Summary of PhD thesis

SYNTHESES AND TRANSFORMATIONS OF DIFUNCTIONAL TETRAHYDROISOQUINOLINES

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A. INTRODUCTION AND AIMS

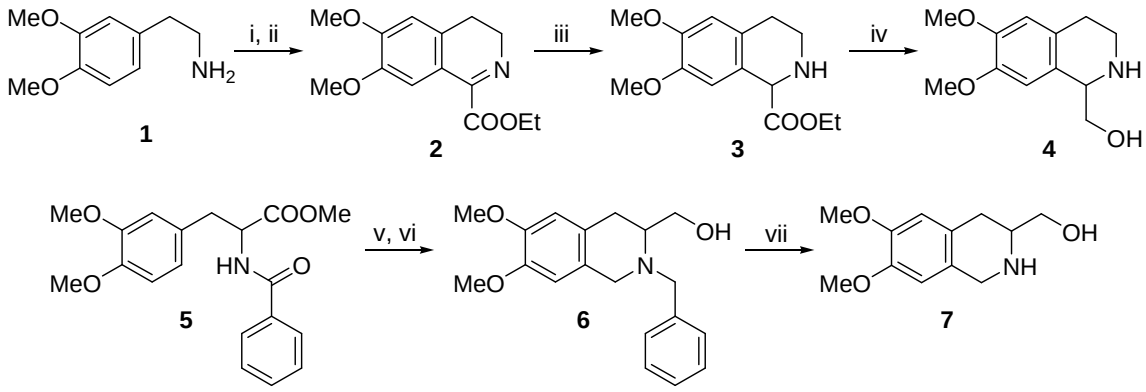
The isoquinoline skeleton is a heterocyclic ring system that frequently occurs among both natural and synthetic bioactive molecules. Isoquinoline derivatives are applied for many therapeutic purposes (*e.g.* the spasmolytic papaverine, the antitussive noscapine, the expectorant emetine, the angiotensin-converting enzyme inhibitor quinapril, the muscle relaxant tubocurarine, the dopaminergic agonist apomorphine, *etc.*). As a consequence of their wide-ranging occurrence among alkaloids and biologically active compounds, great attention has been paid to the synthesis of variously saturated and functionalized isoquinoline derivatives. Asymmetric methods have also been developed for the preparation of enantiomerically pure analogues.

The synthesis and transformations of difunctional 1- and/or 3-substituted 1,2,3,4-tetrahydroisoquinoline derivatives have been research topics at the Institute of Pharmaceutical Chemistry, University of Szeged, in recent decades. During this work, numerous tetrahydroisoquinoline-condensed 5- and 6-membered 1,3-, 1,2,3- and 1,2,3,4-heterocycles have been obtained by cyclization of the corresponding tetrahydroisoquinoline 1,2- and 1,3-amino alcohols, hydrazino alcohols and diamines. The structural analysis of the prepared tricycles revealed that both the conformational and the ring-chain tautomeric equilibria of these ring systems are influenced significantly by the effects of the substituents and the relative configurations of the substituted atoms.

In the frame of my PhD work, in connection with the above-mentioned previous systematic studies on tetrahydroisoquinoline derivatives, our primary aim was to collect further data on the chemistry of difunctional tetrahydroisoquinoline compounds. We planned to investigate the scope and limitations of the ring-closure reactions of tetrahydroisoquinoline 1,2- and 1,3-amino alcohols with S- or P-containing agents; and to study the effects of some structural parameters (C or P substituents and relative configurations) on the predominant conformations of the angularly or linearly-fused *N*-bridged tricycles. A further aim of my PhD work was to devise a new synthetic approach for the preparation of 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid derivatives by utilizing Ugi 3-component reactions with the participation of readily available 3,4-dihydroisoquinolines. We also planned to study the influence of chiral non-racemic acids on the stereochemical outcome of Ugi condensations of dihydroisoquinolines.

B. RESULTS AND DISCUSSION

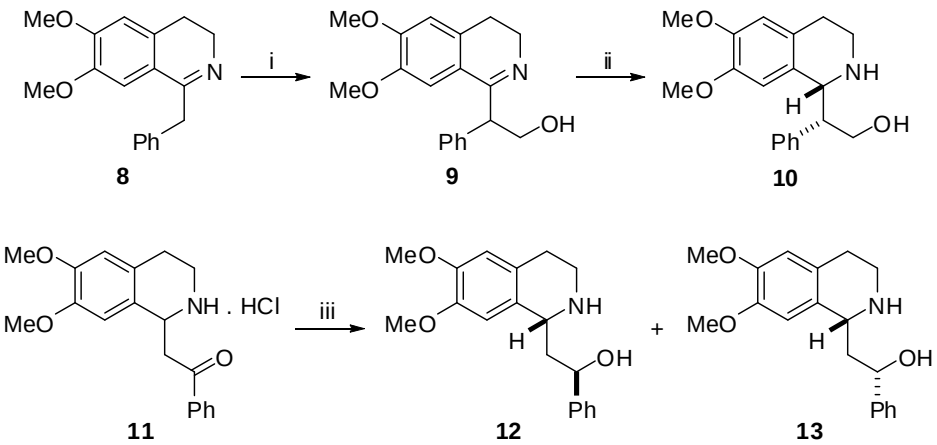
1. Tetrahydroisoquinoline 1,2- and 1,3-amino alcohols **4**, **7**, **10**, **12** and **13**, starting materials for the further cyclizations, were synthetized by using literature methods. The regio-isomeric **4** and **7** were prepared from homoveratrylamine (**1**) or racemic *N*-benzoyl-3,4-dimethoxyphenylalanine methyl ester (**5**) In both cases, the alcoholic function was built by $LiAlH_4$ reduction of the corresponding ester group, which was preceded (for **4**) or followed (for **7**) by construction of the tetrahydroisoquinoline skeleton (Scheme 1).



Reagents and conditions: (i) $(COOEt)_2$, 140 °C; (ii) $POCl_3$, toluene-EtOH; (iii) H_2, 5% Pt/C, EtOH, r.t.; (iv) $LiAlH_4$, THF, (v) $LiAlH_4$, THF, reflux, 5 h; (vi) CH_2O, HCl, H_2O, reflux, 6 h; (vii) H_2, 10% Pd/C, MeOH, 30 bar, 40 °C, 30 h.

Scheme 1

(1*R**,1'*R**)-1-(2'-Hydroxy-1'-phenylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**10**) was prepared by the stereoselective $NaBH_4$ reduction of the hydroxymethylated

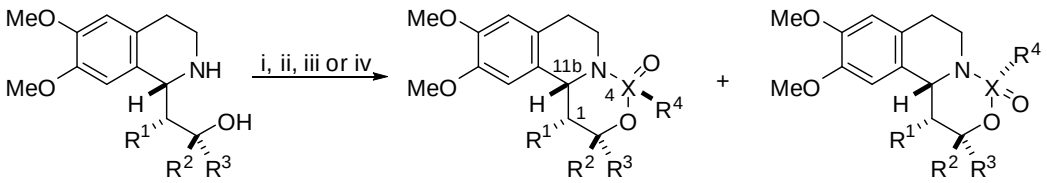


Reagents and conditions: (i) CH_2O, NaOEt, EtOH, r.t.; (ii) $NaBH_4$, MeOH, 0 °C → r.t.; (iii) $NaBH_4$, MeOH, 0 °C → r.t., then r.t., 3 h, then fractional crystallization.

Scheme 2

derivative (**9**) of 1-benzyl-6,7-dimethoxy-3,4-dihydroisoquinoline (**8**). 1-(2'-Hydroxy-2'-phenylethyl)-substituted tetrahydroisoquinoline diastereomers **12** and **13** were obtained from the corresponding β-amino ketone **11** by reduction with $NaBH_4$. In contrast with the literature data, both the (1*R**,2'*R**) and (1*R**,2'*S**) diastereomers (**12** and **13**) could be isolated by fractional crystallization of the crude reduction product (Scheme 2).

2. Novel 1- or 2-phenyl-substituted 4-[bis(2-chloroethyl)amino]- or 4-phenyl-9,10-dimethoxy-1,6,7,11b-tetrahydro-2*H*-1,3,2-oxazaphosphino[4,3-*a*]isoquinoline 4-oxides (**14**-**19**), and 9,10-dimethoxy-1,6,7,11b-tetrahydro-2*H*-1,2,3-oxathiazino[4,3-*a*]isoquinoline 4-oxides (**20**-**22**) and 4,4-dioxides (**23**-**25**) were prepared by the ring closure of phenyl-substituted tetrahydroisoquinoline-1-ethanols (**10**, **12** and **13**) with phenylphosphonic dichloride, bis(2-chloroethyl)phosphoramidic dichloride, thionyl chloride or sulphuryl chloride (Scheme 3).

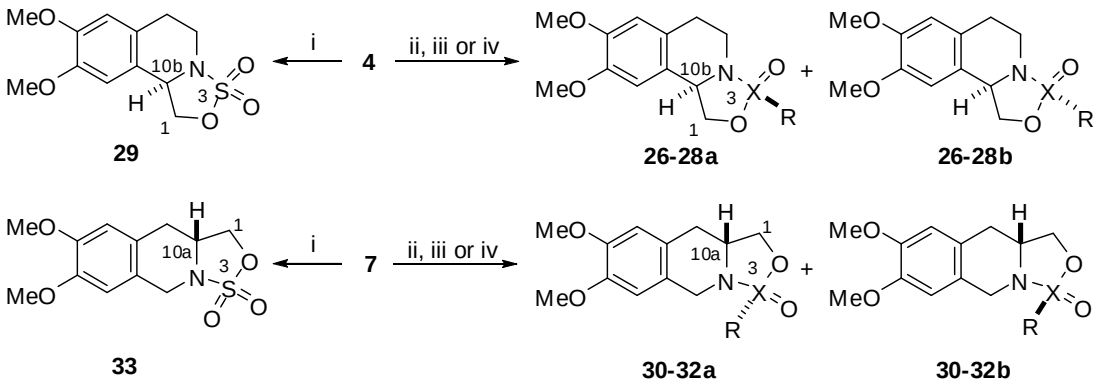


Compound	R^1	R^2	R^3	R^4	X	Diastereomeric ratio (**a** : **b**) in the crude product	Diastereomeric excess (*de*)
14	Ph	H	H	Ph	P	55 : 45	10%
15	Ph	H	H	$N(CH_2CH_2Cl)_2$	P	~0 : ~100	~100%
16	H	Ph	H	Ph	P	55 : 45	10%
17	H	Ph	H	$N(CH_2CH_2Cl)_2$	P	45 : 55	10%
18	H	H	Ph	Ph	P	55 : 45	10%
19	H	H	Ph	$N(CH_2CH_2Cl)_2$	P	45 : 55	10%
20	Ph	H	H	electron pair	S	~0 : ~100	~100%
21	H	Ph	H	electron pair	S	22 : 78	56%
22	H	H	Ph	electron pair	S	16 : 84	68%
23	Ph	H	H	O	S	-	-
24	H	Ph	H	O	S	-	-
25	H	H	Ph	O	S	-	-

Reagents and conditions: (i) $PhPOCl_2$, CH_2Cl_2, Et_3N, 6 °C → r.t., then r.t., 24 h; (ii) $(ClCH_2CH_2)_2NPOCl_2$, CH_2Cl_2, Et_3N, r.t., 48 h. (iii) SO_2Cl_2, Et_3N, CH_2Cl_2, -15 °C → r.t., 2 h, then r.t., 48 h; (iv) $SOCl_2$, Et_3N, CH_2Cl_2, -15 °C → r.t., 2 h, then r.t., 48 h.

Scheme 3

3. The first representatives of new ring systems, 1,5,6,10b-tetrahydro-1,3,2-oxazaphospholo[4,3-*a*]isoquinolines (**26** and **27**), 1,5,10,10a-tetrahydro-1,3,2-oxazaphospholo-[3,4-*b*]isoquinolines (**30** and **31**), 1,5,6,10b-tetrahydro-1,2,3-oxathiazolo[4,3-*a*]isoquinolines (**28** and **29**) and a 1,5,10,10a-tetrahydro-1,2,3-oxathiazolo[3,4-*b*]isoquinoline (**32**), were prepared by cyclizations of regioisomeric tetrahydroisoquinoline 1,2-amino alcohols with the above-mentioned P- or S-containing agents (Scheme 4).



Compound	X	R	Diastereomeric ratio (**a** : **b**) in the crude product	Diastereomeric excess (*de*)
26	P	Ph	50 : 50	0%
27	P	$N(CH_2CH_2Cl)_2$	55 : 45	10%
28	S	electron pair	80 : 20	60%
30	P	Ph	42 : 58	16%
31	P	$N(CH_2CH_2Cl)_2$	43 : 57	14%
32	S	electron pair	~100 : ~0	~100%

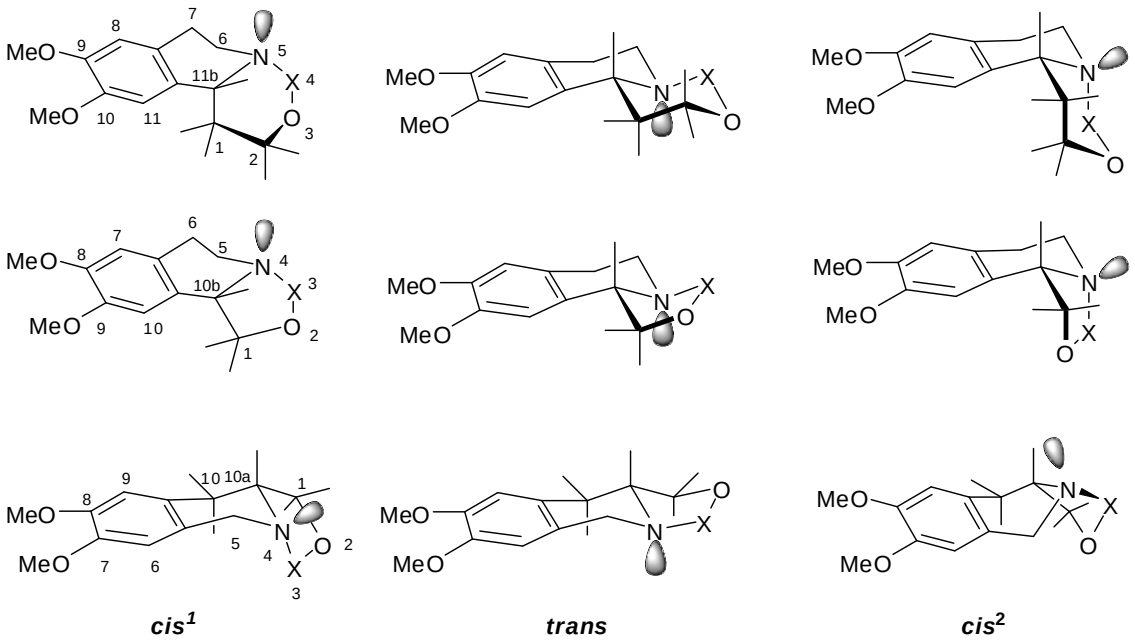
Reagents and conditions: (i) SO_2Cl_2, Et_3N, CH_2Cl_2, -15 °C → r.t., 2 h, then r.t., 48 h, (ii) $PhPOCl_2$, CH_2Cl_2, Et_3N, 6 °C → r.t., then r.t., 24 h; (iii) $(ClCH_2CH_2)_2NPOCl_2$, CH_2Cl_2, Et_3N, r.t., 48 h; (iv) $SOCl_2$, Et_3N, CH_2Cl_2, -15 °C → r.t., 2 h, then r.t., 48 h.

Scheme 4

4. The NMR spectra of the crude ring-closed products indicated that, (with the exception of **15b**) the ratio of the diastereomers, differing in the *cis* or *trans* position of the P substituent and the H atom at the annelation, was only slightly influenced by the substituents on the P or by the type or substituents of the tetrahydroisoquinoline amino alcohols. However, in the ring closures with thionyl chloride, the diastereomers containing the S=O group and with the H atom at the annelation in the *cis* position were formed as

the main products with good to high selectivities (*de*: 66-100%). The diastereomers were separated by column chromatography.

5. NMR analysis and theoretical DFT calculations revealed that the conformations of the 1- or 2-phenyl-substituted tetrahydro-1,3,2-oxazaphosphino[4,3-*a*]isoquinoline 4-oxides (**14**-**19**) depend neither on the position of the phenyl substituent nor on the relative configuration of C-2. The geometry of the connection of rings B/C is influenced only by the relative configuration of P-4, independently of the substituent on the P atom: compounds containing a P=O group in the *trans* position relative to H-11b (diastereomers **a**) could be characterized by the *cis*[1] conformation, while their *cis* counterparts (diastereomers **b**) contained *trans*-connected rings B/C (Scheme 5).



Possible connections of rings B/C in saturated 6- and 5-membered O,X,N heterocycles condensed angularly or linearly to 1,2,3,4-tetrahydroisoquinoline

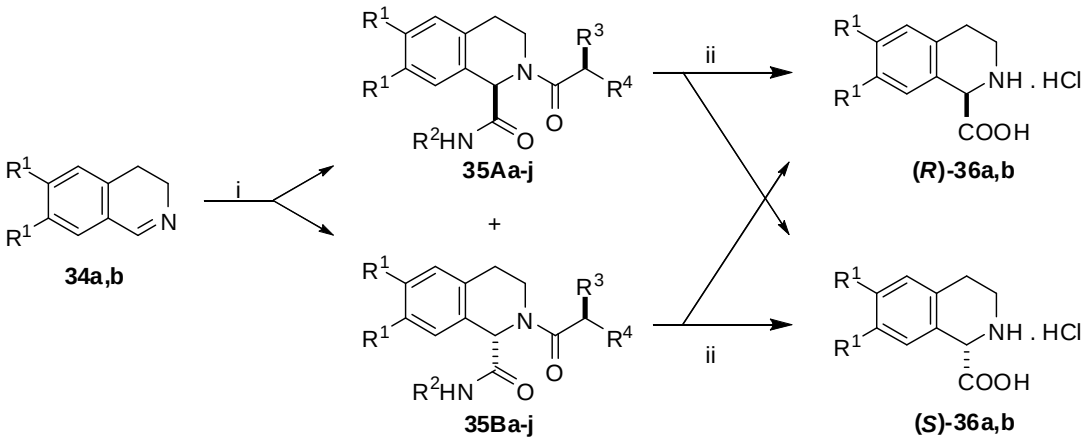
Scheme 5

6. For the 1- or 2-phenyl-substituted tetrahydro-1,2,3-oxathiazino[4,3-*a*]isoquinoline 4-oxides and 4,4-dioxides, the position of the phenyl substitution exerted a significant effect on the predominant conformation: the connection of rings B/C proved to be *trans* for the 1-phenyl-substituted derivatives (**20b** and **23**), while the conformational equilibria of the 2-phenyl-substituted analogues (**21b**, **22b**, **24** and **25**) were found to be shifted towards the *cis*[1] form, independently of the relative configuration of C-2.

7. The NMR spectroscopic conformational analyses on the 1,2,3-oxathiazolidine or 1,3,2-oxazaphospholidine derivatives angularly- or linearly-condensed to tetrahydroisoquinoline

(**26**-**32**) revealed that they exist as conformational equilibria which are fast on the NMR time scale; both the piperidine ring and the 5-membered ring moieties can interconvert. DFT calculations of the structures indicated that, in general two conformers participate in the conformational equilibria. Insertion of the S or P atom caused significant changes in the preferred conformation as compared with the parent oxazolo[4,3-*a*]- and [3,4-*b*]-isoquinoline. Similarly to the homologous **14**-**19**, the stereochemistry of the ring B/C connection (Scheme 5) was found to be dependent on the P configuration relative to that of the C atom at the annelation both for the linear and for the angular 1,3,2-oxaza-phospholidine derivatives (**30**, **31** and **26**, **28**).

8. 1-Unsubstituted 3,4-dihydroisoquinolines proved to be convenient starting materials for Ugi condensations with acids and isocyanides, resulting in 2-acyl- (**35**) or 2-benzyloxy-



34/36	R^1
a	H
b	OMe

35	R^1	R^2	R^3	R^4	Ratio of more mobile and less mobile diastereomers in the crude product (yield)	Enantiomeric excess (*ee*)
a	H	CH_2Ph	OH	Ph	45 (37) : 55 (30)	10%
b	H	CH_2Ph	NPhth	Me	51 (2) : 49 (22)	2%
c	H	cyclohexyl	OH	Ph	50 (32) : 50 (21)	0%
d	H	cyclohexyl	NPhth	Me	47 (12) : 53 (18)	6%
e	H	Bu^t	OH	Ph	50 (25) : 50 (26)	0%
f	OMe	CH_2Ph	OH	Ph	48 (22) : 52 (20)	4%
g	OMe	CH_2Ph	NPhth	Me	45 (8) : 55 (22)	10%
h	OMe	cyclohexyl	OH	Ph	49 (30) : 51 (26)	2%
i	OMe	cyclohexyl	NPhth	Me	50 (0) : 50 (15)	0%
j	OMe	Bu^t	OH	Ph	50 (0) : 50 (19)	0%

Reagents and conditions: (i) R^2NC, $R^3R^4CHCOOH$, MeOH, r.t., 1-4 days; (ii) 10% HCl, reflux, 5-40 h.

Scheme 6

carbonyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamides (**37**) in moderate to good yields. Acidic hydrolysis of the dicarboxamides formed (**35** and **37**) resulted in 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids (**36**). Our two-step procedure (Ugi condensation and subsequent hydrolysis of the carboxamide intermediate) provides a new approach for the synthesis of tetrahydroisoquinoline-1-carboxylic acids (Schemes 6 and 7).

9. The condensations of chiral, non-racemic acids with 3,4-dihydroisoquinolines and isocyanides took place with no or only poor diastereoselectivities (*de*: 0-10%, Table 1). During the hydrolysis of the separated diastereomeric Ugi products, enantiomers of 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (**36a**) and its 6,7-dimethoxy analogue (**36b**) were formed to the accompaniment of a considerable degree of racemization.

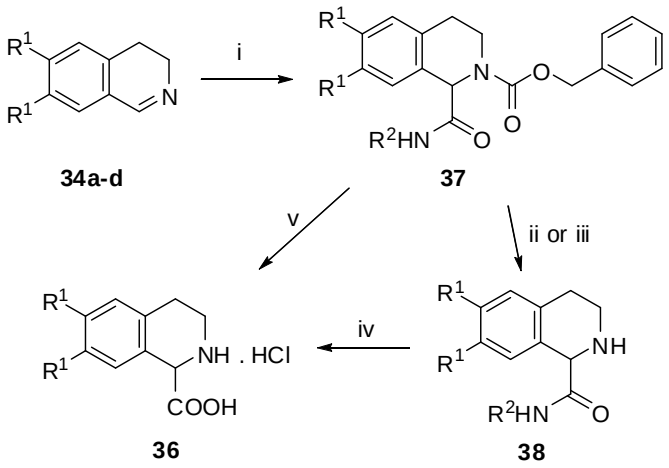
Table 1

Enantiomeric ratios (based on HPLC) of the tetrahydroisoquinolinecarboxylic acids **36a** or **36b** in the crude products formed in the acidic hydrolysis of **35a-g** with 10% HCl

Compound*	Reflux time (h) for 100% conversion	Enantiomeric ratio	Enantiomeric excess (*ee*)
35a (M)	17.5	83 : 17	66%
35a (L)	20	13 : 87	74%
35b (M)	16.5	12 : 88	76%
35b (L)	9	63 : 37	26%
35c (L)	7	33 : 67	34%
35d (M)	40	42 : 58	16%
35d (L)	40	77 : 23	54%
35e (L)	13	27 : 73	46%
35f (M)	15	73 : 27	46%
35f (L)	5	22 : 78	56%
35g (M)	12	20 : 80	60%
35g (L)	40	60 : 40	20%

* (M) = more mobile diastereomer, (L) = less mobile diastereomer

10. The hydrogenolysis of 2-benzyloxycarbonyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamides (**37**) proved to be a convenient procedure for the preparation of 1,2,3,4-tetrahydroisoquinoline-1-carboxamides (**38**). The hydrolysis of the carboxamides (**38**) led to the corresponding 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids (**36**) (Scheme 7).



34/36	R^1
a	H
b	OMe
c	EtO
d	OCH_2O

37	R^1	R^2
a	H	cyclohexyl
b	MeO	cyclohexyl
c	EtO	cyclohexyl
d	OCH_2O	cyclohexyl
e	MeO	CH_2Ph
f	MeO	Bu^t

38	R^1	R^2
a	H	cyclohexyl
b	MeO	cyclohexyl
c	EtO	cyclohexyl
d	OCH_2O	cyclohexyl
e	MeO	CH_2Ph
f	MeO	Bu^t

Reagents and conditions: (i) $PhCH_2OCOCl$, isocyanide, $CHCl_3$, r.t., 5-24 h, then H_2O, r.t., 30 min (46-89%); (ii) 1. 33% HBr in AcOH, 30 min, r.t., 2. NaOH (83-95%); (iii) H_2 (1 atm), Pd/C, EtOH, r.t., 4-6 h (61-89%), (iv) 10% HCl, reflux, 20-25 h (62-76%). (v) 10% HCl, reflux, 20-65 h (36-76%).

Scheme 7

C. PUBLICATIONS

Papers related to the thesis

I. **I. Schuster**, A. Sztojkov-Ivanov, L. Lázár, F. Fülöp:
Synthesis of 1,2,3,4-Tetrahydroisoquinoline-1-carboxylic Acid Derivatives via Ugi Reactions
Lett. Org. Chem., **2007**, *4*, 102. **IF: 0.981**

II. **I. Schuster**, A. Koch, M. Heydenreich, E. Kleinpeter, E. Forró, L. Lázár, R. Sillanpää, F. Fülöp:
Synthesis and Conformational Analysis of Tetrahydroisoquinoline-fused 1,3,2-Oxazaphospholidines and 1,2,3-Oxathiazolidines
Eur. J. Org. Chem., **2008**, 1464-1472. **IF: 3.016**

III. **I. Schuster**, A. Koch, M. Heydenreich, E. Kleinpeter, L. Lázár, F. Fülöp:
Synthesis and Conformational Analysis of Phenyl-substituted 1,3,2-Oxazaphosphino[4,3-*a*]- and 1,2,3-Oxathiazino[4,3-*a*]isoquinolines
J. Mol. Struct., **2008**, *888*, 124-137. **IF: 1.594**

IV. **I. Schuster**, L. Lázár, F. Fülöp:
A Convenient Synthesis of 1,2,3,4-Tetrahydroisoquinoline-1-carboxylic Acid Derivatives via Isocyanide-Based Three-Component Reactions
Synth. Commun., accepted for publication. **IF: 0.981**

Other papers

V. I. Starke, **I. Schuster**, F. Fülöp and E. Kleinpeter:
Mass Spectra of Tetrahydroisoquinoline-fused 1,3,2-O,N,P and 1,2,3-O,S,N-heterocycles – Influence of Ring Size, Ring Fusion, Heteroatom and Substituent Effects, and the Stereochemistry on Fragmentation
Rapid Commun. Mass Spectrom., **2008**, *22*, 1519-1527. **IF: 2.772**

D. CONFERENCE LECTURES

VI. **Schuster Ildikó**:
Tetrahidroizokinolin-1-karbonsav származékok előállítása Ugi-reakcióval
A Szegedi Ifjú Szerves Kémikusok Támogatásáért Alapítvány Tudományos Előadóülése
Szeged, 2005. január 12.

VII. **Schuster Ildikó**, Sztojkov-Ivanov Anita, Lázár László, Fülöp Ferenc:
Ugi-reakció – új szintézismódszer tetrahidroizokinolin-1-karbonsav-származékok előállítására
MTA Heterociklusos Kémiai Munkabizottság ülése
Balatonszemes, 2005. május 25-27.

VIII. **Schuster Ildikó**, Sztojkov-Ivanov Anita, Lázár László, Fülöp Ferenc:
Tetrahidroizokinolin-1-karbonsav származékok előállítása Ugi-reakcióval
MKE Vegyészkonferencia
Hajdúszoboszló, 2005. június 28-30. Abstr.: P-78, p. 128.

IX. Ines Starke, Erich Kleinpeter, **Ildikó Schuster**, László Lázár, Ferenc Fülöp:
Fragmentation of P,S-containing Isoquinolines (*Stereochemical aspects*)
Tagung der Deutschen Gesellschaft für Massenspektrometrie
Mainz, Germany, 3 March 2006. Abstr.: P3-16.

X. **Schuster Ildikó**:
Izokinolinnal kondenzált foszfor- és kéntartalmú heterociklusok szintézise és szerkezetvizsgálata
PhD előadói napok
Szeged, 2006. május 3.

XI. **Schuster Ildikó**, Andreas Koch, Matthias Heydenreich, Erich Kleinpeter, Lázár László, Fülöp Ferenc:
Izokinolinnal kondenzált foszfor- és kéntartalmú heterociklusok szintézise és szerkezetvizsgálata
MTA Heterociklusos Kémiai Munkabizottság ülése
Balatonszemes, 2006. június 7-9.

XII. **Schuster Ildikó**, Andreas Koch, Matthias Heydenreich, Erich Kleinpeter, Lázár László, Fülöp Ferenc:
Régioizomer 1,3,2-oxazafoszfolo- és 1,2,3-oxatiazoloizokinolinok szintézise és konformációanalízise
Centenáriumi Vegyészkonferencia
Sopron, 2007. május 29 - június 1. Abstr. SZ-P-50, p. 368.