SYNTHESES AND TRANSFORMATIONS OF DIFUNCTIONAL TETRAHYDROISOQUINOLINES

PhD Thesis

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CONTENTS

ABBREVIATIONS AND SYMBOLS

Ac	=	Acetyl
Boc	=	*tert*-Butoxycarbonyl
Bu	=	Butyl
Bu^t	=	*tert*-Butyl
Cbz	=	Carboxybenzoyl
DEAD	=	Diethyl azodicarboxylate
DMF	=	Dimethylformamide
DMSO	=	Dimethylsulphoxide
EDDA	=	Ethylene diammonium diacetate
Et	=	Ethyl
EtO	=	Ethoxy
^3J	=	Vicinal scalar coupling constant
MCR	=	Multicomponent reaction
Me	=	Methyl
MeO	=	Methoxy
Ms	=	Mesyl
NMR	=	Nuclear magnetic resonance
NOESY	=	Nuclear Overhauser effect spectroscopy
Ph	=	Phenyl
Phth	=	Phthaloyl
PPA	=	Poly(phenylacetylene)
ppm	=	Parts per million
Pr^i	=	Isopropyl
r.t.	=	Room temperature
TBDMS	=	*Tert*-butyldimethylsilyl
TEBAC	=	Triethylbenzylammonium chloride
Tf	=	Trifluoromethylsulphonyl
THF	=	Tetrahydrofuran
TMS	=	Tetramethylsilane
TMSOTf	=	Tetramethylsilyl triflate
Ts	=	Tosyl
U-4CR	=	Ugi four-component reaction
δ	=	Chemical shift

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*, 102-108.

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.

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.

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
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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
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VI. **Schuster Ildikó**:
Tetrahidroizokinolin-1-karbonsav származékok előállítása Ugi-reakcióval
A Szegedi Ifjú Szerves Kémikusok Támogatásáért Alapítvány Tudományos Előadóülése
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VII. **Schuster Ildikó**, Sztojkov-Ivanov Anita, Lázár László, Fülöp Ferenc:
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MTA Heterociklusos Kémiai Munkabizottság ülése
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VIII. **Schuster Ildikó**, Sztojkov-Ivanov Anita, Lázár László, Fülöp Ferenc:
Tetrahidroizokinolin-1-karbonsav származékok előállítása Ugi-reakcióval
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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.

1. INTRODUCTION

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. The spasmolytic papaverine (**1**), the antitussive noscapine (**2**), the expectorant emetine (**3**), the angiotensin-converting enzyme inhibitor quinapril (**4**), the muscle relaxant tubocurarine (**5**) and the dopaminergic agonist apomorphine (**6**) are only a few examples of the naturally-occurring or synthetic isoquinoline derivatives which have pharmaceutical applications (Fig. 1).[1]

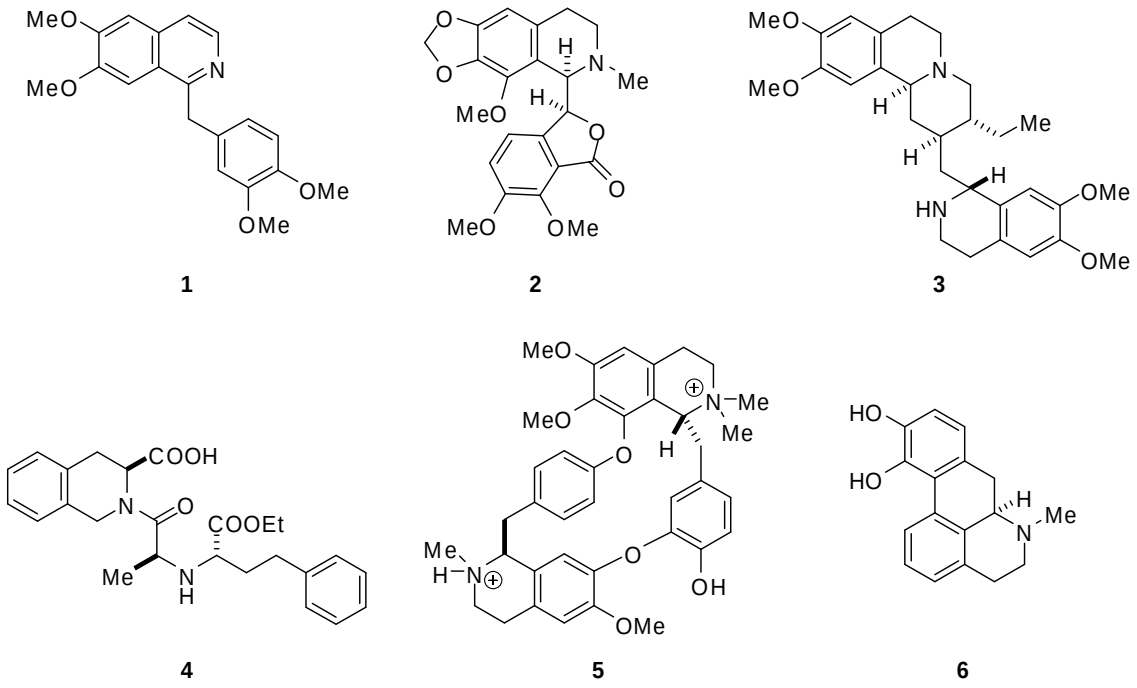
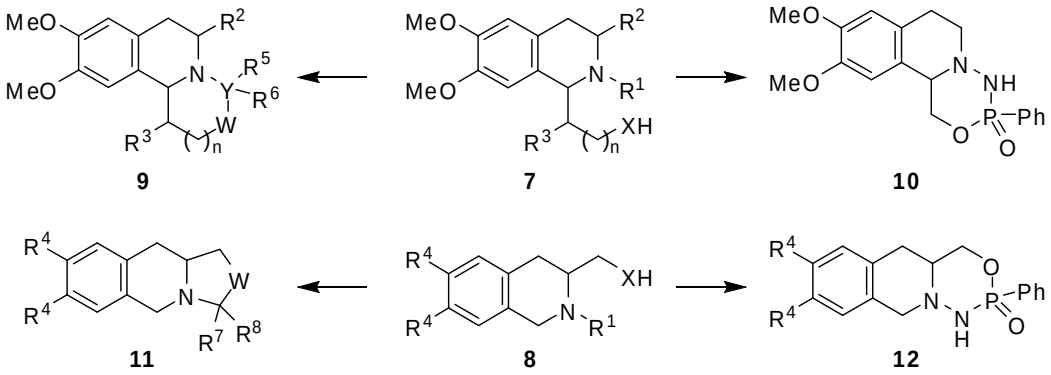


Figure 1

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.[2-6] Asymmetric methods have also been developed for the preparation of enantiomerically pure analogues.[7]

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 tetrahydro-isoquinoline-condensed 5- and 6-membered 1,3-, 1,2,3- and 1,2,3,4-heterocycles (**9**-**12**) have been prepared by cyclization of the corresponding tetrahydroisoquinoline 1,2- and 1,3-amino

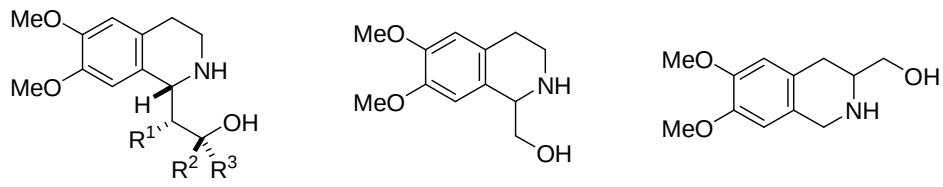
alcohols, hydrazino alcohols and diamines (**7** and **8**) (Scheme 1). The structural analysis of tricycles **9**-**12** revealed that both the conformational and the ring-chain tautomeric equilibria of these ring systems are influenced significantly by the effects of the substituents and the relative configurations of the substituted atoms.[8-18]



R^1 = H, NH_2; R^2 = H, Me; R^3 = H, alkyl, aryl, CH_2OH; R^4 = H, OMe; R^4 = H, Me, Ph;
R^5, R^6 = H, aryl; O; N-alkyl; N-aryl; O, Ph; O, $N(CH_2CH_2Cl)_2$; O, electron pair; O, O;
R^7, R^8 = H, aryl; O; N-alkyl; N-aryl; X = O, NH; Y = C, P, S; W = O, S, NH; n = 0, 1

Scheme 1

In the frame of my PhD work, in connection with the above-mentioned previous systematic studies on tetrahydroisoquinoline derivatives, our 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 **13**-**17** 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 (Fig. 2).[I, II]

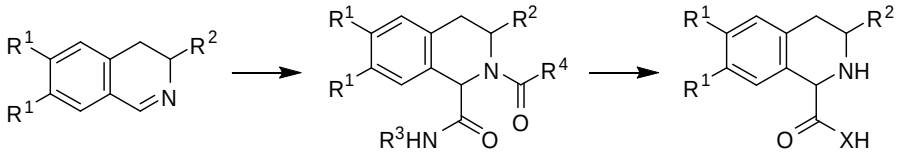


R^1 = Ph, R^2 = R^3 = H: **13**
R^2 = Ph, R^1 = R^3 = H: **14**
R^3 = Ph, R^1 = R^2 = H: **15**

Figure 2

The other part of my PhD work was directed to devising a new approach for the preparation of 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid derivatives **20** by utilizing

Ugi three-component reactions (U-3CRs) with participation of the readily available 3,4-dihydroisoquinolines (**18**), followed by hydrolysis of the diamide intermediates (**19**). An additional aim was to study the influence of chiral non-racemic acids on the stereochemical outcome of the Ugi condensations of dihydroisoquinolines (Scheme 2).[III,IV]



18 **19** **20**

R^1 = H, MeO, EtO, OCH_2O; R^2 = H, Me; R^3 = cyclohexyl, Bu^t, CH_2Ph;

R^4 = cyclohexyl, Ph, CHOHPh (*R*), CHMeN-phthaloyl (*S*), OCH_2Ph; X = O, NR^3

Scheme 2

Details of the syntheses and the physical and analytical data on the new compounds described in the thesis, and descriptions of the NMR spectroscopic analyses, are to be found in the experimental parts of the enclosed publications.

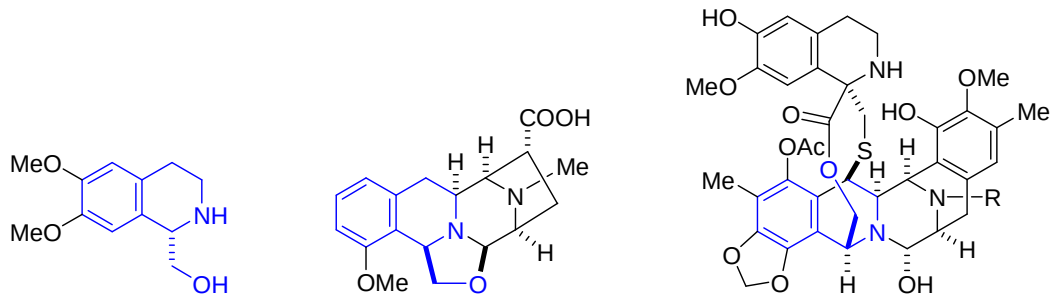
The references to the publications relating to my own research are given as Roman numerals; other literature references are given as Arabic numerals as superscripts.

2. LITERATURE

In this part of my PhD thesis, the most important publications relating to my research topics are discussed. In the first section, some recent results on the synthesis and transformations of 1-(1' or 2'-hydroxyalkyl)-substituted 1,2,3,4-tetrahydroisoquinolines are reported. The second section summarizes the earlier findings on the application of the Ugi reaction for the preparation of isoquinoline derivatives.

2.1. Synthesis and transformations of 1-(hydroxyalkyl)-1,2,3,4-tetrahydroisoquinolines

The 1,2,3,4-tetahydroisoquinoline-1-methanol moiety is a rare structural unit among the naturally-occurring compounds. The 6,7-dimethoxy derivative calycotomine was first isolated from the Australian plant *Calycotome spinosa* Link as the optically active (*S*)-(+) enantiomer [(*S*)-**16**]. Synthetic methods towards calycotomine in racemic and enantiomeric forms were recently reviewed.[19]



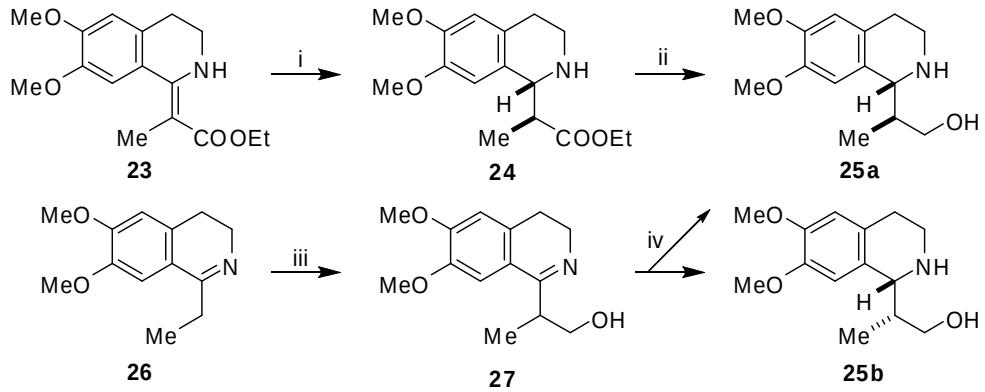
calycotomine [(*S*)-**16**] (-)-quinocarcin (**21**) R = Me: ecteinascidin-743 (**22a**)
R = H: ecteinascidin-729 (**22b**)

Figure 3

More complex isoquinoline alkaloids, such as quinocarcin (**21**), produced by several *Streptomyces* species, and the ecteinascidins (**22**), from the marine tunicate *Ecteinascidia turbinata*, also bear 1-hydroxymethyl substituents attached to a tetrahydroisoquinoline moiety (Fig. 3).[20] Because of their antiproliferative activities, the synthetic opportunities and structural modifications of both quinocarcin and the ecteinascidins have been studied thoroughly, which has contributed considerably to a better understanding of the chemical characteristics of the 1,2,3,4-tetrahydroisoquinoline-1-methanol derivatives.[21-24] Ecteinascidin-743 (**22a**) became the first marine anticancer agent approved in the European Union under the name trabectedin (Yondelis®) for patients with soft tissue sarcoma.[25]

2.1.1. Synthesis

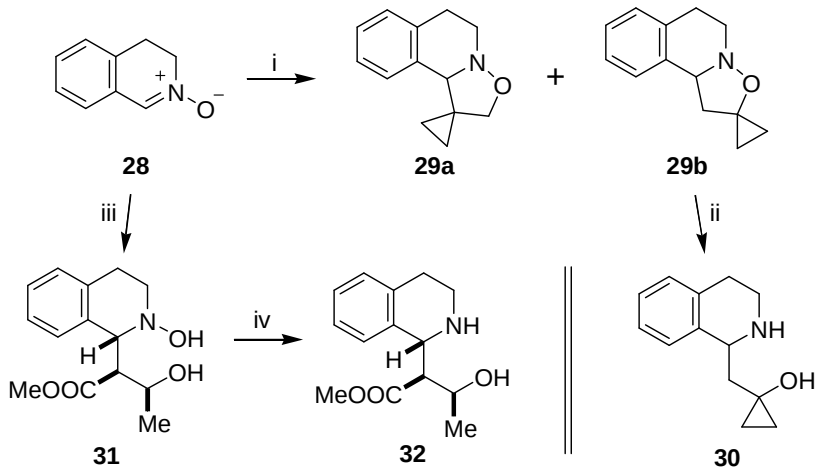
The most frequent methods for the synthesis of 1-(1’ or 2’-hydroxyalkyl)-substituted 1,2,3,4-tetrahydroisoquinolines apply reduction steps to form the alcoholic hydroxy and/or the secondary amine functions of these compounds. Reductions of the appropriate tetrahydro-isoquinoline carboxylic esters or the dihydroisoquinoline alcohols can be the final transformations in these procedures,[26-32] both of which can be illustrated by the preparations of the diastereomeric 1’-methyl-substituted tetrahydroisoquinoline 1,3-amino alcohols **25a** and **25b** (Scheme 3). The reductions of both the enamino ester **23** and the dihydroisoquinoline **27** proceeded with good or excellent diastereoselectivity.[9,10,12,33]



Reagents and conditions: (i) Pt/H_2, EtOH, 30 min; (ii) $LiAlH_4$, THF, reflux, 2 h and fractional crystallization (for **25a**: 44%, i+ii), (iii) HCHO, NaOEt, MeOH, r.t., 5 h; (iv) $NaBH_4$, MeOH, r.t., 3 h and fractional crystallization (for **25b**: 51%, iii+iv).

Scheme 3

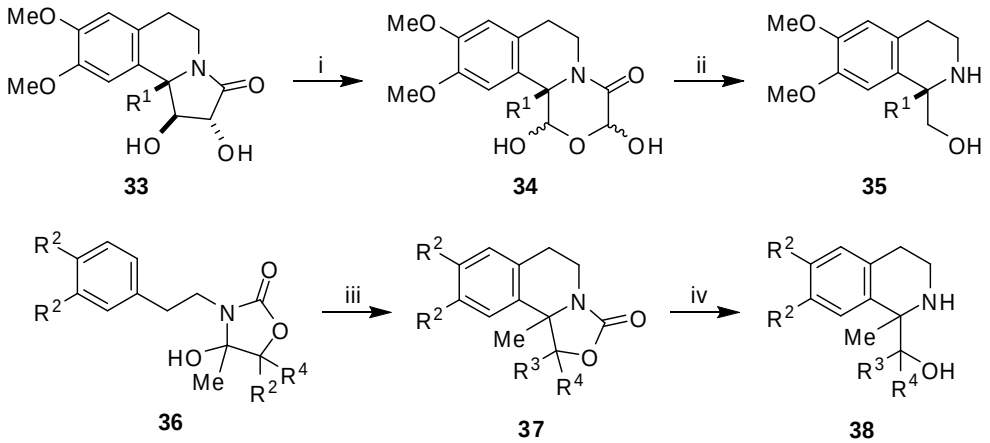
Addition reactions of 3,4-dihydroisoquinoline-2-oxide (**28**) in combination with a subsequent reduction step have also been utilized to prepare tetrahydroisoquinoline 1,3-amino alcohols.[34,35] The 1,3-dipolar cycloadditions of **28** to methylenecyclopropane resulted in the regioisomeric isoxazolidine-spirocyclopropane derivatives (**29a**,**b**). The chemoselective SmI_2 reduction or catalytic hydrogenation of the separated **29b** led to **30** by opening of the isoxazolidine ring and preservation of the fragile cyclopropanol moiety (Scheme 4).[34] Compound **28** underwent addition with a chiral ketene silyl acetal containing a silyl-protected hydroxy group in the presence of a Lewis acid catalyst to give the adduct **31** with high diastereoselectivity. The hydroxylamine function of **31** was reduced by catalytic hydrogenation (Scheme 4).[35]



Reagents and conditions: (i) methylenecyclopropane, toluene, 60 °C, 2 days, (67%, **29a** : **29b** = 7 : 1); (ii) SmI_2, THF, r.t., 2 h (70%); (iii) ZnI_2, CH_2Cl_2, (*R*)-1,3-bis(triethylsilyloxy)-1-methoxy-1-butene, -78 °C → 0 °C, 1 h (71%); (iv) Zn, AcOH, 60 °C, 30 min (80%)

Scheme 4

Hydrolysis of the corresponding lactam or cyclic carbamate moieties of the isoquinoline-condensed 1,3- or 1,4-O,N heterocycles bearing a substituent at the annelation C atom is a step often applied in the synthesis of 1-substituted tetrahydroisoquinoline-1-methanol derivatives. The 10b-substituted pyrrolo[2,1-*a*]isoquinolinones **33**, conveniently available from L-tartaric acid, were converted in a two-step procedure ($NaIO_4$



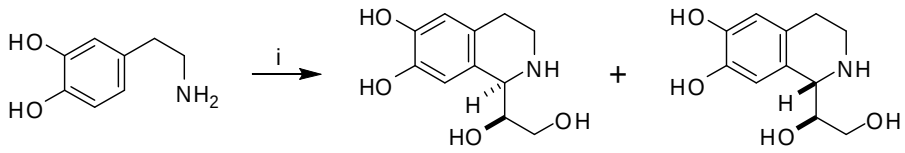
R^1 = Me, Ph; R^2 = H, OMe; R^3, R^4 = Me, Me; Me, Et; $–(CH_2)_5–$

Reagents and conditions: (i) $NaIO_4$, H_2O/MeCN,, r.t., 4-5 days (73-98%); (ii) NaOH, THF/H_2O, r.t., 30 min (84-90%); (iii) PPA, CH_2Cl_2, 120 °C, 4 h (91-98%); (iv) KOH, DMSO : H_2O (1 : 1), 80 °C, 52-155 h (79-97%).

Scheme 5

oxidation followed by an intramolecular Cannizzaro reaction) to 1-substituted calycotomines **35**.[36,37] Hydrolysis of the 1,1,10b-trisubstituted oxazolo[4,3-*a*]isoquinolinon-3-ones **37** furnished the corresponding calycotomine derivatives **38** (Scheme 5).[38]

Pictet–Spengler condensation of dopamine (**39**) and D-glyceraldehyde led to diastereomeric 1-substituted tetrahydroisoquinolines bearing both a 1,2- and a 1,3-amino alcohol moiety (**40a** and **40b**). Transition metal ions (*e.g.* Cu^{2+} and Fe^{3+}) proved to accelerate the formation of **40a** and **40b** markedly, without affecting their product ratio of 2 : 1 (Scheme 6).[39]

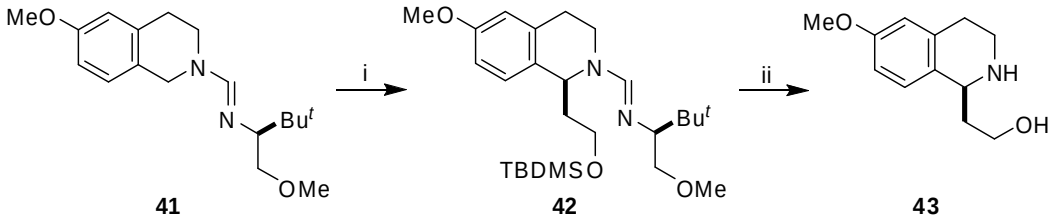


39 **40a** **40b**

Reagents and conditions: (i) D-(+)-glyceraldehyde, pH 8, 37 °C, 3 h (59%)

Scheme 6

The introduction of a 2-hydroxyethyl at moiety to position 1 of the tetrahydroisoquinoline ring was achieved by highly diastereoselective alkylation of **41**, bearing an (*S*)-*tert*-leucine-derived formamidine as a chiral auxiliary group. Removal of the *N* and *O* substituents of **42** led to the tetrahydroisoquinoline amino alcohol **43** as the (*S*) enantiomer (Scheme 7).[40]



41 **42** **43**

Reagents and conditions: (i) BuLi, THF, -78 °C, 20 min, then 2-bromo-1-hydroxyethyl *tert*-butyldimethylsilyl ether, 30 min, EtOH, N_2H_4, 15 °C, 3 h; (ii) HF/H_2O/MeCN, r.t., 3 h.

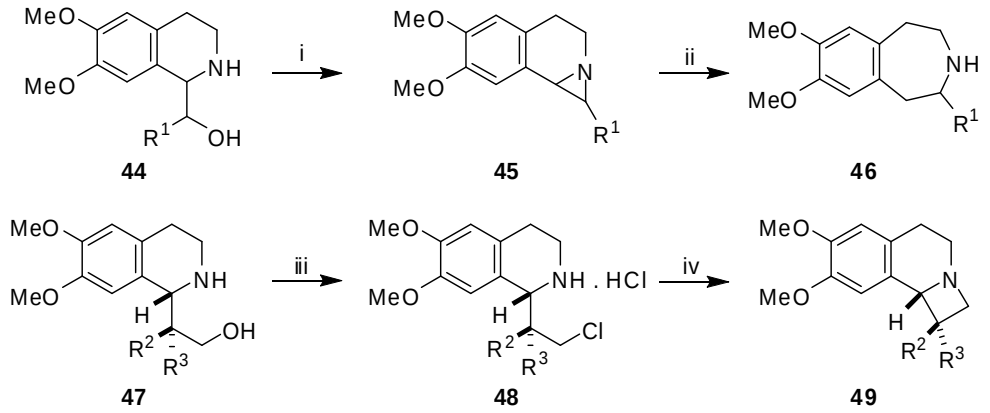
Scheme 7

2.1.2. Ring-closure reactions

The amino alcohol function of the 1-hydroxyalkyl-substituted 1,2,3,4-tetrahydroisoquinolines provides numerous possibilities for the synthesis of various heterocycles condensed angularly to the isoquinoline ring. In many cases, these ring closures are carried

out by insertion of a one-atom-(C, P or S)-containing unit into the amino alcohol moiety, but there are also examples of cyclizations without insertion of any external fragments.

Both 1-hydroxymethyl (**44**) and 1-(2'-hydroxyethyl)-substituted tetrahydroisoquinoline derivatives (**47**) have been cyclized to the corresponding azirino- (**45**) or azeto-[2,1-*a*]isoquinolines (**49**) under Mitsunobu conditions or via a two-step procedure (OH → Cl exchange followed by alkaline treatment), respectively. Catalytic hydrogenation of aziridines **45** led to 3-benzazepine derivatives (**46**) by a ring-enlargement reaction (Scheme 8)[26,29,33]



44 **45** **46**

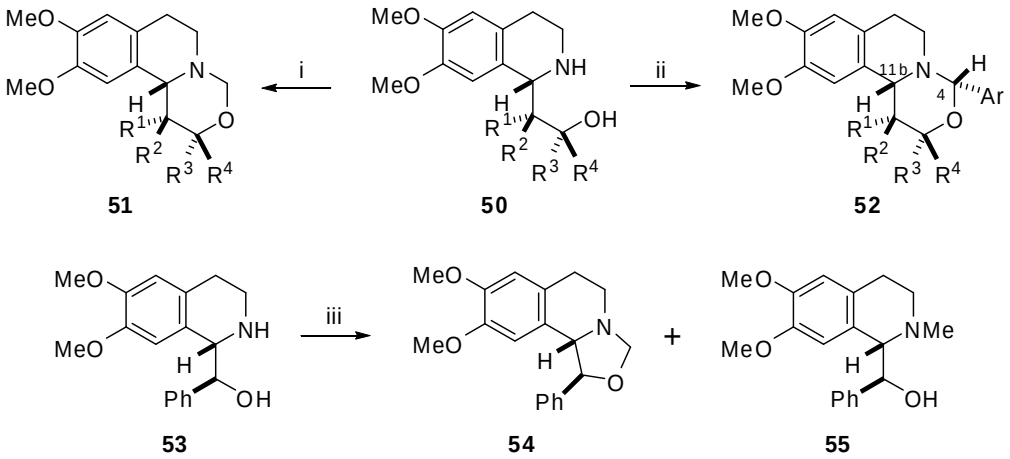
47 **48** **49**

R^1 = CF_3, Ph; R^2 = H, Me, CH_2Ph; R^3 = H, CH_2Ph

Reagents and conditions: (i) ***A****:* PPh_3, CCl_4, Et_3N, MeCN, 30 h (88%) ***B****:* PPh_3, DEAD (72%); (ii) ***A****:* H_2, Pd/C, AcOH/MeOH, r.t., 6 h (98%), ***B****:* H_2, Ra-Ni, MeOH (82%); (iii) $SOCl_2$, reflux, 30 min; (iv) NaOH.

Scheme 8

In the reactions of tetrahydroisoquinoline 1,2- and 1,3-amino alcohols with aldehydes, oxazolo- or 1,3-oxazino[4,3-*a*]isoquinolines were formed as the corresponding cyclic aminals. Ring closure of the methyl- or phenyl-substituted amino alcohols **50** with formaldehyde could be achieved under mild conditions, while the similar reactions with *p*-nitrobenzaldehyde were carried out in refluxing toluene. In the latter cyclizations, diastereomers bearing H-4 and H-11b in the *cis* position were formed as the main or only products. [9,14] It is noteworthy that oxazolo[4,3-*a*]isoquinoline **54** was stable against reductive ring opening, since it was formed as the main product (besides **55**) in the attempted reductive methylation of **53** (Scheme 9).[27]

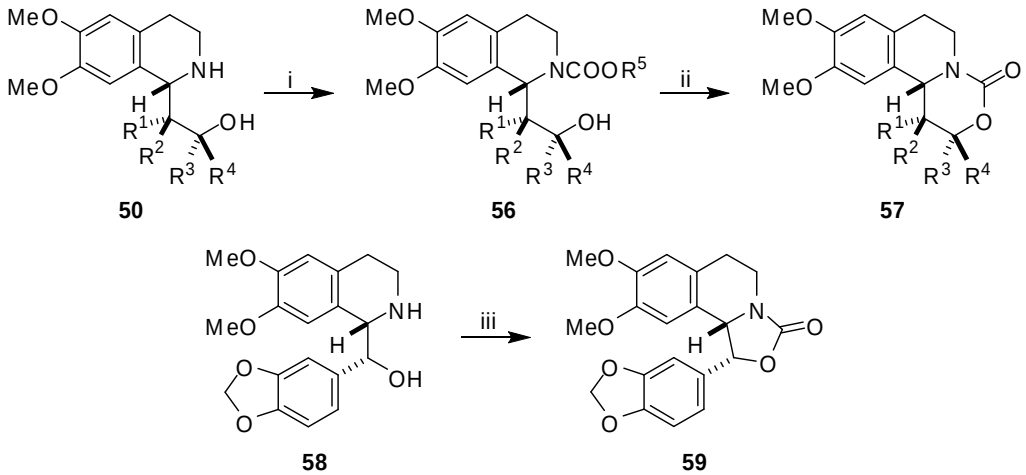


R^1 = H, Me, Ph; R^2 = H, Me; R^3 = H, Me; R^4 = H, Me, Ph; Ar = $C_6H_4NO_2$(*p*)

Reagents and conditions: (i) HCHO, MeOH, H_2O, r.t., 1 h (45-77%); (ii) *p*-nitrobenzaldehyde, toluene, reflux, 6-8 h (35-72%); (iii) HCHO, H_2, Ra-Ni, MeOH, 2.7 atm, r.t., 12 h (67% for **54** and 10% for **55**)

Scheme 9

There are alternative ways to convert tetrahydroisoquinoline 1,2- and 1,3-amino alcohols to the corresponding cyclic urethane derivatives. 1,3-Oxazino[4,3-*a*]isoquinolin-4-ones **57** were prepared via the acyclic ethyl or *tert*-butyl urethanes **56**, by their base-catalysed intramolecular transesterifications,[9,14] while the homologous oxazolone **59** was obtained by a direct cyclization of the amino alcohol **58** with phosgene (Scheme 10).[28]

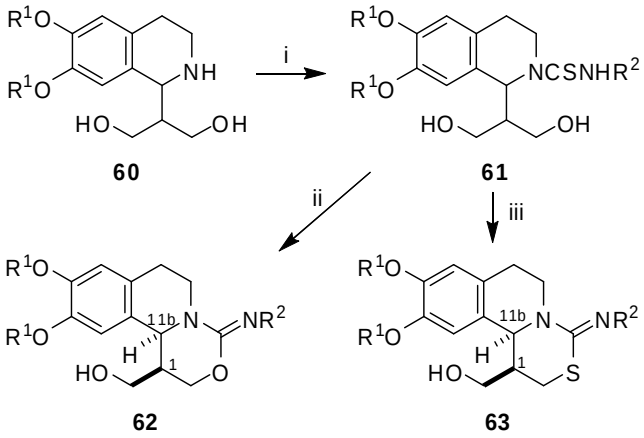


R^1 = H, Me, Ph; R^2 = H, Me; R^3 = H, Me; R^4 = H, Me, Ph; R^5 = Et, Bu^t

Reagents and conditions: (i) ClCOOEt, $NaHCO_3$, 1 h (56-96%) or $(Boc)_2O$, EtOAc, r.t., 16 h (82%); (ii) NaOMe, 160 °C, 45 min (40-53%) or $KOBu^t$, THF, 0 °C. 30 min (83%); (iii) $COCl_2$, Et_3N, THF, r.t., 2 h (73%)

Scheme 10

Thiourea derivatives of 1,2- and 1,3-amino alcohols are conveniently available key intermediates in the synthesis of 2-imino-substituted 1,3-O,N and 1,3-S,N heterocycles (Scheme 11). These transformations are also known among both 1,2- and 1,3-tetrahydroisoquinoline amino alcohols, *e.g.* **60**.[8,13,41] The cyclization of thioureas **61** to the corresponding 4-imino-1,3-oxazino[4,3-*a*]isoquinolines **62** was completed by alkaline treatment of the *S*-methylisothiuronium salts, obtained from **61** with methyl iodide. Under acidic conditions, compounds **61** were transformed to the analogous 4-imino-1,3-thiazino[4,3-*a*]isoquinolines **63**. In both cyclizations, the diastereomers containing H-11b and H-1 in the *cis* position were formed with high diastereoselectivities (Scheme 11).[41]



R^1 = Me, Et; R^2 = Et, cyclohexyl, Ph

Reagents and conditions: (i) R^2NCS, benzene, reflux, 1 h (99%);

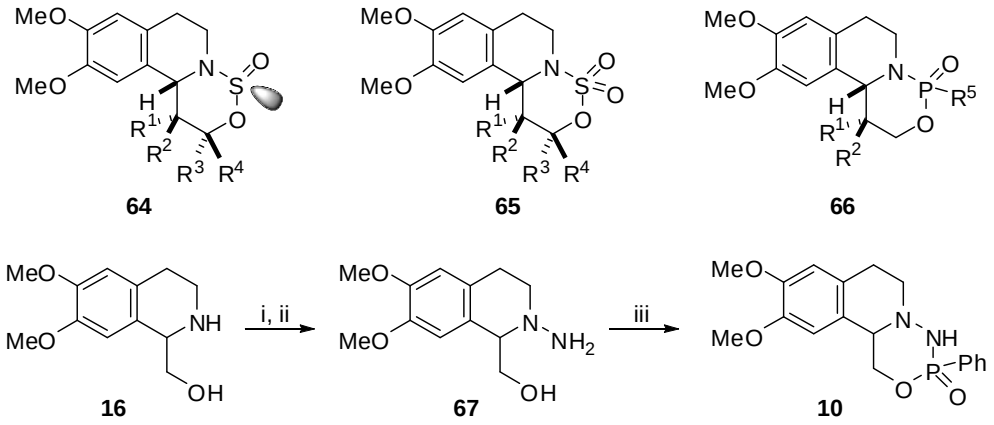
(ii) MeI, r.t. 1 h, then KOH, MeOH, r.t., 3 h (75%);

(iii) 10% HCl in EtOH, reflux, 30 min (67-79%).

Scheme 11

The insertion of a one-S atom-containing unit between the amino and hydroxy functions of (6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-1-yl)ethanol and its methyl-substituted diastereomers resulted in 1,2,3-oxathiazino[4,3-*a*]isoquinoline 4-oxides (**64**) as cyclic sulphamidite, or 4,4-dioxides (**65**) as cyclic sulphamidate derivatives. The similar ring closures of the above amino alcohols or *N*-aminocalycotomine (**67**) with one-P atom-containing building blocks led to the corresponding 1,3,2-oxazaphosphino[4,3-*a*]isoquinolines (**66**) and the 1,3,4,2-oxadizaphosphino[5,4-*a*]isoquinoline derivative **10** (Scheme 12).[11,12,17] The P-epimeric diastereomers of **66** and **10** (formed in a ratio of close to 1 : 1 ratio) were separated by column chromatography. Isoquinoline-condensed cyclic sulphamidates were

also obtained by the treatment of the corresponding *N*-trifluorosulphonyl amino alcohols with NaH.[42,43]

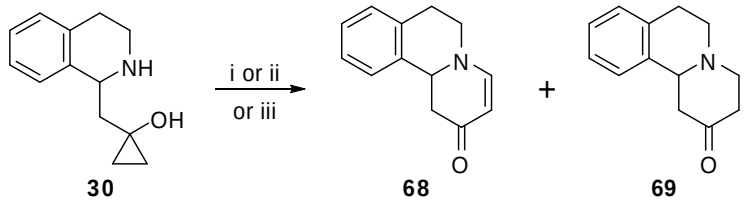


R^1 = H, Me; R^2 = H, Me; R^3 = H, Me; R^4 = H, Me; R^5 = Ph, Cl, $N(CH_2CH_2Cl)_2$

Reagents and conditions: (i) $NaNO_2$, AcOH, H_2O, r.t., 8 h; (ii) $LiAlH_4$, THF, r.t., 2 h (52%); (iii) Cl_2POPh, Et_3N, THF, r.t., 48 h (34%).

Scheme 12

The tetrahydroisoquinoline 1,3-amino alcohol **30**, containing a cyclopropanol moiety, was transformed to pyrido[2,1-*a*]isoquinolin-2-one derivatives (**68** and **69**) through metal-mediated rearrangement/oxidative cyclizations. Treatment of **30** with Pd(II) salts in the presence of an oxidant and a base or with a Pd(0) derivative resulted in mixtures of the unsaturated (**68**) and saturated (**69**) pyridinones in various ratios. Compound **69** was formed in a higher ratio in the reaction when either a Pd(0) catalyst or a Pd(II) salt was applied together with $Cu(OAc)_2$ as a stoichiometric oxidant (Scheme 13).[32,44]

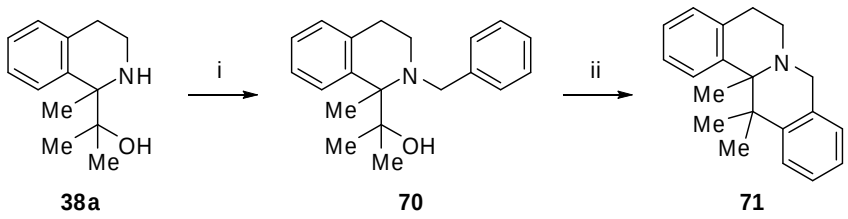


Reagents and conditions: (i) $Pd(OAc)_2$, pyridine, O_2, toluene, 80 °C, 3 h (87%, **68** : **69** = 2 : 3); (ii): $Pd(OAc)_2$, LiOAc, $Cu(OAc)_2$, DMF, 100 °C, 3 h (75%, **68** : **69** = 1 : 5); (iii): Pd(0), MeCN, 50 °C, 20 h (90%, **68** : **69** = 1 : 5).

Scheme 13

There are some examples in which the ring closure of tetrahydroisoquinoline amino alcohol derivatives was utilized in the synthesis of analogues of natural products. 13,13,13a-

Trimethylberbine (**71**) was prepared in a two-step procedure from 1,1',1'-trimethyl-calycotomine (**38a**) through an intramolecular Friedel–Crafts reaction of the *N*-benzyl derivative **70** (Scheme 14).[38]

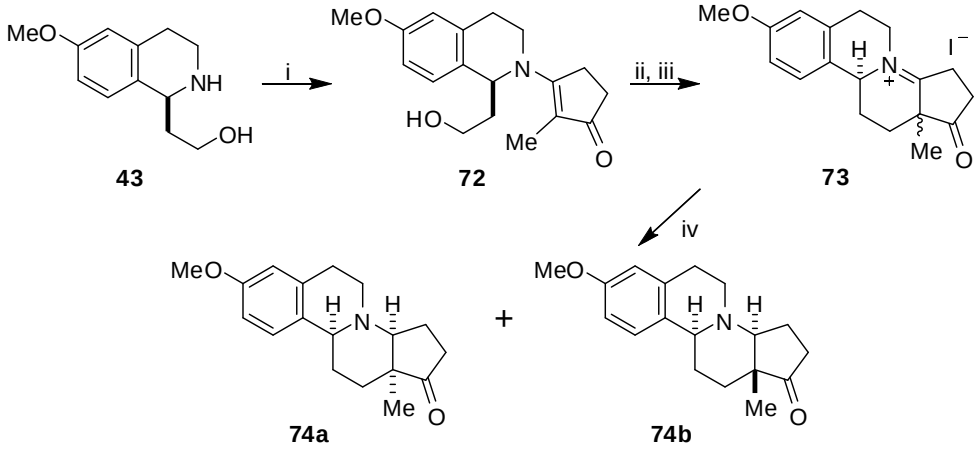


38a **70** **71**

Reagents and conditions: (i) $PhCH_2Cl$, toluene, KI, TEBAC, K_2CO_3, reflux, 20 h (68%); (ii) PPA, 110 °C, 18 h (67%).

Scheme 14

The non-racemic tetrahydroisoquinoline 1,3-amino alcohol **43** was an intermediate in the synthesis of 8-azaestrone derivatives. Ring D of the steroidal skeleton was inserted by enamine (**72**) formation from **43** with 2-methyl-1,3-cyclopentanedione. The construction of ring C was achieved through OH → OMs → I exchange. The relatively unstable iodo derivative was not isolated, but cyclized immediately to iminium salt **73** on heating. Reduction of **73** with tetrabutylammonium cyanoborohydride gave a diastereomeric mixture of 13-epimeric 8-azaestrone-*O*-methyl ethers (**74a**, **74b**), which was separated by fractional crystallization and column chromatography (Scheme 15).[40]



43 **72** **73** **74a** **74b**

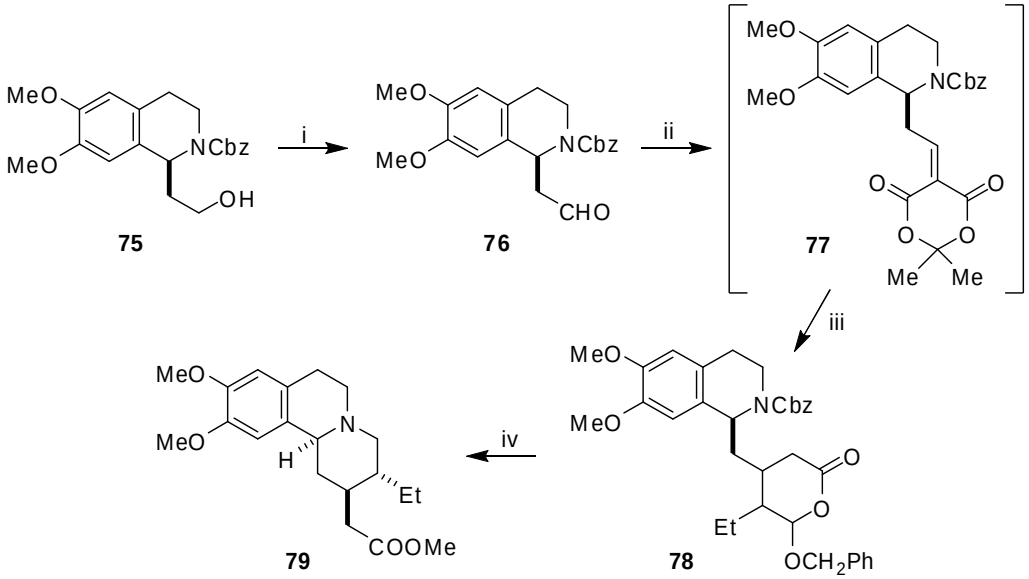
Reagents and conditions: (i) 2-methyl-1,3-cyclopentadienone, *p*-TsOH, toluene, reflux, 70 h (65%); (ii) MsCl, CH_2Cl_2, Et_3N, 0 °C, 10 min (68%); (iii) 1. LiI, DMF, 40 °C, 80 min, 2. 80-90 °C, 6 h; (iv) Bu_4NBH_3CN, 0 °C, 1.5 h (53%, **74a** : **74b** = 45 : 55).

Scheme 15

2.1.3. Other transformations

Both oxidation and reduction of the hydroxy group of tetrahydroisoquinoline amino alcohols were utilized in the total syntheses of natural products.

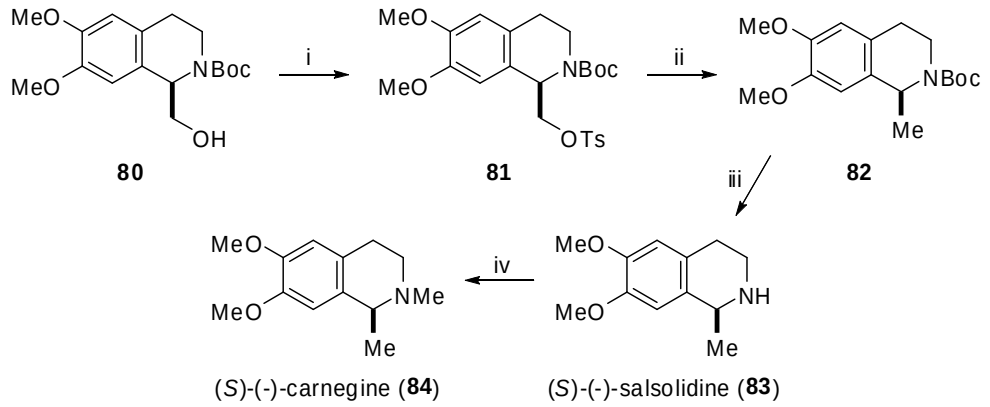
The *N*-Cbz-protected non-racemic amino alcohol **75** was oxidized by Dess–Martin periodinane to the aldehyde **76**. Compound **76** was converted to the pyranone derivative **78** by means of a three-component domino process that combined a Knoevenagel reaction of **76** with Meldrum's acid and a hetero-Diels–Alder reaction of **77** with butyraldehyde benzyl enol ether. The pyrido[2,1-*a*]isoquinoline ester **79**, a key fragment for the synthesis of emetine (**3**), was obtained from **78** by sequential solvolysis, condensation and hydrogenation (Scheme 16).[30]



Reagents and conditions: (i) Dess–Martin periodinane, CH_2Cl_2, 0 °C, 1 h (90%); (ii) Meldrum's acid, EDDA, benzene, 60 °C, 14 h; (iii) but-1-enylbenzyl ether (86%); (iv) K_2CO_3, H_2, Pd/C, MeOH, r.t., 6 h (77%).

Scheme 16

Reductive removal of the hydroxy group from the *N*-Boc-protected (*R*)-calycotomine (**80**) proved to be a convenient approach towards 1-methyltetrahydroisoquinoline alkaloids. Treatment of the *O*-tosyl derivative (**81**) of **80** with $LiAlH_4$ gave the corresponding 1-methyltetrahydroisoquinoline **82** without affecting the *N*-protecting group. Acidic hydrolysis of **82** led to (*S*)-(–)-salsolidine (**83**), which was converted to (*S*)-(–)-carnegine (**53**) by *N*-methylation using formaldehyde and sodium cyanoborohydride (Scheme 17).[31]



80 **81** **82**

(*S*)-(-)-carnegine (**84**) (*S*)-(-)-salsolidine (**83**)

Reagents and conditions: (i) TsCl, pyridine, r.t., 10 h (81%), (ii) $LiAlH_4$, THF, 60 °C, 5 h (56%), (iii) TMSOTf, CH_2Cl_2, r.t., 30 min (86%), (iv) HCHO aq, $NaBH_3CN$, MeCN, r.t., 2 h (87%).

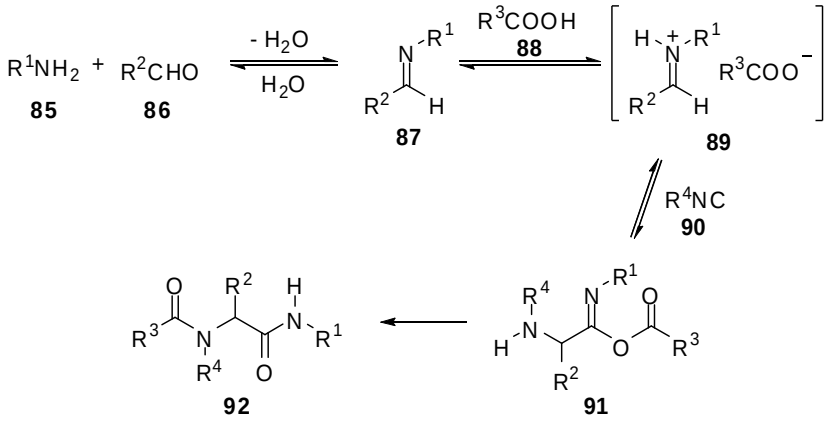
Scheme 17

2.2. The Ugi reaction

Multicomponent reactions (MCRs) are convergent procedures in which three or more starting materials react to form a product, where basically all or most of the atoms contribute to the newly-formed product.[45-47] MCRs are attracting increasing attention because of their applicability in the diversity-oriented parallel syntheses of small molecule libraries, which play an important role in drug research.[48-52]

The first MCR was the Strecker synthesis, introduced in 1850;[53] it was followed by many important named MCRs, such as the Hantzsch reaction, the Biginelli reaction or the Mannich condensation.[48] In 1921, Passerini first applied isocyanide in a 3CR to form α-acyloxy carboxamides,[54] and in 1959, Ugi developed this process further into a 4CR, for the preparation of α-acylamino carboxamides.[55,56] The Ugi reaction is very attractive because it is robust, tolerates a variety of substituents and provides access to a variety of different molecular structures that would otherwise require numerous synthetic steps.

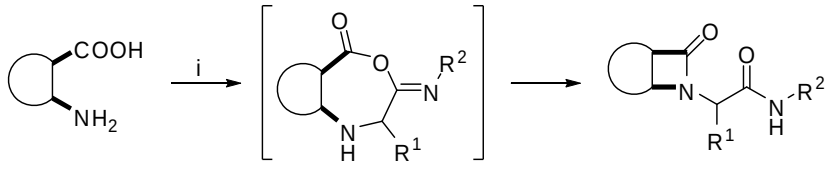
The U-4CR involves a sequence of elementary steps. In the first step, an amine (**85**) reacts with an oxo compound, *e.g.* an aldehyde (**86**), to form an imine **87**, followed by the protonation of **87** by a carboxylic acid (**88**). The third step is α-addition of the electrophilic iminium cation **89** and the nucleophilic carboxylate anion to isocyanide **90**, and subsequently an intramolecular acyl transfer (Mumm rearrangement) takes place to afford an α-acylamino carboxamide (**91** → **92**) (Scheme 18). There is a network of reaction equilibria, which all finally flow into an irreversible step, yielding the product **92**.[47,55]



The Ugi four-component reaction (U-4CR)

Scheme 18

When two of the starting four functionalities required for the Ugi reaction are connected together in a difunctional compound, the condensation results in heterocyclic derivatives. According to this principle, in the Ugi reactions of the alicyclic *cis* β-amino acids **93**, alicycle-condensed azetidinone derivatives **95** were formed (Scheme 19).[57,58]

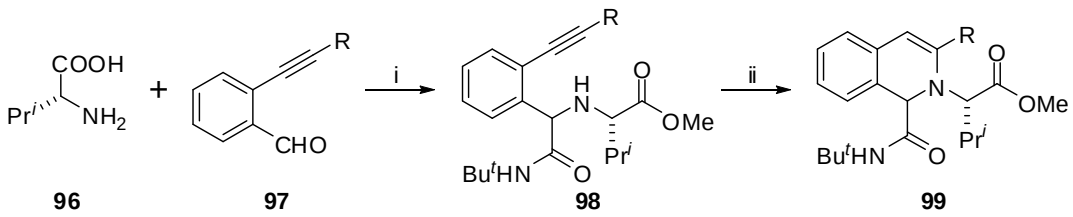


R^1 = Et, Bu^t, $C_6H_4Cl(p)$, $C_6H_4Me(p)$, $C_6H_4OMe(p)$, $C_6H_4NO_2(p)$, $C_6H_4Cl(m)$, $C_6H_4OMe(m)$; R^2 = Bu^t, cyclohexyl

Reagents and conditions: (i) MeOH, r.t., 24 h (43-86%).

Scheme 19

The post-condensation modification or a secondary reaction of the linear Ugi products is often applied for the preparation of various heterocyclic derivatives.[47,49] The combination of the Ugi condensation with a sequential Heck intramolecular reaction proved to be a one-pot two-step synthetic procedure for the synthesis of dihydroisoquinolin-3-one derivatives.[59,60] Highly functionalized non-racemic dihydroisoquinoline-1-carboxamides (**99**) were constructed by an U-4CR with the participation of L-valine (**96**), as a chiral component, and 2-alkynyl-substituted benzaldehydes (**97**), and a subsequent gold-catalysed hydroamination of the Ugi product **98** (Scheme 20).[61]



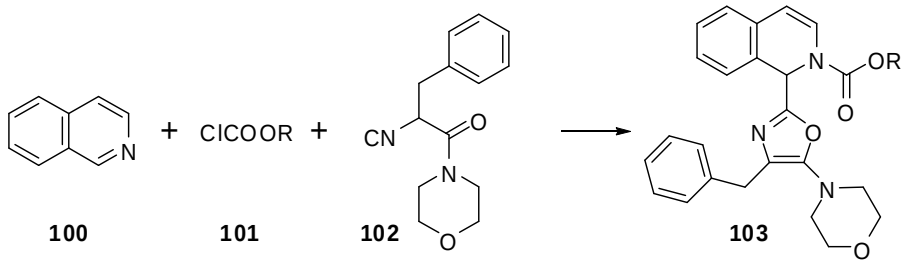
96 **97** **98** **99**

R = Bu, Ph

Reagents and conditions: (i) Bu^{t}NC, MeOH, 6-9 days (68-71%); (ii) MeCN, 3 mol% AuCl, 80 °C, 6 h (23-35%).

Scheme 20

Since the Ugi condensation takes place via an iminium intermediate, the amine and the carbonyl components can be replaced by preformed imines.[47,49] There are numerous examples of the C=N bond of the isoquinoline ring also participating in Ugi reactions (Schemes 21 and 22).



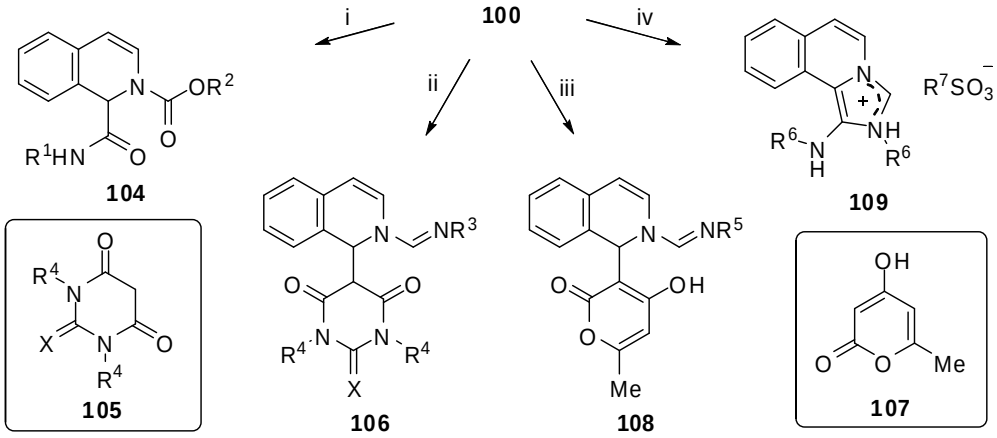
100 **101** **102** **103**

R = Me, Ph, 9-fluorenylmethyl

Reagents and conditions: CH_2Cl_2, -40 °C, 4 Å molecular sieve (31-66%).

Scheme 21

The three-component condensations of isoquinoline (**100**), chloroformates (**101**) and morpholinyl-α-isocyano-β-phenylpropionamide (**102**) took place through the *in situ* formed acylazinium salts, resulting in 1-(oxazol-2-yl)-1,2-dihydroisoquinoline derivatives **103** (Scheme 21).[62] When *tert*-butyl, cyclohexyl or tosylmethyl isocyanide was used instead of **102**, the condensation led to 1,2-dihydroisoquinoline-1-carboxamides **104**.[63] Three-component condensations of isoquinoline (**100**), isocyanides and strong CH-acids, such as barbituric or thiobarbituric acids (**105**) or 6-methyl-3*H*-pyran-2,4-dione (**107**), 2-imino-methyl-1,2-dyhydroisoquinolines bearing a heterocyclic substituent at position 1 (**106** and **108**) were formed under green conditions, in water.[64,65] The application of sulphonic acids in the 1 : 2 condensations of isoquinoline (**100**) with isocyanides led to the formation of 1-aminoimidazo[5,1-*a*]isoquinolinium salts (**109**) (Scheme 22).[66]

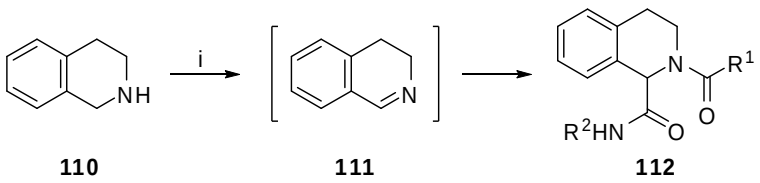


R^1 = Bu^t, cyclohexyl, $TsCH_2$; R^2 = Me, Ph, $C_6H_4Me(p)$; R^3 = Bu^t, cyclohexyl; R^4 = H, Me; R^5 = Bu^t, 1,1,3,3-tetramethylbutyl, cyclohexyl; R^6 = Bu^t, 1,1,3,3-tetramethylbutyl, $PhCH_2$, cyclohexyl, 2,6-dimethylphenyl; R^7 = Me, Ph, $C_6H_4Me(p)$, (–)-camphenyl; X = O, S

Reagents and conditions: (i) R^1NC, R^2COOCl, CH_2Cl_2, r.t., 16-24 h (40-90%); (ii) **105**, R^3NC, H_2O, 70 °C, 12 h (51-95%); (iii) **107**, R^5NC, H_2O, 70 °C, 12 h (59-62%); (iv) R^6NC, R^7SO_3H, CH_2Cl_2, r.t., 24 h (75-96%)

Scheme 22

The imine intermediate for the Ugi condensation can be constructed *in situ* from the corresponding secondary amine by using a mild oxidation method. When 1,2,3,4-tetrahydro-isoquinoline (**110**) was reacted with acids and isocyanides in the presence of 2-iodoxybenzoic acid, 2-acyltetrahydroisoquinoline-1-carboxamides (**112**) were formed (Scheme 23). The yields for **112** in this domino oxidation/U-3CR process was found to be strongly dependent on the solvent applied, among which THF proved to be optimum.[67]



R^1 = Me, Ph, CH_2NHCbz, $C_6H_4I(o)$, CH=CHPh, CH=CHCOOEt, C≡CPh;

R^2 = Bu^t, cyclohexyl, Bn, $CH_2C_6H_4I(o)$;

Reagents and conditions: (i) R^1COOH, R^2NC, 2-iodoxybenzoic acid, DMSO or THF, 60 °C, 20 h, 4 Å molecular sieve (22-87%).

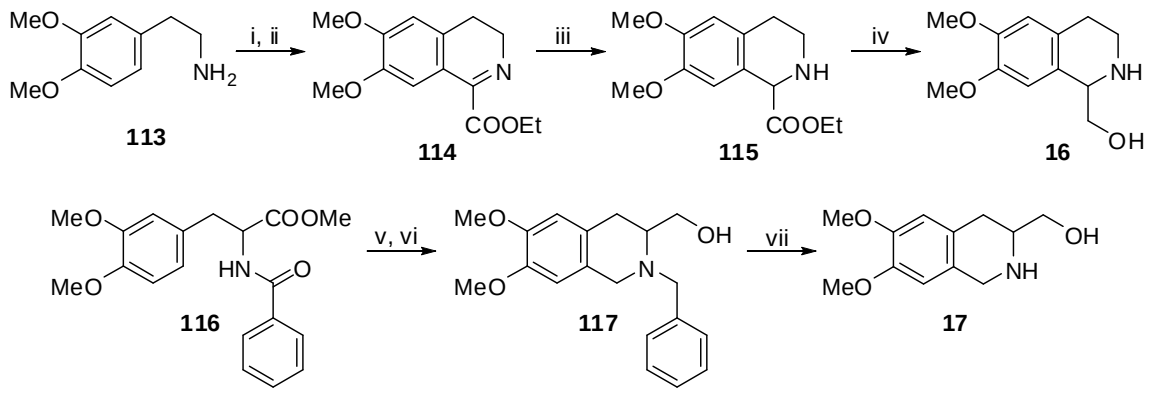
Scheme 23

3. RESULTS AND DISCUSSION

3.1. Synthesis and conformational analysis of isoquinoline-condensed 1,2,3-O,S,N and 1,3,2-O,N,P heterocycles

3.1.1. Synthesis of the amino alcohol starting materials

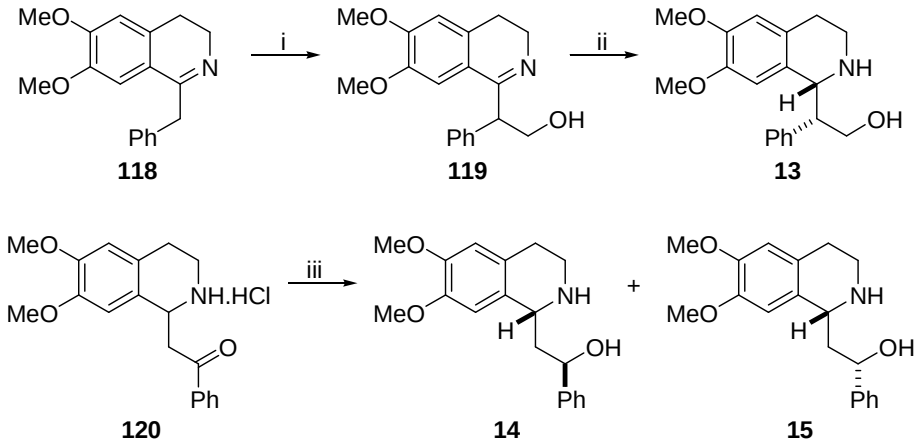
The regioisomeric tetrahydroisoquinoline 1,2-amino alcohols **16** and **17** were prepared from homoveratrylamine (**113**) or the racemic *N*-benzoyl-3,4-dimethoxyphenylalanine methyl ester (**116**) by using literature methods. In both methods,[17] the alcoholic function was built by $LiAlH_4$ reduction of the corresponding ester group, which was preceded (for **16**) or followed (for **17**) by construction of the tetrahydroisoquinoline skeleton (Scheme 24).



Reagents and conditions: (i) $(COOEt)_2$, 140 °C, 6 h; (ii) $POCl_3$, toluene, EtOH, reflux, 3.5 h (81%, i+ii); (iii) H_2, 5% Pt/C, EtOH, r.t., 1 atm, 6 h (82%); (iv) $LiAlH_4$, THF, reflux, 3 h (66%), (v) $LiAlH_4$, THF, reflux, 5 h (78%); (vi) HCHO, HCl, H_2O, reflux, 6 h (92%); (vii) H_2, 10% Pd/C, MeOH, 30 bar, 40 °C, 30 h (~100%).

Scheme 24

For preparation of the 1-(2'-hydroxyethyl)-substituted tetrahydroisoquinolines, bearing a phenyl group at either position 1' or 2', known procedures[14] were applied. (1*R**,1'*R**)-1-(2'-Hydroxy-1'-phenylethyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**13**) was prepared by stereoselective $NaBH_4$ reduction of the hydroxymethylated derivative (**119**) of 1-benzyl-6,7-dimethoxy-3,4-dihydroisoquinoline (**118**). 1-(2'-Hydroxy-2'-phenyl-ethyl)-substituted tetrahydroisoquinolines **14** and **15** were obtained from the corresponding β-amino ketone derivative **120** by reduction with $NaBH_4$. In contrast with the literature data,[14] both the (1*R**,2'*R**) and (1*R**,2'*S**) diastereomers (**14** and **15**) could be isolated by fractional crystallization of the crude reduction product (Scheme 25).



118 **119** **13**

120 **14** **15**

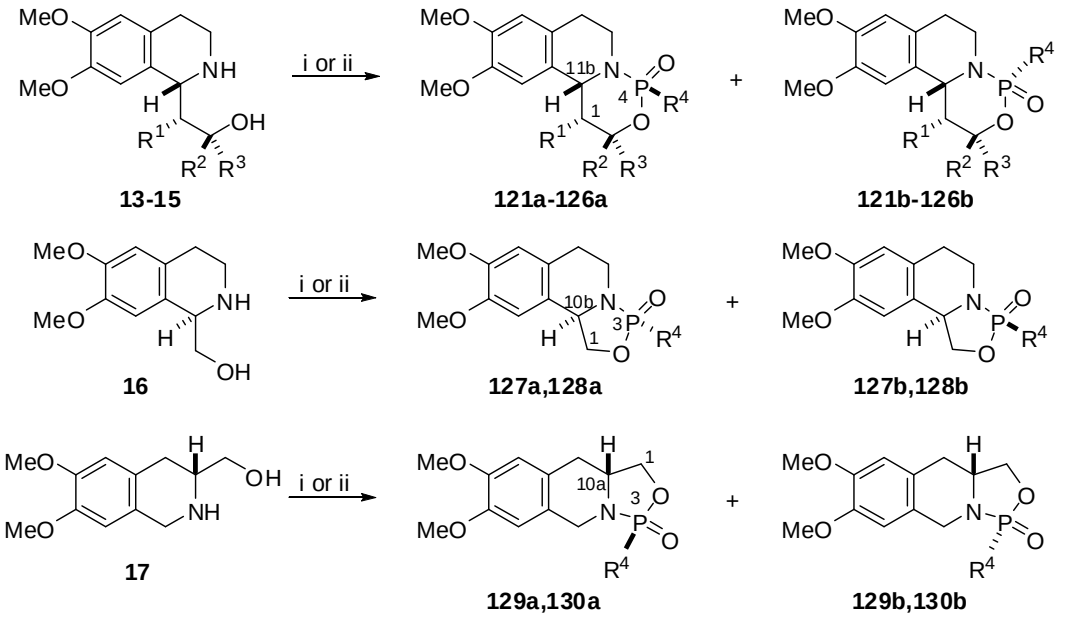
Reagents and conditions: (i) HCHO, NaOEt, EtOH, r.t., 5 h; (ii) $NaBH_4$, MeOH, 0 °C → r.t., 6 h (62%, i+ii); (iii) $NaBH_4$, MeOH, 0°C → r.t., then r.t., 3 h, then fractional crystallization (73%, **14** : **15** = 2 : 1).

Scheme 25

3.1.2. Ring closures of the amino alcohols

When amino alcohols **13**-**17** were reacted with phenylphosphonic dichloride and bis-(2-chloroethyl)phosphoramidic dichloride in anhydrous CH_2Cl_2 in the presence of Et_3N, 1,3,2-oxazaphosphino[4,3-*a*]isoquinolines (**121**–**126**) and the first representatives of two new ring systems, 1,3,2-oxazaphospholo[4,3-*a*]- (**127** and **128**) and 1,3,2-oxazaphospholo[3,4-*b*]-isoquinolines (**129** and **130**), were obtained (Scheme 26).

The NMR spectra of the crude products indicated that the ratio of the diastereomers, differing in the *cis* or *trans* position of the P substituent and the H atom at the annelation point (H-11b for **121**-**126**; H-10b for **127** and **128**; and H-10a for **129** and **130**), was only slightly influenced by the substituents on the P. As the only exception, the ring closure of **13** with bis(2-chloroethyl)phosphoramidic dichloride proved to be highly diastereoselective in favour of the *trans* isomer (**122b**), since the *cis* counterpart (**122a**) could not even be detected in the crude product. For the 5-membered, regioisomeric bis(2-chloroethyl)amino derivatives **128** and **130**, the *major* product for the linearly-condensed regiosomer proved to be the opposite diastereomer to that for the angularly-condensed counterpart (Scheme 26). The P-epimeric diastereomers of **121**, **125** and **126**-**130** could be separated by column chromatography, but all of our efforts to isolate the diastereomers of **123** and **124** failed.

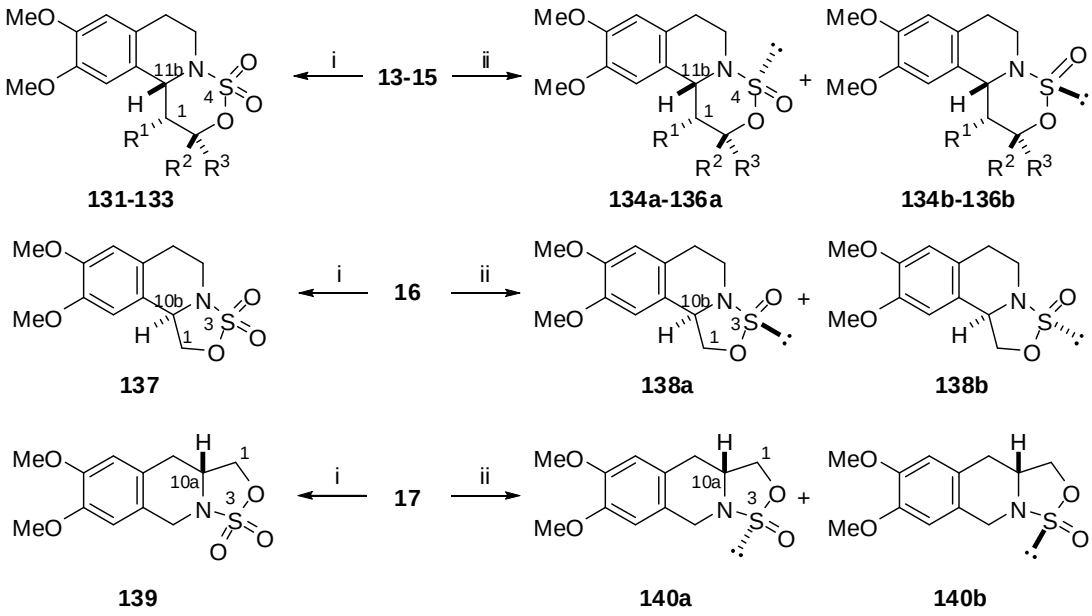


Compound	R^1	R^2	R^3	R^4	Diastereomeric ratio (**a** : **b**) in the crude product	Diastereomeric excess (*de*)
121	Ph	H	H	Ph	55 : 45	10%
122	Ph	H	H	$N(CH_2CH_2Cl)_2$	~0 : ~100	~100%
123	H	Ph	H	Ph	55 : 45	10%
124	H	Ph	H	$N(CH_2CH_2Cl)_2$	45 : 55	10%
125	H	H	Ph	Ph	55 : 45	10%
126	H	H	Ph	$N(CH_2CH_2Cl)_2$	45 : 55	10%
127	-	-	-	Ph	50 : 50	0%
128	-	-	-	$N(CH_2CH_2Cl)_2$	55 : 45	10%
129	-	-	-	Ph	42 : 58	16%
130	-	-	-	$N(CH_2CH_2Cl)_2$	43 : 57	14%

Reagents and conditions: (i) $PhPOCl_2$, CH_2Cl_2, Et_3N,6 °C → r.t., then r.t., 24 h or $(ClCH_2CH_2)_2NPOCl_2$, CH_2Cl_2, Et_3N, r.t., 48 h (6-34%).

Scheme 26

The ring closures of amino alcohols **13**-**17** with thionyl chloride or sulphuryl chloride in the presence of Et_3N in dry CH_2Cl_2 resulted in 1,2,3-oxathiazino[4,3-*a*]isoquinolines (**131**-**136**), and the regioisomeric 1,2,3-oxathiazolo[4,3-*a*]- (**137** and **138**) and [3,4-*b*]isoquinoline derivatives (**140**). The cyclic sulphamidate products (**131**-**133** and **137**) were obtained in only low yields. In the attempted cyclization of **17** with sulphuryl chloride, **139** proved to be decomposed during the purification process. The skeletons of the isoquinoline-condensed 5-membered, 1,2,3-O,S,N heterocycles (**137**, **138** and **140**) are also new ring systems (Scheme 27).



Compound	R^1	R^2	R^3	Diastereomeric ratio (**a** : **b**) in the crude product	Diastereomeric excess (*de*)
131/**134**	Ph	H	H	~100 : ~0	~100%
132/**135**	H	Ph	H	78 : 22	56%
133/**136**	H	H	Ph	84 : 16	68%
138	-	-	-	80 : 20	60%
140	-	-	-	~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 (10-13%); (ii) $SOCl_2$, Et_3N, CH_2Cl_2, -15°C → r.t., 2 h, then r.t., 48 h (7-68%).

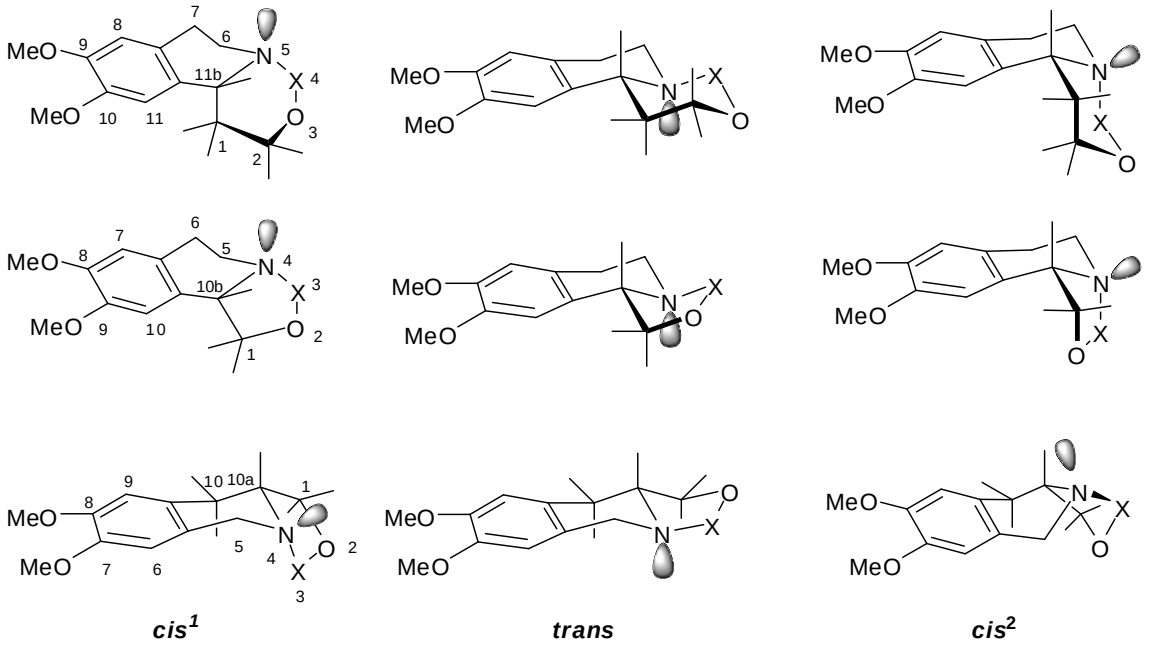
Scheme 27

The ^{1}H NMR spectra of the crude products revealed that the ring closures with $SOCl_2$ were highly diastereoselective. Independently of the size of the 1,2,3-O,S,N ring formed and of the angular or linear connection of the heterocyclic rings, diastereomers containing the S=O bond and the H atom at the annelation (H-11b for **131**-**136**, H-10b for **137** and **138**, and H-10a for **139** and **140**) in the *cis* position predominated. The highest selectivity was found for the 1-phenyl-substituted derivative **134** and for the 5-membered, linearly condensed product **140**, for which only one diastereomer could be observed in the crude product (Scheme 27). For the 2-phenyl-substituted analogues **135** and **136**, although a mixture of S-4 epimeric products was formed, the *minor* diastereomers proved to undergo decomposition during the chromatographic purification process. A similar decomposition of the *minor* diastereomers was observed in the cyclizations towards the analogous 1- or 2-methyl-substituted tetrahydro-2*H*-1,2,3-oxathiazino[4,3-*a*]isoquinoline 4-oxides.[10] However, for the

angularly condensed, 5-membered analogues, both *S*-epimeric diastereomers (**138a**,**b**) could be isolated by column chromatography.

3.1.3. Structure

Similarly to those of N-bridged saturated bi- or polycycles, the stereostructures of the prepared 1,6,7,11b-tetrahydro-2*H*-1,3,2-oxazaphosphino[4,3-*a*]isoquinolines (**121**-**126**), 1,5,6,10b-tetrahydro-1,3,2-oxazaphospholo[4,3-*a*]isoquinolines (**127** and **128**), 1,5,10,10a-tetrahydro-1,3,2-oxazaphospholo[3,4-*b*]isoquinolines (**129** and **130**), 1,6,7,11b-tetrahydro-2*H*-1,2,3-oxathiazino[4,3-*a*]isoquinolines (**131**-**136**), 1,5,6,10b-tetrahydro-1,2,3-oxathiazolo-[4,3-*a*]isoquinolines (**137** and **138**) and 1,5,10,10a-tetrahydro-1,2,3-oxathiazolo[3,4-*b*]-isoquinoline (**140**) can be described by conformational equilibria of *cis*[1]*–trans–cis*[2] type.[10-12] In the *trans* conformation, the hetero rings (ring B refers to the tetrahydropyridine moiety, and ring C to the corresponding 1,2,3-heterocycle) are *trans*-connected with *di-pseudoaxial* arrangements of the *N* lone pair and the H-an (H-an denotes the H atomat the annelation and means H-11b for **121**-**126** and **131**-**136**, H-10b for **127**, **128**, **137** and **138**, and H-10a for **129**, **130**, **139** and **140**). In the two other conformations, the hetero rings are *cis*-connected: for the *cis*[1] conformation, C-1 is in a *pseudoaxial* (inside) position, while for the *cis*[2] conformation, C-1 is in a *pseudoequatorial* (outside) position relative to the tetrahydropyridine ring (Fig. 6).



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

Figure 6

The stereochemistry of the compounds was determined from the characteristic vicinal H,H couplings, the significant differences in the chemical shifts for the indicator nuclei and comparison of the measured and theoretically calculated NMR parameters.

The orientation of H-an was determined by using the vicinal coupling constants $^3J_{\text{H-an,H-1}}$ (Table 1). One large and one small value of $^3J_{\text{H-an,H-1}}$ indicate the *pseudoaxial*, and two moderate values of $^3J_{\text{H-an,H-1}}$ indicate the *pseudoequatorial* position of H-an in the hetero ring. The configuration of the heteroatom was determined from the corresponding chemical shifts. If the S=O or the P=O bond is in the *axial* position and on the same side as H-an and H-2*ax* (only for compounds with a 6-membered ring C), these protons have a higher chemical shift (due to the 1,3-*diaxial* effect; *cf.* Tables 2, 5, 7 and 9).[69] This effect is not so pronounced in 5-membered rings, because the substituents only approximate to the *pseudoaxial* or *pseudoequatorial* orientation.

Table 1

Selected vicinal coupling data (in Hz)

Compd.	H-an[a]–H-1*ax*		H-an[a]–H-1*eq*		Compd.	H-an[a]–H-1*ax*		H-an[a]–H-1*eq*	
	Measd.	Calcd.	Measd.	Calcd.		Measd.	Calcd.	Measd.	Calcd.
121a	–[b]	–[b]	3.1	3.0	**121b**	–[b]	–[b]	3.7	4.1
122a	–[b]	–[b]	–[c]	3.6	**122b**	–[b]	–[b]	1.0	3.0
125a	10.7	9.9	3.8	2.6	**125b**	11.0	9.8	3.3	2.4
126a	11.0	10.1	4.0	1.8	**126b**	11.0	9.9	1.5	2.6
127a	6.4	8.9	5.7	6.3	**127b**	9.9	8.9	6.6	5.6
128a	9.5	9.0	6.8	5.7	**128b**	–[d]	9.2	–[d]	5.8
129a	8.0	8.4	6.3	5.8	**129b**	7.0	7.1	6.5	0.8
130a	7.2	8.6	6.5	5.9	**130b**	11.4	8.5	2.3	6.4
131	–[b]	–[b]	3.2	3.4	**134a**	–[b]	–[b]	3.3	3.6
132	12.0	10.8	3.2	2.2	**135a**	8.8	8.6	6.0	7.6
133	12.2	10.8	3.0	2.9	**136a**	11.8	10.6	2.7	3.1
137	9.6	9.3	6.7	6.4	**140a**	9.2	9.0	6.6	6.2
138a	11.5	9.5	6.5	5.9	**138b**	8.8	4.7	6.8	3.3

[a]H-an is the H atom at the annelation, *i.e.* H-11b for **121**-**126** and **131**-**136**, H-10b for **127**, **128**, **137** and **138,** and H-10a for **129**, **130** and **140**; [b]missing value due to the lack of H-1*ax*; [c]missing value since **122a** was not formed in the ring-closure reaction; [d]overlapping signals.

The P atom can effect distortion in the heterocyclic ring. Earlier studies of the substituent effects on the conformational states of the 1,3,2-oxazaphosphinane ring[68,70] led to the conclusion that this ring could usually be characterized by a chair or a twist conformation.

3.1.3.1. 1,3,2-O,P,N heterocycles

1,6,7,11b-Tetrahydro-2*H*-1,3,2-oxazaphosphino[4,3-*a*]isoquinolines (**121**-**126**)

The configurations of these compounds could be determined from the chemical shifts of the P atom, H-2*ax* and H-11b, since H-2*ax* and H-11b have larger chemical shifts when P=O is *axial*, due to the 1,3-*diaxial* effect (Table 2), which can be observed in the **b** isomers. It suggests the *axial* position of the P=O bond in **b** and the *equatorial* position in the **a** isomers. The diastereomers of **123** and **124** could not be separated, and the NMR spectra of their diastereomeric mixtures contain overlapping signals; thus, their NMR values are not indicated in Table 2.

Table 2

Selected chemical shifts (in ppm; δ_{TMS} = 0 ppm, $\delta_{H_3PO_4}$ = 0 ppm)

Compd.	^{31}P		H-2*ax*		H-11b		C-2		C-6	
	Calcd.	Measd.	Calcd.	Measd.	Calcd.	Measd.	Calcd.	Measd.	Calcd.	Measd.
121a	22.4	19.6	4.39	4.67	4.39	4.90	72.0	71.8	38.1	40.6
121b	31.6	24.1	5.23	5.21	5.45	5.39	68.5	70.4	40.8	42.0
122a	13.3	–[a]	4.51	–[a]	4.83	–[a]	69.1	–[a]	39.9	–[a]
122b	21.8	11.5	4.30	4.80	5.17	5.03	70.1	71.4	40.0	40.0
125a	21.1	19.1	5.00	5.27	4.12	4.67	79.6	79.6	36.6	40.1
125b	30.0	21.8	5.82	5.82	5.29	4.96	76.1	76.9	39.8	41.5
126a	15.3	10.9	5.07	5.46	4.49	4.76	83.9	80.4	39.3	40.7
126b	19.4	15.1	5.24	5.64	4.72	4.78	78.1	78.0	41.5	41.4

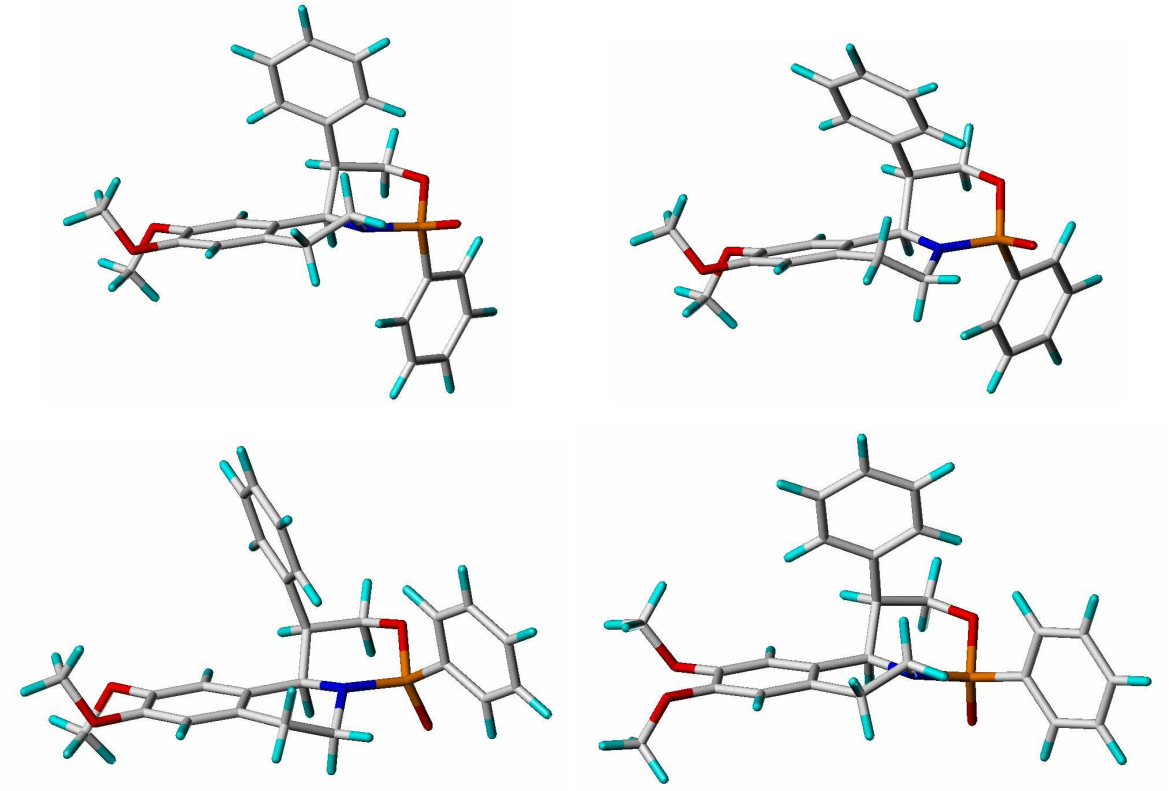
[a]Missing value since **122a** was not formed in the ring-closure reaction.

The 1-phenyl group is *axial* and *trans* to H-11b, because of the small value of $^3J_{H\text{-}1,H\text{-}11b}$ (3.0 Hz for **121a**, 3.7 Hz for **121b** and <1 Hz for **122b**). C-2 has lower and H-2*ax* and H-11b have higher chemical shifts in **121b** as compared with **121a**. C-6 has a higher chemical shift in **121b** than in **121a**, which suggests *trans* ring B/C connections in **121b** and *cis*[1] in **121a**, because the steric hindrance between the 1-phenyl substituent and H-6*ax* causes the downfield shift in the *cis* conformer. The moderate values of $^3J_{H\text{-}6,H\text{-}7}$ in the case of **121a**

indicate the possibility of an equilibrium between two *cis*[1] conformations, which is in accordance with the calculations (Fig. 7).

Although the ring closure of **13** with bis(2-chloroethyl)phosphoramidic dichloride resulted in only one diastereomer (**122b**), the NMR parameters were calculated for both isomers. The same result with respect to the configuration and conformation was obtained both for **122a** and for **122b**; H-2*ax* has a larger chemical shift than H-2*eq* which suggests the *axial* state of the P=O bond. The calculated and the measured values for **122b** correlate good, suggesting the *trans* connection of the B/C rings, which is favourable because of the *axial* 1-phenyl substituent.

Although the diastereomers of **123** and **124** could not be separated, and their ^{1}H NMR spectra contain overlapping multiplets, which does not allow completion of the conformational analysis, calculations were performed on them. These calculations suggest a *trans* B/C connection for isomers **b** with a twisted boat conformation of ring C, and a *cis*[1] B/C connection for isomers **a** with a chair conformation of ring C.



Calculated global (left) and local (right) energy minima of **121a** (top, ΔE = 0.16 kcal mol^{-1}) and **121b** (bottom, ΔE = 3.93 kcal mol^{-1})

Figure 7

Trans-diaxial coupling between H-1*ax* and H-11b excludes the *cis*[2] connenction of rings B/C for **125** and **126** (Table 1). The same result was obtained for the isomers as for **121**. C-6 has a higher chemical shift in **b** than that for **a**, which suggests *trans* ring B/C connections in **b** and *cis*[1] in **a**. The moderate values of $^{3}J_{\text{H-6,H-7}}$ for **125a** and **126a** indicate the possibility of an equilibrium between two *cis*[1] conformations, which is in accordance with the calculations (Table 3).

Our results show that the 1- or 2-phenyl substituent exerts a significant influence on the preferred conformation of 1,3,2-oxazaphosphino[4,3-*a*]isoquinolines. For the 1,2-unsubstituted parent compounds, the B/C connection was always found to be *trans*, independently of the relative configuration or the substituent on the P atom,[11] whereas for the 1- or 2-phenyl-substituted analogues (**121**-**126**), the geometry of the B/C connection proved to depend on the relative configuration of the P atom. For isomers **a**, where the *P* substituent

Table 3

Selected vicinal coupling data (in Hz)

Compd.		H-1*ax*-H-2*ax*	H-1*eq*-H-2*ax*	H-1*eq*-H-2*eq*	H-6*ax*-H-7*ax*	H-6*ax*-H-7*eq*	H-6*eq*-H-7*ax*	H-6*eq*-H-7*eq*	P-H-2*ax*	P-H-2*eq*	P-H-11b
121a	Measd.	–[a]	6.3	2.5	10.7	2.8	4.0	<1	4.5	18.6	3.0
	Calcd.	–[a]	3.5	1.2	10.5	2.9	5.7	1.6	0.6	19.8	1.8
121b	Measd.	–[a]	3.4	1.9	12.3	2.3	5.0	<1	4.0	21.3	3.7
	Calcd.	–[a]	3.4	1.4	10.4	2.6	5.0	1.4	3.6	21.5	4.2
122a	Measd.	–[a]	–[c]	–[c]	–[c]	–[c]	–[c]	–[c]	–[c]	–[c]	–[c]
	Calcd.	–[a]	10.3	3.1	10.7	2.6	5.2	2.1	1.1	21.9	2.0
122b	Measd.	–[a]	6.0	3.0	11.0	3.0	4.5	<1	12.5	13.5	1.0
	Calcd.	–[a]	3.7	1.0	10.4	2.9	5.9	1.6	1.1	21.9	2.0
125a	Measd.	11.3	2.7	–[b]	8.8	3.7	4.3	4.1	1.9	–[b]	<1
	Calcd.	10.0	1.9	–[b]	10.3	2.6	5.1	1.8	2.6	–[b]	3.1
125b	Measd.	11.7	1.6	–[b]	10.0	1.5	<1	<1	1.6	–[b]	2.1
	Calcd.	10.0	2.0	–[b]	9.8	2.0	4.4	2.3	1.7	–[b]	0.1
126a	Measd.	12.0	2.5	–[b]	9.8	4.8	3.0	4.5	3.0	–[b]	3.5
	Calcd.	10.5	0.3	–[b]	9.1	0.9	2.6	2.1	0.8	–[b]	1.8
126b	Measd.	12.0	1.5	–[b]	13.0	<1	4.0	<1	<1	–[b]	<1
	Calcd.	10.2	2.0	–[b]	10.5	2.6	5.1	1.9	2.2	–[b]	2.6

[a]Missing value due to the lack of H-1*ax*; [b]missing value due to the lack of H-2*eq*; [c]missing value since **122a** was not formed in the ring-closure reaction.

and H-11b are in the *cis* position, the connection of rings B/C is *cis*[1], while for diastereomers **b** containing the *P* substituent and H-11b in the *trans* position, rings B/C are *trans*-connected.

1,5,6,10b-Tetrahydro-1,3,2-oxazaphospholo[4,3-*a*]isoquinolines (**127** and **128**)

The 5-membered ring moieties of these compounds readily interconvert by pseudorotation, which is a dynamic process and is too fast on the NMR time scale. For this reason, the preferred conformations of these compounds were obtained by theoretical calculations at the DFT level of theory and were correlated with the NMR spectral data.

The moderate values of the H,H and H,P coupling constants (Table 4) indicate a conformational equilibrium for **127a** involving two preferred *cis* conformers with a flexible tetrahydropyridine ring (Fig. 8).

For the other three compounds, only one conformer (*trans* for **127b**, *cis*[1] for **128a** and *trans* for **128b**) is preferred. As the calculated energy difference between the most stable and the next most stable conformer is >3 kcal mol^{-1}, the preferred conformers of **127b** (*cf.* Fig. 8), **128a** and **128b** were concluded to be the global minimum structures. These findings are supported by the *trans-diaxial* coupling between H-1*ax* and H-10b, furthermore H-5 and H-6. The moderate values of $^{3}J_{\text{H-5,H-6}}$ suggest the flexibility of the 6-membered hetero ring in **128b**.

Table 4

Selected vicinal coupling constants, in Hz

Compd.		H-5*ax*–H-6*ax*	H-5*ax*–H-6*eq*	H-5*eq*–H-6*ax*	H-5*eq*–H-6*eq*	H-10b–P	H-1*ax*–P	H-1*eq*–P	H-5*ax*–P	H-5*eq*–P
127a	Measd.	11.4	6.3	4.2	1.2	<1	15.2	12.4	9.0	7.4
	Calcd.	9.8	5.0	2.2	1.7	1.6	0.8	24.3	15.7	8.4
127b	Measd.	14.4	4.0	<1	<1	<1	0.9	20.7	–[b]	23.7
	Calcd.	10.1	6.3	3.3	1.0	0.3	0.3	14.1	0.8	5.1
128a	Measd.	14.0	4.6	2.2	<1	2.5	<1	22.5	2.2	–[b]
	Calcd.	11.3	7.6	5.0	0.9	1.3	0.4	14.8	0.6	7.5
128b	Measd.	12.3	6.5	3.5	<1	<1	–[a]	21.7	2.3	[b]
	Calcd.	11.4	4.8	2.8	2.2	0.9	0.7	25.6	0.3	4.5

[a]Overlapping signals; [b]multiplets

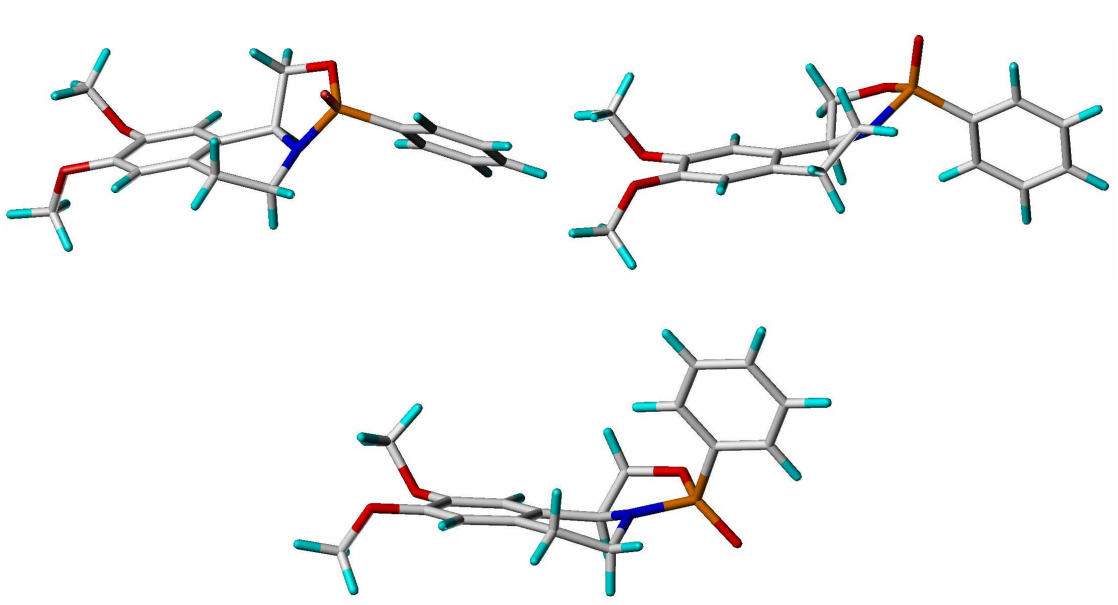
Table 5

Selected chemical shifts in ppm (δ_{TMS} = 0 ppm, $\delta_{H_3PO_4}$ = 0 ppm)

Compound		^{31}P	H-1*ax*	H-1*eq*	H-an*	Compound		^{31}P	H-1*ax*	H-1*eq*	H-an*
127a	Measd.	15.8	4.06	4.70	4.89	**127b**	Measd.	15.9	4.09	4.99	5.01
	Calcd.	35.7	3.71	4.16	4.81		Calcd.	38.7	3.88	4.53	4.74
128a	Measd.	24.2	3.89	4.60	4.80	**128b**	Measd.	25.6	3.81	4.79	4.77
	Calcd.	25.3	3.41	3.52	4.32		Calcd.	29.6	3.43	3.49	4.33
129a	Measd.	35.1	4.06	4.82	3.82	**129b**	Measd.	32.8	4.30	4.62	3.95
	Calcd.	40.8	4.20	4.59	3.48		Calcd.	32.4	4.08	4.21	3.57
130a	Measd.	26.6	3.90	4.14	3.74	**130b**	Measd.	25.1	4.36	4.62	3.78
	Calcd.	28.7	3.77	3.97	3.59		Calcd.	26.7	3.72	4.30	3.22

*H-an is the H atom at the annelation, *i.e.* H-10b for **127** and **128**, and H-10a for **129** and**130**

C → P replacement at position 3 of the 1,5,6,10b-tetrahydro-3*H*-1,3-oxazolo[4,3-*a*]-isoquinoline ring system caused a significant change in the preferred conformation of these tricycles. Whereas the 1,3-oxazolo[4,3-*a*]isoquinoline could be characterized by a *cis*[1] conformation,[71] the ring B/C connection of the analogous 1,3,2-oxazaphospholo[4,3-*a*]-isoquinolines was dependent on the configuration of P relative to C-10b. For isomers **a**, in which the *P* substituent and H-11b were in the *cis* position, *cis*[1] proved to be the preferred conformation, while for isomers **b**, in which the *P* substituent and H-11b were in the *trans* position, rings B/C were found to be *trans*-connected.



Calculated global (left) and local (right) energy minimum conformations for **127a** (top, ΔE = 2.63 kcal mol^{-1}), and calculated global energy minimum conformations for **127b** (bottom)

Figure 8

1,5,10,10a-Tetrahydro-1,3,2-oxazaphospholo[4,3-*b*]isoquinolines (**129** and **130**)

The configuration of the P atom could be determined from the chemical shift of H-10a. If H-10a and the P=O bond are on the same side of the molecule (*cis* position, **b**), it has a higher chemical shift relative to that for the *trans* isomer (**a**) (3.82 ppm for **129a** and 3.95 ppm for **129b**; 3.74 ppm for **130a** and 3.78 ppm for **130b**) due to the 1,3-*diaxial* effect.[69]

Two conformers were indicated by the theoretical calculations as minimum energy structures in the cases of **129a**, **129b** and **130a.** The energy differences were very small (2.10, 0.83 and 0.02 kcal mol^{-1}). From the ^{1}H NMR spectra of **129** and **130**, the interconversion of the 6-membered ring moiety was frozen ($^{3}J_{H\text{-}10a,H\text{-}10ax}$ 10.3-10.9 Hz, $^{3}J_{H\text{-}10a,H\text{-}10eq}$ 2.2-4.2 Hz), which is in complete agreement with the calculational result. However, the 5-membered moiety was still flexible in **129a**, **129b** and **130a** ($^{3}J_{H\text{-}10a,H\text{-}1ax}$ 7.0-8.0 Hz, $^{3}J_{H\text{-}10a,H\text{-}1eq}$ 6.3-6.5 Hz). In the case of **130b**, only one stable conformer was observed, where both hetero rings were frozen (*c. f.* Tables 1 and 6, Fig. 9).

Table 6

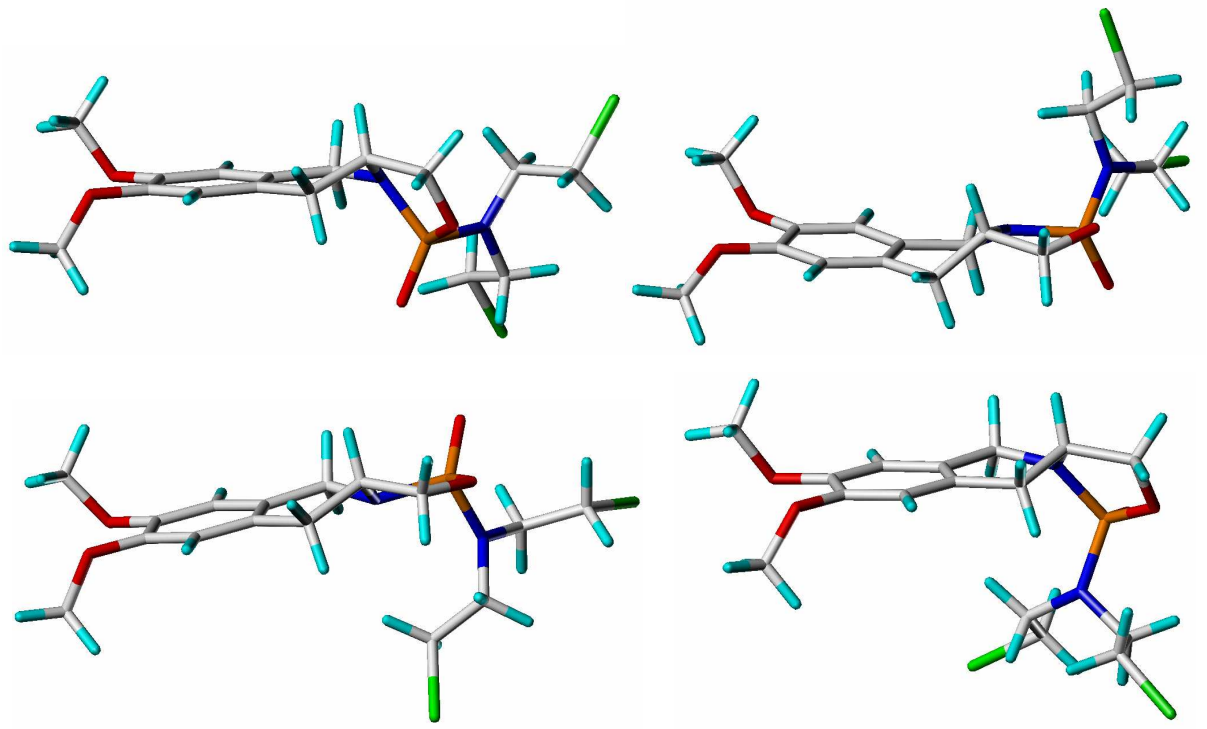
Selected vicinal coupling, in Hz

Compound		H-10*ax* –H-10a	H-10*eq*– H-10a	H-10a –P	H-1*ax* –P	H-1*eq* –P	H-5*ax* –P	H-5*eq* –P
129a	Measd.	10.5	2.4	4.2	5.5	11.7	2.7	2.8
	Calcd.	8.8	3.0	1.3	1.1	20.8	0.7	1.9
129b	Measd.	10.3	4.2	16.7	13.8	5.0	6.1	4.7
	Calcd.	9.5	1.1	4.4	20.8	1.1	0.3	1.2
130a	Measd.	10.9	3.7	3.0	5.2	11.6	6.7	8.3
	Calcd.	9.5	2.9	2.8	0.9	24.4	0.3	1.8
130b	Measd.	10.8	3.3	[a]	6.9	17.0	<1	2.2
	Calcd.	9.2	3.2	1.0	2.3	12.9	0.9	3.1

[a]Multiplet

The calculated energy minima of the conformers and the couplings of H-an suggest a *trans* connection for rings B/C in **129a** and **130b**, and *cis*[1] in **130a** and **129b**. This indicates that both the relative configuration and the type of the substituent on the P atom have a strong influence on the conformational equilibria of these compounds. Since rings B/C are reported to be *trans*-connected in 1,3,10,10a-tetrahydro-5*H*-oxazolo[3,4-*b*]isoquinoline,[71] our results

indicate that the insertion of the P atom caused a change in the geometry of the ring connection.



Calculated global (left) and local (right) energy minima for **130a** (top, ΔE = 0.02 kcal mol^{-1}) and **130b** (bottom, ΔE = 7.99 kcal mol^{-1})

Figure 9

3.1.3.2. 1,2,3-O,S,N heterocycles

1,6,7,11b-Tetrahydro-2*H*-1,2,3-oxathiazino[4,3-*a*]isoquinolines (**131**-**136**)

To determine the configurations of the S atom in the sulphamidites **134**-**136**, the theoretical ^{1}H NMR chemical shifts were analysed. They are nearly the same in the sulphamidites and sulphamidates if the S=O bond is *axial* (*cis* to H-11b). Due to the 1,3-*diaxial* effect, H-11b and H-2*ax* have larger chemical shifts in the **a** isomers, where S=O is *axial*, than in the **b** isomers, where S=O is *equatorial* (Table 7). The experimental values for the isolated isomers of **134**-**136** correlated very well with the calculated chemical results on the **a** isomers. The calculated and experimental chemical shifts of the cyclic sulphamidates **131**-**133** are also given in Table 7. Even if there is no stereochemical assignment, they impressively corroborate the quality of the theoretical calculations.

The 1-phenyl-substituted compounds (**131** and **134a**) have $^{3}J_{\text{H-1,H-11b}}$ values of 3.2 and 3.3 Hz. Consequently, the 1-phenyl group in the preferred conformation must be *axial*.

Table 7

Experimental and calculated characteristic chemical shifts (in ppm; $\delta_{TMS} = 0$)

Compd.	H-11b			H-2*ax*			C-2			C-6		
	Calcd. for **a**	Calcd. for **b**	Exp.	Calcd. for **a**	Calcd. for **b**	Exp.	Calcd. for **a**	Calcd. for **b**	Exp.	Calcd. for **a**	Calcd. for **b**	Exp.
131	5.18		5.36	5.31		5.29	73.3		65.9	40.9		43.1
132	5.22		5.19	_[a]		_[a]	80.8		85.1	39.8		40.9
133	5.16		5.19	5.63		5.85	80.2		84.6	42.0		40.5
134	5.64	4.56	5.43	5.51	4.69	5.47	61.7	68.9	63.7	43.9	39.4	44.0
135	4.46	4.48	4.56	_[a]	_[a]	_[a]	70.6	76.5	70.4	41.9	45.1	40.8
136	5.37	4.53	5.23	5.86	5.06	6.05	68.6	76.0	70.4	39.5	30.5	40.6

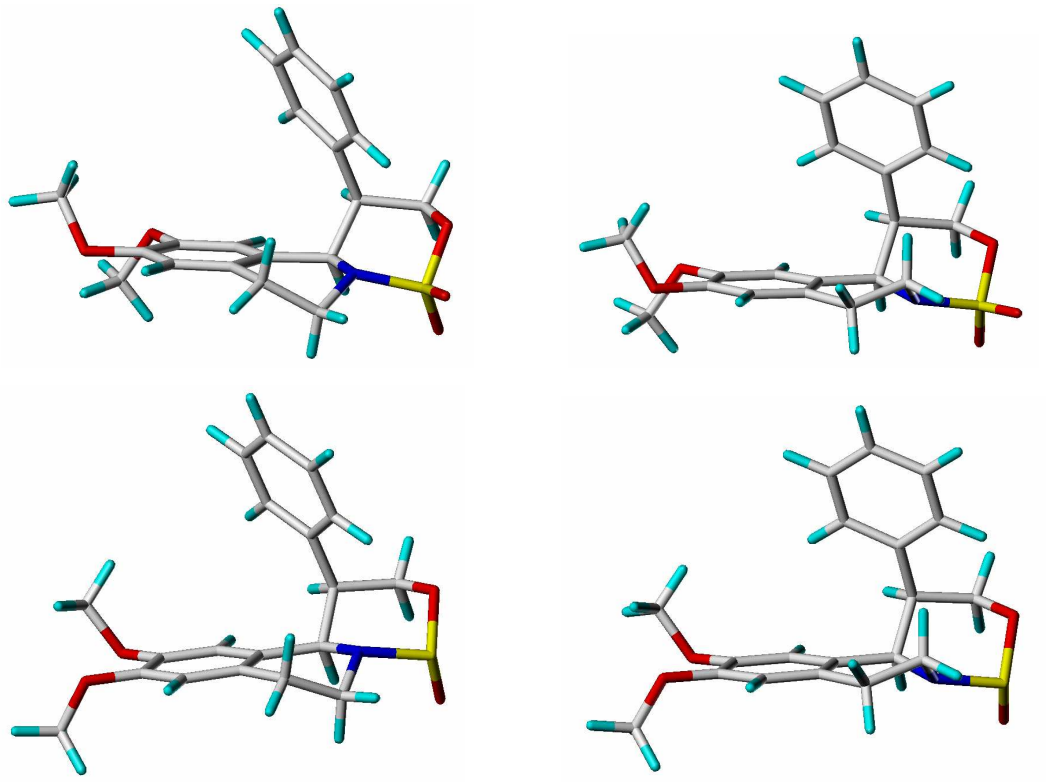
[a]Missing value due to the lack of H-2*ax*.

The chemical shifts of the cyclic sulphamidate **131** and sulphamidite **134a** are similar, except for a large difference (0.67 ppm) for H-2*eq*. This suggests the *axial* position of the S=O bond in **134a** and a similar conformation both for **131** and for **134a** (Fig. 10).

As compared with the 1,2-unsubstituted 1,2,3-oxathiazino[4,3-*a*]isoquinolines, which are characterized by a *cis*[1] conformation,[10] higher chemical shifts of C-6 were observed for **131** and **134a**, which suggests that their rings B/C are *trans*-connected. This was corroborated by the quantum chemical calculations, which showed the *trans* conformation to be more stable than the *cis*[1] form (0.46 kcal mol^{-1} for **131** and 1.76 kcal mol^{-1} for **134a**) (*c. f.* Fig. 10). The moderate values of $^{3}J_{H\text{-}6,H\text{-}7}$ in the ^{1}H NMR spectra of **131** (Table 8) suggest the flexibility of ring B.

Although **134b**-**136b** could not be isolated and studied experimentally, *ab initio* calculations were performed for them. The calculations for **134b** suggest a *cis*[1] connection of rings B/C, which is 1.15 kcal mol^{-1} more stable than the *trans* conformer.

Trans-diaxial coupling between H-1*ax* and H-11b for **132** (Table 1) excluded the *cis*[2] conformation for this compound. In addition, the C-6 chemical shift is similar in **132** and in the unsubstituted sulphamidate (40.9 ppm) Accordingly, the chemical shift of H-2 is larger because of the anisotropic neighbouring effect of the S=O bond in the 1,3-*diaxial* position.[72] Except for the effects of the phenyl substitution (downfield shifts in C-1 and C-2), no significant changes were observed for the ^{1}H and ^{13}C NMR chemical shifts of the unsubstituted compound as compared with **132**.[10] These findings lead to the conclusion that rings B/C in **132** are *cis*[1]-connected.



Calculated global (left) and local (right) energy minimum conformations for **131** (ΔE=0.46 kcal mol^{-1}, top) and for **134a** (ΔE =1.76 kcal mol^{-1}, bottom)

Figure 10

The values of $^{3}J_{\text{H-1,H-11b}}$ (8.8 and 6.0 Hz, Table 1) and $^{3}J_{\text{H-1,H-2}}$ (8.6 and 6.0 Hz, Table 8) for **135a** suggest a boat or a stereoheterogeneous conformation of ring C and the *equatorial* position of H-11b on this ring. Although the *ab initio* calculations showed that the *trans* conformation chair form for ring C was 0.9 kcal mol^{-1} more stable than the *cis*^{1}-connected twisted boat form, the experimental NMR data suggested an equilibrium of these two preferred conformations (Fig. 11).

According to the *ab initio* calculations for **135b**, the *cis*^{1} B/C connection with a twisted ring C was found 0.88 kcal mol^{-1} more stable than the *cis*^{1}-connected chair form.

The observed *trans-diaxial* coupling between H-1*ax* and H-11b (Table 1) excludes the *cis*^{2} conformation for both **133** and **136a**. Apart from the phenyl substituent effects (downfield for C-1, C-2 and H-2), no significant changes were observed for the ^{1}H and ^{13}C chemical shifts of the unsubstituted sulphamidate analogue as compared with **133**; thus, the *cis*^{1} B/C connection can be regarded as the preferred conformer for both compounds. The moderate values of $^{3}J_{\text{H-6,H-7}}$ (Table 8) indicate the flexibility of ring B. With the exception of some small differences (difference in H-2*ax*: 0.20 ppm), the NMR spectral data on **136a** were similar to

those on **133**, which reflects their same preferred conformation (*cis*[1]). The moderate values of the vicinal coupling constants between H-6 and H-7 point to the conformational flexibility of ring B.

Table 8

Selected vicinal coupling data (in Hz)

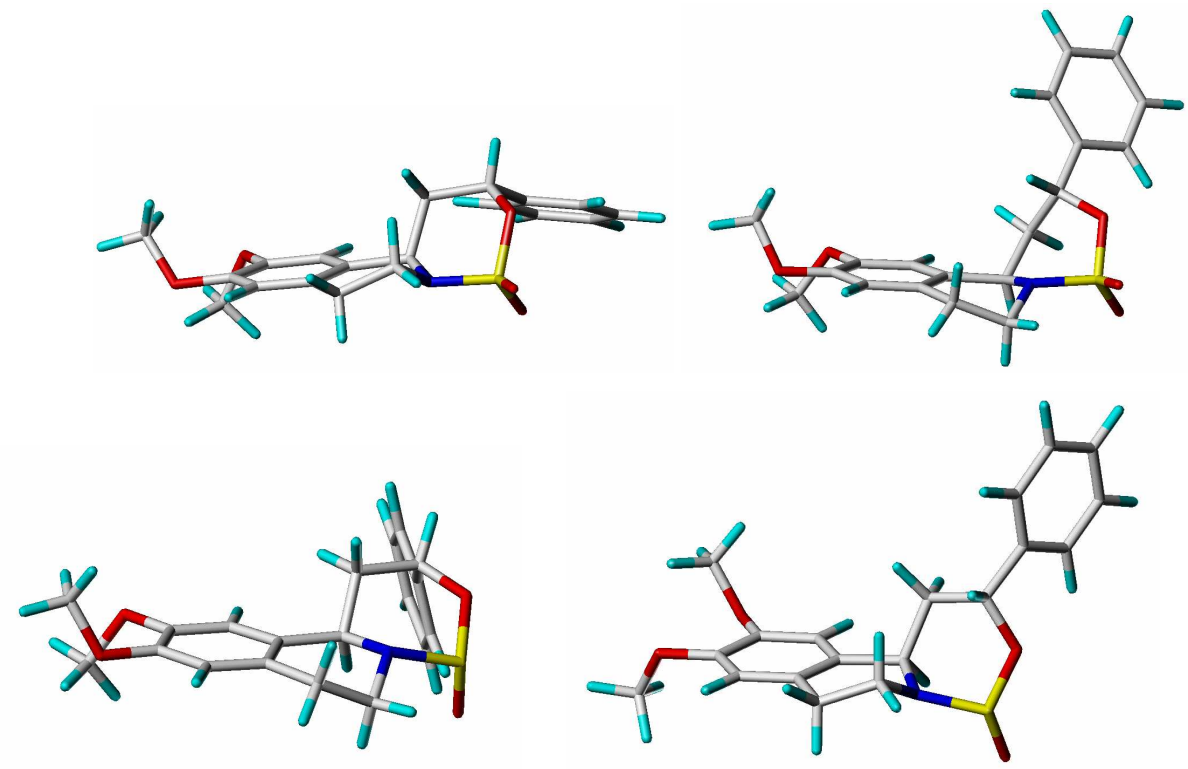
Compd.		H-1*ax*-H-2*ax*	H-1*ax*-H-2*eq*	H-1*eq*-H-2*ax*	H-1*eq*-H-2*eq*	H-6*ax*-H-7*ax*	H-6*ax*-H-7*eq*	H-6*eq*-H-7*ax*	H-6*eq*-H-7*eq*
131	Measd.	–[a]	–[a]	3.2	<1	8.0	4.0	5.6	4.8
	Calcd.	–[a]	–[a]	3.5	1.0	10.3	2.2	4.5	2.4
132	Measd.	–[c]	12.0	–[c]	3.2	11.6	4.0	6.0	2.0
	Calcd.	–[c]	6.2	–[c]	1.1	10.5	1.3	5.9	2.3
133	Measd.	12.0-	–[d]	2.6	–[d]	11.4	3.8	5.8	3.0
	Calcd.	10.3	–[d]	2.4	–[d]	10.6	1.3	5.8	2.3
134a	Measd.	–[a]	–[a]	3.3	1.2	11.2	3.0	4.7	2.7
	Calcd.	–[a]	–[a]	3.5	1.2	10.3	2.4	4.6	2.1
134b	Measd.	–[a]	–[a]	–[b]	–[b]	–[b]	–[b]	–[b]	–[b]
	Calcd.	–[a]	–[a]	3.2	1.2	10.0	2.2	4.4	2.4
135a	Measd.	–[c]	6.0	–[c]	8.6	9.2	4.0	5.4	4.6
	Calcd.	–[c]	5.6	–[c]	9.8	10.2	2.9	5.8	1.4
135b	Measd.	–[c]	–[b]	–[c]	–[b]	–[b]	–[b]	–[b]	–[b]
	Calcd.	–[c]	5.8	–[c]	9.7	10.2	2.1	5.9	2.0
136a	Measd.	12.0	–[d]	2.4	–[d]	8.0	4.6	5.2	5.0
	Calcd.	10.1	–[d]	2.4	–[d]	10.4	1.5	5.9	2.3
136b	Measd.	–[b]	–[d]	–[b]	–[d]	–[b]	–[b]	–[b]	–[b]
	Calcd.	9.7	–[d]	2.0	–[d]	10.6	1.6	5.9	2.1

[a]Missing value due to the lack of H-1*ax*; [b]missing value since **134b**, **135b** and **136b** could not be isolated; [c]missing value due to the lack of H-2*ax*; [d]missing value due to the lack of H-2*eq*.

For **136b**, the calculations suggest that the *cis*[1] conformation is 3.33 kcal mol^{-1} more stable than the energetically next most stable conformer.

Our findings revealed that the position of the phenyl substituent causes significant effects on the preferred conformations of 1,2,3-oxathiazino[4,3-*a*]isoquinolines. For the (11b*R**,1*R**)-1-phenyl-substituted **131** and **134a**, *trans* connection of rings B/C was found, while for the 2-phenyl-substituted **132**, **133**, **135a** and **136a**, *cis*[1] proved to be the preferred conformer, which was not influenced by the relative configuration of C-2. Similar

conformational behaviour was found earlier for the 1- and 2-methyl-substituted 1,2,3-oxathiazino[4,3-*a*]isoquinoline derivatives.[10]



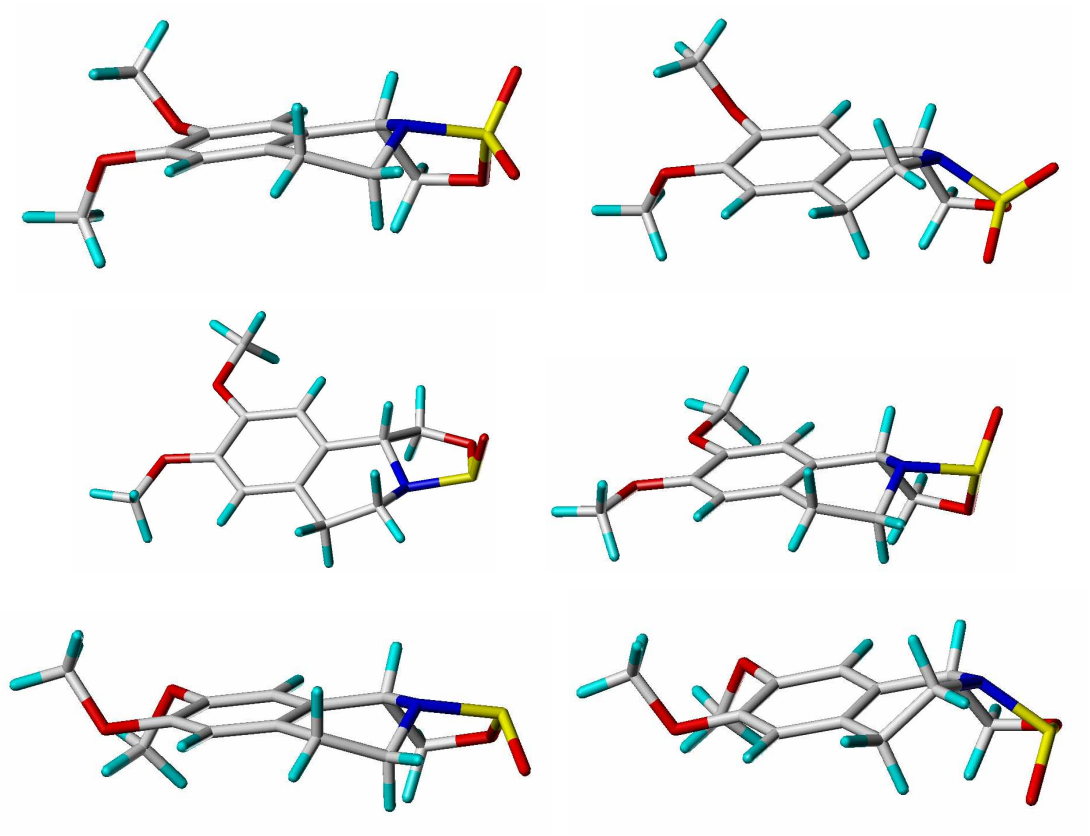
Calculated global (left) and local (right) energy minimum conformations for **132** (ΔE = 0.6 kcal mol^{-1}, top) and **135a** (ΔE = 0.9 kcal mol^{-1}, bottom)

Figure 11

1,5,6,10b-Tetrahydro-1,2,3-oxathiazolo[4,3-*a*]isoquinolines (**137** and **138**)

The configuration of the S atom in the cyclic sulphamidites **138a** and **138b** could be determined from the chemical shift of H-10b. If H-10b and S=O are on the same side of the molecule (*cis* isomer, **138a**), the chemical shift for H-10b is larger (5.03 ppm) than that in the corresponding *trans* isomer (**138b)** (4.35 ppm), due to the 1,3-*diaxial* effect.[69] This effect is perceptible in the cyclic sulphamidate **137**, which has S=O bonds in both *cis* and *trans* positions and the chemical shift of H-10b is 5.07 ppm.

For **137** and **138a**,**b**, two energy minima were calculated, for which the energy differences are rather small (*c. f.* Fig. 13). This suggests conformational equilibria in all three cases, which is corroborated by the moderate values of the coupling constants $^3J_{H,H}$. The corresponding $^3J_{H\text{-}5,H\text{-}6}$ (4.8-8.0 Hz, *c. f.* Table 10) and $^3J_{H\text{-}1,H\text{-}10b}$ values (6.8-9.6 Hz, *c. f.* Table 1) indicate the flexibility of the 6-membered (for **137** and **138a**) or the 5-membered (for **137** and **138b**) hetero rings.



Calculated global (left) and local (right) energy minimum conformations for **137** (bottom, ΔE = 0.40 kcal mol^{-1}, top), **138a** (middle, ΔE = 0.57 kcal mol^{-1}) and **138b** (top, ΔE = 0.88 kcal mol^{-1}, bottom).

Figure 13

Table 9

Selected chemical shifts in ppm (δ_{TMS} = 0 ppm, $\delta_{H_3PO_4}$ = 0 ppm)

Compd.	H-1*ax*		H-1*eq*		H-an[a]	
	Measd.	Calcd.	Measd.	Calcd.	Measd.	Calcd.
137	4.20	3.72	5.07	4.09	5.07	4.69
138a	4.12	3.83	5.07	4.64	5.03	5.03
138b	4.34	4.11	4.75	4.57	4.75	4.94
139	[b]	3.73	[b]	4.36	[b]	3.26
140a	4.07	3.83	4.99	4.56	3.83	3.86
140b	[b]	4.44	[b]	4.23	[b]	3.52

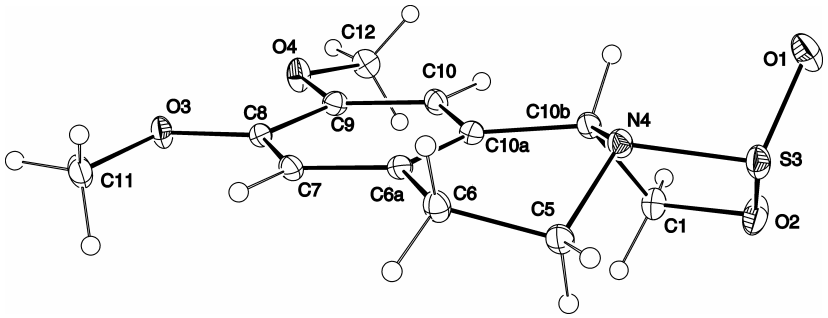
[a]H-an is the H atom at the annelation, *i.e.* H-10b for **137** and **138,** and H-10a for **139** and **140**;
[b]missing value since **139** and **140b** could not be isolated.

Table 10

Selected vicinal coupling constants, in Hz

Compd.	H-5*ax*–H-6*ax*	H-5*ax*–H-6*eq*	H-5*eq*–H-6*ax*	H-5*eq*–H-6*eq*
137	6.8	4.9	6.2	4.8
	10.9	4.9	2.9	2.2
138a	8.0	5.0	5.0	5.0
	10.3	6.3	3.6	1.1
138b	11.2	3.3	5.0	2.6
	10.7	4.6	2.7	2.3

The *cis*[1] conformer involved in the fast conformational equilibrium of **138a** (Table 4) has been revealed in the solid state by X-ray analysis (Fig. 14), whereas the DFT calculations relating to energy and NMR parameters (*cf.* Table 11 and Fig. 13) suggest that the *trans* conformer is the more stable in solution.



Ortep plot (30% ellipsoids) of **138a**, showing the numbering system and the stereochemistry of the compound.

Figure 14

Our results indicate that the heterocyclic ring moieties of 1,2,3-oxathiazolo[4,3-*a*]-isoquinolines are susceptible to undergo ring inversion in the confomational equilibria. For **138a**, where the S=O bond and H-11b are in the *cis* position, different preferred conformations were found in solution (*trans*) and in the solid state (*cis*[1]).

Table 11

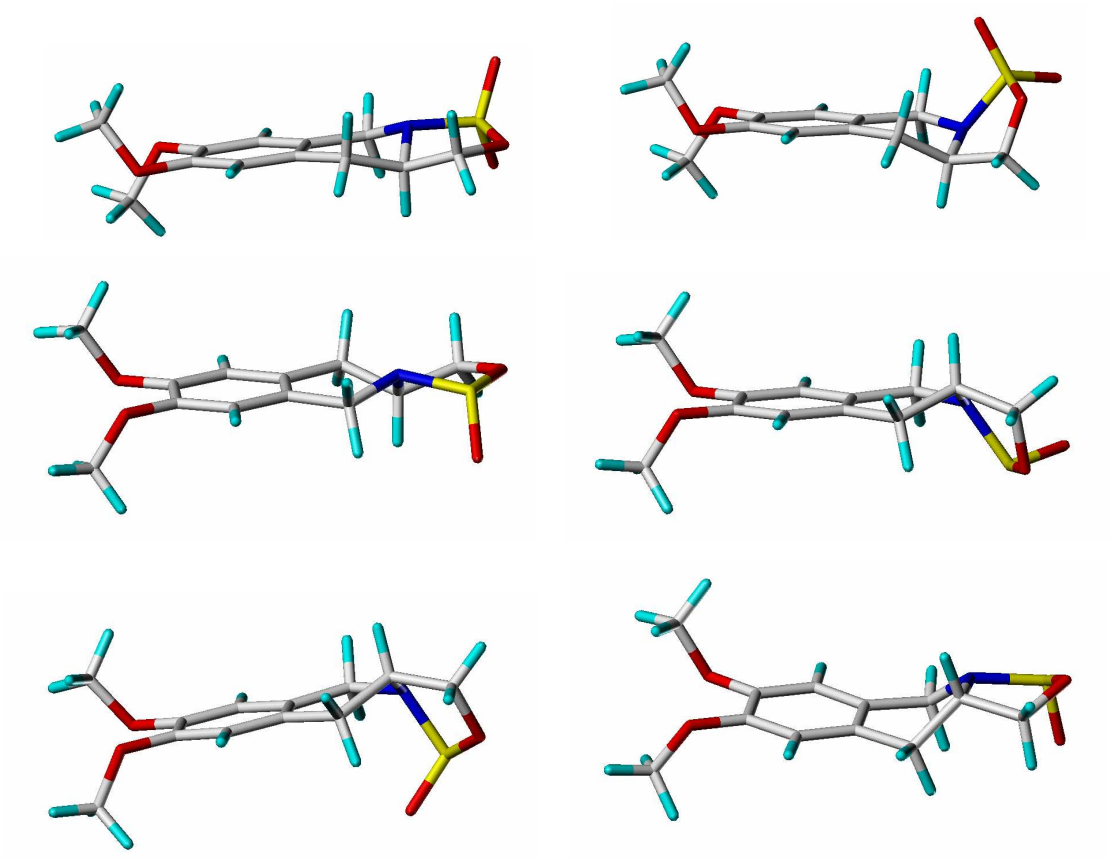
Calculated and experimental characteristic vicinal coupling constants (in Hz) and chemical shifts (in ppm) for **138a**

	Calcd. 1 *trans*	Calcd. 2 *cis*[1]	Measured
H-10b−H-1*eq*	5.9	7.9	6.5
H-10b−H-1*ax*	9.5	8.2	11.5
H-5*ax*−H-6*eq*	6.3	3.1	5.0
H-5*ax*−H-6*ax*	10.3	10.6	8.0
H-5*eq*−H-6*eq*	1.1	1.8	5.0
H-5*eq*−H-6*ax*	3.6	5.0	5.0
H-10b	5.03	5.27	5.03
H-5*ax*	3.00	2.65	3.43
H-5*eq*	3.12	2.75	3.27
H-6*eq*	2.55	2.31	2.95
H-6*ax*	3.06	3.09	2.95
H-1*ax*	3.83	3.69	4.12
H-1*eq*	4.64	4.31	5.07
C-10b	57.7	60.2	57.1
C-5	40.9	40.4	40.1
C-6	31.5	31.0	28.7
C-1	74.4	71.1	76.0

1,5,10,10a-Tetrahydro-1,2,3-oxathiazolo[3,4-*b*]isoquinolines (**139** and **140**)

Similarly to the angularly condensed analogues **138a**,**b**, the configuration of the S atom of the isolated linear sulphamidite diastereomer (**140a**) was determined from the chemical shift of the annelation H atom (H-10a). If H-10a and the S=O group are on the same side of the molecule, *i.e. cis* (**140a**), the chemical shift of H-10a is larger than that in the *trans* isomer (**140b**) due to the 1,3-*diaxial* effect.[69] By comparison of the experimental chemical shift for H-10a (3.83 ppm) with the calculated values of 3.86 ppm for **140a** and 3.52 ppm for **140b**, the *cis* configuration (**140a**) was deduced for the isolated diastereomer.

For **139** and **140**, two conformers were calculated to be most stable, for which the energy difference was rather small (*c. f.* Fig. 15). Although only one isomer (**a**) of **140** could be isolated, calculations were executed for both diastereomers, and for **139**, isolation of which also failed. One large and one small coupling between H-10 and H-10a suggested that the



Calculated global (left) and local (right) energy minima for **139** (ΔE = 1.88 kcal mol^{-1}, top), **140a** (middle, ΔE = 2.92 kcal mol^{-1}) and **140b** (ΔE = 0.10 kcal mol^{-1}, bottom).

Figure 15

6-membered ring was frozen in **140a** and **140b**. The moderate values of $^{3}J_{\text{H-1,H-10a}}$ (Table 1), however, indicated that the corresponding 5-membered rings were flexible. The comparison of the calculated and measured NMR parameters supported the correct stereochemistry of **140a**. Both of the H,H couplings of H-10a in **140a** were of *diaxial* type (Table 12), which suggests the *trans* connection of hetero rings B/C.

Table 12

Calculated and experimental characteristic vicinal coupling constants for **140a**, in Hz

	Calcd. for *trans*	Calcd. for *cis*[2]	Experimental value
H-10*ax*–H-10a	9.3	9.5	10.8
H-10*eq*–H-10a	3.5	3.7	2.8
H-1*ax*–H-10a	9.0	4.1	9.2
H-1*eq*–H-10a	6.2	0.1	6.6

According to the quantum chemical calculations, the *trans* conformation of **139** was 1.88 kcal mol^{-1} more stable than the energetically nearest conformer, with the *cis*[2] B/C connection.

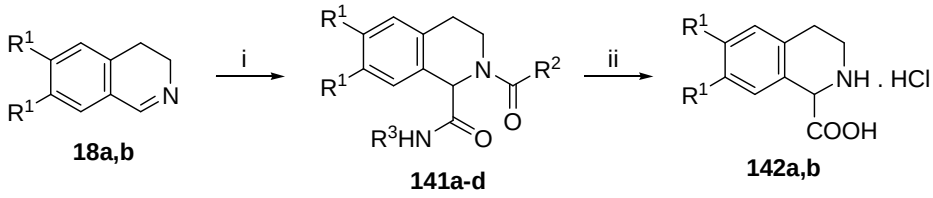
Our findings on 1,2,3-oxathiazolo[3,4-*b*]isoquinolines revealed that the insertion of a S atom into position 3 of the oxazolo[3,4-*b*]isoquinoline ring system caused no change in the preferred conformation, since both tricycles could be characterized by the same (*trans*) connection of rings B/C.

It was also concluded that neither the presence nor the angular or linear position of an annelated benzene ring exerts an influence on the geometry of the connection of the hetero rings, since not only both isolated diastereomers of regioisomeric tetrahydroisoquinoline-fused 1,2,3-oxathiazolidine 2-oxides (**138a** and **140a**), but also the parent 1,5,6,7,8,8a-hexahydro-1,2,3-oxathiazolo[4,3-*a*]pyridine 2-oxide,[73] could be characterized by the *trans* conformation.

3.2. Synthesis of 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids via the Ugi reaction of 3,4-dihydroisoquinolines

1,2,3,4-Tetrahydroisoquinoline-1-carboxylic acids, as conformationally constrained α-amino acids, are of interest as potential building blocks in heterocyclic and peptide chemistry and in drug research.[74-76] On the basis of various successful applications of cyclic imines in Ugi reactions, our aim was to investigate the scope and limitations of this procedure in the case of 3,4-dihydroisoquinolines, with the purpose of devising a new approach for the preparation of tetrahydroisoquinoline-1-carboxylic acid derivatives.

When 3,4-dihydroisoquinolines (**18a,b**) were reacted with achiral carboxylic acids and isocyanide in methanol at room temperature, *N*-acyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamides **141a-d** were formed (Scheme 28) in moderate to good yields. Acidic hydrolysis of **141a** and **141d** with 10% HCl gave the corresponding α-amino acids **142a** and **142b**.



141	R^1	R^2	R^3
a	H	Ph	CH_2Ph
b	OMe	Ph	CH_2Ph
c	OMe	Ph	cyclohexyl
d	OMe	cyclohexyl	cyclohexyl

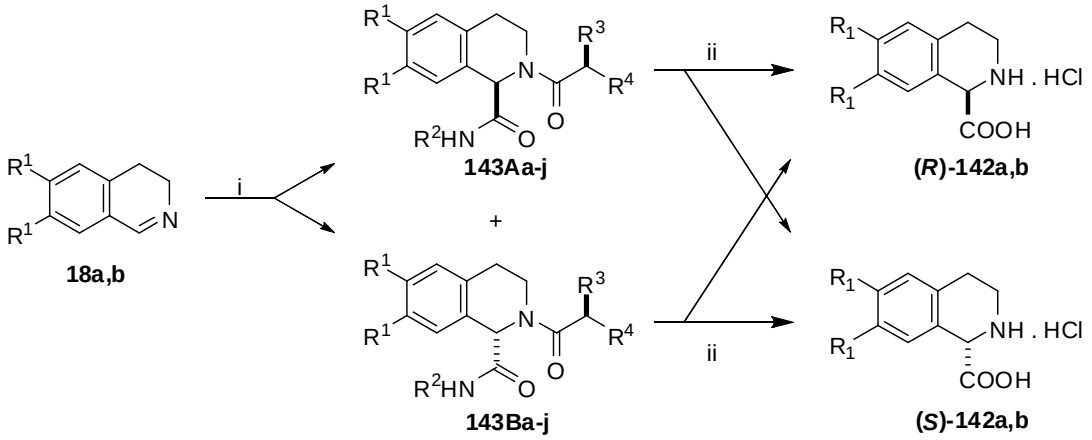
18/142	R^1
a	H
b	OMe

Reagents and conditions: (i) R^2COOH, R^3NC, MeOH, r.t., 1-4 days (49-65%);
(ii) 10% HCl/H_2O, reflux, 1-5 days (70-76%).

Scheme 28

To test the effect of a chiral, non-racemic acid on the stereochemical outcome of the condensation, Ugi reactions of dihydroisoquinolines **18a,b** were also performed by using L-mandelic acid and *N*-phthaloyl-L-alanine. The ^1H NMR spectra of the crude products **143a**-**j** revealed that a significant extent of asymmetric induction could not be achieved and the diastereomeric carboxamides **143A** and **143B** were formed in a ratio of nearly 1 : 1 (Scheme 29). The best (but poor) selectivity (10%, *de*) was achieved in the condensations towards **143a** and **143g**, on the use of benzyl isocyanide and L-mandelic acid for 3,4-dihydro-

isoquinoline, and benzyl isocyanide and *N*-phthaloyl-L-alanine for its 6,7-dimethoxy analogue. Our observations are in accordance with previous results on the applications of chiral, non-racemic acids in the Ugi MCR, since the acid component proved to have no pronounced effect on the stereoselectivity of the reaction, and the diastereomers of the corresponding α-acylaminocarboxamides were formed in a ratio of close to 1 : 1.[47,77,78]



18/142	R^1
a	H
b	OMe

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

Reagents and conditions: (i) R^2NC, $R^3R^4CHCOOH$, MeOH, r.t., 1-4 days;
(ii) 10% HCl, reflux, 5-40 h (70-76%).

Scheme 29

Although the diastereomeric products **143A** and **143B** could be separated by column chromatography in most cases (**a**-**h**), their relative configurations could not be determined from their NMR data as a consequence of the rotation of the bonds and the considerable distance between the asymmetric C atoms in the molecules. All of our attempts to produce appropriate samples of the isolated diastereomers for X-ray crystallography failed. The

isolated isomers of **143a-j** could therefore be referred to only as the more mobile (M) and the less mobile (L) diastereomers.

To prepare enantiopure 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids, the separated diasteromers of the Ugi products **143a-h** were submitted to acidic hydrolysis, under conditions similar to those successfully applied for the racemic compounds. Surprisingly, HPLC analysis of the crude products indicated that each hydrolysis took place with partial racemization, yielding the enantiomers of **142a** and **142b** in only poor to moderate enantiomeric excesses (*ee* 16-76%, *c. f.* Table 13). Even these enantiomeric excesses were totally lost during the chromatographic purification of the hydrolysis products on silica gel. The ready racemization ability of the cyclic α-phenylglycine analogues **142a** and **142b** can be interpreted in terms of the similar process for chiral non-racemic α-phenylglycines, which undergo racemization under acidic conditions.[79]

Table 13

Enantiomeric ratios (based on HPLC) of the tetrahydroisoquinoline carboxylic acids**142a** or **142b** in the crude products formed in the acidic hydrolysis of **143a-g** with 10% HCl

Compound*	Reflux time (h) for 100% conversion	Enantiomeric ratio	Enantiomeric excess (*ee*)
143a (M)	17.5	83 : 17	66%
143a (L)	20	13 : 87	74%
143b (M)	16.5	12 : 88	76%
143b (L)	9	63 : 37	26%
143c (L)	7	33 : 67	34%
143d (M)	40	42 : 58	16%
143d (L)	40	77 : 23	54%
143e (L)	13	27 : 73	46%
143f (M)	15	73 : 27	46%
143f (L)	5	22 : 78	56%
143g (M)	12	20 : 80	60%
143g (L)	40	60 : 40	20%

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

To the best of our knowledge, only two examples have been reported where full physical and analytical data are given on both the (*S*) and (*R*) enantiomers of 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid[80] or its 6,7-dimethoxy analogue.[81] In all other cases, no data have been published either on the $[\alpha]_D$ value or on the optical purity of the

enantiomers of 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid or its 6,7-dimethoxy analogue.[63,82,83] It is interesting that in some cases these enantiomers were prepared as synthetic intermediates by acidic hydrolysis of the corresponding carboxamides,[82,83] a reaction, which is suggested by our results to take place with partial racemization.

To characterize the racemization ability of **142a** under acidic conditions, the hydrolysis of the more mobile diastereomer of **143d** in refluxing 10% HCl was monitored by HPLC. The data in Table 14 show that conversion is followed by relatively rapid racemization, and after 15 h the enantiomeric ratio has reached a constant value (42 : 58). Similar results were obtained when the hydrolysis was performed in 10% trifluoroacetic acid.

Table 14

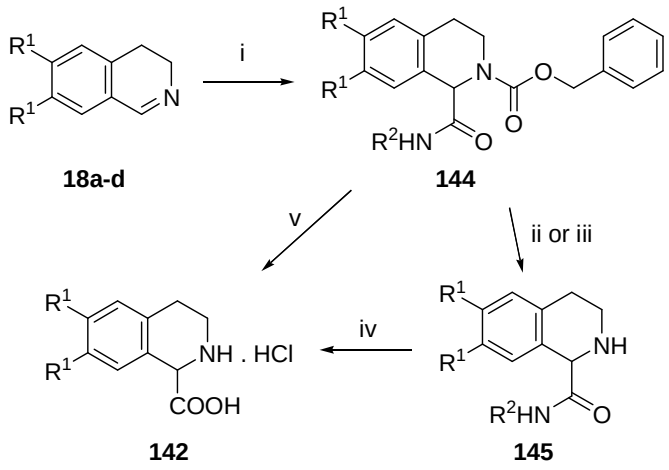
HPLC-based ratios of the enantiomers of 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid in the crude products formed in the acidic hydrolysis (with 10% HCl) of **143Ad**

Time (h)	Conversion (%)	Enantiomeric ratio	Enantiomeric excess (*ee*)
1	~0	–	–
3	~0	–	–
5	~0	–	–
10	15	23 : 77	54%
15	21	42 : 58	16%
25	75	42 : 58	16%
40	100	42 : 58	16%

On the basis of the method described by Díaz *et al.*,[63] who generated acylazinium salts from *N*-containing aromatic heterocycles for isocyanide coupling by using chloroformates, we attempted similar condensations of 3,4-dihydroisoquinolines (**18a-d**) with benzyl, *tert*-butyl or cyclohexyl isocyanide in the presence of benzyl chloroformate. The reactions were performed in $CHCl_3$ solution, at room temperature. The aqueous quenching during the work-up extraction gave diamide **144** in moderate to good yields. As Ugi reactions are known to proceed in aqueous medium,[58,84] coupling of **18b** with benzyl chloroformate and cyclohexyl isocyanide was also attempted in water, but **144b** could then be isolated in only low yield (24%).

It was expected that the presence of the readily and selectively removable *N*-benzyloxycarbonyl (*N*-Cbz) group in the products **144** would promote access to 2-unsubstituted 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid derivatives. As common methods for removal of the benzyl carbamate group,[85] hydrogenolysis and acidic hydrolysis

were investigated for **144a-f** (Scheme 30). Hydrogenation of **144a-f** under atmospheric pressure in the presence of Pd on charcoal catalyst resulted in the corresponding 2-unsubstituted 1,2,3,4-tetrahydroisoquinoline-1-carboxamides **145a-f** in good to moderate yields (61-89%). Somewhat better yields (83-95%) were achieved from the reactions of **144a-f** with 33% HBr in acetic acid, with subsequent alkaline treatment to liberate the free bases **145a-f** from the hydrobromide salts formed.



18/142	R^1
a	H
b	OMe
c	EtO
d	OCH_2O

144	R^1	R^2
a	H	cyclohexyl
b	MeO	cyclohexyl
c	EtO	cyclohexyl
d	OCH_2O	cyclohexyl
e	MeO	benzyl
f	MeO	*tert*-butyl

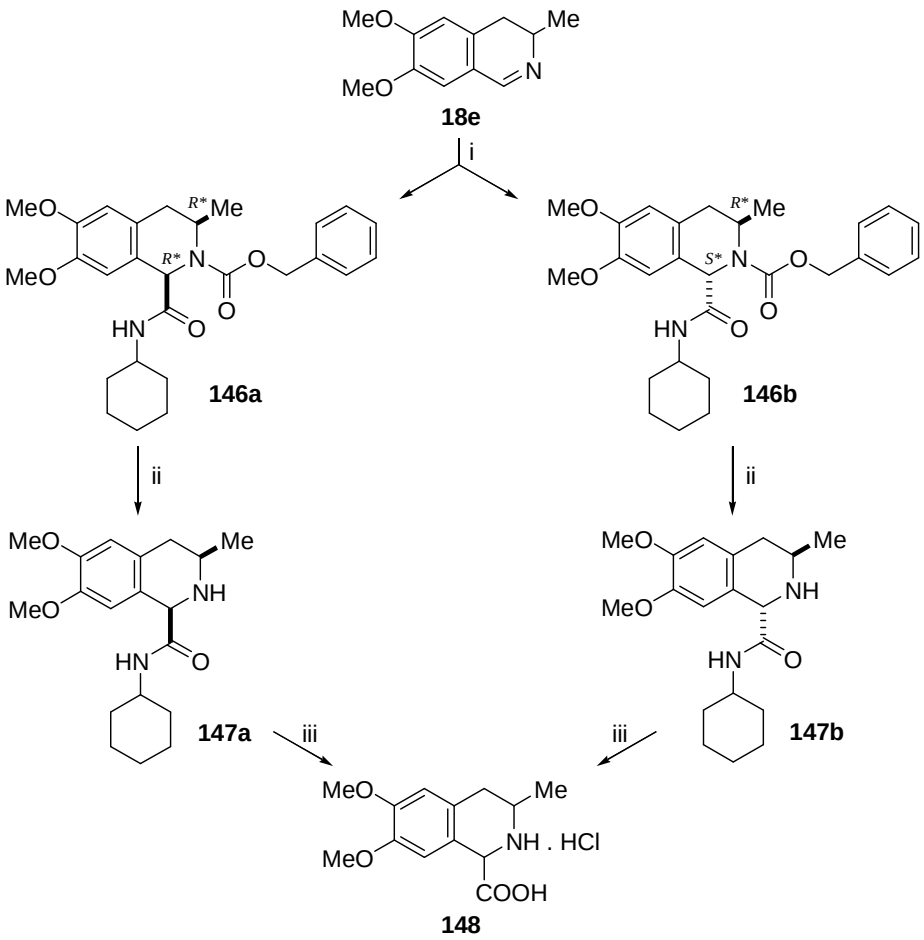
145	R^1	R^2
a	H	cyclohexyl
b	MeO	cyclohexyl
c	EtO	cyclohexyl
d	OCH_2O	cyclohexyl
e	MeO	benzyl
f	MeO	*tert*-butyl

Reagents and conditions: (i) $PhCH_2OCOCl$, R^2NC, $CHCl_3$, 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 30

When **144a**,**d** and **145a**,**d**,**e** were subjected to acidic hydrolysis in refluxing 10% aqueous HCl, the hydrochloride salts of the corresponding 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids **142a-c** were obtained (Scheme 30). **145a**,**d**,**e** underwent hydrolysis in a shorter time and with better yields than for the corresponding reactions of **144a**,**d**. Hydrolysis of the 6,7-methylenedioxy derivatives **144f** and **145f** led to complex mixtures from which the corresponding amino acid could not be isolated; this was probably due to the sensitivity of the 1,3-dioxolane moiety to the harsh reaction conditions.

To test the effect of a 3-methyl substituent on the starting dihydroisoquinoline and to devise a procedure for the synthesis of 3-methyl-substituted tetrahydroisoquinoline-1-carboxylic acid derivatives, coupling of 3-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline (**18e**) was also attempted (Scheme 31). The integrals of the 3-H multiplets in the ^{1}H NMR spectrum of the crude product did not reveal any diastereoselectivity in the formation of the *cis* and *trans* isomers of the corresponding 1,3-disubstituted tetrahydroisoquinolines (**146a,b**). Diastereomers **146a** and **146b** were separated by fractional crystallization, and their relative configurations were determined by NOESY measurements, where NOE interactions were detected between 3-Me and NH in **146a**, and between 3-Me and 1-H in **146b**.



Reagents and conditions: (i) $PhCH_2OCOCl$, cyclohexyl isocyanide, $CHCl_3$, r.t., 24 h, then H_2O, r.t., 30 min, followed by fractional crystallization (**146a**: 31%, **146b**: 44%), (ii) H_2 (1 atm), Pd/C, EtOH, r.t., 6 h (56-68%), (iii) 10% HCl, reflux, 40 h (30-32%).

Scheme 31

Removal of the *N*-Cbz group in **146a,b** by hydrogenolysis afforded the corresponding diastereomeric carboxamides **147a,b**. When either **147a** or **147b** was submitted to acidic hydrolysis in refluxing 10% HCl, the reaction was accompanied by a total loss of diastereomeric purity, and a 1 : 1 mixture of *cis*- and *trans*-6,7-dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid hydrochloride (**148**) was obtained. This phenomenon can be rationalized by the ease with which tetrahydroisoquinoline-1-carboxylic acids undergo racemization in acidic medium.[I,81] All of our efforts to separate the diastereomers of **148** failed.

4. SUMMARY

1. 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 (**121**-**126**), and 9,10-dimethoxy-1,6,7,11b-tetrahydro-2*H*-1,2,3-oxathiazino[4,3-*a*]isoquinoline 4,4-dioxides (**121**-**123**) and 4-oxides (**124**-**126**) were prepared by ring-closure reactions of phenyl-substituted tetrahydroisoquinoline-1-ethanols with phenylphosphonic dichloride, bis(2-chloroethyl)phosphoramidic dichloride, thionyl chloride and sulphuryl chloride.

2. The first representatives of new ring systems, 1,5,6,10b-tetrahydro-1,3,2-oxazaphospholo[4,3-*a*]isoquinolines (**127** and **128**), 1,5,10,10a-tetrahydro-1,3,2-oxazaphospholo-[3,4-*b*]isoquinolines (**129** and **130**), 1,5,6,10b-tetrahydro-1,2,3-oxathiazolo[4,3-*a*]-isoquinolines (**137** and **138**) and a 1,5,10,10a-tetrahydro-1,2,3-oxathiazolo[3,4-*b*]isoquinoline (**140**), were prepared by cyclizations of regioisomeric tetrahydroisoquinoline 1,2-amino alcohols with the above-mentioned P- or S-containing agents.

3. The NMR spectra of the crude ring-closed products indicated that (with the exception of **122b**) 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 the H atom at the annelation in the *cis* position formed as the main products with good to high selectivities (*de*: 66-100%). The diastereomers were separated by column chromatography.

4. 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 (**121**-**126**) 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* conformation, where C-1 is in a *pseudoaxial* position, while their *cis* counterparts (diastereomers **b**) contained *trans*-connected rings B/C.

5. 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 (**131** and **134a**) while the conformational equilibria of the 2-phenyl-substituted analogues (**132**, **133**, **135a** and **136a**) were found to be shifted towards the *cis*[1] form, independently of the relative configuration of C-2.

6. The NMR spectroscopic conformational analyses on the 1,2,3-oxathiazolidine or 1,3,2-oxazaphospholidine derivatives angularly- or linearly-condensed to tetrahydroisoquinoline (**127**-**130** and **138**-**140**) 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. Accordingly, DFT calculations of the structures were processed, indicating that in general two conformers participate in the conformational equilibria. The 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 **121**-**126**, the stereochemistry of the ring B/C connection 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-oxazaphospholidine derivatives (**127**-**130**).

7. 1-Unsubstituted 3,4-dihydroisoquinolines proved to be convenient starting materials for Ugi condensations with acids and isocyanides, resulting in 2-acyl- (**141** and **143**) or 2-benzyloxycarbonyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamides (**144**) in moderate to good yields. The acidic hydrolysis of the formed dicarboxamides (**141**, **143** and **144**) resulted in 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids (**142**). 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.

8. The condensations of chiral, non-racemic acids with 3,4-dihydroisoquinolines and isocyanides took place with no or only poor diastereoselectivities (*de*: 0-10%). During the hydrolysis of the separated diastereomeric Ugi products, enantiomers of 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid (**142a**) and its 6,7-dimethoxy analogue (**142b**) were formed to the accompaniment of a considerable degree of racemization.

9. The hydrogenolysis of 2-benzyloxycarbonyl-1,2,3,4-tetrahydroisoquinoline-1-carboxamides (**144**) proved to be a convenient procedure for the preparation of 1,2,3,4-tetrahydroisoquinoline-1-carboxamides (**145**). The hydrolysis of the carboxamides (**145**) led to the corresponding 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acids (**142**).

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7. ANNEX