Recent advances in the synthesis of polysubstituted 3-pyrazolidinones

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DOI: http://dx.doi.org/10.3998/ark.5550190.p009.129

Abstract

An account of recent developments in the field of 3-pyrazolidinone chemistry is given with special focus on the synthesis and transformations of 5-substituted 4-benzyloxycarbonylamino-3-pyrazolidinones, pyrazolo[1,2-*a*]pyrazole-based peptide analogues, and tetrahydropyrazolo-[1,5-*c*]pyrimidine-2,7-diones. In terms of practical application, polyfunctionalized 3-pyrazolidinones as 'aza-deoxa' analogues of cycloserine, peptide mimetics based on 3-amino-2-oxo-1,5-diazabicyclo[3.3.0]octane-7-carboxylic acid, and 1,6-disubstituted tetrahydropyrazolo[1,5-*c*]-pyrimidine-2,7-diones as the first representatives of a novel saturated heterocyclic system were prepared by these newly developed synthetic methods.

Keywords: pyrazolidinones, cycloadditions, cyclizations, fused pyrimidines, peptide mimetics

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1. Introduction

3-Pyrazolidinone (Figure 1) and its derivatives are cyclic (internal) hydrazides of 3-hydrazinopropanoic acid, which are commonly available by treatment of α,β-unsaturated carboxylic acid derivatives with hydrazine hydrate. In spite of their structural simplicity and ease of preparation, there were almost no reports on 3-pyrazolidinones in the early times of organic chemistry until the second half of the 20th century. The first reports on 3-pyrazolidinones date to the 1940s.[1–6] Since that time, the importance of 3-pyrazolidinones has risen significantly, due to their applicability in industrial processes and biological activity. So far, progress on 3-pyrazolidinone chemistry has been reviewed by Dorn in 1981,[7] Claramunt and Elguero in 1991,[8] and in part by Svete in 2008.[9] Pyrazolidinone derivatives have been employed as dyes in food and other industries.[7,10,11] Their bioactivities range from analgesic and antipyretic (phenazone),[12–14] anti-inflammatory (phenylbutazone),[12–14] and anorectic (BW357U),[15] to inhibitory activities of cyclooxygenase and lipoxygenase in BW755C and phenidone, respectively.[16,17] Bicyclic pyrazolidinones are used, among others, as drugs to relieve Alzheimer's disease[18] and as antibacterial agents.[19–23] Some important 3-pyrazolidinones are presented in (Figure 1).

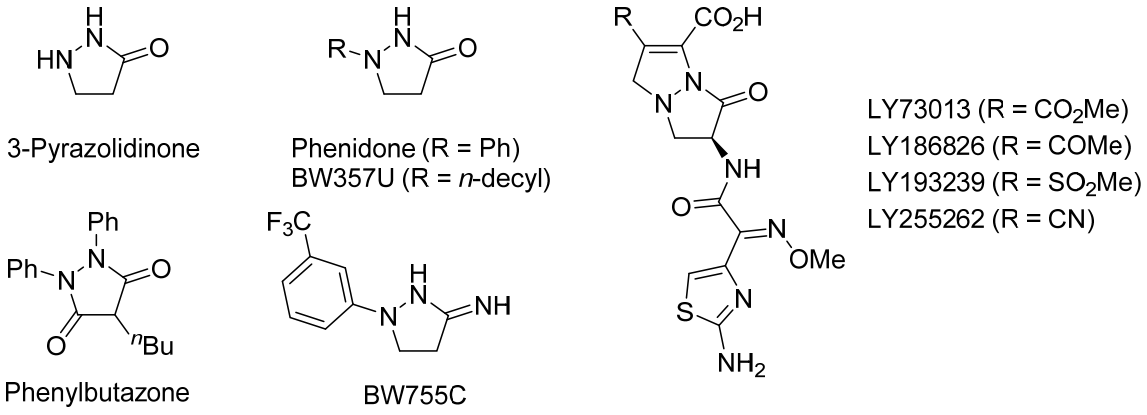


Figure 1. Some important 3-pyrazolidinone derivatives.

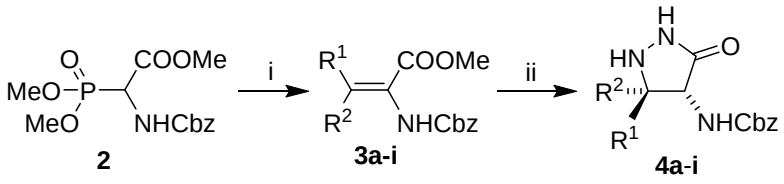
Due to their applicability and biological activity, pyrazolidin-3-one derivatives, both mono- and bi-cyclic, remain attractive synthetic targets. Particular challenge is associated with their enantio- and/or diastereoselective synthesis. Most of the early studies were performed on achiral and on lightly substituted chiral pyrazolidinones.[7,8] Recent studies, however, established the applicability of chiral polysubstituted 3-pyrazolidinones and their derivatives in the stereoselective synthesis of highly functionalized compounds.[24–26] Camphor derived pyrazolidin-3-one has been successfully employed as chiral auxiliary[27] while pyrazolidinone templates have been used in enantioselective Diels-Alder cycloadditions.[28] Several studies demonstrated the potential of pyrazolidin-3-ones as a new scaffold in organocatalysis.[29–35]

In the last two decades, a substantial part of our research interest has also been devoted to the chemistry of 3-pyrazolidinones.[9,36–38] Most of our work in this field was based on chiral racemic (4*R**,5*R**)-4-benzoylamino-5-phenylpyrazolidin-3-one as the model compound, which is easily available from 4-benzylidene-2-phenyl-5(4*H*)-oxazolone by heating with excess hydrazine hydrate.[3,24] This model compound was successfully employed in the synthesis of β-pyrazolylalanine- and β-amino-β-phenylalanine derivatives and pyrazolo[1,2-*a*]pyrazole-based peptide mimetics.[9] In extension, we became interested in the preparation of saturated 6-amino-perhydropyrazolo[1,2-*a*]pyrazole-1(or 2)-carboxylates that could serve as building blocks for incorporation into oligopeptides. Another important issue was the preparation of non-racemic peptide analogues, available either by resolution or by asymmetric synthesis. Finally, literature search revealed that saturated bicyclic pyrazolidinone-based heterocyclic systems are pretty much unknown. In this account, our recent developments in the synthesis of 3-pyrazolidinones and their fused analogs are presented.

2. Synthesis of 3-Pyrazolidinone Derivatives

2.1. From α,β-unsaturated esters

Heating of α,β-unsaturated esters (acrylates) with excess hydrazine hydrate is the most general and straightforward route to 3-pyrazolidinones.[7–9] In the case of functionalized acrylates, however, the use of excess hydrazine hydrate represents a limitation, since nucleophile-sensitive functional groups may also react. This limitation cannot be avoided by the use of nucleophile-resistant protecting groups, since they are usually difficult to remove. Consequently, deprotection and further derivatisations are hardly feasible. For example, the amino function in the products derived from (4*R**,5*R**)-4-benzoylamino-5-phenylpyrazolidin-3-one (**1**) could not be deprotected without destroying the heterocyclic system as well. For this reason, we decided to perform the synthesis of *N*-benzyloxycarbonyl protected compounds to allow N-deprotection and further transformations of the products. First, 3-substituted methyl 2-(benzyloxycarbonylamino)-acrylates **3a**–**i** were prepared by Wittig-Horner condensation of methyl 2-(benzyloxycarbonylamino)-2-(dimethoxyphosphoryl)acetate (**2**) with aldehydes and ketones following a slightly modified procedure by Schmidt and co-workers.[39] Acrylates **3a**–**i** were then treated with excess of $N_2H_4 \cdot H_2O$ in an alcohol (MeOH, EtOH, or ^{n}PrOH) at 20–100 °C to afford the corresponding 3-pyrazolidinones **4a**–**i** in 23–100% yields (Scheme 1).[40–42]

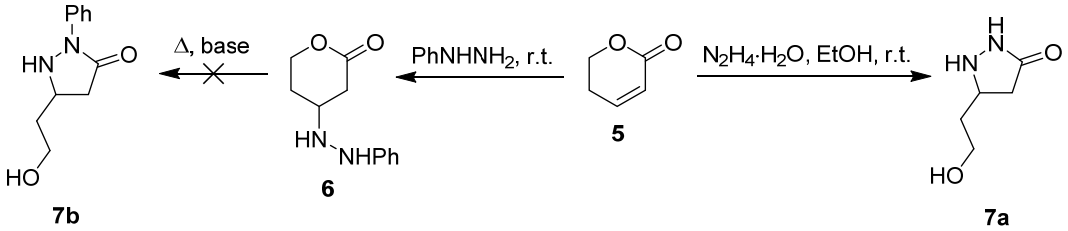


i) R^1R^2C=O, DBU, CH_2Cl_2, r.t.; ii) $N_2H_4 \cdot H_2O$, ROH, r.t. or reflux.

Cpd.	R^1	R^2
4a	1-propyl	H
4b	2-propyl	H
4c	Me	Me
4d	$-(CH_2)_5-$	
4e	Ph	H
4f	3-nitrophenyl	H
4g	4-nitrophenyl	H
4h	4-chlorophenyl	H
4i	2-hydroxyphenyl	H

Scheme 1. Synthesis of 3-pyrazolidinones **4a**–**i**.

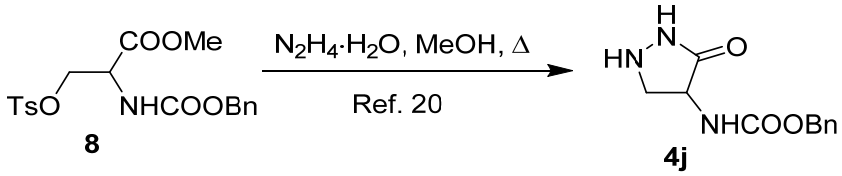
Another recent example of utilization of α,β-unsaturated esters in the synthesis of 3-pyrazolidinones is a 'ring switching' transformation of commercially available 5,6-dihydro-2*H*-pyran-2-one (**5**) with hydrazine hydrate in ethanol at r.t. This reaction gave 5-(2-hydroxyethyl)pyrazolidin-3-one (**7a**)[43] in quantitative yield. It is also noteworthy, that 2-substituted analogues of **7a** could not be prepared in this way. For example, treatment of **5** with phenylhydrazine afforded the 1,4-addition intermediate **6**, which could not be converted into the corresponding pyrazolidinone **7b**, even under forcing conditions (Scheme 2).[43,44]



Scheme 2. Synthesis of 5-(2-hydroxyethyl)pyrazolidin-3-one (**7a**).

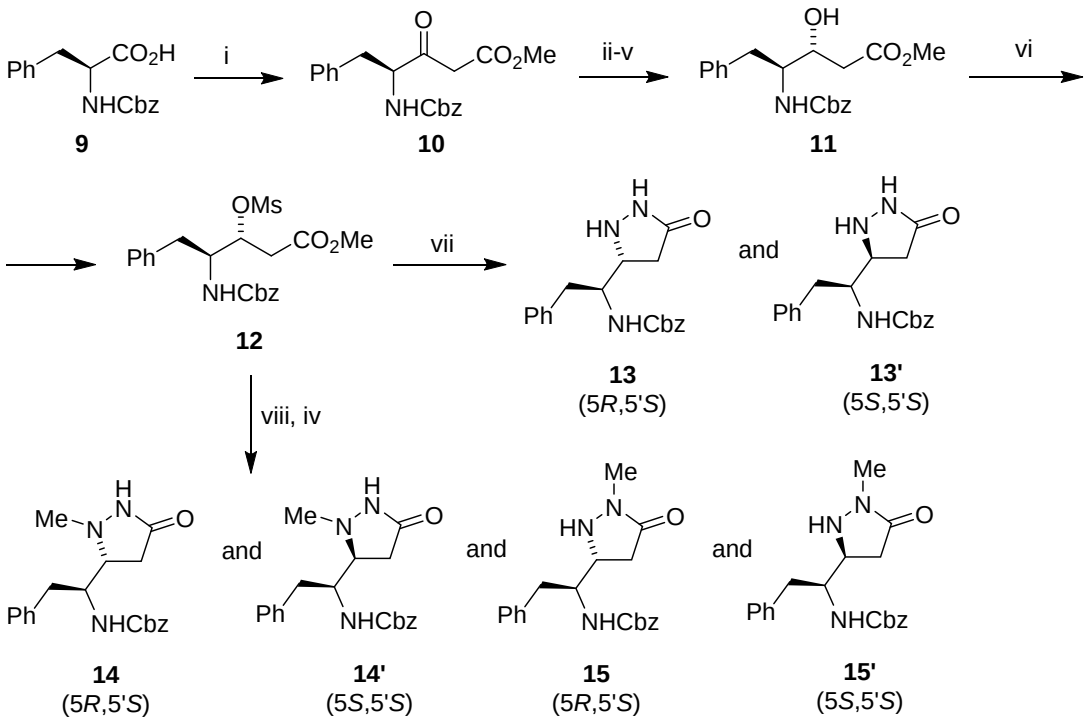
2.2 From β-hydroxy esters

Beside acrylates, β-sulfonyloxy esters are also suitable substrates for the preparation of 3-pyrazolidinones. Preparation of racemic 4-benzyloxycarbonylamino-3-pyrazolidinone **4j** from methyl *N*-benzyloxycarbonyl-*O*-tosylserinate (**8**) and hydrazine hydrate was reported by Jungheim and co-workers in 1987 (Scheme 3).[20]



Scheme 3. Synthesis of 4-benzyloxycarbonylamino-3-pyrazolidinone (**4j**).

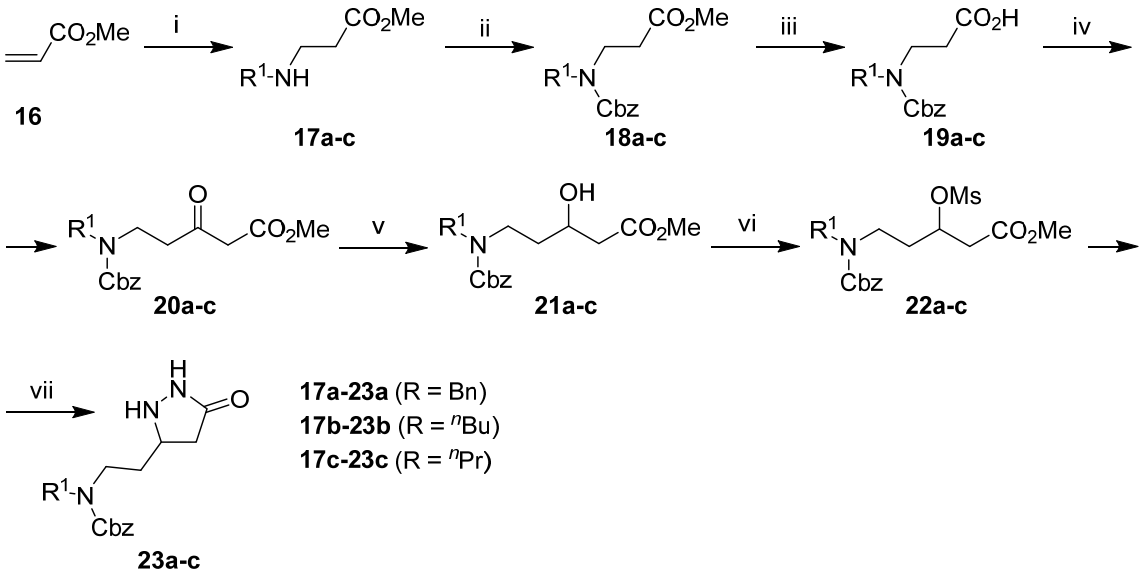
Recently, non-racemic 3-pyrazolidinones have been prepared from L-phenylalanine. N-Cbz-(*S*)-3-phenylalanine (**9**) was converted into the corresponding *β*-keto ester **10**[45] in 43% yield *via* the addition of Li-enolate of methyl acetate to the reactive imidazolide of **9**. Subsequent reduction of **10** with $NaBH_4$, followed by chromatographic separation and re-crystallization gave isomerically pure (3*R*,4*S*)-*β*-hydroxy ester **11**.[46] Mesylation of **11** in pyridine gave **12**, which was further treated with excess hydrazine hydrate in CH_2Cl_2 to yield the desired pyrazolidin-3-one in full conversion as an inseparable mixture of epimers **13** and **13′** in a ratio of 62:38 and in 57% yield. Following the same reaction conditions, cyclization of **12** with methylhydrazine yielded two regioizomeric pyrazolidinones each as a mixture of epimers in 100% conversion. The products **14**, **14′**, **15**, and **15′** were formed in a ratio of 35:26:26:13. Chromatographic separation yielded pure isomers **14**, **14′**, and **15** in 25%, 18%, and 10% yield, respectively. Performing the reaction under identical conditions in DMF did not significantly change the product ratio. The formation of two regioisomers in the reaction of **12** with methylhydrazine was not unexpected. The poor diastereoselectivity of the formation of **13**/**13′**–**15**/**15′** implies that substitution of the mesylate group with hydrazine proceeds, either *via* a mixed S_N1/S_N2 mechanism, or alternatively, *via* initial elimination of mesylate group, followed by 1,4-addition of hydrazine to the so formed *α*,*β*-unsaturated ester intermediate (Scheme 4).[47]



i) CDI, THF, r.t.; ii) MeOAc, LDA, THF, -61 °C; iii) $NaBH_4$, MeOH, -5 °C; iv) chromatographic separation; v) re-crystallization; vi) MsCl, pyridine, -5 °C; vii) $N_2H_4 \cdot H_2O$, CH_2Cl_2, r.t.; viii) $MeNHNH_2$, CH_2Cl_2, r.t.

Scheme 4. Synthesis of non-racemic pyrazolidin-3-ones **13**/**13′**–**15**/**15′**.

Finally, 5-(2-aminoethyl) substituted 3-pyrazolidinones have also been synthesized in six steps from methyl acrylate (**16**). Following literature examples,[48] solvent-free DBU-catalysed Michael addition of benzylamine, 1-butylamine, and 1-propylamine to **16** gave methyl *β*-alaninates **17a**–**c**, which were Cbz-protected and the so formed *N*-alkyl-*N*-Cbz-*β*-alanine esters **18a**–**c** were hydrolyzed to afford *N*-alkyl-*N*-Cbz-*β*-alanines **19a**–**c**[46] in 34–51% yields over three steps. Masamune-Claisen condensation of **19a**–**c** with monomethyl magnesium malonate was carried out according to the literature procedure for homologation of closely related amino acid derivatives[48,50–52] to give the corresponding *β*-keto esters **20a**–**c** in 87–92% yields. Reduction of **20a**–**c** with $NaBH_4$, mesylation of the alcohols **21a**–**c**, and cyclisation of the mesylates **22a**–**c** with hydrazine hydrate furnished 5-{2-[(alkyl)(benzyloxycarbonyl)amino]ethyl}pyrazolidin-3-ones **23a**–**c** in 43–61% yields over three steps (Scheme 5).[53]



i) R^1NH_2, cat. DBU, r.t.; ii) ClCOOBn, CH_2Cl_2, Et_3N, 0-20 °C; iii) aq. NaOH, MeOH, r.t.; iv) CDI, THF, r.t., then potassium monomethyl malonate, $MgCl_2$, r.t.; v) $NaBH_4$, MeOH, 0-20 °C, vi) MsCl, pyridine, 0-20 °C; vii) $N_2H_4{\cdot}H_2O$, MeOH, r.t.

Scheme 5. Synthesis of pyrazolidin-3-ones **23a**–**c**.

3. Transformations of 3-Pyrazolidinone Derivatives

3.1 Transformations on the ring

It is within this context that functionalization at the ring nitrogen atoms is usually performed. On account of the cyclic hydrazide structure of 3-pyrazolidinones, the reactivities of the two nitrogen atoms differ significantly. The more basic and more nucleophilic N(1) is also more reactive. It preferably reacts with sp^2 electrophiles, such as carbonyls, electron-deficient alkenes

and alkynes, and carbocations (S_N1 substrates), whereas reactions with sp^3 type of electrophiles (S_N2 substrates, such as primary alkyl halides) are usually difficult. A better way to obtain the corresponding 1-(primary alkyl)-3-pyrazolidinones is reduction of easily available azomethine imines with complex hydrides, e.g. with $NaBH_4$ or $NaBH_3CN$. Once the N(1) is occupied, the amidic nitrogen N(2) can react with primary alkyl halides in the presence of a base in polar aprotic solvents to give the 1,2-disubstituted derivatives (Figure 2).[7–9,54]

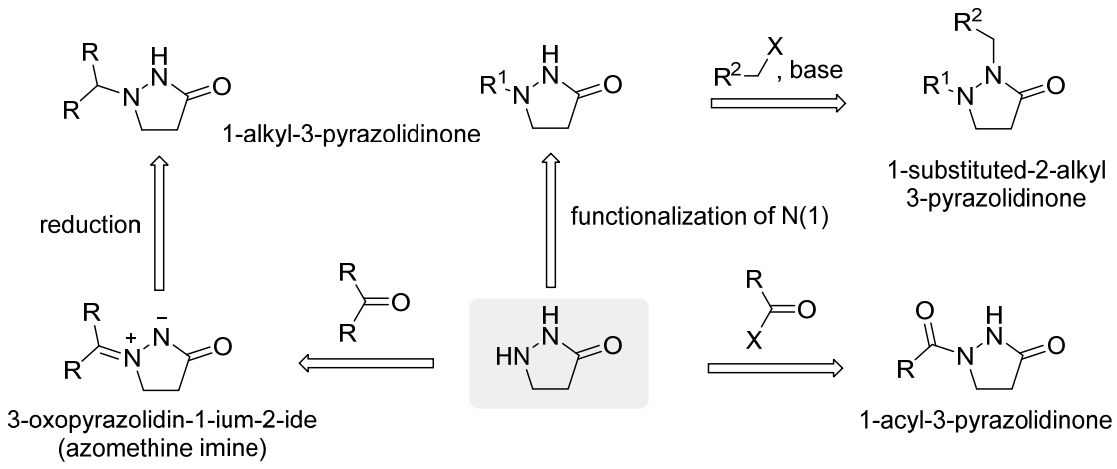


Figure 2. Functionalizations of ring nitrogen atoms with electrophiles.

A recent example of sequential derivatization of 5-substituted (4*R**,5*R**)-4-benzyloxycarbonylamino-3-pyrazolidinones is a simple five-step synthesis of fully substituted (4*R**,5*R**)-4-aminopyrazolidin-3-ones as analogues of D-cycloserine. It comprises a two-step preparation of 5-substituted (4*R**,5*R**)-4-benzyloxycarbonylamino-3-pyrazolidinones **4** (cf. Scheme 1), reductive alkylation at N(1), alkylation of the amidic N(2) with alkyl halides, and simultaneous hydrogenolytic deprotection/reductive alkylation of the primary amino group. The major advantage of the synthesis is that it enables an easy stepwise functionalization of the 3-pyrazolidinone core with only two types of common reagents, aldehydes (or ketones) and alkyl halides (Figure 3).[42]

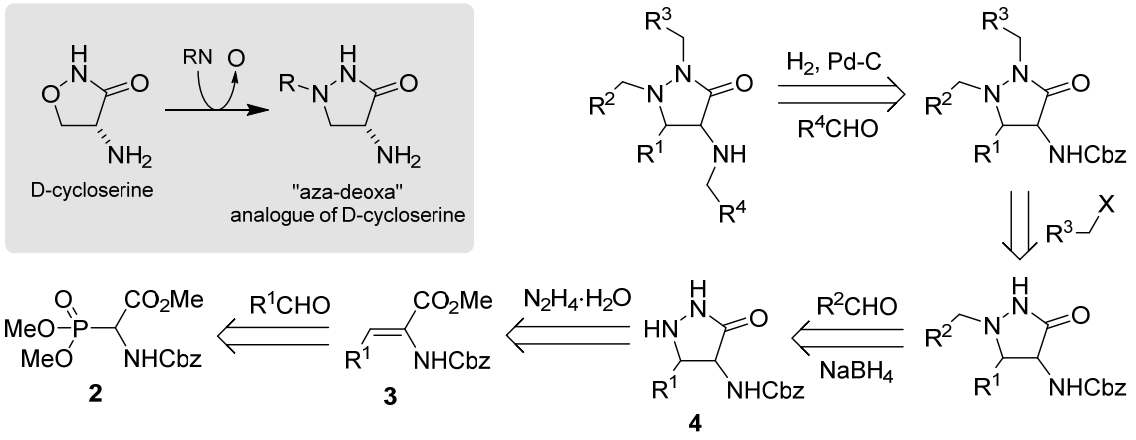
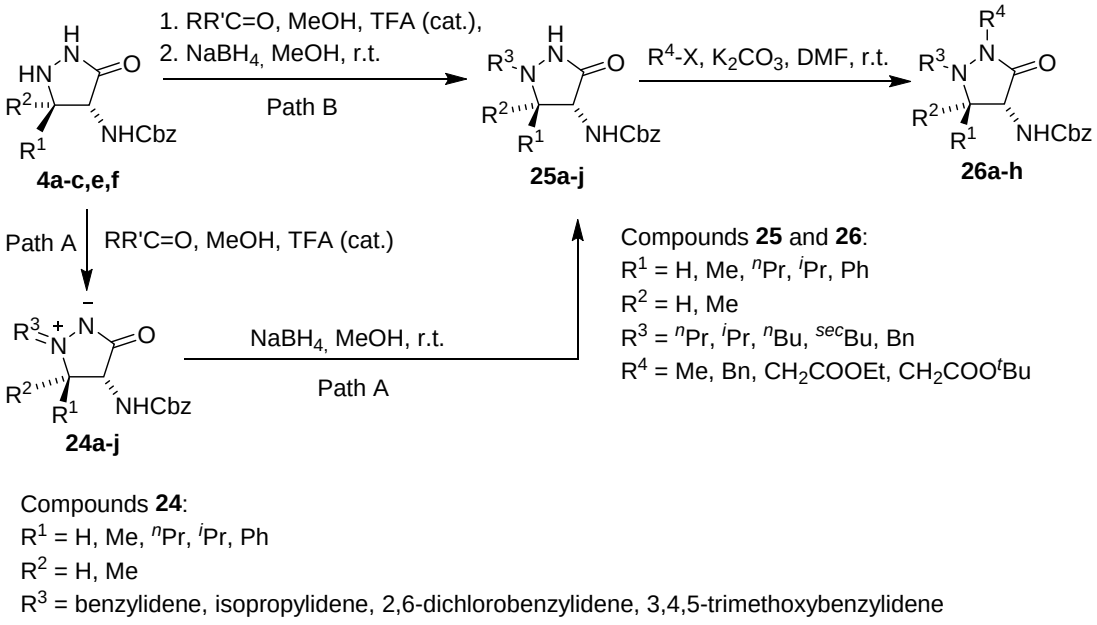


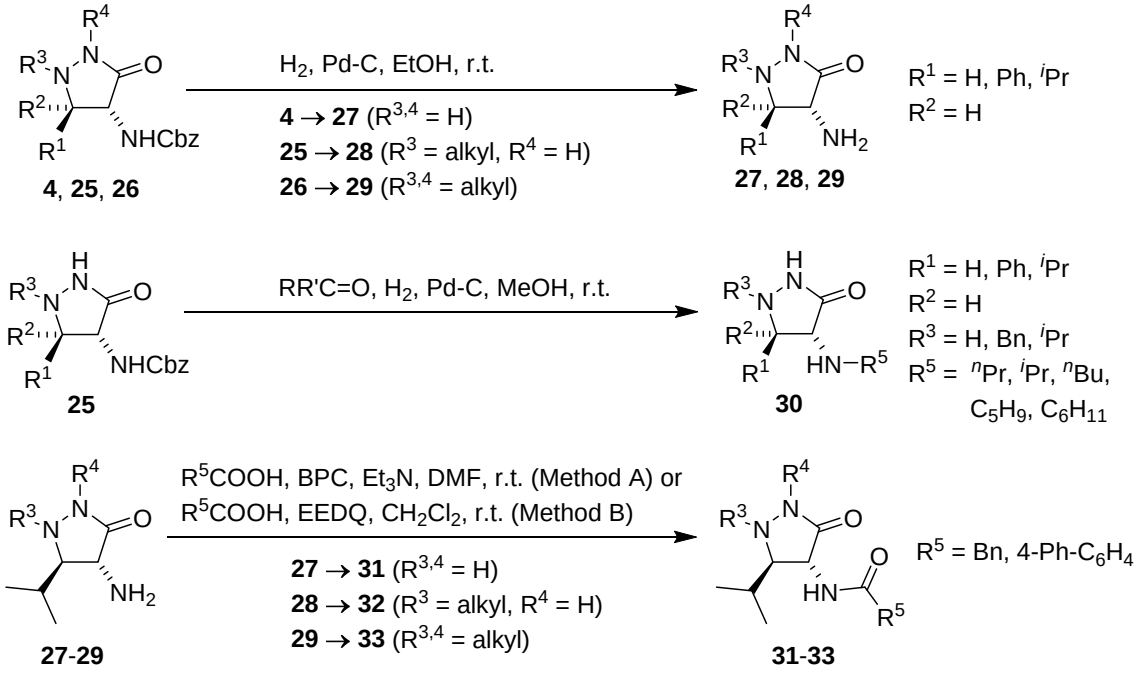
Figure 3. Cycloserine, its 'aza-deoxa' analogues, and their synthesis.

Acid-catalyzed treatment of **4a**–**c**,**e** with acetone and aromatic aldehydes in MeOH gave the corresponding azomethine imines **24a**–**j** in 31–99% yields. Reduction of **24a** (R^1 = ^{i}Pr, R^2 = H, R^3 = benzylidene) with $NaBH_4$ in MeOH at r.t. afforded the 1-benzyl derivative **25a** in 93% yield (Path A). The other N(1)-alkylated derivatives **25** were prepared by an one-pot procedure *via in situ* formation of azomethine imines **24**, followed by subsequent reduction with $NaBH_4$. In this manner, a series of ten N(1)-alkylated 4-(benzyloxycarbonylamino)-3-pyrazolidinones **25a**–**j** were obtained in 21–95% yields (Path B). S_N2-type alkylation of the amidic N(2) was performed with primary alkyl halides in DMF in the presence of K_2CO_3 at r.t. to furnish the fully substituted 4-amino-3-pyrazolidinones **26a**–**h** in 45–97% yields (Scheme 6).[42]



Scheme 6. Synthesis of 1-substituted- (**25**) and 1,2-disubstituted pyrazolidinones **26**.

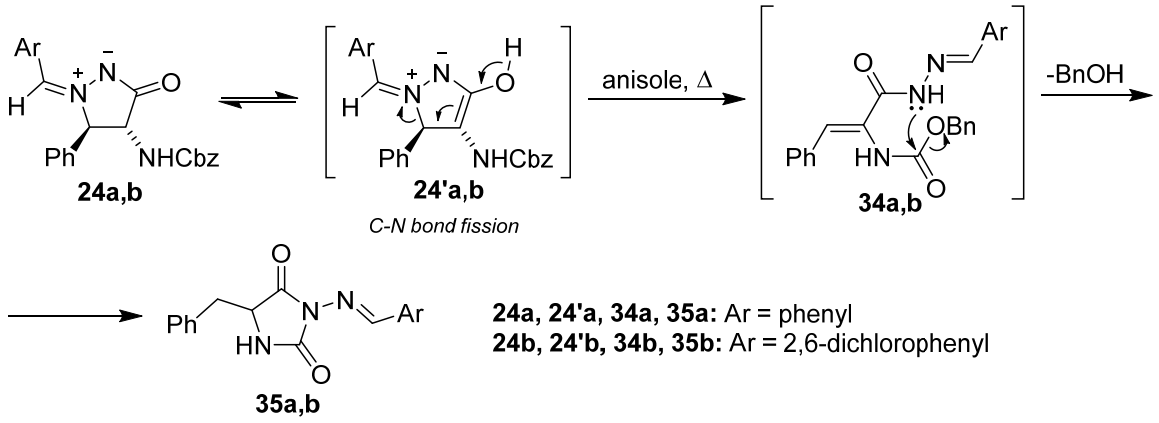
To bring other functionalities to the amino function, transformations of the benzyloxycarbonylamino group at position 4 were studied as well. Hydrogenolytic deprotection of the 4-amino function in the Cbz-protected 4-aminopyrazolidinones **4**, **25**, and **26** gave the free amines **27**, **28**, and **29**, respectively, in almost quantitative yields. When hydrogenolytic deprotection of the 1,5-disubstituted 4-benzyloxycarbonylamino-3-pyrazolidinones **25** was carried out in the presence of an aldehyde or a ketone, the 4-alkylamino-3-pyrazolidinones **30** were obtained in 75–100% yields. Somewhat surprisingly, acylations of the 1,2-unsubstituted (4*R**,5*R**)-4-amino-5-isopropyl-3-pyrazolidinone **27** with acid chlorides or with carboxylic acids in the presence of activating reagents, such as 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) and 1,1′-carbonyldiimidazole (CDI), did not give the desired carboxamides. The only successful N-acylation of **27** was the reaction with [1,1′-biphenyl]-4-carboxylic acid in the presence of bis(pentafluorophenyl) carbonate (BPC) in DMF, which afforded the corresponding *N*-acyl derivative **31** in 10% yield. Though surprising, the difficult acylation of the NH_2 group could be the result of the highly polar character of **27** as cyclic α-amino hydrazide comprising three different amino groups. On the other hand, acylation of the less polar 1-substituted or 1,2-disubstituted pyrazolidinones **28** and **29** with phenylacetic acid and EEDQ in CH_2Cl_2 proceeded smoothly to produce the corresponding carboxamides **32** and **33** in 83% and 82% yield, respectively (Scheme 7).[42]



Scheme 7. Synthesis of polysubstituted pyrazolidinones **27**–**33**.

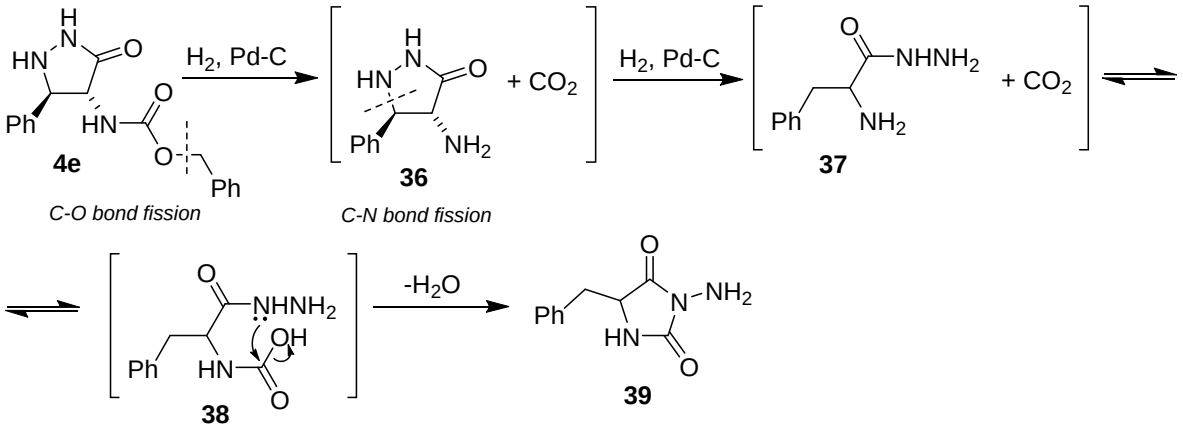
3.2 Ring transformations

5-Aryl-3-pyrazolidinones undergo thermally- or hydrogenolytically-induced 'ring switching' transformation into *N*-aminohydantoins. This reaction was observed for the first time in the course of our studies on cycloadditions of (1*Z*,4*R**,5*R**)-1-arylmethylidene-4-benzyloxycarbonylamino-3-oxo-5-phenylpyrazolidin-1-ium-2-ides **24a**,**b** to *tert*-butyl acrylate in refluxing anisole. Aside from the expected cycloadducts, significant amounts (~25%) of benzylideneiminohydantoins **35** were obtained as side products.[41] Heating **24a**,**b** alone in anisole under reflux furnished the corresponding *N*-iminohydantoins **35a**,**b** as the sole products in good yields. This ring transformation can be rationalized by thermal cleavage of benzylic-type C–N bond in the enol form of azomethine imine **24′**. The so formed α,β-unsaturated hydrazide **34** cyclizes into **35** by nucleophilic attack of the amidic nitrogen to the Cbz group (Scheme 8).[40]



Scheme 8. Ring switching' transformation of pyrazolidinone derivatives **24a**,**b** into the *N*-iminohydantoins **35a**,**b**.

Another, somewhat surprising, transformation was observed in the attempted preparation of (1*Z*,4*R**,5*R**)-2-amino-5-phenyl-3-pyrazolidinone (**36**) by catalytic hydrogenation of the Cbz-protected compound **4e**. Instead of the desired product **36**, the *N*-aminohydantoin **39** was obtained in 69% yield. Also here, the reaction pathway is explainable by sequential hydrogenolytic cleavage of the benzylic C–O and C–N bonds in **4e** to give the α-amino hydrazide **37**. Under slightly elevated pressure (3 bar), the amine **37** and CO_2 are in equilibrium with the carbamic acid **38**, which cyclizes to *N*-amino hydantoin **39**.[40] The proposed mechanism is supported by known, closely related examples of cyclizations of *N*-benzyloxycarbonyl-*α*-amino acid hydrazides[55–57] and α-semicarbazidoacetates[58–60] into 3-aminoimidazolidine-2,4-diones. Besides, the above transformation is also related to Bucherer's synthesis of hydantoins, which proceeds in a closed vessel under slightly elevated pressure utilizing CO_2 (or carbonate) as a C_1-synthon (Scheme 9).[61,62]



Scheme 9. Transformation of the pyrazolidinone **4e** into *N*-aminohydantoin **39**.

4 Synthesis of Bicyclic 3-Pyrazolidinone Derivatives

4.1 Pyrazolo[1,2–*a*]pyrazoles

The synthesis of molecules that can mimic the structure and properties of peptides certainly represents an interesting and important research topic in the fields of organic synthesis and medicinal chemistry.[63–67] An important group of conformationally constrained dipeptide analogues are azabicycloalkane amino acids, comprising various saturated fused heterocycles with a bridgehead nitrogen atom.[68–70] 6-Amino-7-oxotetrahydropyrazolo[1,2-*a*]pyrazole-1-carboxylic acid (**40**) based scaffolds are a subgroup of 5,5-fused azabicycloalkane amino acids. The applicability of **40** for the preparation of biologically active peptide mimetics was successfully demonstrated by researchers at Eli Lilly almost three decades ago.[19–22] Strangely enough, very few other examples of **40**-derived compounds have been reported since 1990, meaning that **40** is a practically unexplored scaffold with reasonable applicative potential. The most general and straightforward synthetic approach towards derivatives of **40** includes stereoselective 1,3-dipolar cycloaddition as the key-step and starting from 4-acylamino-3-pyrazolidinones, which in turn are easily available by simple treatment of α,β-dehydro-α-amino acid derivatives with excess hydrazine hydrate.[7–9,71] Retrosynthetic analysis reveals that derivatives of **40** with up to five stereogenic centers are available in four steps and from four building blocks: a) *N*-acylglycines, b) aldehydes (or ketones) c) hydrazine hydrate, and d) α,β-unsaturated esters. Thus, combination of just four types of widely available building blocks enables an easy access to structurally diverse heterocyclic dipeptides (Figure 4).

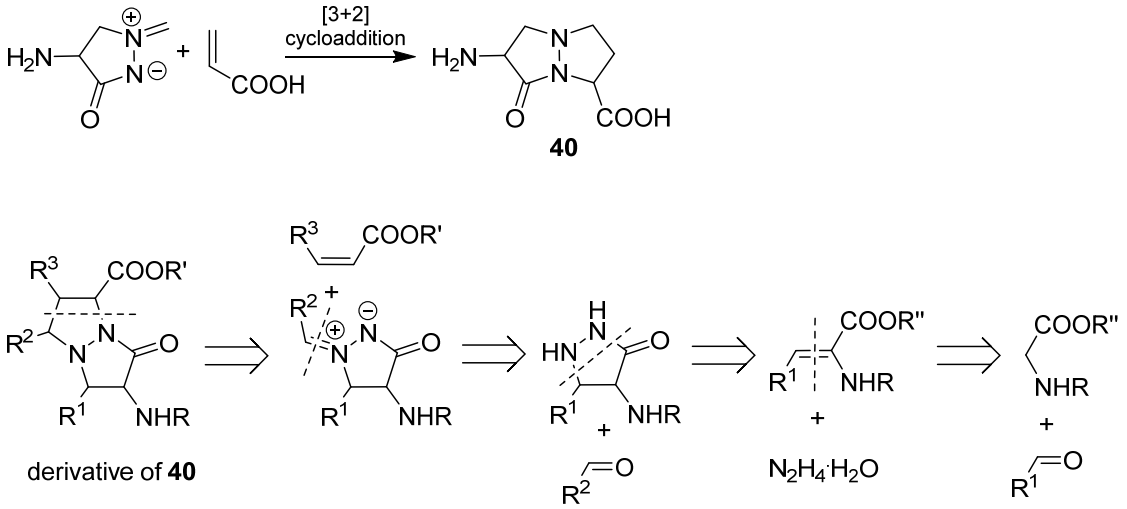
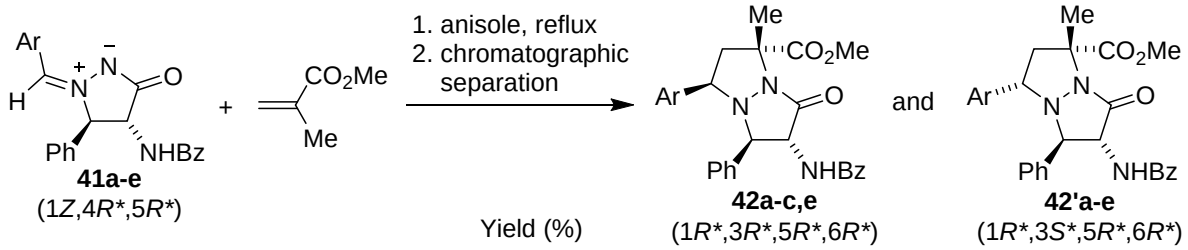


Figure 4. Retrosynthetic analysis of derivatives of **40**.

In the last decade, our studies on [3+2] cycloadditions of (1*Z*,4*R**,5*R**)-1-arylmethylidene-4-benzoylamino-3-oxo-5-phenyltetrahydropyrazol-1-ium-2-ides **41** to various dipolarophiles has revealed the general reactivity and selectivity of these cycloadditions,[9] as well as their applicability in high-throughput synthesis.[72,73] Stereocontrol can be illustrated by cycloadditions of **41** to methyl methacrylate (Scheme 10).[74]



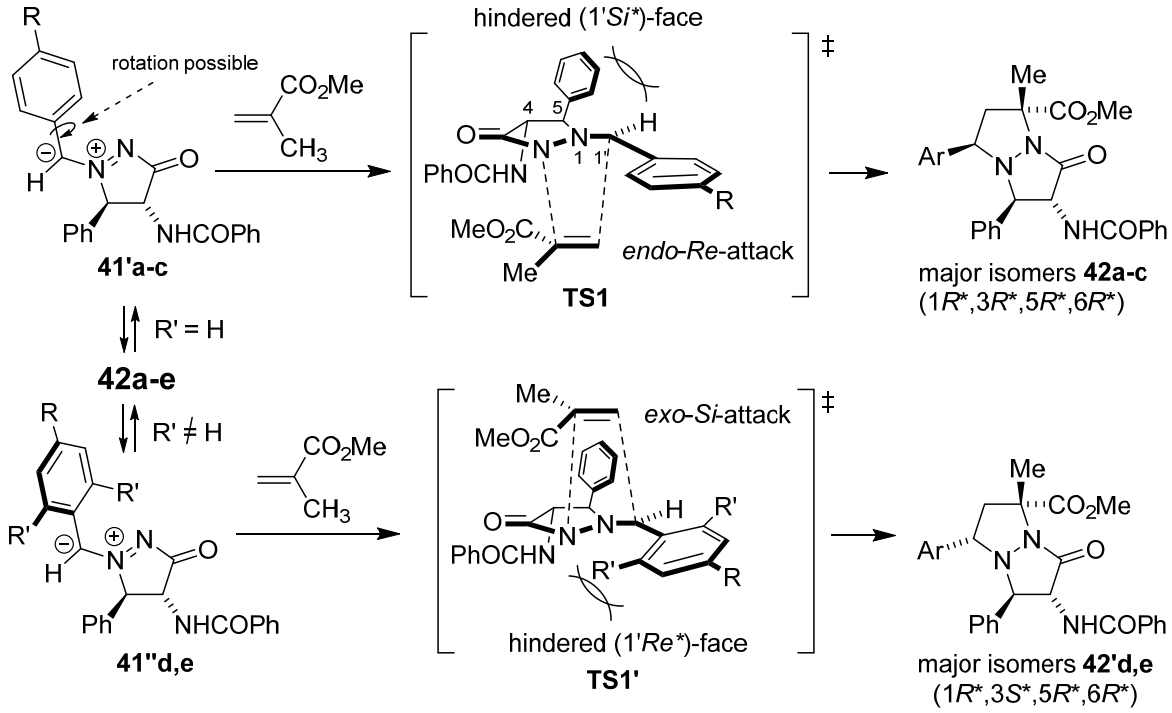
			Yield (%)	
	R	**42 : 42'**	**42**	**42'**
a	phenyl	73:27	67	10
b	4-nitrophenyl	81:19	63	9
c	4-methoxyphenyl	68:32	29	13
d	2,6-dichlorophenyl	0:100	-	50
e	2,4,6-trimethylphenyl	11:89	1	15

Bz = benzoyl

Scheme 10. Cycloadditions of **41a**–**e** to methyl methacrylate.

The stereoselectivity of the cycloadditions of dipoles **41a**–**e** to methyl methacrylate was in agreement with the stereochemistry observed by related cycloadditions[9,72,73,75] and could be explained in the following way: an *ortho*-unsubstituted 1′-aryl group in dipoles **41a**–**c** can rotate around the C(1′)–Ar bond, thus shielding equally both faces of the dipole **41′a**–**c**. Consequently, the phenyl ring at position 5 is the stereodirecting group, which hinders the (1′*Si*)-face of the (*Z*)-

dipole **41′**. Formation of the major (1*R**,3*R**,5*R**,6*R**)-isomers **42a–c** is explainable by preferential *endo*-attack of methyl methacrylate from the less hindered (1′*Re*)-face of dipole **41′a–c** *via* the proposed transition state **TS1**. On the other hand, rotation around the C(1′)–Ar bond is not possible in *ortho*-disubstituted dipoles **41d**,**e**, which presumably adopt a twisted conformation **41″d**,**e**, where steric hindrance of the (1′*Re*)-face by the *ortho*-substituent pointing towards the N(2) becomes stronger than hindrance of the (1′*Si*)-face by the 5-Ph group. Thus, the predominant *exo*-approach of the dipolarophile from the less hindered (1′*Si*)-face of the (*Z*)-dipoles **41″d**,**e** gives the major (1*R**,3*S**,5*R**,6*R**)-isomers **42′d**,**e** *via* the proposed transition state **TS1′** (Scheme 11).[74]

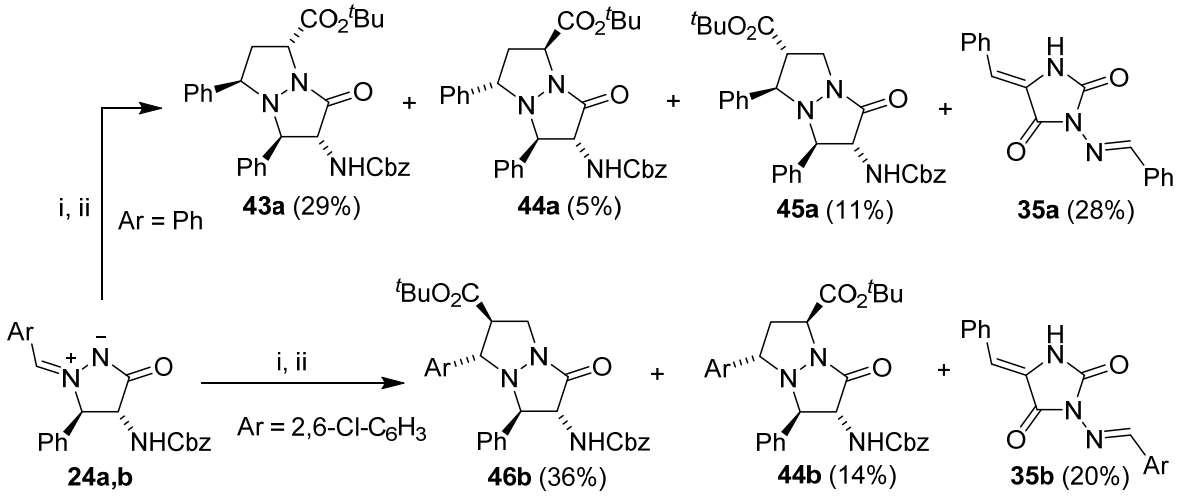


Scheme 11. Proposed stereocontrol in cycloadditions of **41** to methyl methacrylate.

Though very useful for the determination of reactivity and selectivity of the above [3+2] cycloadditions,[9,38] the obtained cycloadducts were not suitable for incorporation into peptides, since carboxy and amino functions (CO_2Me and NHCOPh, respectively) could not be selectively deprotected without cleaving the pyrazolo[1,2-*a*]pyrazolone system as well. Thus, selective deprotection of a heterocyclic dipeptide was mandatory for a viable method for the synthesis of peptide mimetics. To do this, we decided to try out a classical peptide chemistry approach utilizing a combination of Boc and Cbz protecting groups. Cycloadditions of 1-arylmethylidene-4-benzyloxycarbonyl-amino-3-oxopyrazolidin-1-azomethine imines to *tert*-butyl 2-alkenoate would give selectively deprotectable dipeptides enabling derivatization of the carboxy and the amino function. Furthermore, coupling of the racemic dipeptide with an enantiomerically pure

reagent (*e.g.* with *α*-amino acid derivative), followed by separation of the so formed diastereomers would give non-racemic tripeptides.[41]

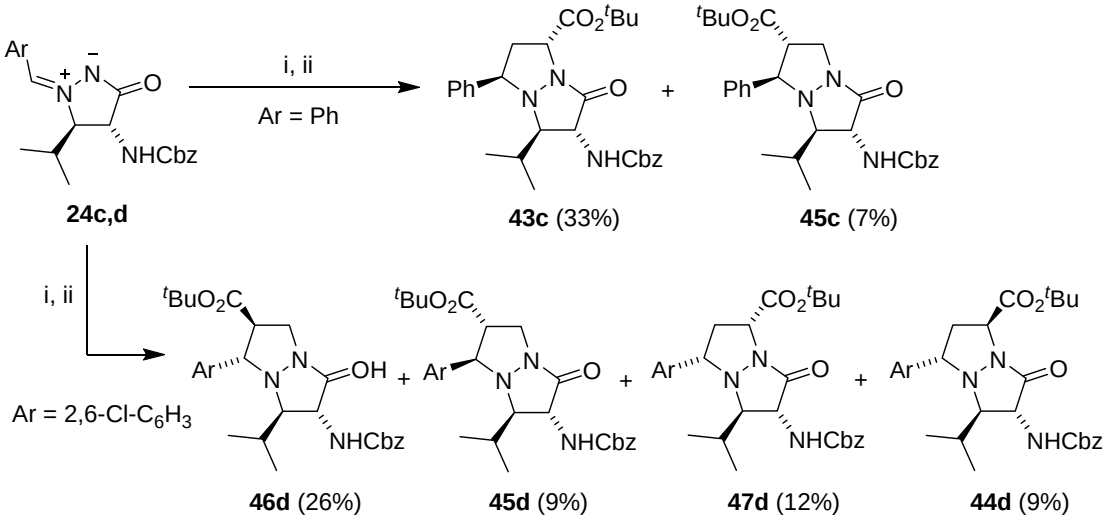
The starting 3-pyrazolidinones **4** and azomethine imines **24** were prepared as described previously (*cf.* Schemes 1 and 6).[40–42] First, cycloadditions of 5-phenyl substituted dipoles **24a,b** to *tert*-butyl acrylate were carried out under standard conditions, *i.e.* in refluxing anisole.[9] Somewhat expectedly,[40] reactions of 5-phenyl substituted dipoles **24a,b** furnished, along with cycloadducts **43**–**46**, the hydantoin derivatives **35a,b** in ~25% yields. Evaporation of the filtrates followed by separation by column chromatography (CC) and medium pressure liquid chromatography (MPLC) then furnished the corresponding cycloadducts **43a**–**45a**, **44b**, and **46b** in 5–36% yields (Scheme 12).[41]



i) *tert*-butyl acrylate, anisole, reflux; ii) chromatographic separation

Scheme 12. Cycloaddition of azomethine imines **24a,b** to *t*-butyl acrylate.

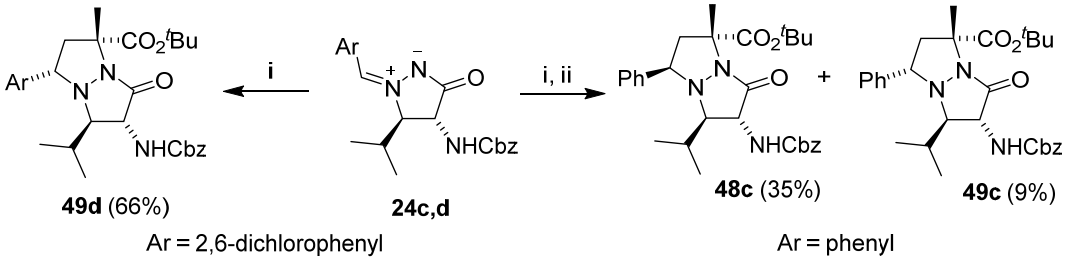
On the other hand, the C(5)–N(1) bond in 5-isopropyl substituted dipoles **24c**,**d** is thermally stable and the formation of hydantoins **35** was not observed in cycloadditions of azomethine imines **24c,d** to *tert*-butyl acrylate, which produced only the corresponding cycloadducts **43**–**47**. Subsequent chromatographic separation of isomeric cycloadducts furnished isomerically pure compounds **43c**, **45c**, and **44d**–**47d** in 7–33% yields (Scheme 13).[41]



i) *tert*-butyl acrylate, anisole, reflux; ii) chromatographic separation.

Scheme 13. Cycloaddition of azomethine imines **24c,d** to *t*-butyl acrylate.

In contrast, cycloadditions of **24c,d** to *tert*-butyl methacrylate were regio- and stereoselective. Cycloaddition to dipole **24c** followed by chromatographic separation furnished diastereomeric cycloadducts **48c** and **49c** in 35% and 9% yield, respectively, while cycloaddition to the *ortho*-disubstituted dipole **24d** gave compound **49d** as the only product in 66% yield (Scheme 14).[41]



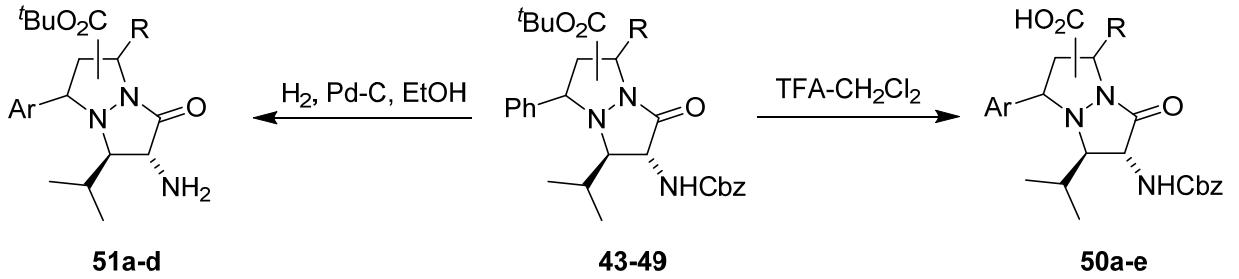
i) *tert*-butyl methacrylate, anisole, reflux; ii) chromatographic separation

Scheme 14. Cycloaddition of azomethine imines **24c,d** to *t*-butyl methacrylate.

The regioselectivity and stereoselectivity of the cycloadditions and configurations of the major isomers **43**, **46**, **48**, and **49** were in agreement with previous results obtained by cycloadditions of closely analogous dipoles to methyl acrylate[75] and methyl methacrylate.[74] Selectivity of these cycloadditions was somewhat lower than expected on the basis of results with analogous reactions.[9,38,72–75] Nevertheless, isolation of multiple isomers may also be advantageous,

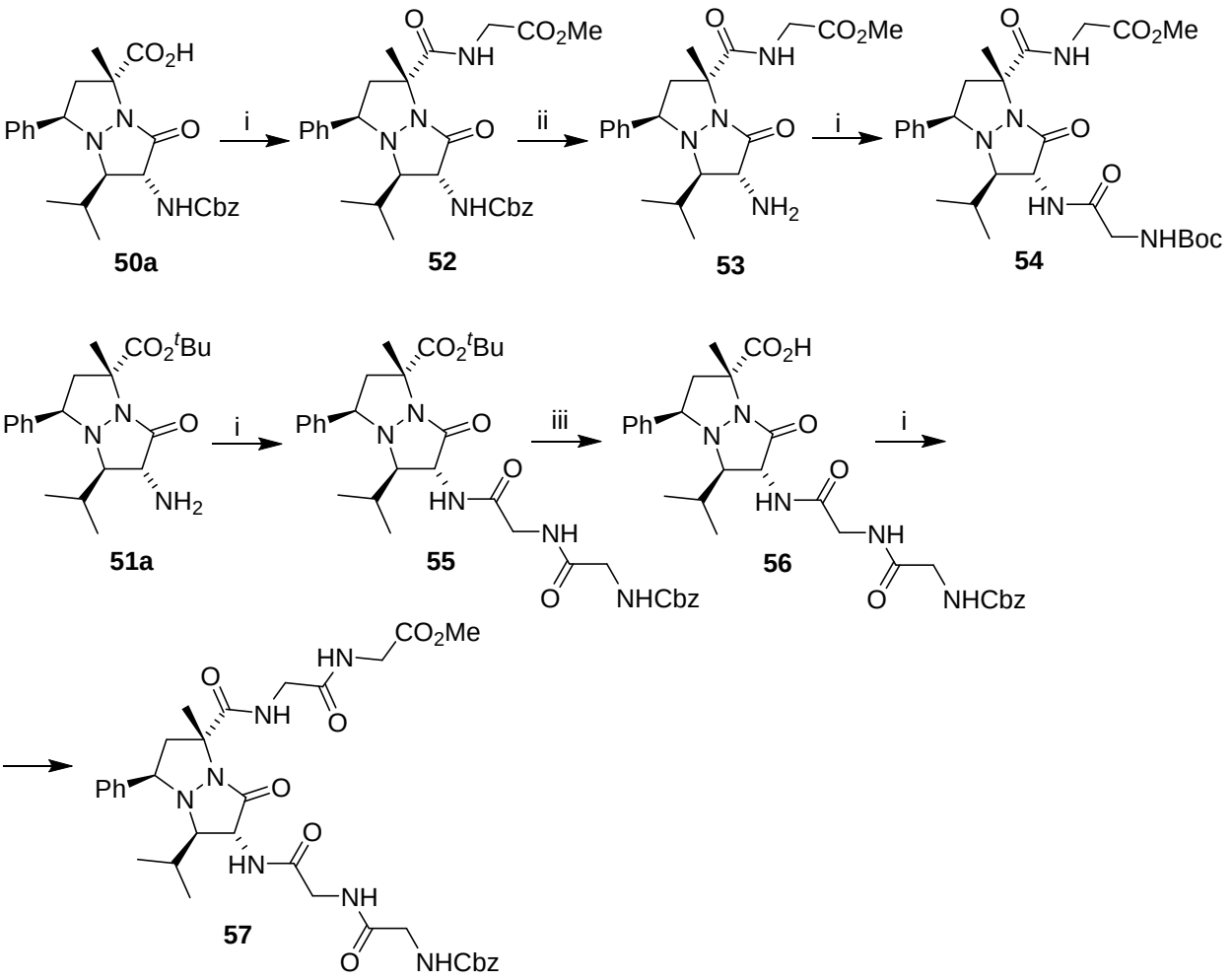
providing more stereochemical diversity of the 6-amino-7-oxotetrahydropyrazolo[1,2-*a*]-pyrazole-1(or 2)-carboxylic acid scaffold (*c*,*f*. Schemes 12–14).[41]

Having this small, stereochemically diverse library of dipeptides **43**–**49** in our hands, we continued with selective deprotection of the amino and the carboxy function. Acidolytic deprotection of the carboxy group afforded the corresponding carboxylic acids **50a**–**e** in 67–100% yields, while hydrogenolytic deprotection of the amino group afforded the corresponding free amines **51a**–**d** in 20–94% yields (Scheme 15).[41]



Scheme 15. Preparation of the carboxy- (**50**) and the amino-building blocks **51**.

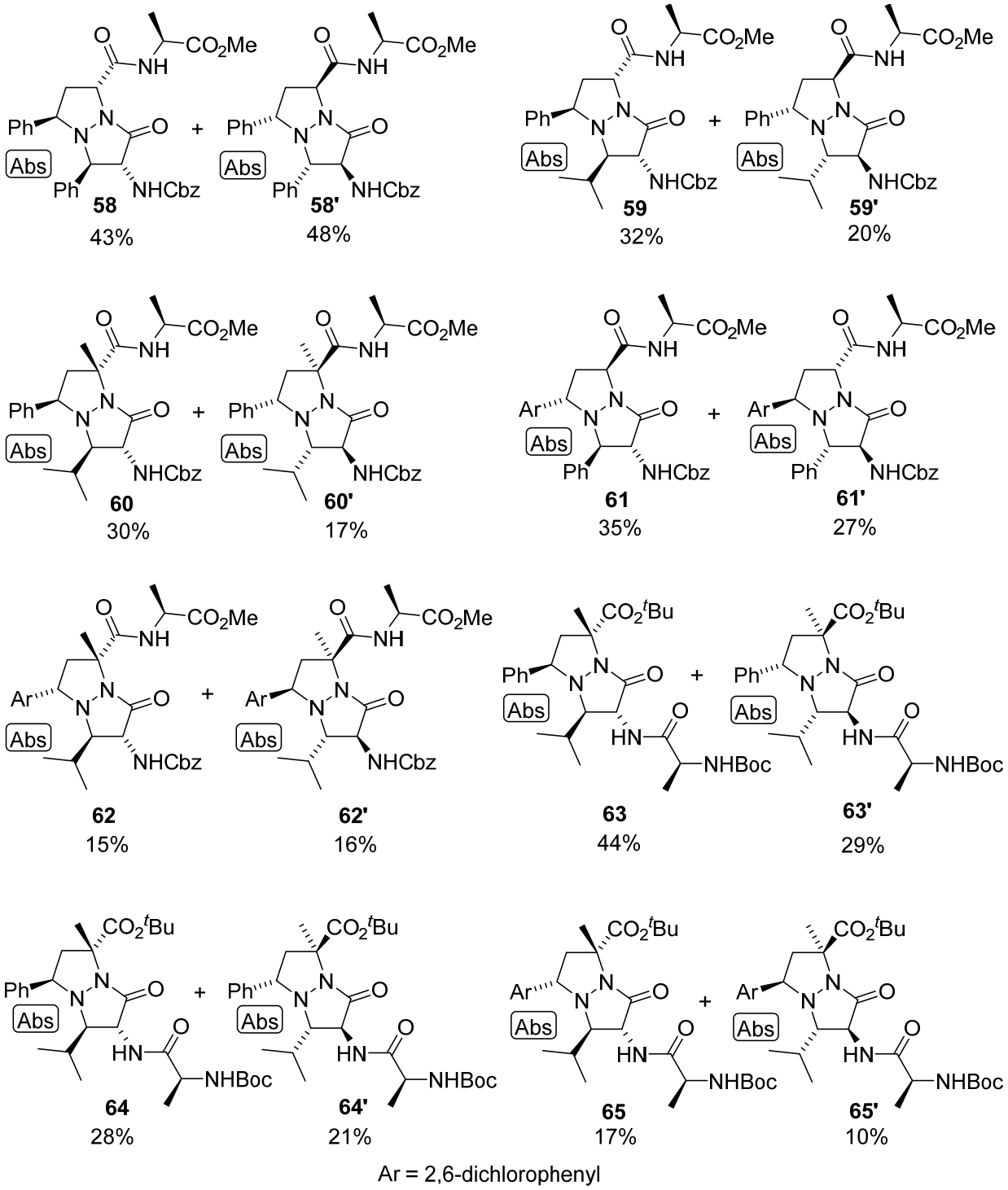
To show that compounds **50** and **51** can serve as useful building blocks for the synthesis of U-shaped peptides, tetrapeptide **54** and hexapeptide **57** with 3-amino-2-oxo-1,4-diaza-bicyclo[3.3.0]octane-7-carboxylic acid (**40**) as the central part of the sequence were prepared. Amidation of dipeptide **50a** with glycine methyl ester gave the tripeptide **52** in 50% yield. Catalytic hydrogenation of **52** followed by acylation of **53** with Boc-glycine in the presence of 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) furnished tetrapeptide **54** in 87% yield. Similarly, acylation of **51a** with *N*-(*N*-benzyloxycarbonylglycyl)glycine gave the tetrapeptide **55** in 74% yield. Treatment of **55** with trifluoroacetic acid in dichloromethane afforded the carboxylic acid **56** in 23% yield. Amidation of the acid **56** with *N*-(glycyl)glycine methyl ester furnished the hexapeptide **57** in 62% yield (Scheme 16).[41]



i) EEDQ, CH_2Cl_2, GlyOMe or GlyGlyOMe, r.t.; (ii) H_2, Pd-C, EtOH, r.t.; (iii) CH_2Cl_2-CF_3CO_2H (2:1), r.t.

Scheme 16. Formation of the hexapeptide **57**.

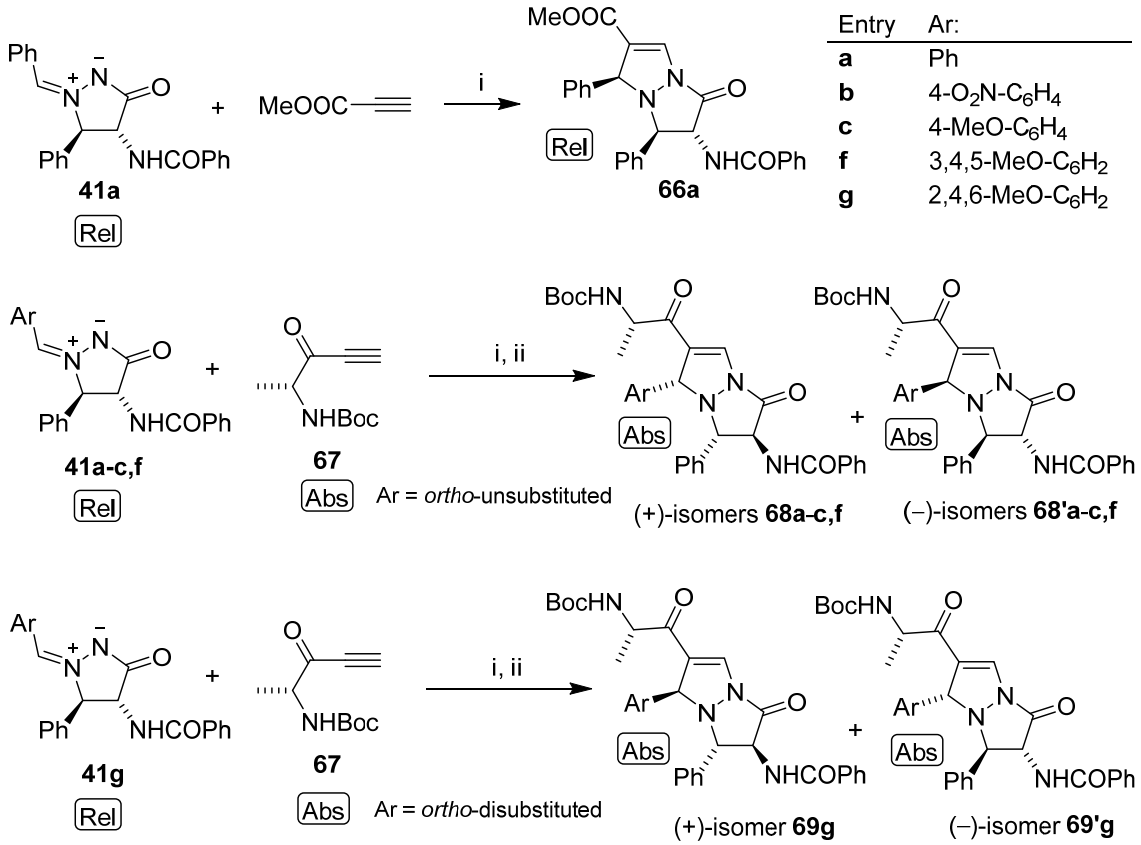
Finally, sixteen non-racemic tripeptides **58**–**65** and **58′**–**65′** were prepared. Amidation of the racemic N-protected dipeptides **50** with methyl (*S*)-alaninate gave diastereomeric tripeptides **58/58′**–**62/62′**, which were separated by MPLC to furnish the non-racemic, diastereomerically pure N-protected tripeptide esters **58**–**62**, and **58′**–**62′**. Similarly, acylation of the racemic C-protected dipeptides **51** with (*S*)-Boc-alanine in the presence of EEDQ followed by separation of diastereomers by MPLC afforded the non-racemic tripeptide esters **63**–**65** and **63′**–**65′** (Scheme 17).[41]



Scheme 17. Non-racemic tripeptides **58**/**58′**–**65**/**65′**obtained by coupling of the racemic building blocks with (*S*)-alanine derivatives followed by chromatographic separation.

However, the weakest link in the above synthesis of peptide analogues was the [3+2] cycloaddition step, which had to be performed in refluxing anisole to assure a complete

conversion of the starting dipole (*cf.* Schemes 10 and 12–14). Since epimerization of an *α*-amino acid (and their derivatives) is usually fast above 100 °C, the use of enantiopure azomethine imines for the synthesis of the non-racemic cycloadducts would not make sense. This serious drawback could by overcome by catalysis, which should significantly lower the required reaction temperature. This has been previously shown by regio- and stereo-selective copper(I) iodide-catalyzed cycloadditions of ethyl propiolate in refluxing dichloromethane.[76] In contrast, the non-catalyzed cycloadditions required harsh thermal activation (~150 °C) and led to mixtures of isomeric cycloadducts.[77] In extension, an optimized Cu-catalyzed method that allowed the preparation of separable non-racemic products under mild conditions was developed. Cycloaddition of azomethine imine **41a** with methyl propiolate was chosen as the model reaction in search for suitable reaction conditions. Since the cycloadduct **66a** is highly fluorescent (bright yellow fluorescence at 375 nm), simple and effective monitoring of the reaction progress was feasible by TLC. Optimization process revealed, that a full conversion of reactants at room temperature was performed at best in acetonitrile in the presence of CuI and Hünig base. Under these optimized conditions, the conversion of **41a** was complete after 12 hours and the cycloadduct **66a** was isolated in 98% yield upon chromatographic workup. Cycloadditions of racemic azomethine imines **41a**–**c**,**f**,**g** to *tert*-butyl (*S*)-(3-oxopent-4-yn-2-yl)carbamate (**67**)[78–80] under the above conditions afforded mixtures of diastereomeric cycloadducts **68a**–**c**,**f**/**68′a**–**c**,**f** and **69g**/**69′g** in 68–95% yields. Subsequently, diastereomers **68a**–**c**,**f**/**68′a**–**c**,**f** and **69g**/**69′g** were separated by medium-performance liquid chromatography (MPLC) to furnish diastereomerically pure non-racemic compounds **68a**–**c**,**f**, **68′a**–**c**,**f**, **69g**, and **69′g** in 3–45% yields.[81] Also here, the regioselectivity and stereoselectivity of the cycloadditions and relative configurations of cycloadducts were in agreement with previous results obtained by closely related cycloadditions (Scheme 18).[9,38,41,76]

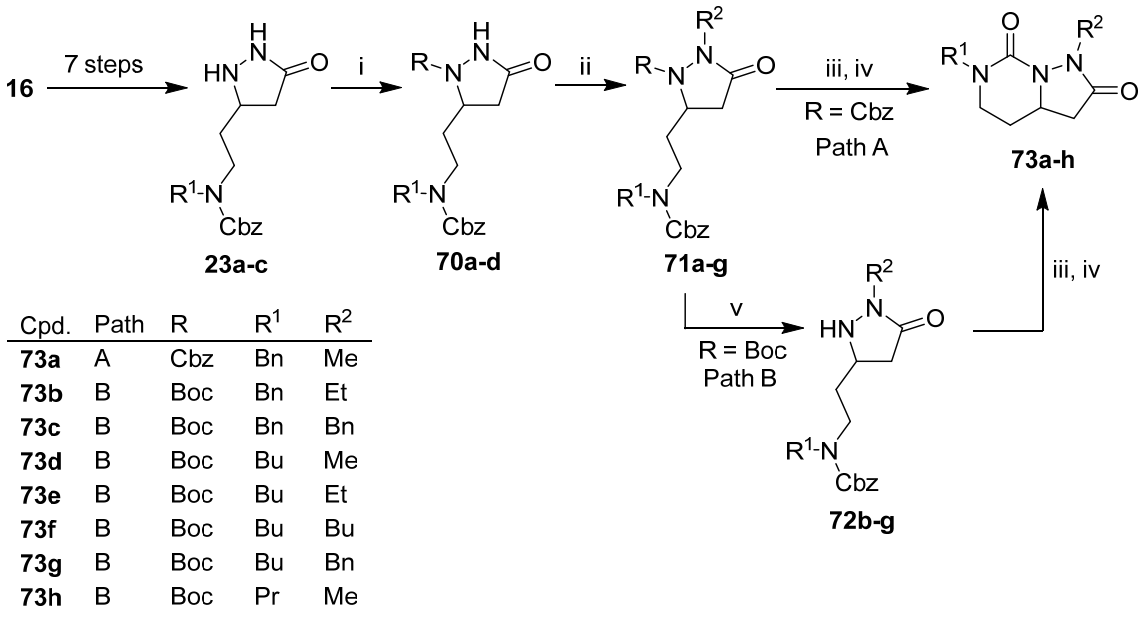


Scheme 18. Formation of non-racemic products **66**, **68**, and **69**.

4.2 Pyrazolo[1,5–*c*]pyrimidines

Recently, a series of tetrahydropyrazolo[1,5-*c*]pyrimidine-2,7(1*H*,3*H*)-diones **73a**–**h**, the first representatives of a so far unexplored saturated heterocyclic system, has been synthesized in twelve steps from methyl acrylate (**16**). The first part of the synthesis comprises a seven-step preparation of 5-{2-[(alkyl)(benzyloxycarbonyl)amino]ethyl}pyrazolidin-3-ones **23a**–**c** (*cf.* Scheme 5). Unfortunately, attempts to prepare N(2)-substituted pyrazolidinones by cyclizations of the mesylates **22** with cyclohexyl-, *tert*-butyl-, and phenylhydrazine failed. Consequently, a different, somewhat longer approach was applied. First, the pyrazolidinone **23a** was treated with ClCOOBn to afford the Cbz-protected derivative **70a** (R = Cbz) in 70% yield. However, subsequent N-methylation with MeI did not proceed to completion and the N-methylated intermediate **71a** was obtained in only 18% yield. Subsequent removal of both Cbz groups by catalytic hydrogenation, cyclisation of the intermediate 1,4-diamine with 1,1′-carbonyldiimidazole (CDI), and chromatographic workup furnished the first final product **73a** in 30% yield over two steps (Path A, Scheme 19). On the other hand, 1-Boc analogues of **70**, prepared by treatment of **23a**–**c** with Boc_2O in 73–97% yields, readily underwent alkylation of the amidic nitrogen N(2) to give the fully substituted intermediates **71b**–**h** in 49–73% yields. Acidolytic

removal of the Boc group gave the 1-unsubstituted pyrazolidinones **72b**–**g** in 77–99% yields. Subsequent hydrogenolysis of the Cbz group followed by cyclisation of the so-formed free 1,4-diamine with CDI, and chromatographic workup furnished title compounds **73b**–**h** in 28–65% yields over the last two steps. This somewhat tedious twelve-step synthesis was simplified by performing it, as far as possible, in a one-pot manner (Path B, Scheme 19).[53]

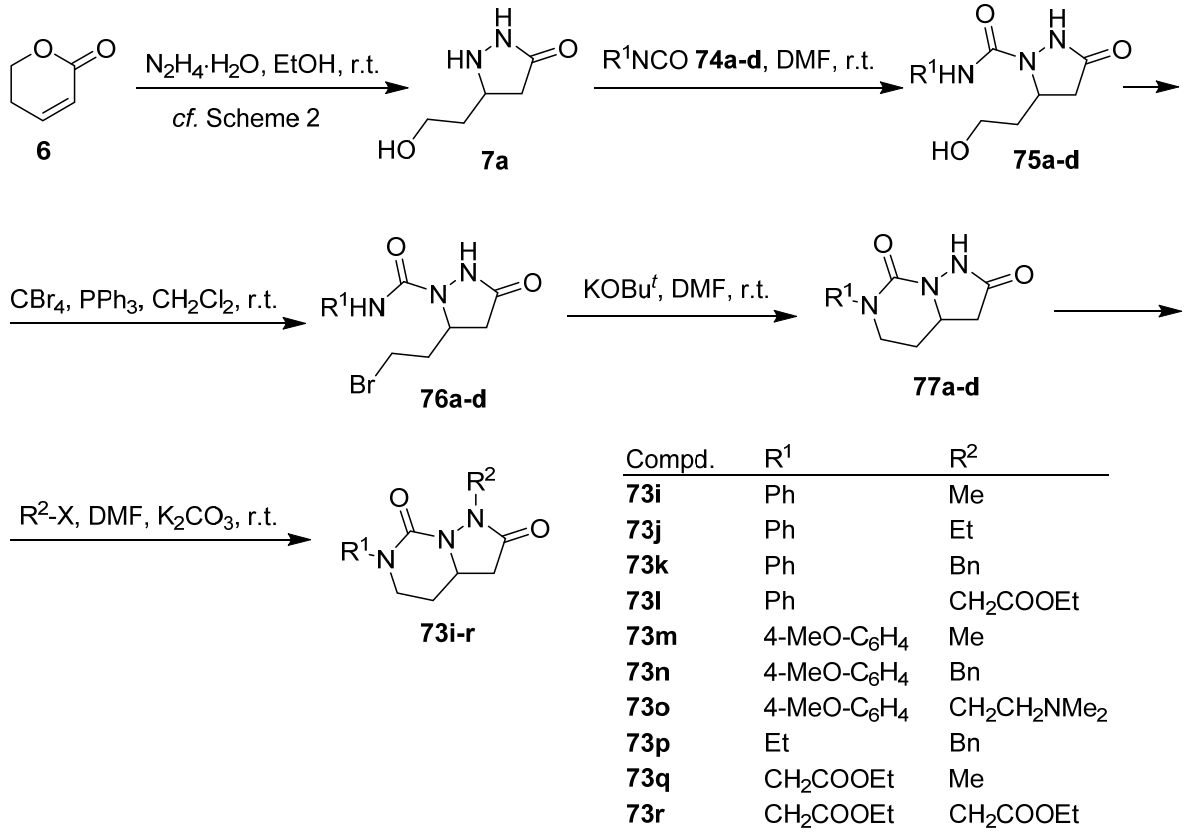


Cpd.	Path	R	R^1	R^2
73a	A	Cbz	Bn	Me
73b	B	Boc	Bn	Et
73c	B	Boc	Bn	Bn
73d	B	Boc	Bu	Me
73e	B	Boc	Bu	Et
73f	B	Boc	Bu	Bu
73g	B	Boc	Bu	Bn
73h	B	Boc	Pr	Me

i) ClCOOBn or Boc_2O, 1,4-dioxane-H_2O, Na_2CO_3, r.t.; ii) R^2-X, DMF, K_2CO_3, r.t.; iii) H_2, Pd-C, MeOH, r.t.; iv) CDI, DMF, r.t.; v) TFA-CH_2Cl_2, r.t.

Scheme 19. Preparation of pyrazolo-pyrimidinediones **73a-h**.

Soon afterwards a novel simpler five-step synthesis of 1,6-disubstituted tetrahydro-pyrazolo[1,5-*c*]pyrimidine-2,7(1*H*,3*H*)-diones **73** was developed. This starts with a 'ring switching' transformation of the commercially available 5,6-dihydro-2*H*-pyran-2-one (**6**) with hydrazine hydrate in ethanol, giving 5-(2-hydroxyethyl)pyrazolidin-3-one (**7a**) in quantitative yield (*cf.* Scheme 2). Subsequent reaction of **7a** with isocyanates **74a**–**d** in anh. DMF at r.t. afforded the urea derivatives **75a**–**d** in 73–97% yields. Appel-type bromination of the alcohols **75** with PPh_3–CBr_4 in CH_2Cl_2 followed by evaporation gave the crude bromoethyl intermediates **76a**–**d**, which were used in the subsequent step without further purification. Cyclisation of **76** with *t*-BuOK in anh. DMF, followed by chromatographic purification gave the 6-substituted tetrahydropyrazolo[1,5-*c*]pyrimidine-2,7(1*H*,3*H*)-diones **77a**–**d** in 40–65% yields over two steps. Finally, S_N2-type alkylation of **77** with primary alkyl halides, followed by isolation by thorough chromatographic workup (FC then MPLC) furnished the final products **73i**–**r** in 22–93% yields (Scheme 20).[44]



Compd.	R^1	R^2
73i	Ph	Me
73j	Ph	Et
73k	Ph	Bn
73l	Ph	CH_2COOEt
73m	4-MeO-C_6H_4	Me
73n	4-MeO-C_6H_4	Bn
73o	4-MeO-C_6H_4	$CH_2CH_2NMe_2$
73p	Et	Bn
73q	CH_2COOEt	Me
73r	CH_2COOEt	CH_2COOEt

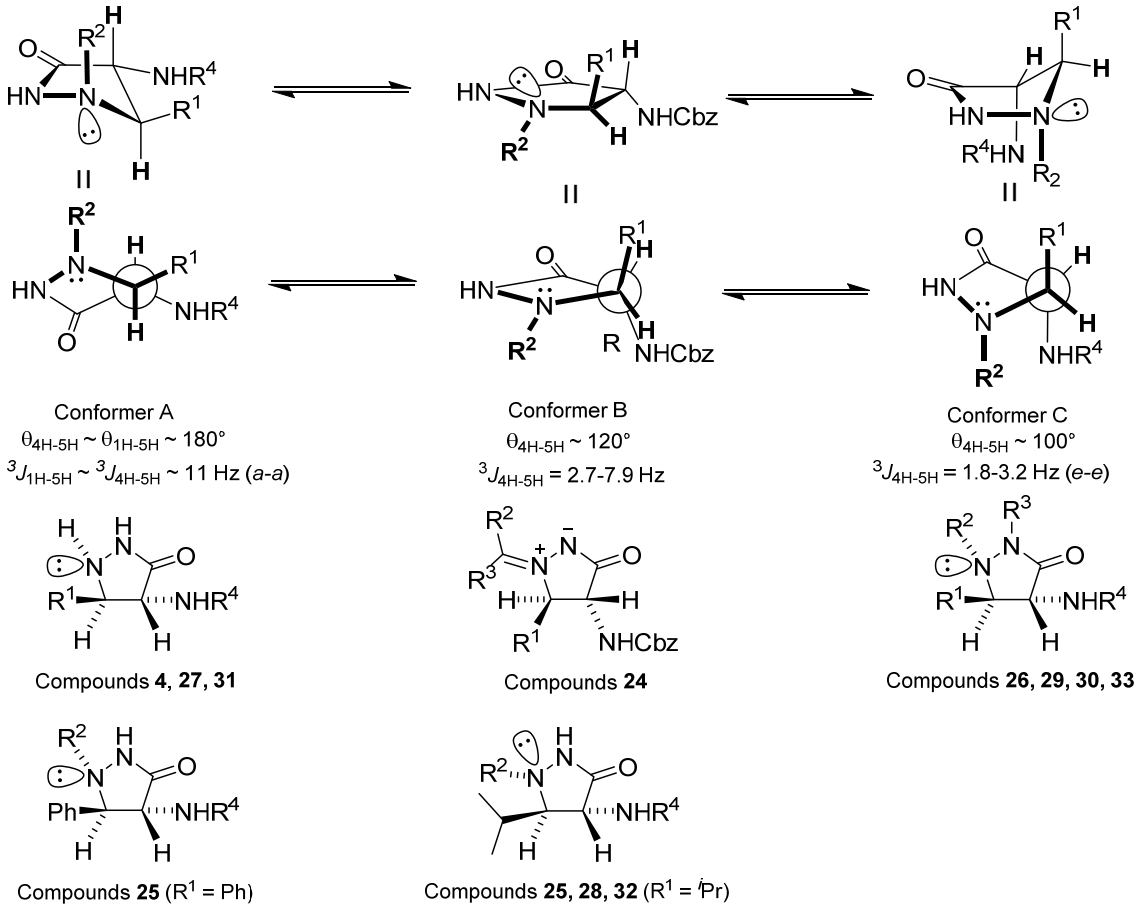
Scheme 20. A five-step synthesis of 1,6-disubstituted tetrahydropyrazolo[1,5-*c*]pyrimidine-2,7(1*H*,3*H*)-diones **73i**–**r**.

5. Structural Features of 3-Pyrazolidinones

The structures of several representative 3-pyrazolidinones and their fused analogues in the solid state have been unambiguously determined by X-ray crystallography.[40–42,44,47,72–77]

The ^{1}H-NMR spectroscopic data of the pyrazolidinones **4** and **25**–**33** and azomethine imines **24** revealed some interesting structural features of these compounds. In solution, these pyrazolidinone derivatives can equilibrate between two envelope conformers A and C *via* the planar conformer B (Scheme 21). The conformations in solution were established on the basis of the magnitude of the vicinal coupling constant. According to the coupling constants, $^3J_{1H–5H} \sim {}^3J_{4H–5H} \sim 11$ Hz, the 4,5-disubstituted compounds **4**, **27**, and **31** exist as envelope conformers A with pseudo axial H–N(1), H–C(4), and H–C(5) ($\theta \sim 180$ °C). In contrast, small vicinal coupling constants, $^3J_{4H–5H} \sim 3$ Hz, in 1,2,4,5-tetrasubstituted pyrazolidinones **26**, **29**, **30**, and **33** were in agreement with conformer C where H–C(4) and H–C(5) were pseudo equatorial ($\theta \sim 100$ °C). The conformation of 1,4,5-trisubstituted compounds **25**, **28**, and **32** was dependent on the substituent at position 5: compounds **25** with a Ph substituent adopted conformation A with

pseudo axial H–C(4) and H–C(5) ($^3J_{4H–5H}$ ~ 11 Hz), while the coupling constant, $^3J_{4H–5H}$ ~ 7 Hz, in 5-isopropylpyrazolidinones **25**, **28**, and **32** is in agreement, either with the flat conformer B (θ ~ 120 °C), or with a rapid equilibrium between the conformers A and C. In the more rigid dipoles **24** with a sp^2-hybridised N(1)-atom, however, the coupling constant, $^3J_{4H–5H}$ ~ 5 Hz, is clearly consistent with the planar conformer B (Scheme 21).[40–42]



Scheme 21. Substituent-dependent conformational equilibrium in solution.

The anticipated U-shaped structure of the pyrazolo[1,2–*a*]pyrazole-based peptides **43**–**65** and **58′**–**65′** was confirmed by X-ray diffraction and by NMR. The X-ray structures of dipeptides **46b** and its free amino derivative, **46d**, and tripeptides **60′**, **61′**, and **63′** exhibit the U-shaped structure of the peptide chain. The U-shape of **60′** is additionally stabilized by intramolecular N-H·O=C hydrogen bond donated by N13 from the alanyl residue and accepted by O9 of the C=O group. In $CDCl_3$ solution, formation of (7′)C=*O*·*H*–N-C(2) intramolecular hydrogen bond in tripeptides **58/58′**–**62/62′** with the C-terminal (*S*)-alanyl residue was supported by ^{1}H NMR spectroscopy. Typically, the signals for the non-hydrogen bonded amidic NH protons appeared at a chemical shift of δ = 5–7 ppm, while the signals for the hydrogen bonded 2-NH protons exhibited higher chemical shift, δ = 7.5–9.3 ppm. For example, in the ^{1}H NMR spectrum of

tripeptide **60′** with the C-terminal (*S*)-alanine residue, a doublet for the H–N-C(2) proton at 8.39 ppm indicates non-covalent interactions of this NH group, explainable by (7′)C=*O*·*H*–N-C(2) intramolecular hydrogen bond. In contrast, a broad singlet for 2-NH proton at 4.94 ppm in the ^{1}H NMR spectrum of tripeptide **64′** with the N-terminal (*S*)-alanine residue does not support hydrogen bonding of this NH group (Figure 5).[41]

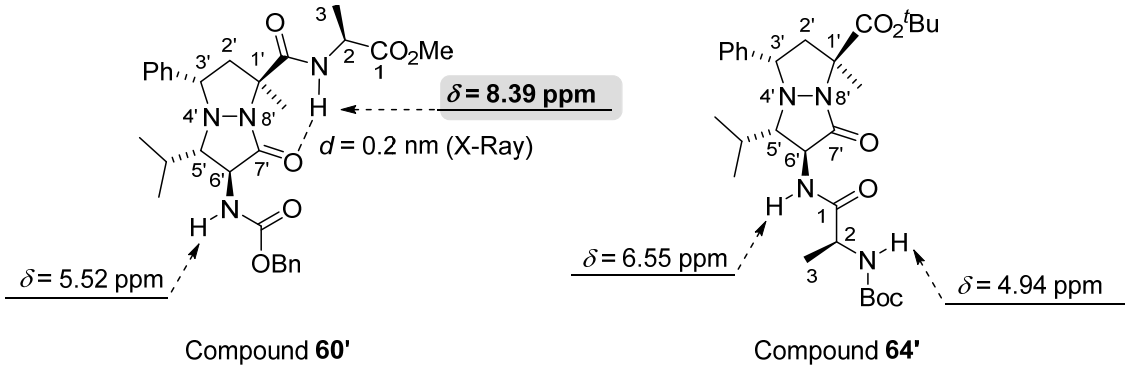


Figure 5. Characteristic chemical shifts of the NH protons in tripeptide **60′** (intramolecular hydrogen bond) and **64′** (without intramolecular hydrogen bond).

The absolute configurations of the non-racemic tripeptides **60′**, **61′**, and **63′** were unambiguously established by X-ray diffraction. Consequently, the configurations of their diastereomers **60**, **61**, and **63** were determined unambiguously as well.[41] Unfortunately, we have so far been unable to prepare single crystals for unambiguous determination of the absolute configuration of the other representative diastereomers. In the absence of a firm proof, tentative configurations were proposed for the other diastereomers on the basis of correlation between specific rotation and absolute configuration.[41,81]

In addition to X-ray structures of the representative tetrahydropyrazolo[1,5-*c*]pyrimidine-2,7(1*H*,3*H*)-diones **73**,[44,53] a more detailed 3D structure of title compounds **73a**–**r** was also established on the basis of characteristic vicinal coupling constants, $^{3}J_{\mathrm{H–H}}$. Large coupling constants, $^{3}J_{\mathrm{3Ha–3aH}} = {}^{3}J_{\mathrm{4Ha–5Hb}}$ = 12.5 Hz and $^{3}J_{\mathrm{4Ha–3aH}}$ = 10.5 Hz are in agreement with antiperiplanar *trans*-orientation of these nuclei. Accordingly, the pyrimidine and the pyrazole part of tetrahydropyrazolo[1,5-*c*]pyrimidine-2,7(1*H*,3*H*)-dione system must both adopt a half-chair conformation in which C(3) and C(4) point out of the plane of the system and 3-Ha, 3a-H, 4-Ha, and 5-Hb are axial (Figure 6).[44,53]

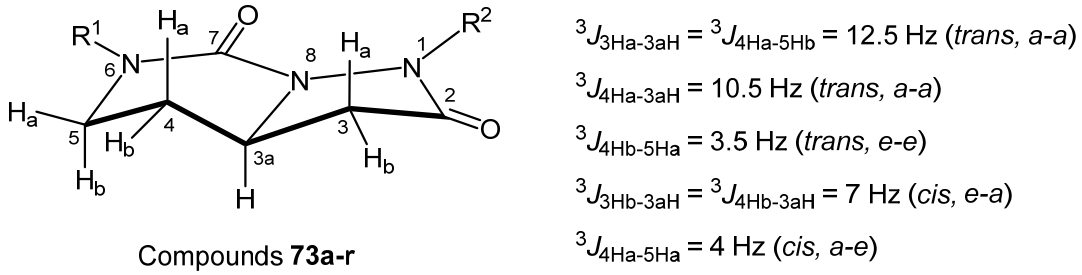


Figure 6. Characteristic NMR data for compounds **73a**–**r**.

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Uroš Grošelj was born in 1975 in Kranj, Slovenia. He studied chemistry at the University of Ljubljana and received his BSc in 2000. He continued his studies under the supervision of Professor Dr. Jurij Svete and received his PhD in 2004. His PhD work focused on the preparation of new camphor derived heterocycles using enaminone methodology. In 2008/2009 he was a post-doctoral fellow in the group of Professor Dr. Dieter Seebach at the ETH Zürich, Switzerland, where he worked on the isolation and X-ray structural characterization of intermediates in organocatalysis with diarylprolinol ethers and imidazolidinones. From 2014 he is employed as Assistant Professor at the Faculty of Chemistry and Chemical Technology, University of Ljubljana. He is author or co-author of 80 scientific papers and recipient of *Futurum Prize* and *Krka Prize* national awards. His research interests encompass synthesis of heterocyclic compounds, stereoselective synthesis, chemistry of terpene enaminones, and organocatalysis.

Jurij Svete was born in Ljubljana, Slovenia in 1962. He studied chemistry at the University of Ljubljana where he received hid PhD in chemistry in 1990 under supervision of Professor Branko Stanovnik. He continued to work as a researcher with the group of Professor Stanovnik. In 1997 he spent one year as a Humboldt Fellow at the University of Stuttgart, Germany, working with Professor Volker Jäger on the synthesis of iminopolyols from furan-nitrile oxide

cycloadducts. In 1996, he became an Assistant Professor, an Associate Professor in 2001, and a Full Professor in 2006. His research interest involve fundamental and applied organic synthesis with emphasis on development of novel reagents and synthetic methods, heterocyclic synthesis, combinatorial synthesis, stereoselective synthesis, 1,3-dipolar cycloaddition reactions, and chemisty of enaminones and 3-pyrazolidinones. He is particularly interested in the synthesis of novel chemical entities based on functionalized heterocycles, such as heterocyclic analogues of peptides.

