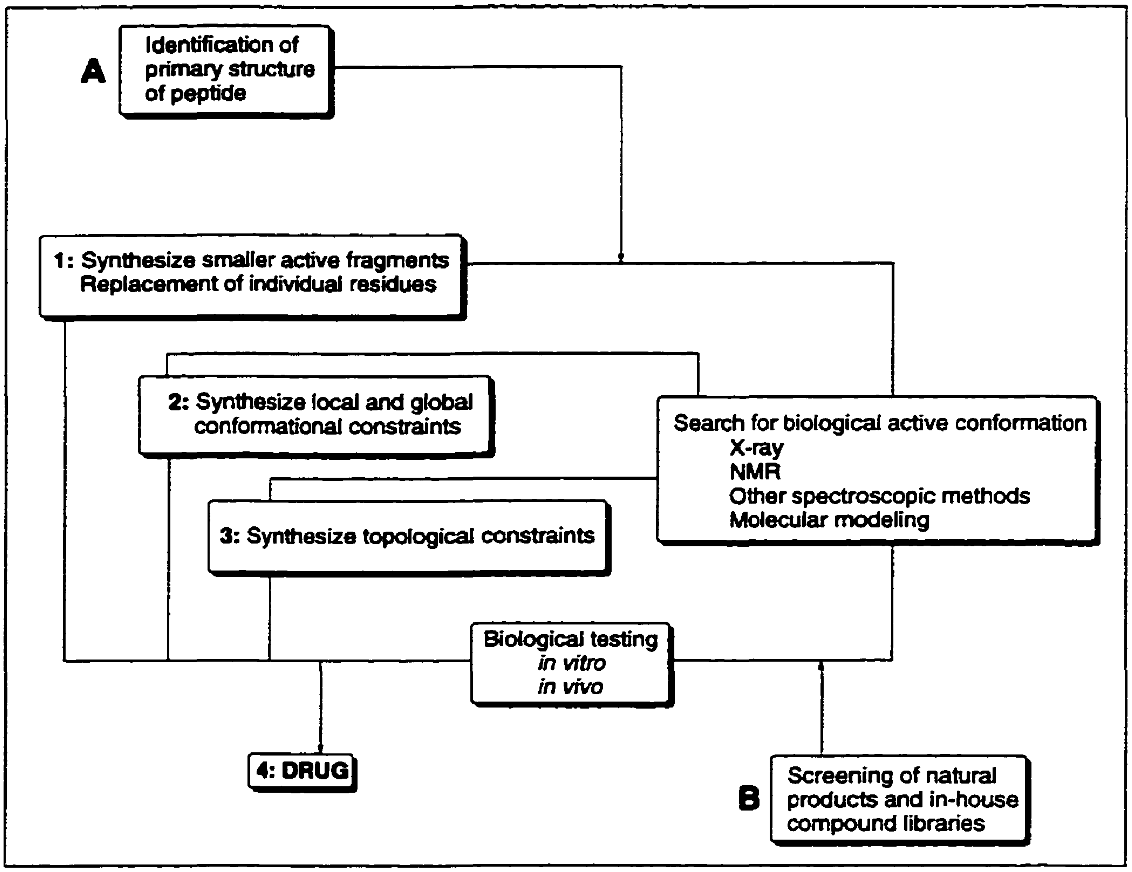

Figure 1: Design Cycle for Peptidomimetics.[8]

Peptidomimetics can be discovered and developed by rational design (entry A) or by an extensive screening process (entry B) as depicted in Figure 1. Whereas the screening of chemical libraries or natural products has met with success,[9] the rational strategy for the discovery of nonpeptide ligands remains elusive.

The rational design of nonpeptide compounds is not feasible without the information obtained from the study of the structure-activity relationships (SAR) and conformational properties of peptide structures. When such information is available and the indication is that the peptide backbone is not an essential feature in receptor binding, the design of a

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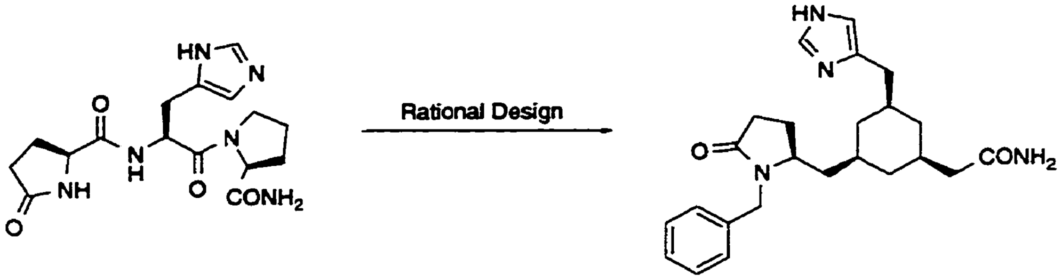
[9] (a) Goetz, M. A.; Lopez, M; Monaghan, R. L.; Chang, R. S. L.; Lotti, V. J.; Chen, T. B., *J. Antibiot.* **1985**, *38*, 177. (b) Evans, B. E.; Bock, M. G.; Rittle, K. E.; DiPardo, R. M.; Whittier, W. L.; Veber, D. F.; Anderson, P. S.; Freidinger, R., *Proc. Natl. Acad. Sci. USA* **1986**, *83*, 4919.

nonpeptide becomes feasible. The transition to a mimetic can then be made rational by adopting some general principles obtained from the pioneer work of Farmer.[10]



I

II

Figure 2: From tripeptide to peptidomimetic.

An illustrative example has been described by Olson *et al.*[11] (Figure 2). They coupled the amino acid side chains of the tripeptide, thyrotropin-releasing hormone (TRH, pGlu-His-Pro-NH_2, **I**) to a cyclohexane ring and obtained compound **II**, which showed affinity for the low affinity TRH receptor sites in the central nervous system (CNS), and exhibited oral activity against a cognitive dysfunction.

The generation of peptidomimetics is based primarily on the knowledge of the conformational, topochemical and electronic properties of the native peptide and that of its target, in other words, the receptor or the active site of the enzyme with which it interacts. The design of peptidomimetics as potential bioactive substances must take account of the following factors:

(a) Replacement as much of the peptide backbone as possible by a nonpeptide framework. If bond surrogates have been shown to retain activity, or peptide bonds are not exposed in the presumed bioactive conformation, then a structural template may be designed to eliminate the amide bond.

(b) Maintain peptide side chain pharmacophoric groups as in the peptide. Rather than completely dispensing with a relationship between peptide and nonpeptide, initially

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[10] Farmer, P. S. Bridging the Gap between Bioactive Peptides and Nonpeptides: Some perspectives in Design. In *Drug Design*, Ariëns, E. J.; Ed.; Academic Press: New York, **1980**; *Vol. X*, pp. 119-143.

[11] Olson, G. L.; Bolin, D. R.; Bonner, M. P.; Bös, M.; Cook, C. M.; Fry, D. C.; Graves, B. J.; Hatada, M.; Hill, D. E.; Michael, K.; Madison, V. S.; Rusiecki, V. K.; Sarabu, R.; Sepinwall, J.; Vincent, G. P., Voss, M. E., *J. Med. Chem.* **1993**, *36*, 3039-3049.

designed mimetics may retain groups as found on the peptide, as these are most likely to be recognized by a receptor.

(c) Retain some conformational flexibility in first-generation mimetics. The probability that a pharmacophore hypothesis will be definitive for rigid peptide side chains is low, making it necessary that the first designs leave some of the side chain pharmacophoric groups unconstrained so that they may adopt conformations analogous to those of the peptide.

(d) Selection of appropriate targets based on availability of a pharmacophore hypothesis. For systems where the biological rationale or medical need is sufficient to justify a peptide mimetic approach, efforts to provide a pharmacophore hypothesis as a lead step is justified and critical to the outcome of the peptide mimetics programs. By following the above requirements, nonpeptide leads might have the following pharmacological properties such as metabolic stability, good bioavailability, high receptor affinity and receptor selectivity, and minimal side effects.

A major problem in the development of mimetics is the discovery of a lead structure that can then be optimized, for example by the use of molecular modeling programs. Information concerning the three-dimensional structure of the peptide-receptor complex, the subsequent signal transduction, and the coordination and interaction with other signal transduction systems and integration in the organism, as well as knowledge of the biosynthesis, transport, release, and inactivation of the peptide are extremely helpful in the discovery of mimetics.

The native peptide itself, the pharmacological properties of which should be optimized, generally serves as lead structure for the development of peptidomimetics. With few exceptions peptides of small to medium size (< 30-50 amino acid units) exist unordered in dilute aqueous solution in a multitude of conformations in dynamic equilibrium (see Figure 3).[12] In solution and in the absence of the receptor, the biologically active conformation can be poorly populated and is frequently quite different from the conformation obtained by, for example X-ray structure analysis in the solid state.[13]

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[12] Giannis, A.; Kolter, T., *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1244.

[13] Kessler, H., *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 512.

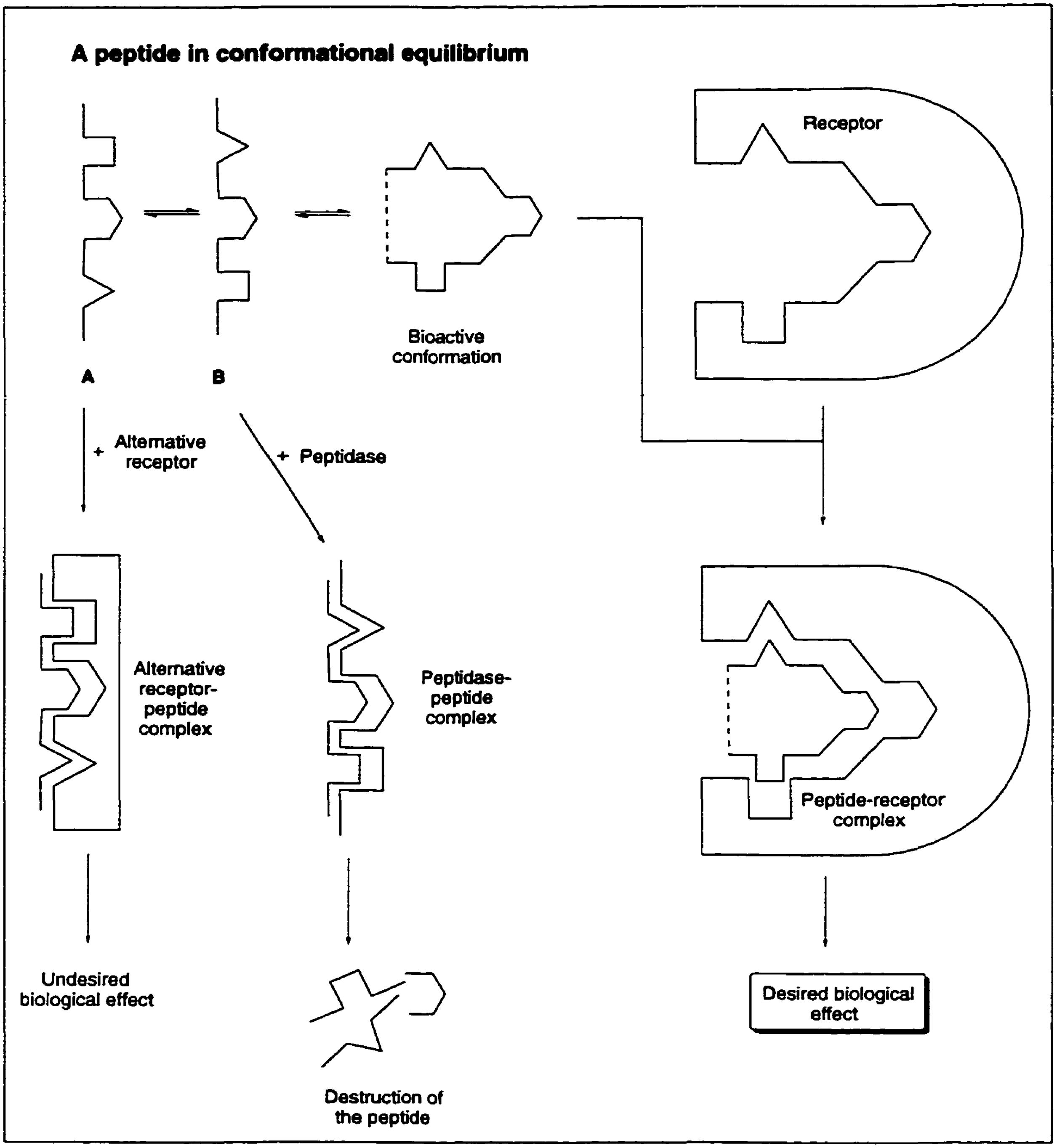
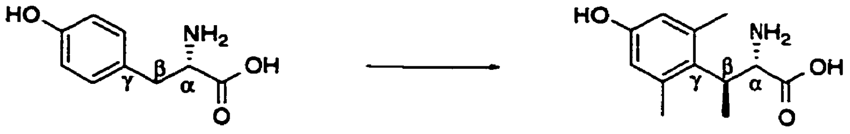


Figure 3: In solution peptides exist in a variety of conformations that are in dynamic equilibrium with each other. If a conformational restriction (broken line) is introduced to the bioactive conformation of the peptide, forms A and B cannot arise. Thus, the interaction with alternative receptors and peptidases is suppressed or does not occur. In this fashion a desired biological effect can be obtained.[12]

The complex problems associated with the rational design of mimetics are being constantly reduced, due to the advances in molecular biology, spectroscopy and computational chemistry. Conformational constraints constitute one of the most promising avenues for a solution to this problem, particularly if the constraints is such that only one conformation of the ligand is significantly populated. Rigid analogs pay a lower entropy cost upon binding to their receptor and therefore should bind more avidly assuming apposite placement of pharmacophoric residues.[14] Proteolytic enzymes generally prefer conformationally adaptable substrates, therefore constrained analogs are generally endowed with increased proteolytic stability. Additionally, selectivity can be enhanced by the exclusion of conformers that produce undesired bioacivity.[15]

1.3 Structural Possibilities for Peptidomimetics

From a structural point of view, peptidomimetics can be prepared by approaches ranging from the slight modification of the initial structure to the generation of a pure nonpeptide. There are several possibilities, and although the list is not exhaustive, I shall try to list the most important ones. Firstly, there is the modification of the side chains of amino acid residues. A strategy adopted is the replacement of natural by unnatural side chains and the exchange of L- for D-amino acids. An interesting example is compound **III**. The modification of the tyrosine side chain by introducing methyl groups in the 2′-, 6′- and β-positions hinders free rotation about the C^{β}-C^{γ} bond and can thus favour the formation of this bioactive conformation.[16]



L-Tyrosine

III

Figure 4: Modification of L-tyrosine.

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[14] Miklavc, A.; Kocjan, D.; Avbelj, F.; Hadzi, D., *QSAR in Drug Design and Toxicology* ed. by Hadzi, D.; Jerman-Blazic, B., **1987**, 185, Amsterdam.

[15] Veber, D. F.; Holly, F. W.; Paleveda, W. J.; Nutt, R. F.; Bergstrand, S. J.; Torchiana, M.; Glitzer, M. S.; Saperstein, R., *Nature* **1979**, *280*, 512.

[16] Jiao, D.; Russell, K. C.; Hruby, V. J., *Tetrahedron* **1993**, *49*, 3511.

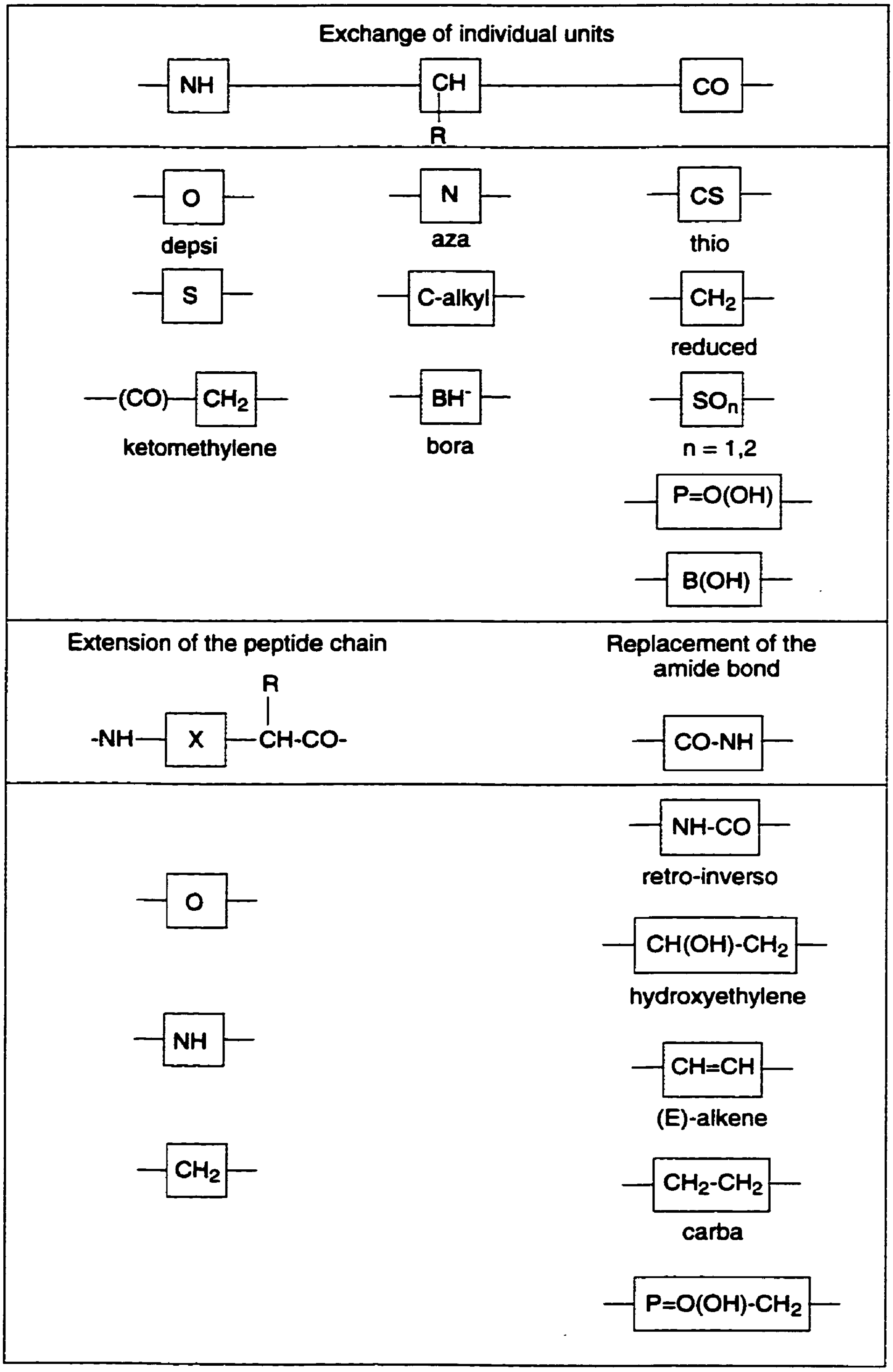

Figure 5: General modifications to the peptide backbone.[18]

Secondly, there is the modification of the peptide backbone. This refers to the general isosteric or isoelectronic exchange of units in the peptide chain and the introduction of additional fragments.[17] General modifications are shown in Figure 5.[18] Thirdly, there is global restrictions of conformation. The conformation of a peptide can be stabilized or fixed by the introduction of bridges of various lengths between different parts of the molecule, thus making the molecule more rigid. The bridging can either occur within a single amino acid residue as in **IV**.[19] The bridge can be linked between two side chains as in **V**,[20] between two backbone units **VI**,[21] or between a side chain and backbone unit **VII**.[22] Additionally, the peptide bond can be completely incorporated into the ring **VIII**.[23]

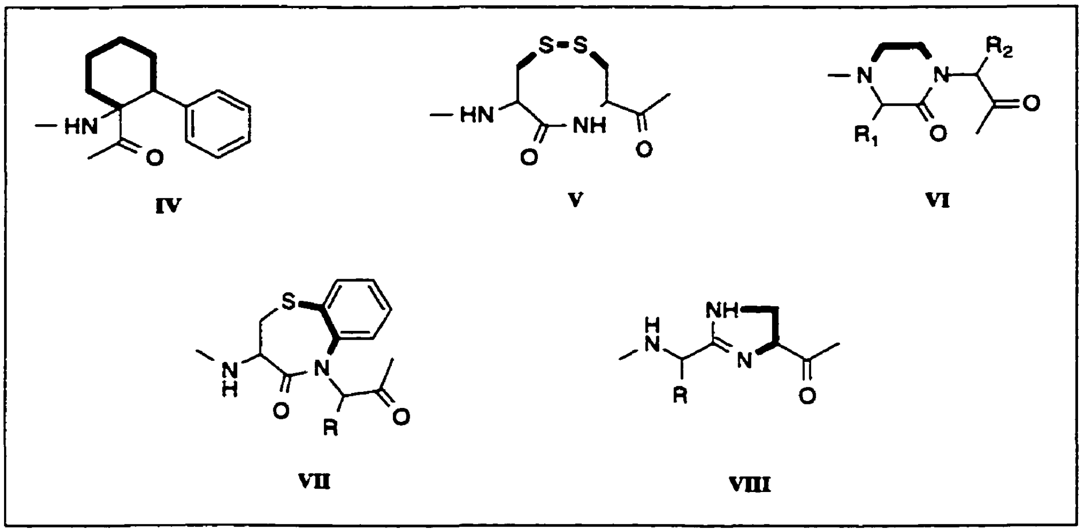

Figure 6: Bridging in peptidomimetics.

Another structural possibility is the imitation of secondary structures. The design of peptidomimetics has been guided by the simple elegance which nature has utilized in the molecular architecture of proteinaceous species. Three basic building blocks, α-helices, β-sheets and reverse turns are utilized for the construction of all proteins. Apparently, the most important is the β-turn which is formed from four amino acids and is stabilized by a

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[17] Spatola, A. F. in *Methods in Neuroscience, Vol 13*. Ed. Conn, P. M., Academic Press, San Diego, **1993**, 19.
[18] Gante, J., *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1699.
[19] Cativiela, C. C.; Diaz de Villegas, M. D.; Avenoza, A.; Peregrina, J. M., *Tetrahedron* **1993**, *49*, 10987.
[20] Suumaran, D. K.; Prorok, M.; Lawrence, D. S., *J. Am. Chem. Soc.* **1991**, *113*, 706.
[21] DiMaio, J.; Belleau, B., *J. Chem. Soc. Perkin Trans. 1* **1989**, 1687.
[22] Gante, J.; Weitzel, R., *Tetrahedron Lett.* **1988**, *29*, 181.
[23] Jones, R. C. F.; Ward, G. F., *Tetrahedron Lett.* **1988**, *29*, 3853.

hydrogen bond between the carbonyl group of the first amino acid and the NH group of the fourth as depicted in Figure 7.

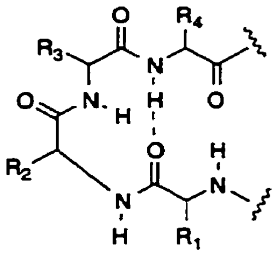
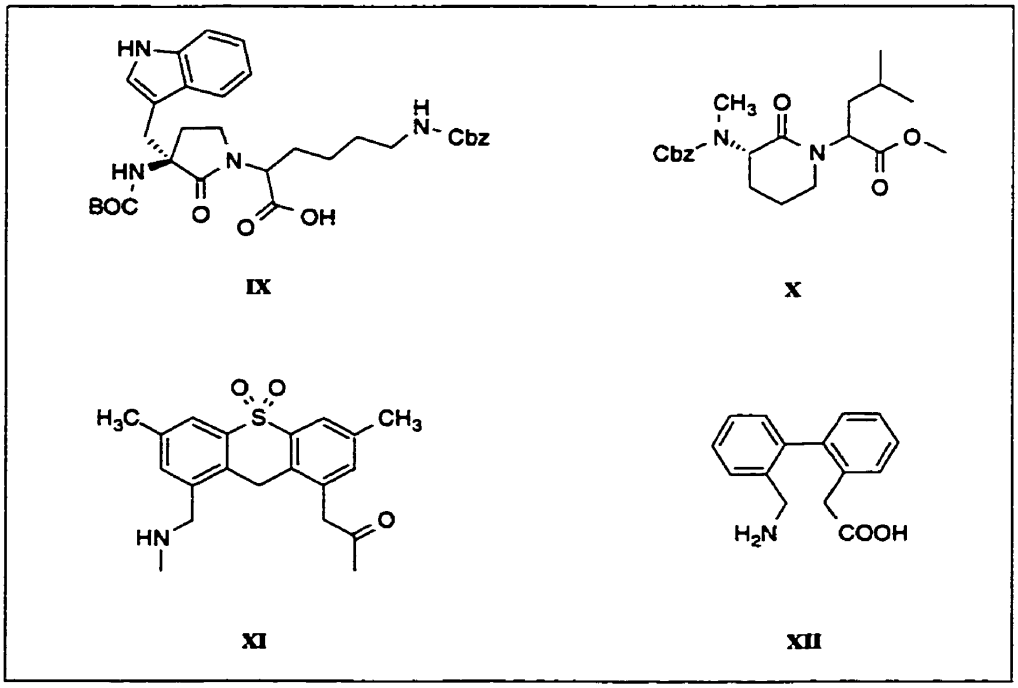


Figure 7: Structure of a typical β-turn.

Some representative examples (Figure 8) demonstrate that the structural motifs range from still recognizable peptide chains (**IX**[24] and **X**[25]) to completely non-peptidic components (**XI**[26] and **XII**[27]).



IX

X

XI

XII

Figure 8: Representative β-turn mimetics.

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[24] Freidinger, R. M., *J. Org. Chem.* **1985**, *50*, 3631.

[25] Aebi, J. D.; Guillaume, D.; Dunlap, B. E.; Rich, D. H., *J. Med. Chem.* **1988**, *31*, 1805.

[26] (a) Feigel, M., *J. Am. Chem. Soc.* **1986**, *108*, 181. (b) Wagner, G.; Feigel, M., *Tetrahedron* **1993**, *49*, 10831. (c) Brandmeier, V.; Sauer, W. H. B.; Feigel, M., *Helv. Chim. Acta* **1994**, *77*, 70.

[27] Brandmeier, V.; Feigel, M., *Tetrahedron* **1989**, *45*, 1365.

1.4 Examples of Peptidomimetics

1.4.1 Tachykinins (Substance P, Neurokinins A and B)

Tachykinins (Figure 9) are peptides with a length of ten or eleven amino acids that act as neurotransmitters or neuromodulators in various parts of the central and peripheral nervous systems.[28] These peptides possess a common C-terminal sequence (Phe-X-Gly-Leu-Met-NH_2, X = Phe, Tyr, Ile, Val) and they have a wide spectrum of similar biological properties[29] which include lowering of blood pressure, initiation of the immune response, transmission of pain and stress to the central nervous system (CNS) and prevention of neurotoxicity of the β-amyloid peptide. The best known and most investigated tachykinin, substance P (SP), was discovered by von Euler and Gaddum in 1931.[30] SP has been shown to be widely distributed in the body. Its presence in the CNS, gastrointestinal tract, blood and blood vessels has been well documented.[31]

Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH_2	Substance P (SP)
His-Lys-Thr-Asp-Ser-Phe-Val-Gly-Leu-Met-NH_2	Neurokinin A (NKA)
Asp-Met-His-Asp-Phe-Phe-Val-Gly-Leu-Met-NH_2	Neurokinin B (NKB)

Figure 9: Structures of some members of the tachykinin family.

There is a general agreement that the multitude of bioactivities induced is mediated through three tachykinin receptor subtypes designed NK-1, NK-2 and NK-3 for which SP, neurokinin A (NKA) and neurokinin B (NKB) are the endogeneous ligands respectively.[32] The characterization of the receptors, the understanding of the pathophysiological roles of tachykinins and the possible relevance of selective compounds to therapeutic indications would be greatly aided by the availability of potent and selective agonists and antagonists. Potential therapeutic indications for tachykinins include[29] rheumatoid arthritis, ulcerative colitis, migraine, schizophrenia, Crohn and Alzheimers diseases to name a selected few.

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[28] (a) Logan, M. E.; Goswami, R.; Tomezuk, B. E.; Venepalli, B. R., *Annu. Rep. Med. Chem.* **1991**, *26*, 43. (b) Maggio, J. E., *Annu. Rev. Neurosci.* **1988**, *11*, 13.

[29] (a) Nicoll, R. A.; Schenker, C.; Leeman, S. E., *Annu. Rev. Neurosci.* **1980**, *3*, 227. (b) Erspamer, V., *Trends Neurosci*, **1981**, *4*, 267. (c) Lowe, J. A.; Snider, R. M., *Ann. Rep. Med. Chem.* **1993**, *28*, 99 and references cited therein.

[30] Von Euler, U. S.; Gaddum, J. H., *J. Physiol.* **1931**, *72*, 74.

[31] (a) Dutta, A. S., *Drugs Fut.* **1987**, *12*, 781. (b) Pernow, B., *Pharmacol. Rev.* **1983**, *24*, 1.

Thus tachykinin analogues are potentially important drugs, if they are potent, highly selective, metabolically stable and bioavailable.

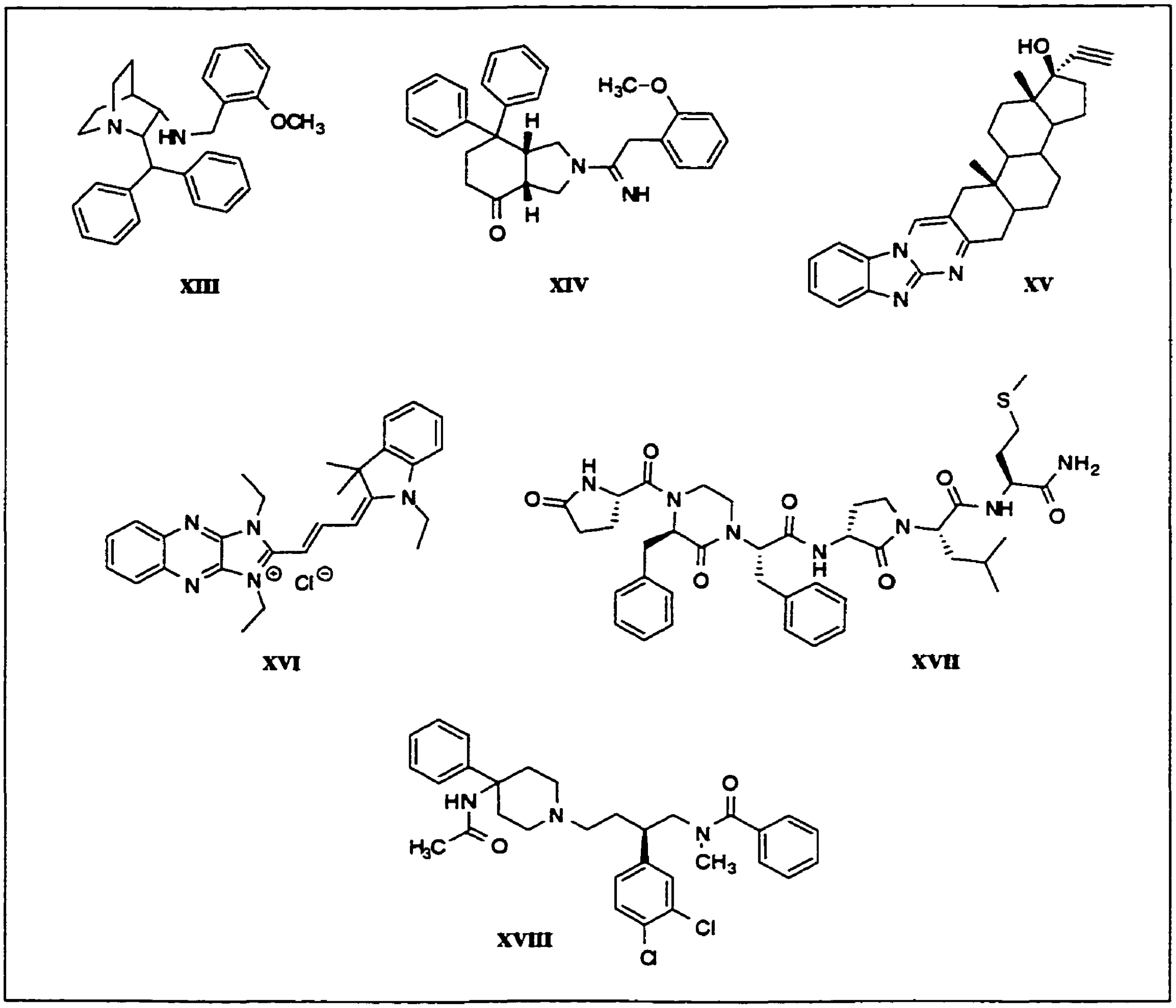

Figure 10: Some tachykinin antagonists.

During the development of antagonists, it became apparent that the residues 7-11 of SP contain the minimal sequence required for biological activity. Exchange of Phe-7 or Gly-9 residue by D-Tyr or other aromatic D-amino acids lead to an antagonistic effect of the resulting peptides.[28a] The first potent, competitive nonpeptide antagonist for the NK-1

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[32] (a) Buck, S. H.; Burcher, E., *Trends Pharmacol. Sci.* **1986**, *7*, 65. (b) Watson, S. P., *Life Sci.* **1984**, *35*, 797.

receptor was CP-96345 (**XIII**)[33] which emerged from a screening process. Of the four possible stereoisomers of **XIII**, only the (2S, 3S) isomer was active. It showed no agonistic activity and had an affinity for the NK-1 receptor comparable to that of its endogeneous ligand, SP. Other potent nonpeptide antagonists for the NK-1 receptor are RP 67580 (**XIV**)[34] and the steroid derivative **XV**.[35] Compound **XVI**[36] is also a nonpeptide NK-1 antagonist, although it is not suitable for further tests because of its lower affinity and high toxicity. More recent examples of NK-2 selective antagonists based on peptides include **XVII**[37] and SR 48968 (**XVIII**).[38]

1.4.2 Angiotensin II (A-II)

The treatment of hypertension by modulation of the renin-angiotensin system (RAS) has focused mainly on the regulation of the concentration of angiotensin II (A-II), which is a potent vasoconstrictor. A-II is the product of the cleavage of angiotensin I (A-I) by the angiotensin-converting enzyme (ACE). A-I itself is produced by the renin-mediated cleavage of angiotensinogen.[39] Inhibition of either ACE or renin will block the formation of A-II and thus lead to lowering of the blood pressure. In addition to its action on blood pressure, A-II transmits numerous other effects,[40] for example release of catecholamines from the adrenal medulla and stimulation of glycogenolysis in the liver. In the kidney, it stimulates the synthesis of prostaglandins and the resorption of sodium ions and inhibits the release of renin and thereby its own biosynthesis. Angiotensin effects

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[33] (a) Snider, R. M.; Constantine, J. W.; Lowe, J. A.; Longo, K. P.; Lebel, W. S.; Woody, H. A.; Drozda, S. E., Desai, M. C.; Vinick, F. J.; Spencer, R. W.; Hess, H.-J., *Science* **1991**, *251*, 435. (b) McLean, S.; Ganong, A. H.; Seeger, T. F.; Bryce, D. K.; Pratt, K. G.; Reynolds, L. S.; Siok, C. J.; Lowe, J. A.; Heym, J., *ibid* **1991**, *251*, 437.

[34] (a) Garret, C.; Carruette, A.; Fardin, V.; Moussaoui, S.; Peyronel, J.-F.; Blanchard, J.-C.; Laduron, P. M., *Proc. Natl. Acad. Sci. USA* **1991**, *88*, 10208. (b) Peyronel, J.-F.; Truchon, A.; Mountonnier, C.; Garret, C., *Bioorg. Med. Chem. Lett.* **1992**, *2*, 37.

[35] (a) Venepalli, B. R.; Aimone, L. D.; Appel, K. C.; Bell, M. R.; Dority, J. A.; Goswami, R.; Hall, P. L.; Kumar, V.; Lawrence, K. B.; Logan, M. E.; Scensny, P. M.; Seelye, J. A.; Tomczuk, B. E., Yanni, J. M., *J. Med. Chem.* **1992**, *35*, 374.

[36] Appel, K. C.; Babb, B. E.; Goswami, R.; Hall, P. L.; Lawrence, K. B.; Logan, M. E.; Przyklek-Elling, R.; Tomczuk, B. E., Venepalli, B. R.; Yanni, J. M., *J. Med. Chem.* **1991**, *34*, 1751.

[37] Dourish, C. T.; Clark, M. L.; Hawley, D.; Williams, B. J.; Iversen, S. D., *Regul. Pept.* **1988**, *22*, 58.

[38] Advenier, C.; Rouissi, N.; Nguyen, Q. T.; Emonds-Alt, X.; Breliere, J.-C.; Neliat, G.; Naline, E.; Regoli, D., *Biochem. Biophys. Res. Commun.* **1992**, *184*, 1418.

[39] Garrison, J. C.; Peach, M. J., In *The Pharmacological Basis of Therapeutics, Chapter 31*, Gilman, G. A.; Rall, T. W.; Nies, A. S.; Taylor, P., Eds., 8th ed., Pergamon Press, New York, **1990**, p. 749.

[40] Greenlee, W. J.; Siegel, P. K. S., *Annu. Rep. Med. Chem.* **1991**, *26*, 63.

contraction of the uterus and stimulates ovulation. In the brain, it stimulates the secretion of vasopressin and adrenocorticotropic hormone (ACTH) by the pituitary gland and also functions as a neuromodulator.

In principle there are numerous possibilities for the pharmacological influence of the renin-angiotensin system, for example by the application of renin inhibitors, ACE inhibitors or of antagonists of the A-II receptor. ACE inhibitors have been proven to be useful in the treatment of hypertension. While A-II agonists are of interest for biochemical and pharmacological investigations, the A-II antagonists are of high therapeutic potential. Some miscellaneous low molecular weight ACE inhibitors are shown in Figure 11.

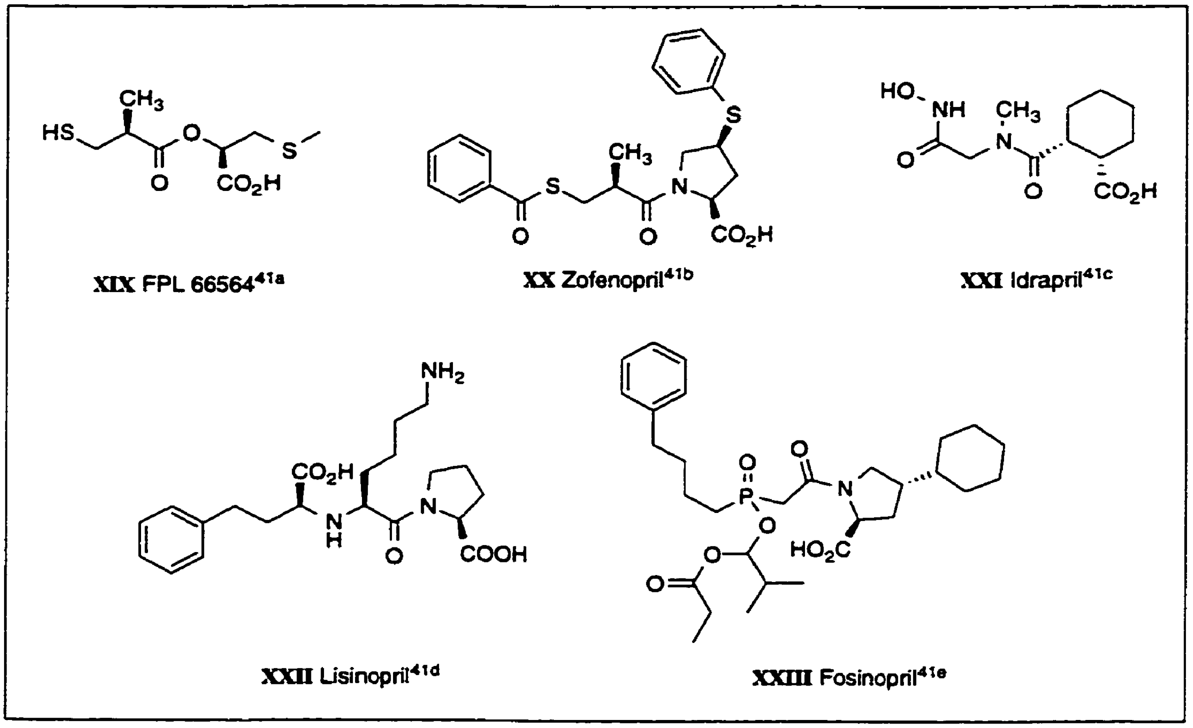

Figure 11: ACE inhibitors.[41]

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[41] (a) Baxter, A. J. G.; Carr, R. D., *Drugs Fut.* **1993**, *18*, 12. (b) Krapcho, J.; Turk, C.; Cushman, D. W.; Powell, J. R.; DeForrest, J. M.; Spitzmiller, E. R.; Karanewsky, D. S.; Duggan, M.; Rounyak, G.; Schwartz, J.; Natarajan, S.; Godfrey, J. D.; Ryono, D. E.; Neubeck, R.; Atwal. K. S.; Petrillo, Jr., E. W., *J. Med. Chem.* **1988**, *31*, 1148. (c) Turbanti, L.; Cerbai, G,.; DiBugno, C.; Giorgi, R.; Garzelli, G.; Criscuoli, M.; Renzetti, A. R.; Subissi, A.; Bramanti, G.; De-Priest, S. A., *J. Med. Chem.* **1993**, *36*, 699. (d) Patchett, A. A.; Harris, E.; Tristram, E. W.; Wyvratt, M. J.; Wu, M. T.; Taub, D.; Peterson, E. R.; Ikeler, T. J.; Ten Broeke, J.; Payne, L. G.; Ondeyka, D. L.; Thorsett, E. D.; Greenlee, W. J., Lohr, N. S.; Hoffsommer, R. D.; Joshua, H.; Ruyle, W. V.; Rothrock, J. W.; Aster, S. D.; Maycock, A. L.; Robinson, F. M.; Hirschmann, R.; Sweet, C. A.; Ulm, E. H.; Gross, D. M.; Vassil, T. C.; Stone, C. A., *Nature* **1980**, *288*, 280. (e) Karanewsky, D. S.; Badia, M. C.; Cushman, D. W.; DeForrest, J. M.; Dejneka, T.; Loots, M. J.; Perri, M. G.; Petrillo, Jr., E. W., Powell, J. R., *J. Med. Chem.* **1988**, *31*, 204.

1.4.3 Miscellaneous mimetics

A series of long-known agents has been shown recently to be mimetics of endogenous peptide ligands. In addition to the examples discussed above, the following are some interesting examples. Somatostatin,[42] a cyclic tetradecapeptide, is formed in the hypothalamus and inhibits the release of the growth hormone (GH) by the pituitary gland. In other parts of the brain, somatostatin acts as a neurotransmitter and as a neuromodulator. Outside the nervous system it has been found in the secretory cells of the intestine and pancreas and in the salivary glands. Its serves in these organs as an autocrine and pancreatic regulator. Somatostatin formed in certain cells in the pancreas, inhibits the release of insulin and glucagon. It can also inhibit motility in the digestive tract and also reduces the secretion of gastric acid and gastrin. The reduction in secretion of pancreatic enzymes and the absorption of carbohydrates, triglycerides and water are other adverse effects. Numerous peptide-based somatostatin agonists have been synthesized and pharmacologically tested, especially by Veber and co-workers.[43] Compound **XXIV**[44] was described as the first nonpeptide somatostatin mimetic.

Gonadotropin-Releasing Hormone (GnRH)[45] is synthesized in the hypothalamus and then secreted. In the anterior lobes of the pituitary gland it acts to release gonadotropins. They stimulate maturation of follicles and estrogen biosynthesis in females and the generation of spermatozoa in males. In females, gonadotropins cause ovulation and formation of corpus luteum and estrogen and in males, the release of testosterone and the biosynthesis of androgens is triggered. Suppression of the release of the gonadotropins is possible by the direct application of GnRH antagonists and thus can be used in the treatment[46] of fertility disorders, endometriosis, polycystic ovarium disease and prostate

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[42] (a) Rens-Domiano, S.; Reisine, T., *J. Neurochem.* **1992**, *58*, 1887. (b) Reichlin, S., *N. Engl. J. Med.* **1983**, *309*, 1495.

[43] Veber, D. F., In *Peptides Chemistry and Biology, Proceedings of the 12th American Peptide Symposium*, Escom, **1992**, p. 3 and references cited therein.

[44] Veber, D. F.; Freidinger, R. M.; Perlow, D. S.; Paleveda Jr., W. J.; Holly, F. W.; Strachan, Nutt, R. F.; Arrison, B. H.; Homnick, C.; Randall, W. C.; Glitzer, M. S.; Saperstein, R.; Hirschmann, R., *Nature* **1981**, *292*, 55.

[45] Conn, P. M.; Crowley Jr., W. F., *N. Engl. J. Med.* **1991**, *324*, 93.

[46] Nestor Jr., J. J.; Vickery, B. H., *Annu. Rep. Med. Chem.* **1988**, *23*, 211.

carcinomas. The antimycotic drug ketoconazole **XXV**,[47] was observed to be a weakly competitive antagonist of the GnRH receptor.

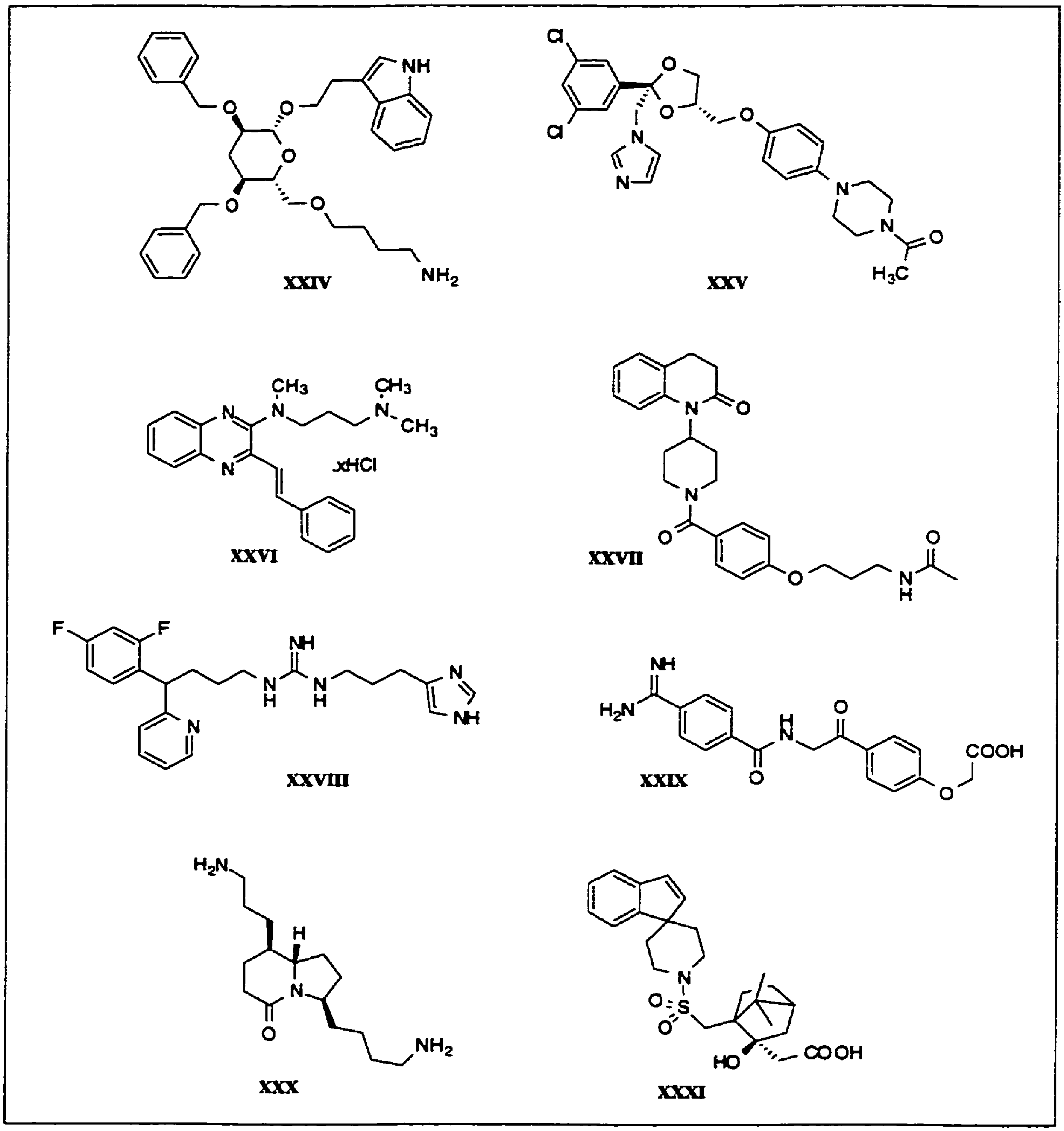

Figure 12: Miscellaneous peptidomimetics.

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[47] Biswanath, D.; Plattner, J. J.; Bush, E. N.; Jae, H.-S.; Diaz, G.; Johnson, E. S.; Perun, T. J., *J Med. Chem.* **1989**, *32*, 2038.

Other nonpeptide ligands for peptide receptors include the glucagon receptor antagonist CP-99711 (**XXVI**),[48] the vasopressin V1 receptor antagonist OPC-21268 (**XXVII**),[49] the neuropeptide Y antagonist He-90481 (**XXVIII**),[50] and the glycoprotein IIb-IIIa antagonist **XXIX**.[51] Also the antagonist **XXX**[52] of the immune-stimulating tetrapeptide tuftsin and the first nonpeptide oxytocin antagonist **XXXI**.[53]

1.5 Project Rationale

The determination of the bioactive conformation of peptides, potentially highly flexible molecules, has often been a key step leading to the synthesis of peptide analogues with greater and more specific biological activity. The determination of peptide bioactive conformations can be achieved by several methods. In addition to classical X-ray crystallography analysis, a plethora of sophisticated spectroscopic and computational methods[54] have been explored. Many building blocks capable of specifically stabilizing some part of the peptide side chains or backbone have been designed.[55] 2-Oxopiperazines **XXXIII** is a fine example of these building blocks in which the N_i and N_{i+1} atoms of the peptide backbone are linked by an ethylene bridge and thus restricting the tortional angles ω_i, ϕ_i and ψ_i as compared to the parent compound **XXXII** (Figure 13).

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[48] Collins, J. L.; Collins, P. J.; Goldstein, S. W.; Faraci, W. S., *Bioorg. Med. Chem. Lett.* **1992**, *2*, 915.
[49] Yamamura, Y.; Ogawa, H.; Chihara, T.; Kondo, K.; Onogawa, T.; Nakamura, S.; Mori, T.; Tominaga, M.; Yabuuchi, Y., *Science* **1991**, *252*, 572.
[50] Motulsky, H. J.; Michel, M. C., International Society of Hypertension, Montreal, Abstract P5.15, **1990**, cited in Doherty, A. M., *Annu. Rep. Med. Chem.* **1991**, *26*, 88.
[51] Alig, L.; Edenhofer, A.; Müller, M.; Trzeciak, A.; Weller, T., US-A 5039805.
[52] Kahn, M.; Devens, B., *Tetrahedron Lett.* **1986**, *27*, 4841.
[53] Evans, b. E.; Leighton, J. L.; Rittle, K. E.; Gilbert, K. F.; Lundell, G. F.; Gould, N. P.; Hobbs, D. W.; DoPardo, R. M.; Veber, D. F.; Pettibone, D. J.; Clineschmidt, B. V.; Anderson, P. S.; Freidinger, R. M., *J Med. Chem.* **1992**, *35*, 3919.
[54] (a) Hruby, V.; Al-Obedi, F.; Kazmierski, W., *Biochem. J.* **1990**, *268*, 249. (b) Fesik, S. W., *J Med. Chem.* **1991**, *34*, 2937. (c) Marshall, G. R., *Tetrahedron* **1993**, *49*, 3547.
[55] (a) Toniolo, C., *Int. J. Peptide Protein Res.* **1990**, *35*, 287. (b) Liskamp, R. M. J., *Recl. Trav. Chim. Pays-Bas* **1994**, *113*, 1.

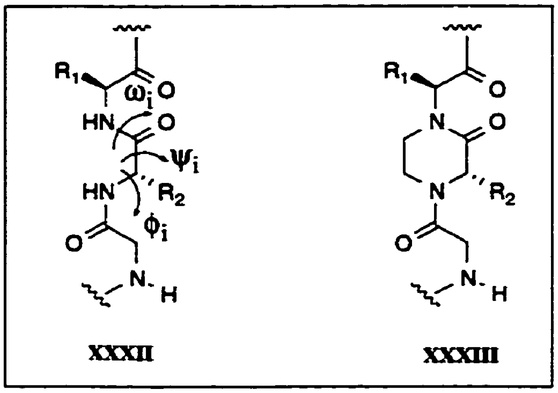

Figure 13: Torsion angles frozen in 2-oxopiperazines.

Although enkephalin analogues containing 3-substituted 2-oxopiperazine skeleton clearly displaying interesting biological activities,[56] very few methods have been available for the synthesis of these kinds of conformationally constrained compounds. Our quest was to develop a short and efficient synthesis of derivatized oxopiperazines from commercially available amino acids. The synthesis of oxopiperazines and analogues have been undertaken by several groups and are described in the following section. Our design for the oxopiperazines synthesis is described in Chapter 2 and our work towards this goal is elaborated in the sections that follow.

1.6 Literature Survey

Interest in the synthesis of derivatized oxopiperazines and related compounds began in the early 1940's. These derivatized oxopiperazines were non-selectively synthesized by alkylation of piperazin-2-one.[57] In 1981, Moon *et al.*[58] synthesized and used N,N'-ethylene-bridged phenylalanyl-leucine as the basic units of enkephalin analogues and examined their opiate activities. The main drawback to their synthesis (Scheme 1) was that the desired compound obtained was a racemic mixture of diastereomers.

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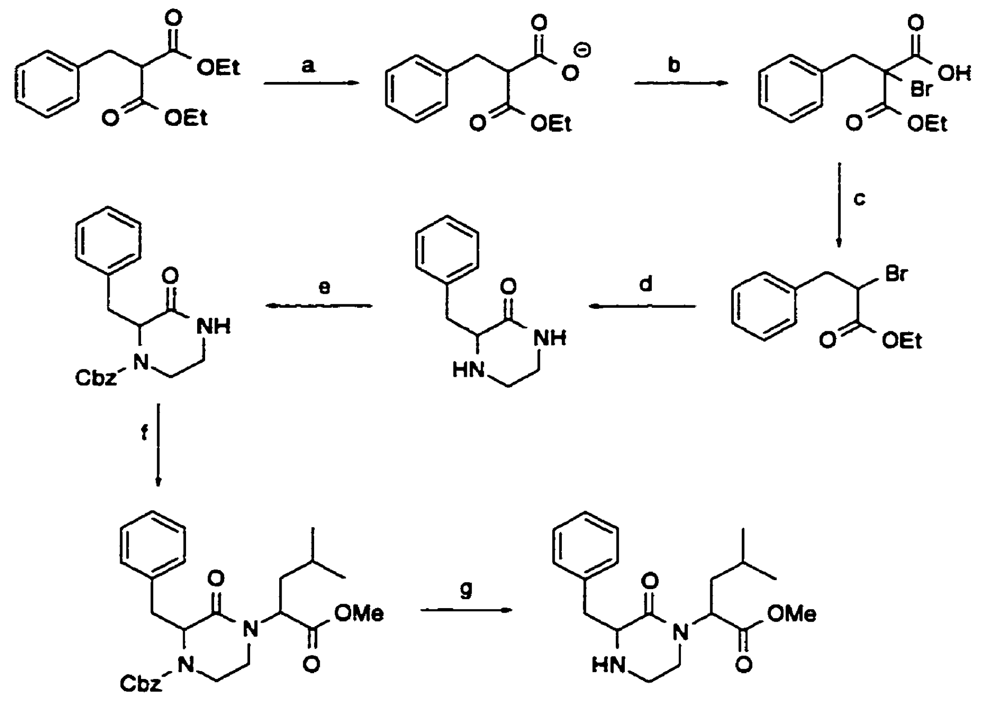
[56] Piercy, M. F.; Moon, M. W.; Blinn, J. R.; Dobry-Scheur, P. J. K., *Brain Res.* **1986**, 74, 385.

[57] (a) Aspinall, S. R., *J. Am. Chem. Soc.* **1940**, *62*, 1202. (b) Uchida, H.; Ohta, M., *Bull. Chem. Soc. Jpn.* **1973**, *46*, 3612.

[58] (a) Moon, M. W.; Lahti, R. A.; Von Voigtlander, P. F.; Samanen, J., In *Peptides: Synthesis, Structure, Function*, eds. Rich, D. H.; Gross, E., Pierce Chem. Co., Rockford, IL, **1981**, p. 641. (b) Moon, M. W., *Piperazinone and piperazine polypeptides.* **1981**, US Patent 4251438.



(a) KOH, EtOH, R.T., 20 hrs. (b) Br_2/CCl_4, 0 °C, 3 hrs. (c) Heated under reduced pressure, 140 °C
(d) $NH_2CH_2CH_2NH_2$, THF/EtOH, R.T., 20 hrs. (e) $ClCO_2Bn$, $CHCl_3$, 30 mins.
(f) NaH, $CH_3CH(CH_3)CH_2CH(Br)CO_2CH_3$, THF, 3 hrs. (g) 10 % Pd/C, 50 p.s.i., MeOH, 30 mins.

Scheme 1: Moon *et al.* synthesis of N,N'-ethylene-bridged phenylalanyl-leucine.[58]

On the other hand, DiMaio and Belleau[21] reported the synthesis of chiral cyclized N,N'-ethylene-bridged tyrosyl-glycine analogues and their enantiomers starting from Cbz-(L)-tyrozine, ethyl 2-amino-3,3-diethoxypropionate[59] and ethyl N-(2,2-dimethoxy-ethyl)glycinate respectively (Scheme 2).

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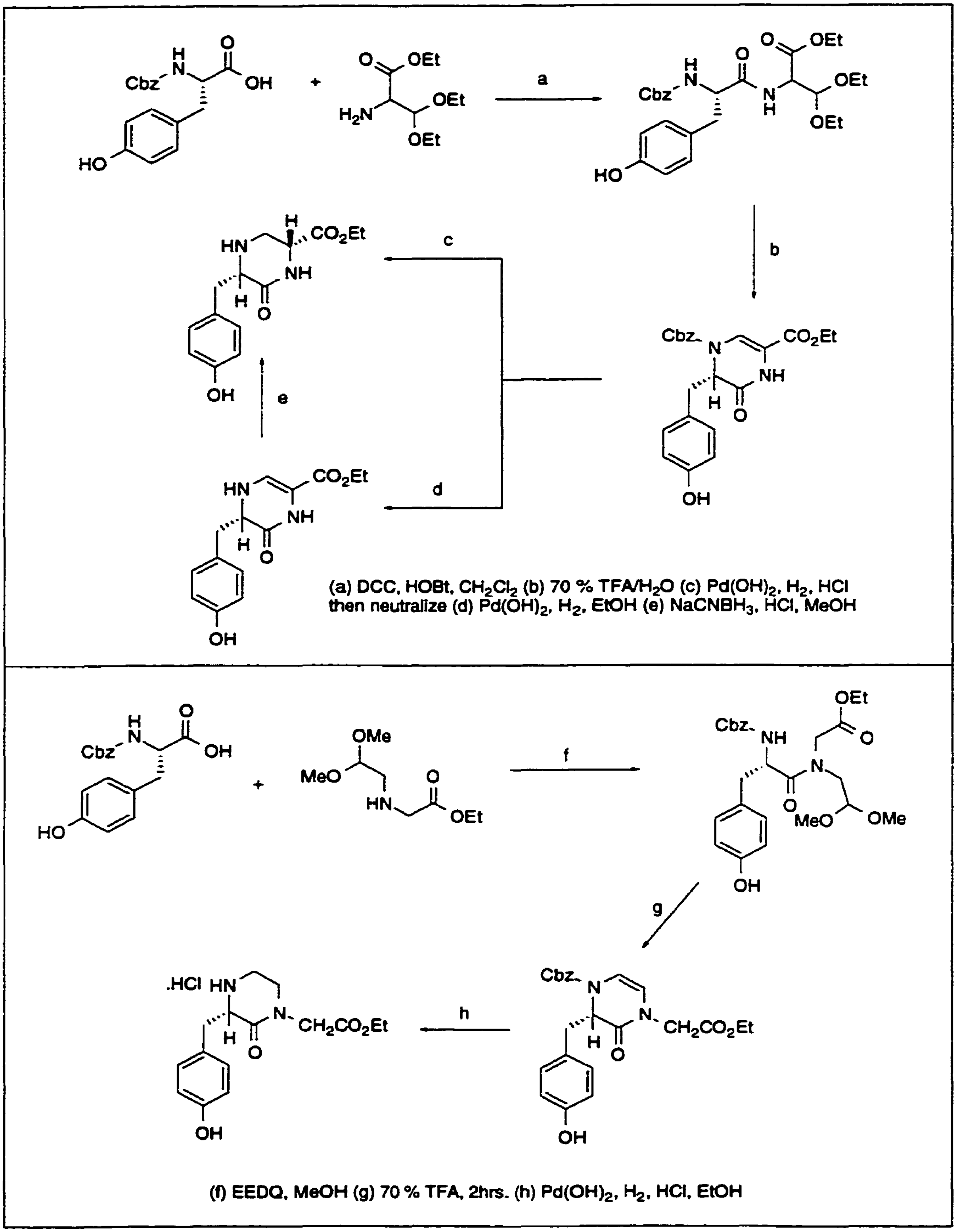
[59] Doyle, T. W.; Belleau, B.; Luh, B. Y.; Conway, T. T.; Menard, M.; Douglas, J. L.; Chu, D. T. W.; Lim, G.; Morris, L. R.; Rivest, P.; Casey, M., *Can. J. Chem.* **1977**, *55*, 484.

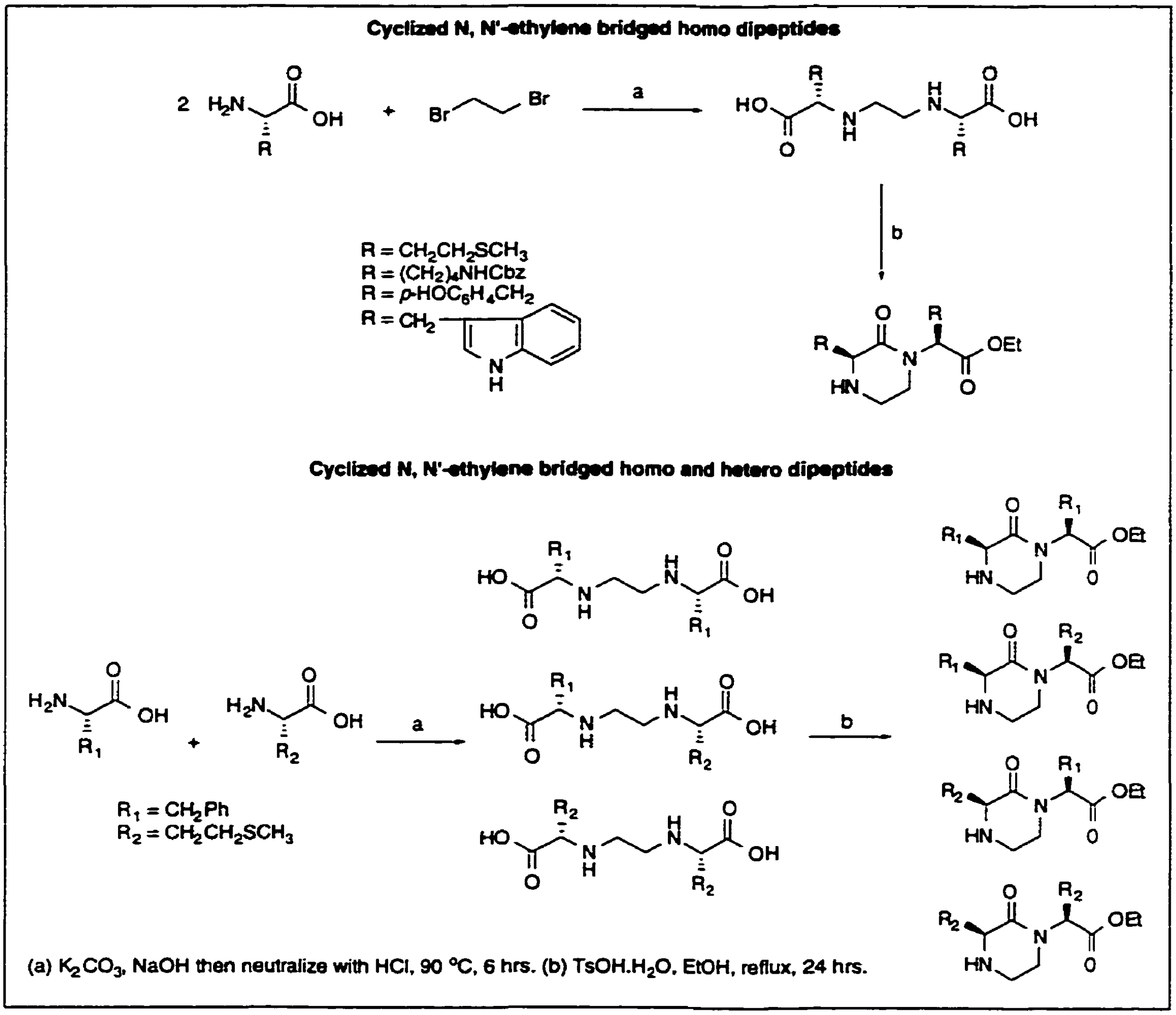


(a) DCC, HOBt, CH_2Cl_2 (b) 70 % TFA/H_2O (c) $Pd(OH)_2$, H_2, HCl then neutralize (d) $Pd(OH)_2$, H_2, EtOH (e) $NaCNBH_3$, HCl, MeOH

(f) EEDQ, MeOH (g) 70 % TFA, 2hrs. (h) $Pd(OH)_2$, H_2, HCl, EtOH

Scheme 2: DiMaio and Belleau synthesis of chiral 2-oxopiperazines.[21]

In 1989, Yamashita *et al.*[60] reported a simple method for preparing optically active N,N'-ethylene-bridged dipeptides through acid catalysed cyclizations (Scheme 3). They started from cheap and readily available amino acids and these conformationally constrained dipeptides were conveniently synthesized in two steps. This method is ideal for the formation of N,N'-ethylene-bridged homo dipeptides. However, in their synthesis of hetero dipeptides a mixture of products were obtained which had to be tediously separated out chromatographically on silica gel.



(a) K_2CO_3, NaOH then neutralize with HCl, 90 °C, 6 hrs. (b) TsOH.H_2O, EtOH, reflux, 24 hrs.

Scheme 3: Yamashita *et al.* synthesis.[60]

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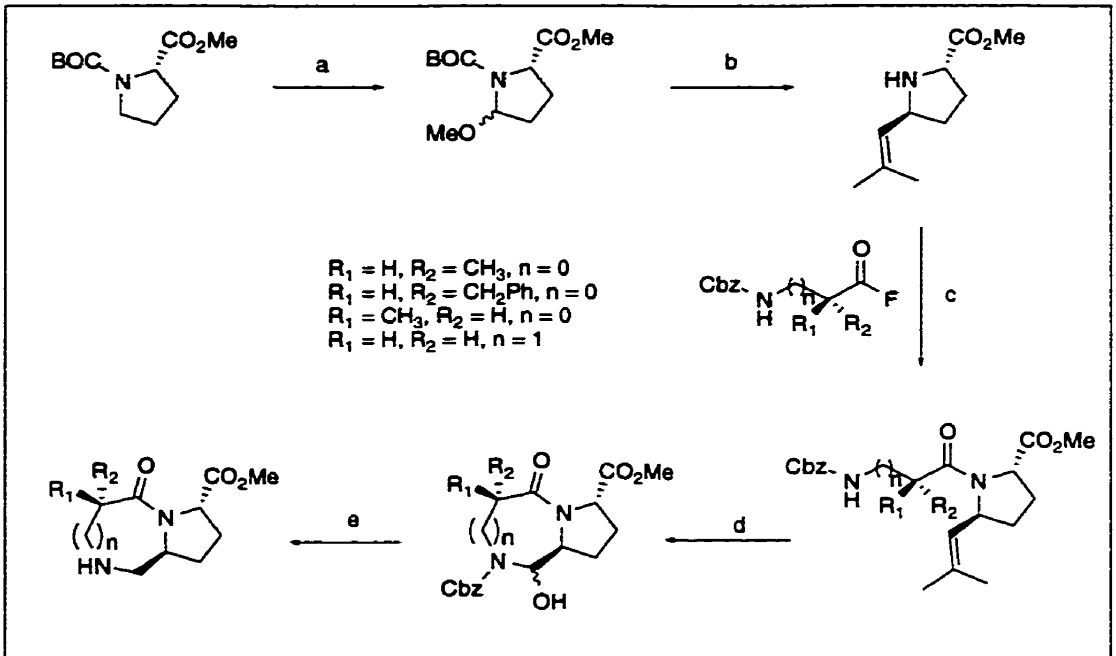
[60] (a) Yamashita, T.; Kojima, Y.; Hirotsu, K.; Ohsuka, A., *Int. J. Peptide Protein Res.* **1989**, *33*, 110. (b) Kojima, Y.; Yamashita, T.; Washizawa, M.; Ohsuka, A., *Makromol, Chem. Rapid, Commun* **1989**, *10*, 1989. (c) Yamashita, T.; Takenaka, H.; Kojima, Y., *Amino Acids* **1993**, *4*, 187. (d) Takenaka, H.; Miyake, H.; Kojima, Y.; Yasuda, M.; Gemba, M.; Yamashita, T., *J. Chem. Soc. Perkin Trans. I* **1993**, 933.

Seven years later, the synthesis of bicyclic piperazinone derivatives was published by Moeller and coworkers (Scheme 4).[61] They reported a facile route for the synthesis of peptide building blocks that constrain the peptide backbone with a diazabicyclic skeleton. The synthesis employed an anodic amide oxidation based approach for generating a functionalized proline derivative, and then utilizing the derivative as a general substrate for rapid assembly of the bicyclic ring system. The advantages of this synthetic method lie in its stereocontrol of all relevant centers and overall very good to excellent yields for each step.



(a) Carbon rod anode, Pt wire cathode, undivided cell, 0.03 M Et_4NOTs in MeOH electrolyte solution, constant current of 26.8 mA (b) i. $(CH_3)_2C{=}CHLi$, $CuBr.Me_2S$, $BF_3.Et_2O$, Et_2O, -78 °C to 0 °C; ii. TBDMSOTf, 2,6-lutidine, CH_2Cl_2; iii. n-Bu_4NF, H_2O, THF, 0 °C (c) N-ethylmorpholine, CH_2Cl_2 (d) O_3, MeOH, -78 °C then Me_2S, R.T. (e) $H_2/Pd(BaSO)_4$, MeOH.

Scheme 4: Synthesis of bicyclic piperazinone derivatives by Moeller *et al.*[61]

During the course of my studies, the synthesis of 2-oxopiperazines via a different route to mine was published by Pohlmann *et al.*(Scheme 5).[62] On their research on the asymmetric synthesis of biologically interesting compounds, they designed a general and

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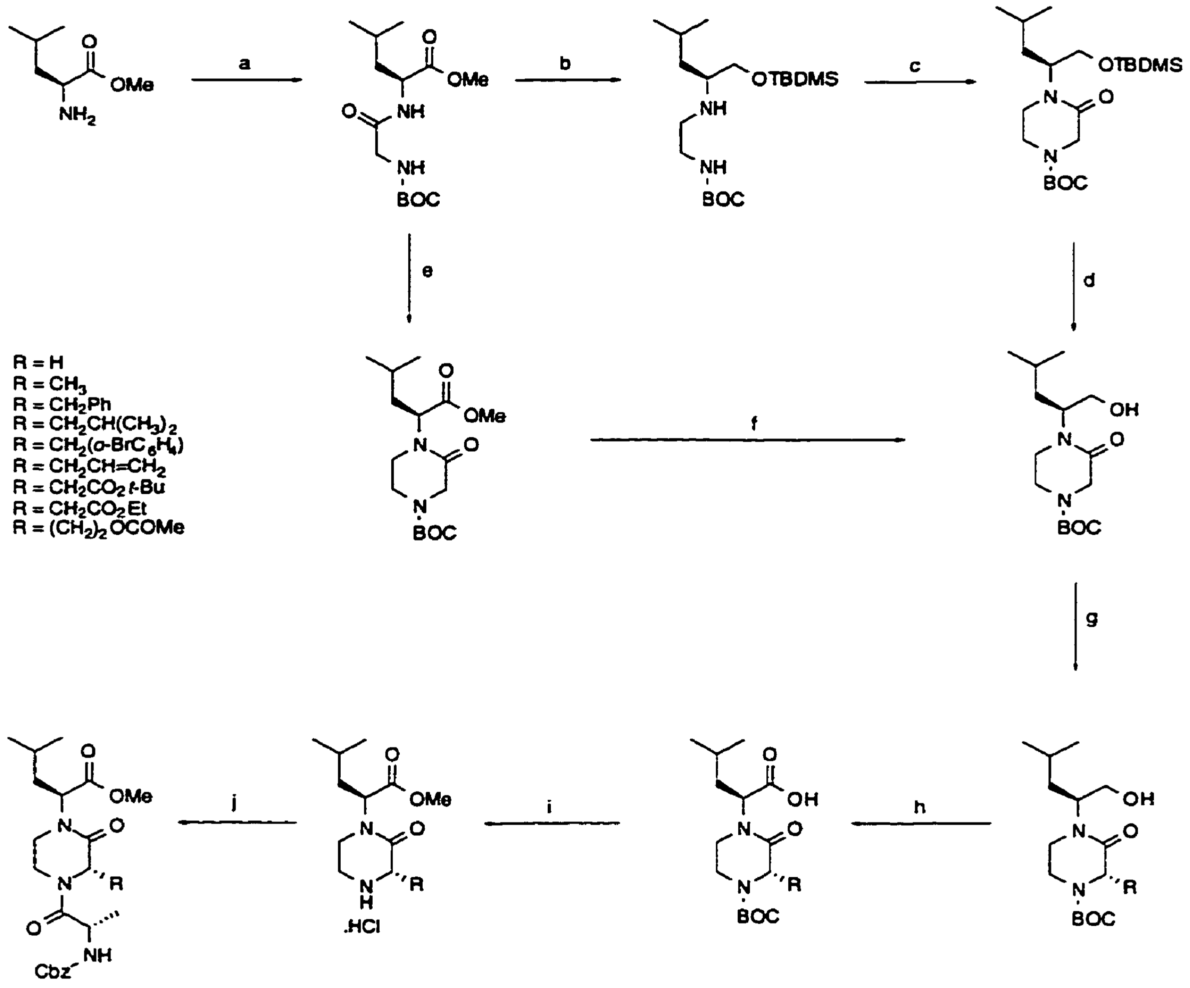
[61] Fobian, Y. M.; d'Avignon, D. A.; Moeller, K. D., *Bioorg. Med. Chem. Lett.* **1996**, *6*, 315.

[62] Pohlmann, A.; Schanen, V.; Guillaume, D.; Quirion, J.-C.; Husson, H.-P., *J. Org. Chem.* **1997**, *62*, 1016.

highly enantioselective synthesis of 3-substituted 2-oxopiperazines.[63] Their synthesis utilized a substituted amino alcohol, whose nitrogen atom is a part of the 2-oxopiperazine, as a chiral inductor. Stereoselective alkylation of the 2-oxopiperazine C-3 atom was accomplished after enolate formation by addition of electrophiles.



(a) BOC-Gly, IBCF (b) i. $LiAlH_4$; ii. TBDMSCl (c) i. $BrCH_2CO_2H$, DCC; ii. NaH, DMF (d) n-Bu_4NF (e) $(TfOCH_2)_2$, NaH (f) $NaBH_4$, LiCl (g) t-BuLi, RX (h) Jones oxidation (i) $SOCl_2$, MeOH (j) Cbz-L-$AlaOC_6F_5$

Scheme 5: Pohlmann *et al.* enantioselective synthesis of oxopiperazines.[62]

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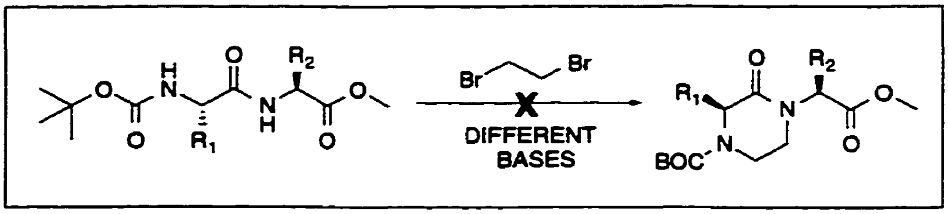
[63] (a) Schanen, V.; Riche, C.; Chiaroni, A.; Quirion, J.-C.; Husson, H.-P., *Tetrahedron Lett.* **1994**, *35*, 2533. (b) Schanen, V.; Cherrier, M. P.; de Melo, S. J.; Quirion, J.-C.; Husson, H.-P., *Synthesis*, **1996**, 833.

CHAPTER 2: RESULTS AND DISCUSSION

2.1 Initial Synthesis of Cyclized N,N'-Ethylene Bridged Homo Dipeptides and Their Analogues

During our initial attempts to make substituted monoketopiperazines, we started from the obvious choice of making a simple dipeptide protected at both ends and cyclizing via the amido-carbamate NH's (Scheme 6). On first glance, this seemed to be a very simple and trivial chemical approach. However, it posed a greater challenge than anticipated. We tried using dibromoethane as the 1,2-dielectrophile under several different conditions without any success. To the best of our knowledge at that time, there was no example of such a reaction conducted on an amidocarbamate compound.



Scheme 6: Attempted cyclization of dipeptide with dibromoethane.

We then focussed our attention on the synthesis of cyclized N,N'-ethylene bridged homo dipeptides and their analogues starting from readily available amino acids. We decided to explore the method of Yamashita and co-workers[60] for the preparation of cyclic dipeptides **3** and **13** (Schemes 7 and 8).

The preparation of chiral oxopiperazine **3** was achieved via two synthetic pathways. Firstly, acyclic dipeptide intermediate **1** was synthesized according to the method similar to that of Schöenberg *et al.*[64] by refluxing for six hours L-leucine in an aqueous solution of potassium carbonate and sodium hydroxide with the slow addition of dibromoethane. After acidification with concentrated hydrochloric acid, acyclic dipeptide **1** was obtained as a white solid. Intermediate **1** was then refluxed with 2.0 eq. of *p*-toluene sulfonic acid monohydrate in excess dry ethanol for 24 hours. This resulted in the simultaneously formation of the cyclization and esterification product which was purified by silica gel

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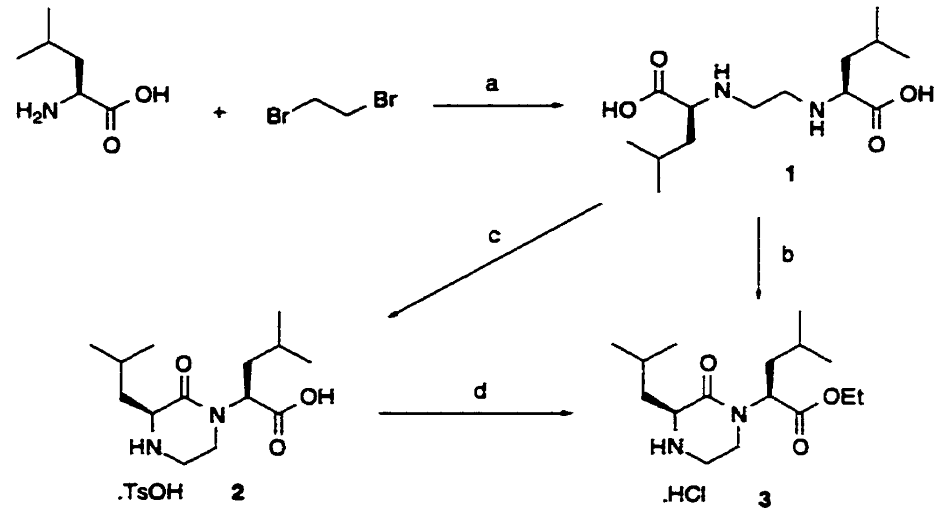
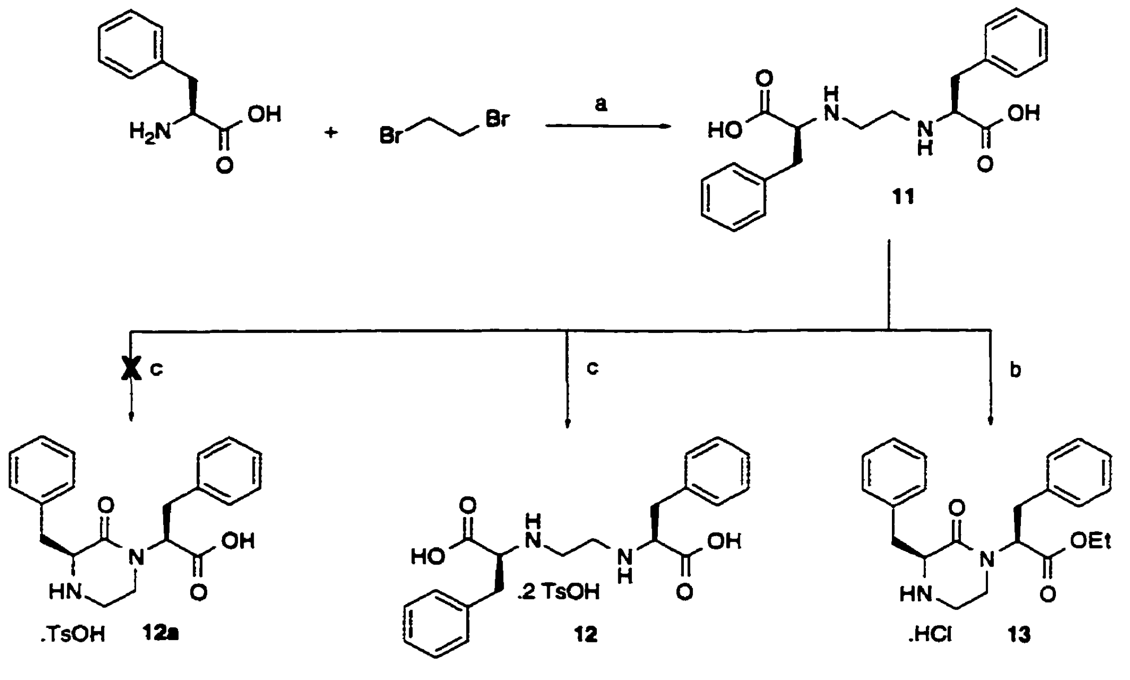
[64] Schöenberg, L. N.; Cooke, D. W.; Liu, C. F., *Inorg. Chem.* **1968**, *7*, 2386.



(a) K_2CO_3, NaOH then neutralize with HCl, 90 °C, 6 hrs. (b) i. 2.0 eq. *p*-TsOH.H_2O, EtOH, reflux, 24 hrs., ii. Et_2O, HCl gas, 3 hrs. (c) 2.0 eq. *p*-TsOH.H_2O, CH_3CN, reflux, 24 hrs. (d) i. 0.1 eq. *p*-TsOH.H_2O, EtOH, reflux, 24 hrs., ii. Et_2O, HCl gas, 3 hrs.

Scheme 7: Synthesis of Cyclized N,N'-ethylene bridged bis-(L)-leucine.

chromatography (benzene/ethyl acetate/methanol, 5/4/1) to produce an oil. Dry hydrogen chloride gas was then bubbled into an ethereal solution of the cyclized ester to prepare its hydrochloride salt **3** in 90 % yield. In the second pathway, acyclic dipeptide **1** was refluxed with 2.0 eq. of *p*-toluene sulfonic acid monohydrate in excess acetonitrile for 24 hours, thus yielding the tosylate salt of the cyclized acid **2** as white fluffy flakes in 95 % yield. This cyclized acid **2** was then refluxed in excess dry ethanol for 24 hours in the presence of a catalytic amount of *p*-toluene sulfonic acid monohydrate (0.1 eq.) and after neutralization with aqueous sodium hydrogen carbonate, provided the free amine of oxopiperazine **3** in quantitative yield.



(a) K_2CO_3, NaOH then neutralize with HCl, 90 °C, 6 hrs. (b) i. 2.0 eq. *p*-TsOH.H_2O, EtOH, reflux, 24 hrs., ii. Et_2O, HCl gas, 3 hrs. (c) 2.0 eq. *p*-TsOH.H_2O, CH_3CN, reflux, 24 hrs.

Scheme 8: Synthesis of CyclizedN,N'-ethylene bridged bis-(L)-phenylalanine.

Utilizing the first synthetic pathway as above, cyclized ester **13** derived from L-phenylalanine was prepared in a similar manner. Interestingly, attempted cyclization of acyclic dipeptide **11** in acetonitrile containing *p*-toluene sulfonic acid monohydrate as carried out above was not successful, and instead, the acyclic ditosylate salt **12** was obtained in quantitative yield.

We then focused our attention in the preparation of tripeptide analogues starting from L-leucine and L-phenylalanine derived cyclized esters **3** and **13** by appending different groups at their N-4 position. According to the three ligand hypothesis of Farmer and Ariëns,[65] three separate groups are required for stereospecific binding to a receptor. The hypothesis is that the peptide backbone is not important for binding. Instead, the affinity of the peptide for its receptor is dependent on the molecular recognition information contained within the side-chains of key amino acids that defined the peptide. Functionalized dipeptides or their analogues, especially when conformationally constrained, may do so quite efficiently. Some excellent examples of theses are captopril, the penicillins and the cephalosporins.

Since we were interested in diverse physical properties where hydrophilicity (z_1) and size (z_2) are the main determinants, but not always the most important factors to exhibit affinity and selectivity for certain receptors, we used the principles adopted by Wold *et al.*[66] to select the appropriate N-terminus blocking groups. For simplicity and clarity, let us take for example a representative dipeptide, where each constituent amino acid is either hydrophilic (z_1 = +) or hydrophobic (z_1 = -) and large (z_2 = +) or small (z_2 = -). Table 1 lists such a set of amino acids. The initial four N-terminus blocking groups selected were succinamic acid (des-amino asparagine), acetic anhydride (des-amino glycine), 3-phenylpropionic acid (des-amino phenylalanine) and 4-methylpentanoic acid (des-amino leucine).

z_1	z_2	Examples
+	+	asparagine or lysine
+	-	glycine or serine
-	+	phenylalanine or tryptophan
-	-	leucine or valine

Table 1: Some amino acids with two of their principal properties.

Scheme 9 shows the des-amino acid derivatives synthesis. For the synthesis of the des-amino glycine derivative **4**, cyclized ester **3** was dissolved in freshly distilled pyridine and an excess of acetic anhydride (10 eq.) was added to the above solution. After 18 hrs., all the starting material was consumed. However, apart from an intense new spot, several

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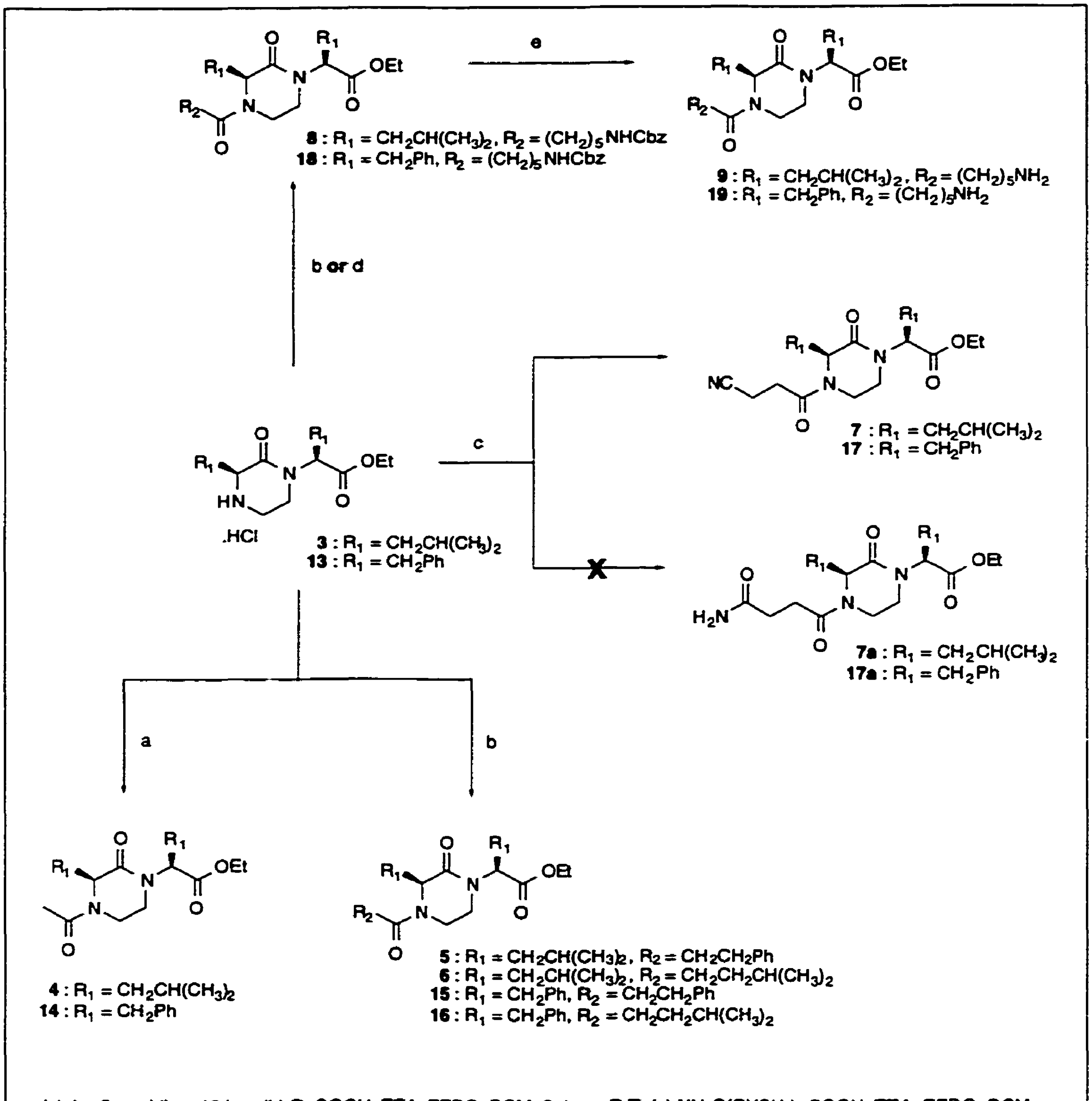
[65] Farmer, P. S.; Ariëns, E. J., *TIPS* **1982**, 362.

small spots were also observed by TLC. Column chromatography was performed to yield the des-glycyl derivative **4** as a white solid in 75 % yield. Des-glycyl derivative **14** was obtained (67 % yield) in a similar fashion from cyclized ester **13**.



(a) Ac_2O, pyridine, 18 hrs. (b) R_2COOH, TEA, EEDQ, DCM, 2 days, R.T. (c) $NH_2C(O)(CH_2)_2COOH$, TEA, EEDQ, DCM, 2 days, R.T. (d) $R_2C(O)F$ (**10**), NEM, DCM,, 24 hrs., R.T. (e) 10 % Pd/C, 45 p.s.i., 3 hrs, $EtOAc/AcOH/H_2O$, 12/2/1 by volume

Scheme 9: Synthesis of des-amino acid derivatives.

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[66] (a) Jonsson, J.; Erikson, L.; Hellburg, S.; Sjöström, M.; Wold, S., *Quant. Struct-Act. Relat.* **1989**, *8*, 204. (b) Hellburg, S.; Erikson, L.; Jonsson, J.; Lindgren, F.; Sjöström, M.; Skagerberg, B.; Wold, S.; Andrews, P., *Int. J. Peptide Protein Res.* **1991**, *37*, 414 and references cited therein.

For the preparation of des-amino leucine derivatives **5** and **6** and des-amino phenylalanine derivatives **15** and **16**, 2-ethoxy-1-(ethoxycarbonyl)-1,2-dihydroquinoline (EEDQ)[67] was used as the coupling reagent for the peptide bond formation. Although several methods[68] exist for the activation of carboxylic acids and subsequent conversion to their derivatives, we choose EEDQ as it allows the coupling step in a single operation. In a typical example, for the formation of des-leucyl derivative **5**, EEDQ was added to a solution of cyclized ester **3** in freshly distilled triethylamine and dichloromethane. After 30 minutes, 3-phenylpropionic acid was added to the above solution which was then left to stir for 2 days. After acidic work up to remove the quinoline which was formed as a by-product, the crude product was purified by flash chromatography to provide **5** in 66 % yield.

Repeating the exact procedure for the preparation of derivative **7a**, using succinamic acid as the des-amino acid, we were unable to isolated the desired product. Instead, we obtained a dehydration product **7** in 33 % yield. The peptide bond formation did occur, however, the unsubstituted amide moiety of succinamic acid was dehydrated to a nitrile. There were several pieces of evidence which alerted us to this transformation. Firstly, in the ^{13}C NMR analysis there were two peaks (due to mixture of rotamers) at 119.06 and 119.18 ppm which are indicative of the presence of a nitrile. Secondly, infra red (IR) analysis of the sample showed a peak for a nitrile at 2254 cm^{-1}. The M^+ peak in the mass spectrum and the elemental analysis confirmed the structural assignment. The same dehydration was observed in the synthesis of derivative **17a**.

It is known that unsubstituted amides can be dehydrated to nitriles[69] by many common dehydrating agents. To the best of our knowledge, EEDQ is not one of these

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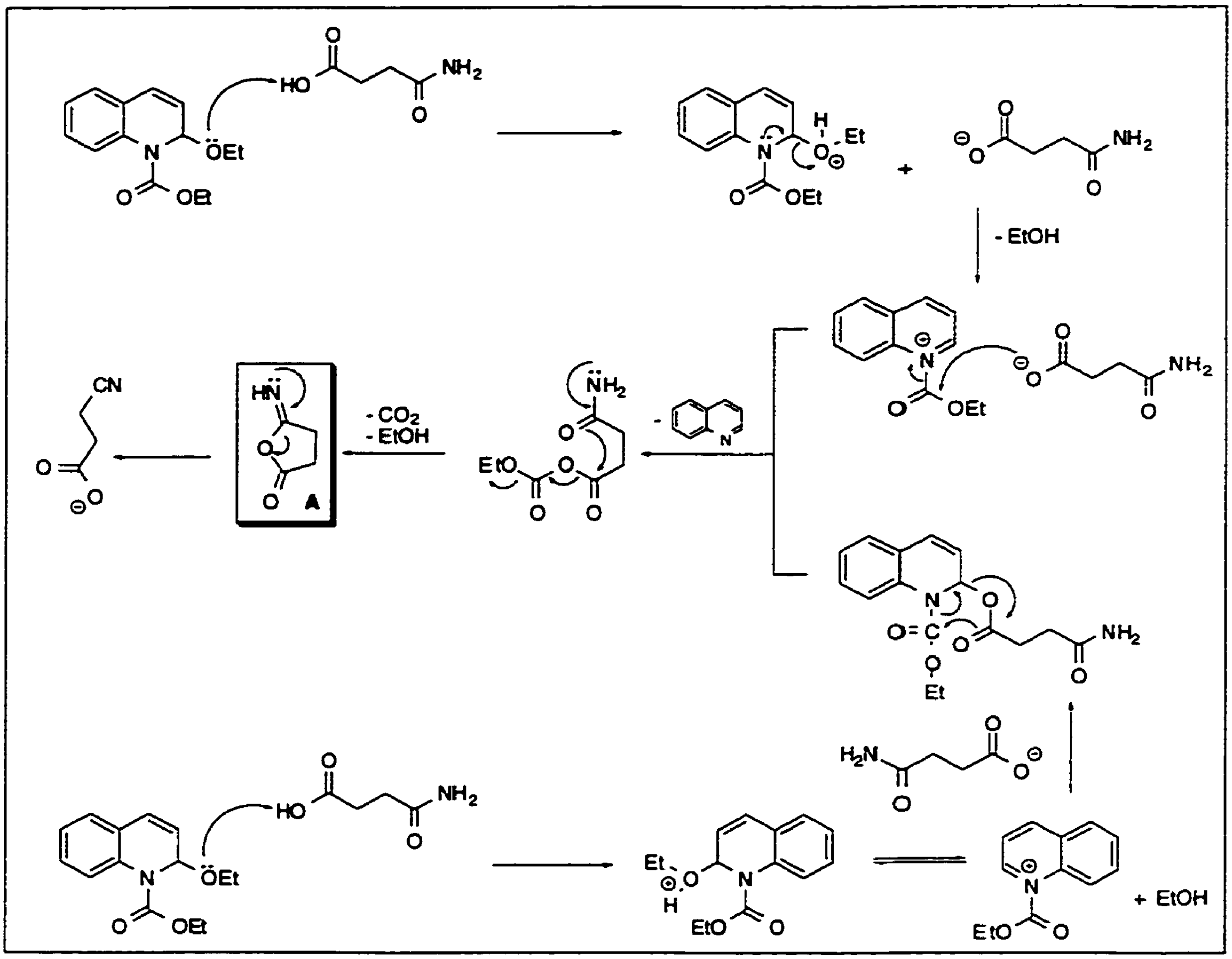
[67] (a) Belleau, B.; Martel, R.; Lacasse, G.; Ménard, M.; Weinberg, N. L.; Perron, Y. G., *J. Am. Chem. Soc.* **1978**, *90*, 823. (b) Belleau, B.; Malek, G., *J. Am. Chem. Soc.* **1968**, *90*, 1651. (c) Dugas, H.; Penny, C., *Bioorganic Chemistry; A Chemical Approach to Enzyme Action*; Springer-Verlag: New York, **1981**.

[68] (a) Brook, M. A.; Chan, T. H., *Synthesis* **1983**, 201. (b) Gorecka, A.; Leplawy, M.; Zabrocki, J.; Zwierzak, A., *Synthesis* **1978**, 474. (c) Paul, R.; Anderson, G. W., *J. Am. Chem. Soc.* **1960**, *82*, 4596. (d) Kim, Y. C.; Lee, J. I., *Tetrahedron Lett.* **1983**, *24*, 3365. (e) Ueda, M.; Oikawa, H.; Teshirogi, T., *Synthesis* **1983**, 908. (f) Cabre, J.; Palomo, A. L., *Synthesis* **1984**, 413. (g) Olah, G. A.; Narang, S. C.; Garcia-Luna, A., *Synthesis* **1981**, 790.

[69] For reviews, see Bieron; Dinan; in Zabicky *The Chemistry of Amides*: Wiley: New York, **1970**, pp. 274-283; Friedrich; Wallenfels, Ref. 377, pp. 96-103; Friedrich, Ref. 377.

dehydrating agents. In Scheme 10 is postulated plausible mechanisms for the dehydration of succinamic acid.



Scheme 10: Possible mechanisms for EEDQ dehydration of succinamic acid.

The above reaction was also repeated using 1-benzotriazolyloxotris-(dimethylamino)phosphonium hexafluorophosphate (BOP reagent) as the coupling agent. BOP reagent, also known as Castro's reagent[70] is widely used in peptide synthesis. It is used in conjunction with 1-hydroxbenzotriazole (HOBt) and N-methyl morpholine, but the degree of coupling efficiency differs between amino acids and the factors that influence the latter are not well understood. When the BOP reagent was used, not surprisingly, the same results as above were obtained. It should be noted that when BOP reagent was used, the chromatographic separation was difficult and tedious due to the presence of active ester and

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[70] Castro, B.; Dormoy, R. J.; Evin, G.; Selve, C., *Tetrahedron Lett.* **1975**, 1219.

symmetric anhydride intermediates. In the work up, a saturated solution of ammonium chloride is normally used. However we found a reported procedure[71] where a 10 % citric acid solution was much more efficient for the removal of any unwanted by-products. The chromatographic purification was thus greatly simplified. This dehydration of the amide moiety using BOP reagent possibly took place via a common intermediate (**A**) as that of the dehydration using EEDQ (see Scheme 10).

Since we still wanted an N-terminus blocking with similar properties to that of des-amino asparagine, we decided to use des-amino lysine. The des-amino acid was N-(benzyloxy-carbonyl)-ε-aminocaproic acid. The benzyloxycarbonyl group can then be easily removed after the coupling step. For the coupling step, two methods were employed. Firstly, the previous typical coupling reagent EEDQ was used for the peptide bond formation. Secondly, the acid fluoride of N-(benzyloxycarbonyl)-ε-aminocaproic acid **10** was made and then coupled with cyclized ester **3**. This increased the yield of this step from 55 % for the first method to 78 %. I shall go in greater details concerning peptide bond formation using acid fluoride coupling later on in this chapter. Tripeptide **18** was invariably made in a similar fashion. The benzyloxycarbonyl groups of **8** and **18** were easily hydrogenated using 10 % Pd/C at 45 p.s.i. for 3 hours in ethyl acetate/acetic acid/ water (12/2/1).

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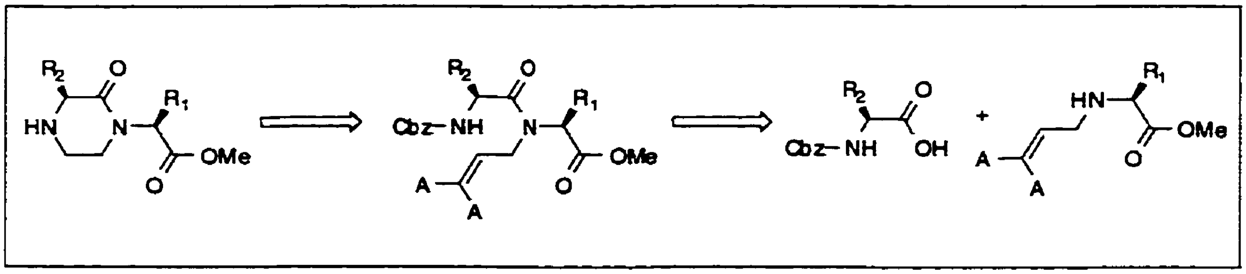
[71] Coste, J.; Frérot, E.; Jouin, P., *J. Org. Chem.* **1994**, *59*, 2437.

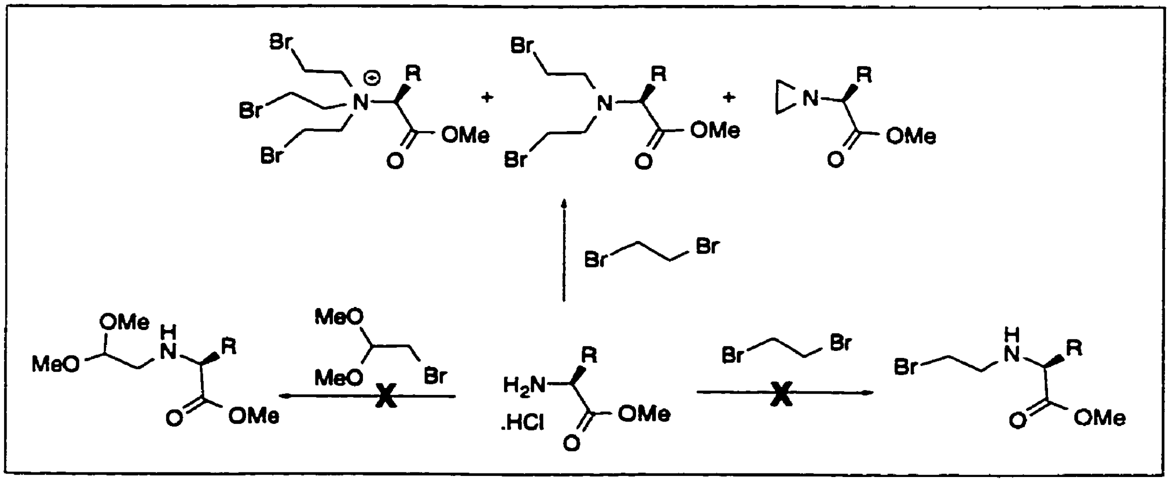
2.2 Synthetic Strategy for the Formation of Cyclized N,N'-Ethylene Bridged Hetero Dipeptides

Our strategy[72] was based on the generation of N-allylic secondary amino acid esters which could then be coupled with other amino acids as depicted in Scheme 11. The aldehyde required for the cyclization could then be generated by oxidation of the alkene functionality.



Scheme 11: Retrosynthesis of oxopiperazines.

In our initial attempts, we decided to simply alkylate an amino acid methyl ester using dibromoethane. However, we were unsuccessful in our endeavours to achieve mono alkylation and ended up with a mixture of possible products such as the tertiary amine and the quaternary ammonium salt as shown in Scheme 12. It is also possible that the aziridine formation also occurred.



Scheme 12: Initial alkylation attempts.

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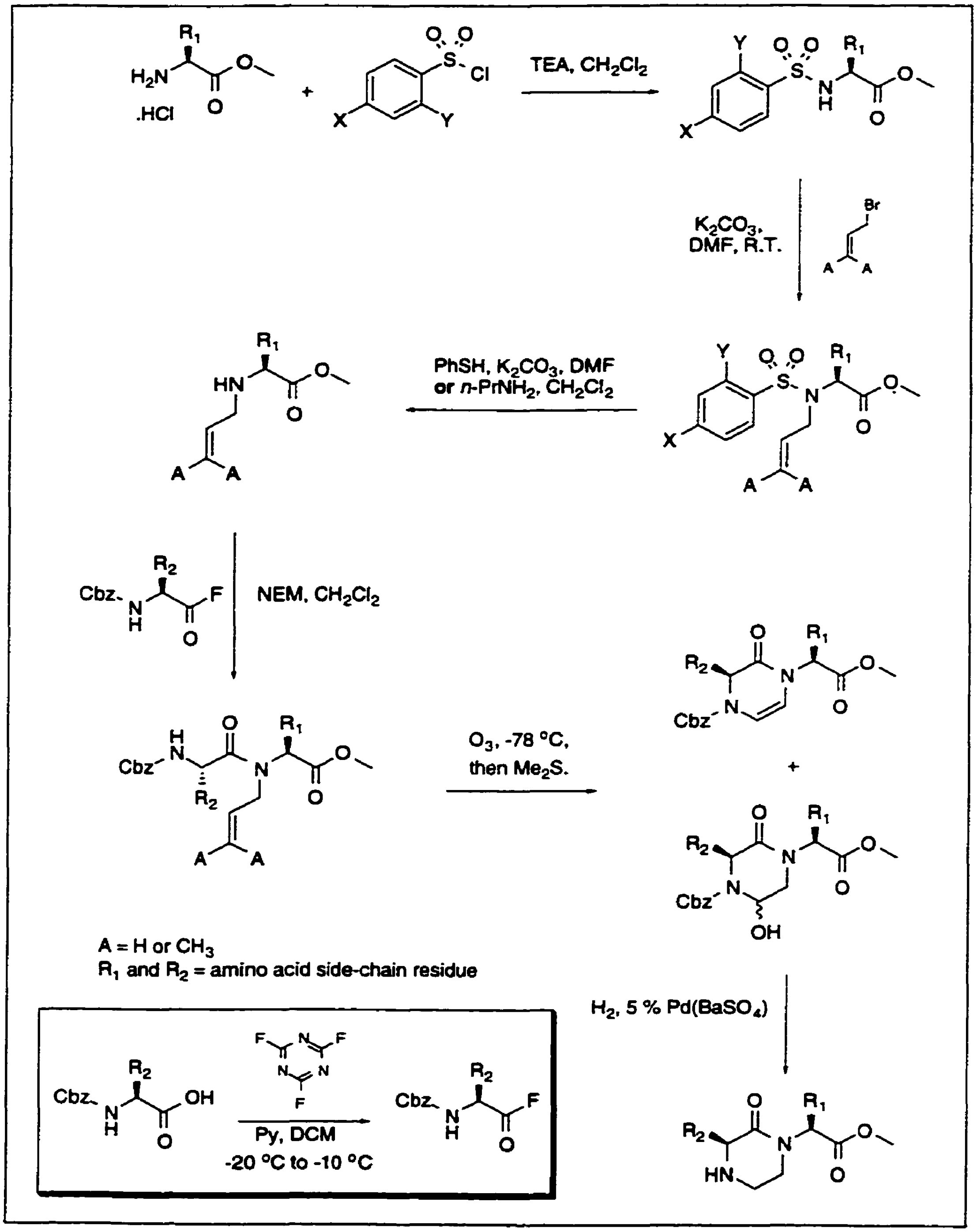
[72] Bhatt, U.; Mohamed, N; Just, J.; Roberts, E., *Tetrahedron Lett.* **1997**, *38*, 3679.

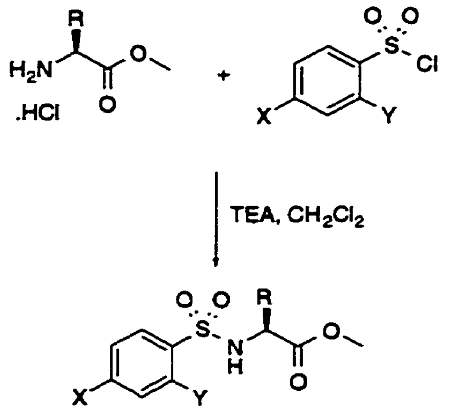
We next looked at the possibility of generating an aldehyde functionality by using a protected aldehyde, bromoacetaldehyde dimethyl acetal to do the above transformation, but was unable to obtain any of the desired product. A full synthetic strategy using the allyl/prenyl system is shown in Scheme 13.



Scheme 13: Total synthesis of oxopiperazines.

2.2.1 Synthesis of Sulfonamides

Our first endeavor was the preparation of secondary allylic amines. The conversion of primary amines to the corresponding secondary amines appears to be deceptively simple.[73] Alkylation of primary amines with alkyl halides or sulfonates frequently leads to the formation of the undesired tertiary amines and/or quaternary ammonium salts. Reductive amination of aldehydes or ketones using sodium cyanoboro hydride ($NaBH_3CN$) often produces tertiary amines to a varying extent unless the desired secondary amine is sterically hindered. Instead, the reduction of N-monoalkyl amides with strong reducing agents such as lithium aluminium hydride or borane could be used. Also, the Mitsunobu alkylations of toluenesulfonamide[74] and trifluoroacetamides[75] have recently been reported.



20 : $R = CH_2Ph$, $X = NO_2$, $Y = H$
21 : $R = CH_2Ph$, $X = H$, $Y = NO_2$
22 : $R = CH_2Ph$, $X = NO_2$, $Y = NO_2$
23 : $R = CH_2CH(CH_3)_2$, $X = NO_2$, $Y = H$
24 : $R = CH_2CH(CH_3)_2$, $X = H$, $Y = NO_2$
25 : $R = CH_2CH(CH_3)_2$, $X = NO_2$, $Y = NO_2$
26 : $R = (CH_2)_4NHCbz$, $X = NO_2$, $Y = H$
27 : $R = CH_2OBn$, $X = NO_2$, $Y = H$
28 : $R = CH(CH_3)_2$, $X = NO_2$, $Y = H$

Scheme 14: Synthesis of sulfonamides.

During our quest for the preparation of secondary allylic amine, Fukuyama *et al.*[76] reported the novel and exceptionally versatile use of 2- and 4-nitrobenzenesulfonamides that provided an efficient way for the synthesis of secondary amines. In a later publication[77] again by the same group, they also used 2,4-dinitrobenzenesulfonamides in a similar fashion. We used 2- and 4-nitrobenzenesulfonamides and 2,4-dinitrobenzenesulfonamides

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[73] For general synthesis of amines, see: Sandler, S. R.; Karo, W., *Organic Functional Group Preparations*. 2nd ed.; Academic, New York, **1983**; Chapter 13.

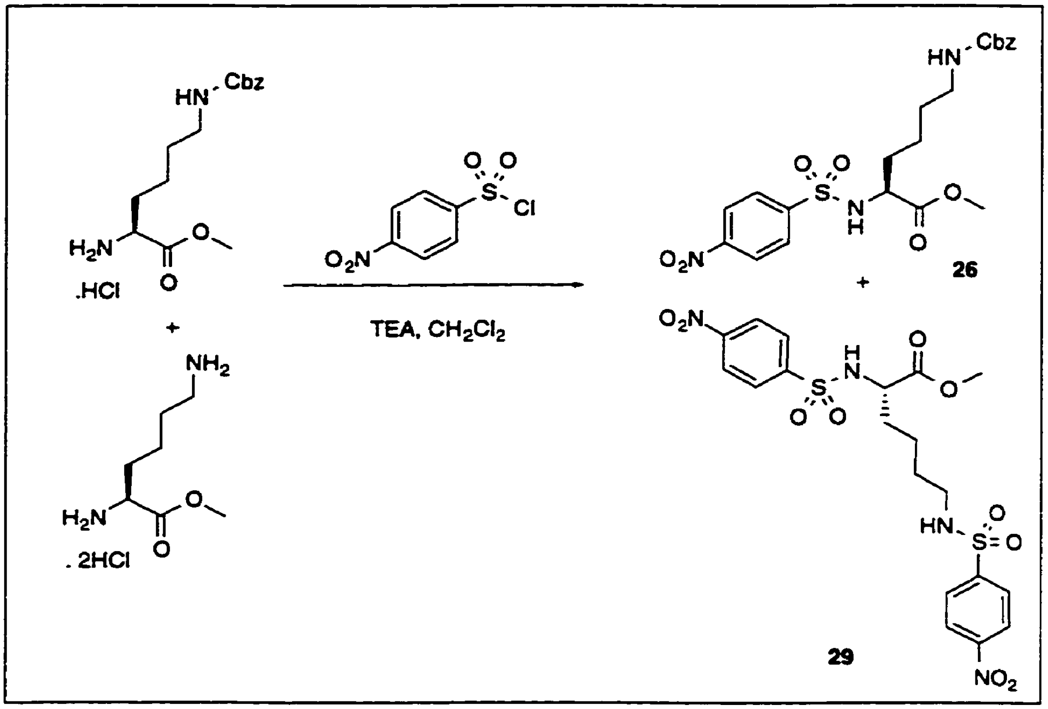
[74] Henry, J. R.; Marcin, L. R.; McIntosh, M. C.; Scola, P. M.; Harris, G. D. Jr.; Weinreb, S. M., *Tetrahedron Lett.* **1989**, *30*, 5709.

[75] Tsunoda, T.; Otsuka, J.; Yamamiya, Y.; Itô, S., *Chem. Lett.* **1994**, 539.

[76] Fukuyama, T.; Jow, C.-K.; Cheung, M., *Tetrahedron Lett.* **1995**, *36*, 6373.

as activating groups for achieving mono-N-alkylation. To a solution of the amino acid methyl ester hydrochloride in dry dichloromethane was added freshly distilled triethylamine followed by the addition of 2- or 4-nitrobenzenesulfonyl chloride (Scheme 14). After six hours at room temperature and typical acid/base workup, the respective sulfonamides were obtained in high purity (^{1}H & ^{13}C NMR analysis) and excellent yields (84-96 %). In the case of the formation of the 2,4-dinitrobenzenesulfonamides, the reaction was performed at -15 °C and slowly warmed up to room temperature. Purification of these sulfonamides was achieved by column chromatography in approximately 70 % yield.

All the sulfonamides obtained above were pure (TLC, ^{1}H and ^{13}C NMR), except for sulfonamide **26** which was found to be contaminated with an impurity.



Scheme 15: By-product **29** formation from the preparation of sulfonamide **26**.

After a very tedious column chromatography (the two spots were overlapping) of 100 mg of crude sulfonamide **26**, we were able to separate the two compounds. From the NMR and mass spectrum analysis we were able to assign the structure of the impurity as that of bis-sulfonamide **29**. We concluded that the starting material, N^{ε}-(benzyloxycarbonyl)-L-

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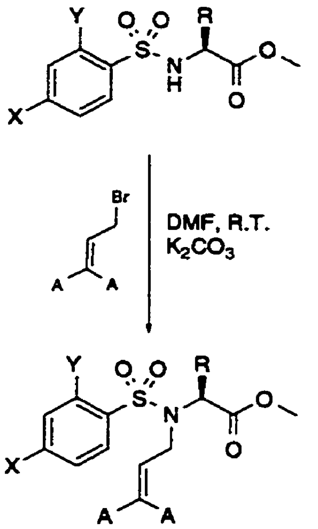
[77] Fukuyama, T.; Cheung, M.; Jow, C.-K.; Hidai, Y.; Kan, T., *Tetrahedron Lett.* **1997**, *33*, 5831.

lysine methyl ester hydrochloride was possibly contaminated with trace amounts of L-lysine methyl ester dihydrochloride (Scheme 15).

2.2.2 Synthesis of Mono-N-Alkylated Sulfonamides

With a number of sulfonamides in hand, we embarked on alkylating them using allyl or prenyl bromide (Scheme 16).



30 : R = CH_2Ph, X = NO_2, Y = H, A = H
31 : R = CH_2Ph, X = NO_2, Y = H, A = CH_3
32 : R = CH_2Ph, X = H, Y = NO_2, A = CH_3
33 : R = CH_2Ph, X = Y = NO_2, A = CH_3
34 : R = $CH_2CH(CH_3)_2$, X = NO_2, Y = H, A = H
35 : R = $CH_2CH(CH_3)_2$, X = NO_2, Y = H, A = CH_3
36 : R = $CH_2CH(CH_3)_2$, X = H, Y = NO_2, A = CH_3
37 : R = $CH_2CH(CH_3)_2$, X =Y = NO_2, A = CH_3
38 : R = $(CH_2)_4NHCbz$, X = NO_2, Y = H, A = CH_3
39 : R = CH_2OBn, X = NO_2, Y = H, A = CH_3
40 : R = $CH(CH_3)_2$, X = NO_2, Y = H, A = CH_3

Scheme 16: N-Alkylation of sulfonamides.

To a solution of the sulfonamide in dry DMF was added 2 mole eq. potassium carbonate. The reaction mixture was then left to stir at R.T. until the solution changed to a yellow color. At this point 5 eq. of allyl or prenyl bromide was slowly injected into the mixture which immediately changed to a dirty brown color. Three hours later, the desired allylated or prenylated sulfonamides were obtained in excellent yields after extraction and evaporation. No chromatography was required for purification. The question why we used both allylated and prenylated sulfonamides will become evident in a section to follow.

Since these sulfonamides can also be alkylated efficiently under Mitsunobu conditions[78] (Scheme 17) we decided to allylate sulfonamide **20** under those conditions. We used standard conditions employed in such reactions.

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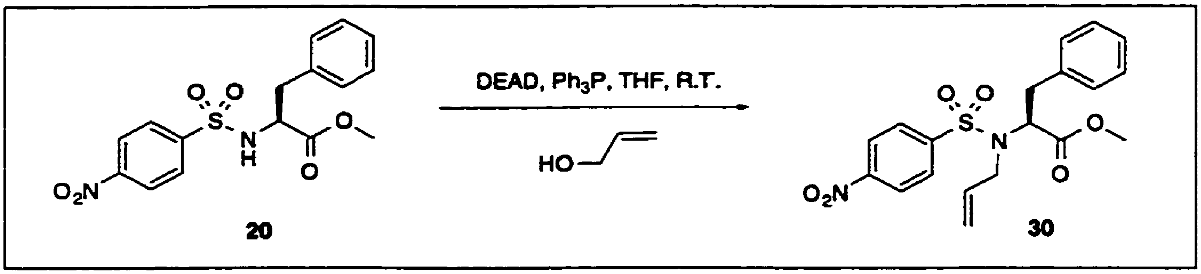
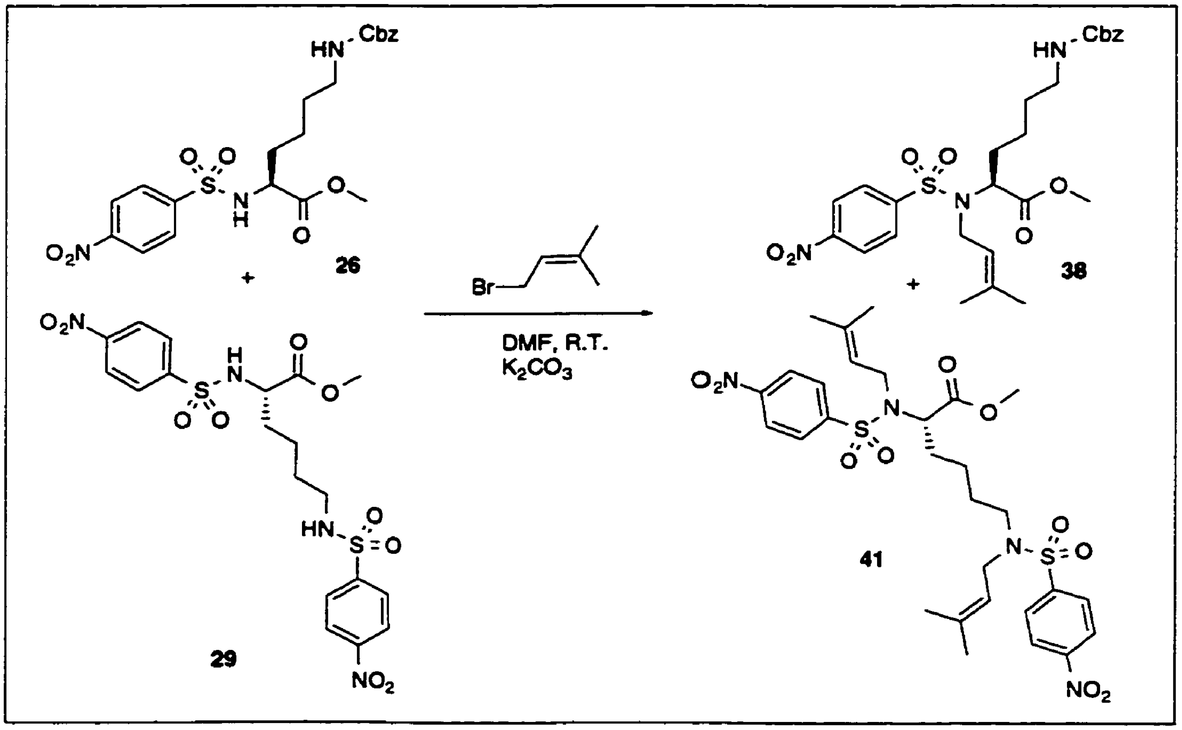
[78] (a) Mitsunobu, O, *Synthesis* **1981**, 1. (b) Hughes, D. L., *Org. React.* **1992**, *42*, 335.



Scheme 17: Allylation under Mitsunobu conditions.

As the desired allylated sulfonamide **30** had to be purified via chromatography and the yield (74 %) was not as good as using the conventional method (99 %), the Mitsunobu coupling method was abandoned.

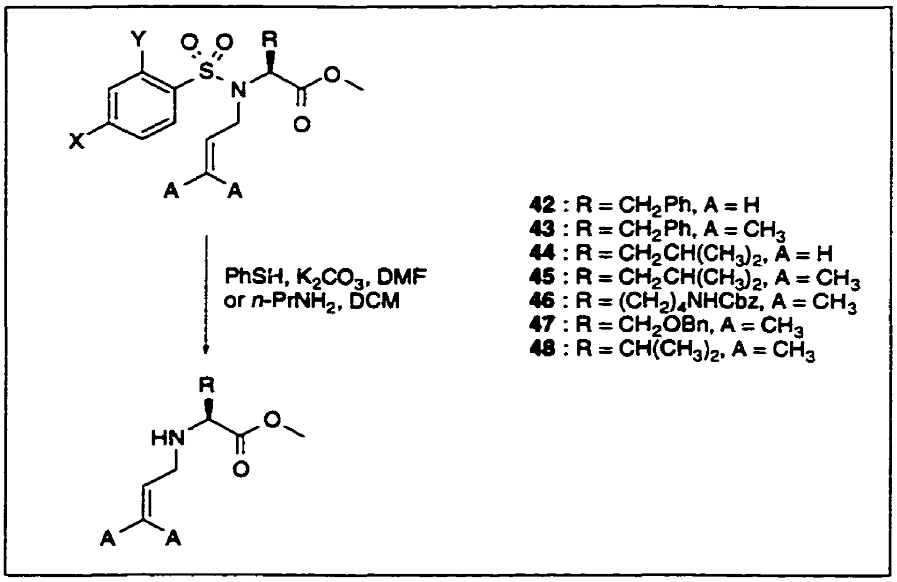


Scheme 18: Prenylation of crude sulfonamide **26**.

As previously mentioned, sulfonamide **26** was contaminated with the bis-sulfonamide by-product **29**. Since the separation of these two products was difficult by chromatography, we decided to prenylate the mixture (Scheme 18) hoping that the difference in R_f of the two possible products would be substantial enough to be easily separated by chromatography. To our delight, our wishes came through and prenylated sulfonamide **38** (R_f = 0.28, ethyl acetate/hexane 1/2) could be easily separated from the diprenylated disulfonamide **41** (R_f = 0.46).

2.2.3 Deprotection of the Alkylated Sulfonamides

The 2- and 4-nitrobenzenesulfonamides were deprotected readily via their Meisenheimer complexes[79] upon treatment with thiolates (thiophenol/K_2CO_3 or mercaptoacetic acid/LiOH) in DMF at room temperature, giving the secondary alkylated amines in high yields (Scheme 19). Thiophenolate gave us better yields and thus was used in preference to the latter. On the other hand, the 2,4-dinitrobenzenesulfonamides were deprotected under even milder conditions. Facile deprotection of these sulfonamides was achieved by treatment with excess *n*-propylamine (20 eq.) in dichloromethane at R.T. While a variety of amine and thiol nucleophiles could be used for the deprotection of 2,4-dinitrobenzenesulfonamides, *n*-propylamine was chosen because it could be removed easily (b.p. 48 °C), it had no stench and it was also inexpensive.



Scheme 19: Deprotection of sulfonamides.

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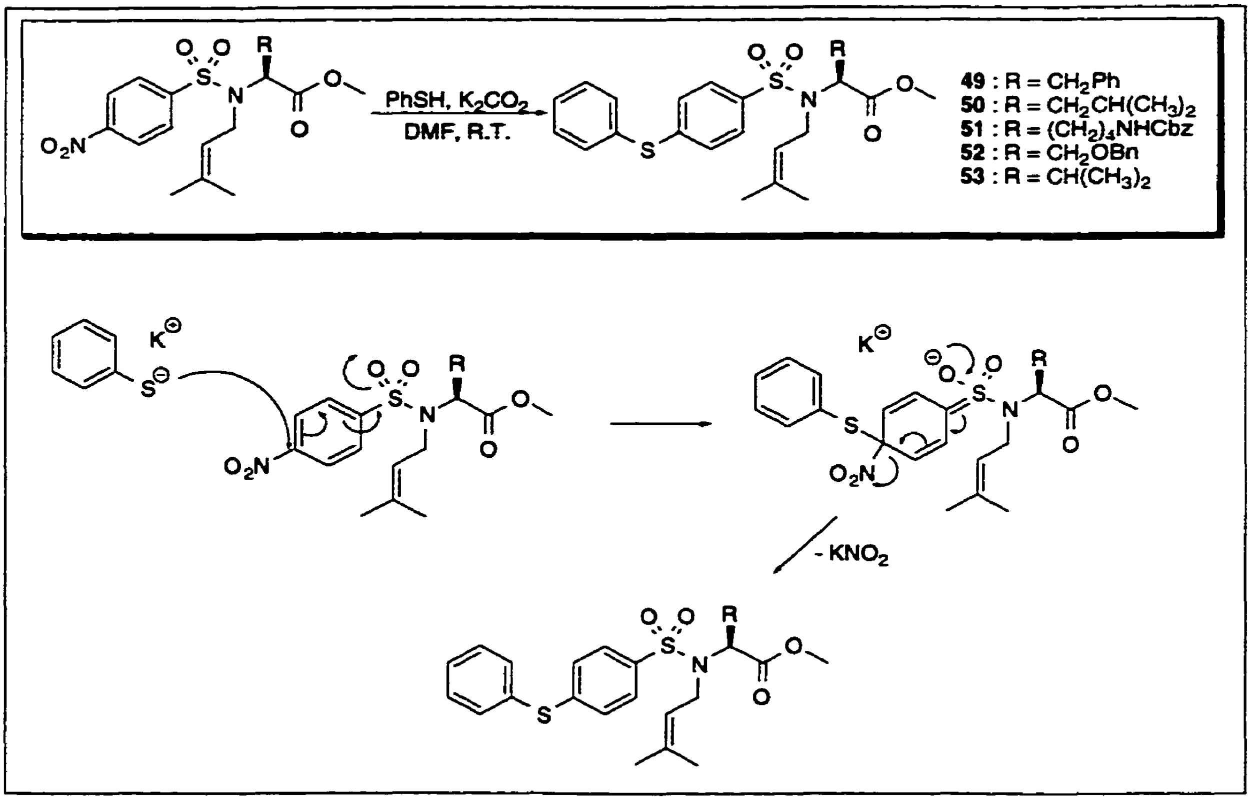
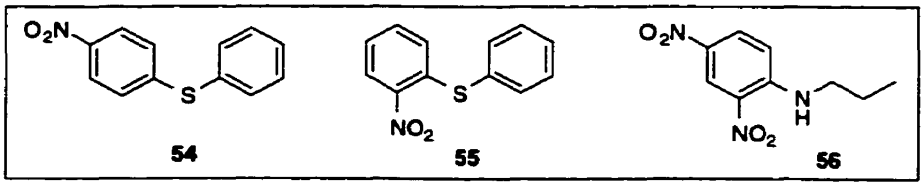
[79] For a monograph on Meisenheimer salts and on this mechanism, see Buncel, E; Crampton, M. R.; Strauss, M. J.; Terrier, F., *Electron Deficient Aromatic- and Heteroaromatic-Base Interactions*; Elsevier: New York, **1984**.

The deprotection of the prenylated 4-nitrobenzenesulfonamide **31** with thiophenoxide yielded the secondary amine **43** and also trace amounts of a by-product. After careful analysis by ^{1}H, ^{13}C NMR and mass spectrum, we were able to deduce the by-product structure **49** and also was able to postulate a mechanism for its formation (Scheme 20). The same type of thiophenoxide by-products were also observed in the deprotection of all the prenylated 4-nitrobenzenesulfonamides.



Scheme 20: Structures and possible mechanism of thiophenoxide by-products.

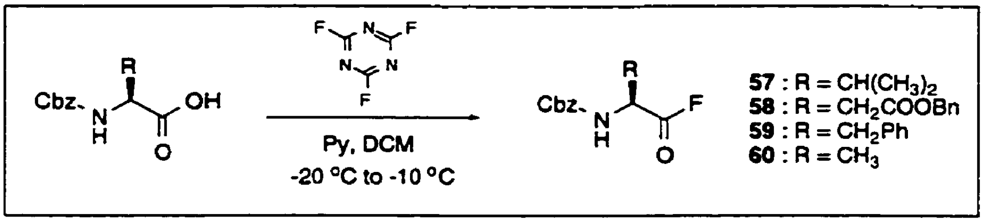
As stated earlier, all the alkylated sulfonamides were deprotected via intermolecular Meisenheimer complexes. The by-products from these deprotections were also isolated and characterized (Scheme 21).



Scheme 21: Intermolecular Meisenheimer by-products.

2.2.4 Synthesis of N-Alkylated Dipeptides

Peptide coupling is an important aspect of synthetic organic chemistry and there are many reagents which are used for this transformation.[80] The coupling of hindered primary amines in peptide synthesis has received some attention.[81] However, the coupling of hindered secondary amines has not been extensively explored apart from those involving N-methylated amino acids.[70,82] In a parallel approach to mine, one of my co-workers, Mr. Ulhas Bhatt[83] was also interested in the coupling of N-allylic secondary amines to form derivatized dipeptides. He tried a plethora of traditional reagents (BOP, EDAC.CH_3I, DCC, PyBrOP, HATU and DIC) for this peptide coupling. However, his yields ranged from (<1 to 57 %). Our attention was then drawn to the use of acid fluorides which have shown promise in coupling hindered amines.[84] The acid fluorides were synthesized by adding 5 eq. cyanuric fluoride to a cooled stirred solution of the desired N^{α}-benzyloxycarbonyl amino acid in pyridine and dichloromethane (Scheme 22). After one hour the reaction was quenched with crushed ice. The acid fluorides were obtained as semi-solids in very good yields (85 to 88 %).



Scheme 22: Preparation of acid fluorides.

These acid fluorides were relatively stable and could be kept at 4 °C (refridgerator temperature) for long-term storage.

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[80] Bodanszky, M.; Bodanszky, A., *The Practice of Peptide Synthesis*, Springer Verlag, **1994**.

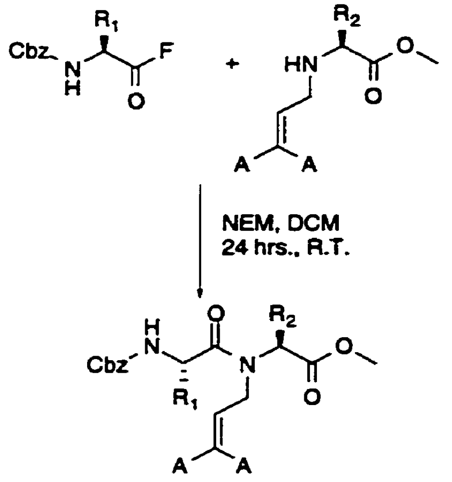
[81] Frérot, E.; Coste, J.; Pantaloni, A.; Dufour, M.-N.; Jouin, P., *Tetrahedron* **1991**, *47*, 259.

[82] Angell, Y. M.; García-Echeverría, C.; Rich, D. H., *Tetrahedron Lett.* **1994**, *35*, 5981.

[83] Bhatt, U., Ph.D. candidate, McGill University, Dept. of Chemistry, **1994-present**.

[84] (a) For a recent review see Carpino, L. A.; Beyermann, M.; Wenschuh, H.; Bienert, M., *Acc. Chem. Res.* **1996**, *29*, 268. (b) Carpino, L. A.; Mansour, E.-S. M. E.; Sadat-Aalaee, D., *J. Org. Chem.* **1991**, *56*, 2611.

The reaction of the N-alkylated amino acids with the acid fluorides was then investigated. To a solution of the secondary amine in N-ethylmorpholine and dichloromethane was added a solution of the acid fluoride (3-5 eq.) in dichloromethane over a period of five minutes (Scheme 23). A color change from yellow to deep red was an indication that the reaction was progressing. After 24 hours stirring at R.T., the functionalized dipeptides were obtained with yields ranging from 65 to 85 %.



61 : $R_1 = CH(CH_3)_2$, $R_2 = CH_2Ph$, $A = H$
62 : $R_1 = CH(CH_3)_2$, $R_2 = CH_2Ph$, $A = CH_3$
63 : $R_1 = CH_2COOBn$, $R_2 = CH_2Ph$, $A = H$
64 : $R_1 = CH_2COOBn$, $R_2 = CH_2Ph$, $A = CH_3$
65 : $R_1 = CH_2Ph$, $R_2 = CH_2CH(CH_3)_2$, $A = H$
66 : $R_1 = CH_2Ph$, $R_2 = CH_2CH(CH_3)_2$, $A = CH_3$
67 : $R_1 = CH_2Ph$, $R_2 = (CH_2)_4NHCbz$, $A = CH_3$
68 : $R_1 = CH_2Ph$, $R_2 = CH_2OBn$, $A = CH_3$
69 : $R_1 = CH_3$, $R_2 = CH(CH_3)_2$, $A = CH_3$

Scheme 23: Preparation of functionalized dipeptides.

2.2.5 Preparation of Cyclized Compounds via Ozonolysis[85]

The olefinic dipeptide was ozonized at -78 °C in methanol for three hours. The excess ozone was then removed by passing in dry nitrogen. For the reductive workup, excess dimethyl sulfide[86] was added at -78 °C and the solution was allowed to warm up slowly to room temperature and left to stir for ten hours. After chromatography, a mixture of cyclized alcohol and alkene **70-75 a/b** was obtained (Scheme 24). It should be noted that for the ozonolysis of all the allylated dipeptides, low yields were obtained compared with that of the prenylated dipeptides. Also, methanol was a much better solvent than dichloromethane in terms of yields obtained.

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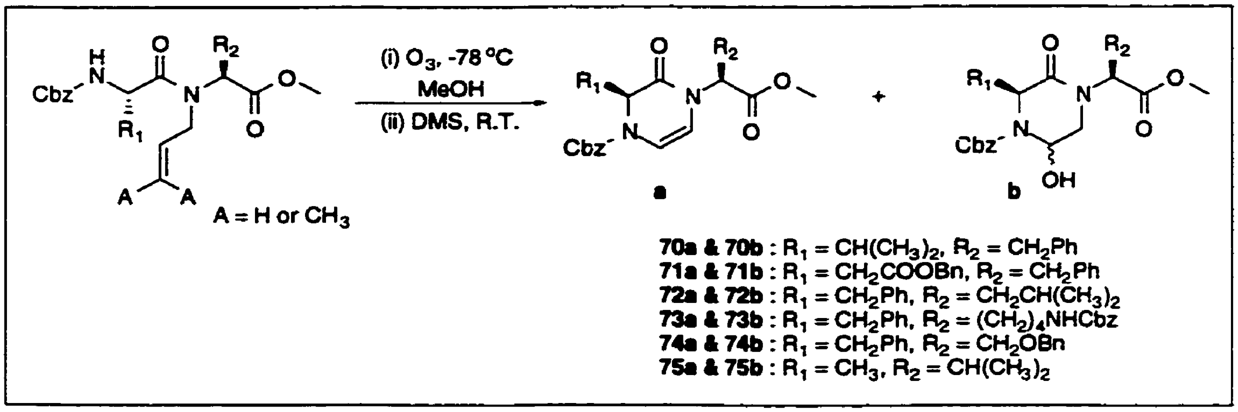
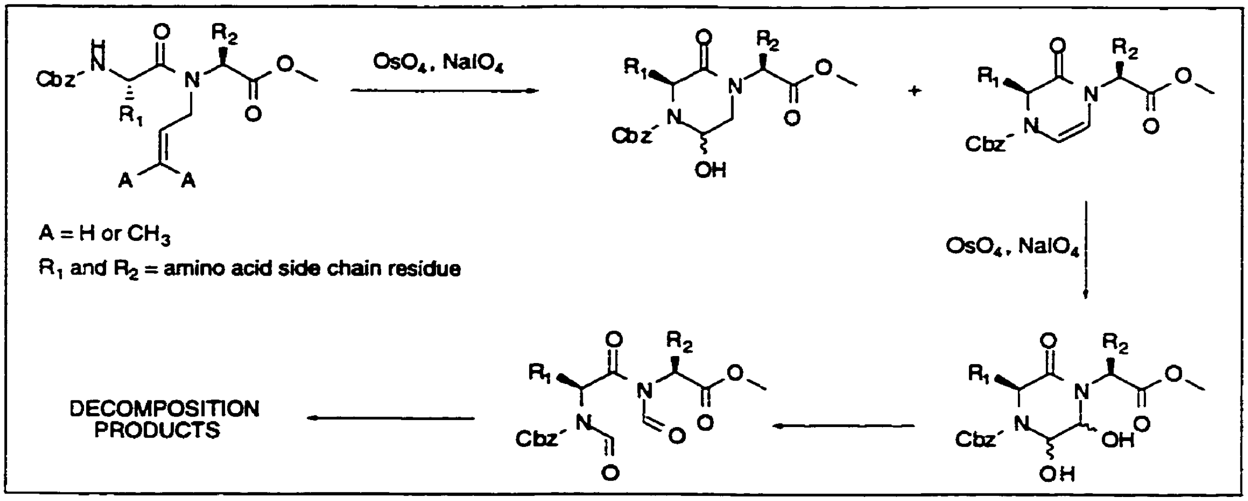
[85] For a monograph, see Razumovskii, S. D.; Zaikov, G. E., *Ozone and its Reactions with Organic Compounds*; Elsevier: New York, **1984**.
[86] Pappas, J. J.; Keaveney, W. P.; Gancher, E.; Berger, M.,*Tetrahedron Lett.* **1966**, 4273.



Scheme 24: Ozonolysis of olefinic dipeptides.

The ^{1}H NMR spectrum of the mixture was highly complex and gave several multiple overlapping signals due to the presence of two diastereomers existing as a number of rotamers. Thus only mass spectra of these mixtures were reported.

We also explored the use of osmium tetroxide and sodium periodate to facilitate the above transformation.[87] However, we were unable to make this reaction work and ended up with unidentified decomposition products. A possible explanation for the decomposition is depicted in Scheme 25.



Scheme 25: Attempted cyclization with osmium tetroxide.

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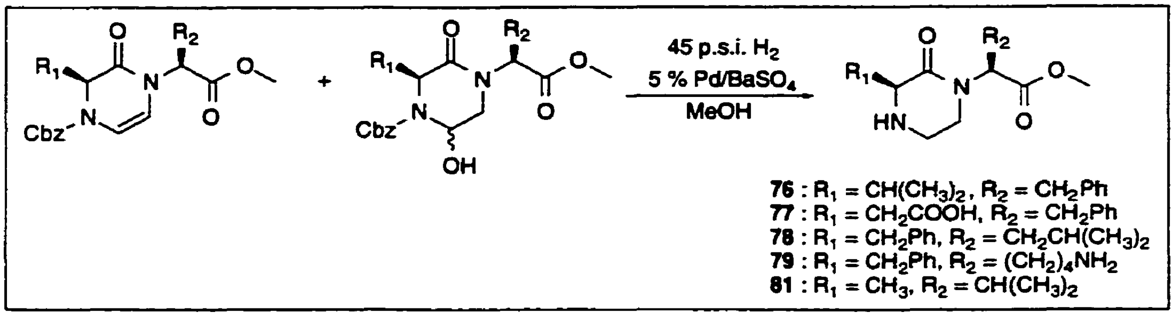
[87] Pappo, R.; Allen, D. S. Jr.; Lemieux, R. U.; Johnson, W. S., *J. Org. Chem.* **1956**, *21*, 478.

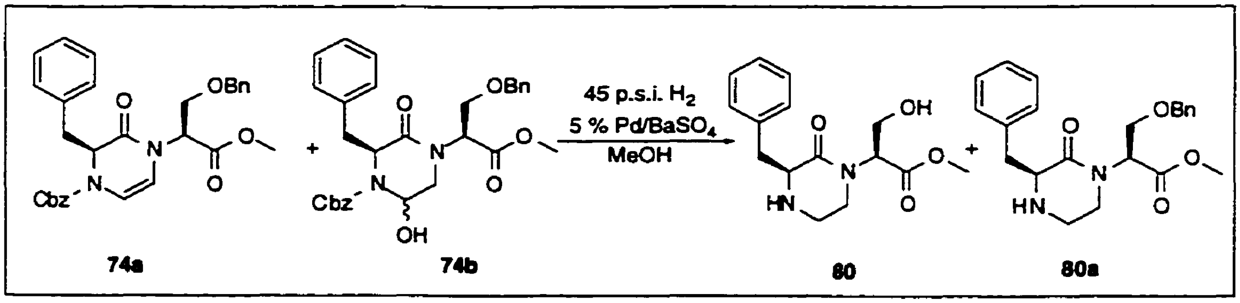
2.2.6 Hydrogenation of Protected Cyclized Alkene and Alcohol.

Hydrogenation[88] of the mixture of cyclized alkene and alcohol using 5 % palladium on barium sulfate for 6 hours at 45 p.s.i. afforded the desired oxopiperazines in good yields (Scheme 26). Under these conditions, the first known cyclized aspartame analog **77** was achieved. Initial tasting of this analogue proved it to be neutral in taste.



Scheme 26: Hydrogenation of cyclized alkene and alcohol.

The hydrogenation of mixture **74a** and **74b** under the same conditions as above, gave a mixture of the desired oxopiperazine **80** and its O-benzyl derivative **80a**. The use of ethyl acetate, ethanol and varying amounts of catalytic agent (10 % Pd/C or 5 % $Pd/BaSO_4$) did not made a difference (Scheme 27). The alcohol moiety, even though it was primary, is possibly a relatively hindered one and condition had to be changed in order to cleave it by hydrogenation. The problem was eventually solved by using a mixture of ethanol, acetic acid and water in a ratio of 12:2:1 and 1.0 eq. of 10 % Pd/C catalyst for 36 hours and under



Scheme 27: Hydrogenation of O-benzyl derivative.

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[88] Genearal references: (a) Freifelder, M., *Catalytic Hydrogenation in Organic Synthesis: Procedures and Commentary*, Wiley-Interscience, New York, **1978**. (b) Rylander, P. N., *Catalytic Hydrogenation in Organic Syntheses*, Academic Press, New York, **1979**. (c) Augustine, R. L., *Catalytic Hydrogenation*, Marcel Dekker, New York, **1965**.

a pressure of 50 p.s.i. of hydrogen, conditions that were developed by Eric Marsault[89] for cleaving hindered secondary benzyl ethers. Only under these conditions were we able to remove this benzyl ether.

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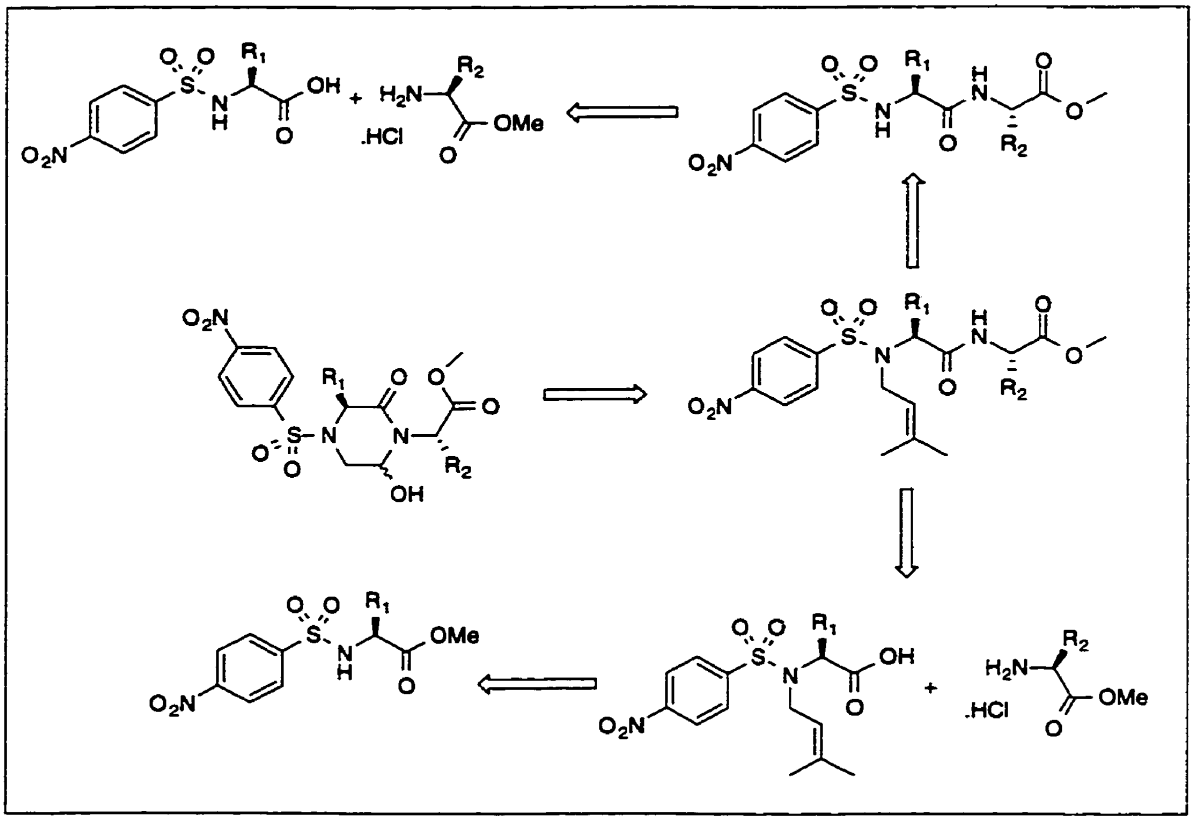
[89] Marsault, E., *Ph.D. Thesis*, McGill University, Dept. of Chemistry, **1996**.

2.3 An Alternative Synthesis for Oxopiperazines Formation

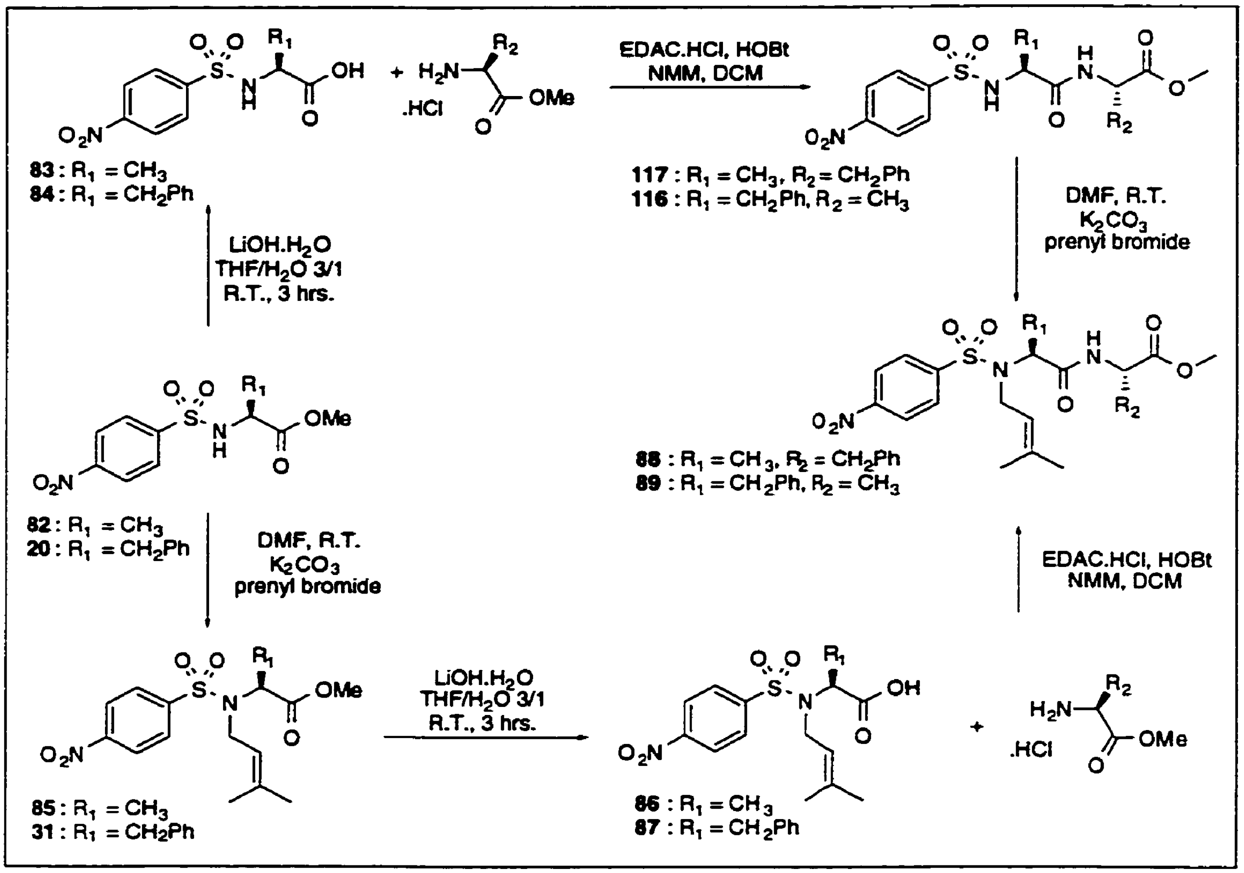
In our previous strategy described in Section 2.2 we reacted N-olefinic amino acids



Scheme 28: Alternative retrosynthesis of oxopiperazines.

with acid fluorides and then after ozonolysis and reductive workup, we cyclized via the carbamate NH. We decided to check the versality of our synthesis by cyclizing via the amide NH instead as depicted in Scheme 28.

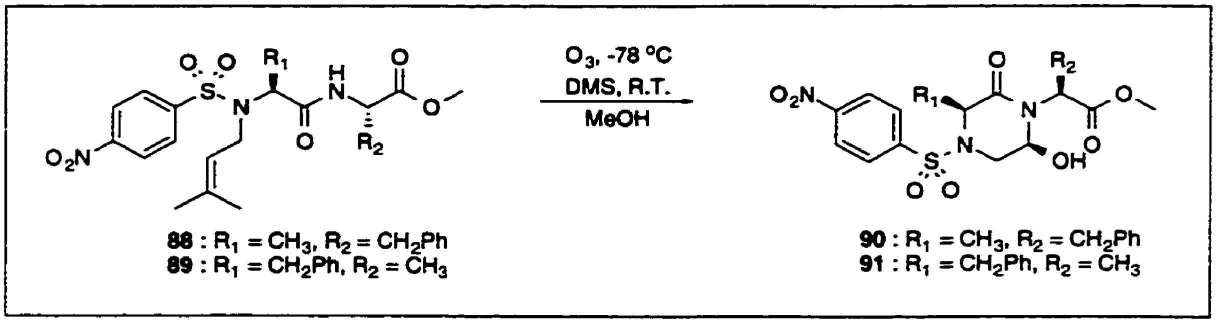
To carry out such a reaction we first needed to generate olefinic dipeptides **88** and **89**, where the amide NH is free (Scheme 29).



Scheme 29: Synthesis of olefinic dipeptides **88** and **89**.

We investigated two possible routes starting from readily available sulfonamides **82** and **20** derived from alanine and phenylalanine respectively. In the first route, sulfonamide methyl esters **82** and **20** were hydrolysed with lithium hydroxide in a mixture of THF and water. After 3 hours stirring at R.T., the reaction was quenched with concentrated hydrochloric acid and the pH of the solution adjusted to 1 to provide acids **83** and **84**. They were then coupled with amino acid methyl esters to yield the sulfonamide dipeptides **117** and **116**, which were then prenylated to give the desired prenylated sulfonamide dipeptides **88** and **89**. The other route was also investigated. The prenylated sulfonamide methyl esters **85** and **31** were hydrolysed as before to yield the acids **86** and **87**. They were then coupled with amino acid methyl esters to yield the prenylated sulfonamide dipeptides **88** and **89**. The first route was better in terms of higher yields and synthetic ease.

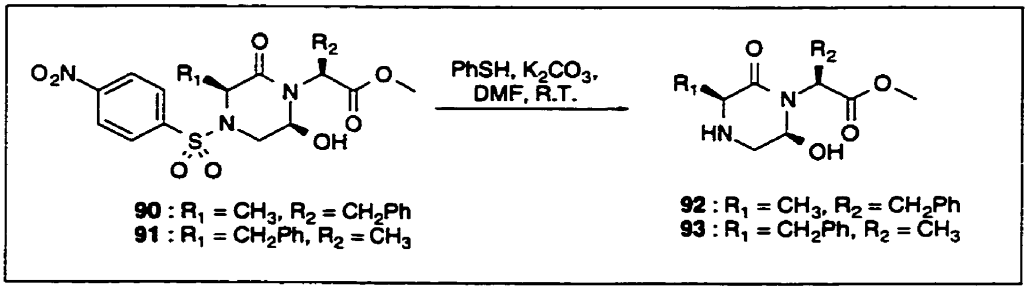
Ozonolysis of **88** and **89** was then accomplished at -78 °C in methanol, followed by reductive work up to yield the functionalized oxopiperazines **90** and **91** (Scheme 30) respectively. Interestingly, we only obtained the cyclized alcohol and none of the elimination product as noticed before. Note that the hydroxyl group is at the 6-position on the oxopiperazine compared to the 5-position as previously seen in our former approach.



Scheme 30: Ozonolysis of prenylated sulfonamide dipeptides.

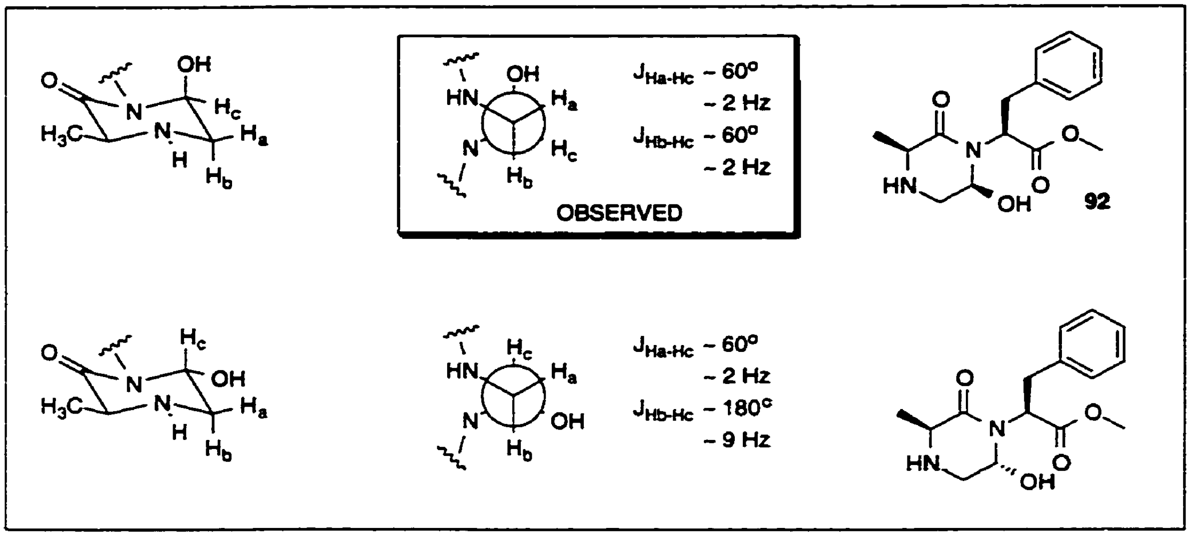
A new stereocenter was generated and we obtained a mixture of diastereomers in which one isomer predominated in a ratio of ~30:1. At this stage it was difficult to assign the right configuration of the new stereocenter due to overlapping ^{1}H NMR signals which complicated matters.

Deprotection of cyclized sulfonamides **90** and **91** using thiophenoxide lead to the desired oxopiperazines **92** and **93** (Scheme 31).



Scheme 31: Deprotection of cyclized sulfonamides.

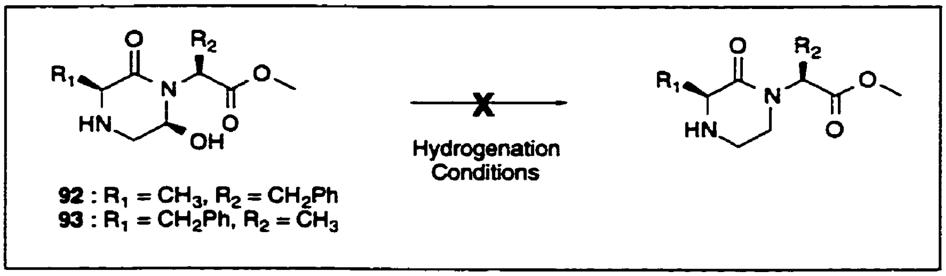
After this deprotection step we were then able to established the relative configuration at the C-6 position of the oxopiperazines (Scheme 32) as the ^{1}H NMR signals were well resolved.



Scheme 32: Relative configuration at C-6.

From the ^1H NMR of the major cyclic carbinolamide, we were able to calculate the coupling constants $J_{Ha\text{-}Hc}$ and $J_{Hb\text{-}Hc}$. Only when the hydroxyl group was in the pseudo axial position were the coupling constants in agreement with known values. Therefore, structure **92** was assigned to it where the hydroxyl group is cis with respect to the methyl group.

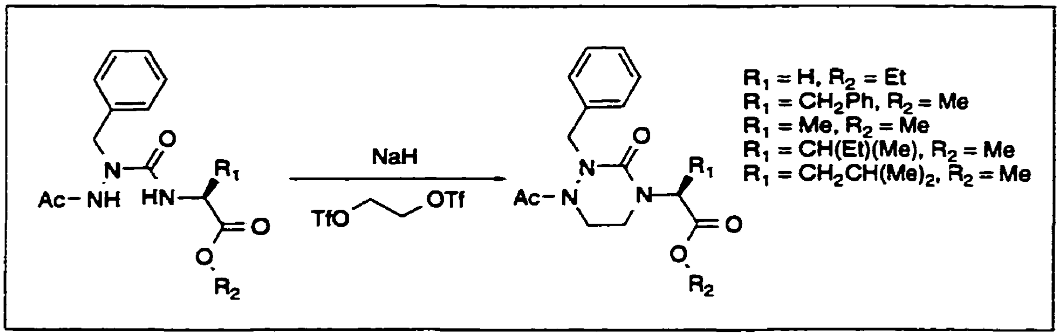
Under several hydrogenation conditions using catalysts such as Pd/C, PtO and solvent systems; methanol, ethyl acetate, ethanol/acetic acid/water, we were unable to remove the hydroxyl group of compounds **92** and **93** and was only able to recover starting material(Scheme 33).



Scheme 33: Attempted hydrogenation of hydroxyl group.

2.4 Amido-Carbamate Cyclization Approach

As mentioned previously in Section 2.1, we attempted cyclization of BOC dipeptides using dibromoethane as the dielectrophile under several different conditions without any success. Using ethylene sulfate[90] as a dielectrophile Pohlmann *et al.*[62] initially tried to do a similar cyclization with a glycyl leucine dipeptide. Unfortunately, they did not observe the formation of the expected cyclic product and recovered the starting material completely. Later, they became aware of a synthesis of 1,2,4-triazinones by Gante *et al.*[91] (Scheme 34) involving N,N-cyclization by the use of ethylene glycol bis-triflate.[92]



Scheme 34: Synthesis of 1,2,4-triazinones.[91]

Pohlmann and co-workers were then able to successfully cyclize BOC-Gly-Leu-OMe using ethylene glycol bis-triflate and sodium hydride as the base in a modest 42 % yield. Note that this group reported the cyclization only of the above dipeptide. Spurred on by this great news and to make our strategy more attractive in terms of a shorter route, we explored their method.

To a cold solution (0 °C) of BOC-glycyl-leucine **98** in anhydrous diethyl ether was added an oily suspension of 1.2 eq. sodium hydride. After stirring for about 20 minutes, a solution of ethylene glycol bis-triflate **94** in dry ether was slowly added over a period of one hour. A further 1.7 eq. of sodium hydride was added and the reaction mixture allowed to stir for 15 hours at R.T. After acidic work up and a very tedious column chromatography, cyclized BOC dipeptide **95** was obtained in 55 % yield. Cyclized dipeptide **97** was prepared in a similar fashion (Scheme 35).

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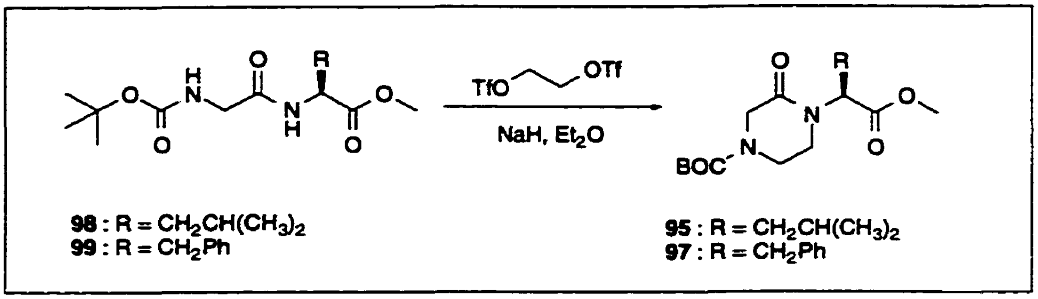
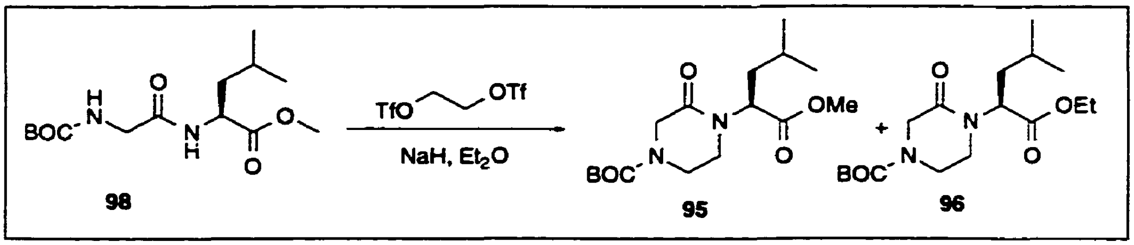
[90] Guillaume, D.; Brum-Bousquet, M.; Aitken, D. J.; Husson, H.-P., *Bull. Soc. Chim. Fr.* **1994**, *131*, 391.

[91] Gante, J.; Neunhoeffer, H.; Schmidt, A., *J. Org. Chem.* **1994**, *59*, 6487.



Scheme 35: Cyclization using bis-triflate.

In our initial attempts for making cyclic dipeptide **95**, we used anhydrous diethyl ether which we obtained from Aldrich Chemical Company. To our surprise, we obtained a by-product **96** in trace amounts (Scheme 36).



Scheme 36: Transesterification.

What alerted us to the formation of this product was its ^{1}H NMR spectrum. The NMR peaks of **96** were almost identical to that of compound **95** with the only exception of the methoxy peak. In the cyclized ethyl ester **96**, there was no singlet at ~3.6 ppm for the OMe peak as in **95**. Instead, the appearance of a triplet at ~1.25 ppm and a quartet at ~4.10 ppm for an OEt group were observed. The mass spectrum also confirmed the assigned structure.

The reason why we observed the transterification product **96** was quite simple. When we did this cyclization reaction, we used ~215 ml of anhydrous diethyl ether which we obtained from Aldrich. When we requested a Certificate of Analysis Report from Aldrich we were not surprised to see that this product contained trace amounts of ethanol and since we used a large amount of ether, there was probably enough ethanol present to cause transterification to occur. Knowing this fact, we prepared our own diethyl ether still

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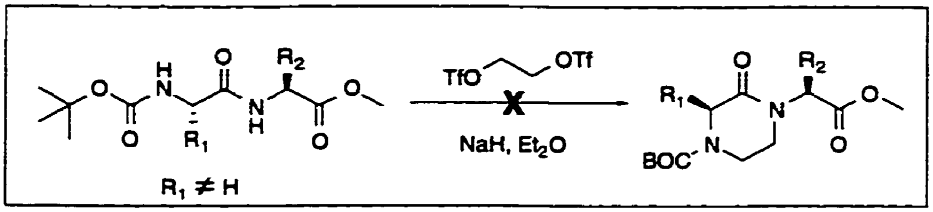
[92] Lindner, E.; von Au, G.; Eberle, H.-J., *Chem. Ber.* **1981**, *114*, 810.

using sodium benzophenone ketyl[93] to produce anhydrous and high purity diethyl ether. All subsequent reactions requiring dry ether was used from this still.

We then attempted to cyclize much more bulky dipeptides (Scheme 37) using the same methodology as above and where $R_1 \neq$ H. To our disappointment we were unable to achieve any of the desired cyclized product. Instead we recovered substantial amount of starting material and some unidentified products. We thus were able only to cyclize glycyl dipeptides



Scheme 37: Attempted cyclization of dipeptide with bis-triflate.

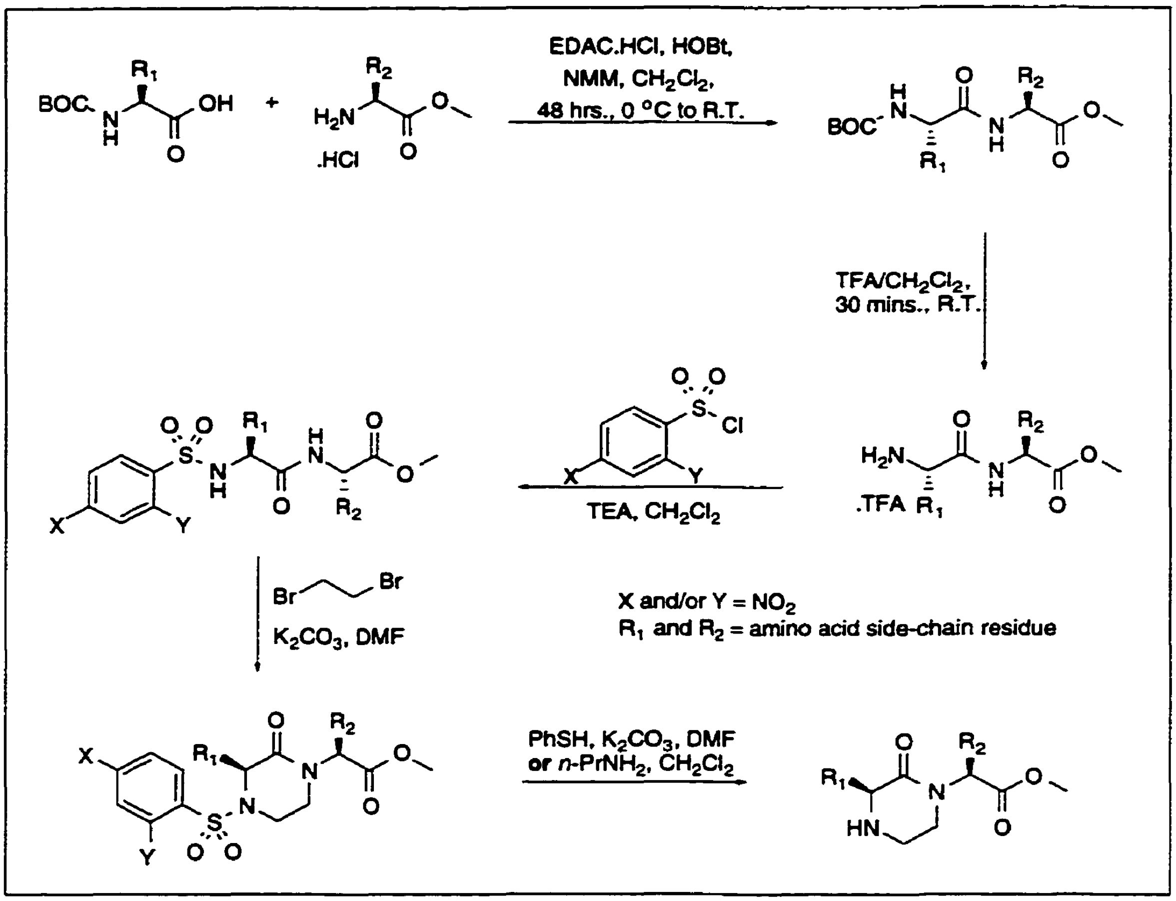
Steric hindrance at the carbamate NH is greater when $R_1 \neq$ H. This could be a possible reason why we did not see any coupling for bulkier dipeptides. This approach was abandoned and the search for a better one was undertaken.

---

[93] Perrin, D. D.; Armarego, W. L. F., *Purification of Laboratory Chemicals* **1988**, 3rd ed., Pergamon Press, pp. 179.

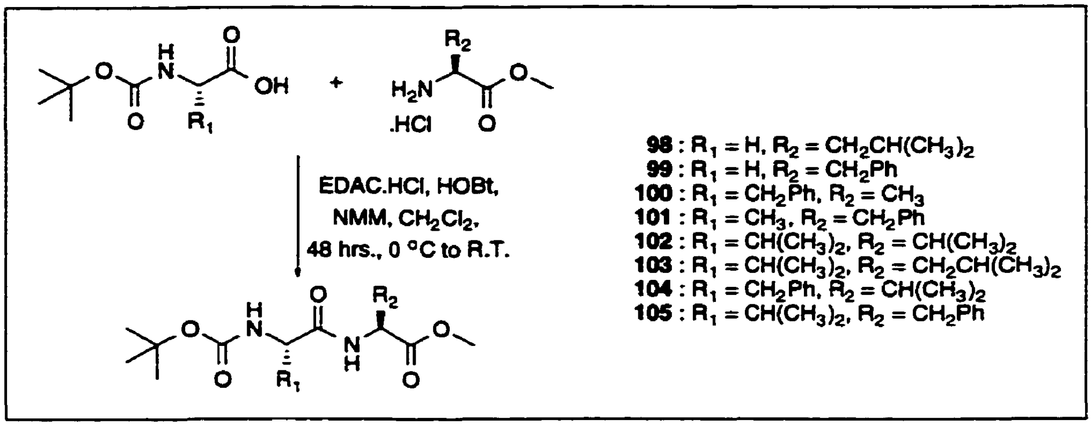
2.5 Amido-Sulfonamide Approach

In our previous section, we knew that sulfonamides can be easily alkylated. We thus decided to explore the cyclization of sulfonamide dipeptides (Scheme 38).



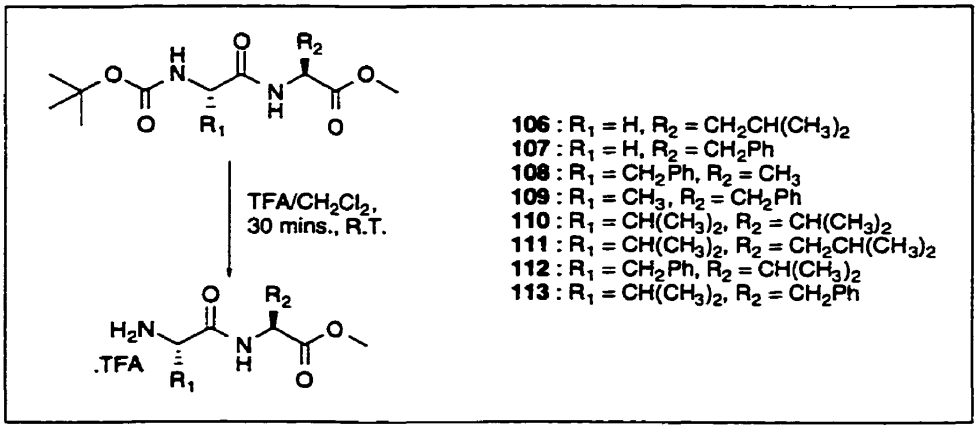
Scheme 38: Cyclization of sulfonamides with dibromoethane.

The first step of the above synthesis was the preparation of BOC-dipeptides (Scheme 39). These were readily prepared using 1-ethyl-3-(3'-dimethylaminopropyl)-carbodiimide hydrochloride, EDAC.HCl as the water soluble condensing reagent. The yields of these reactions were excellent ranging from 92 to 95 %. No column chromatography was required as all the impurities and by-products were removed by a simple acid/base wash. We found that a saturated solution of citric acid was much more effective than 1 N hydrochloric acid. Also a longer reaction time of 48 hours made a great difference in the yields obtained.



Scheme 39: Preparation of BOC-dipeptides.

The second step of the synthesis was the deprotection of the BOC protecting group (Scheme 40). The BOC group is used extensively in peptide synthesis for amine protection.[94] It's removal is facile and the yields are high. This deprotection was readily achieved by the use of a 1:1 ratio of TFA in dichloromethane.[95] After removal of the excess solvent the TFA salt of the dipeptide was obtained in quantitative yields.



Scheme 40: Deprotection of the BOC protecting group.

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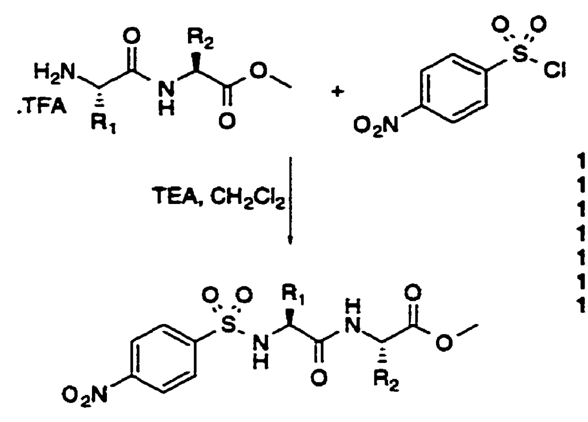
[94] Bodanszky, M., *Principles of Peptide Chemistry*, Springer-Verlag, New York, **1984**, pp 99.

[95] See for example: (a) Bodanszky, M.; Bodanszky, A, *Int. J. Pept. Protein Res.* **1984**, *23*, 565. (b) Masui, Y.; Chino, N.; Sakakibara, S., *Bull. Chem. Soc. Jpn.* **1980**, *53*, 464.

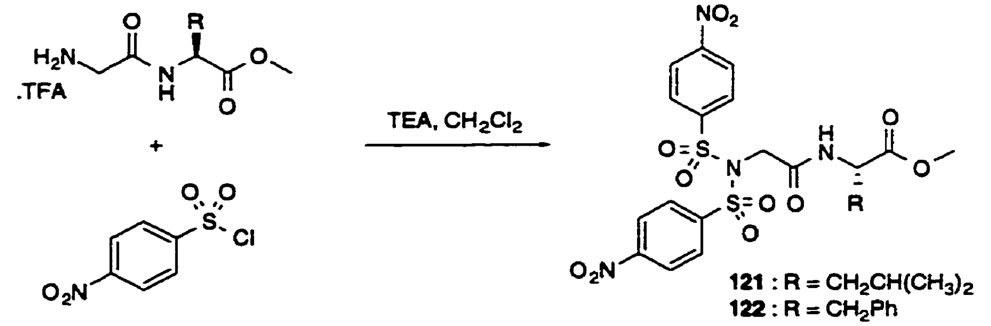
The next step was the formation of the sulfonamides. Since the yields of our previous 4-nitrobenzenesulfonamides were better than the 2- and 2,4-dinitrobenzenesulfonamides we used the former (Scheme 41). In a later study we used all three types.



114 : $R_1 = H$, $R_2 = CH_2CH(CH_3)_2$
115 : $R_1 = H$, $R_2 = CH_2Ph$
116 : $R_1 = CH_2Ph$, $R_2 = CH_3$
117 : $R_1 = CH_3$, $R_2 = CH_2Ph$
118 : $R_1 = CH(CH_3)_2$, $R_2 = CH(CH_3)_2$
119 : $R_1 = CH(CH_3)_2$, $R_2 = CH_2CH(CH_3)_2$
120 : $R_1 = CH_2Ph$, $R_2 = CH(CH_3)_2$

Scheme 41: Formation of 4-nitrobenzenesulfonamides.

The 4-nitrobenzenesulfonamides were prepared as before. During the preparation of glycyl sulfonamides **114** and **115** we isolated a by-product (Scheme 42).

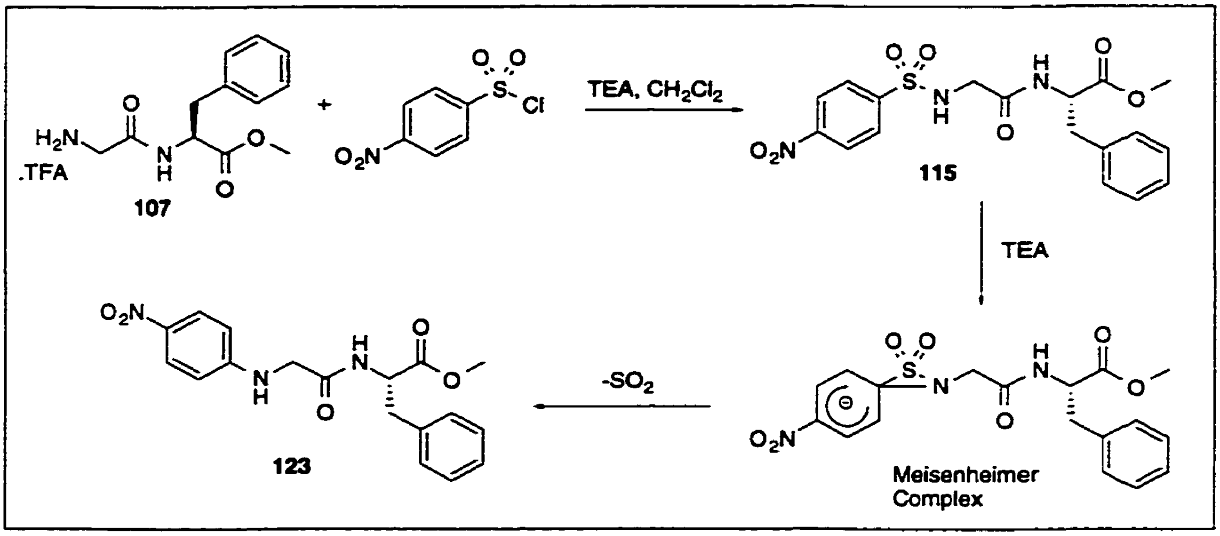


121 : $R = CH_2CH(CH_3)_2$
122 : $R = CH_2Ph$

Scheme 42: Bis-sulfonamide formation.

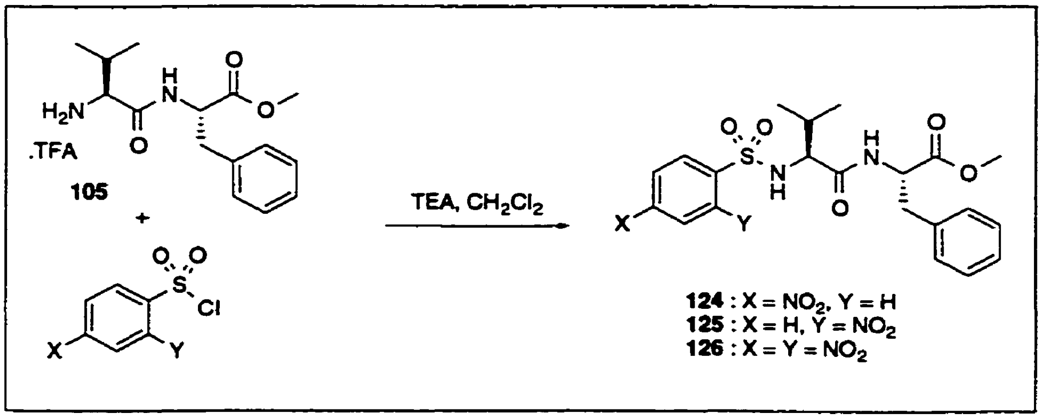
Bis-sulfonamide formation was only observed during the preparation of the above sulfonamides. The yields of bis-sulfonamides **121** and **122** were 10 and 8 % respectively. ^1H NMR showed an extra 4 proton integration in the sulfonamide region and their mass spectra results were confirmed. A plausible answer to this bis-sulfonamide formation is that after the first sulfonyl attachment, the molecule is not that sterically hindered. This is because the first amino acid residue is a hydrogen (i.e. glycyl) as compared to all the other sulfonamide dipeptides we made, where the first amino acid residue is larger than a hydrogen atom.

Another by-product we were able to isolate from the preparation of sulfonamide **115** was assigned the following structure **123** (Scheme 43). The mass spectrum result was the most helpfull as it showed a mass of 64 units less than that of sulfonamide **115**. This loss of 64 mass units was accounted by the expulsion of sulfur dioxide gas due to the concomitant decomposition od **115** via the intramolecular Meisenheimer complex.



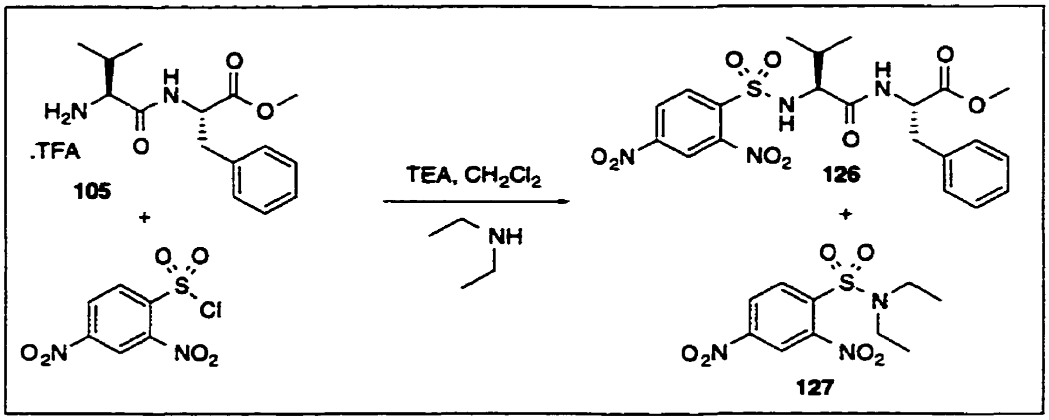
Scheme 43: Formation of compound **123**.

Since we also wanted to check the rates of the cyclization step of the three types of sulfonamides that we have been using, the following series was made (Scheme 44).



Scheme 44: Valine-phenylalanine sulfonamide series.

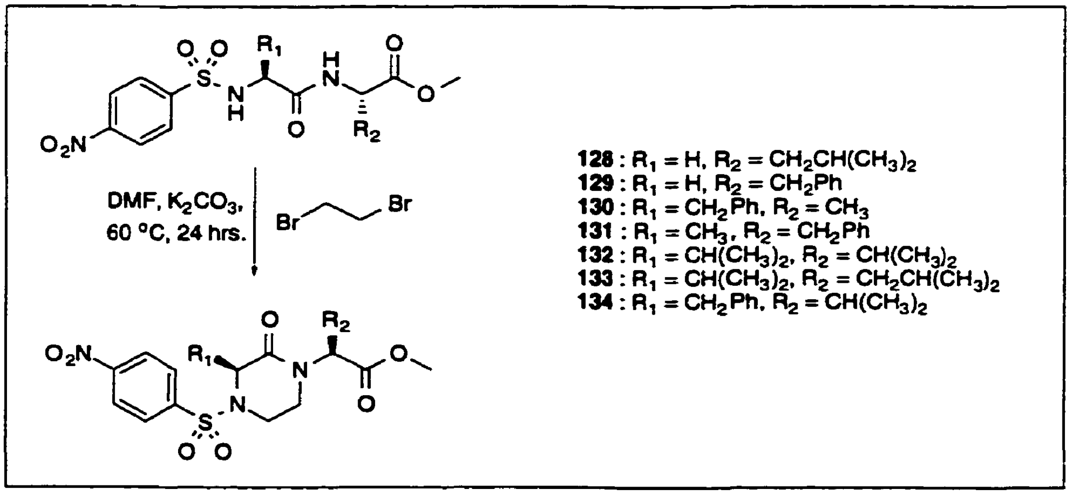
During my haste to prepare the 2,4-dinitrobenzenesulfonamide **126**, I did not use freshly distilled triethylamine, but that of an old batch and we observed yet again the formation of another by-product **127** in trace amounts (Scheme 45).



Scheme 45: Formation of by-product **127**.

We attribute the formation of by-product **127** due to the presence of diethylamine impurity in the old triethylamine.

The most critical step of our strategy was the cyclization step (Scheme 46). To a solution of the sulfonamide dipeptide in DMF was added an excess of potassium carbonate (10 mole eq.) and dibromoethane (10 eq.) and the reaction mixture allowed to stir for 24 hours at 60 °C.

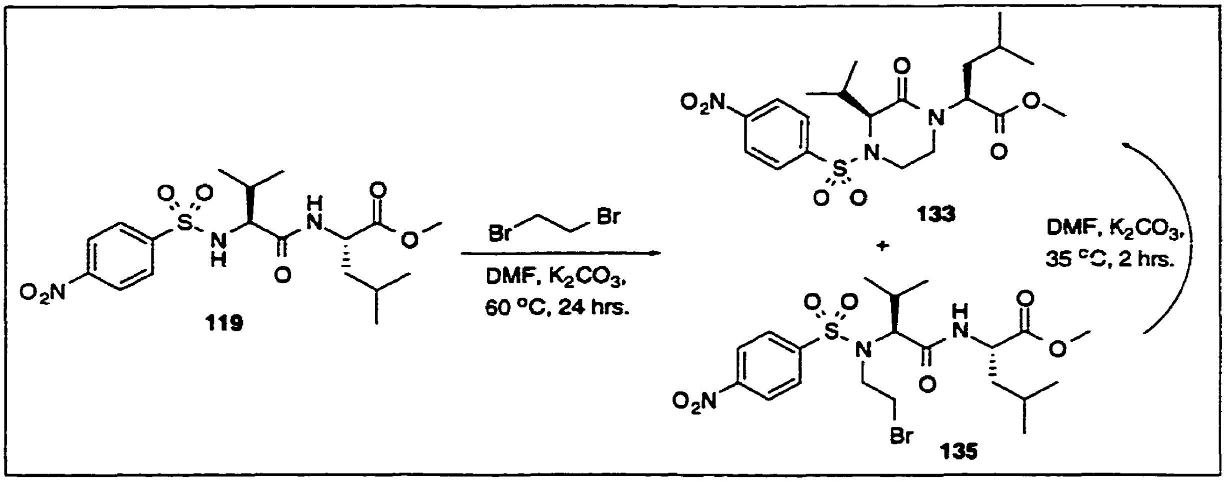


128 : $R_1 = H$, $R_2 = CH_2CH(CH_3)_2$
129 : $R_1 = H$, $R_2 = CH_2Ph$
130 : $R_1 = CH_2Ph$, $R_2 = CH_3$
131 : $R_1 = CH_3$, $R_2 = CH_2Ph$
132 : $R_1 = CH(CH_3)_2$, $R_2 = CH(CH_3)_2$
133 : $R_1 = CH(CH_3)_2$, $R_2 = CH_2CH(CH_3)_2$
134 : $R_1 = CH_2Ph$, $R_2 = CH(CH_3)_2$

Scheme 46: Cyclization of sulfonamide dipeptides.

The desired cyclized dipeptides were obtained in high yields ranging from 88 to 93 % without chromatographic separation

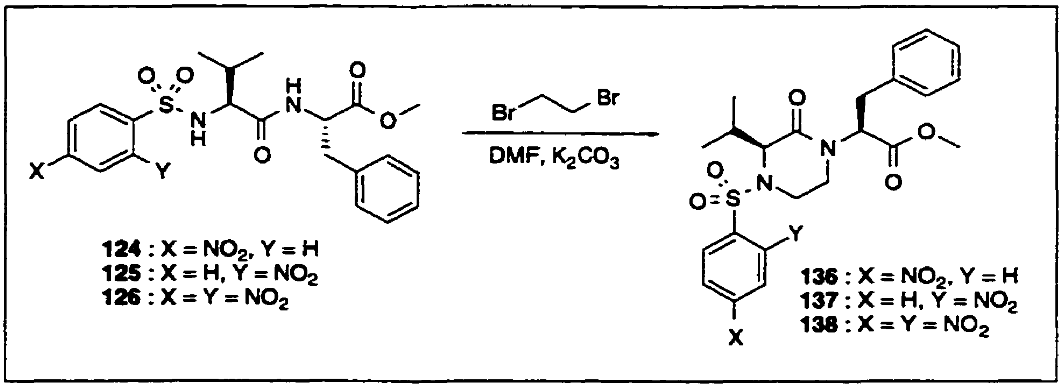
In our initial attempts to do this cyclization step on sulfonamide **119**, we used only 2 mole eq. potassium carbonate and we obtained a mixture of products (Scheme 47).



Scheme 47: Initial attempt to cyclize sulfonamide **119**.

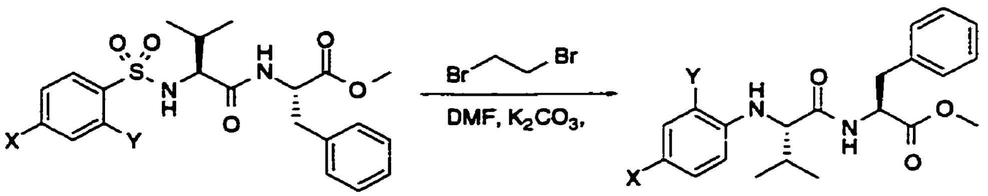
After column chromatography, the desired cyclized compound **133** was obtained and also the bromoethyl intermediate **135**. To a solution of this intermediate **135** in DMF was added 2 mole eq. potassium carbonate and after 2 hours at 35 °C, cyclized compound **133** was obtained in quantitative yield.

The valine-phenylalanine sulfonamide series (Scheme 48) was also prepared. We observed some very interesting side products.



Scheme 48: Cyclization of valine-phenylalanine sulfonamide series.

The cyclization of the 4-nitrobenzenesulfonamide dipeptide **124** proceeded smoothly as before. However, for the cyclization of the 2-nitrobenzenesulfonamide **125** a longer reaction time was required (36 hours compared with the usual 24 hours). Also the reaction was not a clean one and we obtained the intramolecular Meisenheimer complex by-product **139** (Scheme 49). The 2,4-dinitrobenzenesulfonamide dipeptide **126** cyclization was very problematic. Three different reaction temperature were investigated. At R.T. for 24 hours and at 60 °C for two hours, the concomitant intramolecular Meisenheimer complex by-product **140** was isolated with no presence of any of the desired product. A compromise temperature of ~35 °C was reached and only then were we able to obtained the desired product **138** in 45 % yield, but we also obtained the decomposition product **140**.

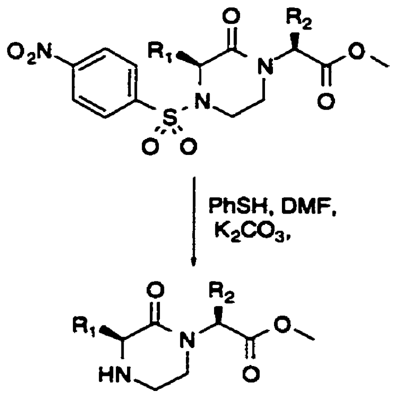


125 : $X = H, Y = NO_2$
126 : $X = Y = NO_2$

139 : $X = H, Y = NO_2$
140 : $X = Y = NO_2$

Scheme 49: Concomitant decomposition products.

The final step was the removal of the sulfonyl group to form the cyclic secondary amines (Scheme 50). Facile deprotection was achieved with thiophenoxide as before.

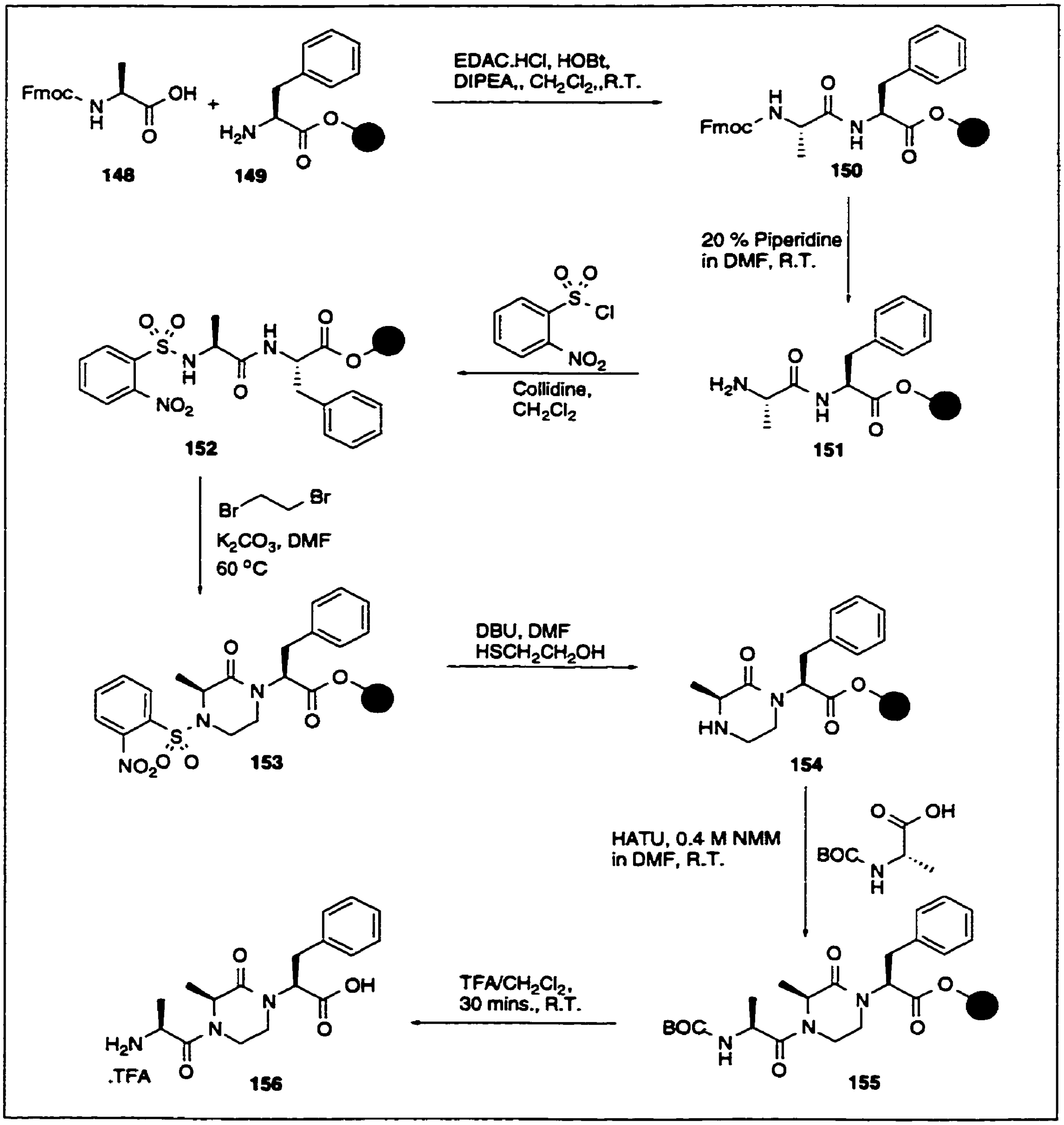


141 : $R_1 = H, R_2 = CH_2CH(CH_3)_2$
142 : $R_1 = H, R_2 = CH_2Ph$
143 : $R_1 = CH_2Ph, R_2 = CH_3$
144 : $R_1 = CH_3, R_2 = CH_2Ph$
145 : $R_1 = CH(CH_3)_2, R_2 = CH(CH_3)_2$
146 : $R_1 = CH(CH_3)_2, R_2 = CH_2CH(CH_3)_2$
147 : $R_1 = CH_2Ph, R_2 = CH(CH_3)_2$

Scheme 50: Facile deprotection using thiophenoxide.

2.6 Synthesis on Solid Support

The cyclization of sulfonamides using dibromoethane as the 1,2-dielectrophile in our last section was very encouraging. The yields for each individual step were high and the reagents and conditions were compatible with solid phase synthesis. Thus we decided to attempt the synthesis of a functionalized oxopiperazine on solid support (Scheme 51).



Scheme 51: Solid phase synthesis of a tripeptide.

We investigated the scope of our reaction by using an amino acid preloaded on the 2-chloro-trityl resin. This resin has been widely used for fully protected peptide fragment synthesis by Fmoc solid phase synthesis. Cleavage of the product from the resin can be achieved under mild conditions such as treatment with 0.5 % TFA in dichloromethane.

It should be noted that I did all the solid support work in the Astra labs, Montreal. All the reverse phase-high performance liquid chromatography and electron spray mass spectrometry of my products were kindly recorded by Dr. Ralf Schmidt, Dr. Brian Takasaki and Dr. Mirek Tomaszewski.

The first step of our synthesis was the coupling of Fmoc-L-alanine **148** to L-phenylalanine-2-chlorotrityl resin **149**. This was accomplished using either 4 eq. of EDAC.HCl, diisopropylethylamine (DIPEA) and HOBt respectively in CH_2Cl_2 for three hours or 4 eq. of O-benzotriazole-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU)[96] in 0.4 M N-methylmorpholine/DMF for 20 minutes to provide Fmoc protected dipeptide **150**. The reaction was also monitored by the Kaiser ninhydrin test[97] until it was negative. The next step was the Fmoc deprotection[98] of **150** which was efficiently achieved with 20 % piperidine in DMF for 20 minutes to yield amine **151**.

For the sulfonylation reaction, amine **151** was swollen in CH_2Cl_2 and then treated with 5 eq. of collidine and 3 eq. of 2-nitrobenzenesulfonyl chloride for 2 hours at R.T. to provide the sulfonamide **152**. We and others[99] have observed that the use of DIPEA in CH_2Cl_2 for the sulfonylation reaction resulted in darkened resin and incomplete reaction even after prolonged reaction time and the addition of excess reagents, presumably because 2-nitrobenzenesulfonyl chloride was unstable under such conditions. A much longer reaction time (1 day) resulted in a slight deterioration of the product.

The cyclization step to form the oxopiperazine **153** was very problematic. Many different conditions were tried. The best condition was dibromoethane (10 eq.) in DMF using finely powdered potassium carbonate (10 eq.) as the base and heating the reaction for 60 °C for 18 hours, then washing the resin and resubmitting the resin to the reaction under

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[96] Dourtoglou, V.; Gross, B., *Synthesis* **1974**, 572.

[97] Kaiser, E.; Colescott, R. L.; Bossinger, C. D.; Cook, P. I., *Anal. Biochem.* **1970**, *34*, 595.

[98] For a review of the use of Fmoc protection in peptide synthesis, see: Atherton, E.; Sheppard, R. C., 'The Fluorenylmethoxycarbonyl Amino Protecting Group,' in *The Peptides.*, Udenfriend, S.; Meienhofer, J., Academic Press, Orlando, FL, **1987**, *Vol 9*, pp. 1-38.

the same conditions as above to give **153**. Other bases were also used such as tetramethylguanidine (TMG), 1,8-diazobicyclo[5.4.0]undec-7-ene (DBU) and 1,3,4,6,7,8-hexahydro-1-methyl-2*H*-pyrimido[1,2-a]pyrimidine (MTBD).[100] Only the use of MTBD gave comparable results to that of potassium carbonate as base. The use of ethylene glycol di-*p*-tosylate as the 1,2-dielectrophile did not yield any of the desired product. The alkylation of the sulfonamide was attempted under Mitsunobu conditions which were recently applied in solid phase synthesis for the alkylation of phenols.[101] However, we did not observe any coupling under those conditions.

Quantitative cleavage of the 2-nitrobenzenesulfonyl group of **153** was effective with β-mercaptoethanol and DBU in DMF to yield the cyclized amine **154**. We used the 2-NBS in preference to the 4-nitrobenzenesulfonyl (4-NBS) group since Miller *et al.*[102] had noted that the 2-NBS group was cleaved more readily than 4-NBS group on solid support. β-Mercaptoethanol was used in preference to the traditional thiophenol, since it cleaved the sulfonamides faster and it is less toxic and noxious. The deprotection step was easily followed via the formation of a bright yellow color. The third amino acid BOC-L-alanine was activated with the recently described coupling reagent, O-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU)[103] to give the BOC-tripeptide **155**. This step was performed twice to ensure complete coupling. The BOC group and the resin were removed simultaneously by treating the resin bound product with 50 % TFA/DCM at R.T. for 30 minutes yielding the deprotected tripeptide oxopiperazine analogue **156**.

The yield of each step was assessed by reverse phase-high performance liquid chromatography (RP-HPLC) and the product structure verified using electron spray mass spectrometry (Table 2).

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[99] Yang, L.; Chiu, K., *Tetrahedron Letts.* **1997**, *38*, 7307.
[100] Schwesinger, R., *Chimia* **1985**, *39*, 269.
[101] (a) Rano, T. A.; Chapman, K. T., *Tetrahedron Lett.* **1995**, *36*, 3789. (b) Krchnak, V.; Flegelova, A.; Weichsel, A. S.; Lebl, M., *Tetrahedron Lett.* **1995**, *36*, 6193. (c) Papaioannou, D.; Athanassopoulos, D.; Magafa, V.; Karamanos, N.; Stravropoulos, G.; Napoli, A.; Sindona, G.; Aksnes, D. W.; Francis, G. W., *Acta Chem. Scand.* **1994**, *48*, 324.
[102] Miller, S. C.; Scanlan, T. S., *J. Am. Chem. Soc.* **1997**, *119*, 2301.
[103] Capino, L. A., *J. Am. Chem. Soc.* **1993**, *115*, 4397.

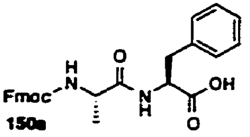
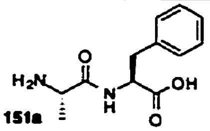
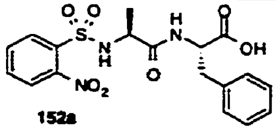
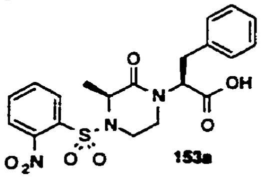
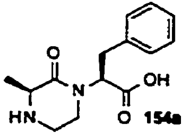
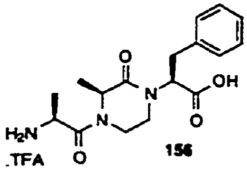
Entry	Structure	Yield (%)	MW	ES-MS (±)
1	 150a	96	458	459 (+)
2	 151a	88	236	235 (-)
3	 152a	87	421	420 (-)
4	 153a	48	447	446 (-)
5	 154a	85†	262	261 (-)
6	 156	80†	333*	334 (+)

Table 2: Yield and mass spectral results.

MW: Molecular Weight

ES-MS (±): Electron Spray-Mass Spectrometry in positive or negative mode

*: Molecular weight of the free amine

†: These are approximate yields which were assessed after compensating for impurities from the previous cyclization step (entry 4)

2.7 Concluding Remarks

As described from our previous sections, we have achieved efficient syntheses of substituted oxopiperazines. The direct approach using sulfonamide dipeptides and dibromoethane as the 1,2-dielectrophile is noteworthy. We have shown that using this approach we were able to synthesize a cyclic tripeptide on solid support. The cyclization step on solid support however, would need to be optimized as the yield for this step was modest (48 %). Mr. Ulhas Bhatt will be continuing this project. When this is accomplished, a cyclized dipeptide library can be synthesized consisting of appropriate amino acids selected for their wide range and variety of physico-chemical properties. This library of compounds can then be screened against a variety of protein substrates in binding assays in the search of micromolar leads for drug design.

CHAPTER 3: CONTRIBUTIONS TO KNOWLEDGE

1. Three novel synthetic methods for the formation of 2-oxopiperazines were achieved. By using one of these methodologies, the first known cyclized aspartame analogue was accomplished.

2. The reaction of N-allyl amino acids with acid fluorides was investigated and was shown to be a superior coupling method for secondary amines.

3. The first known amido-sulfonamide cyclization was achieved.

4. The synthesis of oxopiperazines on solid phase was undertaken.

CHAPTER 4: EXPERIMENTAL

4.1 General Methods.

^1H NMR spectra were recorded on JEOL CFP 270 and Varian UNITY 500 spectrometers at 270 and 500 MHz respectively. Peak assignments were made with homonuclear spin (H-H) decoupling experiments and 2D Correlation Spectroscopy (COSY). ^{13}C NMR spectra were recorded on JEOL CFP 270 and Varian UNITY 500 spectrometers at 67.9 and 125.7 MHz respectively. Peak assignments were made with 2D Heteronuclear Correlation (HETCOR). Chemical shifts are reported on the δ scales in parts per million (ppm) with solvent residues as references. Spin multiplicities are given with the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), br (broad) and m (multiplet). Mass Spectra (MS) were obtained on a KRATOS MS 25RFA spectrometer in the direct-inlet mode. All melting point are uncorrected and were determined on a GallenKamp block. Specific rotation values were measured on a JASCO DIP-140 digital polarimeter using a 10 mm length cell at the indicated wavelength, temperature and concentrations (calculated in g/100 ml solvent). IR spectra were recorded on an Analect FT A25-18 spectrometer between NaCl plates.

Elemental analyses were done by the Guelph Chemical Laboratories Ltd. and Canadian Microanalytical Service Ltd., Vancouver with range being ± 0.4 % of calculated value. Thin Layer Chromatography (TLC) was performed using Kieselgel 60 F_{254} aluminum backed plates (0.2 mm thickness). Column chromatography was performed using the method described by Still *et al.*[104] on Merck silica gel 40 to 63 μm particle size. Visualization methods included exposure by UV light and/or then by dipping in Solution A (ammonium molybdate (2.5 g) and ceric sulfate (1.0 g) in 10% v/v aqueous sulfuric acid (100 ml)) or dipping in a ninhydrin solution ((0.3 % w/v), acetic acid (3 % v/v) and n-butanol (96.7 % v/v)) followed by heating.

All air sensitive experiments were carried out under argon with freshly distilled dried solvents. All reactions involving anhydrous conditions were performed using glassware that was heated overnight in an oven at about 140 °C, then cooled in a dessicator

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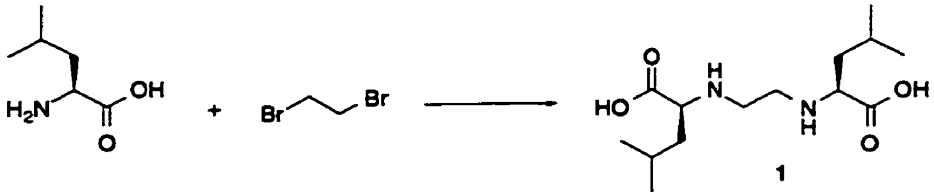
[104] Still, W. C.; Kahn, M.; Mitra, A., *J. Org. Chem.* **1978**, *43*, 2923.

containing drierite. Methylene chloride (CH_2Cl_2) was distilled from P_2O_5, diethyl ether and THF from sodium benzophenone ketyl. Pyridine was dried over KOH and toluene was dried by standing over sodium wire. Triethylamine and acetonitrile were distilled from CaH_2. All other chemicals were purchased from Aldrich Chemical Company Inc., Sigma Chemicals, Chem-Impex International, Novabiochem and Fluka Chemicals where appropriate and were used without further purification. Unless specified, all compounds were obtained as semi-solids or oils.

4.2 Experimental for Section 2.1

N,N'-Ethylene-bridged bis-L-leucine (1)



Sodium hydroxide (4.00 g, 0.10 mol) in water (20 ml) was added to L-leucine (13.12 g, 0.10 mmol). The solution was heated to reflux and 1,2-dibromoethane (4.33 ml, 0.05 mol) and potassium carbonate (6.91 g, 0.50 mol) were slowly added. The solution was stirred under reflux for six hours with some difficulty towards the end due to some undissolved potassium carbonate. Cooling and neutralizing to pH of 5 with concentrated hydrochloric acid resulted in the formation of a solid white product. This was washed well with water and air dried to give **1** as a white powder (4.93 g, 34 %). Mp 244-247 °C; IR (Nujol, cm^{-1}), 2400-2800 (carboxylic OH), 1730 (carboxylic acid C=O); ^{1}H NMR (270 MHz, ND_4OD with DSS as an internal standard): δ 0.86-0.92 (m, 12 H, 2 X $(\mathbf{CH_3})_2CHCH_2$), 1.27-1.77 (m, 6 H, 2 X $(CH_3)_2\mathbf{CHCH_2}$), 2.49-2.65 (m, 4 H, $N(\mathbf{CH_2})_2N$), 3.05 (dd, 2 H, J = 6.2 Hz and 8.4 Hz, 2 X C**H**N); ^{13}C NMR (67.9 MHz, ND_4OD with DSS as an internal standard): δ 24.02, 24.88 (2 X $(CH_3)_2CHCH_2$), 26.97 (2 X $(CH_3)_2CHCH_2$), 44.85 (2 X $(CH_3)_2CHCH_2$), 48.76 (2 X $N(CH_2)_2N$), 64.90 (2 X CHN), 184.58 (2 X COOH); MS (EI) m/e (%) 288 (1.5) [M]$^+$, 214 (100), 197 (24.6), 185 (44.2), 155 (74.6), 113 (34.9), 99 (32.9) Anal. Calcd for $C_{14}H_{28}N_2O_4\cdot 0.5H_2O$: C, 56.54; H, 9.83; N, 9.42; Found: C, 56.84; H, 9.75; N, 9.45.

(2S,3'S)-2-[3'-Isobutyl-2'-oxopiperazin-1'-yl]-4-methylpentanoic acid, *p*-toluenesulfonic acid salt (2)

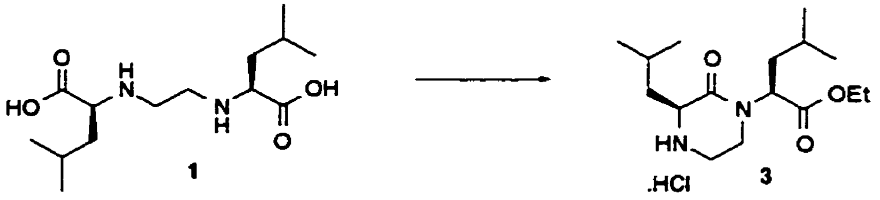
1

.TsOH 2

N,N'-Ethylene-bridged bis-L-leucine **1** (5.76 g, 20 mmol) was refluxed in acetonitrile (300 ml) for 24 hours in the presence of *p*-toluenesulfonic acid monohydrate (7.60 g, 40 mmol). The residue obtained after the removal of the solvent was washed with diethyl ether to give the tosylate salt of the cyclized monoketopiperazine (MKP) acid **2** as white fluffy flakes (8.34 g, 95 %). Mp 225-230 °C; $[\alpha]_D^{20}$ -52.2° (c 0.600, DMF); IR (Nujol, cm^{-1}), 2400-2800 (carboxylic OH), 1730 (carboxylic acid C=O), 1638 (amide C=O); ^1H NMR (270 MHz, DMSO-d_6): δ 0.82, 0.91 (2 d, 12 H, J = 6.2 Hz and 6.2 Hz, 2 X $(C\mathbf{H}_3)_2CHCH_2$), 1.42-1.86 (m, 6 H, 2 X $(CH_3)_2C\mathbf{H}C\mathbf{H}_2$), 2.29 (s, 3 H, $C\mathbf{H}_3C_6H_4$), 3.30-3.55 (m, 4 H, $C\mathbf{H}_2C\mathbf{H}_2$), 4.08 (dd, 1 H, J = 4.0 Hz and 9.6 Hz, α-C**H** on MKP ring), 4.97 (dd, 1 H, J = 4.0 Hz and 11.4 Hz, α-C**H** outside MKP ring), 7.12 (d, 2 H, J = 7.9 Hz, ortho **H**'s to CH_3), 7.48 (d, 2 H, J = 8.0 Hz, meta **H**'s to CH_3); ^{13}C NMR (67.9 MHz, DMSO-d_6): δ 23.46 ($CH_3C_6H_4$), 23.55, 23.58, 25.90, 25.99 (2 X $(CH_3)_2CHCH_2$), 26.87, 27.82 (2 X $(CH_3)_2CHCH_2$), 40.10, 43.25 (2 X $(CH_3)_2CHCH_2$), 44.47, 46.52 (CH_2CH_2), 59.34 (α-CH outside MKP ring), 59.89 (α-CH on MKP ring), 128.44, 132.38 (Aromatics), 145.02 (Quaternary Aromatic), 176.26 (C=O), 180.90 (COOH); MS (FAB, NBA) m/e (%) 713 (2.7) $[MH + Free\ M]^+$, 541 (25.1) $[2\ Free\ M + H]^+$, 443 (1.3) $[MH]^+$, 271 (100) $[Free\ M + H]^+$, 243 (69.7); Anal. Calcd for $C_{21}H_{34}N_2O_6S$: C, 56.99; H, 7.74; N, 6.33; Found: C, 56.59; H, 7.75; N, 6.12.

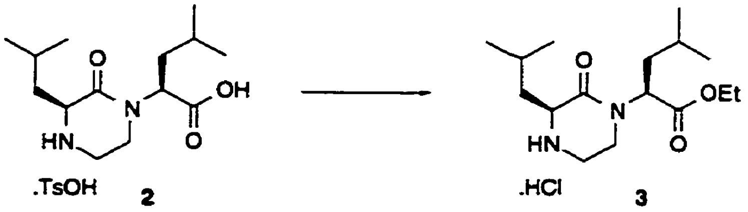
Ethyl (2S,3'S)-2-[3'-isobutyl-2'-oxopiperazin-1'-yl]-4-methylpentanoate, hydrochloride salt (3)

Method 1



N,N'-ethylene-bridged bis-L-leucine **1** (3.46 g, 12.00 mmol) was refluxed with *p*-toluenesulfonic acid monohydrate (4.57 g, 24.00 mmol) in dry ethanol (130 ml) for 24 hours. The tosylate salt obtained after removal of the solvent was neutralized with aqueous sodium hydrogen carbonate (10 % w/v, 130 ml) and extracted with dichloromethane (2 X 130 ml). A crude oily residue thus obtained was purified by silica gel column chromatography (benzene/ethyl acetate/methanol, 5/4/1 v/v/v) to give the free amine as an oil. Dry hydrogen gas was then bubbled into an ethereal solution of the amine to prepare its hydrochloride salt **3** (3.61 g, 90 %).

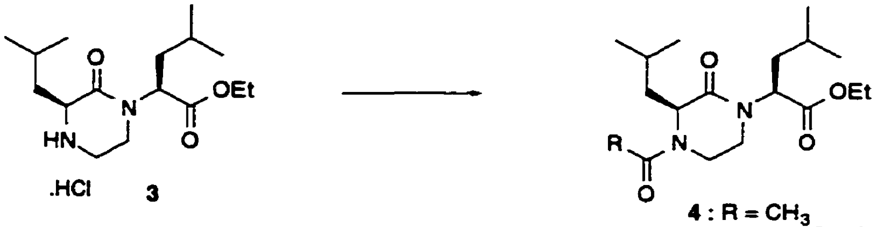
Method 2



Tosylate salt **2** (4.27 g, 9.65 mmol) was refluxed in dry ethanol (120 ml) for 24 hours in the presence of *p*-toluenesulfonic acid monohydrate (184 mg, 0.97 mmol). The tosylate salt obtained after removal of the solvent was neutralized with aqueous sodium hydrogen carbonate (10 % w/v, 120 ml) and extracted with dichloromethane (2 X 130 ml). The organic extracts were dried over anhydrous magnesium sulfate and evaporated to yield the free amine as a yellow oil. Dry hydrogen gas was then bubbled into an etheral solution of the amine to prepare its hydrochloride salt **3** (3.06 g, 95 %). TLC (of free amine) benzene/ethyl acetate/methanol, 5/4/1, R_f 0.54; mp 132-135 °C (Hydrochloride salt); $[\alpha]^{20}_{D}$ -26.6° (c 0.500, $CHCl_3$); IR (Nujol, cm^{-1}), 1730 (ester C=O), 1645 (amide C=O); ^1H

NMR (270 MHz, $CDCl_3$): δ 0.96-1.04 (m, 12 H, 2 X $(C\mathbf{H}_3)_2CHCH_2$), 1.35 (t, 3 H, J = 7.2 Hz, $CH_2C\mathbf{H}_3$), 1.24-1.61 (m, 6 H, 2 X $(CH_3)_2C\mathbf{H}C\mathbf{H}_2$),), 2.79-3.07 (m, 4 H, $C\mathbf{H}_2C\mathbf{H}_2$), 3.60 (dd, 1 H, J = 2.7 Hz and 3.5 Hz, α-C**H** on MKP ring), 4.20-4.28 (m, 2 H, $C\mathbf{H}_2CH_3$), 5.36 (dd, 1 H, J = 7.7 Hz and 11.1 Hz, α-C**H** outside MKP ring); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 14.05 (CH_2CH_3), 21.02, 21.14, 22.56, 23.11 (2 X $(CH_3)_2CHCH_2$), 23.42, 24.37 (2 X $(CH_3)_2CHCH_2$), 24.78, 36.58 (2 X $(CH_3)_2CHCH_2$), 41.97, 44.70 (CH_2CH_2), 53.78 (α-CH outside MKP ring), 57. 58 (α-CH on MKP ring), 60.79 (CH_2CH_3), 171.32, 171.55 (2 X C=O); MS (CI, NH_3) m/e (%) 299 (50.9) [MH, free base]$^+$, 242 (87.9), 213 (40.4), 197 (100), 155 (64.0), 139 (12.5), 113 (43.3); Anal. Calcd for $C_{16}H_{30}N_2O_3 \cdot HCl$: C, 57.39; H, 9.33; N, 8.37; Found: C, 57.15; H, 9.43; N, 8.32.

Ethyl (2S,3'S)-2-[4'-(acetyl)-3'-isobutyl-2'-oxopiperazin-1'-yl]-4-methylpentanoate (4)



4 : R = CH_3
5 : R = CH_2CH_2Ph
6 : R = $CH_2CH_2CH(CH_3)_2$
7 : R = CH_2CH_2CN
8 : R = $(CH_2)_5NHCbz$

To a solution of cyclized compound **3** (111 mg, 0.37 mmol) in freshly distilled pyridine (2 ml) stirred at room temperature under a stream of argon was added acetic anhydride (0.35 ml, 3.7 mmol). After eighteen hours, the pyridine was evaporated *in vacuo*, then the oily residue was dissolved in dichloromethane (10 ml) and washed with ammonium chloride solution (10 % w/v, 2 X 5 ml) and brine (5 ml) respectively. The organic layer was dried over anhydrous magnesium sulfate. The excess solvent was removed under reduced pressure and the crude product obtained was purified by silica gel chromatography (hexane/ethyl acetate, 1/2, v/v) to yield **4** as a white solid (95 mg, 75 %). TLC ethyl acetate/hexane, 2/1, R_f 0.30; mp 83-85 °C; $[\alpha]_D^{20}$ +25.6° (c 0.500, $CHCl_3$); IR

(Nujol, cm^{-1}), 1743 (ester C=O), 1638 (amide C=O); ^{1}H NMR (270 MHz, CDCl$_3$), Mixture of two rotamers: δ 0.90-0.98 (m, 12 H), 1.24 (dt, 3 H, J = 3.5 Hz and 7.2 Hz), 1.40-1.46 (m, 1 H), 1.56-1.76 (m, 5 H), 2.10, 2.11 (2 s, 3 H), 3.15-3.51 (m, 3 H), 3.58 (dd, 1 H, J = 3.7 Hz and 9.0 Hz, α-**CH** on MKP ring), 4.15 (apparent q, 2 H, J = 7.2 Hz), 4.32-4.39 (m, 1 H), 5.20 (ddd, 1 H, J = 5.9 Hz, 10.4 Hz and 16.1 Hz, α-**CH** outside MKP ring), ^{13}C NMR (67.9 MHz, CDCl$_3$): δ 14.21, 21.12, 21.24, 21.28, 21.73, 22.81, 23.29, 24.71, 24.96, 25.14, 25.18, 36.79, 37.30, 41.55, 41.84, 41.89, 42.60, 53.63, 54.09, 54.09, 54.50, 58.46, 61.36, 61.41, 168.72, 168.85, 169.24, 169.51, 170.99, 171.49 (**C**=O); MS (CI, NH$_3$) m/e (%) 341 (17.5) [MH]$^+$, 284 (100), 239 (41.0), 210 (26.6), 167 (24.8), 154 (69.6), 112 (23.5) Anal. Calcd for $C_{18}H_{32}N_2O_4$: C, 63.50; H, 9.47; N, 8.23; Found: C, 63.75; H, 9.66; N, 8.11.

Ethyl (2S,3'S)-2-[3'-isobutyl-4'-(3-phenylpropionyl)-2'-oxopiperazin-1'-yl]-4-methylpentanoate (5)

Freshly distilled triethylamine (46 µl, 0.33 mmol) was added to a solution of cyclized compound **3** (100 mg, 0.30 mmol) in dichloromethane (5 ml). EEDQ (89 mg, 0.34 mmol) was then added and the reaction mixture was allowed to stir at room temperature. After 30 minutes, hydrocinnamic acid (47 mg, 0.31 mmol) was added to the above solution which was left to stir for two days. The solvent was then evaporated under reduced pressure. The residue was dissolved in ethyl acetate (5 ml), washed with hydrochloric acid (5 % v/v, 2 X 5 ml) and dried over anhydrous sodium sulfate. The ethyl acetate was evaporated *in vacuo* to afford the crude product which was purified by silica gel chromatography (hexane/ethyl acetate, 1/2, v/v) to yield a white solid (67 mg, 66 %). TLC ethyl acetate/hexane, 2/1, R$_f$0.62; mp 57-61 °C; $[\alpha]^{20}_{D}$ +88.4° (c 0.285, CHCl$_3$); IR (Nujol, cm^{-1}), 1734 (ester C=O), 1638 (amide C=O); ^{1}H NMR (270 MHz, CDCl$_3$), Mixture of two rotamers: δ 0.90-0.98 (m, 12 H), 1.24 (dt, 3 H, J = 2.9 Hz and 7.2 Hz), 1.41-1.51 (m, 2 H), 1.56-1.79 (m, 5 H), 2.57-2.67 (m, 2 H), 2.95-3.02 (m, 2 H), 3.18-3.33 (m, 1 H), 3.39-3.51 (m, 4 H), 4.14 (apparent q, 2 H, J = 7.2 Hz), 5.19 (ddd, 1 H, J = 5.7 Hz, 10.6 Hz and 16.1 Hz, α-**CH** outside MKP ring), 7.19-7.31 (m, 5 H, **Ph**); ^{13}C NMR (67.9 MHz, CDCl$_3$): δ 14.25, 21.29, 22.54, 22.69, 22.92, 23.31, 24.71, 24.99, 25.14, 25.22, 31.20, 31.34, 34.65, 35.55, 36.92, 37.08, 37.38, 41.22, 41.60, 41.85, 42.06, 53.65, 54.10, 54.10, 54.79, 57.63, 61.39, 126.32, 128.37, 128.47, 128.62 (Aromatics), 140.95, 141.15 (Quaternary Aromatics), 169.52, 171.02, 171.54 (C=O); MS (EI) m/e (%) 430 (43.5) $[M]^+$, 374 (100), 297 (38.6), 241 (61.8), 197 (28.6), 105 (34.2) 91 (41.6); Anal. Calcd for $C_{25}H_{38}N_2O_4$: C, 69.74; H, 8.90; N, 6.51; Found: C, 69.40; H, 8.89; N, 6.29.

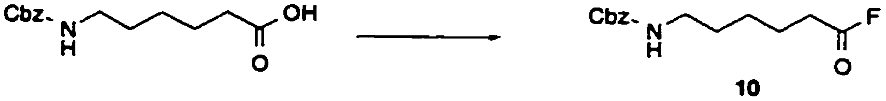
Ethyl (2S,3'S)-2-[3'-isobutyl-4'-(4-methylpentanoyl)-2'-oxopiperazin-1'-yl]-4-methylpentanoate (6)

Similarily prepared as compound **5** in 62 % yield. TLC ethyl acetate/hexane, 2/1, R_f 0.68; mp 46-49 °C; $[\alpha]_D^{20}$ +37.5° (c 0.320, $CHCl_3$); IR (Nujol, cm^{-1}), 1740 (ester C=O), 1636 (amide C=O); ^1H NMR (270 MHz, $CDCl_3$), Mixture of two rotamers: δ 0.88-1.00 (m, 18 H), 1.19-1.28 (m, 3 H), 1.51-1.85 (m, 9 H), 2.18-2.41 (m, 2 H), 3.17-3.36 (m, 2 H), 3.44-3.60 (m, 3 H), 4.14 (apparent q, 2 H, J = 6.9 Hz), 5.20 (ddd, 1 H, J = 5.7 Hz, 10.2 Hz and 15.8 Hz, α-CH outside MKP ring); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 14.23, 21.28, 21.33, 22.36, 22.39, 22.45, 22.47, 22.62, 22.68, 22.85, 23.31, 24.74, 24.99, 25.12, 25.21, 27.88, 28.00, 30.92, 31.55, 33.86, 34.11, 36.75, 36.81, 37.35, 41.21, 41.70, 41.94, 41.97,42.04, 42.66, 53.58, 54.15, 54.62, 56.16, 57.67, 61.32, 61.33, 61.40, 168.84, 169.64, 170.99, 171.58, 171.67, 172.28 (C=O); MS (EI) m/e (%) 396 (3.3) $[M]^+$, 340 (100), 297 (27.6), 241 (41.8), 210 (9.4), 167 (9.9), 99 (4.6); Anal. Calcd for $C_{22}H_{40}N_2O_4$: C, 66.63; H, 10.17; N, 7.06; Found: C, 66.71; H, 10.30; N, 6.91.

Ethyl (2S,3'S)-2-[4'-(3-cyanopropionyl)-3'-isobutyl-2'-oxopiperazin-1'-yl]-4-methylpentanoate (7)

Similarily prepared as compound **5** in 33 % yield. TLC ethyl acetate/hexane, 2/1, R_f 0.47; mp 63-66 °C; $[\alpha]_D^{20}$ +11.4° (c 0.085, $CHCl_3$); IR (Nujol, cm^{-1}), 2254 (nitrile CN), 1735 (ester C=O), 1655 (amide C=O); ^1H NMR (270 MHz, $CDCl_3$), Mixture of two rotamers: δ 0.90-1.02 (m, 12 H), 1.25 (dt, 3 H, J = 4.5 Hz and 7.2 Hz), 1.39-1.49 (m, 1 H), 1.60-1.80 (m, 5 H), 2.63-2.77 (m, 4 H), 3.20-3.61 (m, 4 H), 3.70-3.80 (m, 1 H), 4.15 (q, 2 H, J = 7.2 Hz), 5.20 (ddd, 1 H, J = 5.7 Hz, 10.6 Hz and 16.1 Hz, α-**CH** outside MKP ring); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 12.96, 13.15, 14.25, 21.21, 22.50, 22.69, 22.94, 23.31, 24.86, 25.01, 25.20, 25.30, 28.95, 29.64, 36.92, 37.46, 37.65, 41.28, 41.38, 41.42, 42.10, 42.72, 53.60, 54.10, 55.26, 57.55, 61.50, 119.06, 119.18 (CN), 167.63, 167.63, 168.11, 169.02, 170.99, 171.59 (C=O); MS (EI) m/e (%) 379 (7.1) $[M]^+$, 323 (100), 306 (60.1), 278 (70.2), 249 (19.8), 193 (54.3), 112 (8.7); Anal. Calcd for $C_{20}H_{33}N_3O_4$: C, 63.30; H, 8.77; N, 11.07; Found: C, 62.83; H, 8.68; N, 10.45.

N-(Benzyloxycarbonyl)-ε-aminocaproic acid fluoride (10)



To a stirred solution of N-(benzyloxycarbonyl)-ε-aminocaproic acid (2.00 g, 7.54 mmol) and dry pyridine (610 µl, 7.54 mmol) in dry dichloromethane (10 ml) which was kept under argon was added cyanuric fluoride (1.55 ml, 15.08 mmol) at -20 °C to -10 °C. After stirring at -10 °C for one hour, crushed ice was added along with additional dichloromethane (20 ml). The organic layer was separated and the aqueous layer extracted once with dichloromethane (10 ml). The combined dichloromethane layers were extracted with ice-cold water (20 ml), dried over anhydrous magnesium sulfate and the solvent removed with a rotary evaporator at room temperature. The fluoride was obtained as a yellow oil (1.61 g, 79 %). ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.11-1.25 (m, 2 H, $NHCH_2CH_2\mathbf{CH_2}$), 1.30-1.38 (m, 2 H, $\mathbf{CH_2}CH_2C(O)F$), 1.43-1.51 (m, 2 H, $NHCH_2\mathbf{CH_2}$), 2.30 (t, 2 H, J = 7.2 Hz, $\mathbf{CH_2}C(O)F$), 2.99-3.07 (m, 2 H, $NH\mathbf{CH_2}$), 4.98 (s br, 2 H, $O\mathbf{CH_2}Ph$), 5.58 (s br, 1 H, **NH**), 7.21 (s br, 5 H, **Ph**); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 23.50 ($NHCH_2CH_2CH_2$), 25.66 ($CH_2CH_2C(O)F$), 29.34 ($NHCH_2CH_2$), 31.74 (d, J = 50.2 Hz, $CH_2C(O)F$), 40.64 ($NH\mathbf{CH_2}$), 66.31 (OCH_2Ph), 127.87, 128.46, (Aromatics), 136.94 (Quaternary Aromatic), 156.77 (NHC(O)), 163.59 (d, J = 360.3 Hz, C(O)F).

Ethyl (2S,3'S)-2-[4'-(N-benzyloxycarbonyl-6-aminohexanoyl)-3'-isobutyl-2'-oxopiperazin-1'-yl]-4-methylpentanoate (8)

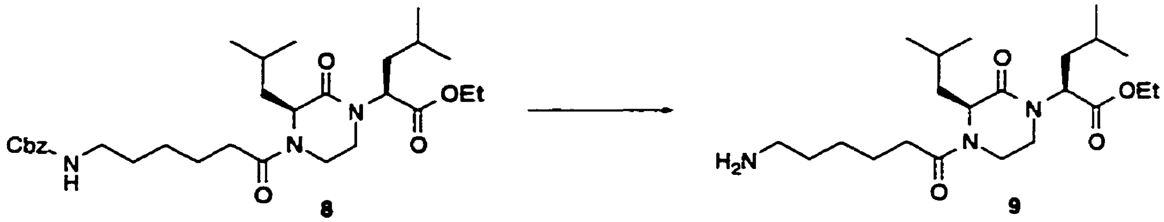
Method 1

Similarily prepared as compound **5** in 55 % yield.

Method 2

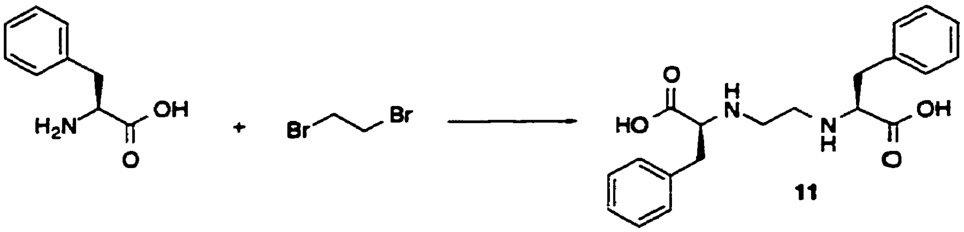
To a solution of cyclized compound **3** (0.28 g, 0.85 mmol) and N-ethylmorpholine (216 μl, 1.70 mmol) in dichloromethane (2.0 ml), a solution of N-(benzyloxycarbonyl)-ε-aminocaproic acid fluoride **10** (0.60 g, 2.25 mmol) in dichloromethane (2.0 ml), was added over a period of one minute and the reaction mixture stirred at room temperature for 24 hours. Color change from yellow to a deep red within 10 minutes. Dichloromethane (10 ml) was added to the crude mixture and was washed well with hydrochloric acid (3 N, 2 X 10 ml), sodium bicarbonate (10 % w/v, 2 X 10 ml) and water (10 ml) respectively. Column chromatography (hexane/ethyl acetate, 1/3) yielded **8** as a yellow sticky solid (0.36 g, 78 %). TLC ethyl acetate/hexane, 3/1, R_f 0.49; $[\alpha]_D^{20}$ +15.5° (c 0.310, $CHCl_3$); IR (Nujol, cm^{-1}), 3325 (NH), 1735 (ester C=O), 1636 (amide C=O); ^1H NMR (270 MHz, $CDCl_3$), Mixture of rotamers: δ 0.88-1.00 (m, 10 H), 1.11-1.75 (m, 17 H), 2.08-2.29 (m, 2 H), 3.02-3.14 (m, 2 H), 3.22-3.51 (m, 4 H), 4.01-4.11 (m, 2 H), 4.22-4.25 (m, 1 H), 4.95-5.30 (m, 4 H), 7.21-7.35 (m, 5 H, **Ph**); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 14.17, 15.28, 21.20, 22.63, 22.80, 23.28, 24.41, 24.72, 24.93, 25.08, 25.15, 26.23, 26.40, 29.73, 31.59, 32.50, 33.20, 33.84, 36.70, 37.26, 40.82, 41.06, 41.51, 41.90, 42.44, 53.60, 54.02, 54.60, 57.64, 61.36, 65.83, 66.48, 66.79, 128.03, 128.49 (Aromatics), 136.78 (Quaternary Aromatic), 156.53, (NC(O)), 168.88, 169.61, 170.98, 171.26, 171.49, 171.82 (C=O); MS (EI) m/e (%) 545 (9.3) $[M]^+$; HRMS (EI) m/e Calcd for $C_{30}H_{47}N_3O_6$: 543.34646; Found: 543.34590.

Ethyl (2S,3'S)-2-[4'-(6-aminohexanoyl)-3'-isobutyl-2'-oxopiperazin-1'-yl]-4-methylpentanoate (9)



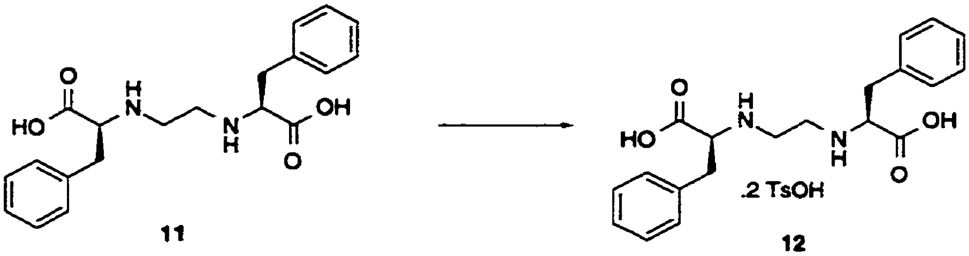
A solution of compound **8** (200 mg, 0.37 mmol) and 10 % palladium on activated carbon (100 mg) in a mixture of ethyl acetate/acetic acid/water (12/2/1 v/v/v, 15 ml) was shaken in a pressure vessel, under a pressure of 45 p.s.i. of gaseous hydrogen for three hours. After that time, the mixture was carefully filtered over a short very compact pad of celite and evaporated to yield an oil. Column chromatography (benzene/ethyl acetate/methanol, 5/4/1) gave **9** as an oil (122 mg, 81 %). TLC benzene/ethyl acetate/methanol, 5/4/1, R_f 0.12; $[\alpha]_D^{20}$ +11.2° (c 0.200, $CHCl_3$); IR (Nujol, cm^{-1}), 3330 (NH), 1740 (ester C=O), 1635 (amide C=O); ^1H NMR (270 MHz, $CDCl_3$), Mixture of rotamers: δ 0.99-1.11 (m, 15 H), 1.45-1.76 (m, 12 H), 2.10-2.27 (m, 2 H), 3.01-3.14 (m, 2 H), 3.25-3.49 (m, 4 H), 4.01-4.10 (m, 2 H), 4.23-4.25 (m, 1 H), 4.95-5.15 (m, 1 H); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 14.55, 15.25, 21.31, 22.73, 22.81, 23.30, 24.41, 24.75, 24.91, 25.18, 25.25, 26.33, 26.40, 29.74, 31.69, 32.50, 33.21, 33.85, 36.74, 37.26, 40.92, 41.16, 41.52, 41.88, 42.44, 53.69, 54.12, 54.62, 57.64, 61.41, 168.86, 169.68, 171.12, 171.25, 171.49, 171.85 (C=O); MS (EI) m/e (%) 411 (15.6) $[M]^+$; HRMS (EI) m/e Calcd for $C_{22}H_{41}N_3O_4$: 411.30971; Found: 411.30960.

N,N'-Ethylene-bridged bis-L-phenylalanine (11)



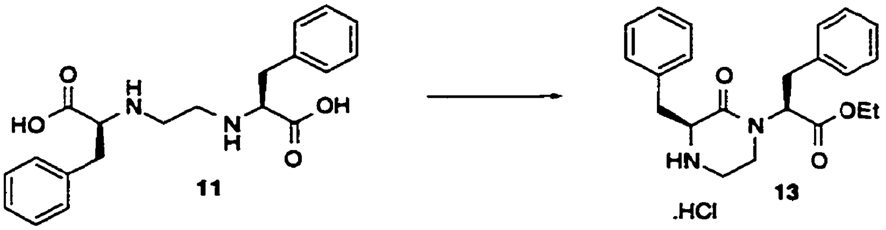
Sodium hydroxide (0.96 g, 24.00 mmol) in water (20 ml) was added to L-phenylalanine (4.00 g, 24.00 mmol). The solution was heated to reflux and 1,2-dibromoethane (1.05 ml, 12.00 mmol) and potassium carbonate (1.66 g, 12.00 mmol) were slowly added. The solution was stirred under reflux for six hours with some difficulty towards the end due to some undissolved potassium carbonate. Cooling and neutralizing to a pH of 5 with concentrated hydrochloric acid resulted in the formation of a solid off-white product. This was washed well with water and air dried to give **11** as an off-white powder (1.30 g, 30 %). mp 223-228 °C; IR (Nujol, cm^{-1}), 2400-2800 (carboxylic OH), 1730 (carboxylic acid C=O); ^{1}H NMR (270 MHz, ND_4OD with DSS as an internal standard): δ 2.44-2.62 (m, 4 H, 2 X $\mathbf{CH_2}$Ph), 2.75-2.90 (m, 4 H, $N(\mathbf{CH_2})_2N$), 3.24 (dd, 2 H, J = 6.2 Hz and 7.6 Hz, 2 X **CH**N), 7.21-7.35 (m, 10 H, 2 X **Ph**); ^{13}C NMR (67.9 MHz, ND_4OD with DSS as an internal standard): δ 41.89 (2 X CH_2Ph), 49.29 ($N(CH_2)_2N$), 68.08 (2 X CHN), 129.30, 131.29, 132.13 (Aromatics), 141.09 (Quaternary Aromatic), 183.42 (2 X COOH); MS (FAB, Glycerol/NaOH) m/e (%) 379 (4.3) $[M + Na]^+$, 357 (2.7) $[MH]^+$, 277 (9.8); Anal. Calcd for $C_{20}H_{24}N_2O_4$: C, 67.40; H, 6.79; N, 7.86; Found: C, 67.53; H, 6.86; N, 7.83.

N,N'-Ethylene-bridged bis-phenylalanine, di-*p*-toluenesulfonic acid salt (12)



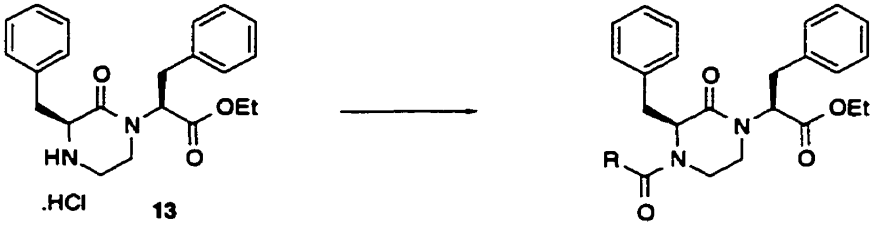
N,N'-Ethylene-bridged bis-L-phenylalanine **11** (5.35 g, 15 mmol)was refluxed in acetonitrile (225 ml) for 24 hours in the presence of *p*-toluenesulfonic acid monohydrate (5.71 g, 30 mmol). The residue obtained after the removal of the solvent was washed well with diethyl ether to give the ditosylate salt of N,N'-ethylene-bridged bis-phenylalanine **12** as a white solid (10.10 g, 96 %). Mp 215-218 °C; IR (Nujol, cm^{-1}), 2400-2800 (carboxylic OH), 1730 (carboxylic acid C=O); ^1H NMR (270 MHz, ND_4OD with DSS as an internal standard): δ 2.39 (s, 6 H, $\mathbf{CH}_3C_6H_4$), 2.52-2.63 (m, 4 H, 2 X $\mathbf{CH}_2Ph$), 2.79-2.95 (m, 4 H, $N(\mathbf{CH}_2)_2N$), 3.28 (dd, 2 H, J = 6.2 Hz and 7.7 Hz, 2 X **CH**N), 7.24-7.33 (m, 10 H, 2 X **Ph**), 7.37 (d, 4 H, J = 8.4 Hz, ortho **H**'s to CH_3), 7.69 (d, 4 H, J = 8.2 Hz, meta **H**'s to CH_3); ^{13}C NMR (67.9 MHz, ND_4OD with DSS as an internal standard): δ 22.79 (2 X $CH_3C_6H_4$), 41.45 (2 X CH_2Ph), 48.84 ($N(CH_2)_2N$), 67.64 (2 X CHN), 127.78, 128.88, 130.86, 131.69 (Aromatics), 140.74, 144.32, 146.77 (Quaternary Aromatics), 182.95 (2 X COOH); MS (FAB, NBA) m/e (%) 885 (0.3) $[2\ Free\ M + TsOH + H]^+$, 713 (0.6) $[2\ Free\ M + H]^+$, 529 (1.0) $[Free\ M + TsOH + H]^+$, 357 (10.9) $[Free\ M + H]^+$, 192 (4.7); Anal. Calcd for $C_{34}H_{40}N_2O_{10}S_2 \cdot H_2O$: C, 56.81; H, 5.89; N, 3.90; Found: C, 56.77; H, 5.57; N, 4.03.

Ethyl (2S,3'S)-2-[3'-benzyl-2'-oxopiperazin-1'-yl]-3-phenylpropanoate, hydrochloride salt (13)



N,N'-Ethylene-bridged bis-phenylalanine **11** (0.10 g, 0.28 mmol) was refluxed with *p*-toluenesulfonic acid monohydrate (0.16 g, 0.84 mmol) in dry ethanol (15 ml) for 24 hours. The tosylate salt obtained after removal of the solvent was neutralized with aqueous sodium hydrogen carbonate (10 % w/v, 30 ml) and extracted with dichloromethane (2 X 30 ml). The crude oily residue thus obtained was purified by silica gel column chromatography (benzene/ethyl acetate/methanol, 5/4/1 v/v/v) to afford the free amine as an oil. Dry hydrogen gas was then bubbled into an ethereal solution of the amine to prepare its hydrochloride salt **13** (83 mg, 74 %). TLC (of free amine) benzene/ethyl acetate/methanol, 5/4/1, R_f 0.44; mp 188-192 °C (Hydrochloride salt); $[\alpha]_D^{20}$ -141.0° (c 0.500, $CHCl_3$); IR (Nujol, cm^{-1}), 1740 (ester C=O), 1640 (amide C=O); ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.26 (t, 3 H, J = 7.2 Hz, $CH_2C\mathbf{H}_3$), 2.80-3.05 (m, 4 H, $C\mathbf{H}_2Ph$ and $C\mathbf{H}_2CH_2$), 3.20-3.38 (m, 3 H, $C\mathbf{H}_2Ph$ and $CH_2C\mathbf{H}_2$), 3.61 (dd, 1 H, J = 6.9 Hz and 8.4 Hz, α-C**H** on MKP ring), 3.89-4.06 (m, 1 H, $CH_2C\mathbf{H}_2$), 4.11-4.25 (m, 2 H, $C\mathbf{H}_2CH_3$), 5.17 (dd, 1 H, J = 5.7 Hz and 10.6 Hz, α-C**H** outside MKP ring), 7.14-7.33 (m, 10 H, 2 X **Ph**); ^{13}C NMR (125.7 MHz, $CDCl_3$): δ 13.62 (CH_2CH_3), 33.72, 37.75 (2 X CH_2Ph), 41.16, 46.16 (CH_2CH_2), 58.25 (α-CH outside MKP ring), 59.92 (α-CH on MKP ring), 60.56 (CH_2CH_3), 125.91, 126.13, 127.91, 127.94, 128.34. 128.71 (Aromatics), 136.71, 137.86 (Quaternary Aromatics), 169.22, 169.81 (2 X C=O); MS (CI, NH_3) m/e (%) 367 (30.5) $[MH]^+$, 275 (100), 265 (9.9), 247 (41.8), 219 (6.6), 189 (7.1), 132 (10.9); Anal. Calcd for $C_{22}H_{26}N_2O_3$·HCl: C, 65.58; H, 6.75; N, 6.95; Found: C, 64.92; H, 6.67; N, 6.71.

Ethyl (2S,3'S)-2-[4'-(acetyl)-3'-benzyl-2'-oxopiperazin-1'-yl]-3-phenylpropanoate (14)



14 : R = CH_3
15 : R = CH_2CH_2Ph
16 : R = $CH_2CH_2CH(CH_3)_2$
17 : R = CH_2CH_2CN
18 : R = $(CH_2)_5NHCbz$

To a solution of cyclized compound **13** (90 mg, 0.25 mmol) in freshly distilled pyridine (2 ml) stirred at room temperature under a stream of argon was added acetic anhydride (0.23 ml, 2.5 mmol). After eighteen hours, the pyridine was evaporated *in vacuo*, then the oily residue was dissolved in dichloromethane (10 ml) and washed with ammonium chloride solution (10 % w/v, 2 X 5 ml) and brine (5 ml) respectively. The organic layer was subsequently dried over anhydrous magnesium sulfate. The excess solvent was removed *in vacuo* and the crude product obtained was purified by silica gel chromatography (hexane/ethyl acetate, 1/2, v/v) to yield **14** as a white solid (68 mg, 67 %). TLC ethyl acetate/hexane, 2/1, R_f 0.31; mp 89-93 °C; $[\alpha]^{20}_{D}$ -40.7° (c 0.290, $CHCl_3$); IR (Nujol, cm^{-1}), 1735 (ester C=O), 1640 (amide C=O); ^1H NMR (270 MHz, $CDCl_3$), Mixture of two rotamers; δ 1.22-1.28 (m, 3 H), 1.95, 2.02 (2 s, 3 H), 2.54 (dd, 1 H, J = 10.4 Hz and 13.9 Hz), 2.62-2.87 (m, 1 H), 2.96-3.31 (m, 6 H), 3.40 (dd, 1 H, J = 5.7 Hz and 14.6 Hz), 4.18-4.32 (m, 2 H), 5.17-5.31 (ddd, 1 H, J = 5.7 Hz, 11.4 Hz and 17.1 Hz, α-**CH** outside MKP ring), 6.94-7.32 (m, 10 H, 2 X **Ph**); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 14.24, 14.27, 20.07, 21.11, 21.52, 34.19, 34.41, 35.04, 36.67, 37.72, 42.05, 43.74, 44.22, 56.84, 57.90, 58.20, 61.62, 61.68, 126.71, 127.05, 127.18, 127.29, 128.33, 128.68, 128.76, 128.88, 128.92, 129.57, 129.74 (Aromatics), 136.45, 136.65, 136.77, 137.15 (Quaternary Aromatics), 167.51, 168.28, 168.54, 169.47, 169.79, 170.11 (C=O); MS (EI) m/e (%) 408 (31.0) $[M]^+$, 317 (40.3), 275 (100), 247 (10.1), 201 (16.0), 91 (7.8); Anal. Calcd for $C_{24}H_{28}N_2O_4 \cdot 0.5H_2O$: C, 69.04; H,7.00; N, 6.71; Found: C, 68.90; H, 6.75; N, 6.54.

Ethyl (2S,3'S)-2-[3'-benzyl-4'-(3-phenylpropionyl)-2'-oxopiperazin-1'-yl]-3-phenylpropanoate (15)

Freshly distilled triethylamine (38 µl, 0.28 mmol) was added to a solution of cyclized compound **13** (100 mg, 0.25 mmol) in dichloromethane (5 ml). EEDQ (86 mg, 0.32 mmol) was then added and the reaction mixture was allowed to stir at room temperature. After 30 minutes, hydrocinnamic acid (45 mg, 0.30 mmol) was added to the above solution which was left to stir for two days. The solvent was then evaporated under reduced pressure. The residue was dissolved in ethyl acetate (5 ml), washed with hydrochloric acid (5 % v/v, 2 X 5 ml) and dried over anhydrous sodium sulfate. The ethyl acetate was evaporated *in vacuo* to afford the crude product which was purified by silica gel chromatography (hexane/ethyl acetate, 1/2, v/v) to yield **15** as a white solid (90 mg, 67 %). TLC ethyl acetate/hexane, 2/1, R_f 0.57; mp 114-117 °C; $[\alpha]_D^{20}$ +120.8° (c 0.255, $CHCl_3$); IR (Nujol, cm^{-1}), 1733 (ester C=O), 1638 (amide C=O); ^1H NMR (270 MHz, $CDCl_3$), Mixture of two rotamers: δ 1.27 (dt, 3 H, J = 4.7 Hz and 7.2 Hz), 1.47-1.58 (m, 1 H), 1.98-2.10 (m, 1 H), 2.31-2.45 (m, 2 H), 2.49-2.71 (m, 2 H), 2.80-3.35 (m, 6 H), 3.41 (dd, 1 H, J = 5.7 Hz and 14.8 Hz), 4.16-4.27 (m, 2 H), 5.28 (dd, 1 H, J = 5.4 Hz and 11.1 Hz), 6.89-7.38 (m, 15 H, 3 X **Ph**); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 14.29, 14.30, 30.83, 31.05, 33.84, 34.23, 34.40, 35.19, 35.23, 36.78, 37.69, 41.22, 43.89, 44.25, 56.94, 57.99, 58.25, 60.54, 61.59, 61.66, 126.09, 126.34, 126.71, 127.07, 127.17, 127.32, 128.11, 128.32, 128.40, 128.51, 128.69, 128.73, 128.89, 128.95, 129.65, 129.77 (Aromatics), 136.50, 13669, 136.84, 137.11, 140.89, 141.07 (Quaternary Aromatics), 167.37, 168.31, 169.78, 170.07, 170.21, 171.12 (C=O); MS (EI) m/e (%) 498 (14.0) $[M]^+$, 407 (30.6), 275 (100), 201 (17.8), 131 (5.3), 105 (17.6), 91 (27.2); Anal. Calcd for $C_{31}H_{34}N_2O_4 \cdot 0.5H_2O$: C, 73.35; H, 6.95; N, 5.52; Found: C, 73.06; H, 6.71; N, 5.38.

Ethyl (2S,3'S)-2-[3'-benzyl-4'-(4-methylpentanoyl)-2'-oxopiperazin-1'-yl]-3-phenylpropanoate (16)

Similarily prepared as compound **15** in 70 % yield. TLC ethyl acetate/hexane, 2/1, R_f 0.66; mp 59-62 °C; $[\alpha]_D^{20}$ +13.9° (c 0.430, $CHCl_3$); IR (Nujol, cm^{-1}), 1735 (ester C=O), 1640 (amide C=O); ^1H NMR (270 MHz, $CDCl_3$), Mixture of two rotamers: δ 0.64-0.69 (m, 6 H), 1.26 (t, 3 H, J = 7.2 Hz), 1.34-1.50 (m, 1 H), 2.14 (dd, 1 H, J = 6.9 Hz and 9.6 Hz), 2.55 (dd, 1 H, J = 10.4 Hz and 13.8 Hz), 2.71-3.21 (m, 10 H), 3.40 (dd, 1 H, J = 5.7 Hz and 14.6 Hz), 4.14-4.26 (m, 2 H), 5.20 (dd, 1 H, J = 5.7 Hz and 11.4 Hz), 6.94-7.31 (m, 10 H, 2 X **Ph**); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 14.27, 22.23, 22.26, 22.33, 22.40, 27.76, 29.99, 31.38, 33.57, 33.95, 34.16, 34.40, 35.04, 36.74, 37.72, 41.23, 44.01, 44.44, 56.69, 58.13, 58.18, 60.75, 61.59, 61.66, 126.67, 127.05, 127.15, 127.24, 128.27, 128.71, 128.86, 128.92, 129.56, 129.80 (Aromatics), 136.53, 136.68, 136.89, 137.16 (Quaternary Aromatics), 167.63, 168.43, 169.79, 170.14, 171.35, 172.41 (C=O); MS (EI) m/e (%) 464 (10.9) $[M]^+$, 373 (17.9), 347 (10.5), 275 (100), 229 (5.4), 201 (17.0), 91 (8.3); Anal. Calcd for $C_{28}H_{36}N_2O_4$: C, 72.39; H, 7.81; N, 6.03; Found: C, 72.13; H, 7.80; N, 6.01.

Ethyl (2S,3'S)-2-[3'-benzyl-4'-(3-cyanopropionyl)-2'-oxopiperazin-1'-yl]-3-phenylpropanoate (17)

Similarily prepared as compound **15** in 40 % yield. TLC ethyl acetate/hexane, 2/1, R_f 0.37; mp 84-87 °C; $[\alpha]_D^{20}$ -49.0° (c 0.140, $CHCl_3$); IR (Nujol, cm^{-1}), 2250 (nitrile CN), 1735 (ester C=O), 1650 (amide C=O); ^1H NMR (270 MHz, $CDCl_3$), Mixture of two rotamers: δ 1.26 (dt, 3 H, J = 3.2 Hz and 7.2 Hz), 1.91-2.15 (m, 2 H), 2.20-2.31 (m, 1 H), 2.39-2.61 (m, 2 H), 2.66-3.36 (m, 7 H), 3.43 (dd, 1 H, J = 10.9 Hz and 13.6 Hz), 4.15-4.27 (m, 2 H), 5.35 (dd, 1 H, J = 5.4 Hz and 11.4 Hz), 6.91-7.31 (m, 10 H, 2 X **Ph**); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 12.71, 12.90, 14.29, 27.97, 29.33, 34.24, 34.44, 35.50, 36.76, 37.59, 41.04, 43.38, 43.79, 53.52, 57.23, 57.58, 58.00, 60.76, 61.71, 61.79, 118.82, 119.22 (CN), 126.91, 127.20, 127.26, 127.67, 128.50, 128.72, 128.78, 128.90, 129.18, 129.55, 129.61 (Aromatics), 136.30, 136.41, 136.61, 136.70 (Quaternary Aromatics), 166.87, 166.98, 167.88, 168.03, 169.74, 170.08 (C=O); MS

(EI) m/e (%) 447 (29.2) $[M]^+$, 356 (59.8), 275 (100), 271 (41.2), 247 (12.3), 201 (25.3), 91 (16.6); Anal. Calcd for $C_{26}H_{29}N_3O_4 \cdot 0.5H_2O$: C, 68.40; H, 6.62; N, 9.20; Found: C, 68.99; H, 6.49; N, 9.21.

Ethyl (2S,3'S)-2-[-3'-benzyl-4'-(N-benzyloxycarbonyl-6-aminohexanoyl)-2'-oxopiperazin-1'-yl]-3-phenylpropanoate (18)

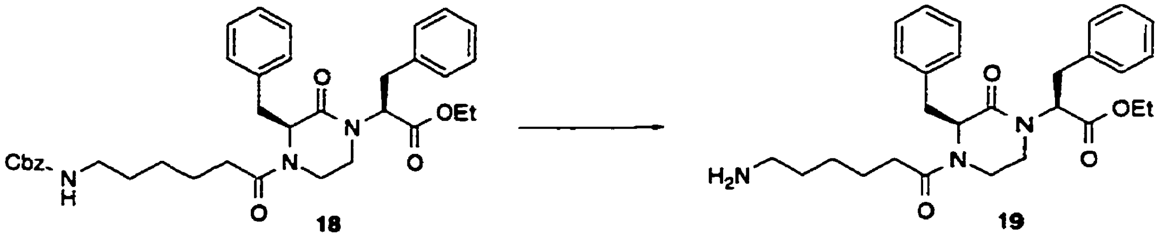
Method 1

Similarily prepared as compound **15** in 52 % yield.

Method 2

To a solution of cyclized compound **13** (0.34 g, 0.85 mmol) and N-ethylmorpholine (216 µl, 1.70 mmol) in dichloromethane (2.0 ml), a solution of N-(benzyloxycarbonyl)-ε-aminocaproic acid fluoride **10** (0.60 g, 2.25 mmol) in dichloromethane (2.0 ml), was added over a period of 60 seconds and the reaction mixture stirred at room temperature for 24 hours. Color change from yellow to a deep red within 10 minutes. Dichloromethane (10 ml) was added to the crude mixture, and the solution was washed well with hydrochloric acid (3 N, 2 X 10 ml), sodium bicarbonate (10 % w/v, 2 X 10 ml) and water (10 ml) respectively. Column chromatography was performed (hexane/ethyl acetate, 1/3) to yield **18** as a white solid (0.39 g, 75 %). TLC ethyl acetate/hexane, 3/1, R_f 0.40; mp 69-72 °C; $[\alpha]^{20}_{D}$ +17.5° (c 0.445, $CHCl_3$); IR (Nujol, cm^{-1}), 3330 (NH), 1738 (ester C=O), 1638 (amide C=O); ^1H NMR (270 MHz, $CDCl_3$), Mixture of rotamers; δ 0.64-0.69 (m, 6 H), 1.26 (t, 3 H, J = 7.2 Hz), 1.34-1.50 (m, 1 H), 2.14 (dd, 1 H, J = 6.9 Hz and 9.6 Hz), 2.55 (dd, 1 H, J = 10.4 Hz and 13.8 Hz), 2.71-3.21 (m, 10 H), 3.38 (dd, 1 H, J = 5.9 Hz and 14.9 Hz), 4.14-4.25 (m, 2 H), 5.07 (s, 2 H, $OC\mathbf{H}_2Ph$), 5.22 (dd, 1 H, J = 5.5 Hz and 11.0 Hz), 7.14-7.34 (m, 15 H, 3 X **Ph**); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 14.26, 24.19, 24.47, 26.19, 26.36, 29.57, 29.72, 31.63, 33.15, 33.89, 34.12, 34.47, 35.06, 36.78, 37.63, 40.84, 41.05, 43.75, 44.35, 56.75, 57.88, 58.18, 60.61, 61.62, 61.72, 66.63, 126.71, 127.07, 127.18, 127.24, 128.14, 128.28, 128.57, 128.69, 128.86, 129.62, 129.74 (Aromatics), 136.43, 136.63, 136.74, 136.83, 137.09 (Quaternary Aromatics), 156.48 (NHC(O)), 167.65, 168.42, 169.81, 170.17, 170.94, 171.90 (C=O); MS (EI) m/e (%) 613 (12.9) $[M]^+$, 275 (100); HRMS (EI) m/e Calcd for $C_{36}H_{43}N_3O_6$: 613.31519; Found: 613.31495.

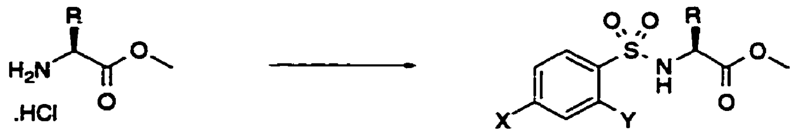
Ethyl (2S,3'S)-2-[4'-(6-aminohexanoyl)-3'-benzyl-2'-oxopiperazin-1'-yl]-3-phenylpropanoate (19)



A solution of compound **18** (200 mg, 0.33 mmol) and 10 % palladium on activated carbon (100 mg) in a mixture of ethyl acetate/acetic acid/water (12/2/1 v/v/v, 15 ml) was shaken in a pressure vessel, under a pressure of 45 p.s.i. of gaseous hydrogen for three hours. After that time, the mixture was carefully filtered over a short very compact pad of celite and evaporated to yield an oil. Column chromatography was performed (benzene/ethyl acetate/methanol, 5/4/1 v/v/v) to yield **19** as a yellowish sticky solid (125 mg, 80 %). TLC benzene/ethyl acetate/methanol, 5/4/1, R_f 0.15; $[\alpha]_D^{20}$ -11.4° (c 0.235, $CHCl_3$); IR ($CHCl_3$, cm^{-1}), 3410, 3320 (NH_2), 1740 (ester C=O), 1635 (amide C=O); ^1H NMR (270 MHz, $CDCl_3$), Mixture of two rotamers: δ 0.69-0.77 (m, 6 H), 1.27 (t, 3 H, J = 7.0 Hz), 1.38-1.55 (m, 1 H), 2.14 (dd, 1 H, J = 7.2 Hz and 9.5 Hz), 2.58 (dd, 1 H, J = 10.2 Hz and 13.8 Hz), 2.69-3.22 (m, 10 H), 3.39 (dd, 1 H, J = 7.0 Hz and 15.0 Hz), 4.14-4.25 (m, 1 H), 5.22 (dd, 1 H, J = 5.6 Hz and 10.9 Hz), 7.24-7.38 (m, 10 H, 2 X **Ph**); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 14.16, 24.27, 24.50, 26.29, 26.36, 29.47, 29.78, 31.65, 33.26, 33.90, 34.22, 34.50, 35.16, 36.79, 37.68, 40.85, 41.12, 43.72, 44.45, 56.65, 57.98, 58.15, 60.91, 61.62, 61.82, 126.61, 127.17, 127.19, 127.26, 128.02, 128.18, 128.38, 128.57, 128.70, 128.89, 129.66, 129.78 (Aromatics), 136.66, 136.79, 136.93, 137.10 (Quaternary Aromatics), 167.66, 168.52, 169.91, 170.27, 170.94, 171.88 (C=O); MS (EI) m/e (%) 479 (15.2) $[M]^+$, 275 (100); HRMS (EI) m/e Calcd for $C_{28}H_{37}N_3O_4$: 479.27841; Found: 479.27818.

4.3 Experimental for Section 2.2

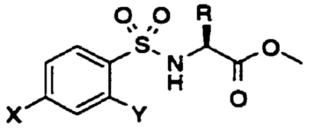
Preparation of sulfonamide amino acid methyl esters (GP 1)



$X = NO_2$, $Y = H$ or
$X = H$, $Y = NO_2$ or
$X = Y = NO_2$

To a solution of the amino acid methyl ester (1.00 mmol) in dry dichloromethane (5 ml) was added freshly distilled triethylamine (2.20 mmol) followed by the addition of 2- or 4-nitrobenzenesulfonyl chloride (1.00 mmol). The reaction mixture was stirred at room temperature under a stream of argon for six hours. The crude mixture was then washed well with hydrochloric acid (10 % v/v, 2 X 10 ml), sodium bicarbonate (10 % w/v, 2 X 10 ml) and brine (10ml) respectively. The organic layer was then dried over anhydrous sodium sulfate and the excess solvent removed under reduced pressure. In the case of the 2,4-dinitrobenzenesulfonamides, the reaction was performed at -15 °C and slowly warmed up to room temperature. Purification of these sulfonamides if necessary was achieved by column chromatography.

N-4-Nitrobenzenesulfonyl-L-phenylalanine methyl ester (20)



20 : $R = CH_2Ph$, $X = NO_2$, $Y = H$
21 : $R = CH_2Ph$, $X = H$, $Y = NO_2$
22 : $R = CH_2Ph$, $X = NO_2$, $Y = NO_2$
23 : $R = CH_2CH(CH_3)_2$, $X = NO_2$, $Y = H$
24 : $R = CH_2CH(CH_3)_2$, $X = H$, $Y = NO_2$
25 : $R = CH_2CH(CH_3)_2$, $X = NO_2$, $Y = NO_2$
26 : $R = (CH_2)_4NHCbz$, $X = NO_2$, $Y = H$
27 : $R = CH_2OBn$, $X = NO_2$, $Y = H$
28 : $R = CH(CH_3)_2$, $X = NO_2$, $Y = H$

Prepared according to **GP 1** in 91 % yield. TLC ethyl acetate/hexane, 1/1, R_f 0.64; mp 147-150 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.96 (A of ABX system, 1 H, J = 7.4 Hz and 13.9 Hz, C**H**$_2$Ph), 3.10 (B of ABX system, 1 H, J = 5.2 Hz and 13.9 Hz, C**H**$_2$Ph), 3.60 (s, 3 H, OC**H**$_3$), 4.20-4.28 (m, 1 H, C**H**), 5.41 (d, 1H, J = 9.4 Hz, N**H**) 7.01-7.24 (m, 5 H, **Ph**), 7.82 (d, 2 H, J = 9.1 Hz, meta **H**'s to -NO_2), 8.20 (d, 2 H, J = 8.9 Hz, ortho **H**'s to -NO_2); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 38.35 (CH_2Ph), 51.69 (OCH_3), 57.92 (CH), 124.17, 126.82, 128.12, 128.41, 129.39 (Aromatics), 136.35, 146.82, 149.90 (Quaternary Aromatics), 171.14 (C=O); MS (FAB, NBA) m/e (%) 365 (2.3) $[MH]^+$.

N-2-Nitrobenzenesulfonyl-L-phenylalanine methyl ester (21)

Prepared according to **GP 1** in 85 % yield. TLC ethyl acetate/hexane, 1/1, R_f 0.44; mp 77-79 °C. ^1H NMR (270 MHz, $CDCl_3$): δ 3.02 (A of ABX system, 1 H, J = 7.4 Hz and 13.9 Hz, C**H**$_2$Ph), 3.13(B of ABX system, 1 H, J = 5.5 Hz and 13.9 Hz, C**H**$_2$Ph), 3.48 (s, 3 H, OC**H**$_3$), 4.39-4.48 (m, 1 H, C**H**), 6.13 (d, 1H, J = 8.6 Hz, N**H**) 7.06-7.18 (m, 5 H, **Ph**), 7.55-7.63 (m, 2 H, para **H**'s to -NO_2 and -SO_2), 7.69-7.76 (m, 1 H, ortho **H** to -SO_2), 7.84-7.91 (m, 1 H, ortho **H** to -NO_2); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 38.99 (CH_2Ph), 52.61 (OCH_3), 58.01 (CH), 125.59, 127.40, 128.69, 129.37, 130.33, 133.21 (Aromatics), 133.72, 135.92, 147.37 (Quaternary Aromatics), 171.01 (C=O); MS (CI, NH_3) m/e (%) 365 (36.3) $[MH]^+$, 335 (21.1), 305 (53.6), 186 (100).

N-2,4-Dinitrobenzenesulfonyl-L-phenylalanine methyl ester (22)

Prepared according to **GP 1** in 71 % yield. TLC ethyl acetate/hexane, 2/1, R_f 0.41. ^1H NMR (270 MHz, $CDCl_3$): δ 3.01 (A of ABX system, 1 H, J = 8.2 Hz and 14.1 Hz, C**H**$_2$Ph), 3.20(B of ABX system, 1 H, J = 4.9 Hz and 14.1 Hz, C**H**$_2$Ph), 3.65 (s, 3 H, OC**H**$_3$), 4.50 (X of ABX system, 1 H, J = 4.9 Hz and 8.2 Hz, C**H**CH$_2$Ph), 6.10 (s br, 1H, N**H**) 7.06-7.20 (m, 5 H, **Ph**), 8.02 (d, 1 H, J = 8.6 Hz, ortho **H** to -SO_2), 8.36 (dd, 1 H, J = 2.2 Hz and 8.6 Hz, **H** para to the 2-NO_2), 8.58 (d, 1 H, J = 2.2 Hz, **H** ortho to the 2-NO_2); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 38.92 (CH_2Ph), 52.91 (OCH_3), 58.33 (CH), 120.87, 127.22, 127.55 128.83, 129.33, 131.83 (Aromatics), 134.94, 139.63, 147.48, 149.60 (Quaternary Aromatics), 170.86 (C=O); MS (CI, NH_3) m/e (%) 427 (93.7) $[M + NH_4]^+$, 410 (3.0) [M + H], 162 (100).

N-4-Nitrobenzenesulfonyl-L-leucine methyl ester (23)

Prepared according to **GP 1** in 88 % yield.TLC ethyl acetate/hexane, 1/1, R_f 0.69; mp 80-82 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.87, 0.89 (2 d, 6 H, J = 4.5 Hz and 4.7 Hz, $CH_2CH(C\mathbf{H}_3)_2$), 1.48-1.54 (m, 2 H, $C\mathbf{H}_2C\mathbf{H}(CH_3)_2$), 1.65-1.82 (m, 1 H, $C\mathbf{H}_2CH(CH_3)_2$) 3.48 (s, 3 H, $OC\mathbf{H}_3$), 3.96-4.04 (m, 1 H, NHC**H**), 5.35 (d, 1 H, J = 9.9 Hz, N**H**CH), 8.01 (d, 2 H, J = 8.9 Hz, meta **H**'s to -NO_2), 8.32 (d, 2 H, J = 8.9 Hz, ortho **H**'s to -NO_2); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 21.40, 22.74 ($CH_2CH(CH_3)_2$), 24.41 ($CH_2CH(CH_3)_2$), 42.25 ($CH_2CH(CH_3)_2$), 52.61 (OCH_3), 54.61 (NHCH), 124.28, 128.58 (Aromatics), 145.74, 150.16 (Quaternary Aromatics), 172.40 (C=O); MS (CI, NH_3) m/e (%) 348 (62.9) $[M + NH_4]^+$, 331 (9.1) $[MH]^+$, 271 (100), 186 (23.5).

N-2-Nitrobenzenesulfonyl-L-leucine methyl ester (24)

Prepared according to **GP 1** in 84 % yield TLC ethyl acetate/hexane, 1/1, R_f 0.47; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.80, 0.83 (2 d, 6 H, J = 2.2 Hz and 2.5 Hz, $CH_2CH(C\mathbf{H}_3)_2$), 1.48-1.54 (m, 2 H, $C\mathbf{H}_2C\mathbf{H}(CH_3)_2$), 1.65-1.80 (m, 1 H, $C\mathbf{H}_2CH(CH_3)_2$) 3.31 (s, 3 H, $OC\mathbf{H}_3$), 4.05-4.15 (m, 1 H, NHC**H**), 5.95 (d, 1 H, J = 9.6 Hz, N**H**CH), 7.65-7.70 (m, 2 H, para **H**'s to -NO_2 and -SO_2), 7.79-7.83 (m, 1 H, ortho **H** to -SO_2), 7.94-7.98 (m, 1 H, ortho **H** to -NO_2); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 21.29, 22.71 ($CH_2CH(CH_3)_2$), 24.34 ($CH_2CH(CH_3)_2$), 41.78 ($CH_2CH(CH_3)_2$), 52.29 (OCH_3), 55.38 (NHCH), 125.54, 130.41, 133.03, 133.74, (Aromatics), 134.00, 147.58 (Quaternary Aromatics), 171.96 (C=O); MS (CI, NH_3) m/e (%) 348 (53.2) $[M + NH_4]^+$, 331 (10.5) $[MH]^+$, 271 (100).

N-2,4-Dinitrobenzenesulfonyl-L-leucine methyl ester (25)

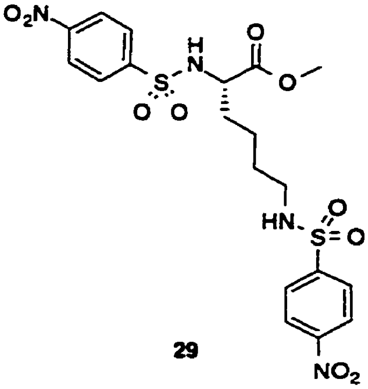
Prepared according to **GP 1** in 72 % yield TLC ethyl acetate/hexane, 1/2, R_f 0.38; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.92, 0.95 (2 d, 6 H, J = 1.5 Hz and 1.2 Hz, $CH_2CH(C\mathbf{H}_3)_2$), 1.59-1.68 (m, 2 H, $C\mathbf{H}_2C\mathbf{H}(CH_3)_2$), 1.75-1.88 (m, 1 H, $C\mathbf{H}_2CH(CH_3)_2$) 3.48 (s, 3 H, $OC\mathbf{H}_3$), 4.21-4.30 (m, 1 H, NHC**H**), 6.01 (d, 1 H, J = 8.9 Hz, N**H**CH), 8.25 (d, 1 H, J= 8.6 Hz, ortho **H** to -SO_2), 8.50 (dd, 1 H, J = 2.2 Hz and

8.6 Hz, **H** para to the 2-NO_2), 8.72 (d, 1 H, J = 2.2 Hz, **H** ortho to the 2-NO_2); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 21.22, 22.80 ($CH_2CH(\mathbf{CH_3})_2$), 24.49 ($CH_2\mathbf{CH}(CH_3)_2$), 41.67 ($\mathbf{CH_2}CH(CH_3)_2$), 52.63 (OCH_3), 55.72 (NHCH), 121.08, 127.18, 132.10, (Aromatics), 139.81, 147.90, 149.83 (Quaternary Aromatics), 172.07 (C=O); MS (CI, NH_3) m/e (%) 393 (100) $[M + NH_4]^+$, 376 (1.3) $[MH]^+$, 316 (47.6), 231 (42.9).

N-4-Nitrobenzenesulfonyl-N^{ε}-(benzyloxycarbonyl)-L-lysine methyl ester (26)

Prepared according to **GP 1** in 86 % yield. TLC ethyl acetate/hexane, 1/1, R_f 0.30; mp 106-108 °C; ^1H NMR(270 MHz, $CDCl_3$): δ 1.31-1.54 (m, 4 H, $CH_2(\mathbf{CH_2})_2CH_2NH$), 1.61-1.85 (m, 2 H, $\mathbf{CH_2}(CH_2)_2CH_2NH$), 3.11-3.16 (m, 2 H, $CH_2(CH_2)_2\mathbf{CH_2}NH$), 3.51 (s, 3 H, $O\mathbf{CH_3}$), 3.92-4.00 (m, 1 H, $NHC\mathbf{H}CH_2$), 4.87 (s br, 1 H, $CH_2N\mathbf{H}$), 5.09 (s, 2 H, $\mathbf{CH_2}Ph$), 5.77 (d, 1 H, J = 8.9 Hz, $N\mathbf{H}CHCH_2$), 7.28-7.35 (m, 5 H, **Ph**), 8.00 (d, 2 H, J = 8.9 Hz, meta **H**'s to -NO_2), 8.31 (d, 2 H, J = 8.9 Hz, ortho **H**'s to -NO_2); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 21.90 ($CH_2CH_2(CH_2)_2NH$), 29.29 ($(CH_2)_2CH_2CH_2NH$), 32.38 ($CH_2(CH_2)_3NH$), 40.25 ($(CH_2)_3CH_2NH$), 52.72 (OCH_3), 55.78 ($NHCHCH_2$), 66.85 (CH_2Ph), 124.33, 128.21, 128.50, 128.61 (Aromatics), 136.58, 145.88, 150.16 (Quaternary Aromatics), 156.80 (NHC(O)), 171.78 ($C(O)OCH_3$); MS (CI, NH_3) m/e (%) 480 (26.3) $[MH]^+$, 389 (63.3), 342 (74.4), 156 (100).

N^{α},N^{ϵ}-Bis-4-nitrobenzenesulfonyl-L-lysine methyl ester (29)



29

Obtained as a by-product from the preparation of compound **26**. TLC ethyl acetate/hexane, 1/1, R_f 0.29; mp 94-97 °C; ^{1}H NMR(270 MHz, $CDCl_3$): δ 1.25-1.55 (m, 4 H, $CH_2(\mathbf{CH_2})_2CH_2NH$), 1.60-1.87 (m, 2 H, $\mathbf{CH_2}(CH_2)_2CH_2NH$), 2.94-3.03 (m, 2 H, $CH_2(CH_2)_2\mathbf{CH_2}NH$), 3.51 (s, 3 H, $O\mathbf{CH_3}$), 3.89-3.97 (m, 1 H, $NH\mathbf{CH}CH_2$), 5.11 (t, 1 H, J = 5.9 Hz, $CH_2N\mathbf{H}$), 5.64 (d, 1 H, J = 9.2 Hz, $N\mathbf{H}CH$), 8.00-8.08 (m, 4 H, meta **H**'s to -NO_2), 8.32-8.38 (m, 4 H, ortho **H**'s to -NO_2); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 21.88 ($CH_2\mathbf{C}H_2(CH_2)_2NH$), 28.85 ($(CH_2)_2\mathbf{C}H_2CH_2NH$), 32.50 ($\mathbf{C}H_2(CH_2)_3NH$), 42.91 ($(CH_2)_3\mathbf{C}H_2NH$), 52.92 ($O\mathbf{C}H_3$), 55.63 ($NH\mathbf{C}H$), 124.43, 124.57, 128.37, 128.51 (Aromatics), 145.40, 145.83, 150.19, 150.28 (Quaternary Aromatics), 171.55 ($\mathbf{C}(O)OCH_3$); MS (CI, NH_3) m/e (%) 531 (36.1) $[MH]^+$, 389 (48.2).

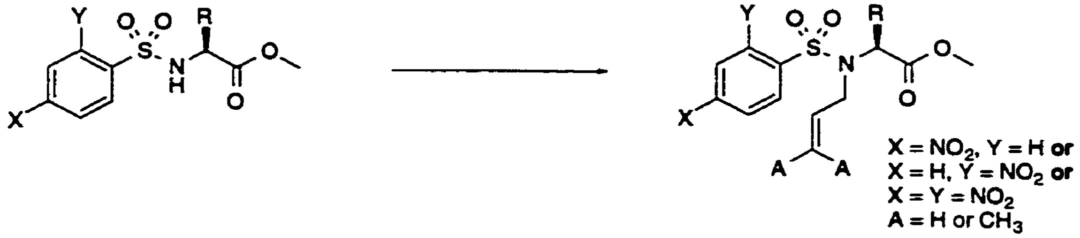
N-4-Nitrobenzenesulfonyl-O-benzyl-L-serine methyl ester (27)

Prepared according to **GP 1** in 88 % yield. TLC ethyl acetate/hexane, 1/1, R_f 0.58; mp 95-98 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.59 (s, 3 H, $O\mathbf{CH_3}$), 3.64 (A of ABX system, 1 H, J = 3.2 Hz and 9.4 Hz, $CH\mathbf{CH_2}$), 3.79 (B of ABX system, 1 H, J = 3.5 Hz and 9.4 Hz, $CH\mathbf{CH_2}$), 4.20-4.26 (m, 1 H, $\mathbf{CH}CH_2$), 4.44 (ABq, 2 H, J = 12.0 Hz, $\mathbf{CH_2}Ph$), 5.74 (d, 1H, J = 8.9 Hz, N**H**) 7.16-7.35 (m, 5 H, **Ph**), 8.00 (d, 2 H, J = 8.9 Hz, meta **H**'s to -NO_2), 8.25 (d, 2 H, J = 9.2 Hz, ortho **H**'s to -NO_2); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 52.98 ($O\mathbf{C}H_3$), 56.35 ($\mathbf{C}HCH_2$), 70.31 ($CH\mathbf{C}H_2$), 73.45 ($O\mathbf{C}H_2Ph$), 124.24, 127.76, 128.16, 128.39, 128.55 (Aromatics), 137.00, 146.28, 150.21 (Quaternary Aromatics), 169.60 (**C**=O); MS (CI, NH_3) m/e (%) 412 (100) $[M + NH_4]^+$, 395 (19.5) $[MH]^+$, 208 (98.0), 162 (29.0).

N-4-Nitrobenzenesulfonyl-L-valine methyl ester (28)

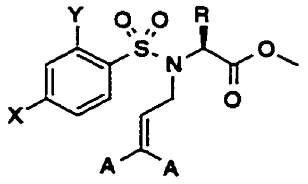
Prepared according to **GP 1** in 96 % yield. TLC ethyl acetate/hexane, 1/2, R$_f$ 0.38; mp 93-96 °C; ^{1}H NMR (270 MHz, CDCl$_3$): δ 0.84, 0.95 (2 d, 6 H, J = 6.7 Hz and 6.9 Hz, CH(C**H**$_3$)$_2$) 2.01-2.13 (m, 1 H, C**H**(CH$_3$)$_2$) 3.49 (s, 3H, OC**H**$_3$), 3.82 (dd, 1 H, J = 5.0 Hz and 9.9 Hz, NHC**H**), 5.52 (d, 1 H, J = 10.1 Hz, N**H**CH), 8.01 (d, 2 H, J = 8.9 Hz, meta **H**'s to -NO$_2$), 8.32 (d, 2 H, J = 8.9 Hz, ortho **H**'s to -NO$_2$); ^{13}C NMR (67.9 MHz, CDCl$_3$): δ 17.36, 19.02 (CH(CH$_3$)$_2$), 31.60 (CH(CH$_3$)$_2$), 52.52 (OCH$_3$), 61.32 (NHCH), 124.28, 128.58 (Aromatics), 145.72, 150.15 (Quaternary Aromatics), 171.45 (C=O); MS (CI, NH$_3$) m/e (%) 334 (66.9) [M + NH$_4$]$^+$, 317 (8.5) [MH]$^+$, 287 (12.3), 274 (7.8), 257 (100), 227 (8.9), 186 (15.0).

Preparation of allylated or prenylated sulfonamides (GP 2)



To a solution of the sulfonamide (1.00 mmol) in dry DMF (5 ml) was added potassium carbonate (2.00 mmol). The reaction mixture was then left to stir under argon at room temperature until the solution changed color (≈ 20 minutes). At this point, allyl or prenyl bromide (5.00 mmol) was slowly injected into the mixture which changed to a dirty brown color and was then left to stir for an additional three hours. The DMF was removed *in vacuo* and the residue dissolved in ethyl acetate (30 ml). This organic layer was then washed with hydrochloric acid (10 % v/v, 2 X 30 ml) and brine (30 ml) respectively. The organic layer was then dried over anhydrous sodium sulfate and the excess solvent removed under reduced pressure to yield the desired compound.

N-(Allyl)-N-4-nitrobenzenesulfonyl-L-phenylalanine methyl ester (30)



30 : R = CH_2Ph, X = NO_2, Y = H, A = H
31 : R = CH_2Ph, X = NO_2, Y = H, A = CH_3
32 : R = CH_2Ph, X = H, Y = NO_2, A = CH_3
33 : R = CH_2Ph, X = Y = NO_2, A = CH_3
34 : R = $CH_2CH(CH_3)_2$, X = NO_2, Y = H, A = H
35 : R = $CH_2CH(CH_3)_2$, X = NO_2, Y = H, A = CH_3
36 : R = $CH_2CH(CH_3)_2$, X = H, Y = NO_2, A = CH_3
37 : R = $CH_2CH(CH_3)_2$, X =Y = NO_2, A = CH_3
38 : R = $(CH_2)_4NHCbz$, X = NO_2, Y = H, A = CH_3
39 : R = CH_2OBn, X = NO_2, Y = H, A = CH_3
40 : R = $CH(CH_3)_2$, X = NO_2, Y = H, A = CH_3

Method 1

Prepared according to **GP 2** in 99 % yield.

Method 2

To a solution of N-4-Nitrobenzenesulfonyl-L-phenylalanine methyl ester **20** (0.50 g, 1.37 mmol) in dry THF (20 ml) was added triphenylphosphine (0.72 g, 2.74 mmol) and diethyl azodicarboxylate (430 µl, 2.74 mmol). To the resulting solution was added freshly distilled allyl alcohol (186 µl, 2.74 mmol) and the solution stirred at room temperature for one hour. The excess solvent was removed under reduced pressure to gave a dark brown oil. Column chromatography performed (hexane/ ethyl acetate, 3/1 v/v) to yield a brown oil (0.41g, 74%).

TLC ethyl acetate/hexane, 1/2, R_f 0.50; ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.97 (A of ABX system, 1 H, J = 8.9 Hz and 14.3 Hz, $\mathbf{CH_2}$Ph) 3.34 (B of ABX system, 1 H, J = 6.2 Hz and 14.3 Hz, $\mathbf{CH_2}$Ph), 3.57 (s, 3 H, O$\mathbf{CH_3}$), 3.78-4.00 (m, 2 H, CH_2=CH$\mathbf{CH_2}$), 4.88 (X of ABX system, 1 H, J = 6.2 Hz and 8.9 Hz, C**H**), 5.07-5.23 (m, 2 H, $\mathbf{CH_2}$=CHCH_2), 5.56-5.71 (m, 1 H, CH_2=C**H**CH_2), 7.13-7.28 (m, 5 H, **Ph**), 7.70 (d, 2 H, J = 9.1 Hz, meta **H**'s to -NO_2), 8.15 (d, 2 H, J = 9.2 Hz, ortho **H**'s to -NO_2); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 36.32 (CH_2Ph), 48.66 (CH_2=CHCH_2), 52.42 (OCH_3), 61.60 (CH), 119.18 (CH_2=CHCH_2), 123.95, 127.16, 128.74, 128.80, 129.29 (Aromatics), 133.57 (CH_2=CHCH_2), 136.59, 145.97, 149.83 (Quaternary Aromatics), 170.57 (C=O); MS (FAB, NBA) m/e (%) 405 (49.9) $[MH]^+$.

N-(Dimethylallyl)-N-4-nitrobenzenesulfonyl-L-phenylalanine methyl ester (31)

Prepared according to **GP 2** in 97 % yield. TLC ethyl acetate/hexane, 1/2, R_f 0.63; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.58, 1.63 (2 s, 6 H, $(C\mathbf{H}_3)_2C{=}CHCH_2$), δ 2.94 (A of ABX system, 1 H, J = 9.1 Hz and 14.3 Hz, $C\mathbf{H}_2Ph$) 3.35 (B of ABX system, 1 H, J = 6.2 Hz and 14.3 Hz, $C\mathbf{H}_2Ph$), 3.61 (s, 3 H, $OC\mathbf{H}_3$), 3.73-4.00 (m, 2 H, $(CH_3)_2C{=}CHC\mathbf{H}_2$), 4.83-4.87 (m, 1 H, $(CH_3)_2C{=}C\mathbf{H}CH_2$), 4.89 (X of ABX system, 1 H, J = 6.2 Hz and 9.1 Hz, C**H**), 7.14-7.30 (m, 5 H, **Ph**), 7.68 (d, 2 H, J = 8.9 Hz, meta **H**'s to $-NO_2$), 8.14 (d, 2 H, J = 9.2 Hz, ortho **H**'s to $-NO_2$); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 17.87, 25.81 ($(\mathbf{C}H_3)_2C{=}CHCH_2$), 36.33 ($\mathbf{C}H_2Ph$), 43.92 ($(CH_3)_2C{=}CH\mathbf{C}H_2$), 52.42 ($O\mathbf{C}H_3$), 61.37 (**C**H) 119.64 ($(CH_3)_2C{=}\mathbf{C}HCH_2$), 123.77, 127.11, 128.65, 128.78, 129.33 (Aromatics), 136.88 ($(CH_3)_2\mathbf{C}{=}CHCH_2$), 137.07, 146.58, 149.68 (Quaternary Aromatics), 170.77 (**C**=O); MS (CI, NH_3) m/e (%) 450 (19.6) $[M + NH_4]^+$, 433 (1.5) $[MH]^+$, 382 (31.5), 365 (15.1), 246 (100), 186 (7.3), 156 (6.7).

N-(Dimethylallyl)-N-2-nitrobenzenesulfonyl-L-phenylalanine methyl ester (32)

Prepared according to **GP 2** in 88 % yield TLC ethyl acetate/hexane, 1/1, R_f 0.65; mp 46-48 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.58, 1.64 (2 s, 6 H, $(C\mathbf{H}_3)_2C{=}CHCH_2$), 3.01 (A of ABX system, 1 H, J = 7.7 Hz and 14.1 Hz, $C\mathbf{H}_2Ph$), 3.33 (B of ABX system, 1 H, J = 7.6 Hz and 14.1 Hz, $C\mathbf{H}_2Ph$), 3.57 (s, 3 H, $OC\mathbf{H}_3$), 3.93-4.06 (m, 2 H, $(CH_3)_2C{=}CHC\mathbf{H}_2$), 4.91 (apparent t, 1 H, J = 7.4 Hz, NC**H**), 5.00-5.07 (m, 1 H, $(CH_3)_2C{=}C\mathbf{H}CH_2$), 7.17-7.27 (m, 5 H, **Ph**), 7.49-7.67 (m, 3 H, para **H**'s to $-NO_2$ and $-SO_2$ and ortho **H** to $-SO_2$), 7.74-7.78 (m, 1 H, ortho **H** to $-NO_2$); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 17.89, 25.79 ($(\mathbf{C}H_3)_2C{=}CHCH_2$), 36.68 ($\mathbf{C}H_2Ph$), 44.37 ($(CH_3)_2C{=}CH\mathbf{C}H_2$), 52.30 ($O\mathbf{C}H_3$), 61.14 (**C**H) 120.48 ($(CH_3)_2C{=}\mathbf{C}HCH_2$), 124.09, 126.99, 128.58, 129.42, 131.10, 131.48, 133.35 (Aromatics), 134.09 ($(CH_3)_2\mathbf{C}{=}CHCH_2$), 136.41, 136.71, 148.12 (Quaternary Aromatics), 170.92 (**C**=O); MS (FAB, NBA/NaCl) m/e (%) 455 (8.2) $[M + Na]^+$, 431 (21.7), 365 (99.2).

N-(Dimethylallyl)-N-2,4-dinitrobenzenesulfonyl-L-phenylalanine methyl ester (33)

Prepared according to **GP 2** in 97 % yield. TLC ethyl acetate/hexane, 1/2, R_f 0.50; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.60, 1.67 (2 s, 6 H, $(C\mathbf{H}_3)_2C=CHCH_2$), 3.01 (A of ABX system, 1 H, J = 8.9 Hz and 14.3 Hz, $C\mathbf{H}_2Ph$), 3.38 (B of ABX system, 1 H, J = 6.4 Hz and 14.3 Hz, $C\mathbf{H}_2Ph$), 3.65 (s, 3 H, $OC\mathbf{H}_3$), 3.92-4.11 (m, 2 H, $(CH_3)_2C=CHC\mathbf{H}_2$), 4.92 (X of ABX system, 1 H, J = 6.4 Hz and 8.9 Hz, NC**H**), 4.99-5.04 (m, 1 H, $(CH_3)_2C=C\mathbf{H}CH_2$), 7.17-7.29 (m, 5 H, **Ph**), 7.84 (d, 1 H, J = 8.7 Hz, ortho **H** to $-SO_2$), 8.25 (dd, 1 H, J = 2.0 Hz and 8.7 Hz, **H** para to the 2-NO_2), 8.35 (d, 1 H, J = 2.0 Hz, **H** ortho to the 2-NO_2); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 17.94, 25.81 ($(\mathbf{CH_3})_2C=CHCH_2$), 36.31 ($\mathbf{C}H_2Ph$), 44.76 ($(CH_3)_2C=CH\mathbf{C}H_2$), 52.62 ($O\mathbf{C}H_3$), 61.69 (**C**H) 119.48 ($(CH_3)_2C=\mathbf{C}HCH_2$), 119.80 125.69, 127.18, 128.71, 129.36, 132.66, (Aromatics), 136.38 ($(CH_3)_2\mathbf{C}=CHCH_2$), 137.49, 139.50, 148.10, 149.38 (Quaternary Aromatics), 170.66 (**C**=O); MS (CI, NH_3) m/e (%) 495 (34.4) $[M + NH_4]^+$, 246 (100).

N-(Allyl)-N-4-nitrobenzenesulfonyl-L-leucine methyl ester (34)

Prepared according to **GP 2** in 95 % yield. TLC ethyl acetate/hexane, 1/2, R_f 0.69; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.86, 0.92 (2 d, 6 H, J = 6.4 Hz and 6.5 Hz, $CH_2CH(C\mathbf{H}_3)_2$), 1.60-1.76 (m, 3 H, $C\mathbf{H}_2C\mathbf{H}(CH_3)_2$), 3.53 (s, 3 H, $OC\mathbf{H}_3$), 3.75-3.98 (m, 2 H, $CH_2=CHC\mathbf{H}_2$), 4.66-4.70 (m, 1 H, NC**H**), 5.05-5.15 (m, 2 H, $C\mathbf{H}_2=CHCH_2$), 5.50-5.65 (m, 1 H, $CH_2=C\mathbf{H}CH_2$), 8.01 (d, 2 H, J = 9.0 Hz, meta **H**'s to $-NO_2$), 8.32 (d, 2 H, J = 9.0 Hz, ortho **H**'s to $-NO_2$); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 21.32, 22.95 ($CH_2CH(\mathbf{C}H_3)_2$), 24.55 ($CH_2\mathbf{C}H(CH_3)_2$), 38.95 ($\mathbf{C}H_2CH(CH_3)_2$), 48.44 ($CH_2=CH\mathbf{C}H_2$), 52.25 ($O\mathbf{C}H_3$), 57.99 (N**C**H), 120.01 ($\mathbf{C}H_2=CHCH_2$), 123.91, 128.87 (Aromatics), 134.12 ($CH_2=\mathbf{C}HCH_2$), 146.00, 149.84 (Quaternary Aromatics), 171.54 (**C**=O); MS (CI, NH_3) m/e (%) 388 (18.1) $[M + NH_4]^+$, 328 (30.2), 212 (100), 152 (20.2).

N-(Dimethylallyl)-N-4-nitrobenzenesulfonyl-L-leucine methyl ester (35)

Prepared according to **GP 2** in 92 % yield. TLC ethyl acetate/hexane, 1/2, R_f 0.71; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.89, 0.96 (2 d, 6 H, J = 6.2 Hz and 6.2 Hz, $CH_2CH(C\mathbf{H}_3)_2$), 1.60-1.76 (m, 9 H, $C\mathbf{H}_2C\mathbf{H}(CH_3)_2$ and $(C\mathbf{H}_3)_2C{=}CHCH_2$), 3.51 (s, 3 H, $OC\mathbf{H}_3$), 3.86 (apparent d, 2 H, J = 6.9 Hz, $(CH_3)_2C{=}CHC\mathbf{H}_2$), 4.63-4.69 (m, 1 H, NC**H**), 5.05-5.12 (m, 1 H, $(CH_3)_2C{=}C\mathbf{H}CH_2$), 7.98 (d, 2 H, J = 8.9 Hz, meta **H**'s to -NO_2), 8.31 (d, 2 H, J = 8.7 Hz, ortho **H**'s to -NO_2); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 17.84 ($(\mathbf{C}H_3)_2C{=}CHCH_2$), 21.29, 22.93 ($CH_2CH(\mathbf{C}H_3)_2$), 24.43 ($CH_2\mathbf{C}H(CH_3)_2$), 25.76 ($(\mathbf{C}H_3)_2C{=}CHCH_2$), 38.81 ($\mathbf{C}H_2CH(CH_3)_2$), 43.78 ($(CH_3)_2C{=}CH\mathbf{C}H_2$), 52.16 ($O\mathbf{C}H_3$), 58.23 (N**C**H), 120.78 ($(CH_3)_2C{=}\mathbf{C}HCH_2$), 123.90, 128.77 (Aromatics), 135.65 ($(CH_3)_2\mathbf{C}{=}CHCH_2$), 146.25, 149.89 (Quaternary Aromatics), 171.64 (**C**=O); MS (CI, NH_3) m/e (%) 416 (16.3) $[M + NH_4]^+$, 348 (34.2), 212 (100), 152 (14.3).

N-(Dimethylallyl)-N-2-nitrobenzenesulfonyl-L-leucine methyl ester (36)

Prepared according to **GP 2** in 97 % yield. TLC ethyl acetate/hexane, 1/1, R_f 0.70; mp 93-96 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.89, 0.96 (2 d, 6 H, J = 6.1 Hz and 6.4 Hz, $CH_2CH(C\mathbf{H}_3)_2$), 1.61-1.80 (m, 9 H, $C\mathbf{H}_2C\mathbf{H}(CH_3)_2$ and $(C\mathbf{H}_3)_2C{=}CHCH_2$), 3.53 (s, 3 H, $OC\mathbf{H}_3$), 3.85-4.06 (m, 2 H, $(CH_3)_2C{=}CHC\mathbf{H}_2$), 4.64-4.71 (m, 1 H, NC**H**), 5.20-5.25 (m, 1 H, $(CH_3)_2C{=}C\mathbf{H}CH_2$), 7.52-7.66 (m, 3 H, para **H**'s to -NO_2 and -SO_2 and ortho **H** to -SO_2), 7.97-8.03 (m, 1 H, ortho **H** to -NO_2); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 17.84 ($(\mathbf{C}H_3)_2C{=}CHCH_2$), 21.26, 22.89 ($CH_2CH(\mathbf{C}H_3)_2$), 24.47 ($CH_2\mathbf{C}H(CH_3)_2$), 25.76 ($(\mathbf{C}H_3)_2C{=}CHCH_2$), 38.90 ($\mathbf{C}H_2CH(CH_3)_2$), 44.37 ($(CH_3)_2C{=}CH\mathbf{C}H_2$), 52.15 ($O\mathbf{C}H_3$), 58.64 (N**C**H), 121.59 ($(CH_3)_2C{=}\mathbf{C}HCH_2$), 124.03, 131.12, 131.39, 133.38, (Aromatics), 133.66 ($(CH_3)_2\mathbf{C}{=}CHCH_2$), 134.95, 148.07 (Quaternary Aromatics), 172.05 (**C**=O); MS (FAB, NBA/NaCl) m/e (%) 421 (31.4) $[M + Na]^+$, 397 (35.8), 331 (100), 271 (97.2).

N-(Dimethylallyl)-N-2,4-dinitrobenzenesulfonyl-L-leucine methyl ester (37)

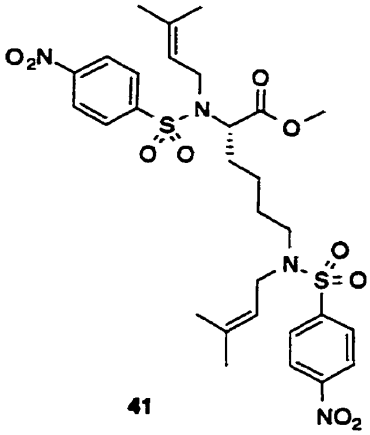
Prepared according to **GP 2** in 98 % yield. TLC ethyl acetate/hexane, 1/2, R_f 0.71; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.88, 0.96 (2 d, 6 H, J = 6.2 Hz and 5.9 Hz, $CH_2CH(C\mathbf{H}_3)_2$), 1.60-1.82 (m, 9 H, $C\mathbf{H}_2C\mathbf{H}(CH_3)_2$ and $(C\mathbf{H}_3)_2C{=}CHCH_2$), 3.59 (s, 3 H, $OC\mathbf{H}_3$), 3.85-4.04 (m, 2 H, $(CH_3)_2C{=}CHC\mathbf{H}_2$), 4.65-4.74 (m, 1 H, NC**H**), 5.20-5.22 (m, 1 H, $(CH_3)_2C{=}C\mathbf{H}CH_2$), 8.23 (d, 1 H, J = 8.6 Hz, ortho **H** to -SO_2), 8.39 (d, 1 H, J = 2.2 Hz, **H** ortho to the 2-NO_2); 8.45 (dd, 1 H, J = 2.2 Hz and 8.6 Hz, **H** para to the 2-NO_2); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 17.90 $(CH_3)_2C{=}CHCH_2$), 21.07, 22.93 ($CH_2CH(CH_3)_2$), 24.52 ($CH_2CH(CH_3)_2$), 25.75 ($(CH_3)_2C{=}CHCH_2$), 38.70 ($CH_2CH(CH_3)_2$), 44.85 ($(CH_3)_2C{=}CHCH_2$), 52.45 (OCH_3), 59.03 (NCH), 119.57 ($(CH_3)_2C{=}CHCH_2$), 120.95, 125.72, 132.86 (Aromatics), 135.82 ($(CH_3)_2\mathbf{C}{=}CHCH_2$), 139.06, 148.11, 149.49 (Quaternary Aromatics), 171.85 (**C**=O); MS (FAB, NBA/NaCl) m/e (%) 466 (27.3) $[M + Na]^+$.

N-4-Nitrobenzenesulfonyl-N^{ε}-(benzyloxycarbonyl)-N-dimethylallyl-L-lysine methyl ester (38)

Prepared according to **GP 2** in 90 % yield. TLC ethyl acetate/hexane, 1/2, R_f 0.28; ^{1}H NMR(270 MHz, $CDCl_3$): δ 1.34-1.54 (m, 4 H, $CH_2(C\mathbf{H}_2)_2CH_2NH$), 1.60 (d, 6 H, J = 2.7 Hz, $(C\mathbf{H}_3)_2C{=}CHCH_2$), 1.67-1.98 (m, 2 H, $C\mathbf{H}_2(CH_2)_2CH_2NH$), 3.14-3.21 (m, 2 H, $CH_2(CH_2)_2C\mathbf{H}_2NH$), 3.51 (s, 3 H, $OC\mathbf{H}_3$), 3.82 (d, 6 H, J = 2.7 Hz, $(CH_3)_2C{=}CHC\mathbf{H}_2$), 4.55 (dd, 1 H, J = 5.2 Hz and J = 9.9 Hz, $NHC\mathbf{H}CH_2$), 4.87 (s br, 1 H, $CH_2N\mathbf{H}$), 4.99-5.06 (m, 1 H, $(CH_3)_2C{=}C\mathbf{H}CH_2$), 5.07 (s, 2 H, $C\mathbf{H}_2Ph$), 7.27-7.34 (m, 5 H, **Ph**), 7.97 (d, 2 H, J = 8.9 Hz, meta **H**'s to -NO_2), 8.30 (d, 2 H, J = 8.9 Hz, ortho **H**'s to -NO_2); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 17.82 ($(CH_3)_2C{=}CHCH_2$), 23.29 ($CH_2CH_2(CH_2)_2NH$), 25.76 ($(CH_3)_2C{=}CHCH_2$), 29.42 ($(CH_2)_2CH_2CH_2NH$), 31.64 ($CH_2(CH_2)_3NH$), 40.74 ($(CH_2)_3CH_2NH$), 43.75 ($(CH_3)_2C{=}CHCH_2$), 52.23 (OCH_3), 59.80 ($NHCHCH_2$), 66.66 (CH_2Ph), 120.15 ($(CH_3)_2C{=}CHCH_2$), 123.91, 128.13, 128.57, 128.78 (Aromatics), 136.35 ($(CH_3)_2C{=}CHCH_2$), 136.71, 146.31, 149.91 (Quaternary Aromatics), 156.47

(NHC(O)), 171.06 ($C(O)OCH_3$); MS (FAB, NBA) m/e (%) 548 (15.2) $[MH]^+$, 480 (22.5), 436 (23.0), 361 (17.9).

N^α,N^ε-Bis-dimethylallyl-N^α,N^ε-bis-4-nitrobenzenesulfonyl-L-lysine methyl ester (41)



41

Obtained as a by-product from the preparation of compound **38**. TLC ethyl acetate/hexane, 1/2, R_f 0.46; ^{1}H NMR(270 MHz, $CDCl_3$): δ 1.30-1.94 (m, 18 H, $C\mathbf{H}_2(C\mathbf{H}_2)_2CH_2N$ and 2 X $(C\mathbf{H}_3)_2C{=}CHCH_2$)), 3.14 (t, 2 H, J = 7.2 Hz, $CH_2(CH_2)_2C\mathbf{H}_2N$), 3.53 (s, 3 H, $OC\mathbf{H}_3$), 3.83 (t, 4 H, J = 5.9 Hz, 2 X $(CH_3)_2C{=}CHC\mathbf{H}_2$), 4.55 (dd, 1 H, J = 4.9 Hz and J = 9.9 Hz, $NC\mathbf{H}CH_2$), 4.86-4.90, 4.98-5.03 (2 m, 2 H, 2 X $(CH_3)_2C{=}C\mathbf{H}CH_2$), 7.92-8.00 (m, 4 H, meta **H**'s to $-NO_2$), 8.30-8.36 (m, 4 H, ortho **H**'s to $-NO_2$); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 17.82, 17.93 (2 X $(\mathbf{C}H_3)_2C{=}CHCH_2$), 23.19 ($CH_2\mathbf{C}H_2(CH_2)_2NH$), 25.19, 25.20 (2 X $(\mathbf{C}H_3)_2C{=}CHCH_2$), 27.97 ($(CH_2)_2\mathbf{C}H_2CH_2NH$), 29.33 ($\mathbf{C}H_2(CH_2)_3NH$), 43.73 ($(CH_2)_3\mathbf{C}H_2N$), 45.43, 46.96 (2 X $(CH_3)_2C{=}CH\mathbf{C}H_2$), 52.29 ($O\mathbf{C}H_3$), 59.72 (N$\mathbf{C}$H), 118.15, 120.15 (2 X $(CH_3)_2C{=}\mathbf{C}HCH_2$), 123.94, 124.33, 128.35, 128.79 (Aromatics), 136.78, 137.93 (2 X $(CH_3)_2\mathbf{C}{=}CHCH_2$), 146.29, 146.42, 149.91, 149.98 (Quaternary Aromatics), 170.92 ($\mathbf{C}(O)OCH_3$); MS (FAB, NBA/NaCl) m/e (%) 689 (14.8) $[M + Na]^+$, 665 (7.5).

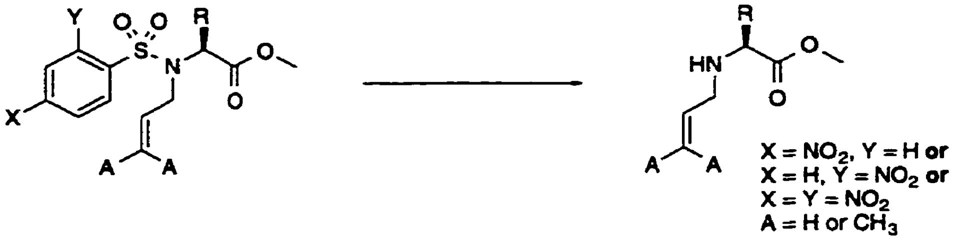
N-4-Nitrobenzenesulfonyl-N-dimethylallyl-O-benzyl-L-serine methyl ester (39)

Prepared according to **GP 2** in 92 % yield. TLC ethyl acetate/hexane, 1/1, R_f 0.76; mp 81-84 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.56, 1.58 (2 s br, 6 H, $(C\mathbf{H}_3)_2C{=}CHCH_2$), 3.69 (s, 3 H, $OC\mathbf{H}_3$), 3.76 (A of ABX system, 1 H, J = 9.1 Hz and 10.4 Hz, $CHC\mathbf{H}_2O$), 3.91 (B of ABX system, 1 H, J = 4.7 Hz and 10.4 Hz, $CHC\mathbf{H}_2O$), 3.84-4.00 (m, 2 H, $(CH_3)_2C{=}CHC\mathbf{H}_2$), 4.39 (ABq, 2 H, J = 11.4 Hz, $C\mathbf{H}_2Ph$), 4.91 (X of ABX system, 1 H, J= 4.7 Hz and 9.1 Hz, $C\mathbf{H}CH_2O$), 4.92-4.99 (m, 1 H, $(CH_3)_2C{=}C\mathbf{H}CH_2$), 7.10-7.31 (m, 5 H, **Ph**), 7.94 (d, 2 H, J = 9.2 Hz, meta **H**'s to $-NO_2$), 8.05 (d, 2 H, J = 9.2 Hz, ortho **H**'s to $-NO_2$); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 17.78, 25.74 ($(\mathbf{C}H_3)_2C{=}CHCH_2$), 44.17 ($(CH_3)_2C{=}CH\mathbf{C}H_2$), 52.61 ($O\mathbf{C}H_3$), 59.40 ($\mathbf{C}HCH_2$), 67.64 ($CH\mathbf{C}H_2$), 73.51 ($O\mathbf{C}H_2Ph$), 119.68 ($(CH_3)_2C{=}\mathbf{C}HCH_2$), 123.62, 128.07, 128.22, 128.51, 128.88 (Aromatics), 136.81 ($(CH_3)_2\mathbf{C}{=}CHCH_2$), 137.12, 146.69, 149.65 (Quaternary Aromatics), 169.59 (C=O); MS (CI, NH_3) m/e (%) 480 (14.8) $[M + NH_4]^+$, 412 (24.1), 395 (14.6), 276 (100).

N-(Dimethylallyl)-N-4-nitrobenzenesulfonyl-L-valine methyl ester (40)

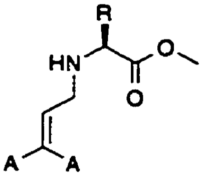
Prepared according to **GP 2** in 95 % yield. TLC ethyl acetate/hexane, 1/1, R_f 0.81; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.89, 0.99 (2 d, 6 H, J = 6.7 Hz and 6.7 Hz, $CH(C\mathbf{H}_3)_2$), 1.56, 1.62 (2 s, 6 H, $(C\mathbf{H}_3)_2C{=}CHCH_2$) 2.04-2.18 (m, 1 H, $C\mathbf{H}(CH_3)_2$), 3.46 (s, 3H, $OC\mathbf{H}_3$), 3.76-3.81 (m, 1 H, $(CH_3)_2{=}CHC\mathbf{H}_2$), 4.04-4.14 (m, 1 H, $(CH_3)_2{=}CHC\mathbf{H}_2$), 4.15 (d, 1 H, J = 10.6 Hz, $NC\mathbf{H}$), 4.85-4.93 (m, 1 H, $(CH_3)_2C{=}C\mathbf{H}CH_2$), 7.95 (d, 2 H, J = 8.9 Hz, meta **H**'s to $-NO_2$), 8.27 (d, 2 H, J = 8.9 Hz, ortho **H**'s to $-NO_2$); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 17.78 ($(\mathbf{C}H_3)_2C{=}CHCH_2$), 19.44, 19.56 ($CH(\mathbf{C}H_3)_2$), 25.71 ($(\mathbf{C}H_3)_2C{=}CHCH_2$), 28.21 ($\mathbf{C}H(CH_3)_2$), 43.26 ($(CH_3)_2C{=}CH\mathbf{C}H_2$), 51.65 ($O\mathbf{C}H_3$), 65.80 ($N\mathbf{C}H$), 120.06 ($(CH_3)_2C{=}\mathbf{C}HCH_2$), 123.71, 128.80 (Aromatics), 136.09 ($(CH_3)_2\mathbf{C}{=}CHCH_2$), 146.68, 149.82 (Quaternary Aromatics), 170.58 (C=O); MS (EI) m/e (%) 384 (60.5) $[M]^+$.

Preparation of the deprotected sulfonamides (GP 3)



To a mixture of potassium carbonate (3.00 mmol) in dry DMF (5 ml) was added thiophenol (1.20 mmol). This mixture was left to stir under argon until the solution changed color (≈ 30 minutes). The desired sulfonamide compound (1.00 mmol) in dry DMF (5 ml) was slowly injected into the above reaction mixture which was then left to stir for an additional six hours. The DMF was removed *in vacuo* and the residue dissolved in ethyl acetate (30 ml). This organic layer was then washed with sodium bicarbonate (10 % w/v, 2 X 30 ml). The organic layer was then dried over anhydrous sodium sulfate and the excess solvent removed under reduced pressure. In the case of the 2,4-dinitrobenzene-sulfonamides (1 mmol), the deprotecting agent was *n*-propylamine (20 mmol) in dichloromethane (5 ml). Purification was achieved by column chromatography.

N-Allyl-L-phenylalanine methyl ester (42)



42 : R = CH_2Ph, A = H
43 : R = CH_2Ph, A = CH_3
44 : R = $CH_2CH(CH_3)_2$, A = H
45 : R = $CH_2CH(CH_3)_2$, A = CH_3
46 : R = $(CH_2)_4NHCbz$, A = CH_3
47 : R = CH_2OBn, A = CH_3
48 : R = $CH(CH_3)_2$, A = CH_3

Method 1

Prepared according to **GP 3** in 85 % yield.

Method 2

To a mixture of lithium hydroxide (24 mg, 0.99 mmol) in dry DMF (0.5 ml) was added mercaptoacetic acid (35 µl, 0.49 mmol). This mixture was left to stir under a stream of Argon until the solution changed to a yellowish color (≈ 30 minutes). The allylated compound **30** (0.10 g, 0.25 mmol) in dry DMF (1.0 ml) was slowly injected into the above reaction mixture which was then left to stir for six hours. There was a color change from yellow to pale mauve. The DMF was removed *in vacuo* and the residue dissolved in ethyl acetate (5 ml). This organic layer was then washed with sodium bicarbonate (10 % w/v, 2 X 5 ml). The organic layer was then dried over anhydrous sodium sulfate and the excess solvent removed under reduced pressure to yield a brownish oil. Column chromatography was performed (hexane/ethyl acetate, 2/1) to yield a yellow oil (30 mg, 55%). TLC hexane/ethyl acetate, 2/1, R_f 0.40; ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.98 (d br, 2 H, J = 6.7 Hz, $\mathbf{CH_2}Ph$), 3.08-3.33 (m, 2 H, CH_2=$CH\mathbf{CH_2}$), 3.57 (apparent t, 1 H, J = 6.9 Hz, CH), 3.63 (s, 3 H, $O\mathbf{CH_3}$), 5.03-5.16 (m, 2 H, $\mathbf{CH_2}$=$CHCH_2$), 5.73-5.88 (m, 1 H, CH_2=$\mathbf{CH}CH_2$), 7.14-7.31 (m, 5 H, **Ph**); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 39.58 (CH_2Ph), 50.60 (CH_2=$CHCH_2$), 51.75 (OCH_3), 61.98 ($PhCH_2CH$), 116.95 (CH_2=$CHCH_2$), 126.86, 128.52, 129.23 (Aromatics), 135.64 (CH_2=$CHCH_2$), 137.06 (Quaternary Aromatic), 174.63 ($C(O)OCH_3$). MS (EI) m/e (%) 219 (1.1) $[M]^+$, 160 (26.3), 128 (100), 119 (3.6), 91 (10.9).

N-Dimethylallyl-L-phenylalanine methyl ester (43)

Prepared according to **GP 3** in 81 % yield. TLC hexane/ethyl acetate, 2/1, R_f 0.41; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.55, 1.67 (2 s, 6 H, $(\mathbf{CH_3})_2C$=$CHCH_2$), δ 2.93 (2 d, 2 H, J = 2.2 Hz and 2.7 Hz, $\mathbf{CH_2}Ph$), 2.99-3.21 (m, 2 H, $(CH_3)_2C$=$CH\mathbf{CH_2}$), 3.52 (t, 1 H, J = 6.9 Hz, **CH**), 3.61 (s, 3 H, $O\mathbf{CH_3}$), 5.11-5.18 (m, 1 H, $(CH_3)_2C$=$\mathbf{CH}CH_2$), 7.13-7.30 (m, 5 H, **Ph**); ^{13}C NMR (67.9 MHz, $CDCl_3$) δ 17.84, 25.79 ($(CH_3)_2C$=$CHCH_2$), 39.83 (CH_2Ph), 45.59 ($(CH_3)_2C$=$CHCH_2$), 51.61 (OCH_3), 62.39 ($PhCH_2CH$), 122.30 ($(CH_3)_2C$=$CHCH_2$), 126.74, 128.47, 129.18 (Aromatics), 135.14 ($(CH_3)_2\mathbf{C}$=$CHCH_2$), 137.33 (Quaternary Aromatic), 175.18 ($\mathbf{C}(O)OCH_3$); MS (FAB, NBA) m/e (%) 248 (100) $[MH]^+$, 192 (61.0), 188 (42.5), 180 (86.6).

N-Allyl-L-leucine methyl ester (44)

Prepared according to **GP 3** in 85 % yield. TLC hexane/ethyl acetate, 2/1, R_f 0.50; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.66 (apparent t, 6 H, J = 6.5 Hz, $CH_2CH(C\mathbf{H}_3)_2$), 1.15-1.20 (m, 3 H, $C\mathbf{H}_2C\mathbf{H}(CH_3)_2$), 3.02 (apparent t, 1 H, J = 6.9 Hz, $NHC\mathbf{H}$), 3.10-3.31 (m, 2 H, $CH_2=CHC\mathbf{H}_2$) 3.52 (s, 3 H, $OC\mathbf{H}_3$), 4.95-5.02 (m, 2 H, $C\mathbf{H}_2=CHCH_2$), 5.61-5.78 (m, 1 H, $CH_2=C\mathbf{H}CH_2$); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 22.13, 22.51 ($CH_2CH(CH_3)_2$), 24.44 ($CH_2CH(CH_3)_2$), 42.78 ($CH_2CH(CH_3)_2$), 49.52 ($CH_2=CHCH_2$), 51.25 (OCH_3), 58.65 (NCH), 120.96 ($CH_2=CHCH_2$), 134.26 ($CH_2=CHCH_2$), 174.22 (C=O); MS (CI, NH_3) m/e (%) 186 (100) $[MH]^+$, 154 (88.2), 146 (30.1), 112 (5.9).

N-Dimethylallyl-L-leucine methyl ester (45)

Prepared according to **GP 3** in 93 % yield. TLC hexane/ethyl acetate, 2/1, R_f 0.52; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.62 (apparent t, 6 H, J = 6.7 Hz, $CH_2CH(C\mathbf{H}_3)_2$), 1.13-1.19 (m, 2 H, $C\mathbf{H}_2C\mathbf{H}(CH_3)_2$), 1.34, 1.42 (2 s, 6 H, $(C\mathbf{H}_3)_2C=CHCH_2$), 1.43-1.52 (m, 1 H, $C\mathbf{H}_2CH(CH_3)_2$), 2.77 (A of ABX system, 1 H, J = 6.9 Hz and 12.6 Hz, $(CH_3)_2C=CHC\mathbf{H}_2$), 2.89 (B of ABX system, 1 H, J = 6.7 Hz and 12.6 Hz, $(CH_3)_2C=CHC\mathbf{H}_2$), 2.98 (apparent t, 1 H, J = 7.2 Hz, $NHC\mathbf{H}$), 3.42 (s, 3 H, $OC\mathbf{H}_3$), 4.90-4.97 (m, 1 H, $(CH_3)_2C=C\mathbf{H}CH_2$); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 17.43 ($(CH_3)_2C=CHCH_2$), 22.03, 22.46 ($CH_2CH(CH_3)_2$), 24.66 ($CH_2CH(CH_3)_2$), 25.41 ($(CH_3)_2C=CHCH_2$), 42.69 ($CH_2CH(CH_3)_2$), 45.33 ($(CH_3)_2C=CHCH_2$), 51.05 (OCH_3), 58.99 (NCH), 122.56 ($(CH_3)_2C=CHCH_2$), 134.26 ($(CH_3)_2C=CHCH_2$), 176.21 (C=O); MS (CI, NH_3) m/e (%) 214 (100) $[MH]^+$, 154 (92.5), 146 (31.3), 138 (3.7).

N$^\varepsilon$-(Benzyloxycarbonyl)-N-dimethylallyl-L-lysine methyl ester (46)

Prepared according to **GP 3** in 90 % yield. TLC ethyl acetate/hexane, 1/1, R_f 0.17; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.14-1.34 (m, 6 H, $C\mathbf{H}_2(C\mathbf{H}_2)_2CH_2NH$), 1.41, 1.51 (2 s, 6 H, $(C\mathbf{H}_3)_2C=CHCH_2$), 2.81-3.04 (m, 5 H, $CH_2(CH_2)_2C\mathbf{H}_2NH$, $(CH_3)_2C=CHC\mathbf{H}_2$ and $NHC\mathbf{H}CH_2$), 3.48 (s, 3 H, $OC\mathbf{H}_3$), 4.87 (s, 2 H, $C\mathbf{H}_2Ph$), 4.99-5.04 (m, 1 H, $(CH_3)_2C=C\mathbf{H}CH_2$), 5.54 (apparent t, 1 H, J = 5.7, Hz, $N\mathbf{H}C=O$), 7.06-7.16 (m, 5 H,

Ph); ^{13}C NMR (67.9 MHz, CDCl$_3$): δ 17.67 ((CH_3)$_2$C=CHCH$_2$), 22.90 ($CH_2CH_2(CH_2)_2NH$), 25.63 ((CH_3)$_2$C=CHCH$_2$), 29.62 (($CH_2)_2CH_2CH_2NH$), 33.05 ($CH_2(CH_2)_3NH$), 40.69 (($CH_2)_3CH_2NH$), 45.46 (($CH_3)_2C=CHCH_2$), 51.43 (OCH_3), 60.49 ($NHCHCH_2$), 66.21 (CH_2Ph), 122.49 (($CH_3)_2C=CHCH_2$), 127.83, 127.91, 128.32, (Aromatics), 134.63 (($CH_3)_2C=CHCH_2$), 136.82, (Quaternary Aromatics), 156.47 (NHC(O)), 175.87 (C(O)OCH$_3$); MS (CI, NH$_3$) m/e (%) 363 (100) [MH]$^+$, 303 (24.0), 255 (21.8), 174 (26.9).

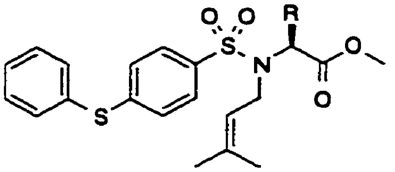
N-Dimethylallyl-O-benzyl-L-serine methyl ester (47)

Prepared according to **GP 3** in 85 % yield. TLC ethyl acetate/hexane, 1/1, R$_f$ 0.42; ^{1}H NMR (270 MHz, CDCl$_3$): δ 1.58, 1.67 (2 s, 6 H, $(C\mathbf{H}_3)_2C=CHCH_2$), 3.11 (A of ABX system, 1 H, J = 7.2 Hz and 12.9 Hz, $CHC\mathbf{H}_2O$), 3.23 (B of ABX system, 1 H, J = 6.9 Hz and 12.9 Hz, $CHC\mathbf{H}_2O$), 3.43-3.67 (m, 3 H, $(CH_3)_2C=CHC\mathbf{H}_2$ and $C\mathbf{H}CH_2O$), 3.69 (s, 3 H, $OC\mathbf{H}_3$), 4.48 (ABq, 2 H, J = 12.1 Hz, $C\mathbf{H}_2Ph$), 4.92-4.99 (apparent t, 1 H, J = 6.9 Hz $(CH_3)_2C=C\mathbf{H}CH_2$), 7.20-7.29 (m, 5 H, **Ph**); ^{13}C NMR (67.9 MHz, CDCl$_3$): δ 17.86, 25.79 (($CH_3)_2C=CHCH_2$), 45.53 (($CH_3)_2C=CHCH_2$), 51.88 (OCH_3), 60.69 ($CHCH_2$), 71.10 ($CHCH_2$), 73.27 (OCH_2Ph), 122.41 (($CH_3)_2C=CHCH_2$), 127.63 127.69, 128.39 (Aromatics), 135.15 (($CH_3)_2C=CHCH_2$), 137.96 (Quaternary Aromatic), 173.75 (C=O); MS (CI, NH$_3$) m/e (%) 278 (100) [MH]$^+$, 218 (19.1), 210 (16.0), 156 (25.1).

N-Dimethylallyl-L-valine methyl ester (48)

Prepared according to **GP 3** in 84 % yield. TLC hexane/ethyl acetate, 5/1, R$_f$ 0.35; ^{1}H NMR (270 MHz, CDCl$_3$): δ 0.79, 0.81 (2 d, 6 H, J = 3.7 Hz and 3.9 Hz, $CH(C\mathbf{H}_3)_2$), 1.48, 1.57 (2 s, 6 H, $(C\mathbf{H}_3)_2C=CHCH_2$) 1.70-1.82 (m, 1 H, $C\mathbf{H}(CH_3)_2$), 2.85 (d, 1 H, J = 5.9 Hz, $NC\mathbf{H}$), 2.87-2.94 (m, 1 H, $(CH_3)_2=CHC\mathbf{H}_2$), 3.01-3.09 (m, 1 H, $(CH_3)_2=CHC\mathbf{H}_2$), 3.58 (s, 3H, $OC\mathbf{H}_3$), 5.05-5.11 (m, 1 H, $(CH_3)_2C=C\mathbf{H}CH_2$); ^{13}C NMR (67.9 MHz, CDCl$_3$): δ 17.68 (($CH_3)_2C=CHCH_2$), 18.71, 19.06 ($CH(CH_3)_2$), 25.60 (($CH_3)_2C=CHCH_2$), 31.60 ($CH(CH_3)_2$), 46.01 (($CH_3)_2C=CHCH_2$), 51.17 (OCH_3), 66.62 (NCH), 122.71 ($(CH_3)_2C=\mathbf{C}HCH_2$), 134.57 ($(CH_3)_2\mathbf{C}=CHCH_2$), 175.70 (**C**=O); MS (CI, NH_3) m/e (%) 200 (15.5) $[MH]^+$, 198 (100), 185 (16.6).

N-(Dimethylallyl)-N-4-thiophenylbenzenesulfonyl-L-phenylalanine methyl ester (49)



49 : R = CH_2Ph
50 : R = $CH_2CH(CH_3)_2$
51 : R = $(CH_2)_4NHCbz$
52 : R = CH_2OBn
53 : R = $CH(CH_3)_2$

Obtained as a side product during the preparation of compound **43**. TLC hexane/ethyl acetate, 2/1, R_f 0.65; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.60 (s br, 6 H, $(C\mathbf{H}_3)_2C=CHCH_2$), 2.93 (A of ABX system, 1 H, J = 8.2 Hz and 14.3 Hz, $C\mathbf{H}_2Ph$) 3.30 (B of ABX system, 1 H, J = 7.2 Hz and 14.3 Hz, $C\mathbf{H}_2Ph$), 3.54 (s, 3 H, $OC\mathbf{H}_3$), 3.73-3.92 (m, 2 H, $(CH_3)_2C=CHC\mathbf{H}_2$), 4.79 (m, 1 H, C**H**), 4.91-4.97 (m, 1 H, $(CH_3)_2C=C\mathbf{H}CH_2$), 7.04-7.49 (m, 14 H, Aromatics); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 17.84, 25.83 ($(\mathbf{C}H_3)_2C=CHCH_2$), 36.57 ($\mathbf{C}H_2Ph$), 43.71 ($(CH_3)_2C=CH\mathbf{C}H_2$), 52.13 ($O\mathbf{C}H_3$), 60.76 (**C**H) 120.52 ($(CH_3)_2C=\mathbf{C}HCH_2$), 126.86, 127.56, 128.04 128.62, 129.04, 129.36, 129.83, 131.93, (Aromatics), 133.96 ($(CH_3)_2\mathbf{C}=CHCH_2$), 136.00, 137.12, 137.67, 144.28 (Quaternary Aromatics), 171.13 (**C**=O); MS (CI, NH_3) m/e (%) 513 (1.6) $[M + NH_4]^+$, 496 (1.3) $[MH]^+$, 249 (33.4), 246 (100), 185 (23.9), 156 (12.8), 120 (3.4).

N-(Dimethylallyl)-N-4-thiophenylbenzenesulfonyl-L-leucine methyl ester (50)

Obtained as a side product during the preparation of compound **45**. TLC ethyl acetate/hexane, 1/6, R_f0.43; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.86, 0.93 (2 d, 6 H, J = 6.4 Hz and 6.2 Hz, $CH_2CH(C\mathbf{H}_3)_2$), 1.55-1.72 (m, 9 H, $C\mathbf{H}_2C\mathbf{H}(CH_3)_2$ and $(C\mathbf{H}_3)_2C=CHCH_2$), 3.48 (s, 3 H, $OC\mathbf{H}_3$), 3.86 (apparent d, 2 H, J = 6.9 Hz, $(CH_3)_2C=CHC\mathbf{H}_2$), 4.55-4.61 (m, 1 H, NC**H**), 5.10-5.16 (m, 1 H, $(CH_3)_2C=C\mathbf{H}CH_2$), 7.20 (d, 2 H, J = 8.6 Hz, meta **H**'s to -SO$_2$), 7.36-7.50 (m, 5 H, **Ph**), 7.64 (d, 2 H, J = 8.7 Hz, ortho **H**'s to -SO$_2$); ^{13}C NMR (67.9 MHz, CDCl$_3$): δ 17.80 ((CH$_3$)$_2$C=CHCH$_2$), 21.40, 22.91 (CH$_2$CH(CH$_3$)$_2$), 24.40 (CH$_2$CH(CH$_3$)$_2$), 25.76 (CH$_3$)$_2$C=CHCH$_2$), 38.93 (CH$_2$CH(CH$_3$)$_2$), 43.40 ((CH$_3$)$_2$C=CHCH$_2$), 51.90 (OCH$_3$), 57.64 (NCH), 121.63 ((CH$_3$)$_2$C=CHCH$_2$), 127.72, 128.04, 128.98, 129.82, 132.44 (Aromatics), 133.88 ((CH$_3$)$_2$C=CHCH$_2$), 134.64, 137.35, 144.37 (Quaternary Aromatics), 172.10 (C=O); MS (CI, NH$_3$) m/e (%) 462 (1.5) [MH]$^+$, 334 (23.2), 249 (32.0), 212 (100).

N-(Dimethylallyl)-N$^{\varepsilon}$-(benzyloxycarbonyl)-N-4-thiophenylbenzenesulfonyl-L- lysine methyl ester (51)

Obtained as a side product during the preparation of compound **46**. TLC ethyl acetate/hexane, 1/1, R$_f$ 0.56; ^{1}H NMR (270 MHz, CDCl$_3$): δ 1.36-1.57 (m, 4 H, CH$_2$(C**H**$_2$)$_2$CH$_2$NH), 1.62 (d, 6 H, J = 2.8 Hz, (C**H**$_3$)$_2$C=CHCH$_2$), 1.66-1.95 (m, 2 H, C**H**$_2$(CH$_2$)$_2$CH$_2$NH), 3.15-3.24 (m, 2 H, CH$_2$(CH$_2$)$_2$C**H**$_2$NH), 3.53 (s, 3 H, OC**H**$_3$), 3.85 (d, 2 H, J = 2.7 Hz, (CH$_3$)$_2$C=CHC**H**$_2$), 4.60 (dd, 1 H, J = 5.4 Hz and J = 10.0 Hz, NC**H**CH$_2$), 4.89 (s br, 1 H, CH$_2$N**H**C=O), 5.00-5.06 (m, 1 H, (CH$_3$)$_2$C=C**H**CH$_2$), 5.07 (s, 2 H, C**H**$_2$Ph), 7.17-7.76 (m, 14 H, Aromatics); ^{13}C NMR (67.9 MHz, CDCl$_3$): δ 17.85 ((CH$_3$)$_2$C=CHCH$_2$), 23.24 (CH$_2$CH$_2$(CH$_2$)$_2$NH), 25.77 ((CH$_3$)$_2$C=CHCH$_2$), 29.55 ((CH$_2$)$_2$CH$_2$CH$_2$NH), 32.66 (CH$_2$(CH$_2$)$_3$NH), 41.54 ((CH$_2$)$_3$CH$_2$NH), 43.66 ((CH$_3$)$_2$C=CHCH$_2$), 52.91 (OCH$_3$), 59.86 (NCHCH$_2$), 66.56 (CH$_2$Ph), 121.15 ((CH$_3$)$_2$C=CHCH$_2$), 123.72, 128.23, 128.45, 128.51, 128.98, 129.34, 129.55, 130.92 (Aromatics), 136.35 ((CH$_3$)$_2$C=CHCH$_2$), 136.75, 137.25, 147.31, 149.96 (Quaternary Aromatics), 156.87 (NHC(O)), 171.17 (C(O)OCH$_3$); MS (CI, NH$_3$) m/e (%) 628 (12.8) [M + NH$_4$]$^+$, 611 (33.1) [MH]$^+$.

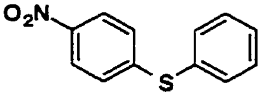
N-Dimethylallyl-O-Benzyl-N-4-thiophenylbenzenesulfonyl-L-serine methyl ester (52)

Obtained as a side product during the preparation of compound **47**. TLC ethyl acetate/hexane, 1/1, R_f 0.47; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.54, 1.59 (2 s, 6 H, $(C\mathbf{H}_3)_2C=CHCH_2$), 3.66 (s, 3 H, $OC\mathbf{H}_3$), 3.72 (A of ABX system, 1 H, J = 9.2 Hz and 10.5 Hz, $CHC\mathbf{H}_2O$), 3.91 (B of ABX system, 1 H, J = 4.6 Hz and 10.5 Hz, $CHC\mathbf{H}_2O$), 3.85-3.99 (m, 2 H, $(CH_3)_2C=CHC\mathbf{H}_2$), 4.40 (ABq, 2 H, J = 11.6 Hz, $C\mathbf{H}_2Ph$), 4.98 (X of ABX system, 1 H, J = 4.6 Hz and 9.2 Hz, $C\mathbf{H}CH_2O$), 4.94-5.02 (m, 1 H, $(CH_3)_2C=C\mathbf{H}CH_2$), 7.07-7.51 (m, 14 H, Aromatics); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 17.75, 25.84 ($(\mathbf{C}H_3)_2C=CHCH_2$), 44.23 ($(CH_3)_2C=CH\mathbf{C}H_2$), 52.55 ($O\mathbf{C}H_3$), 59.37 ($\mathbf{C}HCH_2$), 67.65 ($CH\mathbf{C}H_2$), 73.52 ($O\mathbf{C}H_2Ph$), 119.78 ($(CH_3)_2C=\mathbf{C}HCH_2$), 123.62, 128.07, 128.22, 128.51, 128.88, 129.36, 129.41, 130.11 (Aromatics), 136.82 ($(CH_3)_2\mathbf{C}=CHCH_2$), 137.12, 138.34, 146.69, 149.65 (Quaternary Aromatics), 169.99 ($\mathbf{C}=O$); MS (CI, NH_3) m/e (%) 543 (3.5) $[M + NH_4]^+$, 526 (5.1) $[MH]^+$.

N-(Dimethylallyl)-N-4-thiophenylbenzenesulfonyl-L-valine methyl ester (53)

Obtained as a side product during the preparation of compound **48**. TLC ethyl acetate/hexane, 1/5, R_f0.51; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.87, 0.98 (2 d, 6 H, J = 6.5 Hz and 6.5 Hz, $CH(C\mathbf{H}_3)_2$), 1.54, 1.65 (2 s, 6 H, $(C\mathbf{H}_3)_2C=CHCH_2$) 2.08-2.18 (m, 1 H, $C\mathbf{H}(CH_3)_2$), 3.53 (s, 3H, $OC\mathbf{H}_3$), 3.75-3.85 (m, 1 H, $(CH_3)_2=CHC\mathbf{H}_2$), 4.07-4.14 (m, 1 H, $(CH_3)_2=CHC\mathbf{H}_2$), 4.25 (d, 1 H, J = 10.5 Hz, $NC\mathbf{H}$), 4.86-4.91 (m, 1 H, $(CH_3)_2C=C\mathbf{H}CH_2$), 7.06 (d, 2 H, J = 8.6 Hz, meta **H**'s to $-SO_2$), 7.25-7.29 (m, 5 H, **Ph**), 7.52 (d, 2 H, J = 8.6 Hz, ortho **H**'s to $-SO_2$); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 17.77 ($(\mathbf{C}H_3)_2C=CHCH_2$), 19.51, 19.59 ($CH(\mathbf{C}H_3)_2$), 25.73 ($(\mathbf{C}H_3)_2C=CHCH_2$), 29.21 ($\mathbf{C}H(CH_3)_2$), 42.99 ($(CH_3)_2C=CH\mathbf{C}H_2$), 52.01 ($O\mathbf{C}H_3$), 66.03 ($N\mathbf{C}H$), 120.12 ($(CH_3)_2C=\mathbf{C}HCH_2$), 127.40, 127.97, 128.68, 129.69, 133.75 (Aromatics), 133.98 ($(CH_3)_2\mathbf{C}=CHCH_2$), 134.65, 137.35, 144.47 (Quaternary Aromatics), 171.25 ($\mathbf{C}=O$); MS (CI, NH_3) m/e (%) 465 (17.9) $[M + NH_4]^+$, 448 (6.9) [MH].

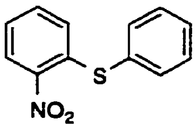
4-Thiophenylnitrobenzene (54)



54

The Meisenheimer by-product from the deprotection of 4-nitrobenzene sulfonamides. TLC ethyl acetate/hexane, 1/6, R_f0.60; ^{1}H NMR (270 MHz, $CDCl_3$): δ 7.16 (d, 2 H, J = 8.9 Hz, meta **H**'s to $-SO_2$), 7.39-7.55 (m, 5 H, **Ph**), 8.04 (d, 2 H, J = 8.9 Hz, ortho **H**'s to $-SO_2$); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 124.11, 126.76, 129.78, 130.13, 130.50 (Aromatics), 134.82, 145.42, 148.60 (Quaternary Aromatics); MS (EI) m/e (%) 231 (100) $[M]^+$, 201 (11.9), 184 (68.2), 152 (10.1).

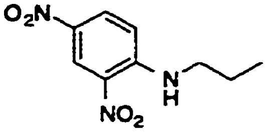
2-Thiophenylnitrobenzene (55)



55

The Meisenheimer by-product from the deprotection of 2-nitrobenzene sulfonamides. TLC ethyl acetate/hexane, 1/5, R_f0.44; ^{1}H NMR (270 MHz, $CDCl_3$): δ 6.85 (dd, 1 H, J = 1.2 Hz and 8.2 Hz para **H** to $-NO_2$), 7.15-7.24 (m, 1 H, para **H** to -SPh), 7.29-7.35 (m, 1 H, ortho **H** to -SPh), 7.43-7.59 (m, 5 H, **Ph**), 8.20 (dd, 1 H, J = 1.5 Hz and 8.2 Hz, ortho **H** to $-NO_2$); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 125.03, 125.79, 128.40, 130.10, 130.19, 131.05, 133.51 (Aromatics), 135.95, 139.50, 145.05 (Quaternary Aromatics); MS (CI, NH_3) m/e (%) 249 (12.1) $[M + NH_4]^+$, 232 (6.5) $[MH]^+$, 184 (21.9), 167 (100).

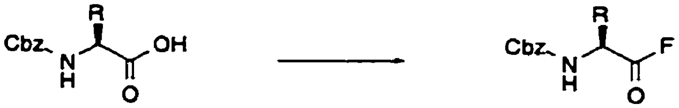
2,4-Dinitrophenylpropylamine (56)



56

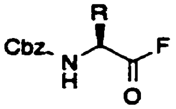
The Meisenheimer by-product from the deprotection of 2,4-dinitrobenzene sulfonamides. TLC ethyl acetate/hexane, 1/3, R_f0.31; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.05 (t, 3 H, J = 7.4 Hz, CH_2**CH_3**), 1.72-1.86 (m, 2 H, **CH_2**CH_3), 3.34-3.41 (m, 2 H, NHC**H_2**), 6.91 (d, 1 H, J= 9.6 Hz, ortho **H** to -NH), 8.21 (dd, 1 H, J = 2.7 Hz and 9.6 Hz, **H** para to the 2-NO_2), 8.55 (s br, 1 H, N**H**CH_2), 9.06 (d, 1 H, J = 2.7 Hz, **H** ortho to the 2-NO_2); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 11.50 (CH_2CH_3), 22.12 (CH_2CH_3), 45.36 ($NHCH_2$), 114.08, 124.33, 130.24 (Aromatics), 130.34, 135.90, 148.52 (Quaternary Aromatics); MS (CI, NH_3) m/e (%) 226 (91.4) $[M + H]^+$, 225 (100), 196 (36.4).

Preparation of acid fluorides (GP 4)



To a stirred solution of N-benzyloxycarbonyl amino acid (1.00 mmol) and dry pyridine (1.00 mmol) in dry dichloromethane (5 ml) which was kept under a stream of argon was added cyanuric fluoride (10 mmol) at -20 °C to -10 °C. After stirring at -10 °C for one hour, crushed ice was added along with additional dichloromethane (10 ml). The organic layer was separated and the aqueous layer extracted once with dichloromethane (5 ml). The combined dichloromethane layers were extracted with ice-cold water (10 ml), dried over anhydrous magnesium sulfate and the solvent removed with a rotary evaporator at room temperature to yield the acid fluoride. **CAUTION:** Cyanuric fluoride is very toxic and safety precautions are advised.

N-(Benzyloxycarbonyl)-L-valine acid fluoride (57)



57 : R = CH(CH$_3$)$_2$
58 : R = CH$_2$COOBn
59 : R = CH$_2$Ph
60 : R = CH$_3$

Prepared according to **GP 4** in 88 % yield. ^{1}H NMR (270 MHz, CDCl$_3$): δ 0.96, 1.04 (2 d, 6 H, J = 6.9 Hz and J = 6.9 Hz, (C**H**$_3$)$_2$CH), 2.12-2.29 (m, 1 H, (CH$_3$)$_2$C**H**), 3.35-4.50 (m, 1 H, C**H**), 5.12 (s, 2 H, OC**H**$_2$Ph), 5.53 (d br, 1 H, J = 8.6 Hz, N**H**), 7.34 (s, 5 H, **Ph**); ^{13}C NMR (67.9 MHz, CDCl$_3$): δ 17.62, 18.83 ((CH$_3$)$_2$CH), 30.37 ((CH$_3$)$_2$CH), 58.39 (d, J = 57.5 Hz, CH), 67.53 (OCH$_2$Ph), 128.24, 128.43, 128.69 (Aromatics), 136.00 (Quaternary Aromatic), 156.31 (NHC=O), 162.46 (d, J = 372.4 Hz, COF).

N-(Benzyloxycarbonyl)-β-(benzyl ester)-L-aspartic acid fluoride (58)

Prepared according to **GP 4** in 85 % yield. ^{1}H NMR (270 MHz, CDCl$_3$): δ 2.89-3.18 (m, 2 H, C**H**$_2$CO), 4.85-4.93 (m, 1 H, C**H**), 5.13, 5.15 (2 s, 4 H, 2 X C**H**$_2$Ph), 5.86 (d, 1 H, J = 8.7 Hz, N**H**), 7.36 (s br, 10 H, 2 X **Ph**); ^{13}C NMR (67.9 MHz, CDCl$_3$): δ 36.21 (CH$_2$CO), 49.34 (d, J = 60.9 Hz, CH), 67.59, 67.70 (2 X CH$_2$Ph), 128.29, 128.52, 128.78 (Aromatics), 134.95, 135.79 (Quaternary Aromatics), 155.79 (NHC=O), 161.24 (d, J = 368.2 Hz, COF), 170.29 (CH$_2$C=O).

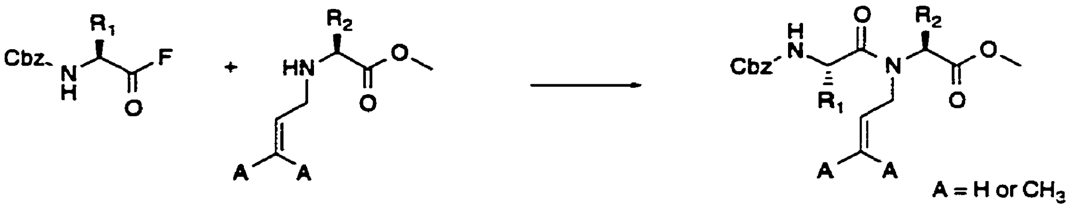
N-(Benzyloxycarbonyl)-L-phenylalanine acid fluoride (59)

Prepared according to **GP 4** in 86 % yield. Mp 85-87 °C; ^{1}H NMR (270 MHz, CDCl$_3$): δ 3.17 (d, 2 H, J = 5.7 Hz, CHC**H**$_2$Ph), 4.78-4.87 (m, 1 H, C**H**CH$_2$Ph), 5.10 (s br, 3 H, OC**H**$_2$Ph and N**H**), 7.13-7.39 (m, 10 H, 2 X **Ph**); ^{13}C NMR (67.9 MHz, CDCl$_3$): δ 36.89 (CHCH$_2$Ph), 53.89 (d, J = 59.9 Hz, CHCH$_2$Ph), 67.59 (OCH$_2$Ph), 127.27, 127.87, 128.29, 128.69, 129.18, (Aromatics), 134.35 135.84 (Quaternary Aromatics), 155.73 (NHC=O), 162.00 (d, J = 365.4 Hz, C(O)F).

N-(Benzyloxycarbonyl)-L-alanine acid fluoride (60)

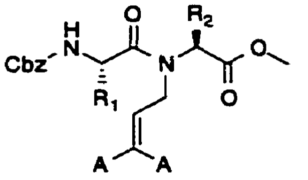
Prepared according to **GP 4** in 87 % yield. Mp 40-42 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.41 (d, 3 H, J = 7.2 Hz, $\mathbf{CH_3}$CH), 4.41-4.55 (m, 1 H, CH_3**CH**), 5.10 (ABq, 2 H, J = 11.9 Hz, O$\mathbf{CH_2}$Ph), 6.00 (d, 1 H, J = 7.2 Hz, N**H**), 7.31 (s br, 5 H, **Ph**); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 16.55 (CH_3CH), 48.62 (d, J = 62.1 Hz, CH_3CH), 67.39 (OCH_2Ph), 128.20, 128.40, 128.65 (Aromatics), 136.07 (Quaternary Aromatic), 156.08 (NHC=O), 163.30 (d, J = 371.2 Hz, COF).

Preparation of dipeptides : Secondary amino acids coupling with acid fluorides (GP 5)



To a solution of N-allylated or prenylated methyl ester (1.00 mmol) and N-ethylmorpholine (1.20 mmol) in dichloromethane (5.00 ml), a solution of N$^\alpha$-benzyloxycarbonyl acid fluoride (3.00-5.00 mmol) in dichloromethane (2.00 ml), was added over a period of 5 minutes and the reaction mixture stirred at room temperature for 24 hours. Color change from yellow to a deep red within 10 minutes. Dichloromethane (20 ml) was added to the crude mixture and the solution was washed well with hydrochloric acid (3 N, 2 X 20 ml), sodium bicarbonate (10 % w/v, 2 X 20 ml) and water (20 ml). Column chromatography was performed (hexane/ethyl acetate) to yield the desired dipeptide.

N-(Benzyloxycarbonyl)-L-valyl-N'-allyl-L-phenylalanine methyl ester (61)



61 : $R_1 = CH(CH_3)_2$, $R_2 = CH_2Ph$, $A = H$
62 : $R_1 = CH(CH_3)_2$, $R_2 = CH_2Ph$, $A = CH_3$
63 : $R_1 = CH_2COOBn$, $R_2 = CH_2Ph$, $A = H$
64 : $R_1 = CH_2COOBn$, $R_2 = CH_2Ph$, $A = CH_3$
65 : $R_1 = CH_2Ph$, $R_2 = CH_2CH(CH_3)_2$, $A = H$
66 : $R_1 = CH_2Ph$, $R_2 = CH_2CH(CH_3)_2$, $A = CH_3$
67 : $R_1 = CH_2Ph$, $R_2 = (CH_2)_4NHCbz$, $A = CH_3$
68 : $R_1 = CH_2Ph$, $R_2 = CH_2OBn$, $A = CH_3$
69 : $R_1 = CH_3$, $R_2 = CH(CH_3)_2$, $A = CH_3$

Prepared according to **GP 5** in 85 % yield. TLC hexane/ethyl acetate, 1/1, R_f 0.60; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.88-0.96 (m, 6 H, $CH(C\mathbf{H}_3)_2$), 1.85-1.97 (m, 1 H, $C\mathbf{H}(CH_3)_2$), 3.11 (dd, 1 H, J = 9.6 Hz and 9.9 Hz, $C\mathbf{H}_2Ph$), 3.34-3.53 (m, 2 H, $C\mathbf{H}_2Ph$ and $CH_2{=}CHC\mathbf{H}_2$), 3.63 (s, 3 H, $OC\mathbf{H}_3$), 3.90 (dd, 1 H, J = 3.8 Hz and 4.9 Hz, $CH_2{=}CHC\mathbf{H}_2$), 4.39-4.51 (m, 2 H, $C\mathbf{H}NH$ and $C\mathbf{H}NCH_2$), 5.08 (s br, 2 H, $OC\mathbf{H}_2Ph$), 5.09-5.18 (m, 2 H, $C\mathbf{H}_2{=}CHCH_2$), 5.41 (d, 1 H, J = 9.4 Hz, N**H**), 5.58-5.71 (m, 1 H, $CH_2{=}C\mathbf{H}CH_2$), 7.14-7.38 (m, 10 H, 2 X **Ph**); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 17.13, 19.95 ($CH(\mathbf{C}H_3)_2$), 31.46 ($\mathbf{C}H(CH_3)_2$), 35.19 ($\mathbf{C}H_2Ph$), 51.30 ($CH_2{=}CH\mathbf{C}H_2$), 52.23 ($O\mathbf{C}H_3$), 55.95 ($\mathbf{C}HNH$), 60.54 ($\mathbf{C}HNCH_2$), 66.85 ($O\mathbf{C}H_2Ph$), 118.79 ($\mathbf{C}H_2{=}CHCH_2$), 126.82, 127.97, 128.14, 128.86, 129.25, 129.49 (Aromatics), 133.36 ($CH_2{=}\mathbf{C}HCH_2$), 136.55, 137.74 (Quaternary Aromatics), 156.31 (NH**C**(O)O), 170.86 (**C**(O)NCH_2), 172.29 (**C**(O)OMe); MS (FAB, NBA) m/e (%) 453 (77.4) $[MH]^+$, 421 (62.0).

N-(Benzyloxycarbonyl)-L-valyl-N'-dimethylallyl-L-phenylalanine methyl ester (62)

Prepared according to **GP 5** in 78 % yield. TLC hexane/ethyl acetate, 2/1, R_f 0.46; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.85-0.92 (m, 6 H, $CH(C\mathbf{H}_3)_2$), 1.41, 1.45 (2 s, 6 H, $(C\mathbf{H}_3)_2C{=}CHCH_2$) 1.88-1.98 (m, 1 H, $C\mathbf{H}(CH_3)_2$), 3.05 (A of ABX system, 1 H, J = 9.8 Hz and 13.5 Hz, $CHC\mathbf{H}_2Ph$), 3.31 (B of ABX system, 1 H, J = 5.1 Hz and 13.5 Hz, $CHC\mathbf{H}_2Ph$), 3.35-3.51 (m, 1 H, $(CH_3)_2C{=}CHC\mathbf{H}_2$), 3.57 (s, 3 H, $OC\mathbf{H}_3$), 3.58-3.85 (m, 1 H, $(CH_3)_2C{=}CHC\mathbf{H}_2$), 4.25 (X of ABX system, 1 H, J = 5.1 Hz and 9.8 Hz, $C\mathbf{H}CH_2Ph$), 4.71-4.84 (m, 2 H, $(CH_3)_2C{=}C\mathbf{H}CH_2$ and $NHC\mathbf{H}$), 5.10 (s br, 2 H, $OC\mathbf{H}_2Ph$), 5.41 (d, 1 H, J = 9.3 Hz, N**H**), 7.16-7.35 (m, 10 H, 2 X **Ph**); ^{13}C NMR (67.9

MHz, $CDCl_3$): δ 17.24 ($(CH_3)_2C=CHCH_2$), 19.98, 20.21 ($CH(CH_3)_2$), 26.11 ($(CH_3)_2C=CHCH_2$), 31.53 ($CH(CH_3)_2$), 36.19 (CH_2Ph), 46.25 ($(CH_3)_2C=CHCH_2$), 51.15 (OCH_3), 56.02 (CHNH), 60.84 ($CHNCH_2$), 65.99 (OCH_2Ph), 119.96 ($(CH_3)_2C=CHCH_2$), 126.86, 128.01, 128.17, 129.05, 129.25, 129.55 (Aromatics), 136.00 ($(CH_3)_2C=CHCH_2$), 136.59, 137.88 (Quaternary Aromatics), 156.52 (NHC(O)O), 171.02 ($C(O)NCH_2$), 172.44 (C(O)OMe); MS (FAB, NBA/NaCl) m/e (%) 503 (32.4) $[M + Na]^+$, 481 (45.8) $[MH]^+$.

N-(Benzyloxycarbonyl)-β-(benzylester)-L-aspartyl-N'-allyl-L-phenylalanine methyl ester (63)

Prepared according to **GP 5** in 75 % yield. TLC ethyl acetate/hexane, 1/4, R_f 0.17; ^1H NMR (270 MHz, $CDCl_3$): δ 2.72 (ddd, 2 H, J = 5.9 Hz, 6.2 Hz and 6.7 Hz , $CH_2C=O$), 3.12-3.50 (m, 3 H, $CHC\mathbf{H}_2Ph$ and $CH_2=CHC\mathbf{H}_2$), 3.66 (s, 3 H, $OC\mathbf{H}_3$), 3.91-4.11 (m, 1 H, $CH_2=CHC\mathbf{H}_2$), 4.38 (dd, 1 H, J = 4.9 Hz and 5.2 Hz, $C\mathbf{H}CH_2Ph$), 4.94-5.15 (m, 7 H, 2 X $PhC\mathbf{H}_2O$, $C\mathbf{H}_2=CHCH_2$ and NHC**H**), 5.50-5.64 (m, 1 H, $CH_2=C\mathbf{H}CH_2$), 5.75 (d, 1 H, J = 9.4 Hz, N**H**), 7.11-7.39 (m, 15 H, 3 X **Ph**); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 35.03, 37.70 (2 X CH_2Ph), 48.46 ($CH_2=CHCH_2$), 51.41 (OCH_3), 52.29 (CHNH), 60.98 ($CHNCH_2$), 66.77, 67.13 (2 X OCH_2Ph), 118.58 ($CH_2=CHCH_2$), 126.85, 127.05, 128.31, 128.59, 129.39 (Aromatics), 132.99 ($CH_2=CHCH_2$), 135.75, 136.33, 137.71 (Quaternary Aromatics), 155.53 (NHC(O)O), 170.21, 170.56, 170.82 (3 X C=O); MS (EI) m/e (%) 558 (62.5) $[M]^+$.

N-(Benzyloxycarbonyl)-β-(benzylester)-L-aspartyl-N'-dimethylallyl-L-phenylalanine methyl ester (64)

Prepared according to **GP 5** in 80 % yield. TLC ethyl acetate/hexane, 1/2, R_f 0.41; ^1H NMR (270 MHz, DMSO-d_6): δ 1.40, 1.48 (2 s, 6 H, $(C\mathbf{H}_3)_2C=CHCH_2$), 2.61 (A of ABX system, 1 H, J = 7.4 Hz and 16.3 Hz, $CHC\mathbf{H}_2C=O$), 2.73 (B of ABX system, 1 H, J = 6.8 Hz and 16.3 Hz, $CHC\mathbf{H}_2C=O$), 3.03 (A of ABX system, 1 H, J = 9.9 Hz and 13.6 Hz, $CHC\mathbf{H}_2Ph$), 3.21 (B of ABX system, 1 H, J = 4.9 Hz and 13.6 Hz,

$\mathrm{CHC\mathbf{H}_2Ph}$), 3.33-3.53 (m, 1 H, $\mathrm{(CH_3)_2C{=}CHC\mathbf{H}_2}$), 3.55 (s, 3 H, $\mathrm{OC\mathbf{H}_3}$), 3.56-3.81 (m, 1 H, $\mathrm{(CH_3)_2C{=}CHC\mathbf{H}_2}$), 4.18 (X of ABX system, 1 H, J = 4.9 Hz and 9.9 Hz, $\mathrm{C\mathbf{H}CH_2Ph}$), 4.68-4.82 (m, 2 H, $\mathrm{(CH_3)_2C{=}C\mathbf{H}CH_2}$ and $\mathrm{NHC\mathbf{H}}$), 4.96-5.16 (m, 4 H, 2 X $\mathrm{OC\mathbf{H}_2Ph}$), 7.11-7.40 (m, 15 H, 3 X **Ph**); ^{13}C NMR (67.9 MHz, DMSO-d_6): δ 17.90, 25.99 ($\mathrm{(CH_3)_2C{=}CHCH_2}$), 34.64, 36.91 (2 X $\mathrm{CH_2Ph}$), 47.11 ($\mathrm{(CH_3)_2C{=}CHCH_2}$), 48.47 ($\mathrm{OCH_3}$), 52.32 (CHNH), 61.67 ($\mathrm{CHNCH_2}$), 66.17 (s br, 2 X $\mathrm{OCH_2Ph}$), 120.55 ($\mathrm{(CH_3)_2C{=}CHCH_2}$), 126.93, 128.14, 128.29, 128.50, 128.89, 129.87 (Aromatics), 135.20 ($\mathrm{(CH_3)_2\mathbf{C}{=}CHCH_2}$), 136.58, 137.46, 138.77 (Quaternary Aromatics), 156.00 (NHC(O)O), 170.51, 170.72, 170.99 (3 X C=O); MS (FAB, NBA) m/e (%) 587 (49.9) $[\mathrm{MH}]^+$, 519 (80.4), 475 (46.0), 268 (20.2), 246 (83.1), 181 (39.8).

N-(Benzyloxycarbonyl)-L-phenylalanyl-N'-allyl-L-leucine methyl ester (65)

Prepared according to **GP 5** in 79 % yield. TLC ethyl acetate/hexane, 1/3, R_f 0.42; ^{1}H NMR (270 MHz, $\mathrm{CDCl_3}$): δ 0.91, 0.96 (2 d, 6 H, J = 6.2 Hz and 6.4 Hz, $\mathrm{CH_2CH(C\mathbf{H}_3)_2}$), 1.44-1.65 (m, 2 H, $\mathrm{C\mathbf{H}_2C\mathbf{H}(CH_3)_2}$), 1.69-1.78 (m, 1 H, $\mathrm{C\mathbf{H}_2CH(CH_3)_2}$), 2.98 (A of ABX system, 1 H, J = 6.5 Hz and 14.4 Hz, $\mathrm{C\mathbf{H}_2Ph}$), 3.13 (B of ABX system, 1 H, J = 7.4 Hz and 14.4 Hz, $\mathrm{C\mathbf{H}_2Ph}$), 3.30-3.54 ($\mathrm{CH_2{=}CHC\mathbf{H}_2}$), 3.59 (s, 3 H, $\mathrm{OC\mathbf{H}_3}$), 4.69-4.85 (m, 2 H, NC**H**, NHC**H**), 5.15 (s, 2 H, $\mathrm{PhC\mathbf{H}_2O}$), 5.76 (d, 1 H, J = 8.9 Hz, N**H**), 7.22-7.35 (m, 10 H, 2 X **Ph**); ^{13}C NMR (67.9 MHz, $\mathrm{CDCl_3}$): δ 22.11, 23.09 ($\mathrm{CH_2CH(CH_3)_2}$), 24.96 ($\mathrm{CH_2CH(CH_3)_2}$), 36.91 ($\mathrm{CHCH_2Ph}$) 39.66 ($\mathrm{CH_2CH(CH_3)_2}$), 51.21 ($\mathrm{CH_2{=}CHCH_2}$), 52.55 ($\mathrm{OCH_3}$), 53.12 ($\mathrm{CHCH_2Ph}$), 56.26 (NCH), 66.85 ($\mathrm{OCH_2Ph}$), 119.85 ($\mathrm{CH_2{=}CHCH_2}$), 126.96, 127.80, 128.51, 128.59, 129.43, 129.72 (Aromatics), 133.56 ($\mathrm{CH_2{=}CHCH_2}$), 136.55, 136.66 (Quaternary Aromatics), 156.12 (NHC(O)O), 172.03, 172.63 (2 X C=O); MS (CI, $\mathrm{NH_3}$) m/e (%) 467 (5.9) $[\mathrm{MH}]^+$, 334 (33.2), 258 (29.0), 212 (100).

N-(Benzyloxycarbonyl)-L-phenylalanyl-N'-dimethylallyl-L-leucine methyl ester (66)

Prepared according to **GP 5** in 77 % yield. TLC ethyl acetate/hexane, 1/3, R_f 0.39; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.85, 0.87 (2 d fine, 6 H, J = 1.7 Hz and 1.5 Hz, $CH_2CH(C\mathbf{H}_3)_2$), 1.41-1.65 (m, 8 H, $\mathbf{CH}_2\mathbf{CH}(CH_3)_2$ and $(\mathbf{CH}_3)_2C{=}CHCH_2$), 1.71-1.82 (m, 1 H, $\mathbf{CH}_2CH(CH_3)_2$), 2.93 (A of ABX system, 1 H, J = 6.4 Hz and 13.3 Hz, $\mathbf{CH}_2Ph$), 3.10 (B of ABX system, 1 H, J= 7.4 Hz and 13.3 Hz, $\mathbf{CH}_2Ph$), 3.62 (s, 3 H, $O\mathbf{CH}_3$), 3.68-3.94 (m, 2 H, $(CH_3)_2C{=}CH\mathbf{CH}_2$), 4.80-4.92 (m, 3 H, N**CH**, NH**CH** and $(CH_3)_2C{=}\mathbf{CH}CH_2$), 5.05 (s, 2 H, $Ph\mathbf{CH}_2O$), 5.70 (d, 1 H, J = 8.6 Hz, N**H**), 7.18-7.33 (m, 10 H, 2 X **Ph**); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 18.03 ($(CH_3)_2C{=}CHCH_2$), 21.93, 23.04 ($CH_2CH(CH_3)_2$), 24.83 ($CH_2\mathbf{CH}(CH_3)_2$), 25.77 ($(CH_3)_2C{=}CHCH_2$), 37.91 ($CHCH_2Ph$) 39.59 ($\mathbf{CH}_2CH(CH_3)_2$), 44.38 $(CH_3)_2C{=}CH\mathbf{CH}_2$), 52.04 ($\mathbf{CH}CH_2Ph$), 52.53 ($OCH_3$), 55.73 (NCH), 66.69 ($OCH_2Ph$), 120.82 ($(CH_3)_2C{=}CHCH_2$), 126.88, 127.90, 128.07, 128.46, 128.52, 129.39, 129.69 (Aromatics), 135.32 $(CH_3)_2\mathbf{C}{=}CHCH_2$), 136.45, 136.59 (Quaternary Aromatics), 155.66 (NH**C**(O)O), 171.99, 172.53 (2 X **C**=O); MS (FAB, NBA) m/e (%) 495 (33.3) $[MH]^+$.

N-(Benzyloxycarbonyl)-L-phenylalanyl-N'-(benzyloxycarbonyl)-N$^\alpha$-dimethylallyl-L-lysine methyl ester (67)

Prepared according to **GP 5** in 67 % yield. TLC ethyl acetate/hexane, 1/3, R_f 0.41; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.18-1.25 (m, 4 H, $CH_2(\mathbf{CH}_2)_2CH_2NH$), 1.60, 1.63 (2 s, 6 H, $(\mathbf{CH}_3)_2C{=}CHCH_2$), 1.68-1.95 (m, 1 H, $\mathbf{CH}_2(CH_2)_3NH$), 2.85-2.95 (m, 1 H, $\mathbf{CH}_2(CH_2)_3NH$), 3.02-3.13 (m, 4 H, $CH_2(CH_2)_2\mathbf{CH}_2NH$ and $\mathbf{CH}_2Ph$), 3.60 (s, 3 H, $O\mathbf{CH}_3$), 3.63-3.71 (m, 1 H, $(CH_3)_2C{=}CH\mathbf{CH}_2$), 3.86-3.99 (m, 1 H, $(CH_3)_2C{=}CH\mathbf{CH}_2$), 4.76-4.86 (m, 2 H, N**CH** and NHC**H**), 4.98-5.11 (m, 3 H, 2 X $Ph\mathbf{CH}_2O$ and $(CH_3)_2C{=}\mathbf{CH}CH_2$), 5.24 (t, 1 H, J = 5.4 Hz, $\mathbf{NH}CH_2$), 5.73 (d, 1 H, J = 8.7 Hz, **NH**CH) 7.15-7.30 (m, 15 H, 3 X **Ph**); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 18.03 ($(CH_3)_2C{=}CHCH_2$), 23.18 ($CH_2CH_2(CH_2)_2NH$), 25.76 ($(CH_3)_2C{=}CHCH_2$), 28.48 ($(CH_2)_2CH_2CH_2NH$), 29.26 ($CH_2(CH_2)_3NH$), 39.40 ($(CH_2)_3CH_2NH$), 40.81 (CH_2Ph) 44.46 ($(CH_3)_2C{=}CHCH_2$), 52.07 (NHCH), 52.53 (OCH_3), 57.12 (NCH), 66.54, 66.77

(2 X CH_2Ph), 120.64 ($(CH_3)_2C=CHCH_2$), 126.93, 127.95, 128.11, 128.53, 129.63, 129.82 (Aromatics), 135.49 ($(CH_3)_2C=CHCH_2$), 136.43, 136.50, 136.84 (Quaternary Aromatics), 155.80, 156.50 (2 X NHC(O)), 171.50, 172.90 (2 X C=O); MS (FAB, NBA) m/e (%) 644 (49.1) $[MH]^+$.

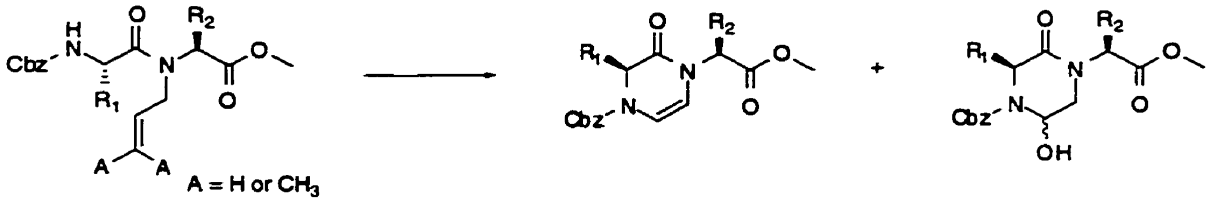
N-(Benzyloxycarbonyl)-L-phenylalanyl-N'-dimethylallyl-O-benzyl-L-serine methyl ester (68)

Prepared according to **GP 5** in 65 % yield. TLC ethyl acetate/hexane, 1/2, R_f 0.31; ^1H NMR (270 MHz, $CDCl_3$): δ 1.64, 1.70 (2 s, 6 H, $(C\mathbf{H}_3)_2C=CHCH_2$), 2.95 (A of ABX system, 1 H, J = 6.2 Hz and 13.6 Hz, $CHC\mathbf{H}_2Ph$), 3.11 (B of ABX system, 1 H, J = 7.2 Hz and 13.6 Hz, $CHC\mathbf{H}_2Ph$), 3.64-3.69 (m with overlapping s, 4 H, $OC\mathbf{H}_3$ and $(CH_3)_2C=CHC\mathbf{H}_2$), 3.84-4.10 (m, 3 H, $(CH_3)_2C=CHC\mathbf{H}_2$ and $CHC\mathbf{H}_2O$), 4.50, 4.51 (2 s, 2 H, $CH_2OC\mathbf{H}_2Ph$), 4.61 (X of ABX system, 1 H, J= 6.2 Hz and 7.2 Hz, $C\mathbf{H}CH_2Ph$), 4.88-5.14 (m, 4 H, $(CH_3)_2C=C\mathbf{H}CH_2$, $NC\mathbf{H}$ and $PhC\mathbf{H}_2OC(O)$), 5.73 (d, 1 H, J = 8.6 Hz, $N\mathbf{H}CH$), 7.22-7.37 (m, 15 H, 3 X $\mathbf{Ph}$); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 18.07, 25.79 ($(CH_3)_2C=CHCH_2$), 39.55 ($CHCH_2Ph$), 46.68 ($(CH_3)_2C=CHCH_2$), 52.21 ($CHCH_2Ph$), 52.36 (OCH_3), 58.91 ($NCHCH_2$), 66.73 ($PhCH_2OC(O)$), 68.35 ($NCHCH_2$), 73.28 (CH_2OCH_2Ph), 120.42 ($(CH_3)_2C=CHCH_2$), 126.95, 127.69, 127.79, 127.98, 128.10, 128.49, 128.56, 129.71 (Aromatics), 135.93 ($(CH_3)_2C=CHCH_2$), 136.32, 136.65, 138.00 (Quaternary Aromatics), 155.63 ($PhCH_2OC(O)$), 169.63, 173.75 (2 X C=O); MS (FAB, NBA) m/e (%) 559 (21.4) $[MH]^+$.

N-(Benzyloxycarbonyl)-L-alanyl-N'-dimethylallyl-L-valine methyl ester (69)

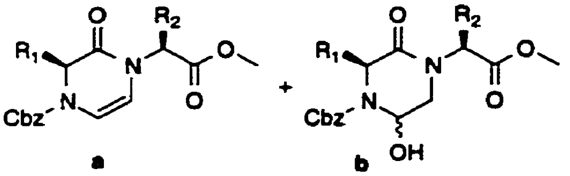
Prepared according to **GP 5** in 72 % yield. TLC ethyl acetate/hexane, 1/5, R_f 0.21; ^1H NMR (270 MHz, $CDCl_3$): δ 0.78, 0.94 (2 d, 6 H, J = 6.7 Hz and 6.7 Hz, $CH(C\mathbf{H}_3)_2$), 1.67 (s br, 6 H, $(C\mathbf{H}_3)_2C=CHCH_2$), 2.11-2.38 (m, 1 H, $C\mathbf{H}(CH_3)_2$), 3.61 (s, 3 H, $OC\mathbf{H}_3$), 3.81-3.91 (m, 1 H, $(CH_3)_2=CHC\mathbf{H}_2$), 4.16-4.25 (m, 1 H, $(CH_3)_2=CHC\mathbf{H}_2$), 4.51-4.59 (m, 2 H, NCH and NHC**H**) 5.01-5.11 (m, 3 H, $(CH_3)_2C=C\mathbf{H}CH_2$ and $PhC\mathbf{H}_2O$), 5.68 (d, 1 H, J = 7.4 Hz, N**H**CH), 7.21-7.35 (m, 5 **H**, Ph); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 17.96 ($(CH_3)_2C=CHCH_2$), 18.93 ($CHCH_3$ and $CH(CH_3)_2$), 20.27 ($CH(CH_3)_2$), 25.73 ($(CH_3)_2C=CHCH_2$), 27.70 ($CH(CH_3)_2$), 43.88 ($(CH_3)_2C=CHCH_2$), 47.07 ($CHCH_3$), 51.80 (OCH_3), 62.36 (NCH), 66.64 ($PhCH_2O$), 120.68 ($(CH_3)_2C=CHCH_2$), 127.91, 128.03, 128.49 (Aromatics), 135.48 ($(CH_3)_2C=CHCH_2$), 136.53 (Quaternary Aromatic), 155.67 (NHC(O)O), 171.31, 174.12 (2 X C=O); MS (CI, NH_3) m/e (%) 405 (6.6) $[MH]^+$, 297 (65.6), 229 (65.7), 198 (100).

Preparation of cyclized compounds via ozonolysis (GP 6)



The allylated or prenylated protected dipeptide (1.00 mmol) was ozonized at -78 °C in methanol (25 ml) for three hours. The excess ozone was then removed by passing in dry nitrogen. Dimethyl sulfide (10.00 mmol) was added at -78 °C and the solution was allowed to warm up slowly to room temperature and left to stir for ten hours. The solvent was removed under reduced pressure and the residue chromatographed on silica gel (hexane/ethyl acetate) to yield the desired cyclized compound.

Cyclized alkene (70a) and alcohol (70b)



70a & 70b : $R_1 = CH(CH_3)_2$, $R_2 = CH_2Ph$
71a & 71b : $R_1 = CH_2COOBn$, $R_2 = CH_2Ph$
72a & 72b : $R_1 = CH_2Ph$, $R_2 = CH_2CH(CH_3)_2$
73a & 73b : $R_1 = CH_2Ph$, $R_2 = (CH_2)_4NHCbz$
74a & 74b : $R_1 = CH_2Ph$, $R_2 = CH_2OBn$
75a & 75b : $R_1 = CH_3$, $R_2 = CH(CH_3)_2$

Prepared according to **GP 6** in 82 % yield. TLC ethyl acetate/hexane, 1/1, R_f 0.37. The ^{1}H NMR spectrum was highly complex and gave several multiple overlapping signals. MS (FAB, NBA) m/e (%) 455 (8.4) [MH, alcohol]$^+$, 437 (7.2) [MH, alkene]$^+$.

Cyclized alkene (71a) and alcohol (71b)

Prepared according to **GP 6** in 82 % yield. TLC ethyl acetate/hexane, 1/1, R_f 0.44. The ^{1}H NMR spectrum was highly complex and gave several multiple overlapping signals. MS (FAB, NBA) m/e (%) 561 (10.2) [MH, alcohol]$^+$, 543 (5.2) [MH, alkene]$^+$.

Cyclized alkene (72a) and alcohol (72b)

Prepared according to **GP 6** in 77 % yield. TLC ethyl acetate/hexane, 1/3, R_f 0.20. The ^{1}H NMR spectrum was highly complex and gave several multiple overlapping signals. MS (FAB, NBA) m/e (%) 469 (12.8) [MH, alcohol]$^+$, 451 (9.0) [MH, alkene]$^+$.

Cyclized alkene (73a) and alcohol (73b)

Prepared according to **GP 6** in 75 % yield. TLC ethyl acetate/hexane, 1/1, R_f 0.27. The ^{1}H NMR spectrum was highly complex and gave several multiple overlapping signals. MS (FAB, NBA) m/e (%) 618 (10.2) [MH, alcohol]$^+$, 600 (100) [MH, alkene]$^+$.

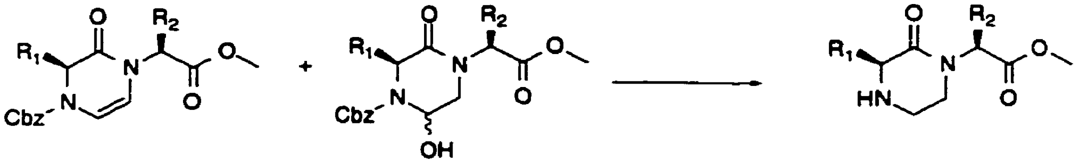
Cyclized alkene (74a) and alcohol (74b)

Prepared according to **GP 6** in 70 % yield. TLC ethyl acetate/hexane, 1/2, R_f 0.17. The ^{1}H NMR spectrum was highly complex and gave several multiple overlapping signals. MS (FAB, NBA) m/e (%) 533 (7.0) [MH, alcohol]$^+$, 515 (55.4) [MH, alkene]$^+$.

Cyclized alkene (75a) and alcohol (75b)

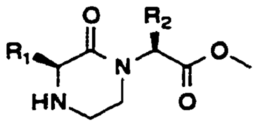
Prepared according to **GP 6** in 76 % yield. TLC ethyl acetate/hexane, 1/3, R_f 0.13. The ^{1}H NMR spectrum was highly complex and gave several multiple overlapping signals. MS (CI, NH_3) m/e (%) 379 (1.3) [MH, alcohol]$^+$, 361 (100) [MH, alkene]$^+$.

Hydrogenation of the cyclized alkene and alcohol mixture (GP 7)



A solution of the mixture of cyclized alkene and alcohol (100 mg) in freshly distilled methanol (10 ml) and 5 % palladium on barium sulphate, reduced (100 mg) was shaken in a pressure vessel, under a pressure of 45 p.s.i. of gaseous hydrogen for six hours. After that time, the mixture was carefully filtered over a short very compact pad of celite and evaporated to yield a brown oil which was column chromatograph (ethyl acetate) to afford the required compound. One exception was the deprotection of the O-benzyl ether derivative which was deprotected using 10 % Pd/C (1 eq.) in a mixture of ethanol, acetic acid and water in a ratio of 12:2:1 for 36 hours under a pressure of 50 p.s.i.

Methyl (2S,3'S)-2-[3'-isopropyl-2'-oxopiperazin-1'-yl]-3-phenylpropanoate (76)



76 : $R_1 = CH(CH_3)_2$, $R_2 = CH_2Ph$
77 : $R_1 = CH_2COOH$, $R_2 = CH_2Ph$
78 : $R_1 = CH_2Ph$, $R_2 = CH_2CH(CH_3)_2$
79 : $R_1 = CH_2Ph$, $R_2 = (CH_2)_4NH_2$
80 : $R_1 = CH_2Ph$, $R_2 = CH_2OH$
81 : $R_1 = CH_3$, $R_2 = CH(CH_3)_2$

Prepared according to **GP 7** in 79 % yield. TLC benzene/ethyl acetate/methanol, 5/4/1, R_f 0.43; ^{1}H NMR (500 MHz, DMSO-d_6): δ 0.45 (d, 1 H, J = 7.0 Hz, ($\mathbf{H}_3$)$_2$CH), 0.76 (d, 1 H, J = 7.0 Hz, (C$\mathbf{H}_3$)$_2$CH), 2.08-2.12 (m, 1 H, (CH$_3$)$_2$C**H**), 2.42-2.46 (m, 1 H, C$\mathbf{H}_2$CH$_2$), 2.66-2.84 (m, 2 H, CH$_2$C$\mathbf{H}_2$), 3.04 (A of ABX system, 1 H, J = 11.0 Hz and 14.0 Hz, CHC$\mathbf{H}_2$Ph), 3.10 (d, 1 H, J = 2.5 Hz, (CH$_3$)$_2$CHC**H**), 3.20 (B of ABX system, 1 H, J = 4.5 Hz and 14.0 Hz, CHC$\mathbf{H}_2$Ph), 3.21-3.25 (m, 1 H, C$\mathbf{H}_2$CH$_2$), 3.61 (s, 3 H, OC$\mathbf{H}_3$), 4.87 (X of ABX system, 1 H, J = 4.5 Hz and 11.0 Hz, C**H**CH$_2$Ph), 7.15-7.25 (m, 5 H, **Ph**); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 16.47, 19.43 ((**C**H$_3$)$_2$CH), 30.13 ((CH$_3$)$_2$**C**H), 33.67 (**C**H$_2$Ph) 41.95, 47.31 (**C**H$_2$**C**H$_2$), 52.19 (O**C**H$_3$), 58.92 (N**C**H), 63.83 (NH**C**H), 126.69, 128.50, 129.19 (Aromatics), 137.67 (Quaternary Aromatic), 170.05, 171.07 (2 X **C**=O); MS (EI) m/e (%) 304 (35.1) [M]$^+$, 261 (100), 233 (20.0), 185 (27.8); HRMS (EI) m/e Calcd for $C_{17}H_{24}N_2O_3$: 304.17868; Found: 304.17840.

(1'S,3S)-1-[(1'-methoxycarbonyl-2'-phenylethyl)-2-oxopiperazin-3-yl] acetic acid (77)

Prepared according to **GP 7** in 76 % yield. ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.15 (A of ABX system, 1 H, J = 8.0 Hz and 16.0 Hz, CHC$\mathbf{H}_2$C(O)), 2.48-2.52 (m, 1 H, CHC$\mathbf{H}_2$C(O)), 2.52-2.58 (m, 1 H, C$\mathbf{H}_2$CH$_2$), 2.72-2.84 (m, 2 H, CH$_2$C$\mathbf{H}_2$), 3.06 (A of ABX system, 1 H, J = 11.0 Hz and 14.0 Hz, CHC$\mathbf{H}_2$Ph), 3.18 (B of ABX system, 1 H, J = 5.5 Hz and 14.0 Hz, CHC$\mathbf{H}_2$Ph), 3.24-3.30 (m, 1 H, C$\mathbf{H}_2$CH$_2$), 3.54 (X of ABX system, 1 H, J = 3.5 Hz and 8.0 Hz, C**H**CH$_2$C(O)), 3.63 (s, 3 H, OC$\mathbf{H}_3$), 4.84 (X of ABX system, 1 H, J = 5.5 Hz and 11.0 Hz, C**H**CH$_2$Ph), 7.17-7.30 (m, 5 H, **Ph**); ^{13}C NMR (125.7 MHz, DMSO-d_6): δ 33.37, 36.98 (2 X CH**C**H$_2$), 40.90, 46.92 (**C**H$_2$**C**H$_2$),

51.95 (OCH$_3$), 55.64 (NHCH), 58.73 (NCH), 126.43, 128.20, 128.95 (Aromatics), 137.41 (Quaternary Aromatic), 168.86, 170.50, 172.61 (3 X C=O); MS (EI) m/e (%) 320 (79.0) [M]$^+$, 275 (32.9), 229 (100), 157 (74.4); HRMS (EI) m/e Calcd for $C_{16}H_{20}N_2O_5$: 320.13721; Found: 320.13750.

Methyl (2S,3'S)-2-[3'-benzyl-2'-oxopiperazin-1'-yl]-4-methylpentanoate (78)

Prepared according to **GP 7** in 81 % yield. TLC ethyl acetate, R$_f$ 0.22; ^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 0.81, 0.83 (2 d, 6 H, J = 6.5 Hz and 6.5 Hz, CH$_2$CH(C**H**$_3$)$_2$), 1.23-1.29 (m, 1 H, CH$_2$C**H**(CH$_3$)$_2$), 1.48-1.54 (m, 1 H, C**H**$_2$CH(CH$_3$)$_2$), 1.63-1.70 (m, 1 H, C**H**$_2$CH(CH$_3$)$_2$), 2.29 (s, 1 H, N**H**), 2.71-2.76 (m, 1 H, NC**H**$_2$CH$_2$N), 2.84 (A of ABX system, 1 H, J = 8.0 Hz and 14.0 Hz, C**H**$_2$Ph), 2.93-2.96 (m, 1 H, NC**H**$_2$CH$_2$N), 3.01-3.10 (m, 3 H, NCH$_2$C**H**$_2$N and C**H**$_2$Ph), 3.56 (X of ABX system, 1 H, J = 3.0 Hz and 8.0 Hz, C**H**CH$_2$Ph), 3.61 (s, 3 H, OC**H**$_3$), 5.08 (dd, 1 H, J = 4.5 Hz and 12.0 Hz, NC**H**), 7.16-7.24 (m, 5 H, **Ph**); ^{13}C NMR (67.9 MHz, CDCl$_3$): δ 21.42, 23.33 (CH$_2$CH(CH$_3$)$_2$), 24.76 (CH$_2$CH(CH$_3$)$_2$), 36.73 (CHCH$_2$Ph) 38.51 (CH$_2$CH(CH$_3$)$_2$), 42.36, 44.72 (NCH$_2$CH$_2$N), 52.22 (CHCH$_2$Ph), 53.86 (OCH$_3$), 61.00 (NCH), 126.71, 128.62 129.54 (Aromatics), 138.27 (Quaternary Aromatic), 170.04, 172.34 (2 X C=O); MS (EI) m/e (%) 318 (1.5) [M]$^+$, 287 (2.0), 227 (100), 199 (52.4); HRMS (EI) m/e Calcd for $C_{18}H_{26}N_2O_3$: 318.19433; Found: 318.19400.

Methyl (2S,3'S)-2-[3'-benzyl-2'-oxopiperazin-1'-yl]-6-aminohexanoate (79)

Prepared according to **GP 7** in 81 % yield. ^{1}H NMR (270 MHz, CD$_3$OD): δ 1.14-1.55 (m, 6 H, C**H**$_2$(C**H**$_2$)$_2$CH$_2$NH$_2$), 1.75-1.98 (m, 2 H, CH$_2$(CH$_2$)$_2$C**H**$_2$NH$_2$), 2.41 (s, 1 H, N**H**), 2.55-2.66 (m, 1 H, NC**H**$_2$CH$_2$N), 2.93 (dd, 1 H, J = 8.4 Hz and 13.6 Hz, CH$_2$Ph), 2.99-3.09 (m, 2 H, NC**H**$_2$CH$_2$N), 3.18-3.29 (m, 2 H, C**H**$_2$Ph and NCH$_2$C**H**$_2$N), 3.70-3.74 (m with overlapping s, 4 H, NHC**H** and OC**H**$_3$), 4.98 (dd, 1 H, J = 4.7 Hz and 10.7 Hz, NC**H**), 7.10-7.32 (m, 5 H, **Ph**); ^{13}C NMR (67.9 MHz, CD$_3$OD):

δ 23.14 ($CH_2CH_2(CH_2)_2NH_2$), 27.23 ($(CH_2)_2CH_2CH_2NH_2$), 30.98 ($CH_2(CH_2)_3NH_2$), 34.44 ($(CH_2)_3CH_2NH_2$), 37.82 (CH_2Ph), 41.34, 44.85 (NCH_2CH_2N), 51.46 (OCH_3), 56.59 (NHCH), 60.40 (NCH), 126.47, 128.30, 129.35 (Aromatics), 137.82 (Quaternary Aromatic), 171.07, 171.39 (2 X C=O); MS (EI) m/e (%) 333 (17.5) $[M]^+$, 256 (50.0), 242 (100), 189 (17.1); HRMS (EI) m/e Calcd for $C_{18}H_{27}N_3O_3$: 333.20523; Found: 333.20550.

Methyl (2S,3'S)-2-[3'-benzyl-2'-oxopiperazin-1'-yl]-3-hydroxypropanoate (80)

Prepared according to **GP 7** in 80 % yield. TLC benzene/ethyl acetate/methanol, 5/4/1, R_f 0.20; ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.88 (A of ABX system, 1 H, J = 9.5 Hz and 13.7 Hz, $CHC\mathbf{H}_2Ph$), 2.92-3.12 (m, 2 H, $CHC\mathbf{H}_2Ph$ and $NC\mathbf{H}_2CH_2N$), 3.34-3.45 (m, 3 H, $NC\mathbf{H}_2C\mathbf{H}_2N$), 3.71 (X of ABX system, 1 H, J = 4.9 Hz and 9.5 Hz, $\mathbf{C}HCH_2Ph$), 3.73 (s, 3 H, $OC\mathbf{H}_3$), 3.88 (A of ABX system, 1 H, J = 3.9 Hz and 10.5 Hz, $C\mathbf{H}_2OH$), 3.95 (B of ABX system, 1 H, J = 7.8 Hz and 10.5 Hz, $C\mathbf{H}_2OH$), 5.24 (X of ABX system, 1 H, J = 3.9 Hz and 7.8 Hz, $C\mathbf{H}CH_2OH$), 7.21-7.38 (m, 5 H, **Ph**); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 38.88 ($CHCH_2Ph$), 42.25, 46.21 (NCH_2CH_2N), 52.44 (OCH_3), 58.91 ($CHCH_2Ph$), 61.31 ($NCHCH_2$), 62.32 ($NCHCH_2$), 127.21, 128.54, 129.71 (Aromatics), 135.32 (Quaternary Aromatic), 169.53, 172.73 (2 X C=O); MS (EI) m/e (%) 292 (16.1) $[M]^+$, 183 (39.0), 105 (84.2), 91 (100); HRMS (EI) m/e Calcd for $C_{15}H_{20}N_2O_4$: 292.14230; Found: 292.14209.

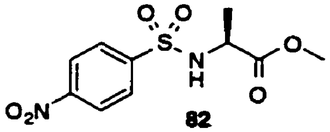
Methyl (2S,3'S)-2-[3'-methyl-2'-oxopiperazin-1'-yl]-3-methylbutanoate (81)

Prepared according to **GP 7** in 73 % yield. TLC benzene/ethyl acetate/methanol, 5/4/1, R_f 0.19; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.91, 1.00 (2 d, 6 H, J = 6.7 Hz and 6.7 Hz, $CH(C\mathbf{H}_3)_2$), 1.35 (d, 3 H, J = 6.7 Hz, $CHC\mathbf{H}_3$), 2.20-2.34 (m, 1 H, $C\mathbf{H}(CH_3)_2$), 2.93-3.03, 3.12-3.21 (2 m, 2 H, $NC\mathbf{H}_2CH_2N$), 3.42-3.50 (m, 2 H, $NCH_2C\mathbf{H}_2N$), 3.54 (q, 1 H, J = 6.7 Hz, $\mathbf{C}HCH_3$), 3.70 (s, 3 H, $OC\mathbf{H}_3$), 4.67 (d, 1 H, J = 10.4 Hz, $NC\mathbf{H}$); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 17.20 ($CHCH_3$), 18.08, 18.99 ($CH(CH_3)_2$), 26.85

($CH(CH_3)_2$), 40.88, 44.57 (NCH_2CH_2N), 51.09 (OCH_3), 54.46 ($CHCH_3$), 62.11 (NCH), 170.94, 171.68 (2 X C=O); MS (EI) m/e (%) 228 (16.8) $[M]^+$, 157 (34.9), 141 (100), 113 (74.3); HRMS (EI) m/e Calcd for $C_{11}H_{20}N_2O_3$: 228.14738; Found: 228.14750.

4.4 Experimental for Section 2.3

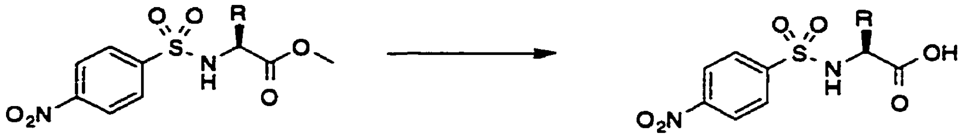
N-4-Nitrobenzenesulfonyl-L-alanine methyl ester (82)



82

Prepared according to **GP 1** in 90 % yield. TLC ethyl acetate/hexane, 1/2, R_f 0.27; mp 103-105 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.37 (d, 3 H, J = 7.2 Hz, $CHC\mathbf{H}_3$), 3.56 (s, 3H, $OC\mathbf{H}_3$), 4.00-4.11 (m, 1 H, NHC**H**), 5.78 (d, 1 H, J = 8.2 Hz, N**H**CH), 8.03 (d, 2 H, J = 8.9 Hz, meta **H**'s to $-NO_2$), 8.31 (d, 2 H, J = 8.9 Hz, ortho **H**'s to $-NO_2$); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 19.71 ($CHCH_3$), 51.74 (OCH_3), 52.87 (NHCH), 124.38, 128.47 (Aromatics), 146.00, 150.16 (Quaternary Aromatics), 172.32 (C=O); MS (CI, NH_3) m/e (%) 306 (100) $[M + NH_4]^+$, 289 (4.9) $[MH]^+$, 259 (38.4), 229 (33.2), 199 (20.0), 186 (43.8), 156 (26.2).

N-4-Nitrobenzenesulfonyl-L-alanine (83)



83 : R = CH_3
84 : R = CH_2Ph

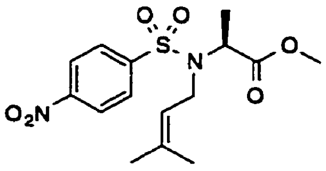
A solution of N-4-nitrobenzenesulfonyl-L-alanine methyl ester, **82** (1.00 g, 3.47 mmol) in a THF/water mixture (3/1 v/v, 20 ml) was treated with lithium hydroxide monohydrate (0.44 g, 10.41 mmol) and stirred at room temperature for three hours. Water (30 ml) was then added and the mixture extracted with dichloromethane (2 X 30 ml) to remove any organic soluble impurities. The aqueous layer was then quenched with concentrated hydrochloric acid and the pH of the solution adjusted to 1. This solution was then extracted with dichloromethane (3 X 30 ml) and the combined organic layers were dried over anhydrous magnesium sulfate, filtered and concentrated *in vacuo* to yield a pale brown solid (0.90 g, 95 %). Mp 142-145 °C; ^{1}H NMR (270 MHz, DMSO-d_6): δ 1.19 (d, 3

H, J = 7.2 Hz, CHC**H**$_3$), 3.82-3.93 (m, 1 H, NHC**H**), 8.01 (d, 2 H, J = 8.9 Hz, meta **H**'s to -NO$_2$), 8.39 (d, 2 H, J = 8.9 Hz, ortho **H**'s to -NO$_2$), 8.60 (d, 1 H, J = 8.4 Hz, NHCH),; ^{13}C NMR (67.9 MHz, DMSO-*d*$_6$): δ 19.00 (CHCH$_3$), 51.84 (NHCH), 124.93, 128.59 (Aromatics), 147.49, 149.99 (Quaternary Aromatics), 173.46 (C=O); MS (EI) m/e (%) 274 (20.0) [M]$^+$.

N-4-Nitrobenzenesulfonyl-L-phenylalanine (84)

Prepared as compound **83** in 93 % yield.Mp 162-165 °C. ^{1}H NMR (270 MHz, DMSO-*d*$_6$): δ 2.70 (A of ABX system, 1 H, J = 10.1 Hz and 13.8 Hz, C**H**$_2$Ph), 3.00 (B of ABX system, 1 H, J = 4.7 Hz and 13.8 Hz, C**H**$_2$Ph), 3.92-4.01 (m, 1 H, C**H**), 7.06-7.17 (m, 5 H, **Ph**), 7.75 (d, 2 H, J = 8.9 Hz, meta **H**'s to -NO$_2$), 8.20 (d, 2 H, J = 8.9 Hz, ortho **H**'s to -NO$_2$), 8.74 (d, 1H, J = 9.2 Hz, N**H**); ^{13}C NMR (67.9 MHz, DMSO-*d*$_6$): δ 38.11 (CH$_2$Ph), 58.20 (CH), 124.69, 126.94, 128.19, 128.66, 129.74 (Aromatics), 137.22, 147.18, 149.65 (Quaternary Aromatics), 172.69 (C=O); MS (CI, NH$_3$) m/e (%) 368 (37.8) [M + NH$_4$]$^+$, 351 (3.9) [MH]$^+$, 305 (51.3), 148 (100).

N-(Dimethylallyl)-N-4-nitrobenzenesulfonyl-L-alanine methyl ester (85)

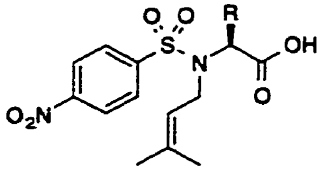


85

Prepared according to **GP 2** in 91 % yield. TLC ethyl acetate/hexane, 1/2, R$_f$ 0.59; mp 82-84 °C; ^{1}H NMR (270 MHz, CDCl$_3$): δ 1.40 (d, 3 H, J = 7.4 Hz, CHC**H**$_3$), 1.58, 1.59 (2 s, 6 H, (C**H**$_3$)$_2$C=CHCH$_2$), 3.56 (s, 3 H, OC**H**$_3$), 3.75-3.93 (m, 2 H, (CH$_3$)$_2$=CHC**H**$_2$), 4.65 (q, 1 H, J = 7.4 Hz, C**H**CH$_3$), 4.95-5.01 (m, 1 H, (CH$_3$)$_2$=C**H**CH$_2$), 7.97 (d, 2 H, J = 8.9 Hz, meta **H**'s to -NO$_2$), 8.28 (d, 2 H, J = 8.9 Hz, ortho **H**'s to -NO$_2$); ^{13}C NMR (67.9 MHz, CDCl$_3$): δ 16.56 ((CH$_3$)$_2$C=CHCH$_2$), 17.78 (CHCH$_3$), 25.73 ((CH$_3$)$_2$C=CHCH$_2$), 43.79 ((CH$_3$)$_2$C=CHCH$_2$), 52.36 (OCH$_3$), 55.31

(NCH), 120.18 ($(CH_3)_2C{=}CHCH_2$), 124.00, 128.64 (Aromatics), 136.55 ($(CH_3)_2C{=}CHCH_2$), 146.58, 149.89 (Quaternary Aromatics), 171.52 (C=O); MS (FAB, NBA) m/e (%) 357 (20.4) $[MH]^+$.

N-(Dimethylallyl)-N-4-nitrobenzenesulfonyl-L-alanine (86)



86 : R = CH_3
87 : R = CH_2Ph

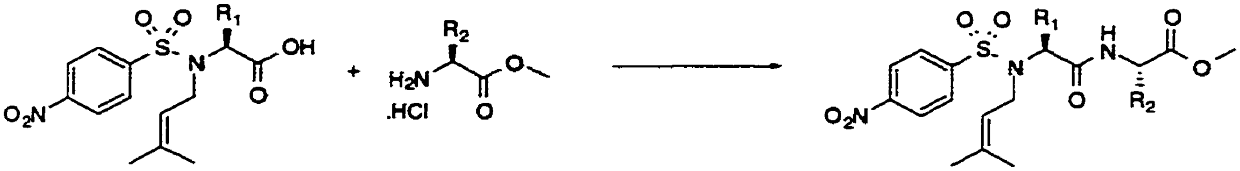
Similarily prepared as compound **83** in 82 % yield. Mp 123-126 °C. ^{1}H NMR (270 MHz, DMSO-d_6): δ 1.40 (d, 3 H, J = 7.4 Hz, $CHC\mathbf{H}_3$), 1.59 (s br, 6 H, $(C\mathbf{H}_3)_2C{=}CHCH_2$), 3.76 (A of ABX system, 1 H, J = 6.7 Hz and 16.1 Hz, $(CH_3)_2{=}CHC\mathbf{H}_2$), 3.95 (B of ABX system, 1 H, J = 6.9 Hz and 16.1 Hz, $(CH_3)_2{=}CHC\mathbf{H}_2$), 4.58 (q, 1 H, J = 7.4 Hz, $C\mathbf{H}CH_3$), 4.99-5.05 (m, 1 H, $(CH_3)_2{=}C\mathbf{H}CH_2$), 8.04 (d, 2 H, J = 8.9 Hz, meta **H**'s to $-NO_2$), 8.38 (d, 2 H, J = 8.9 Hz, ortho **H**'s to $-NO_2$); ^{13}C NMR (67.9 MHz, DMSO-d_6): δ 16.95 ($(CH_3)_2C{=}CHCH_2$), 18.06 ($CHCH_3$), 25.92 ($(CH_3)_2C{=}CHCH_2$), 44.10 ($(CH_3)_2C{=}CHCH_2$), 55.78 (NCH), 121.50 ($(CH_3)_2C{=}CHCH_2$), 124.82, 129.10 (Aromatics), 135.45 ($(CH_3)_2C{=}CHCH_2$), 146.63, 150.10 (Quaternary Aromatics), 172.69 (C=O); MS (FAB, NBA) m/e (%) 343 (18.2) $[MH]^+$.

N-(Dimethylallyl)-N-4-nitrobenzenesulfonyl-L-phenylalanine (87)

Similarily prepared as compound **83** in 90 % yield. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.56, 1.62 (2 s, 6 H, $(C\mathbf{H}_3)_2C{=}CHCH_2$), 2.99 (A of ABX system, 1 H, J = 9.6 Hz and 14.6 Hz, $C\mathbf{H}_2Ph$) 3.45 (B of ABX system, 1 H, J = 5.5 Hz and 14.6 Hz, $C\mathbf{H}_2Ph$), 3.74-4.06 (m, 2 H, $(CH_3)_2C{=}CHC\mathbf{H}_2$), 4.83-4.87 (m, 1 H, $(CH_3)_2C{=}C\mathbf{H}CH_2$), 4.92 (X of ABX system, 1 H, J= 5.5 Hz and 9.6 Hz, C**H**), 7.15-7.28 (m, 5 H, **Ph**), 7.49 (d, 2 H, J = 8.9 Hz, meta **H**'s to $-NO_2$), 7.66 (d, 2 H, J = 8.9 Hz, ortho **H**'s to $-NO_2$); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 17.89, 25.73 ($(CH_3)_2C{=}CHCH_2$), 36.18 (CH_2Ph), 44.43

($(CH_3)_2C=CHCH_2$), 61.70 (CH) 119.48 ($(CH_3)_2C=CHCH_2$), 123.83, 127.19, 128.83, 129.34, 130.29 (Aromatics), 134.05 ($(CH_3)_2C=CHCH_2$), 137.56, 146.44, 149.89 (Quaternary Aromatics), 170.77 (C=O); MS (EI) m/e (%) 418 (1.2) $[M]^+$, 122 (90.5), 105 (100), 77 (62.1).

Preparation of prenylated sulfonamide dipeptides (GP 8)

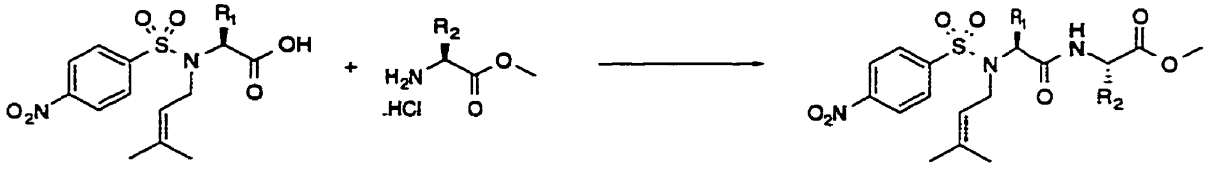


To a cooled solution (0 °C) of the prenylated sulfonamide amino acid (1.00 mmol), amino acid methyl ester hydrochloride (1.10 mmol), N-hydroxybenzotriazole, HOBt (1.10 mmol) and N-methyl morpholine, NMM (1.10 mmol) in dry dichloromethane (5 ml) was added 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride, EDAC.HCl (1.10 mmol). The reaction mixture was slowly warmed to room temperature and stirred under argon for 48 hours. The crude mixture was washed with water (10 ml), saturated citric acid solution (2 X 10 ml), water (10 ml), sodium bicarbonate solution (10 % w/v, 2 X 10 ml) and water (10 ml) respectively. The organic layer was then dried over anhydrous magnesium sulfate and the excess solvent removed under reduced pressure to afford the desired dipeptide which was used without any further purification.

N-(Dimethylallyl)-N-4-nitrobenzenesulfonyl-L-alanyl-L-phenylalanine methyl ester (88)

Method 1

Prepared according to **GP 8** in 63 % yield.



88 : $R_1 = CH_3, R_2 = CH_2Ph$
89 : $R_1 = CH_2Ph, R_2 = CH_3$

Method 2

88 : $R_1 = CH_3, R_2 = CH_2Ph$
89 : $R_1 = CH_2Ph, R_2 = CH_3$

Prepared according to **GP 2** in 75 % yield. TLC ethyl acetate/hexane, 1/2, R_f 0.32; ^1H NMR (270 MHz, $CDCl_3$): δ 1.10 (d, 3 H, J = 7.2 Hz, $CHC\mathbf{H}_3$), 1.53, 1.57 (2 s, 6 H, $(C\mathbf{H}_3)_2C{=}CHCH_2$), 2.97 (A of ABX system, 1 H, J = 7.9 Hz and 13.9 Hz, $C\mathbf{H}_2Ph$), 3.14 (B of ABX system, 1 H, J = 5.2 Hz and 13.9 Hz, $C\mathbf{H}_2Ph$), 3.45-3.75 (m with overlapping s, 5 H, $OC\mathbf{H}_3$ and $(CH_3)_2{=}CHC\mathbf{H}_2$), 4.43 (q, 1 H, J = 7.2 Hz, $C\mathbf{H}CH_3$), 4.65-4.75 (m, 2 H, $NHC\mathbf{H}$ and $(CH_3)_2{=}C\mathbf{H}CH_2$), 6.73 (d, 1 H, J = 7.7 Hz, $N\mathbf{H}CH$), 7.09-7.32 (m, 5 H, **Ph**), 7.89 (d, 2 H, J = 8.9 Hz, meta **H**'s to $-NO_2$), 8.25 (d, 2 H, J = 8.9 Hz, ortho **H**'s to $-NO_2$); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 14.27 ($(CH_3)_2C{=}CHCH_2$), 17.84 ($CHCH_3$), 25.69 ($(CH_3)_2C{=}CHCH_2$), 37.83 (CH_2Ph), 43.24 ($(CH_3)_2C{=}CHCH_2$), 52.46 (OCH_3), 53.69 (NHCH), 55.70 (NCH), 119.58 ($(CH_3)_2C{=}CHCH_2$), 124.34, 127.27, 128.39, 128.88, 129.31 (Aromatics), 135.97 ($(CH_3)_2C{=}CHCH_2$), 137.03, 146.29, 150.02 (Quaternary Aromatics), 169.95, 171.67 (C=O); MS (CI, NH_3) m/e (%) 504 (11.7) $[MH]^+$, 436 (46.1), 317 (100).

N-(Dimethylallyl)-N-4-nitrobenzenesulfonyl-L-phenylalanyl-L-alanine methyl ester (89)

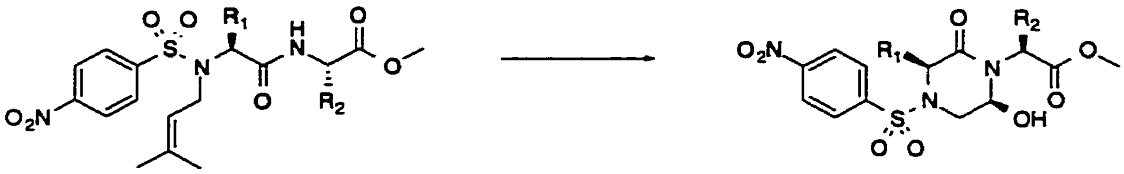
Method 1

Prepared according to **GP 8** in 72 % yield.

Method 2

Prepared according to **GP 2** in 77 % yield. TLC ethyl acetate/hexane, 1/1, R_f 0.67; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.40 (d, 3 H, J = 7.2 Hz, $CHC\mathbf{H}_3$), 1.63, 1.69 (2 s, 6 H, $(C\mathbf{H}_3)_2C=CHCH_2$), 2.80 (A of ABX system, 1 H, J= 9.4 Hz and 14.6 Hz, $C\mathbf{H}_2Ph$), 3.26 (B of ABX system, 1 H, J = 5.7 Hz and 14.6 Hz, $C\mathbf{H}_2Ph$), 3.71 (s, 3 H, $OC\mathbf{H}_3$), 3.94-4.14 (m, 2 H, $(CH_3)_2=CHC\mathbf{H}_2$), 4.41-4.53 (m, 1 H, $C\mathbf{H}CH_3$), 4.63 (X of ABX system, 1 H, J = 5.7 Hz and 9.4 Hz, $C\mathbf{H}CH_2Ph$), 5.01-5.07 (m, 1 H, $(CH_3)_2=C\mathbf{H}CH_2$), 6.95-7.14 (m, 5 H, **Ph**), 7.53 (d, 2 H, J = 8.9 Hz, meta **H**'s to $-NO_2$), 8.03 (d, 2 H, J = 8.9 Hz, ortho **H**'s to $-NO_2$); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 17.92 ($(\mathbf{C}H_3)_2C=CHCH_2$), 17.99 ($CH\mathbf{C}H_3$), 25.79 ($(\mathbf{C}H_3)_2C=CHCH_2$), 34.56 ($\mathbf{C}H_2Ph$), 43.27 ($(CH_3)_2C=CH\mathbf{C}H_2$), 48.47 (NHCH), 52.55 ($OCH_3$), 61.73 (NCH), 119.87 ($(CH_3)_2C=\mathbf{C}HCH_2$), 124.01, 126.78, 128.14, 128.64, 129.17 (Aromatics), 137.01 ($(CH_3)_2\mathbf{C}=CHCH_2$), 137.11, 145.93, 149.68 (Quaternary Aromatics), 169.00, 172.80 (C=O); MS (FAB, NBA) m/e (%) 504 (54.1) $[M + H]^+$.

Methyl (2S,3'S,6'S)-2-[6'-hydroxy-3'-methyl-4'-(4-nitrobenzenesulfonyl)-2'-oxopiperazin-1'-yl]-3-phenylpropanoate (90)



90 : $R_1 = CH_3$, $R_2 = CH_2Ph$
91 : $R_1 = CH_2Ph$, $R_2 = CH_3$

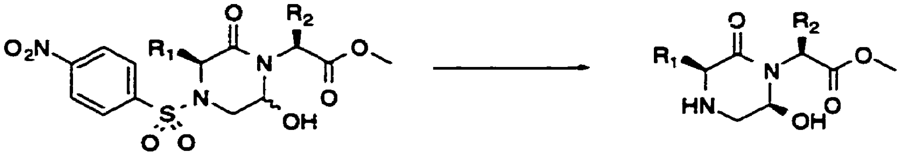
Prepared according to **GP 6** in 78 % yield. TLC ethyl acetate/hexane, 1/1, R_f 0.29; ^{1}H NMR (270 MHz, DMSO-d_6): δ 1.27 (d, 3 H, J = 6.9 Hz, $C\mathbf{H}_3CH$), 2.95 (A of ABX system, 1 H, J= 10.2 Hz and 13.6 Hz, $C\mathbf{H}_2Ph$), 3.16-3.23 (m, 3 H, $NC\mathbf{H}_2CH(OH)$ and $C\mathbf{H}_2Ph$), 3.56 (s, 3 H, $OC\mathbf{H}_3$), 4.00-4.07 (m, 1 H, $NCH_2C\mathbf{H}(OH)$), 4.19 (q, 1 H, J = 6.9 Hz, $CH_3C\mathbf{H}$), 4.43 (X of ABX system, 1 H, J = 5.2 Hz and 10.2 Hz, $C\mathbf{H}CH_2Ph$), 6.70 (d, 1 H, J = 7.2 Hz, $NCH_2CH(O\mathbf{H})$), 7.05-7.20 (m, 5 H, **Ph**), 8.06 (d, 2 H, J = 8.9 Hz, meta **H**'s to $-NO_2$), 8.41 (d, 2 H, J = 8.9 Hz, ortho **H**'s to $-NO_2$); ^{13}C NMR (67.9 MHz, DMSO-d_6): δ 18.01 ($CHCH_3$), 34.68 (CH_2Ph), 45.73 ($NCH_2CH(OH)$), 52.50 (OCH_3), 54.32 (NCH), 57.98 (CH_3CH), 78.34 ($NCH_2CH(OH)$), 125.45, 126.92, 128.83, 129.05, 129.61 (Aromatics), 138.16, 144.51, 150.58 (Quaternary Aromatics), 167.80, 170.46 (C=O); MS (CI) m/e (%) 478 (7.0) $[M+H]^+$, 460 (56.9), 446 (40.8), 291 (100); HRMS (EI) m/e Calcd for $[M-H_2O]^+$, $C_{21}H_{21}N_3O_7S$: 459.11001; Found: 459.11030.

Methyl (2S,3'S,6'S)-2-[3'-benzyl-6'-hydroxy-4'-(4-nitrobenzenesulfonyl)-2'-oxopiperazin-1'-yl]propanoate (91)

Prepared according to **GP 6** in 82 % yield. TLC ethyl acetate/hexane, 1/1, R_f 0.46; ^{1}H NMR (270 MHz, DMSO-d_6): δ 0.99 (d, 3 H, J = 6.9 Hz, $C\mathbf{H}_3CH$), 3.03 (A of ABX system, 1 H, J= 4.9 Hz and 14.1 Hz, $C\mathbf{H}_2Ph$), 3.17 (B of ABX system, 1 H, J = 9.4 Hz and 14.2 Hz, $C\mathbf{H}_2Ph$), 3.31-3.43 (m, 1 H, $NC\mathbf{H}_2CH(OH)$), 3.58 (s, 3 H, $OC\mathbf{H}_3$), 3.94-4.03 (m, 1 H, $NC\mathbf{H}_2CH(OH)$), 4.17 (q, 1 H, J = 6.9 Hz, $CH_3C\mathbf{H}$), 4.43 (X of ABX system, 1 H, J = 4.9 Hz and 9.4 Hz, $C\mathbf{H}CH_2Ph$), 4.65-4.74 (m, 1 H, $NCH_2C\mathbf{H}(OH)$), 6.73 (d, 1 H, J = 7.7 Hz, $NCH_2CH(O\mathbf{H})$), 7.11-7.26 (m, 5 H, **Ph**), 7.92 (d, 2 H, J = 8.6

Hz, meta **H**'s to -NO_2), 8.30 (d, 2 H, J = 8.6 Hz, ortho **H**'s to -NO_2); ^{13}C NMR (67.9 MHz, DMSO-d_6): δ 15.36 ($CHCH_3$), 37.84 (CH_2Ph), 47.45 ($NCH_2CH(OH)$), 52.30 (OCH_3), 56.27 (NCH), 59.51 (CH_3CH), 79.47 ($NCH_2CH(OH)$), 125.31, 127.29, 128.82, 129.04, 130.16 (Aromatics), 136.98, 145.98, 150.45 (Quaternary Aromatics), 166.29, 171.36 (C=O); MS (FAB, NBA) m/e (%) 478 (4.3) $[M + H]^+$.

Methyl (2S,3'S,6'S)-2-[6'-hydroxy-3'-methyl-2'-oxopiperazin-1'-yl]-3-phenylpropanoate (92)



92 : $R_1 = CH_3$, $R_2 = CH_2Ph$
93 : $R_1 = CH_2Ph$, $R_2 = CH_3$

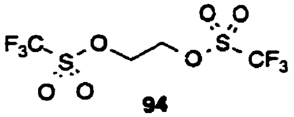
Prepared according to **GP 3** in 65 % yield. TLC benzene/ethyl acetate/methanol, 5/4/1, R_f 0.21; ^1H NMR (270 MHz, $CDCl_3$): δ 1.32 (d, 3 H, J = 6.9 Hz, $C\mathbf{H}_3CH$), 2.54 (A of ABX system, 1 H, J = 2.2 Hz and 12.9 Hz, $NC\mathbf{H}_2CH(OH)$), 2.83 (A of ABX system, 1 H, J = 2.0 Hz and 12.9 Hz, $NC\mathbf{H}_2CH(OH)$), 3.31 (A of ABX system, 1 H, J = 5.5 Hz and 13.9 Hz, $C\mathbf{H}_2Ph$), 3.36-3.47 (m, 2 H, $CH_3C\mathbf{H}$ and $C\mathbf{H}_2Ph$), 3.75 (s, 3 H, $OC\mathbf{H}_3$), 3.86-3.90 (m, 1 H, $NCH_2C\mathbf{H}(OH)$), 4.06 (X of ABX system, 1 H, J = 5.4 Hz and 10.4 Hz, $C\mathbf{H}CH_2Ph$), 7.08-7.34 (m, 5 H, **Ph**); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 18.10 ($CHCH_3$), 34.80 (CH_2Ph), 49.31 ($NCH_2CH(OH)$), 52.66 (OCH_3), 56.14 (CH_3CH), 62.59 (NCH), 81.25 ($NCH_2CH(OH)$), 126.83, 128.59, 129.27 (Aromatics), 138.09 (Quaternary Aromatic), 171.11, 171.48 (C=O); MS (FAB, NBA/NaCl) m/e (%) 315 (40.1) $[M+Na]^+$, HRMS (EI) m/e Calcd for $[M-H_2O]^+$, $C_{15}H_{18}N_2O_3$: 274.13173; Found: 274.13230.

Methyl (2S,3'S,6'S)-2-[3'-benzyl-6'-hydroxy-2'-oxopiperazin-1'-yl]propanoate (93)

Prepared according to **GP 3** in 69 % yield. TLC 100 % ethyl acetate R_f 0.18; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.53 (d, 3 H, J = 7.4 Hz, C**H**$_3$CH), 2.82 (A of ABX system, 1 H, J = 9.4 Hz and 13.6 Hz, C**H**$_2$Ph), 2.99-3.08 (m, 2 H, NC**H**$_2$CH(OH)), 3.38 (B of ABX system, 1 H, J = 3.5 Hz and 13.6 Hz, C**H**$_2$Ph), 3.67 (X of ABX system, 1 H, J = 3.5 Hz and 9.4 Hz, C**H**CH$_2$Ph), 3.72 (s, 3 H, OC**H**$_3$), 4.75-4.83 (m, 2 H, NCH$_2$C**H**(OH) and CH$_3$C**H**), 7.21-7.34 (m, 5 H, **Ph**); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 15.36 (CH**C**H$_3$), 39.00 (**C**H$_2$Ph), 49.92 (N**C**H$_2$CH(OH)), 52.43 (O**C**H$_3$), 53.06 (PhCH$_2$**C**H), 61.54 (N**C**H), 77.39 (NCH$_2$**C**H(OH)), 126.94, 128.72, 129.57 (Aromatics), 137.88 (Quaternary Aromatic), 169.82, 172.76 (**C**=O); MS (EI) m/e (%) 292 (0.8) [M]$^+$, 272 (20.4), 201 (48.0), 183 (100); HRMS (EI) m/e Calcd for $C_{15}H_{20}N_2O_4$: 292.14230; Found: 292.14452.

4.5 Experimental for Section 2.4

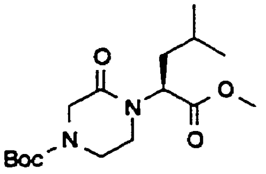
Ethylene glycol bis-triflate (94)



94

A solution of ethylene glycol (1.22 ml, 17.72 mmol), pyridine (2.87 ml, 35.44 ml) in dichloromethane (14 ml) was added dropwise over a period of 70 minutes to a solution of triflic anhydride (5.96 ml, 35.44 ml) in dichloromethane (36 ml) which was maintained at 0 °C. The reaction mixture was then filtered and washed with water (50 ml). The organic layer was separated and dried over anhydrous sodium sulfate. The dried solution was evaporated *in vacuo* to yield a brown liquid which was column chromatographed (dichloromethane) to gave a pale brown liquid (4.92 g, 86 %). TLC dichloromethane, R_f 0.72; ^{1}H NMR (270 MHz, $CDCl_3$): δ 4.73 (s, 4 H, 2 X CH_2); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 72.17 (2 X CH_2), 118.52 (q, J = 318.4 Hz, 2 X CF_3); MS (CI, NH_3) m/e (%) 344 (16.4) $[M + NH_4]^+$, 327 (0.9) $[MH]^+$,177 (100).

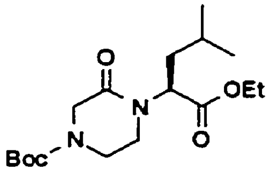
Methyl (2S)-2-[4'-(*tert*-butoxycarbonyl)-2'-oxopiperazin-1'-yl]-4-methylpentanoate (95)



95

To a solution of compound **98** (1.19 g, 3.92 mmol) in anhydrous diethyl ether (200 ml) was added an oily suspension of sodium hydride in mineral oil (60 % w/w, 0.19 g, 4.76 mmol) at 0 °C. The suspension was stirred for 20 minutes, and then a solution of ethylene glycol bis-triflate (1.55 g, 4.76 mmol) in anhydrous diethyl ether (15 ml) was slowly added over a period of one hour. The mixture was then stirred for one hour at 0 °C and then a second portion of an oily suspension of sodium hydride in mineral oil (60 % w/w, 0.27 g, 6.78 mmol) was added. The reaction was stirred for one hour at 0 °C and 15 hours at room temperature and then poured into a hydrochloric acid solution (1 N, 15 ml) containing some ice. The phases were separated, the aqueous phase was extracted with ether (100 ml) and the organic phases dried ($MgSO_4$) and concentrated *in vacuo*. The oily residue purified by silica gel chromatography (ethyl acetate/cyclohexane, 1/2 v/v) yielding an oil that crystallized from cyclohexane to give a pale yellow solid (0.71 g, 55 %). TLC ethyl acetate/cyclohexane, 2/1, R_f 0.33; mp 79-80 °C $[\alpha]_D^{20}$ -30.5° (c 0.500, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 0.80 (d, 3 H, J = 6.5 Hz, $(C\mathbf{H}_3)_2CH$), 0.82 (d, 3 H, J = 6.5 Hz, $(C\mathbf{H}_3)_2CH$), 1.35 (s, 9 H, $(C\mathbf{H}_3)_3C$), 1.36-1.39 (m, 1 H, $(CH_3)_2C\mathbf{H}$), 1.57-1.62 (m, 2 H, $CHC\mathbf{H}_2$), 3.15-3.19 (m, 1 H, $NC\mathbf{H}_2CH_2N$), 3.21-3.27 (m, 1 H, $NC\mathbf{H}_2CH_2N$), 3.36-3.41 (m, 1 H, $NC\mathbf{H}_2CH_2N$), 3.57 (s, 3 H, OCH_3), 3.61-3.65 (m, 1 H, $NC\mathbf{H}_2CH_2N$), 3.92 (A of AB, 1 H, J = 18.0 Hz, $NC\mathbf{H}_2C(O)$) 4.05 (B of AB, 1 H, J = 18.0 Hz, $NC\mathbf{H}_2C(O)$); 5.21 (dd, 1 H, J = 6.5 Hz and 9.5 Hz, $NC\mathbf{H}$); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 21.23 ($(CH_3)_2CH$), 23.11, 24.86 ($(CH_3)_2CH$), 28.23 ($(CH_3)_3C$), 36.76 ($CHCH_2$), 40.26, 42.43 (NCH_2CH_2N), 47.77 ($NCH_2C(O)$), 52.16 (OCH_3), 53.55 (NCH), 80.54 ($(CH_3)_3C$), 153.69 (NC(O)O), 166.32, 171.68 (2 X C=O); MS (EI) m/e (%) 328 (2.6) $[M]^+$, 297 (3.3), 272 (20.7), 213 (100); HRMS (EI) m/e Calcd for $C_{16}H_{28}N_2O_5$: 328.19981; Found: 328.19950.

Ethyl (2S)-2-[4'-(*tert*-butoxycarbonyl)-2'-oxopiperazin-1'-yl]-4-methylpentanoate (96)

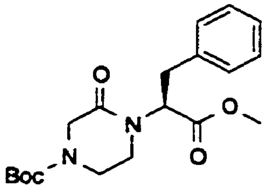


96

Obtained as a by-product from the preparation of compound **95**. TLC ethyl acetate/cyclohexane, 2/1, R_f 0.34; $[\alpha]_D^{20}$ -41.5° (c 0.100, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$): δ 0.90 (d, 3 H, J = 3.2 Hz, $(C\mathbf{H}_3)_2CH$), 0.92 (d, 3 H, J = 3.5 Hz, $(C\mathbf{H}_3)_2CH$), 1.24 (t, 3 H, J = 7.0 Hz, $C\mathbf{H}_3CH_2$), 1.44 (s, 9 H, $(C\mathbf{H}_3)_3C$), 1.45-1.50 (m, 1 H, $(CH_3)_2C\mathbf{H}$), 1.67-1.78 (m, 2 H, $CHC\mathbf{H}_2$), 3.15-3.19 (m, 1 H, $NC\mathbf{H}_2CH_2N$), 3.22-3.41

(m, 2 H, $NC\mathbf{H}_2CH_2N$), 3.45-3.55 (m, 1 H, $NC\mathbf{H}_2CH_2N$), 3.71-3.80 (m, 1 H, NCH_2CH_2N), 3.99-4.22 (m, 4 H, $CH_3C\mathbf{H}_2$ and $NC\mathbf{H}_2C(O)$), 5.31 (dd, 1 H, J = 5.9 Hz and 9.9 Hz, $NC\mathbf{H}$); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 14.24 (CH_3CH_2O), 21.40 ($(CH_3)_2CH$), 23.28, 25.08 ($(CH_3)_2CH$), 28.40 ($(CH_3)_3C$), 36.96 ($CHCH_2$), 40.52, 42.57 (NCH_2CH_2N), 48.01 ($NC\mathbf{H}_2C(O)$), 53.55 (NCH), 61.41 (CH_3CH_2O), 80.85 ($(CH_3)_3C$), 153.94 (NC(O)O), 166.54, 171.48 (2 X C=O); MS (EI) m/e (%) 342 (2.4) $[M]^+$, 297 (3.9), 286 (12.9), 213 (100); HRMS (EI) m/e Calcd for $C_{17}H_{30}N_2O_5$: 342.21546; Found: 342.21510.

Methyl (2S)-2-[4'-(*tert*-butoxycarbonyl)-2'-oxopiperazin-1'-yl]-3-phenylpropanoate (97)

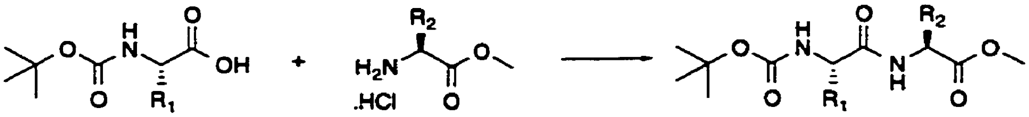


97

Similarly prepared as compound **95** in 39 % yield. TLC ethyl acetate/hexane, 1/1, R_f 0.38; ^1H NMR (270 MHz, $CDCl_3$): δ 1.39 (s, 9 H, $(C\mathbf{H}_3)_3C$), 3.05 (A of ABX system, 1 H, J = 11.1 Hz and 14.6 Hz, $CHC\mathbf{H}_2Ph$), 3.16-3.32 (m, 4 H, $NC\mathbf{H}_2C\mathbf{H}_2N$), 3.39 (B of ABX system, 1 H, J = 5.4 Hz and 14.6 Hz, $CHC\mathbf{H}_2Ph$), 3.71 (s, 3 H, $OC\mathbf{H}_3$), 3.94 (ABq, 2 H, J = 18.3 Hz), 5.17 (B of ABX system, 1 H, J = 5.4 Hz and 11.1 Hz, $CHCH_2Ph$), 7.13-7.28 (m, 5 H, **Ph**); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 28.34 ($(CH_3)_3C$), 34.36 (CH_2Ph), 40.11, 44.47 (NCH_2CH_2N), 47.77 ($NC\mathbf{H}_2C(O)$), 52.52 (OCH_3), 58.07 (NCH), 80.07 ($(CH_3)_3C$), 127.04, 128.73 (Aromatics), 136.54 (Quaternary Aromatic), 153.74, 166.29, 170.73 (2 X C=O); MS (EI) m/e (%) 362 (6.2) $[M]^+$, 247 (26.8), 143 (79.5), 100 (100); HRMS (EI) m/e Calcd for $C_{19}H_{26}N_2O_5$: 362.18416; Found: 362.18450.

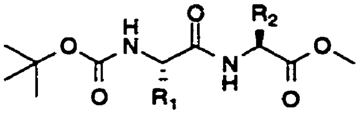
4.6 Experimental for Section 2.5

Preparation of BOC dipeptides (GP 9)



To a cooled solution (0 °C) of BOC amino acid (1.00 mmol), amino acid methyl ester hydrochloride (1.10 mmol), N-hydroxybenzotriazole, HOBt (1.10 mmol) and N-methyl morpholine, NMM (1.10 mmol) in dry dichloromethane (5 ml) was added 1-ethyl-3-(3′-dimethylaminopropyl)carbodiimide hydrochloride, EDAC.HCl (1.10 mmol). The reaction mixture was slowly warmed to room temperature and stirred under argon for 48 hours. The crude mixture was washed with water (10 ml), saturated citric acid solution (2 X 10 ml), water (10 ml), sodium bicarbonate solution (10 % w/v, 2 X 10 ml) and water (10 ml) respectively. The organic layer was then dried over anhydrous magnesium sulfate and the excess solvent removed under reduced pressure to afford the desired dipeptide which was used without any further purification.

N-(*tert*-Butoxycarbonyl)-L-glycyl-L-leucine methyl ester (98)



98 : $R_1 = H$, $R_2 = CH_2CH(CH_3)_2$
99 : $R_1 = H$, $R_2 = CH_2Ph$
100 : $R_1 = CH_2Ph$, $R_2 = CH_3$
101 : $R_1 = CH_3$, $R_2 = CH_2Ph$
102 : $R_1 = CH(CH_3)_2$, $R_2 = CH(CH_3)_2$
103 : $R_1 = CH(CH_3)_2$, $R_2 = CH_2CH(CH_3)_2$
104 : $R_1 = CH_2Ph$, $R_2 = CH(CH_3)_2$
105 : $R_1 = CH(CH_3)_2$, $R_2 = CH_2Ph$

Prepared according to **GP 9** in 92 % yield. TLC ethyl acetate/hexane, 1/1, R_f 0.31; ^{1}H NMR (270 MHz, DMSO-d_6): δ 0.82, 0.87 (2 d, 6 H, J = 6.4 Hz and 6.4 Hz), 1.37 (s, 9 H), 1.40-1.60 (m, 3 H), 3.55 (d, 2 H, J = 6.2 Hz), 3.61 (s, 3 H), 4.26-4.34 (m, 1 H), 6.90 (t, 1 H, J = 6.2 Hz), 8.10 (d, 1 H, J = 7.9 Hz); ^{13}C NMR (67.9 MHz, DMSO-d_6): δ 15.68, 21.84, 23.27, 24.66, 28.69, 40.51, 43.44, 50.64, 52.32, 64.46, 78.50, 156.26, 169.99, 173.45; MS (CI, NH_3) m/e (%) 303 (23.2) $[MH]^+$, 247 (100), 203 (86.7), 187 (21.0), 144 (22.0).

N-(*tert*-Butoxycarbonyl)-L-glycyl-L-phenylalanine methyl ester (99)

Prepared according to **GP 9** in 92 % yield. TLC ethyl acetate/hexane, 1/1, R_f 0.29; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.36 (s, 9 H), 2.92-3.08 (m, 2 H), 3.58 (s, 3 H), 3.65-3.68 (m, 2 H), 4.74-4.82 (m, 1 H), 5.60 (t, 1 H, J = 5.7 Hz), 7.03-7.24 (m, 5 H); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 28.33, 37.89, 44.09, 52.26, 53.30, 79.90, 127.06, 128.25, 128.57, 129.03, 129.26, 129.60, 135.96, 156.13, 169.64, 171.93; MS (CI, NH_3) m/e (%) 337 (4.9) $[MH]^+$, 281 (34.9), 237 (47.8), 162 (100).

N-(*tert*-Butoxycarbonyl)-L-phenylalanyl-L-alanine methyl ester (100)

Prepared according to **GP 9** in 91 % yield. TLC ethyl acetate/hexane, 1/2, R_f 0.28; mp 100-103 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.32 (d, 3 H, J = 7.2 Hz), 1.38 (s, 9 H), 3.10 (d, 2 H, J = 6.7 Hz), 3.68 (s, 3 H), 4.31-4.55 (m, 2 H), 5.06 (d, 1 H, J = 6.7 Hz), 6.54 (d, 1 H, J = 6.9 Hz), 7.16-7.30 (m, 5 H); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 18.38, 28.31, 38.44, 48.15, 52.47, 55.72, 80.26, 126.97, 128.67, 129.43, 136.61, 155.41, 170.88, 172.92; MS (FAB, NBA) m/e (%) 351 (65.3) $[MH]^+$.

N-(*tert*-Butoxycarbonyl)-L-alanyl-L-phenylalanine methyl ester (101)

Prepared according to **GP 9** in 93 % yield. TLC ethyl acetate/hexane, 1/1, R_f 0.44; mp 78-82 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.21 (d, 3 H, J = 6.9 Hz), 1.37 (s, 9 H), 2.98 (dd, 1 H, J = 6.4 Hz and 13.6Hz), 3.06 (dd, 1 H, J = 5.9 Hz and 13.6 Hz), 3.60 (s, 3 H), 4.12-4.18 (m, 1 H), 4.72-4.81 (m, 1 H), 5.34 (d, 1 H, J = 5.7 Hz), 6.88 (d, 1 H, J = 6.2 Hz), 7.04-7.24 (m, 5 H); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 18.42, 28.35, 37.92, 50.08, 52.26, 53.32, 79.86, 127.05, 128.53, 129.30, 135.98, 155.40, 171.85, 172.66; MS (FAB, NBA) m/e (%) 351 (72.5) $[MH]^+$.

N-(*tert*-Butoxycarbonyl)-L-valyl-L-valine methyl ester (102)

Prepared according to **GP 9** in 95 % yield. TLC ethyl acetate/hexane, 1/1, R_f 0.38; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.87-0.95 (m, 12 H), 1.41 (s, 9 H), 2.03-2.21 (m, 2 H), 3.71 (s, 3 H), 3.90 (dd, 1 H, J = 6.7 Hz and 8.4 Hz), 4.51 (dd, 1 H, J = 4.9 Hz and 8.6 Hz), 5.08 (d, 1 H, J = 8.6 Hz), 6.43 (d, 1 H, J = 8.4 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 17.83, 17.96, 18.96, 19.31, 28.33, 30.70, 31.24, 52.13, 57.13, 60.16, 79.87, 155.88, 171.72, 172.21.

N-(*tert*-Butoxycarbonyl)-L-valyl-L-leucine methyl ester (103)

Prepared according to **GP 9** in 92 % yield. TLC ethyl acetate/hexane, 1/1, R_f 0.70; mp 127-130 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.86-0.92 (m, 12 H), 1.39 (s, 9 H), 1.46-1.62 (m, 2 H), 2.00-2.10 (m, 1 H), 3.67 (s, 3 H), 3.86-3.93 (m, 1 H), 4.51-4.60 (m, 1 H), 5.13 (d, 1 H, J = 8.9 Hz), 6.47 (d, 1 H, J = 7.9 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 17.96, 19.21, 21.87, 22.81, 24.79, 28.32, 30.92, 41.40, 50.70, 52.22, 59.90, 79.79, 155.88, 171.60, 173.22. MS (CI, NH_3) m/e (%) 345 (36.8) $[MH]^+$, 289 (100), 245 (99.1), 172 (41.8).

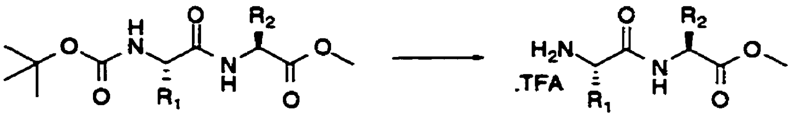
N-(*tert*-Butoxycarbonyl)-L-phenylalanyl-L-valine methyl ester (104)

Prepared according to **GP 9** in 93 % yield. TLC ethyl acetate/hexane, 1/2, R_f 0.48; mp 117-120 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.80, 0.84 (2 d, 6 H, J = 6.9 Hz and 6.9 Hz), 1.38 (s, 9 H), 1.98-2.12 (m, 1 H), 3.04 (d, 2 H, J = 6.9 Hz), 3.65 (s, 3 H), 4.29-4.36 (m, 1 H), 4.44 (dd, 1 H, J = 5.2 Hz and 8.6 Hz), 5.09 (d, 1 H, J = 7.9 Hz), 6.45 (d, 1 H, J = 8.4 Hz), 7.17-7.29 (m, 5 H); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 17.83, 18.88, 28.30, 31.31, 38.10, 52.10, 55.89, 57.30, 80.24, 126.92, 128.67, 129.38, 136.72, 155.48, 171.27, 171.84; MS (CI, NH_3) m/e (%) 379 (20.0) $[MH]^+$, 323 (53.7), 279 (75.4).

N-(*tert*-Butoxycarbonyl)-L-valyl-L-phenylalanine methyl ester (105)

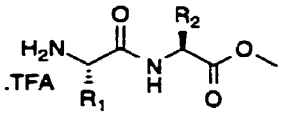
Prepared according to **GP 9** in 92 % yield. TLC ethyl acetate/hexane, 1/1, R_f 0.56; mp.109-111 °C; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.84, 0.90 (2 d, 6 H, J = 6.4 Hz and 6.9 Hz), 1.42 (s, 9 H), 2.00-2.15 (m, 1 H), 3.09 (dd, 2 H, J = 3.2 Hz and 5.8 Hz), 3.69 (s, 3 H), 3.88 (dd, 1 H, J = 6.2 Hz and 8.3 Hz), 4.85 (dd, 1 H, J = 5.9 Hz and 13.8 Hz), 5.00 (d, 1 H, J = 7.9 Hz), 6.31 (d, 1 H, J = 6.7 Hz), 7.11-7.29 (m, 5 H); ^{13}C NMR ($CDCl_3$, 67.9 MHz) 17.72, 19.22, 28.36, 30.92, 38.06, 52.35, 53.16, 59.97, 79.94, 127.24, 128.68, 129.29, 135.74, 155.74, 171.24, 171.73; MS (CI, NH_3) m/e (%) 379 (10.4) $[MH]^+$, 323 (37.7), 279 (100).

Preparation of deprotected dipeptides (GP 9)



To the desired dipeptide (1.00 mmol) was added a solution mixture of TFA/CH_2Cl_2 (1/1 v/v, 5 ml) and the reaction mixture stirred at room temperature for 30 minutes. The excess solvent was evaporated *in vacuo* to yield the desired trifluoroacetate salt.

L-Glycyl-L-leucine methyl ester trifluoroacetate (106)



106 : R_1 = H, R_2 = $CH_2CH(CH_3)_2$
107 : R_1 = H, R_2 = CH_2Ph
108 : R_1 = CH_2Ph, R_2 = CH_3
109 : R_1 = CH_3, R_2 = CH_2Ph
110 : R_1 = $CH(CH_3)_2$, R_2 = $CH(CH_3)_2$
111 : R_1 = $CH(CH_3)_2$, R_2 = $CH_2CH(CH_3)_2$
112 : R_1 = CH_2Ph, R_2 = $CH(CH_3)_2$
113 : R_1 = $CH(CH_3)_2$, R_2 = CH_2Ph

Prepared according to **GP 9** in quantitative yield. Mp 123-126 °C; ^{1}H NMR (270 MHz, DMSO-d_6): δ 0.84, 0.89 (2 d, 6 H, J = 6.4 Hz and 6.2 Hz), 1.44-1.70 (m, 3 H), 3.54-3.69 (m with overlapping s, 5 H), 4.30-4.39 (m, 1 H), 8.13 (s br, 3 H), 8.83 (d, 1 H, J = 7.7 Hz); ^{13}C NMR (67.9 MHz, DMSO-d_6): δ 21.75, 23.17, 24.65, 40.49, 50.95, 52.49, 117.44 (q, J = 299.2 Hz), 159.01 (q, J = 33.1 Hz), 166.71, 173.01.

L-Glycyl-L-phenylalanine methyl ester trifluoroacetate (107)

Prepared according to **GP 9** in quantitative yield. ^{1}H NMR (270 MHz, CDCl$_3$): δ 2.88-3.07 (m, 2 H), 3.54 (s, 3 H), 3.58-3.81 (m, 2 H), 4.69-4.77 (m, 1 H), 7.05-7.21 (m, 5 H), 7.86 (d, 1 H, J = 6.9 Hz), 8.04 (s br, 3 H); ^{13}C NMR (67.9 MHz, CDCl$_3$): δ 37.57, 40.87, 52.47, 54.15, 116.21 (q, J = 295.1 Hz), 127.14, 128.59, 129.20, 160.11 (q, J = 38.2 Hz), 166.38, 172.19.

L-Phenylalanyl-L-alanine methyl ester trifluoroacetate (108)

Prepared according to **GP 9** in quantitative yield. ^{1}H NMR (270 MHz, DMSO-d_6): δ 1.30 (d, 3 H, J = 7.2 Hz), 2.95 (dd, 1 H, J = 7.4 Hz and 13.9 Hz), 3.11 (dd, 1 H. J = 5.9 Hz and 13.9 Hz), 3.63 (s, 3 H), 4.02-4.08 (m, 1 H), 4.30-4.40 (m, 1 H), 7.22-7.36 (m, 5 H), 8.27 (s br, 3 H), 9.00 (d, 1 H, J = 6.9 Hz); ^{13}C NMR (67.9 MHz, DMSO-d_6): δ 17.45, 37.37, 48.26, 52.59, 53.79, 116.60 (q, J = 290.2 Hz), 127.66, 129.02, 130.11, 135.38, 161.17 (q, J = 41.2 Hz), 168.44, 172.83.

L-Alanyl-L-phenylalanine methyl ester trifluoroacetate (109)

Prepared according to **GP 9** in quantitative yield. Mp 168-170 °C; ^{1}H NMR (270 MHz, DMSO-d_6): δ 1.33 (d, 3 H, J = 6.9 Hz), 2.95 (dd, 1 H, J = 9.2 Hz and 13.9 Hz), 3.10 (dd, 1 H, J = 5.2 Hz and 13.9 Hz), 3.61 (s, 3 H), 3.78-3.89 (m, 1 H), 4.48-4.56 (m, 1 H), 7.20-7.33 (m, 5 H), 8.19 (s br, 3 H), 8.90 (d, 1 H, J = 7.4 Hz); ^{13}C NMR (67.9 MHz, DMSO-d_6): δ 17.61, 36.80, 48.46, 52.57, 54.50, 116.55 (q, J = 294.3 Hz), 127.24, 128.90, 129.60, 137.50, 161.44 (q, J = 39.6 Hz), 170.40, 171.97.

L-Valyl-L-valine methyl ester trifluoroacetate (110)

Prepared according to **GP 9** in quantitative yield. ^{1}H NMR (270 MHz, CDCl$_3$): δ 0.87-1.05 (m, 12 H), 2.08-2.15 (m, 2 H), 3.68 (s, 3 H), 4.11-4.23 (m, 2 H), 7.82 (d, 1 H, J = 5.2 Hz), 8.21 (s br, 3 H); ^{13}C NMR (67.9 MHz, CDCl$_3$): δ 17.82, 18.61, 30.19, 30.47, 52.04, 58.64, 58.82, 116.21 (q, J = 289.9 Hz), 161.52 (q, J = 40.7 Hz), 169.28, 171.54.

L-Valyl-L-leucine methyl ester trifluoroacetate (111)

Prepared according to **GP 9** in quantitative yield. Mp 151-152 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.83-0.87 (m, 6 H), 1.00, 1.04 (2 d, 6 H, J = 6.7 Hz and 6.9 Hz), 1.52-1.64 (m, 3 H), 2.10-2.22 (m, 1 H), 3.69 (s, 3 H), 4.02-4.05 (m, 1 H), 4.33-4.41 (m, 1 H), 7.63 (d, 1 H, J = 6.7 Hz), 8.06 (s br, 3 H); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 17.71, 17.74, 21.50, 22.36, 24.65, 30.48, 40.17, 51.91, 52.33, 58.76, 116.88 (q, J = 286.5 Hz), 161.02 (q, J = 39.2 Hz), 168.77, 172.59.

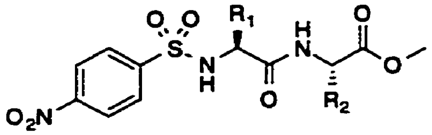
L-Phenylalanyl-L-valine methyl ester trifluoroacetate (112)

Prepared according to **GP 9** in quantitative yield. Mp 165-168 °C; ^{1}H NMR (270 MHz, DMSO-d_6): δ 0.87, 0.90 (2 d, 6 H, J = 5.4 Hz and 5.4 Hz), 1.97-2.10 (m, 1 H), 2.97 (dd, 1 H, J = 7.4 Hz and 13.9 Hz), 3.09 (dd, 1 H, J = 6.2 Hz and 13.9 Hz), 3.62 (s, 3 H), 4.16-4.22 (m, 2 H), 7.17-7.34 (m, 5 H), 8.33 (s br, 3 H), 8.78 (d, 1 H, J = 7.9 Hz); ^{13}C NMR (67.9 MHz, DMSO-d_6): δ 18.71, 19.34, 30.57, 37.48, 52.24, 53.61, 58.21, 116.52 (q, J = 287.6 Hz), 127.61, 128.96, 130.07, 135.34, 161.59 (q, J = 40.3 Hz), 168.88, 171.72.

L-Valyl-L-phenylalanine methyl ester trifluoroacetate (113)

Prepared according to **GP 9** in quantitative yield. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88, 0.93 (2 d, 6 H, J = 7.0 Hz and J = 7.0 Hz), 2.10-2.24 (m, 1 H), 2.95 (dd, 1 H, J = 8.5 Hz and12.0 Hz), 3.05 (dd, 1 H, J = 5.5 Hz and 14.0 Hz), 3.58 (s, 3 H), 3.60-3.62 (s br, 1 H), 4.54 (dd, 1 H J = 7.0 Hz and 14.1 Hz), 7.19-7.29 (m, 5 H), 8.01-8.10 (s br, 3 H), 8.85 (d, 1 H, J = 7.5 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 18.63, 19.24, 30.67, 37.55, 52.21, 54.01, 59.00, 116.75 (q, J = 289.2 Hz), 127.66, 129.01, 130.12, 135.35, 161.88 (q, J = 41.2 Hz), 169.88, 172.61.

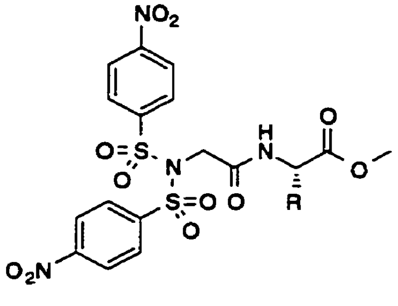
N-4-Nitrobenzenesulfonyl-L-glycyl-L-leucine methyl ester (114)



114 : R_1 = H, R_2 = $CH_2CH(CH_3)_2$
115 : R_1 = H, R_2 = CH_2Ph
116 : R_1 = CH_2Ph, R_2 = CH_3
117 : R_1 = CH_3, R_2 = CH_2Ph
118 : R_1 = $CH(CH_3)_2$, R_2 = $CH(CH_3)_2$
119 : R_1 = $CH(CH_3)_2$, R_2 = $CH_2CH(CH_3)_2$
120 : R_1 = CH_2Ph, R_2 = $CH(CH_3)_2$

Prepared according to **GP 1** in 83% yield. TLC ethyl acetate/hexane, 1/1, R_f 0.34; mp 115-118 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.85, 0.87 (2 d, 6 H, J = 5.7 Hz and J = 5.4 Hz), 1.47-1.66 (m, 1 H), 3.63-3.79 (m with overlapping s, 5 H), 4.47-4.56 (m, 1 H), 6.25 (t, 1 H, J = 5.7 Hz), 6.65 (d, 1 H, J = 8.2 Hz), 8.04 (d, 2 H, J = 8.9 Hz), 8.32 (d, 2 H, J = 8.9 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 21.74, 22.79, 24.86, 41.17, 45.51, 51.01, 52.65, 124.53, 128.59, 145.00, 150.23, 167.57, 173.41; MS (FAB, NBA) m/e (%) 388 (100) $[MH]^+$.

N,N-Bis-4-nitrobenzenesulfonyl-L-glycyl-L-leucine methyl ester (121)



121 : R = $CH_2CH(CH_3)_2$
122 : R = CH_2Ph

Obtained as a by-product from the preparation of compound **114** in 10% yield. TLC ethyl acetate/hexane, 1/1, R_f0.71; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.86, 0.88 (2 d, 6 H, J = 5.9 Hz and J = 5.9 Hz), 1.39-1.65 (m, 1 H), 3.71 (s, 3 H), 4.46-4.56 (m with overlapping s, 3 H), 6.26 (d, 1 H, J = 8.2 Hz), 8.26 (d, 4 H, J = 9.2 Hz), 8.38 (d, 4 H, J = 9.2 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 21.91, 22.77, 24.84, 41.60, 50.53, 51.14, 52.60, 124.33, 130.41, 144.09, 151.05, 165.21, 173.21; MS (FAB, NBA) m/e (%) 573 (7.1) $[MH]^+$.

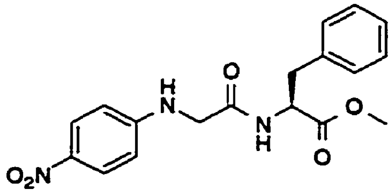
N-4-Nitrobenzenesulfonyl-L-glycyl-L-phenylalanine methyl ester (115)

Prepared according to **GP 1** in 75% yield. TLC ethyl acetate/hexane, 1/1, R_f 0.25; ^{1}H NMR (270 MHz, $CDCl_3$): δ 2.97-3.11 (m, 2 H), 3.58-3.72 (m with overlapping s, 5 H), 4.71-4.78 (m, 1 H), 6.67 (d, 1 H, J = 7.9 Hz), 7.03-7.29 (m, 5 H), 7.98 (d, 2 H, J = 9.2 Hz), 8.27 (d, 2 H, J = 9.2 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 37.71, 45.45, 52.69, 53.44, 124.52, 127.44, 128.50, 128.82, 129.24, 135.40, 145.10, 150.25, 167.31, 171.84; MS (CI, NH_3) m/e (%) 422 (72.5) $[MH]^+$, 392 (15.5), 235 (16.3), 162 (100).

N,N-Bis-4-nitrobenzenesulfonyl-L-glycyl-L-phenylalanine methyl ester (122)

Obtained as a by-product from the preparation of compound **115** in 8% yield. TLC ethyl acetate/hexane, 1/1, R_f 0.64; ^{1}H NMR (270 MHz, $CDCl_3$): δ 3.08-3.14 (m, 2 H), 3.74 (s, 3 H), 4.39 (ABq, 2 H, J = 17.8 Hz), 4.76-4.82 (m, 1 H), 6.25 (d, 1 H, J = 7.7 Hz), 7.04-7.29 (m, 5 H), 8.22 (d, 4 H, J = 8.9 Hz), 8.34 (d, 4 H, J = 8.9 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 37.61, 50.41, 52.68, 53.47, 124.33, 127.43, 128.81, 129.44, 130.39, 135.26, 143.89, 151.04, 165.09, 171.50; MS (FAB, NBA/NaCl) m/e (%) 629 (1.2) [M + Na], 607 (8.4) $[M + H]^+$.

N-4-Nitrophenyl-L-glycyl-L-phenylalanine methyl ester (123)



123

Obtained as a by-product from the preparation of compound **115** in 10% yield. TLC ethyl acetate/hexane, 1/1, R_f0.42; ^{1}H NMR (270 MHz, DMSO-d_6): δ 2.90 (dd, 1 H, J = 8.7 Hz and 13.6 Hz), 3.03 (dd, 1 H, J = 5.9 Hz and 13.8 Hz), 3.60 (s, 3 H), .3.71-3.88 (m, 2 H), 4.45-4.53 (m, 1 H), 7.20-7.28 (m, 5 H), 8.05 (d, 2 H, J = 8.4 Hz), 8.39 (d, 2 H, J = 8.4 Hz), 8.56 (d, 1 H, J = 7.7 Hz), 9.56 (t, 1 H , J = 5.7 Hz); ^{13}C NMR (67.9 MHz, DMSO-d_6): δ 37.36, 42.02, 52.39, 54.23, 124.87, 127.78, 128.78, 129.59, 137.44, 149.70, 150.04, 167.64, 172.23; MS (CI, NH_3) m/e (%) 371 (0.4) $[M + NH_4]^+$, 333 (43.3), 273 (15.7), 162 (100).

N-4-Nitrobenzenesulfonyl-L-phenylalanyl-L-alanine methyl ester (116)

Prepared according to **GP 1** in 80 % yield. TLC ethyl acetate/hexane, 1/1, R_f 0.32; ^{1}H NMR (270 MHz, DMSO-d_6): δ 1.21 (d, 3 H, J = 7.4 Hz), 2.64 (dd, 1 H, J = 10.6 Hz and 13.8 Hz), 2.88 (dd, 1 H, J = 3.9 Hz and 13.8 Hz), 3.59 (s, 3 H), 4.00-4.12 (m, 2 H), 7.08-7.19 (m, 5 H), 7.72 (d, 2 H, J = 8.9 Hz), 8.21 (d, 2 H, J = 8.9 Hz), 8.56 (d, 1 H, J = 6.9 Hz), 8.65 (s br, 1 H); ^{13}C NMR (67.9 MHz, DMSO-d_6): δ 17.30, 38.66, 41.01, 48.00, 52.44, 58.06, 124.53, 126.77, 128.24, 129.79, 137.55, 147.20, 149.64, 170.68, 173.16; MS (FAB, NBA) m/e (%) 436 (81.3) $[M + H]^+$.

N-4-Nitrobenzenesulfonyl-L-alanyl-L-phenylalanine methyl ester (117)

Prepared according to **GP 1** in 82 % yield. TLC ethyl acetate/hexane, 1/1, R_f 0.32; ^{1}H NMR (270 MHz, DMSO-d_6): δ 1.00 (d, 3 H, J = 6.9 Hz), 2.81 (dd, 1 H, J = 8.6 Hz and 13.6 Hz), 2.93 (dd, 1 H, J = 5.7 Hz and 13.6 Hz), 3.54 (s, 3 H), 3.88-4.01 (m, 1 H), 4.13-4.21 (m, 1 H), 7.15-7.33 (m, 5 H), 7.86 (d, 2 H, J = 9.2 Hz), 8.22 (d, 2 H, J = 9.2 Hz), 8.39 (d, 1 H, J = 7.7 Hz), 8.45 (d, 1 H, J = 6.4 Hz); ^{13}C NMR (67.9 MHz, DMSO-d_6): δ 19.66, 37.03, 52.11, 52.39, 54.19, 124.69, 127.20, 128.53, 128.81, 129.61, 137.54, 147.22, 149.86, 171.50, 172.08; MS (FAB, NBA) m/e (%) 436 (37.9) $[MH]^+$.

N-4-Nitrobenzenesulfonyl-L-valyl-L-valine methyl ester (118)

Prepared according to **GP 1** in 83 % yield. TLC ethyl acetate/hexane, 1/1, R_f 0.56; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.63, 0.71, 0.84, 0.95 (4 d, 12 H, J = 6.7 Hz, 6.7 Hz, 6.7 Hz and 6.7 Hz), 1.87-2.08 (m, 2 H), 2.67 (dd, 1 H, J = 5.2 Hz and 8.9 Hz), 3.70 (s, 3 H), 4.32 (dd, 1 H, J = 4.7 Hz and 8.7 Hz), 5.91 (d, 1 H, J = 8.9 Hz), 6.22 (d, 1 H, J = 8.4 Hz), 8.04 (d, 2 H, J = 8.6 Hz), 8.30 (d, 2 H, J = 8.6 Hz); ^{13}C NMR (67.9 MHz,

$CDCl_3$): δ 17.30, 17.63, 18.61, 19.10, 31.13, 32.08, 52.44, 57.36, 62.11, 124.31, 128.61, 145.91, 150.11, 169.92, 171.94; MS (CI, NH_3) m/e (%) 416 (100) $[MH]^+$, 356 (31.8), 257 (81.9).

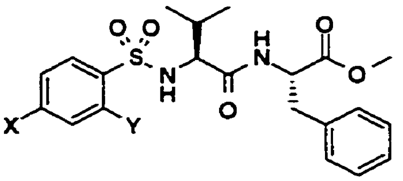
N-4-Nitrobenzenesulfonyl-L-valyl-L-leucine methyl ester (119)

Prepared according to **GP 1** in 85 % yield. TLC ethyl acetate/hexane, 1/2, R_f 0.32; mp 47-49 °C; ^1H NMR (270 MHz, $CDCl_3$): δ 0.71, 0.78, 0.84, 0.97 (4 d, 12 H, J = 6.4 Hz, 6.4 Hz, 6.7 Hz and 6.7 Hz), 1.11-1.51 (m, 3 H), 1.97-2.09 (m, 1 H), 3.64 (dd, 1 H, J = 3.9 Hz and 8.9 Hz), 3.68 (s, 3 H), 4.33-4.43 (m, 1 H), 5.84 (d, 1 H, J = 8.9 Hz), 6.05 (d, 1 H, J = 8.2 Hz), 8.03 (d, 2 H, J = 8.9 Hz), 8.29 (d, 2 H, J = 8.9 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 17.14, 19.22, 21.63, 22.61, 24.79, 32.17, 41.46, 50.87, 52.53, 61.91, 124.24, 128.62, 145.88, 150.07, 169.70, 172.90; MS (CI, NH_3) m/e (%) 447 (0.5) $[M + NH_4]^+$, 430 (43.8) $[MH]^+$, 370 (24.5), 257 (100).

N-4-Nitrobenzenesulfonyl-L-phenylalanyl-L-valine methyl ester (120)

Prepared according to **GP 1** in 81 % yield. TLC ethyl acetate/hexane, 1/2, R_f 0.20; ^1H NMR (270 MHz, $CDCl_3$): δ 0.80, 0.83 (2 d, 6 H, J =3.2 Hz and 3.2 Hz), 1.99-2.12 (m, 1 H), 2.92 (dd, 1 H, J = 8.6 Hz and 14.1 Hz), 3.05 (dd, 1 H, J = 5.4 Hz and 14.1 Hz), 3.71 (s, 3 H), 3.91-4.10 (m, 1 H), 4.38-4.47 (m, 1 H), 6.05 (s br, 1 H), 6.58 (d, 1 H, J = 8.2 Hz), 6.99-7.19 (m, 5 H), 7.76 (d, 2 H, J = 8.9 Hz), 8.12 (d, 2 H, J = 8.9 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 17.76, 18.80, 31.35, 38.93, 52.39, 57.59, 58.64, 124.26, 127.34, 128.18, 128.87, 129.31, 135.48, 145.27, 149.94, 170.14, 171.71; MS (CI, NH_3) m/e (%) 464 (100) $[MH]^+$, 434 (35.5), 404 (15.5), 261 (37.6).

N-4-Nitrobenzenesulfonyl-L-valyl-L-phenylalanine methyl ester (124)



124 : X = NO_2, Y = H
125 : X = H, Y = NO_2
126 : X = Y = NO_2

Prepared according to **GP 1** in 86 % yield. TLC ethyl acetate/hexane, 1/1, R_f 0.65; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.77, 0.88 (2 d, 6 H, J = 6.7 Hz and 6.7 Hz), 1.92-2.08 (m, 1 H), 2.92 (d, 2 H, J = 5.9 Hz), 3.63-3.69 (m with overlapping s, 4 H), 4.59-4.68 (m, 1 H), 6.00 (d, 1 H, J = 8.9 Hz), 6.31 (d, 1 H, J = 7.6 Hz), 6.92-7.25 (m, 5 H), 7.95 (d, 2 H, J = 8.9 Hz), 8.20 (d, 2 H, J = 8.9 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 17.24, 19.16, 31.91, 37.79, 52.54, 53.52, 62.17, 124.27, 127.44, 128.44, 128.79, 129.06, 135.39, 145.98, 150.05, 169.84, 171.54; MS (CI, NH_3) m/e (%) 464 (10.3) $[MH]^+$, 375 (67.8), 162 (100).

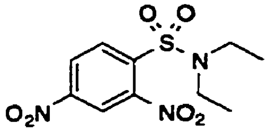
N-2-Nitrobenzenesulfonyl-L-valyl-L-phenylalanine methyl ester (125)

Prepared according to **GP 1** in 75 % yield. TLC ethyl acetate/hexane, 1/1, R_f 0.42; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.74, 0.81 (2 d, 6 H, J = 6.9 Hz and 6.9 Hz), 2.06-2.18 (m, 1 H), 2.86-3.01 (m, 2 H), 3.65 (s, 3 H), 3.78 (dd, 1 H, J = 4.7 Hz and 7.9 Hz), 4.63-4.71 (m, 1 H), 6.02 (d, 1 H, J = 7.9 Hz), 6.50 (d, 1 H, J = 7.7 Hz), 7.01-7.29 (m, 5 H), 7.61-7.72 (m, 2 H), 7.85-7.88 (m, 1 H), 8.00-8.03 (m, 1 H); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 16.95, 19.17, 31.25, 37.95, 52.44, 53.40, 63.10, 125.68, 127.31, 128.76, 129.16, 130.59, 132.92, 133.77, 133.90, 135.71, 147.81, 169.66, 171.41; MS (CI, NH_3) m/e (%) 464 (100) $[MH]^+$, 434 (55.2), 257 (64.0), 162 (76.8).

N-2,4-Dinitrobenzenesulfonyl-L-valyl-L-phenylalanine methyl ester (126)

Prepared according to **GP 1** in 63 % yield. TLC ethyl acetate/hexane, 1/1, R_f 0.56; mp 116-117 °C; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.80, 0.94 (2 d, 6 H, J = 6.9 Hz and 6.9 Hz), 2.08-2.20 (m, 1 H), 2.87 (dd, 1 H, J = 7.4 Hz and 13.8 Hz), 3.01 (dd, 1 H, J = 5.2 Hz and 13.8 Hz), 3.65 (s, 3 H), 3.88 (d, 1 H, J = 4.7 Hz), 456-4.64 (m, 1 H), 6.10 (s br, 1 H), 6.24 (d, 1 H, J = 7.9 Hz), 7.00-7.30 (m, 5 H), 8.05 (d, 1 H, J = 8.6 Hz), 8.33 (dd, 1 H, J = 2.2 Hz and 8.6 Hz), 8.62 (d, 1 H, J = 2.2 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 17.12, 19.35, 30.89, 37.56, 52.66, 52.98, 63.96, 118.86, 124.21, 127.45, 128.52, 128.89, 130.55, 131.82, 137.45, 147.86, 169.68, 171.46; MS (EI) m/e (%) 508 (1.0) $[M]^+$, 302 (31.7), 238 (36.9), 162 (100);

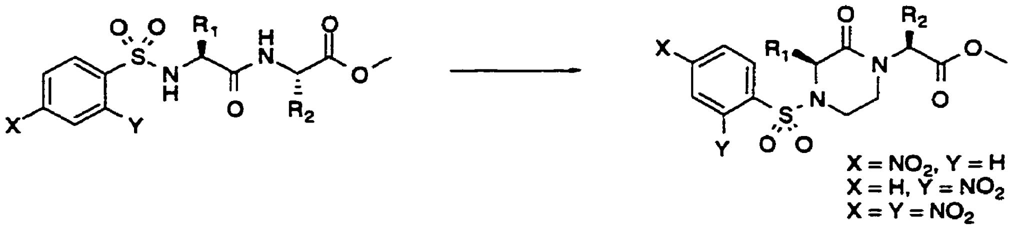
N,N-Diethyl-N-2,4-dinitrobenzenesulfonamide (127)



127

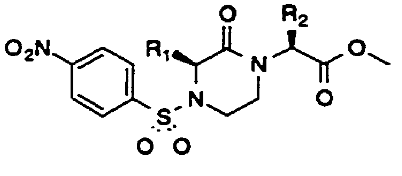
Obtained as a by-product from the preparation of compound **126**. TLC ethyl acetate/hexane, 1/1, R_f 0.69; ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.17 (t, 6 H, J = 7.2 Hz), 3.39 (q, 4 H, J = 7.2 Hz), 8.21 (d, 1 H, J = 8.9 Hz), 8.43 (d, 1 H, J = 2.2 Hz), 8.46 (dd, 1 H, J = 2.2 Hz and 8.9 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 13.90, 41.92, 119.74, 126.06, 132.38, 139.56, 148.12, 149.63; MS (FAB, NBA) m/e (%) 304 (16.5) $[M + H]^+$.

Preparation of cyclized sulfonamide dipeptides (GP 11)



To a solution of 4-nitrobenzenesulfonamide dipeptide (1.00 mmol) in DMF (75ml) was added K_2CO_3 (10.00 mmol.) and the reaction mixture was allowed to stir at 60 °C for 30 minutes; 1,2-dibromoethane (10.00 mmol) was added to the above solution which was left to stir at 60 °C for 24 hours. The DMF was removed *in vacuo* and the residue dissolved in ethyl acetate (30 ml). This organic layer was then washed with hydrochloric acid (10 % v/v, 2 X 30 ml) and brine (30 ml) respectively. The organic layer was then dried over anhydrous sodium sulfate and the excess solvent removed under reduced pressure to yield the desired compound. For the formation of the 2-nitrobenzenesulfonamide cyclized dipeptide a longer reaction time was required (36 hours). For the 2,4-dinitrobenzenesulfonamide cyclized dipeptide, the reaction time was 2 hours and the temperature was maintained at 35 °C.

Methyl (2S)-2-[4'-(4-nitrobenzenesulfonyl)-2'-oxopiperazin-1'-yl]-4-methylpentanoate (128)



128 : $R_1 = H, R_2 = CH_2CH(CH_3)_2$
129 : $R_1 = H, R_2 = CH_2Ph$
130 : $R_1 = CH_2Ph, R_2 = CH_3$
131 : $R_1 = CH_3, R_2 = CH_2Ph$
132 : $R_1 = CH(CH_3)_2, R_2 = CH(CH_3)_2$
133 : $R_1 = CH(CH_3)_2, R_2 = CH_2CH(CH_3)_2$
134 : $R_1 = CH_2Ph, R_2 = CH(CH_3)_2$

Prepared according to **GP 11** in 88 % yield. TLC ethyl acetate/hexane, 1/1, R_f 0.40; ^{1}H NMR (270 MHz, $CDCl_3$); δ 0.85, 0.87 (2 d overlapping, 6 H, J = 6.9 Hz and 7.4 Hz), 1.29-1.41 (m, 1 H), 1.60-1.68 (m, 2 H), 3.15-3.24 (m, 1 H), 3.31-3.47 (m, 2 H), 3.50-3.59 (m, 1 H), 3.63 (s, 3 H), 3.85 (ABq, 2 H, J = 16.6 Hz), 5.21 (dd, 1 H, J = 5.9 Hz and 10.4 Hz), 7.96 (d, 2 H, J = 8.9 Hz), 8.38 (d, 2 H, J = 8.9 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 21.20, 23.19, 24.96, 36.72, 42.59, 43.36, 48.55, 52.45, 53.71, 124.75, 129.03, 141.39, 150.63, 163.97, 171.58; MS (EI) m/e (%) 413 (1.5) $[M]^+$, 354 (68.7), 326 (100), 301 (30.2).

Methyl (2S)-2-[4'-(4-nitrobenzenesulfonyl)-2'-oxopiperazin-1'-yl]-3-phenylpropanoate (129)

Prepared according to **GP 11** in 89 % yield. TLC ethyl acetate/hexane, 1/1, R_f 0.35; ^{1}H NMR (270 MHz, $CDCl_3$); δ 2.95 (dd, 1 H, J = 11.1 Hz and 14.6 Hz), 3.01-3.36 (m, 5 H), 3.65 (s, 3 H), 3.67 (ABq, 2 H, J = 16.8 Hz), 5.10 (dd, 1 H, J = 5.2 Hz and 11.1 Hz), 7.07-7.24 (m, 5 H), 7.85 (d, 2 H, J = 8.4 Hz), 8.29 (d, 2 H, J = 8.4 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 34.17, 43.09, 44.44, 48.30, 52.62, 58.05, 124.72, 127.15, 128.28, 128.59, 128.78, 128.92, 129.10, 136.26, 141.37, 150.54, 163.85, 170.34; MS

(EI) m/e (%) 447 (6.5) [M]$^+$, 388 (15.7), 328 (63.4), 162 (100); HRMS (EI) m/e Calcd for $C_{20}H_{21}N_3O_7S$: 447.11001; Found: 447.10970.

Methyl (2S,3'S)-2-[3'-benzyl-4'-(4-nitrobenzenesulfonyl)-2'-oxopiperazin-1'-yl]propanoate (130)

Prepared according to **GP 11** in 95 % yield. TLC ethyl acetate/hexane, 1/1, R_f 0.33; ^{1}H NMR (270 MHz, $CDCl_3$); δ 1.20 (d, 3 H, J = 7.4 Hz), 2.59-2.65 (m, 1 H), 3.05-3.44 (m, 5 H), 3.60 (s, 3 H), 4.52 (t, 1 H, J = 5.0 Hz), 5.08 (q, 1 H, J = 7.4 Hz), 7.18-7.29 (m, 5 H), 7.80 (d, 2 H, J = 8.4 Hz), 8.27 (d, 2 H, J = 8.4 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 14.01, 39.59, 41.31, 41.41, 51.75, 52.43, 59.99, 124.63, 127.34, 128.56, 128.65, 130.16, 136.09, 143.81, 150.40, 166.55, 171.21; MS (FAB, NBA) m/e (%) 462 (20.0) [M + H]$^+$.

Methyl (2S,3'S)-2-[3'-methyl-4'-(4-nitrobenzenesulfonyl)-2'-oxopiperazin-1'-yl]-3-phenylpropanoate (131)

Prepared according to **GP 11** in 93 % yield. TLC ethyl acetate/hexane, 1/1, R_f 0.34; mp 124-127 °C; ^{1}H NMR (270 MHz, $CDCl_3$); δ 1.08 (d, 3 H, J = 6.9 Hz), 2.90 (dd, 1 H, J = 11.9 Hz and 14.8 Hz), 3.06-3.47 (m, 5 H), 3.64 (s, 3 H), 4.25 (q, 1 H, J = 6.9 Hz), 5.36 (dd, 1 H, J = 5.4 Hz and 11.9 Hz), 7.08-7.27 (m, 5 H), 7.93 (d, 2 H, J = 9.2 Hz), 8.34 (d, 2 H, J = 9.2 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 19.31, 34.40, 40.40, 42.43, 52.54, 54.68, 56.35, 124.77, 127.24, 128.34, 128.62, 128.74, 135.82, 144.80, 150.36, 168.05, 170.32; MS (EI) m/e (%) 461 (8.5) [M]$^+$, 374 (17.2), 342 (44.7), 162 (100); HRMS (EI) m/e Calcd for $C_{21}H_{23}N_3O_7S$: 461.12566; Found: 461.12540.

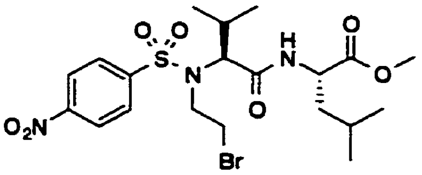
Methyl (2S,3'S)-2-[3'-isopropyl-4'-(4-nitrobenzenesulfonyl)-2'-oxopiperazin-1'-yl]-3-methylbutanoate (132)

Prepared according to **GP 11** in 88 % yield. TLC ethyl acetate/hexane, 1/2, R_f 0.33; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.75, 0.88, 0.99, 1.08 (4 d, 12 H, J = 6.7 Hz, 6.7 Hz, 6.9 Hz and 6.7 Hz), 1.93-2.17 (m, 2 H), 3.21-3.37 (m, 2 H), 3.42 (s, 3 H), 3.48-3.68 (m, 2 H), 4.03 (d, 1 H, J = 8.9 Hz), 4.57 (d, 1 H, J = 10.2 Hz), 7.94 (d, 2 H, J = 8.9 Hz), 8.28 (d, 2 H, J = 8.9 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 19.30, 19.50, 28.05, 31.60, 40.07, 42.15, 51.67, 60.30, 65.61, 124.47, 128.73, 144.16, 150.26, 167.57, 171.03; MS (EI) m/e (%) 441 (1.4) $[M]^+$, 398 (100), 153 (63.6), 141 (79.9); HRMS (EI) m/e Calcd for $C_{19}H_{27}N_3O_7S$: 441.15696; Found: 441.15650.

Methyl (2S,3'S)-2-[3'-isopropyl-4'-(4-nitrobenzenesulfonyl)-2'-oxopiperazin-1'-yl]-4-methylpentanoate (133)

Prepared according to **GP 11** in 84 % yield. TLC ethyl acetate/hexane, 1/2, R_f 0.50; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.82, 0.86, 1.02, 1.12 (4 d, 12 H, J = 6.4 Hz, 6.7 Hz, 6.7 Hz and 6.9 Hz), 1.18-1.57 (m, 3 H), 2.01-2.19 (m, 1 H), 3.17-3.21 (m, 2 H), 3.47 (s, 3 H), 3.58-3.75 (m, 2 H), 4.06 (d, 1 H, J = 8.6 Hz), 4.99 (dd, 1 H, J = 5.4 Hz and 10.9 Hz), 7.97 (d, 2 H, J = 8.9 Hz), 8.30 (d, 2 H, J = 8.9 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 19.43, 20.18, 20.83, 23.28, 25.14, 31.85, 37.19, 39.76, 42.06, 52.08, 53.33, 65.46, 124.60, 128.77, 144.22, 150.51, 167.68, 171.46; MS (EI) m/e (%) 455 (1.1) $[M]^+$, 412 (43.7), 167 (13.3), 84 (100); HRMS (EI) m/e Calcd for $C_{20}H_{29}N_3O_7S$: 455.17261; Found: 455.17340.

N-2-Bromoethyl-N-4-nitrobenzenesulfonyl-L-valyl-L-leucine methyl ester (135)



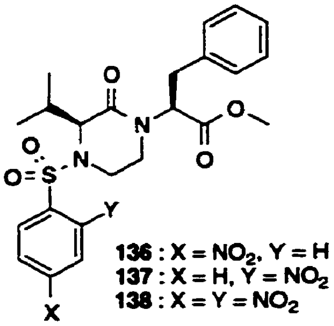
135

Obtained as a side-product from the preparation of compound **133**. TLC ethyl acetate/hexane, 1/2, R_f 0.56; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.40, 0.88, 0.92, 0.94 (4 d, 12 H, J = 6.4 Hz, 6.4 Hz, 5.9 Hz and 5.9 Hz), 1.51-1.71 (m, 3 H), 2.12-2.26 (m, 1 H), 3.39-3.68 (m, 4 H), 3.72 (s, 3 H), 3.76-3.84 (m, 1 H), 4.46-4.54 (m, 1 H), 6.39 (d, 1 H, J = 7.9 Hz), 8.01 (d, 2 H, J = 8.9 Hz), 8.35 (d, 2 H, J = 8.9 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 19.06, 19.56, 21.77, 22.82, 24.85, 27.07, 28.81, 41.06, 46.35, 50.92, 52.47, 66.47, 124.59, 128.46, 145.23, 150.47, 169.47, 172.9; MS (EI) m/e (%) 456 (14.8) $[M-Br]^+$, 412 (47.9), 227 (100), 209 (34.7); HRMS (EI) m/e Calcd for $[M-Br]^+$, $C_{20}H_{30}N_3O_7S$: 456.18043; Found: 456.18010.

Methyl (2S,3'S)-2-[3'-benzyl-4'-(4-nitrobenzenesulfonyl)-2'-oxopiperazin-1'-yl]-3-methylbutanoate (134)

Prepared according to **GP 11** in 93 % yield. TLC ethyl acetate/hexane, 1/1, R_f 0.32; mp 124-128 °C; ^{1}H NMR (270 MHz, $CDCl_3$); δ 0.65, 0.88 (2 d, 6 H, J = 6.7 Hz and 6.7 Hz), 1.91-2.05 (m, 1 H), 2.82-3.06 (m, 2 H), 3.16-3.26 (m with overlapping d, 3 H, J = 5.7 Hz), 3.52 (s, 3 H), 3.54-3.62 (m, 1 H), 4.57 (t, 1 H, J = 5.7 Hz), 4.70 (d, 1 H, J = 10.4 Hz), 7.05-7.18 (m, 5 H), 7.74 (d, 2 H, J = 8.7 Hz), 8.17 (d, 2 H, J = 8.7 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 19.06, 19.71, 26.92, 39.19, 40.85, 42.02, 51.94, 60.01, 61.40, 124.54, 127.21, 128.46, 128.64, 129.94, 136.21, 144.62, 150.17, 166.72, 170.54; MS (EI) m/e (%) 489 (2.3) $[M]^+$, 398 (100), 370 (17.3), 153 (17.7); HRMS (EI) m/e Calcd for $C_{23}H_{27}N_3O_7S$: 489.15696; Found: 489.15750.

Methyl (2S,3'S)-2-[3'-isopropyl-4'-(4-nitrobenzenesulfonyl)-2'-oxopiperazin-1'-yl]-3-phenylpropanoate (136)



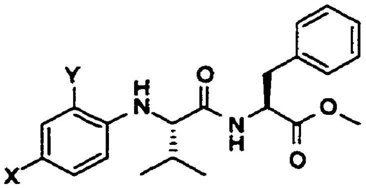
136 : X = NO_2, Y = H
137 : X = H, Y = NO_2
138 : X = Y = NO_2

Prepared according to **GP 11** in 90 % yield. TLC ethyl acetate/hexane, 1/2, R_f 0.38; ^{1}H NMR (270 MHz, $CDCl_3$); δ 0.53, 0.82 (2 d, 6 H, J = 6.7 Hz and 6.7 Hz), 1.49-1.65 (m, 1 H), 2.70 (dd, 1 H, J = 13.3 Hz and 14.8 Hz), 3.08-3.18 (m, 2 H), 3.24-3.42 (m, 2 H), 3.49-3.56 (m with overlapping s, 4 H), 3.87 (d, 1 H, J = 8.7 Hz), 5.36 (dd, 1 H, J = 4.9 Hz and 12.3 Hz), 7.03-7.21 (m, 5 H), 7.94 (d, 2 H, J = 8.9 Hz), 8.28 (d, 2 H, J = 8.9 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 19.05, 19.85, 31.51, 34.68, 40.13, 41.87, 52.29, 55.63, 65.21, 124.55, 127.21, 128.49, 128.72, 128.78, 135.87, 144.27, 150.34, 167.36, 170.36; MS (EI) m/e (%) 489 (2.9) $[M]^+$, 446 (14.3), 162 (81.9), 84 (100); HRMS (EI) m/e Calcd for $C_{23}H_{27}N_3O_7S$: 489.15696; Found: 489.15730.

Methyl (2S,3'S)-2-[3'-isopropyl-4'-(2-nitrobenzenesulfonyl)-2'-oxopiperazin-1'-yl]-3-phenylpropanoate (137)

Prepared according to **GP 11** in 65 % yield. TLC ethyl acetate/hexane, 1/2, R_f 0.11; ^{1}H NMR (270 MHz, $CDCl_3$); δ 0.68, 0.71 (2 d, 6 H, J = 6.2 Hz and 6.2 Hz), 1.69-1.84 (m, 1 H), 2.90 (dd, 1 H, J = 11.9 Hz and 14.8 Hz), 3.09-3.20 (m, 2 H), 3.29-3.40 (m, 2 H), 3.60 (s, 3 H), 3.75-3.85 (m, 1 H), 4.05 (d, 1 H, J = 7.9 Hz), 5.29 (dd, 1 H, J = 4.9 Hz and 11.6 Hz), 7.10-7.25 (m, 5 H), 7.59-7.73 (m, 3 H), 7.91-7.95 (m, 1 H); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 19.50, 19.68, 31.65, 34.32, 40.74, 42.51, 52.37, 57.16, 64.62, 124.37, 127.07, 128.70, 128.77, 130.86, 132.12, 132.96, 133.94, 136.33, 148.25, 167.24, 170.36; MS (EI) m/e (%) 489 (9.8) $[M]^+$, 446 (23.0), 284 (51.9), 186 (100); HRMS (EI) m/e Calcd for $C_{23}H_{27}N_3O_7S$: 489.15696; Found: 489.15740.

N-2-Nitrophenyl-L-valyl-L-phenylalanine methyl ester (139)



139 : X = H, Y = NO_2
140 : X = Y = NO_2

Obtained as a by-product from the preparation of compound **137** in 9 % yield. TLC ethyl acetate/hexane, 1/1, R_f0.44; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.77, 0.83 (2 d, 6 H, J = 6.7 Hz and 6.7 Hz), 2.16-2.28 (m, 1 H), 2.82-3.01 (m, 2 H), 3.66 (s, 3 H), 3.81 (dd, 1 H, J = 5.2 Hz and 8.0 Hz), 4.69-4.75 (m, 1 H), 6.12 (d, 1 H, J = 7.6 Hz), 6.52 (d, 1 H, J = 8.0 Hz), 7.04-7.29 (m, 5 H), 7.62-7.74 (m, 2 H), 7.86-7.89 (m, 1 H), 8.02-8.04 (m, 1 H); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 17.21, 19.28, 32.25, 37.96, 52.45, 53.50, 63.23, 125.77, 127.56, 128.75, 129.12, 131.21, 132.94, 133.79, 133.92, 135.85, 147.79, 169.78, 171.54; MS (CI, NH_3) m/e (%) 426 (5.8) $[MH]^+$, 400 (36.4), 382 (17.3), 193 (100).

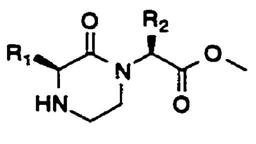
Methyl (2S,3'S)-2-[4'-(2,4-dinitrobenzenesulfonyl)-3'-isopropyl-2'-oxopiperazin-1'-yl]-3-phenylpropanoate (138)

Prepared according to **GP 11** in 45 % yield. TLC ethyl acetate/hexane, 1/2, R_f 0.13; ^{1}H NMR (270 MHz, $CDCl_3$); δ 0.71, 0.85 (2 d, 6 H, J = 6.7 Hz and 6.7 Hz), 1.71-1.85 (m, 1 H), 2.98 (dd, 1 H, J = 10.7 Hz and 14.6 Hz), 3.10-3.21 (m, 2 H), 3.28-3.40 (m, 2 H), 3.62 (s, 3 H), 3.75-3.85 (m, 1 H), 4.10 (d, 1 H, J = 8.0 Hz), 5.29 (dd, 1 H, J = 4.9 Hz and 10.7 Hz), 7.12-7.25 (m, 5 H), 8.12 (dd, 1 H, J = 2.5 Hz and 9.6 Hz), 8.66 (d, 1 H, J = 9.6 Hz), 9.05 (d, 1 H, J = 2.5 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 17.92, 19.45, 31.22, 37.96, 52.60, 53.12, 64.56, 119.25, 124.12, 128.26, 129.01, 130.35, 131.56, 135.33, 137.52, 148.21, 169.52, 171.50; MS (FAB, NBA) m/e (%) 535 (6.2) $[M + H]^+$.

N-2,4-Dinitrophenyl-L-valyl-L-phenylalanine methyl ester (140)

Obtained as a by-product from the preparation of compound **138** in 50 % yield. TLC ethyl acetate/hexane, 1/2, R_f 0.15; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.96, 1.00 (2 d, 6 H, J = 6.9 Hz and 6.9 Hz), 2.28-2.39 (m, 1 H), 3.01 (dd, 1 H, J = 7.2 Hz and 14.3 Hz), 3.15 (dd, 1 H, J = 5.4 Hz and 14.3 Hz), 3.69 (s, 3 H), 3.84 (dd, 1 H, J = 5.2 Hz and 5.9 Hz), 4.81-4.89 (m, 1 H), 6.22 (d, 1 H, J = 8.2 Hz), 6.71 (d, 1 H, J = 9.7 Hz), 7.00-7.24 (m, 5 H), 8.18 (dd, 1 H, J = 2.7 Hz and 9.4 Hz), 8.70 (d, 1 H, J = 9.4 Hz), 9.11 (d, 1 H, J = 2.7 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 17.70, 19.42, 31.21, 37.54, 52.61, 52.75, 64.05, 114.96, 123.99, 127.50, 128.85, 128.98, 130.54, 131.46, 135.32, 137.40, 147.70, 169.49, 171.46; MS (FAB, NBA) m/e (%) 445 (15.4) $[M + H]^+$.

Methyl (2S)-2-(2'-oxopiperazin-1'-yl)-4-methylpentanoate (141)



141 : R_1 = H, R_2 = $CH_2CH(CH_3)_2$
142 : R_1 = H, R_2 = CH_2Ph
143 : R_1 = CH_2Ph, R_2 = CH_3
144 : R_1 = CH_3, R_2 = CH_2Ph
145 : R_1 = $CH(CH_3)_2$, R_2 = $CH(CH_3)_2$
146 : R_1 = $CH(CH_3)_2$, R_2 = $CH_2CH(CH_3)_2$
147 : R_1 = CH_2Ph, R_2 = $CH(CH_3)_2$

Prepared according to **GP 3** in 82 % yield. TLC 100 % ethyl acetate, R_f 0.16; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.86 (d, 3 H, J = 6.5 Hz), 0.91 (d, 3 H, J = 6.0 Hz), 1.41-1.50 (m, 1 H), 1.64-1.73 (m, 2 H), 3.40-3.61 (m, 4 H), 3.67 (s, 3 H), 3.80-3.91 (s br, 2 H); 5.25 (dd, 1 H, J = 4.5 Hz and 9.0 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 21.07, 22.91, 24.74, 36.59, 39.57, 40.91, 44.88, 52.55, 54.06, 162.74, 171.22; MS (EI) m/e (%) 228 (9.5) $[M]^+$, 172 (25.8), 169 (14.3), 141 (100); HRMS (EI) m/e Calcd for $C_{11}H_{20}N_2O_3$: 228.14738; Found: 228.14710.

Methyl (2S)-2-(2'-oxopiperazin-1'-yl)-3-phenylpropanoate (142)

Prepared according to **GP 3** in 85 % yield. TLC 100 % ethyl acetate, R_f 0.12; ^{1}H NMR (270 MHz, $CDCl_3$); δ 2.75-2.84 (m, 2 H), 2.95-3.21 (m, 3 H), 3.20-3.30 (m, 1 H), 3.40 (ABq, 2 H, J = 17.3 Hz), 3.69 (s, 3 H), 5.07 (dd, 1 H, J = 5.4 Hz and 10.6 Hz), 7.14-7.28 (m, 5 H); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 34.16, 43.01, 46.44, 50.12, 52.42, 58.17, 126.89, 128.60, 128.85, 136.98, 168.31, 170.94; MS (EI) m/e (%) 262 (13.3) $[M]^+$, 175 (43.5), 143 (85.1), 100 (100); HRMS (EI) m/e Calcd for $C_{14}H_{18}N_2O_3$: 262.13173; Found: 262.13150.

Methyl (2S,3'S)-2-[3'-benzyl-2'-oxopiperazin-1'-yl]propanoate (143)

Prepared according to **GP 3** in 83 % yield. TLC 100 % ethyl acetate, R_f 0.25; ^1H NMR (270 MHz, $CDCl_3$); δ 1.39 (d, 3 H, J = 7.4 Hz), 2.83 (dd, 1 H, J = 9.6 Hz and 13.6 Hz), 2.98-3.36 (m, 4 H), 3.45 (dd, 1 H, J = 3.5 Hz and 13.6 Hz), 3.68 (dd, 1 H, J = 3.5 Hz and 9.6 Hz), 3.71 (s, 3 H), 5.20 (q, 1 H, J = 7.4 Hz), 7.18-7.32 (m, 5 H); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 14.12, 38.49, 42.26, 44.70, 51.84, 52.35, 60.88, 126.78, 128.72, 129.42, 138.30, 169.62, 172.22; MS (CI) m/e (%) 277 (60.3) $[M+H]^+$, 249 (5.8), 185 (100), 157 (26.1); HRMS (EI) m/e Calcd for $[M-OCH_3]^+$, $C_{14}H_{17}N_2O_2$: 245.12899; Found: 245.12860.

Methyl (2S,3'S)-2-[3'-methyl-2'-oxopiperazin-1'-yl]-3-phenylpropanoate (144)

Prepared according to **GP 3** in 85 % yield. TLC 100 % ethyl acetate, R_f 0.17; ^1H NMR (270 MHz, $CDCl_3$); δ 1.17 (d, 3 H, J = 6.9 Hz), 2.78-2.99 (m, 3 H), 3.10 (dd, 1 H, J = 11.1 Hz and 14.6 Hz), 3.23-3.32 (m, 1 H), 3.36 (dd, 1 H, J = 5.2 Hz and 14.6 Hz), 3.48 (q, 1 H, J = 6.9 Hz), 3.72 (s, 3 H), 5.08 (dd, 1 H, J = 5.2 Hz and 11.1 Hz), 7.17-7.31 (m, 5 H); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 18.57, 34.27, 41.77, 46.91, 52.40, 55.03, 58.21, 126.87, 128.57, 128.88, 137.00, 171.11, 171.26; MS (EI) m/e (%) 276 (41.9) $[M]^+$, 189 (45.6), 157 (96.7), 114 (100); HRMS (EI) m/e Calcd for $C_{15}H_{20}N_2O_3$: 276.14738; Found: 276.14760.

Methyl (2S,3'S)-2-[3'-isopropyl-2'-oxopiperazin-1'-yl]-3-methylbutanoate (145)

Prepared according to **GP 3** in 79 % yield. TLC 100 % ethyl acetate, R_f 0.19; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.85, 0.89, 0.95 (3 d, 12 H, J = 6.9 Hz, 6.7 Hz and 6.7 Hz), 2.09-2.24 (m, 1 H), 2.40-2.52 (m, 1 H), 2.86-2.97 (m, 1 H), 3.10-3.18 (m, 1 H), 3.23-3.33 (m, 1 H), 3.42 (d, 1 H, J = 3.2 Hz), 3.44-3.50 (m, 1 H), 3.66 (s, 3 H), 4.87 (d, 1 H, J = 10.6 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 16.73, 19.36, 19.74, 26.97, 30.35, 42.70, 44.66, 51.79, 61.11, 64.82, 170.44, 171.77; MS (EI) m/e (%) 256 (18.8) $[M]^+$, 213 (100), 185 (44.2), 169 (28.0); HRMS (EI) m/e Calcd for $C_{13}H_{24}N_2O_3$: 256.17868; Found: 256.17890.

Methyl (2S,3'S)-2-[3'-isopropyl-2'-oxopiperazin-1'-yl]-4-methylpentanoate (146)

Prepared according to **GP 3** in 79 % yield. TLC 100 % ethyl acetate, R_f 0.18; ^{1}H NMR (270 MHz, $CDCl_3$): δ 0.83, 0.90, 0.93, 0.97 (4 d, 12 H, J = 6.9 Hz, 6.9 Hz, 7.2 Hz and 7.2 Hz), 1.44-1.79 (m, 3 H), 2.42-2.53 (m, 1 H), 2.98-3.31 (m, 4 H), 3.46 (d, 1 H, J = 3.0 Hz), 3.68 (s, 3 H), 5.31 (dd, 1 H, J = 5.4 Hz and 10.9 Hz); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 16.49, 19.34, 21.05, 23.45, 24.88, 30.26, 36.74, 42.57, 44.77, 52.19, 53.81, 64.73, 170.57, 172.43; MS (EI) m/e (%) 270 (6.1) $[M]^+$, 227 (100), 141 (34.9), 99 (13.4); HRMS (EI) m/e Calcd for $C_{14}H_{26}N_2O_3$: 270.19433; Found: 270.19460.

Methyl (2S,3'S)-2-[3'-benzyl-2'-oxopiperazin-1'-yl]-3-methylbutanoate (147)

Prepared according to **GP 3** in 86 % yield. TLC 100 % ethyl acetate, R_f 0.15; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.83, 0.96 (2 d, 6 H, J = 6.7 Hz and 6.7 Hz), 2.11-2.22 (m, 1 H), 2.85-2.90 (m, 1 H), 2.91-3.01 (m, 1 H), 3.04-3.10 (m, 1 H), 3.21-3.31 (m, 1 H), 3.35 (dd, 1H, J = 3.5 Hz and 13.5 Hz), 3.40-3.46 (m, H), 3.69 (s, 3 H), 3.70-3.72 (m, 1H), 4.92 (d, 1 H, J = 10.8 Hz), 7.22-7.39 (m, 5 H); ^{13}C NMR (67.9 MHz, $CDCl_3$): δ 19.14, 19.73, 26.90, 38.59, 42.21, 44.50, 51.89, 61.02, 61.11, 126.75, 128.68, 129.57, 138.19, 169.91, 171.62; MS (EI) m/e (%) 304 (32.1) $[M]^+$, 261 (100), 233 (27.8); HRMS (EI) m/e Calcd for $C_{17}H_{24}N_2O_3$: 304.17868; Found: 304.17855.

4.7 Experimental for Section 2.6

Peptide Synthesis

Peptide synthesis was conducted in small round bottom flasks using a mechanical shaker on 0.1 mmol scale using standard Fmoc SPPS. The amino acid preloaded on 2-chloro-trityl resin was used. A Fmoc amino acid was coupled to the amino acid resin in four-fold excess using either 4 equivalents of HBTU in 0.4 M NMM/DMF for 20 minutes or 4 equivalents of EDAC.HCl, DIPEA and HOBt respectively in dichloromethane for 3 hours until the Kaiser ninhydrin test was negative. The resin was then drained and washed with CH_2Cl_2 (2X), DMF (2X), MeOH (2X), DMF (2X) and CH_2Cl_2 (2X) respectively. Fmoc deprotection was accomplished with 20 % piperidine in DMF (2 X 10 minutes) and the resin washed as before.

The Fmoc deprotected dipeptide resin was swollen in CH_2Cl_2, treated with 5 equivalents of collidine and 3 equivalents of 2-nitrobenzenesulfonyl chloride. The resulting mixture was agitated at room temperature for 2 hours until the Kaiser ninhydrin test was negative. The resin was washed again as above. The resin-bound sulfonamide was resuspended in DMF and treated with dibromoethane (10 eq.) and fine potassium carbonate powder (10 mole eq.) The mixture was then agitated at 60 °C for 12-18 hours. Again the resin was washed as above with the inclusion of washing with water (2X) to remove any inorganic salts.

After the washing, the resin was again suspended in DMF and treated with 5 equivalents of DBU and 10 equivalents of 2-mercaptoethanol for 1 hour at room temperature. A bright yellow colour was indicatice of oNBS cleavage. Following cleavage, the resin was extensively washed with DMF. The third amino acid in the peptide synthesis was coupled to the resin using HATU in place of HBTU (2 X 20 minutes). At each step of the synthesis, a small sample of the resin was removed and cleaved for LC-MS analysis.

Product Cleavage

The resin bound products after each step were treated with 0.5 % TFA/ CH_2Cl_2 for 10 minutes. The resin was washed with 0.5 % TFA/ CH_2Cl_2 and the solution was evaporated to yield the product.

Product Analysis

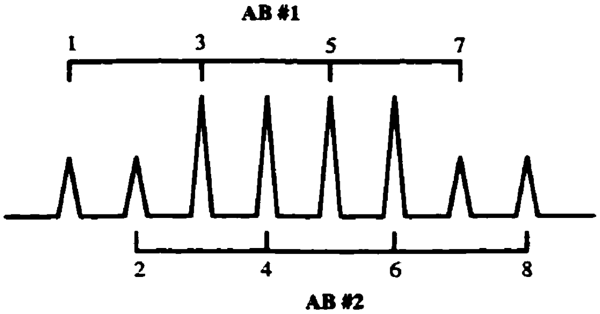
% yield assessed by RP-HPLC (Micromass Platform LC) at 215 nm (10-50 % CH_3CN in water containing 0.1 % TFA). Product structure verified using electron spray mass spectrometry (Hewlett Packard Series 1100).

APPENDICES

Appendix I: Analysis of ABX Systems in ^{1}H NMR Spectra.

The chemical shifts and coupling constants of second order AB portions of ABX systems were calculated by the method shown below.[105]

The ABX spectrum is divided into two AB systems.



$J_{A,B} = (8 - 6) = (7 - 5) = (4 - 2) = (3 - 1)$

AB #1	**AB #2**
$v_1 = (1 + 3 + 5 + 7)/4$	$v_2 = (2 + 4 + 6 + 8)/4$
$(\Delta v_1)/2 = [(1 - 7)(3 - 5)]^{1/2}/2$	$(\Delta v_2)/2 = [(2 - 8)(4 - 6)]^{1/2}/2$
$\Delta 1^+ = v_1 + (\Delta v_1)/2$	$\Delta 2^+ = v_2 + (\Delta v_2)/2$
$\Delta 1^- = v_1 - (\Delta v_1)/2$	$\Delta 2^- = v_2 - (\Delta v_2)/2$

$v_A = (\Delta 1^+ + \Delta 2^+)/2$

$J_{AX} = \Delta 1^+ - \Delta 2^+$

or

$v_A = (\Delta 1^+ + \Delta 2^-)/2$

$J_{AX} = \Delta 1^+ - \Delta 2^-$

$v_B = (\Delta 1^- + \Delta 2^-)/2$

$J_{BX} = \Delta 1^- - \Delta 2^-$

or

$v_B = (\Delta 1^- + \Delta 2^+)/2$

$J_{BX} = \Delta 1^- - \Delta 2^+$

Two possible set of values are generated, but one gives unrealistic coupling constants.

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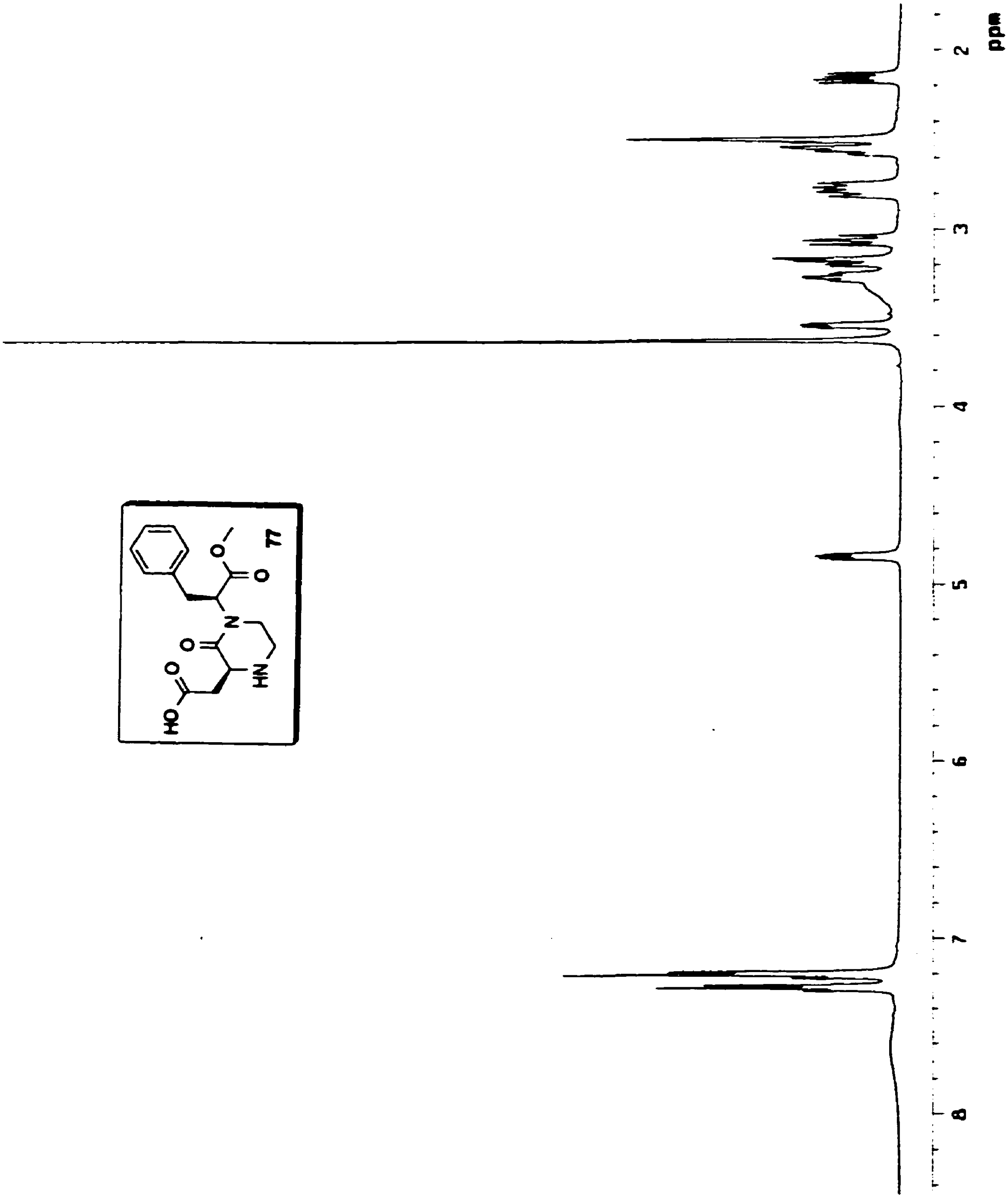
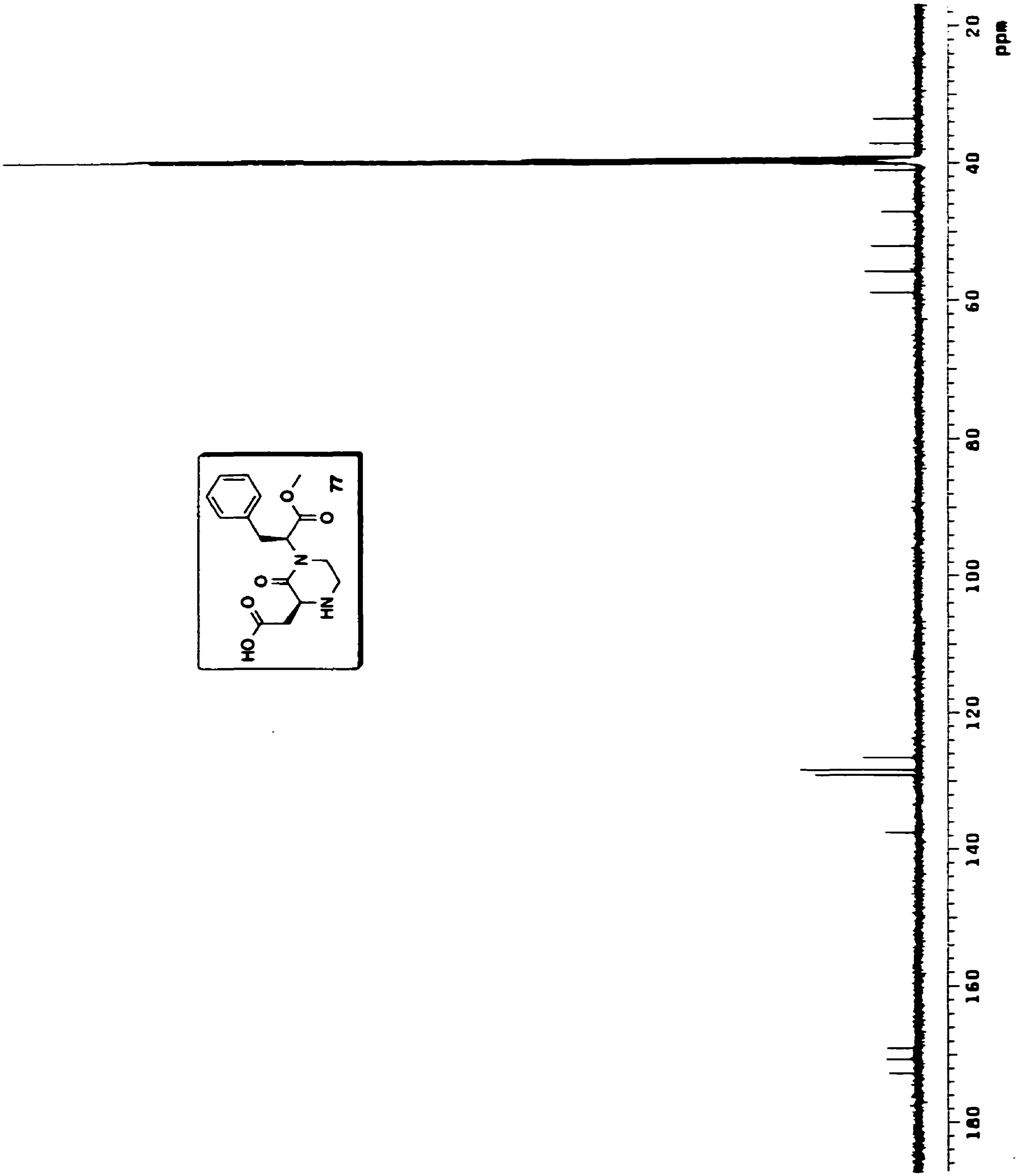
[105] Becker, E. D. ed., *High Resolution NMR-Theory and Chemical Applications* **1980**, *Chapter 7*, Academic Press, Inc., London.

Appendix II: NMR Spectra

1. ^{1}H NMR spectrum (500 MHz, DMSO-d_6) of cyclized aspartame analogue **77**.



2. ^{13}C NMR spectrum (125.7 MHz, DMSO-d_6) of cyclized aspartame analogue **77**.



3. 2D-COSY map (500 MHz, DMSO-d_6) of cyclized aspartame analogue **77**.