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

Inaugural-Dissertation

Zur Erlangung der Doktorwürde
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Eingericht von
Diplom-Chemikerin IVANA S. VELJKOVIĆ
aus Knjaževac, Serbien und Montenegro

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

2. Gutachter: Prof. Dr. Beate Koksch

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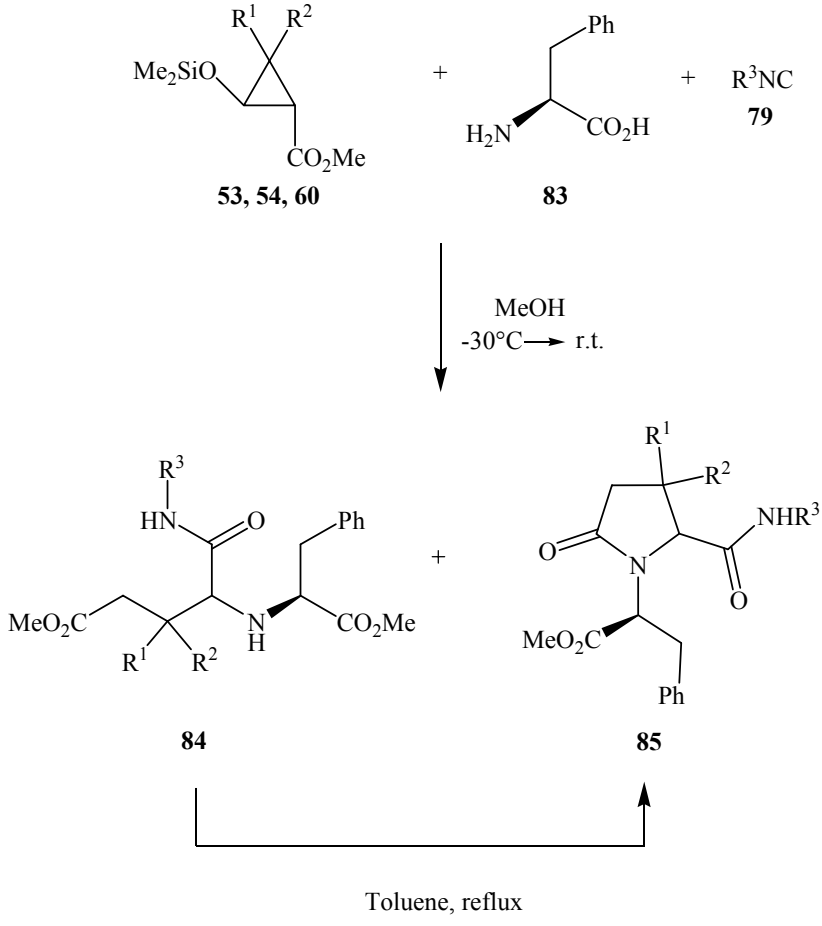
CONTENT

ABBREVIATIONS

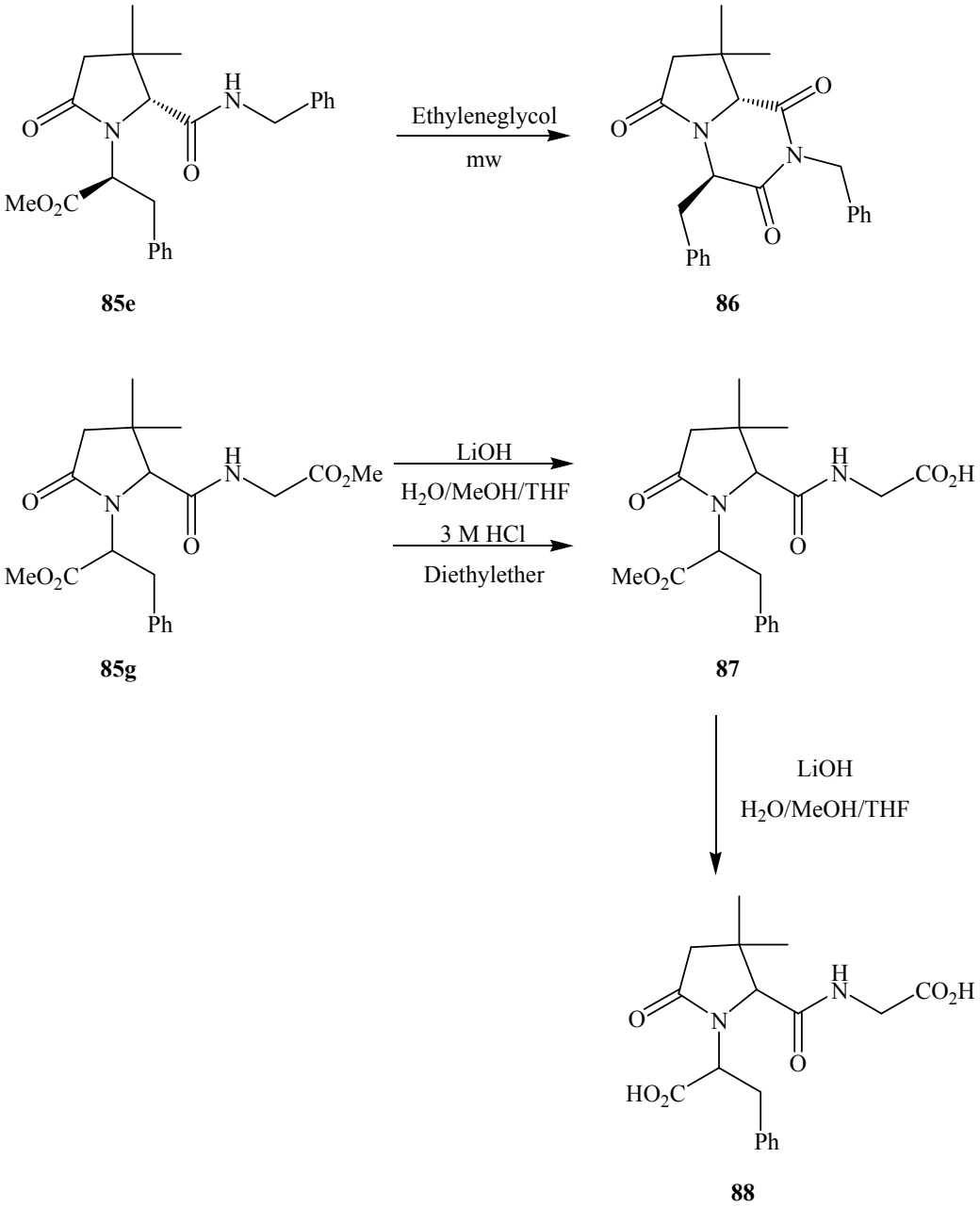
Ac	Acetyl
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
BOC-ON	2-(*tert*-Butoxycarbonyloxyimino)-2-phenylacetonitrile
BOP	Benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate
BSE	Bovine Spongiform Encelopathy
Bu	n-butyl
^{t}Bu	*tert*-butyl
3CC	three component condensation
COSY	^{1}H,^{1}H-NMR 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	^{1}H,^{13}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	*o*-Benzotriazol-1-yl-N,N,N′,N′-tetramethyluronium tetrafluoroborate
TCFH	Tetramethyl chloroformamidinium hexafluorophosphate
TFA	Trifluoroacetic acid
TFFH	Tetramethyl fluoroformamidinium hexafluorophosphate
THF	Tetrahydofuran
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 α-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.

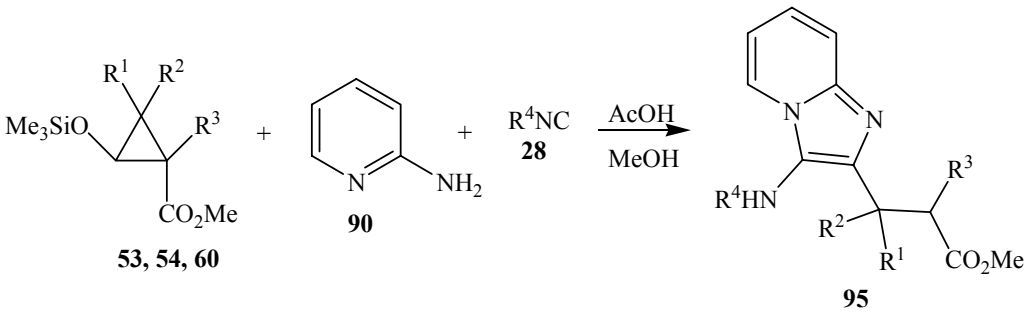


85e **86**

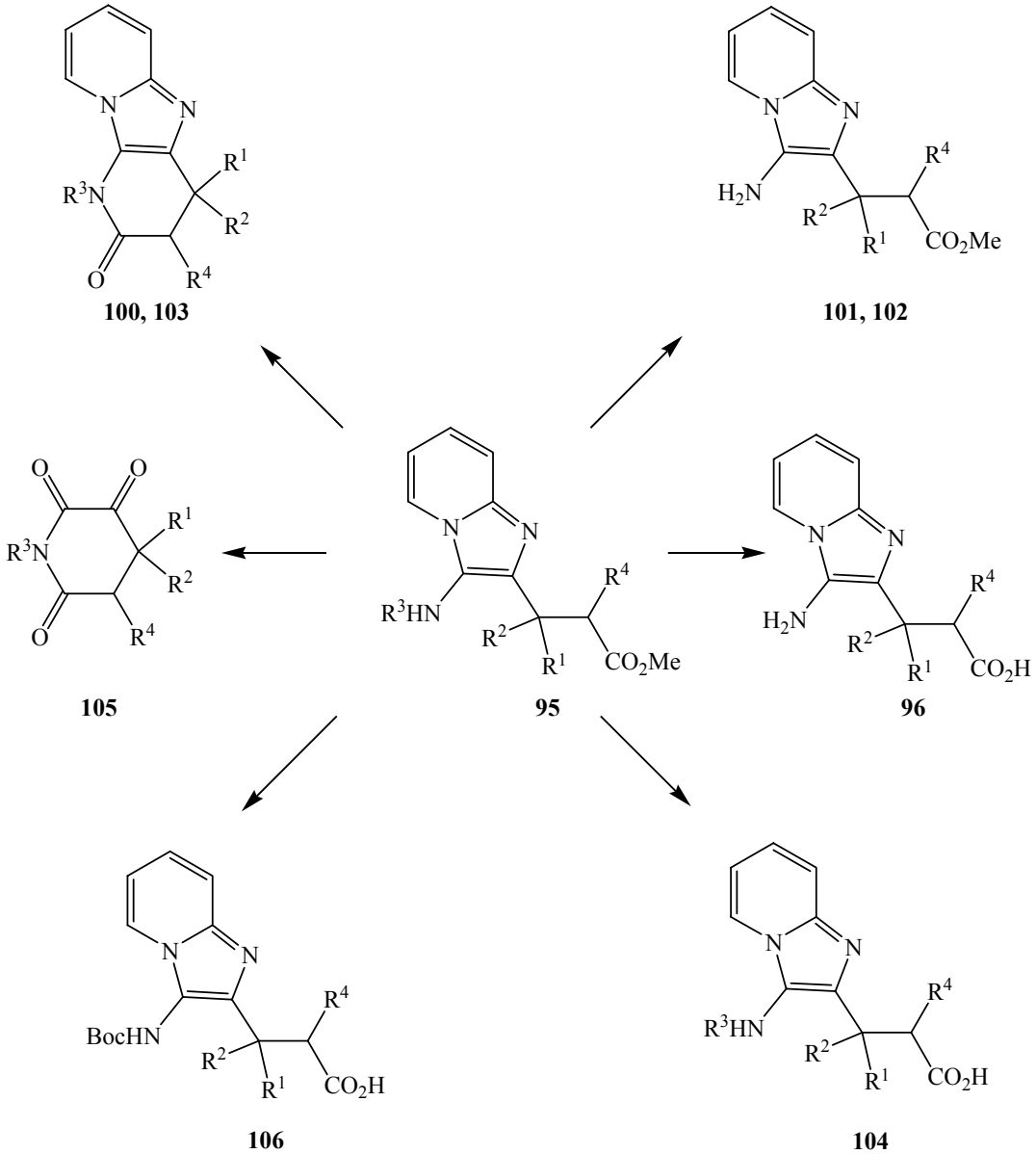
85g **87**

88

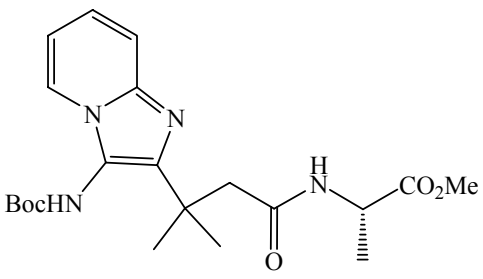
3. A number of 3-aminoimidazo[1,2-*a*]pyridines **95** have been synthesized exploiting the Ugi-type three component condensation of methyl 2-siloxycyclopropanecarboxylates **53**, **54** and **60** with 2-aminopyridine **90** and four isocyanides **28** in moderate to good yields.



4. These compounds could be further converted into several products, for example lactams **100** and **103**, δ-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.



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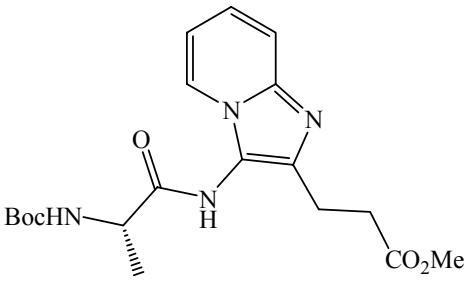

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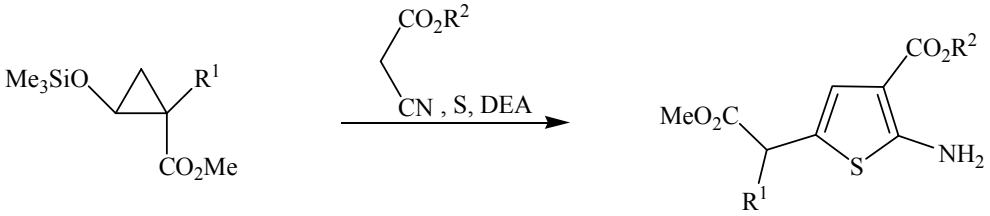
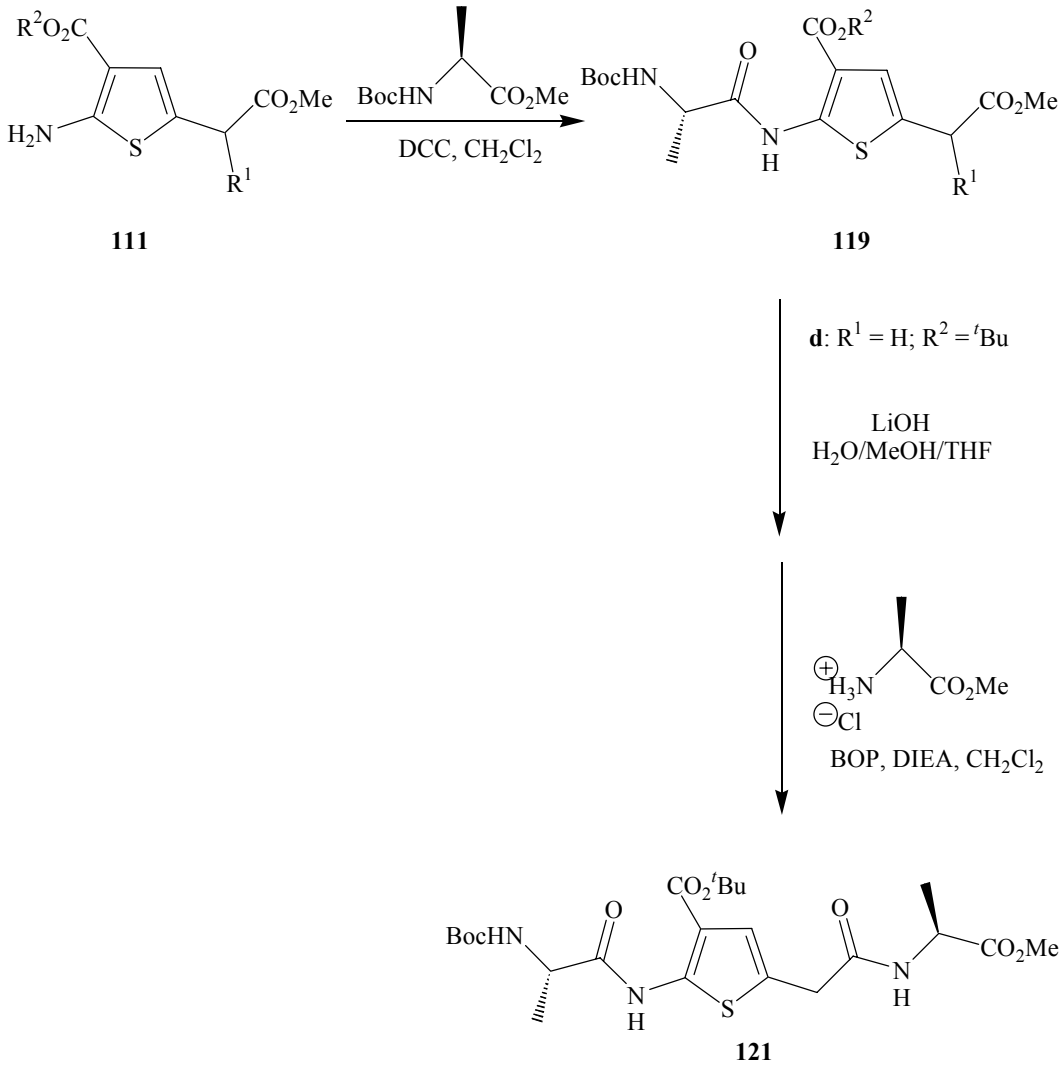
6. Methyl 2-siloxycyclopropanecarboxylates **53**, **55** and **57** have been utilized as precursor compounds in the Gewald's reaction of cyanoacetic ester derivatives with sulfur to synthesize 2-aminothiophenes **111**.



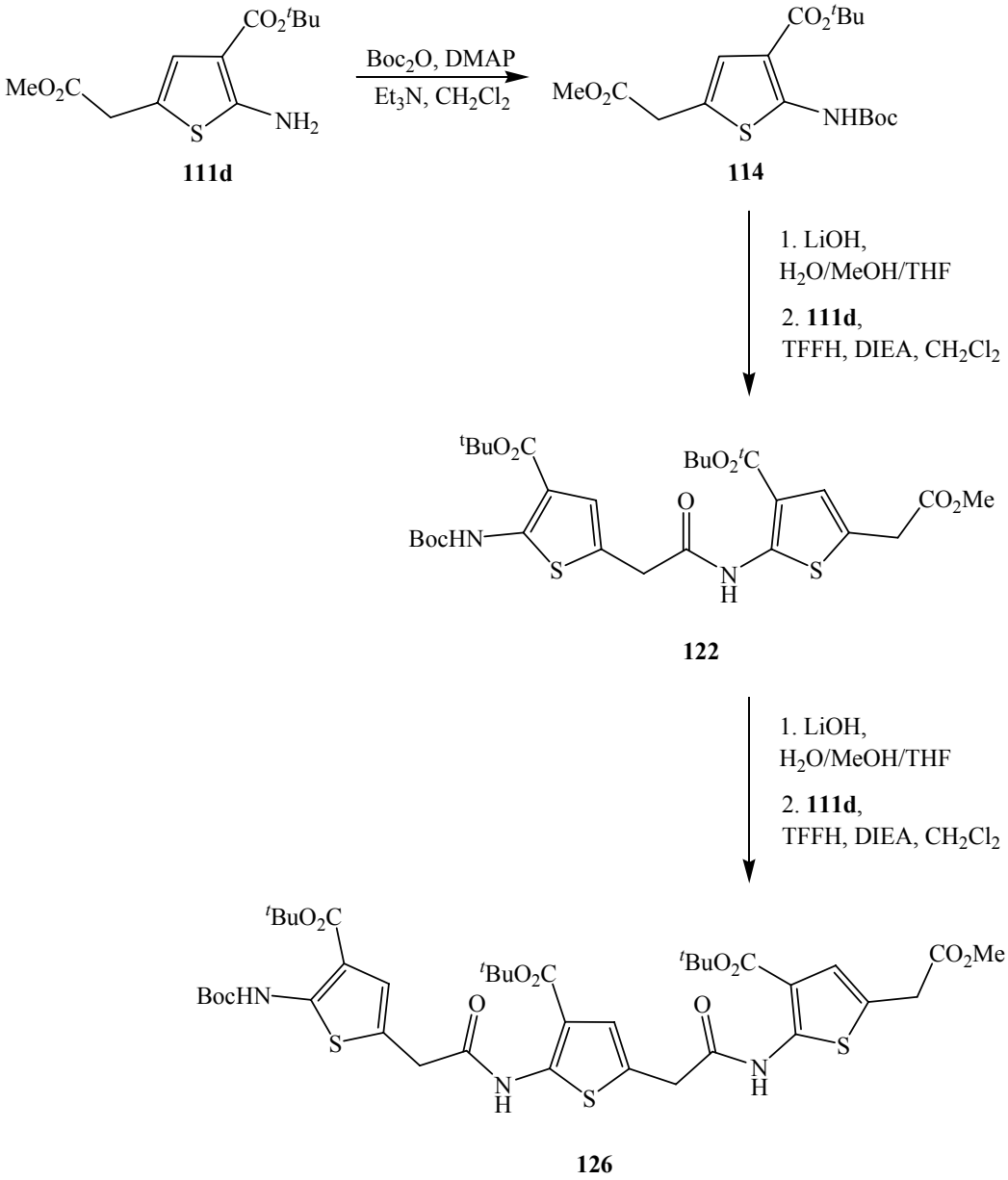
53, 55, 57 **111**

7. δ-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**.



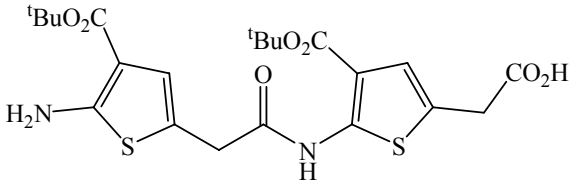
111 **119** **121**

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 δ-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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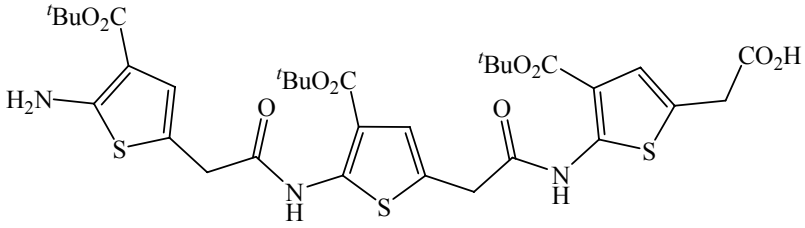

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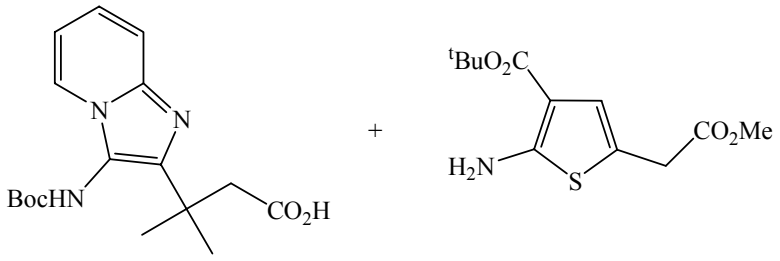
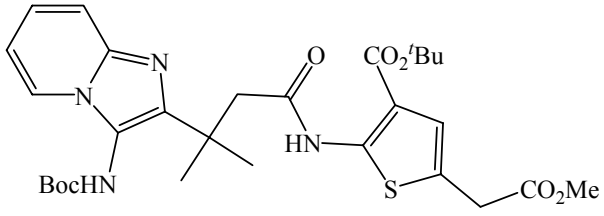
10. δ-Amino ester **111** was coupled with compound **96**, which incorporates a pyridinoimidazolo moiety, and tetrapeptide analogue **130** was obtained in the presence of TFFH and DIEA.



96 **111d**



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CURRICULUM VITAE

Name: Ivana S. Veljković

Date of Birth: 6th 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"