

**Multicomponent reactions of  
siloxycyclopropanes for synthesis of  
unnatural amino acids and their application  
in synthesis of peptidomimetics**

Inaugural-Dissertation

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Des Fachbereiches Biologie, Chemie, Pharmazie  
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Diplom-Chemikerin IVANA S. VELJKOVIĆ  
aus Knjaževac, Serbien und Montenegro

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1. Gutachter: Prof. Dr. Hans-Ulrich Reissig

2. Gutachter: Prof. Dr. Beate Kokschi

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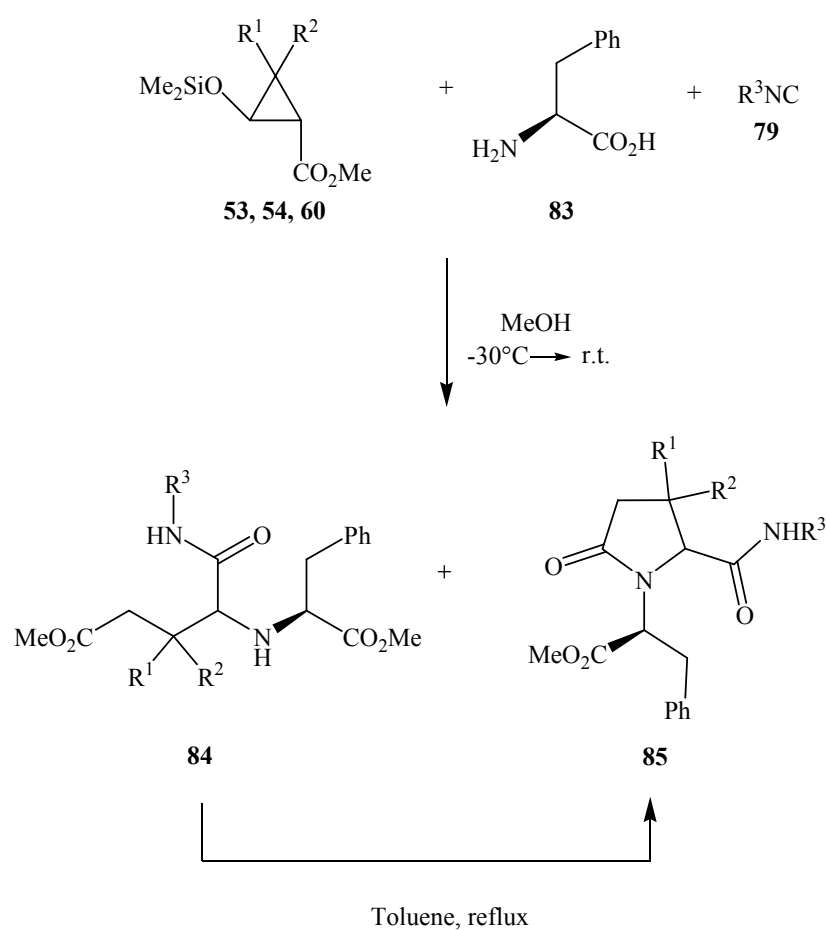
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## ABBREVIATIONS

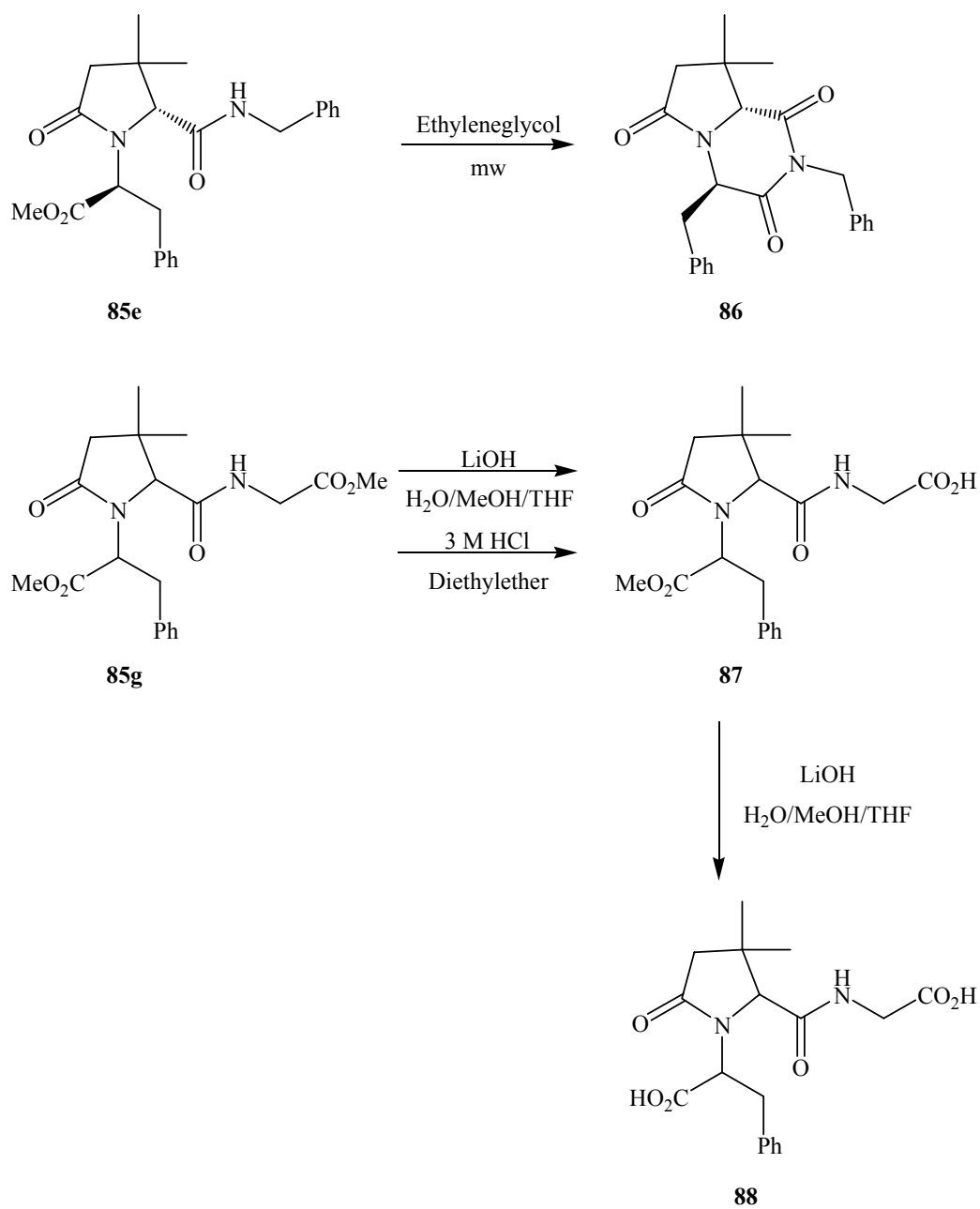
Ac	Acetyl
Bn	Benzyl
Boc	<i>tert</i> -Butoxycarbonyl
BOC-ON	2-( <i>tert</i> -Butoxycarbonyloxyimino)-2-phenylacetoneitrile
BOP	Benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate
BSE	Bovine Spongiform Encephalopathy
Bu	n-butyl
<sup>t</sup> Bu	<i>tert</i> -butyl
3CC	three component condensation
COSY	<sup>1</sup> H, <sup>1</sup> H-NMR correlated spectroscopy
DCC	1,3-Dicyclohexylcarbodiimide
DEA	N,N-Diethylamine
DIEA	Diisopropylethylamine
DMAP	N,N-Dimethylaminopyridine
DMF	N,N-Dimethylformamide
DMSO	Dimethylsulfoxid
DNA	Deoxyribonucleic acid
Et	Ethyl
Fmoc	Fluorenyl-9-methoxy-carbonyl
h	hour (hours)
HMBC	Heteronuclear Multiple-Bond Correlation
HMPA	Hexamethylphosphoramide
HETCORR	<sup>1</sup> H, <sup>13</sup> C-NMR correlated spectroscopy
HOBt	1-Hydroxybenzotriazole
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectroscopy
IR	Infrared Spectroscopy
LDA	Lithium diisopropylamide
MCR	multicomponent reaction
Me	Methyl
ml	mililiter
MS	Mass Spectroscopy
NMR	Nuclear Magnetic Resonance Spectroscopy
Ph	Phenyl
RNA	Ribonucleic acid
SAR	structure activity relationship
TBTU	<i>o</i> -Benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate
TCFH	Tetramethyl chloroformamidinium hexafluorophosphate
TFA	Trifluoroacetic acid
TFFH	Tetramethyl fluoroformamidinium hexafluorophosphate
THF	Tetrahydrofuran
TMS	Trimethylsilyl
U-4CR	Ugi Four-component reaction
U5-4CR	Ugi Five-center four-component reaction

## 8 Summary

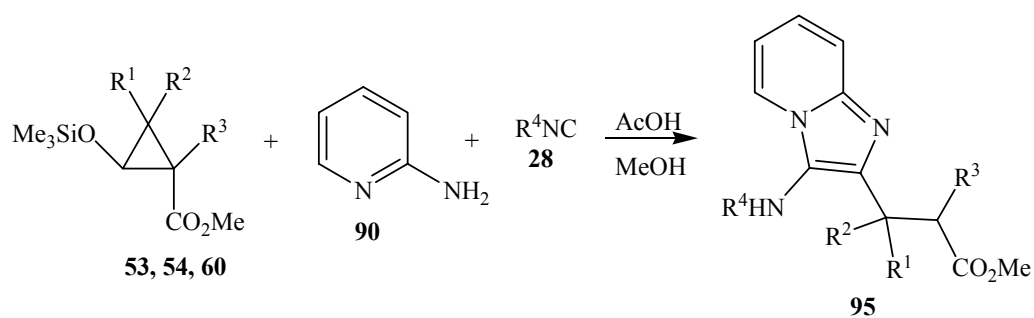
1. The Ugi 5-center 4-component reaction was used to synthesize a number of  $\alpha$ -acylaminoimides **84** and functionalized pyrrolidinones **85** with moderate to good diastereoselectivity utilizing 2-siloxycyclopropanecarboxylates **53**, **54** and **60**, L-phenylalanine **83** and isocyanides **79** as starting materials. The best yields were obtained in reactions of 2-siloxycyclopropane **54**. The cyclized products **85** could be obtained in higher yields in a one-pot sequence, which can be classified as a 6-center 4-component reaction.



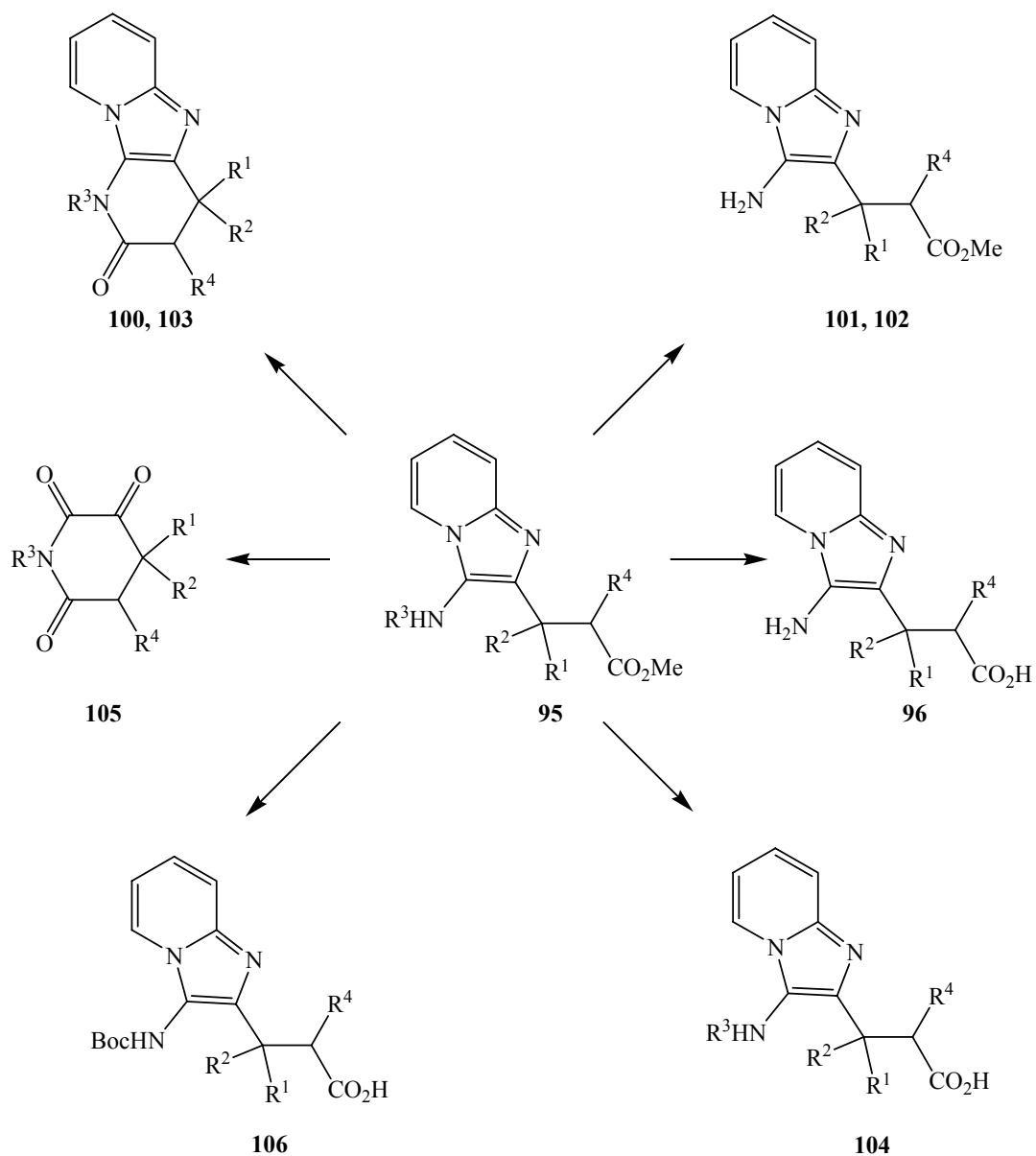
2. Starting from the corresponding pyrrolidinones **85e** and **85g**, interesting bicyclic compounds such as **86** and mono- and diacid derivatives like **87** and **88** could be prepared.



3. A number of 3-aminoimidazo[1,2-*a*]pyridines **95** have been synthesized exploiting the Ugi-type three component condensation of methyl 2-siloxycyclopropanecarboxylates **53**, **54** and **60** with 2-aminopyridine **90** and four isocyanides **28** in moderate to good yields.

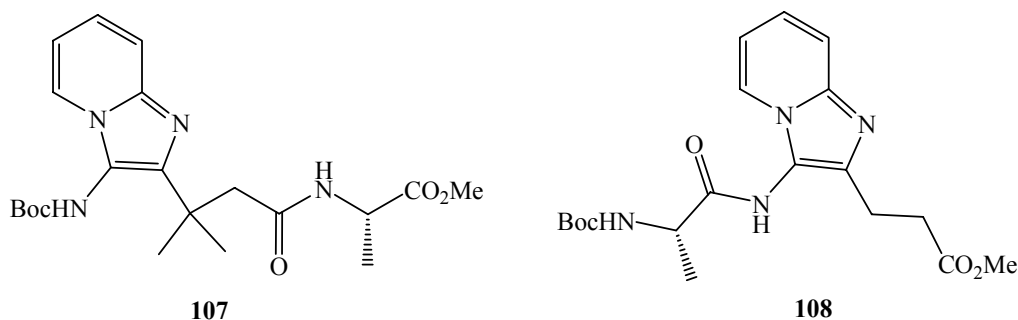


4. These compounds could be further converted into several products, for example lactams **100** and **103**,  $\delta$ -amino esters **101** and **102**, carboxylic acids **96**, **104** and **106** and compound **105**.

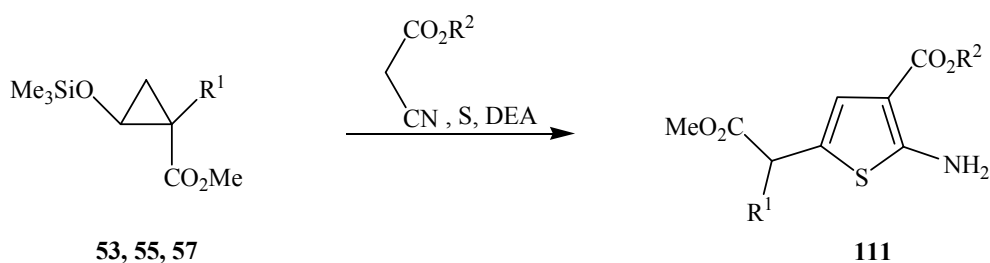




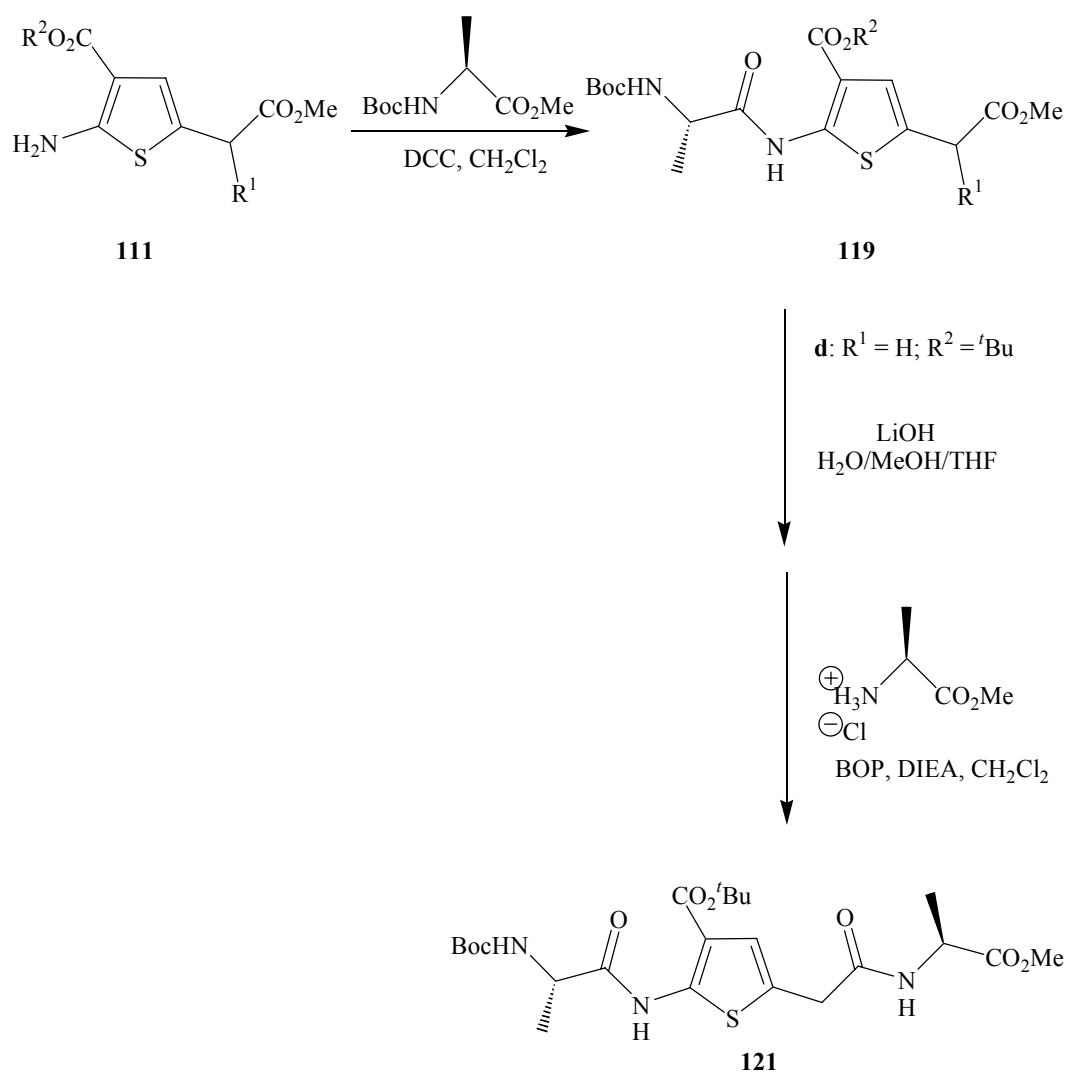
5. The novel building blocks have been utilized for the synthesis of peptidomimetics **107** and **108** applying the coupling reagents BOP and TFFH, respectively.



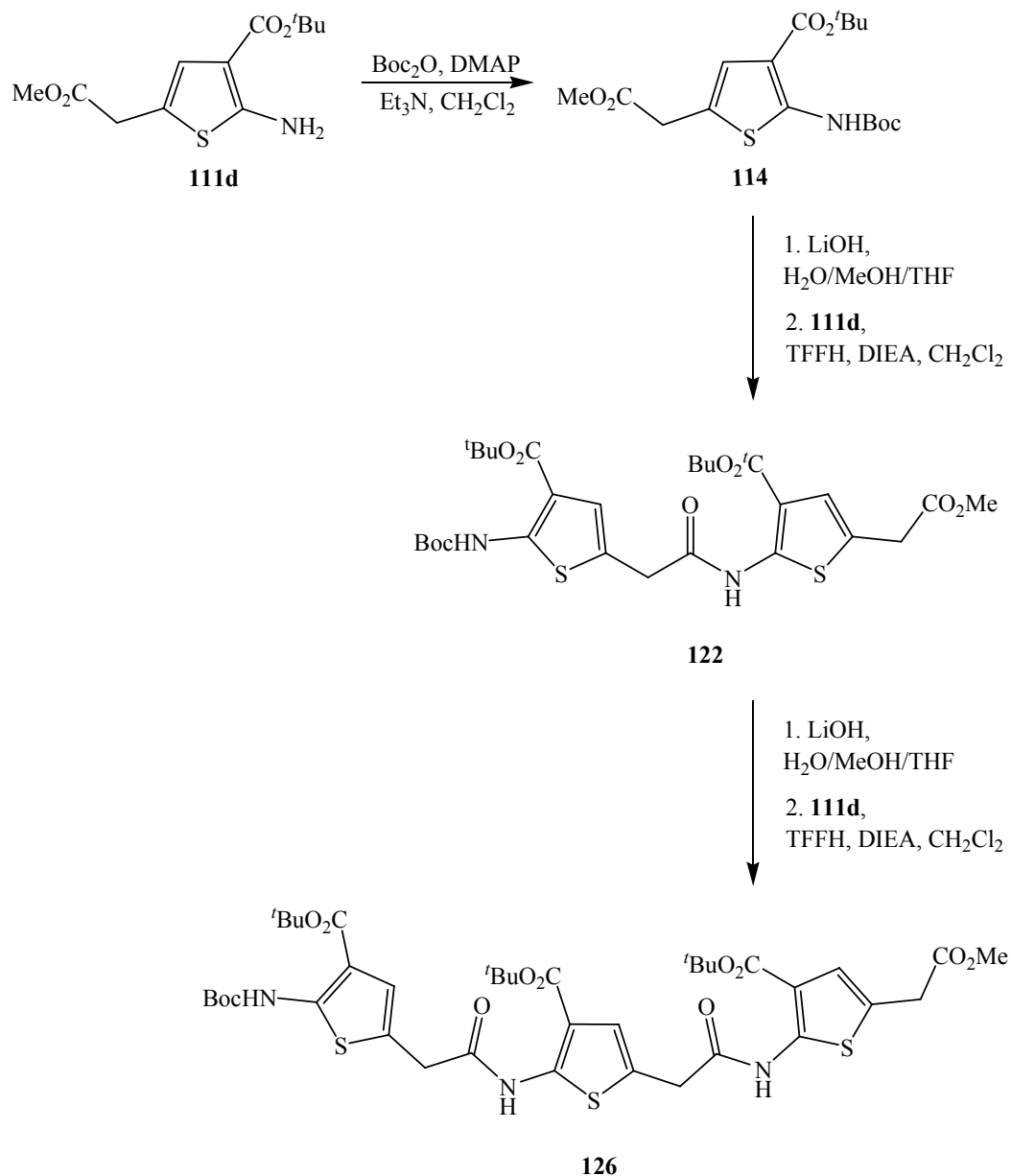
6. Methyl 2-siloxycyclopropanecarboxylates **53**, **55** and **57** have been utilized as precursor compounds in the Gewald's reaction of cyanoacetic ester derivatives with sulfur to synthesize 2-aminothiophenes **111**.



7.  $\delta$ -Amino esters **111** could be coupled with N-Boc L-alanine to obtain tripeptide analogues **119**. The compound **119d** has also been obtained in a one-pot procedure starting from siloxycyclopropanecarboxylate **53**. Base-mediated hydrolysis of methyl ester **119d** provided free carboxylic acid which could be coupled with L-alanine methyl ester to obtain tetrapeptide analogue **121**.

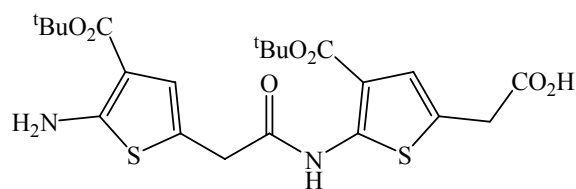


8. The amino-group of compound **111d** was N-Boc-protected. Subsequent base-mediated hydrolysis of the methoxycarbonyl group afforded N-Boc protected carboxylic acid which could be coupled with  $\delta$ -amino ester **111d** to obtain tetrapeptide analogue **122** utilizing TFFH in the presence of DIEA. A subsequent base-mediated hydrolysis and coupling with **111d** afforded hexapeptide analogue **126**.

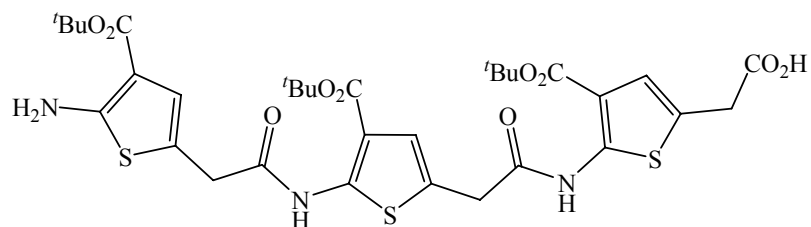


9. Chemoselective deprotection of N-Boc-group with trimethylsilyltrifluoromethanesulfonate in the presence of 2,6-lutidine and saponification of the ester with lithium hydroxide allowed preparation of deprotected tetra- and hexapeptide analogues **125** and **128**.

Cyclization of trimer **128** has been attempted utilizing TFFH in the presence of DIEA, and BOP in the presence of DMAP. Unfortunately no cyclic trimer was obtained.

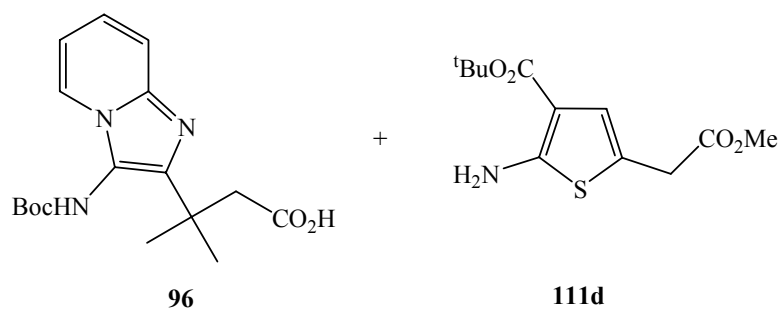


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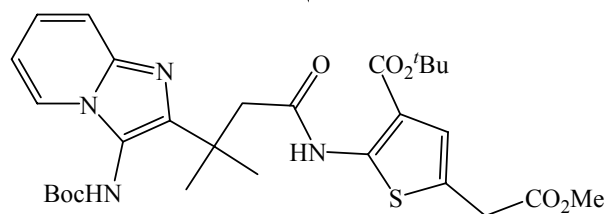
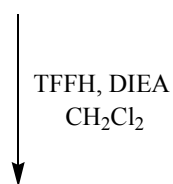
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10.  $\delta$ -Amino ester **111** was coupled with compound **96**, which incorporates a pyridinoimidazolo moiety, and tetrapeptide analogue **130** was obtained in the presence of TFFH and DIEA.



96

111d



130

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## **CURRICULUM VITAE**

Name: Ivana S. Veljković

Date of Birth: 6<sup>th</sup> October 1974

Country of Birth: Yugoslavia

Marital Status: Married

### **EDUCATION**

- 09/1981- 06/1989 Primary school “Dimitrije Todorović Kaplar” , Knjaževac
- 09/1989- 06/1992 Gymnasium “Ivo Lola Ribar”, Knjaževac
- 10/1992- 06/1998 Undergraduate studies, Faculty of Chemistry, University of Belgrade, Yugoslavia
- 06/1998 Diploma in Chemistry, Faculty of Chemistry, University of Belgrade, Yugoslavia, Supervisor: Dr Dušanka Milojković-Opsenica  
Diploma thesis: Planar chromatography of some 1,4-benzodiazepines
- 11/1998- 11/2001 Postgraduate studies, Faculty of Chemistry, University of Belgrade, Yugoslavia, Supervisor: Prof. Dr Ivan O. Juranić
- 11/2001- 02/2005 Doctorate studies, Freie Universität Berlin, Berlin, Germany  
Doctoral thesis advisor: Prof. Dr Hans-Ulrich Reissig

### **EMPLOYMENT AND STUDENTSHIPS**

- 11/1998- 10/2001 Junior research associate  
Institute of Chemistry, Technology and Metallurgy  
Njegoševa 12, Belgrade, Serbia and Montenegro (ex-Yugoslavia)
- 10/2000- 01/2001 DAAD Fellowship for short term research at FU Berlin under supervision of Prof. Dr Hans-Ulrich Reissig
- 11/2001- 12/2001 Financial support from Volkswagen Stiftung
- 01/2002- 12/2004 DFG studentship Graduirtenkolleg Nr. 788 “Wasserstoffbrücken und Wasserstofftransfer“