Synthesis of Diverse Polyfunctional Amides as Precursors to Potentially Interesting Peptidomimetics

DISSERTATION

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Meinem Lehrer, Herr Prof. Armin de Meijere danke ich herzlich für die interessante Themenstellung, für hilfreiche Diskussionen und Anregungen und die während dieser Arbeit erwiesene Unterstützung.

to my family

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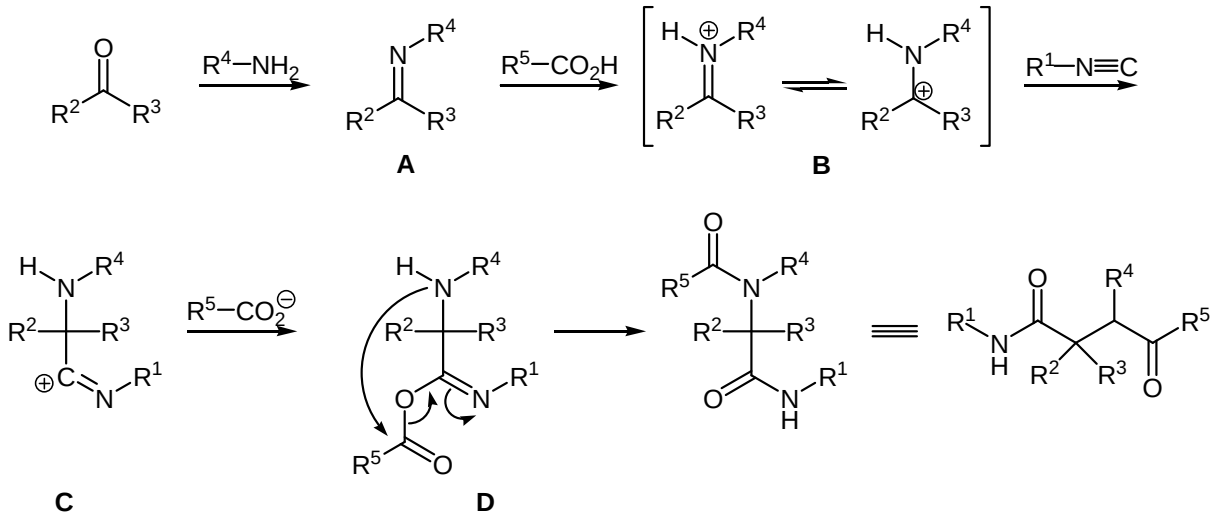
A Introduction

1. Ugi Multicomponent Condensation as a Convenient Reaction for the Synthesis of Biological Active Compounds

The Ugi multicomponent reaction has been known only since 1959.[1] Since that time multicomponent reactions such as Ugi and Passerini attract more and more attention because of their applicability in combinatorial chemistry as well as in the synthesis of natural products and their analogues. The Ugi four-component condensation is widely used because it provides various dipeptide-type products according to a very simple experimental procedure under mild conditions.[2] Many of these products might be considered as potential biological active substances, in particular, peptidemimetics.

The mechanism of the classical version of the Ugi multicomponent reaction 4CC (four centers, four components) is well known[2] and can be represented in simple form as it shown in Schema 1.



Scheme 1. Mechanism of the Ugi multicomponent reaction (4CC).

In the first step, an aldehyde (or ketone) **1** and an amine **2** undergo condensation to form an imine **A**, which can be protonated by the acid **3** to yield cation **B**. An isonitrile **4** then attacks cation **B** to give cation **C**. The latter couples with the anion of the starting acid **3** and forms the intermediate **D**. Intramolecular acyl transfer from the iminoacyl to the secondary amino moiety eventually leads to the final Ugi product **5.**

Since many natural products and their synthetic biologically active analogues contain small ring systems such as cyclopropane and epoxy moieties, it was decided to prepare some dipeptides containing three-membered ring residues. Since natural isonitriles show strong antibiotic, fungicidal, or antineoplastic activity,[2] synthesis of them was especially interesting and thus, as a

donor of cyclopropane moiety the cyclopropaneisonitriles were chosen. As a convenient donor of the epoxy residue in Ugi reaction epoxy acids were established.

The synthesis of bicyclic ketopiperazines, represented in Figur 1, are interesting due to their potential biological activity as peptide β-turn mimetics.[3] Thus, it was decided to apply the multicomponent reactions to their synthesis.

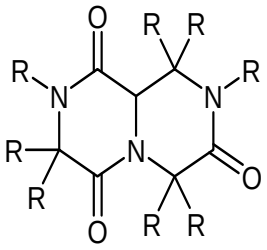
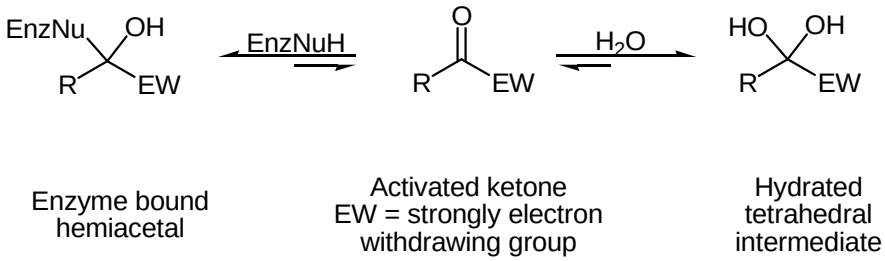


Figure 1. Bicyclic ketopiperazine scaffold **6**.

2. Biological Role of Keto Amides in Living Organisms

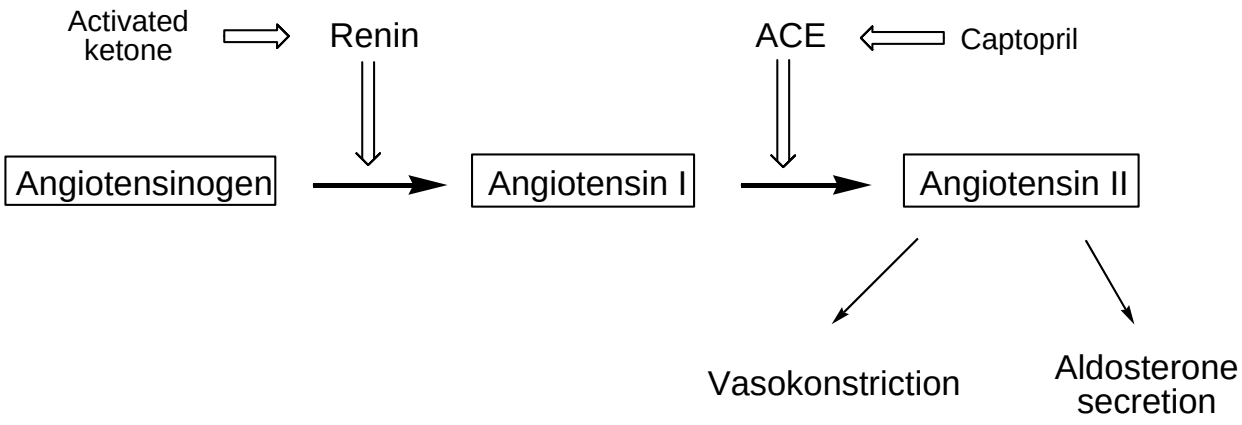
Activated ketone based inhibitors have found application for all classes of proteases.[4] This versatility arises from the fact that they exist as hydrates in aqueous media and can thus directly serve as transition-state analogs and they can react with a nucleophilic residue (serine hydroxyl or cysteine thiol) to form a reversible, hemiacetal-type intermediate (see Scheme 2). Either pathway leads to mimic of the tetrahedral intermediate formed during peptide-bond hydrolysis and thus, such compound can be viewed as transition-state-analogous inhibitors.



Scheme 2. Reactions of activated ketones in nature.

Renin is an aspartyl protease that cleaves angiotensinogen to decapeptide angiotensin I, which itself is inactive but is hydrolyzed by angiotensin converting enzyme (ACE) to the octapeptide angiotensin II, a potent vasoconstrictor and stimulant of aldosterone secretion (see Scheme 3). Captopril, the first orally active ACE inhibitor, has demonstrated that interruption of the renin-angiotensin system is of therapeutic benefit in hypertension and congestive heart failure.[5] Inhibitors of renin would be expected to produce the same result and therefore might constitute a

novel alternative to ACE inhibitors. This has resulted in intensive research in this area in several laboratories over the last decade.[6]



Scheme 3. Renin-angiotensin system.

Calpains are calcium-dependent cysteine proteases which are widely distributed in mammalian cells, with platelets being a particularly rich sources of the enzyme. There are two distinct classes of calpains: the first class requires micromolar concentrations of calcium for optimal enzymatic activity and is referred to as calpain I or μ-calpain. A second class requires millimolar concentrations of calcium and is referred to a calpain II or m-calpain.[7] Calpains have many possible biological roles including the development of long-term memory, the breakdown of neurofilaments at axon terminals, muscle protein turnover, breakdown of membrane proteins, cytoskeletal modification and cleavage of surface proteins during platelet activation, the metabolism of neuropeptides, and the regulation of meiosis.[8] Since calpains are involved in such a diversity of important physiological processes, calpain inhibitors may be useful for the treatment of a variety of disease states especially those involving neurodegeneration such as stroke.[9]

A wide variety of inhibitor structures such as peptide-like ketones, namely α-keto acids, α-keto esters, α-keto amides, α-diketones and fluoroalkyl derivates, have now been reported. The most interesting as potential biological active compounds are activated amides as they mimic natural peptides. Thus, it was decided to synthesize a variety of α-keto amides which are already known as a human renin and calpains inhibitors, and γ-keto amides, the biological activity of which is unknown but might be interesting.

In these terms this work is directed towards the following aims:

– Synthesis of cyclopropaneisonitriles and applying them to the synthesis of new cyclopropane containing dipeptides *via* Ugi condensation

– Synthesis of epoxy containing dipeptides *via* Ugi multicomponent reaction

– Applying of the Ugi multicomponent reaction to the synthesis of bicyclic diketopiperazines

– Synthesis of a number of substituted α-keto amides

– Synthesis of a number of substituted 3-keto amides

B Main Part

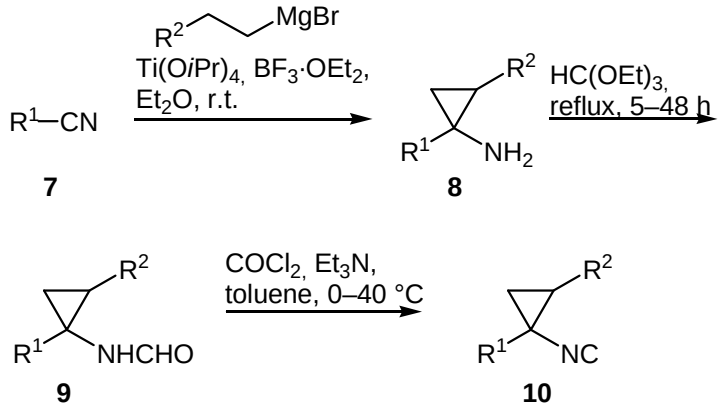
1. Ugi Multicomponent Reactions for the Synthesis of Potential Biologically Active Peptides

1.1. Considerations

Multicomponent reactions attract more and more attention because of their applicability in the combinatorial construction of small molecule libraries as well as in the synthesis of natural products and their analogues. In particular, the Ugi four-component condensation has been widely employed because it provides various dipeptide-type products according to a very simple experimental procedure under mild conditions.[2] Many of these products have drug-like structures and might therefore exhibit a variety of interesting biological activities. Many natural isonitriles show strong antibiotic, fungicidal, or antineoplastic effects.[2] Compounds containing a cyclopropane moiety also often exhibit interesting biological activities. Since cyclopropylamines are now easily available,[10,11,12] several of them were transformed to a number of new cyclopropylisonitriles, and were applied in Ugi multicomponent reactions.

1.2. Synthesis of New Cyclopropylisonitriles

Cyclopropylisonitriles **10a**–**c** were synthesized from the corresponding cyclopropylamines **8a**–**c** *via* the *N*-formyl derivatives **9a**–**c** according to an established protocol (Scheme 1.1 and Table 1.1).[2]



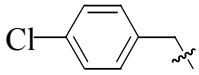
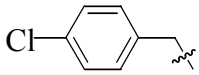
Scheme 1.1. Synthesis of some substituted cyclopropylisonitriles. For further details see Table 1.1.

Primary cyclopropylamines can conveniently be prepared by reductive cyclopropanation of *N*,*N*-dibenzylcarboxamides with ethyl- or substituted ethylmagnesium bromide in the presence of titanium tetraisopropoxide with subsequent hydrogenative debenzylation,[11] or directly from certain nitriles.[12] Thus, the commercially available nitriles **7a**–**c** were treated with ethyl-, butyl- and phenylethylmagnesium bromide, respectively, in the presence of Ti(O*i*Pr)$_4$ according to an

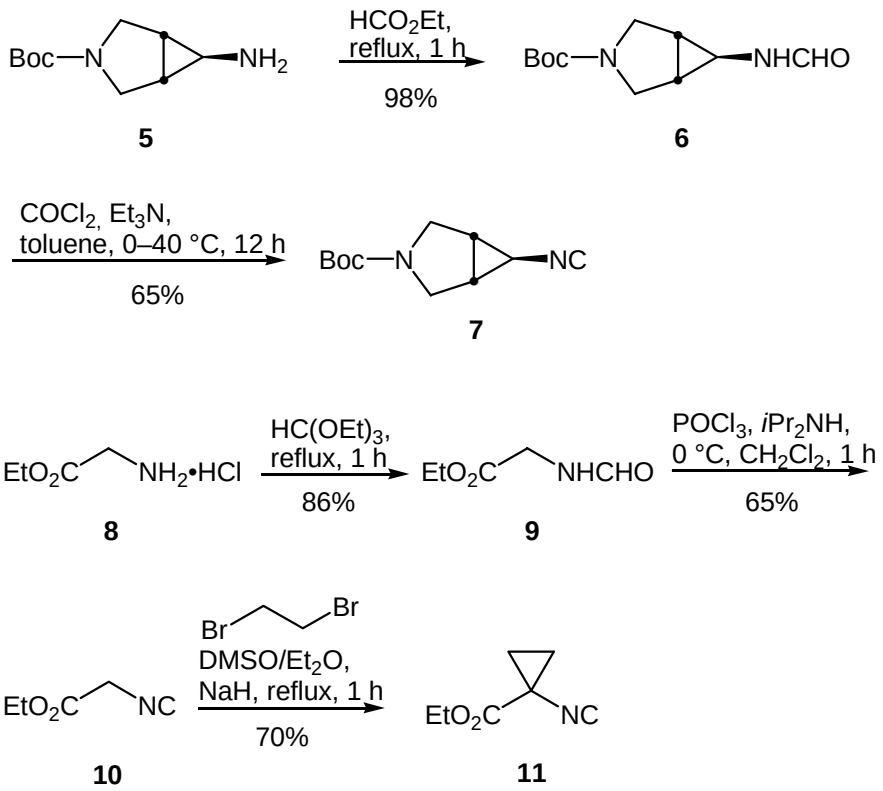
established protocol,[12] to give the correspondingly substituted cyclopropylamines **8a**–**c** in 47, 57 and 30% yield, respectively (see Table 1.1).

The latter were heated under reflux with triethyl orthoformate analogously to the method suggested by Chancellor et al.[13] to give the *N*-formyl derivatives **9a**–**c** (97, 64 and 61% yield), which were dehydrated by treatment with a solution of phosgene in toluene to yield **10a**–**c** (71, 88 and 68%, Table 1.1).

Table 1.1. Synthesis of some substituted cyclopropylisonitriles **10** from nitriles **7** (see Scheme 1.1).

			Yields (%)		
	R^1	R^2	**8**	**9**	**10**
a		H	47	97	71
b		Et	57	64	88
c	$BnOCH_2$	Ph	30	61	68

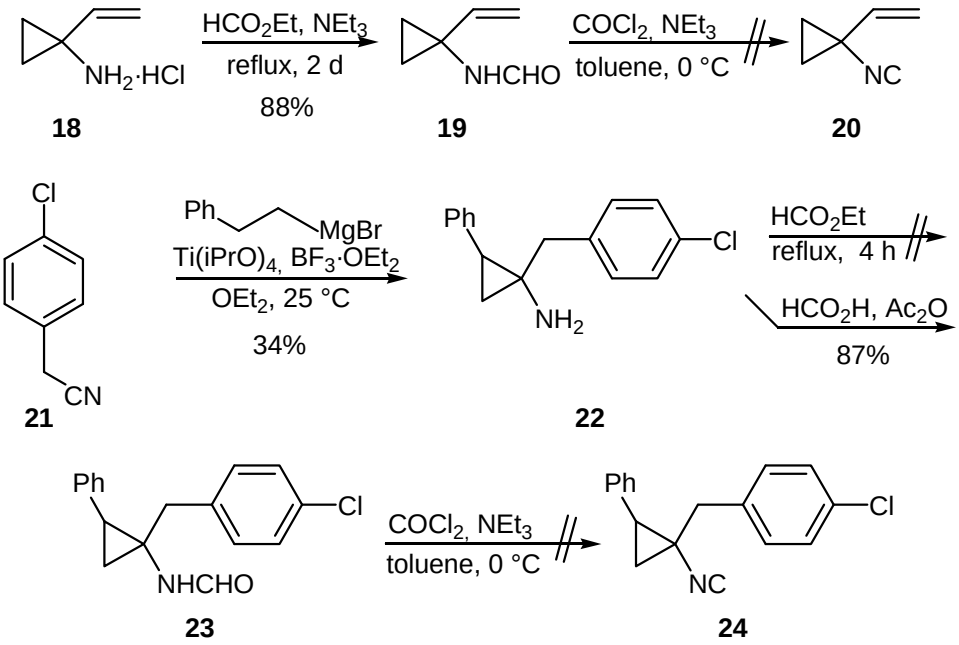
The bicyclic isonitrile **13** was synthesized analogously from the mono-*N*-Boc-protected bicyclic diamine **11** which had been obtained from the corresponding *N*,*N*-dibenzyl derivative according to an established protocol.[14] The formylation of **11** with ethyl formate proceeded virtually quatitatively, and the dehydration of the *N*-formyl derivative **12** with phosgene furnished **7** in 65% yield (Scheme 1.3).



Scheme 1.2. Synthesis of *tert*-butyl 6-isocyano-3-aza-bicyclo[3.1.0]hexane-3-carboxylate (**13**) and ethyl 1-isocyanocyclopropanecarboxylate (**17**).

Ethyl 1-isocyanocyclopropanecarboxylate **17** was prepared by bisalkylation of ethyl isocyanoacetate (**16)** with formation of the three-membered ring.[15,16]

Attempts to synthesize 1-vinylisonitrile **20** from the corresponding 1-vinylcyclopropylamine **18** were unsuccessful, perhaps because isonitrile **20** whis its activated vinyl group is prone to undergo polymerization (see Scheme 1.3).

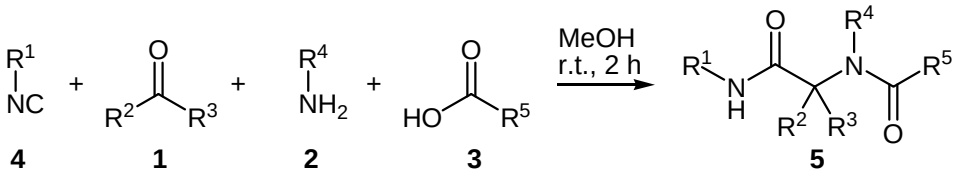


Scheme 1.3. Attempts to synthesize cyclopropylisonitriles **20** and **24**.

The synthesis of isonitrile **24** was hampered for sterical reasons. Obviously, the two phenyl groups on the cyclopropane ring retard the reactivity of the reaction center. At the step of the formylation it was possible to avoid this difficulty by using a mixed anhydride as suggested by Liegeois et al.[17] But the dehydration of the *N*-formyl derivative **23** proved to be impossible, only the starting material was reisolated (see Scheme 1.3).

1.3. Ugi Four-Component Reactions with Cyclopropylisonitriles

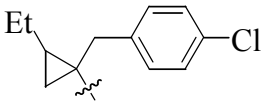
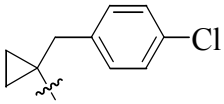
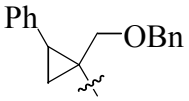
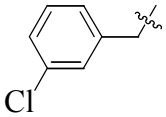
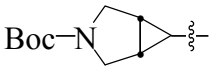
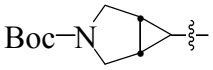
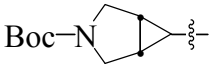
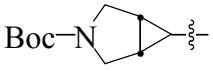
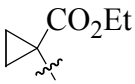
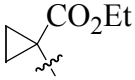
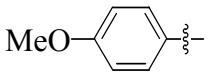
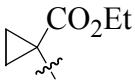
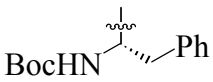
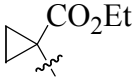
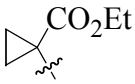
The reactivities of the new cyclopropylisonitriles were tested in the classic version of the 4CC Ugi reaction. Thus, isonitrile **4** an aldehyde or a ketone **1**, a primary amine **2** and a carboxylic acid **3** in MeOH react at ambient temperature to give a dipeptide **5**.[2]



Scheme 1.4. The 4CC Ugi reaction applied to the new cyclopropylisonitriles. For further details see Table 1.2.

A total of 12 new cyclopropyl-group containing dipeptides were synthesized from the cyclopropylisonitriles **10a–c**, **13**, **17** and a variety of ketones, amines and carboxylic acids. The results are represented in Table 1.2.

Table 1.2. New cyclopropyl-group containing dipeptides **5** prepared by the 4CC Ugi reaction employing cyclopropylisonitriles **10a–c**, **13**, **17** (see Scheme 1.4).

5	R^1	R^2	R^3	R^4	R^5	Yield (%)
a			H	Bn		69
b			H	Bn		55
c		–$(CH_2)_5$–			CH_2NHBoc	86
d			H	Bn		81
e			H	Ph		76
f			H	H	Me	52
g		–$(CH_2)_5$–		H	Me	68
h			H	Bn		81
i			H			86
j		–$(CH_2)_5$–		H		75
k		–$(CH_2)_5$–		H	Ph	66
l			H	H	Ph	38

The geometries and conformations of dipeptides **5b**,**d**,**h** and **i** in the solid state were established by X-ray crystal structure analyses.[18] The conformations of the dipeptide fragments in all four compounds studied by X-ray crystallography, are closed to each other. The orientation of the

substituents R^2, R^4 and R^5 is also similar. However, the orientation of cyclopropyl moiety of R^1 in compound **15b** is different in compare to it in molecules **5d,h,i** – corresponding torsion φ-angles are –78.5 and –70.1, –84.1°, respectively.

The structure of **5b** also differs from others by an arrangement of molecules in the crystal. Whereas the molecules **5b** in the crystal are linked in chains by N–H…O=C hydrogen bonds (carbonyl group adjacent to NH), the molecules of **5d,h,i** form centrosymmetrical dimers by hydrogen bonds pairs N–H…O=C (carbonyl of the other peptide group).

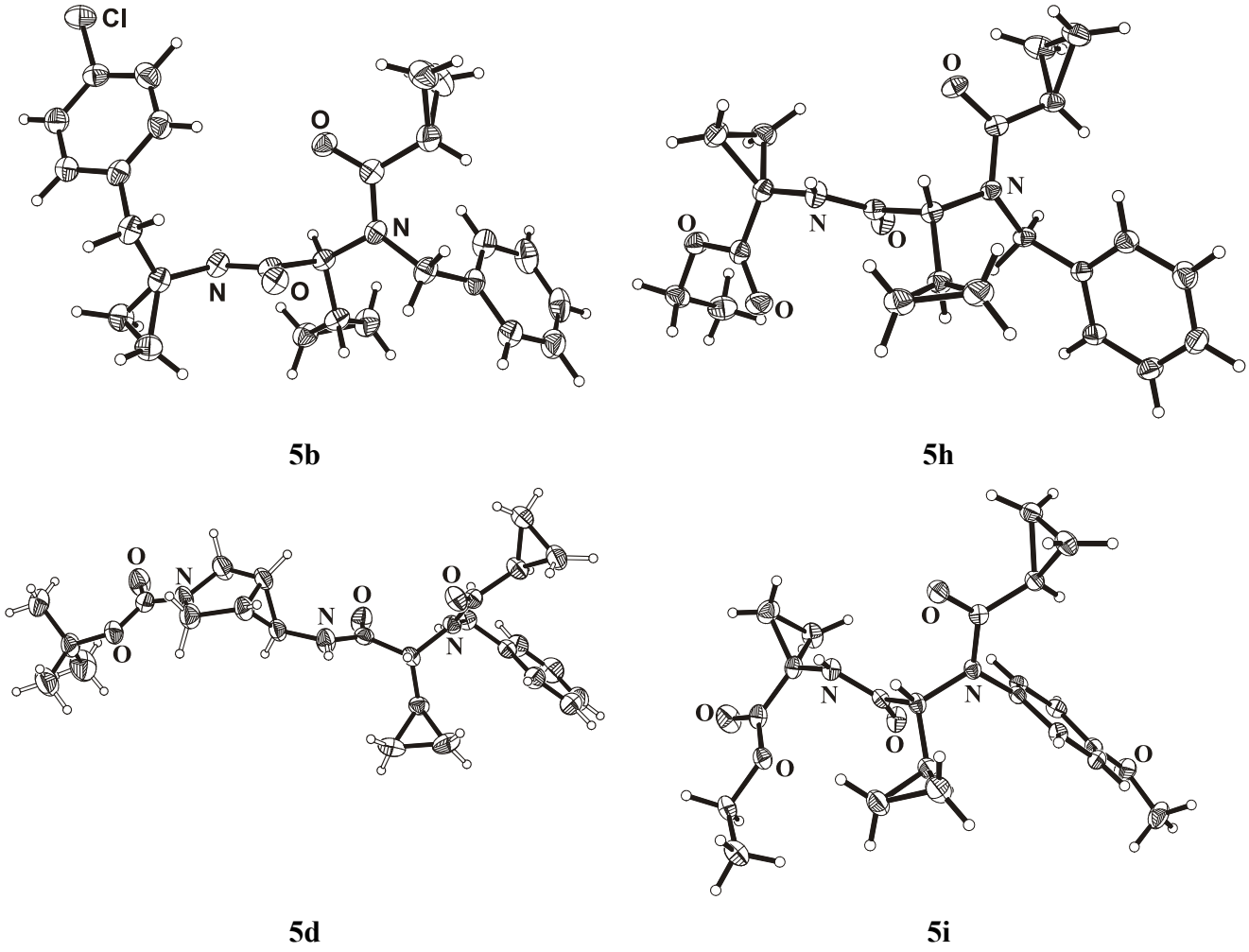
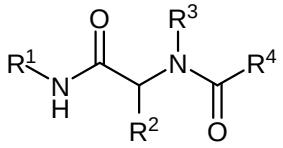


Figure 1.1. Structures of the cyclopropyl-group containing dipeptides **5b**,**d**,**h**,**i** in the crystals.[18]

A simple and convenient access to new dipeptides, each containing at least one cyclopropyl moiety, based on the 4CC Ugi reaction applying cyclopropylisonitriles has been developed.

1.4. Ugi Four-Component Reactions with Oxirane Containing Acids

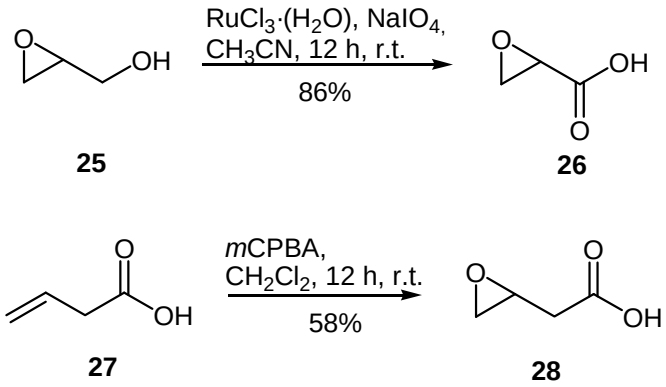
Very often introduction of the oxirane ring in a molecule leads to an increase of the biological activity of a substance. By varying of the reagents in Ugi multicomponent condensation it is easy to prepare many oxirane-group containing dipeptides. Especially it was interesting to vary the substituents R^1, R^2 and R^3 in dipeptide **5** if R^4 is a rest of the starting acid containing the oxirane moiety (see Figure 1.2).



5

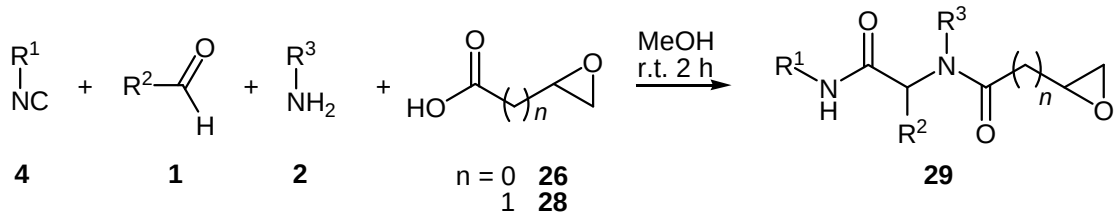
Figure 1.2. Dipeptide, the product of the Ugi 4CC reaction.

The starting acids, oxiran-2-carboxylic acid[19] (**26)** and oxyranylacetic acid[20] (**28**), were successfully synthesized according to the literature procedure from oxyranyl methanol **25** by catalytic oxidation of alcohol and from vinylacetic acid **27** by oxidation of double bond with *m*CPBA, correspondently.



Scheme 1.5. Synthesis of oxirane-2-carboxylic acid[19] (**26**) and oxiranylacetic acid[20] (**28**).

The obtained acids **26** and **28** were subjected the Ugi multicomponent condensation with different amines, aldehydes and isonitriles to afford oxirane-containing dipeptides **29** in moderate to good yields (42–78%) (see Scheme 1.6 and Table 1.3).



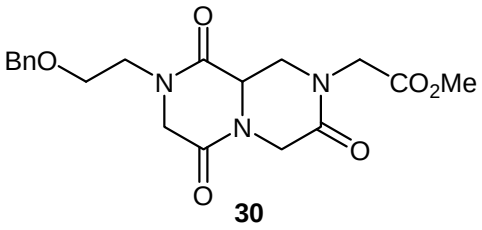
Scheme 1.6. Synthesis of new oxirane containing dipeptides **29** by the 4CC Ugi reaction. For further details see Table 1.3.

Table 1.3. New oxirane-containing dipeptides **29** prepared by the 4CC Ugi reaction (see Scheme 1.6).

29	R^1	R^2	R^3	*n*	Yield (%)
a	MeO_2CCH_2	*t*Bu	Bn	0	78
b	MeO_2CCH_2	*t*Bu	Ph	0	64
c	MeO_2CCH_2	*t*Bu	MeO_2CCH_2	0	42
d	Bn	*t*Bu	Ph	0	75
e	Bn	*t*Bu	Bn	0	73
f	Bn	*t*Bu	MeO_2CCH_2	0	62
g	Bn	Ph	Ph	0	74
h	Bn	Ph	Bn	0	74
i	MeO_2CCH_2	Ph	Ph	0	61
j	Ph	*t*Bu	Ph	1	46

1.5. Attempted Application of the Ugi Reaction towords the Synthesis of a Peptide β-Turn Mimetic

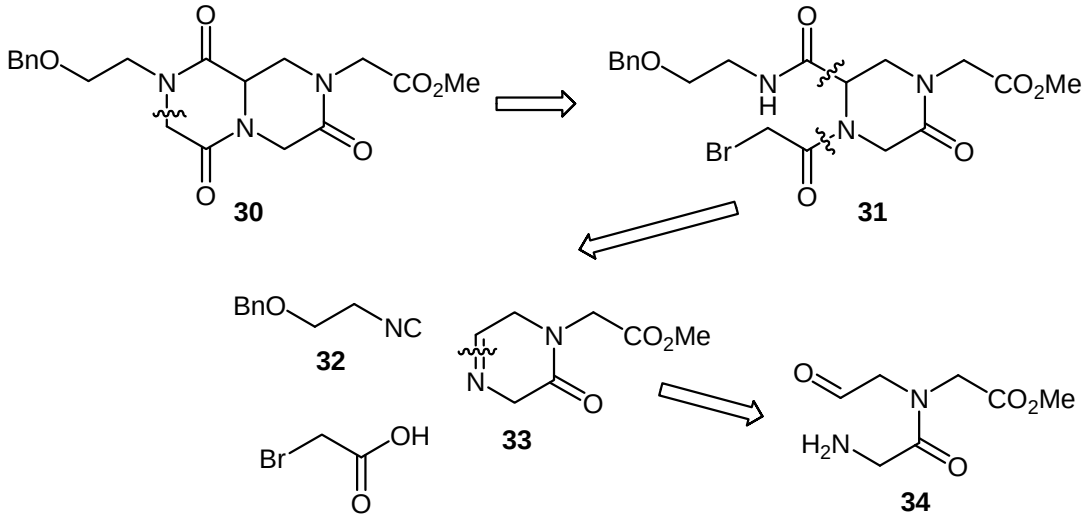
The Ugi multicomponent reactions are often used in the synthesis of biological active compounds. Substituted bicyclic ketopiperazines are known as peptide β-turn mimetics.[21] Thus, it was decided to test the Ugi condensation in applying to the synthesis of bicyclic ketopiperazine **30**, which might exhibit biological activity.



30

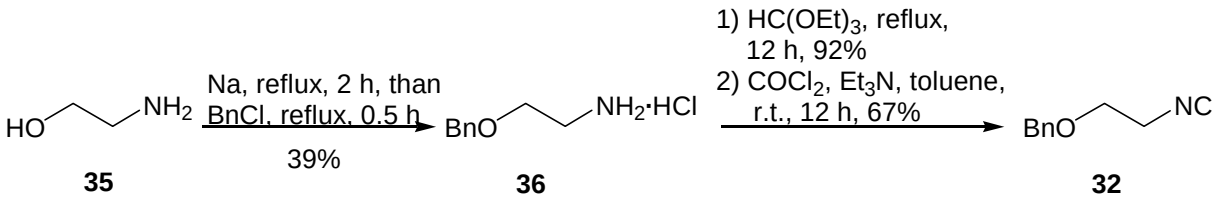
Figure 1.3. Potential biological active β-turn mimetic **30**.

Retrosynthetically the bicyclic peptide **30** can be represented as a substituted piperazine **31** which can be theoretically easily available by Ugi multicomponent condensation of isonitrile **32**, bromoacetic acid and cyclic imine **33** which in its turn is a product of condensation of respective amino aldehyde **34** (see Scheme 1.7).



Scheme 1.7. Retrosynthesis considiration of the bicyclic peptide **30**.

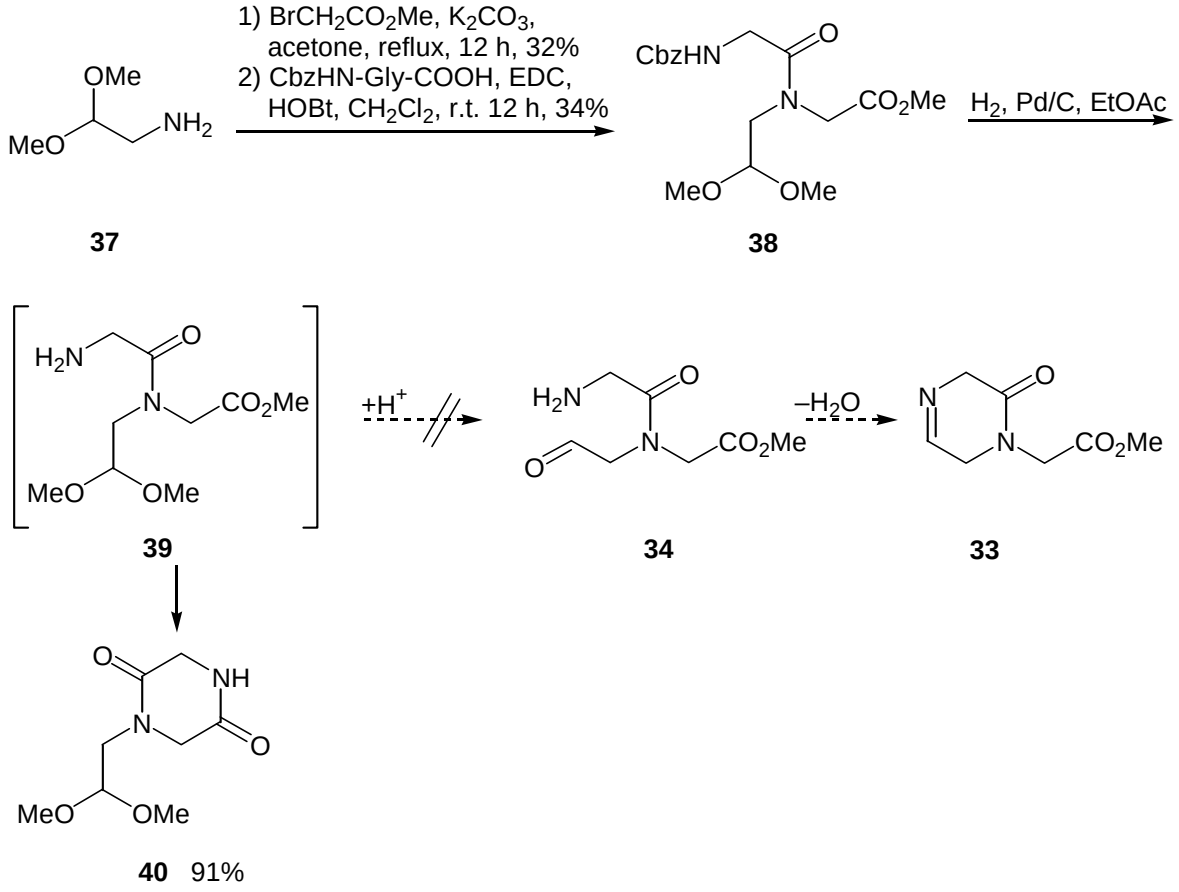
Isonitrile **32** was prepared analogously to the cyclopropyl isonitriles as stated above from respective aminoetanol **35**, hydroxy group of which was protected with benzyl moiety according to known procedure[22] in moderate yield (39%). The following formyl derivative, prepared by refluxing with triethyl orthoformate, was dehydrated by treatment with a solution of phosgene in toluene to afforded required isonitrile **32** in good overall yield (62%) in two steps.



35 **36** **32**

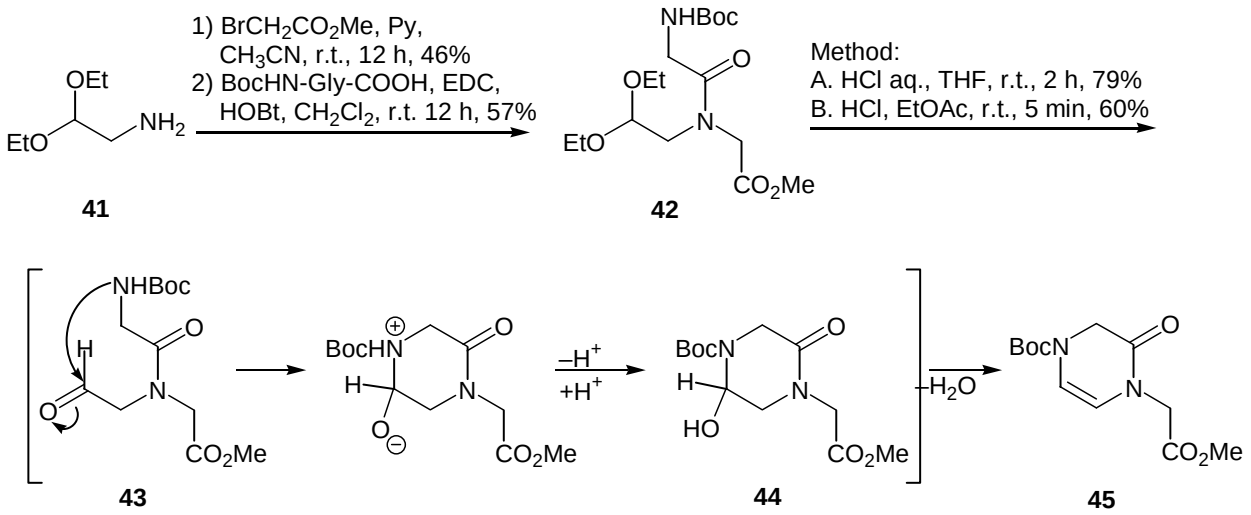
Scheme 1.8. Synthesis of isonitrile **32**.

The synthesis of imine **33** was based on the synthesis of respective amino aldehyde, having cyclization as a key step. Thus, starting 2,2-dimethoxyethylamine **37** was treated with methyl bromoacetate to yield the mixture of bi- and mono- alkylated amines from which desired mono product was separated by distillation (see Scheme 1.9). The latter was coupled with *N*-Cbz-glycine to afford amide **38**. The deprotection of amino group of **38** should give free amine **39** which after cleavage of aldehyde group should cyclilyze into desired imine **33**. However, palladium-catalyzed hydrogenation proceeded smoothly resulting only piperazine **40** in excellent yield (91%). Obviously, the presence of ester group in molecule causes nucleophyl attack of free amine residue on carbonyl moiety to form stable piperazine **40**.



Scheme 1.9. Attempted synthesis of imine **33** employing Cbz-protection.

After ineffective attempt of applying of Cbz-protection it was decided to test Boc group which can be removed at the same time with acetale protection of aldehyde. Thus, starting 2,2-diethoxyethylamine **41** was converted into *N*-Boc-protected amide **42** similar to the methods which were used for the synthesis of *N*-Cbz-protected amide **38** (see Scheme 1.10). Alkylation with methyl bromoacetate at the presence of pyridine[23] instead of K_2CO_3 afforded more mono alkylated product, 46% and 32%, correspondently. Following coupling of mono-alkylated amine with *N*-Boc-glycine gave desired *N*-Boc-protected amide **42**. Treatment of the latter with hydrochloric acid furnished 3-oxo-3,4-dihydropyrazine **45** in good yield.



Scheme 1.10. Attempted synthesis of imine **33** employing Boc-protection.

Evidently, hydrochloric acid cleaves aldehyde group first to afford free aldehyde **43**, which after nucleophyl addition of amino group on carbonyl moiety converts into alcohol **44**. Elimination of water from the latter leads to 3,4-dihydropyrazine **45**.

Since it has proved to be impossible to obtain imine **33**, it was no possibility to apply the Ugi multicomponent condensation for the synthesis of cyclic peptide **30**.

2. Synthesis of α-Keto Amides and Their Implementation in the Synthesis of Dipeptides as Potential Peptidomimetics

2.1. Considerations

A variety of carbonyl-homologized ketones, acids, esters, amides, and fluoroalkyl derivates, have recently been reported to be potent inhibitors of human renin and calpains (calcium-dependent cysteine proteases).[4] In line with this trend, it was decided to extend this variety of α-oxocarbonyl compounds towards the yet unknown class of α-keto amides, which would contain leucine- and isoleucine-residue (Figure 2.1). The choice of the alkyl substitutents was made basedon an analysis of preliminary results of a bioscreening of libraries of similarly functionalized substances containing various alkyl residues. Thus, it was shown that compounds with a leucine-moiety clearly overcome their homologues bearing the same set of functionalities in terms of biological activity.[24] Moreover, there was no information concerning any activity of the similarly functionalized α-isoleucine derivatives published elsewhere.

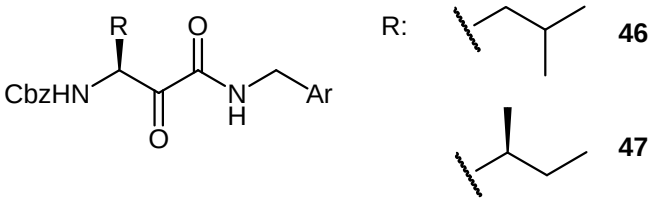


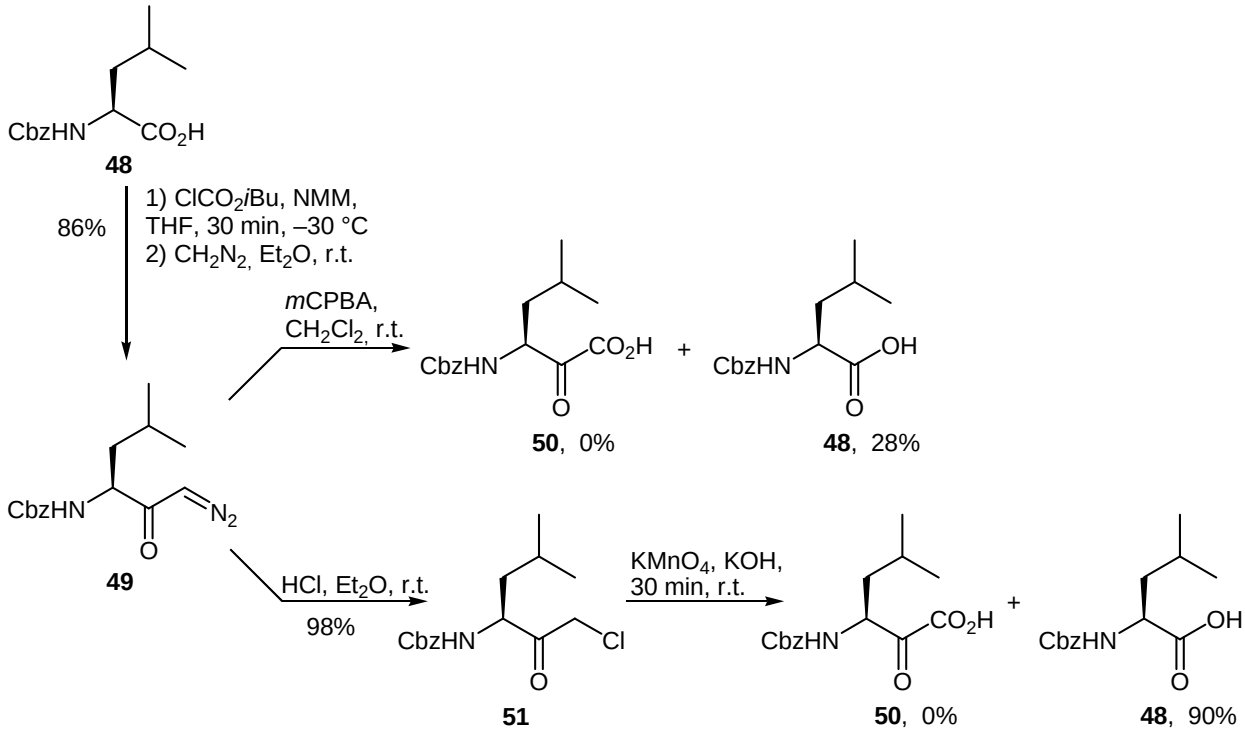
Figure 2.1. α-Keto amides, bearing leucine and isoleucine moieties.

At a first glance, the target β-amino α-keto amides might be retrosynthetically reduced to the corresponding β-amino α-keto acids, the preparation of which appeared to be straightforward in view of a relatively wide arsenal of synthetic procedures that might lead to the target compounds.

2.2. Synthesis of *N*-Protected β-Amino-α-keto Amides Containing Leucine Moiety

Starting from commercially available *N*-protected L-leucine, at least three different methods for substitution of its hydroxy function against the methoxycarbonyl synthone equivalent might be suggested.

According the first one, the starting *N*-Cbz-protected leucine **48** was converted into diazo derivative **49** by treatment of mixed anhydride with diazomethane (see Scheme 2.1). Several attempts to perform a direct oxidation of the diazoketone **49** into the corresponding α-keto-acid **50** have been undertaken.

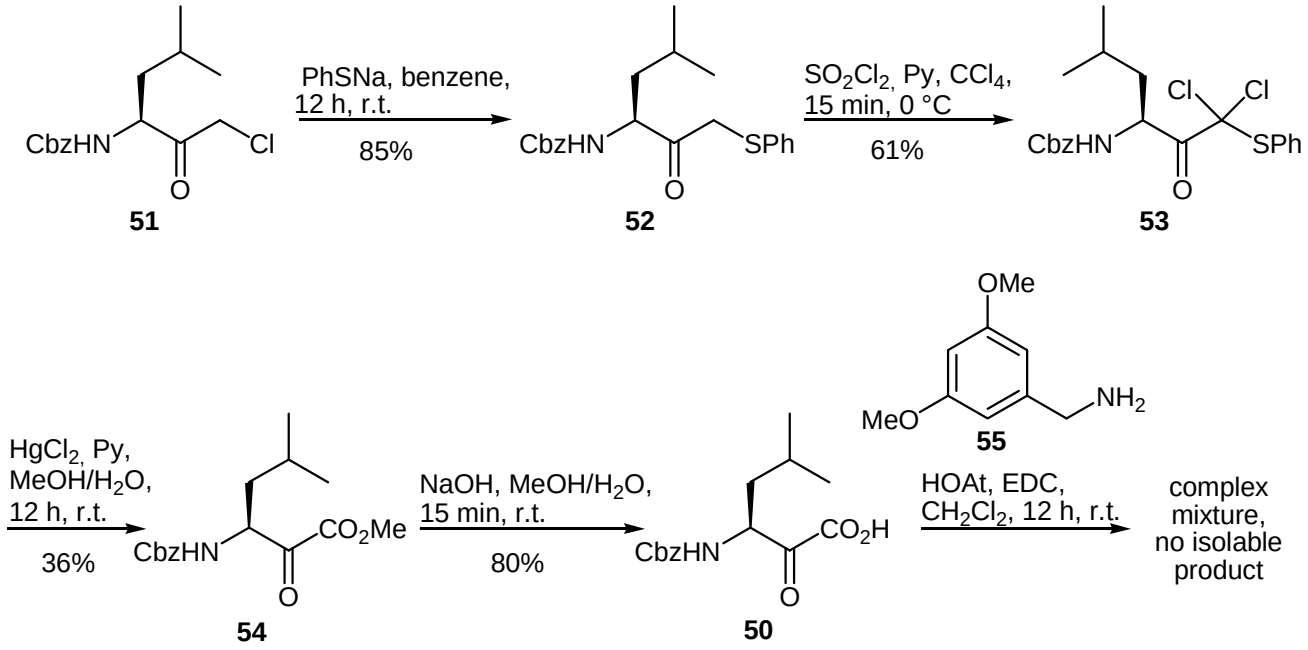


Scheme 2.1. Attempts to oxidize the diazoketone **49**.

At first, *m*CPBA was tried as the most commonly oxidizing reagent used for similar purposes, but only starting *N*-protected amino acid **48** was isolated from the reaction mixture that has unambiguously evidenced an occured overoxidation. Then, $KMnO_4$ was tested for this purpose, since aromatic chloroketones are well documented to be transformed into the respective α-keto acids by oxidation with potassium permanganate.[25] Thus, the chloroketone **51** was subjected to the standard oxidation procedure with $KMnO_4$, that, however, resulted again in the same overoxidized product, namely acid **48**.

Thus, the above described attempts to oxidize a diazomethyl or chloromethyl moieties adjacent to the α-keto-group towards the desired α-keto acid **50** failed.

The second approach to convert a chloromethylketone into the respective α-keto ester is based on the methodology developed by Fortes et al. [26] which comprised formation of thiophenyl ketones with subsequent oxidation and hydrolysis of the intermediately formed α-dichlorothiophenyl derivates, thus accomplishing elaboration of the required α-keto ester function.

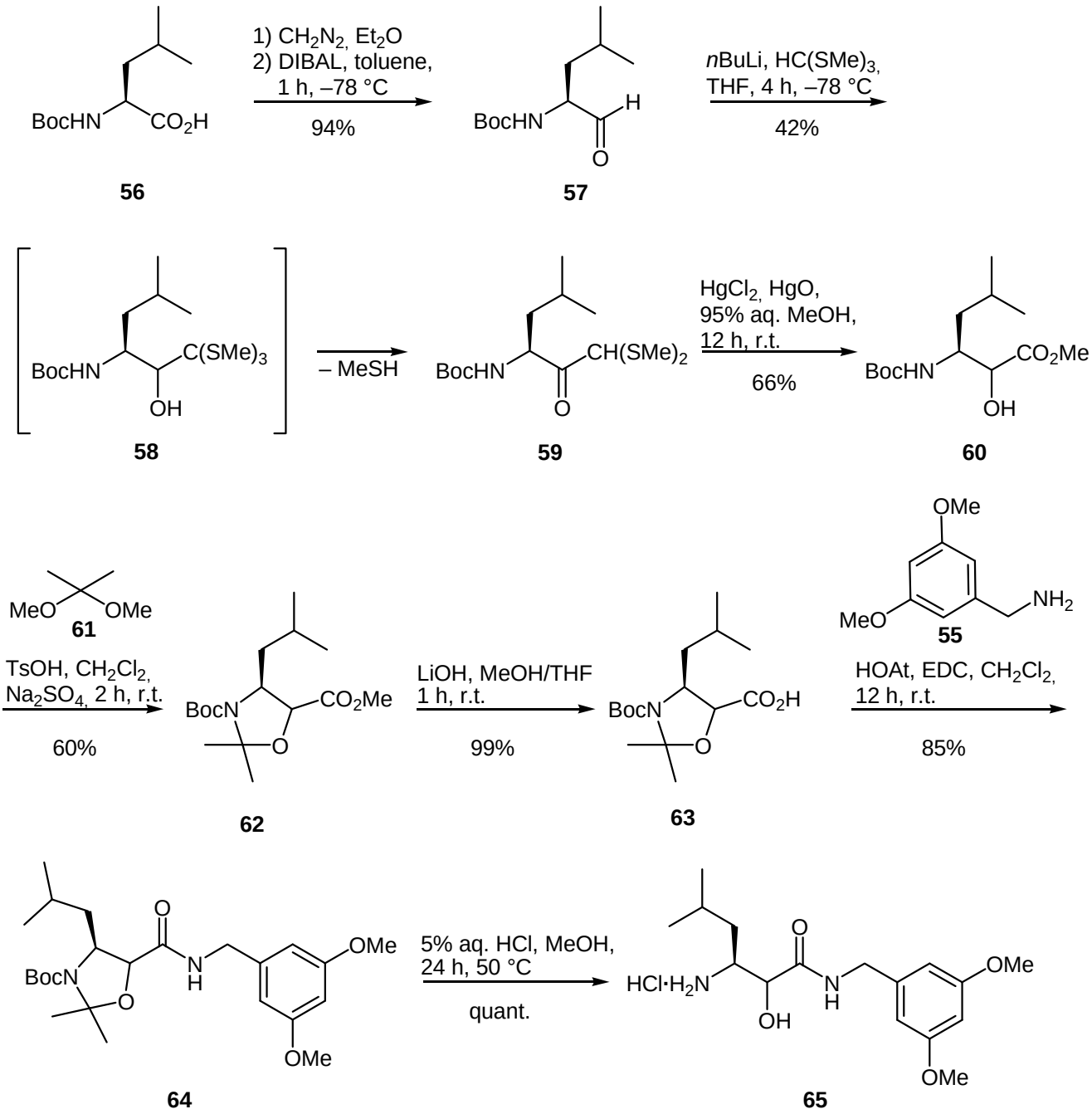


Scheme 2.2. Synthesis of α-keto acid **50**.

Thus, according to this protocol, α-chloro ketone **51** was smoothly converted to the corresponding α-thiopenyl ketone **52** (see Scheme 2.2), which in turn underwent an oxidation of the α-methylene group by sulfuryl chloride affording the respective dichlorothiophenyl derivative **53** that after subsequent mercury-catalyzed alcoholysis and following basic hydrolysis gave α-keto acid **50** with overall yield of 13 % after 7 steps, starting from *N*-protected amino acid **48**. The reaction of the latter with 3,5-dimethoxybenzylamine **55** under standard conditions provided a complex mixture, in which no product has been found. It might be referred to the significantly increased nucleophilicity of the α-keto group in **50** in comparison with even activated carboxylic group of this substrate that can interfere in reaction of **50** with amines.

The third route for elaboration of the α-keto ester moiety is based on the nucleophilic addition of an ester anion equivalent to aldehydes as suggested by Patel et al.[27](see Scheme 2.3), since the classical cyanohydrine formation – Pinner alcoholysis sequence obviously would not be tolerated by the protective groups in the side-chains of the concerned substrates. An essential advantage of

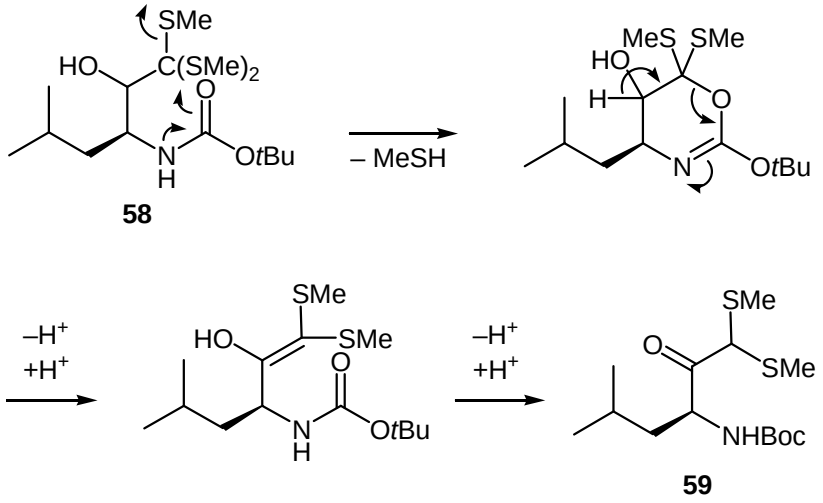
this approach is that it allows to provide an easy access to the corresponding α-hydroxy esters under mild conditions, which can be also considered as potential biological active substances.[28]



Scheme 2.3. Synthesis of hydrochloride **65**.

Condensation of the ester anion equivalent tris(methylthio)methide with the aldehyde **57**,[29] obtained by reduction of the methyl ester of *N*-Boc-protected leucine **56**, had to give the α-hydroxy-ortho thioester **58** but only α-keto dithiomethyl derivate **59** was isolated in a moderate yield of 42%. In the ^{1}H-NMR spectrum there are only two and different singlets from SMe groups and the in ^{13}C-NMR spectrum there is a distinct signal at 200.0 ppm which can be answer only to keto group. The

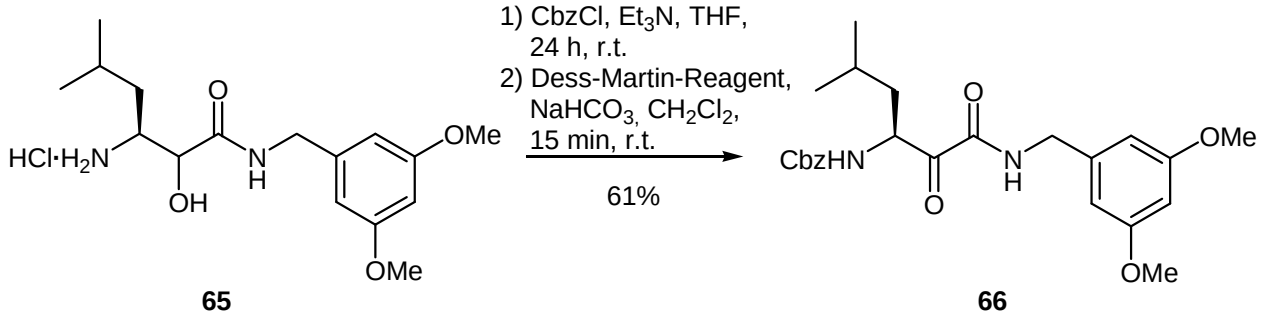
reason of such facile elimination might originate from the opportunity for anchimeric assistance of the adjacent Boc-group for the leave of a thiomethyl group, as it shown on the Scheme 2.4.



Scheme 2.4. Mechanistic rationalization of formation of the α,α-dithiomethylketone **59**.

Nevertheless, the mercury-catalyzed hydrolysis[30] of α-keto dithiomethyl derivate **59** afforded the corresponding α-hydroxy ester **60** in good yield (66%) (see Scheme 2.4). To prevent a possible cyclisation which may be caused by intramolecular attack of the hydroxy-group onto Boc-moiety (see below) it was protected by treatment of the α-hydroxy ester **60** with 2,2-dimethoxypropane **61** in the presence of catalytic amounts of TsOH[31] to provide the respective oxazolidine derivate **62**. Then, the ester group of the latter was hydrolyzed with lithium hydroxide according to Wei et al.[32], giving the acid **63** in quantitative yield. The reaction of acid **63** with 3,5-dimethoxybenzyl amine **55** under standard conditions, namely, in the presence of equimolar amounts of EDC and HOAt, proceeded smoothly to provide amide **64** in good yield (85%). The final deprotection of **64** has been accomplished by treatment with aqueous hydrochloric acid in methanol to afford the hydrochloride **65** in quantitative yield. The hydrochloride **65** is going to be used as multipurpose building block for the synthesis of *N*-protected amide **46** as well as for its further condensation with animoacids to prepare dipeptides.

After standard Cbz-protection of the amino group of the hydrochloride **65** and an ineffective attempted oxidation of α-hydroxy group according to standard Swern protocol, use of Dess-Martin periodinane (DMP) had become rather successful thus furnishing the target α-keto amide **66** in good yield (see Scheme 2.5).

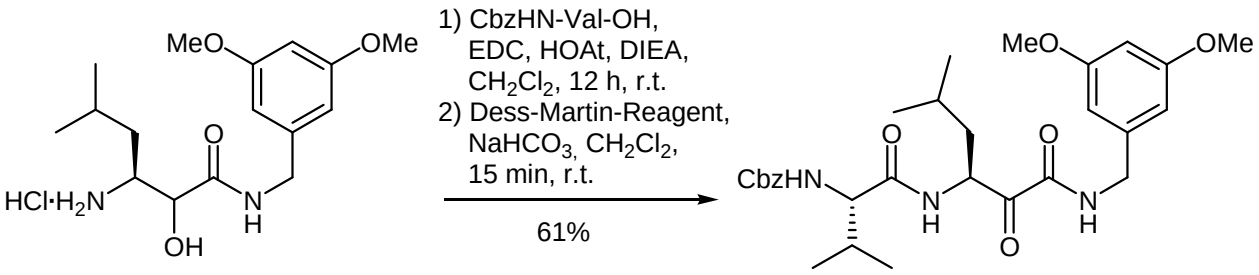


Scheme 2.5. Synthesis of α-keto amide **66** from hydrochloride **65**.

Overall, the desired α-keto amide **66** was synthesized from *N*-Boc-protected leucine **56** in ten steps with an overall yield of 8%. An obvious advantage of this route is that it resembles a rather general convergent strategy as outlined above.

2.3. Synthesis of Dipeptides Containing α-Keto Groups

A possibility to apply hydrochloride **65** as a building block for the synthesis of peptides containing α-keto group was tested in coupling with *N*-protected amino acid.

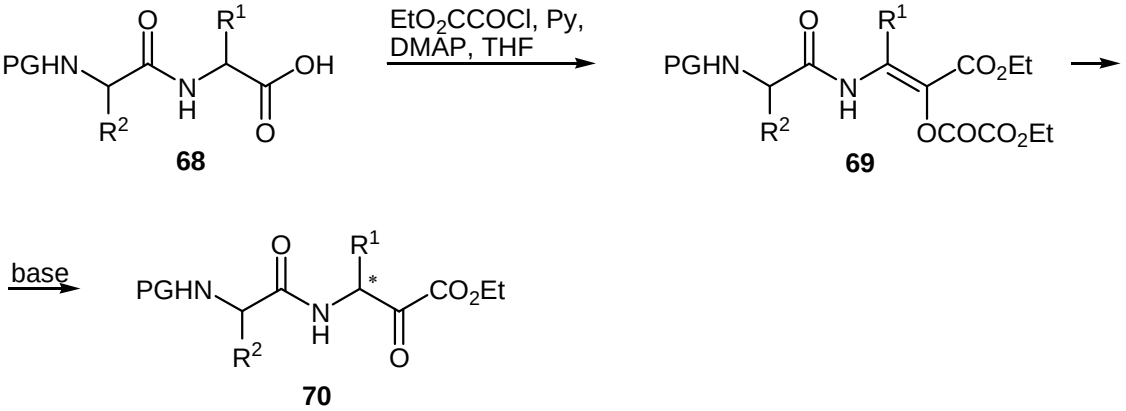


65 **67**

Scheme 2.6. Synthesis of peptide **67** from the hydrochloride **65**.

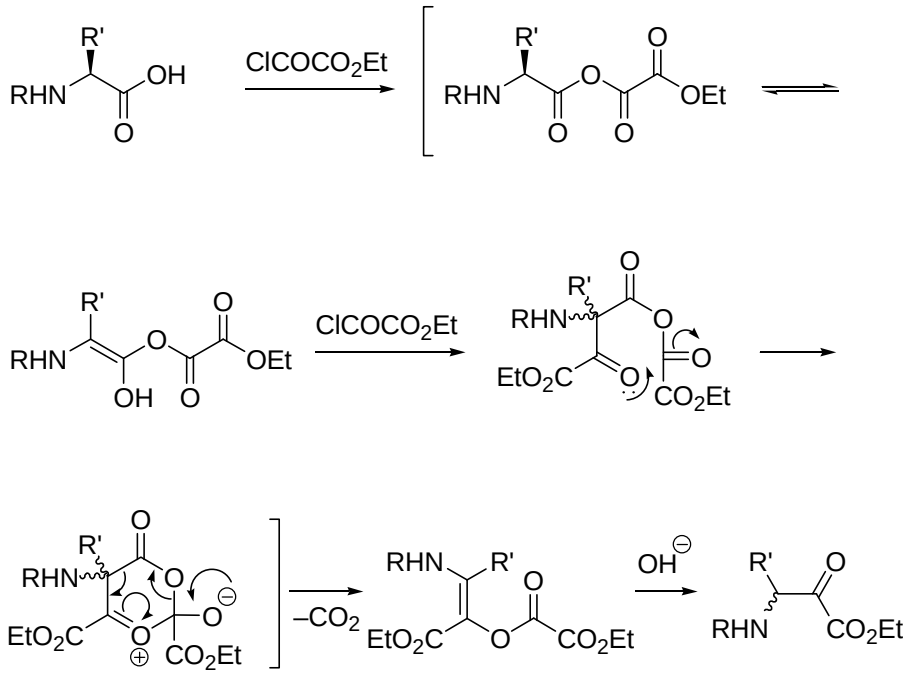
Thus, dipeptide **67** was obtained from hydrochloride **65** *via* coupling with *N*-Cbz-protected valine and following oxidation with Dess-Martin periodinane (DMP) in 61% yield (see Scheme 2.6).

Alternatively, α-keto containing peptides might be also prepared by modified Dakin-West reaction.[33] Thus, according to this protocol, *N*-protected oligopeptide **68** should react with an excess of ethyl oxalyl chloride to afford intermediate mixed ethyl enoloxalate **69** which after subsequent basic hydrolysis, resulted into the required α-keto ester **70** (see Scheme 2.7).[34]



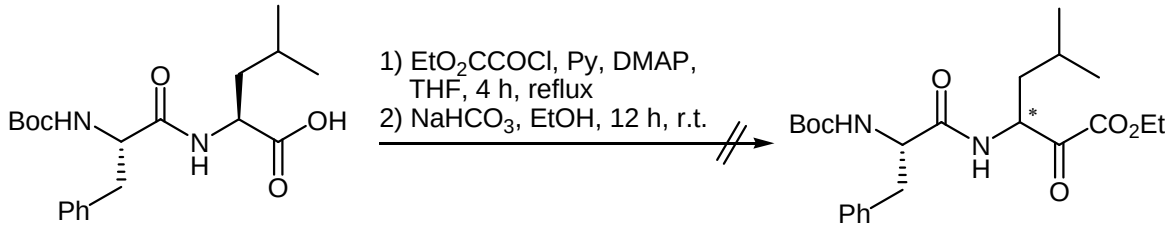
Scheme 2.7. Preparation of α-keto containing dipeptides **70** by a modified Dakin-West reaction.

However, this reaction has a significant drawback, since in its course a racemization of one stereogenic center must occur (see Scheme 2.8).



Scheme 2.8. Mechanistic rationalization of modified Dakin-West reaction.

Nevertheless, several attempts to prepare peptide **72** containing α-keto group using this protocol were undertaken (see Scheme 2.9). But neither of those did not afforded the desired α-keto modified dipeptide **72**.

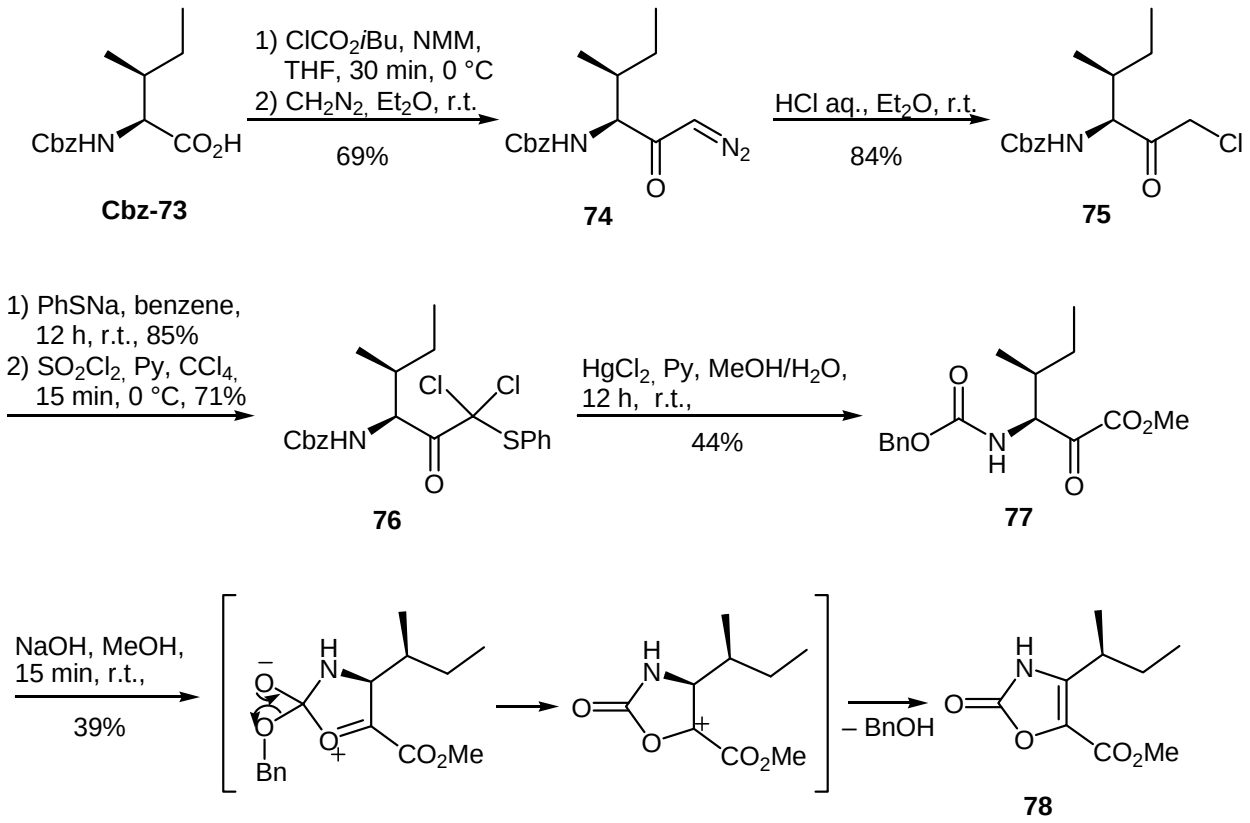


Scheme 2.9. Attempt to synthesize α-keto containing dipeptides **72** by a modified Dakin-West reaction.

Indeed it is well documented that use of modified Dakin-West reaction does not proceed cleanly, affording the respective α-keto dipeptides in low to moderate yields only after rigorous optimization of the reaction conditions for both steps. After several unsuccessful attempts to find an appropriate reaction conditions, it was decided to give up further efforts, since the hydrochloride **65** had been already shown to be successfully applied for the synthesis of the respective dipeptides (see Scheme 2.6).

2.4. Attempts to Synthesis of *N*-Protected β-Amino-α-keto Amides with Isoleucine Residue

Simultaneously to the transformation of leucine according to the Scheme 2.2 *N*-protected isoleucine **Cbz-73** was subjected to the similar reactions (see Scheme 2.10).



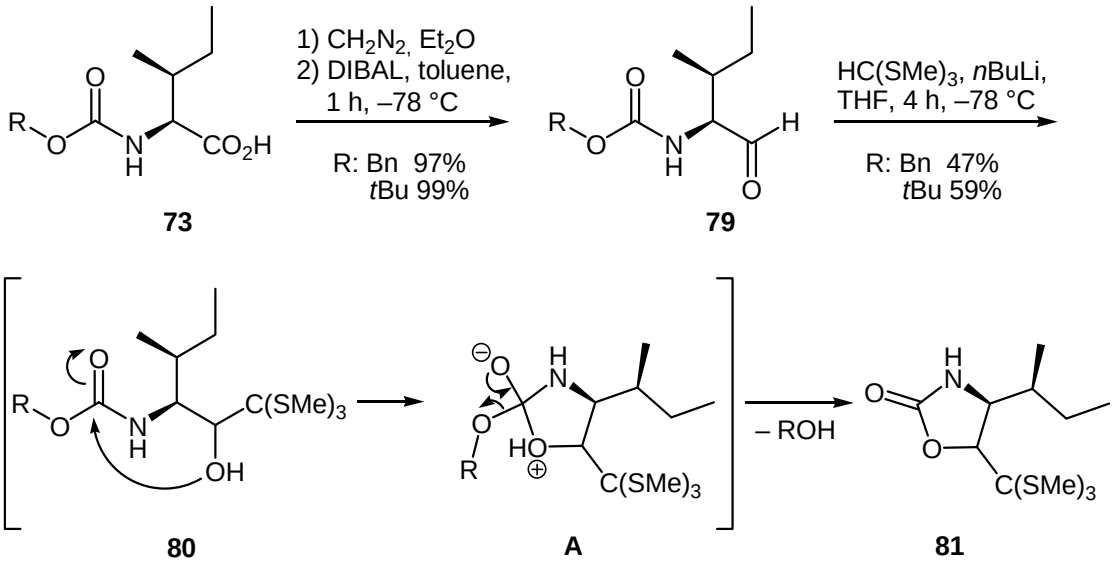
Cbz-73 **74** **75** **76** **77** **78**

Scheme 2.10. Attempt to synthesis of α-keto amide containing isoleucine residue **47** by a diazo compound **74**.

The starting *N*-Cbz-protected isoleucine **Cbz-73** by a mixed anhydride was converted into diazo ketone **74** which was treated with aqueous hydrochloric acid to afford the α-chloro ketone **75**. The chloro residue of the latter was substituted for thiophenyl moiety and the methylene group was oxidized with sulfuryl chloride to give dichlorothiophenyl derivate **76**. The hydrolysis of **76** to the α-keto methyl ester **77** proceeded with moderated yield 44% but the following hydrolysis of the methyl ester gave no α-keto acid, only oxazole **78** was isolated. Apparently, the presence of methyl group in 4-position causes such conformation of α-keto ester **77** in which oxygen atom of α-keto group attacks the carbon atom of benzyloxocarbonyl group. The following benzyl alcohol elimination provides the formation of the oxazole **78**.

The route based on nucleophyl addition of ester anion sinthon to aldehyde[27] and successfully applied to *N*-Boc-protected leucine **56** (see Scheme 2.3) in the case of *N*-protected isoleucine **73** did not bring expected results (see Scheme 2.11). From *N*-Cbz- or *N*-Boc-protected isoleucines **Cbz-,**

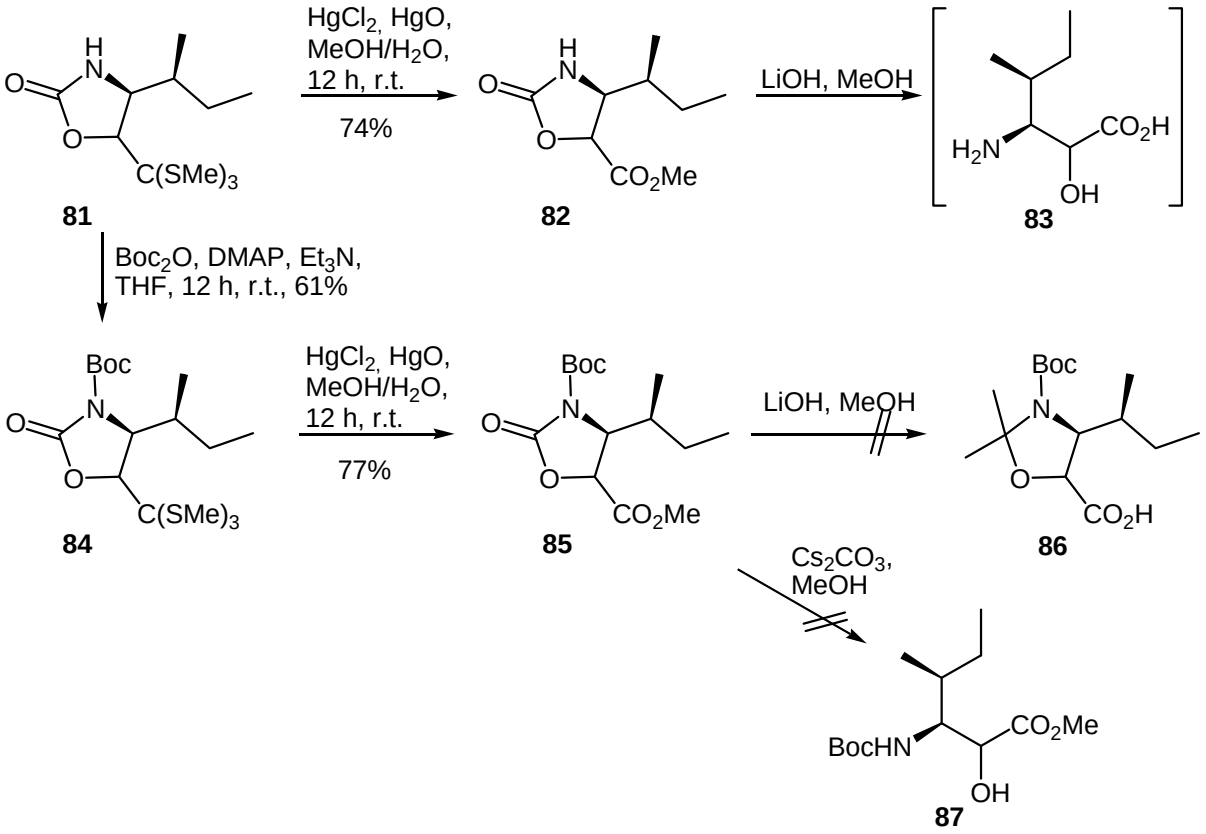
Boc-73 by a reduction of their methyl esters corresponding aldehydes **Cbz-, Boc-79** were prepared. Condensations of the latters with the ester anion synthon tris(methylthio)methane led to oxazolidin-2-one **81**. Obviously, the first product of this reaction is α-hydroxy ortho thioester **80** but the sterical influence of methyl group in the 4-position causes the nucleophyl attack of hydroxy group on carbon atom of benzyl-or *tert*-butyloxocarbonyl group to give intermediate **A**. The latter transforms by a alcohol elimination into oxazolidin-2-one **81**. Changing the sequence of addition of the reagents, addition of tris(methylthio)methane anion to the solution of aldehyde, does not provide to desired α-hydroxy orthothioester **80**. After decreasing the time of reaction to 1 hour only starting aldehyde was isolated. That demonstrates that desired α-hydroxy orthothioester **80** is unstable and can not be isolated while it converts into corresponding oxazolidin-2-one **81** immediately after formation.



73 **79** **80** **A** **81**

Scheme 2.11. Attempted synthesis of the α-hydroxy orthothioester **80**.

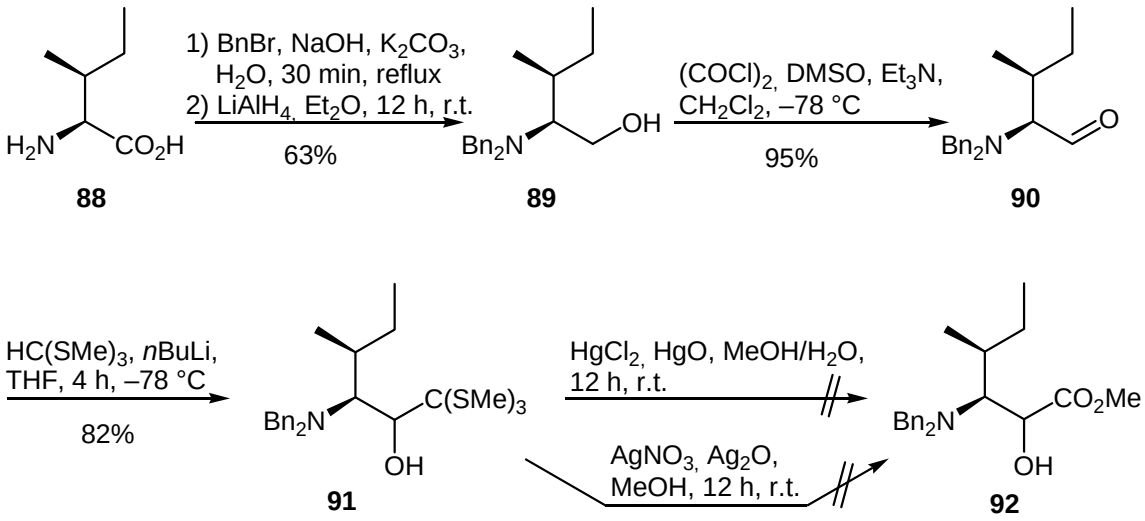
In literature several examples of transformation of the oxazolidin-2-ones are described. Thus, obtained oxazolidin-2-one **81** was mercury-catalyzed hydrolyzed to methyl ester **82** (see Scheme 2.12). By attempt to hydrolyze the ester group of **82** the latter decomposed, probably, into free amino acid **83** which can not be isolated from water solution.



Scheme 2.12. Attempted transformations of **(**4*S*)-4-((*S*)-*sec*-butyl)-5-(tris(methylthio)methyl)-oxazolidin-2-one **81**.

Protection of nitrogen atom of the oxazolidin-2-one **81** with *tert*-butyloxocarbonyl and following hydrolysis of orthothioester group afforded Boc-protected oxazolidin-2-one **85**, which was unsuccessfully attempted to hydrolyze to the acid **86**. Principally possible ring opening by treating with catalytically amount of cesium carbonate[35] did not proceed in the case of the oxazolidin-2-one **85**. Increasing of the amount of cesium carbonate to 1 equiv. led to complete decomposition of starting oxazolidin-2-one **85**. Probably, the product of this decomposition was again free amino acid **83**.

After unsuccessful attempts of using oxocarbonyl protective groups (Cbz and Boc) it was necessary to choose principal new one which has no carbonyl group. One of the most useful such protection group for nitrogen is dibenzyl protection.



Scheme 2.13. Synthesis of α-hydroxy orthothioester **91** and attempts its transformation into α-hydroxy methyl ester **92**.

Thus, isoleucine **88** was dialkylated with benzyl bromide and reduced to alcohol **89** which was subjected the Swern oxidation to afford *N*-dibenzyl protected isoleucinale **90** (see Scheme 2.13). Condensation of the latter with tris(methylthio)methane anion proceeded smoothly to give α-hydroxy ortho thioester **91** with good yield 82%. But the further mercury-catalyzed hydrolysis to the α-hydroxy methyl ester **91** gave only yellow mixture in which no product was revealed by NMR spectroscopy. Using alternative procedure with silver nitrate[36] also did not bring any results. The presence of tertiary amino group in molecule makes the hydrolysis impossible, obviously, while possible complex building of free electron pair of nitrogen with free orbital of transition metal (mercury or silver).

Thus, it was shown that method successfully applied to the synthesis of α-keto amides containing leucine residue can not be applied to the synthesis of α-keto amides containing isoleucine residue, probably, due to sterical influence of methyl group in 4-position.

3. Synthesis of 3-Keto Amides and Their Structural Analogues as Potential Peptidomimetics

3.1. Consideration

Many natural and synthetic biological by active substances are amides. The presence of other functional group in molecule can change an intensively or a direction of biological activity. In the past years, the keto amides and their structural analogs, such as epoxy and unsaturated amides, attract more and more attention of scientists by their pharmacological properties. Since in literature there are no information about biological activity of activated 3-keto amides and their similar structural analogs, represented in Figure 3.1, it was decided to prepare them.

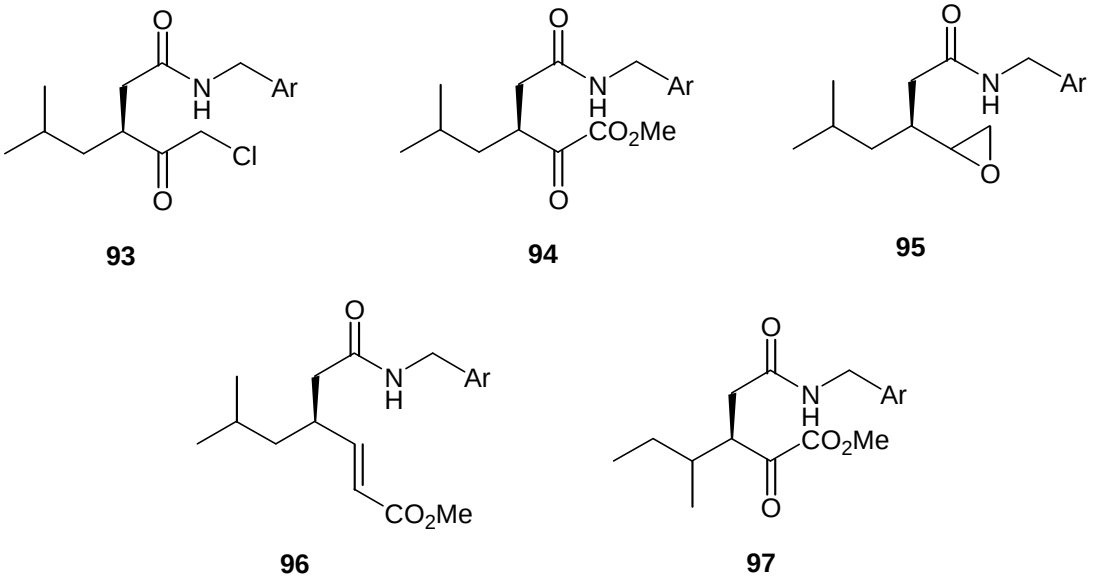
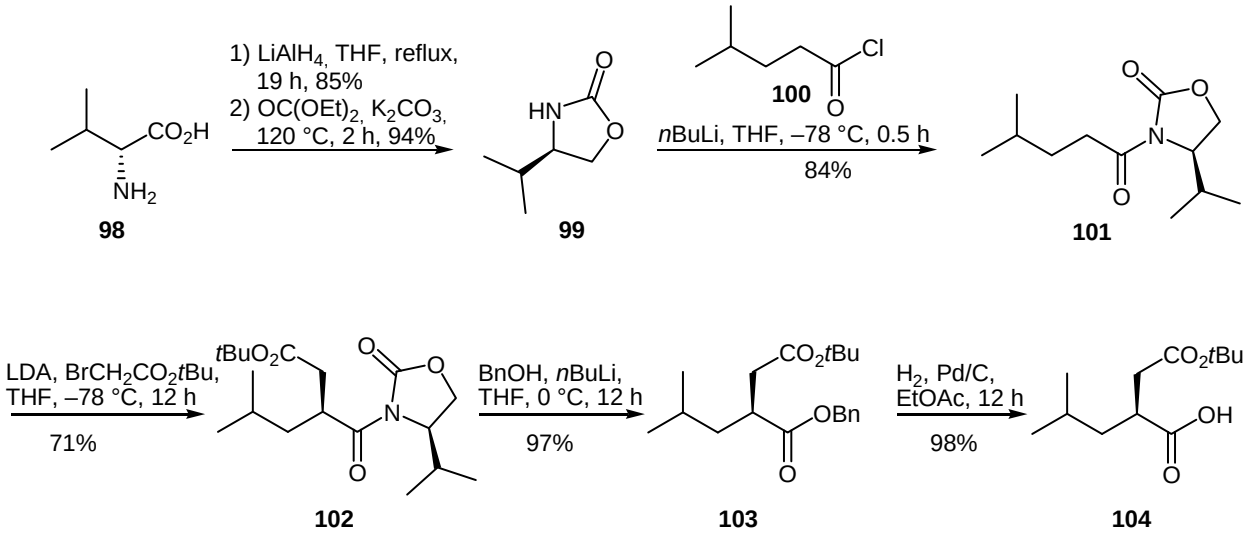


Figure 3.1. Potentially biologically active amides.

First four amides have the same carbon skeleton and the same configuration of optical active center. That's why the next synthetical strategy was convenient: to form the optical center in carbon skeleton at first and then to construct the desired rest of molecule. The most common way to obtain the chiral center in this case is 4-substituted oxazolidin-2-ones described by Evans.[37] 4-Substituted oxazolidin-2-one reacts with acid chloroanhydride to give amide which can be stereoselectively alkylated in alpha position to carbonyl group. Then the oxazolidin-2-one auxiliarity can be easily cleaved off by treatment with lithium hydroxide and hydrogen peroxide, affording the appropriately modified with the required configuration of the α-carbon center.

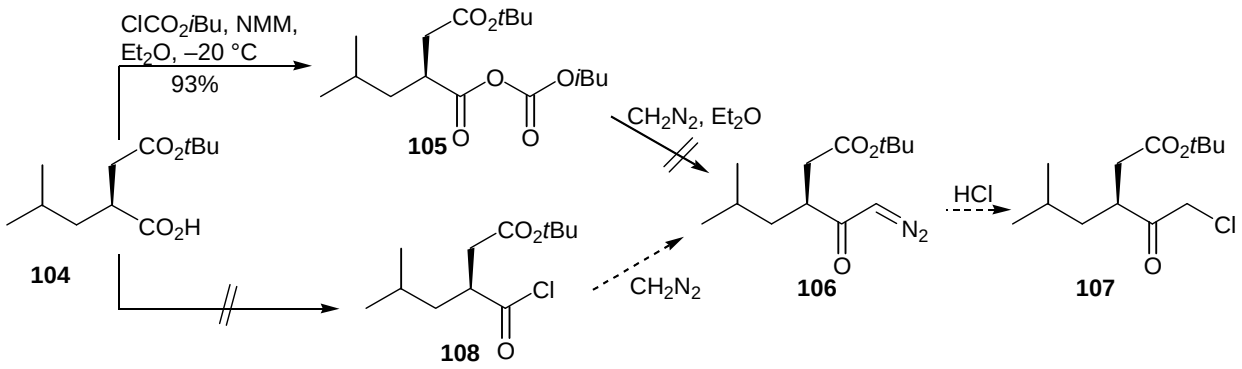
3.2. Attempted Synthesise of 5-Chloro-3-keto Amide **93**

Taking in consideration the literature date about the stereochemistry of the similar transformation,[38] (*R*)-4-isopropyloxazolidin-2-one **99** was selected as suitable auxiliarity to obtain desired configuration of the chiral center. Thus, the starting (*R*)-4-isopropyloxazolidin-2-one **99** was prepared in two steps according to known procedures[37,39] from D-valine **98** by the reduction[39] of amino acid with lithium aluminumhydride and subsequent condensation[37] of the obtained vicinal hydroxyamine with diethylcarbonate (see Scheme 3.1). Acylation of (*R*)-4-isopropyloxazolidin-2-one **99** with 4-methylpentanoic acid chloride **100**[40] under standard conditions gave amide **101** in good yield (84%). The latter was stereoselectively alkylated in α-position with *tert*-butyl bromacetat to give only one (*S*)-isomer of amide **102**. The following removal of the auxiliarity, however, turned out to be a bit complicated as it was expected first. Thus, after the standard cleavage protocol based on combination of oxygen peroxide with LiOH[41] has been applied, only staring material has been recovered. Thus, complication was circumvented when the amide **102** was converted into benzyl ester **103**[42] which was successfully cleaved by catalytic hydrogenation on 10% Pd/C at atmosphere pressure. This sequence afforded the desired acid **104** in 95% overall yield after two steps.



Scheme 3.1. Synthesis of acid **104**.

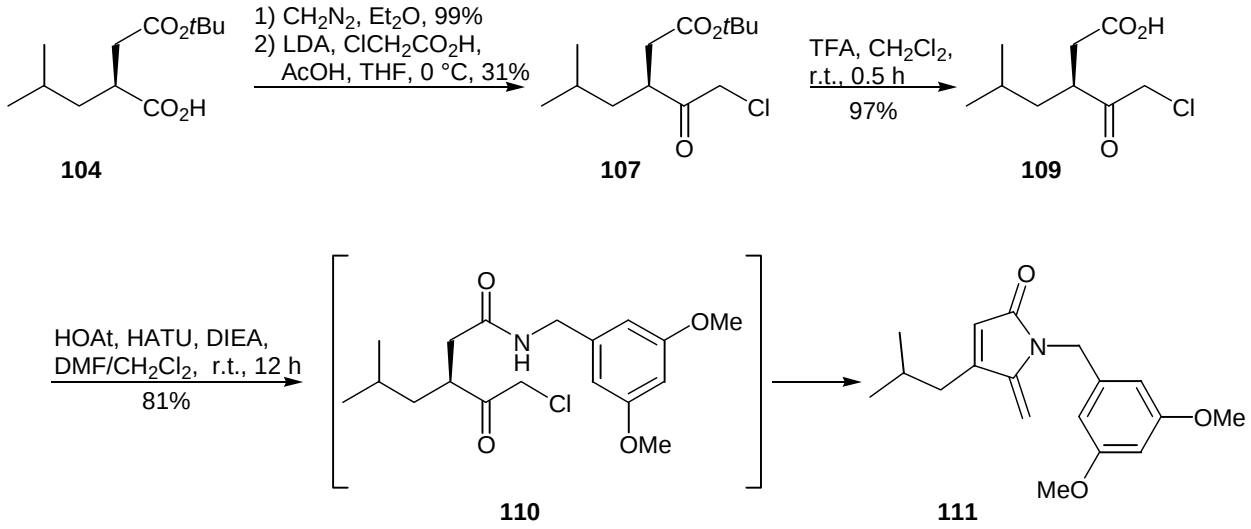
Further notification of the obtained acid **104** towards 5-chloro-3-keto ester **107** might performed by acylation of diazomethane with subsequent substitution of the diazo group for chloride atom. Thus, the starting acid **104** was converted into mixed anhydride **105** as has been previously described[43]. But the obtained anhydride **105** turned out to be not electrophilic enough to acylate the diazomethane (see Scheme 3.2). On the other hand, any attempts to prepare the respective acid chloride **108** have been also failed because of presence of the acid-labile *t*Bu-ester moiety.



Scheme 3.2. Attempted synthesis of chloro ketone **107** by a diazo compound **106**.

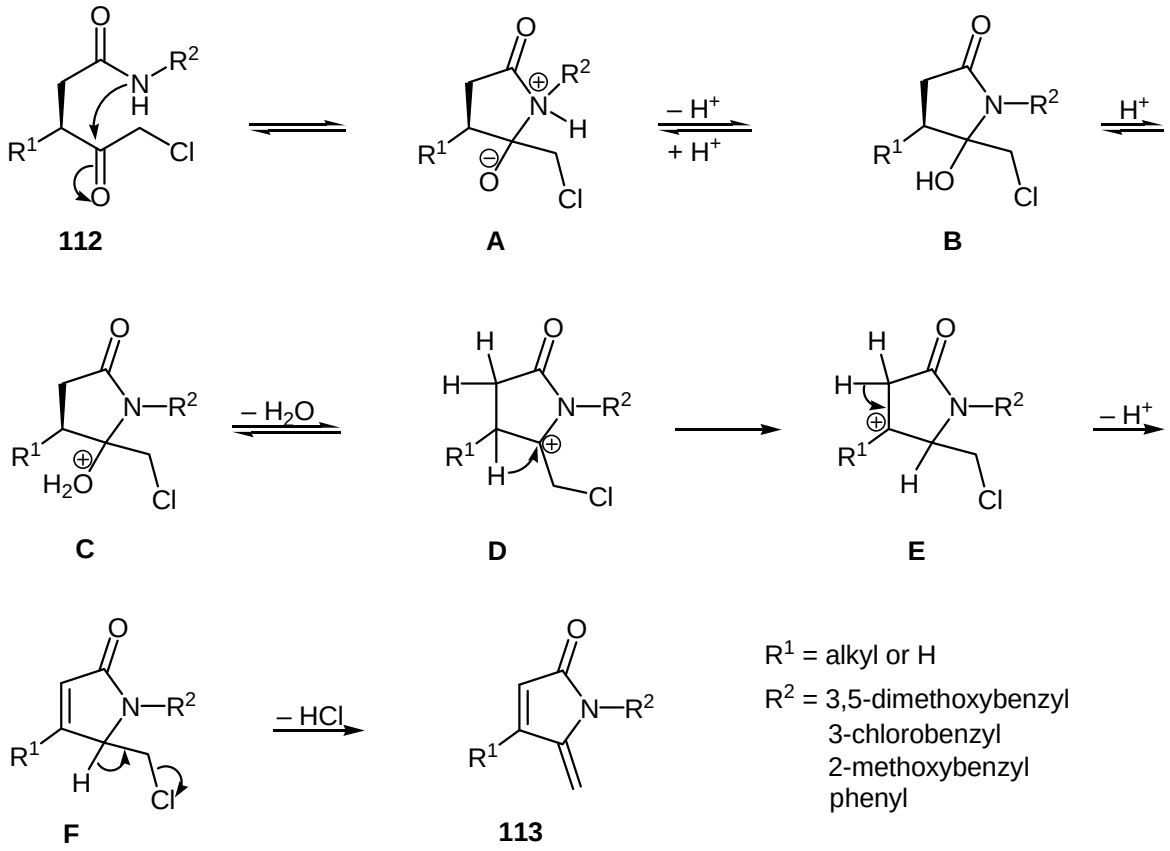
The reaction of esters with chloroacetic acid, so-called Claisen reaction, was an alternative possibility to obtain chloro ketones.[44] Thus, the acid **104** was converted into methyl ester by treatment with diazomethane and after the Claisen condensation with chloroacetic acid in the presence of 3.5 equiv. LDA, (*S*)-*tert*-butyl 3-(2-chloroacetyl)-5-methylhexanoate **107** was obtained (see Scheme 3.3) in moderate yield (31%), probably because of leak in chemoselectivity of the last step.

The *tert*-butyl ester group of ester **107** was removed by treatment with trifluoroacetic acid to give acid **109** which was then coupled with 3,5-dimethoxybenzyl amine **55** under standard conditions affording desired amide **110** in good yield (81%) (see Scheme 3.3). The product, however, proved to be not stable and at ambient temperature even in solution, within 1 h was completely converted into cyclic amide **111**. Without solvent this transformation required longer exposition at ambient temperature (2 h) and resulted significantly contradicted product. There are no examples of such reaction pattern in the literature.



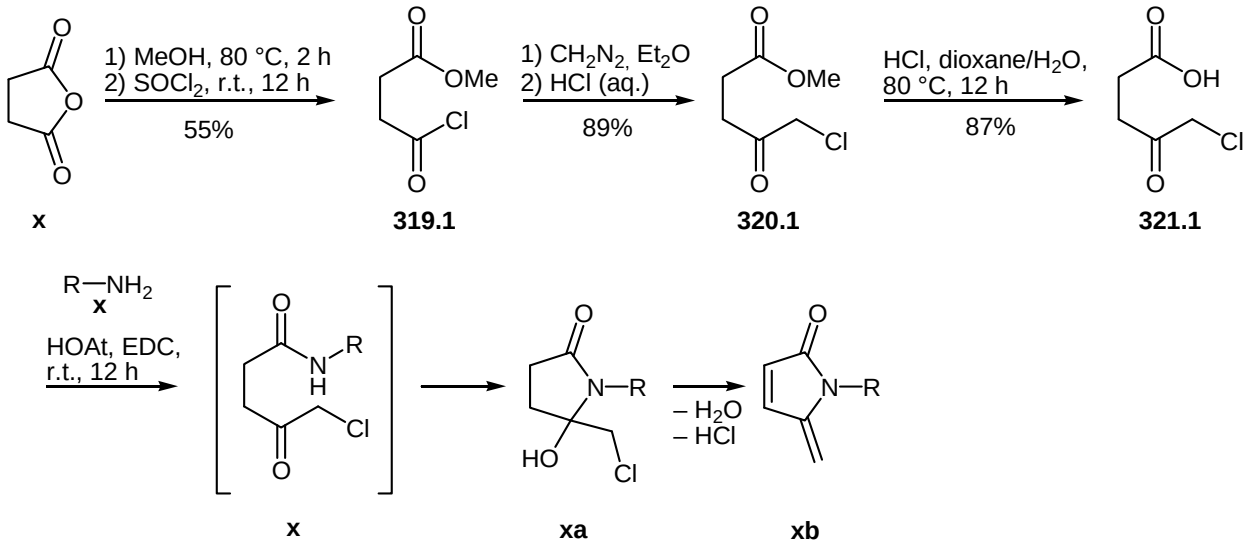
Scheme 3.3. Attempted synthesis of 5-chloro-3-keto amide **110**.

For the conversion of amide **110** into cyclic amide **111** the following mechanism can be proposed (see Scheme 3.4). Intramoleculare nucleophyl attack of carbonyl moiety with nitrogen atom of the amide residue of 5-chloro-3-keto amine **112** affords the pyrrolidinone **B**. Following protonation of hydroxy group causes the elimination of water and formation of cation **D**. 1,2-Hydride shift proceeds irreversiblely and gives after the proton loss unstable intermediate **F**, which converts into pyrrole **113** by a hydrochloric acid elimination. It can be supported that the motion force of this transformation is a formation of the conjugated electron system.



Scheme 3.4. Assumed mechanism of the conversion of amides **112** into pyrroles **113**.

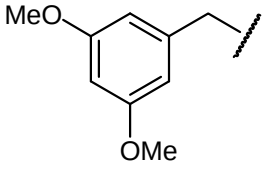
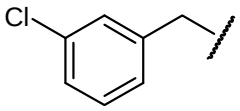
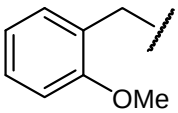
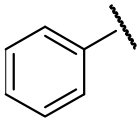
New cyclization of 5-chloro-3-keto amides was also confirmed in the simplest case (see Scheme 3.5). 4-Chloro-4-oxobutanoate[45] **115** prepared from succinic acid anhydride **114** in overall yield 55% as follows, according to the literature.[46] Chloroanhydride **115** was then treated with diazomethane to give diazocompound which was converted into the corresponding 5-chloro-3-keto ester **116** with hydrochloric acid. Acid **117** obtained after acidic hydrolysis of methyl ester **116** was coupled with four different amines: 3,5-dimethoxybenzylamine **55**, 3-chlorobenzylamine, 2-methoxybenzylamine and aniline (see Table 3.1).



Scheme 3.5. Synthesis of amides **119** and **120** (for details see Table 3.1).

In contrast to the case of 5-chloro-3-keto amide **110** there are no uncyclized amides **118** it was found among the reaction products, probably, because of 1,2-hydride shift in **110** occurs less readily due to statistic reason (in contrast to **118**, in **110** there is only one hydrogen in γ-position which is available for migration).

Table 3.1. Synthesis of the amides **119** and **120** (see Scheme 3.5).

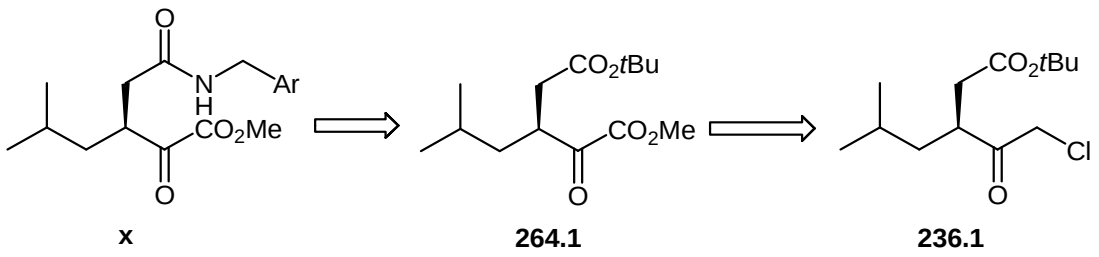
Entry			Yields (%)		
		R	**118**	**119**	**120**
1	**a**		–	58	24
2	**b**		–	52	47
3	**c**		–	–	12
4	**d**		–	52	44

In three reactions (Entry 1, 2 and 4, see Table 3.1) it was possible to isolate γ-lactams **119** with yields 52–58% but they are not stable at room temperature and quickly convert into pirrol-2-ones **120**. The yields of this conversion are not high, only 12–44% regarding to lactams **119** as a stating

material. As the pirrol-2-ones **120** were not the goal of this investigation, the yields of this transformation are not optimized. But basing on the ^{1}H NMR spectra of **119** obtained for the same sample immediately after purification and after 2 h in solution of $CDCl_3$ at ambient temperature, it can be concluded that conversion of **119** into **120** in the solution proceeds in quantitative yield.

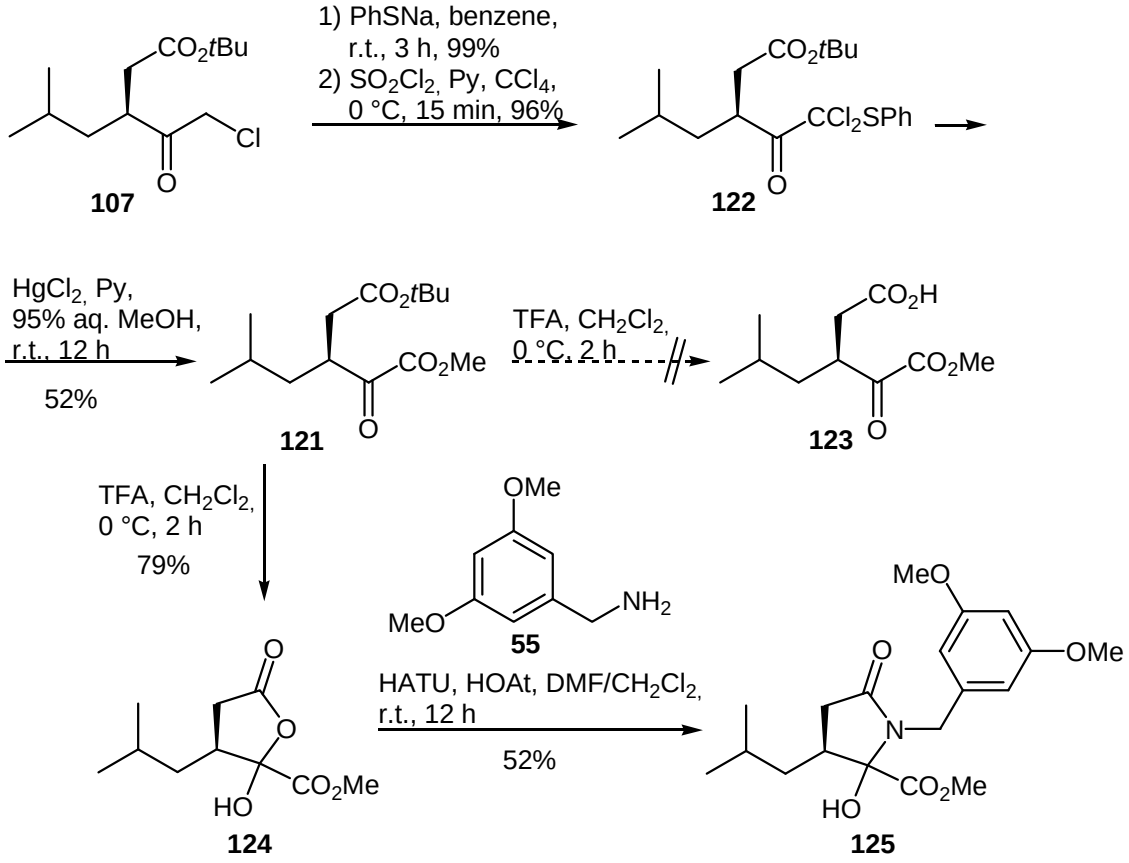
3.3. Attempted Synthesis of 5-Carboxy-3-keto Amide **94**

5-Chloro-3-keto ester **107** is a convenient building block for synthesis of 5-carboxy-3-keto amide **94**.



Scheme 3.6. Retrosynthesis of the amide **94**.

Retrosynthetically amide **94** can be conceded as a respective ester **121** which is modified derivative of 5-chloro-3-keto ester **107**.



Scheme 3.7. Synthesis of amide **125**.

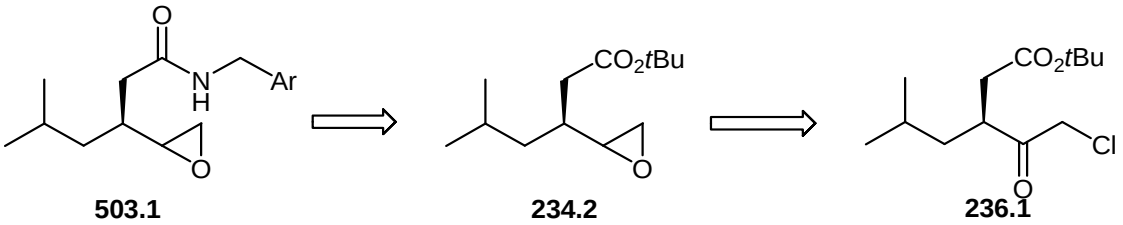
According to the method described by Fortes et al.[26] the chloromethyl group of the **107** was oxidized to methyl ester **121** as follows (see Scheme 2.5). Oxidation of the thiophenyl derivative with sulfuryl chloride and its subsequent alcoholysis afforded (*S*)-5-*tert*-butyl 1-methyl 3-isobutyl-2-oxopentanedioate **121** in 49% overall yield. However, the cleavage of the *tert*-butyl ester did not

liberate the required acid **123**, affording instead of that **(**3*S*)-methyl 2-hydroxy-3-isobutyl-5-oxotetrahydrofuran-2-carboxylate **124** in good yield (79%). Following water elimination as in the case of 5-chloro-3-keto amide **110** (see mechanism in Scheme 3.4) is not possible here while acceptor character of ester group prevent the adjacent cation **D**.

Since the required acid **123** was found to exist exclusively as its tetrahydrofurane tautomer **124**, it was decided to subject the latter to the reaction with amine **55**. Indeed, the reaction took place, giving the corresponding pirrolidinone **125** in moderate yield (52%), biological activity of which is currently screened.

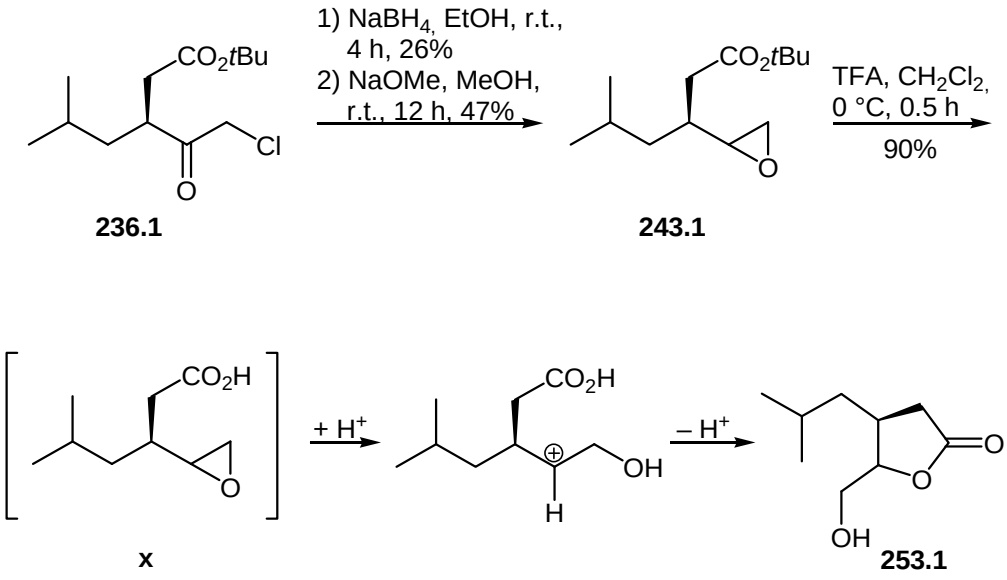
3.4. Attempted Synthesis of β-Epoxyethyl Amide **95**

5-Chloro-3-keto ester **107** can be considered to be a starting material for the synthesis of β-epoxyethyl amide **95**.



Scheme 3.8. Retrosynthetical synthesis of amide **95**.

Retrosynthetically epoxyamide **95** can be represented as β-epoxyethane ester **126** which can be easily prepared from ester **107** (see Scheme 3.8).

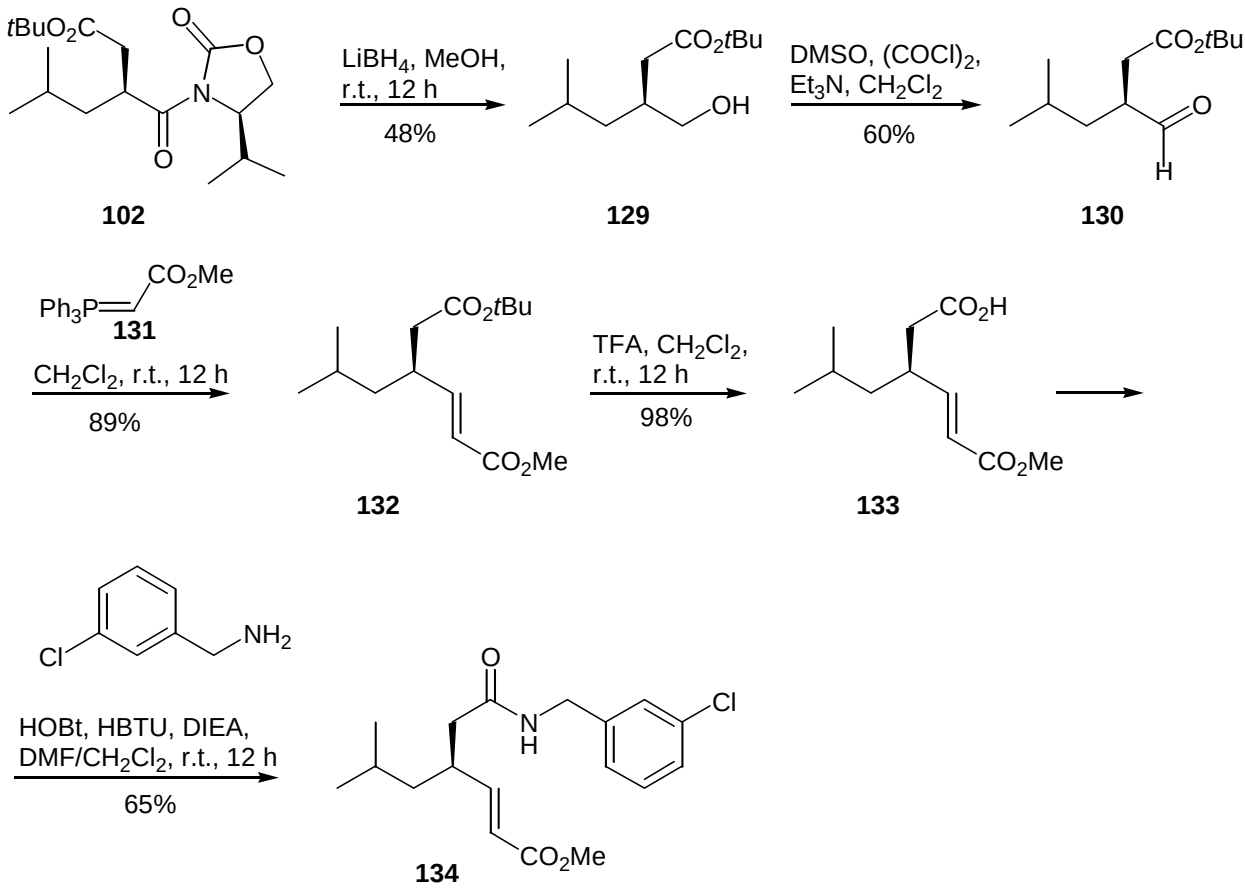


Scheme 3.9. Attempted synthesis of β-epoxyethyl amide **95**.

Chloroketone moiety of **107** was converted into the epoxide group by reduction of keto group with $NaBH_4$ and subsequent cyclization of the formed chlorohydrine in the presence of sodium methylate[47] (see Scheme 3.9). And again, during the cleavage of *tert*-butyl ester group of **126,** the epoxy group has intramolecular captured the liberating carboxylate function, affording instead of the expected acid **127**, γ-lactone **128**.

3.5. Synthesis of 4,5-Unsaturated Amide **96**

For the synthesis of amide **96** the strategy based on reduction-oxidation sequence applied to the amide **102** followed by Wittig olefination as the key step (see Scheme 3.10).

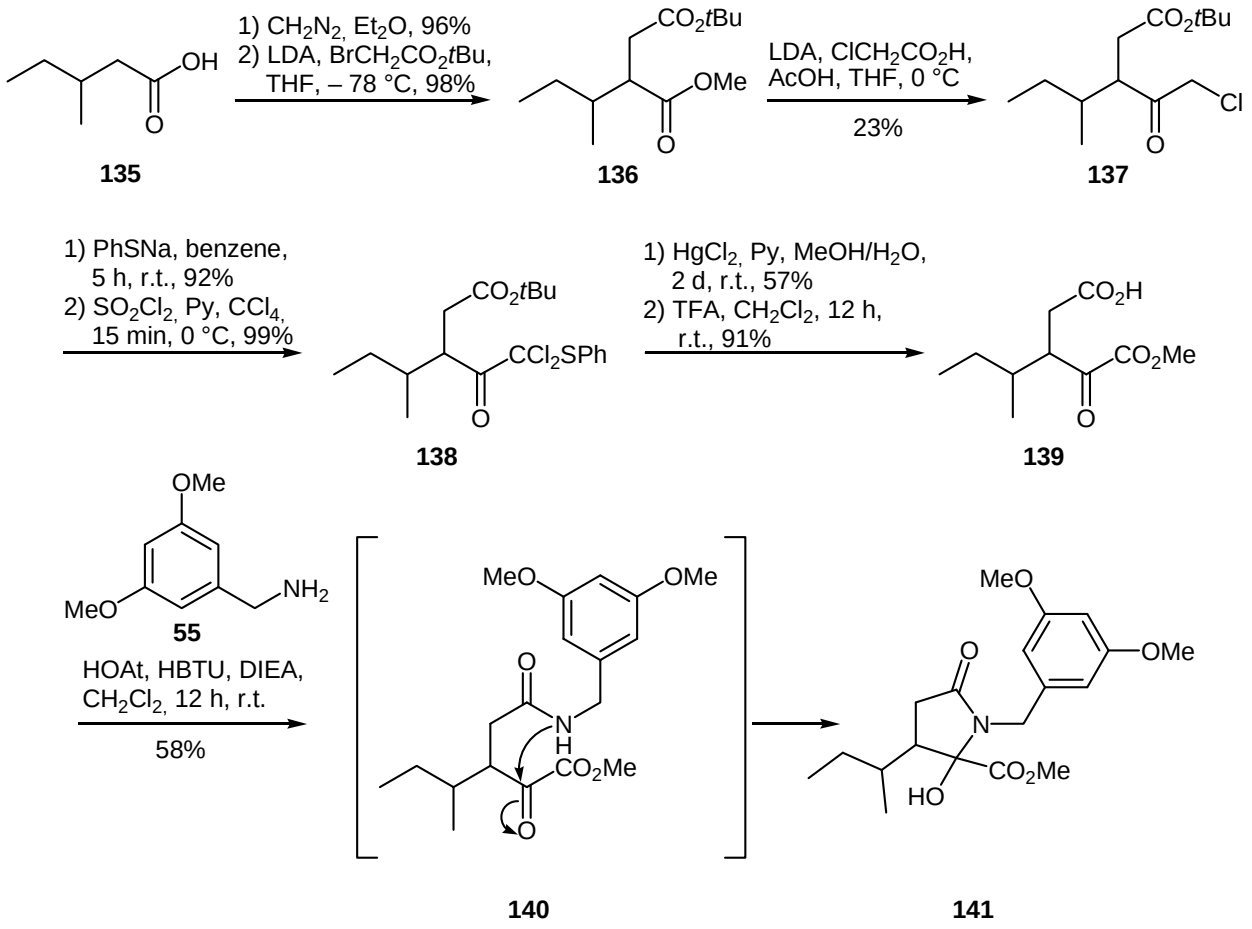


Scheme 3.10. Synthesis of 4,5-unsaturated amide **134**.

Thus, amide **102** was reduced into alcohol **129** with lithium borhydride according to Martin et al.[43] resulting in the required alcohol in moderate yield (48%). The decrease of the yield of alcohol **129** apparently caused by lactone formation under the reaction conditions. The following Swern oxidation[48] of alcohol **129** gave aldehyde **130** in good yield (60%). The latter was coupled with Wittig reagent **131** under standard conditions to give (*S*,*E*)-6-*tert*-butyl 1-methyl 4-isobutylhex-2-enedioate **132** in 89% yield. The following cleavage of *tert*-butyl ester in this case proceeded smoothly, and without any complications afforded desired acid **133** in excellent yield (98%). The latter was finally coupled with 3-chlorobenzylamine to give (*S*,*E*)-methyl 4-(2-(3-chlorobenzylamino)-2-oxoethyl)-6-methylhept-2-enoate **134** in good yield (65%).

3.6. Attempted Synthesis of 5-Carboxy-3-keto Amide **97**

Taking in consideration the previous results regarding stability of the target amides (**110, 94, 95)**, formation of a pyrrolidine derivative was anticipated. Therefore, it was decided to synthesize first racemic product with aim to decrease the quantity of steps of the whole synthesis.



Scheme 3.11. Attempted synthesis of the amide **140**.

The starting 3-methylpentanoic acid **135** was quantitatively converted into methyl ester by treatment with diazomethane, and than alkylated with *tert*-butyl bromacetate with the good overall yield (94%) (see Scheme 3.11). The Claisen reaction of the ester **136** proceeded in this case with lower yield (23%) compared to the ester of acid **104** (31%) (see Scheme 3.3), respectively. The chloro moiety of the obtained 5-chloro-3-keto ester **137** was substituted for thiophenyl residue, the methylene group was oxidized with sulfuryl chloride to afford dichlorothiophenyl derivative **138** which was subjected the mercury-catalyzed alcoholysis. Subsequent acidic hydrolysis of the *tert*-butyl ester gave acid **139**. The latter was coupled with 3,5-dimethoxybenzyl amine **55** under standard conditions, giving in good yield (58%) pyrrolidine **141**, as it was predicted on basic consideration of the previous synthetic efforts.

C Experimental Part

1. General Notes

IR: Bruker IFS 66 (FT-IR) spectrophotometer, measured as KBr pellets or oils between KBr plates. – NMR spectra were recorded on a Varian UNITY-200 (200 MHz for ^{1}H and 50.3 MHz for ^{13}C NMR), Varian Mercury-200 (200 MHz for ^{1}H and 50.3 MHz for ^{13}C NMR), a Bruker AM 250 (250 MHz for ^{1}H and 62.9 MHz for ^{13}C NMR), a Varian UNITY-300 (300 MHz for ^{1}H and 75.5 MHz for ^{13}C NMR) or a Varian Inova 500 (500 MHz for ^{1}H and 125.7 MHz for ^{13}C NMR) instruments in $CHCl_3$ if not otherwise specified. Multiplicities were determined by APT (Attached Proton Test), DEPT (Distortionless Enhancement by Polarization Transfer) or HSQC (Heteronuclear Single Quantum Coherence) measurements. Chemical shifts are reported in ppm relative to residual peaks of the deuterated solvent: δ = 2.50 ppm for $[D_6]$-DMSO, 5.98 for $[D_2]$-1,1,2,2-Tetrachlorethan, 7.26 for $[D_1]$-$CDCl_3$. The signals were characterized: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, dd = double of doublets, ddd = double of dd, dt = double of triplets, m = multiplet. Abbreviations: cPr-H = cyclopropyl proton, cHex-H = cyclohexyl proton, Ph-H = phenyl proton, Ar-H = aromatic proton, * = the assignment is exchangeable. The signals were characterized: + = primary or tertiary (positive DEPT-signal), – = secondary (negative DEPT-signal), Cquat = quaternary carbon atom (zero DEPT-signal) or + = primary or tertiary (positive APT-signal), – = secondary or quaternary carbon atom (negative APT-signal). Abbreviations: cPr-C = cyclopropyl carbon, cHex-C = cyclohexyl carbon, Ph-C = phenyl carbon, Ar-C = aromatic carbon, * = the assignment is exchangeable. – MS (EI at 70 eV) or DCI (with NH_3 or HCOOH): Finnigan MAT 95 spectrometer. High resolution mass data (HRMS) were obtained by preselected-ion peak matching at *R* ca. 10000 to be within ± 2 ppm of the exact mass, ESI: APEX IV 7T FTICR Brucker Daltonic. – Melting points: Büchi 510 capillary melting point apparatus, uncorrected values. – TLC: Macherey-Nagel precoated sheets, 0.25 mm Sil G/UV_{254}, developed with molybdenum phosphoric acid solution (10% in ethanol), ninhydrine (300 mg ninhydrine, 3.00 g acetic acid, 100 mL *n*-butanol) or iodine. – Column chromatography: Merck silica gel, grad 60, 230-400 mesh. – Element analyses: Mikroanalytisches Laboratorium des Instituts für Organische und Biomoleculare Chemie der Universität Göttingen, Germany. – Solvents were dried and purified according to conventional laboratory methods under Argon atmosphere. – All chemicals were used as commercially available, unless otherwise noted. – Abbreviations: Ac = acetate, Ar = aryl, HOAt = 7-aza-1-hydroxybenzotriazole, Bn = benzyl, Boc = *tert*-butoxycarbonyl, *t*Bu = *tert*-butyl, Bz = benzoyl, *m*CPBA = *meta*-chlorperbenzoic acid, cHex = cyclohexyl, DMAP = N,N-dimethylaminopyridine, DMF = dimethylformamide, Et = ethyl, Me = methyl, MeCN = acetonirtile, Ph = phenyl, THF = tetrahydrofurane, HATU = 1-[bis(dimethylamino)methylen]-1H-

1,2,3-triazo[4,5-b]pyridinium-3-oxidhexafluorphosphat, EDC = 1-(2-dimethylaminopropyl)-3-ethylcarbodiimid, HOBt = 1-hydroxybenyotriayol, NMM = *N*-methylmorpholine. The following substances were prepared according to literature procedures: benzylisonitrile[49], phenylisonitrile[50], HOAt[51].

2. Procedures for the Synthesis and Spectral Data of the Compounds

2.1. Synthesis of Compounds in Chapter 1

General Procedure for the Preparation of Amines (GP 1.1)

To a stirred solution of respective nitrile (20 mmol) and Ti(O*i*Pr)$_4$ (22 mmol) in anhydrous Et_2O (20 mL) a solution of the respective Grignard reagent in Et_2O (40 mmol) was added dropwise within 30 min at ambient temperature., After stirring for 30 min, a solution of boron trifluoride etherate (40 mmol, 48% in Et_2O) was added dropwise within 30 min. After stirring for an additional 15 min, the reaction mixture was cooled to 0 °C, and a 10% aq. solution of NaOH (50 mL) was added dropwise within 15 min. The obtained suspension was extracted with Et_2O (3 × 40 mL), the combined organic phases were dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by distillation or crystallization or *via* hydrochloride.

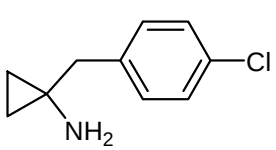
General Procedure for the Preparation of *N*-Formamides (GP 1.2)

A mixture of respective amine (3.0 mmol) and ethyl orthofomate (12.6 mmol) was heated under reflux for the indicated time. The excess of ethyl orthofomate was removed *in vacuo*, the solid residue was filtered off and washed with Et_2O or purified by column chromatography on silica gel.

General Procedure for the Preparation of Isonitriles (GP 1.3)

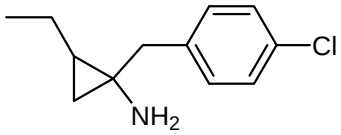
To a stirred solution of respective *N*-formamide (9.1 mmol) and triethylamine (2.8 mmol) in anhydrous toluene (20 mL) a solution of phosgene (9.1 mmol, 20% in toluene) was added dropwise within 10 min at 0 °C. After heating at 40 °C for 30 min and stirring at ambient temperature for an additional 4 h, the solid $Et_3N{\cdot}HCl$ was filtered off and washed with toluene (10 mL). The residue, obtained after concentration of the filtrate under reduced pressure, was purified by distillation, filtration through a pad of silica gel or column chromatography on silica gel.

1-(4-Chlorobenzyl)cyclopropylamine (8a): Distillation on Kugelrohr (100–120 °C, 0.005 Torr) of the residue, obtained from ethylmagnesium bromide (27.0 mL, 40.0 mmol, 1.5 M in Et_2O), 4-chlorobenzyl cyanide (2.57 mL, 20.0 mmol), Ti(O*i*Pr)$_4$ (6.58 mL, 22.0 mmol) and boron trifluoride etherate (5.10 mL, 40.0 mmol,



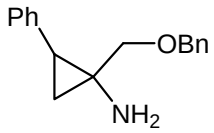
48% in Et_2O) according to the GP 1.1, gave pure amine **8a** (1.72 g, 47%) as a pale yellow oil. – IR (film): ν = 3366, 3281, 3083, 3003, 2965, 2916, 2853, 1595, 1491, 1091, 1016 cm^{-1}. – ^1H NMR (250 MHz, $CDCl_3$): δ = 0.50–0.70 (m, 2 H, *c*Pr-H), 0.80–0.90 (m, 1 H, *c*Pr-H), 1.20–1.40 (m, 3 H, *c*Pr-H, NH_2), 2.65 (s, 2 H, CH_2Ph), 7.10–7.30 (m, 4 H, Ph-H). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.1 (*c*Pr-CH_2), 34.7 (C, *c*Pr-C), 45.7 (CH_2), 128.1, 128.5, 131.8, 137.9 (6 C, Ph-C). – MS (DCI): *m/z* (%) 201/199 (9/44) [M + NH_4^+], 184/182 (17/55) [M + H^+]. – HRMS-DCI: *m/z* calcd for $C_{10}H_{13}ClN$ [M + H^+]: 182.0737; found: 182.0731. – Anal. Calcd for $C_{10}H_{12}ClN$: C, 66.12; H, 6.66; N, 7.71. Found: C, 66.16; H, 6.93; N, 7.48.

1-(4-Chlorobenzyl)-2-ethylcyclopropylamine (8b): To the solution of the residue, obtained from



butylmagnesium bromide (70 mL, 109 mmol, 1.55 M in Et_2O), 4-chlorobenzyl cyanide (7.0 mL, 54.5 mmol), Ti(O*i*Pr)$_4$ (18.0 mL, 60.0 mmol) and boron trifluoride etherate (13.8 mL, 109 mmol, 48% in Et_2O) according to the GP 1.1, aq. HCl (20 mL, 5 N) was added, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL), then the aqueous layer was basified with aq. NaOH (30 mL, 5 N) and extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers from the last extraction were dried over Na_2SO_4 and the solution concentrated under reduced pressure to give the amine **8b** (6.47 g, 57%) as pale yellow oil. – IR (film): ν = 3369, 3067, 2990, 2959, 2929, 2871, 1898, 1596, 1491, 1092, 1016 cm^{-1}. – ^1H NMR (200 MHz, 2 diastereomers, $CDCl_3$): δ = 0.00–0.10 (m, 2 H, *c*Pr-H), 0.40–1.50 (m, 18 H, CH_2CH_3, *c*Pr-H, NH_2), 2.30–2.70 (m, 4 H, CH_2), 6.90–7.20 (m, 8 H, Ph-H). – ^{13}C NMR (75.5 MHz, APT, 2 diastereomers, $CDCl_3$): δ = 14.2, 14.4 (+, *c*Pr-CH), 19.2, 20.4 (–, *c*Pr-CH_2), 21.7, 23.4 (–, *C*H_2CH$_3$), 26.8, 28.3 (+, CH_2*C*H_3), 38.2, 38.5 (–, *c*Pr-C_{quat}), 40.9, 47.3 (–, *C*H_2Ph), 128.4, 128.5 (+, Ph-C), 130.5, 130.6 (+, Ph-C), 2 × 132.1 (–, Ph-C_{quat}), 2 × 138.1 (–, Ph-C_{quat}). – MS (EI): *m/z* (%) 211/209 (<1/2) [M^+], 182/180 (32/100), 127/125 (10/31).

1-Benzyloxymethyl-2-phenylcyclopropylamine (8c): The solid residue, obtained from 2-



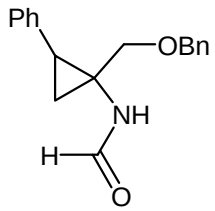
phenylethylmagnesium bromide (51 mL, 51 mmol, 1.00 M in Et_2O), benzyloxyacetonitrile (3.70 g, 25.2 mmol), Ti(O*i*Pr)$_4$ (8.3 mL, 28 mmol) and boron trifluoride etherate (6.40 mL, 50.4 mmol, 48% in Et_2O) according to the GP 1.1, was filtered off and washed with Et_2O/hexane (1:1, 20 mL) to yield **8c** (1.94 g, 30%) as a yellow solid, m.p. 95–97 °C. – IR (KBr): ν = 3431, 3023, 2853, 2683, 2589, 1495, 1453, 1095, 733, 689 cm^{-1}. – ^1H NMR (250 MHz, $CDCl_3$): δ = 1.26 (t, 1 H, *J* = 7.3 Hz, *c*Pr-H), 1.94 (dd, 1 H, *J* = 7.0 Hz, *J* = 10.0 Hz, *c*Pr-H), 3.14 (dd, 1 H, *J* = 7.5 Hz, *J* = 10.0 Hz, *c*Pr-H), 3.33 (d, 1 H, *J* = 11.0 Hz, CH_2), 3.40 (d, 1 H, *J* = 11.0 Hz, CH_2), 4.37 (d, 1 H, *J* = 12.0 Hz, CH_2), 4.45 (d, 1 H, *J* = 12.0 Hz, CH_2), 7.10–7.30 (m, 10 H, Ph-H), 8.69 (br s, 2 H, NH_2). – ^{13}C NMR (50.3 MHz, APT, $CDCl_3$): δ =

13.1 (–, *c*Pr-CH_2), 26.1 (+, *c*Pr-CH), 39.4 (–, *c*Pr-C_{quat}), 68.9, 73.1 (–, CH_2), 127.1, 127.5, 128.3, 128.4, 128.5, 129.2 (+, 10 C, Ph-C), 134.6, 137.3 (–, Ph-C_{quat}). – MS (EI): *m/z* (%) 253 (5) [M^+], 162 (12), 144 (9), 132 (27), 105 (16), 91 (100), 77 (12). – HRMS-EI: *m/z* calcd for $C_{17}H_{20}NO$ [M + H^+]: 254.1545; found: 254.1539.

***N*-[1-(4-Chlorobenzyl)cyclopropyl]formamide (9a):** Formamide **9a** (611 mg, 97%) was obtained according to GP 1.2 (reflux for 6 h) from amine **8a** (545 mg, 3.00 mmol) and ethyl orthoformate (2.1 mL, 12.6 mmol) as a colorless solid, m.p. 70–71 °C. – IR (film): ν = 3435, 3314, 2873, 1662, 1522, 1490, 1014, 533 cm^{-1}. – ^{1}H NMR (200 MHz, 2 tautomers, $CDCl_3$): δ = 0.75–0.95 (m, 8 H, *c*Pr-CH_2), 2.75 (s, 2 H, CH_2Ph), 2.88 (s, 2 H, CH_2Ph) 5.80 (br s, 1 H, N*H*CHO), 6.10 (d, 1 H, *J* = 12.5 Hz, N*H*CHO), 7.10–7.35 (m, 8 H, Ph-H), 7.85 (d, 1 H, *J* = 12.7 Hz, NHC*H*O), 7.98 (d, 1 H, *J* = 2.0 Hz, NHC*H*O). – ^{13}C NMR (50.3 MHz, 2 tautomers, $CDCl_3$): δ = 12.8, 13.2 (*c*Pr-CH_2), 33.3, 34.8 (*c*Pr-C_{quat}), 40.5, 44.3 (CH_2), 128.5, 128.8, 130.6, 130.8 (Ph-CH), 132.4, 132.9, 135.8, 137.2 (Ph-C_{quat}), 161.5, 165.9 (NHCHO). – MS (EI): *m/z* (%) 211/209 (10/28) [M^+], 166/164 (14/23), 129 (88), 127/125 (21/45), 56 (100). – Anal. Calcd for $C_{11}H_{12}ClNO$: C, 63.01; H, 5.77; N, 6.68. Found: C, 62.95; H, 5.51; N, 6.79.

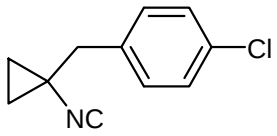
***N*-[1-(4-Chlorobenzyl)-2-ethylcyclopropyl]formamide (9b):** Formamide **9b** (4.68 g, 64%) was obtained according to the GP 1.2 (reflux for 48 h) from amine **8b** (6.47 g, 30.9 mmol) and ethyl orthoformate (15.0 mL, 90 mmol) as a colorless solid, m.p. 61–62 °C. – IR (KBr): ν = 3293, 3072, 3006, 2961, 2873, 2760, 1662, 1529, 1492, 1390, 1091 cm^{-1}. – ^{1}H NMR (250 MHz, 2 diastereomers, 2 tautomers, $CDCl_3$): δ = 0.04–0.06 (m, 4 H, *c*Pr-CH), 0.80–1.90 (m, 28 H, CH_2CH_3, *c*Pr-CH_2), 2.60–3.25 (m, 8 H, CH_2Ph), 5.35–5.95 (m, 4 H, N*H*CHO), 7.00–7.20 (m, 16 H, Ph-H), 7.80–8.10 (m, 4 H, NHC*H*O). – ^{13}C NMR (75.5 MHz, APT, 2 diastereomers, 2 tautomers, $CDCl_3$): δ = 13.69, 13.73, 13.83, 13.91 (+, CH_2CH_3), 18.53, 18.56, 18.76, 19.08, 21.93, 21.98, 22.83, 23.03 (–, *c*Pr-CH_2, CH_2CH_3), 25.42, 26.07, 27.72, 28.30 (+, *c*Pr-CH), 35.97, 37.03, 37.77, 38.30, 38.83, 39.82, 41.52, 45.75 (–, *c*Pr-C_{quat}, CH_2Ph), 128.46, 128.49, 128.80, 128.84, 130.58, 130.62, 130.71, 130.85 (+, 16 C, Ph-CH), 132.19, 132.32,132.75, 132.86, 135.93, 136.01, 137.37, 137.63 (–, 8 C, Ph-C_{quat}), 161.10, 161.84, 165.93, 166.52 (+, 4 C, NCHO). – MS (EI): *m/z* (%) 239/237 (14/52) [M^+], 210/208 (26/65), 165/163 (16/39), 127/125 (33/100), 116 (82), 91/98 (19/62), 84 (42). – Anal. Calcd for $C_{13}H_{16}ClNO$: C, 65.68; H, 6.78; N, 5.89. Found: C, 65.42; H, 6.55; N, 5.96.

***N*-(1-Benzyloxymethyl-2-phenylcyclopropyl)formamide (9c):** Column chromatography



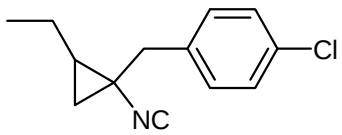
(EtOAc/hexane, 1:2) of the residue, obtained from **8c** (1.86 g, 7.34 mmol) and ethyl orthoformate (3.6 mL, 22.0 mmol) according to the GP 1.2 (reflux for 5 h), gave pure **9c** (1.26 g, 61%, R_f = 0.17) as yellow oil. – IR (film): ν = 3276, 3061, 3027, 2860, 1659, 1495, 1295, 1098, 738, 698 cm^{-1}. – ^1H NMR (250 MHz, 2 tautomers, $CDCl_3$): δ = 1.35 (dd, 4 H, *J* = 6.3 Hz, *J* = 14.6 Hz, *c*Pr-CH_2), 2.54 (dd, 2 H, *J* = 7.3 Hz, *J* = 15.8 Hz, *c*Pr-CH), 3.07 (d, 1 H, *J* =10.3 Hz, CH_2), 3.14 (d, 1 H, *J* =10.3 Hz, CH_2), 3.26 (d, 1 H, *J* = 10.3 Hz, CH_2), 3.46 (d, 1 H, *J* =10.3 Hz, CH_2), 4.21 (d, 1 H, *J* = 12.0 Hz, CH_2), 4.23 (d, 1 H, *J* = 12.0 Hz, CH_2), 4.32 (d, 1 H, *J* = 12.0 Hz, CH_2), 4.34 (d, 1 H, *J* = 12.0 Hz, CH_2), 6.27 (br s, 2 H, NH), 7.00–7.20 (m, 20 H, Ph-H), 8.14 (d, 1 H, *J* = 1.3 Hz, CHO), 8.46 (d, 1 H, *J* = 11.8 Hz, CHO). – ^{13}C NMR (75.5 MHz, APT, 2 tautomers, $CDCl_3$): δ = 15.4, 16.5 (–, *c*Pr-CH_2), 29.8, 30.0 (+, *c*Pr-CH), 37.3, 39.1 (–, *c*Pr-C_{quat}), 71.5, 72.4, 73.0, 73.1 (–, CH_2), 126.7, 127.0, 127.3, 127.5, 127.7, 127.8, 128.2, 128.3, 128.4, 128.6, 129.0, 129.1 (+, 20 C, Ph-CH), 135.7, 136.6, 137.7, 137.9 (–, Ph-C_{quat}), 161.6, 166.7 (+, CHO). – MS (EI): *m/z* (%) 281 (<1) [M^+], 197 (15), 173 (34), 172 (33), 128 (29), 105 (26), 91 (100), 77 (22). – HRMS-EI: *m/z* calcd for $C_{18}H_{20}NO_2$ [M + H^+]: 282.1494; found: 282.1489.

1-(4-Chlorobenzyl)cyclopropylisonitrile (10a): Distillation on Kugelrohr (80–100 °C, 0.005 Torr)



of the residue, obtained from **9a** (1.00 g, 4.77 mmol), triethylamine (1.3 mL, 9.33 mmol) and phosgene (2.3 mL, 4.79 mmol, 20% in toluene) according to the GP 1.3, gave pure **10a** (651 mg, 71%) as a colorless oil, which turned brown immediately. – IR (film): ν = 3358, 2972, 2928, 2861, 2133, 1653, 1491, 1256, 1093, 1016, 738 cm^{-1}. – ^1H NMR (250 MHz, $CDCl_3$): δ = 0.84–0.95 (m, 2 H, *c*Pr-H), 1.10–1.20 (m, 2 H, *c*Pr-H), 2.88 (s, 2 H, CH_2), 7.20–7.40 (m, 4 H, Ar). – ^{13}C NMR (75.5 MHz, $CDCl_3$): δ = 14.4 (*c*Pr-CH_2), 34.5 (*c*Pr-C_{quat}), 41.2 (CH_2), 128.7, 130.5, 133.2, 134.7 (6 C, Ph-C), 153.3 (NC). – MS (EI): *m/z* (%) 193/191 (<1/2) [M^+], 153/151 (9/29), 116 (100). – HRMS-EI: *m/z* [M^+] calcd for $C_{11}H_{10}ClN$: 191.0502; found: 191.0502. – Anal. Calcd for $C_{11}H_{10}ClN$: C, 68.94; H, 5.26; N, 7.31. Found: C, 68.84; H, 5.25; N, 7.14.

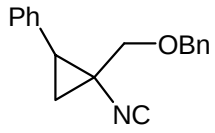
1-(4-Chlorobenzyl)-2-ethylcyclopropylisonitrile (10b): The residue, obtained from **9b** (2.17 g,



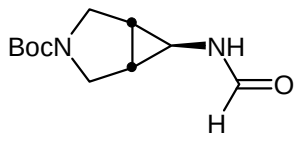
9.13 mmol), triethylamine (3.2 mL, 22.8 mmol) and phosgene (4.8 mL, 9.1 mmol, 20% in toluene) according to the GP 1.3, was filtered through a pad of silica gel (10 g), the filtrate was concentrated under reduced pressure to give **10b** (1.75 g, 88%) as a yellow oil, which turned brown immediately. – IR (film): ν = 2964, 2932, 2874, 2129, 1684, 1492, 1456, 1092, 1016 cm^{-1}. – ^1H NMR (250 MHz, 2

diastereomers, $CDCl_3$): δ = 0.58–0.64 (m, 1 H, *c*Pr-H), 0.80–0.90 (m, 1 H, *c*Pr-H), 0.95–1.15 (m, 7 H, CH_2CH_3, *c*Pr-H), 1.10–1.70 (m, 7 H, CH_2CH_3, *c*Pr-H), 2.68–3.06 (m, 4 H, CH_2Ph), 7.10–7.38 (m, 8 H, Ph-H). – ^{13}C NMR (62.9 MHz, 2 diastereomers, $CDCl_3$): δ = 12.9, 13.4 (*c*Pr-CH_2), 20.1, 20.4, 22.4, 22.7, 26.0, 28.9 (CH_2CH_3, *c*Pr-CH), 38.5 (CH_2), 38.4, 38.6 (*c*Pr-C_{quat}), 42.1 (CH_2), 128.5, 128.6, 130.2, 130.4 (8 C, Ph-C), 132.8, 132.9, 135.0, 135.2 (Ph-C_{quat}), 157.2, 157.3 (NC). – MS (EI): *m/z* (%) 221/219 (9/27) [M^+], 179/177 (9/35), 155/153 (12/42), 142 (82), 127/125 (30/100), 115 (64). – Anal. Calcd for $C_{13}H_{14}ClN$: C, 71.07; H, 6.42; N, 6.37. Found: C, 70.81; H, 6.29; N, 6.18.

1-Benzyloxymethyl-2-phenylcyclopropylisonitrile (10c): To the toluene solution of the residue, obtained from **9c** (1.16 g, 4.12 mmol), triethylamine (1.43 mL, 10.3 mmol) and a solution of phosgene (2.2 mL, 4.1 mmol, 20% in toluene) according to GP 1.3, water (30 mL) was added, and the reaction mixture was extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (2 × 10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to leave a black oil which was purified by column chromatography on silica gel (EtOAc/hexane, 1:2) to give compound **10c** (738 mg, 68 %, R_f = 0.69) as a colorless oil. – IR (film): ν = 3029, 2864, 2134, 1735, 1497, 1453, 1102, 740, 698 cm^{-1}. – ^1H NMR (250 MHz, $CDCl_3$): δ = 1.54 (dd, 1 H, *J* = 6.3 Hz, *J* = 7.8 Hz, *c*Pr-CH_2), 1.69 (dd, 1 H, *J* = 6.3 Hz, *J* =9.8 Hz, *c*Pr-CH_2), 2.89 (t, 1 H, *J* = 8.8 Hz, *c*Pr-CH), 3.27 (s, 2 H, CH_2O), 4.33 (d, 1 H, *J* = 12.3 Hz, CH_2Ph), 4.39 (d, 1 H, *J* = 12.3 Hz, CH_2Ph), 7.10–7.30 (m, 10 H, Ph-H). – ^{13}C NMR (75.5 MHz, APT, $CDCl_3$): δ = 17.2 (–, *c*Pr-CH_2), 31.0 (+, *c*Pr-CH), 39.5 (–, *c*Pr-C_{quat}), 69.7, 72.9 (–, CH_2), 127.4, 127.5, 127.7, 128.4, 128.5, 128.0 (+, 8 C, Ph-CH), 134.1, 137.4 (–, Ph-C_{quat}), 153.8 (–, NC). – MS (DCI): *m/z* (%) 263 (3) [M^+], 157 (25), 118 (18), 115 (14), 91 (100).



(1*S*,5*R*,6*S*)-*tert*-Butyl 6-Formamido-3-aza-bicyclo[3.1.0]hexane-3-carboxylate (12): A mixture of the amine **11** (396 mg, 2.00 mmol) and ethyl formate (5 mL, 62 mmol) was heated under reflux for 1 h. The excess of the ethyl formate was removed *in vacuo* to leave **12** (442 mg, 98 %) as a colorless solid, m.p. 168–170 °C. – IR (film): ν = 3291, 3056, 2977, 2935, 2877, 1695, 1426, 1394, 1174, 1122, 735 cm^{-1}. – ^1H NMR (250 MHz, 2 tautomers, $CDCl_3$): δ = 1.40 [s, 18 H, $C(CH_3)_3$], 1.65–1.82 [m, 4 H, CH(bicycle)], 2.45 (s, 2 H, CHN), 3.30–3.44 [m, 4 H, CH_2(bicycle)], 3.60–3.80 [d, 4 H, *J* = 11.1 Hz, CH_2(bicycle)], 6.16 (s, 1 H, NH), 6.35 (d, 1 H, *J* = 11.0 Hz, NH), 8.00–8.30 (m, 2 H, CHO). – ^{13}C NMR (62.9 MHz, 2 tautomers, $CDCl_3$): δ = 23.3, 24.8 [CH(bicycle)], 28.3, 28.4 [$C(CH_3)_3$], 31.2, 32.8 [CH(bicycle)], 47.3, 47.6 [CH_2(bicycle)], 79.7, 79.9 [$C(CH_3)_3$], 154.3, 154.4 (NCOO),



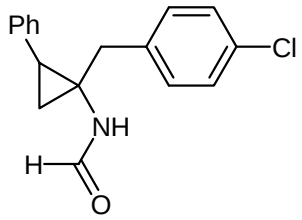
162.2, 166.4 (CHO). – MS (DCI): *m/z* (%) 470 (5) [2M + NH_4^+], 453 (5) [2M + H^+], 244 (100) [M + NH_4^+], 227 (59) [M + H^+], 188 (75).

(1*S*,5*R*,6*S*)-*tert*-Butyl 6-Isocyano-3-aza-bicyclo[3.1.0]hexane-3-carboxylate (13): Column chromatography (Et_2O/hexane, 1:1) of the residue, obtained from **12** (226 mg, 1.00 mmol), triethylamine (0.35 mL, 2.50 mmol) and phosgene (0.53 mL, 1.00 mmol, 20% in toluene) according to the GP 1.3, gave pure **7** (135 mg, 65%, R_f = 0.43) as a colorless solid, m.p. 51–52 °C. – IR (KBr): ν = 3447, 2982, 2941, 2878, 2145, 1697, 1415, 1394, 1113 cm^{-1}. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.39 [s, 9 H, $C(CH_3)_3$], 2.06 (s, 2 H, CH), 2.52 (t, 1 H, *J* = 2.4 Hz, CHNC), 3.33 (d, 2 H, *J* = 11.5 Hz, CH_2), 3.5–3.7 (m, 2 H, CH_2). – ^{13}C NMR (50.3 MHz, APT, $CDCl_3$): δ = 25.6 (+, CH), 26.3 (+, CH), 28.3 [+, $C(CH_3)_3$], 30.5 (+, *C*HNC), 46.8 (–, CH_2), 46.9 (–, CH_2), 80.1 [–, $C(CH_3)_3$], 154.2 (–, COO), 155.0 (–, NC). – MS (EI): *m/z* (%) 208 (3) [M^+], 153 (14), 135 (7), 57 (100). – HRMS-EI: *m/z* calcd for $C_{11}H_{16}N_2O_2$ [M^+]: 208.1212; found: 208.1212.

***N*-(1-Vinylcyclopropyl)formamide (19):** A mixture of the 1-vinylcyclopylamine hydrochloride **18** (359 mg, 3.00 mmol), ethyl formate (1.6 mL, 20 mmol) and triethylamine (0.42 mL, 3.00 mmol) was heated under reflux for 24 h. After cooling EtOAc (30 mL) was added, the reaction mixture was washed with brine (1 × 10 mL) and dried over Na_2SO_4. The solution was concentrated *in vacuo* to leave **19** (293 mg, 88 %) as a yellow oil. – ^{1}H NMR (250 MHz, 2 tautomers, $CDCl_3$): δ = 0.90–1.10 (m, 8 H, *c*Pr-H), 5.00–5.15 (m, 4 H, CH_2), 5.35–5.50 (m, 2 H, CH), 6.18 (bs, 1 H, NH), 6.45 (br s, 1 H, NH), 8.05–8.25 (m, 2 H, CHO). – ^{13}C NMR (62.9 MHz, 2 tautomers, $CDCl_3$): δ = 15.4, 16.2 (4 C, *c*Pr-CH_2), 33.4, 35.1 (*c*Pr-C_{quat}), 111.3, 112.4 (=CH_2), 139.1, 141.7 (=CH), 161.4, 167.1 (CHO).

1-(4-Chlorobenzyl)-2-phenylcyclopropylamine (22): Recrystallized from Et_2O of the residue, obtained from phenylmagnesium bromide (90.0 mL, 107 mmol, 1.185 M in Et_2O), 4-chlorobenzyl cyanide (6.87 mL, 53.5 mmol), Ti(O*i*Pr)$_4$ (17.6 mL, 58.9 mmol) and boron trifluoride etherate (13.6 mL, 107 mmol, 48% in Et_2O) according to the GP 1.1, gave **22** (4.67 g, 34%) as a pale yellow solid which turned brown on the air. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.40 (t, 1 H, *J* = 8.0 Hz, *c*Pr-CH_2), 1.70–1.85 (m, 1 H, *c*Pr-CH_2), 2.38 (d, 2 H, *J* = 17.0 Hz, CH_2), 2.90–3.15 (m, 3 H, CH_2, *c*Pr-CH), 7.05 (d, 2 H, *J* = 8.0 Hz, Ph-H), 7.18 (d, 2 H, *J* = 8.0 Hz, Ph-H), 7.25–7.40 (m, 5 H, Ph-H), 8.32 (bs, 2 H, NH_2). – ^{1}H NMR (62.9 MHz, $CDCl_3$): δ = 14.5, 26.8 (*c*Pr-CH_2), 36.2 (*c*Pr-CH), 40.7 (CH_2), 127.5, 128.7, 129.2, 129.3, 130.9, 133.1, 133.6, 134.6 (12 C, Ph-C).

***N*-[1-(4-Chlorobenzyl)-2-phenylcyclopropyl]formamide (23):** Formic acid (1.4 mL) was added

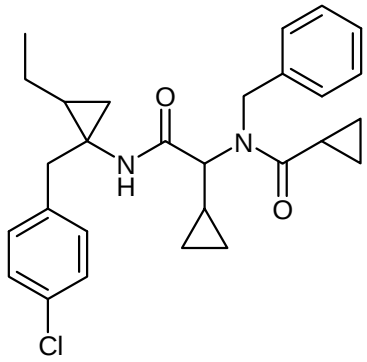


dropwise to cooled acetic anhydride (3.1 mL). The mixture was heated at 50 °C for 15 min, cooled to 0 °C and amine **22** (1.05 g, 4.08 mmol) was added. After overnight stirring at ambient temperature the mixture was poured into cold water (50 mL), made basic with 30% aq. solution of ammonia and extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was recrystallized from Et_2O/hexane (1:1) to give **23** (1.02 g, 87%) as a colorless solid. – ^{1}H NMR (250 MHz, 2 tautomers, $CDCl_3$): δ = 1.10–1.50 (m, 4 H, *c*Pr-CH_2), 1.95–2.10 (m, 2 H, CH_2, *c*Pr-CH), 2.31 (d, 1 H, *J* = 14.3 Hz, CH_2), 2.45–2.75 (m, 2 H, *c*Pr-CH, CH_2), 2.99 (d, 1 H, *J* = 14.3 Hz, CH), 5.78 (br s, 1 H, N*H*CHO), 6.12 (br s, 1 H, N*H*CHO), 6.70–7.50 (m, 18 H, Ph-H), 8.05 (d, 1 H, *J* = 7.9 Hz, NHC*H*O), 8.08 (d, 1 H, *J* = 0.8 Hz, NHC*H*O). – ^{13}C NMR (62.9 MHz, 2 tautomers, $CDCl_3$): δ = 30.6, 30.9 (4 C, *c*Pr-CH_2, *c*Pr-CH), 36.5, 38.5 (CH_2), 39.8, 40.2 (*c*Pr-C), 126.8, 128.2, 128.3, 128.4, 128.6, 128.7, 128.9, 129.2, 130.5, 130.8, 132.2, 135.5, 136.9, 137.3 (24 C, Ph-CH, Ph-C), 155.6, 161.3 (NHCHO).

General Procedure for the Preparation of Dipeptides 5a-l (GP 1.4)

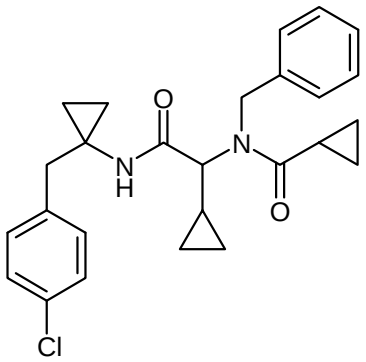
A solution of the respective aldehyde (or ketone), the amine, the isonitrile and the acid in MeOH (5 mL) was stirred for 2 h at ambient temperature. The solvent was removed *in vacuo*, and the crude product was purified by recrystallization or column chromatography on silica gel.

Cyclopropanecarboxylic Acid Benzyl{[1-(4-chlorobenzyl)-2-ethylcyclopropylcarbamoyl] cyclopropylmethyl}amide (5a):

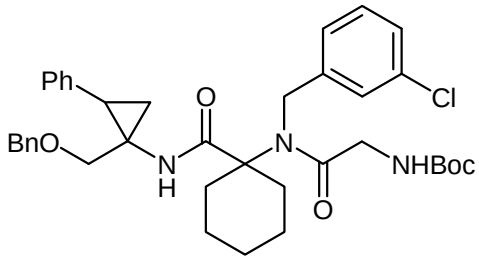


Column chromatography (Et_2O/hexane, 1:1) of the residue, obtained from cyclopropanecarbaldehyde (210 mg, 3.00 mmol), benzylamine (107 mg, 1.00 mmol), isonitrile **10b** (220 mg, 1.00 mmol) and cyclopropanecarboxylic acid (129 mg, 1.50 mmol) according to GP 1.4, gave pure **5a** (322 mg, 69%, R_f = 0.45) as a pale yellow oil. – IR (film): ν = 3313, 3067, 3006, 2961, 2930, 2873, 1739, 1684, 1617, 1492, 1430, 1241 cm^{-1}. – ^{1}H NMR (300 MHz, mixture of the 8 diastereomers, $CDCl_3$): δ = 0.05–0.20 (m, 4 H, *c*Pr-CH), 0.30–1.80 (m, 32 H, *c*Pr-CH, CH_2CH_3), 2.55–3.25 (m, 4 H, CH_2Ph-Cl), 3.82 (t, 2 H, *J* = 12.0 Hz, CH), 4.65–4.75 (m, 4 H, NCH_2Ph), 6.40–6.75 (m, 2 H, NH), 7.05–7.35 (m, 18 H, Ph-H). – ^{13}C NMR (50.3 MHz, mixture of the 8 diastereomers, $CDCl_3$): δ = 4.78, 4.83, 4.91, 5.04, 5.14, 5.29, 8.09, 8.29, 8.36, 8.53, 8.78, 8.89, 8.94, 9.03, 10.06, 10.14, 10.18, 10.30, 11.90, 11.97, 12.01, 12.54, 12.94, 13.70, 13.80, 13.82, 18.72, 18.79, 19.21, 19.32, 21.85, 21.94, 23.06,

23.15, 25.92, 26.06, 28.03, 28.19, 35.84, 35.94, 37.07, 37.30, 38.01, 38.06, 41.27, 41.37, 48.63, 48.74, 48.85 (*c*Pr-C,CH_2CH_3, CH_2Ph, CH_2-*p*-Cl-Ph), 63.40, 63.56, 63.90, 64.04 (CH), 126.14, 126.20, 126.97, 127.03, 128.22, 128.25, 128.30, 128.33, 128.40, 128.43, 128.73, 130.46, 130.50, 130.55, 130.63, 130.73, 131.91, 132.01, 137.80, 137.92, 137.97, 138.01, 138.04 (Ph-C), 170.70, 170.82, 171.13, 171.63, 175.72, 175.80 (CNO), (it's not possible to single out all carbon signals). – MS (EI): *m/z* (%) 466/464 (<1/<1) [M^+], 291/289 (6/21), 256 (98), 228 (42), 160 (100), 91 (89). – Anal. Calcd for $C_{28}H_{33}ClN_2O_2$: C, 72.32; H, 7.15; N, 6.02. Found: C, 72.10; H, 6.99; N, 5.88.



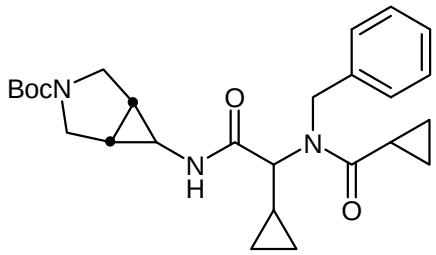
Cyclopropanecarboxylic Acid Benzyl-{[1-(4-chlorobenzyl)cyclopropylcarbamoyl]-cyclopropylmethyl}amide (5b): Column chromatography (Et_2O/hexane, 1:1) of the residue, obtained from cyclopropanecarbaldehyde (350 mg, 5.00 mmol), benzylamine (107 mg, 1.00 mmol), isonitrile **10a** (287 mg, 1.50 mmol) and cyclopropanecarboxylic acid (129 mg, 1.50 mmol) according to GP 1.4, gave pure **5b (**242 mg, 55%, R_f = 0.23) as a colorless solid, m.p. 112–114 °C. – IR (KBr): ν = 3429, 3307, 3083, 3022, 2953, 2929, 2853, 1640, 1533, 1431 cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): δ = 0.10–0.20 (m, 2 H, *c*Pr-H), 0.50–1.10 (m, 11 H, *c*Pr-H), 1.50–1.60 (m, 1 H, *c*Pr-H), 2.78 (d, 1 H, *J* = 13.2 Hz, C*H*$_2$-*p*-Cl-Ph), 2.98 (d, 1 H, *J* = 13.2 Hz, C*H*$_2$-*p*-Cl-Ph), 3.82 (d, 1 H, *J* = 10.8 Hz, CH), 4.74 (s, 2 H, C*H*$_2$Ph), 6.52 (s, 1 H, NH), 7.10–7.40 (m, 9 H, Ph). – ^{13}C NMR (50.3 MHz, APT, $CDCl_3$): δ = 4.8, 5.3, 8.3, 8.9 (–, *c*Pr-CH_2), 10.1, 11.9 (+, *c*Pr-CH), 13.3, 13.4 (–, *c*Pr-CH_2), 33.7 (–, *c*Pr-C_{quat}), 40.4 (–, *C*H_2Ph), 48.8 (–, CH_2-*p*-Cl-Ph), 63.7 (+, CH), 126.2, 127.0, 128.6, 128.4, 130.6 (+, 9 C, Ph-C), 132.2, 137.6, 137.9 (–, Ph-C), 171.2, 175.8 (–, CON). – MS (EI): *m/z* (%) 438/436 (<1/<1) [M^+], 256 (54), 228 (43), 160 (100), 91 (60). – Anal. Calcd for $C_{26}H_{29}ClN_2O_2$: C, 71.46; H, 6.69; N, 6.41. Found: C, 71.65; H, 6.60; N, 6.53.



***N*-*tert*-Butoxycarbonylglycinyl [(1-benzyloxymethyl-2-phenylcyclopropylcarbamoyl)-cycloxehyl]-(3-chlorobenzyl)amine (5c):** Column chromatography (Et_2O/hexane, 1:1) of the residue, obtained from cyclohexanone (49 mg, 0.5 mmol), 3-chlorobenzylamine (71 mg, 0.5 mmol), isonitrile **10c** (132 mg, 0.50 mmol) and *N*-Boc-Gly-OH (88 mg, 0.5 mmol) according to GP 1.4, gave **5c (**285 mg, 86%, R_f = 0.13) as a colorless solid, m.p. 57–59 °C. – IR (KBr): ν = 3428, 3358, 3067, 3028, 2979, 2933, 2865, 1684, 1497, 1165 cm^{-1}. – ^1H NMR (300 MHz): δ = 1.05–1.44 (m, 11 H, *t*Bu, *c*Pr-H), 1.48–1.64 (m, 8 H, *c*Hex-H), 2.42 (m, 2 H, *c*Hex-H),

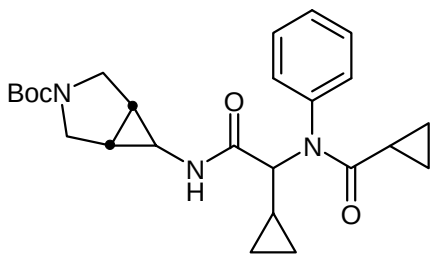
2.48 (t, 1 H, *J* = 7.2 Hz, *c*Pr-H), 3.08 (d, 1 H, *J* = 10.8 Hz, CH_2O), 3.51 (d, 1 H, *J* = 10.8 Hz, CH_2O), 3.84 (br s, 2 H, NCOCH_2NHCOO), 4.25 (d, 1 H, *J* = 12.0 Hz, CH_2Ph), 4.33 (d, 1 H, *J* = 12.0 Hz, CH_2Ph), 4.55 (s, 2 H, CH_2Ph-Cl), 5.38 (br s, 1 H, NH), 6.70 (s, 1 H, NH), 7.08–7.42 (m, 14 H, Ph-H). – ^{13}C NMR (75.5 MHz, APT, add. HSQC, $CDCl_3$): δ = 16.4 (–, *c*Pr-CH_2), 22.8 (–, *c*Hex-CH_2), 25.3 (–, *c*Hex-CH_2), 28.3 [+, C(*C*H_3)$_3$], 29.7 (+, *c*Pr-CH), 32.8 (–, *c*Hex-CH_2), 38.2 (–, *c*Pr-C_{quat}), 43.7 (–, NCO*C*H_2NHCOO), 46.5 (–, CH_2-Ph-*m*-Cl), 66.5 (–, *c*Hex-C_{quat}), 71.6 (–,*c*Pr-CH_2-O), 72.9 (–, Ph-CH_2-O), 79.6 [–, *C*(CH_3)$_3$], 124.0, 126.0, 126.4, 127.4, 127.5, 127.8, 128.0, 128.2, 129.3, 130.4 (+, 14 C, Ph-CH), 135.0, 137.2, 138.3, 139.9 (–, Ph-C_{quat}), 155.6, 170.1, 173.2 (–, CON). – MS (ESI): *m/z* (%) 1345/1343/1341 (8/39/71) [2 M + Na^+], 684/682 (5/19) [M + Na^+]. – Anal. Calcd for $C_{38}H_{46}ClN_3O_5$: C, 69.13; H, 7.02; N, 6.36. Found: C, 68.94; H, 6.89; N, 6.08.

(1*R*,5*S*)-*tert*-Butyl 6-(2-(*N*-Benzylcyclopropanecarboxamido)-2-cyclopropylacetamido)-3-aza-bicyclo[3.1.0]hexane-3-carboxylate (5d):



Column chromatography (Et_2O/Hexane, 1:1) of the residue, obtained from cyclopropanecarbaldehyde (107 mg, 1.53 mmol), benzylamine (54.6 mg, 0.51 mmol), isonitrile **13** (161 mg, 0.77 mmol) and cyclopropanecarboxylic acid (66.2 mg, 0.77 mmol) according to GP 1.4, gave pure **5d (**186 mg, 81%, R_f= 0.08) as a colorless solid, m.p. 122–124 °C. – IR (KBr): ν = 3440, 3281, 3067, 2973, 2932, 2859, 1705, 1612, 1420, 1394, 1114 cm^{-1}. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.10–0.30 (m, 3 H, *c*Pr-H), 0.40–1.30 (m, 5 H, *c*Pr-H), 1.39 (s, 9 H, *t*Bu), 1.50–1.70 [m, 4 H, *c*Pr-H, CH (bicycle)], 2.37 [m, 1 H, C*H*NH (bicycle)], 3.30–3.40 [m, 2 H, CH_2 (bicycle)], 3.55–3.70 [m, 2 H, CH_2 (bicycle)], 3.93 (d, 1 H, *J* = 10.3 Hz, CH), 4.92 (s, 2 H, CH_2Ph), 6.77 (s, 1 H, NH), 7.10–7.35 (m, 5 H, Ph-H). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 5.1, 8.3, 8.7, 9.0, 10.4, 12.2 (*c*Pr-CH), 23.7, 24.2 [CH (bicycle)], 28.4 [C(*C*H_3)$_3$], 32.3 [CHNH (bicycle)], 47.4, 47.6 [CH_2 (bicycle)], 48.9 (*C*H_2Ph), 63.5 (CH), 79.4 (*C*(CH_3)$_3$), 126.1, 127.0, 128.4, 137.9 (6 C, Ph-C), 154.4 (NCOO), 171.8, 175.9 (CON). – MS (ESI): *m/z* (%) 498 (57) [M + $HCOO^-$], 452 [M – H^+]. – Anal. Calcd for $C_{26}H_{35}N_3O_4$: C, 68.85; H, 7.78; N, 9.26. Found: C, 68.64; H, 7.51; N, 9.04.

(1*R*,5*S*)-*tert*-Butyl 6-(2-Cyclopropyl-2-(*N*-phenylcyclopropanecarboxamido)acetamido)-3-aza-bicyclo[3.1.0]hexane-3-carboxylate (5e):



Column chromatography (Et_2O/hexane, 1:1) of the residue, obtained from cyclopropanecarbaldehyde (105 mg, 1.50 mmol), aniline (47 mg, 0.5 mmol), isonitrile **13** (156 mg, 0.75 mmol) and cyclopropanecarboxylic acid (64.5 mg, 0.75 mmol) according to GP 1.4, gave pure **5e (**168 mg, 76%, R_f= 0.05) as a colorless solid, m.p. 184–185 °C. – IR (KBr): ν

= 3434, 3369, 3317, 3059, 3012, 2979, 2927, 2882, 1694, 1627, 1541, 1424, 1388, 1114 cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): δ = 0.20–0.35 (m, 2 H, *c*Pr-CH), 0.35–0.50 (m, 1 H, *c*Pr-CH), 0.55–0.70 (m, 3 H, *c*Pr-CH), 0.80–1.00 (m, 3 H, *c*Pr-CH), 1.15–1.30 (m, 1 H, *c*Pr-CH), 1.38 (s, 9 H, *t*Bu), 1.60–1.70 [m, 2 H, 2 CH (bicycle)], 2.42–2.48 (m, 1 H, C*H*NH), 3.35 [d, 2 H, *J* = 12.0 Hz, CH_2 (bicycle)], 3.68 [dd, 2 H, *J* = 3.0 Hz, *J* = 4.5 Hz, CH_2 (bicycle)], 3.95 (d, 1 H, *J* = 6.0 Hz, CH), 6.78 (s, 1 H, NH), 7.30–7.45 (m, 5 H, Ph-H). – ^{13}C NMR (50.3 MHz, APT, $CDCl_3$): δ = 4.3, 5.5, 8.6, 9.0 (–, *c*Pr-CH_2), 10.6, 12.9 (+, *c*Pr-CH), 23.8, 24.1 [+, CH (bicycle)], 28.4 [+, C(*C*H_3)$_3$], 32.5 [+, CHNH (bicycle)], 47.5 [–, CH_2N (bicycle)], 65.3 (+, CH), 79.4 [*C*(CH_3)$_3$], 128.3, 129.2, 129.9 (+, 5 C, Ph-C), 139.8 (–, Ph-C_{quat}), 154.4 (–, NCOO), 171.9, 174.7 (–, CON). – MS (ESI): *m/z* (%) 901 (100) [2 M + Na^+], 462 (6) [M + Na^+]. – Anal. Calcd for $C_{25}H_{33}N_3O_4$: C, 68.31; H, 7.57; N, 9.56. Found: C, 68.00; H, 7.51; N, 9.29.

(1*R*,5*S*)-*tert*-Butyl 6-(2-Acetamido-2-cyclopropylacetamido)-3-aza-bicyclo[3.1.0]hexane-3-carboxylate (5f): Recrystallization (Et_2O/hexane, 1:1) of the residue, obtained from cyclopropanecarbaldehyde (35 mg, 0.5 mmol), aq. ammonium hydroxide (0.1 mL, 0.7 mmol, 28–30 wt% in H_2O), isonitrile **13** (104 mg, 0.50 mmol) and acetic acid (36 mg, 0.6 mmol) according to GP 1.4, gave pure **5f (**86 mg, 52%) as a colorless solid, m.p. 202–204 °C. – IR (KBr): ν = 3440, 3245, 3069, 2978, 2933, 2886, 1700, 1634, 1559, 1395, 1120 cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): δ = 0.25–0.40 (m, 2 H, *c*Pr-CH), 0.44–0.56 (m, 2 H, *c*Pr-CH), 1.00–1.10 (m, 1 H, *c*Pr-CH), 1.39 (s, 9 H, *t*Bu), 1.62 [s, 2 H, CH (bicycle)], 1.98 (s, 3 H, CH_3), 2.42 [s, 1 H, CH (bicycle)], 3.30–3.40 [m, 2 H, CH_2 (bicycle)], 3.56–3.70 [m, 2 H, CH_2 (bicycle)], 3.82 (t, 1 H, *J* = 9.0 Hz, CH), 6.96 (d, 1 H, *J* = 7.0 Hz, NH), 7.42 (d, 1 H, *J* = 21 Hz, NH). – ^{13}C NMR (50.3 MHz, APT, $CDCl_3$): δ = 3.1, 3.2 (–, *c*Pr-CH_2), 14.1 (+, *c*Pr-CH), 23.1 (+, CH_3), 23.3, 24.3 [+, CH (bicycle)], 28.4 [+, C(*C*H_3)$_3$], 32.5 [+, CH (bicycle)], 47.4, 47.6 [–, CH_2 (bicycle)], 56.5 (+, CH), 79.5 [–, *C*(CH_3)$_3$], 154.4 (–, COO), 170.3, 172.5 (–, CONH). – MS (ESI): *m/z* (%) 697 (100) [2M + Na^+], 360 (63) [M + Na^+]. – HRMS-ESI: *m/z* calcd for $C_{17}H_{27}N_3NaO_4$ [M + Na^+]: 360.1899; found: 360.1894.

(1*R*,5*S*)-*tert*-Butyl 6-(1-Acetamidocyclohexanecarboxamido)-3-aza-bicyclo[3.1.0]hexane-3-carboxylate (5g): Recrystallization (Et_2O/hexane, 1:1) of the residue, obtained from cyclohexanone (49 mg, 0.5 mmol), aq. ammonium hydroxide (0.1 mL, 0.7 mmol, 28–30 wt% in H_2O), isonitrile **13** (104 mg, 0.5 mmol) and acetic acid (36 mg, 0.6 mmol) according to GP 1.4, gave pure **5g (**124 mg, 68%) as a colorless solid, m.p. 104–105 °C. –

IR (KBr): ν = 3440, 3304, 3056, 2974, 2932, 2869, 1710, 1653, 1540, 1394, 1172, 1117 cm^{-1}. – ^1H NMR (250 MHz, $CDCl_3$): δ = 1.20–1.40 (m, 12 H, *t*Bu, *c*Hex-CH_2), 1.40–1.70 (m, 5 H, *c*Hex-CH_2), 1.70–1.90 (m, 2 H, *c*Hex-CH_2), 1.90–2.10 [m, 5 H, CH_3, CH (bicycle)], 2.35–2.40 [m, 1 H, CH (bicycle)], 3.25–3.40 [m, 2 H, CH_2 (bicycle)], 3.56–3.70 [m, 2 H, CH_2 (bicycle)], 5.65 (br s, 1 H, NH), 7.35 (br s, 1 H, NH). – ^{13}C NMR (75.5 MHz, APT, $CDCl_3$): δ = 21.5 (–, 2 C, *c*Hex-CH_2), 23.6 [+, CH (bicycle)], 24.0 (+, CH_3), 24.7 [+, CH (bicycle)], 25.1 (–, *c*Hex-CH_2), 28.4 [+, C(*C*H_3)$_3$], 32.1, 32.3 (–, *c*Hex-CH_2), 32.6 (+, CHNH), 47.4, 47.7 [–, CH_2 (bicycle)], 60.2 (–, C_{quat}), 79.4 [–,*C*$(CH_3)_3$], 154.4 (COO), 171.1, 175.3 (CONH). – MS (EI): *m/z* (%) 365 (<1) [M^+], 265 (9), 168 (43), 140 (82), 98 (100), 69 (76).

Ethyl 1-[2-(Benzylcyclopropanecarbonylamino)-2-cyclopropylacetylamino]cyclopropane carboxylate (5h): Column chromatography (Et_2O/hexane, 1:1) of the residue, obtained from cyclopropanecarbaldehyde (210 mg, 3.00 mmol), benzylamine (107 mg, 1.00 mmol), isonitrile **17** (209 mg, 1.50 mmol) and cyclopropanecarboxylic acid (129 mg, 1.50 mmol) according to GP 1.4, gave pure **5h (**312 mg, 81%, R_f = 0.17) as a colorless solid, m.p. 92–93 °C. – IR (KBr): ν = 3429, 3267, 3089, 3039, 3006, 2985, 1738, 1690, 1605, 1539, 1179 cm^{-1}. – ^1H NMR (250 MHz, $CDCl_3$): δ = 0.10–0.30 (m, 3 H, *c*Pr-H), 0.60–1.00 (m, 5 H, *c*Pr-H), 1.05–1.35 (m, 5 H, CH_2CH_3, *c*Pr-H), 1.40–1.50 (m, 1 H, *c*Pr-H), 1.55–1.70 (m, 3 H, *c*Pr-H), 4.08–4.18 (m, 3 H, CH, CH_2CH_3), 4.80 (d, 1 H, *J* = 18.0 Hz, CH_2Ph), 4.96 (d, 1 H, *J* = 18.0 Hz, CH_2Ph), 7.02 (s, 1 H, NH), 7.20–7.40 (m, 5 H, Ph). – ^{13}C NMR (50.3 MHz, APT, $CDCl_3$): δ = 4.7, 5.4, 8.0, 8.9 (–, *c*Pr-CH_2), 9.9, 12.2, 14.2 (+, *c*Pr-CH, CH_2CH_3), 17.2, 17.5, 33.4 (–, *c*Pr-C), 48.8 (–, CH_2Ph), 61.2 (–, CH_2CH_3), 63.3 (+, CH), 126.2, 126.9, 128.4 (+, 5 C, Ph-C), 138.1 (–, Ph-C), 171.6, 172.1, 176.3 (–, CON, COO). – MS (EI): *m/z* (%) 384 (2) [M^+], 256 (18), 228 (78), 160 (100), 91 (40), 69 (37). – Anal. Calcd for $C_{22}H_{28}N_2O_4$: C, 68.73; H, 7.34; N, 7.29. Found: C, 68.41; H, 7.08; N, 7.48.

Ethyl 1-{2-[Cyclopropanecarbonyl-(4-methoxyphenyl)amino]-2-cyclopropylacetylamino}cyclopropanecarboxylate (5i): Column chromatography (Et_2O/hexane, 1:1) of the residue, obtained from cyclopropanecarbaldehyde (105 mg, 1.50 mmol), 4-methoxyaniline (62 mg, 0.5 mmol), isonitrile **17** (104 mg, 0.75 mmol) and cyclopropanecarboxylic acid (105 mg, 1.22 mmol) according to GP 1.4, gave pure **5i (**171 mg, 86%, R_f = 0.22) as a colorless solid, m.p. 132–134 °C. – IR (KBr): ν = 3324, 3299, 3083, 3034, 3000, 2957, 2908, 2835, 1722, 1694,

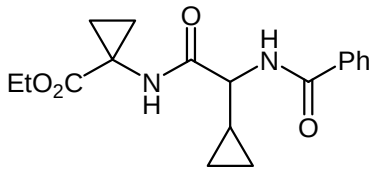
1620, 1510, 1420, 1250, 1179 cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): δ = 0.30–0.50 (m, 3 H, *c*Pr-CH), 0.60–0.75 (m, 3 H, *c*Pr-CH), 0.90–1.10 (m, 4 H, *c*Pr-CH), 1.10–1.40 (m, 5 H, CH_2CH_3, *c*Pr-CH), 1.42–1.50 (m, 1 H, *c*Pr-CH), 1.60–1.70 (m, 1 H, *c*Pr-CH), 3.79 (s, 3 H, OCH_3), 4.05–4.20 (m, 3 H, CH, CH_2CH_3), 6.90 (dd, 2 H, *J* = 1.4 Hz, *J* = 7.6 Hz, Ph-H), 7.20–7.45 (m, 3 H, Ph-H, NH). – ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 5.8, 8.4, 9.0, 10.1, 12.9, 14.3, 17.6, 17.8, 33.4 (*c*Pr-C, CH_2CH_3), 55.5 (OCH_3), 61.3(CH_2CH_3), 64.5 (CH), 114.3, 131.1, 132.2, 159.3 (5 C, Ph-C), 171.7, 172.4, 175.3 (CON, COO). – MS (EI): *m/z* (%) 400 (3) [M^+], 272 (7), 244 (45), 176 (100), 69 (34). – Anal. Calcd for $C_{22}H_{28}N_2O_5$: C, 65.98; H, 7.07; N, 6.99. Found: C, 65.77; H, 6.74; N, 6.64.

(*S*)-Ethyl 1-(1-(2-(*tert*-Butoxycarbonyl)-3-phenylpropanamido)cyclohexanecarboxamido)cyclopropanecarboxylate (5j): Column chromatography (Et_2O/hexane, 1:1) of the residue, obtained from cyclohexanone (49 mg, 0.5 mmol), aq. ammonium hydroxide (0.1 mL, 0.7 mmol, 28–30 wt% in H_2O), isonitrile **17** (70 mg, 0.5 mmol) and N-Boc-Pha-OH (135 mg, 0.51 mmol) according to GP 1.4, gave pure **5j (**187 mg, 75%, R_f = 0.13) as a colorless solid, m.p. 93–94 °C. – IR (KBr): ν = 3437, 3287, 3034, 3006, 2981, 2930, 2866, 1714, 1672, 1509, 1163 cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): δ = 1.00–1.30 (m, 7 H, CH_2CH_3, *c*Pr-CH), 1.30–1.60 (m, 15 H, *t*Bu, *c*Hex-CH_2), 1.78–2.05 (m, 4 H, *c*Hex-CH_2), 2.96 (dd, 1 H, *J* = 7.2 Hz, *J* = 14.0 Hz, CH_2Ph), 3.09 (dd, 1 H, *J* = 7.2 Hz, *J* = 14.0 Hz, CH_2Ph), 4.06 (q, 2 H, *J* = 14.3 Hz, CH_2CH_3), 4.18 (dd, 1 H, *J* = 7.1 Hz, *J* = 13.5 Hz, CH), 5.05 (d, 1 H, *J* = 6.1 Hz, NHBoc), 6.01 (s, 1 H, NH), 7.15–7.35 (m, 5 H, Ph-H), 7.42 (s, 1 H, NH). – ^{13}C NMR (50.3 MHz, APT, $CDCl_3$): δ = 14.1 (+, CH_3), 17.3, 17.5 (–, *c*Pr-CH_2), 21.0, 24.9, (–, *c*Hex-CH_2), 28.2 [+, $C(CH_3)_3$], 31.8, 33.4, 37.3 (–, *c*Hex-CH_2, CH_2Ph, CH_2CH_3), 56.9 (+, CH), 60.4, 61.1 (–, *c*Hex-CH_2, *c*Pr-C), 80.9 [–, $C(CH_3)_3$], 127.2, 128.9, 129.1 (+, 5 C, Ph-CH) 136.3 (–, Ph-C), 155.9 (–, HNCOO), 171.1, 172.5, 174.9 (–, COO, CONH). – MS (EI): *m/z* (%) 501 (4) [M^+], 289 (10), 237 (9), 120 (10), 98 (100). – Anal. Calcd for $C_{27}H_{39}N_3O_6$: C, 64.65; H, 7.84; N, 8.38. Found: C, 64.85; H, 7.78; N, 9.15.

Ethyl 1-[(1-Benzoylaminocyclohexanecarbonyl)amino]cyclopropanecarboxylate (5k): Column chromatography (Et_2O/hexane, 1:1) of the residue, obtained from cyclohexanone (98 mg, 1.0 mmol), ammonium benzoate (70 mg, 0.5 mmol) and isonitrile **17** (70 mg, 0.5 mmol) according to GP 1.4, gave pure **5k (**118 mg, 66%, R_f = 0.07) as a colorless solid, m.p. 207–209 °C. – IR (KBr): ν = 3347, 3266, 3028, 2979, 2935, 2858, 1725, 1663, 1637, 1521, 1339, 1185 cm^{-1}. – ^1H NMR (250 MHz, $CDCl_3$): δ = 1.10–1.20 (m, 5 H, *c*Pr-H, *c*Hex-H), 1.30–1.75 (m, 8

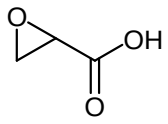
H, CH_2CH_3, *c*Hex-H), 2.00 (t, 2 H, *J* = 11.0 Hz, *c*Hex-H), 2.26 (d, 2 H, *J* = 14.0 Hz, *c*Hex-H), 4.06 (q, 2 H, *J* = 14.3 Hz, CH_2CH_3), 6.11 (s, 1 H, NH), 7.40–7.60 (m, 3 H, Ph-H), 7.70–7.80 (m, 2 H, Ph-H), 7.95 (s, 1 H, NH). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 14.0, 17.5, 21.6, 25.2, 32.1, 33.5 (*c*Pr-CH, *c*Hex-CH_2, CH_2CH_3), 60.6, 61.2 (*c*Pr-C_{quat}, *c*Hex-C_{quat}), 126.8, 128.7, 131.9, 134.4 (6 C, Ph-C), 168.1, 172.4, 174.9 (COO, CONH). – MS (EI): *m/z* (%) 358 (6) [M^+], 237 (20), 230 (17), 202 (70), 105 (100), 77 (20). – Anal. Calcd for $C_{20}H_{26}N_2O_4$: C, 67.02; H, 7.31; N, 7.82. Found: C, 66.71; H, 7.23; N, 7.70.

Ethyl 1-(2-Benzoylamino-2-cyclopropylacetylamino)cyclopropanecarboxylate (5l):

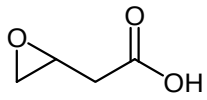


Recrystallization from EtOAc/hexane (1:1) of the residue, obtained from cyclopropanecarbaldehyde (105 mg, 1.50 mmol), ammonium benzoate (70 mg, 0.5 mmol) and isonitrile **17** (70 mg, 0.5 mmol) according to GP 1.4, gave pure **5l (**62 mg, 38%) as a colorless solid, m.p. 158–160 °C. – IR (KBr): ν = 3429, 3282, 3177, 3057, 2930, 2858, 1733, 1684, 1634, 1534, 1449 cm^{-1}. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.45–0.60 (m, 4 H, *c*Pr-H), 1.05–1.35 (m, 6 H, *c*Pr-H, CH_2CH_3), 1.40–1.60 (m, 2 H, *c*Pr-H), 4.08 (q, 2 H, *J* = 13.8 Hz, CH_2CH_3), 4.25 (t, 1 H, *J* = 7.8 Hz, CH), 7.42–7.58 (m, 4 H, Ph-H, NH), 7.75–7.86 (m, 3 H, Ph-H). – ^{13}C NMR (125.7 MHz, APT, $CDCl_3$): δ = 3.1, 3.3 (–, *c*Pr-CH_2), 13.9, 14.1 (+, CH_2CH_3, *c*Pr-CH), 17.2, 17.5 (–, *c*Pr-CH_2), 33.5 (–, *c*Pr-C_{quat}), 56.7 (+, CH), 61.3 (–, CH_2CH_3), 127.2, 128.4, 131.8 (+, 5 C, Ph-CH), 133.6 (–, Ph-C), 167.3, 172.1, 172.7 (–, CON, COO). – MS (EI): *m/z* (%) 330 (4) [M^+], 174 (29), 122 (14), 105 (100). – Anal. Calcd for $C_{18}H_{22}N_2O_4$: C, 65.44; H, 6.71; N, 8.48. Found: C, 65.17; H, 6.43; N, 8.39.

Oxirane-2-carboxylic Acid (26): The solution of oxiranylmethanol (2.25 g, 31.0 mmol), sodium periodate (19.9 g, 93.0 mmol) and $RuCl_3 \cdot (H_2O)$ (178 mg, 0.68 mmol) in CH_3CN (100 mL) were stirred at ambient temperature for 1 h. Than water (1.4 mL, 77.5 mmol) was added and the reaction mixture was stirred overnight. The solvent was removed *in vacuo*, to the residue Et_2O (150 mL) was added and the mixture was filtered through a pad of Celite. The residue after concentration under reduced pressure was purified by column chromatography on silica gel (Et_2O) to give **26** (2.34 g, 86%, R_f = 0.81) as a colorless oil. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.90–3.10 (m, 2 H, CH_2), 3.40–3.50 (m, 1 H, CH), 9.20 (s, 1 H, COOH).



Oxiranylacetic Acid (28): To the solution of vinylacetic acid **27** (1.29 g, 15.0 mmol) in CH_2Cl_2 (120 mL) 55% *m*CPBA (5.15 g, 16.4 mmol) was added portionwise at ambient temperature. After overnight stirring the solvent was removed *in vacuo* and the

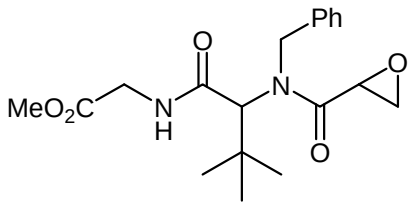


residue was purified by column chromatography on silica gel (EtOAc/hexane, 2:1) to give **28** (892 mg, 58%, R_f = 0.61) as a colorless oil. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.50–2.70 (m, 3 H, CH_2), 2.80–2.90 (m, 1 H, CH_2), 3.20–3.40 (m, 1 H, CH), the signal of COOH group is not detectable.

General Procedure for the Preparation of Peptides 29 (GP 1.5).

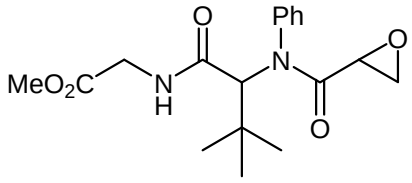
A solution of aldehyde (1.1 mmol), amine (1.0 mmol) or (amine hydrochloride (1.0 mmol) and triethylamine (1.0 mmol)), isonitrile (1.0 mmol) and acid (1.0 mmol) in MeOH (5 mL) was stirred at ambient temperature for 2 h. The solvent was removed *in vacuo*, the residue was dissolved in CH_2Cl_2 (15 mL), washed with 1 M aq. solution of $KHSO_4$ (1 × 5 mL), saturated aq. solution of $NaHCO_3$ (1 × 5 mL), brine (1 × 5 mL) and dried over Na_2SO_4. After concentration under reduced pressure the crude product was purified by column chromatography on silica gel.

Methyl [2-(Methoxycarbonylmethyloxiranecarbonylamino)-3,3-dimethylbutyrylamino]acetate (29a):



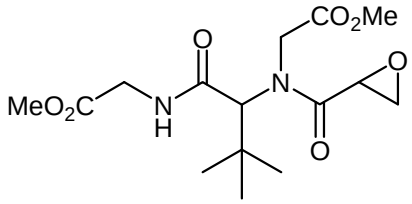
Column chromatography (EtOAc/hexane, 1:1) of the residue, obtained from trimethylacetaldehyde (284 mg, 3.30 mmol), benzylamine (321 mg, 3.00 mmol), methyl isocyanoacetate (297 mg, 3.00 mmol) and oxirane-2-carboxylic acid **26** (264 mg, 3.00 mmol) according to GP 1.5, gave pure **29a** (851 mg, 78%, R_f = 0.33) as a colorless oil. – IR (film): ν = 3304, 3058, 2956, 2864, 1733, 1652, 1558, 1448, 1295, 1201, 1111, 1028 cm^{-1}. – ^{1}H NMR (300 MHz, 2 diastereomers, $CDCl_3$): δ = 1.05–1.20 (m, 18 H, *t*Bu), 2.33 (dd, 1 H, *J* = 4.5 Hz, *J* = 6.4 Hz, OCH_2), 2.27 (dd, 1 H, *J* = 2.6 Hz, *J* = 6.4 Hz, OCH_2), 2.67 (dd, 1 H, *J* = 4.5 Hz, *J* = 6.8 Hz, OCH_2), 2.77 (dd, 1 H, *J* = 2.3 Hz, *J* = 6.4 Hz, OCH_2), 3.35–3.40 (m, 2 H, OCH), 3.65–3.80 (m, 8 H, CH_2CO_2Me), 4.78–4.96 (m, 2 H, CH_2Ph), 5.30–5.60 (m, 4 H, CH_2Ph, C*H*t*Bu*), 7.10–7.30 (m, 10 H, Ph-H), 7.78 (t, 1 H, *J* = 5.3 Hz, NH), 8.01 (t, 1 H, *J* = 5.2 Hz, NH). – ^{13}C NMR (75.5 MHz, APT, 2 diastereomers, $CDCl_3$): δ = 27.5 (+, 6 C, *t*Bu), 36.4, 36.6 (–, CH_2Ph), 40.7 (–, 2 C, *C*H_2CO_2Me), 46.7, 46.8 (–, OCH_2), 47.5, 48.4 (+, OCH), 49.2, 49.4 (–, *t*Bu), 52.0, 52.1 (+, CH_3), 60.4 (+, 2 C, *C*H*t*Bu), 125.5, 125.9, 127.0, 127.1, 128.7, 128.8 (+, 10 C, Ph-CH), 137.9, 138.4 (–, Ph-C), 169.3, 169.5, 170.2, 170.7, 170.8 (–, 6 C, *C*O_2Me, CON). – MS (EI): *m/z* (%) 362 (<1) [M^+], 291 (6), 176 (12), 172 (8), 91 (100). – $C_{19}H_{25}N_2O_5$ (362.43): calcd; C 62.97, H 7.23, N 7.73; found C 62.69, H 6.95, N 7.61.

Methyl [3,3-Dimethyl-2-(oxiranecarbonylphenylamino)butyrylamino]acetate (29b):



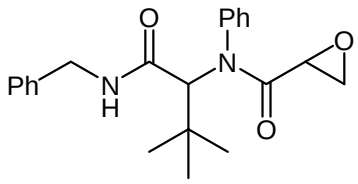
Column chromatography (EtOAc/hexane, 1:1) of residue, obtained from trimethylacetaldehyde (284 mg, 3.30 mmol), aniline (279 mg, 3.00 mmol), methyl isocyanoacetate (297 mg, 3.00 mmol) and

oxirane-2-carboxylic acid **26** (264 mg, 3.00 mmol) according to GP 1.5, gave pure **29b** (672 mg, 64%, R_f = 0.39) as a colorless solid, m.p. 96–98 °C. – IR (KBr): ν = 3287, 3093, 2957, 2880, 1757, 1665, 1562, 1492, 1408, 1369, 1284, 1215, 1174, 1016 cm^{-1}. – ^1H NMR (300 MHz, 2 diastereomers, $CDCl_3$): δ = 0.96 (s, 9 H, *t*Bu), 0.97 (s, 9 H, *t*Bu), 2.61 (dd, *J* = 4.1 Hz, *J* = 6.8 Hz, OCH_2), 2.71 (dd, *J* = 4.2 Hz, *J* = 6.8 Hz, OCH_2), 2.94 (dt, *J* = 2.6 Hz, *J* = 6.8 Hz), 3.09 (dd, *J* = 2.3 Hz, *J* = 4.2 Hz, OCH_2), 3.22 (dd, *J* = 2.6 Hz, *J* = 4.5 Hz, OCH_2), 3.72 (s, 3 H, CH_3), 3.73 (s, 3 H, CH_3), 3.81 (dd, 1 H, *J* = 4.6 Hz, *J* = 17.7 Hz, C*H*$_2$CO$_2$Me), 3.99 (dd, 1 H, *J* = 5.7 Hz, *J* = 18.0 Hz, C*H*$_2$CO$_2$Me), 4.07 (dd, 1 H, *J* = 6.1 Hz, *J* = 17.7 Hz, C*H*$_2$CO$_2$Me), 4.20 (dd, 1 H, *J* = 6.8 Hz, *J* = 17.7 Hz, C*H*$_2$CO$_2$Me), 4.93 (s, 1 H, C*Ht*Bu), 4.95 (s, 1 H, C*Ht*Bu), 7.20 (br s, 2 H, NH), 7.40 (br s, 10 H, Ph-H). – ^{13}C NMR (75.5 MHz, APT, 2 diastereomers, $CDCl_3$): δ = 27.9 (+, 6 C, *t*Bu), 34.5, 34.6 (–, CH_2CO_2Me), 40.7, 40.9 (–, OCH), 46.8, 46.9 (–, *t*Bu), 47.6, 47.8 (+, CH_3), 52.2, 52.3 (+, *C*H*t*Bu), 67.7 (+, OCH), 129.0, 129.2, 129.4, 129.6, 129.9 (+, 10 C, Ph-CH), 139.6, 139.7 (–, Ph-C), 169.8, 170.1, 170.2, 170.5 (–, 6 C, *C*O$_2$Me, CON). – MS (EI): *m/z* (%) 348 (9) [M^+], 292 (18), 232 (100), 203 (20), 162 (37), 146 (22), 104 (73), 77 (30), 69 (24). – $C_{18}H_{24}N_2O_5$ (348.40): calcd; C 62.05, H 6.94, N 8.04; found C 61.83, H 6.71, N 7.88.

Methyl [2-(Methoxycarbonylmethyloxiranecarbonylamino)-3,3-dimethylbutyrylamino]- acetate (29c): 

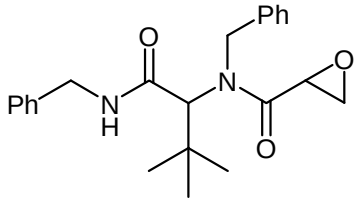
Column chromatography (EtOAc/hexane, 1:1) of the residue, obtained from trimethylacetaldehyde (190 mg, 2.21 mmol), glycine methyl ester hydrochloride (251 mg, 2.00 mmol), triethylamine (202 mg, 2.00 mmol), methyl isocyanoacetate (198 mg, 2.00 mmol) and oxirane-2-carboxylic acid **26** (176 mg, 2.00 mmol) according to GP 1.5, gave pure **29c** (291 mg, 42%, R_f = 0.16) as a colorless solid, m.p. 90–92 °C. – IR (KBr): ν = 3287, 3064, 2957, 2880, 1752, 1654, 1542, 1437, 1368, 1211 cm^{-1}. – ^1H NMR (300 MHz, 2 diastereomers, $CDCl_3$): δ = 0.95–1.15 (m, 18 H, *t*Bu), 2.75–2.90 (m, 3 H, OCH_2), 3.00–3.10 (m, 1 H, OCH_2), 3.35–3.42 (m, 1 H, OCH), 3.45–50 (m, 1 H, OCH), 3.80–4.30 (m, 16 H, CH_2CO_2Me), 4.40–4.82 (m, 4 H, CH_2), 5.15 (s, 1 H, CH), 5.25 (s, 1 H, CH), 7.47 (br s, 1 H, NH), 7.92 (br s, 1 H, NH). – ^{13}C NMR (125.7 MHz, APT, 2 diastereomers, $CDCl_3$): δ = 27.2, 27.4, [+, C(*C*H$_3$)$_3$], 35.9, 36.1, [–, *C*(CH$_3$)$_3$], 40.8, 40.9, 41.0, 46.7, 46.9 (–, CH_2, OCH_2), 47.2 (+, CH), 47.9 (–, OCH_2), 48.2 (+, CH), 51.9, 52.0, 52.4, 52.5 (+, OMe), 61.6, 65.8 (+, OCH), 169.2, 169.4, 169.91, 169.96, 170.11, 170.15, 170.21 (–, 8 C, CON, COO). – MS (EI): *m/z* (%) 344 (24) [M^+], 288 (94), 256 (13), 228 (100), 217 (29), 199 (45), 158 (49), 98 (37). – $C_{15}H_{24}N_2O_7$ (344,37): calcd; C 52.32, H 7.02, N 8.13; found C 52.03, H 6.76, N 7.89.

Oxirane-2-carboxylic Acid (1-Benzylcarbamoyl-2,2-dimethylpropyl)phenyl Amide (29d):



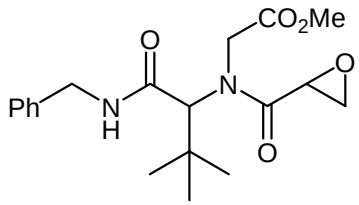
Column chromatography (EtOAc/hexane, 1:3) of the residue, obtained from trimethylacetaldehyde (190 mg, 2.21 mmol), aniline (186 mg, 2.00 mmol), benzylisonitrile (234 mg, 2.00 mmol) and oxirane-2-carboxylic acid **26** (176 mg, 2.00 mmol) according to GP 1.5, gave pure **29d** (551 mg, 75%, R_f = 0.29) as a colorless solid, m.p. 75–77 °C. – IR (KBr): ν = 3319, 3062, 3030, 2960, 2870, 1651, 1594, 1491, 1411, 1292, 1245, 1208, 1178 cm^{-1}. – ^1H NMR (300 MHz, 2 diastereomers, $CDCl_3$): δ = 0.95 (s, 9 H, *t*Bu), 0.98 (s, 9 H, *t*Bu), 2.49 (dd, 1 H, *J* = 4.3 Hz, *J* = 6.5 Hz, OCH_2), 2.60–2.70 (m, 2 H, OCH_2), 2.80 (dd, 1 H, *J* = 2.5 Hz, *J* = 6.5 Hz, OCH_2), 2.95 (dd, 1 H, *J* = 2.5 Hz, *J* = 6.8 Hz, OCH), 3.07 (dd, 1 H, *J* = 2.5 Hz, *J* = 4.0 Hz, OCH), 4.25–4.35 (m, 2 H, CH_2Ph), 4.40–4.50 (m, 2 H, CH_2Ph), 4.87 (s, 1 H, CH), 4.98 (s, 1 H, CH), 7.05–7.15 (br s, 2 H, NH), 7.15–7.35 (m, 20 H, Ph-H). – ^{13}C NMR (75.5 MHz, APT, 2 diastereomers, $CDCl_3$): δ = 27.7, 27.9 [+, C(*C*H_3)$_3$], 34.6 [–, 2 C, *C*(CH_3)$_3$], 43.1, 43.2 (–, CH_2Ph), 46.8 (–, 2 C, OCH_2), 47.3, 47.4 (+, CH), 66.6, 67.6 (+, OCH), 127.2, 127.3, 127.8, 128.5, 128.9, 129.4, 129.9 (+, 20 C, Ph-CH), 138.3, 138.4, 139.2, 139.4 (–, Ph-C), 169.4, 169.6, 169.7 (–, 4 C, CON). – MS (EI): *m/z* (%) 366 (11) [M^+], 278 (10), 232 (85), 161 (39), 146 (29), 104 (49), 91 (100). – $C_{22}H_{26}N_2O_3$ (366.46): calcd; C 72.11, H 7.15, N 7.64; found C 71.93, H 6.91, N 7.40.

Oxirane-2-carboxylic Acid Benzyl-(1-benzylcarbamoyl-2,2-dimethylpropyl)amide (29e):



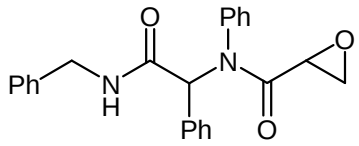
Column chromatography (EtOAc/hexane, 1:1) of the residue, obtained from trimethylacetaldehyde (190 mg, 2.21 mmol), benzylamine (214 mg, 2.00 mmol), benzylisonitrile (234 mg, 2.00 mmol) and oxirane-2-carboxylic acid **26** (176 mg, 2.00 mmol) according to GP 1.5, gave pure **29e** (557 mg, 73%, R_f = 0.72) as a colorless solid, m.p. 166–167 °C. – IR (KBr): ν = 3261, 3086, 3034, 2960, 2869, 1659, 1566, 1467, 1369, 1248, 1185, 1029 cm^{-1}. – ^1H NMR (300 MHz, $CDCl_3$): δ = 1.08 (s, 9 H, *t*Bu), 2.36 (dd, 1 H, *J* = 4.3 Hz, *J* = 6.3 Hz, OCH_2), 2.44 (dd, 1 H, *J* = 2.5 Hz, *J* = 6.5 Hz, OCH_2), 3.34 (dd, 1 H, *J* = 2.5 Hz, *J* = 4.3 Hz, OCH), 4.29 (d, 2 H, *J* = 5.8 Hz, PhC*H*$_2$NH), 4.79 (d, 1 H, *J* = 17.3 Hz, $PhCH_2N$), 5.22 (s, 1 H, CH), 5.58 (d, 1 H, *J* = 17.5 Hz, $PhCH_2N$), 7.00–7.30 (m, 10 H, Ph-H), 7.57 (br s, 1 H, NH). – ^{13}C NMR (75.5 MHz, APT, $CDCl_3$): δ = 27.5 [+, C(*C*H_3)$_3$], 36.5 [–, *C*(CH_3)$_3$], 43.1, 46.6 (–, CH_2), 48.3 (+, CH), 49.3 (–, OCH_2), 63.0 (+, OCH), 125.8, 126.9, 127.2,128.0, 128.4, 128.6 (+, 10 C, Ph-CH), 138.3, 138.6 (–, Ph-C), 168.8, 170.4 (–, CON). – MS (DCI): *m/z* (%) 380 (14) [M^+], 309 (18), 273 (10), 246 (36), 242 (21), 205 (57), 190 (67), 176 (14), 91 (100). – $C_{23}H_{28}N_2O_3$ (380.49): calcd; C 72.61, H 7.42, N 7.36; found C 72.65, H 7.15, N 7.48.

Methyl [(1-Benzylcarbamoyl-2,2-dimethylpropyl)oxiranecarbonylamino]acetate (29f):



Column chromatography (EtOAc/hexane, 1:1) of the residue, obtained from trimethylacetaldehyde (190 mg, 2.21 mmol), glycine methyl ester hydrochloride (251 mg, 2.00 mmol), triethylamine (202 mg, 2.00 mmol), benzylisonitrile (234 mg, 2.00 mmol) and oxirane-2-carboxylic acid **26** (176 mg, 2.00 mmol) according to GP 1.5, gave pure **29f** (451 mg, 62%, R_f = 0.42) as a colorless solid, m.p. 81–82 °C. – IR (KBr): ν = 3304, 3063, 3032, 2959, 2874, 1751, 1653, 1540, 1455, 1368, 1243, 1209, 1181, 1074 cm^{-1}. – ^1H NMR (300 MHz, 2 diastereomers, $CDCl_3$): δ = 0.90–1.00 (m, 18 H, *t*Bu), 2.60–2.85 (m, 3 H, OCH_2), 2.90–3.00 (m, 1 H, OCH_2), 3.35–3.45 (m, 2 H, OCH), 3.62 (s, 3 H, OMe), 3.65 (s, 3 H, OMe), 4.15–4.95 (m, 8 H, CH_2), 5.02 (s, 1 H, CH), 5.08 (s, 1 H, CH), 7.08 (br s, 1 H, NH), 7.15–7.30 (m, 10 H, Ph-H), 7.37 (br s, 1 H, NH). – ^{13}C NMR (75.5 MHz, APT, 2 diastereomers, $CDCl_3$): δ = 27.1 [+, C(*C*H_3)$_3$], 36.0, 36.1 [–, *C*(CH_3)$_3$], 43.1, 43.2, 43.3, 46.3, 46.8 (–, 6 C, CH_2), 47.4, 48.3 (+, CH), 52.2, 52.3 (+, OMe), 61.9 (+, 2 C, OCH), 127.2, 127.3, 127.4, 127.8, 127.93, 127.95, 128.5, 128.7 (+, 10 C, Ph-H), 138.2, 138.4 (–, Ph-C), 168.7, 168.9, 169.9, 170.3 (–, 6 C, CON, COO). – MS (EI): *m/z* (%) 362 (69) [M^+], 306 (69), 274 (100), 256 (14), 235 (15), 228 (66), 158 (29), 91 (52). – $C_{19}H_{26}N_2O_5$ (362.43): calcd; C 62.97, H 7.23, N 7.73; found C 62.82, H 6.92, N 7.50.

Oxirane-2-carboxylic Acid (Benzylcarbamoylphenylmethyl)phenyl Amide (29g):

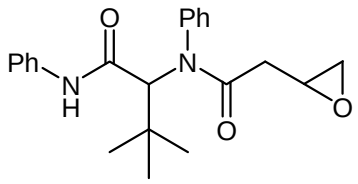


Column chromatography (EtOAc/hexane, 1:1) of the residue, obtained from benzaldehyde (233 mg, 2.19 mmol), aniline (186 mg, 2.00 mmol), benzylisonitrile (234 mg, 2.00 mmol) and oxirane-2-carboxylic acid **26** (176 mg, 2.00 mmol) according to GP 1.5, gave pure **29g** (573 mg, 74%, R_f = 0.35) as a colorless solid, m.p. 150–152 °C. – IR (KBr): ν = 3252, 3063, 3028, 2934, 2879, 1679, 1557, 1493, 1415, 1280, 1245, 1079 cm^{-1}. – ^1H NMR (300 MHz, 2 diastereomers, $CDCl_3$): δ = 2.62–2.70 (m, 2 H, OCH_2), 2.90–3.00 (m, 2 H, OCH_2), 3.05–3.15 (m, 2 H, OCH), 4.35–4.55 (m, 4 H, CH_2Ph), 6.03 (s, 1 H, CH), 6.24 (s, 1 H, CH), 6.30–6.40 (m, 2 H, NH), 7.10–7.35 (m, 20 H, Ph-H). – ^{13}C NMR (75.5 MHz, APT, 2 diastereomers, $CDCl_3$): δ = 43.7, 43.8, 46.7, 46.9 (–, CH_2), 47.5, 47.6 (+, CHPh), 65.1, 66.2 (+, OCH), 127.4, 127.5, 127.6, 128.5, 128.60, 128.64, 128.67, 128.73, 128.78, 128.80, 129.0, 129.3, 130.3, 130.4, 130.7, 131.0 (+, 30 C, Ph-CH), 133.6, 133.9, 137.9, 138.1, 138.8 (–, 6 C, Ph-C), 168.1, 168.2, 169.0, 169.5 (–, CON). – MS (EI): *m/z* (%) 386 (<1) [M^+], 252 (100), 223 (17), 182 (98), 146 (18), 104 (10), 91 (38).

Oxirane-2-carboxylic Acid Benzyl(benzylcarbamoylphenylmethyl) Amide (29h): Column chromatography (EtOAc/hexane, 1:1) of the residue, obtained from benzaldehyde (233 mg, 2.19 mmol), benzylamine (214 mg, 2.00 mmol), benzylisonitrile (234 mg, 2.00 mmol) and oxirane-2-carboxylic acid **26** (176 mg, 2.00 mmol) according to GP 1.5, gave pure **29h** (573 mg, 74%, R_f = 0.39) as a pale yellow oil. – IR (film): ν = 3308, 3062, 3031, 2930, 1655, 1540, 1496, 1453, 1266, 1233, 1204 cm^{-1}. – ^1H NMR (300 MHz, 2 diastereomers, $CDCl_3$): δ = 2.60 (dd, 1 H, *J* = 4.3 Hz, *J* = 6.0 Hz, OCH_2), 2.75 (dd, 1 H, *J* = 4.3 Hz, *J* = 6.0 Hz, OCH_2), 2.80–2.90 (m, 2 H, OCH_2), 3.40–3.50 (m, 2 H, OCH), 4.46 (d, 4 H, *J* = 5.3 Hz, $PhCH_2NH$), 4.69 (t, 2 H, *J* = 17.8 Hz, $PhCH_2N$), 4.96 (t, 2 H, *J* = 17.8 Hz, $PhCH_2N$), 5.97 (s, 1 H, CH), 6.12 (s, 1 H, CH), 6.23 (br s, 2 H, NH), 7.00–7.40 (m, 30 H, Ph-H). – ^{13}C NMR (75.5 MHz, APT, 2 diastereomers, $CDCl_3$): δ = 43.7, 43.8 (–, CH_2Ph), 46.5, 46.7 (–, CH_2Ph), 47.8 (+, 2 C, CH), 49.0, 49.8 (–, OCH_2), 62.6, 63.5 (+, OCH), 126.0, 126.2, 126.3, 127.2, 127.3, 127.5, 127.7, 127.8, 128.3, 128.4, 128.5, 128.6, 128.7, 128.8, 128.91, 128.95, 128.99, 129.8, 129.9 (+, 30 C, Ph-CH), 133.9, 134.4, 137.0, 137.1, 137.8 (–, 6 C, Ph-C), 168.9, 169.2, 169.5, 169.8 (–, CON). – MS (EI): *m/z* (%) 400 (<1) [M^+], 266 (17), 225 (30), 176 (7), 118 (9), 91 (100).

Methyl [2-(Oxiranecarbonylphenylamino)-2-phenylacetylamino]acetate (29i): Column chromatography (EtOAc/hexane, 2:1) of the residue, obtained from benzaldehyde (233 mg, 2.20 mmol), aniline (186 mg, 2.00 mmol), methyl isocyanoacetate (198 mg, 2.00 mmol) and oxirane-2-carboxylic acid **26** (176 mg, 2.00 mmol) according to GP 1.5, gave pure **29i** (446 mg, 61%, R_f = 0.31) as a colorless solid, m.p. 122–124 °C. – IR (KBr): ν = 3286, 3101, 3001, 2956, 2853, 1744, 1669, 1574, 1421, 1246, 1174, 1028 cm^{-1}. – ^1H NMR (300 MHz, 2 diastereomers, $CDCl_3$): δ = 2.60–2.70 (m, 2 H, OCH_2), 2.97 (dt, 2 H, *J* = 2.5 Hz, *J* = 6.5 Hz, OCH_2), 3.05 (dd, 1 H, *J* = 2.3 Hz, *J* = 4.0 Hz, OCH), 3.08 (dd, 1 H, *J* = 2.5 Hz, *J* = 4.0 Hz, OCH), 3.70 (s, 3 H, CH_3), 3.72 (s, 3 H, CH_3), 4.00–4.15 (m, 4 H, CH_2CO_2Me), 6.07 (s, 1 H, CH), 6.29 (s, 1 H, CH), 6.40 (t, 1 H, *J* = 3.0 Hz, NH), 6.48 (t, 1 H, *J* = 3.0 Hz, NH), 7.10–7.30 (m, 20 H, Ph-H). – ^{13}C NMR (75.5 MHz, APT, 2 diastereomers, $CDCl_3$): δ = 41.3, 41.4 (–, CH_2CO_2Me), 46.6, 46.8 (–, OCH_2), 47.3, 47.5, 52.2, 52.3 (+, CH_3, CH), 64.6, 65.7 (+, OCH), 128.4, 128.5, 128.62, 128.68, 128.7, 128.8, 128.9, 129.2, 129.4, 129.8, 130.0, 130.3, 130.6, 130.67, 130.70 (+, 20 C, Ph-CH), 133.0, 133.4, 137.6, 138.5 (–, Ph-C), 168.1, 168.2, 169.1, 169.4, 169.9, 170.0 (–, CON, COO). – MS (EI): *m/z* (%) 368 (3) [M^+], 252 (100), 182 (89), 180 (31), 146 (18), 118 (14), 91 (23), 77 (37). – $C_{20}H_{20}N_2O_5$ (368.39): calcd; C 65.21, H 5.47, N 7.60; found C 64.96, H 5.21, N 7.47.

3,3-Dimethyl-2-[(2-oxiranylacetyl)phenylamino]-*N*-phenylbutyramide (29j): Column



chromatography (EtOAc/hexane, 1:3) of the residue, obtained from trimethylacetaldehyde (190 mg, 2.21 mmol), aniline (186 mg, 2.00 mmol), phenylisonitrile (206 mg, 2.00 mmol) and oxiranylacetic acid **28** (204 mg, 2.00 mmol) according to GP 1.5, gave pure **29j** (339 mg, 46%, R_f = 0.37) as a pale yellow solid, m.p. 115–117 °C. – IR (KBr): ν = 3321, 3286, 3231, 3135, 3057, 3001, 2963, 2870, 1690, 1607, 1536, 1443, 1240, 1163 cm^{-1}. – ^1H NMR (300 MHz, 2 diastereomers, $CDCl_3$): δ = 0.98 (s, 9 H, *t*Bu), 1.02 (s, 9 H, *t*Bu), 2.18–2.50 (m, 6 H, OCH_2, CH_2), 2.70–2.80 (m, 2 H, OCH_2), 3.20–3.30 (m, 2 H, OCH), 5.05 (s, 1 H, CH), 5.09 (s, 1 H, CH), 7.09 (t, 2 H, *J* = 6.0 Hz, Ph-H), 7.22–7.40 (m, 14 H, Ph-H), 7.57 (d, 4 H, *J* = 7.2 Hz, Ph-H), 8.80 (br s, 2H, NH). – ^{13}C NMR (75.5 MHz, APT, 2 diastereomers, $CDCl_3$): δ = 27.8, 27.9 [+, C(CH_3)$_3$], 34.6, 34.7 [–, C(CH_3)$_3$], 38.2, 38.4 (–, CH_2CO), 46.6, 46.7 (–, OCH_2), 48.6, 48.7 (+, CH), 67.8 (+, 2 C, OCH), 119.8, 119.9, 124.1, 124.2, 128.5, 128.76, 128.78, 128.92, 128.93, 129.1, 129.37, 129.43, 129.6, 129.7, 129.8 (+, 20 C, Ph-CH), 137.9, 138.0, 140.5, 140.8 (–, Ph-C), 168.5, 168.6, 172.6, 172.7 (–, CON). – MS (EI): *m/z* (%) 366 (<1) [M^+], 274 (75), 246 (21), 162 (100), 132 (17), 104 (21), 77 (25). – $C_{22}H_{26}N_2O_3$ (366.46): calcd; C 72.11, H 7.15, N 7.64; found C 71.93, H 6.86, N 7.61.

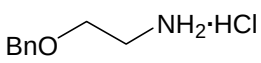
General Procedure for Alkylation of Amine with Alkyl Bromoacetate (GP 1.6).

To the ice cold mixture of 2,2-dimethoxyethylamine (20.0 mmol) and K_2CO_3 (0.2 mol) in acetone (100 mL) the solution of alkyl bromoacetate (20.0 mmol) in acetone (20 mL) was added dropwise and the mixture was stirred additional 12 h at ambient temperature. Acetone was removed *in vacuo*, the residue was dissolved in CH_2Cl_2 (100 mL), washed with water (2 × 30 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was distilled in Kugelrohr or purified by column chromatography on silica gel.

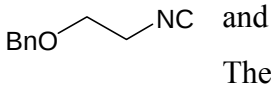
General Procedure for Preparation of Amides (GP 1.7).

To the ice cold suspension of acid (1 mmol) and HOBt×H_2O (1 mmol) in dichloromethane (10 mL) EDC (1 mmol) was added. In 30 min amine (1 mmol) was added and reaction mixture was stirred at ambient temperature for 12 h. The reaction mixture was washed with 1 M aq. solution of $KHSO_4$ (3 × 5 ml), saturated aq. solution of $NaHCO_3$ (3 × 5 ml), brine (5 mL) and dried over $MgSO_4$. After filtration the solution was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel.

2-(Benzyloxy)ethanamine hydrochloride (36): The mixture of sodium (3.45 g, 0.15 mol) and aminoethanol (9.15 g, 0.15 mol) in toluene (50 mL) was heated under reflux for 2 h. Then the solution of benzyl chloride (17.3 mL, 0.15 mol) was added dropwise and the reaction mixture was heated under reflux additional 30 min. The mixture was cold in the ice bath, the solid NaCl was filtered off and the filtrate was concentrated *in vacuo*. To the residue 2 M solution of HCl in EtOAc (100 mL) was added and the solid hydrochloride **36** (10.92 g, 39%) was filtered off, m.p. 143–145 °C. – ^{1}H NMR (250 MHz, CD_3OD): δ = 3.10–3.30 (m, 2 H, CH_2N), 3.70–3.80 (m, 2 H, OCH_2), 4.64 (s, 2 H, CH_2Ph), 4.95 (br s, 2 H, NH_2), 7.30–7.50 (m, 5 H, Ph-H). – ^{13}C NMR (62.9 MHz, CD_3OD): δ = 43.2 (CH_2N), 69.3 (OCH_2*), 76.6 (CH_2Ph*), 131.4, 131.6, 132.0 (5 C, Ph-CH), 141.5 (Ph-C).

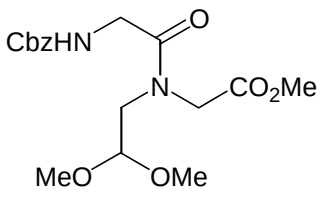


1-((2-Isocyanoethoxy)methyl)benzene (32): The mixture of hydrochloride **36** (9.18 g, 49.0 mmol) and triethyl ortho formaite (24.2 mL, 147 mmol) was heated under reflux for 12 h. The volatiles were removed *in vacuo*, the residue was dissolved in CH_2Cl_2 (150 mL) and washed with water (2 × 50), brine (2 × 50), dried over Na_2SO_4 and concentrated under reduced pressure to give formate (8.07 g, 92%) as a pale yellow solid. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.40–3.70 (m, 4 H, CH_2CH_2), 4.52 (s, 2 H, CH_2Ph), 6.06 (br s, 1 H, NH), 7.30–7.40 (m, 5 H, Ph-H), 8.16 (s, 1 H, CHO).



To the ice cold solution of formamide (941 mg, 5.26 mmol) and triethylamine (2.21 mL, 15.9 mmol) in toluene (10 mL) the 20% toluene solution of phosgene (2.79 mL, 5.3 mmol) was added dropwise. After stirring overnight the solid Et_3N×HCl was filtered off and to the residue CH_2Cl_2 (20 mL) was added, the mixture was washed with water (2 × 10 mL), dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (Et_2O/hexane, 1:1) to give **32** (575 mg, 67%, R_f = 0.66) as a colorless oil which turns brown quickly. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.50–3.65 (m, 2 H, CH_2N*), 3.65–3.75 (m, 2 H, OCH_2*), 4.60 (s, 2 H, CH_2Ph), 7.30–7.40 (m, 5 H, Ph-CH). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 43.1 (CH_2N), 67.2 (OCH_2*), 73.4 (CH_2Ph*), 127.7, 128.0, 128.5 (5 C, Ph-CH), 137.2 (Ph-C), 156.8 (NC).

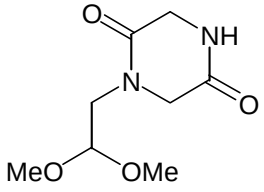
Methyl 2-(2-(Benzyloxycarbonyl)-*N*-(2,2-dimethoxyethyl)acetamido)acetate (38): Distillation (100 C, 1 Torr) of the residue, obtained from 2,2-dimethoxyethylamine **37** (2.2 mL, 20.0 mmol), K_2CO_3 (27.6 g, 0.2 mol) and methyl bromoacetate (1.84 mL, 20.0 mmol) according to GP 1.6, gave pure amine (1.13 g, 32%) as a colorless oil. – ^{1}H NMR (250 MHz, $CDCl_3$): δ



= 2.09 (s, 1 H, NH), 2.76 (d, 2 H, *J* = 5.5 Hz, C*H*$_2$CH), 3.34 (s, 6 H, OMe), 3.45 (s, 2 H, CH$_2$COO), 3.72 (s, 3 H, COOMe), 4.60 (t, 1 H, *J* = 5.5 Hz, CH$_2$C*H*).

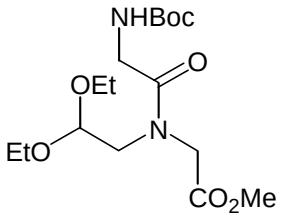
Column chromatography (EtOAc/hexane, 4:1) of the residue obtained from amine (1.19 g, 6.72 mmol), EDC (901 mg, 6.72 mmol), HOBt×H$_2$O (1.03 g, 6.72 mmol) and CbzHN-glicine (1.40 g, 6.72 mmol) according to GP 1.7, gave pure **38** (849 mg, 34%, R_f = 0.57) as a colorless oil. – ^{1}H NMR (250 MHz, CDCl$_3$): δ = 3.30-3.45 (m, 8 H, OMe, CH$_2$), 3.50 (d, 1 H, *J* = 7.5 Hz, CH$_2$), 3.72 (s, 3 H, COOMe), 3.97 (d, 1 H, *J* = 4.3 Hz, CH$_2$), 4.05-4.25 (m, 2 H, CH$_2$), 4.30-4.50 [m, 1 H, C*H*(OMe)$_2$], 5.11 (s, 2 H, CH$_2$Ph), 5.73 (s, 1 H, NH), 7.35 (s, 5 H, Ph-CH).

1-(2,2-Dimethoxyethyl)piperazine-2,5-dione (40): The amide **38** (849 mg, 2.31 mmol) was hydrated on palladium on carbon (50 mg) in EtOAc (20 mL) to give after filtration through a pad of Celite pure **170.1** (424 mg, 91%) as a colorless oil. – ^{1}H NMR (250 MHz, CDCl$_3$): δ = 3.38 (s, 6 H, OMe), 3.46 (d, 2 H, *J* = 5.3 Hz, CH$_2$), 4.00 (s, 2 H, CH$_2$), 4.08 (s, 2 H, CH$_2$), 4.50 (t, 1 H, *J* = 12.5 Hz, CH), 7.57 (br s, 1 H, NH). – ^{13}C NMR (62.9 MHz, CDCl$_3$): δ = 44.9, 48.2, 51.3 (CH$_2$), 54.7 (2 C, OMe), 102.4 (CH), 163.8, 166.6 (CON).

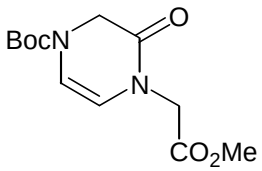


Methyl 2-(2-(*tert*-Butoxycarbonyl)-*N*-(2,2-diethoxyethyl)acetamido)acetate (42): To the ice cold mixture of 2,2-diethoxyethylamine **41** (399 mg, 3.00 mmol) and pyridine (237 mg, 3.00 mmol) in acetonitrile (10 mL) the solution of methyl bromoacetate (459 mg, 3.00 mmol) in acetonitrile (3 mL) was added dropwise during 10 min and the mixture was stirred additional 12 h at ambient temperature. Acetonitrile was removed *in vacuo* and the residue was purified by column chromatography on silica gel (EtOAc/hexane, 2:1) to give amine (281 mg, 46%, R_f = 0.26) as a colorless oil. – ^{1}H NMR (250 MHz, CDCl$_3$): δ = 1.20 (t, 3 H, *J* = 7.0 Hz, CH$_2$C*H*$_3$), 1.21 (t, 3 H, *J* = 7.0 Hz, CH$_2$C*H*$_3$), 2.25 (br s, 1 H, NH), 2.70–2.85 (m, 2 H, CHC*H*$_2$), 3.40–3.80 (m, 9 H, C*H*$_2$CH$_3$, C*H*$_2$CO$_2$C*H*$_3$), 4.60 (br s, 1 H, C*H*CH$_2$).

From amine (552 mg, 2.69 mmol), EDC (360 mg, 2.69 mmol), HOBt×H$_2$O (412 mg, 2.69 mmol) and BocHN-glicine (471 mg, 2.69 mmol) according to GP 1.7 amide **42** (541 mg, 57%) was prepared and was used without further purification. – ^{1}H NMR (250 MHz, CDCl$_3$): δ = 1.10–1.30 (m, 6 H, CH$_2$C*H*$_3$), 1.43 (s, 9 H, *t*Bu), 3.30–3.80 (m, 11 H, C*H*$_2$CH$_3$, C*H*$_2$CO$_2$C*H*$_3$, CHC*H*$_2$), 4.05–4.15 (m, 2 H, C*H*$_2$NH), 4.45–4.60 (m, 1 H, C*H*CH$_2$), 5.42 (br s, 1 H, NH).



***tert*-Butyl 4-(2-Methoxy-2-oxoethyl)-3-oxo-3,4-dihydropyrazine-1(2H)-carboxylate (45):**



Method A. The mixture of the crude **42** (487 mg, 1.35 mmol) and 2 M aq. solution of HCl (2 mL) in THF (10 mL) was stirred at ambient temperature for 2 h. The volatiles were removed *in vacuo* to leave amide **45** (278 mg, 79%) as a pale yellow solid.

Method B. The solution of crude **42** (120 mg, 0.33 mmol) in EtOAc (10 mL) the 1 M solution of HCl in EtOAc (5 ml) was added, in 5 min the reaction mixture was concentrated *in vacuo* to give **45** (53 mg, 60%).

– ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.48 (s, 9 H, *t*Bu), 3.74 (s, 3 H, OMe), 4.23 (s, 2 H, CH_2CO_2Me*), 4.29 (s, 2 H, CH_2CO*), 5.37 (d, 0.5 H, *J* = 6.0 Hz, =C*H*NCH_2), 5.47 (d, 0.5 H, *J* = 6.0 Hz, =C*H*NCH_2), 6.29 (d, 0.5 H, *J* = 6.0 Hz, =C*H*NBoc), 6.44 (d, 0.5 H, *J* = 6.0 Hz, =C*H*NBoc). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 28.1 [$C(CH_3)_3$], 46.8, 47.5 (CH_2), 52.4 (OMe), 82.2 [$C(CH_3)_3$], 110.4, 111.3 (=CH), 163.4 (NCOO), 168.3 (NCO), 176.5 (COO). – MS (ESI): *m/z* (%) 270 (<1), 214 (8), 170 (4), 141 (4), 97 (6), 83 (13), 57 (100).

2.2. Synthesis of Compounds in Chapter 2

General Procedure for the Preparation of α-Diazoketones from *N*-Protected Amino Acids (GP 2.1). To a stirred solution of acid (10 mmol) and *N*-methylmorpholine (11 mmol) in anhydrous THF (10 mL) chilled to –30 °C *iso*-butylchorformate (10.5 mmol) was added all at once. After stirring by cooling for an additional 30 min, the reaction mixture was allowed to warm to ambient temperature and solution of diazomethane in Et_2O (~1 M) was added dropwise until the yellow color did not disappeared anymore. After stirring at ambient temperature for an additional 30 min, the reaction mixture was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel.

General Procedure for the Preparation of α-Chloroketones from α-Diazoketones (GP 2.2). To a stirred solution of the respective diazocompound (5 mmol) in Et_2O (25 mL) a 35–37% aq. solution of HCl (2.0 mL) was carefully added (N_2 evolution) at ambient temperature and, after stirring for an additional 10 min, the reaction mixture was washed with saturated aq. solution of $NaHCO_3$ (1 × 10 mL), brine (1 × 10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was used further either without an additional purification, or purified by column chromatography on silica gel.

General Procedure for the Preparation of α-Thiophenylmethylketones (GP 2.3). To a stirred suspension of sodium thiophenolate (1.5 mmol) in anhydrous benzene (5 mL) the respective chloroketone (1.0 mmol) was added, and the reaction mixture was stirred at ambient temperature for 12 h. The reaction mixture was washed with H_2O (2 × 5 mL), brine (1 ×5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was used further either without an additional purification, or purified by column chromatography on silica gel.

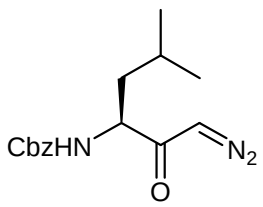
General Procedure for Oxidation of the Methylene Group of α-Thiophenylmethylketones with Sulfuryl Chloride (GP 2.4). To a stirred solution of thiophenyl derivateve (1 mmol) and anhydrous pyridine (5 mmol) in CCl_4 (25 mL) the solution of sulfuryl chloride (2 mmol) in CCl_4 (5 mL) was added dropwise at 0 °C within 5 min. After an additional stirring for 15 min water (10 mL) was added, the layers were separated and the aqueous layer was extracted with CCl_4 (3 × 10 mL). The combined organic layers were washed with 1 M aq. solution of $KHSO_4$ (2 × 10 mL), brine (2 × 10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was used further either without an additional purification, or purified by column chromatography on silica gel.

General Procedure for Hydrolysis of Dichlorothiophenyl Derivatives (GP 2.5). To the stirred solution of dichlorothiophenyl derivative (1 mmol) and pyridine (4 mmol) in 95% aq. MeOH (20 mL) mercury (II) chloride (2 mmol) was added all at once. After stirring at ambient temperature for an additional 12 h, the reaction mixture was concentrated *in vacuo*, to the residue CH_2Cl_2 (20 mL) was added and the obtained suspension was filtered through a pad of Celite. The filtrate was washed with 1 M aq. solution of $KHSO_4$ (2 × 10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was further used without an additional purification or purified by column chromatography on silica gel.

General Procedure for Condensation of Aldehydes with Tris(methylthio)methane (GP 2.6). To a stirred solution of tris(methylthio)methane (24 mmol) in anhydrous THF (25 mL) solution of *n*BuLi (8.9 mL, 23 mmol, 2.6 M in cyclohexane) was added dropwise at –70 °C within 15 min. After stirring at the same temperature for an additional 30 min, respective aldehyde (10 mmol) dissolved in anhydrous THF (15 mL) was added dropwise within 30 min. After stirring under cooling for an additional 4 h, the reaction mixture was quenched with saturated aq. solution of NH_4Cl (10 mL) and allowed to warm to ambient temperature. Two layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel.

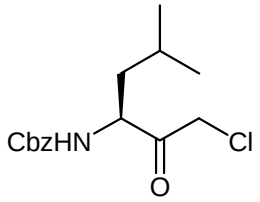
General Procedure for Hydrolysis of Trimethylthioformates into Methyl Esters (GP 2.7). The suspension of the respective orhtothioester (1 mmol), HgO (2 mmol) and $HgCl_2$ (4 mmol) in 95% aq. MeOH (25 mL) was stirred at ambient temperature for 12 h. Then the solvents were removed under reduced pressure, the residue was triturated with CH_2Cl_2 (30 mL) and filtered through a pad of Celite. The filtrate was washed with water, 75% aq. solution of NH_4OAc (20 mL), brine (2 × 10 mL), and dried over $MgSO_4$. The residue, left after the solvent removal, was subjected to column chromatography on silica gel or crystallization to a pure product.

(*S*)-Benzyl 1-Diazo-5-methyl-2-oxohexan-3-ylcarbamate (49): Column chromatography (Et_2O/hexane, 1:1) of the residue, obtained from ZHN-Leu-COOH **48** (295 mg, 1.10 mmol), *iso*-butylchorformate (0.15 mL, 1.15 mmol) and *N*-methylmorpholine (0.13 mL, 1.20 mmol) according to GP 2.1, gave **49** (275 mg, 86%, R_f = 0.21) as a pale yellow oil. – ^{1}H NMR (250 MHz, $CDCl_3$): δ =

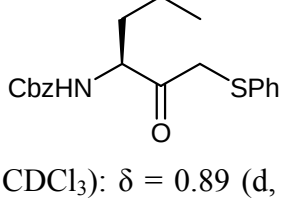


0.80–1.00 (m, 6 H, CH_3), 1.30–1.80 (m, 3 H, CH_2CH), 4.26 (br s, 1 H, NHC*H*), 5.10 (s, 2 H, CH_2Ph), 5.22 (br s, 1 H, NH), 5.42 (br s, 1 H, CHN_2), 7.30–7.40 (m, 5 H, Ph-CH).

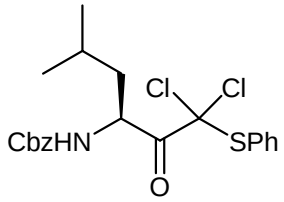
(*S*)-Benzyl 1-Chloro-5-methyl-2-oxohexan-3-ylcarbamate (51): From diazoketone **49** (1.19 g, 4.10 mmol) and 35–37% aq. solution of HCl (2 mL) **a**ccording to GP 2.2, **51** (1.20 g, 98%) was prepared and was further used without an additional purification. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.80–1.05 (m, 6 H, CH_3), 1.35–1.80 (m, 3 H, $CHCH_2$), 4.27 (s, 2 H, CH_2Cl), 4.55–4.70 (m, 1 H, C*H*NH), 5.10 (s, 2 H, CH_2Ph), 5.16 (d, 1 H, *J* = 9.0 Hz, NH), 7.30–7.45 (m, 5 H, Ph-H).



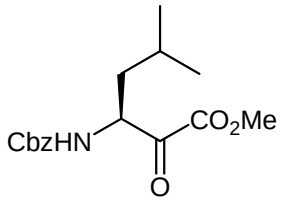
(*S*)-Benzyl 5-Methyl-2-oxo-1-(phenylthio)hexan-3-ylcarbamate (52): Column chromatography (Et_2O/hexane, 1:1) of the residue, obtained from **51** (1.20 g, 4.03 mmol) and sodium thiophenolate (799 mg, 6.05 mmol) according to GP 2.3, gave pure **52** (1.27 g, 85%, R_f = 0.47) as a colorless oil. – IR (film): ν = 3333 cm^{-1}, 3063, 3033, 2957, 2870, 1700, 1521, 1259, 1027. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (d, 3 H, *J* = 6.8 Hz, CH_3), 0.93 (d, 3 H, *J* = 6.8 Hz, CH_3), 1.30–1.80 (m, 3 H, CH_2CH), 3.82 (s, 2 H, CH_2SPh), 4.65 (dt, 1 H, *J* = 2.8 Hz, *J* = 9.3 Hz, NHC*H*), 5.10 (s, 2 H, CH_2Ph), 5.18 (d, 1 H, *J* = 9.3 Hz, NH), 7.20–7.40 (m, 10 H, Ph-CH). – ^{13}C NMR (75.6 MHz, APT, $CDCl_3$): δ = 21.5, 23.2, 24.7 [+, $CH(CH_3)_2$], 40.6, 41.9 (–, *C*H_2CH, *C*H_2SPh), 56.7 (+, CH), 66.9 (–, CH_2Ph), 127.1, 128.0, 128.2, 128.5, 129.1, 130.1 (+, 10 C, Ph-CH), 134.3, 136.1 (–, Ph-C), 155.9 (–, NHCOO), 204.3 (–, CO). – MS (EI), *m/z* (%) = 371 (8), 220 (20), 176 (33), 91 (100).



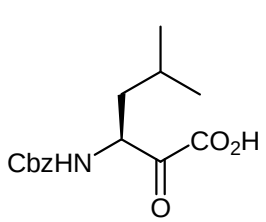
(*S*)-Benzyl 1,1-Dichloro-5-methyl-2-oxo-1-(phenylthio)hexan-3-ylcarbamate (53): Column chromatography (Et_2O/hexane, 1:1) of the residue, obtained from sulfuryl chloride (918 mg, 6.80 mmol), pyridine (1.34 g, 17.0 mmol) and **52** (1.20 g, 3.2 mmol) according to GP 2.4, gave pure **53** (859 mg, 61%, R_f = 0.54) as a colorless oil. – IR (film): ν = 3389 cm^{-1}, 3061, 2955, 2872, 1733, 1506, 1217, 1047. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.94 (d, 3 H, *J* = 5.8 Hz, CH_3), 1.03 (d, 3 H, *J* = 5.8 Hz, CH_3), 1.40–1.60 (m, 1 H, $CHCH_2$), 1.70–1.90 (m, 2 H, CH_2), 5.05–5.25 (m, 3 H, CH_2Ph, NH), 5.39 (t, 1 H, *J* = 10.3 Hz, NHC*H*), 7.30–7.60 (m, 10 H, Ph-CH).– ^{13}C NMR (75.6 MHz, APT, $CDCl_3$): δ = 21.2, 23.4, 25.0 [+, $CH(CH_3)_2$], 43.6 (–, $CHCH_2$), 52.9 (+, NHCH), 67.2 (–, CH_2Ph), 91.8 (–, CCl_2), 128.2, 128.3, 128.6, 129.1, 131.2 (+, 10 C, Ph-CH), 136.1 (–, Ph-C), 137.3 (+, Ph-CH), 155.3 (–, NHCOO), 194.3 (–, CO). – MS (DCI), *m/z* (%) = 904/902/900/898/896 (16/23/55/90/62) [2 M + NH_4^+], 461/459/457 (14/73/100) [M + NH_4^+].



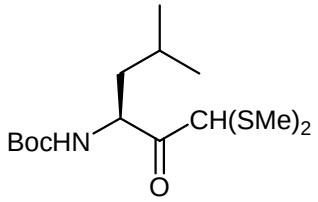
(*S*)-Methyl 3-(Benzyloxycarbonyl)-5-methyl-2-oxohexanoate (54): Column chromatography (Et_2O/hexane, 1:1) of the residue, obtained from **53** (385 mg, 0.86 mmol), mercury (II) chloride (544 mg, 2.00 mmol) and pyridine (316 mg, 4.00 mmol) according to GP 2.5, gave **54** (96 mg, 36%, R_f = 0.32) as a colorless oil. – IR (film): ν = 3482 cm^{-1}, 3415, 3240, 2256, 2129, 1653, 1026. – ^1H NMR (300 MHz, DMSO): δ = 0.87 [d, 6 H, *J* = 6.5 Hz, $CH(CH_3)_2$], 0.40–0.70 (m, 3 H, CH_2CH), 3.77 (s, 3 H, OMe), 4.68–4.70 (m, 1 H, CH), 5.01 (d, 2 H, *J* = 2.0 Hz, CH_2Ph), 7.30–7.45 (m, 5 H, Ph-CH), 7.86 (d, 1 H, *J* = 7.5 Hz, NH).– ^{13}C NMR (75.6 MHz, APT, DMSO): δ = 20.9, 23.0, 24.4 [+, $CH(CH_3)_2$], 37.4 (–, CH_2CH), 52.8, 55.4 (+, CH, OMe), 127.4, 127.7, 128.4 (+, 5 C, Ph-CH), 136.8 (–, Ph-C), 156.1 (–, NHCOO), 193.5 (–, CO). – MS (DCI), *m/z* (%) = 632 (20) [2 M + NH_4^+], 325 (100) [M + NH_4^+], 308 (2) [M + H^+].



(*S*)-3-(Benzyloxycarbonyl)-5-methyl-2-oxohexanoic Acid (50): To a stirred solution of **54** (89 mg, 0.29 mmol) in MeOH (3 mL) solution of NaOH in MeOH/H_2O (1:1) (1 M, 0.35 mL) was added at ambient temperature all at once. After stirring for an additional 15 min, the reaction mixture was quenched with water (10 mL), acidified with 1 M solution of HCl to pH ~ 1 and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to give **50** (68 mg, 80%) as a colorless oil. – ^1H NMR (250 MHz, $CDCl_3$): δ = 0.90–1.05 (m, 6 H, CH_3), 1.30–1.80 [m, 3 H, $CH_2CH(CH_3)_2$], 5.00–5.20 (m, 3 H, CH_2Ph, CH), 5.31 (d, 1 H, *J* = 8.0 Hz, NH), 7.10 (br s, 1 H, COOH), 7.30–7.40 (m, 5 H, Ph-CH).



(*S*)-*tert*-Butyl 5-Methyl-1,1-bis(methylthio)-2-oxohexan-3-ylcarbamate (59): Column chromatography (Et_2O/hexane, 1:5) of the residue, obtained from tris(methylthio)methane (2.97 mL, 22.3 mmol), 2.6 M solution of *n*BuLi in cyclohexane (8.20 mL, 21.4 mmol) and **57** (2.00 g, 9.3 mmol) according to GP 2.6, gave pure **59** (1.26 g, 42%, R_f = 0.41) as a colorless oil. – IR (film): ν = 3374 cm^{-1}, 2989, 2966, 2936, 2870, 1685, 1513, 1369, 1270, 1173. – ^1H NMR (300 MHz, $CDCl_3$): δ = 0.88–0.96 (m, 6 H, CH_3), 1.41 [s, 9 H, $C(CH_3)_3$], 1.50–1.76 (m, 3 H, CH_2CH), 1.98 (s, 3 H, SMe), 2.04 (s, 3 H, SMe), 4.62–4.70 [m, 2 H, CH, $CH(SMe)_2$], 4.85 (d, 1 H, *J* = 9.0 Hz, NH). – ^{13}C NMR (300 MHz, APT, $CDCl_3$): δ = 11.8, 12.6, 21.6, 23.2, 24.9 [+, $CH(CH_3)_2$, SMe], 28.2 [+, $C(CH_3)_3$], 41.2 (–, CH_2), 55.3, 57.9 [+, CH, $CH(SMe)_2$], 80.0 [–, $C(CH_3)_3$], 155.4 (–, HNCOO), 200.0 (–, CO). – MS (ESI) *m/z* (%) = 664 (4) [2 M + Na^+], 344 (100) [M + Na^+].



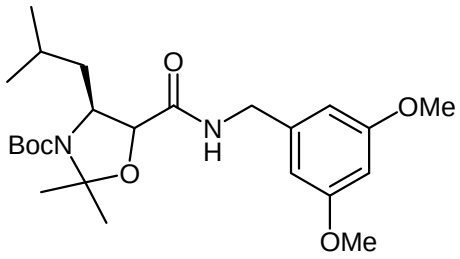
(3*S*)-Methyl 3-(*tert*-Butoxycarbonyl)-2-hydroxy-5-methylhexanoate (60): According to GP 2.7 from **59** (369 mg, 1.00 mmol), mercury (II) oxide (434 mg, 2.00 mmol) and mercury (II) chloride (1.09 g, 4.00 mmol) in 95% MeOH (25 mL) and after crystallization pure ester **60** (181 mg, 66%) was obtained as colorless solid, m.p. 69–70 °C. – IR (film): ν = 3489 cm^{-1}, 3410, 2979, 2957, 2871, 1738, 1688, 1513, 1386, 1249, 1173, 1091. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.92 (d, 6 H, *J* = 6.0 Hz, CH_3), 1.30–1.70 [m, 12 H, CH_2CH, $C(CH_3)_3$], 3.78 (s, 3 H, OMe), 4.00–4.15 (m, 2 H, C*H*CHO*H*), 4.59 (d, 1 H, *J* = 9.0 Hz, C*H*OH). – ^{13}H NMR (50.3 MHz, APT, $CDCl_3$): δ = 22.1, 22.8, 24.8 [+, $(CH_3)_2CH$], 28.3 [+, $C(CH_3)_3$], 41.0 (–, CH_2), 51.1 (+, *C*HCHOH), 52.8 (+, OMe), 72.3 (+, CH*C*HOH), 79.4 [–, $C(CH_3)_3$], 155.3 (–, NCO), 174.3 (–, COO). – MS (DCI): *m/z* (%) = 568 (100) [2 M + NH_4^+], 293 (61) [M + NH_4^+], 276 (6) [M + H^+]. – $C_{13}H_{25}NO_5$ (275.35): calcd; C 56.71, H 9.15, N 5.09; found C 56.46, H 8.99, N 4.92.

(4*S*)-3-*tert*-Butyl 5-Methyl 4-Isobutyl-2,2-dimethyloxazolidine-3,5-dicarboxylate (62): To a stirred solution of **60** (325 mg, 1.24 mmol) and 2,2-dimethoxypropane **61** (0.77 mL, 6.20 mmol) in CH_2Cl_2 (10 mL) toluene-4-sulfonic acid monohydrate (25 mg, 0.13 mmol) and Na_2SO_4 (150 mg) were added all at once. After stirring at ambient temperature for an additional 2 h the reaction mixture was washed with saturated solution of $NaHCO_3$ (1 × 5 mL), brine (1 × 5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (Et_2O/hexane, 1:1) to give **62** (233 mg, 60%, R_f = 0.72) as a colorless oil. – IR (film): ν = 2958 cm^{-1}, 2935, 2875, 2231, 1751, 1685, 1392, 1006. – ^{1}H NMR (300 MHz, $C_2D_2Cl_4$, 100 °C): δ = 0.99 (d, 3 H, *J* = 3.0 Hz, CHC*H*$_3$), 1.02 (d, 3 H, *J* = 3.0 Hz, CHC*H*$_3$), 1.48 [s, 9 H, $C(CH_3)_3$], 1.50–1.75 (m, 9 H, CH_3, CH_2CH), 3.76 (s, 3 H, OMe), 4.28 (dt, 1 H, *J* = 3.0 Hz, *J* = 9.0 Hz, NCH), 4.32 (d, 1 H, *J* = 3.0 Hz, OCH). – ^{13}H NMR (75.6 MHz, APT, $C_2D_2Cl_4$, 100 °C): δ = 21.3, 23.3, 25.4, 26.5, 27.9 (+, CH_3, CH), 28.2 [+, $C(CH_3)_3$], 43.4 (–, CH_2), 51.7 (+, OCH_3), 58.9 (+, NCH), 78.4 (+, OCH), 79.7 [–, $C(CH_3)_3$], 95.7 [–, $C(CH_3)_2$], 150.9 (–, NCO), 171.7 (–, COO). – MS (DCI): *m/z* (%) = 338 (100) [M + Na^+], 298 (9), 223 (8). – $C_{16}H_{29}NO_5$ (315.41): calcd; C 60.93, H 9.27, N 4.44; found C 60.69, H 9.05, N 4.29.

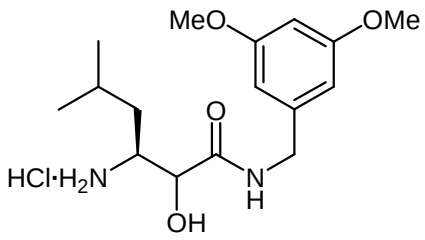
(4*S*)-3-(*tert*-Butoxycarbonyl)-4-isobutyl-2,2-dimethyloxazolidine-5-carboxylic Acid (63): A solution of **62** (200 mg, 0.64 mmol) and $LiOH·H_2O$ (29 mg, 0.70 mmol) in MeOH/THF (1.2 mL/4.8 ml) was stirred at ambient temperature for 1 h, the solvents were removed *in vacuo* and the residue was dissolved in EtOAc (20 mL). The organic solution was washed with 10% aq. solution of citron acid (1

× 5 mL), brine (1 × 5 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give **63** (190 mg, 99%) as a pale yellow oil. – IR (film): ν = 2957 cm^{-1}, 2935, 2875, 2231, 1723, 1690, 1392, 1006. – ^{1}H NMR (300 MHz, $C_2D_2Cl_4$, 100 °C): δ = 1.01 (d, 3 H, *J* = 5.0 Hz, CH_3), 1.04 (d, 3 H, *J* = 5.0 Hz, CH_3), 1.50 [s, 9 H, $C(CH_3)_3$], 1.55–1.80 (m, 9 H, CH_3, CH_2CH), 4.30–4.40 (m, 2 H, NCH, OCH). – ^{13}H NMR (75.6 MHz, APT, $C_2D_2Cl_4$, 100 °C): δ = 21.2, 23.3, 25.4, 26.8, 27.8 (+, CH_3, CH), 28.2 [+, $C(CH_3)_3$], 43.5 (–, CH_2), 58.9 (+, NCH), 78.0 (+, OCH), 80.2 [–, $C(CH_3)_3$], 96.2 (–, C_{quat}), 151.0 (–, NCOO), 173.1 (–, COOH).– MS (ESI): *m/z* (%) = 346 (100) [M – H + 2 Na^+], 324 (16) [M + Na^+].

(4*S*)-*tert*-Butyl 5-((3,5-Dimethoxybenzyl)carbamoyl)-4-isobutyl-2,2-dimethyloxazolidine-3-carboxylate (64): To a suspension of acid **63** (164 mg, 0.55 mmol) and HOAt (83 mg, 0.61 mmol) in CH_2Cl_2 (10 mL) EDC (82 mg, 0.61 mmol) was added at 0 °C within 5 min. After stirring under cooling for an additional 30 min, 3,5-dimethoxybenzylamine **55** (110 mg, 0.66 mmol) dissolved in CH_2Cl_2 (5 mL) was added all at once. After stirring at ambient temperature for 12 h the reaction mixture was washed with 1 M aq. solution of $KHSO_4$ (3 × 10 ml), saturated aq. solution of $NaHCO_3$ (3 × 10 ml), brine (10 mL) and dried over $MgSO_4$. After filtration the solution was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (Et_2O/hexane, 1:2) to give pure amide **64** (210 mg, 85%, R_f = 0.44) as a colorless oil. – IR (film): ν = 3427 cm^{-1}, 3363, 2956, 2875, 2837, 1701, 1598, 1522, 1458, 1386, 1205, 1068. – ^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.94 (d, 3 H, *J* = 5.0 Hz, CH_3), 0.99 (d, 3 H, *J* = 5.0 Hz, CH_3), 1.44 [s, 9 H, $C(CH_3)_3$], 1.50–1.80 (m, 9 H, $CHCH_3$, CH_3), 3.62 (s, 6 H, OMe), 4.23 (s, 1 H, NCH), 4.32–4.40 (m, 3 H, CH_2, OCH), 6.32–6.35 (m, 1 H, Ph-H), 6.35–6.40 (m, 2 H, Ph-H), 6.84 (br s, 1 H, NH).– MS (ESI): *m/z* (%) = 923 (100) [2 M + Na^+], 473 (29) [M + Na^+].

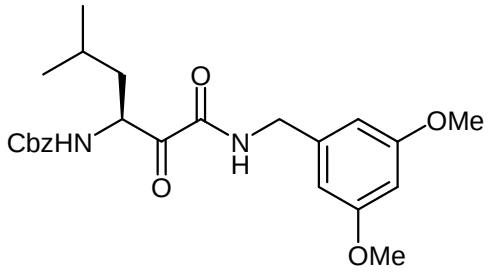


(3*S*)-*N*-(3,5-Dimethoxybenzyl)-3-amino-2-hydroxy-5-methylhexanamide Hydrochloride (65): To a stirred solution of **64** (189 mg, 0.42 mmol) in MeOH (5 mL) 5 % aq. solution of HCl (0.25 mL) was added all at once. After heating at 50 °C for an additional 24 h, the reaction mixture was concentrated under reduced pressure to leave **65** (146 mg, quant.) as colorless solid. – IR (KBr): ν = 3359 cm^{-1}, 2968, 2493, 2071, 1653, 1457, 1201, 1122, 976.– ^{1}H NMR (300 MHz, CD_3OD): δ = 0.95 (t, 6 H, *J* = 5.5 Hz, CH_3), 1.40–1.80 (m, 3 H, CH_2CH), 3.55 (dt, 1 H, *J* = 3.5 Hz, *J* = 5.5 Hz, C*H*NH_2), 3.75 (s, 6 H, OMe), 4.20–4.30 (m, 2 H, C*H*OH, CH_2Ph), 4.56 (d, 1 H, *J* = 15.0 Hz, CH_2Ph), 6.41 (t, 1 H,



J = 3.0 Hz, Ph-H), 6.53 (d, 2 H, J = 3.0 Hz, Ph-H), OH and NH signals were not detectable. – ^{13}C NMR (75.6 MHz, CD_3OD): δ = 22.5, 22.7 (+, CH_3), 25.2 [+, $CH(CH_3)_2$], 39.3 (–, CH_2CH), 43.9 (–, CH_2Ph), 53.1 (+, NCH), 55.8 (+, 2 C, OMe), 71.1 (+, CHOH), 99.9, 106.7 (+, 3 C, Ph-CH), 141.9, 162.5, 173.4 (–, 4 C, Ph-C, CON).– MS (ESI): *m/z* (%) = 621 (60) [2 M + H^+], 311 (100) [M + H^+].

(*S*)-Benzyl 1-(3,5-Dimethoxybenzylamino)-5-methyl-1,2-dioxohexan-3-ylcarbamate (66): To a stirred solution of **65** (50 mg, 0.144 mmol) and triethylamine (43 mg, 0.43 mmol) in THF (5 mL) benzyloxycarbonyl chloride was added at ambient temperature in one portion. After stirring at ambient temperature for an additional 24 h, the reaction mixture was quenched with water (10 mL). Two layers were separated and aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combained organic phases were washed with brine (1 × 5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (Et_2O/hexane, 4:1) to give α-hydroxyamide (54 mg, 84%, R_f = 0.20) as a colorless oil. – ^{1}H NMR (300 MHz, $C_2D_2Cl_4$, 100 °C): δ = 0.80–1.00 (m, 6 H, CH_3), 1.30–1.50 (m, 1 H, CHCH_2), 1.55–1.80 (m, 2 H, $CHCH_2$), 3.77 (s, 6 H, OMe), 3.90–4.05 (m, 1 H, C*H*NH), 4.16 (d, 1 H, J = 2.7 Hz, C*H*OH), 4.33 (dq, J = 6.0 Hz, J = 14.8 Hz, J = 31.8 Hz, CH_2Ph), 5.03 (s, 2 H, CH_2Ph), 5.60 (d, 1 H, NH), 6.34 (t, 1 H, J = 2.3 Hz, Ph-H), 6.39 (d, 2 H, J = 2.0 Hz, Ph-H), 7.17 (br s, 1 H, NH), 7.28–7.40 (m, 5 H, Ph-H), OH signal was not detectable.



To a stirred solution of α-hydroxyamide (11 mg, 0.025 mmol) in CH_2Cl_2 (5 mL) solid $NaHCO_3$ (3 mg, 0.035 mmol) and the Dess-Martin reagent (13 mg, 0.03 mmol) were added at ambient temperature, correspondently. After stirring for an additional 15 min, the solution was concentrated under reduced pressure and the residue was purified by column chromatography on silica gel (Et_2O/hexane, 4:1) to give pure **66** (8 mg, 73%, R_f = 0.58) as a colorless oil. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.91 (d, 3 H, J = 6.0 Hz, CH_3), 1.03 (d, 3 H, J = 6.0 Hz, CH_3), 1.35–1.45 (m, 1 H, CH_2), 1.65–1.85 (m, 2 H, $CHCH_2$), 3.75 (s, 6 H, OMe), 4.38 (d, 2 H, J = 6.0 Hz, NHCH_2Ph), 5.08 (s, 2 H, OCH_2Ph), 5.12–5.35 (m, 2 H, CH, NH), 6.35–6.44 (m, 3 H, Ph-H), 7.12 (br s, 1 H, NH), 7.30–7.40 (m, 5 H, Ph-H). – ^{13}C NMR (75.5 MHz, APT, HSQC, $CDCl_3$): δ = 21.4, 23.2 (+, CH_3), 25.2 [+, $CH(CH_3)_2$], 40.8 (–, CH_2CH), 43.5 (–, NHCH_2Ph), 54.9 (+, CH), 55.4 (+, OMe), 67.1 (–, CH_2Ph), 99.7, 105.8 (+, 3 C, $NHCH_2$Ph-*C*H), 128.1, 128.2, 128.5 (+, 5 C, Ph-CH), 136.1, 138.9, 155.9, 158.8, 161.1 (–, $NHCH_2$Ph-*C*, Ph-C, CONH, NHCOO), 196.7 (–, *C*OCONH). – MS (EI): *m/z* (%) = 442 (10) [M^+], 414 (11), 307 (7), 220 (8), 194 (10), 176 (41), 151 (59), 91 (100).

Benzyl (*S*)-1-((*S*)-1-(3,5-Dimethoxybenzylamino)-5-methyl-1,2-dioxohexan-3-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (67): To a stirred suspension of ZNH-Val-COOH (20 mg, 0.08 mmol), HOAt (11 mg, 0.08 mmol) and DIEA (14 mg, 0.11 mmol) in CH_2Cl_2 (5 mL) EDC (11 mg, 0.08 mmol) was added at 0 °C all at once and after stirring for an additional 30 min, hydrochloride **65** (24 mg, 0.07 mmol) was added in one portion. After stirring at ambient temperature for an additional 12 h, the reaction mixture was washed with 1 M aq. solution of $KHSO_4$ (3 × 5 ml), saturated aq. solution of $NaHCO_3$ (3 × 5 ml), brine (5 mL), dried over $MgSO_4$ and concentrated under reduced pressure. To the residue dissolved in CH_2Cl_2 (1 ml), $NaHCO_3$ (8 mg, 0.10 mmol) and Dess-Martin reagent (36 mg, 0.08 mmol) were added at ambient temperature, correspondently. After stirring for an additional15 min, the reaction mixture was concentrated under reduced pressure and purified by column chromatography on silica gel (EtOAc/hexane, 1:1) to give **67** (23 mg, 61%, R_f = 0.61) as a colorless oil. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85–1.00 (m, 12 H, CH_3), 1.40–1.80 (m, 3 H, $CHCH_2$), 2.02–2.16 [m, 1 H, C*H*$(CH_3)_2$], 3.74 (s, 6 H, OMe), 3.95–4.05 [m, 1 H, NHC*H*$CH(CH_3)_2$], 4.38 (d, 2 H, *J* = 6.0 Hz, $NHCH_2Ph$), 5.08 (s, 2 H, CH_2Ph), 5.28–5.38 [m, 2 H, C*H*$CH_2CH(CH_3)_2$, NH], 6.32–6.42 (m, 3 H, $NHCH_2Ph$-C*H*), 7.14 (br s, 1 H, NH), 7.35–7.38 (m, 5 H, Ph-CH). – ^{13}C NMR (75.5 MHz, APT, $CDCl_3$): δ = 17.7, 19.1, 21.4, 23.1, 25.2, 30.9 [+, $CH(CH_3)_2$], 40.4 (–, *C*H_2CH), 43.5 (–, $NHCH_2Ph$), 53.3 [+, *C*$HCH_2CH(CH_3)_2$], 55.4 (+, OMe), 60.2 [+, *C*$HCH(CH_3)_2$], 67.1 (–, CH_2Ph), 99.7, 105.8 (+, 3 C, $NHCH_2Ph$-*C*H), 128.0, 128.2, 128.5 (+, 5 C, Ph-CH), 136.1, 138.9, 156.4, 158.0, 161.1 (–, 6 C, NHCOO, CO*C*ONH, $NHCH_2Ph$-C, Ph-C), 171.0 (–, NHCO), 196.0 (–, *C*OCONH). – MS (ESI) *m/z* (%) = 1080 (48) [2 M – H$^-$], 540 (27) [M – H$^-$], 432 (100).

Benzyl (3*S*,4*S*)-1-Diazo-4-methyl-2-oxohexan-3-ylcarbamate (74): Column chromatography (Et_2O/hexane, 1:1) of the residue, obtained from ZHN-Ile-COOH **73** (2.00 g, 7.55 mmol), *N*-methylmorpholine (0.99 mL, 9.06 mmol) and isobutylchorformate (1.08 mL, 8.31 mmol) according to GP 2.1, gave pure **74** (1.51 g, 69%, R_f = 0.37) as a colorless oil. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, 3 H, *J* = 7.3 Hz, *J* = 7.3 Hz, CH_2CH_3), 0.99 (d, 3 H, *J* = 6.8 Hz, $CHCH_3$), 1.00–1.20 (m, 1 H, C*H*$_2CH_3$), 1.35–1.50 (m, 1 H, C*H*$_2CH_3$), 1.70–1.90 (m, 1 H, C*H*CH_3), 4.60 (br s, 1 H, NHC*H*CO), 5.10 (s, 2 H, CH_2Ph), 5.38 (br s, 2 H, NH, CHN_2), 7.30–7.40 (m, 5 H, Ph-H). – ^{13}C NMR (75.5 MHz, APT, $CDCl_3$): δ = 11.5, 15.6 (+, CH_3), 24.5 (–, *C*H_2CH_3), 37.7 (+, C*H*CH_3), 54.9, 62.3 (+, NH*C*HCO, CHN_2), 128.1, 128.2, 128.5 (+, 5 C, Ph-CH), 136.2 (–, Ph-C), 156.2 (–,

NHCOO), 193.3 (–, CO). – MS (DCI) *m/z* (%) = 596 (60) [2 M + NH_4^+], 551 (100), 397 (46), 307 (25) [M + NH_4^+], 262 (53).

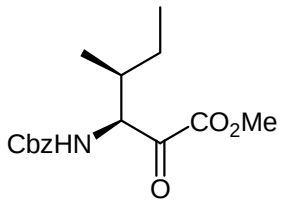
Benzyl (3*S*,4*S*)-1-Chloro-4-methyl-2-oxohexan-3-ylcarbamate (75): Column chromatography (Et_2O/hexane, 1:1) of the residue, obtained from **74** (1.44 g, 4.99 mmol) and 35–37% aq. solution of HCl (2.0 mL) according to GP 2.2, gave pure **75** (1.24 g, 84%, R_f = 0.63) as a colorless oil. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, 3 H, *J* = 7.3 Hz, *J* = 7.3 Hz, CH_2CH_3), 1.00 (d, 3 H, *J* = 6.8 Hz, $CHCH_3$), 1.05–1.20 (m, 1 H, CH_2CH_3), 1.20–1.40 (m, 1 H, CH_2CH_3), 1.80–2.00 (m, 1 H, $CHCH_3$), 4.21 (d, 1 H, *J* = 15.0 Hz, CH_2Cl), 4.30 (d, 1 H, *J* = 15.0 Hz, CH_2Cl), 4.54 (dd, 1 H, *J* = 5.0 Hz, *J* = 8.5 Hz, NHCHCO), 5.10 (s, 2 H, CH_2Ph), 5.30 (d, 1 H, *J* = 8.5 Hz, NH), 7.30–7.40 (m, 5 H, Ph-H). – ^{13}C NMR (75.5 MHz, APT, $CDCl_3$): δ = 11.4, 16.0 (+, CH_3), 24.2 (–, CH_2CH_3), 36.9 (+, $CHCH_3$), 47.5 (–, CH_2Cl), 62.2 (+, NHCHCO), 67.3 (–, CH_2Ph), 128.1, 128.3, 128.6 (+, 5 C, Ph-CH), 135.9 (–, Ph-C), 156.3 (–, NHCOO), 201.5 (–, CO). – MS (ESI) *m/z* (%) = 614/612 (<1/1) [2 M + NH_4^+], 317/315 (28/82) [M + NH_4^+], 281 (100).

Benzyl (3*S*,4*S*)-1,1-Dichloro-4-methyl-2-oxo-1-(phenylthio)hexan-3-ylcarbamate (76): The thiophenyle derivative (1.24 g, 85%), obtained from **75** (1.16 g, 3.90 mmol) and sodium thiophenolate (779 mg, 5.90 mmol) according to GP 2.3, was further used without an additional purification. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84 (t, 3 H, *J* = 7.3 Hz, *J* = 7.3 Hz, CH_2CH_3), 0.95 (d, 3 H, *J* = 6.8 Hz, $CHCH_3$), 0.98–1.10 (m, 1 H, CH_2CH_3), 1.18–1.30 (m, 1 H, CH_2CH_3), 1.80–2.00 (m, 1 H, $CHCH_3$), 3.82 (s, 2 H, CH_2S), 4.63 (dd, 1 H, *J* = 4.8 Hz, *J* = 9.0 Hz, NHCHCO), 5.10 (s, 2 H, CH_2Ph), 5.30 (d, 1 H, *J* = 9.0 Hz), 7.10–7.40 (m, 10 H, Ph-H). – ^{13}C NMR (75.5 MHz, APT, $CDCl_3$): δ = 11.5, 16.0 (+, CH_3), 24.0 (–, CH_2CH_3), 37.0 (+, $CHCH_3$), 43.0 (–, CH_2S), 62.8 (+, NHCHCO), 67.1 (–, CH_2Ph), 127.2, 128.1, 128.2, 128.5, 129.1, 130.4 (+, 10 C, Ph-CH), 134.2, 136.2 (–, Ph-C), 156.2 (–, NHCOO), 203.6 (–, CO).

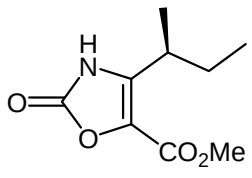
Column chromatography (Et_2O/hexane, 1:1) of residue, obtained from thiophenyle derivative (1.41g, 3.08 mmol), pyridine (1.22 g, 15.4 mmol) and sulfuryl chloride (832 mg, 6.16 mmol) according to GP 2.4, gave pure **76** (963 mg, 71%, R_f = 0.69) as a colorless oil. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, 3 H, *J* = 7.5 Hz, *J* = 7.5 Hz, CH_2CH_3), 0.95–1.10 (m, 4 H, CH_2CH_3, $CHCH_3$), 1.30–1.50 (m, 1 H, CH_2CH_3), 2.00–2.20 (m, 1 H, $CHCH_3$), 5.05–5.35 (m, 4 H, CH_2Ph, NHCHCO), 7.30–7.60 (m, 10 H, Ph-H). – ^{13}C NMR (75.5 MHz, APT, $CDCl_3$): δ = 11.4, 16.4 (+, CH_3), 22.9 (–, CH_2CH_3), 38.3 (+, $CHCH_3$), 59.0 (+, NHCHCO), 76.2 (–, CH_2Ph), 91.8 (–, CCl_2),

128.2, 128.3, 128.6, 129.1, 131.2 (+, 8 C, Ph-CH), 136.1 (–, 2 C, Ph-C), 137.4 (+, 2 C, Ph-CH), 155.6 (–, NHCOO), 193.7 (–, CO).

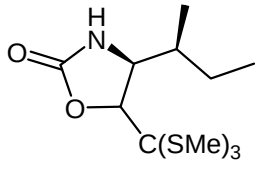
(3*S*,4*S*)-Methyl 3-(Benzyloxycarbonyl)-4-methyl-2-oxohexanoate (77): The ester **77** (272 mg, 44%), obtained from **76** (895 mg, 2.00 mmol), mercury (II) chloride (1.09 g, 4.00 mmol) and pyridine (632 mg, 8.00 mmol) according to GP 2.5, was further used without an additional purification. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.88 (t, 3 H, *J* = 7.0 Hz, CH_2CH_3), 1.01 (d, 3 H, *J* = 6.8 Hz, $CHCH_3$), 1.15–1.40 (m, 2 H, CH_2CH_3), 1.90–2.10 (m, 1 H, $CHCH_3$), 3.89 (s, 3 H, OMe), 4.95–5.05 (m, 1 H, NHC*H*), 5.10 (s, 2 H, CH_2Ph), 5.30 (d, 1 H, *J* = 9.3 Hz, NH), 7.30–7.45 (m, 5 H, Ph-H).



(*S*)-Methyl 4-*sec*-Butyl-2-oxo-2,3-dihydrooxazole-5-carboxylate (78): To the stirred solution of ester **77** in MeOH (5 mL) 1 M solution of NaOH in MeOH (3 mL) was added all at once at ambient temperature. After stirring for an additional 15 min, methanol was removed *in vacuo* and to the residue water (10 mL) was added. The obtained solution was washed with CH_2Cl_2 (3 × 5 mL), acidified with 1 N aq. solution of HCl to pH = 1 and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic phases from second extraction were dried over Na_2SO_4 and concentrated under reduced pressure to leave **78** (69 mg, 39%) as a colorless solid. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, 3 H, *J* = 7.5 Hz, *J* = 7.5 Hz, CH_2CH_3), 1.23 (d, 3 H, *J* = 7.5 Hz, $CHCH_3$), 1.50–1.65 (m, 2 H, CH_2CH_3), 3.30–3.45 (m, 1 H, $CHCH_3$), 3.82 (s, 3 H, OMe), 10.73 (br s, 1 H, NH). – ^{13}C NMR (75.5 MHz, HMBC, COSY, HSQC, $CDCl_3$): δ = 11.7 (CH_2CH_3), 18.5 ($CHCH_3$), 28.1 (CH_2), 31.0 (CH), 51.8 (OMe), 126.4 (=CCO$_2$Me), 142.4 (=CNH), 155.6 (NHCOO), 158.6 (COOMe). – MS (DCI) *m/z* (%) = 615 (6) [3 M + NH_4^+], 416 (79) [2 M + NH_4^+], 234 (28) [M + NH_3 + NH_4^+], 217 (100) [M + NH_4^+].



(4*S*)-4-((*S*)-*sec*-Butyl)-5-(tris(methylthio)methyl)oxazolidin-2-one (81): Column chromatography (Et_2O/hexane, 1:1) of the residue, obtained from tris(methylthio)methane (1.12 mL, 8.38 mmol), 2.6 M solution of *n*BuLi in cyclohexane (3.08 mL, 8.03 mmol) and BocHN-Ile-CHO **79** (870 mg, 3.49 mmol) according to GP 2.6, gave **81** (660 mg, 80%, R_f = 0.38) as a colorless oil. – IR (film): ν = 3262 cm^{-1}, 3149, 2963, 2921, 2876, 1751, 1386, 1235, 1064. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.80–1.00 (m, 6 H, CH_3), 1.00–1.20 (m, 1 H, $CHCH_2$), 1.30–1.55 (m, 2 H, $CHCH_2$), 2.21 (s, 9 H, SMe), 3.94 (t, 1 H, *J* = 2.3 Hz, NHC*H*), 4.44 (d, 1 H, *J* = 3.5 Hz, OCH), 7.05 (br s, 1 H, NH). – ^{13}C NMR (75.6 MHz, APT, $CDCl_3$): δ = 11.7 (+, CH_3), 13.5 (+, 3 C, SMe), 15.5 (+, CH_3), 22.9 (–, CH_2), 39.5



(+, *C*HCH$_3$), 60.0 (+, NCH), 72.1 [–, C(SMe)$_3$], 84.6 (+, OCH), 159.2 (–, NCOO). – MS (ESI): *m/z* (%) = 612 (40) [2 M + Na$^+$], 318 (100) [M + Na$^+$].

(4*S*)-Methyl 4-((*S*)-*sec*-Butyl)-2-oxooxazolidine-5-carboxylate (82): According to GP 2.7 from orhtothioester **81** (660 mg, 2.24 mmol), mercury (II) oxide (972 mg, 4.48 mmol) and mercury (II) chloride (2.44 g, 8.96 mmol) and after crystallization pure **82** (331 mg, 74%) was obtained as colorless solid, m.p. 147–148 °C. – IR (KBr): ν = 3297 cm^{-1}, 2967, 2935, 2880, 1755, 1422, 1382, 1226, 1076. – ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.90–1.00 (m, 6 H, CH$_3$), 1.10–1.25 (m, 1 H, CHC*H*$_2$), 1.40–1.70 (m, 2 H, C*H*C*H*$_2$), 3.72 (dd, 1 H, *J* = 4.0 Hz, *J* = 6.0 Hz, NHC*H*), 3.83 (s, 3 H, OMe), 4.68 (d, 1 H, *J* = 4.0 Hz, OCH), 6.47 (br s, 1 H, NH). – ^{13}H NMR (75.6 MHz, APT, CDCl$_3$): δ = 11.0, 13.8 (+, CH$_3$), 24.4 (–, CH$_2$), 39.1 (+, *C*HCH$_2$), 52.9 (+, NHCH), 60.4 (+, OCH), 75.5 (+, OMe), 158.4 (–, NHCOO), 169.8 (–, *C*OOMe). – MS (DCI): *m/z* (%) = 420 (2) [2 M + NH$_4^+$], 219 (100) [M + NH$_4^+$], 202 (3) [M + H$^+$].

(4*S*)-*tert*-Butyl 4-(*sec*-Butyl)-2-oxo-5-(tris(methylthio)methyl)oxazolidine-3-carboxylate (84): A solution of **81** (283 mg, 0.96 mmol), Boc$_2$O (283 mg, 1.29 mmol), DMAP (25 mg, 0.2 mmol) and Et$_3$N (0.17 mL, 1.20 mmol) in THF (25 mL) was stirred at ambient temperature for 12 h. NaOH (160 mg, 4.00 mmol), EtOH (10 mL) and H$_2$O (10 mL) were then added. The resulting mixture was stirred for 15 min, quenched with saturated aq. solution of NH$_4$Cl (30 mL) and extracted with CH$_2$Cl$_2$ (3 × 20 mL). The combined organic phases were dried over Na$_2$SO$_4$, concentrated *in vacuo* and the residue was purified by column chromatography on silica gel (Et$_2$O/hexane, 1:1) to give **84** (230 mg, 61%, R_f = 0.67) as a colorless oil. – IR (film): ν = 2969 cm^{-1}, 2923, 2877, 1824, 1726, 1370, 1324, 1159, 1056. – ^{1}H NMR (300 MHz, CDCl$_3$): δ = 0.89 (d, 3 H, *J* = 7.0 Hz, CHC*H*$_3$), 0.98 (t, 3 H, *J* = 7.0 Hz, CH$_2$C*H*$_3$), 1.10–1.50 (m, 2 H, CH$_2$), 1.55 [s, 9 H, C(CH$_3$)$_3$], 1.80–2.00 (m, 1 H, C*H*CH$_3$), 2.22 (s, 9 H, SMe), 4.35 (d, 1 H, *J* = 1.8 Hz, OCH), 4.47 (dd, 1 H, *J* = 1.8 Hz, *J* = 3.5 Hz, NCH). – ^{13}C NMR (75.6 MHz, APT, HSQC, CDCl$_3$): δ = 12.1, 13.3 (+, CH$_3$), 13.6 (+, SMe), 25.1 (–, CH$_2$), 28.0 [+, C(*C*H$_3$)$_3$], 37.7 (+, *C*HCH$_3$), 60.8 (+, NCH), 71.4 [–, *C*(SMe)$_3$], 79.8 (+, OCH), 83.7 [–, *C*(CH$_3$)$_3$], 149.1, 151.9 (–, NCOO).– MS (ESI): *m/z* (%) = 812 (100) [2 M + Na$^+$], 418 (16) [M + Na$^+$].

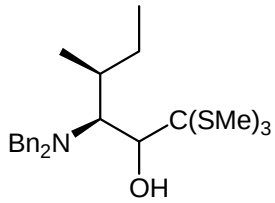
(4S)-3-*tert*-Butyl 5-Methyl 4-((*S*)-*sec*-Butyl)-2-oxooxazolidine-3,5-dicarboxylate (85): Column chromatography (Et_2O/hexane, 1:2) of the residue, obtained from **84** (454 mg, 1.15 mmol), mercury (II) oxide (499 mg, 2.30 mmol) and mercury (II) chloride (1.25 g, 4.60 mmol) according to GP 2.7, gave pure **85** (269 mg, 77%, R_f = 0.16) as a colorless solid, m.p. 82–83 °C. – IR (KBr): ν = 3434 cm^{-1}, 2983, 2935, 2886, 1800, 1762, 1722, 1327, 1202, 1157, 1065. – ^1H NMR (300 MHz, $CDCl_3$): δ = 0.87 (d, 3 H, *J* = 6.6 Hz, CHC*H*$_3$), 0.98 (t, 3 H, *J* = 6.6 Hz, CH_2CH_3), 1.20–1.40 (m, 2 H, CH_2), 1.52 [s, 9 H, $C(CH_3)_3$], 2.06–2.18 (m, 1 H, C*H*CH_3), 3.83 (s, 3 H, OMe), 4.30 (dd, *J* = 3.0 Hz, *J* = 3.6 Hz, NCH), 4.55 (d, 1 H, *J* = 3.0 Hz, OCH). – ^{13}H NMR (50.3 MHz, HSQC, $CDCl_3$): δ = 11.6 (CH_2CH_3), 12.3 ($CHCH_3$), 25.3 (CH_2), 27.9 [$C(CH_3)_3$], 36.2 (CH), 53.2(OCH_3), 61.5 (NCH), 70.0 (OCH), 84.4 [$C(CH_3)_3$] 148.8, 150.9 (NCOO, CO), 169.4 (COO). – MS (DCI): *m/z* (%) = 323 (23) [M + Na^+], 625 (100) [2 M + Na^+].

(2*S*,3*S*)-2-(Dibenzylamino)-3-methylpentan-1-ol (89): To a boiling solution of NH_2-Ile-CO_2H **88** (3.90 g, 30.0 mmol), NaOH (2.40 g, 60.0 mmol) and K_2CO_3 (8.28 g, 60.0 mmol) in water (55 mL) benzyl bromide (10.8 mL, 90.0 mmol) was added dropwise within 20 min. After refluxing for an additional 30 min, the reaction mixture was cooled to 0 °C and extracted with Et_2O (3 × 30 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was dissolved in anhydrous Et_2O (40 mL) and added all at once to the ice cold stirred suspension of $LiAlH_4$ (3.81 g, 93 mmol) in anhydrous Et_2O (50 mL). After stirring at ambient temperature for an additional 12 h, to the reaction mixture water (2 mL), 4 M aq. solution of NaOH (2 mL) and water (6 mL) were added consecutively and after 30 min obtained suspension was filtered through a pad of Celite. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography on silica gel (Et_2O/hexane, 1:1) to give pure **89** (5.63 g, 63%) as a colorless oil. – ^1H NMR (250 MHz, $CDCl_3$): δ = 0.80–1.00 (m, 6 H, CH_3), 1.20–1.40 (m, 1 H, C*H*$_2CH_3$), 1.50–1.70 (m, 1 H, C*H*$_2CH_3$), 1.80–2.00 (m, 1 H, C*H*CH_3), 2.60–2.70 (m, 1 H, NCH), 2.95 (s, 1 H, OH), 3.54 (d, 2 H, *J* = 7.3 Hz, CH_2OH), 3.60 (d, 2 H, *J* = 13.3 Hz, CH_2Ph), 3.90 (d, 2 H, *J* = 13.3 Hz, CH_2Ph), 7.15–7.40 (m, 10 H, Ph-H).

(2*S*,3*S*)-2-(Dibenzylamino)-3-methylpentanal (90): A solution of DMSO (3.10 g, 39.7 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dropwise to a solution of oxalyl chloride (2.88 mg, 22.7 mmol) in anhydrous CH_2Cl_2 (20 mL) at –70 °C. After stirring under the same temperature for 20 min, the solution of alcohol **89** (5.63 g, 18.9 mmol) in anhydrous CH_2Cl_2 (15 mL) was added dropwise at a rate such, that the temperature

of the reaction mixture was not above –60 °C. After stirring at –70 °C for an additional 30 min, triethylamine (13.1 mL, 94.5 mmol) was slowly added, the reaction mixture was allowed to warm to ambient temperature and quenched with water (30 mL). After stirring at ambient temperature for 10 min, the reaction mixture was extracted with CH_2Cl_2 (3 × 30 mL), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to leave **90** (5.32 g, 95%) as a pale yellow oil. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.75–0.95 (m, 6 H, CH_3), 1.00–1.30 (m, 1 H, C*H*$_2$CH$_3$), 1.80–2.00 (m, 1 H, C*H*$_2$CH$_3$), 2.00–2.20 (m, 1 H, C*H*CH$_3$), 2.82 (dd, 1 H, *J* = 3.8 Hz, *J* = 10.0 Hz, NCH), 3.69 (d, 2 H, *J* = 13.8 Hz, CH_2Ph), 4.03 (d, 2 H, *J* = 13.8 Hz, CH_2Ph), 7.20–7.40 (m, 10 H, Ph-H), 9.86 (d, 1 H, *J* = 4.0 Hz, CHO).

(3*S*,4*S*)-3-(Dibenzylamino)-4-methyl-1,1,1-tris(methylthio)hexan-2-ol (91): Column



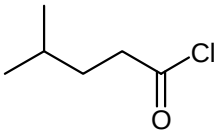
chromatography (Et_2O/hexane, 1:20) of the residue, obtained from tris(methylthio)methane (0.64 mL, 4.80 mmol), 2.6 M solution of *n*BuLi in cyclohexane (1.77 mL, 4.60 mmol) and Bn_2N-Ile-CHO **90** (590 mg, 2.00 mmol) according to GP 2.6, gave **91** (732 mg, 82%, R_f = 0.40) as a colorless solid, m.p. 50–52 °C. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.70 (d, 3 H, *J* = 6.8 Hz, CHC*H*$_3$), 0.85 (t, 3 H, *J* = 7.3 Hz, *J* = 7.3 Hz, CH$_2$C*H*$_3$), 1.20–1.40 (m, 2 H, C*H*$_2$CH$_3$), 1.95–2.10 (m, 1 H, C*H*CH$_3$), 2.24 (s, 9 H, SMe), 3.00 (br s, 1 H, CHN*), 3.17 (br s, 1 H, OH*), 3.55 (d, 2 H, *J* = 14.3 Hz, CH_2Ph), 4.01 (d, 2 H, *J* = 14.0 Hz, CH_2Ph), 4.29 (br s, 1 H, C*H*OH*), 7.15–7.30 (m, 6 H, Ph-H), 7.40–7.50 (m, 4 H, Ph-H).). – ^{13}H NMR (50.3 MHz, APT, $CDCl_3$): δ = 12.3 (+, CH_3), 14.2 (+, 3 C, SMe), 18.5 (+, CH_3), 25.7 (–, *C*H$_2$CH$_3$), 37.8 (+, *C*HCH$_3$), 56.8 (–, 2 C, CH_2Ph), 63.6 (+, CHN), 75.2 (+, CHOH), 75.5 [–, *C*(SMe)$_3$], 126.7, 127.9, 129.3 (+, 10 C, Ph-CH), 140.6 (–, 2 C, Ph-C). – MS (DCI): *m/z* (%) = 450 (48) [M + H$^+$], 402 (53), 358 (22), 312 (100), 296 (40), 266 (83).

2.3. Synthesis of Compounds in Chapter 3

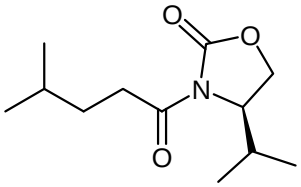
General Procedure for Preparation of Amides Using EDC (GP 3.1): To the stirred suspension of acid (1.0 mmol) and HOAt (or HOBt×H_2O) (1.1 mmol) in CH_2Cl_2 (10 ml) EDC (1.1 mmol) was added at 0 °C at one portion. After an additional stirring at the same temperature for 30 min amine (1.1 mmol) was added dropwise within 5min and the reaction mixture was stirred at ambient temperature overnight. Then the reaction mixture was washed with 1 M aq. solution of $KHSO_4$ (3 × 10 ml), aq. solution of $NaHCO_3$ (3 × 10 ml), brine (1 × 10 mL) and dried over $MgSO_4$. After filtration the solution was concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel.

General Procedure for Preparation of Amides Using HATU or HBTU (GP 3.2): To a stirred solution of HATU (or HBTU) (1.1 mmol), HOAt (or HOBt×H_2O) (1.1 mmol), DIEA (1.1 mmol) and respective acid (1.1 mmol) in anhydrous DFM (5mL) the solution of respective amine (1.0 mmol) in anhydrous CH_2Cl_2 (5 mL) was added at 0 °C within 5 min. After stirring at ambient temperature overnight, the reaction mixture was quenched with 1 M aq. solution of $KHSO_4$ (20 mL) and extracted with CH_2Cl_2 (3 × 15 mL), the combined organic phases were washed with saturated aq. solution of $NaHCO_3$ (3 × 15 mL), brine (2 × 5 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel.

4-Methylpentanoyl chloride (100): Thionyl chloride (8.00 ml, 0.11 mol) was added dropwise to 4-methylpentanoic acid (11.60 g, 0.10 mol) and reaction mixture was stirred overnight at ambient temperature. Volatiles were removed *in vacuo*, the residue was distillated (b.p. 144 °C, 0.005 Torr) to give chloranhydride **100** (12.13 g, 90%) as a colorless liquid.



(*R*)-4-Isopropyl-3-(4-methylpentanoyl)oxazolidin-2-one (101): To a solution of (*R*)-4-isopropyloxazolidin-2-one **99** (11.85 g, 0.101 mol) in anhydrous THF (200 mL) the solution of *n*BuLi (40.5 mL, 0.101 mol, 2.5 M in hexane) was added dropwise within 1 h at –78 °C. After stirring for 30 min the solution of chloranhydride **100** (16.36g, 0.122 mol) in anhydrous THF (50 mL) was added dropwise at the temperature below –70 °C within 15 min. After stirring at the same temperature for an additional 30 min, the reaction mixture was allowed to warm to ambient temperature and saturated aq. solution of NH_4Cl (80 mL) was added. Volatiles were removed *in vacuo* and the residue was quenched with water (50 mL). The obtained mixture was extracted with CH_2Cl_2 (3 × 50 ml) and the combined organic phases were washed with 1 M solution of NaOH (50 mL), water (50 mL), brine (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure.



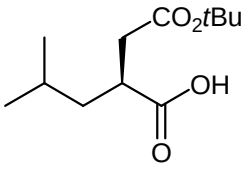
The crude product was purified by column chromatography on silica gel (Et_2O/hexane, 1:3) to give **101** (18.35 g, 84%, R_f = 0.32) as a colorless solid. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.80–1.00 (m, 12 H, CH_3), 1.45–1.70 [m, 3 H, C*H*(CH_3)$_2$, C*H*$_2$C*H*(CH_3)$_2$], 2.30–2.50 [m, 1 H, C*H*$_2$CH(CH_3)$_2$], 2.80–3.10 (m, 2 H, CH_2CON), 4.15–4.30 (m, 2 H, CH_2O), 4.40–4.50 (m, 1 H, CHN). – ^{13}C NMR (62.9 MHz, DEPT, $CDCl_3$): δ = 14.6, 17.9, 22.3 (+, 4 C, CH_3), 27.7, 28.3 [+, *C*H(CH_3)$_2$], 33.2, 33.6 (–, CH_2), 58.3 (+, CHN), 63.2 (–, CH_2O), 154.0 (–, NCOO), 173.6 (–, CON).

(*S*)-*tert*-Butyl 3-((*R*)-4-Isopropyl-2-oxooxazolidine-3-carbonyl)-5-methylhexanoate (102): To a stirred solution of diisopropylamine (14.5 mL, 103 mmol) in anhydrous THF (75 mL) the solution of *n*BuLi (37.6 mL, 94.0 mmol, 2.5 M in hexane) was added at –78 °C within 30 min under N_2. After stirring under cooling for an additional 1 h, to the reaction mixture solution of amide **101** (18.35 g, 85.4 mmol) in anhydrous THF (150 mL) was added dropwise within 1 h. After stirring for an additional 2 h, the solution of *tret*-butyl bromacetate (16.4 mL, 111 mmol) in anhydrous THF (150 mL) was added dropwise within 1 h. The reaction mixture was allowed to warm to ambient temperature overnight and was quenched with brine (70 mL) and neutralized with 1 M solution of HCl. Two layers were separated and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic phases were washed with water (1 × 50 mL), brine (1 × 50 mL), dried over $MgSO_4$, concentrated under reduced pressure to leave solid, which was filtered off and washed with hexane (50 mL) to give **102** (11.19 g, 71%) as a colorless solid. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.80–0.95 (m, 12 H, CH_3), 1.20–1.35 [m, 1 H, C*H*(CH_3)$_2$], 1.40 [s, 9 H, C(CH_3)$_3$], 1.42–1.60 [m, 2 H, C*H*$_2$C*H*(CH_3)$_2$], 2.30–2.45 [m, 2 H, CH_2COO, C*H*$_2$CH(CH_3)$_2$], 2.67 (dd, 1 H, *J* = 9.8 Hz, *J* = 16.5 Hz, CH_2COO), 4.15–4.25 (m, 3 H, CH_2O, CHCON), 4.35–4.43 (m, 1 H, CHN). – ^{13}C NMR (300 MHz, APT, $CDCl_3$): δ = 14.5, 18.0, 21.7, 23.3, 25.7 [+, CH(CH_3)$_2$], 28.0 [+, C(*C*H$_3$)$_3$], 28.1 [+, *C*H(CH_3)$_2$], 37.2 (–, CH*C*H$_2$CH), 37.6 (+, *C*HCON), 40.6 (–, *C*H$_2$COO), 58.7 (+, CHN), 63.0 (–, CH_2O), 80.5 [–, *C*(CH_3)$_3$], 153.5 (–, NCOO), 171.2, 176.3 (–, COO, CON).

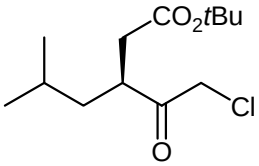
(*S*)-1-Benzyl 4-*tert*-Butyl 2-isobutylsuccinate (103): To the icecold stirred solution of benzyl alcohol (3.18 g, 29.4 mmol) in anhydrous THF (40 mL) the solution of *n*BuLi (8.8 mL, 22.1 mmol, 2.5 M in hexane) was added within 10 min. After stirring for an additional 30 min, the reaction mixture was added to the ice cold solution of amide **102** (5.00 g, 14.7 mmol) in anhydrous THF (40 mL) in one portion. After stirring at ambient temperature for 12 h the reaction mixture was quenched with 1 M aq. solution of $KHSO_4$ (50 mL) and organic solvents were removed *in vacuo*. The residue was extracted with EtOAc (3 × 30 mL) and the combined organic phases were washed with brine (1 ×

30 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (Et_2O/hexan, 1:4) to give **103** (4.57 g, 97%, R_f = 0.85) as a colorless oil. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.80–1.00 (m, 6 H, CH_3), 1.20–1.38 [m, 1 H, C*H*(CH_3)$_2$], 1.40 (s, 9 H, *t*Bu), 1.50–1.70 (m, 2 H, C*H*$_2$CH), 2.35 (dd, 1 H, *J* = 5.3 Hz, *J* = 16.3 Hz, CH_2COO), 2.62 (dd, 1 H, *J* = 9.0 Hz, *J* = 16.3 Hz, CH_2COO), 2.80–3.00 (m, 1 H, CHCOO), 5.10 (d, 1 H, *J* = 12.5 Hz, CH_2Ph), 5.16 (d, 1 H, *J* = 12.5 Hz, CH_2Ph), 7.35 (br s, 5 H, Ph-H).

(*S*)-2-(2-*tert*-Butoxy-2-oxoethyl)-4-methylpentanoic Acid (104): Ester **103** (2.40 g, 7.50 mmol) was hydrogenated over 10% palladium on carbon (300 mg) in EtOAc (50 mL) at atmospheric pressure to give, after filtration of the reaction mixture though a pad of Celite and concentration of the filtrate, pure acid **104** (1.70 g, 98%) as a colorless oil. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.80–1.00 (m, 6 H, CH_3), 1.20–1.40 [m, 1 H, C*H*(CH_3)$_2$], 1.43 (s, 9 H, *t*Bu), 1.50–1.70 [m, 2 H, C*H*$_2$CH(CH_3)$_2$], 2.37 (dd, 1 H, *J* = 5.3 Hz, *J* = 16.5 Hz, C*H*$_2$COO*t*Bu), 2.59 (dd, 1 H, *J* = 9.3 Hz, *J* = 16.5 Hz, C*H*$_2$COO*t*Bu), 2.80–2.90 (m, 1 H, CHCOOH), the signal of COOH group is not detectable.



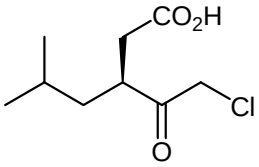
(*S*)-*tert*-Butyl 3-(2-Chloroacetyl)-5-methylhexanoate (107): To a solution of acid **104** (2.16 g, 9.39 mmol) in Et_2O (50 mL) a solution of diazomethane (~ 20 mL, ~ 1 M in Et_2O) was added until the yellow color did not disappeared. The volatiles were removed *in vacuo* to give ester (2.23 g, 97%) as a colorless oil. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.80–1.00 (m, 6 H, CH_3), 1.10–1.40 [m, 1 H, C*H*(CH_3)$_2$], 1.42 (s, 9 H, *t*Bu), 1.50–1.65 [m, 2 H, C*H*$_2$CH(CH_3)$_2$], 2.33 (dd, 1 H, *J* = 5.3 Hz, *J* = 16.3 Hz, CH_2COO), 2.59 (dd, 1 H, *J* =9.3 Hz, *J* = 16.3 Hz, CH_2COO), 2.80–2.90 (m, 1 H, CHCOO), 3.69 (s, 3 H, OMe).



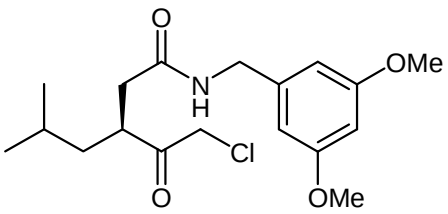
To a strirred solution of diisopropylamine (3.32 g, 32.9 mmol) in anhydrous THF (20 mL) the solution of *n*BuLi (14.0 mL, 34.8 mmol, 2.5 M in hexane) was added at –78 °C within 15 min under N_2. After stirring for 15 min, to the reaction mixture a solution of chloracetic acid (1.56 g, 16.5 mmol) in anhydrous THF (10 mL) was added dropwise at a rate such that the temperature of the reaction mixture was not above –70 °C. After an additional stirring at the same temperature for 15 min the reaction mixture was added to the solution of ester (1.15 g, 4.70 mmol) in anhydrous THF (10 mL) at 0 °C and in 10 min the solution of acetic acid (4 ml) in THF (4 mL) was added in one portion. After an additional stirring at ambient temperature for 12 h, the reaction mixture was quenched with water (100 mL) and EtOAc (100 mL), two layers were separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with the mixture of 1 M aq. solution of $KHSO_4$ and brine (1:1, 2 × 30 mL), the mixture of saturated aq.

solution of $NaHCO_3$ and brine (1:1, 2 × 30 mL), brine (2 × 30 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (Et_2O/hexane, 1:20) to give **107** (386 mg, 31%, R_f = 0.31) as a colorless oil. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.80–1.00 (m, 6 H, CH_3), 1.10–1.30 [m, 1 H, C*H*$(CH_3)_2$], 1.40 (s, 9 H, *t*Bu), 1.45–1.70 [m, 2 H, C*H*$_2$CH$(CH_3)_2$], 2.39 (dd, 1 H, *J* = 4.0 Hz, *J* = 17.3 CH_2COO), 2.70 (dd, 1 H, *J* = 10.5 Hz, *J* = 17.3 CH_2COO), 3.05–3.25 (m, 1 H, CHCO), 4.28 (d, 1 H, *J* = 16.3 Hz, CH_2Cl), 4.40 (d, 1 H, *J* = 16.3 Hz, CH_2Cl).

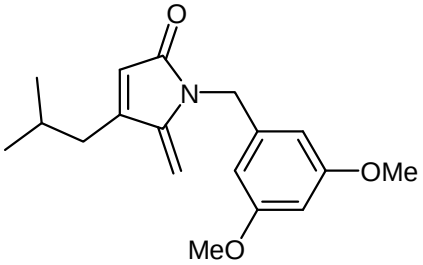
(*S*)-3-(2-Chloroacetyl)-5-methylhexanoic Acid (109): A mixture of ester **107** (371 mg, 1.41 mmol) and trifluoracetic acid (1.07 mL, 14.0 mmol) in CH_2Cl_2 (3 mL) was stirred at ambient temperature for 30 min. The volatiles were removed under reduced pressure to leave acid **109** (279 mg, 97%) as a colorless oil. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.80–1.00 (m, 6 H, CH_3), 1.10–1.30 [m, 1 H, C*H*$(CH_3)_2$], 1.40–1.70 (m, 2 H, C*H*$_2$CH$(CH_3)_2$], 2.52 (dd, 1 H, *J* = 3.8 Hz, *J* = 17.5 Hz, CH_2COO), 2.86 (dd, 1 H, *J* = 10.5 Hz, *J* = 17.5 Hz, CH_2COO), 3.76 (s, 1 H, COOH), 4.25 (d, 1 H, *J* = 16.3 Hz, CH_2Cl), 4.33 (d, 1 H, *J* = 16.3 Hz, CH_2Cl).



(*S*)-*N*-(3,5-Dimethoxybenzyl)-3-(2-chloroacetyl)-5-methylhexanamide (110): According to GP 2.1 from HATU (418 mg, 1.10 mmol), HOAt (150 mg, 1.10 mmol), DIEA (142 mg, 1.10 mmol), acid **109** (227 mg, 1.10 mmol) and 3,5-dimethoxybenzyl amine **55** (167 mg, 1.00 mmol) and after purification by column chromatography on silica gel (EtOAc/hexane, 1:4) pure amide **110** (288 mg, 81%, R_f = 0.55) was obtained as a colorless oil which turns green. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.96 (d, 6 H, *J* = 6.5 Hz, CH_3), 1.80–2.00 [m, 3 H, C*H*$_2$C*H*$(CH_3)_2$], 2.30 (d, 1 H, *J* = 1.3 Hz, CH_2CON), 2.33 (d, 1 H, *J* = 1.0 Hz, CH_2CON), 3.70–3.85 (m, 7 H, OMe, CHCO), 4.73 (s, 2 H, CH_2Cl), 4.77 (d, 1 H, *J* = 1.5 Hz, CH_2Ph), 4.84 (d, 1 H, *J* = 2.3 Hz, CH_2Ph), 6.01 (s, 1 H, NH), 6.33 (s, 3 H, Ph-CH).

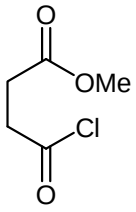


1-(3,5-Dimethoxybenzyl)-4-isobutyl-5-methylene-1H-pyrrol-2(5H)-one (111): – ^{1}H NMR (300 MHz, CD_3CN): δ = 0.94 (d, 6 H, *J* = 5.0 Hz, CH_3), 1.90–2.00 (m, 1 H, CH_2CH), 2.35–2.40 (m, 2 H, C*H*$_2$CH), 3.72 (s, 6 H, OMe), 4.71 (s, 2 H, CH_2Ph), 4.91 (d, 1 H, *J* = 2.5 Hz, =CH_2), 5.09 (d, 1 H, *J* = 2.5 Hz, =CH_2), 6.05 (d, 1 H, *J* = 2.0 Hz, =CHCO), 6.25–6.40 (m, 3 H, Ph-H). – ^{13}C NMR (62.0 MHz, CD_3CN): δ = 22.6 (2 C, CH_3), 29.3 [*C*H$(CH_3)_2$], 35.7 (*C*H$_2$CH), 43.2 (CH_2Ph), 55.9 (2 C, OMe),

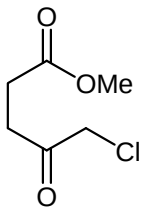


96.4 (=CH_2), 99.6 (Ph-CH), 105.6 (2 C, Ph-CH), 121.1 (=CH), 141.1 (Ph-C), 147.2 (=CN), 152.8 (=C), 162.1 (2 C, Ph-C), 171.1 (CON).

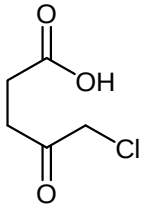
Methyl 4-Chloro-4-oxobutanoate (115): A suspension of succinic acid anhydride **114** (5.00 g, 50.0 mmol) in methanol (2.0 mL, 50.0 mmol) was stirred at 80 °C for 2 h until complete dissolving of anhydride. The reaction mixture was cold to 0 °C and tionyl chloride (4.0 mL, 55.0 mmol) was added dropwise within 10 min. After overnight stirring at ambient temperature the reaction mixture was distillated *in vacuo* to give **115** (4.16 g, 55%) as a colorless oil, b.p. 93 °C (18 Torr). – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.68 (t, 2 H, *J* = 6.8 Hz, CH_2), 3.22 (t, 2 H, *J* = 6.8 Hz, CH_2), 3.72 (s, 3 H, OMe).



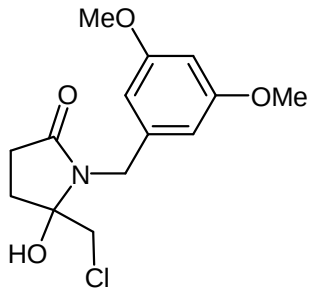
Methyl 5-chloro-4-oxopentanoate (116): To a stirred solution of chloro anhydride **115** (1.05 g, 7.00 mmol) in Et_2O (10 mL) the solution of diazomethane (~ 10 mL, ~ 1 M in Et_2O) was added until the yellow color of the solution did not disappeared. Then to the reaction mixture concentrated hydrochloric acid (0.6 ml, 7.00 mmol) was added dropwise (Caution: N_2 evolution). After complete nitrogen evolution (5 min) water (20 ml) was added, two layers were separated and the aqueous one was extracted with Et_2O (2 × 10 mL). The combined organic phases were washed with saturated aq. solution of $NaHCO_3$ (2 × 10 mL), water (1 × 10 mL), brine (1 × 10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give **116** (1.02 mg, 89%) as a colorless oil. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.66 (t, 2 H, *J* = 6.5 Hz, CH_2), 2.90 (t, 2 H, *J* = 6.5 Hz, CH_2), 3.68 (s, 3 H, OMe), 4.15 (s, 2 H, CH_2Cl).



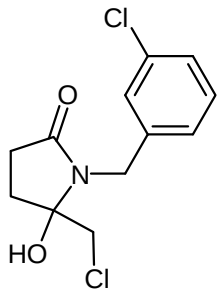
5-Chloro-4-oxopentanoic Acid (117): To a stirred solution of **116** (2.70 g, 16.4 mmol) in dioxane (5 mL) the 6 N aq. solution of hydrochloric acid (7 mL) was added in one portion and the reaction mixture was stirred at 80 °C overnight. Dioxane was removed *in vacuo* and the residue was extracted with CH_2Cl_2 (8 × 5 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to leave acid **117** (2.15 g, 87%) as a colorless solid, m.p. 73 °C. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.71 (t, 2 H, *J* = 6.5 Hz, CH_2), 2.90 (t, 2 H, *J* = 6.5 Hz, CH_2), 4.14 (s, 2 H, CH_2Cl), 5.38 (br s, 1 H, COOH).



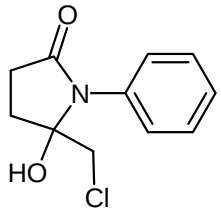
1-(3,5-Dimethoxybenzyl)-5-(chloromethyl)-5-hydroxypyrrolidin-2-one (119a): According to the GP 3.1 from EDC (141 mg, 1.05 mmol), HOAt (143 mg, 1.05 mmol), 3,5-dimethoxybenzylamine **55** (175 mg, 1.05 mmol) and acid **117** (143 mg, 0.95 mmol) and after purification by column chromatography on silica gel (EtOAc/hexane, 1:1) pure **119a** (165 mg, 58%, R_f = 0.20) was obtained as a colorless oil which turned brawn immediately. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.20–2.80 (m, 4 H, CH_2CH_2), 3.48 (d, 1 H, *J* = 11.5 Hz, CH_2Cl), 3.57 (d, 1 H, *J* = 11.5 Hz, CH_2Cl), 3.75 (s, 6 H, OMe), 4.43 (br s, 1 H, CH_2Ph), 4.57 (s, 1 H, CH_2Ph), 6.30–6.50 (m, 3 H, Ph-CH), the signal of OH group is not detectable.



1-(3-Chlorobenzyl)-5-(chloromethyl)-5-hydroxypyrrolidin-2-one (119b): According to the GP 3.1 from EDC (341 mg, 2.20 mmol), HOBt×H_2O (337 mg, 2.20 mmol), 3-chlorobenzylamine (310 mg, 2.20 mmol) and acid **117** (301 mg, 2.00 mmol) and after purification by column chromatography on silica gel (EtOAc/hexane, 1:1) pure **119b** (286 mg, 52%, R_f = 0.17) was obtained as a colorless oil which turned rot. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.00–2.20 (m, 1 H, CH_2), 2.40–2.90 (m, 3 H, CH_2CH_2), 3.45 (d, 1 H, *J* = 11.5 Hz, CH_2Cl), 3.55 (d, 1 H, *J* = 11.5 Hz, CH_2Cl), 4.42 (d, 1 H, *J* = 17.0 Hz, CH_2Ph), 4.50 (d, 1 H, *J* = 17.0 Hz, CH_2Ph), 7.15–7.35 (m, 4 H, Ph-CH), the signal of OH group is not detectable.



5-(Chloromethyl)-5-hydroxy-1-phenylpyrrolidin-2-one (119d): According to GP 3.1 from EDC (295 mg, 2.20 mmol), HOAt (299 mg, 2.20 mmol), aniline (205 mg, 2.20 mmol) and acid **117** (301 mg, 2.00 mmol) and after purification by column chromatography on silica gel (EtOAc/hexane, 1:1) pure **119d** (177 mg, 52%, R_f = 0.07) was obtained as a colorless oil which turneed brawn immediately. – ^{1}H NMR (300 MHz, CD_3CN): δ = 2.10–2.80 (m, 4 H, CH_2CH_2), 3.44 (d, 1 H, *J* = 11.8 Hz, CH_2Cl), 3.57 (d, 1 H, *J* = 11.8 Hz, CH_2Cl), 4.68 (br s, 1 H, OH), 7.20–7.60 (m, 5 H, Ph-CH). – ^{13}C NMR (75.6 MHz, CD_3CN): δ = 30.0, 31.8 (–, CH_2), 48.8 (–, CH_2Cl), 92.7 (–, COH), 128.8, 129.7, 129.8 (+, 5 C, Ph-CH), 136.5 (–, Ph-C), 175.4 (–, CON). – MS (EI), *m*/*z* (%): 227/225 (6/20) [M^+], 176 (100), 120 (10), 93 (54), 77 (13).

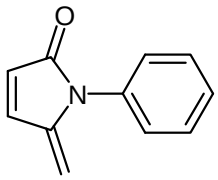


1-(3,5-Dimethoxybenzyl)-5-methylene-1H-pyrrol-2(5H)-one (120a): The amide **119a** (165 mg, 0.55 mmol) converts into **120a** (32 mg, 24%, R_f = 0.52, EtOAc/hexane, 1:1) without any solvent at ambient temperature during 1 h.– ^{1}H NMR (300 MHz, $CDCl_3$): δ = 3.74 (s, 6 H, OMe), 4.75 (s, 2 H, =CH_2), 4.80 (d, 1 H, *J* = 1.5 Hz, CH_2Ph), 4.84 (br s, 1 H, CH_2Ph), 6.25 (dd, 1 H, *J* = 1.3 Hz, *J* = 5.8 Hz, =CH), 6.32 (s, 3 H, Ph-CH), 6.99 (d, 1 H, *J* = 5.8 Hz, =CH). – ^{13}C NMR (75.6 MHz, APT, $CDCl_3$): δ = 42.6 (–, CH_2Ph), 55.2 (+, 2 C, OMe), 97.8 (–, =CH_2), 98.9 (+, Ph-CH), 104.9 (+, 2 C, Ph-CH), 124.8 (+, =*C*HCO), 137.5 (+, =CH), 139.4 (–, Ph-C), 145.1 (–, =C), 161.0 (–, 2 C, Ph-C), 170.3 (–, CON). – MS (EI), *m*/*z* (%): 245 (100) [M^+], 216 (29), 151 (83), 58 (55).

1-(3-Chlorobenzyl)-5-methylene-1H-pyrrol-2(5H)-one (120b): The amide **119b** (286 mg, 1.04 mmol) converts into **120b** (107 mg, 47%, R_f = 0.69, EtOAc/hexane, 1:1) without any solvent at ambient temperature during 3 h. – ^{1}H NMR (300 MHz, CD_3CN): δ = 4.77 (s, 2 H, =CH_2), 4.86 (s, 2 H, CH_2Ph), 6.23 (d, 1 H, *J* = 6.0 Hz, =CH), 7.10–7.35 (m, 5 H, Ph-CH, =CH). – ^{13}C NMR (75.6 MHz, APT, CD_3CN): δ = 42.3 (–, CH_2Ph), 98.1 (–, =CH_2), 118.3, 125.4, 126.3, 127.7, 128.2, 131.2 (+, Ph-CH, =*C*HCO), 134.8 (–, Ph-CCl), 139.0 (+, =CH), 141.1 (–, Ph-C), 146.1 (–, =C), 171.0 (–, CON). – MS (EI), *m*/*z* (%): 221/219 (40/83) [M^+], 192/190 (7/21), 184 (100), 156 (17), 127/125 (21/66), 89 (25).

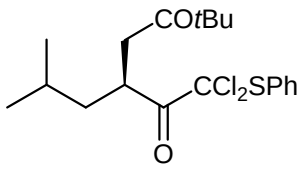
1-(2-Methoxybenzyl)-5-methylene-1H-pyrrol-2(5H)-one (120c): According to the GP 3.1 from EDC (341 mg, 2.20 mmol), HOAt (299 mg, 2.20 mmol), 2-methoxybenzylamine (302 mg, 2.20 mmol) and acid **117** (301 mg, 2.00 mmol) and after purification by column chromatography on silica gel (EtOAc/hexane, 1:1) pure **120c** (53 mg, 12%, R_f = 0.71) was obtained as a colorless oil which turned brawn. – ^{1}H NMR (300 MHz, CD_3CN): δ = 3.85 (s, 3 H, OMe), 4.77 (s, 2 H, =CH_2), 4.86 (s, 1 H, CH_2Ph), 4.90 (s, 1 H, CH_2Ph), 6.23 (dd, 1 H, *J* = 6.0 Hz, *J* = 1.0 Hz, =CH), 6.80–7.05 (m, 3 H, Ph-CH), 7.17 (d, 1 H, *J* = 6.0 Hz, =CH), 7.20–7.30 (m, 1 H, Ph-CH). – ^{13}C NMR (75.6 MHz, APT, CD_3CN): δ = 37.7 (–, CH_2Ph), 56.1 (+, OMe), 97.9 (–, =CH_2), 111.5, 121.4 (+, Ph-CH), 125.5 (+, =*C*HCO), 126.3 (–, Ph-C), 128.1, 129.3 (+, Ph-CH), 138.8 (+, =CH), 146.5 (–, =C), 157.7 (–, Ph-*C*OMe), 171.1 (–, CON). – MS (EI), *m*/*z* (%): 215 (100) [M^+], 184 (39), 136 (25), 121 (57), 91 (90).

5-Methylene-1-phenyl-1H-pyrrol-2(5H)-one (120d): The amide **119d** (177 mg, 0.79 mmol)



converts into **120d** (59 mg, 44%, R_f = 0.53, EtOAc/hexane, 1:1) without any solvent at ambient temperature during 1 h. – ^{1}H NMR (300 MHz, CD_3CN): δ = 4.82 (br s, 1 H, =CH_2), 4.96 (br s, 1 H, =CH_2), 6.36 (dd, 1 H, *J* = 5.5 Hz, *J* = 1.0 Hz, =CH), 7.20–7.60 (m, 6 H, Ph-CH, =CH). – ^{13}C NMR (75.6 MHz, APT, CD_3CN): δ = 98.6 (–, =CH_2), 125.1 (+, Ph-CH), 128.6 (+, =*C*HCON), 128.8, 130.2 (+, 4 C, Ph-CH), 135.6 (–, Ph-C), 139.1 (+, =CH), 147.4 (–, =C), 170.4 (–, CON). – MS (EI), *m*/z (%): 171 (100), 143 (46), 117 (25), 77 (25).

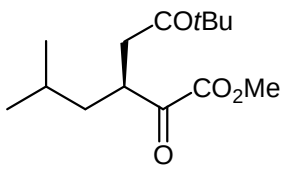
(*S*)-*tert*-Butyl 3-(2,2-Dichloro-2-(phenylthio)acetyl)-5-methylhexanoate (122): To a solution of



chloroketone **107** (500 mg, 1.90 mmol) in benzene (10 mL) sodium thiophenolate (383 mg, 2.90 mmol) was added in one portion. After stirring at ambient temperature for an additional 3 h, the reaction mixture was quenched with water (10 mL) and extracted with benzene (3 × 5 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to give thiophenolate derivative (630 mg, 99%) as a colorless oil which was further used without an additional purification. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.80–1.00 (m, 6 H, CH_3), 1.10–1.30 [m, 1 H, C*H*(CH_3)$_2$], 1.30–1.60 (m, 11 H, *t*Bu, CHC*H*$_2$CH), 2.35 (dd, 1 H, *J* = 4.5 Hz, *J* = 16.8 Hz, CH_2COO), 2.63 (dd, 1 H, *J* = 9.8 Hz, *J* = 16.8 Hz, CH_2COO), 3.10–3.30 (m, 1 H, CHCO), 3.91 (d, 1 H, *J* = 16.3 Hz, CH_2S), 4.00 (d, 1 H, *J* = 16.3 Hz, CH_2S), 7.10–7.40 (m, 5 H, Ph-CH).

To the ice cold solution of tiophenolate derivative (630 mg, 1.88 mmol) and pyridine (750 mg, 9.49 mmol) in CCl_4 (20 mL) the solution of sulfuryl chloride (513 mg, 3.80 mmol) in CCl_4 (5 mL) was added dropwise within 10 min. After stirring for an additional 15 min, to the reaction mixture water (15 mL) was added, two layers were separated, the aqueous layer was washed with 1 M aq. solution of $KHSO_4$ (2 × 5 mL), brine (2 × 5 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give **122** (729 mg, 96%) as a pale yellow oil which was further used without an additional purification. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.90–1.00 (m, 6 H, CH_3), 1.10–1.50 [m, 10 H, *t*Bu, C*H*(CH_3)$_2$], 1.50–1.90 (m, 2 H, CHC*H*$_2$CH), 2.41 (dd, 1 H, *J* = 7.3 Hz, *J* = 16.3 Hz, CH_2COO), 2.73 (dd, 1 H, *J* = 6.0 Hz, *J* = 16.3 Hz, CH_2COO), 3.90–4.05 (m, 1 H, CHCO), 7.30–7.70 (m, 5 H, Ph-CH).

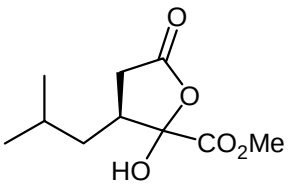
(*S*)-5-*tert*-Butyl 1-Methyl 3-Isobutyl-2-oxopentanedioate (121): A suspension of mercury



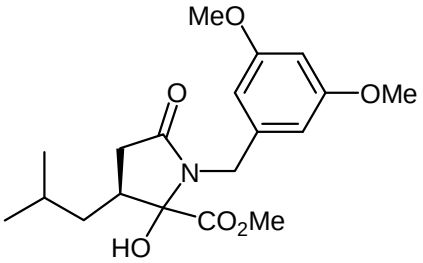
chloride (II) (190 mg, 0.70 mmol), pyridine (111 mg, 1.41 mmol) and **122** (140 mg, 0.35 mmol) in MeOH/H_2O (99:1, 20 mL) was stirred at ambient temperature for 12 h, methanol was removed *in vacuo* and to the residue

EtOAc (30 mL) was added. The reaction mixture was filtered thought a pad of Celite, the filtrate was washed with 1 M aq. solution of $KHSO_4$ (2 × 10 mL), brine (2 × 10 mL), dried over Na_2SO_4 and concentrated under reduce pressure. The residue was purified by column chromatography on silica gel (Et_2O/hexane, 1:10) to give **121** (49 mg, 52%, R_f = 0.42) as a colorless oil. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.80–1.00 (m, 6 H, CH_3), 1.10–1.30 [m, 1 H, C*H*(CH_3)$_2$], 1.39 (s, 9 H, *t*Bu), 1.40–1.70 (m, 2 H, CHC*H*$_2$CH), 2.47 (dd, 1 H, *J* = 4.5 Hz, *J* = 17.0 Hz, CH_2COO), 2.73 (dd, 1 H, *J* = 10.5 Hz, *J* = 17.0 Hz, CH_2COO), 3.60–3.70 (m, 1 H, CHCO), 3.88 (s, 3 H, OMe). – ^{13}C NMR (300 MHz, APT, CDCl3): δ = 22.1, 22.8, 25.9 [+, CH(CH_3)$_2$], 27.9 [+, C(*C*H$_3$)$_3$], 37.4, 40.0 (–, CH_2), 41.2 (+, *C*HCO), 52.9 (+, OMe), 81.3 [–, *C*(CH_3)$_3$], 161.3, 171.0 (–, COO), 196.4 (–, *C*OCOO).

(3*S*)-Methyl 2-Hydroxy-3-isobutyl-5-oxotetrahydrofuran-2-carboxylate (124): A solution of ester **121** (35 mg, 0.13 mmol) and trifluoracetic acid (0.1 mL, 1.30 mmol) was stirred at 0 °C for 2 h. The volatiles were removed *in vacuo* and the residue was purified by column chromatography on silica gel (CH_2Cl_2/MeOH, 30:1) to give **124** (22 mg, 79%) as a colorless oil. – ^{1}H NMR (300 MHz, 2 diastereomers, $CDCl_3$): δ = 0.80–1.00 (m, 6 H, CH_3), 1.10–1.60 [m, 3 H, C*H*$_2$C*H*(CH_3)$_2$], 2.44 (dd, 1 H, *J* = 11.8 Hz, *J* = 17.0, CH_2COO), 2.66 (dd, 1 H, *J* = 8.3 Hz, *J* = 17.0, CH_2COO), 2.90–3.10 (m 1 H, C*H*COH), 3.91 (s, 3 H, OMe), 4.61 (br s, 1 H, OH). – ^{13}C NMR (75.6 MHz, 2 diastereomers, APT, $CDCl_3$): δ = 22.5, 26.0 [+, 3 C, CH(CH_3)$_2$], 33.6, 37.3 (–, CH_2), 39.5, 42.9 (+, CH, OMe), 101.7 (–, COH), 169.1, 174.2 (–, COO).

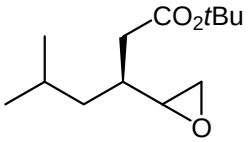


(3*S*)-Methyl 1-(3,5-Dimethoxybenzyl)-2-hydroxy-3-isobutyl-5-oxopyrrolidine-2-carboxylate (125): According to GP 3.2 from HATU (34 mg, 0.09 mmol), HOAt (12 mg, 0.09 mmol), DIEA (12 mg, 0.09 mmol), acid **124** (20 mg, 0.09 mmol) and 3,5-dimethoxybenzyl amine **55** (13 mg, 0.08 mmol) and after purification by column chromatography on silica gel (EtOAc/hexane, 1:2) pure amide **125** (15 mg, 52%, R_f = 0.42) was obtained as a colorless oil. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.80–0.90 (m, 6 H, CH_3), 1.30–1.50 [m, 3 H, C*H*$_2$C*H*(CH_3)$_2$], 2.10–2.30 (m, 1 H, CH_2CON), 2.55–2.85 (m, 2 H, CH_2CON, CHCOH), 3.60 (s, 3 H, COOMe), 3.76 (s, 6 H, OMe), 3.94 (d, 1 H, *J* = 14.0 Hz, CH_2Ph), 4.18 (br s, 1 H, NH), 5.68 (d, 1 H, *J* = 14.0 Hz, CH_2Ph), 6.30–6.50 (m, 3 H, Ph-CH), the signal of OH group is not detectable. – ^{13}C NMR (75.6 MHz, APT, $CDCl_3$): δ = 22.3, 22.8, 25.7 [+, CH(CH_3)$_2$], 35.2, 37.9 (–, CH_2), 38.5 (+, CH_2*C*HCH_2), 43.2 (–, CH_2Ph), 53.3 (+, OMe), 55.3 (+, 2



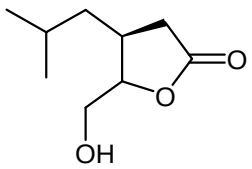
C, OMe), 89.9 (–, COH), 99.6 (+, Ph-CH), 106.5 (+, 2 C, Ph-CH), 138.9 (–, Ph-C), 160.7 (–, 2 C, Ph-C), 173.0, 175.1 (–, COO, CON).

(3*S*)-*tert*-Butyl 5-Methyl-3-(oxiran-2-yl)hexanoate (126): A solution of **107** (415 mg, 1.58 mmol) and sodium borhydride (68 mg, 1.79 mmol) in EtOH (10 mL) was stirred at ambient temperature for 4 h, than water (15 mL) was added and the obtained mixture was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (Et_2O/hexane, 1:20) to give alcohol (109 mg, 26%, R_f = 0.19) as a colorless oil.

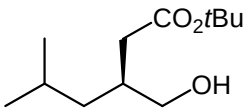


To a solution of alcohol (100 mg, 0.38 mmol) in MeOH (2 mL) the solution of sodium methylate (0.40 mL, 0.40 mmol, 1 M) was added and the reaction mixture was stirred at ambient temperature overnight. Than water (10 mL) was added and the mixture was extracted with CH_2Cl_2 (3 × 5 mL), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (Et_2O/hexane, 1:2) to give **126** (41 mg, 47%, R_f = 0.48) as a colorless oil. – ^{1}H (250 MHz, $CDCl_3$): δ = 0.80–1.00 (m, 6 H, CH_3), 1.10–1.30 [m, 1 H, C*H*(CH_3)$_2$], 1.30–1.50 (m, 11 H, *t*Bu, $CHCH_2CH$), 1.70–1.90 (m, 2 H, CH_2COO), 2.20 (dd, 1 H, *J* = 3.8 Hz, *J* = 6.5 Hz, OCH_2), 2.54 (dd, 1 H, *J* = 2.3 Hz, *J* = 5.0 Hz, OCH), 2.70 (dd, 1 H, *J* = 3.8 Hz, *J* = 5.0 Hz, OCH_2), 2.75–2.85 (m, 1 H, C*H*CHO).

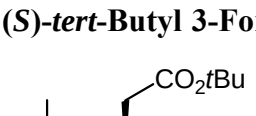
(4*S*)-5-(Hydroxymethyl)-4-isobutyldihydrofuran-2(3H)-one (128): A solution of **126** (42 mg, 0.18 mmol) and trifluoracetic acid (0.14 mL, 1.80 mmol) was stirred at 0 °C for 1 h. The volatiles were removed *in vacuo* and the residue was purified by column chromatography on silica gel (Et_2O/hexane, 1:1) to give **128** (28 mg, 90%, R_f = 0.79) as a colorless oil. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.90–1.00 (m, 6 H, CH_3), 1.30–1.70 [m, 3 H, C*H*$_2$C*H*(CH_3)$_2$], 2.31 (dd, 1 H, *J* = 8.5 Hz, *J* = 17.5 Hz, CH_2COO), 2.40–2.60 (m, 1 H, CH_2CHCH_2), 2.83 (dd, 1 H, *J* = 8.5 Hz, *J* = 17.5 Hz, CH_2COO), 3.73 (dd, 1 H, *J* = 4.5 Hz, *J* = 13.0 Hz, C*H*$_2$OH), 4.00 (dd, 1 H, *J* = 2.5 Hz, *J* = 13.0 Hz, C*H*$_2$OH), 4.20–4.35 (m, 1 H, C*H*CH_2OH), 6.80 (br s, 1 H, OH). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.8, 22.9 (CH_3), 26.2, 34.2, 35.7 ($CHCH_2CH$), 42.3 (*C*H_2COO), 62.5 (CH_2OH), 86.9 (*C*HCH_2OH), 179.3 (COO).



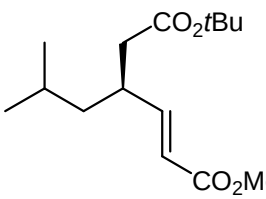
(*S*)-*tert*-Butyl 3-(Hydroxymethyl)-5-methylhexanoate (129): To a suspension of **102** (1.02 g, 3.00 mmol) in Et_2O (18 mL) methanol (96 mg, 3.0 mmol) and $LiBH_4$ (66 mg, 3.0 mmol) were added at 0 °C, consecutively. After stirring at ambient temperature overnight to the reaction mixture was quenched with saturated aq. solution of Na_2CO_3 (20 mL), two layers were separated, the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (Et_2O/hexane, 1:1) to give alcohol **129** (314 mg, 48%, R_f = 0.50) as a colorless oil. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.80–1.00 (m, 6 H, CH_3), 1.00–1.30 [m, 2 H, C*H*$_2$C*H*$(CH_3)_2$], 1.45 (s, 9 H, *t*Bu), 1.50–1.70 [m, 1 H, C*H*$_2$CH$(CH_3)_2$], 1.90 (s, 1 H, OH), 2.00–2.20 (m, 1 H, C*H*CH_2OH), 2.30–2.40 (m, 2 H, CH_2COO), 3.46 (dd, 1 H, *J* = 6.8 Hz, *J* = 10.8 Hz, C*H*$_2$OH), 3.65 (dd, 1 H, *J* = 4.3 Hz, *J* = 10.8 Hz, C*H*$_2$OH). MS (DCI): *m/z* (%) 450 (<1) [2 M + NH_4^+], 251 (8) [M + NH_3 + NH_4^+], 234 (100) [M + NH_4^+], 217 (21) [M + H^+], 195 (14), 177 (79), 160 (76).



(*S*)-*tert*-Butyl 3-Formyl-5-methylhexanoate (130): A solution of DMSO (281 mg, 3.60 mmol) in anhydrous CH_2Cl_2 (2 mL) was added dropwise to a solution of oxalyl chloride (216 mg, 1.70 mmol) in anhydrous CH_2Cl_2 (5 mL) at –70 °C within 5 min. After stirring for 20 min the solution of alcohol **129** (298 mg, 1.38 mmol) in anhydrous CH_2Cl_2 (3 mL) was added at a rate such that the temperature of the reaction mixture was not above –60 °C. After stirring for an additional 30 min at –70 °C triethylamine (0.97mL, 7.00 mmol) was slowly added, the reaction mixture was allowed to warm to ambient temperature and quenched with water (5 mL). After stirring for 10 min the reaction mixture was extracted with CH_2Cl_2 (3 × 10 mL), the combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (Et_2O/hexane, 1:4) to give aldehyde **130** (179 mg, 60%, R_f = 0.62) as a colorless oil. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.80–1.00 (m, 6 H, CH_3), 1.10–1.30 (m, 1 H, CHC*H*$_2$CH), 1.43 (s, 9 H, *t*Bu), 1.50–1.70 [m, 2 H, C*H*$_2$C*H*$(CH_3)_2$], 2.34 (dd, 1 H, *J* = 5.3 Hz, *J* = 16.3 Hz, CH_2COO), 2.58 (dd, 1 H, *J* = 8.3 Hz, *J* = 16.3 Hz, CH_2COO), 2.70–2.90 (m, 1 H, CHCO), 9.69 (d, 1 H, *J* = 1.5 Hz, COH).

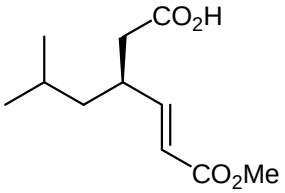


(*S*,*E*)-6-*tert*-Butyl 1-Methyl 4-Isobutylhex-2-enedioate (132): A mixture of aldehyde **130** (64 mg, 0.30 mmol) and Wittig reagent **131** (100 mg, 0.30 mmol) in CH_2Cl_2 (2 mL) was stirred at ambient temperature for 12 h. The solvent was removed *in vacuo* and the residue was purified by column chromatography on silica gel (Et_2O/hexane, 1:5) to give **132** (72 mg, 89%, R_f = 0.45) as a colorless oil. –

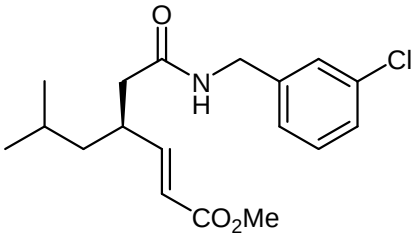


^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.80–1.00 (m, 6 H, CH_3), 1.10–1.40 [m, 2 H, CH_2CH(CH_3)$_2$], 1.42 (s, 9 H, *t*Bu), 1.50–1.70 (m, 1 H, CHCH_2CH), 2.15–2.40 (m, 2 H, CH_2COO), 2.70–2.80 (m, 1 H, CHCH=), 3.72 (s, 3 H, OMe), 5.84 (dd, 1 H, *J* = 0.8 Hz, *J* = 15.8 Hz, =CHCOOMe), 6.76 (dd, 1 H, *J* = 9.0 Hz, *J* = 15.8 Hz, =CHCOOMe).

(*S*,*E*)-3-Isobutyl-6-methoxy-6-oxohex-4-enoic Acid (133): A solution of ester **132** (68 mg, 0.25 mmol) and trifluoracetic acid (0.19 ml, 2.50 mmol) in CH_2Cl_2 (3 mL) was stirred at ambient temperature overnight. The volatiles were removed *in vacuo* to leave acid **133** (53 mg, 98%) as a colorless oil. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.80–1.00 (m, 6 H, CH_3), 1.20–1.40 [m, 2 H, CH_2CH(CH_3)$_2$], 1.40–1.60 (m, 1 H, CH_2CH(CH_3)$_2$], 2.30–2.60 (m, 2 H, CH_2COO), 2.70–2.90 (m, 1 H, CHCH=), 3.74 (s, 3 H, OMe), 5.88 (d, 1 H, *J* = 15.8 Hz, =CHCOO), 6.77 (dd, 1 H, *J* = 8.5 Hz, *J* = 15.8 Hz, =CHCH), 6.95 (br s, 1 H, COOH). – ^{13}C NMR (75.6 MHz, APT, $CDCl_3$): δ = 21.5, 23.2, 25.4 [+, CH(CH_3)$_2$], 36.5 (+, CH_2*C*HCH_2), 39.1, 43.1 (–, CH_2), 51.7 (+, OMe), 121.5 (+, =*C*HCOO), 150.9 (+, =*C*HCH), 167.2 (–, *C*OOMe), 177.1 (–, COOH). – MS (DCI): *m/z* (%) 446 (11) [2 M + NH_4^+], 249 (2) [M + NH_3 + NH_4^+], 232 (100) [M + NH_4^+].



(*S*,*E*)-Methyl 4-(2-(3-Chlorobenzylamino)-2-oxoethyl)-6-methylhept-2-enoate (134): According to GP 3.2 from HOBt×H_2O (46 mg, 0.3 mmol), HBTU (114 mg, 0.30 mmol), DIEA (39 mg, 0.3 mmol), 2-chlorbenzylamine (43 mg, 0.3 mmol) and acid **133** (53 mg, 0.25 mmol) and after purification by column chromatography on silica gel (EtOAc/hexane, 1:2) pure **134** (55 mg, 65%, R_f = 0.35) was obtained as a colorless oil. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.80–1.00 (m, 6 H, CH_3), 1.20–1.40 [m, 2 H, CH_2CH(CH_3)$_2$], 1.40–1.60 (m, 1 H, CH_2CH(CH_3)$_2$], 2.16 (dd, 1 H, *J* = 8.5 Hz, *J* = 14.3 Hz, CH_2CON), 2.32 (dd, 1 H, *J* = 5.8 Hz, *J* = 14.3 Hz, CH_2CON), 2.80–3.00 (m, 1 H, CHCH=), 3.72 (s, 3 H, OMe), 4.30–4.50 (m, 2 H, CH_2Ph), 5.77 (br s, 1 H, NH), 5.87 (d, 1 H, *J* = 15.8 Hz, =CHCOO), 6.74 (dd, 1 H, *J* = 9.3 Hz, *J* = 15.8 Hz, =CHCH), 7.00–7.30 (m, 4 H, Ph-CH). – ^{13}C NMR (75.6 MHz, APT, $CDCl_3$): δ = 21.5, 23.4, 25.5 [+, CH(CH_3)$_2$], 37.3 (+, CH_2*C*HCH_2), 42.2, 43.0, 43.4 (–, CH_2), 51.5 (+, OMe), 121.5 (+, =CHCOO), 125.9, 127.7, 127.8, 129.9 (+, Ph-CH), 134.5 (–, Ph-CCl), 140.2 (–, Ph-C), 166.8 (–, COO), 170.7 (–, CON).



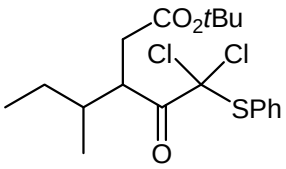
2-*sec*-Butylsuccinic Acid 4-*tert*-Butyl Ester 1-Methyl Ester (136): To a stirred solution of 3-methylpentanoic acid **135** (2.00 g, 17.2 mmol) in Et_2O the solution of diazomethane (~ 20 mL, ~ 1 M in Et_2O) was added until the yellow color of the solution did not disappear anymore. The reaction mixture was concentrated under reduced pressure to give methyl ester (2.13 g, 96%) as a colorless oil. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.80–0.90 (m, 6 H, CH_3), 1.10–1.40 (m, 2 H, CH_2CH$_3$), 1.90–2.00 (m, 1 H, CHCH$_3$), 2.10 (dd, 1 H, *J* = 8.3 Hz, *J* = 14.8 Hz, CH_2CO$_2$Me), 2.31 (dd, 1 H, *J* = 6.3 Hz, *J* = 14.8 Hz, CH_2CO$_2$Me), 3.66 (s, 3 H, CO_2Me).

To a stirred solution of diisopropilamine (1.94 g, 19.2 mmol) in anhydrous THF (15 mL) the solution of *n*BuLi (7.2 mL, 18 mmol, 2.5 M in hexane) was added dropwise at –78 °C withi 10 min under N_2. After stirring for 1 h the solution of 3-methylpentanoic acid methyl ester (2.13 g, 16.4 mmol) in anhydrous THF (25 mL) was added dropwise within 15 min. After stirring for an additional 2 h, *tert*-butyl bromacetate **x** (3.1 mL, 21 mmol) dissolved in anhydrous THF (25 mL) was added dropwise within 30 min. After stirring at ambient temperature overnight, the reaction mixture was quenched with brine (30 mL) and neutralized with 1 M aq. solution of HCl. Two layers were separated, the aqueous layer was extracted with EtOAc (3 × 20 mL), combined organic phasess were dried over $MgSO_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc/hexane, 1:5) to give **136** (3.83 g, 98%, R_f = 0.44) as a colorless oil. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.80–1.00 (m, 6 H, CH_3), 1.00–1.30 (m, 2 H, CH_2CH$_3$), 1.42 (s, 9 H, *t*Bu), 1.60–1.80 (m, 1 H, CHCH$_3$), 2.20–2.40 (m, 1 H, CHCO$_2$Me), 2.50–2.90 (m, 2 H, CH$_2$CO$_2$*t*Bu), 3.68 (s, 3 H, CO_2Me).

***tert*-Butyl 3-(2-Chloroacetyl)-4-methylhexanoate (137):** To a solution of diisopropilamine (2.83 g, 28.0 mmol) in anhydrous THF (6 mL) the solution of *n*BuLi (12.0 mL, 30.0 mmol, 2.5 M in hexane) was added dropwise at –78 °C within 30 min under N_2. After stirring at the same temperature for 15 min the solution of chloroacetic acid (3.88 g, 41.1 mmol) in anhydrous THF (6 mL) was added dropwise within 10 min. After stirring by cooling for an additional 15 min the reaction mixture was added to the solution of **136** (2.85 g, 11.7 mmol) in anhydrous THF (30 mL) at 0 °C. After stirring at ambient temperature for an additional 12 h, the reaction mixture was quenched with water (100 mL) and EtOAc (100 mL), two layers were separated and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic phases were washed with the mixture of 1 M aq. solution of $KHSO_4$ and brine (1:1, 2 × 30 mL), the mixture of saturated aq. solution of $NaHCO_3$ and brine (1:1, 2 × 30 mL), brine (2 × 30 ml), dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (Et_2O/hexane, 1:5) to

give **137** (698 mg, 23%, R_f = 0.53) as a colorless oil. – ^{1}H NMR (300 MHz, 2 diastereomers, $CDCl_3$): δ = 0.70–1.00 (m, 6 H, CH_3), 1.00–1.50 (m, 13 H, *t*Bu, CH_2CH_3), 1.50–1.80 (m, 1 H, $CHCH_3$), 2.20–2.45 (m, 1 H, CH_2CO_2tBu), 2.60–2.85 (m, 1 H, CH_2CO_2tBu), 2.90–3.20 (m, 1 H, CHCO), 4.26 (d, 1 H, *J* = 15.3 Hz, CH_2Cl), 4.35 (d, 1 H, *J* = 15.3 Hz, CH_2Cl). – maj. ^{13}C NMR (300 MHz, APT, $CDCl_3$): δ = 11.9, 15.2 (+, CH_3), 27.8 (–, CH_2CH_3), 28.0 [+, $C(CH_3)_3$], 32.5 (–, CH_2CO_2tBu), 35.7 (+, $CHCH_3$), 48.6 (+, CHCO), 48.9 (–, CH_2Cl), 81.1 [–, $C(CH_3)_3$], 171.9 (–, CO_2tBu), 204.3 (–, CO). min. ^{13}C NMR (300 MHz, APT, $CDCl_3$): δ = 11.4, 16.8 (+, CH_3), 25.9 (–, CH_2CH_3), 28.0 [+, $C(CH_3)_3$], 34.7 (–, CH_2CO_2tBu), 36.4 (+, $CHCH_3$), 49.6 (+, CHCO), 49.9 (–, CH_2Cl), 81.1 [–, $C(CH_3)_3$], 171.8 (–, CO_2tBu), 204.5 (–, CO).

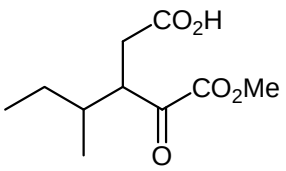
***tert*-Butyl 3-(2,2-Dichloro-2-(phenylthio)acetyl)-4-methylhexanoate (138):** A solution of **137**



(698 mg, 2.66 mmol) and sodium tiophenolate (528 mg, 4.00 mmol) in benzene (20 mL) was stirred at ambient temperature for 5 h. To the reaction mixture water (30 mL) was added, two layers were separated and the aqueous layer was extracted with benzene (3 × 10 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure to give tiophenol derivative (822 mg, 92%, R_f = 0.69, Et_2O/hexane, 1:5) as a pale yellow oil which was further used without an additional purification.

To a solution of tiophenol derivative (822 mg, 2.45 mmol) and pyridine (972 mg, 12.3 mmol) in CCl_4 (20 mL) the solution of sulfuryl chloride (662 mg, 4.90 mmol) in CCl_4 (5 mL) was added dropwise at 0 °C. After stirring for an additional 15 min the reaction mixture was quenched with water (15 mL), two layers were separated and the aqueous layer was extracted with CCl_4 (3 × 10 mL). The combined organic phases were washed with 1 M aq. solution of $KHSO_4$ (2 × 10 mL), brine (2 × 10 mL), dried over Na_2SO_4 and concentrated under reduced pressure to give **138** (979 mg, 99%) as a yellow oil which was further used without an additional purification. – ^{1}H NMR (250 MHz, 2 diastereomers, $CDCl_3$): δ = 0.80–1.10 (m, 6 H, CH_3), 1.20–1.50 (m, 11 H, *t*Bu, CH_2CH_3), 2.00–2.30 (m, 1 H, $CHCH_3$), 2.30–2.50 (m, 1 H, CH_2CO_2tBu), 2.60–2.80 (m, 1 H, CH_2CO_2tBu), 3.90–4.10 (m, 1 H, CHCO), 7.40–7.60 (m, 3 H, Ph-CH), 7.70–7.80 (m, 2 H, Ph-CH).

3-(2-Methoxy-2-oxoacetyl)-4-methylhexanoic Acid (139): The suspension of mercury chloride

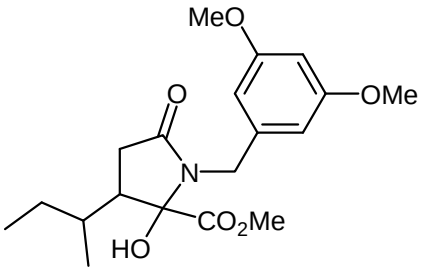


(II) (1.33 g, 4.89 mmol), pyridine (766 mg, 9.70 mmol) and **139** (979 mg, 2.42 mmol) in MeOH/H_2O (99:1, 40 mL) was stirred for 2 d, methanol was removed *in vacuo* and to the residue EtOAc (30 mL) was added. The reaction mixture was filtered thought a pad of Celite, the filtrate was washed with 1 M aq. solution of $KHSO_4$ (2 × 10 mL), brine (2 × 10 mL), dried over Na_2SO_4 and

concentrated under reduce pressure to give ester (374 mg, 57%) as a colorless oil which was used without further purification. – ^{1}H NMR (250 MHz, 2 diastereomers, $CDCl_3$): δ = 0.70–1.00 (m, 6 H, CH_3), 1.15–1.50 (m, 11 H, CH_2, *t*Bu), 1.60–1.90 (m, 1 H, C*H*CH_3), 2.30–2.50 (m, 1 H, CH_2CO_2*t*Bu), 2.60–2.90 (m, 1 H, CH_2CO_2*t*Bu), 3.60–3.80 (m, 1 H, CHCO), 3.88 (s, 3 H, OMe). – maj ^{13}C NMR (300 MHz, 2 diastereomers, APT, $CDCl_3$): δ = 11.9, 15.0 (+, CH_3), 27.8 (–, *C*H_2CH_3), 27.9 [+, C(*C*H_3)$_3$], 31.9 (–, *C*H_2CO_2*t*Bu), 34.9 (+, *C*HCH_3), 46.8 (+, *C*HCO_2Me), 52.9 (+, OMe), 81.1 [–, *C*$(CH_3)_3$], 161.4, 171.5 (–, COO), 195.9 (–, COCOO). min. ^{13}C NMR (300 MHz, 2 diastereomers, APT, $CDCl_3$): δ = 11.5, 16.8 (+, CH_3), 25.8 (–, *C*H_2CH_3), 27.9 [+, C(*C*H_3)$_3$], 34.3 (–, *C*H_2CO_2*t*Bu), 36.1 (+, *C*HCH_3), 47.5 (+, *C*HCO_2Me), 53.0 (+, OMe), 81.2 [–, *C*$(CH_3)_3$], 161.5, 171.4 (–, COO), 196.2 (–, COCOO). – MS (DCI): *m/z* (%) 562 (2) [2 M + NH_4^+], 290 (100) [M + NH_4^+].

A solution of ester (140 mg, 0.51 mmol) and trifluoracetic acid (593 mg, 5.20 mmol) in CH_2Cl_2 (5 mL) was stirred at ambient temperature overnight, the volatiles were removed *in vacuo* to give **139** (102 mg, 91%) as a pale yellow oil which was further used without an additional purification. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.70–1.05 (m, 6 H, CH_3), 1.10–1.60 (m, 2 H, $CHCH_2$), 1.70–1.90 (m, 1 H, $CHCH_2$), 2.30–2.90 (m, 3 H, C*H*C*H*$_2CO_2$H), 3.91 (s, 3 H, OMe), 4.72 (br s, 1 H, COOH). – MS (DCI): *m/z* (%) 450 (29) [2 M + NH_4^+], 251 (89) [M + NH_3 + NH_4^+], 234 [M + NH_4^+].

Methyl 1-(3,5-Dimethoxybenzyl)-3-*sec*-butyl-2-hydroxy-5-oxopyrrolidine-2-carboxylate (141):



According to GP 3.2 from HOAt (34 mg, 0.25 mmol), HBTU (95 mg, 0.25 mmol), 3,5-dimethoxybenzylamine **55** (42 mg, 0.25 mmol), DIEA (32 mg, 0.25 mmol) and acid **139** (43 mg, 0.20 mmol) and after purification by column chromatography on silica gel (EtOAc/hexane, 1:2) pure **141** (42 mg, 58%, R_f = 0.54) was obtained as a colorless oil. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.70–0.90 (m, 6 H, CH_3), 1.10–1.80 (m, 3 H, $CHCH_2$), 2.30 (br s, 1 H, CH_2CON), 2.52 (br s, 2 H, $CHCH_2CON$), 3.35 (s, 3 H, CO_2Me), 3.76 (s, 6 H. OMe), 3.93 (dd, 1 H, *J* = 4.0 Hz, *J* = 15.0 Hz, CH_2Ph), 4.26 (br s, 1H, NH), 4.64 (d, 1 H, *J* = 15.0 Hz, CH_2Ph), 6.32 (s, 1 H, Ph-CH), 6.37 (s, 2 H, Ph-CH), the signal of OH group can not be detected. – ^{13}C NMR (300 MHz, APT, 2 diastereomeres, $CDCl_3$): δ = 10.5, 10.7, 16.3, 16.4 (+, CH_3), 26.7, 26.8 (–, 4 C, *C*H_2CH_3, *C*H_2CON), 43.03, 34.05 (+, *C*HCH_3), 43.0 (–, 2 C, CH_2Ph), 45.2, 45.9 (+, *C*HCHOH), 53.4 (+, 2 C, CO_2CH_3), 55.5 (+, 4 C, Ph-OMe), 89.3, 89.4 (–, CHOH), 99.5, 99.7 (+, Ph-CH), 106.4, 106.5 (+, 4 C, Ph-CH), 138.8, 138.9 (–, Ph-C), 160.6 (–, 4 C, Ph-C), 173.4, 173.5 (–, 4 C, COO, CONH).

D Summary

During elaboration of this thesis, a number of different potential biologically active compounds have been prepared.

First chapter is dedicated to the applying of the Ugi multicomponent reaction for the synthesis of compounds containing small ring systems such as cyclopropane and its structure analogs oxirane moieties. A number of new dipeptides **5a-l**, containing at list one cyclopropane residue, were prepared *via* the Ugi multicomponent condensation of new cyclopropaneisonitriles **10a-c, 13** with variety of other three components (acid, aldehyde, amine) in a good yields (38–86%). New cyclopropaneisonitriles **10a-c, 13** were prepared according to the standard procedure from respective cyclopropaneamines, obtained from nitiles *via* titanium catalysis, by formylation of the latters and subsequent dehydration of the *N*-formyl derivatives.

Synthesis of the oxirane containing peptides was based on the applying of the acid component of the Ugi condensation as a donor of oxirane moiety. Thus, two acids **26** and **28** were prepared according to established protocols and subjected the Ugi condensations with different amines, aldehydes and isonitriles to afford a number of new dipeptides **29a-j** in good yields (42–78%).

Synthesis of potential beta-turn mimetic **30** *via* Ugi multicomponent reaction proved to be unable since all attempt to obtain one of the required components, namely imine **33**, were unsuccessful.

The second chapter is dedicated to the synthesis of activated besed ketones, namely, α-keto amides **46** and **47**. After several unsuccessful attempts desired amide **66** containing leucine moiety and corresponding dipeptide **67** were prepared from respective leucinal **57**. Condensation of the ester anion tris(methylthio)methane with the carbonyl group of the latter and following hydrolysis of the obtained α-keto dithiomethyl derivate **59** afforded α-hydroxymethyl ester **60** which was protected with 2,2-dimethoxypropane **61** to give the respective oxazolidine derivate **62**. After hydrolysis of the ester group, subsequent coupling with 3,5-dimethoxybenzylamine **55** and following remove of the both protection groups, the hydrochloride **65**, a multipurpose building block, was obtained. On the one hand, amino group of latter was protected with Cbz-protection and α-hydroxy group was oxidized into α-keto group to afford desired amide **66**. On the other hand, the hydrochloride **65** was subjected to the coupling with *N*-protected amino acid, namely *N*-Cbz-valine, and following oxidation to give required dipeptide **67**.

Applying the same protocol to the isoleucinal **79** provided to the α-hydroxy orthothioester **80**, which proved to be unstable and cyclezed into oxazolidine derivative **81**, probably, due to sterical influence of methyl group in 4-position. All attempts to open the ring of the latter were unsuccessful. Uging another protection for amino group of the starting aldehyde, namely dibenzyl

protection, afforded to the desired α-hydroxy orthothioester **91**, but the following mercury-catalezed hydrolysis led to complete decomposition of the latter.

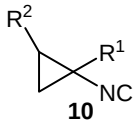
The third chapter is dedicated to the synthesis of 3-keto amides and their analogs. From respective acid chloride **100** by Evans protocol, chiral scaffold **104** was prepared which was converted into 5-chloro-3-keto ester **107** by Cleisen reaction. The *tert*-butyl ester group of the latter was cleaved and subsequent coupled with 3,5-dimethoxybenzylamine **55** to afford amide **110** which proved to be unstable and converted into pyrrole **111** by elimination of water and hydrochloric acid. Mechanism suggested for the new cyclization was confirmed by a number of the simple examples.

5-Chloro-3-keto ester **107** was oxidativly converted into respective 5-carboxy-3-keto ester **121** by substitution of chloro moiety for thiophenyl, oxidation of the methylene group and subsequent mercury-catalyzed hydrolysis. The following hydrolysis of *tert*-butyl ester group resulted, instead of the expected acid, only substituted tetrahydrofuran **124** which was subjected the reaction with amine to give pirrolidinone **125**.

The cloroketone moiety in **107** was converted into an epoxide group by reduction of the keto group and subsequent cyclization of the formed chlorohydrine. Obtained *tert*-butyl ester **126** under acidic condition of cleavage of ester group cyclized into γ-lactone **128**.

The synthesis of 4,5-unsaturated amide **134** was based on the reduction-oxidation sequence applied to the amide **102** followed by Wittig olefination as the key step. Thus, *tert*-butyl ester group of the obtained ester **132** was cleaved and coupled with amine resulting desired amide **134**.

Taking in consideration the previous results regarding stability of the target amides, it was decided to synthesize a recemic mixture of required amide **140**. Thus, methyl ester of acid **135** was alkylated with *tert*-butyl bromacetate to afford ester which was transformed by Claisen reaction into respective 5-chloro-3-keto ester **137**. The latter was converted into 5-carboxy-3-keto acid **139** according to the procedure described for synthesis of amide **110**, and coupled with 3,5-dimethoxybenzylamine **55** to result, as it was predicted, only pyrrolidine **141**.



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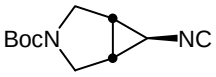

13

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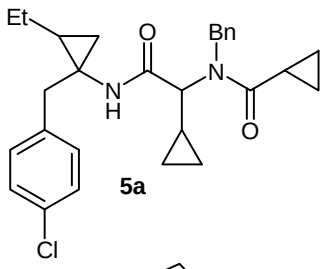
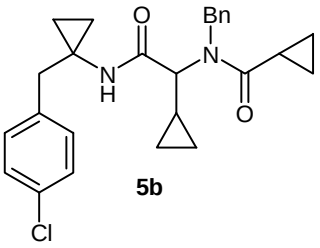
b R^1= 4-Cl-Bn R^2= Et
c R^1= $BnOCH_2$ R^2= Ph



5a



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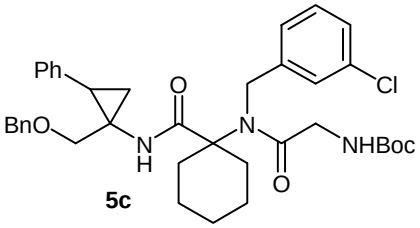

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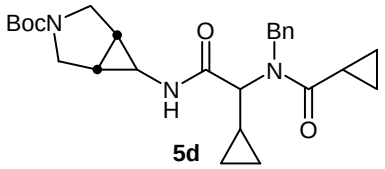

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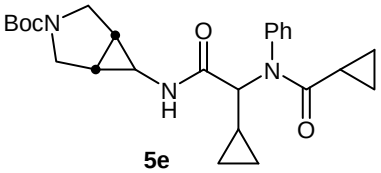

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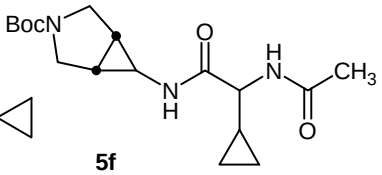

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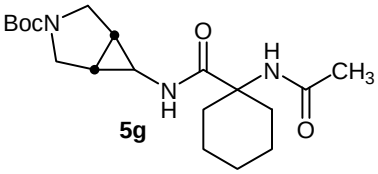
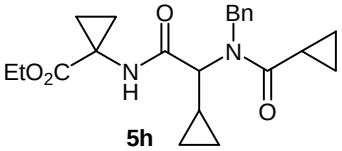


5g



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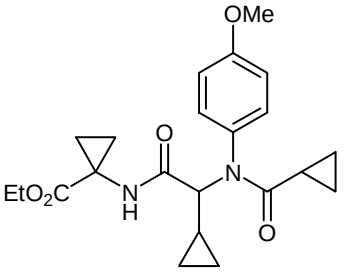

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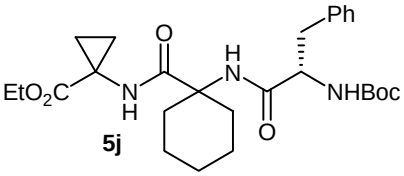

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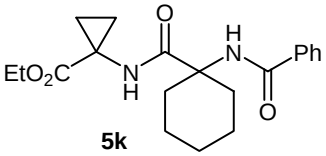

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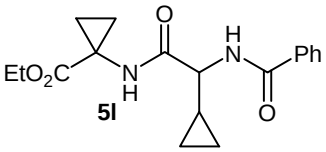
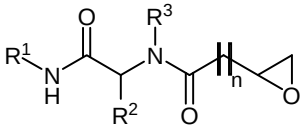
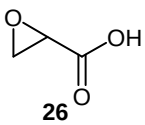


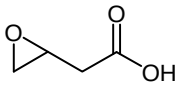
5l



29a-j

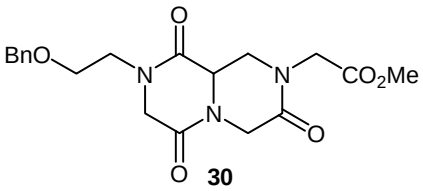


26



28

a R^1 = MeO_2CCH_2 R^2 = *t*Bu R^3 = Bn *n*= 0
b R^1 = MeO_2CCH_2 R^2 = *t*Bu R^3 = Ph *n*= 0
c R^1 = MeO_2CCH_2 R^2 = *t*Bu R^3 = MeO_2CCH_2 *n*= 0
d R^1 = Bn R^2 = *t*Bu R^3 = Ph *n*= 0
e R^1 = Bn R^2 = *t*Bu R^3 = Bn *n*= 0
f R^1 = Bn R^2 = *t*Bu R^3 = MeO_2CCH_2 *n*= 0
g R^1 = Bn R^2 = Ph R^3 = Ph *n*= 0
h R^1 = Bn R^2 = Ph R^3 = Bn *n*= 0
i R^1 = MeO_2CCH_2 R^2 = Ph R^3 = Ph *n*= 0
j R^1 = Ph R^2 = *t*Bu R^3 = Ph *n*= 1



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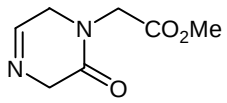
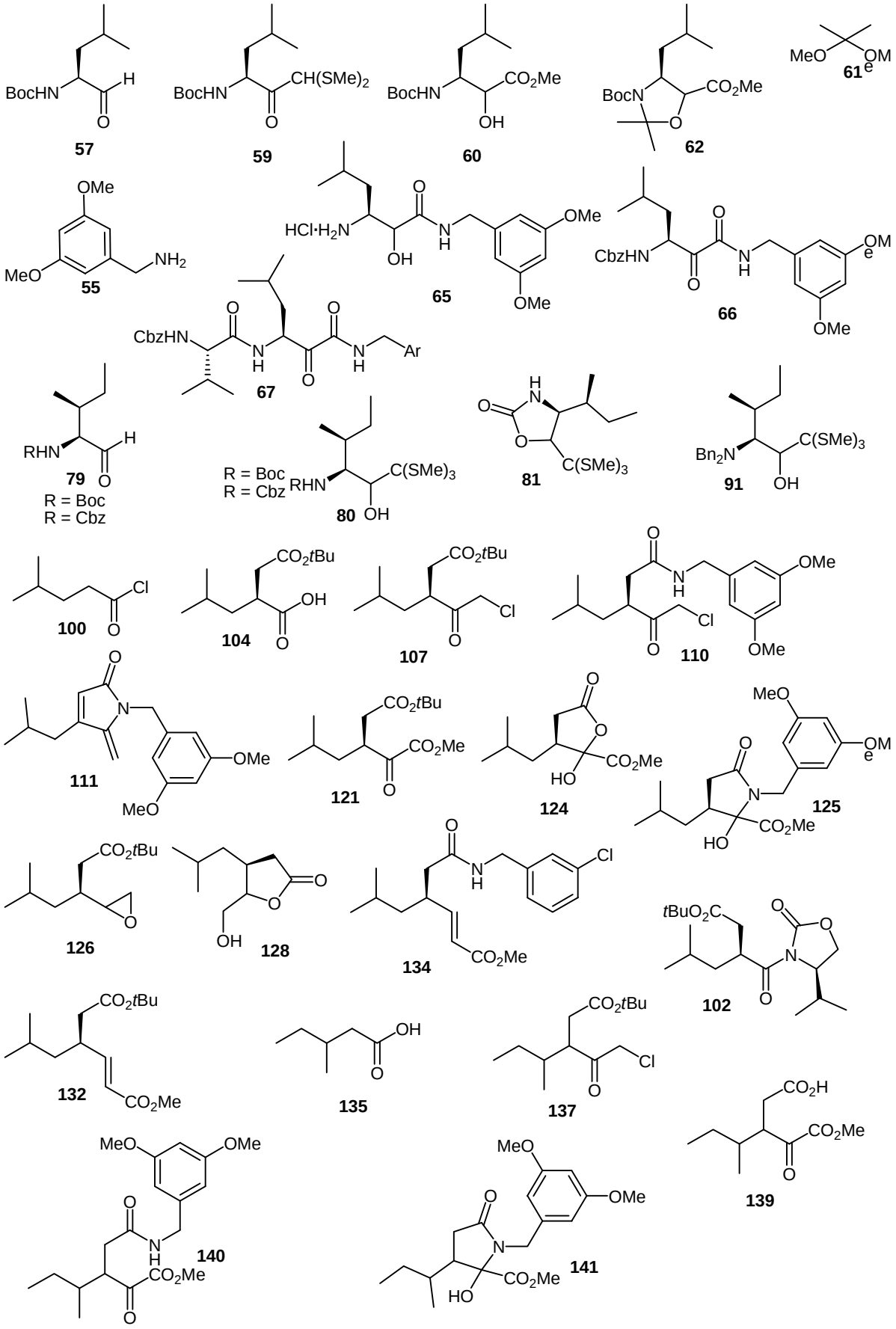


33


BocHN
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BocHN
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OH
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CO2Me
O
62
MeO
OMe
61
OMe
MeO
NH2
55
HCl·H2N
O
N
H
OH
OMe
65
OMe
CbzHN
O
N
H
OMe
66
OMe
CbzHN
O
N
H
O
N
H
Ar
67
RHN
H
O
79
R = Boc
R = Cbz
R = Boc
R = Cbz
RHN
C(SMe)3
OH
80
H
N
O
O
C(SMe)3
81
Bn2N
C(SMe)3
OH
91
Cl
O
100
CO2tBu
OH
O
104
CO2tBu
Cl
O
107
O
N
H
OMe
Cl
O
OMe
110
O
N
OMe
MeO
111
CO2tBu
CO2Me
O
121
O
O
CO2Me
HO
124
MeO
OMe
O
N
CO2Me
HO
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CO2tBu
O
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141

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[18] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited as supplementary publication no. CCDC 604790 (**5b**), CCDC 604791 (**5d**), CCDC 604792 (**5h**), CCDC 604703 (**5i**) with the Cambridge Crystallographic Data Centre. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (+44)1223-336-033; E-mail: deposit@ccdc.cam.ac.uk

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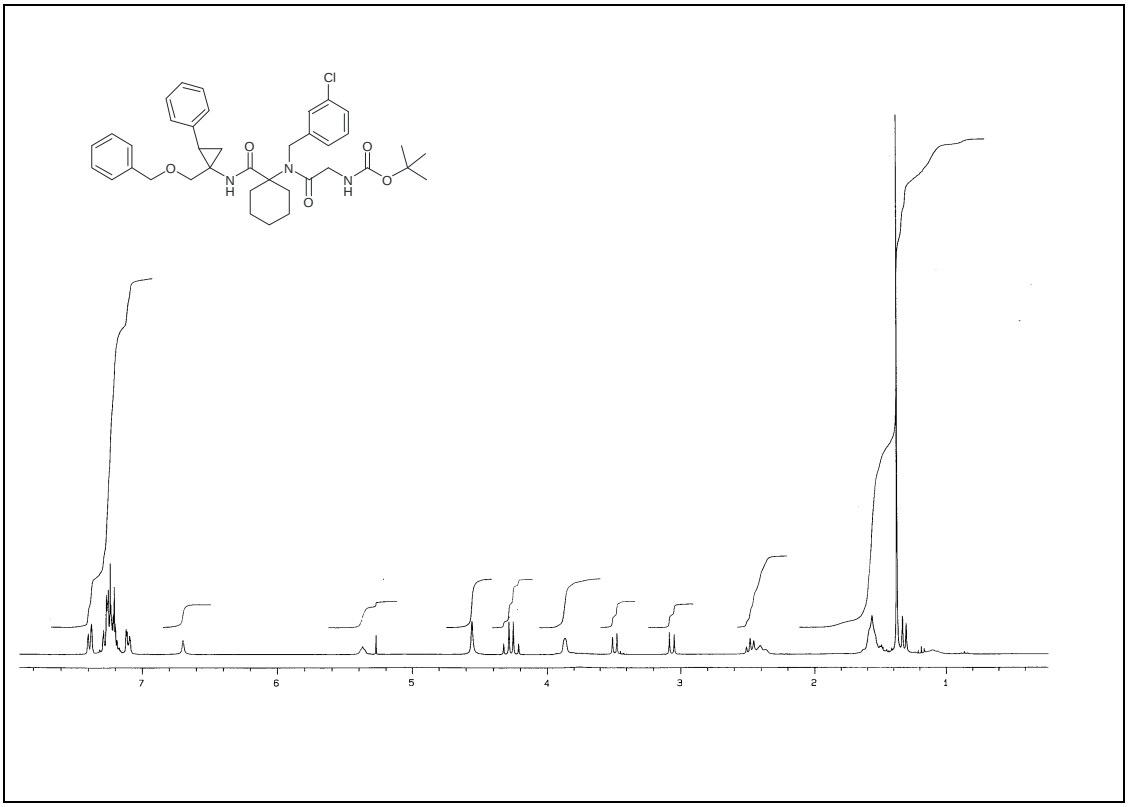
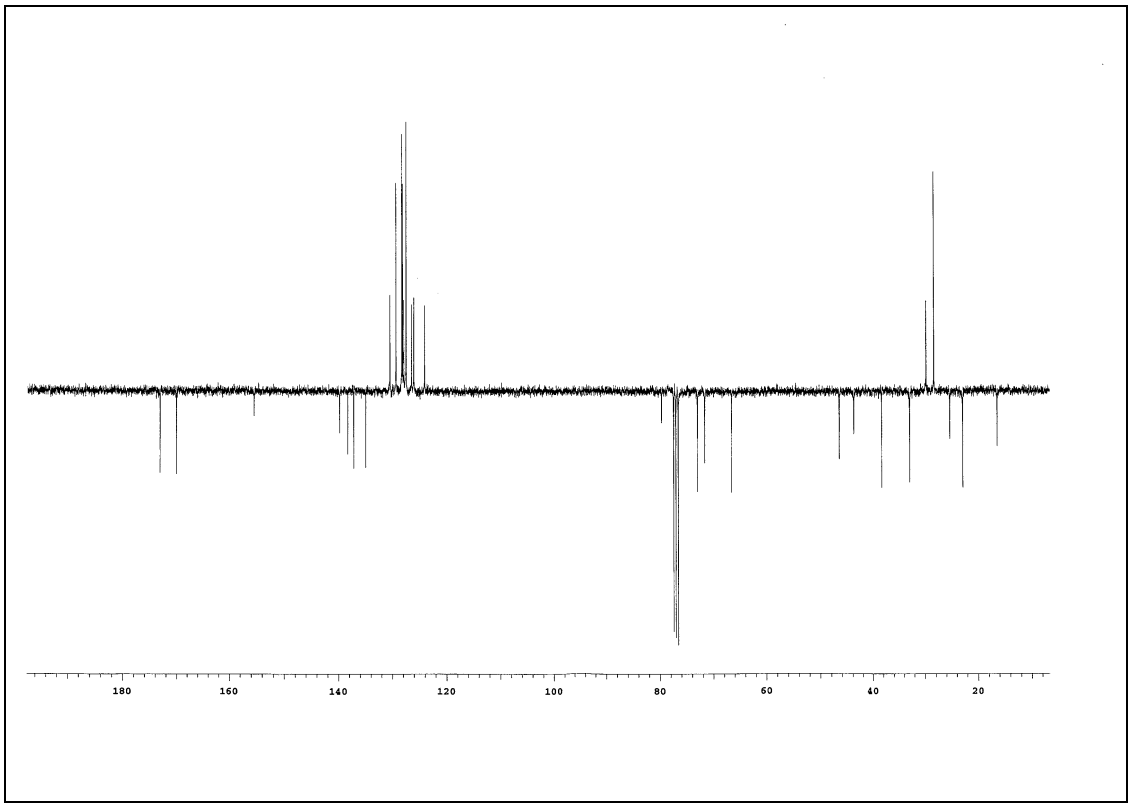
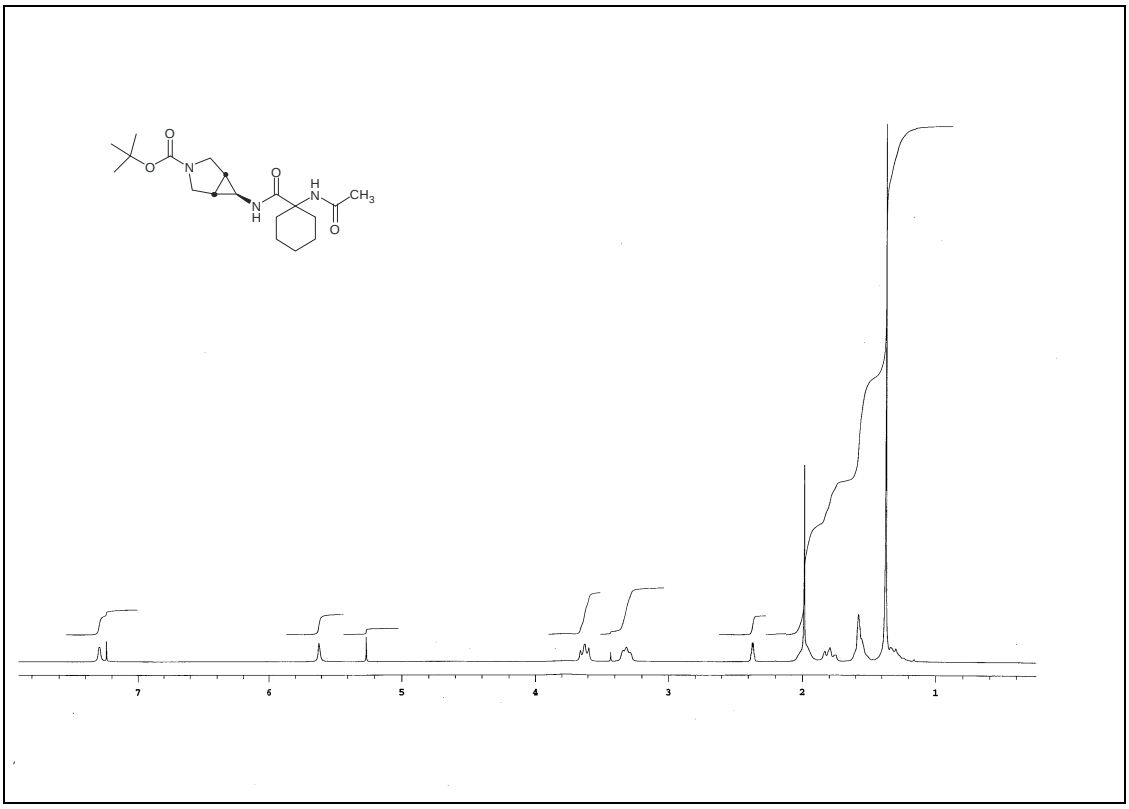
F Spectral Data

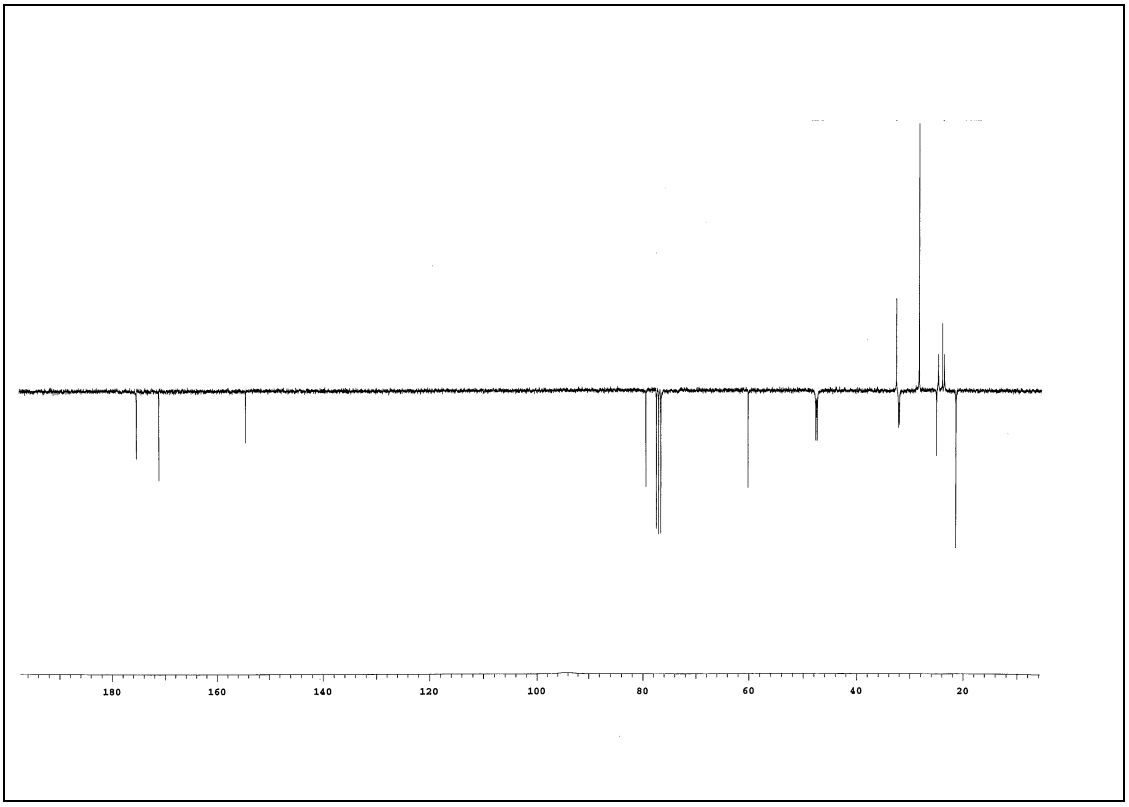
N-*tert*-Butoxycarbonylglycinyl [(1-benzyloxymethyl-2-phenylcyclopropylcarbamoyl)-cycloxehyl]-(3-chlorobenzyl)amine (**5c**):



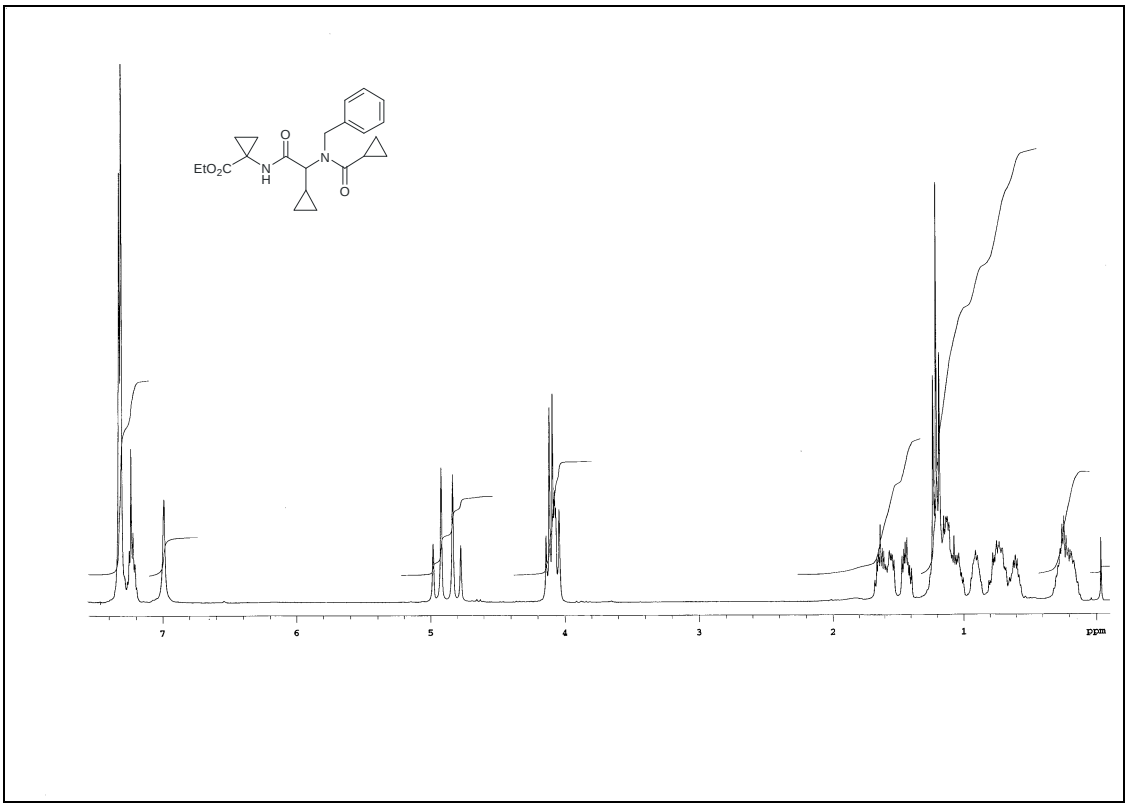


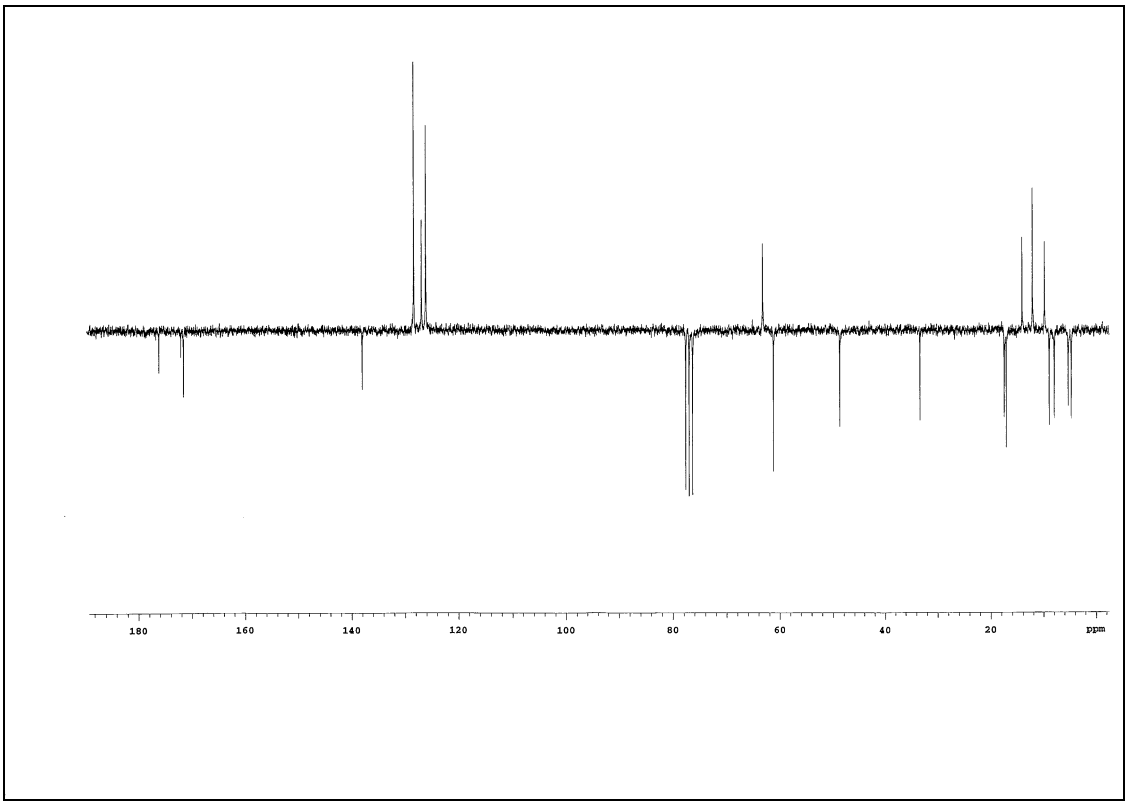
(1*R*,5*S*)-*tert*-Butyl 6-(1-Acetamidocyclohexanecarboxamido)-3-aza-bicyclo[3.1.0]hexane-3-carboxylate (**5g**):



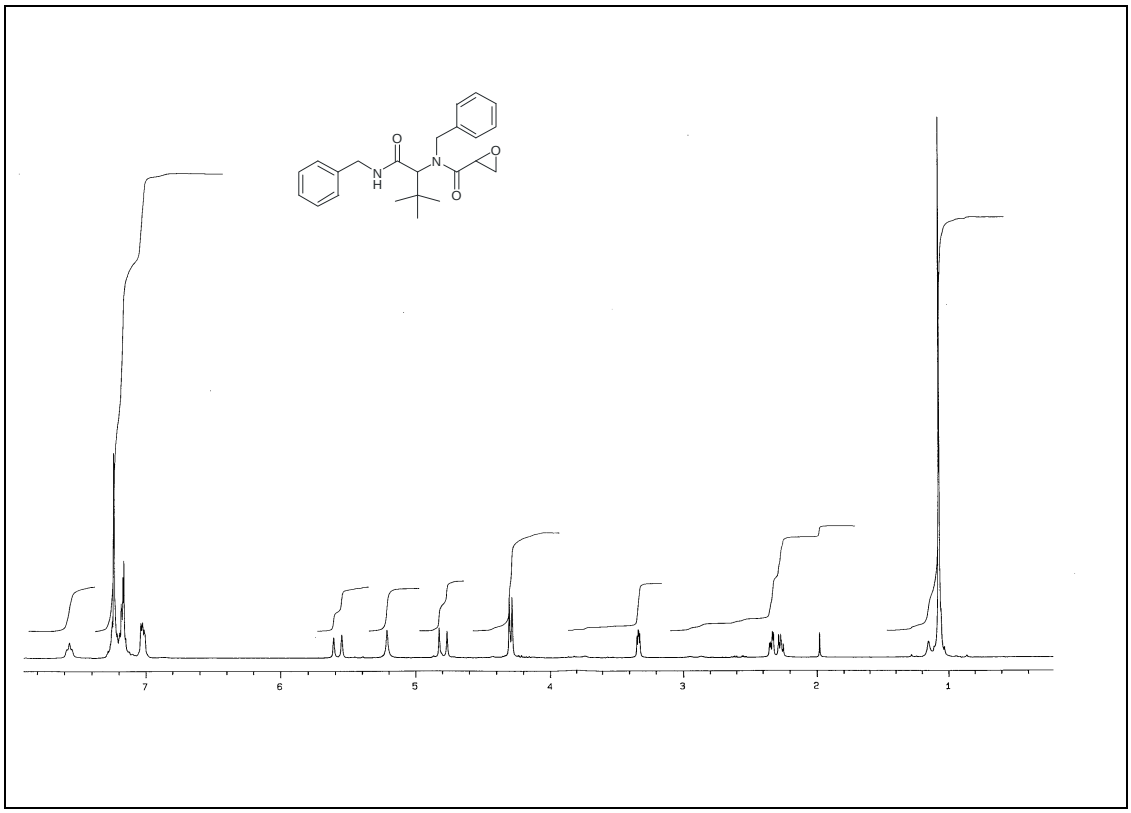


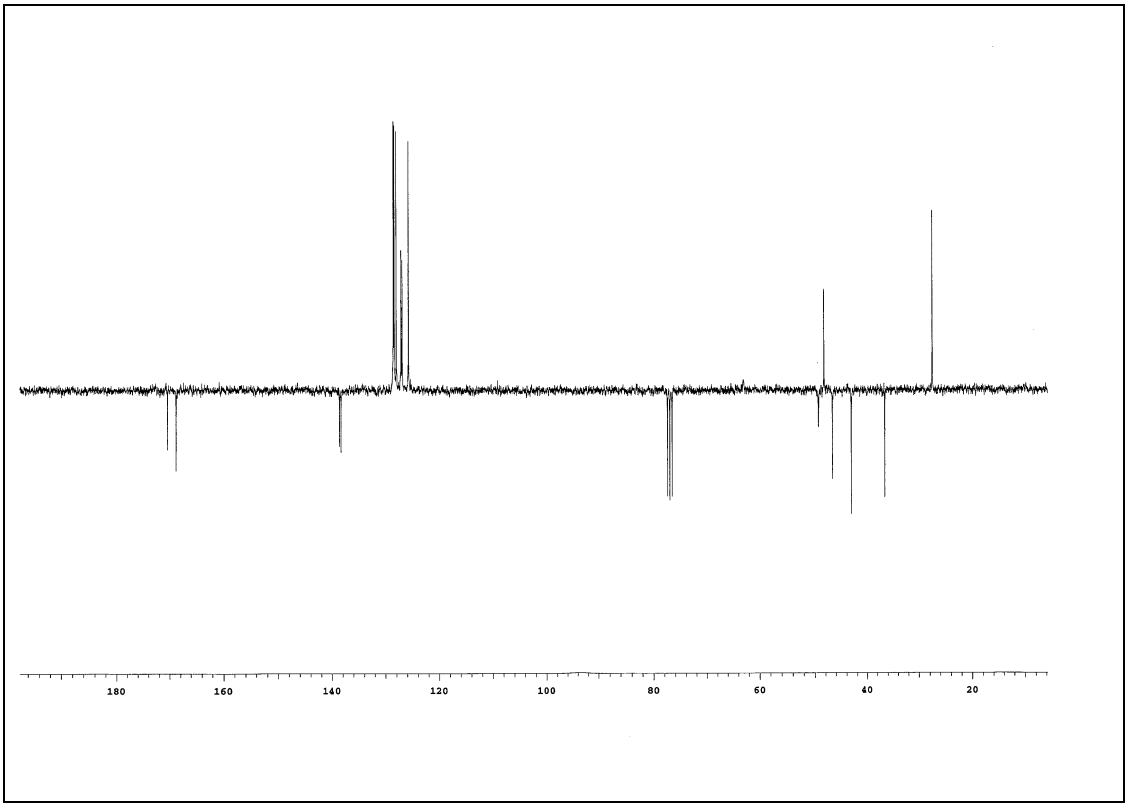
Ethyl 1-[2-(Benzylcyclopropanecarbonylamino)-2-cyclopropylacetylamino]cyclopropane-carboxylate (**5h**)



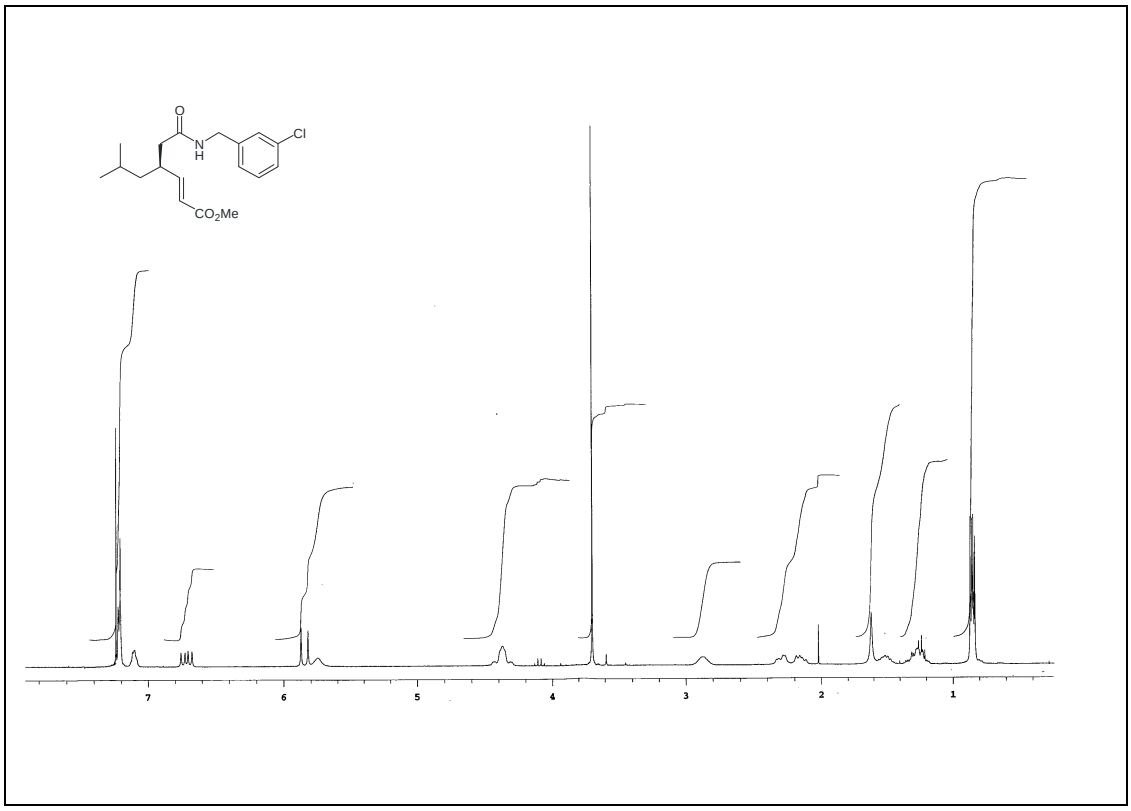


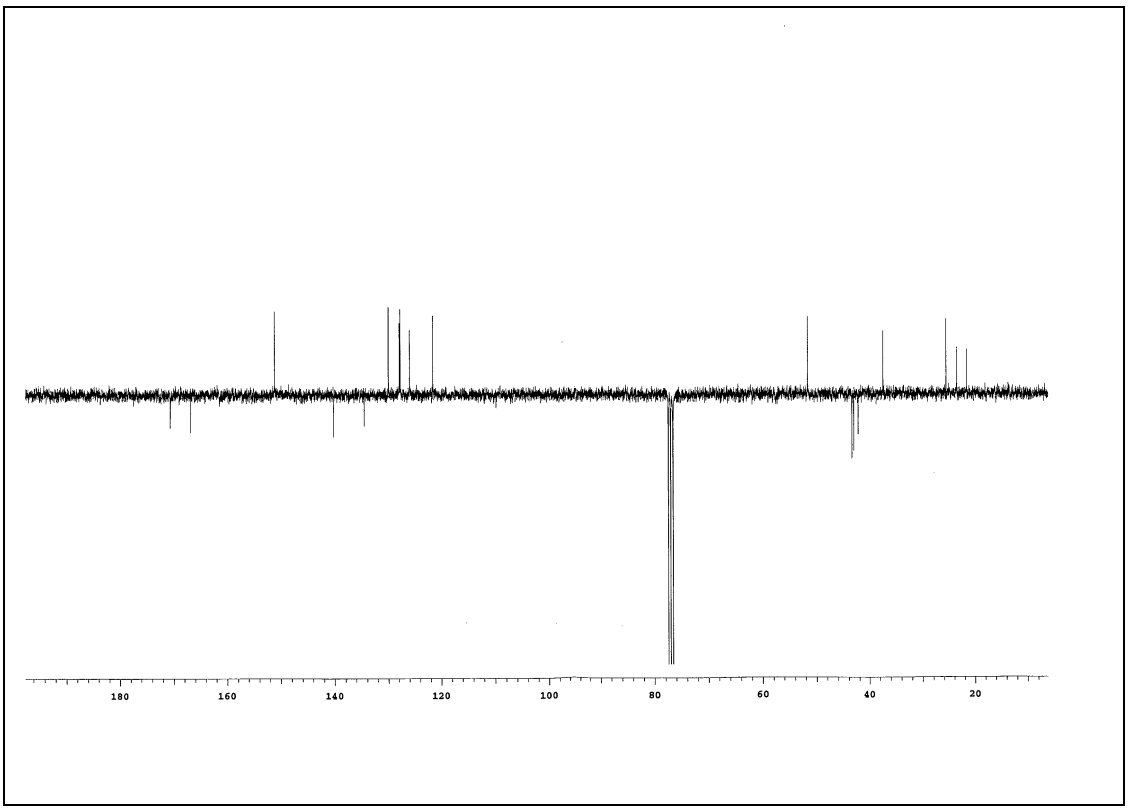
Oxirane-2-carboxylic Acid Benzyl-(1-benzylcarbamoyl-2,2-dimethylpropyl)amide (**29e**):



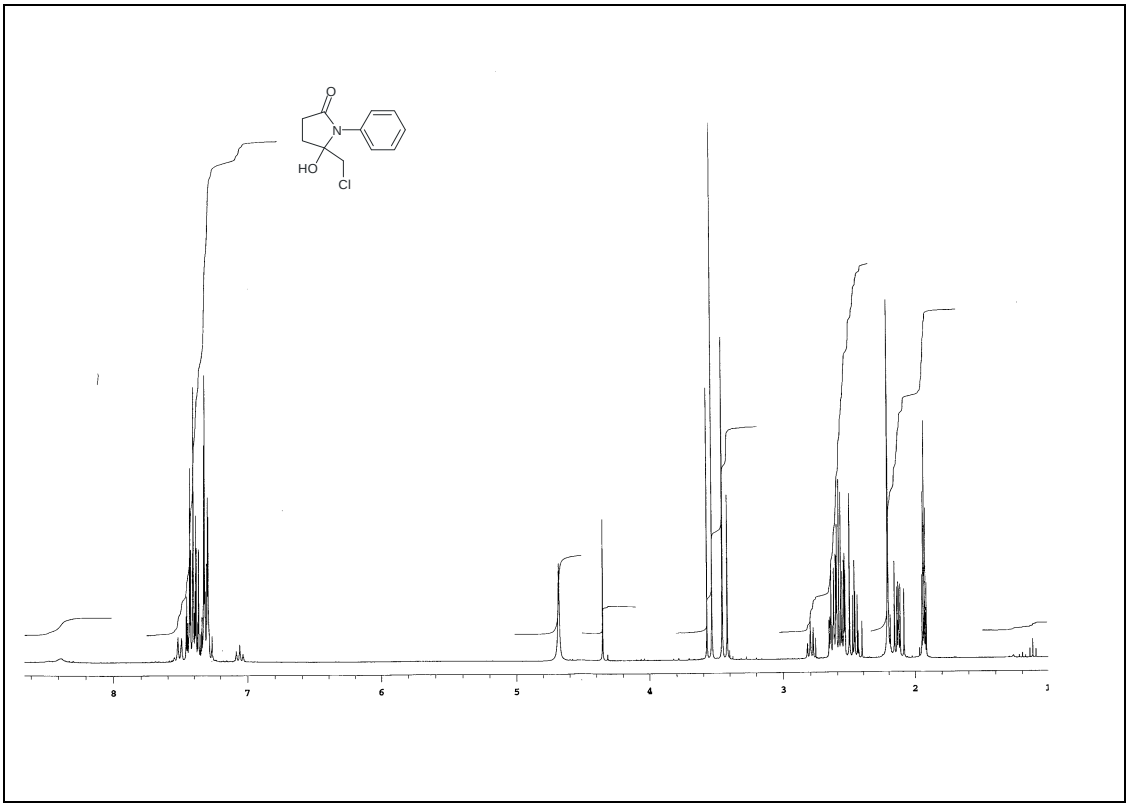


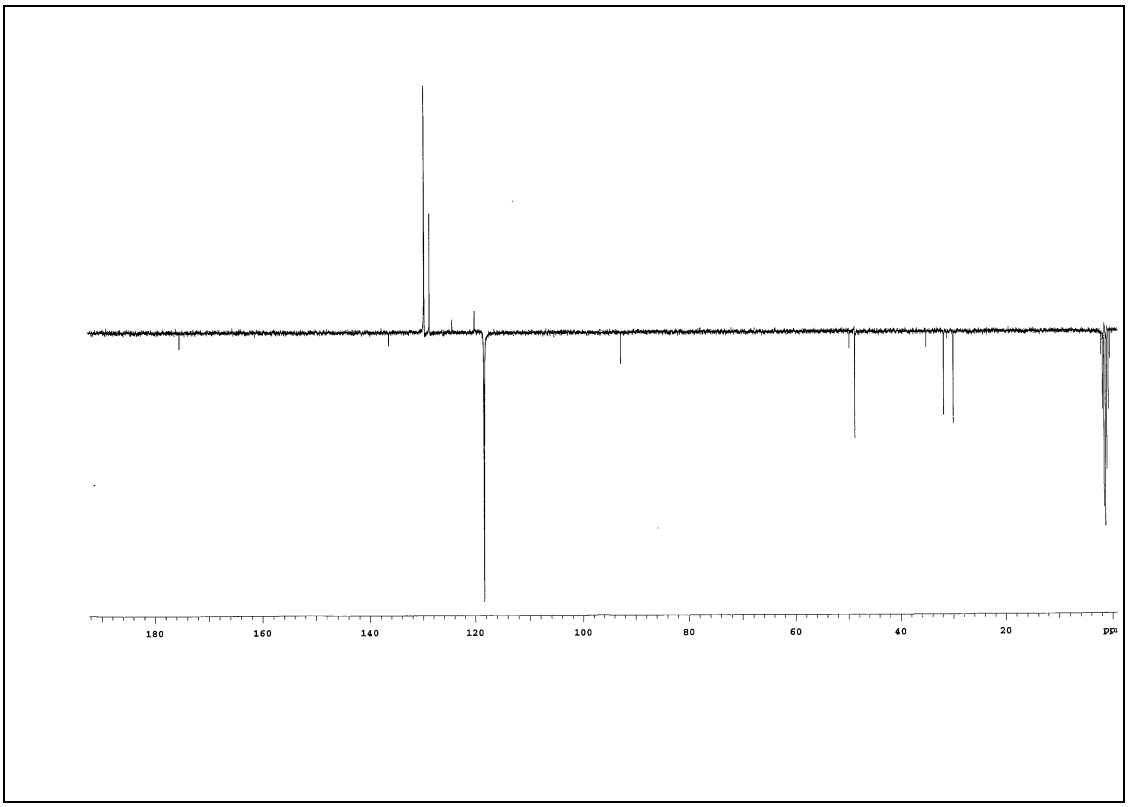
(*S*,*E*)-Methyl 4-(2-(3-Chlorobenzylamino)-2-oxoethyl)-6-methylhept-2-enoate (**134**):



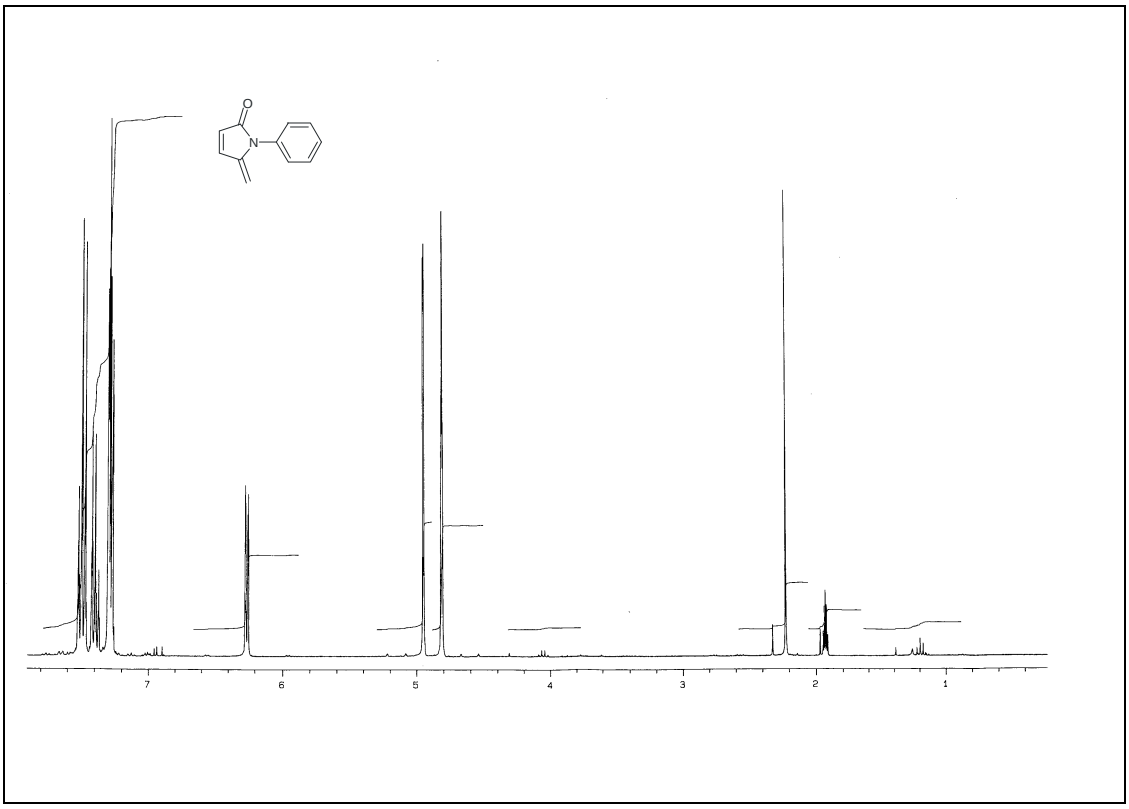


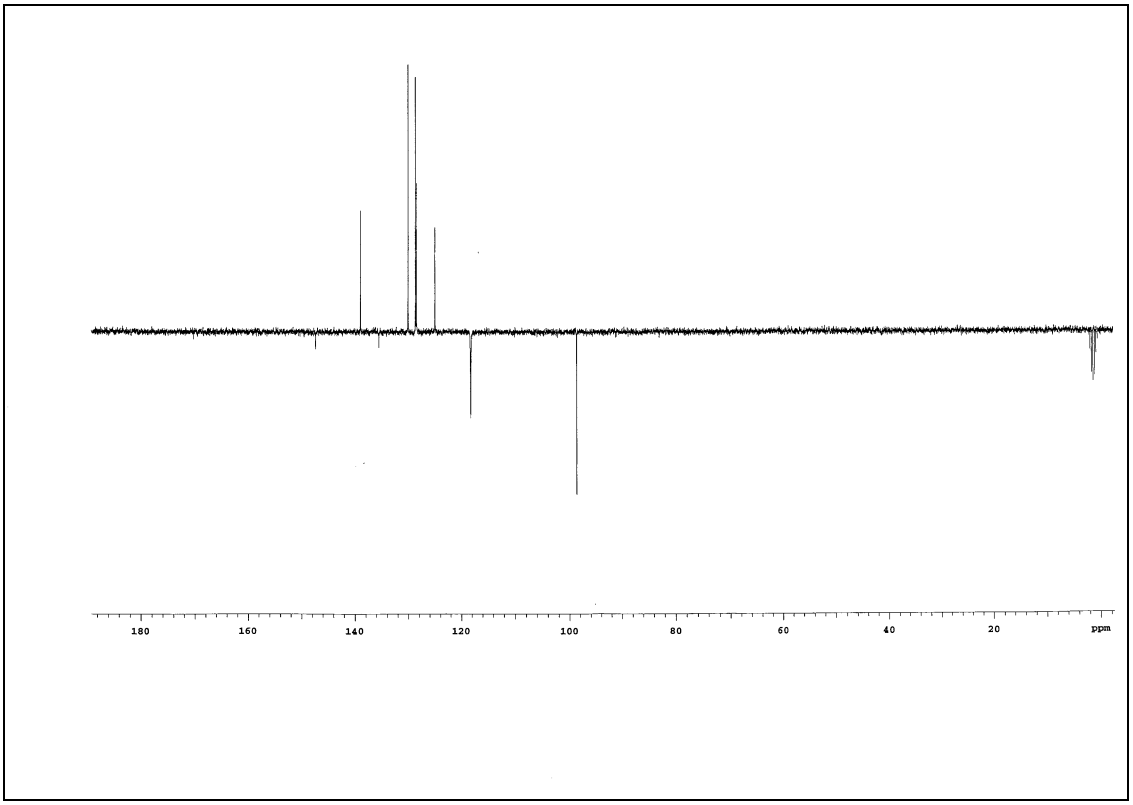
5-(Chloromethyl)-5-hydroxy-1-phenylpyrrolidin-2-one (**119d**):



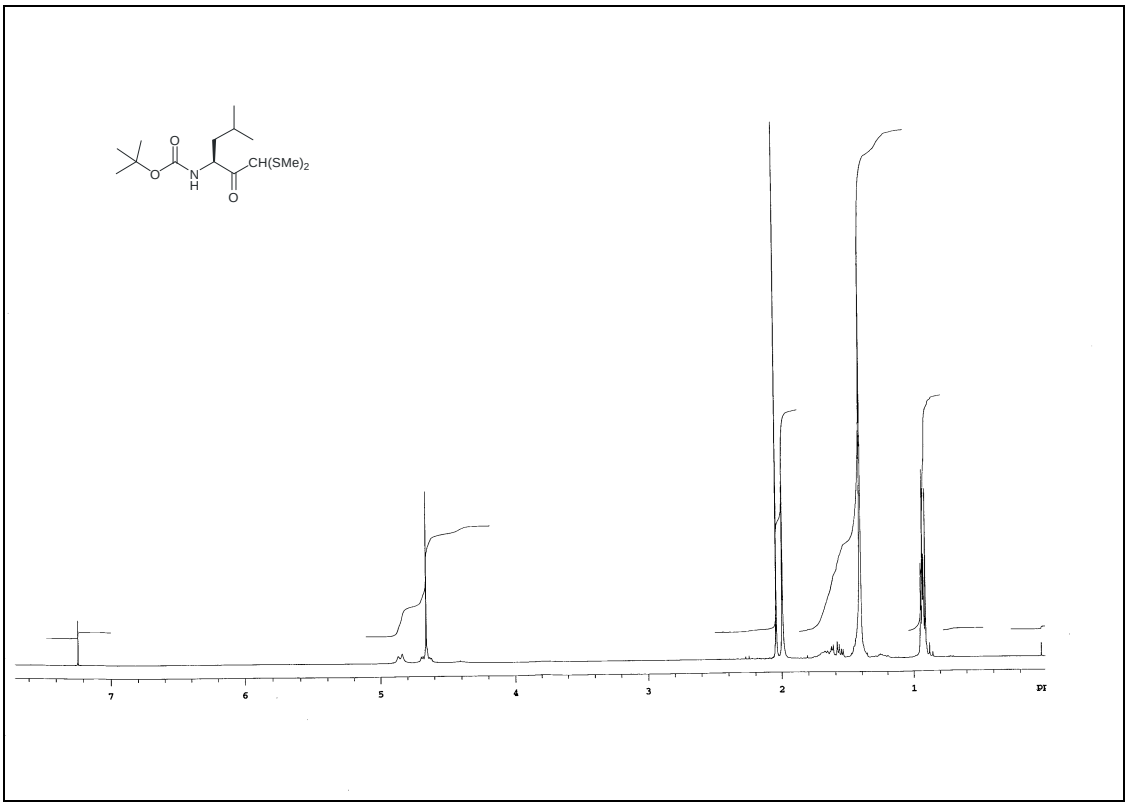


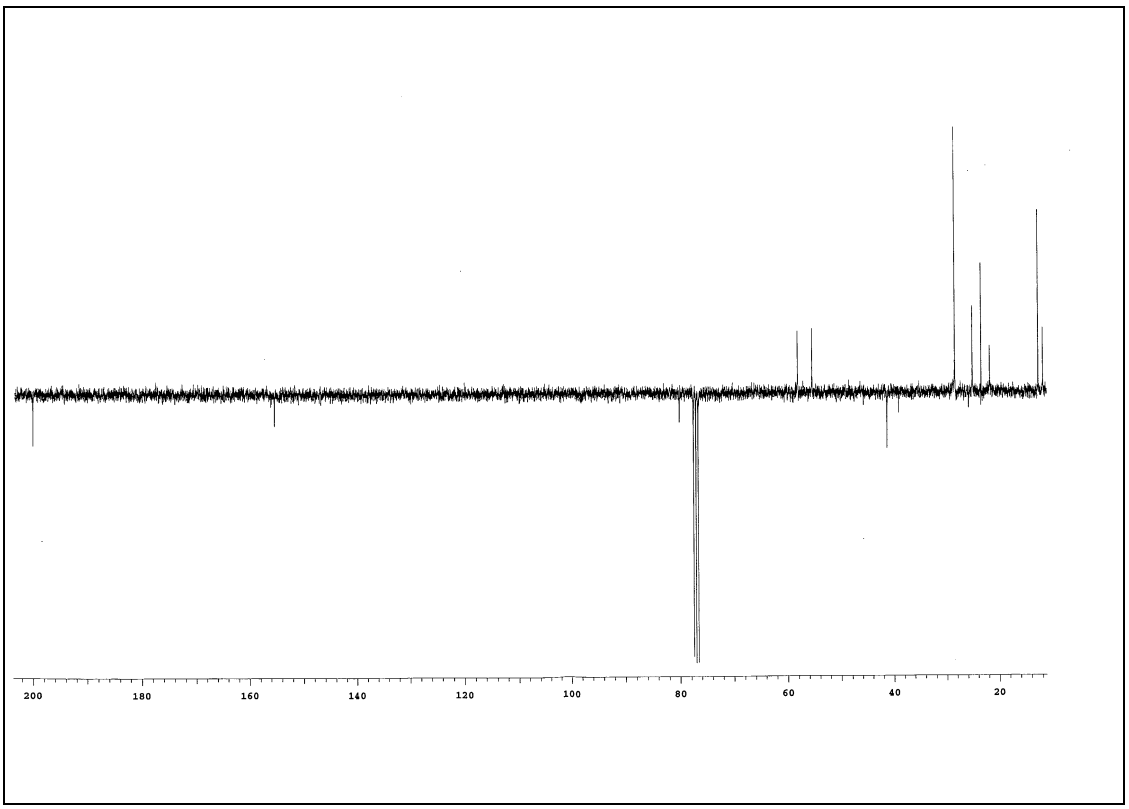
5-Methylene-1-phenyl-1H-pyrrol-2(5H)-one (**120d**):



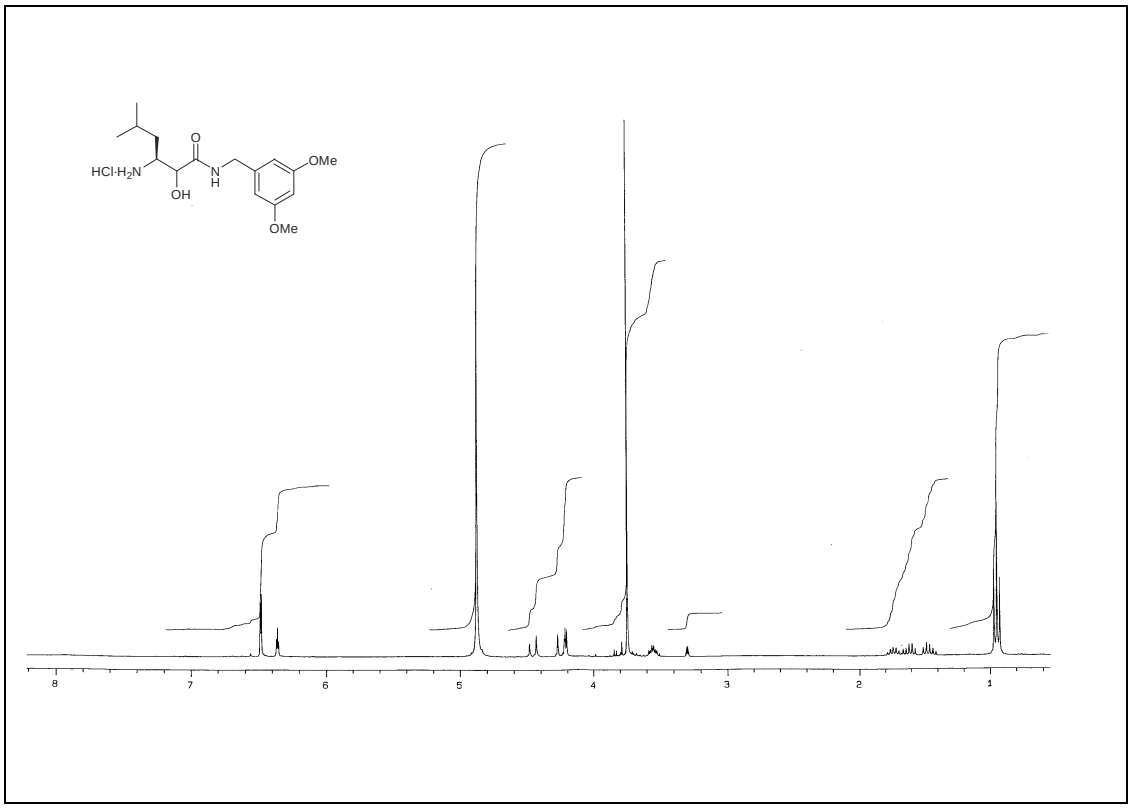


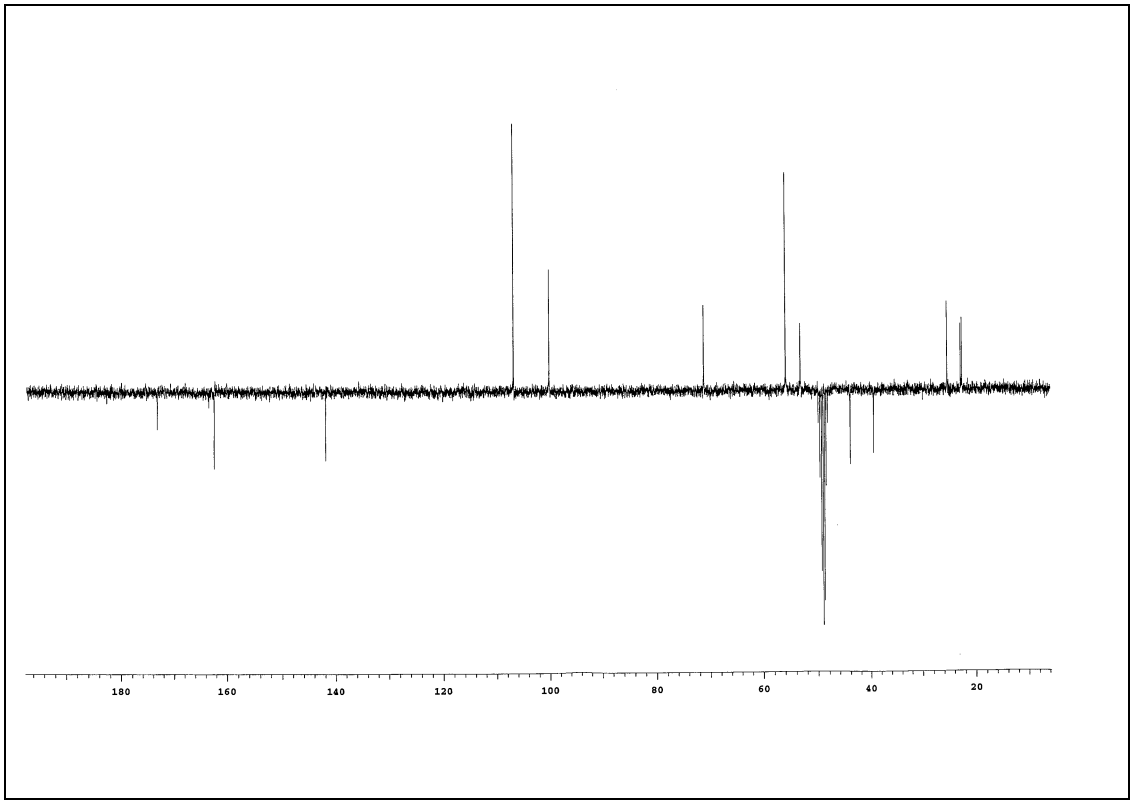
(*S*)-*tert*-Butyl 5-Methyl-1,1-bis(methylthio)-2-oxohexan-3-ylcarbamate (**59**):



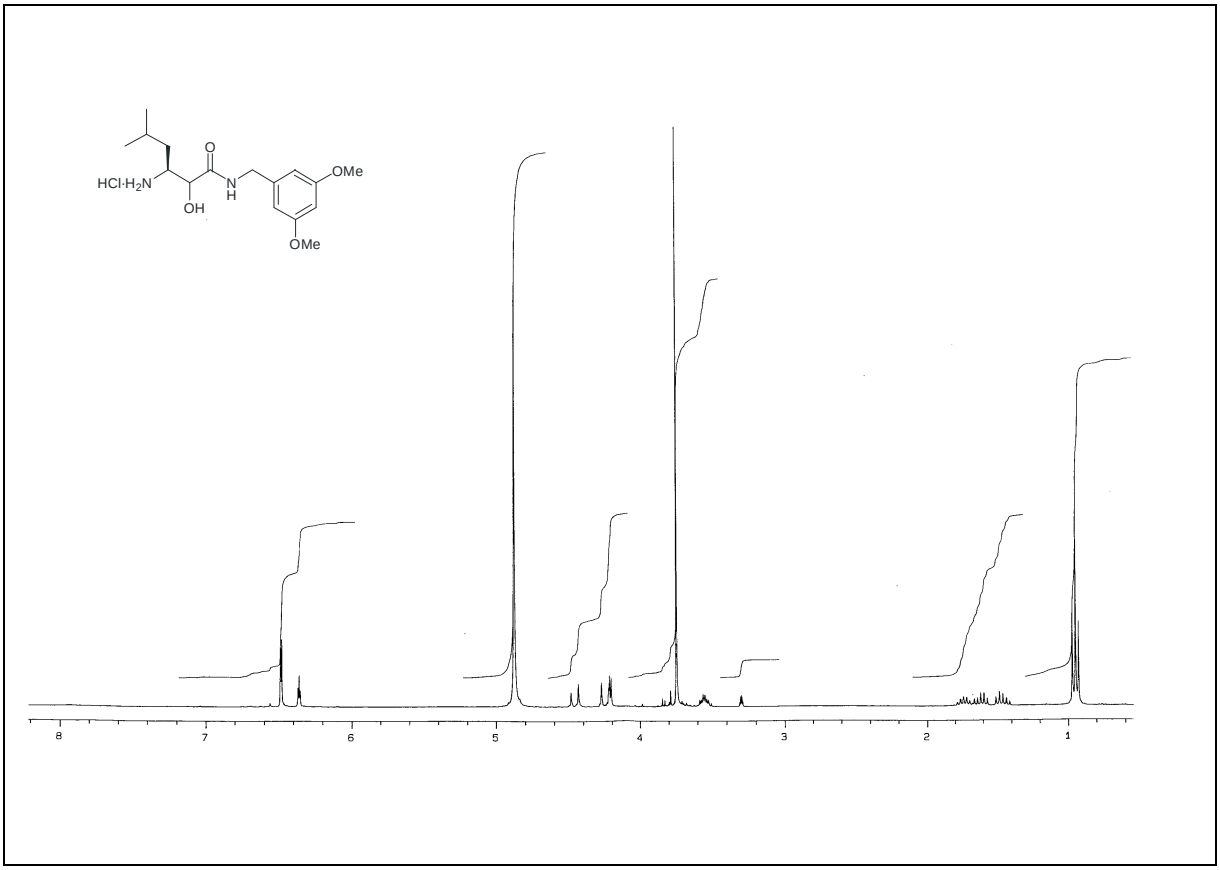


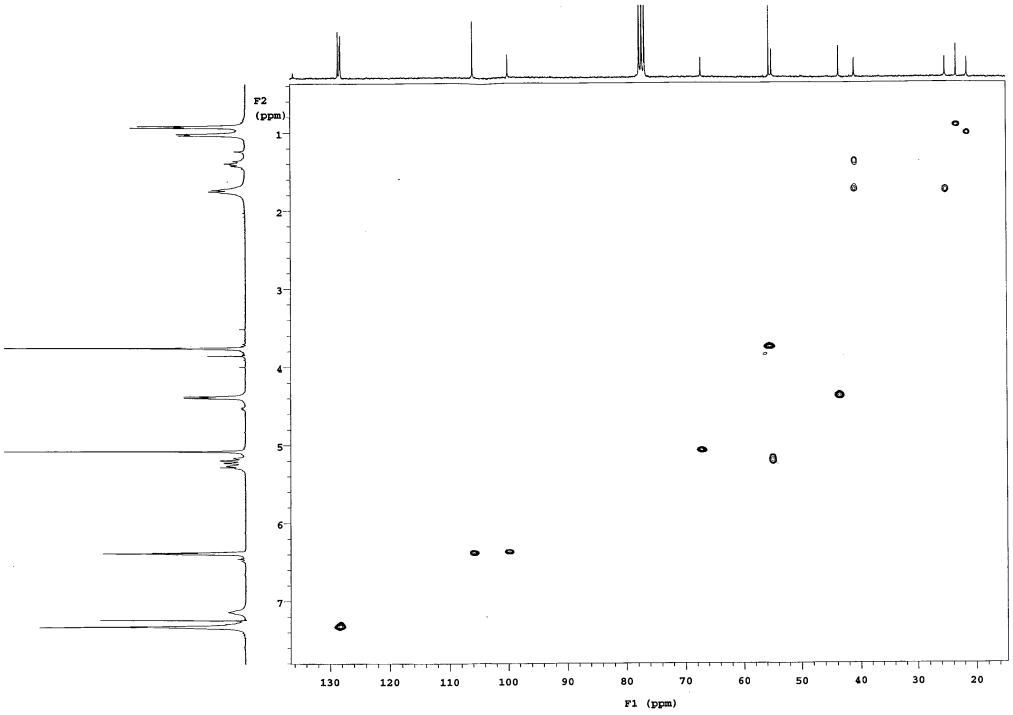
(3*S*)-*N*-(3,5-Dimethoxybenzyl)-3-amino-2-hydroxy-5-methylhexanamide Hydrochloride (**65**):



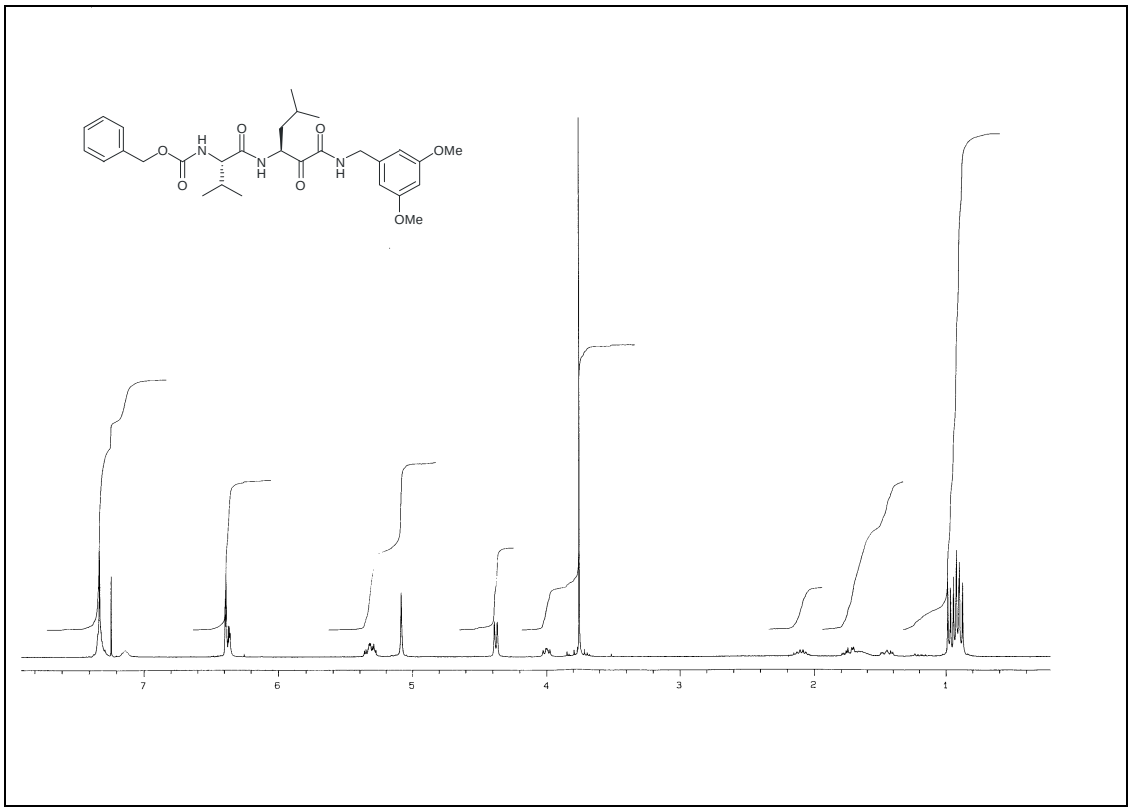


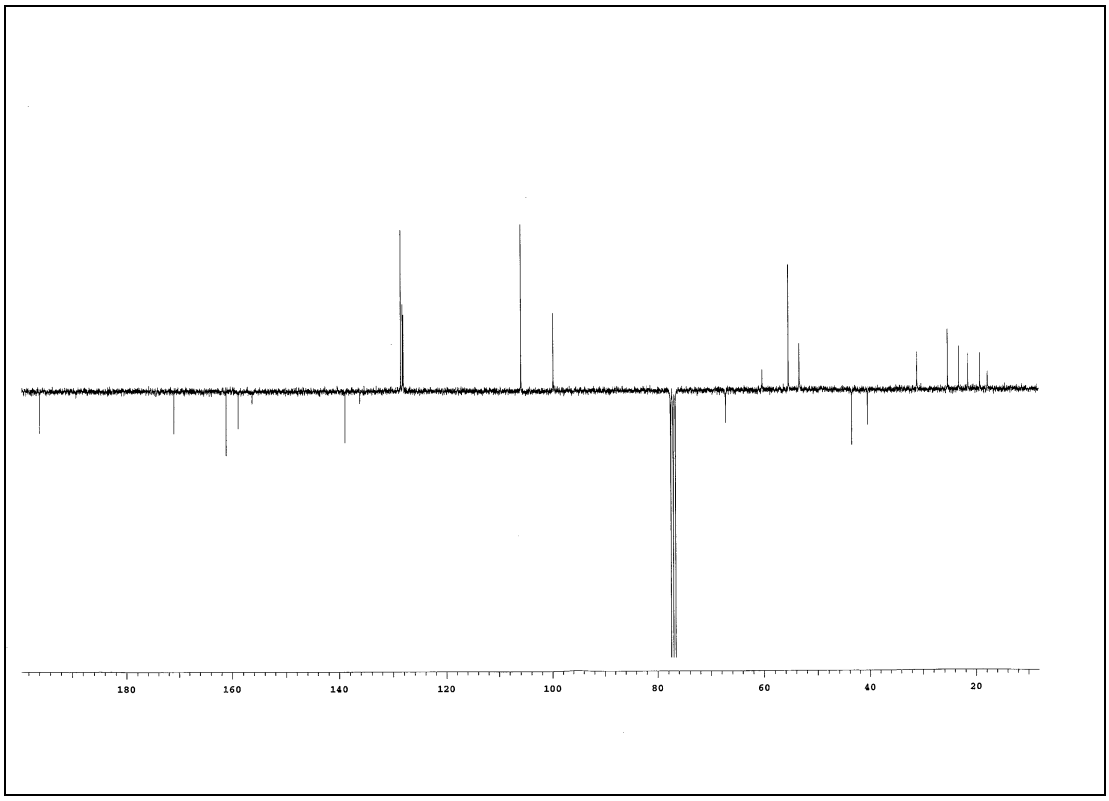
(*S*)-Benzyl 1-(3,5-Dimethoxybenzylamino)-5-methyl-1,2-dioxohexan-3-ylcarbamate (**66**):





Benzyl (*S*)-1-((*S*)-1-(3,5-Dimethoxybenzylamino)-5-methyl-1,2-dioxohexan-3-ylamino)-3-methyl-1-oxobutan-2-ylcarbamate (**67**):





G Crystal Structural Data

1. Cyclopropanecarboxylic Acid Benzyl-{[1-(4-chlorobenzyl)cyclopropylcarbamoyl]-cyclopropylmethyl}amide (5b)

Table 1.1. Crystal data and structure refinement for **5b**.

Identification code	**5b**	
Empirical formula	$C_{26}\ H_{29}\ Cl\ N_2\ O_2$	
Formula weight	436.96	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1/c$	
Unit cell dimensions	a = 11.7811(2) Å	α = 90°.
	b = 19.5913(3) Å	β = 95.03(1)°.
	c = 10.0373(2) Å	γ = 90°.
Volume	2307.8(1) $Å^3$	
Z	4	
Density (calculated)	1.258 Mg/m^3	
Absorption coefficient	0.191 mm^{-1}	
F(000)	928	
Crystal size	0.44 x 0.30 x 0.14 mm^3	
Theta range for data collection	1.74 to 29.00°.	
Index ranges	-16<=h<=16, -26<=k<=26, -13<=l<=13	
Reflections collected	21118	
Independent reflections	6123 [R(int) = 0.0458]	
Completeness to theta = 29.00°	99.9 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	6123 / 0 / 396	
Goodness-of-fit on F^2	1.053	
Final R indices [I>2sigma(I)]	R_1 = 0.0400, wR_2 = 0.1022	
R indices (all data)	R_1 = 0.0577, wR_2 = 0.1121	
Largest diff. peak and hole	0.282 and -0.253 $e.Å^{-3}$	

Table 1.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **5b**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
Cl(1)	3649(1)	473(1)	3622(1)	41(1)
O(1)	1072(1)	-1629(1)	-1038(1)	31(1)
O(2)	3312(1)	-2413(1)	-2490(1)	28(1)
N(1)	1048(1)	-2688(1)	-1921(1)	27(1)
N(2)	3852(1)	-2381(1)	-265(1)	25(1)
C(1)	611(1)	-2049(1)	-1823(1)	28(1)
C(2)	-485(1)	-1887(1)	-2615(2)	37(1)
C(3)	-756(1)	-1154(1)	-2925(2)	41(1)
C(4)	-1349(1)	-1500(1)	-1876(2)	48(1)
C(5)	716(1)	-3143(1)	-3044(1)	30(1)
C(6)	-172(1)	-3674(1)	-2788(1)	29(1)
C(7)	-223(1)	-4269(1)	-3553(2)	38(1)
C(8)	-1034(1)	-4764(1)	-3374(2)	45(1)
C(9)	-1792(1)	-4679(1)	-2429(2)	44(1)
C(10)	-1765(1)	-4088(1)	-1672(2)	45(1)
C(11)	-957(1)	-3583(1)	-1851(1)	37(1)
C(12)	4991(1)	-2144(1)	-396(1)	27(1)
C(13)	5785(1)	-2649(1)	-959(1)	35(1)
C(14)	5899(1)	-2487(1)	517(1)	35(1)
C(15)	3114(1)	-2513(1)	-1323(1)	23(1)
C(16)	5076(1)	-1393(1)	-720(1)	30(1)
C(17)	4688(1)	-939(1)	369(1)	29(1)
C(18)	3583(1)	-681(1)	322(1)	35(1)
C(19)	3251(1)	-252(1)	1319(2)	37(1)
C(20)	4027(1)	-88(1)	2379(1)	31(1)
C(21)	5114(1)	-350(1)	2478(2)	36(1)
C(22)	5438(1)	-771(1)	1465(1)	35(1)
C(23)	2022(1)	-2867(1)	-970(1)	24(1)
C(24)	2270(1)	-3623(1)	-911(1)	30(1)
C(25)	1575(1)	-4093(1)	-122(2)	40(1)
C(26)	2775(1)	-3920(1)	395(2)	35(1)

Table 1.3. Selected bond lengths [Å] and angles [°] for **5b**.

Cl(1)-C(20)	1.749(1)	C(5)-C(6)	1.513(2)	C(16)-C(17)	1.510(2)
O(1)-C(1)	1.233(1)	C(6)-C(11)	1.386(2)	C(17)-C(22)	1.389(2)
O(2)-C(15)	1.231(1)	C(6)-C(7)	1.394(2)	C(17)-C(18)	1.393(2)
N(1)-C(1)	1.360(2)	C(7)-C(8)	1.384(2)	C(18)-C(19)	1.389(2)
N(1)-C(5)	1.463(2)	C(8)-C(9)	1.369(2)	C(19)-C(20)	1.379(2)
N(1)-C(23)	1.470(2)	C(9)-C(10)	1.384(2)	C(20)-C(21)	1.375(2)
N(2)-C(15)	1.337(2)	C(10)-C(11)	1.395(2)	C(21)-C(22)	1.389(2)
N(2)-C(12)	1.438(2)	C(12)-C(13)	1.504(2)	C(23)-C(24)	1.510(2)

C(1)-C(2)	1.490(2)	C(12)-C(14)	1.504(2)	C(24)-C(25)	1.503(2)
C(2)-C(3)	1.498(2)	C(12)-C(16)	1.514(2)	C(24)-C(26)	1.507(2)
C(2)-C(4)	1.514(2)	C(13)-C(14)	1.509(2)	C(25)-C(26)	1.501(2)
C(3)-C(4)	1.478(2)	C(15)-C(23)	1.530(2)		

C(1)-N(1)-C(5)	122.66(11)	C(14)-C(12)-C(16)	120.58(11)
C(1)-N(1)-C(23)	116.81(10)	C(12)-C(13)-C(14)	59.89(9)
C(5)-N(1)-C(23)	119.71(10)	C(12)-C(14)-C(13)	59.89(9)
C(15)-N(2)-C(12)	122.45(10)	O(2)-C(15)-N(2)	124.12(11)
O(1)-C(1)-N(1)	120.85(12)	O(2)-C(15)-C(23)	121.80(11)
O(1)-C(1)-C(2)	120.75(12)	N(2)-C(15)-C(23)	113.87(10)
N(1)-C(1)-C(2)	118.25(11)	C(17)-C(16)-C(12)	112.79(10)
C(1)-C(2)-C(3)	118.30(13)	C(22)-C(17)-C(18)	117.93(13)
C(1)-C(2)-C(4)	115.71(13)	C(22)-C(17)-C(16)	120.00(12)
C(3)-C(2)-C(4)	58.79(10)	C(18)-C(17)-C(16)	122.06(12)
C(4)-C(3)-C(2)	61.15(11)	C(19)-C(18)-C(17)	121.15(13)
C(3)-C(4)-C(2)	60.06(10)	C(20)-C(19)-C(18)	119.14(13)
N(1)-C(5)-C(6)	115.45(10)	C(21)-C(20)-C(19)	121.25(13)
C(11)-C(6)-C(7)	118.81(13)	C(21)-C(20)-Cl(1)	118.50(11)
C(11)-C(6)-C(5)	122.63(12)	C(19)-C(20)-Cl(1)	120.25(11)
C(7)-C(6)-C(5)	118.53(12)	C(20)-C(21)-C(22)	118.90(13)
C(8)-C(7)-C(6)	120.76(15)	C(21)-C(22)-C(17)	121.59(13)
C(9)-C(8)-C(7)	120.27(15)	N(1)-C(23)-C(24)	113.36(10)
C(8)-C(9)-C(10)	119.82(14)	N(1)-C(23)-C(15)	111.50(9)
C(9)-C(10)-C(11)	120.36(15)	C(24)-C(23)-C(15)	106.86(10)
C(6)-C(11)-C(10)	119.96(15)	C(25)-C(24)-C(26)	59.83(9)
N(2)-C(12)-C(13)	116.01(11)	C(25)-C(24)-C(23)	120.64(12)
N(2)-C(12)-C(14)	114.79(11)	C(26)-C(24)-C(23)	118.19(11)
C(13)-C(12)-C(14)	60.22(9)	C(26)-C(25)-C(24)	60.23(9)
N(2)-C(12)-C(16)	114.44(11)	C(25)-C(26)-C(24)	59.94(9)
C(13)-C(12)-C(16)	120.26(11)		

Table 1.4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **5b**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1)	50(1)	39(1)	36(1)	2(1)	11(1)	9(1)
O(1)	39(1)	28(1)	26(1)	-2(1)	-1(1)	1(1)
O(2)	35(1)	33(1)	18(1)	1(1)	6(1)	-3(1)
N(1)	30(1)	27(1)	24(1)	-1(1)	1(1)	-3(1)
N(2)	32(1)	27(1)	17(1)	1(1)	5(1)	-5(1)
C(1)	33(1)	29(1)	24(1)	2(1)	3(1)	-2(1)
C(2)	37(1)	37(1)	35(1)	-2(1)	-5(1)	1(1)
C(3)	40(1)	41(1)	42(1)	8(1)	-1(1)	5(1)
C(4)	32(1)	64(1)	46(1)	8(1)	5(1)	6(1)
C(5)	34(1)	32(1)	24(1)	-3(1)	5(1)	-7(1)
C(6)	29(1)	30(1)	26(1)	3(1)	-3(1)	-4(1)

C(7)	37(1)	34(1)	42(1)	-4(1)	-2(1)	-3(1)
C(8)	43(1)	33(1)	56(1)	0(1)	-10(1)	-5(1)
C(9)	40(1)	43(1)	47(1)	16(1)	-13(1)	-15(1)
C(10)	34(1)	67(1)	34(1)	9(1)	1(1)	-12(1)
C(11)	36(1)	44(1)	31(1)	-1(1)	4(1)	-8(1)
C(12)	31(1)	29(1)	22(1)	0(1)	3(1)	-4(1)
C(13)	36(1)	38(1)	31(1)	-3(1)	6(1)	0(1)
C(14)	36(1)	38(1)	30(1)	2(1)	-1(1)	0(1)
C(15)	31(1)	19(1)	21(1)	0(1)	5(1)	0(1)
C(16)	35(1)	32(1)	25(1)	3(1)	3(1)	-8(1)
C(17)	35(1)	24(1)	27(1)	5(1)	1(1)	-6(1)
C(18)	35(1)	37(1)	32(1)	5(1)	-6(1)	-3(1)
C(19)	32(1)	39(1)	40(1)	6(1)	1(1)	3(1)
C(20)	37(1)	26(1)	31(1)	5(1)	8(1)	1(1)
C(21)	36(1)	36(1)	34(1)	-4(1)	-4(1)	0(1)
C(22)	30(1)	34(1)	39(1)	-6(1)	-2(1)	0(1)
C(23)	30(1)	23(1)	21(1)	0(1)	5(1)	-1(1)
C(24)	38(1)	23(1)	30(1)	-2(1)	5(1)	-1(1)
C(25)	45(1)	29(1)	45(1)	10(1)	2(1)	-9(1)
C(26)	43(1)	25(1)	38(1)	4(1)	0(1)	-1(1)

Table 1.5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **5b**.

Atom	x	y	z	U(eq)
H(2N)	3664(13)	-2429(8)	495(17)	33(4)
H(2)	-811(14)	-2206(10)	-3235(18)	52(5)
H(31)	-1194(15)	-1056(9)	-3753(18)	49(5)
H(32)	-172(15)	-866(9)	-2621(17)	48(5)
H(41)	-2082(17)	-1626(10)	-2122(19)	57(5)
H(42)	-1118(16)	-1404(10)	-958(19)	55(5)
H(51)	435(12)	-2863(8)	-3810(16)	36(4)
H(52)	1408(12)	-3369(8)	-3320(14)	31(4)
H(7)	333(14)	-4345(9)	-4164(17)	44(4)
H(8)	-1070(15)	-5201(10)	-3915(19)	58(5)
H(9)	-2330(15)	-5037(10)	-2267(18)	58(5)
H(10)	-2247(15)	-3982(9)	-1053(18)	57(5)
H(11)	-929(13)	-3184(8)	-1325(15)	34(4)
H(131)	6362(14)	-2468(8)	-1514(17)	42(4)
H(132)	5480(13)	-3077(9)	-1233(16)	40(4)
H(141)	5652(13)	-2821(9)	1104(17)	41(4)
H(142)	6569(15)	-2206(9)	829(17)	48(5)
H(161)	5888(13)	-1293(8)	-867(15)	39(4)
H(162)	4612(13)	-1307(8)	-1538(16)	38(4)
H(18)	3072(14)	-801(8)	-395(17)	40(4)
H(19)	2467(14)	-65(9)	1247(16)	48(5)
H(21)	5615(14)	-242(9)	3209(18)	47(5)
H(22)	6213(15)	-929(9)	1512(17)	49(5)
H(23)	1847(11)	-2713(7)	-120(14)	25(3)
H(24)	2570(13)	-3819(8)	-1713(17)	41(4)
H(251)	973(15)	-3867(9)	341(17)	48(5)

H(252)	1477(16)	-4542(10)	-490(20)	62(6)
H(261)	2874(13)	-3611(8)	1158(16)	39(4)
H(262)	3388(15)	-4255(9)	334(17)	49(5)

Table 1.6. Torsion angles [°] for **5b**.

C(5)-N(1)-C(1)-O(1)	-164.30(11)	C(12)-N(2)-C(15)-O(2)	-4.00(18)
C(23)-N(1)-C(1)-O(1)	5.31(17)	C(12)-N(2)-C(15)-C(23)	170.68(10)
C(5)-N(1)-C(1)-C(2)	20.08(17)	N(2)-C(12)-C(16)-C(17)	62.97(14)
C(23)-N(1)-C(1)-C(2)	-170.30(11)	C(13)-C(12)-C(16)-C(17)	-151.66(12)
O(1)-C(1)-C(2)-C(3)	26.63(19)	C(14)-C(12)-C(16)-C(17)	-80.52(15)
N(1)-C(1)-C(2)-C(3)	-157.75(12)	C(12)-C(16)-C(17)-C(22)	83.95(15)
O(1)-C(1)-C(2)-C(4)	-40.17(19)	C(12)-C(16)-C(17)-C(18)	-95.55(15)
N(1)-C(1)-C(2)-C(4)	135.45(13)	C(1)-N(1)-C(23)-C(24)	165.74(10)
C(1)-C(2)-C(3)-C(4)	-104.46(15)	C(5)-N(1)-C(23)-C(24)	-24.32(15)
C(1)-C(2)-C(4)-C(3)	108.88(15)	C(1)-N(1)-C(23)-C(15)	-73.62(13)
C(1)-N(1)-C(5)-C(6)	-98.78(14)	C(5)-N(1)-C(23)-C(15)	96.32(12)
C(23)-N(1)-C(5)-C(6)	91.89(14)	O(2)-C(15)-C(23)-N(1)	-35.07(15)
N(1)-C(5)-C(6)-C(11)	25.97(19)	N(2)-C(15)-C(23)-N(1)	150.12(10)
N(1)-C(5)-C(6)-C(7)	-155.90(12)	O(2)-C(15)-C(23)-C(24)	89.30(13)
C(15)-N(2)-C(12)-C(13)	-68.45(15)	N(2)-C(15)-C(23)-C(24)	-85.51(12)
C(15)-N(2)-C(12)-C(14)	-135.90(12)	N(1)-C(23)-C(24)-C(25)	-79.47(15)
C(15)-N(2)-C(12)-C(16)	78.45(14)	C(15)-C(23)-C(24)-C(25)	157.30(12)
N(2)-C(12)-C(13)-C(14)	-104.97(12)	N(1)-C(23)-C(24)-C(26)	-149.27(11)
C(16)-C(12)-C(13)-C(14)	110.17(13)	C(15)-C(23)-C(24)-C(26)	87.50(13)
N(2)-C(12)-C(14)-C(13)	107.00(12)	C(23)-C(24)-C(25)-C(26)	-106.90(14)
C(16)-C(12)-C(14)-C(13)	-109.64(13)	C(23)-C(24)-C(26)-C(25)	110.93(14)

Table 1.7. Hydrogen bonds for **5b** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(2)-H(2N)...O(2)#1	0.817(17)	2.123(17)	2.9380(13)	175.2(15)

Symmetry transformations used to generate equivalent atoms: #1 x,-y-1/2,z+1/2

2. (1*R*,5*S*)-*tert*-Butyl 6-(2-(*N*-Benzylcyclopropanecarboxamido)-2-cyclopropyl-acetamido)-3-azabicyclo[3.1.0]hexane-3-carboxylate (5d)

Table 2.1. Crystal data and structure refinement for **5d**.

Identification code	**5d**	
Empirical formula	$C_{26}H_{35}N_3O_4$	
Formula weight	453.57	
Temperature	200(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 8.0801(9) Å	α = 94.697(3)°.
	b = 9.947(1) Å	β = 91.886(4)°.
	c = 15.668(2) Å	γ = 92.197(4)°.
Volume	1253.3(3) $Å^3$	
Z	2	
Density (calculated)	1.202 Mg/m^3	
Absorption coefficient	0.081 mm^{-1}	
F(000)	488	
Crystal size	0.22 x 0.11 x 0.03 mm^3	
Theta range for data collection	2.52 to 28.00°.	
Index ranges	-10<=h<=10, -13<=k<=13, -20<=l<=20	
Reflections collected	11581	
Independent reflections	5833 [R(int) = 0.0685]	
Completeness to theta = 28.00°	96.3 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5833 / 0 / 427	
Goodness-of-fit on F^2	0.964	
Final R indices [I>2sigma(I)]	R_1 = 0.0398, wR_2 = 0.0545	
R indices (all data)	R_1 = 0.1446, wR_2 = 0.0814	
Largest diff. peak and hole	0.144 and -0.159 e.$Å^{-3}$	

Table 2.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **5d**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
O(1)	9626(2)	6955(2)	10189(1)	52(1)
O(2)	12218(2)	7898(2)	10033(1)	41(1)
O(3)	7858(2)	6557(2)	6021(1)	45(1)
O(4)	7936(2)	10005(2)	4387(1)	36(1)

N(1)	7532(2)	7741(2)	4377(1)	27(1)
N(2)	9908(3)	8136(2)	6344(1)	38(1)
N(3)	10233(3)	8143(2)	9058(1)	41(1)
C(1)	10402(3)	9244(3)	7806(2)	38(1)
C(2)	11282(4)	9133(3)	8660(2)	43(1)
C(3)	10605(3)	7611(3)	9803(2)	39(1)
C(4)	8554(4)	7967(4)	8668(2)	48(1)
C(5)	8735(3)	8515(3)	7805(2)	40(1)
C(6)	10055(3)	7957(3)	7247(2)	35(1)
C(7)	12978(3)	7345(3)	10786(2)	43(1)
C(8)	12170(5)	7912(5)	11590(2)	60(1)
C(9)	14753(4)	7887(5)	10767(2)	64(1)
C(10)	12877(4)	5814(3)	10694(2)	75(1)
C(11)	8864(3)	7390(3)	5797(2)	30(1)
C(12)	9120(3)	7638(3)	4854(2)	28(1)
C(13)	7094(3)	8962(3)	4153(2)	30(1)
C(14)	5546(3)	9045(3)	3622(2)	37(1)
C(15)	5459(4)	10184(3)	3049(2)	45(1)
C(16)	4478(4)	10230(3)	3831(2)	44(1)
C(17)	6458(3)	6515(3)	4203(2)	31(1)
C(18)	6559(3)	5760(2)	3329(2)	30(1)
C(19)	7504(3)	6186(3)	2678(2)	39(1)
C(20)	7546(4)	5423(3)	1896(2)	47(1)
C(21)	6617(4)	4236(3)	1768(2)	53(1)
C(22)	5646(4)	3809(3)	2404(2)	52(1)
C(23)	5601(3)	4564(3)	3181(2)	42(1)
C(24)	10174(3)	6567(3)	4445(2)	31(1)
C(25)	12025(3)	6737(3)	4620(2)	43(1)
C(26)	11292(4)	6920(3)	3743(2)	47(1)

Table 2.3. Selected bond lengths [Å] and angles [°] for **5d**.

O(1)-C(3)	1.213(3)	C(1)-C(6)	1.502(4)	C(14)-C(16)	1.508(4)
O(2)-C(3)	1.354(3)	C(1)-C(5)	1.505(4)	C(15)-C(16)	1.480(4)
O(2)-C(7)	1.469(3)	C(1)-C(2)	1.509(3)	C(17)-C(18)	1.514(3)
O(3)-C(11)	1.219(3)	C(4)-C(5)	1.509(4)	C(18)-C(19)	1.378(3)
O(4)-C(13)	1.241(3)	C(5)-C(6)	1.495(4)	C(18)-C(23)	1.393(3)
N(1)-C(13)	1.349(3)	C(7)-C(9)	1.514(4)	C(19)-C(20)	1.390(4)
N(1)-C(17)	1.470(3)	C(7)-C(8)	1.516(4)	C(20)-C(21)	1.372(4)
N(1)-C(12)	1.475(3)	C(7)-C(10)	1.517(4)	C(21)-C(22)	1.373(4)
N(2)-C(11)	1.341(3)	C(11)-C(12)	1.537(3)	C(22)-C(23)	1.379(4)
N(2)-C(6)	1.442(3)	C(12)-C(24)	1.505(3)	C(24)-C(26)	1.502(3)
N(3)-C(3)	1.350(3)	C(13)-C(14)	1.488(3)	C(24)-C(25)	1.512(4)
N(3)-C(2)	1.465(3)	C(14)-C(15)	1.504(4)	C(25)-C(26)	1.506(4)
N(3)-C(4)	1.468(3)				

C(3)-O(2)-C(7)	120.9(2)	O(3)-C(11)-N(2)	123.4(2)
C(13)-N(1)-C(17)	122.9(2)	O(3)-C(11)-C(12)	123.3(2)
C(13)-N(1)-C(12)	118.69(19)	N(2)-C(11)-C(12)	113.3(2)

C(17)-N(1)-C(12)	118.4(2)	N(1)-C(12)-C(24)	112.4(2)
C(11)-N(2)-C(6)	123.5(2)	N(1)-C(12)-C(11)	111.90(19)
C(3)-N(3)-C(2)	125.0(2)	C(24)-C(12)-C(11)	109.9(2)
C(3)-N(3)-C(4)	120.4(2)	O(4)-C(13)-N(1)	121.7(2)
C(2)-N(3)-C(4)	113.5(2)	O(4)-C(13)-C(14)	119.9(2)
C(6)-C(1)-C(5)	59.65(18)	N(1)-C(13)-C(14)	118.4(2)
C(6)-C(1)-C(2)	117.1(2)	C(13)-C(14)-C(15)	117.3(2)
C(5)-C(1)-C(2)	108.7(2)	C(13)-C(14)-C(16)	117.4(2)
N(3)-C(2)-C(1)	103.0(2)	C(15)-C(14)-C(16)	58.83(19)
O(1)-C(3)-N(3)	124.1(2)	C(16)-C(15)-C(14)	60.71(19)
O(1)-C(3)-O(2)	126.1(2)	C(15)-C(16)-C(14)	60.46(19)
N(3)-C(3)-O(2)	109.8(2)	N(1)-C(17)-C(18)	116.8(2)
N(3)-C(4)-C(5)	103.3(2)	C(19)-C(18)-C(23)	118.8(3)
C(6)-C(5)-C(1)	60.09(17)	C(19)-C(18)-C(17)	124.5(2)
C(6)-C(5)-C(4)	117.6(2)	C(23)-C(18)-C(17)	116.7(2)
C(1)-C(5)-C(4)	107.9(2)	C(18)-C(19)-C(20)	121.0(3)
N(2)-C(6)-C(5)	117.5(2)	C(21)-C(20)-C(19)	119.4(3)
N(2)-C(6)-C(1)	114.2(2)	C(20)-C(21)-C(22)	120.4(3)
C(5)-C(6)-C(1)	60.26(18)	C(21)-C(22)-C(23)	120.3(3)
O(2)-C(7)-C(9)	101.9(2)	C(22)-C(23)-C(18)	120.1(3)
O(2)-C(7)-C(8)	109.7(2)	C(26)-C(24)-C(12)	119.0(2)
C(9)-C(7)-C(8)	110.4(3)	C(26)-C(24)-C(25)	59.94(18)
O(2)-C(7)-C(10)	111.0(2)	C(12)-C(24)-C(25)	116.9(2)
C(9)-C(7)-C(10)	111.4(3)	C(26)-C(25)-C(24)	59.70(18)
C(8)-C(7)-C(10)	112.0(3)	C(24)-C(26)-C(25)	60.36(18)

Table 2.4. Anisotropic displacement parameters ($Å^2$x 10^3) for **5d**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	49(1)	70(2)	39(1)	22(1)	-2(1)	-9(1)
O(2)	41(1)	53(1)	30(1)	8(1)	-5(1)	5(1)
O(3)	46(1)	54(1)	35(1)	8(1)	4(1)	-17(1)
O(4)	35(1)	31(1)	43(1)	8(1)	-8(1)	-3(1)
N(1)	23(1)	30(1)	28(1)	3(1)	0(1)	-1(1)
N(2)	35(1)	50(2)	31(1)	12(1)	-2(1)	-10(1)
N(3)	34(1)	60(2)	29(1)	17(1)	-4(1)	-3(1)
C(1)	41(2)	41(2)	31(2)	13(1)	-4(1)	1(1)
C(2)	44(2)	52(2)	34(2)	10(2)	-3(1)	0(2)
C(3)	42(2)	45(2)	29(2)	-1(1)	-2(1)	10(1)
C(4)	34(2)	72(3)	40(2)	18(2)	-3(1)	-1(2)
C(5)	30(2)	57(2)	34(2)	12(1)	-6(1)	6(1)
C(6)	33(2)	43(2)	29(1)	9(1)	-5(1)	2(1)
C(7)	51(2)	47(2)	31(2)	9(1)	-9(1)	11(2)
C(8)	66(3)	82(3)	32(2)	1(2)	-3(2)	4(2)
C(9)	50(2)	95(3)	50(2)	18(2)	-12(2)	5(2)
C(10)	97(3)	54(2)	74(2)	10(2)	-21(2)	22(2)
C(11)	28(1)	30(2)	32(1)	5(1)	2(1)	6(1)
C(12)	24(1)	30(2)	30(1)	9(1)	-3(1)	0(1)
C(13)	28(1)	37(2)	26(1)	7(1)	3(1)	2(1)
C(14)	31(2)	36(2)	42(2)	3(1)	-8(1)	3(1)

C(15)	37(2)	60(2)	39(2)	15(2)	-5(1)	7(2)
C(16)	38(2)	54(2)	43(2)	10(2)	-2(2)	14(2)
C(17)	28(2)	32(2)	34(2)	7(1)	3(1)	-5(1)
C(18)	27(1)	29(2)	33(1)	3(1)	-3(1)	1(1)
C(19)	35(2)	41(2)	38(2)	1(1)	-1(1)	-4(1)
C(20)	42(2)	61(2)	39(2)	2(2)	3(1)	4(2)
C(21)	58(2)	56(2)	42(2)	-11(2)	-11(2)	14(2)
C(22)	57(2)	38(2)	59(2)	-6(2)	-8(2)	-3(2)
C(23)	36(2)	44(2)	45(2)	3(2)	0(1)	-7(1)
C(24)	29(1)	32(2)	35(2)	9(1)	4(1)	5(1)
C(25)	29(2)	39(2)	61(2)	8(2)	8(1)	6(1)
C(26)	47(2)	47(2)	48(2)	7(2)	22(2)	4(2)

Table 2.5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (Å^{2}x 10^3) for **5d**.

Atom	x	y	z	U(eq)
H(101)	11715	5495	10694	90
H(102)	13491	5468	11174	90
H(103)	13361	5489	10153	90
H(1)	10550(30)	10040(20)	7522(14)	35(7)
H(2N)	10660(30)	8660(20)	6149(15)	41(8)
H(21)	12500(30)	8760(30)	8599(15)	58(9)
H(22)	11310(30)	10020(30)	9006(15)	44(8)
H(41)	7730(30)	8500(30)	9022(15)	50(9)
H(42)	8240(30)	6980(30)	8639(15)	51(9)
H(5)	7760(30)	8860(20)	7544(14)	44(8)
H(6)	10600(30)	7070(20)	7390(13)	38(7)
H(81)	11010(30)	7510(30)	11597(16)	57(9)
H(82)	12770(30)	7610(30)	12089(18)	68(10)
H(83)	12230(40)	8880(30)	11630(20)	102(15)
H(91)	14830(40)	8910(30)	10774(18)	73(12)
H(92)	15370(30)	7580(30)	11269(18)	73(10)
H(93)	15310(40)	7590(30)	10240(20)	98(14)
H(12)	9670(20)	8540(20)	4861(12)	18(6)
H(14)	4920(30)	8240(30)	3425(15)	50(8)
H(151)	4890(30)	9950(20)	2467(16)	53(8)
H(152)	6440(30)	10730(30)	3064(15)	51(9)
H(162)	3240(30)	10010(30)	3731(17)	72(10)
H(162)	4820(30)	10840(30)	4279(17)	62(10)
H(171)	6780(20)	5920(20)	4658(13)	24(6)
H(172)	5320(30)	6770(20)	4347(13)	28(6)
H(191)	8150(30)	6980(20)	2779(14)	36(7)
H(201)	8220(30)	5750(30)	1436(16)	60(9)
H(211)	6660(30)	3720(30)	1257(17)	64(10)
H(221)	4960(30)	2960(30)	2315(15)	51(8)
H(231)	4860(30)	4280(20)	3655(15)	48(8)
H(24)	9690(30)	5640(20)	4401(14)	40(7)
H(251)	12590(30)	5930(30)	4678(15)	48(8)
H(252)	12420(30)	7620(20)	4973(14)	45(8)
H(261)	11410(30)	6230(20)	3284(15)	44(8)
H(262)	11240(30)	7890(30)	3565(16)	60(9)

Table 2.6. Torsion angles [°] for **5d**.

C(3)-N(3)-C(2)-C(1)	173.1(3)	C(17)-N(1)-C(12)-C(11)	-69.6(3)
C(4)-N(3)-C(2)-C(1)	-18.7(3)	O(3)-C(11)-C(12)-N(1)	46.1(3)
C(6)-C(1)-C(2)-N(3)	-54.7(3)	N(2)-C(11)-C(12)-N(1)	-136.8(2)
C(5)-C(1)-C(2)-N(3)	10.1(3)	O(3)-C(11)-C(12)-C(24)	-79.5(3)
C(2)-N(3)-C(3)-O(1)	168.3(3)	N(2)-C(11)-C(12)-C(24)	97.6(3)
C(4)-N(3)-C(3)-O(1)	0.9(5)	C(17)-N(1)-C(13)-O(4)	172.0(2)
C(2)-N(3)-C(3)-O(2)	-12.9(4)	C(12)-N(1)-C(13)-O(4)	-4.9(3)
C(4)-N(3)-C(3)-O(2)	179.8(3)	C(17)-N(1)-C(13)-C(14)	-7.0(3)
C(7)-O(2)-C(3)-O(1)	3.7(4)	C(12)-N(1)-C(13)-C(14)	176.1(2)
C(7)-O(2)-C(3)-N(3)	-175.2(2)	O(4)-C(13)-C(14)-C(15)	28.7(4)
C(3)-N(3)-C(4)-C(5)	-171.9(3)	N(1)-C(13)-C(14)-C(15)	-152.2(2)
C(2)-N(3)-C(4)-C(5)	19.4(4)	O(4)-C(13)-C(14)-C(16)	-38.4(4)
C(2)-C(1)-C(5)-C(6)	-111.0(3)	N(1)-C(13)-C(14)-C(16)	140.6(2)
C(6)-C(1)-C(5)-C(4)	112.1(3)	C(13)-C(14)-C(15)-C(16)	-107.0(3)
C(2)-C(1)-C(5)-C(4)	1.0(4)	C(13)-C(14)-C(16)-C(15)	106.9(3)
N(3)-C(4)-C(5)-C(6)	53.4(3)	C(13)-N(1)-C(17)-C(18)	85.3(3)
N(3)-C(4)-C(5)-C(1)	-11.7(4)	C(12)-N(1)-C(17)-C(18)	-97.8(3)
C(11)-N(2)-C(6)-C(5)	-77.4(3)	N(1)-C(17)-C(18)-C(19)	-4.1(4)
C(11)-N(2)-C(6)-C(1)	-145.1(2)	N(1)-C(17)-C(18)-C(23)	177.0(2)
C(1)-C(5)-C(6)-N(2)	-103.6(3)	C(23)-C(18)-C(19)-C(20)	-1.9(4)
C(4)-C(5)-C(6)-N(2)	160.7(3)	C(17)-C(18)-C(19)-C(20)	179.1(3)
C(4)-C(5)-C(6)-C(1)	-95.7(3)	C(18)-C(19)-C(20)-C(21)	0.7(4)
C(5)-C(1)-C(6)-N(2)	109.1(2)	C(19)-C(20)-C(21)-C(22)	0.5(5)
C(2)-C(1)-C(6)-N(2)	-154.2(2)	C(20)-C(21)-C(22)-C(23)	-0.4(5)
C(2)-C(1)-C(6)-C(5)	96.8(3)	C(21)-C(22)-C(23)-C(18)	-0.8(5)
C(3)-O(2)-C(7)-C(9)	178.0(3)	C(19)-C(18)-C(23)-C(22)	1.9(4)
C(3)-O(2)-C(7)-C(8)	-64.9(3)	C(17)-C(18)-C(23)-C(22)	-179.1(3)
C(3)-O(2)-C(7)-C(10)	59.3(3)	N(1)-C(12)-C(24)-C(26)	85.9(3)
C(6)-N(2)-C(11)-O(3)	5.4(4)	C(11)-C(12)-C(24)-C(26)	-148.8(2)
C(6)-N(2)-C(11)-C(12)	-171.7(2)	N(1)-C(12)-C(24)-C(25)	154.7(2)
C(13)-N(1)-C(12)-C(24)	-128.3(2)	C(11)-C(12)-C(24)-C(25)	-79.9(3)
C(17)-N(1)-C(12)-C(24)	54.7(3)	C(12)-C(24)-C(25)-C(26)	-109.5(3)
C(13)-N(1)-C(12)-C(11)	107.5(2)	C(12)-C(24)-C(26)-C(25)	106.1(3)

Table 2.7. Hydrogen bonds for **5d** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(2)-H(2N)...O(4)#1	0.87(2)	1.97(2)	2.828(3)	171(2)

Symmetry transformations used to generate equivalent atoms: #1 -x+2,-y+2,-z+1

3. Ethyl 1-[2-(Benzylcyclopropanecarbonylamino)-2-cyclopropylacetylamino]-cyclopropanecarboxylate (5h)

Table 3.1. Crystal data and structure refinement for **5h**.

Identification code	**5h**	
Empirical formula	$C_{22}H_{28}N_2O_4$	
Formula weight	384.46	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 9.7358(5) Å	α = 70.078(2)°.
	b = 9.8306(5) Å	β = 71.432(2)°.
	c = 12.2647(6) Å	γ = 82.394(2)°.
Volume	1045.77(9) $Å^3$	
Z	2	
Density (calculated)	1.221 Mg/m^3	
Absorption coefficient	0.084 mm^{-1}	
F(000)	412	
Crystal size	0.36 x 0.24 x 0.12 mm^3	
Theta range for data collection	2.81 to 29.00°.	
Index ranges	-13<=h<=13, -13<=k<=13, -16<=l<=15	
Reflections collected	8373	
Independent reflections	5153 [R(int) = 0.0322]	
Completeness to theta = 29.00°	92.5 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5153 / 0 / 365	
Goodness-of-fit on F^2	0.945	
Final R indices [I>2sigma(I)]	R_1 = 0.0407, wR_2 = 0.0991	
R indices (all data)	R_1 = 0.0535, wR_2 = 0.1041	
Largest diff. peak and hole	0.317 and -0.187 $e.Å^{-3}$	

Table 3.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **5h**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
O(1)	4645(1)	2290(1)	4937(1)	26(1)
O(2)	3911(1)	3665(1)	6174(1)	32(1)
O(3)	3185(1)	-1335(1)	10968(1)	24(1)
O(4)	2080(1)	1202(1)	8485(1)	27(1)
N(1)	4485(1)	1402(1)	8094(1)	22(1)
N(2)	1670(1)	619(1)	10938(1)	18(1)
C(1)	4401(1)	2541(1)	5994(1)	23(1)
C(2)	4803(1)	1250(1)	6919(1)	22(1)
C(3)	4644(2)	-250(1)	6886(1)	29(1)
C(4)	6119(1)	318(2)	6541(1)	31(1)
C(5)	4134(2)	3409(1)	4008(1)	30(1)
C(6)	2552(2)	3242(2)	4238(2)	38(1)
C(7)	1949(1)	-825(1)	11336(1)	19(1)
C(8)	786(1)	-1790(1)	12253(1)	24(1)
C(9)	1275(2)	-3125(1)	13128(1)	33(1)
C(10)	789(2)	-3276(1)	12145(2)	36(1)
C(11)	188(1)	1242(1)	11031(1)	20(1)
C(12)	-407(1)	1982(1)	11991(1)	20(1)
C(13)	-110(1)	1477(1)	13098(1)	25(1)
C(14)	-733(1)	2144(1)	13980(1)	29(1)
C(15)	-1664(1)	3337(1)	13765(1)	28(1)
C(16)	-1968(1)	3860(1)	12665(1)	28(1)
C(17)	-1343(1)	3187(1)	11785(1)	24(1)
C(18)	3108(1)	1351(1)	8801(1)	19(1)
C(19)	2897(1)	1504(1)	10048(1)	19(1)
C(20)	2707(1)	3072(1)	9993(1)	23(1)
C(21)	3058(2)	3495(1)	10940(1)	33(1)
C(22)	4046(1)	3912(1)	9663(1)	29(1)

Table 3.3. Selected bond lengths [Å] and angles [°] for **5h**.

O(1)-C(1)	1.3439(14)	C(2)-C(4)	1.5151(16)	C(12)-C(17)	1.3981(15)
O(1)-C(5)	1.4543(15)	C(2)-C(3)	1.5187(16)	C(13)-C(14)	1.3887(17)
O(2)-C(1)	1.2063(13)	C(3)-C(4)	1.4890(19)	C(14)-C(15)	1.3881(17)
O(3)-C(7)	1.2456(13)	C(5)-C(6)	1.496(2)	C(15)-C(16)	1.3836(19)
O(4)-C(18)	1.2245(13)	C(7)-C(8)	1.4807(16)	C(16)-C(17)	1.3903(17)
N(1)-C(18)	1.3408(14)	C(8)-C(10)	1.5106(17)	C(18)-C(19)	1.5333(16)
N(1)-C(2)	1.4299(15)	C(8)-C(9)	1.5172(17)	C(19)-C(20)	1.5090(15)
N(2)-C(7)	1.3559(14)	C(9)-C(10)	1.484(2)	C(20)-C(21)	1.5033(18)
N(2)-C(19)	1.4743(14)	C(11)-C(12)	1.5126(15)	C(20)-C(22)	1.5055(16)

N(2)-C(11)	1.4758(13)	C(12)-C(13)	1.3882(17)	C(21)-C(22)	1.502(2)
C(1)-C(2)	1.4908(17)				

C(1)-O(1)-C(5)	116.33(9)	C(10)-C(9)-C(8)	60.42(9)
C(18)-N(1)-C(2)	119.77(9)	C(9)-C(10)-C(8)	60.86(9)
C(7)-N(2)-C(19)	115.85(8)	N(2)-C(11)-C(12)	114.93(9)
C(7)-N(2)-C(11)	122.68(9)	C(13)-C(12)-C(17)	118.17(11)
C(19)-N(2)-C(11)	118.40(9)	C(13)-C(12)-C(11)	122.56(10)
O(2)-C(1)-O(1)	124.33(11)	C(17)-C(12)-C(11)	119.21(10)
O(2)-C(1)-C(2)	124.34(11)	C(12)-C(13)-C(14)	120.88(11)
O(1)-C(1)-C(2)	111.33(9)	C(15)-C(14)-C(13)	120.37(13)
N(1)-C(2)-C(1)	114.57(9)	C(16)-C(15)-C(14)	119.54(12)
N(1)-C(2)-C(4)	116.88(10)	C(15)-C(16)-C(17)	119.91(11)
C(1)-C(2)-C(4)	119.93(10)	C(16)-C(17)-C(12)	121.13(12)
N(1)-C(2)-C(3)	116.46(10)	O(4)-C(18)-N(1)	123.12(11)
C(1)-C(2)-C(3)	119.06(10)	O(4)-C(18)-C(19)	121.61(10)
C(4)-C(2)-C(3)	58.79(8)	N(1)-C(18)-C(19)	115.26(9)
C(4)-C(3)-C(2)	60.48(8)	N(2)-C(19)-C(20)	112.75(9)
C(3)-C(4)-C(2)	60.73(8)	N(2)-C(19)-C(18)	108.96(8)
O(1)-C(5)-C(6)	109.73(11)	C(20)-C(19)-C(18)	111.14(10)
O(3)-C(7)-N(2)	120.51(10)	C(21)-C(20)-C(22)	59.89(9)
O(3)-C(7)-C(8)	120.05(10)	C(21)-C(20)-C(19)	118.51(11)
N(2)-C(7)-C(8)	119.40(9)	C(22)-C(20)-C(19)	118.05(10)
C(7)-C(8)-C(10)	116.08(11)	C(22)-C(21)-C(20)	60.13(8)
C(7)-C(8)-C(9)	115.95(10)	C(21)-C(22)-C(20)	59.98(8)
C(10)-C(8)-C(9)	58.71(9)		

Table 3.4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **5h**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	32(1)	27(1)	23(1)	-11(1)	-10(1)	5(1)
O(2)	45(1)	22(1)	31(1)	-12(1)	-9(1)	1(1)
O(3)	18(1)	24(1)	35(1)	-13(1)	-10(1)	4(1)
O(4)	20(1)	39(1)	28(1)	-14(1)	-9(1)	-4(1)
N(1)	17(1)	31(1)	22(1)	-12(1)	-7(1)	-2(1)
N(2)	15(1)	18(1)	22(1)	-7(1)	-5(1)	0(1)
C(1)	20(1)	25(1)	24(1)	-11(1)	-4(1)	-4(1)
C(2)	20(1)	24(1)	23(1)	-11(1)	-5(1)	-1(1)
C(3)	38(1)	23(1)	28(1)	-11(1)	-9(1)	0(1)
C(4)	28(1)	34(1)	28(1)	-13(1)	-7(1)	8(1)
C(5)	40(1)	25(1)	24(1)	-6(1)	-12(1)	0(1)
C(6)	40(1)	35(1)	42(1)	-11(1)	-21(1)	6(1)
C(7)	18(1)	20(1)	24(1)	-9(1)	-11(1)	0(1)
C(8)	20(1)	20(1)	29(1)	-5(1)	-10(1)	0(1)
C(9)	32(1)	27(1)	35(1)	0(1)	-13(1)	0(1)
C(10)	43(1)	20(1)	45(1)	-6(1)	-17(1)	-7(1)
C(11)	16(1)	19(1)	25(1)	-7(1)	-8(1)	2(1)
C(12)	15(1)	18(1)	24(1)	-5(1)	-4(1)	-2(1)

C(13)	23(1)	24(1)	26(1)	-6(1)	-8(1)	2(1)
C(14)	28(1)	34(1)	24(1)	-8(1)	-8(1)	0(1)
C(15)	27(1)	28(1)	29(1)	-14(1)	-2(1)	-1(1)
C(16)	26(1)	23(1)	33(1)	-10(1)	-7(1)	4(1)
C(17)	24(1)	22(1)	25(1)	-6(1)	-8(1)	3(1)
C(18)	19(1)	18(1)	23(1)	-7(1)	-8(1)	-1(1)
C(19)	17(1)	19(1)	23(1)	-7(1)	-7(1)	-2(1)
C(20)	23(1)	20(1)	26(1)	-7(1)	-7(1)	-1(1)
C(21)	47(1)	24(1)	32(1)	-15(1)	-13(1)	-2(1)
C(22)	29(1)	22(1)	38(1)	-10(1)	-10(1)	-6(1)

Table 3.5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **5h**.

Atom	x	y	z	U(eq)
H(1N)	5195(16)	1446(15)	8376(13)	31(4)
H(31)	4299(16)	-315(15)	6230(14)	35(4)
H(32)	4290(15)	-953(15)	7671(14)	33(4)
H(41)	6696(15)	-51(15)	7124(13)	35(4)
H(42)	6661(15)	596(15)	5706(14)	34(4)
H(51)	4720(15)	3213(15)	3234(13)	30(4)
H(52)	4338(15)	4348(16)	4008(12)	32(4)
H(61)	1983(17)	3419(16)	4991(15)	42(4)
H(62)	2203(17)	3952(18)	3575(15)	50(5)
H(63)	2352(17)	2256(19)	4304(15)	51(5)
H(8)	-149(15)	-1350(15)	12566(12)	30(4)
H(91)	597(17)	-3426(16)	13975(14)	39(4)
H(92)	2305(16)	-3228(15)	13021(13)	35(4)
H(101)	1542(16)	-3446(15)	11445(14)	36(4)
H(102)	-147(18)	-3657(18)	12359(15)	48(4)
H(111)	171(13)	1963(13)	10220(12)	19(3)
H(112)	-459(14)	488(14)	11183(12)	22(3)
H(13)	559(15)	668(16)	13257(13)	35(4)
H(14)	-494(15)	1763(15)	14747(14)	34(4)
H(15)	-2110(14)	3803(14)	14384(12)	29(3)
H(16)	-2618(15)	4692(15)	12520(13)	31(4)
H(17)	-1552(14)	3556(15)	11001(13)	30(4)
H(19)	3767(13)	1128(13)	10310(11)	19(3)
H(20)	1889(15)	3616(15)	9689(12)	31(4)
H(211)	2391(17)	4209(18)	11247(14)	47(4)
H(212)	3405(16)	2722(17)	11568(14)	43(4)
H(221)	4988(15)	3416(14)	9522(12)	28(3)
H(222)	4012(15)	4937(17)	9163(14)	39(4)

Table 3.6. Torsion angles [°] for **5h**.

C(5)-O(1)-C(1)-O(2)	-6.61(16)	C(19)-N(2)-C(11)-C(12)	-93.92(12)
C(5)-O(1)-C(1)-C(2)	172.97(9)	N(2)-C(11)-C(12)-C(13)	-36.24(15)
C(18)-N(1)-C(2)-C(1)	73.88(13)	N(2)-C(11)-C(12)-C(17)	146.55(10)
C(18)-N(1)-C(2)-C(4)	-138.25(11)	C(17)-C(12)-C(13)-C(14)	0.46(17)
C(18)-N(1)-C(2)-C(3)	-71.62(14)	C(11)-C(12)-C(13)-C(14)	-176.78(11)

O(2)-C(1)-C(2)-N(1)	3.52(16)	C(12)-C(13)-C(14)-C(15)	-0.29(18)
O(1)-C(1)-C(2)-N(1)	-176.07(9)	C(13)-C(14)-C(15)-C(16)	0.03(18)
O(2)-C(1)-C(2)-C(4)	-143.30(12)	C(14)-C(15)-C(16)-C(17)	0.05(18)
O(1)-C(1)-C(2)-C(4)	37.12(14)	C(15)-C(16)-C(17)-C(12)	0.14(18)
O(2)-C(1)-C(2)-C(3)	148.06(12)	C(13)-C(12)-C(17)-C(16)	-0.39(17)
O(1)-C(1)-C(2)-C(3)	-31.52(14)	C(11)-C(12)-C(17)-C(16)	176.95(11)
N(1)-C(2)-C(3)-C(4)	-106.79(12)	C(2)-N(1)-C(18)-O(4)	-1.26(17)
C(1)-C(2)-C(3)-C(4)	109.31(12)	C(2)-N(1)-C(18)-C(19)	179.15(9)
N(1)-C(2)-C(4)-C(3)	106.08(12)	C(7)-N(2)-C(19)-C(20)	-158.77(10)
C(1)-C(2)-C(4)-C(3)	-107.84(12)	C(11)-N(2)-C(19)-C(20)	40.51(13)
C(1)-O(1)-C(5)-C(6)	-81.86(13)	C(7)-N(2)-C(19)-C(18)	77.35(11)
C(19)-N(2)-C(7)-O(3)	1.04(15)	C(11)-N(2)-C(19)-C(18)	-83.37(11)
C(11)-N(2)-C(7)-O(3)	160.85(10)	O(4)-C(18)-C(19)-N(2)	33.99(14)
C(19)-N(2)-C(7)-C(8)	178.60(9)	N(1)-C(18)-C(19)-N(2)	-146.41(10)
C(11)-N(2)-C(7)-C(8)	-21.59(16)	O(4)-C(18)-C(19)-C(20)	-90.84(12)
O(3)-C(7)-C(8)-C(10)	-36.63(16)	N(1)-C(18)-C(19)-C(20)	88.75(12)
N(2)-C(7)-C(8)-C(10)	145.79(11)	N(2)-C(19)-C(20)-C(21)	80.69(13)
O(3)-C(7)-C(8)-C(9)	29.48(16)	C(18)-C(19)-C(20)-C(21)	-156.64(10)
N(2)-C(7)-C(8)-C(9)	-148.09(11)	N(2)-C(19)-C(20)-C(22)	149.75(11)
C(7)-C(8)-C(9)-C(10)	-106.05(12)	C(18)-C(19)-C(20)-C(22)	-87.58(13)
C(7)-C(8)-C(10)-C(9)	105.81(12)	C(19)-C(20)-C(21)-C(22)	107.68(12)
C(7)-N(2)-C(11)-C(12)	106.76(12)	C(19)-C(20)-C(22)-C(21)	-108.43(13)

Table 3.7. Hydrogen bonds for **5h** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(1N)...O(3)#1	0.878(15)	1.962(15)	2.8367(13)	174.3(13)

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,-y,-z+2

4. Ethyl 1-{2-[Cyclopropanecarbonyl-(4-methoxyphenyl)amino]-2-cyclopropyl-acetylamino}cyclopropanecarboxylate (5i)

Table 4.1. Crystal data and structure refinement for **5i**.

Identification code	**5i**	
Empirical formula	C_{22} H_{28} N_2 O_5	
Formula weight	400.46	
Temperature	120(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 11.3239(5) Å	□= 90.008(2)°.
	b = 13.8172(6) Å	□= 93.736(2)°.
	c = 14.2573(6) Å	□ = 111.296(2)°.
Volume	2073.34(16) $Å^3$	
Z	4	
Density (calculated)	1.283 Mg/m^3	
Absorption coefficient	0.091 mm^{-1}	
F(000)	856	
Crystal size	0.36 x 0.14 x 0.12 mm^3	
Theta range for data collection	2.86 to 29.50°.	
Index ranges	-15<=h<=15, -19<=k<=19, -19<=l<=19	
Reflections collected	18232	
Independent reflections	10701 [R(int) = 0.0375]	
Completeness to theta = 29.50°	92.6 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	10701 / 0 / 747	
Goodness-of-fit on F^2	0.954	
Final R indices [I>2sigma(I)]	R_1 = 0.0410, wR_2 = 0.0771	
R indices (all data)	R_1 = 0.0628, wR_2 = 0.0818	
Largest diff. peak and hole	0.295 and -0.223 e.$Å^{-3}$	

Table 4.2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for **5i**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Atom	x	y	z	U(eq)
O(1)	4825(1)	7898(1)	1730(1)	40(1)
O(2)	3921(1)	7505(1)	3105(1)	24(1)
O(3)	4354(1)	3604(1)	4896(1)	25(1)
O(4)	-2340(1)	1208(1)	2450(1)	31(1)
O(5)	2344(1)	4951(1)	2646(1)	28(1)
O(11)	-553(1)	-2662(1)	3372(1)	36(1)
O(12)	588(1)	-2368(1)	2100(1)	23(1)
O(13)	823(1)	1582(1)	50(1)	24(1)
O(14)	7658(1)	3903(1)	2140(1)	31(1)
O(15)	2346(1)	293(1)	2518(1)	26(1)
N(1)	4353(1)	5735(1)	3296(1)	21(1)
N(2)	2458(1)	3456(1)	4158(1)	18(1)
N(11)	407(1)	-531(1)	1760(1)	19(1)
N(12)	2658(1)	1603(1)	814(1)	17(1)
C(1)	4522(1)	7326(1)	2387(1)	26(1)
C(2)	4801(1)	6353(1)	2498(1)	23(1)
C(3)	6065(1)	6399(1)	2162(1)	33(1)
C(4)	4873(1)	5792(1)	1608(1)	32(1)
C(5)	3642(1)	8458(1)	3060(1)	28(1)
C(6)	3012(2)	8527(1)	3937(1)	32(1)
C(7)	3321(1)	3050(1)	4507(1)	18(1)
C(8)	2998(1)	1915(1)	4394(1)	21(1)
C(9)	4095(1)	1539(1)	4371(1)	25(1)
C(10)	3349(1)	1351(1)	5218(1)	27(1)
C(11)	-3441(1)	1030(1)	2954(1)	40(1)
C(12)	1220(1)	2821(1)	3738(1)	17(1)
C(13)	194(1)	2479(1)	4289(1)	21(1)
C(14)	-1016(1)	1928(1)	3884(1)	23(1)
C(15)	-1190(1)	1714(1)	2926(1)	21(1)
C(16)	-150(1)	2016(1)	2375(1)	21(1)
C(17)	1045(1)	2583(1)	2778(1)	19(1)
C(18)	3126(1)	5105(1)	3316(1)	19(1)
C(19)	2777(1)	4592(1)	4262(1)	19(1)
C(20)	1728(1)	4870(1)	4637(1)	23(1)
C(21)	2109(2)	5895(1)	5159(1)	32(1)
C(22)	1639(2)	4896(1)	5680(1)	33(1)
C(31)	-74(1)	-2113(1)	2736(1)	23(1)
C(32)	-176(1)	-1082(1)	2559(1)	20(1)
C(33)	-1411(1)	-988(1)	2819(1)	29(1)
C(34)	-229(1)	-463(1)	3420(1)	26(1)
C(35)	674(1)	-3394(1)	2188(1)	26(1)
C(36)	1281(1)	-3578(1)	1338(1)	29(1)
C(37)	1917(1)	2080(1)	381(1)	18(1)
C(38)	2461(1)	3229(1)	333(1)	23(1)
C(39)	1567(2)	3801(1)	476(1)	31(1)
C(40)	1995(1)	3733(1)	-475(1)	26(1)

C(41)	8684(1)	3925(1)	1595(1)	32(1)
C(42)	3960(1)	2186(1)	1151(1)	17(1)
C(43)	4252(1)	2561(1)	2073(1)	21(1)
C(44)	5491(1)	3150(1)	2378(1)	24(1)
C(45)	6456(1)	3349(1)	1764(1)	22(1)
C(46)	6164(1)	2985(1)	842(1)	24(1)
C(47)	4915(1)	2401(1)	538(1)	22(1)
C(48)	1655(1)	72(1)	1795(1)	18(1)
C(49)	2153(1)	453(1)	836(1)	18(1)
C(50)	3129(1)	5(1)	610(1)	22(1)
C(51)	2665(2)	-1059(1)	154(1)	35(1)
C(52)	3325(2)	-124(1)	-408(1)	34(1)

Table 4.3. Selected bond lengths [Å] and angles [°] for **5i**.

O(1)-C(1)	1.2098(14)	N(12)-C(42)	1.4488(14)	C(21)-C(22)	1.5024(19)
O(2)-C(1)	1.3360(15)	N(12)-C(49)	1.4810(14)	C(31)-C(32)	1.4907(16)
O(2)-C(5)	1.4613(15)	C(1)-C(2)	1.4940(18)	C(32)-C(34)	1.5120(18)
O(3)-C(7)	1.2353(13)	C(2)-C(4)	1.5095(19)	C(32)-C(33)	1.5199(17)
O(4)-C(15)	1.3676(13)	C(2)-C(3)	1.5184(18)	C(33)-C(34)	1.4825(19)
O(4)-C(11)	1.4228(18)	C(3)-C(4)	1.4784(19)	C(35)-C(36)	1.496(2)
O(5)-C(18)	1.2233(13)	C(5)-C(6)	1.498(2)	C(37)-C(38)	1.4836(16)
O(11)-C(31)	1.2073(14)	C(7)-C(8)	1.4821(16)	C(38)-C(40)	1.5104(16)
O(12)-C(31)	1.3373(15)	C(8)-C(9)	1.5119(17)	C(38)-C(39)	1.5161(18)
O(12)-C(35)	1.4615(14)	C(8)-C(10)	1.5184(17)	C(39)-C(40)	1.4840(19)
O(13)-C(37)	1.2383(13)	C(9)-C(10)	1.4876(19)	C(42)-C(47)	1.3825(17)
O(14)-C(45)	1.3689(14)	C(12)-C(13)	1.3822(16)	C(42)-C(43)	1.3872(17)
O(14)-C(41)	1.4308(17)	C(12)-C(17)	1.3920(16)	C(43)-C(44)	1.3826(17)
O(15)-C(48)	1.2215(13)	C(13)-C(14)	1.3892(17)	C(44)-C(45)	1.3933(17)
N(1)-C(18)	1.3470(15)	C(14)-C(15)	1.3834(18)	C(45)-C(46)	1.3831(18)
N(1)-C(2)	1.4295(15)	C(15)-C(16)	1.3929(17)	C(46)-C(47)	1.3895(17)
N(2)-C(7)	1.3614(13)	C(16)-C(17)	1.3796(17)	C(48)-C(49)	1.5323(17)
N(2)-C(12)	1.4452(14)	C(18)-C(19)	1.5306(16)	C(49)-C(50)	1.5008(17)
N(2)-C(19)	1.4828(14)	C(19)-C(20)	1.5015(17)	C(50)-C(52)	1.5020(19)
N(11)-C(48)	1.3523(15)	C(20)-C(22)	1.4988(19)	C(50)-C(51)	1.5025(18)
N(11)-C(32)	1.4302(15)	C(20)-C(21)	1.5045(18)	C(51)-C(52)	1.498(2)
N(12)-C(37)	1.3620(13)				

C(1)-O(2)-C(5)	115.78(10)	C(20)-C(19)-C(18)	109.97(9)
C(15)-O(4)-C(11)	116.89(11)	C(22)-C(20)-C(19)	118.57(11)
C(31)-O(12)-C(35)	116.00(9)	C(22)-C(20)-C(21)	60.03(9)
C(45)-O(14)-C(41)	116.68(11)	C(19)-C(20)-C(21)	116.94(11)
C(18)-N(1)-C(2)	121.09(10)	C(22)-C(21)-C(20)	59.80(9)

C(7)-N(2)-C(12)	122.86(9)	C(20)-C(22)-C(21)	60.17(9)
C(7)-N(2)-C(19)	118.34(9)	O(11)-C(31)-O(12)	123.92(11)
C(12)-N(2)-C(19)	118.71(9)	O(11)-C(31)-C(32)	123.79(12)
C(48)-N(11)-C(32)	121.96(10)	O(12)-C(31)-C(32)	112.28(10)
C(37)-N(12)-C(42)	121.29(9)	N(11)-C(32)-C(31)	117.67(10)
C(37)-N(12)-C(49)	118.25(9)	N(11)-C(32)-C(34)	118.46(10)
C(42)-N(12)-C(49)	120.09(8)	C(31)-C(32)-C(34)	116.05(10)
O(1)-C(1)-O(2)	123.63(12)	N(11)-C(32)-C(33)	117.69(10)
O(1)-C(1)-C(2)	123.95(13)	C(31)-C(32)-C(33)	115.09(10)
O(2)-C(1)-C(2)	112.41(10)	C(34)-C(32)-C(33)	58.54(8)
N(1)-C(2)-C(1)	117.95(11)	C(34)-C(33)-C(32)	60.46(8)
N(1)-C(2)-C(4)	117.26(11)	C(33)-C(34)-C(32)	60.99(9)
C(1)-C(2)-C(4)	116.91(11)	O(12)-C(35)-C(36)	107.03(10)
N(1)-C(2)-C(3)	117.18(11)	O(13)-C(37)-N(12)	121.80(11)
C(1)-C(2)-C(3)	115.54(11)	O(13)-C(37)-C(38)	120.80(10)
C(4)-C(2)-C(3)	58.45(9)	N(12)-C(37)-C(38)	117.39(10)
C(4)-C(3)-C(2)	60.47(9)	C(37)-C(38)-C(40)	118.03(10)
C(3)-C(4)-C(2)	61.08(9)	C(37)-C(38)-C(39)	116.73(11)
O(2)-C(5)-C(6)	107.18(11)	C(40)-C(38)-C(39)	58.73(8)
O(3)-C(7)-N(2)	121.73(11)	C(40)-C(39)-C(38)	60.45(9)
O(3)-C(7)-C(8)	120.29(10)	C(39)-C(40)-C(38)	60.83(9)
N(2)-C(7)-C(8)	117.97(10)	C(47)-C(42)-C(43)	119.74(11)
C(7)-C(8)-C(9)	116.99(10)	C(47)-C(42)-N(12)	119.58(11)
C(7)-C(8)-C(10)	117.56(11)	C(43)-C(42)-N(12)	120.64(11)
C(9)-C(8)-C(10)	58.80(8)	C(44)-C(43)-C(42)	120.20(12)
C(10)-C(9)-C(8)	60.82(8)	C(43)-C(44)-C(45)	120.00(12)
C(9)-C(10)-C(8)	60.38(8)	O(14)-C(45)-C(46)	124.42(11)
C(13)-C(12)-C(17)	119.75(11)	O(14)-C(45)-C(44)	115.78(11)
C(13)-C(12)-N(2)	119.63(11)	C(46)-C(45)-C(44)	119.80(11)
C(17)-C(12)-N(2)	120.58(11)	C(45)-C(46)-C(47)	119.91(12)
C(12)-C(13)-C(14)	120.31(12)	C(42)-C(47)-C(46)	120.33(12)
C(15)-C(14)-C(13)	119.70(12)	O(15)-C(48)-N(11)	123.85(11)
O(4)-C(15)-C(14)	124.67(12)	O(15)-C(48)-C(49)	121.86(10)
O(4)-C(15)-C(16)	115.19(11)	N(11)-C(48)-C(49)	114.28(10)
C(14)-C(15)-C(16)	120.14(11)	N(12)-C(49)-C(50)	112.07(9)
C(17)-C(16)-C(15)	119.80(12)	N(12)-C(49)-C(48)	111.15(10)
C(16)-C(17)-C(12)	120.19(12)	C(50)-C(49)-C(48)	109.41(9)
O(5)-C(18)-N(1)	123.76(11)	C(49)-C(50)-C(52)	117.86(11)
O(5)-C(18)-C(19)	122.02(11)	C(49)-C(50)-C(51)	117.68(11)
N(1)-C(18)-C(19)	114.22(10)	C(52)-C(50)-C(51)	59.83(9)

N(2)-C(19)-C(20)	113.21(10)	C(52)-C(51)-C(50)	60.07(9)
N(2)-C(19)-C(18)	109.73(10)	C(51)-C(52)-C(50)	60.10(9)

Table 4.4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for **5i**. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

Atom	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	59(1)	34(1)	29(1)	12(1)	17(1)	16(1)
O(2)	29(1)	19(1)	22(1)	2(1)	3(1)	7(1)
O(3)	23(1)	22(1)	28(1)	-4(1)	-8(1)	7(1)
O(4)	20(1)	32(1)	37(1)	-8(1)	-7(1)	5(1)
O(5)	27(1)	28(1)	22(1)	5(1)	-6(1)	3(1)
O(11)	58(1)	25(1)	24(1)	6(1)	14(1)	14(1)
O(12)	33(1)	17(1)	22(1)	1(1)	3(1)	12(1)
O(13)	21(1)	24(1)	25(1)	-3(1)	-4(1)	9(1)
O(14)	19(1)	34(1)	36(1)	-7(1)	-1(1)	5(1)
O(15)	26(1)	28(1)	19(1)	1(1)	-3(1)	4(1)
N(1)	22(1)	22(1)	17(1)	1(1)	-1(1)	5(1)
N(2)	19(1)	15(1)	18(1)	0(1)	-2(1)	5(1)
N(11)	22(1)	18(1)	16(1)	0(1)	0(1)	6(1)
N(12)	18(1)	16(1)	17(1)	1(1)	-1(1)	6(1)
C(1)	26(1)	24(1)	21(1)	0(1)	1(1)	2(1)
C(2)	24(1)	23(1)	19(1)	1(1)	3(1)	3(1)
C(3)	29(1)	36(1)	33(1)	2(1)	10(1)	9(1)
C(4)	40(1)	28(1)	23(1)	-2(1)	6(1)	8(1)
C(5)	35(1)	18(1)	29(1)	2(1)	-1(1)	7(1)
C(6)	44(1)	26(1)	27(1)	-2(1)	-2(1)	16(1)
C(7)	20(1)	20(1)	14(1)	0(1)	0(1)	7(1)
C(8)	20(1)	18(1)	23(1)	-1(1)	-5(1)	6(1)
C(9)	25(1)	23(1)	29(1)	-2(1)	0(1)	12(1)
C(10)	34(1)	24(1)	26(1)	6(1)	1(1)	12(1)
C(11)	18(1)	42(1)	51(1)	13(1)	-2(1)	2(1)
C(12)	18(1)	15(1)	19(1)	0(1)	-2(1)	7(1)
C(13)	25(1)	19(1)	17(1)	0(1)	2(1)	6(1)
C(14)	20(1)	20(1)	28(1)	0(1)	6(1)	6(1)
C(15)	19(1)	16(1)	28(1)	-2(1)	-3(1)	7(1)
C(16)	26(1)	23(1)	17(1)	-3(1)	-3(1)	12(1)
C(17)	20(1)	19(1)	20(1)	1(1)	2(1)	10(1)
C(18)	24(1)	15(1)	20(1)	-1(1)	0(1)	8(1)
C(19)	21(1)	15(1)	18(1)	0(1)	-2(1)	5(1)
C(20)	26(1)	18(1)	25(1)	0(1)	3(1)	8(1)
C(21)	41(1)	21(1)	35(1)	-1(1)	8(1)	11(1)
C(22)	46(1)	28(1)	29(1)	4(1)	12(1)	15(1)
C(31)	30(1)	19(1)	19(1)	-2(1)	-1(1)	7(1)
C(32)	25(1)	17(1)	18(1)	0(1)	4(1)	6(1)
C(33)	27(1)	27(1)	31(1)	0(1)	9(1)	9(1)
C(34)	34(1)	22(1)	23(1)	-1(1)	7(1)	10(1)
C(35)	36(1)	18(1)	26(1)	0(1)	-3(1)	13(1)
C(36)	36(1)	25(1)	32(1)	-3(1)	-3(1)	17(1)

C(37)	21(1)	21(1)	13(1)	-2(1)	1(1)	10(1)
C(38)	25(1)	18(1)	27(1)	-2(1)	-5(1)	10(1)
C(39)	45(1)	28(1)	28(1)	0(1)	4(1)	23(1)
C(40)	31(1)	24(1)	25(1)	5(1)	3(1)	14(1)
C(41)	19(1)	27(1)	49(1)	1(1)	2(1)	8(1)
C(42)	19(1)	16(1)	18(1)	1(1)	0(1)	8(1)
C(43)	23(1)	23(1)	19(1)	1(1)	3(1)	11(1)
C(44)	26(1)	26(1)	19(1)	-3(1)	-1(1)	9(1)
C(45)	19(1)	20(1)	28(1)	0(1)	-1(1)	7(1)
C(46)	22(1)	23(1)	26(1)	1(1)	7(1)	7(1)
C(47)	25(1)	22(1)	18(1)	-1(1)	2(1)	8(1)
C(48)	23(1)	13(1)	20(1)	-1(1)	1(1)	9(1)
C(49)	20(1)	15(1)	17(1)	0(1)	-1(1)	5(1)
C(50)	26(1)	22(1)	21(1)	-2(1)	2(1)	12(1)
C(51)	43(1)	26(1)	40(1)	-8(1)	5(1)	17(1)
C(52)	41(1)	41(1)	26(1)	-3(1)	8(1)	21(1)

Table 4.5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for **5i**.

Atom	x	y	z	U(eq)
H(2N)	4797(12)	5876(10)	3810(10)	29(4)
H(11N)	26(11)	-740(10)	1214(9)	23(4)
H(31)	6572(12)	7025(11)	1906(10)	35(4)
H(32)	6490(12)	6029(11)	2538(10)	35(4)
H(41)	4575(12)	5044(11)	1645(9)	35(4)
H(42)	4684(12)	6069(10)	1001(10)	30(4)
H(51)	4470(12)	9053(11)	3021(9)	32(4)
H(52)	3102(11)	8413(10)	2486(9)	29(4)
H(61)	2244(13)	7886(12)	4009(10)	40(4)
H(62)	2723(12)	9128(11)	3905(10)	41(4)
H(63)	3598(13)	8633(11)	4481(11)	43(4)
H(8)	2263(11)	1533(9)	4021(8)	19(3)
H(91)	4947(12)	2083(10)	4434(9)	26(3)
H(92)	3966(11)	965(10)	3927(9)	29(4)
H(101)	3764(12)	1760(10)	5785(10)	29(4)
H(102)	2733(12)	656(11)	5325(9)	36(4)
H(111)	-3501(12)	501(11)	3478(10)	43(4)
H(112)	-4166(14)	758(11)	2495(11)	45(4)
H(113)	-3429(14)	1740(13)	3247(11)	61(5)
H(13)	321(11)	2637(9)	4938(9)	22(3)
H(14)	-1691(12)	1704(10)	4258(9)	27(4)
H(16)	-280(11)	1843(10)	1729(9)	25(3)
H(17)	1771(12)	2836(10)	2392(9)	25(3)
H(19)	3506(10)	4842(8)	4703(8)	11(3)
H(20)	935(11)	4663(9)	4254(9)	22(3)
H(211)	3011(13)	6316(11)	5238(9)	36(4)
H(212)	1534(13)	6290(11)	5055(10)	40(4)
H(221)	2246(13)	4707(10)	6063(10)	37(4)
H(222)	773(15)	4667(12)	5907(11)	58(5)
H(331)	-2043(12)	-1613(11)	3074(9)	32(4)

H(332)	-1710(12)	-562(10)	2397(10)	32(4)
H(341)	-125(11)	-779(10)	4024(9)	30(4)
H(342)	185(12)	285(11)	3388(9)	30(4)
H(351)	-204(12)	-3906(10)	2240(9)	25(3)
H(352)	1203(11)	-3366(9)	2775(9)	24(3)
H(361)	2103(13)	-3037(11)	1288(9)	30(4)
H(362)	744(12)	-3614(10)	772(9)	28(4)
H(363)	1419(13)	-4246(12)	1411(10)	47(4)
H(38)	3301(12)	3565(10)	565(9)	25(3)
H(391)	677(13)	3350(11)	574(9)	34(4)
H(392)	1937(14)	4454(12)	837(11)	51(5)
H(401)	1381(12)	3267(10)	-934(9)	25(3)
H(402)	2630(12)	4334(11)	-749(9)	33(4)
H(411)	9460(13)	4198(11)	2036(10)	38(4)
H(412)	8732(11)	4383(10)	1032(9)	29(4)
H(413)	8575(12)	3186(11)	1361(9)	36(4)
H(43)	3591(12)	2399(10)	2510(10)	34(4)
H(44)	5725(11)	3425(10)	3011(9)	25(3)
H(46)	6790(12)	3126(10)	406(9)	26(4)
H(47)	4713(11)	2144(10)	-86(9)	25(3)
H(49)	1455(10)	208(8)	368(8)	11(3)
H(50)	3861(11)	177(9)	1045(9)	23(3)
H(511)	1721(13)	-1411(11)	28(10)	38(4)
H(512)	3132(13)	-1493(12)	344(10)	46(4)
H(521)	2818(12)	113(10)	-851(10)	32(4)
H(522)	4190(13)	-1(11)	-550(10)	40(4)

Table 4.6. Torsion angles [°] for **5i**.

C(5)-O(2)-C(1)-O(1)	-0.28(18)	C(15)-C(16)-C(17)-C(12)	2.34(18)	O(13)-C(37)-C(38)-C(40)	-28.95(18)
C(5)-O(2)-C(1)-C(2)	178.52(10)	C(13)-C(12)-C(17)-C(16)	0.65(17)	N(12)-C(37)-C(38)-C(40)	152.05(11)
C(18)-N(1)-C(2)-C(1)	77.97(15)	N(2)-C(12)-C(17)-C(16)	-177.13(10)	O(13)-C(37)-C(38)-C(39)	38.07(17)
C(18)-N(1)-C(2)-C(4)	-70.21(15)	C(2)-N(1)-C(18)-O(5)	6.11(18)	N(12)-C(37)-C(38)-C(39)	-140.92(12)
C(18)-N(1)-C(2)-C(3)	-136.81(12)	C(2)-N(1)-C(18)-C(19)	-173.56(11)	C(37)-C(38)-C(39)-C(40)	-108.04(12)
O(1)-C(1)-C(2)-N(1)	-178.12(12)	C(7)-N(2)-C(19)-C(20)	-131.75(11)	C(37)-C(38)-C(40)-C(39)	105.83(14)
O(2)-C(1)-C(2)-N(1)	3.09(16)	C(12)-N(2)-C(19)-C(20)	44.96(14)	C(37)-N(12)-C(42)-C(47)	-84.30(14)
O(1)-C(1)-C(2)-C(4)	-29.82(19)	C(7)-N(2)-C(19)-C(18)	104.98(11)	C(49)-N(12)-C(42)-C(47)	88.57(13)
O(2)-C(1)-C(2)-C(4)	151.38(11)	C(12)-N(2)-C(19)-C(18)	-78.31(13)	C(37)-N(12)-C(42)-C(43)	93.42(14)

O(1)-C(1)-C(2)-C(3)	36.11(18)	O(5)-C(18)-C(19)-N(2)	67.41(14)	C(49)-N(12)-C(42)-C(43)	-93.71(13)
O(2)-C(1)-C(2)-C(3)	-142.68(11)	N(1)-C(18)-C(19)-N(2)	-112.91(11)	C(47)-C(42)-C(43)-C(44)	0.21(18)
N(1)-C(2)-C(3)-C(4)	106.79(13)	O(5)-C(18)-C(19)-C(20)	-57.74(15)	N(12)-C(42)-C(43)-C(44)	-177.51(10)
C(1)-C(2)-C(3)-C(4)	-107.16(13)	N(1)-C(18)-C(19)-C(20)	121.93(11)	C(42)-C(43)-C(44)-C(45)	-1.51(18)
N(1)-C(2)-C(4)-C(3)	-106.66(13)	N(2)-C(19)-C(20)-C(22)	84.93(14)	C(41)-O(14)-C(45)-C(46)	-12.61(17)
C(1)-C(2)-C(4)-C(3)	104.82(13)	C(18)-C(19)-C(20)-C(22)	-151.93(11)	C(41)-O(14)-C(45)-C(44)	166.90(11)
C(1)-O(2)-C(5)-C(6)	-178.22(11)	N(2)-C(19)-C(20)-C(21)	153.76(10)	C(43)-C(44)-C(45)-O(14)	-177.37(11)
C(12)-N(2)-C(7)-O(3)	-177.22(11)	C(18)-C(19)-C(20)-C(21)	-83.11(13)	C(43)-C(44)-C(45)-C(46)	2.17(18)
C(19)-N(2)-C(7)-O(3)	-0.65(17)	C(19)-C(20)-C(21)-C(22)	-109.04(13)	O(14)-C(45)-C(46)-C(47)	177.98(11)
C(12)-N(2)-C(7)-C(8)	3.89(17)	C(19)-C(20)-C(22)-C(21)	106.35(13)	C(44)-C(45)-C(46)-C(47)	-1.51(18)
C(19)-N(2)-C(7)-C(8)	-179.55(10)	C(35)-O(12)-C(31)-O(11)	2.23(17)	C(43)-C(42)-C(47)-C(46)	0.44(18)
O(3)-C(7)-C(8)-C(9)	-25.42(17)	C(35)-O(12)-C(31)-C(32)	-176.65(10)	N(12)-C(42)-C(47)-C(46)	178.19(11)
N(2)-C(7)-C(8)-C(9)	153.49(11)	C(48)-N(11)-C(32)-C(31)	-84.07(14)	C(45)-C(46)-C(47)-C(42)	0.21(18)
O(3)-C(7)-C(8)-C(10)	41.63(17)	C(48)-N(11)-C(32)-C(34)	63.95(15)	C(32)-N(11)-C(48)-O(15)	-8.76(18)
N(2)-C(7)-C(8)-C(10)	-139.46(11)	C(48)-N(11)-C(32)-C(33)	131.25(12)	C(32)-N(11)-C(48)-C(49)	170.37(10)
C(7)-C(8)-C(9)-C(10)	107.37(13)	O(11)-C(31)-C(32)-N(11)	-178.09(12)	C(37)-N(12)-C(49)-C(50)	135.98(11)
C(7)-C(8)-C(10)-C(9)	-106.40(13)	O(12)-C(31)-C(32)-N(11)	0.79(15)	C(42)-N(12)-C(49)-C(50)	-37.10(14)
C(7)-N(2)-C(12)-C(13)	92.31(14)	O(11)-C(31)-C(32)-C(34)	33.13(18)	C(37)-N(12)-C(49)-C(48)	-101.24(11)
C(19)-N(2)-C(12)-C(13)	-84.24(13)	O(12)-C(31)-C(32)-C(34)	-147.99(10)	C(42)-N(12)-C(49)-C(48)	85.68(12)
C(7)-N(2)-C(12)-C(17)	-89.91(14)	O(11)-C(31)-C(32)-C(33)	-32.51(18)	O(15)-C(48)-C(49)-N(12)	-61.07(14)

C(19)-N(2)-C(12)-C(17)	93.54(13)	O(12)-C(31)-C(32)-C(33)	146.37(11)	N(11)-C(48)-C(49)-N(12)	119.78(10)
C(17)-C(12)-C(13)-C(14)	-2.17(17)	N(11)-C(32)-C(33)-C(34)	-108.05(12)	O(15)-C(48)-C(49)-C(50)	63.22(14)
N(2)-C(12)-C(13)-C(14)	175.63(10)	C(31)-C(32)-C(33)-C(34)	106.38(12)	N(11)-C(48)-C(49)-C(50)	-115.93(11)
C(12)-C(13)-C(14)-C(15)	0.69(18)	N(11)-C(32)-C(34)-C(33)	106.74(12)	N(12)-C(49)-C(50)-C(52)	-82.34(14)
C(11)-O(4)-C(15)-C(14)	9.69(18)	C(31)-C(32)-C(34)-C(33)	-104.73(12)	C(48)-C(49)-C(50)-C(52)	153.91(11)
C(11)-O(4)-C(15)-C(16)	-170.48(11)	C(31)-O(12)-C(35)-C(36)	171.94(10)	N(12)-C(49)-C(50)-C(51)	-150.95(11)
C(13)-C(14)-C(15)-O(4)	-177.87(11)	C(42)-N(12)-C(37)-O(13)	176.43(11)	C(48)-C(49)-C(50)-C(51)	85.30(14)
C(13)-C(14)-C(15)-C(16)	2.31(18)	C(49)-N(12)-C(37)-O(13)	3.43(17)	C(49)-C(50)-C(51)-C(52)	107.78(13)
O(4)-C(15)-C(16)-C(17)	176.34(10)	C(42)-N(12)-C(37)-C(38)	-4.59(16)	C(49)-C(50)-C(52)-C(51)	-107.49(13)
C(14)-C(15)-C(16)-C(17)	-3.83(18)	C(49)-N(12)-C(37)-C(38)	-177.58(10)		

Table 4.7. Hydrogen bonds for **5i** [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
N(1)-H(2N)...O(3)#1	0.841(13)	2.028(14)	2.8570(13)	168.0(13)
N(11)-H(11N)...O(13)#2	0.861(13)	2.119(13)	2.9623(13)	166.2(12)

Symmetry transformations used to generate equivalent atoms:
#1 -x+1,-y+1,-z+1 #2 -x,-y,-z

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Publications

1) **"***Manganese reactivity in the synthesis of magneto-resisting complex oxides***",** Chezhina, N.; Mikhailova, M.; Osipova, A., *Solid State Ionics* **2001**,*141-142*, 617-621.

2) **"***Magnetic behavior of manganese in complex oxides with perovskite and pyrochlore structure***",** Chezhina, N.; Piir, I.; Osipova, A. *Physica Status Solidi A: Applied Research* **2002**, *189*, 1069-1072.

3) **"***Atom states and interatomic interactions in complex perovskite-like oxides: XV. Magnetic susceptibility of La0.67Ca0.33MnO3 - LaAlO3 solid solutions***",** Chezhina, N. V.; Mikhailova, M. V.; Osipova, A. S. *Russian Journal of General Chemistry* (Translation of Zhurnal Obshchei Khimii) **2001**, *71*, 1351-1354.

Lebenslauf

Ich wurde am 3. März 1981 als einziges Kind des Ingenieurs Sergei Osipov und der Dipl. Chemikerin Galina Osipova, geb. Jakovleva, in Sankt-Petersburg geboren.

Von 1988 bis 1992 besuchte ich die Schule № 31 in Sankt-Petersburg und anschließend wechselte ich auf die Schule № 201 in Sankt-Petersburg, die ich von 1992 bis 1998 besuchte.

Zum Herbstsemester 1998 nahm ich das Studium der Chemie an der Sankt-Petersburger Staatlichen Universität auf. Während meines Studium arbeitete ich von Oktober 1998 bis Mai 2001 in der Gruppe von Prof. N. V. Chezhina und erhielt im Jahr 2000 des Soros Stipendium. Unter der wissenschaftlichen Anleitung von Prof. M. A. Kuznetsov fertigte ich von September 2001 bis Mai 2002 meine Diplomarbeit mit dem Titel „Neue Umlagerung bei der Reaktion von aromatischen *o*-Aminoaldehyden mit 3,5-Dionpyrazolidin-Derivaten“ an, die mit der Note „sehr gut“ bewertet wurde. Am 11. Juli 2003 wurde mir der akademische Grad Diplom-Chemikerin verliehen.

Seit August 2003 arbeite ich im Arbeitskreis von Prof. Dr. Armin de Meijere an meiner Dissertation. In der Zeit von August 2003 bis Juli 2006 wurde ich mit der Betreuung von Studierenden im Rahmen des chemischen Praktikums für Mediziner und Zahnmediziner, zweimal mit der Betreuung von Übungsgruppen zur Vorlesung „Experimentalchemie II, Organische Chemie“, sowie der Betreuung von Praktikanten während des „Organisch-chemischen Grundpraktikums, Teil A“ und der Betreuung der Übungen zur Vorlesung „Reaktionsmechanismen in der Organischen Chemie“ beauftragt.

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