Synthesis of New Spirocyclopropanated β-Lactams and Their Application as Building Blocks for β-Amino Acid Peptides

DISSERTATION

zur Erlangung des Doktorgrades
der Mathematisch-Naturwissenschaftlichen Fakultäten
der Georg-August Universität zu Göttingen

vorgelegt von

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aus

Florenz (Italien)

Göttingen 2005

D7

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Tag der mündlichen Prüfung: 02 November 2005

Die vorliegende Arbeit wurde in der Zeit von Oktober 2002 bis September 2005 im Institut für Organische und Biomolekulare Chemie der Georg-August-Universität Göttingen unter der wissenschaftlichen Anleitung von Herrn Prof. Dr. Armin de Meijere angefertigt.

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

Herrn Prof. Dr. A. Brandi danke ich herzlich für die hilfreichen Diskussionen und seine stetige Unterstützung.

To my mother

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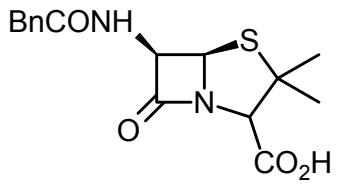
A. Introduction

β-Lactam antibiotics are the most frequently employed kind of antimicrobial agents. The first example ever observed was discovered by Sir A. Fleming in 1929.[1] He found out how the growth of some bacteria stams was significantly stopped from a mold, belonging to the genus *Penicillium*, and named it Penicillin. In the year 1943 the group of investigators E. Chain, H. W. Florey and E. P. Abraham succeeded to isolate Penicillin G (**1**) (Figure 1), and postulated the structure of penicillin derivatives **2** (Figure 2).[2] In 1945 Hodgkin and Law could obtain the X-Ray crystal analysis of Penicillin G (**1**).[3]



1

Figure 1. Penicillin G.

During the nineteenfifties Cephalosporin derivatives **3** were isolated (Figure 3),[4] after *Cephalosporium acremonium* was isolated by Brotzu from the sea near a sewer outlet off the Sardinian coast. Crude filtrates of this fungus were found to inhibit the growth of some bacteria and to cure infections in humans.

In the subsequent decades, the researchers working with the microbiological sources as well as in the synthetic field could collect a very large number of β-lactam antibiotics. Sometimes the addition of side chains to natural nuclei made possible to produce semisynthetic compounds with greater antibacterial activity than that of the parent natural substance.

The actually available β-lactam antibiotics could be separated in nine classes: Penicillins **2**, Cephalosporins **3**, Penems **4**, Clavulanic acid **5**, *trans*-Carbapenems **6**, *cis*-Carbapenems **7**, en-Carbapenems **8**, Nocardicines **9**, Monobactams **10** (Figure 2).

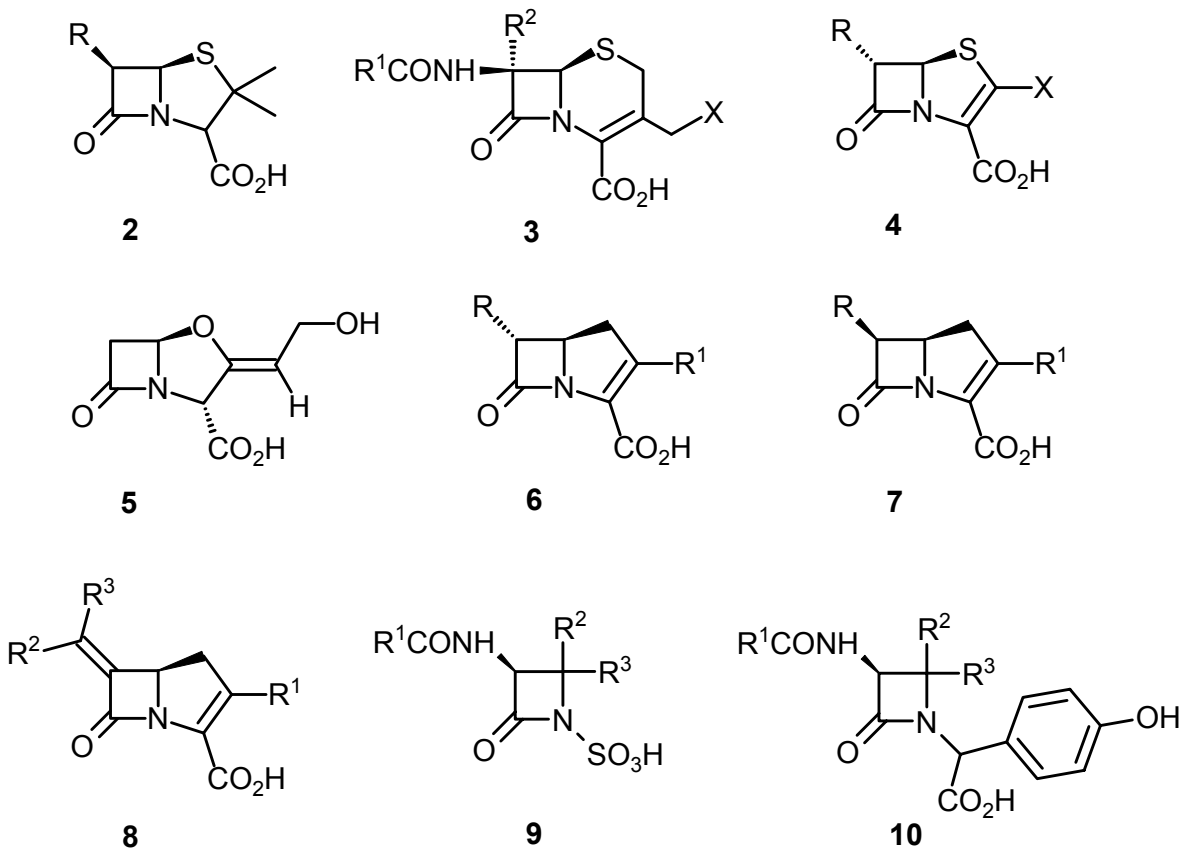


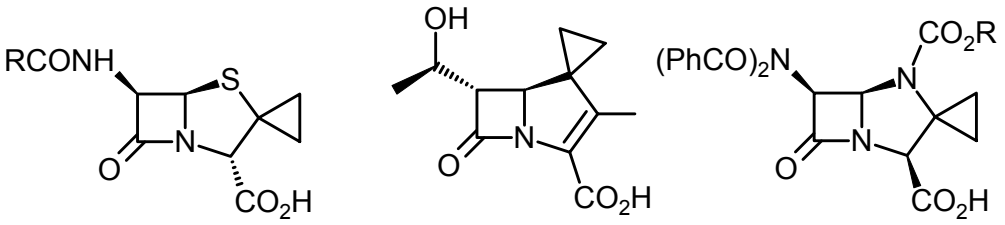
Figure 2. Basic structures of the most important classes of β-lactam antibiotics.

A typical aspect of the research in this field is the limited number of original skeletons. The class of antibiotics received its name from the four-membered heterocycle, the β-lactam ring. This 2-azetidinone skeleton is the center of the activity respect to biological substrates.[5]

The antibacterial activity derives from inhibition of enzymes, called "Penicillin binding proteins" (PBPs) that are important for the peptidoglycan layer construction, by stabilyzing the bacterial membrane. These enzymes are transpeptidases and interact with the β-lactam ring through amide bond breaking (N1-C2 fragmentation). The reactivity toward PBPs is strongly influenced by the presence of substituents on the β-lactam or by eventually present fused rings.[6] The latter ones can increase the ring strain energy and so, favour the interaction with the transpeptidases, whose activity release this additional strain.[5,7]

Because of its unusual electronic and sterical properties, expecially cyclopropyl rings are able to influence the conformational constraint of a molecule and so its biological activity.[6] For this reason, the spirocyclopropane unit has been several times introduced onto β-lactam antibiotics skeletons, trying to modify their reactivity, respect to biological systems.

The spirocyclopropane has been introduced on the five-membered ring in penicillin derivatives **11**,[8,9] in carbapenems **12**[10] and in azapenames **13**[11] (Figure 3).

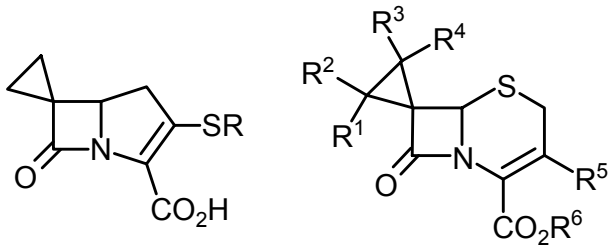


11 **12** **13**

Figure 3. β-Lactam antibiotics containing a spiroanellated cyclopropyl moiety.

A geminal disubstitution is known to generate a decrease in angle deformation, incurred upon a cyclization (Thorpe-Ingold effect). In analogy, a spirocyclopropane ring, resembling this kind of substitution, gives to the system an additional strain, which is expected to be released in the interaction toward the transpeptidases.

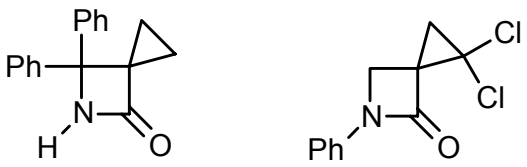
For this reason the spirocyclopropane moiety has already been introduced on the 2-azetidinone ring in penem systems **14** and cephem systems **15** (Figure 4).[12]



14 **15**

Figure 4. β-Lactam antibiotics in which the cyclopropane ring is spirofused to the β-lactam ring.

Some monocyclic spirocyclopropanated β-lactam derivatives **16** and **17** have also already been prepared by carbene addition to a preformed heterocycle, containing an exocyclic double bond (Figure 5).[13]



16 **17**

Figure 5. First examples of monocyclic spirocyclopropanated 2-azetidinones.

Already in the middle of the last century, the first strains of bacteria became resistent against penicillin, requiring the discovery and development of new derivatives. During the years bacterial resistance against the β-lactam antibiotics continues to increase at a dramatic rate. Although most bacteria contain PBPs, β-lactam antibiotics cannot kill or inhibit all bacteria and various mechanisms of bacterial resistance to these agents are operative. Because the β-lactam antibiotics inhibit many different PBPs in a single bacterium, the affinity for β-lactam antibiotics of several PBPs must decrease for the organism to be resistant. Altered PBPs with decreased affinity for β-lactam antibiotics are acquired by homologous recombination between PBP genes of different bacterial species. Other instances of bacterial resistance are caused by the inability of the agent to penetrate to its site of action.

Bacteria can as well destroy β-lactam antibiotics enzymatically. β-Lactamases are capable of inactivating certain antibiotics and may be present in large quantities in the cell.

For this reason new classes of antibiotics are nowadays applied in medicine as for example Aminoglycosides, Tetracyclines, Macrolides in combination with the traditionally widely used β-lactams.

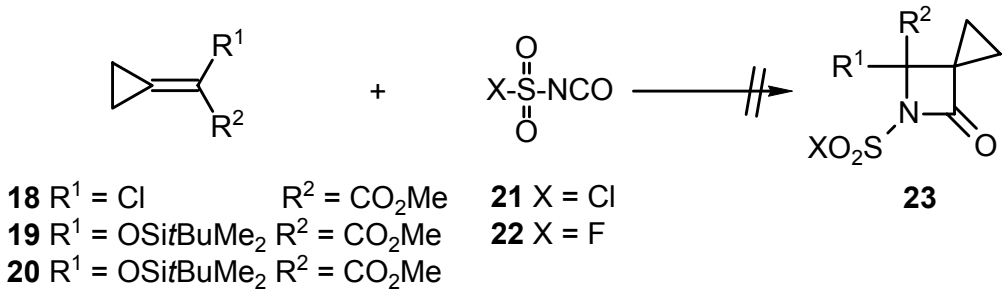
In this sense the exploitation of combinatorial chemistry is very important and with that, the rapid access to differently substituted molecules, once the necessary type of structure has been recognized. Random screening allows the selection of the best structure and in addition the best substitution pattern.

Even if the oriented synthesis of β-lactam structures, with the aim to prepare a special antibiotic, might look like an overcome research, it may not be forgot how useful are this derivatives as intermediates for the organic synthesis. In fact, every single bond in a β-lactam can selectively be cleaved,[14] favoring the 2-azetidinone nucleus for various applications.[15] α- and β-amino acids, peptides, peptidomimetics, but also several kinds of heterocycles can be prepared. The expression *"β-lactam synton method"*[16] is generally accepted for all that synthetical methodologies based on β-lactam ring-fragmentations.

For all this application the presence of the cyclopropyl ring offers new interesting hints, but of course it does require more complicated synthetical approaches to the reactive nucleus.

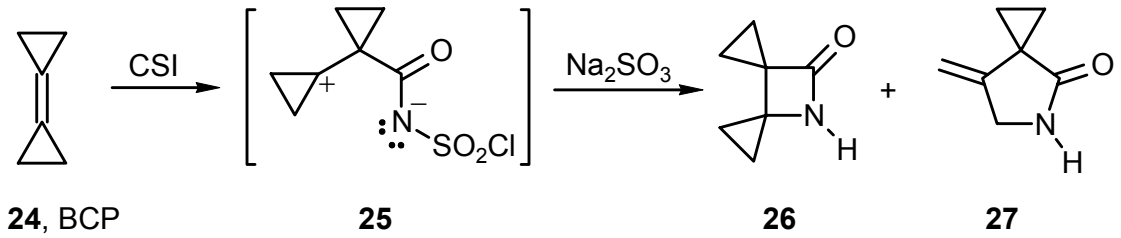
If a cyclic molecule is chosen as a target, it is possible to obtain it *via* cycloaddition of two fragments or *via* cyclization of a preformed chain.

An attempted approach to monocyclic spirocyclopropane-2-azetidinones by [2+2] cycloaddition has already been described previously, using different alkylidenecyclopropanes and reactive sulfonyl isocyanates as, for example, chloro- or fluorosulfonylisocyanates (**21,** CSI or **22**, FSI). Methyl 2-chloro-2-cyclopropylideneacetate (**18**) does not react with CSI, even under high pressure, and other derivatives (**19-20**) just decompose, under these harsh conditions (Scheme 1).[17]



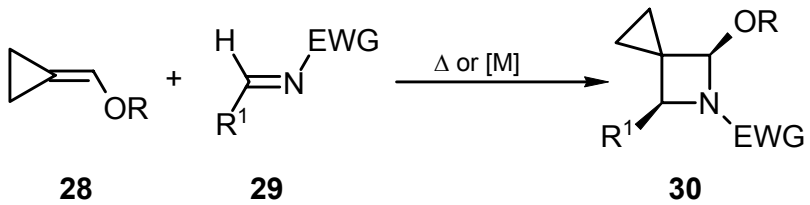
Scheme 1. Attempted [2+2] cycloadditions of alkylidenecyclopropanes onto activated isocyanates **21** and **22**.

When bicyclopropylidene (**24**),[18] is added to CSI, the cyclopropyl cation rest in the zwitterionic intermediate **25**, rearranges and the desired 3,4-dispirocyclopropane-2-azetidinone **26** is formed just in a mixture with the γ-lactam **27** (Scheme 2).[19]



Scheme 2. [2+2] Cycloaddition of bicyclopropylidene (**24**) to chlorosulfonylisocyanates (CSI).

A more promising, but not fully investigated, way of synthesis, developed by de Meijere, Yamamoto et al.,[20] consists in the thermal or metal-catalyzed [2+2] cycloaddition of alkoxy-methylenecyclopropanes **28** to acceptor substituted imines **29** (Scheme 3).



Scheme 3. Synthesis of substituted 3-spirocyclopropane-azetidines 30.[20]

The oxidation of the alkoxy group to a carbonyl group may offer a rather facile two-step access to 3-spirocyclopropanated 2-azetidinones.

Because of the easy interconversion between β-amino acids and β-lactams, cyclopropyl-modified β-alanines[21] **31** can also be imagined as precursors for the synthesis of spirocyclo-propanated monocyclic β-lactams **33** (Figure 6).

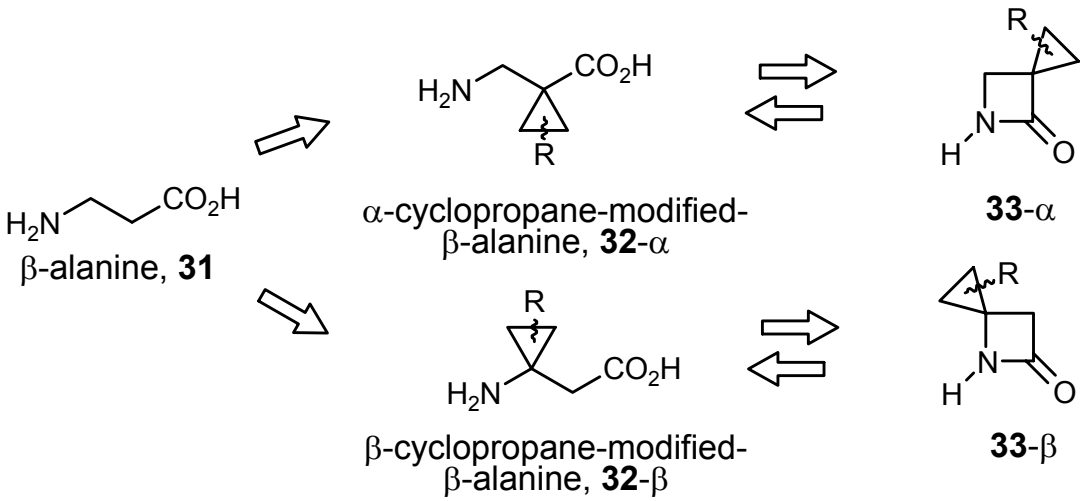
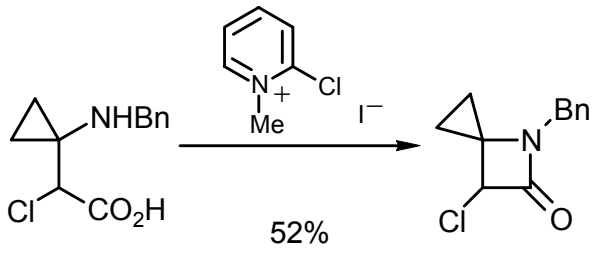


Figure 6. α- or β-Cyclopropyl-modified β-alanine interconversion with 3- or 4-spiro-cyclopropanated β-lactams **33**-α or -β, respectively.

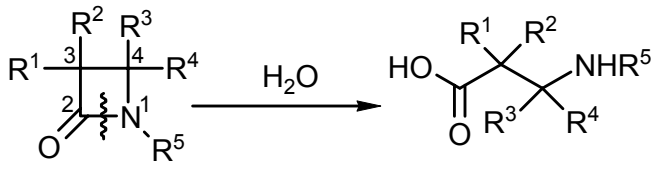
The synthesis of a spirocyclopropane-anellated β-lactam **35,** has been described by de Meijere et al.,[22,23] through cyclization of the β-alanine derivative **34** (Scheme 4).



34 **35**

Scheme 4. Synthesis of a 4-spirocyclopropanated-2-azetidinone **35**.

Since β-lactams may be considered as cyclized forms of β-amino acids in which the amino and the carboxyl groups are simultaneously protected, an application of the *"β-lactam synton method"*[16] is the ring opening at the N1-C2 bond for the synthesis of β-amino acids.[24]
Starting from the pioneer work of Bose,[25] cleavage of the amide bond (N1-C2) has been the subject of many investigations. It is well known that cleavage of the 2-azetidinone ring **36**, with nucleophilic reagents including water, usually takes place at the N1-C2 bond (Figure 7).



36 **37**

Figure 7. N1-C2 opening of the β-lactam ring leading to β-amino acids.

β-Amino acids are also present in nature, even as components of naturally occurring biologically active peptides,[26] and their incorporation into peptides of pharmacological interest has often been found advantageous in terms of biological activity and metabolic stability.[27]
Taxol (**38**), which is the lead compound applied for the cancer chemotherapy, consists of a (–)-*N*-benzoyl-(2*R*,3*S*)-3-phenylisoserine side chain, and a second part, called 10-deacetylbaccatin, presenting the diterpenic, more complex structure. The β-amino acidic chain, essential for Taxol (**38**) biological activity, is normally synthetically coupled with the precursor 10-deacetylbaccatin, obtained from natural sources (Figure 8). The natural reserve are scarce and not easily accessible. This process has consequently sparked the interest in the field of α-hydroxy-β-amino acids.[28] α-Hydroxy-β-amino acids, for example, are also present in various peptidic enzyme inhibitors such as Bestatin (**39**) (Figure 8).[29]

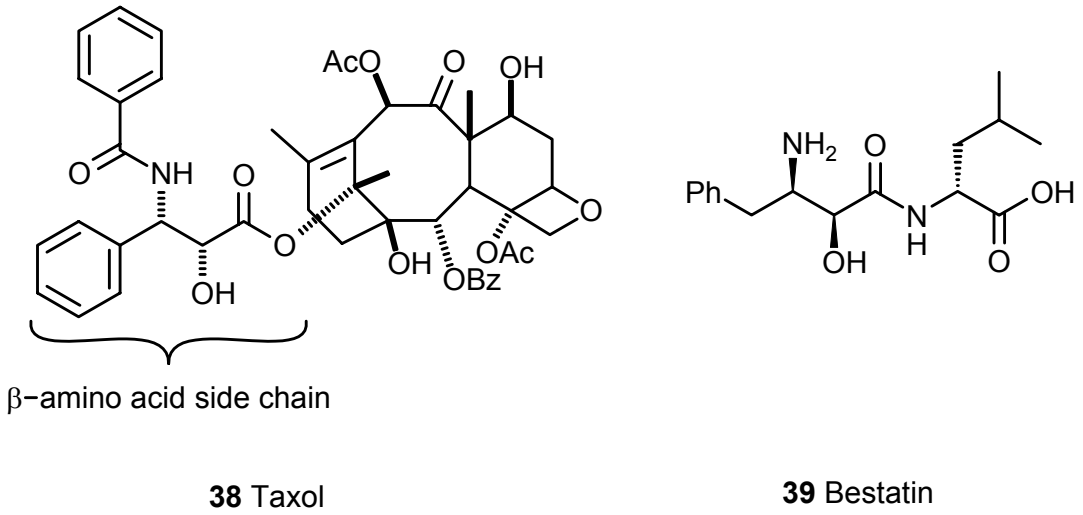


Figure 8. Bestatin and Taxol are important biologically active molecules, both containing β-amino acid moieties.

In addition, recent studies concerning oligo-β-peptides have revealed new opportunities for the development of specific helical conformations and β-sheet type structures.[27]
Oligomers **40a-d**, derived from geminally C(α)-disubstituted β-amino acids ($\beta^{2,2}$-units), have been prepared from 1-(aminomethyl)cyclopropanecarboxylic acid (**41**).[30]

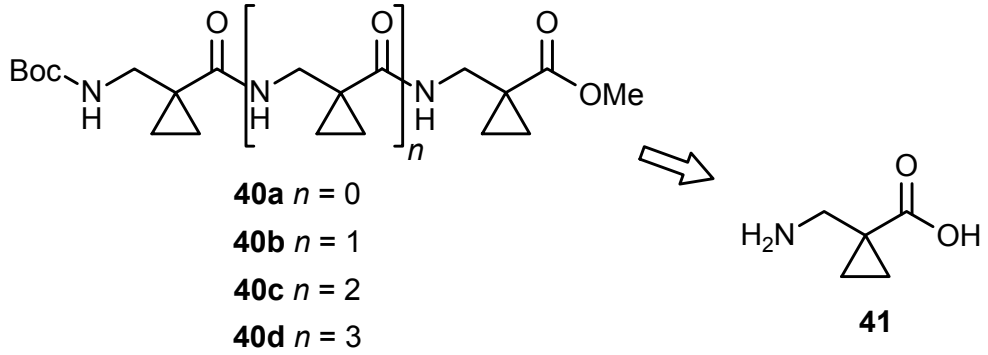


Figure 9. β-Oligopeptides **40** consisting of 1-(aminomethyl)cyclopropane carboxylic acid (**41**) units.

The presence of an additional anchor on the β-amino acid chain, like a cyclopropane ring, has shown interesting consequences for the helical supramolecular structure. Cyclopropane-carbonyl derivatives (like cyclopropyl carbenium ions) are subjected to a hyperconjugative effect, favoring the so-called bisecting conformation. Both the *s* - *cis* and the *s* - *trans*-form are stabilized by interaction of the HOMO, π-type Walsh orbitals of the cyclopropane ring

with the LUMO, antibonding π* orbital of the C=O bond. A search in the *Cambridge Files* (CCDC) for structures like **42**, has shown that seven of the eleven there found, have the *s - cis* conformation, that, according to theoretical and spectroscopic data, is the more stable.[31] All cyclopropane-carbonyl moieties in the oligomers **40** have the *s - cis* conformation **42a** with the C=O group pointing over the three-membered ring. The rotational barrier for the interconversion of the s - *cis* **42a** and *s - trans* **42b** conformations is about 6 Kcal/mol and becomes zero, increasing the ring-size from cyclopropane to cyclohexane (Figure 10).

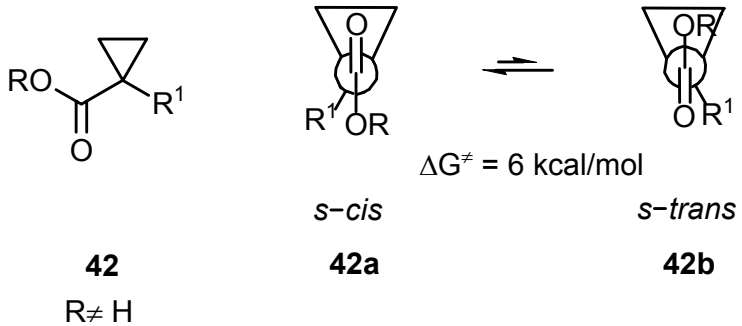


Figure 10. Conformational considerations about cyclopropylcarbonyl moieties **42**.

The bisecting effect and the large exocyclic bond angle (120 º) are proposed to provide the "ordering elements", which lead to the secondary structural motif in the oligomers **40a-d**. Five atoms H–N–C(O)–C(H_2)–C(H_2) of a single amino acid result fixed in a common plane by H-bonding, to form a boat-like eight-membered ring with three atoms N(H)–C=O of a neighbor unit (Figure 11).

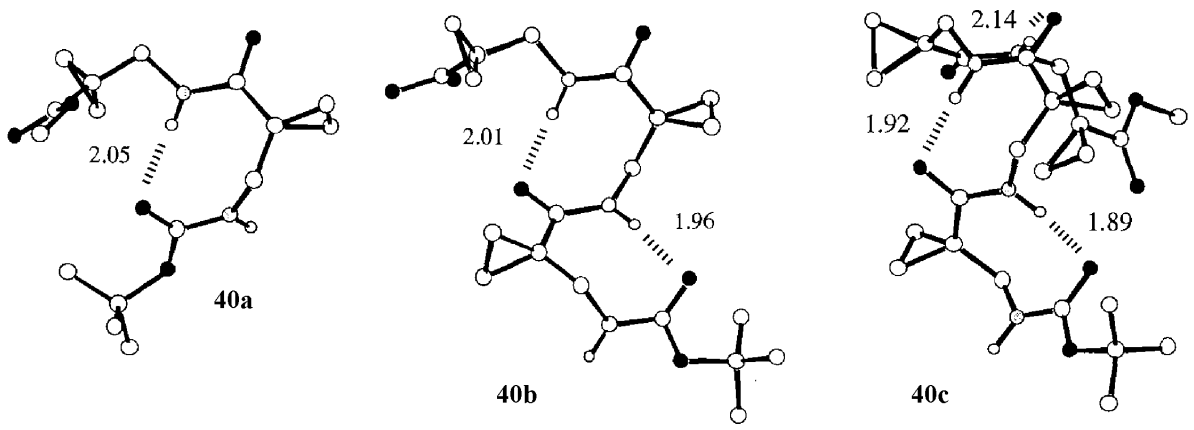


Figure 11. X-Ray crystal structures of the β-amino-acid derivative $\beta^{2,2}$-di-, $\beta^{2,2}$-tri- and $\beta^{2,2}$-tetrapeptides **40a**, **40b**, and **40c**.[30]

It might be interesting to examin if this regularity and high organization are reproducible in much longer chains, like in a poly-β-amino acid.

In this sense this work is directed towards the following aims:

- The synthesis of several different 3-spirocyclopropanated-2-azetidinones **33**-α, formally derived from 1-(aminomethyl)cyclopropane carboxylic acid (**41**).

- Development of a fast one-step synthesis of 3-spirocyclopropanated-2-azetidinones **33**-α, using the microwave technology, and optimization of the reaction conditions.

- The synthesis of dipeptides containing α-cyclopropyl-β-alanine units **32**-α, via N1-C2 ring-opening in the synthesized β-lactams **33**-α, using the amino group nucleophilicity of amino esters.

- The attempt to obtain spirocyclopropanated-poly-β-propiolactams **40**.

B. Main Part

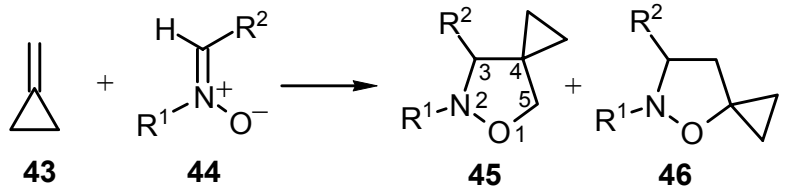
1. Synthesis of 3-Spirocyclopropanated-2-Azetidinones

1.1. Considerations

Because of the wide-ranging significance of β-lactams in organic synthesis and in pharmacology, the development of efficient methods for their preparation plays an important role.

The feature of a spirocyclopropyl ring bonded to the azetidinone renders this molecular skeleton even more interesting. From the pharmacological point of view the spiro-fused small ring might be important, because it is expected to introduce additional ring-strain,[5-7] which is decisive to favour the interaction with the PBPs, and so the weakening of the cell-wall in bacteria. From the synthetic point of view the spirocyclopropane moiety would enrich in number and in interest the applications included in the *"β-lactam synton method"*.[16]

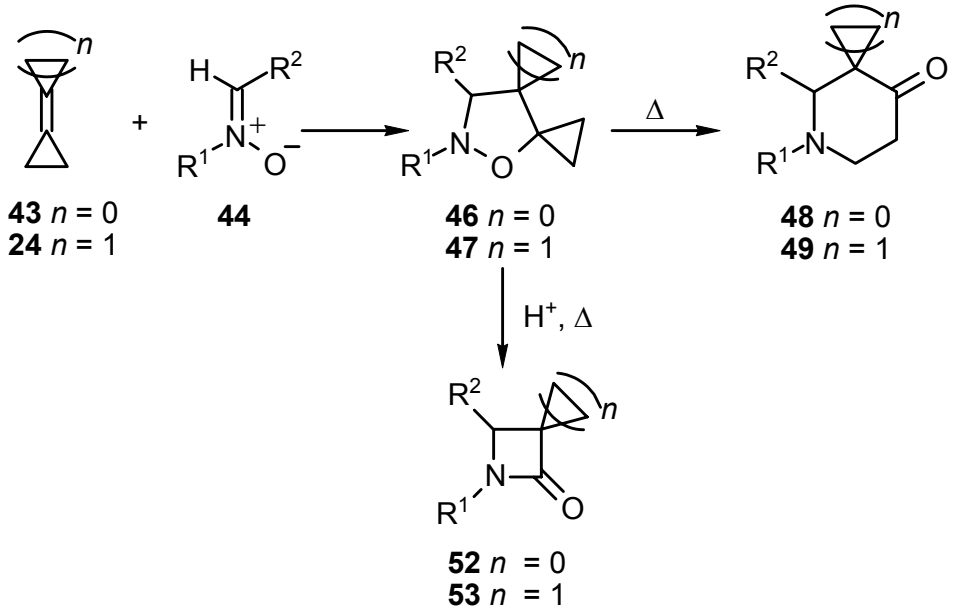
Brandi et al. have investigated the chemistry of nitrones **44**, whose 1,3-dipolar cycloaddition to the alkylidenecyclopropane **43** leads to a mixture of isoxazolidine regioisomers **45** and **46**, where the cyclopropane ring is located on the C-4 or on the C-5, respectively (Scheme 5).[32]



Scheme 5. 1,3-Dipolar cycloaddition of nitrones **44** to methylenecyclopropane (**43**).

As the result of the combination of the strained small ring and the adjacent weak N-O bond, isoxazolidines **46** show a distinctive chemistry and can be converted by thermal rearrangement, which is generally named Brandi-Guarna reaction,[33] to tetrahydropyridones **48** (Scheme 6).[32]

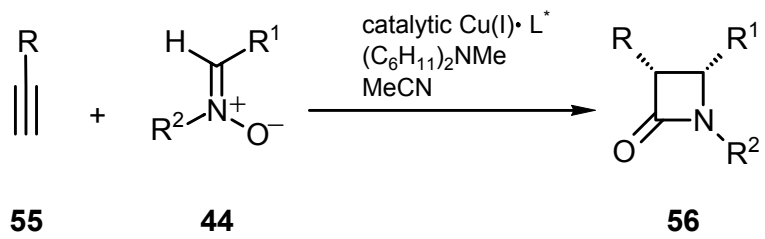
More recently it was reported by the same group, that 5-spirocyclopropanated isoxazolidines **46**, can rearrange to azetidin-2-ones **52**, by heating in the presence of a protic acid (Scheme 6).[34]



Scheme 6. Formation of isoxazolidines 46 and 47 and their possible rearrangement pathways.

If bicyclopropylidene (**24**) is used as dipolarophile, the cycloaddition with nitrone **44** furnishes **47** as only product. The thermal rearrangement of **47** leads to spirocyclopropanated tetrahydropyridones **49**.[32] If the same isoxazolidine **47** is heated under acidic conditions, should occur the rearrangement to β-lactam **53**, still bearing a spirocyclopropane ring in α - position respect to the carbonyl group (Scheme 6).

A variation of the nitrone chemistry in which β-lactams are the final products, is the copper catalyzed Kinugasa-Miura reaction.[35a,b] Terminal alkynes **55** react with 1,3-dipoles **44** in the presence of a catalytic amount of the metal to give azetidin-2-ones **56** (Scheme 7). An enantioselective variation of this process has been recently presented by Fu et al., who prepared several β-lactams **56** introducing in the synthesis the use of chiral bis(azaferrocene) ligands.[35c]



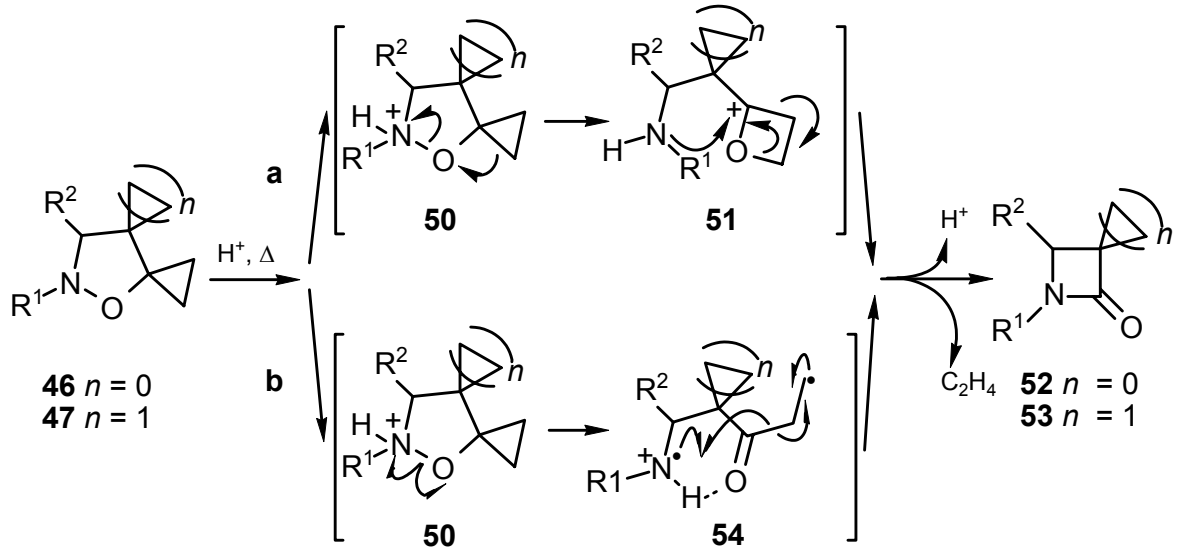
Scheme 7. The Kinugasa-Miura reaction.

However even this newly developed method cannot substitute the rearrangement of 5-spiro-cyclopropanated isoxazolidine, when 24 is used as dipolarophile. The final structure complexity (product 53, Scheme 6) is increased from the presence of a spirocyclopropyl group, which cannot be introduced with the Kinugasa-Miura reaction.

1.2. Background and Mechanicistic Aspects

Two different mechanisms have been proposed for the acid catalyzed rearrangement of **46** and **47**. After protonation of the nitrogen atom to form **50**, the reaction can proceed following a ionic mechanism (Scheme 8, pathway a), in which the labile N-O bond is broken and a contemporary ring enlargement takes place, with formation of an oxetane in **51**. The latter can undergo a retro Paternó-Büchi reaction, which liberates ethylene, while the carbonyl group is attacked from the lone electron pair of the nitrogen atom to give the four-membered rings **52** or **53**, respectively (Scheme 8).

As a second possible pathway a radical process can be imagined (Scheme 8, pathway b). After protonation of the nitrogen atom to form **50**, the N-O bond can break homolitically, followed by rearrangement of the cyclopropyloxy radical to an oxoethyl radical. Supported by a strong intramolecular hydrogen bond, radical ricombination in **48**-**49** is suppressed, producing exclusively ring closure to the two β-lactams **52** and **53**, which is accompanied by liberation of ethylene (Scheme 8).[34a]



Scheme 8. Proposed mechanisms for the rearrangement under acidic conditions.

Detailed studies have shown that the radical mechanism (Scheme 8, patway b), seems to be the most probable one.[34b] Cyclization reaction of aminium radical intermediates as **54** are already well known from the Hoffman-Löffler reaction.[36]

Some other known ring contraction from isoxazolidine to β-lactam have been reported,[37-39] but no cyclopropyl-fragment rearrangements have ever been involved. The known examples refer to 5-nitroisoxazolidine **57**, 5-cyanoisoxazolidine **58** and 5-thioisoxazolidines **59**, whose rearrangement requests strongly basic conditions to deprotonate the position 5 (Figure 12).

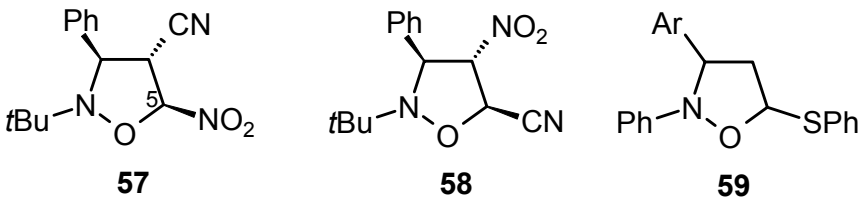


Figure 12. Isoxazolidine capable to rearrange to β-lactams.

The rearrangement of isoxazolidine **46** and **47** is totally new in synthetic chemistry, but reminds a process that occurs in nature: the enzymatic conversion of 1-aminocyclopropane carboxylic acid ACC **60** into ethylene during the plant growth regulation and the maturation of fruits (Figure 13).[6b,40]

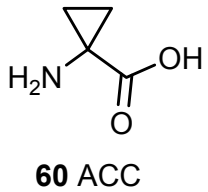


Figure 13. 1-Aminocyclopropane carboxylic acid.

1.3. Synthesis of Nitrones

In order to obtain 3-spirocyclopropanated-2-azetidinones several differently substituted nitrones **44a-i** have been prepared (Figure 14), and subsequently their 1,3-dipolar cycloadditions with bicyclopropylidene (**24**) have been performed.

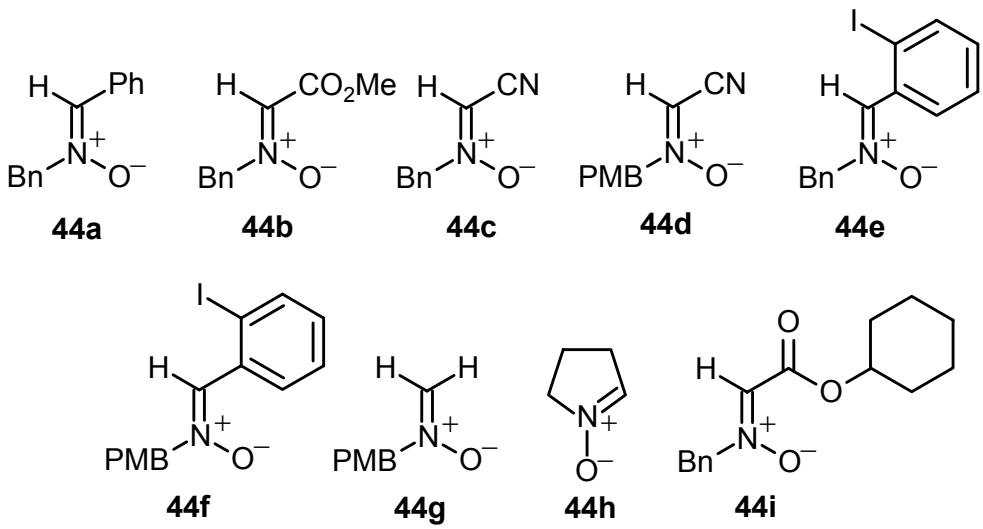
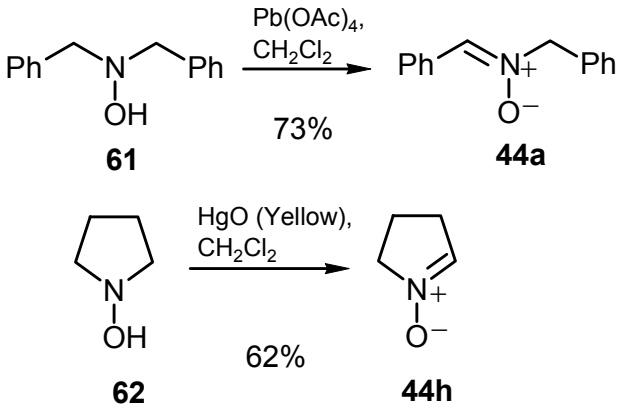


Figure 14. Structures of synthetized nitrones used for the 1,3-dipolar cycloaddition.

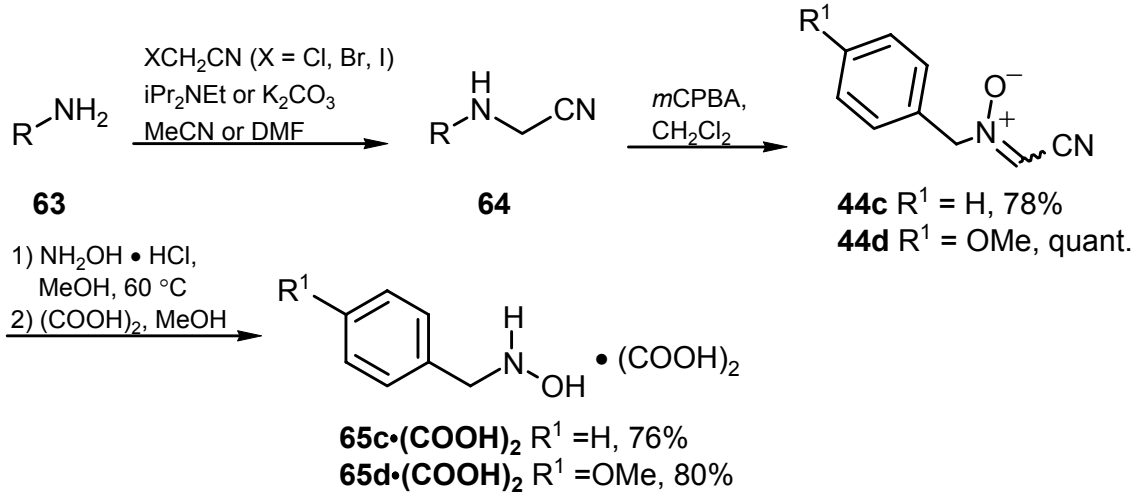
The nitrones **44a** and **44h** were obtained under dehydrogenation of *N*,*N*-dibenzyl-hydroxylamine[41] and *N*-hydroxypyrrolidine.[42] The reactions were performed using lead acetate and yellow mercury oxide, respectively, following known procedures (Scheme 9).



Scheme 9. Synthesis of nitrones by oxidation of symmetrically *N*,*N*-disubstituted hydroxylamines **61** and **62**.

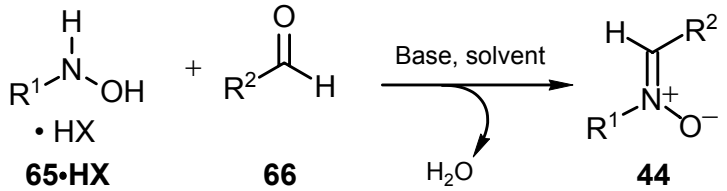
The *N*-benzyl-*C*-cyanonitrone (**44c**) and *N*-(*p*-methoxybenzyl)-*C*-cyanonitrone **(44d)** were obtained using the first two steps of a process, that has been developed for the synthesis of hydroxylamines starting from primary amines. This method consists in three steps. First the primary amine **63** is mono-cyanomethylated, the formed adduct **64** is oxidized to the nitrone using *m*CPBA and finally the hydroxylaminolysis is achieved with hydroxylamine hydrochloride (Scheme 10).[43]

The reported yield for **44c** (78%) was reproduced and nitrone **44d** was obtained as a 1:4 mixture of *E*- and *Z*-isomers, in quantitative yield.



Scheme 10. Synthesis of primary *N*-hydroxylamine salts **65**.

The hydroxylamine **65c·(COOH)$_2$** was prepared reproducing the reference yield (76%),[43] while **65d·(COOH)$_2$** was obtained with the same method in 80% yield (Scheme 10). The nitrones **44b**,**e-g**, **i** were obtained by means of traditional condensation methods, i.e. reacting *N*- alkyl hydroxylamines with a carbonyl derivative (Scheme 11).[44]



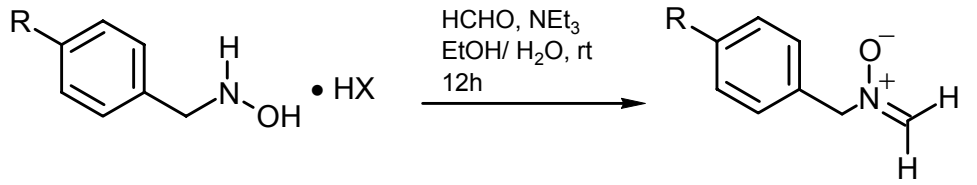
Scheme 11. Synthesis of nitrones **44b, e-g, i** *via* condensation of a *N*-hydroxylamine salt **65·HX** with a carbonyl derivative **66**.

Entry	**44**	R^1	HX	R^2	Solvent	Temp [°C]	Base	Yield [%]
1	**b**	Bn	$(COOH)_2$	CO_2Me	Et_2O	0	K_2CO_3	63
2	**e**	Bn	HCl	oC_6H_4I	EtOH	100	NaOAc	68
3	**f**	PMB	$(COOH)_2$	oC_6H_4I	THF	25	Et_3N	89
4	**g**	PMB	$(COOH)_2$	H	EtOH	25	Et_3N	88
5	**i**	Bn	—	CO_2cHex	C_6H_6	80	—	76

Table 1. Conditions for the condensation to nitrones **44**.

The conditions necessary for the condensation (Scheme 11) depended on the derivative and varied in a wide range from 0 ºC in dry ether for **44b**, to refluxing benzene requested for the synthesis of **44i** (Table 1).

N-(*p*-Methoxybenzyl)-methyleneamine-*N*-oxide (44g) was synthesized according to the literature, but using triethylamine as the base instead of sodium acetate (Scheme 12 and Table 1, Entry 4).[45] Formaldehyde-*N*-benzyloxime (44j) was not isolated following the literature procedure.[46] The white solid initially obtained after solvent evaporation under reduced pressure, turned to a yellow oil, during the attempt to collect it from the flask with a simple trituration-suction procedure (Scheme 12).



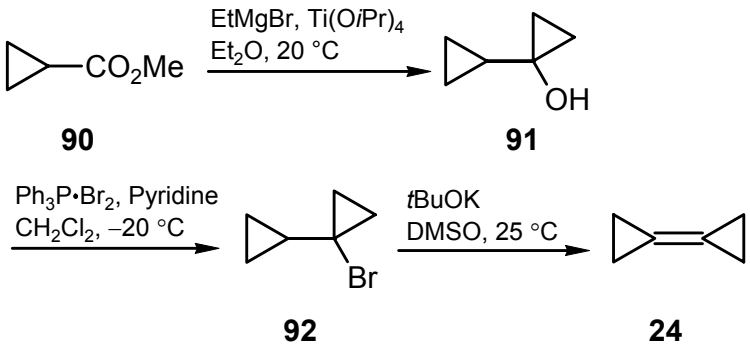
65c•HCl R = H
65d•(COOH)$_2$ R = OMe

44j R = H,
44g R = OMe, 88%

Scheme 12. Condensation of formaldehyde 66-H as a solution 8 M in water to give nitrones 44g and 44j.

1.4. 1,3-Dipolar Cycloaddition of Nitrones to Bicyclopropylidene

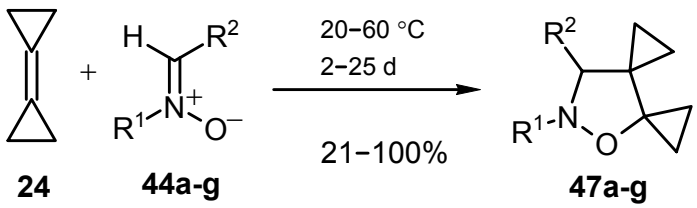
The olefine **24** is easily available even in large scale for synthetic purposes, with a relatively new three steps synthesis.[18] This process was optimized by de Meijere et al., and applies as key step the Ti-mediated cyclopropanation, developed by Kulinkovich (Scheme 13).[47]



Scheme 13. Synthesis of bicyclopropylidene **24**.

Bicyclopropylidene (**24**) shows a distinctive behaviour respect to other tetraalkyl-substituted olefines, which are not able to undergo 1,3-dipolar cycloadditions with nitrones.[48]

As could be expected according to literature precedents,[34,49,50] 1,3-dipolar cycloaddition of **44a-g,**[41-47] to **24** in benzene or without any solvent, at ambient or elevated temperature, gave the corresponding cycloadducts **47a-g** in 21 to 100% yield (Scheme 14 and Table 2). As in the previous cases, very long reaction times were necessary for these cycloadditions to go to completion, because they have to be carried out at moderate temperatures to avoid the thermal rearrangement of the cycloadducts at elevated temperature.[32]



Scheme 14. 1,3-Dipolar cycloaddition of nitrones **44a-g** onto bibyclopropylidene (**24**).

Entry	**44**	R^1	R^2	Temp.[°C]	Time[d]	**47**	Yield [%]
1	**a**	Ph	Bn	60	25	**a**	95
2	**b**	CO_2Me	Bn	45	2	**b**	100
3	**c**	CN	Bn	20	8	**c**	94
4	**d**	CN	PMB	20	8	**d**	100
5	**e**	*o*IC_6H_4	Bn	60	6	**e**	88
6	**f**	*o*IC_6H_4	PMB	65	4	**f**	75
7	**g**	H	PMB	20	6	**g**	21

Table 2. Reaction conditions and yields for the 1,3-dipolar cycloadditions to bicyclopropylidene (**24**) of nitrones **44a-g**.

The structures of **47a-g** were assigned on the basis of their NMR spectra. However, initially no signals of the benzylic CH_2 group as well as nitrile and quaternary spirocyclopropane carbon atoms in position 4 were found in the ^{13}C NMR spectra of 8-benzyl-9-cyano-8-aza-7-oxadispiro[2.0.2.3]nonane (**47c**) and 9-cyano-8-(4-methoxybenzyl)-8-aza-oxadispiro-[2.0.2.3]nonane (**47d**) at room temperature under standard conditions. Additional high temperature measurement (100 °C in $C_2D_2Cl_4$) were run to complete the characterization. The

structural features of the cycloadduct **47b** were established by an X-Ray crystal structure analysis (Figure 15).

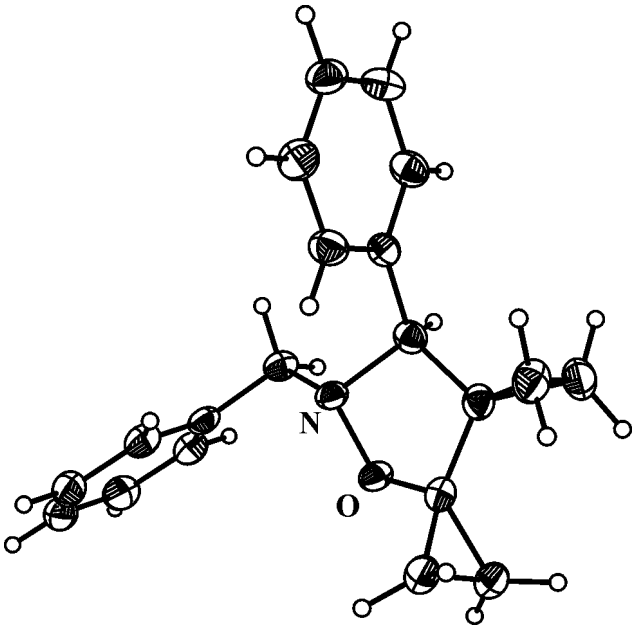
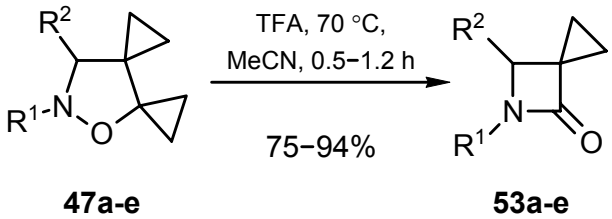


Figure 15. X-Ray crystal structure analysis of 8-benzyl-9-phenyl-8-aza-7-oxadi-spiro[2.0.2.3]nonane (**47a**).

1.5. Thermal Rearrangement of Spirocyclopropanated Isoxazolidines Under Acidic Conditions

Treatment of the compounds **47a-e** with trifluoroacetic acid (TFA) in acetonitrile at 70 °C furnished the corresponding 3-spirocyclopropanated β-lactams **53a-e** in yield ranging from 75 to 94%, respectively, after purification by column chromatography (Scheme 15 and Table 3). Thus, the overall yields of this two step process from nitrones **44a-e** to 5-azaspiro[2.3]hexan-4-ones **53a-e**, range from 70 to 94 %.

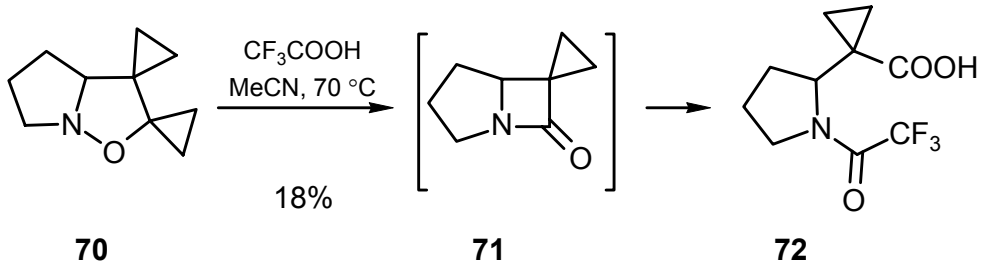


Scheme 15. Thermal rearrangement under acidic conditions for the cycloadducts **47a-e**.

Entry	**47**	R^1	R^2	Time[h]	**53**	Yield [%]
1	**a**	Ph	Bn	3	**a**	75
2	**b**	CO_2Me	Bn	12	**b**	78
3	**c**	CN	Bn	12	**c**	75
4	**d**	CN	PMB	12	**d**	94
5	**e**	*o*IC_6H_4	Bn	1	**e**	89

Table 3. Reaction conditions and yields for the rearrangements to **53a-e**.

In the case of the pyrroline-*N*-oxide (**44h**), the cycloadduct **70**,[50] afforded, instead of the expected carbapenem **71**, the β-homoproline derivative **72** (Scheme 16). This kind of process has already been observed for the thermal rearrangement under acidic condition of 5-spiro-cyclopropanated isoxazolidines **46** derived from cyclic nitrones.[51]



Scheme 16. Rearrangement of **70** and ring-opening to *N*-protected β-amino acid **72**.

The final product **72** is supposed to be formed through a carbapenem intermediate **71**, that immediatly undergoes opening of the β-lactam ring, followed by acylation of the nitrogen atom with trifluoroacetate. An analogous reaction has previously been observed by Stoodley et al. for β-lactams fused to five-membered ring in the presence of trifluoracetic acid at room temperature.[52]

2. New One-Pot Approach to 3-Spirocyclopropanated Monocyclic β-Lactams

2.1. Considerations

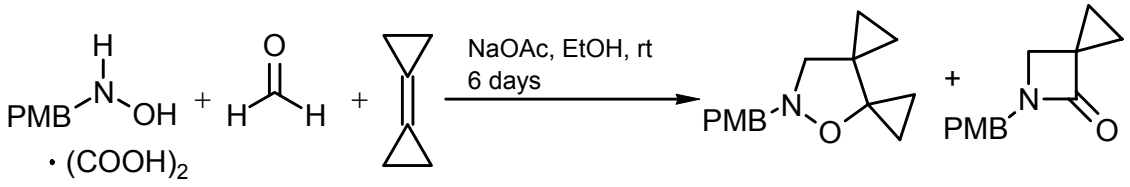
Nitrone **44j**, synthesized by condensation of formaldehyde **66**-H with N-benzyl hydroxylamine hydrochloride **65c·HCl** in the presence of a base,[46] started decomposing during the isolation procedures (Scheme 12, Chapter 1).

Moreover, when *N*-(*p*-methoxybenzyl)-methyleneamine-*N*-oxide (**44g)** was subjected to 1,3-dipolar cycloaddition to bicyclopropylidene (**24)**, the yield was just 21%, while the results normally obtained in the cycloadditions of linear nitrones to **24** vary in the range between 75 and 100% (Table 1, Chapter 1).

In order to get over the problems, which in the case of nitrones derived from formaldehyde **66**-H, are related with their instability, a different strategy was applied. The nitrones **44g** and **44j** were used *in situ* in the cycloaddition to the dipolarophile, like a more detailed literature research suggested.[53,54] The generation of nitrones, by condensing a hydroxylamine **65·HX** and an aldehyde **66** (Scheme 10, Chapter 1), and their *in situ* addition to a dipolarophile has recently been applied in the synthesis of skeletal congeners of antitumor, antibiotic natural products.[55] Nevertheless this method is used since longer, when the carbonyl derivative is particularly reactive, as in the case of formaldehyde.[54]

2.2. Development of a Selective One-Pot Synthesis for 2-Azetidinones

When the hydroxylamine **65d·(COOH)$_2$**, formaldehyde **66**-H and the base sodium acetate were stirred in a sovirell glass with the dipolarophile **24** for 6 days at room temperature, a mixture of the expected cycloadduct 8-(*p*-methoxybenzyl)-7-oxa-8-aza-di-spiro[2.0.2.3]nonane (**47g**) and surprisingly, of the relative β-lactam derivative 5-(*p*-methoxy-benzyl)-5-azaspiro[2.3]hexan-4-one (**53g)** was obtained, in 8 and 22% yield respectively, after purification by column cromatography (Scheme 17).

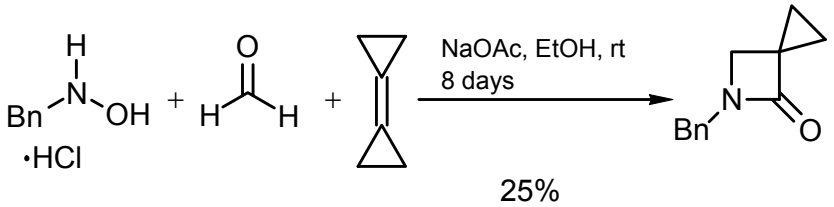


65d•(COOH)$_2$ **66**-H **24** **47g**, 8% **53g**, 22%

Scheme 17. Synthesis of **47g** and **53g**, by BCP addition to the *in situ* generated nitrone **44g**.

Probably, the acidity furnished by the buffered system acetate/ ammonium gave the product **53g**, whose formation requires the rearrangement of **47g** in the presence of acidic protons (Scheme 8, Chapter 1). To test the riproducibility of this result, further studies were conducted.

The experiment was repeated with benzylhydroxylamine hydrochloride (**65c·HCl**) and with the same aldehyde **66**-H. 5-Benzyl-5-azaspiro[2.3]hexan-4-one **53j** was obtained after 8 days at room temperature, in a comparable yield (25%) with **53g** but without any trace of the relative isoxazolidine (Scheme 18).



65c•HCl **66**-H **24** **53j**

Scheme 18. Synthesis of **53j**, by BCP addition to the *in situ* generated nitrone **44j**.

When the procedure was run at higher temperature (45 or 50 °C) or at high pressure (10 Kbar), no significant improvement in yield were achieved, although the β-lactam was always the only isolated product (Table 4). No mixture with isoxazolidines, piperidones or other fragmentation products was observed.

Reagents	Conditions temp[°C]/pressure[KBar]	Time[d]	Product	Yield [%]
65d•(COOH)$_2$ (1 eq), **24** (1.5 eq), NaOAc (1 eq), **66**-H (1.5 eq)	45/ 1	7	**53g**	30
65c•HCl (1 eq), **24** (1.5 eq) NaOAc (1 eq), **66**-H (1.5 eq)	50/ 1	5	**53j**	33
65d•(COOH)$_2$ (1 eq), **24** (2 eq) NaOAc (1 eq), **66**-H (2 eq)	25/ 10	1	**53g**	28
65c•HCl (1 eq), **24** (2 eq) NaOAc (1 eq), **66**-H (2 eq),	25/ 10	1	**53j**	22

Table 4. Attempts to improve the selective one-pot synthesis of 2-azetidinones **53g** and **53j**.

2.3. Extension of the One-Pot 2-Azetidinone Synthesis to Different Substrates

In view of the multiple beneficial effects of microwave heating on organic synthetic transformations reported in recent years,[56] we tried out the possibility of reducing the reaction times by using microwaves. The main difference with the traditional sources of energy (oil and sand bath, heating mantles, etc) is that reactants and solvents are heated directly, without the vessel's interference. By the use of microwave technology, the energy is more efficiently used and the necessary amount of it is furnished in a faster and more homogeneous way.

After the first application in a laboratory in 1986,[57] and after the exhaustive treatments about interections between bodies and microwave-rays dued to Rippel[58] and Mingos,[59] modern single mode cavity ovens have been produced from several companies, with the achievement of high reproducibility and predictability in results.

The *in situ* 1,3-dipolar cycloaddition of the generated unstable and reactive nitrones[53] **44g** and **44j** to bicyclopropylidene (**24**) could be enhanced by the use of microwave technology in terms of velocity and yields.

For this reason several different conditions were tried. In particular, the stechiometry was changed and the reaction temperature increased, this last parameter allowing a shorter reaction time.

The hydroxylamines salt **65d·(COOH)$_2$** and **65c·HCl** gave the desired products in better yields in comparison to the previously used methods (Scheme 17 and 18 and Table 4), and in much less time (from 6 days to 45 minutes for **53g** and from 8 days to 60 minutes for **53j**) (Table 5).

Reagents	Temperature [°C]	Time[min]	Product	Yield[%]
65d•(COOH)$_2$ (1 eq), **24** (2 eq) NaOAc (1 eq), **66**-H (2 eq)	60	60	**53g**	26
65d•(COOH)$_2$ (2 eq), **24** (1 eq) NaOAc (2 eq), **66**-H (2 eq)	80	45	**53g**	53[a]
65c•HCl (1 eq), **24** (2 eq) NaOAc (1 eq), **66**-H (2 eq)	60	195	**53j**	34
65c•HCl (1 eq), **24** (2 eq) NaOAc (1 eq), **66**-H (2 eq)	100	60	**53j**	48
65c•HCl (2 eq), **24** (1 eq) NaOAc (2 eq), **66**-H (2 eq)	100	60	**53j**	68[a]

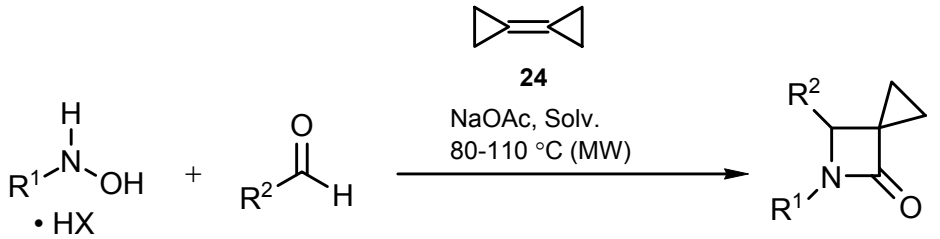
[a] GP 6, exp.part

Table 5. Attempts to increase the microwave assisted one-pot synthesis of 2-azetidinones **53g** and **53j**.

The best results were obtained using a twofold excess of hydroxylamine salt **65**, of formaldehyde **66**-H and of sodium acetate respect to the olefine **24**. Using microwaves, 2-azetidinone **53g** was thus obtained in 53% yield, instead of 30%, running the reaction at 80 ºC for 45 min, instead of 7 days (see Table 4) and compound **53j** was obtained in 68% yield, running the reaction at 100 ºC for 60 min (without microwaves the yield was 33% after 5 days) (see Table 4). It is noteworthy that hydroxylamines **65**, formaldehyde **66**-H, and

sodium acetate are used in excess, but they are cheaper, and often commercially available, while bicyclopropylidene (**24**) needs more complex steps to be prepared.[18]

The next step was to prove the generality of the new process for preparing 3-spiro-cyclopropanated-2-azetidinones in a single step. The reactions were performed in sealed vessels for the microwave system from Personal Chemistry. The reaction volumes were never bigger than 5 mL and high concentrations (0.75 to 2.5 M) of reactants were used to accelerate the cycloaddition step. The solid starting materials were usually not completely solved. The reaction controls were performed with NMR measurments because the limiting reagent (the olefine) is volatile and cannot be observed on TLC. Once found the right conditions, the reaction was repeated to determine the yield.
Several different hydroxylamines **65** and carbonyl compounds **66**, **73-76** were heated under microwave irradiation in the presence of **24** (see Experimental Part, General Notes).

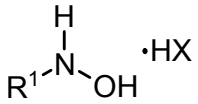


65•HX	**66**-H	R^2 = H	**53**	R^2 = H
	73-Me	R^2 = CO_2Me	**77**-Me	R^2 = CO_2Me
	73-cHex	R^2 = CO_2cHex	**77**-cHex	R^2 = CO_2cHex
	73-Et	R^2 = CO_2Et	**77**-Et	R^2 = CO_2Et
	74	R^2 = CHO	**78**	R^2 = CHO
	75	R^2 = *m*-$NO_2C_6H_4$	**79**	R^2 = *m*-$NO_2C_6H_4$
	76	R^2 = *o*-IC_6H_4	**53e**	R^2 = *o*-IC_6H_4

Scheme 19. One-Pot three component synthesis of 3-spirocyclopropanated-2-azetidinones under microwave heating.

The hydroxylamine salts **65c, f**, and **g** are commercially available, while **65d, e, h, i** were prepared following known procedures.[43,60] *N*-Monosubstituted hydroxylamines are sold and isolated like salts, because of their low stability in the free form (Table 6).

65	R^1	HX
c	Bn	HCl
d	PMB	$(COOH)_2$
e	Bnh	HCl
f	*t*Bu	HCl
g	Me	HCl
h	Ph	HCl
i	$pBrC_6H_4$	HCl



65

Bnh = $CH(Ph)_2$

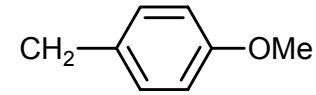
PMB = 

Table 6. Hydroxylamines used in the one-pot process for the synthesis of β-lactams.

Azaspiro[2.3]hexanones **53g,j** and **53e**,**f**-H were obtained in yields ranging from 49 to 73 %, with formaldehyde **66**-H (a titrated solution of formaline was used)[61] and changing the nature of the hydroxylamine **65·HX** (Table 7, Entry 1-4).

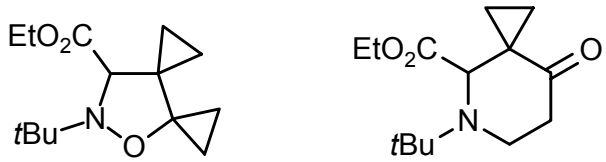
In the case of **53j** and **53e**-H also paraformaldehyde was used, but lower yields were obtained in comparison with the stabilized solution of the monomer in water: respectively 56 and 37%, instead of 68 and 49% (Table 7, Entry 1 and 3).

The use of glyoxylates **73**-Me and **73**-Et gave also good results. The pure methyl derivative **73**-Me[62] gave **77d**-Me in 78% yield (Table 7, Entry 7). Ethyl glyoxylate **73**-Et was used as a commercially available solution in toluene. The latter did not interfere with the reaction course, that led to the desired products **77c**-Et in 72% yield and **77f**-Et in 53% yield (Table 7, Entry 5 and 6).

Entry	Start. Mat.	R^1	R^2	Time [min]	Temp [°C]	Prod.	Yield[%]
1	**65d** + **66**-H	PMB	H	45	80	**53g**	53
2	**65c** + **66**-H	Bn	H	60	100	**53j**	68
3	**65e** + **66**-H	Bnh	H	30	100	**53e**-H	49
4	**65f** + **66**-H	*t*Bu	H	30	80	**53f**-H	73
5	**65c** + **73**-Et	Bn	CO_2Et	15	80	**77c**-Et	72
6	**65f** + **73**-Et	*t*Bu	CO_2Et	105	80	**77f**-Et	53
7	**65d** + **73**-Me	PMB	CO_2Me	120	80	**77d**-Me	78

Table 7. One-pot three-component reaction under microwave heating for the direct conversion of **65**, carbonyl derivatives and bicyclopropylidene (**24**) to 3-spiro-cyclopropanated 2-azetidinones **53** (see Scheme 19).

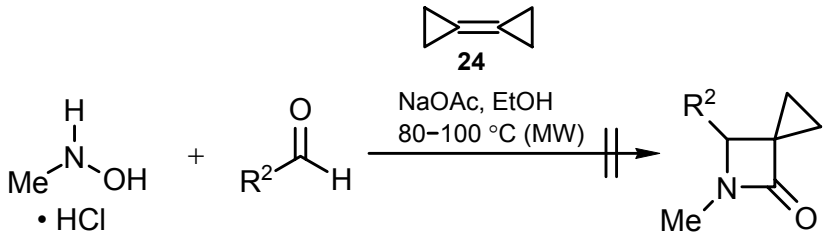
In this last case, the yield was lower because side products were found: some unreacted isoxazolidine **47f**-Et and the thermal rearrangement product 5-*tert*-butyl-8-oxo-5-aza-spiro[2.5]octane-4-carboxylate **49f**-Et (Figure 16). Changing the conditions to lower temperature and longer reaction time did not avoid the formation of these side products. Probably, the bulk of the *tert*butyl group creates hinderance and makes the nitrogen protonation not so easy like with other *N*-protecting groups.



47f-Et **49f**-Et

Figure 16. Side products in the reaction of ethyl glyoxylate **73**-Et and *tert*-butylhydroxylamine **65f·HCl**.

The very good results obtained with the hydroxylamines **65c-f** were not repeated with **65g-i**. With *N*-methylhydroxylamine hydrochloride, formaldehyde (**66**-H) and **24**, the yield of the corresponding *N*-methylazetidinone **53g**-H was at best 10% and using the same hydroxyl-amine derivative with ethyl glyoxylate (**73**-Et) and **24**, the corresponding azetidinone **77g**-Et could not be detected even in the crude reaction mixture (Scheme 20).



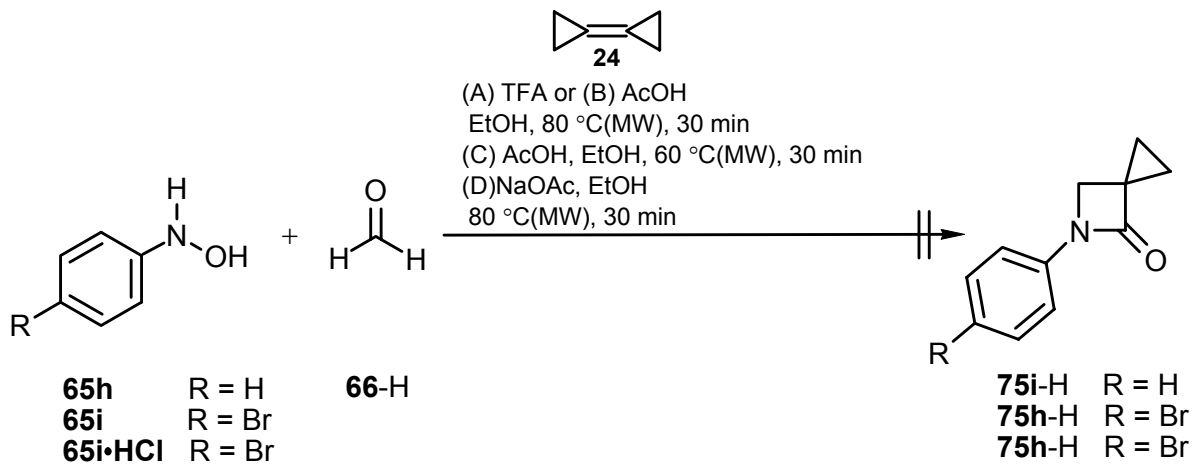
65g **66**-H R^2 = H **53g**-H
73-Et R^2 = CO_2Et **77g**-Et

Scheme 20. Methyl hydroxylamine hydrochloride **65g·HCl** reactions.

The particularly reactive methyl nitrone, formed in the first step of the cascade, is probably involved in further equilibria with water or with the hydroxylamine itself, like reported in a work of Fornefeld,[54b] so that the compond **53g**-H was found just in traces.

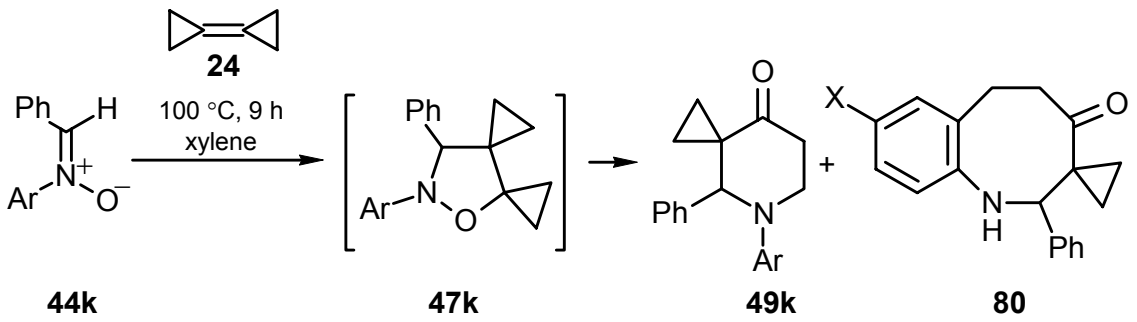
When *N*-aryl hydroxylamines **65h** and **65i** were heated in the microwave oven with formaldehyde **66**-H in ethanol under different conditions, the reaction control via NMR

spectrometry never presented signals, which could be assigned to defined structures and also attempts to solve the mixture by column cromatography failed (Scheme 21).



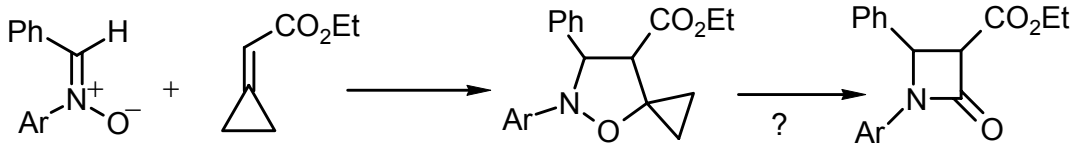
Scheme 21. Attempts of preparation of *N*-aryl substituted β-lactams **75h,i**-H.

Bicyclopropylidene (**24**) has already been added to nitrones **44k**, derived from *N*-aryl hydroxylamines, but the cycloadduct **47k** has never been isolated. The mixture of **24** and **44k** has been heated at high temperature to isolate the thermal rearrangement products **49k** and **80** (Scheme 22).[32b]



Scheme 22. 1,3-Dipolar cycloaddition of *N*-aryl nitrones 44k to BCP (24).

Isoxazolidines of type **83** have already been isolated from the cycloaddition of nitrones **44k** to alkylidenecyclopropane **82**, but their thermal rearrangement under acidic conditions for the synthesis of *N*-aryl substituted β-lactams of type **84** has never been tried (Scheme 23).[63]



44k **82** **83** **84**

Scheme 23. 1,3-Dipolar cycloaddition to 82 and the never tried rearrangement to 84 under traditional heating in the presence of acid.

It can be supposed that the electron pair on the nitrogen atom in isoxazolidines **47k** is too much influenced by the aromatic ring, to be prone to protonation, and this can be the reason for the unsuccessful attempts of synthesis under the one-pot microwave-assisted process (Scheme 21).

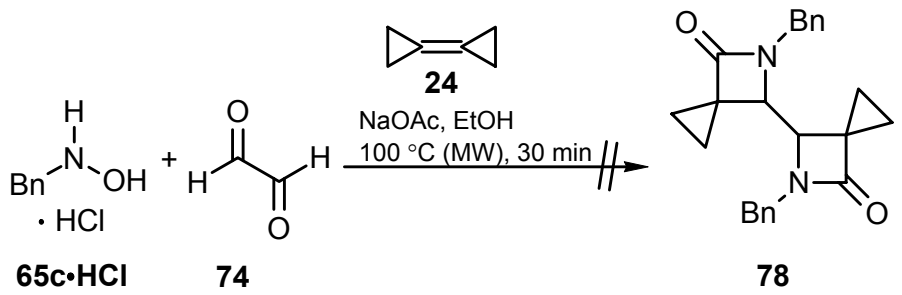
Moreover *N*-aryl hydroxylamines are known to be particularly sensitive materials.[64] They are susceptible toward oxidation, particularly in the presence of a base, and are also prone toward redox disproportionation reaction: ionic or zerovalent metals can catalyze the formation of nitrosobenzene and aniline derivatives, starting from 35 °C. Impurities deriving from zerovalent metals are impossible to avoid because these are necessary for the synthesis.[64a]

Even acidic conditions can damage *N*-aryl hydroxylamine, that can in this conditions rearrange to aminophenol, when not para-substituted.[64b]

From the complex mixtures obtained after the microwave experiments and their work-up, it was very hard to distinguish if there were a particular problematic step, within the requested ones for the one-pot procedure, or if the hydroxylamines themselves decomposed, under one of the possible suggested processes, eventually catalyzed from the microwave irradiation.

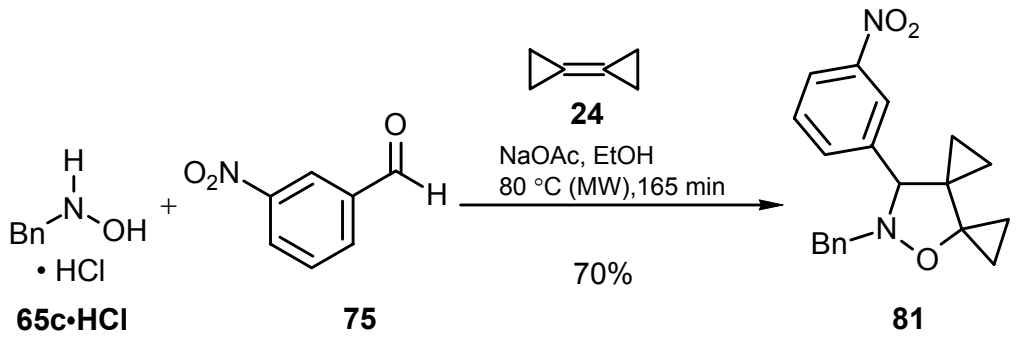
In order to extend to different substrates the discovered microwave assisted process for the synthesis of β-lactams, were tried also the activated carbonyl derivatives **73**-cHex and **74**, **75, 76**.

Glyoxale **74** gave no positive results and the symmetrical expected product **78** was not recovered after column cromatography of the crude mixture obtained by heating **65c·HCl**, **74** and sodium acetate, under microwave irradiation (Scheme 24).



Scheme 24. Failed attempt to follow the one-pot microwave assisted procedure with glyoxale 74.

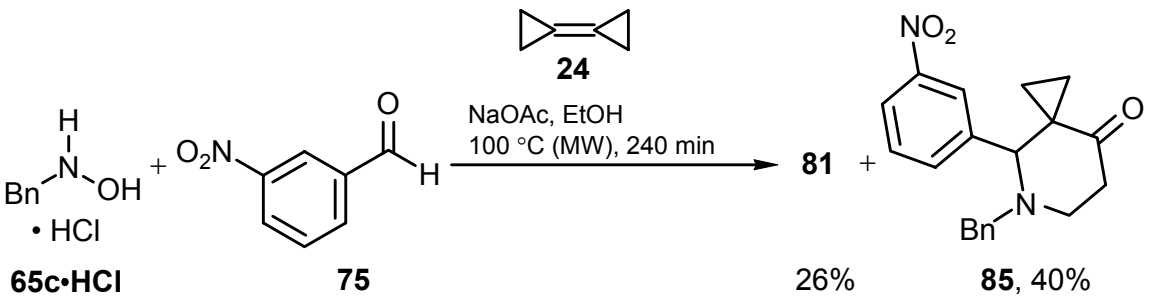
The hydroxylamine **65c·HCl** and the benzaldehyde **75**, heated in the microwave system for 165 min at 80 °C, gave as final product just the cycloadduct **81** in 70% yield (Scheme 25), while no trace of the azetidinone **79** was detected (Scheme 19).



Scheme 25. Synthesis of the adduct 81 under microwave heating.

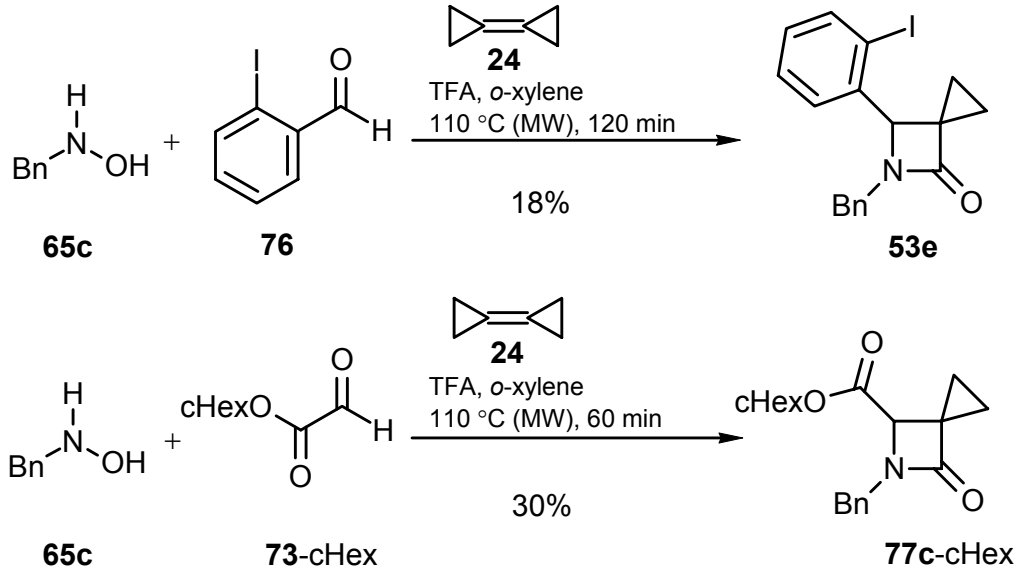
It's well known that the cycloaddition of *C*-aryl-nitrones to bicyclopropylidene are particularly slow and probably this step restrained the intire process.[65]

A higher temperature was tried, with the aim to accelerate the cycloaddition step, but a mixture of cycloadduct **81** and piperidone **85**, respectively in 27% and 40% yield, was obtained after column cromatography (Scheme 25).



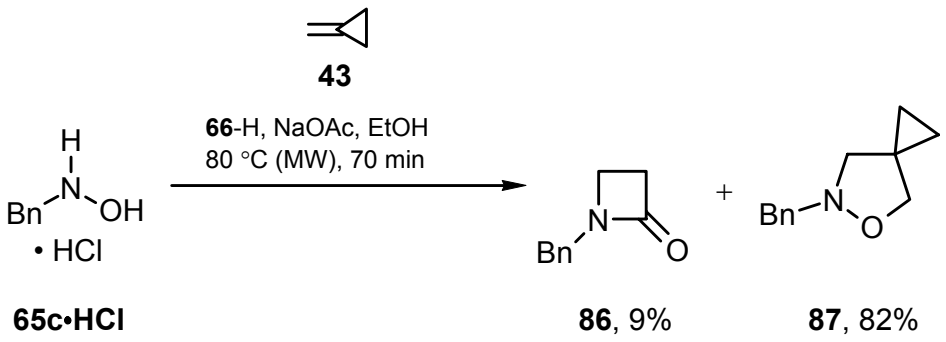
Scheme 26. Partial thermal rearrangement to **85**.

When the strong trifluoacetic acid (TFA) was introduced as the source of protons in the mixture of free hydroxylamine and carbonyl derivative in *o*-xylene, heating at 110 °C, the desired azetidinones **53e** and **77c**-cHex were isolated in 18 and 30% yield, respectively. The aldehyde **76** needed 2 hours, while the more activated glyoxylate **73**-cHex[62] led to the final product in just half that time (Scheme 27).



Scheme 27. Microwave assisted approach to β-lactams **53e** and **77c**-cHex.

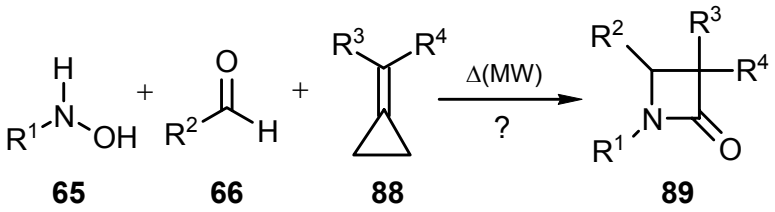
When methylenecyclopropane (**43**)[18] was employed as dipolarophile in this three-component reaction with **65c·HCl** and formaldehyde (**66**-H), the expected product **86** was isolated in only 9% yield along with 4-spirocyclopropaneisoxazolidine (**87**), which was formed along with the fragmented 5-spirocyclopropanated regioisomer, and cannot undergo acid-catalyzed fragmentative rearrangement (Scheme 28).



Scheme 28. One-pot three-component reaction under microwave heating starting from methylencyclopropane **43**.

The identification of the end of the process was particularly treaky, because compound **87** as well as its 5-spiro-regioisomer show rotamers in the NMR spectra, the alkyl signals of which are broad and overlapping. Just after isolating the mixture of regioisomers and measuring a spectrum at 100 ºC, was possible to identify the single signals and to repeat the reaction with the comprehension of its course.

Theorethically, under this strategy could also be synthethyzed 2-azetidinones **89,** lacking in the spirocyclopropane. The synthesis of such derivatives can nevertheless be achieved by different methodologies, that don't need expensive starting material like the alkylidenecyclopropanes **88** (Scheme 29).



Scheme 29. Possible synthesis under microwave assisted one-pot process of general β-lactams **89**.

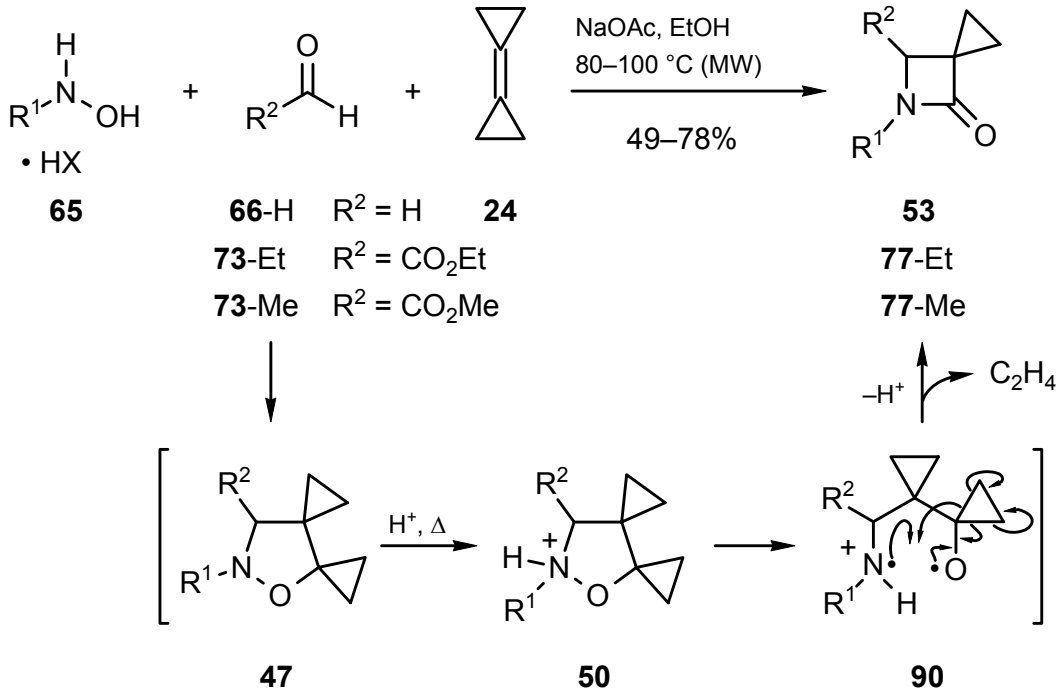
2.4. Conclusions about the newly developed one-pot reaction

Because of the wide-ranging significance of β-lactams, the development of efficient methods for their synthesis is an important objective. The synthesis just proposed (Scheme 19) can furnish monocyclic β-lactam derivatives in one step, by using microwave irradiation and short

times, starting in most cases from commercially available reagents (hydroxylamine **65** and carbonyl derivatives **66**), except the alkylidenecyclopropane **88**. Using bicyclopropylidene **24**, spirocyclopropanated derivatives **53** and **77** can be prepared.

Using as energy source the microwave heating, a cascade of reactions takes place in a well defined sequence, so that it is possible to name it a multicomponent process.[66]

Apparently, the nitrone initially formed from the aldehyde (**66**) and the hydroxylamine (**65**), undergo 1,3-dipolar cycloaddition to **24**, and the resulting isoxazolidine **47**, under the slightly acidic conditions of the hydroxylamine hydrochloride/sodium acetate buffered system fragments via intermediates **50**, **84**[32] to ethylene and the β-lactam **53** (Scheme 30).



65	R^1	HX
a	Bn	HCl
b	PMB	$(COOH)_2$
c	BnH	HCl
d	*t*Bu	HCl

PMB = 4-$MeOC_6H_4CH_2$
BnH = $CHPh_2$

Scheme 30. One-pot three-component reaction under microwave heating for the direct conversion of alkylhydroxylamine hydrochlorides **65**, aldehydes **66-73** and bicyclopropylidene (**24**) to 3-spirocyclopropanated 2-azetidinones **53** and **77**.

The fragmentative rearrangement of 5-spirocyclopropanated isoxazolidines **46** and **47** previously had been carried out with reasonably strong acids such as trifluoroacetic, *p*-toluenesulfonic or hydrochloric acid, like shown in the previous chapter (Scheme 15). To better understand, why this new one-pot three-component reaction worked without any of these strong free acids present, control experiments were carried out with the isolated dispirocyclopropanated **47c**-Et. When the latter compound was heated with added acetic acid in acetonitrile at 70 °C overnight, none of the azetidinone **77c**-Et was detected, but heating **47c**-Et under the same conditions with benzylhydroxylamine hydrochloride **65c·HCl** did furnish **77c**-Et (59%). For the overall transformation to occur, the added sodium acetate is essential as well. An experiment with all the components for the formation of **77c**-Et, except for the added sodium acetate, carried out in the microwave oven, gave no trace of product. In fact, not even the condensation of the hydroxylamine and the aldehyde to the nitrone took place.

Since this one-pot three-component reaction has no precedent, it is difficult to estimate the role of the microwave heating. In any case, it is remarkable that the time required for the overall reaction is never longer than 2 hours, whereas with traditional heating at 45 °C the 1,3-dipolar cycloaddition of the most reactive *N*-methyl-*C*-(ethoxycarbonyl)nitrone onto bicyclopropylidene (**24**) requires 16 d, and at higher temperatures only the corresponding spirocyclopropanated piperidone derivative is formed.[50]

3. Microwave Heating to Accelerate the 1,3-Dipolar Cycloadditions of Nitrones to Bicyclopropylidene

3.1. Considerations

The synthetical methodology based on the nitrone cycloaddition to methylenecyclopropane (**43**) or bicyclopropilydene (**24**), followed by thermal rearrangement of the resulting adducts to give functionalized pyridones (Scheme 6, Chapter 1) has already been demonstrated as a versatile strategy to obtain alkaloids like for example **91** and **92**, or different azaheterocycles like the rare amino acid **93** (Figure 17).[32a]

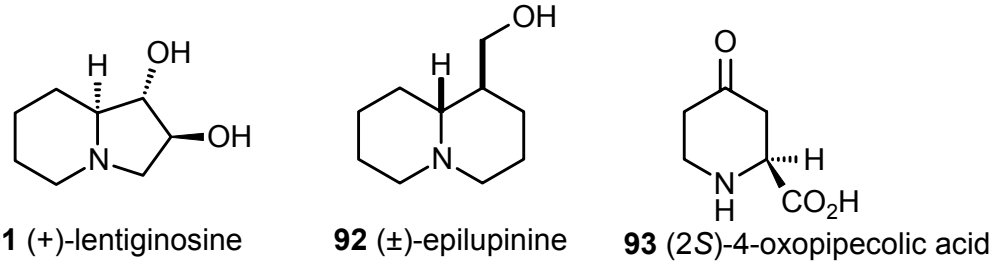


Figure 17. Different natural compounds obtained with the thermal rearrangement of 5-spirocyclopropanated isoxazolidines.

With the same strategy were also prepared biologically active compounds able to cleave a supercoiled DNA plasmid,[67] for their structural analogy with naturally occurring cytotoxic compounds, like illudines **94** and ptaquiloside **95** (Figure 18).

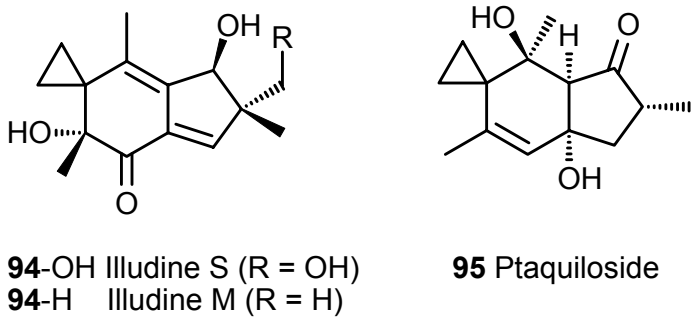
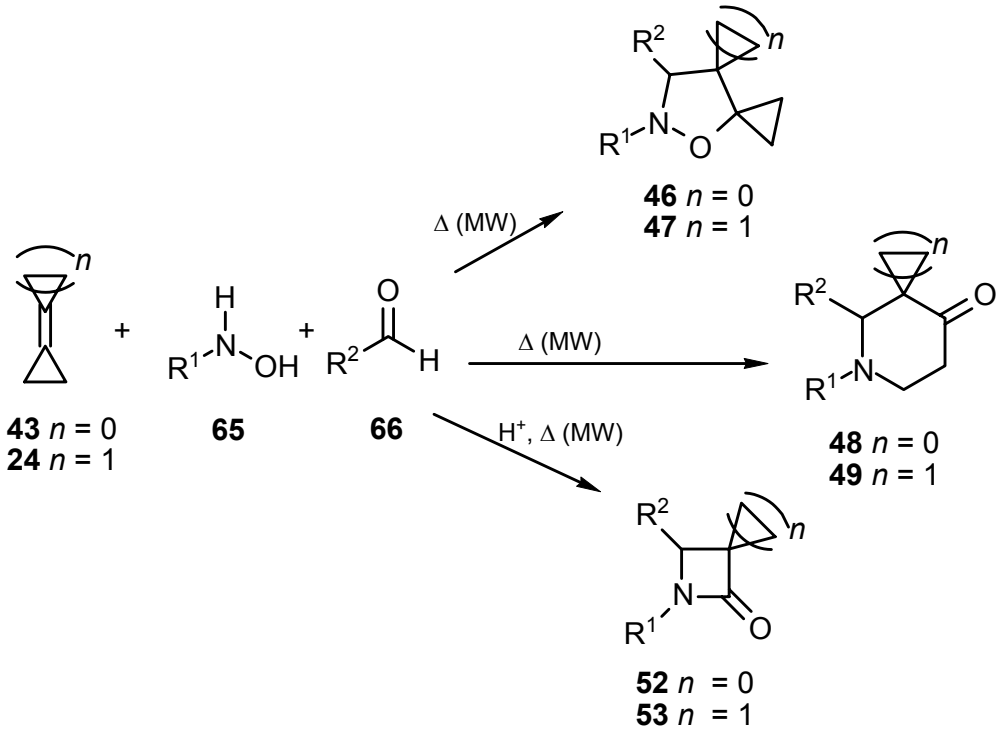


Figure 18. Spirocyclopropanated citotoxic, naturally occurring compounds.

Quite a large number of β-lactams in the spirocyclopropanated form has been prepared, applying the rearrangement under acidic conditions of BCP-derived cycloadducts **47** (Scheme 18, Chapter 1) and that preparation was accelerated and simplified to one-step with

the development of the one-pot microwave assisted synthesis (Scheme 19, Chapter 2). Moreover, it would be interesting to show if it is possible to obtain indipendentely not only the β-lactams **53** but also the isoxazolidine-cycloadducts **46** and **47** or the piperidones **48** and **49**, starting from the same three components olefine, hydroxylamine and carbonyl derivative (Scheme 31). In that case it would be possible the selective synthesis of three different azaheterocycle with the same starting materials, just changing the reaction conditions.



Scheme 31. Possible one pot syntheses of three different kinds of azaheterocycle starting from the same components **65**, **66** in the presence of **24** or **43**, with microwave irradiations.

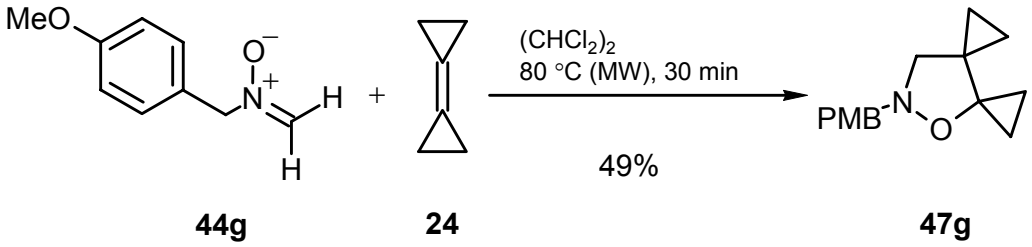
Moreover the cycloaddition of **24** onto nitrones **44** suffers unfortunately of prolongued reaction times. The introduction of microwave technology as source of heat for 1,3-dipolar cycloaddition of **24** and for the rearrangement of the obtained cycloadducts **47**, could probably reduce the time required for these reactions, making the processes faster usable.

3.2. Synthesis of Isoxazolidine or Piperidone Derivatives

In the case of nitrone **44g** it was possible, by selecting the conditions, to obtain indipendentely the cycloadduct **47g** or the piperidone **49g**. The target molecules were prepared, starting from

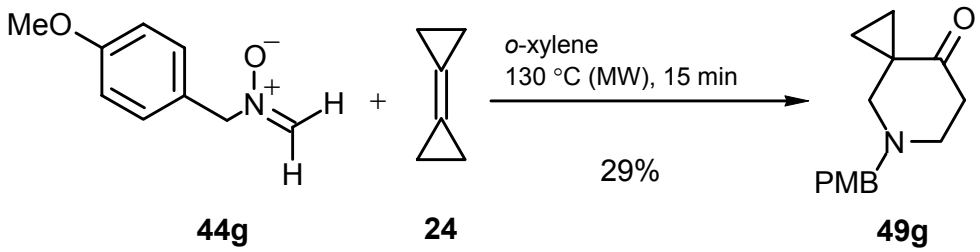
the nitrone (Scheme 32 and 33 for **47g** and **49g**, respectively) or after condensation of hydroxylamine **65d** and aldehyde **66**-H and *in situ* addition to the dipolarophile (Scheme 34 and 35 for **47g** and **49g**, respectively).

N-(*p*-Methoxybenzyl)methyleneamine-*N*-oxide (**44g**) reacted with bicyclopropylidene (**24**) in 30 minutes at 80 °C, using tetrachloroethane as a solvent. After column cromatography the desidered 8-(*p*-methoxybenzyl)-7-oxa-8-aza-dispiro[2.0.2.3]nonane **(47g)** was obtained in 49% yield (Scheme 32).



Scheme 32. 1,3-Dipolar cycloaddition of **44g** and **24** under microwave heating.

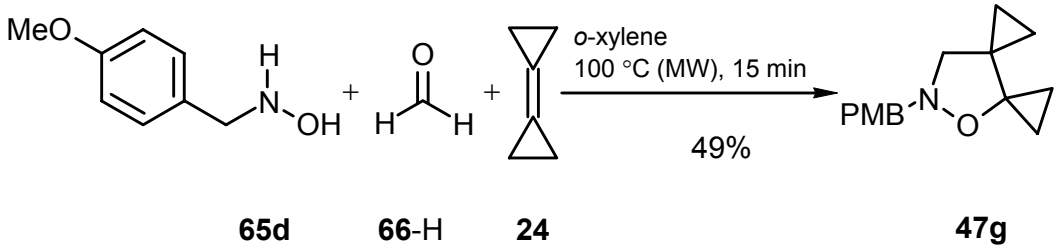
The same components **44g** and **24**, if heated at a higher temperature, led selectively to the thermal rearrangement product 5-(*p*-methoxybenzyl)-5-azaspiro[2.5]octan-8-one (**49g**) in 15 minutes. The yield after purification by column cromatography was 29% (Scheme 33).



Scheme 33. Thermal rearrangement to **49g** under microwave heating.

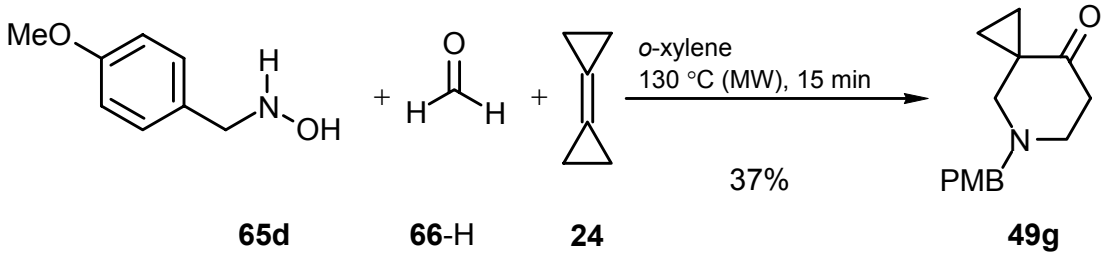
The cycloadduct **47g** and the rearranged product **49g** were obtained as well by the *in situ* generation of the unstable nitrone **44g** but no significant improvement in yield was observed.

For both processes, the free hydroxylamine **65d** was stirred with formaldehyde **66**-H and dipolarophile **24** in the absence of acids. The presence of free protons would in fact favour the rearrangement of the cycloadduct to β-lactams (Chapter 2). When the reaction components were heated for 15 minutes in xylene at 100 ºC, the cycloadduct **47g** was obtained in 49% yield after column cromatography purification (Scheme 34).



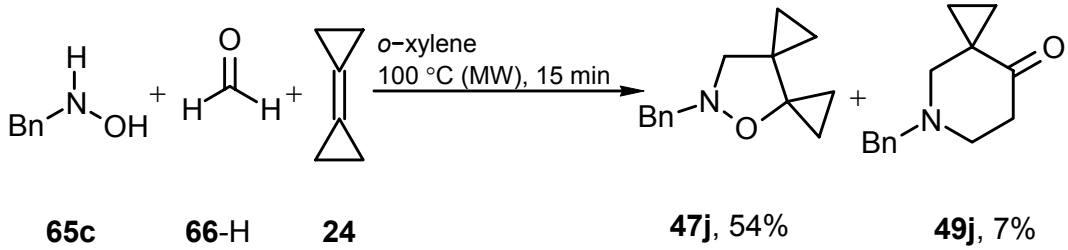
Scheme 34. Generation of the nitrone and *in situ* cycloaddition to **24**.

The same reagents, heated at a higher temperature, gave the piperidone **49g** in 37% yield after purification (Scheme 35).



Scheme 35. Generation of the nitrone and *in situ* thermal rearrangement to **49g**.

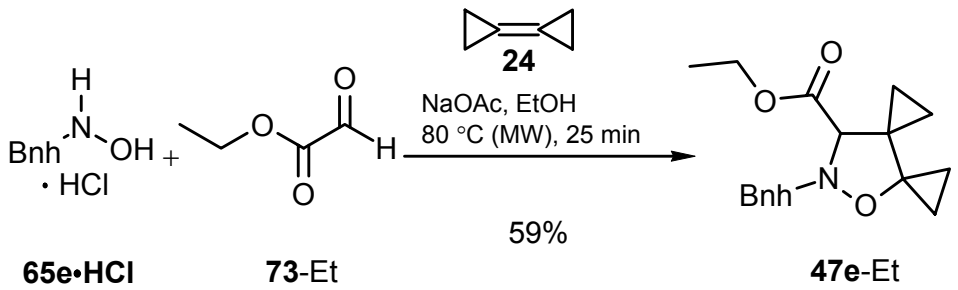
The free *N*-benzyl hydroxylamine (**65c**) as well, reacted with formaldehyde **66**-H and bicyclopropylidene (**24**) to give **47j** in 54% yield and **49j** in 7% yield (Scheme 36).



Scheme 36. Generation of the nitrone and *in situ* cycloaddition to **24** and partial rearrangement to tetrahydropyridone **49j**.

Compounds **47g** and **47j** needed (like **87**, described in the last chapter) a high temperature NMR measurement (100 ºC in $C_2D_2Cl_4$) to obtain well resolved signals. The molecules dynamic, in relation with the instrument time-scale, when the C(α) respect to the nitrogen atom on the ring (C-9) is unsubstituted, is the reason of very broad peaks in the room temperature measurements.

Ethyl glyoxylate **73**-Et and the hydroxylamine **65e·HCl** reacted under the reaction-conditions normally used for the synthesis of β-lactams (G P 6, Exp. Part) to give ethyl 8-benzhydryl-7-oxa-8-azadispiro[2.0.2.3]nonane-9-carboxylate (**47e**-Et): the good couple of ethanol with microwave irradiation,[68] results in a very fast synthesis (25 minutes) (Scheme 37).



Scheme 37. Synthesis of isoxazolidine **47e**-Et.

The use of microwave irradiation resulted in very short reaction times for cycladditions and rearrangements. Like for the one-pot three component synthesis of β-lactams, it's here impossible to make comparisons with the traditional heating, because these are the first experiments on these substrates. As for the cycloaddition of nitrones **44** to **24** under traditional heating, it is very important to select carefully temperature and time, to avoid the obtainment of mixtures (Scheme 36). In the case of microwave experiments, the higher reaction velocity renders the choice of those parameters in some case more difficult than with normal energy sources. The good results obtained expecially with formaldehyde allow to hope for further applications of the microwave heating in this field, for the obtainment in one step of different azaheterocycles, by selecting the reaction conditions, using the same starting materials.

4. β-Lactam Ring-Opening with *N*- and *O*-Nucleophiles and Formation of Dipeptides Containing 1-(Aminomethyl)cyclopropanecarboxylic Acid Residues

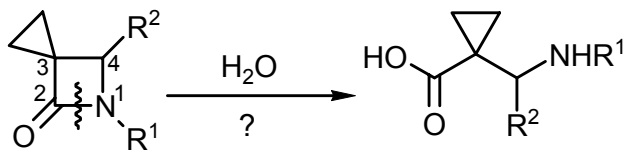
4.1. Considerations

Many β-amino acids are building blocks for peptides and antibiotics[69a] which were isolated from plants and, more often, from marine microorganisms.[69b] Recently, the biosynthesis of the phenylisoserine side chain of Taxol (**38**) was studied (Figure 8, Introduction).[70,71]

Early studies by Abderholden, for example, suggested that peptide bonds involving β-amino acids are resistent to enzymatic hydrolysis.[72] Certain β-amino acids have been incorporated into naturally occurring peptides with important pharmacological properties to improve resistance against degradation.[73]

β-amino acids and β-oligopeptides proved resistence to diverse and highly potent peptidases (pronase, proteinase K, 20S proteosoma) and to microorganisms (*Pseudomonas aeruginosa* and *Pseudomonas putida*).[74]

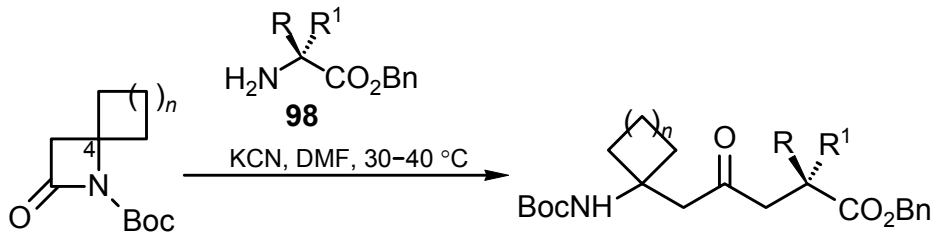
In the past years, de Meijere et al. have shown how β-amino acids containing a cyclopropane ring in the β position ($\beta^{3,3}$- or C(β)-modified-β-alanines **32**-β) can be used to obtain 4-spiro-cyclopropanated-2-azetidinones **33**-β (Figure 6, Introduction).[22,23] With an inverse process the spirocyclopropyl-β-lactams **53**, obtained with the rearrangement of isoxazolidines **47,** can be opened to obtain β-amino acids **96** (Scheme 38).



53 **96**

Scheme 38. Spirocyclopropyl-$\beta^{2,2}$-Modified-β-alanine **96** synthesis, *via* ring opening of β-lactam **53**.

The ring-opening of 2-azetidinones with *N*-nucleophiles has been already published from the group of Bhupathy,[75] and Palomo et al. performed a coupling of α-amino acid esters **98** with activated *N*-Boc protected β-lactams **97a-c**, containing a spirocycloalkyl group in position 4 (Scheme 39).[76]



97a *n* = 1
97b *n* = 2
97c *n* = 3

99a *n* = 1
99b *n* = 2
99c *n* = 3

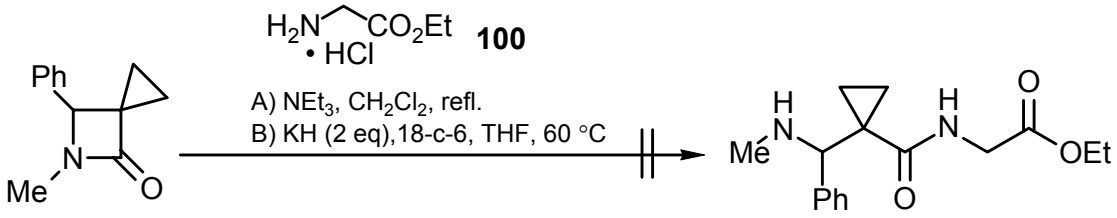
Scheme 39. Ring opening of Boc-protected β-lactams 97a-c with the amino ester 98.

The coupling of suitable protected glycine and β-lactams **53** could directly give simple dipeptides,[65] in which the β-alanine part would act as a conformational lock.

4.2. Attempted Ring-Opening of β-Lactams with *N*-Nucleophiles

Some experiments were conducted to perform the coupling of α-amino acids and 3-spiro-cyclopropanated-β-lactams **53**. 5-Methyl-6-phenyl-5-azaspiro[2.3]hexane-4-one (**53f**)[65] did not react with the ethyl ester of glycyne **100**. The amino ester **100** was used as hydrochloride. A first experiment was conducted using triethylamine in refluxing dichloromethane,[77] but just starting material was recovered after 4 days (method A, Scheme 40).

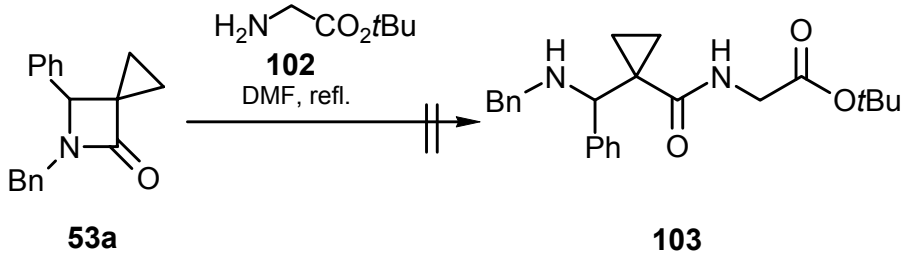
After that, it was tried the generation *in situ* of an amide base, adding under argon atmosphere the amino ester hydrochloride to a flask containing KH in anhydrous THF. The mixture was heated at 60 ºC, but no reaction was observed (method B, Scheme 40).[78]



53f **101**

Scheme 40. Failed attempts of N1-C2 ring opening of compound **53f**.

It was also tried the *tert*-Butylester of glycine **102** as *N*-nucleophile on 5-benzyl-6-phenyl-5-azaspiro[2.3]hexane-4-one (**53a**), but only starting material was recovered (Scheme 41).



Scheme 41. Failed attempt of N1-C2 ring opening of compound **53a**.

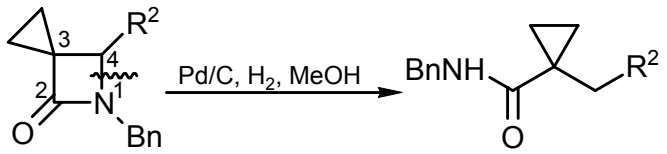
Without any further activation of the substrate, like it could be conferred from a different substitution at the nitrogen atom, the ring opening at the N1-C2 bond does not take place.
These experimental results suggest that the presence of the spirocyclopropyl ring in position 3 on the β-lactam is not able to introduce on the heterocycle enough strain to render it prone to the ring opening, i.e. to the coupling with an amino esters, *via* amide-bond breaking.

4.3. Changing the Character of the *N*-Protecting Group

Since in the literature no *N*-nucleophilic ring-openings are known for *N*-alkylprotected-2-azetidinones, like **53a** and **53f**, one possible way to make this transformation could be the activation of the β-lactams **53** toward this reaction introducing an acyl group at the nitrogen atom. In order to create the suitable substrate, (see Scheme 39) two different strategies have been applied:

1. Deprotection-reprotection sequence: the N1 on the ring must be deprotected from the alkyl group and reprotected with a more electron-withdrawing group.
2. Oxidation of the benzylic CH_2 to C=O: the alkyl protecting group had to be transformed, so that its electronical properties are inverted.

Unfortunately, attempted debenzylation of *N*-benzyl protected compounds **53a-b** and **53c**-H, by hydrogenation under palladium catalysis led to hydrogenolytic opening of the N–C(R^2) bond on the lactam ring when R^2 = Ph (**53a**) and no reaction occurred for $R^2 \neq$ Ph (**53b,j**) (Scheme 42).

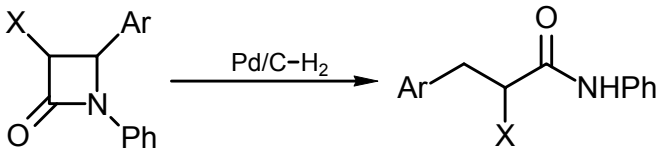


53a R^2 = Ph
53b R^2 = CO_2Me
53j R^2 = H

104 R^2 = Ph
53b R^2 = CO_2Me
53j R^2 = H

Scheme 42. Attempted debenzylation with palladium on carbon.

The former result was not surprising, because Ojima and co-workers found that cleavage of the C4-N1 bond in 2-azetidinones **105** proceeds by palladium-catalysed hydrogenolysis, when an aryl substituent is attached to the C4 position (Scheme 43).[79]

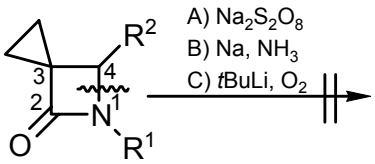


105
X = N_3, OBn

106
X = NH_2, OH

Scheme 43. N1-C4 ring-opening in the presence of aryl-substituents on the C4.

Attempted debenzylations of **53a** by buffered sodium persulfate[80a] or of **53c** under Birch conditions (sodium in ammonia)[80b] only led to no reaction or decomposition of the starting material, respectively. A procedure[80c] that uses *t*BuLi and bubbled dry-oxygen, destroyed 5-(benzyl)-5-azaspiro[2.3]hexan-4-one (**53j**) (Scheme 44).



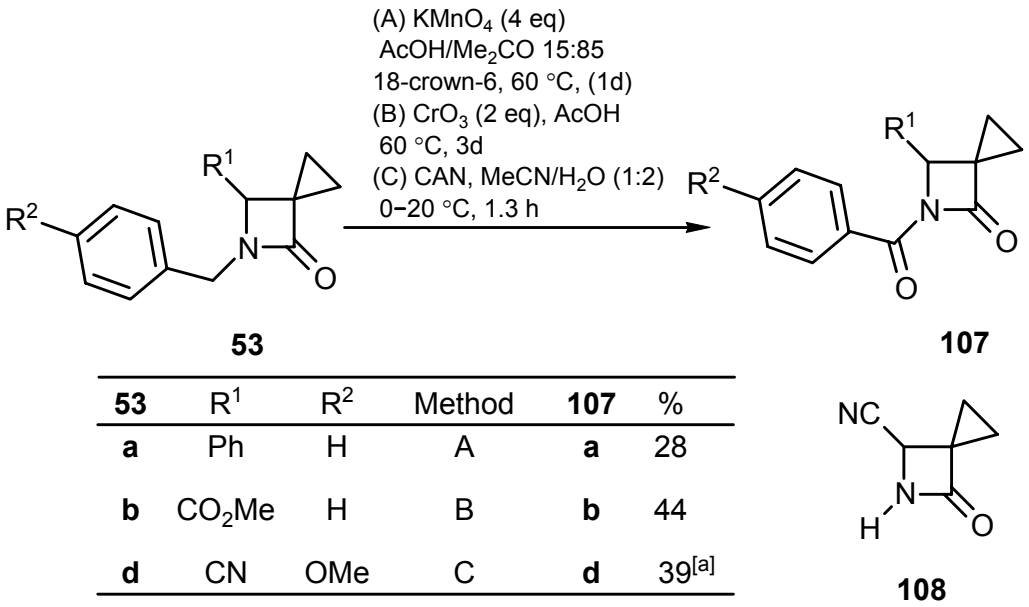
53

53	R^2	Method	Result
a	Ph	A	No reac.
c	CN	B	decompos.
j	H	C	decompos.

Scheme 44. Attempted debenzylation by other methods than hydrogenation.

However, the alternative approach by oxidation of the benzylic methylene to carbonyl group turned out to be more successful (Scheme 45). This type of oxidation was achieved for

compounds **53a**,**b** with potassium permanganate in acetic acid/acetone mixture (method A)[81a] or chromium trioxide in acetic acid (method B)[81b] which furnished the corresponding *N*-benzoyl-β-lactams **107a**,**b** in 28 and 44% yield (Scheme 45). The methylene group in the more labile *p*-methoxybenzyl group of the β-lactam **53d** can be oxidized using cerium ammonium nitrate (CAN) in aqueous acetonitrile (method C).[81c] However, this oxidation was accompanied by oxidative *N*-deprotection of **53d** to give *N*-(*p*-methoxybenzoyl)-β-lactam **107d** and *N*-deprotected β-lactam **108** in almost equal yield (39 and 38%, respectively) (Scheme 45).



53	R^1	R^2	Method	107	%
a	Ph	H	A	**a**	28
b	CO_2Me	H	B	**b**	44
d	CN	OMe	C	**d**	39[a]

[a] Plus **108** (38%)

Scheme 45. Oxidation of the benzylic methylene group in β-lactams **53a**,**b**,**d**

The structure of the *N*-benzoyl-β-lactam **107b** was rigorously proved by an X-Ray crystal structure analysis (Figure 19).

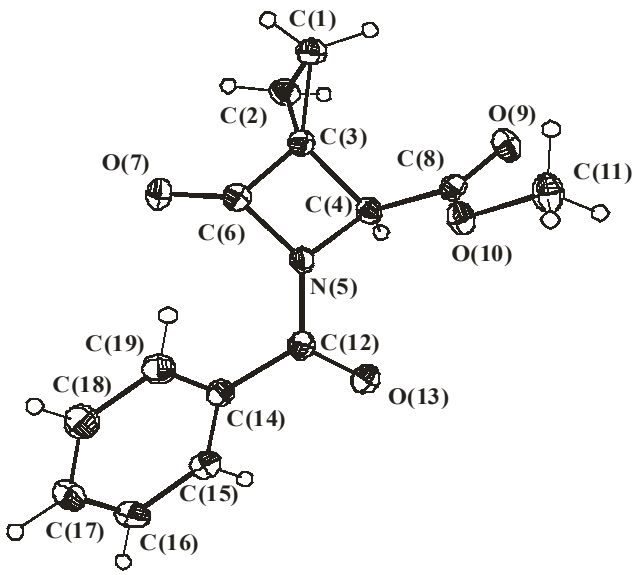


Figure 19. X-Ray crystal structure analysis Methyl 5-Benzoyl-6-oxo-5-aza-spiro[2.3]hexane-4-carboxylate (**107b**).

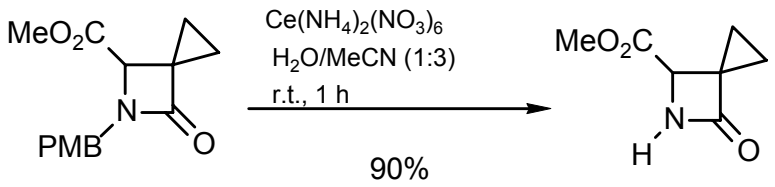
Bond	lenght [pm]	angles	amplitude [°]
C(3)−C(4)	153.7(2)	C(6)−C(3)−C(4)	88.6(8)
C(4)−N(5)	148.2(2)	N(5)−C(4)−C(3)	87.2(8)
N(5)−C(6)	142.9(2)	C(6)−N(5)−C(4)	93.1(8)
C(3)−C(6)	148.9(2)	N(5)−C(6)−C(3)	91.0(8)
C(6)−O(7)	120.0(1)		
N(5)-C(12)	139.4(2)		

Table 8. Values from the X-Ray crystal structure analysis of 107b.

The structure of **107b** in hand allows some considerations. A precedent X-Ray analysis of an analogue, methyl (6-oxo-5-azaspiro[2.3]hex-4-yl) acetate,[17] had already shown how the introduction of the small spiro alkyl ring doesn't increase the ring strain so much that it can be recognised in bond lenghts or angles. The values found in that case were the typicals for monocyclic β-lactams.[82] In fact, because of the supposed newly introduced strain (the spirofused ring), it could have been expected an increase in N(5)-C(6) bond lenght and a decrease in C(6)-O(7) lenght, but this was not observed.

In the case of **107b**, the N(5)-C(6) bond is 6.7 pm longer than for the just cited analogue and this has to be ascribed to the presence of the additional C=O: the C(12)-N(5) bond lenght is infact 139.4 pm (Table 8) and, like expected, the *N*-atom lone pair forms the resonance structure with the exocyclic carbonyl instead than with the endocyclic one.

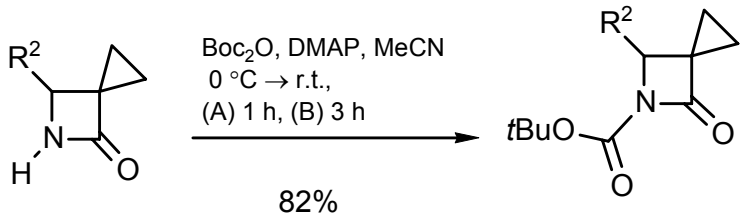
Treatment of **77d**-Me with ceric ammonium nitrate (CAN) in aqueous acetonitrile (1:3) at room temperature did indeed furnish **109** in 90% yield (Scheme 46). In this case the deprotection occurred with no trace of cooxidation product, like for **53d** (Scheme 45).



77d-Me **109**

Scheme 46. Deprotection from the *para*methoxybenzyl group in oxidative conditions.

The accessibility of deprotected derivatives like **108** and **109** allowed the synthesis of the *tert*-butoxycarbonyl protected derivatives **110** and **111**, that were obtained in 78 and 82% yield, respectively, applying an estabilished procedure (Scheme 47).[83]



108 R^2 = CN
109 R^2 = CO_2Me

110 R^2 = CN
111 R^2 = CO_2Me

Scheme 47. Protection of **108** and **109** with the "activating"-group Boc.

This *N*-protection offered β-lactams that, like the **107** derivatives, present an exocyclic carbonyl group bounded with the nitrogen atom.

The consequent minor double bond carachter for N1-C2 (N(5)-C(6)) means a reduced importance of the resonance structure **113** (Figure 20). This should induce a major reactivity, toward the ring opening with amino acid esters, for this kind of β-lactams in comparison with the alkyl substituted ones (**53a** and **53f**).

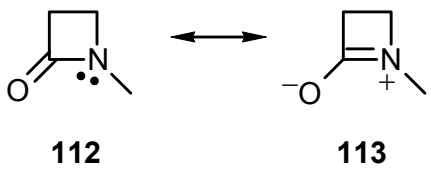
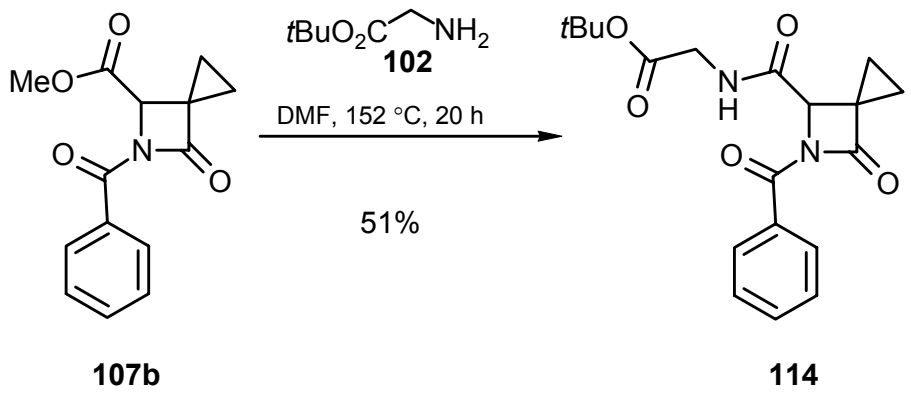


Figure 20. Amide-bond resonance in the β-lactam ring **112**.

4.4. Dipeptides Containing 1-(Aminomethyl)cyclopropanecarboxylic Acid Residues

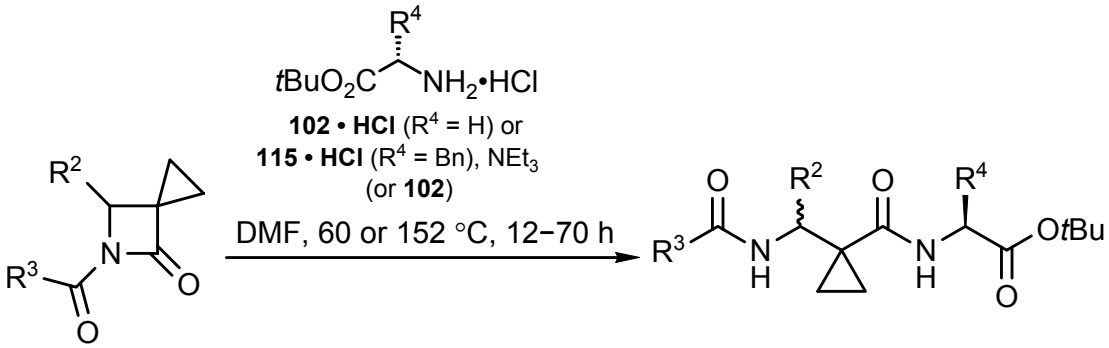
The β-lactams **107b** and **110** were treated in the presence of **102**. The electronwithdrawing groups benzoyl and *tert*butoxycarbonyl on the nitrogen atom should make the internal-ring amide bond easier to break.

The β-lactams **107a, 107b** and **110** did not react with *tert*-butyl glycinate (**102**) in DMF at ambient temperature. Upon heating of **107b** with **102** in DMF under reflux (152 °C) the ester group was transformed into a *tert*-butoxycarbonylmethylenamido group to give the new lactam **114** (Scheme 48) without ring opening even after prolonged heating with an excess of **102**.



Scheme 48. Reaction of *N*-acylated β-lactams **107b** with *tert*-butyl glycinate (**102**)

However, the β-lactams **107a** and **110** under these conditions reacted with **102** in the desired mode to give the corresponding β-dipeptides **116** and **117** in 61 and 84% yield, respectively (Scheme 49 and Table 9), as pure colorless solids after column chromatography (**116**) or without any additional purification (**117**).



Scheme 49. Reactions of *N*-acylated β-lactams **107a** and **110** with *tert*-butyl glycinate (**102**) and *tert*-butyl (*S*)-phenylalaninate (**115**)

Starting Materials	R^1	R^3	Product	R^4	%
107a	Ph	Ph	**116**	H	61
110	CN	O*t*Bu	**117**	H	84
110	CN	O*t*Bu	**118**	Bn	81

Table 9. Results for the ring-opening with amino esters 102 and 115.

Under the same conditions, a 1.1 : 1 mixture of the diastereomeric dipeptides (2*S*,2'*S*)-**118** and (2*S*,2'*R*)-**118** was obtained from the β-lactam **110** and *tert*-butyl (*S*)-phenylalaninate (**115**). These diastereomeric dipeptides (2*S*,2'*S*)-**118**, (2*S*,2'*R*)-**118** could easily be separated by column chromatography (see Experimental Section), and the structure of the latter was established by an X-Ray crystal structure analysis (Figure 21). Absolute configuration of the dipeptide (2*S*,2'*R*)-**118** was assigned on the basis of the known (*S*)-configuration of the *tert*-butyl (*S*)-phenylalaninate (**115**), used in the synthesis of **118**.

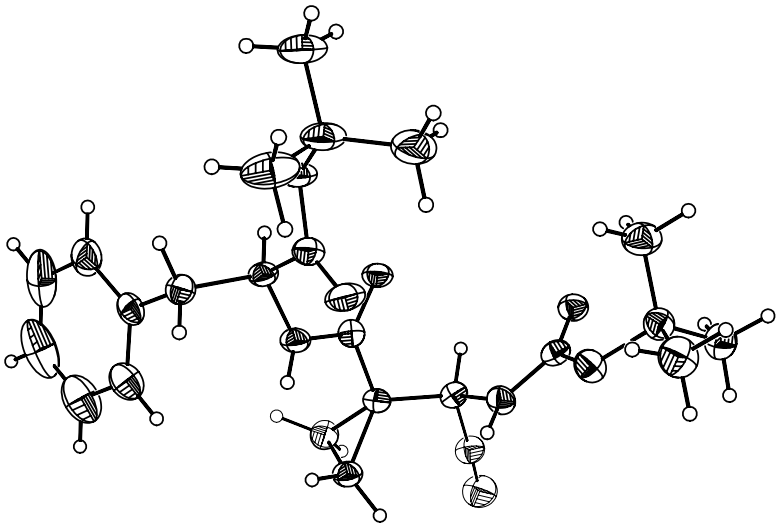
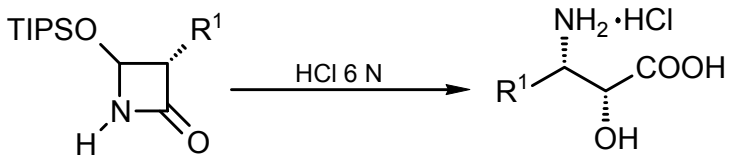


Figure 21. Molecular structure of *tert*-butyl (2*S*,2'*R*)-2-{[1-(*tert*-butoxycarbonylamino-cyanomethyl)cyclopropylcarbonyl]amino}-3-phenylpropionate [(2*S*,2'*R*)-**118**] in the crystal.

4.5. Ring Opening of β-Lactams with *O*-Nucleophiles

Norstatine (**120**) (R^1 = *i*Bu) and analogues (with different R^1 substituents) have been used extensively as crucial amino acid residues in peptide-based inhibitors of such enzymes as renin and HIV-I protease. A method, developed from Ojima, can lead with high enantiomeric purity to those products *via* the key intermediate β-lactam **119**, which is opened at the N1-C2 bond with water as *O*-Nucleophile in stongly acidic conditions (Scheme 50).[83]



119 R^1 = *i*Bu **120**

Scheme 50. Synthesis of Norstatine **120** (R^1 = *i*Bu).

The β-amino acidic chain, essential for Taxol (**38**) biological activity (Figure 8, Introduction), is normally synthetically coupled with the precursor 10-deacetylbaccatin **121**, *via O*-Nucleophilic ring-opening of a preformed β-lactam **122**, performed by the deprotonated hydroxy group at the C-13 atom on **121** (Figure 22).[83]

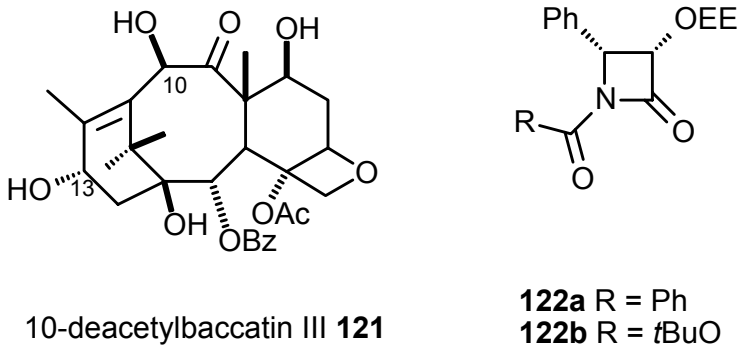
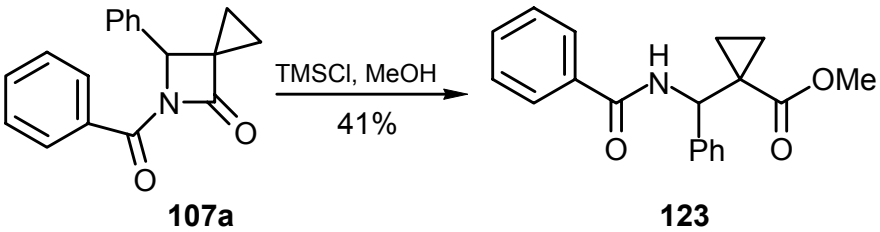


Figure 22. Starting materials for the semisynthesis of Taxol (38).

Methyl 1-(Benzoylamino-phenyl-methyl)cyclopropane carboxylate (**123**) was obtained, just treating the compound **107a** in stongly acidic conditions with trimethylchlorosilane in methanol (Scheme 51).



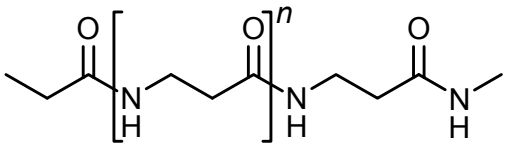
Scheme 51. Ring-opening to Methyl 1-(Benzoylamino-phenyl-methyl)cyclopropane carboxylate (123).

The purification by cromatography gave **123** as a colorless solid in 41% yield. The structure of **107a** reminds to the compound **122a** used from Ojima for the semisynthesis of Taxol and analogues,[83] with the only difference on the position 3, where it's located a cyclopropyl group instead of a protected hydroxy group (EE = ethoxy-ethoxy) (Figure 22).

5. Attempted Synthesis of a Poly(β-peptide), Consisting of 1-(Aminomethyl)cyclopropanecarboxylic Acid

5.1. Considerations

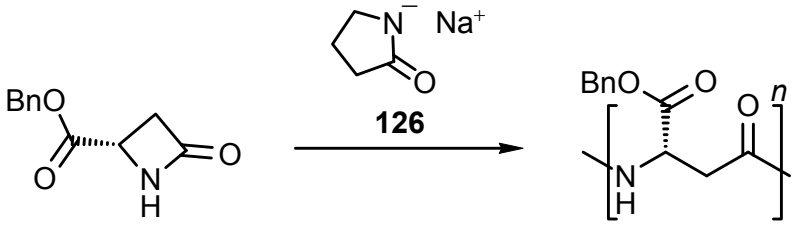
Before the detailed studies conducted by Seebach on folding of β-peptides of different kinds, the structure of monodisperse β-peptides had not accurately been estabilished.[84] Just controversal reports on the structure of β-peptides and of β-amino acids polymers have appeared in the literature since the early 60‘s, based on IR, CD, fiber X-Ray and NMR methods. A β-sheet conformation was assigned to several polydisperse poly(β-amino acid)s, the so called nylon-3 derivatives **124**, constituted of a 3-carbonbackbone polyamide (Figure 23).[85]



124

Figure 23. Nylon-3 structure.

However, more recently it was shown from fiber X-ray scattering that poly(α-alkyl-β-*L*-aspartate)s adopt helical structures.[86] Poly-β-aspartates **127** are biologically degradable polymers, obtainable by anionic polymerization of readily available β-lactam **125** of *L*-aspartic acid (Scheme 52).[86]



125 **127**

Scheme 52. Anionic polymerization of **125** to give poly-β-aspartate **127**.

While the mechanism of formation and the parameters determining the stability of secondary structures of proteins (including the helix, the pleated sheet and the turn) are not yet totally understood, β-peptides adopt well-defined secondary structures that can also be predicted by calculations, when their backbones are not conformationally restricted by cyclic residues.[87] Part of the huge work due to the group of Seebach has furnished the informations about the folding of β-peptides, derived from couplings of 1-(aminomethyl)cyclopropane carboxylic acid (**41**) units (Figure 24 and Figure 11, Introduction).[30]

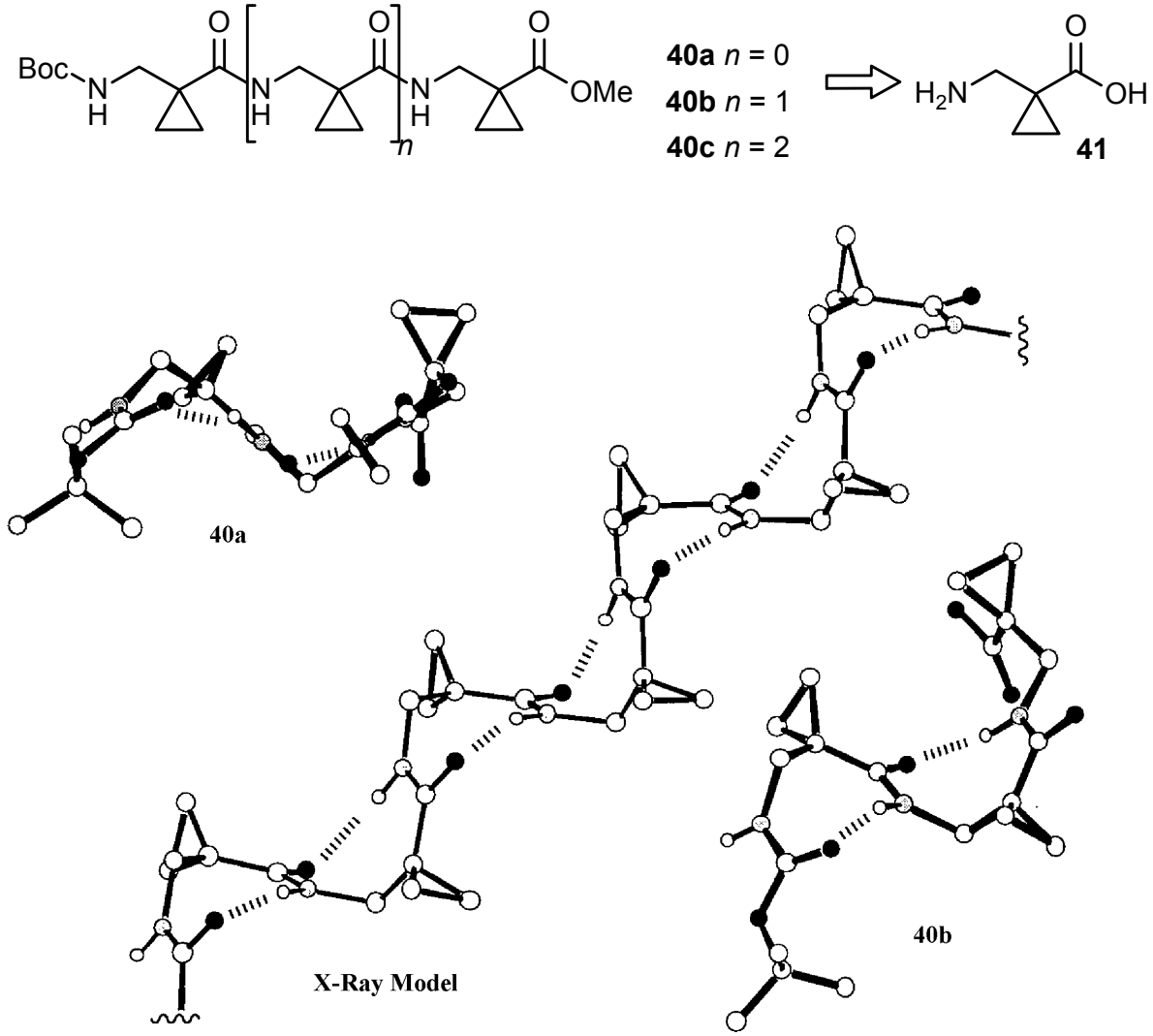
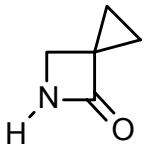


Figure 24. X-Ray structures of oligomers **40a,b** and model for a polymer.

Collecting the parameters from X-Ray analyses of the oligomers **40**, a polymer model has been created, on which the carbonyl groups adjacent to the cyclopropane create the ordering factor, that leads to the formation of eight-membered rings between neighbour units.

Real poly(β-peptides) can been prepared *via* condensation of short peptides,[88-90] polymerization of β-amino acid-N-carboxyanhydrides,[91-95] copolymerization of carbon monoxide and aziridine,[96] and polymerization of β-lactam,[86,87,97-99] which is the best method that can furnish high molecular weight polymers. The best reported control in β-lactam polymerizations was obtained by Šebenda and Hashimoto, who prepared narrow molecular weight distribution, low-molecular weight poly(β-peptides) anionically, using *N*-acyl-lactam activators,[97,98] and by Cheng and Deming[100] who used metal-amido complexes to control the polymerization.

The anionic polymerization of 5-aza-spiro[2.3]hexan-4-one (128) (Figure 25), would lead to structures, whose folding should resumble the calculated model (Figure 24).

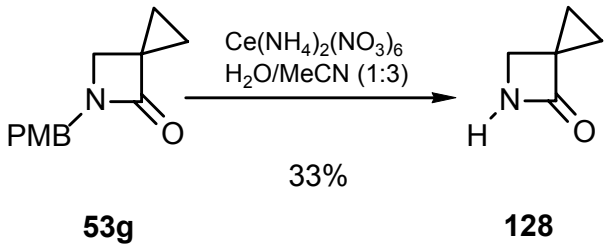


128

Figure 25. Monomer 128 for the anionic polymerization to poly-β-cyclopropanated-amide.

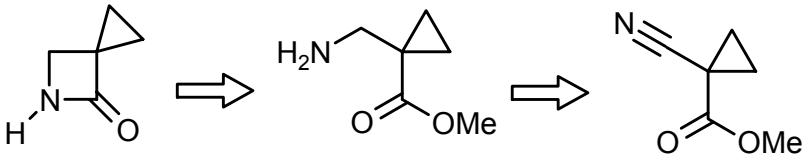
5.2. Synthesis of 5-Azaspiro[2.3]hexan-4-one

The synthesis of the monomer **128** for the anionic polymerization, was obtained *via* deprotection with ceric ammonium nitrate of the analogue **53g**, in 33% yield (Scheme 53). The amount of starting material necessary for this deprotection step is limited from the volume of the vessels disposable for the microwave oven (3.5-5 mL) and no more than a 5 mmol scale can be used for this reaction. The low yield, obtained for the deprotection, cannot furnish amount of **128** sufficient for a polymerization on larger scale.



Scheme 53. Synthesis of 5-aza-spiro[2.3]hexan-4-one (**128**) via deprotection of **53g**.

The monomer 5-aza-spiro[2.3]hexan-4-one (**128**) can also be imagined as deriving from the ring-closure of the corresponding β-alanine derivative methyl 1-(aminomethyl)-cyclopropane carboxylate (**130**) (Scheme 54).

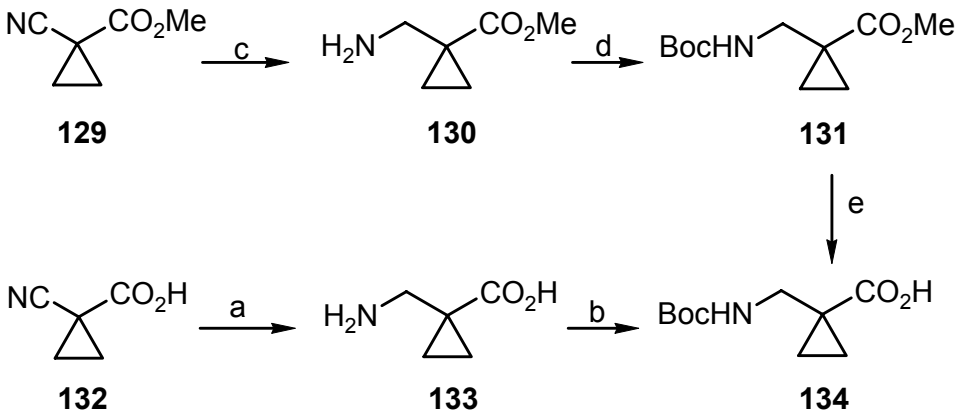


128 **130** **129**

Scheme 54. A different synthetic strategy to **128**.

α-Cyclopropyl-modified β-alanines **32**-α (Figure 6, Introduction) can be easily prepared. Commercially available 1-cyanocyclopropanecarboxylic acid **132**, also easily prepared from dialkylation of methyl cyanoacetate with 1,2-dibromoethane in DMF with K_2CO_3[101] or from trimethylsilylacetonitrile,[102] offers a simple, but most effective entry, into a α-cyclopropyl-modified β-alanine (Scheme 55).

The cyano group can be reduced with catalytic hydrogenation in the presence Platinum oxide to lead to **133** (conditions a, Scheme 55), and subsequent protection of the amino group (conditions b, Scheme 55) gives rise to the *N*-Boc-protected amino acid **134**, being suitably functionalized to be incorporated into peptides.



129 **130** **131**

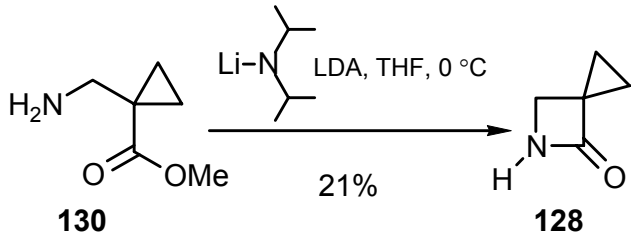
132 **133** **134**

Scheme 55. Reagents and conditions: (a) H_2, PtO_2, HOAc, 86%; (b) Boc_2O, NaOH, dioxane, 93%; (c) H_2, Raney-Ni, MeOH, 1 bar, rt, 4 h; (d) Boc_2O, MeCN, NEt_3, 0 °C, 2 h, 80% (2 steps); (e) LiOH, MeOH, rt, 3d, 48%.

Likewise, the methyl ester **129** can be converted to the aminoester **130** by catalytic hydrogenation over Raney-Nickel (conditions c, Scheme 55), freshly prepared, followed by *N*-Boc protection (conditions d, Scheme 55) to **131** and subsequent saponification to **134** (conditions e, Scheme 55).[30,103]

5.3. Ring Closure of Methyl 1-(Aminomethyl)cyclopropane carboxylate

Ring closures to 4-membered lactam through reaction of the amino group with the ester function on the same molecule are well known reactions. Several C(α)-mono- and -di-substituted β-amino esters give easliy the cyclization upon treating with strong bases in ethereal solvents. Following the work from Kise and Ueda,[104] a first attempt consisted in addition at 0 °C of a 0.3 M solution of **130** in THF to a 0.3 M solution of LDA in THF/hexane, freshly prepared from the amine and buthyl lithium at –78 °C. The desired azetidinone **128** was obtained in 21% yield (Scheme 56). The rest of **130** polymerized to an unsoluble colorless solid.



Scheme 56. Cyclization to 5-aza-spiro[2.3]hexan-4-one (**128**).

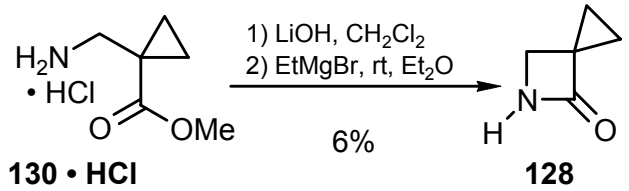
Since **130** seemed to be not perfectly soluble in THF, the previous reaction was tried adding a solution 0.09 M of it in diethyl ether to a LDA solution in tetrahydrofurane. Unfortunatly also in this case polymerization was observed.

EtMgBr was used as base at room temperature or at 0 °C, but no improvement respect to the first tried method was observed.[105]

The methyl 1-(aminomethyl)cyclopropane carboxylate (**130**) was transformed in his hydrochloric salt, because of the lower lability of the latter respect to the free amine. After ricrystallization from petrol ether, the pure salt **130·HCl** was obtained in 91% yield.

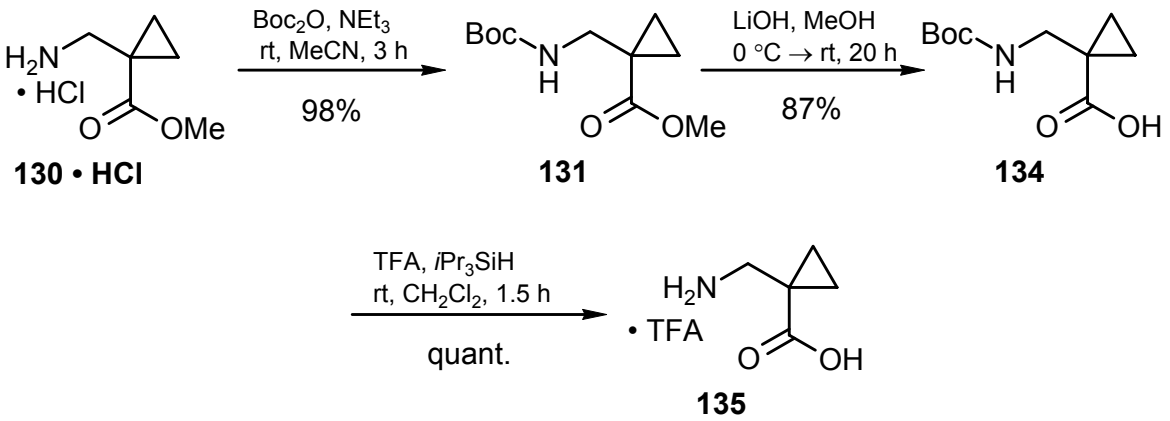
The free amino ester **130**, prepared from the latter and directly used for the reactions, should be more free from impurities than the same compound stored for a long time after distillation.

The procedure of Avenoza[106] was repeated, adding very slowly (4 h) a solution of the starting material **130** in CH_2Cl_2, obtained from **130·HCl**, to the Grignard reagent solution, but only 6% yield in **128** was obtained (Scheme 57).



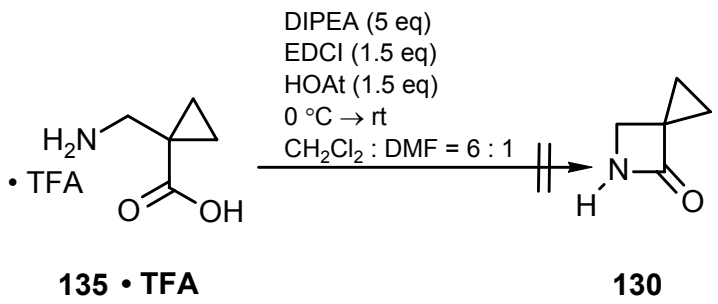
Scheme 57. Cyclization to 5-aza-spiro[2.3]hexan-4-one (128) with a different strong base.

The compound **130·HCl** was transformed into the trifluoroacetic acid salt of 1-(amino-methyl)-cyclopropane carboxylic acid (**135**), modifying known procedures,[103] so that the yield in the single steps were improved (Scheme 58).



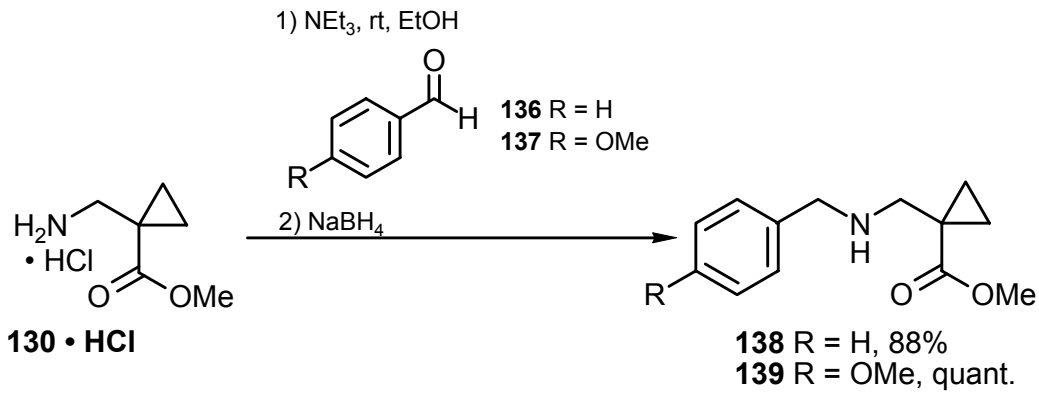
Scheme 58. Modification on known procedures to obtain 135.

The substrate **135** was supposed to be suitable for an intramolecular coupling between the free amino and the carboxylic functions. Typical strong coupling reactants like EDTA and HOAt promoted just the polymerization of **135**, even working with a 0.02 M solution of it or with a ten times more diluted solution. It was impossible to isolate any trace of the ring closure product **128** (Scheme 59).



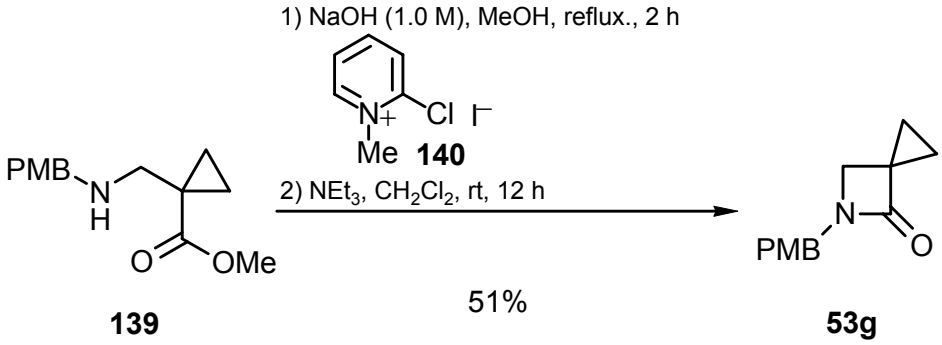
Scheme 59. Failed cyclization with coupling reagents.

Just the protection of **130** with a benzyl group, under a known procedure,[107] to **138** and **139** (Scheme 60) and the subsequent Mukayama condensation protocol applied on **135**,[108] gave finally the ring closure to **53g** in a 51% yield, over two steps (Scheme 61).



Scheme 60. Benzylic protection at the amino group in **130·HCl**.

The procedure was not applied for the benzyl protected derivative **138**, because problems correlated with the debenzylation of 5-benzyl-5-aza-spiro[2.3]hexan-4-one derivatives (Scheme 42 and 44, Chapter 4).

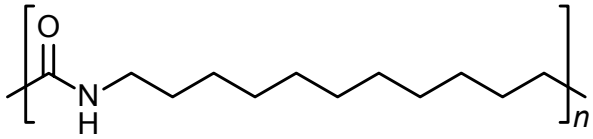


Scheme 61. Cyclization of the *N*-protected amino ester **139** under Mukajama's conditions.

The long procedure could give just **53g** and not directly the *N*-deprotected spirocyclopropyl derivative **128**. Moreover the deprotection step on a large scale presents some problem for the isolation of the product **128**.

5.4. Polymerizations

Among polymerizable heterocyclic compounds, lactams represent the most versatile group. Polymerizable lactams include four and heigher-membered rings, which may be substituted both at the carbon atoms and at the amide nitrogen, or may contain other ring-atoms beside carbon and nitrogen. The different ring size and substitution affect very strongly the reactivity of lactams as well as the properties of the resulting polymer: polymers from four-membered lactams are close to polypeptides (i.e. polypropiolactam **124**, Figure 23), and polymers from very large lactams approach the characteristics of polyethylene (i.e. polylaurolactam **141**, Figure 26).



polylaurolactam **141**

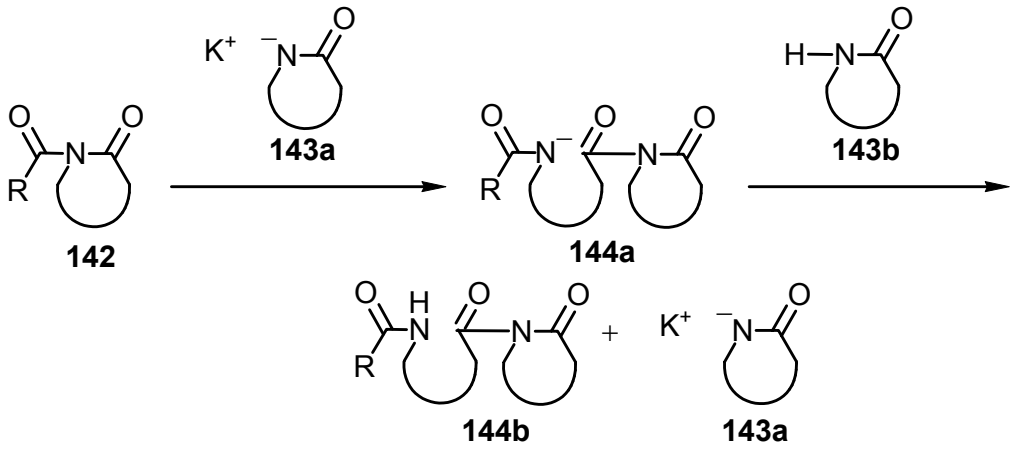
Figure 26. Polylactam with the properties of polyethylene.

Three different kinds of process are known: cationic, hydrolytic and anionic polymerization.[99] The last one has been the most successfull in the field of β-lactams polymerization.[97,98,100]

The anionic ring opening polymerization consists in a chain-growth reaction, where are involved two activated species: the lactam anions **143a** (particles of increased nucleophilicity) and *N*-acylated lactam units **142**, **144b**, **145b** etc. (i.e. growth centers of increasing acylating ability) (Scheme 62 and 63).

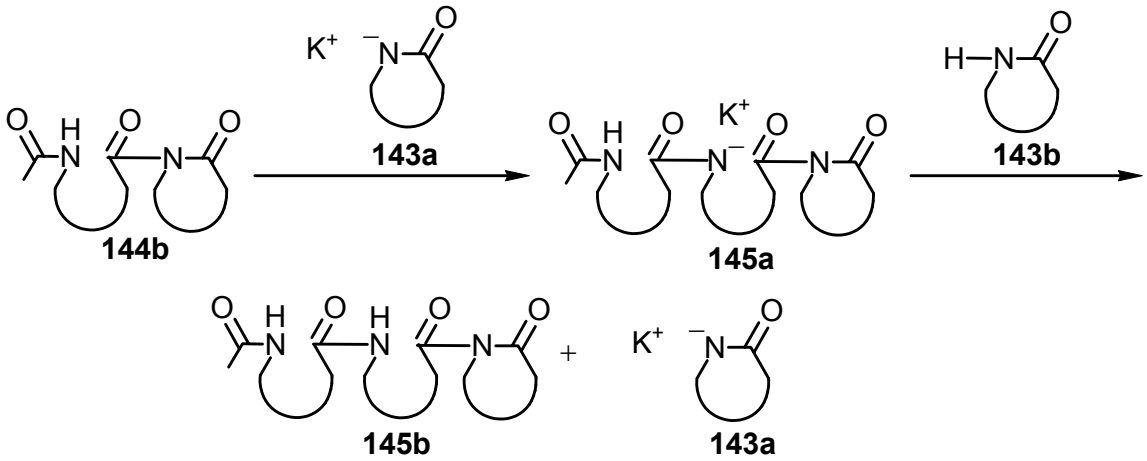
Lactams anions **143a** are able to produce growth center and thus can initiate an anionic polymerization (Scheme 62). Therefore lactamates (i.e. salts of lactams in which the anion is

derived from the lactam, like **143a** or **126**) and strong bases (e.g. NaH, *tert*-BuOK) are designated initiators.



Scheme 62. Initiation step.

Acyl lactams or precursors of growth centers like **142** are termed activators, because they significantly enhance the effect of initiators. The polymerization proceeds through the nucleophilic attack of the lactamates on the monomeric unit **143b**, to increase the chain length (Scheme 63).



Scheme 63. Propagation step.

The work of Hashimoto on 4,4-dimethyl-2-azetidinone (**147a**)[98] show the best results in terms of narrow molecular weight distribution for low-molecular weight poly(β-peptides) but already Graf et al.,[85a] Bestian[85b] and Schmidt[87a] studied the polymerization of a series of 2-azetidinones and the properties of the resulting polymers. Their chemical resistence and melting temperature depend on the chain stereoregularity and on the nature of substituents. More recently, using a variety of initiators, the polymerization of 3-butyl-3-methyl-2-

azetidinone **146d**,[99] of a series of 3-alkyl-3-methyl-2-azetidinones **146a-d**,[97] and of a series of 4-alkyl-4-methyl-2-azetidinones **147a-d**,[109] was reported, confirming the general behavior mentioned above (Figure 27).

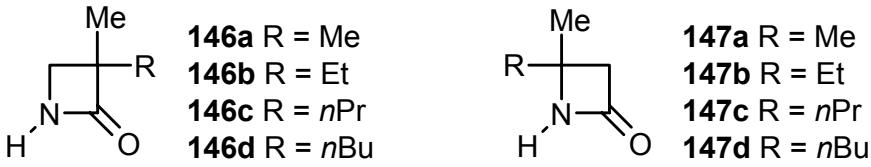


Figure 27. Derivatives on which has been tried the anionic polymerization.

5.5. Synthesis and Characterization of New Poly(2-Azetidinones)

Compound **108** and its benzoyl derivative **107d** were prepared according to the oxidative process conducted on β-lactam **53d** (Scheme 45, Chapter 4), while 4-Phenyl-2-azetidinone **148** and its benzoyl derivative **149** were prepared by following known procedures (Figure 28).[110]

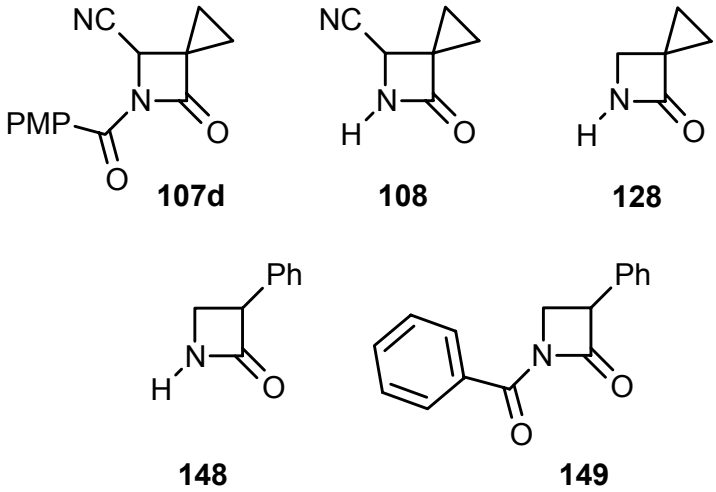
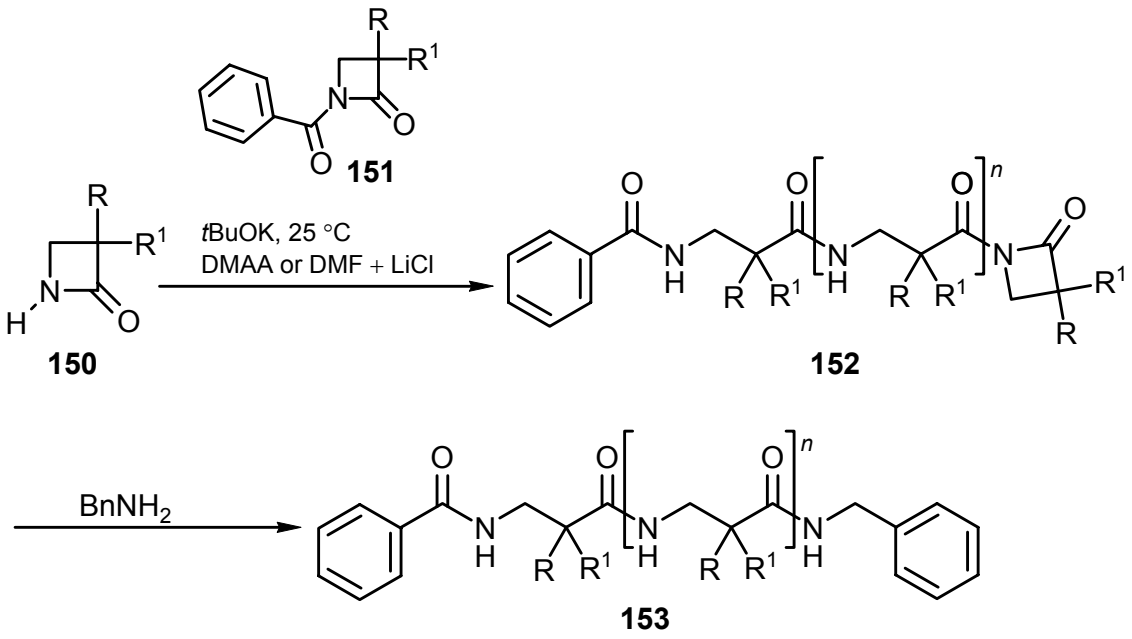


Figure 28. Monomers for the anionic polymerization.

The derivative **148** and the 3-spirocyclopropanated-2-azetidinones **108** and **128**, were subjected to polymerization-protocols, following the work of Hashimoto.[98] The β-lactam **150** and the base catalyst *t*BuOK are stirred in the presence of the activator **151** and benzylamine is added to stop the process and get the polymer **153**. Mild condition and dissolution of the polyamide during the process are achieved with a solution of lithium chloride in dry DMAA or DMF (Scheme 64).[98a]

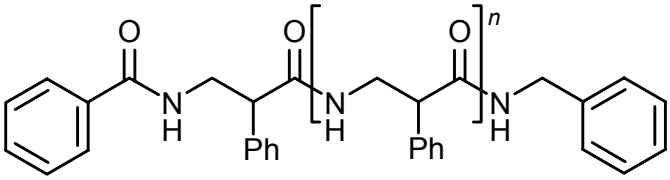


Scheme 64. Hashimoto conditions for the anionic polymerization of β-lactams.

The living anionic polymerization of **148** was tried (5 mmol scale), using **149** as activator. The salt (5% mol. respect to the starting material) was previously dried *in vacuo* at high temperature. Potassium *tert*-butoxide, freshly sublimated, was used as catalyst in small amount (0.5% mol.), to decrease the polymerization rate and with it the broadening of molecular weight distribution. The polymer was precipitated adding to the flask a mixture acetone/water 5:1 and purified and isolated through dissolution in trifluoroethanol and replicated precipitation with the same mixture of solvents. The powder was collected by centrifugation and shows a melting point higher than 260 ºC.

The polymer IR spectrum shows respect to the monomer's one, a larger band for the free N-H stretching at 3291 cm^{-1} and the C=O strong band has moved from 1745 cm^{-1} (typical value for a β-lactam amidic carbonyl) to 1648 cm^{-1}, with a second strong band at 1528 cm^{-1}, that is characteristic of polyamides.

The ESI mass spectrum shows a regular distribution of peaks, and this confirms the formation of a totally new poly-β-peptide. It's possible to find peacks every 146 m/z and 294 m/z, corresponding respectively at the molecular weight of one and two monomers. The maximum observed value corresponds to 945, the molecular weight of **154**, in which four monomer-units (n = 4) are bound with an initiator molecule and a benzyl rest at the chain end (Figure 29).



154

Figure 29. Polymerization product 154.

In the case of compound **108** dry dimethylacetamide was used as solvent, toghether with lithium chloride, previously dried *in vacuo*. The mixture acetone/water, used for 148, could not precipitate the polymer and diethyl ether was used. After purification, a white powder was collected *via* centrifugation. Its IR spectrum shows a large band for the free N-H (3273 cm^{-1}) but the β-lactamic C=O stretch (1753 cm^{-1}) is not completely disappeared from the spectrum, although it seems like a shoulder of the bigger band by 1672 cm^{-1}, due to acyclic amidic C=O.

The polymer was not soluble in the solvent suitable for the ESI measurement, so that it does not really represent the mass distributions for the polymer but just the soluble impurities, collected during the procedures that allow the polymer isolation. Also attempts to determine the molecular weight distribution with GPC failed for the same reason.

A last attempt was tried with **128**. A solution of lithium chloride in dry dimethyl acetamide was used as the solvent and freshly sublimated potassium *tert*-butoxide was used as the catalyst. No acylated-activator was added to the flask. The mixture acetone/water could precipitate the polymer, that was treated like as usual for purification and isolation.

The polymer IR spectrum shows that the amidic carbonyl strong band, typical for β-lactams, has moved to 1635 cm^{-1}, with a second strong band by 1576 cm^{-1}, that is characteristic of polyamides.

Even if the IR measurements give positive results, no full characterization was possible for the polymers obtained from **128**, as well as for **108**, because the isolated solids were impossible to solve for the necessary spectral analysis (NMR, mass spectrometry, Gel Permeation Cromatography).

The low solubility is a quite common property of polyamides[98a] but, in the presence of reactive groups like the strained cyclopropyl ring or the nitrile, could also derive from reaction between different formed chains.

Probably, the used conditions cannot avoid reactions between different chains, expecially because of the presence of the strained small ring or of the nitrile group. This phenomenon could explain the practical impossibility to dissolve again the isolated polymers.

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 Bruker AM 250 (250 MHz for ^{1}H and 62.9 MHz for ^{13}C NMR), a Varian Mercury 200 (200 MHz for ^{1}H and 50.3 MHz for ^{13}C NMR), a Unity 300 (300 MHz for ^{1}H and 75.5 MHz for ^{13}C NMR) and an Inova 600 (600 MHz for ^{1}H, 150 MHz for ^{13}C NMR) instruments in $CDCl_3$ if not otherwise specified. Multiplicities were determined by DEPT (Distortionless Enhancement by Polarization Transfer) or APT (Attached Proton Test) measurements. 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, cPr-H = cyclopropyl proton, cHex-H = cyclohexyl proton, Ar-H = aromatic proton, * = the assignment is exchangeable. The signals were characterized: + = primary or tertiary (positive DEPT-signal), – = secondary (negative DEPT-signal), C_{quat} = quaternary carbon atom (zero DEPT-signal) or + = primary or tertiary (positive APT-signal), – = secondary or quaternary carbon atom (negative APT-signal). The signals were characterized: cPr-C = cyclopropyl carbon, cHex-C = cyclohexyl carbon, Ar-C = aromatic carbon, * = the assignment is exchangeable. – MS (EI, 70 eV) or DCI (with NH_3): 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. – M.p.: melting point instrument according to Dr Tottoli: 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, grade 60, 70–230 or 230–400 mesh. – Elemental analysis: Mikroanalytisches Laboratorium des Instituts für Organische und Biomolekulare Chemie der Universität Göttingen, Germany. – X-Ray structure analysis of compounds **47a**, **107b**, and [(2*S*,2'*R*)-**118**] were collected at 133(2) K on a STOE-IPDS 2 Image Plate diffractometer using graphite monochromated Mo-K_{α} radiation. The structure solutions and refinements on F^2 were performed with the Bruker SHELXTL program suite. – Microwave: the reactions under microwave heating were carried out in a Smith Creator, part

of Coherent SynthesisTM, Personal Chemistry. Emission frequency of 2.45 GHz and reactor with on-line temperature, pressure and microwave power control. Reaction temperature in the range of 60 to 250 ºC, reaction pressures up to 2 MPa (20 bar). The temperature increase varies in the range 2–5 ºC/sec, depending on the solvent. The reactions are performed under magnetic stirring, in vials with caps supplied by Personal Chemistry. – 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, Bnh = benzhydryl, Boc = *tert*butoxycarbonyl, *t*Bu = *tert*butyl, Bz = benzoyl, *m*CPBA = *meta*-chloroperbenzoic acid, cHex = cyclohexyl, DEAD = diethylazodicarboxylate, DMAA = *N*,*N*-dimethylacetamide, DMAP = *N*,*N*-dimethylaminopyridine, DMF = dimethylformamide, EE = ethoxy-ethoxy, Et = ethyl, , Me = methyl, MeCN = acetonitrile, Ph = phenyl, PMB = 4-methoxybenzyl, THF = tetrahydrofurane, TIPS = tri*iso*propylsilyl. The following substances were prepared according to literature procedures: biciclopropylidene (**24**),[18] methylenecyclopropane (**43**),[18] *N*-benzyl-*C*-phenylnitrone (**44a**),[41] *N*-benzyl-*C*-(methoxycarbonyl)-nitrone (**44b**),[44] *N*-benzyl-*C*-cyanonitrone (**44c**),[43] *N*-(*p*-methoxybenzyl)-methyleneammine *N*-oxide (**44g**),[45] formaldehyde-*N*-benzyloxime (**44j**),[46] dispiro[cyclopropane-1,2'-hexahydropyrrolo[1,2-b]isoxazole-3,1''-cyclopropane] (**70**),[50] benzylhydroxylamine oxalate (**65c·(COOH)$_2$**),[43] benzhydrylhydroxylamine hydrochloride (**65e·HCl**),[43] cyclohexylglyoxylate (**73**-cHex) and methylglyoxylate (**73**-Me),[63] phenylhydroxylamine hydrochloride (**65h·HCl**), 4-bromophenylhydroxylamine hydrochloride (**65i·HCl**),[60] 5-Methyl-6-phenyl-5-azaspiro[2.3]hexan-4-one (**53f**),[65] *tert*butylglycinate (**102**),[111] 4-Phenyl-2-azetidinone (**148**).[110]

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

2.1. Synthesis of the Compounds in Chapter 1

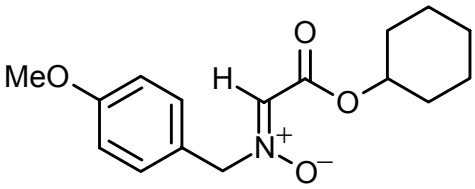
***N*-(*p*-Methoxybenzyl)-*C*-cyanonitrone (44d)**: Chloroacetonitrile (22.6 g, 18.9 mL, 0.30 mol) and K_2CO_3 (55.3 g, 0.40 mol) were added to a vigorously stirred solution of *p*-methoxybenzylamine (27.4 g, 26.1 mL, 0.20 mol) in acetonitrile (2 L). After an additional stirring for 12 h at 60 °C, the suspension was filtered through a pad of Celite, and the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (R_f = 0.20, 660 g of silica gel, 7.5 × 20 cm column, hexane/Et_2O 1:2) to give **44d** (28.0 g, 80%) as a dark oil. To the solution of the latter (28.0 g, 0.160 mol) in anhydrous CH_2Cl_2 (760 mL) was added *m*CPBA (60.7 g, 0.352 mol) in small portions at 0 °C. After an additional stirring for 30 min at 0 °C and for 1 h at ambient temperature, a 10% aq. solution of $Na_2S_2O_3$ (300 mL) and sat. aq. $NaHCO_3$ solution (300 mL) were added, and the mixture was stirred for an additional 1 h. The aqueous phase was extracted with CH_2Cl_2 (2 × 200 mL); the combined organic layers were washed with brine (2 × 200 mL), dried and concentrated under reduced pressure. Nitrone **44d** (30.4 g, 100%, 1:4 mixture of *E*- and *Z*-isomers) was obtained as a yellow solid and used without purification. An analytical sample was obtained by column chromatography (R_f = 0.24, 20 g of silica gel, 2 × 13 cm column, hexane/Et_2O 1:3); m.p. 74–75 °C. – IR (KBr): $\tilde{\nu}$ = 3102 cm^{-1}, 2994, 2964, 2937, 2838, 2222, 1616, 1587, 1544, 1520, 1462, 1414. – ^1H NMR (250 MHz, $CDCl_3$): δ = 3.82 (s, 3 H, OCH_3, *E*-isomer), 3.84 (s, 3 H, OCH_3, *Z*-isomer), 4.94 (s, 2 H, CH_2, *Z*-isomer), 5.24 (s, 2 H, CH_2, *E*-isomer), 6.53 (s, 1 H, =CH, *Z*-isomer), 6.62 (s, 1 H, =CH, *E*-isomer), 6.90–6.99 (m, 4 H, Ar-H, *Z*- and *E*-isomers), 7.29–7.33 (m, 2 H, Ar-H, *Z*-isomer), 7.44–7.48 (m, 2 H, Ar-H, *E*-isomer). – ^{13}C NMR (50.3 MHz, $CDCl_3$, additional DEPT): δ = 55.3 (+, CH_3, *E*-isomer), 55.4 (+, CH_3, *Z*-isomer), 69.4 (–, CH_2, *E*-isomer), 71.1 (–, CH_2, *Z*-isomer), 106.8 (+, =CH, *Z*-isomer), 107.0 (+, =CH, *E*-isomer), 112.1 (C_{quat}, CN, *Z*-isomer), 114.3 (+, 2 CH, Ar-C, *E*-isomer), 114.8 (+, 2 CH, Ar-C, *Z*-isomer), 115.3 (C_{quat}, CN, *E*-isomer), 122.4 (C_{quat}, Ar-C, *Z*-isomer), 123.5 (C_{quat}, Ar-C, *E*-isomer), 131.0 (+, 2 CH, Ar-C, *E*-isomer), 131.5 (+, 2 CH, Ar-C, *Z*-isomer), 160.7 (C_{quat}, Ar-C, *E*-isomer), 161.0 (C_{quat}, Ar-C, *Z*-isomer). – MS (EI): *m/z* (%) = 190 (2) [M^+], 121 (100), 77 (12), 51 (8). – $C_{10}H_{10}N_2O_2$ (190.2): calcd. C 63.15, H 5.30, N 14.73; found C 62.88, H 5.49, N 14.93.

***N*-(*p*-Methoxybenzyl)hydroxylamine oxalate (65d):** To a solution of *N*-(*p*-methoxybenzyl)-*C*-cyanonitrone **44d** (4.70 g, 25.0 mmol) in MeOH (125 mL) was added $NH_2OH{\cdot}HCl$ (8.70 g, 125 mmol). After stirring for 2 h at 60 °C, the resulting mixture was cooled to r.t., methanol was evaporated in vacuo, and $CHCl_3$ (100 mL) was added. The mixture containing some undissolved solids was filtered through a pad of Celite. The filtrate was concentrated, and the residue was partitioned with $CHCl_3$ (150 mL) and a satd. solution of $NaHCO_3$ (150 mL). The acqueous layer was extracted with $CHCl_3$ (2 × 70 mL), and the combined extracts were washed with satd. solution of NaCl (150 mL), dried ($MgSO_4$) and filtered. To the filtrate was added a solution of oxalic acid (3.15 g, 250.0 mmol) in 25 mL of methanol, and the resulting suspension was evaporated to dryness. The solid obtained was triturated with ether/pentane, and collected by suction. After drying in vacuo, analytically pure **65d** (4.84 g, 80%) was obtained as a yellowish solid, m.p. 145 °C. – IR (KBr): $\tilde{\nu}$ = 3424 cm^{-1}, 2932, 2837, 1721, 1612, 1515, 1454, 1306, 1253, 826, 710. – ^{1}H NMR (250 MHz, CD_3OD): δ = 3.85 (s, 3 H, CH_3), 4.35 (s, 2 H, CH_2), 7.01–7.05 (m, 2 H, Ar-H), 743–7.47 (m, 2 H, Ar-H). – ^{13}C NMR (62.9 MHz, CD_3OD, additional DEPT): δ = 56.0 (+, CH_3), 56.4 (–, CH_2), 115.7 (+, 2 CH, Ar-C), 122.1 (C_{quat}, Ar-C), 133.6 (+, 2 CH, Ar-C), 162.1 (C_{quat}, Ar-C), 165.5 (C=O, $(COOH)_2$). – $C_{10}H_{13}NO_6$ (243.22): calcd. C 49.38, H 5.39, N 5.76; found C 49.13, H 5.61, N 5.90.

***N*-(*p*-Methoxybenzyl)-*C*-(2-iodophenyl)-nitrone (44f):** To a suspension of *p*-methoxybenzylhydroxylamine oxalate **65d·(COOH)$_2$** (1.19 g, 4.90 mmol) and triethylamine (0.496 g, 0.68 mL, 4.90 mmol) in dry THF (25 mL) was added *o*-Iodobenzaldehyde (1.14 g, 4.90 mmol). After an additional stirring for 36 hours at 25 °C in the presence of molecular sieves, diethyl ether was added (25 mL) and the suspension was filtered through a pad of Celite®. Water (40 mL) was added and the phases were separated. The aqueous phase was extracted with ether (2 × 50 mL); the combined organic layers were washed with HCl 2 M (2 × 100 mL), dried and concentrated under reduced pressure. The nitrone **44f** (1.60 g, 89%) was obtained as a yellow solid, m.p. 81–82 °C. – IR (KBr): $\tilde{\nu}$ = 3060 cm^{-1}, 2935, 2838, 1516, 1290, 1248, 1033. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.79 (s, 3 H, CH_3O), 4.99 (s, 2 H, CH_2), 6.92–7.04 (m, 3 H, Ar-H), 7.33–7.43 (m, 3 H, Ar-H), 7.70 (s, 1 H, =CH), 7.82–7.85 (m, 1 H, Ar-H), 9.14–9.17 (m, 1 H, Ar-H). – ^{13}C NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 53.3 (+, CH_3), 71.2 (–,

NCH_2), 99.3 (C_{quat}, Ar-C), 114.3 (+, 2 CH, Ar-C), 124.8 (C_{quat}, Ar-C), 128.2 (+, CH, *), 129.0 (+, CH, *), 131.0 (+, 2 CH, Ar-C), 131.3 (+, CH, *), 132.1 (C_{quat}, Ar-C), 137.3 (+, CH, *), 139.4 (+, CH, *), 160.1 (C_{quat}, Ar-C). – MS (EI): *m/z* (%) = 367 (2) [M^+], 351 (2), 232 (2), 203 (1), 121 (100), 91 (4), 77 (4). – $C_{15}H_{14}INO_2$ (367.18): calcd. C 49.07, H 3.84, N 3.81; found C 48.84, H 3.82, N 3.72.

***N*-Benzyl-*C*-(Cyclohexyloxycarbonyl)-nitrone (44i):** Cyclohexylglyoxylate (0.687 g, 4.40 mmol) was added to a solution of benzylhydroxylamine **65c** (0.448 g, 3.64 mmol) in benzene (19 mL). After refluxing for 14 h, the solvent was evaporated under reduced pressure. The residue was purified by column chromatography (R_f = 0.17, 85 g of silica gel, 3.5 × 18 cm column, hexane/Et_2O 2:1) to give **44i** (0.723 g, 76%, 1:1.8 mixture of *E*- and *Z*- isomers) as a colorless solid with m.p. 69–70 °C. – IR (KBr): $\tilde{\nu}$ = 3072 cm^{-1}, 2937, 2857, 1717, 1559, 1261, 1018. – ^1H NMR (250 MHz, $CDCl_3$): δ = 1.25–1.90 (m, 20 H, cHex-H, *E*- and *Z*- isomers), 4.82–4.85 (m, 2 H, OcHex-H, *E*- and *Z*- isomers), 4.98 (s, 2 H, NCH_2, *Z*-isomer), 5.70 (s, 2 H, NCH_2, *E*-isomer), 7.04 (s, 1 H, =CH, *Z*-isomer), 7.18 (s, 1 H, =CH, *E*-isomer), 7.31–7.43 (m, 6 H, Ar-H, *E*- and *Z*- isomers), 7.51–7.59 (m, 4 H, Ar-H, *E*- and *Z*- isomers). – ^{13}C NMR (62.9 MHz, $CDCl_3$, additional APT): δ = 23.6 (–, 2 CH_2, cHex-C, *E*- and *Z*- isomers), 25.1 (–, CH_2, cHex-C, *Z*-isomer), 25.2 (–, CH_2, cHex-C, *E*-isomer), 31.2 (–, 2 CH_2, cHex-C, *E*-isomer), 31.4 (–, 2 CH_2, cHex-C, *Z*-isomer), 66.1 (–, NCH_2, *Z*-isomer), 73.1 (–, NCH_2, *E*-isomer), 73.4 (+, OCH, cHex-C, *E*-isomer), 74.2 (+, OCH, cHex-C, *Z*-isomer), 125.7 (+, =CH, *E*-isomer), 127.5 (+, =CH, *Z*-isomer), 128.5 (+, 2 CH, Ar-C, *Z*-isomer), 128.7 (+, 2 CH, Ar-C, *E*-isomer), 129.0 (+, 2 CH, Ar-C, *E*-isomer), 129.2 (+, 2 CH, Ar-C, *Z*-isomer), 129.4 (+, CH, Ar-C, *E*-isomer), 129.6 (+, CH, Ar-C, *Z*-isomer), 131.6 (–, C_{quat}, Ar-C, *E*-isomer), 133.3 (–, C_{quat}, Ar-C, *Z*-isomer), 159.3 (–, C_{quat}, C=O, *E*-isomer), 160.3 (–, C_{quat}, C=O, *Z*-isomer). – MS (EI): *m/z* (%) = 261 (10) [M^+], 244 (2), 162 (12), 91 (100), 83 (14), 65 (8), 55 (12).



Cycloaddition of Nitrones 44a–g to Bicyclopropylidene (24). General Procedure 1.

(GP 1) : A solution of the respective nitrone (5 mmol) and bicyclopropylidene (**24**) (0.85 g, 1.0 mL, 10.6 mmol) was stirred in a hermetically closed tube at the indicated temp. for the indicated time. After cooling to ambient temp., the solution was concentrated under reduced pressure, and the crude product was purified by column chromatography on silica gel.

8-Benzyl-9-phenyl-7-oxa-8-azadispiro[2.0.2.3]nonane (47a): Column chromatography (R_f = 0.44, 165 g of silica gel, 5 × 17 cm column, hexane/Et_2O 10:1) of the residue obtained from nitrone **44a** (3.76 g, 18.0 mmol) and bicyclopropylidene **24** (1.60 g, 1.87 mL, 20.0 mmol) according to GP 1 (60 °C, 25 d) gave the cycloadduct **47a** (5.0 g, 95%) as a colorless solid, m.p. 70 °C. – IR (KBr): $\tilde{\nu}$ = 3067 cm^{-1}, 2998, 2845, 1653, 1636, 1456, 1437. – ^1H NMR (250 MHz, $CDCl_3$): δ = 0.12–0.35 (m, 2 H, CH_2, cPr-H), 0.34–0.53 (m, 4 H, CH_2, cPr-H), 0.85–0.98 (m, 2 H, CH_2, cPr-H), 4.14 (s, 1 H, CH), 4.08 (m, 2 H, CH_2), 7.20–7.40 (m, 10 H, Ar-H). – ^{13}C NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 6.7 (–, CH_2, cPr-C), 7.3 (–, CH_2, cPr-C), 7.7 (–, CH_2, cPr-C), 8.6 (–, CH_2, cPr-C), 33.0 (C_{quat}, C-3), 61.3 (–, NCH_2), 66.5 (C_{quat}, C-6), 76.3 (+, CH), 126.8 (+, CH, Ar-C), 127.6 (+, CH, Ar-C), 127.9 (+, 2 CH, Ar-C), 128.1 (+, 2 CH, Ar-C), 128.5 (+, 4 CH, Ar-C), 137.7 (C_{quat}, Ar-C), 138.1 (C_{quat}, Ar-C). – MS (EI): *m/z* (%) = 291 (10) [M^+], 262 (5), 235 (5), 129 (30), 115 (18), 91 (100). – $C_{20}H_{21}NO$ (291.4): calcd C 82.44, H 7.27, N 4.81; found C 82.19, H 6.97, N 4.76.

Methyl 8-Benzyl-8-aza-7-oxadispiro[2.0.2.3]nonane-9-carboxylate (47b): Column chromatography (R_f = 0.14, 115 g of silica gel, 4.5 × 15 cm column, hexane/Et_2O 5:1) of the residue obtained from nitrone **44b** (1.0 g, 5.18 mmol) and bicyclopropylidene **24** (832 mg, 0.97 mL, 10.4 mmol) according to GP1 (45 °C, 2 d) gave the cycloadduct **47b** (1.40 g, 100%) as a yellow oil. – IR (film): $\tilde{\nu}$ = 3064 cm^{-1}, 3031, 3006, 2953, 1766, 1456, 1437. – ^1H NMR (250 MHz, $CDCl_3$): δ = 0.27–0.36 (m, 2 H, CH_2, cPr-H), 0.40–0.46 (m, 1 H, CH_2, cPr-H), 0.61–0.78 (m, 3 H, CH_2, cPr-H), 0.91–0.94 (m, 2 H, CH_2, cPr-H), 3.65 (s, 3 H, OCH_3), 3.68 (s, 1 H, CH), 4.14 (d, $^2J_{H,H}$ = 12.5 Hz, 1 H, NCH_2), 4.37 (d, $^2J_{H,H}$ = 12.5 Hz, 1 H, NCH_2), 7.23–7.41 (m, 5 H, Ar-H). – ^{13}C NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 5.5 (–, CH_2, cPr-C), 6.8 (–, CH_2, cPr-C), 8.6 (–, CH_2, cPr-C), 10.7 (–, CH_2, cPr-C), 30.0 (C_{quat}, C-3), 52.1 (+, CH_3), 62.8 (–, NCH_2), 66.4 (C_{quat}, C-6), 72.7 (+, CH), 127.7 (+, CH, Ar-H), 128.4 (+, 2 CH, Ar-H), 129.4 (+, 2 CH, Ar-H), 136.0 (C_{quat}, Ar-C), 170.6 (C_{quat}, C=O). – MS (EI): *m/z* (%) = 273 (10) [M^+], 214 (90), 105 (19), 91 (100). – $C_{16}H_{19}NO_3$ (273.3): calcd. C 70.31, H 7.01, N 5.12; found C 70.10, H 6.80, N 5.01.

8-Benzyl-9-cyano-8-aza-7-oxadispiro[2.0.2.3]nonane (47c): Column chromatography (R_f = 0.20, 54 g of silica gel, 4 × 10 cm column, hexane/Et_2O 2:1) of the residue obtained from the nitrone **44c** (1.46 g, 9.12 mmol) and bicyclopropylidene **24** (1.60 g, 1.9 mL, 20 mmol) according to GP 1 (20 °C, 8 d) gave the cycloadduct **47c** (2.07 g, 94%) as a colorless oil. – IR (film): $\tilde{\nu}$ = 3066 cm^{-1}, 3031, 2959, 2863, 2246, 1497, 1454. – ^1H NMR (300 MHz, $CDCl_3$): δ = 0.30–0.49 (m, 2 H, CH_2, cPr-H), 0.51–0.60 (m, 2 H, CH_2, cPr-H), 0.80–0.97 (m, 4 H, CH_2, cPr-H), 3.78 (s, 1 H, CH), 4.11–4.26 (m, 2 H, NCH_2), 7.20–7.37 (m, 5 H, Ar-H). – ^{13}C NMR (50.3 MHz, $CDCl_3$, additional APT): δ = 7.3 (–, CH_2, cPr-C), 7.7 (–, CH_2, cPr-C), 8.2 (–, CH_2, cPr-C), 11.2 (–, CH_2, cPr-C), 62.5 (+, CH), 66.6 (C_{quat}, C-6), 128.0 (+, CH, Ar-C), 128.6 (+, 2 CH, Ar-C), 129.2 (+, 2 CH, Ar-C), 135.0 (C_{quat}, Ar-C), three carbon atoms were not detectable at this temp. – ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$, 100 °C): δ = 7.0 (–, CH_2, cPr-C), 7.4 (–, CH_2, cPr-C), 7.7 (–, CH_2, cPr-C), 10.5 (–, CH_2, cPr-C), 30.6 (C_{quat}, C-3), 60.8 (–, NCH_2), 62.5 (+, CH), 66.2 (C_{quat}, C-6), 116.1 (C_{quat}, CN), 127.6 (+, CH, Ar-C), 128.3 (+, 2 CH, Ar-C), 128.8 (+, 2 CH, Ar-C), 135.3 (C_{quat}, Ar-C). – MS (EI): *m/z* (%) = 239 (20) [M^+ – H], 214 (10), 211 (20), 105 (50), 91 (100). – MS (DCI): *m/z* (%) = 481 (5) [2 M + H^+], 258 (8) [M + NH_4^+], 241 (100) [M + H^+]. – $C_{15}H_{16}N_2O$ (240.3): calcd. C 74.97, H 6.71, N 11.66; found C 74.76, H 6.65, N 11.63;

9-Cyano-8-(4-methoxybenzyl)-8-aza-7-oxadispiro[2.0.2.3]nonane (47d): Column chromatography (R_f = 0.34, 55 g of silica gel, 3 × 17 cm column, hexane/Et_2O 10:1) of the residue obtained from the nitrone **44d** (2.5 g, 13 mmol) and bicyclopropylidene **24** (2.10 g, 2.46 mL, 26.2 mmol) according to GP 1 (20 °C, 8 d) gave the cycloadduct **47d** (3.50 g, 100%) as a colorless solid, m.p. 70–71 °C. – IR (KBr): $\tilde{\nu}$ = 3075 cm^{-1}, 3010, 2934, 2868, 2838, 2246, 1611, 1585, 1512, 1468. – ^1H NMR (250 MHz, $CDCl_3$): δ = 0.36–0.70 (m, 4 H, CH_2, cPr-H), 0.82–1.04 (m, 4 H, CH_2, cPr-H), 3.80 (s, 3 H, OCH_3), 3.81 (s, 1 H, CH), 4.04–4.28 (m, 2 H, NCH_2), 6.85–6.91 (m, 2 H, Ar-H), 7.30–7.37 (m, 2 H, Ar-H). – ^{13}C NMR (50.3 MHz, $CDCl_3$, additional APT): δ = 7.2 (–, CH_2, cPr-C), 7.7 (–, CH_2, cPr-C), 8.2 (–, CH_2, cPr-C), 11.2 (–, CH_2, cPr-C), 55.2 (+, OCH_3), 62.3 (+, CH), 66.5 (C_{quat}, C-6), 114.0 (+, 2 CH, Ar-C), 126.9 (C_{quat}, Ar-C), 130.5 (+, 2 CH, Ar-C), 159.4 (C_{quat}, Ar-C), three carbon atoms were not detectable at this temp. – ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$, 100 °C): δ = 6.9 (–, CH_2, cPr-C), 7.4 (–, CH_2, cPr-C), 7.7 (–, CH_2, cPr-C), 10.5 (–, CH_2, cPr-

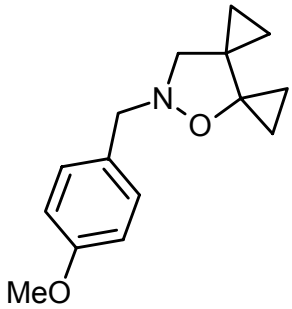
C), 30.5 (C_{quat}, C-3), 55.2 (+, OCH_3), 60.2 (–, NCH_2), 62.3 (+, CH), 66.2 (C_{quat}, C-6), 114.1 (+, 2 CH, Ar-C), 116.2 (C_{quat}, CN), 127.3 (C_{quat}, Ar-C), 130.1 (+, 2 CH, Ar-C), 159.4 (C_{quat}, Ar-C). – MS (EI): *m/z* (%) = 270 (20) [M^+], 241 (8), 135 (25), 121 (100). – $C_{16}H_{18}N_2O_2$ (270.3): calcd. C 71.09, H 6.71, N 10.36; found C 70.97, H 6.58, N 10.12.

8-Benzyl-9-(2-iodophenyl)-7-oxa-8-azadispiro[2.0.2.3]nonane (47e): Column chromatography (R_f = 0.37, 50 g of silica gel, 3 × 14 cm column, hexane/Et_2O 5:1) of the residue obtained from nitrone **44e** (0.920 g, 2.73 mmol) and bicyclopropylidene **24** (0.219 g, 0.26 mL, 2.73 mmol) according to GP 1 (60 °C, 6 d) gave the cycloadduct **47e** (1.00 g, 88%) as a yellow oil. – IR (film): $\tilde{\nu}$ = 3053 cm^{-1}, 3031, 2998, 2871, 2831, 1497, 1456, 1425. – ^1H NMR (250 MHz, $CDCl_3$): δ = 0.10–0.22 (m, 2 H, CH_2, cPr-H), 0.36–0.45 (m, 2 H, CH_2, cPr-H), 0.55–0.57 (m, 1H, CH_2, cPr-H), 0.89–0.99 (m, 3 H, CH_2, cPr-H), 4.07–4.13 (d, $^2J_{H,H}$ = 15.0 Hz, 1 H, NCH_2), 4.22–4.28 (d, $^2J_{H,H}$ = 15.0 Hz, 1 H, NCH_2), 4.64 (s, 1 H), 6.92–6.96 (td, $^3J_{H,H}$ = 7.5, $^4J_{H,H}$ = 2.5 Hz, 1 H, Ar-H), 7.19–7.36 (m, 6 H, Ar-H), 7.71–7.74 (dd, $^3J_{H,H}$ = 7.5, $^4J_{H,H}$ = 1.2 Hz, 1 H, Ar-H), 7.80–7.84 (dd, $^3J_{H,H}$ = 7.5, $^4J_{H,H}$ = 2.5 Hz, 1 H, Ar-H). – ^{13}C NMR (62.9 MHz, $CDCl_3$, additional APT): δ = 6.5 (–, CH_2, cPr-C), 7.1 (–, CH_2, cPr-C), 8.9 (–, CH_2, cPr-C), 9.3 (–, CH_2, cPr-C), 33.5 (–, C_{quat}, C-3), 61.8 (–, NCH_2), 66.9 (–, C_{quat}, C-6), 78.5 (+, CH), 100.1 (–, C_{quat}, Ar-C), 127.0 (+, CH, Ar-C), 128.1 (+, 2 CH, Ar-C), 128.3 (+, CH, Ar-C), 128.8 (+, 2 CH, Ar-C), 129.2 (+, CH, Ar-C), 131.1 (+, CH, Ar-C), 137.5 (–, C_{quat}, Ar-C), 138.8 (+, CH, Ar-C), 141.5(–, C_{quat}, Ar-C). – MS (EI): *m/z* (%) = 417 (20), 348 (5), 307 (5), 214 (15), 129 (60), 106 (10), 91 (100), 65 (15). – $C_{20}H_{20}INO$ (417.28): calcd; C 57.57, H 4.8, N 3.36; found C 57.65, H 4.66, N 3.28.

8-(*p*-Methoxybenzyl)-9-(2-iodophenyl)-7-oxa-8-azadispiro[2.0.2.3]nonane (47f): Column chromatography (R_f = 0.4, 38 g of silica gel, 6 × 4 cm column, hexane/Et_2O 4:1) of the residue obtained from nitrone **44f** (0.906 g, 2.46 mmol) and bicyclopropylidene **24** (0.197 g, 0.230 mL, 2.46 mmol) according to GP 1 (65 °C, 4 d) gave the cycloadduct **47f** (0.827 g, 75%) as a yellow solid, m.p = 84–85 °C. – IR (film): $\tilde{\nu}$ = 3066 cm^{-1}, 2996, 2837, 1616, 1513, 1245, 1030, 1008. – ^1H NMR (250 MHz, $CDCl_3$): δ = 0.13–0.22 (m, 2 H, CH_2, cPr-H), 0.36–0.56 (m, 3 H, CH_2, cPr-H), 0.88–1.00 (m, 3 H, CH_2, cPr-H), 3.76 (s, 3 H, OCH_3), 4.02–

4.07 (d, $^2J_{H,H}$ = 14.0 Hz, 1 H, NCH_2), 4.17–4.22 (d, $^2J_{H,H}$ = 14.0 Hz, 1 H, NCH_2), 4.78 (s, 1 H), 6.76–6.82 (m, 2 H, Ar-H), 6.89–6.95 (td, $^3J_{H,H}$ = 7.7, $^4J_{H,H}$ = 1.6 Hz, 1 H, Ar-H), 7.24–7.37 (m, 3 H, Ar-H), 7.70–7.74 (dd, $^3J_{H,H}$ = 8.0, $^4J_{H,H}$ = 1.0 Hz, 1 H, Ar-H), 7.78–7.82 (dd, $^3J_{H,H}$ = 8.0, $^4J_{H,H}$ = 1.6 Hz, 1 H, Ar-H). – ^{13}C NMR (62.9 MHz, $CDCl_3$, additional APT): δ = 6.5 (–, CH_2, cPr-C), 7.1 (–, CH_2, cPr-C), 8.8 (–, CH_2, cPr-C), 9.4 (–, CH_2, cPr-C), 33.5 (–, C_{quat}, C-3), 55.2 (+, OCH_3), 61.3 (–, NCH_2), 66.9 (–, C_{quat}, C-6), 78.2 (+, CH), 100.1 (–, C_{quat}, Ar-C), 113.5 (+, 2 CH, Ar-C), 128.3 (+, CH, Ar-C), 129.1 (+, CH, Ar-C), 129.5 (–, C_{quat}, Ar-C), 130.1 (+, 2 CH, Ar-C), 131.0 (+, CH, Ar-C), 138.8 (+, CH, Ar-C), 141.7 (–, C_{quat}, Ar-C), 158.7 (–, C_{quat}, Ar-C). – MS (EI): *m/z* (%) = 447 (8) [M^+], 337 (8), 244 (10), 162 (6), 135 (24), 121 (100), 91 (10), 77 (16). – $C_{21}H_{22}INO_2$ (447.31): calcd; C 56.39, H 4.96, N 3.13; found C, H, N.

8-(*p*-Methoxybenzyl)-7-oxa-8-aza-dispiro[2.0.2.3]nonane (47g): Column chromatography



(R_f = 0.27, 42 g of silica gel, 3 × 12 cm column, hexane/Et_2O 2:1) of the residue obtained from the nitrone **44g** (0.176 g, 1.06 mmol) and bicyclopropylidene **24** (0.424 g, 0.50 mL, 5.3 mmol) according to GP 1 in CH_2Cl_2 (20 °C, 6 d) gave the cycloadduct **47g** (0.055 g, 21%) as a colorless oil. – IR (film): $\tilde{\nu}$ = 3072 cm^{-1}, 3000, 2934, 2835, 1612, 1586, 1513, 1463, 1442. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.29 (bs, 4 H, CH_2, cPr-H), 0.56 (bs, 2 H, CH_2, cPr-H), 0.78 (bs, 2 H, CH_2, cPr-H), 2.90 (bs, 1 H, NCH_2), 3.3 (bs, 1 H, NCH_2), 3.7 (s, 3 H, OCH_3), 3.88 (bs, 1 H, NCH_2Ph), 4.15 (bs, 1 H, NCH_2Ph), 6.74–6.79 (m, 2 H, Ar-H), 7.19–7.22 (m, 2 H, Ar-H). – ^{1}H NMR (300 MHz, $C_2D_2Cl_4$, 100 °C): δ = 0.35–0.40 (m, 2 H, CH_2, cPr-H), 0.43–0.47 (m, 2 H, CH_2, cPr-H) 0.66–0.70 (m, 2 H, CH_2, cPr-H), 0.84–0.89 (m, 2 H, CH_2, cPr-H), 3.22 (s, 2 H, NCH_2), 3.82 (s, 3 H, OCH_3), 4.12 (s, 2 H, NCH_2Ph), 6.86–6.91 (m, 2 H, Ar-H), 7.28–7.32 (m, 2 H, Ar-H). – ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$, 100 °C): δ = 7.3 (2 CH_2, cPr-C), 8.1 (2 CH_2, cPr-C), 26.4 (C_{quat}, C-3), 55.1 (OCH_3), 62.2 (CH_2, *), 62.9 (CH_2, *), 65.6 (C_{quat}, C-6), 113.7 (2 CH, Ar-C), 129.7 (C_{quat}, Ar-C), 130.0 (2 CH, Ar-C), 158.8 (C_{quat}, Ar-C). – MS (EI): *m/z* (%) = 245 (85), 230 (22), 216 (25), 188 (15), 135 (45), 121 (100). – $C_{15}H_{19}NO_2$ (245.32): calcd. C 73.44, H 7.81, N 5.71; found C 73.22, H 8.06, N 5.61.

Preparation of β-Lactams 53a–e. General Procedure 2.

(GP 2): To the solution of the respective isoxazolidine **47** in acetonitrile was added trifluoroacetic acid (TFA), and the resulting mixture was stirred at 70 °C for the indicated time. After cooling to ambient temp., the mixture was filtered through a pad of Celite, concentrated under reduced pressure, and the crude product was purified by column chromatography on silica gel.

5-Benzyl-6-phenyl-5-azaspiro[2.3]hexane-4-one (53a): Column chromatography (R_f = 0.15, 40 g of silica gel, 3 × 14 cm column, hexane/Et_2O 3:1) of the residue obtained from the isoxazolidine **47a** (1.48 g, 5.08 mmol) and TFA (698 mg, 0.472 mL, 6.12 mmol) in acetonitrile (32 mL) according to GP 2 (3 h) gave the β-lactam **53a** (1.0 g, 75%) as a colorless solid, m.p. 64–65 °C. – IR (KBr): $\tilde{\nu}$ = 3029 cm^{-1}, 1745, 1653, 1559, 1494, 1456. – ^1H NMR (250 MHz, $CDCl_3$): δ = 0.37–0.43 (ddd, $^2J_{H,H}$ = 10.0, $^3J_{H,H}$ = 7.5, 5.0 Hz, 1 H, CH_2, cPr-H), 1.01–1.06 (ddd, $^2J_{H,H}$ = 10.0, $^3J_{H,H}$ = 7.5, 5.0 Hz, 1 H, CH_2, cPr-H), 1.09–1.18 (ddd, $^2J_{H,H}$ = 10.0, $^3J_{H,H}$ = 7.5, 5.0 Hz, 1 H, CH_2, cPr-H), 1.24–1.32 (ddd, $^2J_{H,H}$ = 10.0, $^3J_{H,H}$ = 7.5, 5.0 Hz, 1 H, CH_2, cPr-H), 3.85 (d, $^2J_{H,H}$ = 15.0 Hz, 1 H, NCH_2), 4.48 (s, 1 H, CH), 4.88 (d, $^2J_{H,H}$ = 15.0 Hz, 1 H, NCH_2), 7.15–7.21 (m, 4 H, Ar-H), 7.24–7.43 (m, 6 H, Ar-H). – ^{13}C NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 7.2 (–, CH_2, cPr-C), 8.2 (–, CH_2, cPr-C), 40.3 (C_{quat}, C-3), 44.5 (–, NCH_2), 61.4 (+, CH), 127.5 (+, CH, Ar-C), 127.6 (+, CH, Ar-C), 128.4 (+, 4 CH, Ar-C), 128.6 (+, 2 CH, Ar-C), 128.7 (+, 2 CH, Ar-C), 135.8 (C_{quat}, Ar-C), 136.3 (C_{quat}, Ar-C), 172.4 (C_{quat}, C=O). – MS (EI): *m/z* (%) = 263 (36) [M^+], 172 (10), 130 (100), 129 (85), 115 (42), 91 (65). – $C_{18}H_{17}NO$ (263.3): calcd. C 82.10, H 6.51, N 5.32; found C 82.0, H 6.25, N 5.12.

Methyl 5-Benzyl-6-oxo-5-azaspiro[2.3]hexane-4-carboxylate (53b): Column chromatography (R_f = 0.21, 40 g of silica gel, 3 × 14 cm column, hexane/Et_2O 1:1) of the residue obtained from the isoxazolidine **47b** (1.41 g, 5.16 mmol) and TFA (0.710 g, 0.480 mL, 6.22 mmol) in acetonitrile (32 mL) according to GP 2 (12 h) gave the β-lactam **53b** (990 mg, 78%) as a yellow oil. – IR (film): $\tilde{\nu}$ = 3065 cm^{-1}, 3029, 3003, 2953, 2849, 1756, 1729, 1455, 1436. – ^1H NMR (250 MHz, $CDCl_3$): δ = 0.84–0.92 (m, 1 H, CH_2, cPr-H), 1.06–1.16 (m, 1 H,

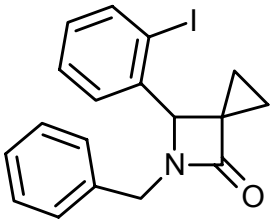
CH_2, cPr-H), 1.18–1.29 (m, 2 H, CH_2, cPr-H), 3.71 (s, 3 H, OCH_3), 4.02 (s, 1 H, CH), 4.24 (d, $^2J_{H,H}$ = 15.0 Hz, 1 H, NCH_2), 4.91 (d, $^2J_{H,H}$ = 15.0 Hz, 1 H, NCH_2), 7.25–7.39 (m, 5 H, Ar-H). – ^{13}C NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 6.5 (–, CH_2, cPr-C), 8.0 (–, CH_2, cPr-C), 37.2 (C_{quat}, C-3), 45.5 (–, NCH_2), 52.1 (+, CH), 57.4 (+, OCH_3), 127.7 (+, CH, Ar-C), 128.3 (+, 2 CH, Ar-C), 128.7 (+, 2 CH, Ar-C), 135.2 (C_{quat}, Ar-C), 170.0 (C_{quat}, C=O, *), 170.9 (C_{quat}, C=O, *). – MS (EI): *m/z* (%) = 245 (4) [M^+], 217 (20), 186 (30), 158 (40), 91 (100). – $C_{14}H_{15}NO_3$ (245.3): calcd. C 68.56, H 6.16, N 5.71; found C 68.45, H 6.08, 5.49.

5-Benzyl-6-oxo-5-azaspiro[2.3]hexane-4-carbonitrile (53c): Column chromatography (R_f = 0.11, 41 g of silica gel, 3 × 12 cm column, hexane/Et_2O 2:1) of the residue obtained from the isoxazolidine **47c** (627 mg, 2.61 mmol) and TFA (357 mg, 0.24 mL, 3.13 mmol) in acetonitrile (15 mL) according to GP 2 (12 h) gave the β-lactam **53c** (415 mg, 75%) as a colorless oil. – IR (film): $\tilde{\nu}$ = 3065 cm^{-1}, 3032, 3009, 2923, 2243, 1772, 1496, 1456, 1382, 1355. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.17–1.29 (m, 2 H, CH_2, cPr-H), 1.32–1.44 (m, 2 H, CH_2, cPr-H), 4.14 (s, 1 H, CH), 4.25 (d, $^2J_{H,H}$ = 15.1 Hz, 1 H, NCH_2), 4.81 (d, $^2J_{H,H}$ = 15.1 Hz, 1 H, NCH_2), 7.27–7.42 (m, 5 H, Ar-H). – ^{13}C NMR (75.5 MHz, $CDCl_3$, additional APT): δ = 8.2 (–, CH_2, cPr-C), 9.1 (–, CH_2, cPr-C), 38.3 (–, C_{quat}, C-3), 46.0 (–, NCH_2), 46.7 (+, CH), 115.6 (–, C_{quat}, CN), 128.3 (+, CH), 128.4 (+, 2 CH, Ar-C), 129.0 (+, 2 CH, Ar-C), 133.9 (–, C_{quat}, Ar-C), 169.8 (–, C_{quat}, C=O). – MS (EI): *m/z* (%) = 212 (85) [M^+], 183 (32), 122 (32), 91 (100), 80 (45), 69 (50). – $C_{13}H_{12}N_2O$ (212.25): calcd. C 73.56, H 5.70, N 13.20; found C 73.74, H 5.77, N 13.08.

5-(*p*-Methoxybenzyl)-6-oxo-5-azaspiro[2.3]hexane-4-carbonitrile (53d): Column chromatography (R_f = 0.10, 44 g of silica gel, 3 × 13 cm column, hexane/Et_2O 1.5:1) of the residue obtained from the isoxazolidine **47d** (2.00 g, 7.40 mmol) and TFA (1.01 g, 0.68 mL, 8.88 mmol) in acetonitrile (45 mL) according to GP 2 (12 h) gave the β-lactam **53d** (1.68 g, 94%) as a colorless solid, m.p. 54–56 °C. – IR (KBr): $\tilde{\nu}$ = 3003 cm^{-1}, 2973, 2913, 2867, 2841, 2249, 1754, 1613, 1585, 1515. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.14–1.27 (m, 2 H, CH_2, cPr-H), 1.30–1.44 (m, 2 H, CH_2, cPr-H), 3.80 (s, 3 H, OCH_3), 4.10 (s, 1 H, CH), 4.18 (d, $^2J_{H,H}$ = 15.0 Hz, 1 H, NCH_2), 4.75 (d, $^2J_{H,H}$ = 15.0 Hz, 1 H, NCH_2), 6.84–6.93 (m, 2 H, Ar-H), 7.20–7.26 (m, 2 H, Ar-H). – ^{13}C NMR (62.9 MHz, $CDCl_3$,

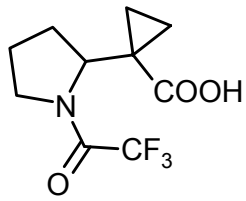
additional DEPT): δ = 8.2 (–, CH_2, cPr-C), 9.0 (–, CH_2, cPr-C), 38.2 (C_{quat}, C-3), 45.5 (–, NCH_2), 46.4 (+, CH), 55.2 (+, OCH_3), 114.3 (+, 2 CH, Ar-C), 115.7 (C_{quat}, CN), 125.9 (C_{quat}, Ar-C), 129.8 (+, 2 CH, Ar-C), 159.5 (C_{quat}, Ar-C), 169.6 (C_{quat}, C=O). – MS (EI): *m/z* (%) = 242 (40) [M^+], 213 (15), 121 (100). – $C_{14}H_{14}N_2O_2$ (242.3): calcd. C 69.41, H 5.82, N 11.56; found C 69.14, H 5.61, N 11.37.

5-Benzyl-6-(2-iodophenyl)-5-azaspiro[2.3]hexane-4-one (53e): Column chromatography



(R_f = 0.26, 35 g of silica gel, 3 × 10 cm column, hexane/Et_2O 2:1) of the residue obtained from the isoxazolidine **47e** (0.350 g, 0.840 mmol) and TFA (0.144 g, 0.1 mL, 1.26 mmol) in acetonitrile (10 mL) according to GP 2 (1 h) gave the β-lactam **53e** (0.290 g, 89%) as colorless oil. – IR (film): $\tilde{\nu}$ = 3062 cm^{-1}, 3029, 3001, 2916, 1761, 1584, 1563, 1455, 1437. – ^1H NMR (250 MHz, $CDCl_3$): δ = 0.37–0.43 (m, 1 H, cPr-H), 1.05 (m, 1 H, cPr-H), 1.25–1.33 (m, 2 H, cPr-H), 3.96–4.02 (d, $^2J_{H,H}$ = 15.0 Hz, 1 H, NCH_2), 4.88–4.94 (d, $^2J_{H,H}$ = 15.0 Hz, 1 H, NCH_2), 4.91 (s, 1 H), 6.98–7.04 (m, 1 H, Ar-H), 7.22–7.38 (m, 7 H, Ar-H), 7.77–7.81 (m, 1 H, Ar-H). – ^{13}C NMR (62.9 MHz, $CDCl_3$, additional APT): δ = 6.9 (–, CH_2, cPr-C), 9.0 (–, CH_2, cPr-C), 41.1 (–, C_{quat}, C-3), 45.3 (–, NCH_2), 64.2 (+, CH), 98.4 (–, C_{quat}, Ar-C), 127.4 (+, CH, Ar-C), 127.7 (+, CH, Ar-C), 128.5 (+, 2 CH, Ar-C), 128.7 (+, CH, Ar-C), 128.8 (+, 2 CH, Ar-C), 129.8 (+, CH, Ar-C), 135.6 (–, C_{quat}, Ar-C), 139.1 (–, C_{quat}, Ar-C), 139.5 (CH, Ar-C), 172.9 (–, C_{quat}, C=O). – MS (EI): *m/z* (%) = 389 (8), 262 (10), 129 (100), 91 (80), 77 (10), 65 (20), 51 (10), 41 (5). – $C_{18}H_{16}INO$ (389.23): calcd; C 55.54, H 4.14, N 3.6; found C 55.80, H 4.16, N 3.73.

1-[1-(2,2,2-Trifluoroacetyl)-pyrrolidin-2-yl]-cyclopropane carboxylic acid (72): Column



chromatography (R_f = 0.13, 160 g of silica gel, 5 × 17 cm column, CH_2Cl_2/MeOH 60:1 + 1% NH_3) of the residue obtained from the isoxazolidine **70** (6.28 g, 38.0 mmol) and TFA (5.24 g, 3.5 mL, 46.0 mmol) in acetonitrile (210 mL) according to GP 2 (12 h) gave the product **72** (1.70 g, 18%) as a colorless solid, m.p. 127–128 °C. – IR (KBr): $\tilde{\nu}$ = 3423 cm^{-1}, 2979, 1690, 1458, 1141. – ^1H NMR (250 MHz, $CDCl_3$): δ = 0.77–0.83 (m, 1 H, CH_2, cPr-H), 1.31–1.44 (m, 2 H, CH_2, cPr-H), 1.50–1.56 (m, 1 H, CH_2, cPr-H), 1.71–1.87 (m, 1 H), 2.03–2.26 (m, 3 H), 3.69–3.86 (m, 3H). – ^{13}C NMR (75.5 MHz, $CDCl_3$, additional APT): δ = 15.3 (–, CH_2, cPr-C), 18.3 (–, CH_2, cPr-C), 24.9(–, *), 25.3 (–, *), 29.6 (–, *), 48.2 (–, q, $^4J_{C,F}$ =

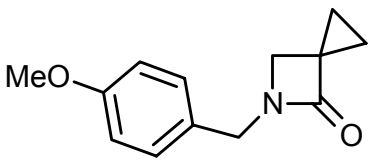
3.8 Hz, C-3), 62.2 (+, C-1), 116.4 (–, q, $^{1}J_{C,F}$ = 287.6 Hz, CF_3), 156.2 (–, q, $^{2}J_{C,F}$ = 36.2 Hz, $COCF_3$), 179.6 (–, C=O). – MS (EI): *m/z* (%) = 251 (15) [M^+], 206 (45), 182 (50), 166 (100), 154 (40), 136 (20), 69 (60), 41 (50). – MS (DCI): m/z (%) = 520 (10) [2 M + NH_4^+], 286 (10) [M + NH_3 + NH_4^+], 269 (100) [M + NH_4^+], 252 (5) [M + H^+].

2.2. Synthesis of Compounds in Chapter 2

Reaction of Bicyclopropylidene with *in situ* generated nitrones. General Procedure 3 (GP 3): The hydroxylamine salt (1 equiv.), sodium acetate (1 equiv.), formaline (1.5 equiv.) and bicyclopropylidene (1.5 equiv.) were stirred in ethanol (solution 0.3 M) at room temperature in a sealed tube. After the indicated time the reaction mixture was transferred to a flask and the solvent evaporated to dryness. Equal amounts of water and ethyl acetate were added. The two phases were separated and the water phase was extracted thrice with ethyl acetate, after being basified to pH = 8 with a sat. solut. of $NaHCO_3$.The combined organic layers were washed with brine and dried over Na_2SO_4, and the crude product was purified by column cromatography.

5-(*p*-Methoxybenzyl)-5-azaspiro[2.3]hexan-4-one (53g) and 8-(*p*-Methoxybenzyl)-7-oxa-8-aza-dispiro[2.0.2.3]nonane (47g): Column chromatography (42 g of silica gel, 12 × 3 cm column, hexane/Et_2O 3:1) of the residue obtained from hydroxylamine 65d·$(COOH)_2$ (0.998 g, 4.10 mmol), formaldehyde 66-H solution (12.3 M) in water (0.5 mL, 6.15 mmol), bicyclopropylidene (24) (0.58 mL, 0.493 g, 6.15 mmol), and NaOAc (0.336 g, 4.10 mmol) in 13.7 mL of ethanol according to GP 3 (25 °C, 6 days) gave the product 53g (R_f = 0.28, 0.201 g, 22%) and 47g (R_f = 0.33, 0.082 g, 8%) as yellow oils.

53g: – IR (KBr): $\tilde{\nu}$ = 3080 cm^{-1}, 3001, 2936, 2894, 2839, 1732, 1512, 1401. – ^1H NMR (250 MHz, $CDCl_3$): δ = 0.90–0.95 (m, 2 H, cPr-H), 1.16–1.21 (m, 2 H, cPr-H), 3.30 (s, 2 H), 3.80 (s, 3 H), 4.40 (s, 2 H), 6.85–6.91 (m, 2 H, Ar-H), 7.17–7.23 (m, 2 H, Ar-H). – ^{13}C NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 7.33 (–, 2 CH_2, cPr-H), 31.8 (C_{quat}, C-3), 45.6 (–, NCH_2, *), 47.7 (–, NCH_2, *), 55.1 (+, CH_3), 113.9 (+, 2 CH, Ar-C), 127.8 (C_{quat}, Ar-C), 129.2 (+, 2 CH, Ar-C), 158.9 (C_{quat}, Ar-C), 172.3 (C_{quat}, C=O). – MS (EI): *m/z* (%) = 217 (100), 186 (8), 163 (10), 121 (85), 78 (10). – $C_{13}H_{15}NO_2$ (217.26): calcd. C 71.87, H 6.96, N 6.45; found C 72.07, H 7.10, N 6.30.



5-Benzyl-5-azaspiro[2.3]hexan-4-one (53j): Column chromatography (25 g of silica gel, 15 × 2 cm column, hexane/Et_2O 2:1) of the residue obtained from hydroxylamine **65c·HCl** (0.499 g, 3.13 mmol), formaldehyde **66**-H solution (12.3 M) in water (0.380 mL, 4.67 mmol), bicyclopropylidene (**24**) (0.440 mL, 0.374 g, 4.67 mmol), and NaOAc (0.257 g, 3.13 mmol) in 10.9 mL of ethanol according to GP 3 (25 °C, 8 days) gave the product **53j** (R_f = 0.23, 0.144 g, 25%) as a yellow oil. – IR (film): $\tilde{\nu}$ = 3064 cm^{-1}, 3004, 2890, 1751, 1496, 1455, 1395, 1354. – ^1H NMR (250 MHz, $CDCl_3$): δ = 0.92–0.97 (m, 2 H, cPr-H), 1.18–1.23 (m, 2 H, cPr-H), 3.33 (s, 2 H, CH_2), 4.47 (s, 2 H, CH_2), 7.17–7.39 (m, 5 H, Ar-H). – ^{13}C NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 7.6 (–, 2 CH_2, cPr-C), 32.1 (C_{quat}, C-3), 46.3 (–, NCH_2, *), 48.1 (–, NCH_2, *), 127.6 (+, CH, Ar-C), 128.1 (+, 2 CH, Ar-C), 128.7 (+, 2 CH, Ar-C), 136.0 (C_{quat}, Ar-C), 172.6 (C_{quat}, C=O). – MS (EI): *m/z* (%) = 187 (44), 131 (10), 91 (100), 54 (21). – $C_{12}H_{13}NO$ (187.24): calcd. C 76.98, H 7.00, N 7.48; found C 76.83, H 7.13, N 7.25.

Synthesis of β-lactams by reaction of Bicyclopropylidene with *in situ* generated nitrones under traditional heating. General Procedure 4

(GP 4): The hydroxylamine salt (1 equiv.), sodium acetate (1 equiv.), formaline (1.5 equiv.) and bicyclopropylidene (1.5 equiv.) were stirred in ethanol (solution 0.3 M) at the indicated temperature in a sealed tube. After the indicated time the reaction mixture was transferred to a flask and the solvent evaporated to dryness. Equal amounts of water and ethyl acetate were added. The two phases were separated and the water phase was extracted thrice with ethyl acetate, after being basified to pH = 8 with a sat. solution of $NaHCO_3$. After that, the combined organic layers were washed with brine, dried over sodium sulfate, and the crude product was purified by column cromatography.

5-(*p*-Methoxybenzyl)-5-azaspiro[2.3]hexan-4-one (53g): Column chromatography (20 g of silica gel, 12 × 1 cm column, hexane/Et_2O 3:1) of the residue obtained from hydroxylamine **65d·(COOH)$_2$** (0.280 g, 1.15 mmol), formaldehyde (**66**-H) solution (12.3 M) in water (0.14 mL, 1.72 mmol), bicyclopropylidene (**24**) (0.16 mL, 0.138 g, 1.72 mmol), and NaOAc (0.094 g, 1.15 mmol) in 4.0 mL of ethanol according to GP 4 (45 °C, 7 days) gave the product **53g** (R_f = 0.28, 0.075 g, 30%) as a yellow oil.

5-Benzyl-5-azaspiro[2.3]hexan-4-one (53j): Column chromatography (25 g of silica gel, 15 × 2 cm column, hexane/Et_2O 2:1) of the residue obtained from hydroxylamine **65c·HCl** (0.499 g, 3.13 mmol), formaldehyde **66**-H solution (12.3 M) in water (0.380 mL, 4.67 mmol), bicyclopropylidene (**24**) (0.440 mL, 0.374 g, 4.67 mmol), and NaOAc (0.257 g, 3.13 mmol) in 10.9 mL of ethanol according to GP 4 (50 °C, 5 days) gave the product **53j** (R_f = 0.23, 0.194 g, 33%) as a yellow oil.

Synthesis of β-lactams by reaction of Bicyclopropylidene with *in situ* generated nitrones under high pressure. General Procedure 5

(GP 5): The hydroxylamine salt (1 equiv.), sodium acetate (1 equiv.), formaline (2.0 equiv.) and bicyclopropylidene (2.0 equiv.) were mantained in ethanol (solution 0.3 M) at room temperature in a sealed teflon-tube under 10 Kbar pressure. After 24 h the reaction mixture was transferred to a flask and the solvent evaporated to dryness. Equal amounts of water and ethyl acetate were added. The two phases were separated and the water phase was washed thrice with ethyl acetate, after being basified to pH = 8 with a sat. solution of $NaHCO_3$. After that the combined organic layers were washed with brine, dried over sodium sulfate and the crude product was purified by column cromatography.

5-(*p*-Methoxybenzyl)-5-azaspiro[2.3]hexan-4-one (53g): Column chromatography (25 g of silica gel, 2 × 15 cm column, hexane/Et_2O 3:1) of the residue obtained from hydroxylamine **65d·(COOH)$_2$** (0.243 g, 1.00 mmol), formaldehyde (**66**-H) solution (8 M) in water (0.25 mL, 2.00 mmol), bicyclopropylidene (**24**) (0.19 mL, 0.160 g, 2.00 mmol), and NaOAc (0.082 g, 1.00 mmol) in 3.5 mL of ethanol according to GP 5 (25 °C) gave the product **53g** (R_f = 0.28, 0.062 g, 28%) as a yellow oil.

5-Benzyl-5-azaspiro[2.3]hexan-4-one (53j): Column chromatography (20 g of silica gel, 11 × 2 cm column, hexane/Et_2O 2:1) of the residue obtained from hydroxylamine **65c·HCl** (0.160 g, 1.00 mmol), formaldehyde **66**-H solution (8.0 M) in water (0.25 mL, 2.00 mmol), bicyclopropylidene (**24**) (0.190 mL, 0.160 g, 2.00 mmol), and NaOAc (0.082 g, 1.00 mmol) in 3.5 mL of ethanol according to GP 5 (25 °C) gave the product **53j** (R_f = 0.23, 0.041 g, 22%) as a yellow oil.

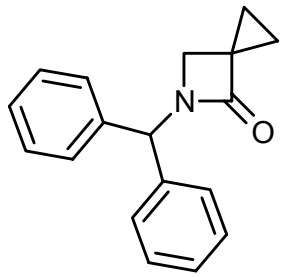
Microwave assisted one-pot three-component synthesis of β-lactams 53g,j, 53e-H,f-H, 77c-Et,f-Et and 77d-Me. General Procedure 6

(GP 6): A solution of the hydroxylamine salt (2 equiv.), the aldehyde (2 equiv.), bicyclopropylidene (**24**) (1 equiv.), and NaOAc (2 equiv.) in ethanol was sealed in a screw-capped vial for the microwave apparatus and heated at the indicated temperature for the indicated time. After cooling down to room temperature, the solution was concentrated under reduced pressure. An equal amount each of water and ethyl acetate was added, and the two phases were separated. The water phase was made basic with a satd. solution of $NaHCO_3$ and extracted three times with ethyl acetate. The combined organic layers were then washed with brine, dried over Na_2SO_4 and the crude product was purified by column cromatography.

5-(*p*-Methoxybenzyl)-5-azaspiro[2.3]hexan-4-one (53g): Column chromatography (R_f = 0.28, 30 g of silica gel, 12 × 2.5 cm column, hexane/Et_2O 3:1) of the residue obtained from hydroxylamine **65d·(COOH)$_2$** (0.780 g, 3.20 mmol), formaldehyde (**66**-H) solution (8.0 M) in water (0.250 mL, 2.00 mmol), bicyclopropylidene (**24**) (0.190 mL, 0.160 g, 2.00 mmol), and NaOAc (0.263 g, 3.20 mmol) in 2.50 mL of ethanol according to GP 6 (80 °C, 45 min) gave the product **53g** (0.232 g, 53%) as a yellow oil.

5-Benzyl-5-azaspiro[2.3]hexan-4-one (53j): Column chromatography (R_f = 0.29, 45 g of silica gel, 12 × 3 cm column, hexane/Et_2O 2:1) of the residue obtained from hydroxylamine **65·HCl** (0.638 g, 4.00 mmol), formaldehyde **66**-H solution (8.0 M) in water (0.250 mL, 2.00 mmol), bicyclopropylidene (**24**) (0.190 mL, 0.160 g, 2.00 mmol), and NaOAc (0.328 g, 4.00 mmol) in 1.75 mL of ethanol according to GP 6 (100 °C, 60 min) gave the product **53j** (0.255 g, 68%) as a yellow oil.

5-(Benzhydryl)-5-azaspiro[2.3]hexan-4-one (53e-H): Column chromatography (R_f = 0.18, 36 g of silica gel, 15 × 2.5 cm column, hexane/Et_2O 2:1) of the residue obtained from hydroxylamine **65e·HCl** (0.707 g, 3.00 mmol), formaldehyde (**66**-H) solution (8.0 M) in water (0.375 mL, 3.00 mmol), bicyclopropylidene (**24**) (0.140 mL, 1.50 mmol), and NaOAc (0.246 g, 3.00 mmol) in 2.00 mL of ethanol according to GP 6 (100 °C, 30 min) gave the product **53e**-H (193 mg, 49%) as a colorless solid, m.p. 95–96 °C. – IR (KBr): $\tilde{\nu}$ = 3080 cm^{-1}, 3060, 2962, 2892, 1888, 1745, 1597, 1581, 1494, 1446, 1384, 1364. – ^{1}H NMR (250 MHz, $CDCl_3$):



δ = 0.93–0.98 (m, 2 H, cPr-H), 1.20–1.25 (m, 2 H, cPr-H), 3.39 (s, 2 H, CH_2), 6.25 (s, 1 H, CH), 7.02–7.28 (m, 5 H, Ar-H), 7.30–7.40 (m, 5 H, Ar-H). – ^{13}C NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 7.8 (–, 2 CH_2, cPr-H), 31.4 (C_{quat}, C-3), 47.4 (–, CH_2), 59.3 (+, CH), 127.6 (+, 2 CH, Ar-C), 128.1 (+, 4 CH, Ar-C), 128.6 (+, 4 CH, Ar-C), 139.2 (2 C_{quat}, Ar-C), 172.5 (C_{quat}, C=O). – MS (EI): *m/z* (%) = 263 (45), 186 (20), 167 (100), 165 (25), 152 (18), 91 (18). – $C_{18}H_{17}NO$ (263.33): calcd. C 82.10, H 6.51, N 5.32; found C 82.12, H 6.25, N 5.16.

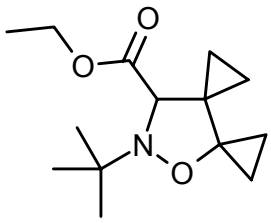
5-*tert*-Butyl-5-azaspiro[2.3]hexan-4-one (53f-H): Column chromatography (R_f = 0.19, 25 g of silica gel, 12 × 2 cm column, hexane/Et_2O 2:1) of the residue obtained from hydroxylamine **65f·HCl** (0.251 g, 2.00 mmol), formaldehyde (**66**-H) solution (8.0 M) in water (0.25 mL, 2.00 mmol), bicyclopropylidene (**24**) (0.09 mL, 1.00 mmol), and NaOAc (0.164 g, 2.00 mmol) in 0.5 mL of ethanol according to GP 6 (80 °C, 30 min) gave the product **53f**-H (0.111 g, 73%) as a colorless oil. – IR (film): $\tilde{\nu}$ = 2970 cm^{-1}, 2935, 2885, 2839, 1753, 1379, 1336. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.87–0.91 (m, 2 H, cPr-H), 1.09–1.14 (m, 2 H, cPr-H), 1.35 (s, 9 H, 3 CH_3), 3.35 (s, 2 H). – ^{13}C NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 7.3 (–, 2 CH_2, cPr-C), 27.9 (+, 3 CH_3), 30.2 (C_{quat}, C-3), 45.5 (–, NCH_2), 64.3 (C_{quat}), 171.3 (C_{quat}, C=O). – MS (EI): *m/z* (%) = 153 (10), 138 (100), 84 (5), 70 (100), 57 (40). – HRMS (EI) calcd. for $C_9H_{15}NO$ 153.1154 [M^+], found 153.1154.

Ethyl 5-benzyl-6-oxo-5-azaspiro[2.3]hexane-4-carboxylate (77c-Et**):** Column chromatography (R_f = 0.29, 35 g of silica gel, 12 × 2.5 cm column, hexane/Et_2O 3:1) of the residue obtained from hydroxylamine **65c·HCl** (0.479 g, 3.00 mmol), ethyl glyoxylate (**73**-Et) as a solution in toluene (50% weight) (0.60 mL, 3.00 mmol), bicyclopropylidene (**24**) (0.140 mL, 1.50 mmol), and NaOAc (0.246 g, 3.00 mmol) in 0.70 mL of ethanol according to GP 6 (80 °C, 15 min) gave the product **77c**-Et (0.279 g, 72%) as a yellow oil. – IR (film): $\tilde{\nu}$ = 2981 cm^{-1}, 1775, 1744, 1496, 1456, 1388, 1199. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.84–0.90 (ddd, $^2J_{H,H}$ = 9.4, $^3J_{H,H}$ = 7.8, 4.2 Hz, 1 H, cPr-H), 1.04–1.28 (m, 3 H, cPr-H), 1.20–1.25 (t, $^3J_{H,H}$ = 9.0 Hz, 3 H, CH_3), 3.98 (s, 1 H), 4.10–4.21 (m, 2 H, OCH_2), 4.21–4.25 (d, $^2J_{H,H}$ = 12.0 Hz, 1 H, NCH_2), 4.86–4.91 (d, $^2J_{H,H}$ = 12.0 Hz, 1 H, NCH_2), 7.22–7.36 (m, 5 H, Ar-H). – ^{13}C NMR (75.5 MHz, $CDCl_3$, additional APT): δ = 6.4 (–, CH_2, cPr-C), 8.0 (–, CH_2, cPr-C), 14.2 (+, CH_3), 37.2 (–, C_{quat}, C-3), 45.6 (–, NCH_2), 57.5 (+, CH), 61.3 (–, OCH_2),

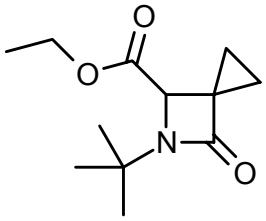
127.8 (+, CH, Ar-C), 128.4 (+, 2 CH, Ar-C), 128.8 (+, 2 CH, Ar-C), 135.3 (–, C_{quat}, Ar-C), 169.6 (–, C=O, *), 171.1 (–, C=O, *). – MS (EI): *m/z* (%) = 259 (4), 231 (18), 186 (5), 158 (39), 91 (100), 65 (15). – $C_{15}H_{17}NO_3$ (259.30): calcd. C 69.48, H 6.61, N 5.40; found C 68.76, H 6.72, N 5.52. – HRMS (EI) calcd. for $C_{15}H_{17}NO_3$ 260.1281 [$M+H^+$], found 260.1281.

One-pot protocol applied to hydroxylamine 65f·HCl and ethyl glyoxylate 73-Et*:* A solution of *tert*-butylhydroxylamine hydrochloride (**65f·HCl**) (250 mg, 2.00 mmol), ethyl glyoxylate (**73**-Et) as a toluene solution (50% ww) (0.408 g, 0.40 mL, 2.0 mmol), bicyclopropylidene (**24**) (80 mg, 0.090 mL, 1.00 mmol) and NaOAc (164 mg, 2.0 mmol) in ethanol (0.50 mL), was sealed in a screw capped vial for the microwave oven and heated at 80 ºC for 105 min. After cooling to room temperature, the solution was concentrated under reduced pressure. An equal amount each of water and ethyl acetate (30 mL) was added, and the two phases were separated. The water phase was made basic with $NaHCO_3$ (satd. solution) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were then washed with brine and dried over Na_2SO_4. The crude product was purified by column chromatography (50 g of flash silica gel, 3 × 15 cm column, hexane/Et_2O 3:1) to give ethyl 8-*tert*-butyl-7-oxa-8-azadispiro[2.0.2.3]nonane-9-carboxylate (**47f**-Et) and ethyl 5-*tert*-butyl-8-oxo-5-azaspiro[2.5]octane-4-carboxylate (**49f**-Et) (0.111 g, 44%) in a ratio **47f**-Et: **49f**-Et of 1.3:1 and ethyl 5-*tert*-butyl-6-oxo-5-azaspiro[2.3]hexane-4-carboxylate (**77f**-Et) (0.119 g, 53%) as a yellow solid. The product **49f**-Et couldn't be separated from the mixture and characterized.

(**47f**-Et): M.p. 58–60 °C. – IR (film): $\tilde{\nu}$ = 3076 cm^{-1}, 2977, 2936, 1757, 1724, 1465, 1363, 1275. – ^1H NMR (600 MHz, $CDCl_3$): δ = 0.09– 0.13 (ddd, $^2J_{H,H}$ = 10.5, $^3J_{H,H}$ = 7.2, 6.3 Hz, 1 H, cPr-H), 0.15–0.18 (m, 1 H, cPr-H), 0.50–0.54 (ddd, $^2J_{H,H}$ = 10.5, $^3J_{H,H}$ = 7.1, 5.6 Hz, 1 H, cPr-H), 0.65–0.70 (m, 3 H, cPr-H), 0.82–0.86 (dt, $^2J_{H,H}$ = 11.2, $^3J_{H,H}$ = 6.7 Hz, 1 H), 0.90–0.94 (ddd, $^2J_{H,H}$ = 11.2, $^3J_{H,H}$ = 7.2, 5.6 Hz, 1 H, cPr-H), 1.13 (s, 9 H, 3 CH_3), 1.24–1.26 (t, $^3J_{H,H}$ = 7.2 Hz, 3 H, CH_3), 3.69 (s, 1 H), 4.14–4.19 (dq, $^3J_{H,H}$ = 10.5, $^2J_{H,H}$ = 7.1 Hz, 1 H, CH_2), 4.23–4.28 (dq, $^3J_{H,H}$ = 10.5, $^2J_{H,H}$ = 7.1 Hz, 1 H, CH_2). – ^{13}C NMR (62.9 MHz, $CDCl_3$, additional APT): δ = 4.7 (–, CH_2, cPr-C), 5.1 (–, CH_2, cPr-C), 11.4 (–, CH_2, cPr-C), 12.2 (–, CH_2, cPr-C), 14.3 (+, CH_3), 25.4 (+, 3 CH_3), 31.3 (–, C_{quat}, C-3), 58.8 (–, C_{quat}), 60.9 (–, OCH_2), 65.7 (–, C_{quat}, C-6), 67.9 (+, CH), 171.7 (C_{quat}, C=O). – MS (EI): *m/z* (%) = 253 (15), 210 (5), 180 (40), 124 (100), 96 (45), 57 (100), 41 (75). – $C_{14}H_{23}NO_3$ (253.34): calcd. C 66.37, H 9.15, N 5.53; found C 66.15, H 9.09, N 5.47.

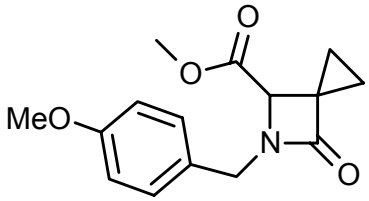


(77f-Et): (R_f = 0.7, hexane/Et_2O 3:1). – IR (film): $\tilde{\nu}$ = 2937 cm^{-1}, 1766, 1749, 1368, 1186. –



^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.68–0.74 (m, 1 H, cPr-H), 1.05–1.24 (m, 3 H, cPr-H), 1.28 (t, $^3J_{H,H}$ = 7.5 Hz, 3 H, CH_3), 1.37 (s, 9 H, 3 CH_3), 4.18 (s, 1 H), 4.21 (dq, $^2J_{H,H}$ = 7.5, $^3J_{H,H}$ = 2.5 Hz, 2 H). – ^{13}C NMR (62.9 MHz, $CDCl_3$, additional APT): δ = 6.4 (–, CH_2, cPr-C), 8.0 (–, CH_2, cPr-C), 14.3 (+, CH_3), 27.9 (+, 3 CH_3), 35.6 (–, C_{quat}, C-3), 54.3 (–, *), 57.8 (+, CH), 61.3 (–, *), 170.5 (–, C=O, *), 171.0 (–, C=O, *). – MS (EI): *m/z* (%) = 225 (15), 210 (80), 182 (100), 152 (35), 136 (20), 96 (40), 41 (35). – $C_{12}H_{19}NO_3$ (225.29): calcd. C 63.98, H 8.50, N 6.22; found C 64.07, H 8.73, N 6.01.

Methyl 5-(4-methoxybenzyl)-6-oxo-5-azaspiro[2.3]hexane-4-carboxylate (77d-Me): Co-



lumn chromatography (R_f = 0.12, 70 g of flash silica gel, 20 × 3 cm column, hexane/Et_2O 3:2) of the residue obtained from hydroxylamine **65d·(COOH)$_2$** (0.486 g, 2.00 mmol), methyl glyoxylate **73**-Me (0.176 g, 2.00 mmol), bicyclopropylidene (**24**) (0.090 mL, 1.00 mmol), and NaOAc (0.164 g, 2.00 mmol) in 1.10 mL of ethanol according to GP 6 (80 °C, 120 min) gave the product **77d**-Me (0.215 g, 78%) as a light-yellow oil. – IR (film): $\tilde{\nu}$ = 2954 cm^{-1}, 2837, 1775, 1735, 1612, 1514, 1392, 1248. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.84–0.91 (m, 1 H, cPr-H), 1.04–1.30 (m, 3 H, cPr-H), 3.71 (s, 3 H), 3.80 (s, 3 H), 3.99 (s, 1 H), 4.14–4.20 (d, $^2J_{H,H}$ = 15.0 Hz, 1 H, NCH_2), 4.82–4.88 (d, $^2J_{H,H}$ = 15.0 Hz, 1 H, NCH_2), 6.84–6.90 (m, 2 H, Ar-H), 7.15–7.21 (m, 2 H, Ar-H). – ^{13}C NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 6.6 (–, CH_2, cPr-C), 8.0 (–, CH_2, cPr-C), 37.1 (–, C_{quat}, C-3), 45.1 (–, NCH_2), 52.2 (+, CH), 55.3 (+, CH_3, *), 57.3 (+, CH_3, *), 114.1 (+, 2 CH, Ar-C), 127.2 (–, C_{quat}, Ar-C), 129.8 (+, 2 CH, Ar-C), 159.2 (–, C_{quat}, Ar-C), 170.2 (C_{quat}, C=O, *), 170.9 (C_{quat}, C=O, *). – MS (EI): *m/z* (%) = 275 (4), 243 (5), 215 (5), 188 (25), 148 (10), 121 (100), 78 (15). – $C_{15}H_{17}NO_4$ (275.30): calcd. C 65.44, H 6.22, N 5.09; found C 65.17, H 6.20, N 4.91.

One-pot three-component applied on methyl hydroxylamine 65g·HCl. General Procedure 7

(GP 7): A solution of the methyl hydroxylamine salt (2 equiv.), the aldehyde (2 equiv.), bicyclopropylidene (**24**) (1 equiv.), and NaOAc (2 equiv.) in ethanol was sealed in a screw-capped vial for the microwave apparatus and heated at the indicated temperature for the indicated time. After cooling down to room temperature, the solution was concentrated under reduced pressure. Equal amounts of water and ethyl acetate were added, and the two phases were separated. The water phase was made basic with a satd. solution of $NaHCO_3$ and extracted three times with ethyl acetate. The combined organic layers were then washed with brine and dried over Na_2SO_4.

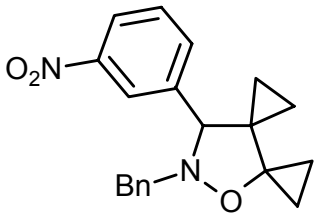
Reaction with formaldehyde 66-H: Column chromatography (25 g of silica gel, 15 × 2 cm column, hexane/Et_2O 2:1) of the residue obtained from hydroxylamine **65g·HCl** (0.251 g, 3.00 mmol), formaldehyde **66**-H solution (8.0 M) in water (0.375 mL, 3.00 mmol), bicyclopropylidene (**24**) (0.140 mL, 0.120 g, 1.50 mmol), and NaOAc (0.246 g, 3.00 mmol) in 1.75 mL of ethanol according to GP 7 (80 °C, 30 min) gave the product **53g**-H in trace.

Reaction with ethyl glyoxylate 73-Et: Column chromatography (40 g of silica gel, 12 × 2.5 cm column, hexane/Et_2O 3:1) of the residue obtained from hydroxylamine **65g·HCl** (0.251 g, 3.00 mmol), ethyl glyoxylate (**73**-Et) as a solution in toluene (50% weight) (0.60 mL, 3.00 mmol), bicyclopropylidene (**24**) (0.140 mL, 0.120 g, 1.50 mmol), and NaOAc (0.246 g, 3.00 mmol) in 0.70 mL of ethanol according to GP 7 (100 °C, 70 min) gave no product.

One-pot protocol applied to hydroxylamine 65c·HCl and *meta*-nitrobenzaldehyde 75. 8-Benzyl-9-(3-nitrophenyl)-7-oxa-8-azadispiro[2.0.2.3]nonane (81): A solution of 65c·HCl (479 mg, 3.00 mmol), *meta*-nitrobenzaldehyde (75) (453 mg, 3.00 mmol), bicyclopropylidene (24) (0.14 mL, 120 mg, 1.5 mmol) and NaOAc (246 mg, 2.00 mmol) in ethanol (0.6 mL), was sealed in a screw capped vial for the microwave oven and heated at 80 ºC for 165 min. After cooling to room temperature, the solution was concentrated under reduced pressure. Equal amounts of water and ethyl acetate (30 mL) were added, and the two phases were separated. The water phase was made basic with $NaHCO_3$ (satd. solution) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were then washed with brine and

dried over Na_2SO_4. The crude product was purified by column chromatography (50 g of flash silica gel, 3 × 12 cm column, hexane/Et_2O 3:1) to give 81 (0.351 g, 69%).

– IR (KBr): $\tilde{\nu}$ = 3075 cm^{-1}, 3006, 2997, 1531, 1526, 1353, 737. ^1H NMR (250 MHz, $CDCl_3$): δ = 0.10–0.24 (m, 2 H, cPr-H), 0.38–0.52 (m, 2 H, cPr-H), 0.61–0.69 (m, 2 H, cPr-H), 0.98–1.02 (m, 2 H, cPr-H), 4.11 (d, $^2J_{H,H}$ = 12.5 Hz, 1 H, CH_2), 4.19 (s, 1 H, CH), 4.28 (d, $^2J_{H,H}$ = 12.5 Hz, 1 H, CH_2), 7.20–7.33 (m, 5 H, Ar-H), 7.44–7.51 (m, 1 H, Ar-H), 7.73-7.82 (m, 1 H, Ar-H), 8.10-8.17 (m, 2 H, Ar-H).



– ^{13}C NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 6.6 (–, CH_2, cPr-C), 7.3 (–, CH_2, cPr-C), 8.8 (–, CH_2, cPr-C), 9.3 (–, CH_2, cPr-C), 33.1 (C_{quat}, C-3), 62.0 (–, CH_2), 75.5 (C_{quat}, C-6), 76.6 (+, CH), 122.7 (+, CH, Ar-C), 123.4 (+, CH, Ar-C), 127.4 (+, CH, Ar-C), 128.3 (+, 2 CH, Ar-C), 129.0 (+, 2 CH, Ar-C), 129.2 (+, CH, Ar-C), 134.7 (+, CH, Ar-C), 136.4 (C_{quat}, Ar-C), 141.4 (C_{quat}, Ar-C), 148.1 (C_{quat}, Ar-C). MS (EI): *m/z* (%) = 336 (5), 307 (2), 214 (8), 180 (10), 128 (30), 105 (20), 91 (100). – $C_{20}H_{20}N_2O_3$ (336.38): calcd. C 71.41, H 5.99, N 8.33; found C 71.32, H 6.04, N 8.15.

One-pot protocol applied to hydroxylamine 65c·HCl and *meta*-nitrobenzaldehyde (75): A solution of **65c·HCl** (479 mg, 3.00 mmol), *meta*-nitrobenzaldehyde **75** (453 mg, 3.00 mmol), bicyclopropylidene (**24**) (0.14 mL, 120 mg, 1.5 mmol) and NaOAc (246 mg, 2 mmol) in ethanol (0.6 mL), was sealed in a screw capped vial for the microwave oven and heated at 100 ºC for 240 min. After cooling to room temperature, the solution was concentrated under reduced pressure. Equal amount of water and ethyl acetate (30 mL) were added, and the two phases were separated. The water phase was made basic with $NaHCO_3$ (satd. solution) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were then washed with brine and dried over Na_2SO_4. The crude product was purified by column chromatography (50 g of flash silica gel, 3 × 12 cm column, hexane/Et_2O 3:1) to give **81** (R_f = 0.37, 0.135 g, 27%) and **5-(Benzyl)-4-(3-nitrophenyl)-5-azaspiro[2.5]octan-8-one** (**85**) (R_f = 0.20, 0.201 g, 40%).

(85): – IR (film): $\tilde{\nu}$ = 3086 cm^{-1}, 2822, 1698, 1530, 1350, 1143, 1099. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.32–0.37 (m, 1 H, cPr-H), 0.92–0.97 (m, 1 H, cPr-H), 1.20–1.27 (m, 1 H, cPr-H), 1.56–1.62 (m, 1 H, cPr-H), 2.46–2.55 (m, 1 H, CH_2–CH_2), 2.70–2.73 (m, 1 H, CH_2–CH_2), 2.91–3.02 (m, 2 H, CH_2–CH_2), 3.64–3.69 (d, $^{2}J_{H,H}$ = 13.5 Hz, 1 H, NCH_2Ph), 3.72 (s, 1 H, CH), 3.85–3.90 (d, $^{2}J_{H,H}$ = 13.5 Hz, 1 H, NCH_2Ph), 7.29–7.68 (m, 7 H, Ar-H), 8.14–8.15 (m, 2 H, Ar-H). – ^{13}C NMR (62.9 MHz, $CDCl_3$, additional APT): δ = 12.4 (–, CH_2, cPr-C), 21.0 (–, CH_2, cPr-C), 30.7 (–, *), 37.6 (–, *), 45.4 (–, *), 58.5 (–, *), 68.4 (+, CH), 122.5 (+, CH, Ar-C), 123.8 (+, CH, Ar-C), 127.5 (+, CH, Ar-C), 128.6 (+, 2 CH, Ar-C), 128.6 (+, 2 CH, Ar-C), 129.1 (+, CH, Ar-C), 134.6 (+, CH, Ar-C), 138.1 (C_{quat}, Ar-C), 142.2 (C_{quat}, Ar-C), 148.1 (C_{quat}, Ar-C), 208.3 (C_{quat}, C=O). – MS (EI): *m/z* (%) = 336 (20), 245 (15), 230 (5), 218 (15), 214 (80), 150 (40), 105 (10), 91 (100), 77 (20). – HRMS (EI) calcd. for $C_{20}H_{20}N_2O_3$ 337.1547 [M+H^{+}], found 337.1548.

One-pot three-component synthesis of β-lactams 77c-cHex and 53e, applied at the free hydroxylamine. General Procedure 8

(GP 8): A solution of the hydroxylamine (1.7 equiv.), the aldehyde (1.7 equiv.), bicyclopropylidene (**24**) (1 equiv.), and TFA (1 equiv.) in *o*-xylene was sealed in a screw-capped vial for the microwave apparatus and heated at 110 °C for the indicated time. After cooling down to room temperature, the reaction mixture was filtered through a short pad of silica gel, eluting initially with pentane, to remove the high boiling-solvent, then with methanol to recover the mixture. The solvent was evaporated and the crude was purified by column cromatography.

Cyclohexyl 5-benzyl-6-oxo-5-azaspiro[2.3]hexane-4-carboxylate (77c-cHex): Column chromatography (R_f = 0.21, 35 g of flash silica gel, 14 × 2.5 cm column, hexane/Et_2O 3:2) of the residue obtained from **65c·HCl** (0.304 g, 2.50 mmol), cyclohexyl glyoxylate **73-cHex** (0.390 g, 2.50 mmol), bicyclopropylidene (**24**) (0.140 mL, 0.120 g, 1.50 mmol), and TFA (0.11 mL, 1.50 mmol) in *o*-xylene (1.50 mL) according to GP 8 (110 °C, 60 min) gave the product **77c-cHex** (0.141 g, 30%) as a light-yellow oil. – IR (film): $\tilde{\nu}$ = 3063 cm^{-1}, 2936, 2858, 1771, 1455, 1393, 1353, 1201, 1013.

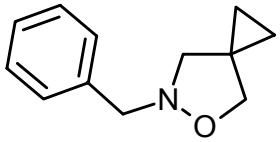
– ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.82–0.95 (m, 1 H, cPr-H), 1.07–1.42 (m, 9 H, cPr-H, cHex-H), 1.71–1.83 (m, 4 H, cHex-H), 3.97 (s, 1 H), 4.19–4.25 (d, $^2J_{H,H}$ = 15.0 Hz, 1 H, NCH_2Ph), 4.73–4.95 (m, 1 H, OCH, cHex-H), 4.89–4.95 (d, $^2J_{H,H}$ = 15.0 Hz, 1 H, NCH_2Ph), 7.24–7.39 (m, 5 H, Ar-H). – ^{13}C NMR (62.9 MHz, $CDCl_3$, additional APT): δ = 6.36 (–, CH_2, cPr-C), 7.93 (–, CH_2, cPr-C), 23.6 (–, CH_2, *), 23.6 (–, *), 25.1 (–, *), 31.5 (–, *), 31.7 (–, *), 37.1 (–, *), 45.6 (–, *), 57.5 (+, CH), 74.0 (+ ,OCH), 127.8 (+, CH, Ar-C), 128.4 (+, 2 CH, Ar-C), 128.8 (+, 2 CH, Ar-C), 135.3 (–, C_{quat}, Ar-C), 169.1 (–, C_{quat}, Ar-C), 171.2 (–, C=O). – MS (EI): *m/z* (%) = 285 (1), 186 (30), 158 (25), 91 (100), 55 (35), 41 (22). – MS (DCI): *m/z* (%) = 644 (10) [2 M + NH_4^+], 627 (5) [2 M+ H^+], 331 (100) [M + NH_4^+], 314 (40) [M + H^+]. – $C_{19}H_{23}NO_3$ (313.39): calcd. C 72.82, H 7.40, N 4.47; found C 72.63, H 7.44, N 4.31.

5-Benzyl-6-(2-iodophenyl)-5-azaspiro[2.3]hexane-4-one (53e): Column chromatography (R_f = 0.26, 35 g of silica gel, 2.5 × 12 cm column, hexane/Et_2O 2:1) of the residue obtained from **65c·HCl** (0.346 g, 2.80 mmol), *o*-iodobenzaldehyde (**76**) (0.650 g, 2.80 mmol), bicyclopropylidene (**24**) (0.150 mL, 0.120 g, 1.60 mmol), and TFA (0.12 mL, 0.182 g, 1.60 mmol) in *o*-xylene (1.60 mL) according to GP 8 (110 °C, 120 min) gave the product (0.112 g, 18%) as colorless oil.

One-pot protocol applied to hydroxylamine 65c·HCl and formaldehyde (66-H) with Methylenecyclopropane (43) as dipolarophile: A solution of 65c·HCl (0.479 g, 3.00 mmol), formaldehyde (66-H) solution (8 M) in water (0.375 mL, 3.00 mmol), methylenecyclopropane (43) (0.1 mL, 81 mg, 1.5 mmol) and NaOAc (0.246 g, 3.0 mmol) in ethanol (1.0 mL), was sealed in a screw-capped vial for the microwave oven, and heated at 80 ºC for 70 min. After cooling to room temperature, the solution was concentrated under reduced pressure. An equal amount each of water and ethyl acetate (30 mL) was added, and the two phases were separated. The water phase was made basic with $NaHCO_3$ (satd. solution) and extracted with ethyl acetate (3 × 30 mL). The combined organic layers were then washed with brine (2 × 30 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent a crude mixture was obtained, containing 1-benzylazetidin-2-one (86, R^1 = Bn; R^2 = H) and 6-benzyl-5-oxa-6-azaspiro[2.4]heptane (87). Column chromatography (35 g of silica gel, 15 × 2.5 cm column, hexane/Et_2O 3:1) of the residue gave 87 (0.234 g, 82%, R_f = 0.28). A second column

chromatography (12 g of silica gel, 8 × 2 cm, column, hexane/Et_2O 2:1) was necessary to separate 86 (21 mg, 9%, R_f = 0.12) from benzylhydroxylamine

6-benzyl-5-oxa-6-azaspiro[2.4]heptane (87): – IR (film): $\tilde{\nu}$ = 3087 cm^{-1}, 3068, 2997, 2867, 1496, 1454, 1030, 1018. – ^1H NMR (300 MHz, $C_2D_2Cl_4$, 100 °C): δ = 0.73–0.81 (m, 4 H, cPr-H), 2.97 (s, 2 H), 3.88 (s, 2 H), 4.09 (s, 2 H), 7.28–7.43 (m, 5 H, Ar-H). – ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$, 100 °C): δ = 10.2 (2 CH_2, cPr-C), 24.8 (C_{quat}, C-3), 61.8 (CH_2, *), 62.2 (CH_2, *), 72.9 (CH_2, *), 126.9 (CH, Ar-C), 128.0 (2 CH, Ar-C), 128.8 (2 CH, Ar-C), 137.4 (C_{quat}, Ar-C). – MS (EI): *m/z* (%) = 190 (2) [M + H^+], 189 (12), 161 (2), 106 (4), 91 (100), 77 (5). – $C_{12}H_{15}NO$ (189.25): calcd; C 76.16, H 7.99, N 7.40; found C 76.18, H 7.72, N 7.22.

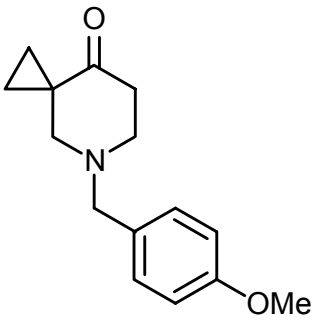


2.3. Synthesis of Compounds in Chapter 3

8-(*p*-Methoxybenzyl)-7-oxa-8-azadispiro[2.0.2.3]nonane (47g): A solution of the nitrone **44g** (0.166 mg, 1.00 mmol), bicyclopropylidene (**24**) (0.19 mL, 0.160 g, 2.00 mmol), in tetrachloroethane (2 mL) was sealed in a screw-capped vial and heated at 80 °C for 30 minutes under microwaves irradiation. After cooling down to room temperature, the solution was concentrated under reduced pressure. After column cromatography ($R_f = 0.27$, 25 g of silica gel, 2 × 15 cm column, hexane/Et_2O 2:1) **47g** was obtained (120.0 mg, 49%).

5-(4-Methoxybenzyl)-5-azaspiro[2.5]octan-8-one (49g): A solution of the nitrone **44g** (0.130 mg, 0.79 mmol), bicyclopropylidene (**24**) (0.15 mL, 0.126 g, 1.57 mmol), in *o*-xylene (1.00 mL) was sealed in a screw-capped vial and heated at 130 °C for 15 minutes under microwaves irradiation. After cooling down to room temperature the reaction mixture was filtered through a short pad of silica gel, eluting initially with pentane, to remove the high boiling-solvent, then with methanol to recover the mixture. The solvent was evaporated and the crude was purified by column cromatography ($R_f = 0.17$, 25 g of silica gel, 2 × 15 cm column, hexane/Et_2O 1:1) to give **49g** (57.0 mg, 29%) as a yellow oil.

49g: – IR (KBr): $\tilde{\nu} = 3000\ cm^{-1}$, 2952, 2904, 2806, 2756, 1688, 1606, 1511. – ^1H NMR (250 MHz, $CDCl_3$): δ = 0.60–0.70 (m, 2 H, cPr-H), 1.23–1.28 (m, 2 H, cPr-H), 2.50–2.55 (m, 4 H, CH_2–CH_2), 2.82–2.87(m, 2 H, NCH_2), 3.54 (s, 2 H, NCH_2Ph), 3.79 (s, 3 H, CH_3), 6.83–6.88 (m, 2 H, Ar-H), 7.24–7.27 (m, 2 H, Ar-H). – ^{13}C NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 17.6 (–, 2 CH_2, cPr-C), 28.4 (C_{quat}, C-3), 39.3 (–, CH_2, *), 52.0 (–, CH_2, *), 55.2 (+, CH_3), 59.8 (–, CH_2, *), 61.5 (–, CH_2, *), 113.6 (+, 2 CH, Ar-C), 129.9 (C_{quat}, Ar-C), 130.0 (+, 2 CH, Ar-C), 158.8 (C_{quat}, Ar-C), 176.5 (C_{quat}, C=O). – MS (EI): *m/z* (%) = 245 (25), 124 (10), 121 (100), 91 (5), 77 (5). – $C_{15}H_{19}NO_2$ (245.32): calcd. C 73.44, H 7.81, N 5.71; found C 73.12, H 7.72, N 5.65.



Reaction of Bicyclopropylidene with *In situ* Generated Nitrones under Microwave Heating

8-(*p*-Methoxybenzyl)-7-oxa-8-aza-dispiro[2.0.2.3]nonane (47g): A solution of the free hydroxylamine **65d** (0.613 mg, 4.00 mmol), bicyclopropylidene (**24**) (0.19 mL, 0.160 g, 2.00 mmol), formaldehyde **66**-H as a solution (8 M) in water (0.50 mL, 4.00 mmol) in *o*-xylene (1.75 mL) was sealed in a screw-capped vial and heated at 100 °C for 15 minutes. After cooling down to room temperature, the reaction mixture was filtered through a short pad of silica gel, eluting initially with pentane, to remove the high boiling-solvent, then with methanol to recover the mixture. The solvent was evaporated in vacuo and the crude was purified by column cromatography cromatography (R_f = 0.27, 42 g of silica gel, 3 × 15 cm column, hexane/Et_2O 2:1) to give **47g** (243.0 mg, 49%).

5-(*p*-Methoxybenzyl)-5-azaspiro[2.5]octan-8-one (49g): A solution of the free hydroxylamine **65d** (0.298 mg, 0.080 g, 1.94 mmol), bicyclopropylidene (**24**) (0.090 mL, 1.00 mmol), and formaldehyde **66**-H as a solution (8 M) in water (0.125 mL, 1.00 mmol) in *o*-xylene (1.00 mL) was sealed in a screw-capped vial and heated at 130 °C for 15 minutes. After cooling down to room temperature the reaction mixture was filtered through a short pad of silica gel, eluting initially with pentane, to remove the high boiling-solvent, then with methanol to recover the mixture. The solvent was evaporated and the crude was purified by column cromatography (R_f = 0.17, 25 g of silica gel, 15 × 2 cm column, hexane/Et_2O 1:1) to give **49g** (90.0 mg, 37%).

8-Benzyl-7-oxa-8-azadispiro[2.0.2.3]nonane (47j) and 5-benzyl-5-azaspiro[2.5]octan-8-one (49j): A solution of the benzyl hydroxylamine **65c** (0.276 mg, 2.20 mmol), bicyclo-propylidene (**24**) (0.10 mL, 0.080 g, 1.00 mmol), and formaldehyde **66**-H as a solution (8 M) in water (0.27 mL, 2.20 mmol) in *o*-xylene (2.0 mL) was sealed in a screw-capped vial and heated at 100 °C for 20 minutes. After cooling down to room temperature the solvent was evaporated and the crude product was purified by column cromatography (34 g of silica gel, 12 × 3 cm column, hexane/Et_2O 2:1) to give **47j** (R_f = 0.24, 0.117 g, 54%) and **49j** (R_f = 0.16, 180.0 mg, 7%).

(47j): – IR (film): $\tilde{\nu}$ = 3064 cm^{-1}, 3000, 2931, 2868, 1653, 1496, 1454, 1027. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.23–0.52 (bs, 4 H, cPr-H), 0.67 (bs, 2 H, cPr-H), 0.87 (bs, 2 H, cPr-H), 3.03 (bs, 1 H, CH_2), 3.43 (bs, 1 H, CH_2), 4.02 (bs, 1H, CH_2), 4.30 (bs, 1 H, CH_2), 7.13–7.53 (m, 5 H, Ar-H). – ^{1}H NMR (300 MHz, $C_2D_2Cl_4$, 100 °C): δ = 0.37–0.41 (m, 2 H, cPr-H), 0.44–0.48 (m, 2 H, cPr-H) 0.67–0.71 (m, 2 H, cPr-H), 0.85–0.90 (m, 2 H, cPr-H), 3.25 (s, 2H, CH_2), 4.19 (s, 2 H, CH_2), 7.25–7.45 (m, 5 H, Ar-H). – ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$, 100 °C): δ = 7.3 (2 CH_2, cPr-C), 8.1 (2 CH_2, cPr-C), 26.4 (C_{quat}), 62.8 (CH_2, *), 63.1 (CH_2, *), 65.6 (C_{quat}, C-6), 126.9 (+, CH, Ar-C), 128.0 (+, 2 CH, Ar-C), 128.8 (+, 2 CH, Ar-C), 137.5 (C_{quat}, Ar-C). – MS (EI): *m/z* (%) = 216 (1) [M + H$^+$], 215 (5), 187 (2), 186 (10), 158 (10), 105 (40), 91 (100), 77 (10), 65 (22), 54 (25). – HRMS (EI) calcd. for $C_{14}H_{17}NO$ 216.1383 [M + H$^+$], found 216.1384.

(49j): – IR (film): $\tilde{\nu}$ = 3066 cm^{-1}, 2948, 2808, 1753 (weak), 1699, 1495, 1454, 1357, 1152, 1028. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.62–0.66 (m, 2 H, cPr-H), 1.26–1.30 (m, 2 H, cPr-H), 2.40–2.58 (m, 4 H, CH_2–CH_2), 2.86–2.91 (m, 2 H, CH_2), 3.62 (s, 2 H, NCH_2Ph), 7.26–7.41 (m, 5 H, Ar-H). – ^{13}C NMR (75.5 MHz, $CDCl_3$, additional DEPT): δ = 17.6 (–, 2 CH_2, cPr-C), 28.5 (C_{quat}, C-3), 39.3 (–, CH_2), 52.2 (–, NCH_2, *), 60.0 (–, NCH_2, *), 62.2 (–, NCH_2, *), 127.3 (+, CH, Ar-C), 128.4 (+, 2 CH, Ar-C), 128.8 (+, 2 CH, Ar-C), 138.0 (C_{quat}, Ar-C), 209.0 (C_{quat}, C=O). – MS (EI): *m/z* (%) = 215 (20), 138 (10), 124 (25), 91 (100), 65 (15), 42 (8). – HRMS (EI) calcd. for $C_{14}H_{17}NO$ 216.1383 [M+H$^+$], found 216.1384.

Ethyl 8-benzhydryl-7-oxa-8-azadispiro[2.0.2.3]nonane-9-carboxylate (47e-Et): Column chromatography (R_f = 0.33, 42 g of silica gel, 12 × 3 cm column, hexane/Et_2O 4:1) of the residue obtained from **65e·HCl** (0.550 g, 2.33 mmol), ethyl glyoxylate **73-Et** as a solution (50 % weight) in toluene (0.50 mL, 2.33 mmol), bicyclopropylidene (**24**) (0.150 mL, 0.130 g, 1.63 mmol), and NaOAc (0.191 g, 2.33 mmol) in ethanol (0.6 mL) according to GP 6 (80 °C, 25 min) gave the product **47e-Et** (0.351 g, 59%) as a colorless solid.

(47e-Et): – M.p = 70 °C. – IR (KBr): $\tilde{\nu}$ = 3066 cm^{-1}, 2998, 2896, 1752, 1452, 1162. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.34–0.40 (m, 3 H, cPr-H), 0.55–0.75 (m, 3 H, cPr-H), 0.81–0.88 (m, 2 H, cPr-H), 1.16 (t, $^{3}J_{H,H}$ = 7.0 Hz, 3 H, CH_3), 3.75 (s, 1 H, CH), 4.02 (q, $^{3}J_{H,H}$ = 7.0 Hz, 2 H, CH_2), 5.29 (s, 1 H, CH), 7.18–7.31 (m, 6 H, Ar-H), 7.43–7.46 (m, 2 H, Ar-H), 7.55-7.59 (m, 2 H, Ar-H). – ^{13}C NMR (62.9 MHz, $CDCl_3$, additional APT): δ = 6.0 (–, CH_2, cPr-C), 7.2 (–, CH_2, cPr-C), 7.6 (–, CH_2, cPr-C), 9.9 (–, CH_2, cPr-C), 14.2 (+, CH_3), 30.3 (–, C_{quat}, C-3), 60.6 (–, OCH_2), 66.3 (–, C_{quat}, C-6), 72.2 (+, CH, *), 75.8 (+, CH, *), 126.8 (+, CH, Ar-C), 127.3 (+, 2 CH, Ar-C), 127.7 (+, CH, Ar-C), 128.2 (+, 2 CH, Ar-C), 128.3 (+, 2 CH, Ar-C), 128.6 (+, 2 CH, Ar-C), 140.9 (–, C_{quat}, Ar-C), 142.3 (–, C_{quat}, Ar-C), 170.2 (–, C=O). – MS (EI): *m/z* (%) = 363 (5), 334 (5), 306 (5), 290 (45), 262 (15), 181 (25), 167 (100), 105 (30), 77 (20). – $C_{23}H_{25}NO_3$ (363.45): calcd. C 76.01, H 6.93, N 3.85; found C 75.79, H 6.80, N 4.06.

2.4. Synthesis of Compounds in Chapter 4

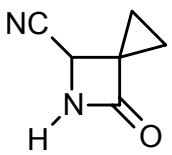
5-Benzoyl-6-phenyl-5-azaspiro[2.3]hexane-4-one (107a): $KMnO_4$ (721 mg, 4.56 mmol) and 18-crown-6 (15.0 mg, 0.057 mmol, 5 mol%) were added to a stirred solution of β-lactam **53a** (0.300 g, 1.14 mmol) in a mixture of acetone/acetic acid 85:15 (30 mL). The solution was stirred at 60 °C for 24 h. After cooling to room temperature, the mixture was diluted with diethyl ether (30 mL), then an aq. sat. solution of $NaHCO_3$ (50 mL) was added in small portions under vigorous stirring, and the reaction mixture was stirred until the carbon dioxide evolution ceased. The organic phase was washed with brine (2 × 20 mL), dried and concentrated under reduced pressure. Column chromatography (R_f = 0.26, 12 g of silica gel, 2 × 10 cm column, hexane/Et_2O 3:1) of the residue gave **107a** (90.0 mg, 28%) as a colorless solid, m.p. 121–123 °C. – IR (KBr): $\tilde{\nu}$ = 3065 cm^{-1}, 3010, 2950, 1800, 1675, 1653, 1448. – ^1H NMR (250 MHz, $CDCl_3$): δ = 0.66–0.76 (m, 1 H, cPr-H), 1.28–1.39 (m, 2 H, cPr-H), 1.43–1.53 (m, 1 H, cPr-H), 5.35 (s, 1 H, CH, 6-H), 7.29–7.43 (m, 5 H, Ar-H), 7.45–7.51 (m, 2 H, Ar-H), 7.55–7.62 (m, 1 H, Ar-H), 8.04–8.11 (m, 2 H, Ar-H). – ^{13}C NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 10.6 (–, cPr-C), 11.7 (–, cPr-C), 37.9 (C_{quat}, C-3), 59.7 (+, CH, C-6), 126.9 (+, 2 CH, Ar-C), 128.1 (+, 2 CH, Ar-C), 128.5 (+, CH, Ar-C), 128.7 (+, 2 CH, Ar-C), 129.9 (+, 2 CH, Ar-C), 132.2 (C_{quat}, Ar-C), 133.1 (+, CH, Ar-C), 136.4 (C_{quat}, Ar-C), 164.8 (C=O, *), 170.4 (C=O, *). – MS (EI): *m/z* (%) = 277 (36) [M^+], 249 (25), 129 (32), 105 (100), 77 (50). – $C_{18}H_{15}NO_2$ (277.3): calcd. C 77.96, H 5.45, N 5.05; found C 77.69, H 5.35, N 4.82. Some starting material **53a** (200 mg, 67%) was also recovered by column chromatography (R_f = 0.11).

Methyl 5-Benzoyl-6-oxo-5-azaspiro[2.3]hexane-4-carboxylate (107b): Finely powdered CrO_3 (0.202 g, 0.202 mmol) was added in one portion to a stirred solution of β-lactam **53b** (247 mg, 1.01 mmol) in acetic acid (20 mL) at ambient temp., and the resulting mixture was stirred at 60 °C for an additional 3 days. After cooling to room temperature and dilution with diethyl ether (20 mL), $NaHCO_3$ (15.0 g, 179 mmol) was added to the solution in several portions, and the reaction mixture was stirred until the carbon dioxide evolution ceased. The organic phase was washed with aq. sat. $NaHCO_3$ solution in 20 mL portions until the evolution of carbon dioxide ceased, dried and concentrated under reduced pressure. Column chromatography (R_f = 0.20, 42 g of

silica gel, 3 × 13 cm column, hexane/Et_2O 2:1) of the residue gave **107b** (113 mg, 44%) as a colorless solid, m.p. 92–93 °C. – IR (KBr): $\tilde{\nu}$ = 3090 cm^{-1}, 3077, 2987, 2961, 1796, 1734, 1676, 1601, 1581, 1481, 1441. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.07–1.33 (m, 2 H, cPr-H), 1.34–1.56 (m, 2 H, cPr-H), 3.80 (s, 3 H, OCH_3), 4.80 (s, 1 H, CH, 6-H), 7.44–7.49 (m, 2 H, Ar-H), 7.54–7.68 (m, 1 H, Ar-H), 8.06–8.15 (m, 2 H, Ar-H). – ^{13}C NMR (50.3 MHz, $CDCl_3$, additional APT): δ = 9.6 (–, CH_2, cPr-C), 11.4 (–, CH_2, cPr-C), 34.4 (–, C_{quat}, C-3), 52.6 (+, *), 56.0 (+, *), 128.1 (+, 2 CH, Ar-C), 129.9 (+, 2 CH, Ar-C), 131.2 (–, C_{quat}, Ar-C), 133.3 (+, CH, Ar-C), 164.5 (–, C=O, *), 167.6 (–, C=O, *), 168.7 (–, C=O, *). – MS (EI): *m/z* (%) = 259 (2) [M^+], 228 (5), 200 (97), 105 (100), 77 (45). The structure of this β-lactam **107b** was verified by X-ray crystal structure analysis. Some starting material **53b** (72 mg, 29%) was also recovered by column chromatography (R_f = 0.12).

Deprotection of β-Lactam 53d: To a stirred solution of β-lactam **53d** (900 mg, 3.72 mmol) in acetonitrile (40 mL) was added a solution of CAN (6.63 g, 12.1 mmol) in water (85 mL) at 0 °C. After an additional stirring for 20 minutes at the same temp. and for 1 h at ambient temp., the mixture was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were washed successively with a 10% aq. Na_2SO_3 solution (2 × 50 mL), a 5% aq. $NaHCO_3$ solution (2 × 50 mL) and brine (50 mL), dried and concentrated under reduced pressure. Column chromatography (hexane/Et_2O 1:2, 75 g of silica gel, 3.5 × 16 cm column) of the residue gave **6-oxo-5-azaspiro[2.3]hexane-4-carbonitrile** (**108**) (172 mg, 38%) as a colorless solid, m.p. 72–73 °C, R_f = 0.15, and **5-(*p*-methoxybenzoyl)-6-oxo-5-aza-spiro[2.3]hexane-4-carbonitrile** (**107d**) (371 mg, 39%) as a colorless solid, m.p. 109–110 °C, R_f = 0.38 (hexane/Et_2O 1:4).

108: – IR (KBr): $\tilde{\nu}$ = 3250 cm^{-1}, 3097, 2720, 2249, 1763, 1331. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.26–1.37 (m, 2 H, cPr-H), 1.41–1.48 (m, 2 H, cPr-H), 4.44 (s, 1 H, CH, 4-H), 6.40 (s, 1 H, NH). – ^{13}C NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 9.1 (–, cPr-C), 9.8 (–, cPr-C), 39.8 (C_{quat}, C-3), 43.6 (+, CH), 116.9 (C_{quat}, CN), 171.5 ($C_{quat,}$ C=O). – MS (EI): *m/z* (%) = 122 (12) [M^+], 79 (50), 52 (100). – $C_6H_6N_2O$ (122.1) calcd. C 59.01, H 4.95, N 22.94; found C 59.20, H 5.08, N 22.81.



107d: – IR (KBr): $\tilde{\nu}$ = 3084 cm^{-1}, 3005, 2977, 2938, 2843, 2251, 1798, 1666, 1603, 1576, 1514. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.47–1.67 (m, 4 H, cPr-H), 3.89 (s, 3 H, OCH_3), 4.92 (s, 1 H, CH, H-4), 6.95–7.01 (m, 2 H, Ar-H), 8.08–8.14 (m, 2 H, Ar-H). – ^{13}C NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 11.4 (–, cPr-C), 12.2 (–, cPr-C), 34.8 (C_{quat}, C-3), 44.4 (+, CH, C-4), 55.5 (+, CH_3), 113.8 (+, 2 CH, Ar-C), 115.4 (C_{quat}, CN), 122.2 (C_{quat}, Ar-C), 132.6 (+, 2 CH, Ar-C), 163.3 (C_{quat}, *), 164.3 (C_{quat}, *), 166.3 (C_{quat}, *). – MS (EI): *m/z* (%) = 256 (20) [M^+], 135 (100), 92 (9), 77 (9). – $C_{14}H_{12}N_2O_3$ (256.3): calcd. C 65.62, H 4.72, N 10.93; found C 65.75, H 4.61, N 11.15.

Methyl 6-oxo-5-azaspiro[2.3]hexane-4-carboxylate (109): To a stirred solution of β-lactam **77d**-Me (0.114 g, 0.41 mmol), in acetonitrile (3.0 mL) was added a solution of ceric ammonium nitrate (CAN) (0.50 g, 0.90 mmol) in water/acetonitrile (2.0/3.0 mL). After 1 h of stirring at room temperature additional CAN (0.110 g, 0.20 mmol) was added. After 30 min, $Na_2S_2O_3 \cdot 5 \cdot H_2O$ (0.273 g, 1.1 mmol) was added, and the color of the suspension turned to a lighter yellow. $NaHCO_3$ was also added until the pH turned from 1 to 7. The suspension was evaporated to dryness, methanol (15 mL) was added, and the suspension obtained was filtered through a pad of silica gel (soaked with diethyl ether) to eliminate salts. The column was washed with methanol (~200 mL), and the 68 mg of crude product, obtained after evaporation of the solvent, was purified by column chromatography. The β-lactam **109** (R_f = 0.47, 70 g of flash silica gel, 20 × 3 cm column, CH_2Cl_2/MeOH (1 vol% NH_4OH conc.) 50:1) was obtained as a light-yellow oil (58 mg, 90%). – IR (film): $\tilde{\nu}$ = 3006 cm^{-1}, 2955, 1792, 1733, 1438, 1289. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.87–0.97 (m, 1 H, cPr-H), 1.08–1.31 (m, 3 H, cPr-H), 3.73 (s, 3 H, OCH_3), 4.24 (s, 1 H, H-4). – ^{13}C NMR (62.9 MHz, $CDCl_3$, additional DEPT): δ = 7.2 (–, cPr-C), 8.5 (–, cPr-C), 38.3 (C_{quat}, C-3), 52.3 (+, *), 54.9 (+, *), 170.7 (C=O, *), 172.8 (C=O, *). – MS (EI): *m/z* (%) = 155 (1), 135 (15), 112 (22), 96 (30), 85 (62), 83 (100), 82 (8), 69 (8), 48 (50), 46 (22). – $C_7H_9NO_3$ (155.15): calcd. C 54.19, H 5.85, N 9.03; found C 53.94, H 5.74, N 8.78.

***tert*-Butyl 4-Cyano-6-oxo-5-azaspiro[2.3]hexane-5-carboxylate (110)**: Di-*tert*-butyl pyrocarbonate (Boc_2O) (873 mg, 4.00 mmol) and DMAP (24.0 mg, 0.196 mmol) were added in one portion to a stirred solution of β-lactam **108** (245 mg, 2.01 mmol) in anhydrous acetonitrile (30 mL) at 0 °C. The reaction mixture was stirred at ambient temperature for an additional 3 h, diluted with dichloromethane (30 mL), washed successively with 10% aq. Na_2SO_3 solution (2 × 20 mL), aq. sat. $NaHCO_3$ solution of (2 × 20 mL) and brine (2 × 20 mL), dried and concentrated under reduced pressure. Column chromatography (R_f = 0.10, 12 g of silica gel, 2 × 10 cm column, hexane/Et_2O 2:1) furnished **110** (346 mg, 78%) as a colorless solid, m.p. 87 °C. – IR (KBr): $\tilde{\nu}$ = 3012 cm^{-1}, 2992, 2250, 1823, 1717. – ^1H NMR (300 MHz, $CDCl_3$): δ = 1.35–1.46 (m, 2 H, cPr-H), 1.48–1.64 (m, 2 H, cPr-H), 1.56 (s, 9 H, 3 CH_3), 4.64 (s, 1 H, CH, 4-H). – ^{13}C NMR (50.3 MHz, $CDCl_3$, additional DEPT): δ = 10.6 (–, cPr-C), 11.4 (–, cPr-C), 28.0 (+, 3 CH_3), 37.0 (C_{quat}, C-3), 45.9 (+, CH, C-4), 85.1 (C_{quat}, *t*Bu), 115.0 (CN), 145.7 (C=O, *), 166.6 (C=O, *). – MS (EI): *m/z* (%) = 223 (1) [M + H^+], 167 (9), 149 (30), 57 (100). – MS (DCI): *m/z* (%) = 684 (5) [3 M + NH_4^+], 462 (40) [2 M + NH_4^+], 257 (72) [M + NH_3 + NH_4^+], 240 (100) [M + NH_4^+]. – $C_{11}H_{14}N_2O_3$ (222.2): calcd. C 59.45, H 6.35, N 12.61; found C 59.55, H 6.14, N 12.47.

5-*tert*-Butyl-4-methyl 6-oxo-5-azaspiro[2.3]hexane-4,5-dicarboxylate (111): Di-*tert*-butyl pyrocarbonate (Boc_2O) (0.113 g, 0.52 mmol) and DMAP (3 mg, 0.03 mmol) were added in one portion to β-lactam **109** (40.0 mg, 0.26 mmol) in anhydrous acetonitrile (3.90 mL) at 0 °C. After 1 h, the starting material was no longer detectable by TLC. The reaction mixture was stirred at ambient temperature for an additional 13 h, diluted with dichloromethane (20 mL), washed successively with 5% aq. $NaHSO_3$ solution (3 × 20 mL), aq. satd. $NaHCO_3$ solution (1 × 20 mL), dried and concentrated under reduced pressure. Column chromatography (R_f = 0.17, 12 g of silica gel, 2 × 8 cm column, hexane/Et_2O 2:1) furnished **111** (54 mg, 82%) as a colorless solid, m.p. 69–70 °C. – IR (film): $\tilde{\nu}$ = 2978 cm^{-1}, 2950, 1814, 1743, 1723, 1382, 1319, 1151. – ^1H NMR (250 MHz, $CDCl_3$): δ = 0.95–1.01 (m, 1 H, cPr-H), 1.24–1.44 (m, 3 H, cPr-H), 1.51 (s, 9 H, 3 CH_3), 3.78 (s, 3 H, OCH_3), 4.48 (s, 1 H, 4-H). – ^{13}C NMR (50.3 MHz, $CDCl_3$, additional DEPT): δ = 8.7 (–, cPr-C), 10.5 (–, cPr-C), 27.9 (+, 3 CH_3), 36.1 (C_{quat}, C-3), 51.5 (+, *), 57.2 (+, *), 83.6 (C_{quat}, *t*Bu), 168.4 (C=O, *), 168.7 (2 C=O, *). – MS (EI): *m/z* (%) = 200 (1), 140 (19), 96 (10), 57 (100). – MS (DCI): *m/z*

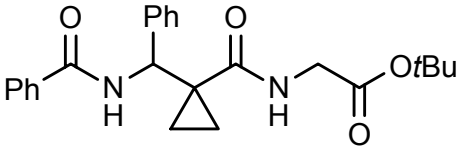
(%) = 273 (100) [M + NH_4^+]. – $C_{12}H_{17}NO_5$ (255.3): calcd. C 56.46, H 6.71, N 5.49; found C 56.50, H 6.89, N 5.54.

Reaction of N-Acylated β-Lactams 107a,b, 11 with tert-Butyl Glycinate (102) and tert-Butyl (S)-Phenylalaninate (115). General Procedure 9

(GP 9)*: tert*-Butyl aminoester **102** [or its hydrochloride in the presence of triethylamine (1 equiv.)] was added to a solution of the respective β-lactam **107a,b** or **110** in DMF, and the resulting mixture was stirred at 152 °C (if not otherwise specified) for the indicated time. After cooling to ambient temperature, diethyl ether (20 mL) was added, and the organic layer was washed with water (10 mL), brine (2 × 10 mL), and dried over Na_2SO_4. After filtration, the solution was concentrated under reduced pressure, and the crude product was purified by column chromatography on silica gel.

***tert*-Butyl [(5-Benzoyl-6-oxo-5-azaspiro[2.3]hexane-4-carbonyl)amino]acetate (114):** Column chromatography (R_f = 0.10, 12 g of silica gel, 2 × 10 cm column, hexane/Et_2O 1:1) of the residue obtained from the β-lactam **107b** (113 mg, 0.436 mmol) and glycinate **102** (171 mg, 1.31 mmol) in DMF (10 mL) according to GP 9 (20 h) gave **114** (80 mg, 51%) as a colorless solid, m.p. 112–115 °C. – IR (KBr): $\tilde{\nu}$ = 3400 cm^{-1} (br.), 2982, 2925, 2853, 1790, 1719, 1644, 1604, 1581, 1516, 1487. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.08–1.19 (m, 1 H, cPr-H), 1.31–1.45 (m, 2 H, cPr-H), 1.48 (s, 9 H, 3 CH_3), 1.58–1.66 (m, 1 H, cPr-H), 4.27 (s, 2 H, CH_2CO), 5.03 (d, $^3J_{H,H}$ = 7.4 Hz, 1 H, CH, 4-H), 6.91 (d, $^3J_{H,H}$ = 7.4 Hz, 1 H, NH), 7.39–7.47 (m, 2 H, Ar-H), 7.5–7.57 (m, 3 H, Ar-H), 7.75–7.81 (m, 2 H, Ar-H). – ^{13}C NMR (150 MHz, $CDCl_3$, additional APT): δ = 13.3 (–, CH_2, cPr-C), 15.2 (–, CH_2, cPr-C), 27.2 (–, C_{quat}, C-3), 28.0 (+, 3 CH_3), 40.7 (–, CH_2, C-1), 53.4 (+, CH, C-4), 83.2 (–, C_{quat}, *t*Bu), 127.2 (+, 2 CH, Ar-C), 128.7 (+, 2 CH, Ar-C), 132.3 (+, CH, Ar-C), 132.5 (–, C_{quat}, Ar-C), 165.9 (C=O, *), 167.8 (C=O, *), 174.7 (C=O, *), 177.4 (C=O, *). – MS (DCI): *m/z* (%) = 734 (10) [2 M + NH_4^+], 376 (100) [M + NH_4^+]. – $C_{19}H_{22}N_2O_5$ (358.39) calcd. C 63.67, H 6.19 N 7.82; found C 63.33, H 5.95, N 7.71.

***tert*-Butyl {[1-(Benzoylaminophenylmethyl)cyclopropylcarbonyl]amino}acetate (116):**



Column chromatography (R_f = 0.17, 15 g of silica gel, 2 × 10 cm column, hexane/Et_2O 1:2) of the residue obtained from the β-lactam **107a** (243 mg, 0.877 mmol) and glycinate **102** (354 mg, 2.7 mmol) in DMF (35 mL) according to GP 9 (12 h) gave **116** (217 mg, 61%) as a colorless solid, m.p. 133–134 °C. – IR (KBr): $\tilde{\nu}$ = 3311 cm^{-1}, 3238, 3064, 2974, 1754, 1734, 1656, 1636. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.99–1.29 (m, 4 H, cPr-H), 1.36 (s, 9 H, 3 CH_3), 3.71 (dd, $^2J_{H,H}$ = 18.3, $^3J_{H,H}$ = 5.0 Hz, 1 H, CH_2CO), 3.78 (dd, $^2J_{H,H}$ = 18.3, $^3J_{H,H}$ = 5.0 Hz, 1 H, CH_2CO), 4.76 (d, $^3J_{H,H}$ = 8.7 Hz, 1 H, CH, 2'-H), 5.81 (t, $^3J_{H,H}$ = 5.0 Hz, 1 H, NH), 7.12–7.27 (m, 3 H, Ar-H), 7.32–7.47 (m, 5 H, Ar-H), 7.85–7.89 (m, 2 H, Ar-H), 8.66 (d, $^3J_{H,H}$ = 8.7 Hz, 1 H, NH). – ^{13}C NMR (75.5 MHz, $CDCl_3$, additional APT): δ = 13.1 (–, CH_2, cPr-C), 14.1 (–, CH_2, cPr-C), 27.9 (+, 3 CH_3), 29.5 (–, C_{quat}), 41.8 (–, CH_2, C-1), 58.3 (+, CH, C-2'), 82.5 (–, C_{quat}, *t*Bu), 126.5 (+, 2 CH, Ar-C), 127.2 (+, 2 CH, Ar-C), 127.4 (+, CH, Ar-C), 128.5 (+, 4 CH, Ar-C), 131.5 (+, CH, Ar-C), 134.1 (–, C_{quat}, Ar-C), 140.2 (–, C_{quat}, Ar-C), 166.5 (–, C=O, *), 168.8 (–, C=O, *), 173.5 (–, C=O, *). – MS (EI): *m/z* (%) = 408 (2) [M^+], 335 (10), 277 (85), 250 (15), 210 (15), 105 (100), 77 (30), 57 (22). – MS (DCI): *m/z* (%) = 426 (55) [M + NH_4^+], 409 (100) [M + H^+]. – $C_{24}H_{28}N_2O_4$ (408.5): calcd. C 70.57, H 6.91, N 6.86; found C 70.76, H 7.10, N 7.26.

***tert*-Butyl{[1(*tert*-Butoxycarbonylaminocyanomethyl)cyclopropylcarbonyl]amino}acetate (117)**: The colorless solid (0.20 g, 84%) obtained from β-lactam **110** (150 mg, 0.67 mmol), *tert*-butyl glycinate hydrochloride (**12·HCl**) (195 mg, 1.16 mmol) and triethylamine (118 mg, 162 µL, 1.16 mmol) in DMF (16 mL) according to GP 9 (12 h) after evaporation of the solvent was essentially pure acetate **117**. An analytical sample was obtained by column chromatography (R_f = 0.70, 20 g of silica gel, 2 × 16 cm column, Et_2O), m.p. 86–88 °C. – IR (KBr): $\tilde{\nu}$ = 3311 cm^{-1}, 3096, 2989, 2939, 1751, 1688, 1638, 1550, 1511. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.08–1.16 (m, 1 H, cPr-H), 1.17–1.28 (m, 2 H, cPr-H), 1.30–1.37 (m, 1 H, cPr-H), 1.44 (s, 9 H, 3 CH_3), 1.47 (s, 9 H, 3 CH_3), 3.87 (dd, $^2J_{H,H}$ = 18.4, $^3J_{H,H}$ = 4.4 Hz, 1 H, CH_2CO), 3.94 (dd, $^2J_{H,H}$ = 18.4, $^3J_{H,H}$ = 4.4 Hz, 1 H, CH_2CO), 4.24 (d, $^3J_{H,H}$ = 9.2 Hz, 1 H, CH, 2'-H), 5.83 (br. t, $^3J_{H,H}$ = 4.4 Hz, 1 H, NH), 6.20 (br. d, $^3J_{H,H}$ = 9.2 Hz, 1 H, NH). – ^{13}C NMR (50.3 MHz, $CDCl_3$, additional APT): δ = 13.2 (–, CH_2, cPr-C), 14.8 (–, CH_2, cPr-C),

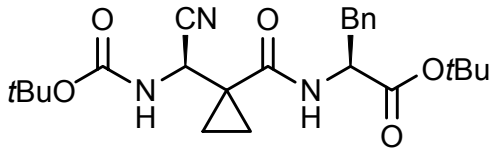
27.9 (–, C_{quat}), 28.0 (+, 3 CH_3), 28.2 (+, 3 CH_3), 41.9 (–, CH_2, C-1), 47.0 (+, CH, C-2'), 81.2 (–, C_{quat}, *t*Bu), 82.8 (–, C_{quat}, *t*Bu), 117.4 (–, CN), 168.8 (–, 2 C=O, *), 171.2 (–, C=O, *). – MS (EI): *m/z* (%) = 353 (2) [M^+], 297 (15), 224 (28), 197 (42), 57 (100). – MS (DCI): *m/z* (%) = 724 (10) [2 M + NH_4^+], 707 (18) [2 M + H^+], 371 (85) [M + NH_4^+], 354 (100) [M + H^+]. – $C_{17}H_{27}N_3O_5$ (353.41): calcd. C 57.77, H 7.70, N 11.89; found C 57.49, H 7.58, N 11.81.

***tert*-Butyl (2*S*,2'*S*)-2-{[1-(*tert*-Butoxycarbonylaminocyanomethyl)cyclopropylcarbo-nyl]-amino}-3-phenylpropionate [(2*S*,2'*S*)-118] and *tert*-Butyl (2*S*,2'*R*)-2-{[1-(*tert*-Butoxy-carbonylaminocyanomethyl)cyclopropylcarbonyl]amino}-3-phenylpropionate [(2*S*,2'*R*)-118]**: Column chromatography (44 g of silica gel, 3 × 13 cm column, hexane/Et_2O 1:1) of the residue obtained from the β-lactam **110** (184 mg, 0.83 mmol), *tert*-butyl (*S*)-phenylalaninate hydrochloride (**14·HCl**) (428 mg, 1.66 mmol) and Et_3N (168 mg, 230 µL, 1.66 mmol) in DMF (33 mL) according to GP 9 (60 °C, 12 h) gave **(2*S*,2'*S*)-118** (155 mg, 42%) and **(2*S*,2'*R*)-118** (143 mg, 39%) as colorless solids.

The diastereoisomer **(2*S*,2'*S*)-118**: R_f = 0.34, m.p. 101–102 °C, – $[\alpha]_D^{20}$ = +53.4 (*c* = 0.5 in $CHCl_3$). – IR (KBr): $\tilde{\nu}$ = 3438 cm^{-1}, 3426, 3090, 2981, 2935, 2247, 1738, 1719, 1650, 1540, 1524, 1370. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.00–1.22 (m, 4 H, cPr-H), 1.41 (s, 9 H, 3 CH_3), 1.43 (s, 9 H, 3 CH_3), 3.06 (dd, $^2J_{H,H}$ = 15.0, $^3J_{H,H}$ = 5.0 Hz, 1 H, CH_2Ph), 3.15 (dd, $^2J_{H,H}$ = 15.0, $^3J_{H,H}$ = 5.0 Hz, 1 H, CH_2Ph), 4.18 (d, $^3J_{H,H}$ = 8.7 Hz, 1 H, CH, 2'-H), 4.65 (dd, $^3J_{H,H}$ = 12.5, 5.0 Hz, 1 H, CH, 2-H), 5.71 (br. d, $^3J_{H,H}$ = 8.7 Hz, 1 H, NH), 6.12 (br. d, $^3J_{H,H}$ = 7.6 Hz, 1 H, NH), 7.11–7.14 (m, 2 H, Ar-H), 7.23–7.29 (m, 3 H, Ar-H). – ^{13}C NMR (75.5 MHz, $CDCl_3$, additional APT): δ = 13.2 (–, CH_2, cPr-C), 14.7 (–, CH_2, cPr-C), 27.9 (+, 3 CH_3), 28.2 (+, 3 CH_3), 37.4 (–, CH_2, C-3). 46.9 (+, CH, *), 53.4 (+, CH, *), 81.1 (–, C_{quat}, *t*Bu), 82.7 (–, C_{quat}, *t*Bu), 117.3 (–, CN), 127.1 (+, CH, Ar-C), 128.4 (+, 2 CH, Ar-C), 129.4 (+, 2 CH, Ar-C), 135.6 (–, C_{quat}, Ar-C), 170.2 (–, C=O, *), 170.7 (–, C=O, *), two carbon atoms were not detectable at this temp. – ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$, 100 °C): δ = 12.5 (CH_2, cPr-C), 13.9 (CH_2, cPr-C), 27.5 (C_{quat}), 27.7 (3 CH_3), 28.0 (3 CH_3), 37.4 (CH_2, C-3), 47.1 (CH, *), 53.5 (CH, *), 81.1 (C_{quat}, *t*Bu), 82.5 (C_{quat}, *t*Bu), 117.0 (CN), 126.9 (CH, Ar-C), 128.2 (2 CH, Ar-C), 129.1 (2 CH, Ar-C), 135.7 (C_{quat},

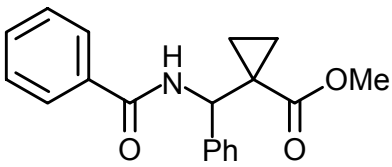
Ar-C), 154.3 (C_{quat}, Ar-C), 169.8 (C=O, *), 170.2 (C=O, *), 170.7 (C=O, *). MS (EI): *m/z* (%) = 443 (9) [M^+], 387 (10), 331 (28), 314 (30), 286 (22), 242 (10), 148 (100), 120 (85), 91 (15), 57 (40). $C_{24}H_{33}N_3O_5$ (443.5): calcd. C 64.99, H 7.50, N 9.47; found C 64.76, H 7.76, N 9.60.

The diastereoisomer **(2*S*,2'*R*)-118**: R_f = 0.27, m.p. 142–143 °C, $[\alpha]_D^{20}$ = +22.5 (*c* = 0.16 in



$CHCl_3$). – IR (KBr): $\tilde{\nu}$ = 3374 cm^{-1}, 3281, 3036, 2970, 2250, 1739, 1690, 1649, 1535, 1369. – ^1H NMR (250 MHz, $CDCl_3$): δ = 0.99–1.26 (m, 4 H, cPr-H), 1.43 (s, 9 H, 3 CH_3), 1.46 (s, 9 H, 3 CH_3), 3.04 (dd, $^2J_{H,H}$ = 12.5, $^3J_{H,H}$ = 5.0 Hz, 1 H, CH_2Ph), 3.12 (dd, $^2J_{H,H}$ = 12.5, $^3J_{H,H}$ = 7.5 Hz, 1 H, CH_2Ph), 4.10 (d, $^3J_{H,H}$ = 10.0 Hz, 1 H, CH, 2'-H), 4.71 (dd, $^3J_{H,H}$ = 12.5, 5.0 Hz, 1 H, CH, 2-H), 5.67 (br. d, $^3J_{H,H}$ = 10.0 Hz, 1 H, NH), 6.15 (br. d, $^3J_{H,H}$ = 12.5 Hz, 1 H, NH), 7.06–7.10 (m, 2 H, Ar-H), 7.24–7.31 (m, 3 H, Ar-H). – ^{13}C NMR (75.5 MHz, additional APT): δ = 13.3 (–, CH_2, cPr-C), 14.7 (–, CH_2, cPr-C), 27.9 (+, 3 CH_3), 28.2 (+, 3 CH_3), 37.7 (–, CH_2, C-3), 47.1 (+, CH, *), 53.3 (+, CH, *), 81.1 (–, C_{quat}, *t*Bu), 83.0 (–, C_{quat}, *t*Bu), 117.5 (–, CN), 127.1 (+, CH, Ar-C), 128.4 (+, 2 CH, Ar-C), 129.4 (+, 2 CH, Ar-C), 135.8 (–, C_{quat}, Ar-C), 170.2 (–, C=O, *), 170.3 (–, C=O, *), two carbon atoms were not detectable at this temp. ^{13}C NMR (75.5 MHz, $C_2D_2Cl_4$, 100 °C): δ = 12.5 (CH_2, cPr-C), 13.9 (CH_2, cPr-C), 27.6 (C_{quat}), 27.7 (3 CH_3), 28.0 (3 CH_3), 37.7 (CH_2, C-3), 47.1 (CH), 53.4 (CH), 81.1 (C_{quat}, *t*Bu), 82.7 (C_{quat}, *t*Bu), 117.0 (CN), 126.8 (CH, Ar-C), 128.2 (2 CH, Ar-C), 129.1 (2 CH, Ar-C), 135.8 (Ar-C), 154.3 (C_{quat}, Ar-C), 169.9 (C=O, *), 170.1 (C=O, *). – MS (EI): *m/z* (%) = 443 (38), 387 (35), 331 (75), 314 (65), 286 (68), 240 (25), 184 (22), 148 (100), 120 (55), 57 (50). – $C_{24}H_{33}N_3O_5$ (443.5): calcd. C 64.99, H 7.50, N 9.47; found C 64.77, H 7.62, N 9.42.

Methyl 1-(Benzoylaminophenylmethyl)-cyclopropane carboxylate (123): In argon



atmosphere trimethylsilylchloride (0.37 mL, 2.92 mmol) was added to a stirred solution of **53a** (0.325 g, 1.17 mmol) in MeOH (30 mL). The mixture was refluxed for 24 hours. After cooling to room temperature, CH_2Cl_2 (60 mL) was added and the resulting solution was washed with $NaHCO_3$ solution (2 × 50 mL). The organic phase was dried over $MgSO_4$ and after filtration and evaporation of the solvent under reduced pressure, the crude residue was purified by column cromatography (R_f = 0.26, 25 g of silica gel, 2 × 15 cm column, hexane/Et_2O 2:1) and gave **123** (0.148 g, 41%) as a colorless solid,

m.p. 139–140 °C. – IR (film): $\tilde{\nu}$ = 3340 cm^{-1}, 3033, 2959, 1734, 1717, 1635, 1521, 1313, 1140. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.09–1.28 (m, 3 H, cPr-H), 1.61–1.70 (m, 1 H, cPr-H), 3.57 (s, 3 H, OCH_3), 4.83–4.88 (d, $^{3}J_{H,H}$ = 9.2 Hz, 1 H, CH), 7.18–7.29 (m, 3 H, Ar-H), 7.35–7.47 (m, 5 H, Ar-H), 7.80–7.89 (m, 4 H, 3 Ar-H and NH). – ^{13}C NMR (50.3 MHz, $CDCl_3$, additional APT): δ = 15.2 (–, CH_2, cPr-C), 16.1 (–, CH_2, cPr-C), 27.7 (–, C_{quat}), 52.0 (+, *), 56.6 (+, *), 126.6 (+, 2 CH, Ar-C), 127.1 (+, 2 CH, Ar-C), 127.3 (+, CH, Ar-C), 128.4 (+, 2 CH, Ar-C), 128.6 (+, 2 CH, Ar-C), 131.6 (+, CH, Ar-C), 134.3 (–, C_{quat}, Ar-C), 140.3 (–, C_{quat}, Ar-C), 166.5 (–, C=O, *), 174.7 (–,C=O, *). – MS (EI): *m/z* (%) = 309 (18), 276 (25), 250 (10), 204 (92), 105 (100), 77 (40).

2.5. Synthesis of Compounds in Chapter 5

5-aza-spiro[2.3]hexan-4-one (128): To a solution of **53g** (0.178 g, 0.82 mmol) in acetonitrile (10.5 mL) was slowly added a solution of ceric ammonium nitrate (CAN) (0.877 g, 1.60 mmol) in water (3.5 mL) at room temperature. After 1 h additional CAN (0.438 g, 0.80 mmol) was added in portions. After additional 30 minutes the reaction was stopped and water (50 mL) and ethyl acetate (50 mL) were added into the reaction flask. The two phases were separated and the water extracted were washed with ethyl acetate (3 × 50 mL). The organic layers were than washed with a solution of $NaHCO_3$ and then dried over $MgSO_4$. After filtration and evaporation of the solvent under reduced pressure, the crude product was purified by column cromatography (R_f = 0.12, 15 g of silica gel, 2 × 8 cm column, hexane/Et_2O 1:6) to give **128** (26.0 mg, 33%) as a colorless oil. ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.87–1.11 (m, 2 H, cPr-H), 1.16–1.28 (m, 2 H, cPr-H), 3.43–3.45 (d, $^3J_{H,H}$ = 5.0 Hz, 2 H, CH_2), 7.09 (bs, NH). – ^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 8.2 (2 CH_2, cPr-C), 31.5 (C_{quat}, C-3), 48.2 (CH_2, C-6), 172.5 (C=O, C-4).

Cyclization of Methyl 1-(aminomethyl)-cyclopropane carboxylate 130. 5-aza-spiro[2.3]hexan-4-one (128): A solution of 130 (0.258 g, 2.00 mmol) in THF (6 mL) was added at 0 ºC to a solution of LDA (0.42 mL, 0.304 g, 3.00 mmol of diisopropylamine) in THF/hexane (10 mL). The resulting mixture was stirred at 25 ºC, overnight. The mixture was diluted with a 1.0 M sol. of NH_4Cl (20 mL) and extracted with CH_2Cl_2 (2 × 20 mL). The organic layers were then dried over Na_2SO_4. Column cromatography of the residue obtained after filtration and evaporation of the solvent (R_f = 0.1, 15 g of silica gel, 2 × 10 cm column, MeOH/Et_2O 1:6) gave 128 (40.0 mg, 21%).

Cyclization of 130·HCl. 5-aza-spiro[2.3]hexan-4-one (128): To a solution of 130·HCl (0.564 g, 3.40 mmol) in CH_2Cl_2 was added LiOH (3.6 mL of a 1.0 M solution) in water (20 mL) at 0 ºC. The mixture was stirred for additional 2 h at 25 ºC. The two phases were separated and the organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvent, the residue obtained (0.335 g, 2.59 mmol) was solved in diethyl ether (40 mL) and added in 4 hours to a solution of EtMgBr (1.2 mL of a 3.20 M sol., 3.84 mmol) in diethyl ether (160.0 mL). The mixture was stirred overnight at room temperature. A solution of NH_4Cl sat. (200 mL) was added and the two phases separated. The water phase was washed

with CH_2Cl_2 (2 × 60 mL) and the combined organic layers dried over Na_2SO_4. Just traces of 128 (15.0 mg, 6%) were obtained after evaporation of the solvent.

Methyl 1-({[*tert*-Butoxycarbonyl]amino}methyl)cyclopropane-1-carboxylate (131): To a suspension of 130·HCl (0.828 g, 5.00 mmol) in acetonitrile (5 mL) were added at 25 ºC triethylamine (0.70 mL, 0.506 g, 5.00 mmol) and in 20 minutes a solution of Boc_2O (1.09 g, 5.00 mmol) in acetonitrile (5 mL). After 3 hours no more starting material was observed in the mixture and diethyl ether (20 mL) and $NaHCO_3$ (20 mL) were added to the flask. The two phases were separated and the water phase was washed with ether (3 × 10 mL). The combined organic layers dried over $MgSO_4$ and then filtered. Evaporation of the solvent gave 131 (1.13 g, 98%).

1-({[*tert*-Butoxycarbonyl]amino}methyl)cyclopropane-1-carboxylic acid (134): A solution of LiOH (0.599 g, 2.50 mmol) in water (8 mL) was dropped to a solution of **131** (1.10 g, 5.00 mmol) in MeOH (6 mL), mantained at 0 ºC. The mixture was left under stirring for 20 hours at room temperature. After evaporating MeOH *in vacuo* water (20 mL) was added to the flask and the pH turned to 4, with a 0.02 M solution of HCl. The water phase was extracted with ether (3 × 30 mL). The organic layers were dried over $MgSO_4$. Filtration and evaporation of the solvent to dryness gave **134** (0.939 g, 87%).

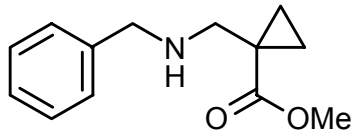
1-(Aminomethyl)-cyclopropane carboxylic acid trifluoroacetate (135·TFA): Trifluoroacetic acid (1.243 g, 0.84 mL, 10.9 mmol) was added at room temperature to a suspension of **134** (0.216 g, 1.0 mmol) and iPr_3SiH (0.458 g, 0.59 mL, 2.9 mmol) in dry CH_2Cl_2 (3 mL). After 1.5 hours the solvent was removed *in vacuo* and TFA was removed, adding toluene and evaporating to dryness (3 × 5 mL). **135·TFA** was obtained in quantitative yield (0.229 g).

Attempt of Ring Closure of 135·TFA with Coupling Reagents: To a solution of 135·TFA (0.229 g, 1.00 mmol) in CH_2Cl_2:DMF = 6:1 (43/7 mL) mantained at 0 ºC, were added DIPEA (0.646 g, 0.85 mL, 5.00 mmol), EDCI (0.287 g, 1.50 mmol), HOAt (0.204 g, 1.50 mmol). By adding the last reagent the solution turned to a fine suspension. After 12 hours at 0 ºC the solution was washed with $NaHSO_4$ (10% sol.) (6 × 20 mL). The organic phase was dried over $MgSO_4$. No trace of the cyclization product was found in the NMR spectrum, measured after evaporation of the solvent.

Benzylic protection of Methyl 1-(aminomethyl)-cyclopropane carboxylate hydrochloride (130·HCl). General Procedure 10

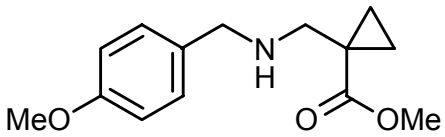
(GP 10): To a solution of **130·HCl** (1 equiv.) and triethylamine (1 equiv.) in MeOH, was added the aldehyde (1.5 equiv.) and the mixture was stirred for 1.5 hours. $NaBH_4$ (2 equiv.) was added in portions in 1 hour. After 1 night at 25 ºC the solvent was evaporated *in vacuo*, water and AcOEt were added. After separation, the water phase was washed with AcOEt and the organic layers dried over Na_2SO_4.

Methyl 1-(Benzylamino-methyl)-cyclopropane carboxylate (138): Column cromatography



(R_f = 0.17, 30 g of silica gel, 3 × 8 cm column, hexane/Et_2O 1:3) of the residue obtained from **130·HCl** (0.497 g, 3.00 mmol), triethylamine (0.304 g, 0.40 mL, 3.00 mmol), $NaBH_4$ (0.227 g, 6.00 mmol) in MeOH (7 mL), under the GP 10 gave **138** (0.580 g, 88%) as a colorless oil. – IR (film): $\tilde{\nu}$ = 3333 cm^{-1}, 3086, 2951, 2848, 1718, 1454, 1437. – ^1H NMR (200 MHz, $CDCl_3$): δ = 0.74–0.79 (m, 2 H, cPr-H), 1.22–1.25 (m, 2 H, cPr-H), 2.68 (s, 2 H, CH_2), 3.63 (s, 3 H, OCH_3), 3.79 (s, 2 H, NCH_2Ph), 7.19–7.31 (m, 5 H, Ar-H). – ^{13}C NMR (50.3 MHz, $CDCl_3$, additional APT): δ = 14.9 (–, 2 CH_2, cPr-C), 23.8 (–, C_{quat}), 51.7 (+, OCH_3), 52.6 (–, CH_2, *), 53.6 (–, CH_2, *), 126.8 (+, CH, Ar-C), 127.9 (+, 2 CH, Ar-C), 128.3 (+, 2 CH, Ar-C), 140.2 (–, C_{quat}, Ar-C), 175.3 (–, C=O). – MS (EI): m/z (%) = 218 (2), 204 (5), 128 (25), 120 (10), 106 (100), 96 (18), 91 (90), 65 (10). – $C_{13}H_{17}NO_2$ (219.28): calcd. C 71.21, H 7.81, N 6.39; found C 70.96, H 7.75, N 6.17.

Methyl 1-[(*p*-Methoxybenzylamino)-methyl]-cyclopropane carboxylate (139): Column



cromatography (R_f = 0.12, 50 g of silica gel, 3 × 15 cm column, hexane/Et_2O 1:3) of the residue obtained from **130·HCl** (0.828 g, 5.00 mmol), triethylamine (0.506 g, 0.70 mL, 5.00 mmol), $NaBH_4$ (0.378 g, 10.0 mmol) in MeOH (8 mL), under the GP 10 gave **139** (1.20 g, 96%) as a colorless oil. – IR (film): $\tilde{\nu}$ = 3331 cm^{-1}, 3005, 2951, 2835, 1721, 1611, 1585, 1512, 1437. – ^1H NMR (200 MHz, $CDCl_3$): δ = 0.74–0.77 (m, 2 H, cPr-H), 1.20–1.24 (m, 2 H, cPr-H), 2.18 (s, 2 H, CH_2), 2.66 (s, 3 H, OCH_3), 3.72 (s, 2 H, NCH_2Ph), 3.76 (s, 3 H, OCH_3), 6.81–6.84 (m, 2 H, Ar-H), 7.20–7.24 (m, 2 H, Ar-H). – ^{13}C NMR (50.3 MHz, $CDCl_3$, additional APT): δ = 14.9 (–, 2 CH_2, cPr-C), 23.8 (–, C_{quat}), 51.7 (+, CH_3, *), 52.5 (–, CH_2, *), 53.0 (–, CH_2, *), 55.2 (+, CH_3, *),

113.7 (+, 2 CH, Ar-C), 129.1 (+, 2 CH, Ar-C), 132.2 (–, C_{quat}, Ar-C), 158.5 (–, C_{quat}, Ar-C), 175.3 (–, C=O). – MS (EI): m/z (%) = 248 (5), 136 (100), 121 (88), 96 (5), 78 (8), 41 (2). – $C_{14}H_{19}NO3$ (249.31): calcd. C 67.45, H 7.68, N 5.62; found C 67.55, H 7.83, N 5.56.

5-(*p*-Methoxybenzyl)-5-azaspiro[2.3]hexan-4-one (53g): Compound 139 (0.625 g, 2.50 mmol) was solved in 25 mL NaOH 1.0 M in methanol. The mixture was refluxed for 2 h, When the starting material disappeared from the TLC, the mixture was cooled to room temperature and made neutral with a 0.5 N H_2SO_4 solution: a solid precipitates and water was evaporated *in vacuo*. The solid obtained was solved in $CHCl_3$ and dried over Na_2SO_4. After filtration and evaporation *in vacuo* of the solvent a colorless solid (1.12 g) was obtained. To a suspension of it in CH_2Cl_2 (250 mL) were added 2-chloro-*N*-methyl-pyridinium iodide 140 (0.703 g, 2.75 mmol) and triethylamine (0.885 g, 1.20 mL, 8.75 mmol). The mixture was stirred at room temperature until the starting material disappeared from the TLC (12 h). Column cromatography of the residue obtained after evaporation of the solvent (R_f = 0.28, 50 g silica gel, 3 × 15 cm column, hexane/Et_2O 1:3) gave 53g (0.277 g, 51%).

Poly(3-Phenyl-2-azetidinone) (154): LiCl (0.140 g, 3.4 mmol) was first dried in vacuo at 140 ºC for 30 minutes in a schlenk flask. After cooling at room temperature, the monomer **148** (1.00 g, 6.79 mmol) and the activator **149** (0.040 g, 0.160 mmol) were dissolved in DMF (3.40 mL) under nitrogen atmosphere. The base *t*BuOK (4.0 mg, 0.034 mmol) was added and the mixtutre stirred for 30 minutes at 25 ºC. Benzylamine (98.0 mg, 0.1 mL, 0.92 mmol) was then added and the mixture was stirred for additional 72 h. When a mixture acetone : water = 5 : 1 (10 mL) was added, a white solid precipitated. The latter was collected by centrifugation and dried *in vacuo*. The white solid (0.825 g) obtained, had melting point >260 ºC. – IR (KBr): $\tilde{\nu}$ = 3291 cm^{-1}, 3060, 3028, 1648, 1528, 1494, 1452, 697. – MS (ESI) (+): m/z (%) = 570 (20), 643 (20), 717 (20), 822 (60), 937 (20), 969 (100), 1011 (20), 1116 (80), 1158 (10), 1263 (40), 1306 (10), 1410 (20), 1558 (10) and MS (ESI) (–): m/z (%) = 651 (20), 798 (80), 945 (100), 1092 (70), 1139 (30), 1240 (30), 1386 (20), 1432 (10).

Anionic Polymerization of 108: LiCl (0.014 g, 0.325 mmol) was first dried *in vacuo* at 130 ºC for 3 h in a schlenk flask. A solution of **108** (0.080 g, 0.650 mmol) in dry DMAA

(2.0 mL) was added under nitrogen atmosphere. The activator **107c** (4.00×10^{-3} g, 0.016 mmol) and *t*BuOK (1.0×10^{-3} g, 0.9×10^{-5} mmol) were added to the solution. After 1 h at 25 ºC benzylamine was added (1 drop) and the mixture stirred for additional 72 h. The latter was poured in a mixture acetone : water = 5 : 1 and diethyl ether was added to obtain the precipitation of a solid, that was collected by centrifugation. The white solid was solved in 2,2,2-trifluoroethanol and then precipitated again. The solid was collected and dried *in vacuo*. 50.0 mg of a colorless solid were obtained. The solid obtained had melting point >260 ºC. IR (KBr): $\tilde{\nu}$ = 3604 cm^{-1}, 3273, 3010, 1754, 1672, 1530, 1416, 1351, 1146. The polymer was not soluble in the solvents suitable for a more detailed carachterization.

Anionic Polymerization of 128: LiCl (0.108 g, 2.55 mmol) was first dried *in vacuo* at 130 ºC for 3 h in a schlenk flask. A solution of **128** (0.124 g, 1.28 mmol) in dry DMAA (1.2 mL) was added under nitrogen atmosphere. *t*BuOK (1.0×10^{-3} g, 0.9×10^{-5} mmol) was added to the solution. After 1 h at 25 ºC benzylamine was added (1 drop) and the mixture stirred for additional 72 h. The latter was poured in a mixture acetone : water = 5 : 1 and diethyl ether was added to obtain the precipitation of a solid, that was collected by centrifugation. The white solid is solved in 2,2,2-trifluoroethanol and then precipitated again. The solid is collected and dried *in vacuo*. 124.0 mg of a colorless solid were obtained. The solid obtained had melting point >260 ºC. IR (KBr): $\tilde{\nu}$ = 3081 cm^{-1}, 3005, 2934, 1635, 1576, 1365, 1203. The polymer was not soluble in the solvents suitable for a more detailed carachterization.

D. Summary

During the elaboration of this thesis, several differently substituted monocyclic 3-spirocyclopropanated-β-lactams **53**, which are formally derived from the α-cyclopropyl-modified β-alanine **41**, have been prepared. The synthesis of these derivatives was achieved through the rearrangement of 4,5-dispirocyclopropanated isoxazolidines **47** in the presence of an acid. The compounds **47** were obtained by means of 1,3-dipolar cycloadditions of linear nitrones **44** on bicyclopropylidene (**24**). The 3-spirocyclopropanated β-lactams **53** have subsequently been introduced into oligopeptides, in which the presence of the small ring adjacent to the carbonyl function introduces a conformational lock.

In the first part of this work, the synthesis of nitrones **44a-j** was described. The derivatives **44d-g**, and **i** were not yet known in the literature and were obtained in 68% up to quantitative yield. The 1,3-dipolar cycloadditions of **44a-f** furnished the 4,5-dispirocyclopropanated-isoxazolidines **47a-f** in 75% up to quantitative yield. The nitrone **44g,** which was proved to be unstable**,** gave the cycloadduct **47g** in 21% yield. The rearrangement under acidic conditions of isoxazolidines **47a-e**, using the methodology of Brandi et al., led to the desired monocyclic β-lactams **53a-e** in 75 to 94% yields. The cycloadduct **70**, derived from the cyclic nitrone **44h**, did not lead to a β-lactam, but furnished the β-spirocyclopropanated homoproline **72** in low yield (18%).

Furthermore, a new one-pot procedure for the synthesis of the monocyclic β-lactam derivatives **53** was developed and optimized, applying microwave heating. In particular, the azaspiro[2.3]hexanones **53g,j**, **53e**-H**,f**-H, **77c**-Et**,f**-Et and **77d**-Me were prepared in 49 up to 78% yield by a three-component cascade reaction, in which a *N*-hydroxylamine salt **65·HCl**, formaldehyde **66**-H or an alkyl glyoxylate **73**-alk and bicyclopropylidene (**24**) yielded the final products in the presence of sodium acetate. Attempts to apply this methodology to *N*-methyl hydroxylamines **65g** and *N*-aryl hydroxylamines **65h**,**i** were unsuccessful. In the case of cyclohexyl glyoxylate **73-cHex** and *orto*-iodobenzaldehyde **76**, different conditions were found to be necessary for the formation of β-lactams **77c**-cHex and **53e** respectively. These compounds could only be obtained by a one-pot reaction, using the hydroxylamine in its free form and adding a strong protic acid.

It was subsequenly shown how it is possible to obtain selectively the cyclopropanated isoxazolidines **47g,j**, **47e**-Et and **81** (in 49 to 70% yields), or the corresponding piperidones

49g,j and **85** (in 7 to 37% yield). In the absence of acids, but with the same components used in the microwave assisted one-pot synthesis of β-lactams **53**, it was in fact possible to obtain these other two kinds of azaheterocycles, just varying the reaction parameters, time and temperature.

The preparation of β-lactams **107a,b**, **110** and **111**, protected at the nitrogen atom with electron-withdrawing groups, was undertaken to apply them in the peptide-synthesis. The derivatives **107a,b** were obtained by oxidation of the benzylic methylene carbon in **53a,b**. The derivatives **110** and **111** were prepared by deprotection-reprotection sequences through introduction of the Boc group on **108** and **109**, obtained from **53d** and **77d**-Me. The β-lactam derivatives **107a** and **110** were coupled with *tert*-butyl glycinate **102** and/or *tert*-butyl (*S*)-phenylalaninate **115** by *N*-nucleophilic ring-opening of the azetidinone nucleus to obtain the dipeptides **116-118** in 61 to 84% yields. The separation of the two diasteroisomers (2*S*,2'*S*)-**118** and (2*S*,2'*R*)-**118**, and the analysis of the X-Ray crystal structure of one of them, allowed the assignment of the absolute configurations. The derivative **107b**, when treated with **102**, did not undergo ring-opening reaction, but the coupling took place at the methoxycarbonyl function, to give **114** in 51% yield. The ring opening of **53a**, under strongly acidic conditions with methanol as an *O*-nucleophile, led to the compound **123**.

In the final part of this project, a synthesis of **128** was carried out via ring-closing of cyclopropyl-β-alanine **130**. This approach allowed to obtain **128** in reasonable yields only after benzylic protection of **130** to get **138** and **139**. Subsequently, *via* ring-closure of **139**, the *para*-methoxybenzyl protected β-lactam **53g** was obtained and its deprotection led to the target β-lactam **128**. The possibility to synthesize *N*-deprotected-3-spirocyclopropanated β-lactam derivatives like **108** or **128** furnished ideal starting materials, to try an anionic polymerization protocol in order to obtain spirocyclopropanated poly-β-propiolactams.

The anionic polymerization of **108** and **128** was performed, and white, high melting solids were obtained. The analysis of their IR spectra showed positive results, but the impossibility to dissolve the obtained solids, limited their further characterization by GPC or ESI mass spectrometry. Additionally, the new polymer **154** was prepared by anionic polymerization of the β-lactam **148**, in the presence of **149**, as activator.

E. References

[1] A. Fleming, *Br. J. Exp. Pathol*. **1929**, *10*, 226–229.

[2] E. P. Abraham, E. Chain, W. Baker, R. Robinson, *Pen. Report* No 103, **1943**.

[3] D. Crowfoot, C. W. Bunn, B. W. Rogers-Low, A. Turner-Jones in *The Chemistry of Penicillin*, Princeton University Press, Princeton, New Jersey, **1949**, p. 310.

[4] G. G. F. Newton, E. P. Abraham, *Nature* **1955**, *175*, 548.

[5] [a] R. B. Morin, M. Gorman, *Chemistry and Biology of* β-*Lactam Antibiotics*, Academic Press, New York **1982**; [b] D. B. Boyd, *Penicillins and Cephalosporins*, Vol. 1, from *Chemistry and Biology of* β-*Lactam Antibiotics*, Academic Press, New York **1982**; [c] R. B. Morin, M. Gorman, *Nontraditional* β-*Lactam Antibiotics*, Vol. 2, from *Chemistry and Biology of* β-*Lactam Antibiotics*, Academic Press, New York **1982**; [d] R. B. Morin, M. Gorman, *The Biology of* β-*Lactam Antibiotics*, Vol. 3, from *Chemistry and Biology of* β-*Lactam Antibiotics*, Academic Press, New York **1982**.

[6] [a] H.–W. Liu, C. T. Walsh in *The Chemistry of the cyclopropyl group* (Ed. Z. Rappoport), Wiley **1987**, pp. 959–1021; [b] J. Salaün, *Top. Curr. Chem*. **2000**, *207*, 1–67.

[7] [a] D. B. Boyd *Penicillins and Cephalosporins*, Vol. 1, from *Chemistry and Biology of* β-*Lactam Antibiotics*, Academic Press, New York **1982**, pp. 567–577; [b] N. C. Cohen *Actual. Chim.* (May **1983**), 7; [c] M. Takasuka, J. Nishikawa, K. Tori *J. Antibiot.* **1982**, *35*, 1729–1733; [d] D. B. Boyd *J. Med. Chem.* **1983**, *26*, 1010–1013.

[8] N. F. Osborne, *J. Chem. Soc. Perkin Trans. I* **1982**, 1435–1439.

[9] D. H. Shih, J. A. Fayter, B. G. Christensen, *Tetrahedron Lett.* **1984**, *25*, 1639–1642.

[10] C. U. Kim, P. F. Misco, B. Y. Luh, *Heterocycles* **1987**, *26*, 1193–1196.

[11] M. Es-Sayed, T. Heiner, A. de Meijere, *Synthesis* **1993**, 57–58.

[12] D.H. Shih, F. Baker, L. Cama, B. G. Christensen, *Heterocycles* **1984**, *21*, 29–40.

[13] [a] T. J. Barton, R. J. Rogido, *Tetrahedron Lett.* **1972**, 3901–3902; [b] S. R. Fletcher, I. T. Kay, *J. Chem. Soc., Chem. Commun*. **1978**, 903–904.

[14] B. Alcaide, P. Almendros, *Synlett*, **2002**, *3*, 381–393.

[15] [a] I. Ojima, S. Suga, R. Abe, *Chem. Lett.* **1980**, 853–856; [b] I. Ojima, X. Qiu, *J. Am. Chem. Soc.* **1987**, *109*, 6537–6538; [c] I. Ojima, M. Zhao, T. Yamato, K. Nakahashi, M. Yamashita, R. Abe, *J. Org. Chem.* **1991**, *56*, 5263–5277; [d] B. Alcaide, P. Almendros, C. Aragoncillo, N. R. Salgado, *J. Org. Chem.* **1999**, *64*, 9596–9604; [e] B. Alcaide, N. R. Salgado, M. A. Sierra, *Tetrahedron Lett.* **1998**, *39*, 467–470; [f] B. Alcaide, Y. Martín-Cantalejo, J. Rodríguez-López, M. A. Sierra, *J. Org. Chem.* **1993**, *58*, 4767–4770; [g] B. Alcaide, P. Almendros, N. R. Salgado, A. Rodríguez-Vicente, *J. Org. Chem.* **2000**, *65*, 4453–4455; [h] F. P. Cossío, C. Lopez, M. Oiarbide, C. Palomo, D. Aparicio, G. Rubiales, *Tetrahedron Lett.* **1988**, *29*, 3133–3136; [i] C. Palomo, M. Oiarbide, A. Landa, A. Esnal, A. Linden, *J. Org. Chem*. **2001**, *66*, 4180–4186.

[16] I. Ojima, F. Delaloge, *Chem. Soc. Rev.* **1997**, *26*, 377–386.

[17] F. Graupner, *Dissertation*, Universität Göttingen, **1993**.

[18] The preparation and chemical transformations of methylenecyclopropane (**43**) and its close relative bicyclopropylidene (**24**) have been reviewed extensively. [a] P. Binger, H. M. Büch, *Top. Curr. Chem*. **1987**, *135*, 77–151; [b] P. Binger, T. Schmidt, in *Houben-Weyl*, *Methods of Organic Chemistry*, (Ed.: A. de Meijere) Vol. E 17c, Thieme, Stuttgart, **1997**, pp. 2217–2294; [c] A. Brandi, A. Goti, *Chem. Rev*. **1998**, *98*, 589–635; [d] A. de Meijere, S. I. Kozhushkov, A. F. Khlebnikov, *Zh. Org. Khim*. **1996**, *32*, 1607–1626; *Russ. J. Org. Chem.* (*Engl. Transl.*) **1996**, *32*, 1555–1575; [e] A. de Meijere, S. I. Kozhushkov, A. F. Khlebnikov, *Top. Curr. Chem.* **2000**, *207*, 89–147; [f] A. de Meijere, S. I. Kozhushkov, T. Späth, M. von

Seebach, S. Löhr, H. Nüske, T. Pohlmann, M. Es-Sayed, S. Bräse, *Pure Appl. Chem*. **2000**, *72*, 1745–1756.

[19] W. Weber, I. Erden, A. de Meijere, *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 387–388.

[20] I. Nakamura, T. Nemoto, A. de Meijere, Y. Yamamoto, *Angew. Chem.* **2005**, to be submitted.

[21] F. Gnad, O. Reiser, *Chem. Rev*. **2003**, *103*, 1603–1623.

[22] S. Teichmann, *Dissertation*, Universität Hamburg, **1988**.

[23] A. de Meijere, S. Teichmann, D. Yu, J. Kopf, M. Oly, N. von Thienen, *Tetrahedron* **1989**, *45*, 2957–2968.

[24] C. Palomo, J. M. Aizpurua, I. Ganboa, Chapter 14 in *Enantioselective Synthesis of* β-*Amino Acids* (Ed.: E. Juaristi), Wiley-VCH, New York, **1997**, p. 279.

[25] M. S. Manhas, S. G. Amin, A. K. Bose, *Heterocycles* **1976**, *5*, 669–690.

[26] [a] J. M. Waisvizs, M. G. van der Hoeven, B. te Nijenhuis, *J. Am. Chem. Soc.* **1957**, *79*, 4524–4527; [b] K. S. Chu, G. R. Negrete, J. P. Konopelski, *J. Org. Chem.* **1991**, *56*, 5196–5206.

[27] [a] Stachowiak, M. C. Khosla, K. Plucinska, F. M. Bumpus, *J. Med. Chem*. **1979**, *22*, 1128–1130; [b] T. Jamazaki, A. Probstl, P. Schiller, M. Goodman, *Int. J. Pept. Protein Res.* **1991**, *37*, 364–381; [c] Z. Huang, A. Probstl, J. R. Spencer, T. Yamazaki, M. Goodman, *Int. J. Pept. Protein Res.* **1993**, *42*, 352–365; [d] D. H. Appella, L. A. Christianson, D. A. Klein, D. R. Powell, X. Huang, J. J. Barchi, S. H. Gellman, *Nature* **1997**, *387*, 381–384; [e] S. H. Gellman, *Acc. Chem. Res*. **1998**, *31*, 173–180; [f] E. A. Porter, X. Wang, H. Lee, B. Weisblum, S. H. Gellman, *Nature* **2000**, *404*, 565; [g] D. Seebach, M. Overhand, F. N. M. Kühnle, B. Martinoni, L. Oberer, U. Hommel, H. Widmer, *Helv. Chim. Acta* **1996**, *79*, 913–941; [h] S. Abele, G. Guichard, D. Seebach, *Helv. Chem. Acta* **1998**, *81*, 2141–2156; [i]

K. Gademann, M. Ernst, D. Hoyer, D. Seebach, *Angew. Chem.* **1999**, *111*, 1302–1304; *Angew. Chem., Int. Ed.* **1999**, *38*, 1223–1226; [j] B. W. Gung, D. Zou, A. M. Stalcup, C. E. Cottrell, *J. Org. Chem.* **1999**, *64*, 2176–2177; [k] Y. Hamuro, J. P. Schneider, W. F. DeGrado, *J. Am. Chem. Soc.* **1999**, *121*, 12200–12201.

[28] [a] N. Katayama, Y. Nozaki, S. Tsubotani, M. Kondo, S. Harada, H. Ono, *J. Antibiot*. **1990**, *33*, 1128–1137; [b] J. N. Denis, A. E. Greene, D. Guenard, F. Gueritte–Voegelein, L. Mangatal, P. Potier, *J. Am. Chem. Soc.* **1988**, *110*, 5917–5919; [c] H. Umezawa, T. Aoyagi, H. Suda, M. Hamada, T. Takeuchi, *J. Antibiot.* **1976**, *29*, 97.

[29] K. Iizuka, H. Harada, K. Akahane, T. Kubota, H. Umeyawa, Y. J. Kiso, *J. Chem. Soc. Chem. Commun*. **1989**, 1678–1680;

[30] S. Abele, P. Seiler, D. Seebach, *Helv. Chem. Acta* **1999**, *82*, 1559–1571.

[31] [a] H. G. Richey Jr *chapter 25* in*, Carbonium Ions* Eds. G. A. Olah and P. v. R. Schleyer, Wiley-Interscience. New York, **1972**, Vol. III; [b] A. D. Walsh, *Trans. Faraday Soc.* **1949**, *45*, 179–190; [c] T. M. Sugden, *Nature* **1947**, *160*, 367–368; [d] S. A. Monti, *J. Org. Chem*. **1970**, *35*, 380–383; [e] A. de Meijere, *Angew. Chem*. **1979**, *11*, 867–884; *Angew. Chem. Int. Ed.* **1979**, *18*, 809–826; [f] Z. Rappoport in *The Chemistry of the Cyclopropyl group*, John Wiley & Sons, Chichester, **1987**, Vol. 2; [g] F. H. Allen, *Acta Crystallogr., Sect. B* **1980**, *36*, 81; [h] M. Pellissier, A. Serafini, J. Devanneaux, J.-F. Labarre, J.–F. Tocanne, *Tetrahedron* **1971**, *27*, 3271–3284; [i] J. –F. Tocanne, *Tetrahedron* **1972**, *28*, 389–416.

[32] [a] A. Brandi, F. M. Cordero, A. Goti, F. De Sarlo, A. Guarna, *Synlett* **1993**, 1–8; [b] F. M. Cordero, F. De Sarlo, A. Brandi, *Monatsh. Chem.* **2004**, *135*, 649–669.

[33] A. Hassner, C. Stumer, *Organic Synthesis Based on Name Reactions*–2nd Ed., Tetrahedron Organic Chemistry Series, 22; Pergamon, Oxford, UK, **2002**, p. 42.

[34] [a] F. M. Cordero, F. Pisaneschi, A. Goti, J. Ollivier, J. Salaün, A. Brandi, *J. Am. Chem. Soc.* **2000**, *122*, 8075–8076; [b] F. M. Cordero, F. Pisaneschi, M. Salvati, V. Paschetta, J. Ollivier, J. Salaün, A. Brandi, *J. Org. Chem.* **2003**, *68*, 3271–3278.

[35] [a] M. Miura, M. Enna, K. Okuro, M. Nomura, *J. Org. Chem*. **1995**, *60*, 4999–5004; [b] M. Kinugasa, S. Hashimoto, *J. Chem. Soc., Chem. Commun*. **1972**, 466–467; [c] R. Shintani, G. C. Fu, *Angew. Chem.* **2003**, *115*, 4216–4219; *Angew. Chem. Int. Ed.* **2003**, *42*, 4082–4085.

[36] [a] L. Stella, *Angew. Chem. Int. Ed.* **1983**, *22*, 337–350; [b] M. E. Wolff, *Chem. Rev* **1963**, *63*, 55–64.

[37] [a] A. Padwa, K. K. Koehler, A. Rodriguez, *J. Org. Chem*. **1984**, *49*, 282–288; [b] A. Padwa, K. K. Koehler, A. Rodriguez, *J. Am. Chem. Soc*. **1981**, *103*, 4974–4975.

[38] H. G. Aurich, J. –L. Ruiz Quintero, *Tetrahedron* **1994**, *50*, 3943–3950.

[39] L. W. A. van Berkom, G. J. T. Kuster, R. de Gelder, H. W. Scheeren, *Eur. J. Org. Chem.* **2004**, 4397–4404.

[40] J. Salaun, M. S. Baird, *Curr. Med. Chem*. **1995**, *2*, 511–542.

[41] S. Cicchi, M. Corsi, A. Goti, *J. Org. Chem*. **1999**, *64*, 7243–7245.

[42] F. M. Cordero, F. Machetti, F. De Sarlo, A. Brandi, *Gazz. Chim. Ital*. **1997**, *127*, 25–29.

[43] H. Tokuyama, T. Kuboyama, A. Amano, T. Yamashita, T. Fukuyama, *Synthesis* **2000**, 1299–1304.

[44] O. Tamura, T. Okabe, T. Yamaguchi, K. Gotanda, K. Noe, M. Sakamoto, *Tetrahedron* **1995**, *51*, 107–118.

[45] A. Hassan, M. Waseer, A. Sk. Asrof, *J. Chem. Soc., Perkin Trans. II* **1998**, 393–400.

[46] R. Annunziata, M. Cinquini, F. Cozzi, P. Giaroni, L. Raimondi, *Tetrahedron Let*. **1991**, *32*, 1659–1662.

[47] O. G. Kulinkovich, S. V. Sviridov, D. A. Vasilevski, *Synthesis* **1991**, 234.

[48] A. de Meijere, S. I. Kozhushkov, T. Spaeth, N. S. Zefirov, *J. Org. Chem*. **1993**, *58*, 502−505.

[49] A. Goti, F. M. Cordero, A. Brandi, *Top. Curr. Chem*. **1996**, *178*, 1−97.

[50] A. Goti, B. Anichini, A. Brandi, *J. Org. Chem*. **1996**, *61*, 1665−1672.

[51] F. M. Cordero, M. Salvati, F. Pisaneschi, A. Brandi, *Eur. J. Org. Chem*. **2004**, 2205−2213.

[52] [a] R. Sharma, R. J. Stoodley, A. Whiting, *J. Chem. Soc., Perkin Trans. I* **1987**, 2361−2369; [b] P. H. Crackett, C. M. Pant, R. J. Stoodley, *J. Chem. Soc., Perkin Trans. I* **1984**, 2785−2793; [c] J. Brennan, G. Richardson, R. J. Stoodley, *J. Chem. Soc., Perkin Trans. I* **1983**, 649−655.

[53] C. M. Tice, B. Ganem, *J. Org. Chem*. **1983**, *48*, 5048−5050.

[54] [a] A. Vasella, *Helv. Chim. Acta* **1977**, *60*, 1273−1295; [b] E. J. Fornefeld, A. J. Pike, *J. Org. Chem.* **1979**, *44*, 835−839; [c] W. Oppolzer, *Tetrahedron Lett*. **1979**, 4391−4394.

[55] I. S. Young, J. L. Williams, M. A. Kerr, *Org. Lett*. **2005**, *7*, 953–955.

[56] C. O. Kappe, *Angew. Chem*. **2004**, *116*, 6408–6443; *Angew. Chem. Int. Ed*. **2004**, *43*, 6250–6284.

[57] R. Gedey, F. Smith, K. Westaway, H. Ali, L. Baldisera, L. Laberge, J. Roussel, *Tetrahedron Lett.* **1986**, *27*, 279–282.

[58] A. R. von Rippel, *Dielectric Materials and Applications*, MIT Press, Cambridge, MA, **1954**.

[59] C. Gabriel, S. Gabriel, E. H. Grant, B. S. J. Halstead, D. M. P. Mingos, *Chem. Soc. Rev*. **1998**, *27*, 213–223.

[60] [a] P. R. West, G. C. Davis, *J. Org. Chem*. **1989**, *54*, 5176–5180; [b] I. D. Entwistle, T. Gilkerson, R. A. W. Johnstone, R. P. Telford, *Tetrahedron* **1978**, *34*, 213–215.

[61] [a] R. Signer, *Helv. Chim. Acta* **1930**, *13*, 43–46; [b] P. F. Schuda, C. B. Ebner, S. J. Potlock, *Synthesis* **1987**, *12*, 1055–1057.

[62] T. R. Kelly, T. E. Schmidt, J. G. Haggerty, *Synthesis* **1972**, 544–545.

[63] F. M. Cordero, I. Barile, F. De Sarlo, A. Brandi, *Tetrahedron Lett.* **1999**, *40*, 6657–6660.

[64] [a] Y. Ogata, T. J. Morimoto, *J. Org. Chem*. **1965**, *30*, 597–600; [b] V. D. Simonou, T. V. Denisenko, V. I. Savchenko, S. Y. Sklyar, *J. Org. Chem. USSR* **1976**, *12*, 1048–1050.

[65] A. Zanobini, M. Gensini, J. Magull, D. Vidović, S. I. Kozhushkov, A. Brandi, A. de Meijere, *Eur. J. Org. Chem.* **2004**, 4158–4166.

[66] A. Dömling, I. Ugi, *Angew. Chem*. **2000**, *112*, 3300–3344; *Angew. Chem. Int. Ed*. **2000**, *39*, 3168–3210.

[67] C. Zorn, B. Anichini, A. Goti, A. Brandi, S. I. Kozhushkov, A. de Meijere, L. Citti, *J. Org. Chem.* **1999**, *64*, 7846–7855.

[68] P. Lindström, J. Tierney, B. Wathey, J. Westmann, *Tetrahedron* **2001**, *57*, 9225–9283.

[69] [a] C. N. C. Drey, Chapter 3 *in Chemistry and Biochemistry of Amino Acids, Peptides, and Proteins* (Ed. G. C. Barnet), Chapman and Hall, London **1985**, p. 25; [b] A. F. Spatola in *Chemistry and Biochemistry of Amino Acids, Peptides and Proteins* (Ed. B. Winstein), Marcel Dekker, New York, **1983**, Vol. 7, p. 267.

[70] [a] G. Cardillo, C. Tomasini, *Chem. Soc. Rev*. **1996**, *25*, 117–128; [b] T. Yasumoto, M. Satake, *Chimia* **1998**, *52*, 63–68; [c] C. A. Bewley, D. J. Faulkner, *Angew. Chem*. **1998**, *110*, 2280–2297; *Angew. Chem. Int. Ed.* **1998**, *37*, 2163–2178.

[71] K. D. Walker, H. G. Floss, *J. Am. Chem. Soc* **1998**, *120*, 5333–5334.

[72] [a] E. Abderhalden, F. Reich, *Fermentforschung* **1929**, *11*, 319–329; [b] E. Abderhalden, R. Fleischmann, *Fermentforschung* **1928**, *10*, 195–212.

[73] [a] R. P. Nargund, K. H. Barakat, K. Cheng, W. W.–S. Chen, B. R. Butler, R. G. Smith, A. A. Patchett, *Bioorg. Med. Chem. Lett.* **1996**, *6*, 1265–1270; [b] M. Llinares, C. Devin, J. Azay, G. Berge, J. A. Fehrentz, J. Martinez, *Eur. J. Med. Chem*. **1997**, *32*, 767–780; [c] K. Iijima, J. Katada, Y. Hayashi, *Bioorg. Med. Chem. Lett.* **1999**, *9*, 413–418.

[74] [a] T. Hintermann, D. Seebach, *Chimia* **1997**, *50*, 244–247; [b] D. Seebach, S. Abele, J. V. Schreiber, B. Martinoni, A. K. Nussbaum, H. Schild, H. Schulz, H. Henneke, R. Wössner, F. Bitsch, *Chimia* **1998**, *52*, 734–739.

[75] M. Bhupathy, J. J. Bergan, J. M. McNamara, R. P. Volanta, P. J. Reider, *Tetrahedron Lett*. **1995**, *36*, 9445–9448.

[76] C. Palomo, M. Oiarbide, S. Bindi, *J. Org. Chem*. **1998**, *63*, 2469–2474.

[77] I. Ojima, C. M. Sun, Y. H. Park, *J. Org. Chem*. **1994**, *59*, 1249–1250.

[78] M. Es-Sayed, *Dissertation*, Universität Hamburg, **1992**.

[79] Ring opening of β-lactams with aryl substituents at C-4 under hydrogenolytic conditions has previously been observed: [a] I. Ojima, S. Suga, R. Abe, *Tetrahedron Lett*. **1980**, *21*, 3907–3910. [b] I. Ojima, N. Hatanaka, N. Yodo, R. Abe, M. Yatabe, M. Yamashita in *Peptide Chemistry* **1982** (Ed.: S. Sakakibara), Protein Research Foundation, Osaka, 1983, pp. 29–34; [c] I. Ojima, in *Advances in Asymmetric Synthesis* (Ed. Hassner), Jai Press Inc. Greenwich, CT, **1995**, Vol. 1, pp. 95.

[80] [a] J. Aszodi, A. Bonnet, G. Teutsch, *Tetrahedron* **1990**, *46*, 1579–1586; [b] G. D. Annis, E. M. Hebblethwaite, S. T. Hodgson, D. M. Hollinshead, S. V. Ley, *J. Chem. Soc. Perkin Trans. 1* **1983**, 2851–2856; [c] R. M. Williams, E. Kwast, *Tetrahedron Lett*. **1989**, *30*, 451–454.

[81] [a] V. Moreaux, H. Warren, J. M. Williams, *Tetrahedron Lett*. **1997**, *38*, 4655–4658. [b] J. M. Blanco, O. Caamanno, F. Fernandez, X. Garsia Mera, C. Lopez, G. Rodriguez, J. E. Rodriguez-Borges, A. Rodriguez-Hergueta, *Tetrahedron Lett*. **1998**, *39*, 5663–5666. [c] B. Alcaide, A. Gomez, J. Plumet, J. Rodrigez-Lopez, *Tetrahedron* **1989**, *45*, 2751–2762.

[82] M. I. Page, *Adv. Phys. Org. Chem* **1987**, *23*, 165–270.

[83] I. Ojima, *Acc. Chem. Res*. **1995**, *28*, 383–389.

[84] [a] X. Daura, W. F. van Gusteren, D. Rigo, B. Jaun, D. Seebach, *Chem. Eur. J.* **1997**, *3*, 1410–1417; [b] X. Daura, B. Jaun, D. Seebach, W. F. van Gunsteren, A. E. Mark, *J. Mol. Biol.* **1998**, *280*, 925–932; [c] X. Daura, K. Gademann, B. Jaun, D. Seebach, W. F. van Gunsteren, A. E. Mark, *Angew. Chem.* **1999**, *111*, 249–253; *Angew. Chem. Int. Ed.* **1999**, *38*, 236–240.

[85] [a] R. Graf, G. Lohaus, K. Börner, E. Schmidt, H. Bestian, *Angew. Chem*. **1962**, *74*, 523; *Angew. Chem. Int. Ed.* **1962**, *1*, 481–488; [b] H. Bestian, *Angew. Chem*. **1968**, *80*, 304–312; *Angew. Chem. Int. Ed.* **1968**, *7*, 278–285 [c] E. Schmidt, *Angew. Makromol. Chem*. **1970**, *14*, 185–202.

[86] [a] A. Rodíguez-Galán, S. Muñoz-Guerra, J. A. Subirana, B. Chuong, H. Sekiguchi, *Makromol. Chem., Makromol. Symp*. **1986**, *6*, 277–284; [b] S. Muñoz-Guerra, F. López-Carrasquero, J. M. Fernández-Santin, J. A. Subirana in *Encyclopedia of Polymeric Materials* (Ed.: J. C. Salamone), CRC Press: Boca Raton, FL, **1996**, pp 4694–4700; [c] A. M. Ilarduya, C. Alaman, M. Garcia-Alvarez, F. López-Carrasquero, S. Muñoz-Guerra, *Macromolecules* **1999**, *32*, 3257–3263.

[87] [a] F. Chen, G. Lepore, M. Goodmann, *Macromolecules* **1974**, *7*, 779–783; [b] H. W. Siesler, *Polymer* **1974**, *15*, 146–148; [c] S. R. Turner, R. C. Schulz, *Makromol. Chem.* **1975**, *176*, 501–506; [d] H. R. Krichelsdorf, G. Schilling, *Makromol. Chem*. **1978**, *179*, 2667–2674; [e] H. Yuki, Y. Okamoto, Y. Taketani, T. Tsubota, Y. Marubayashi, *J. Polym. Chem. Ed.* **1978**, *16*, 2237–2251; [f] J. Masamoto, K. Sasaguri, C. Ohizumi, H. Kobayashi, *J. Polym. Sci., Part A-2* **1978**, *8*, 1703; [g] E. J. Günster, R. C. Schulz, *Makromol. Chem*. **1980**, *181*, 643–649.

[88] J. Kovacs, R. Ballina, R. Rodin, D. Balasubramanian, J. Applequist, *J. Am. Chem. Soc.* **1965**, *87*, 119–120.

[89] P. M. Hardy, J. Haylock, H. Rydon, *J. Chem. Soc., Perkin Trans. 1* **1972**, 605–611.

[90] H. Yuki, Y. Okamoto, Y. Taketani, T. Tsubota, Y. Marubayashi, *J. Polym. Sci., Polym. Chem. Ed.* **1978**, *16*, 2237–2251.

[91] [a] J. M. Fernández-Santin, J. Aymami, A. Rodíguez-Galán, S. Muñoz-Guerra, J. A. Subirana, *Nature* **1984**, *311*, 53–54; [b] J. M. Fernández-Santin, S. Muñoz-Guerra, A. Rodíguez-Galán, J. Aymami, J. Lloveras, J. A. Subirana, E. Giralt, M. Ptak, *Macromolecules* **1987**, *20*, 62–68.

[92] [a] J. Cheng, J. W. Ziller, T. J. Deming, *Org. Lett.* **1999**, *2*, 1943–1946; [b] J. Cheng, T. J. Deming, *Macromolecules* **2001**, *34*, 5169–5174.

[93] [a] L. Birkofer, R. Modic, *Liebigs Ann. Chem*. **1957**, *604*, 56; [b] L. Birkofer, R. Modic, *Liebigs Ann. Chem*. **1959**, *628*, 162–172.

[94] A. Zilkha, Y. Burstein, *Biopolymers* **1964**, *2*, 147–161.

[95] H. Kricheldorf, α-*Aminoacid-N-carboxyanhydrides and Related Heterocycles*; Springer-Verlag: Berlin, New York, **1987**.

[96] L. Jia, E. Ding, W. R. Anderson, *Chem. Commun*. **2001**, 1436–1437.

[97] [a] C. D. Eisenach, R. W. Lenz, *Macromolecules* **1976**, *9*, 227–230; [b] C. D. Eisenach, R. W. Lenz, *Makromol. Chem*. **1979**, *180*, 429–440.

[98] [a] K. Hashimoto, M. Okata, S. Nagata, *J. Polym. Sci., Part A: Polym. Chem*. **1995**, *33*, 1995–1999; [b] K. Hashimoto, T. Oi, J. Yasuda, K. Hotta, M. Okata, *J. Polym. Sci., Part A: Polym. Chem.* **1997**, *35*, 1831–1838; [c] K. Hashimoto, J. Yasuda, M. Kobayashi, *J. Polym. Sci., Part A: Polym. Chem.* **1999**, *37*, 909–915.

[99] J. Šebenda, J. Hauer, *Polym. Bull*. **1981**, *5*, 529–534.

[100] J. Cheng, T. J. Deming, *J. Am. Chem. Soc*. **2001**, *123*, 9457–9458.

[101] D. A. White, *Synth. Commun*. **1977**, *7*, 559.

[102] [a] L. W. Jones, A. W. Scott, *J. Am. Chem. Soc.* **1922**, *44*, 407–423; [b] A. D. Mitchell, J. F. Thorpe, *J. Chem. Soc*. **1910**, *97*, 997–1004.

[103] D. Seebach, S. Abele, T. Sifferlen, M. Hänggi, S. Gruner, P. Seiler, *Helv. Chim. Acta* **1998**, *81*, 2218–2243.

[104] N. Kise, N. Ueda, *J. Org. Chem*. **1999**, *64*, 7511–7514.

[105] T. Shono, K. Tsubata, N. Okinaga, *J. Org. Chem*. **1984**, *49*, 1056–1059.

[106] A. Avenoza, C. Cativiela, M. París, J. M. Peregrina, *Tet. Asymmetry* **1995**, *6*, 1409–1418.

[107] M. A. Bonache, G. Gerona Navarro, C. García Apparicio, M. Alías, M. Martín Martínez, M. T. García Lopez, D. Lopez, C. Cativiela, R. Gonzalez–Muñiz, *Tet. Asymmetry* **2003**, *14*, 2161–2169.

[108] T. Mukaiyama, *Angew. Chem*. **1976**, *4*, 111–120.

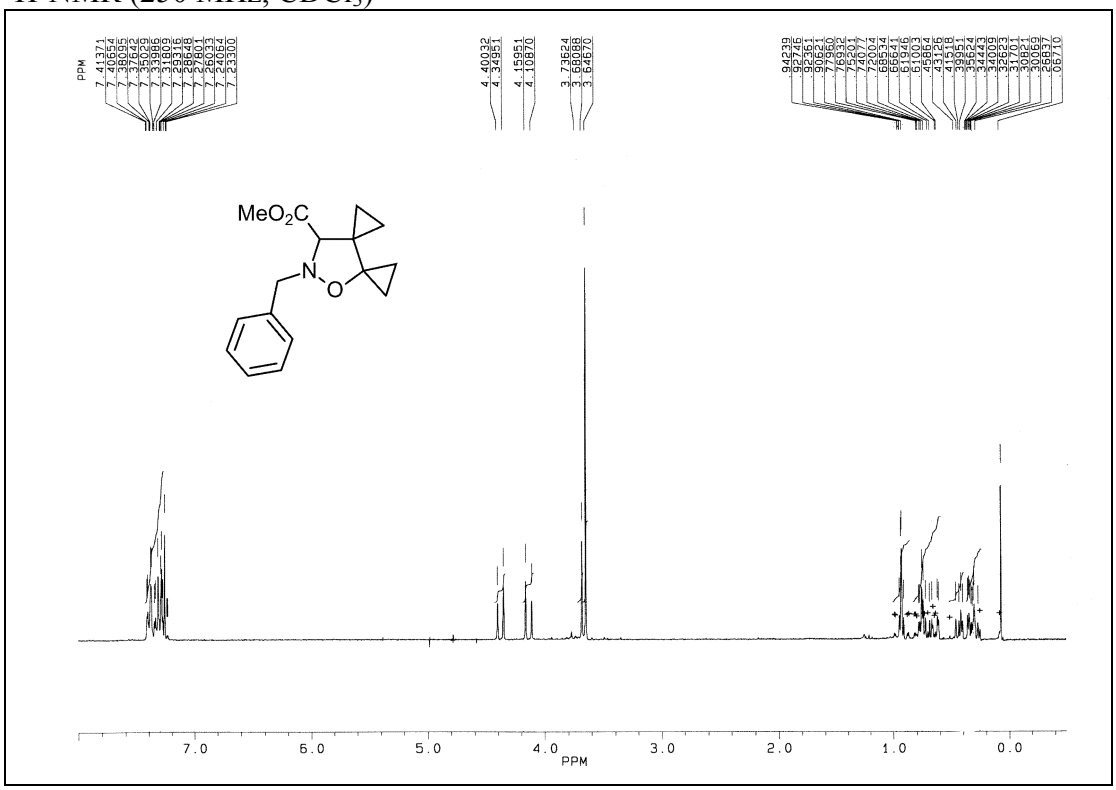
[109] M. Fournier, R. E. Prud'homme, *J. Polym. Sci., Part A: Polym. Chem.* **1999**, *37*, 761–769.

[110] A. Vollmar, M. S. Dunn, *J. Org. Chem*. **1960**, *25*, 387–390.

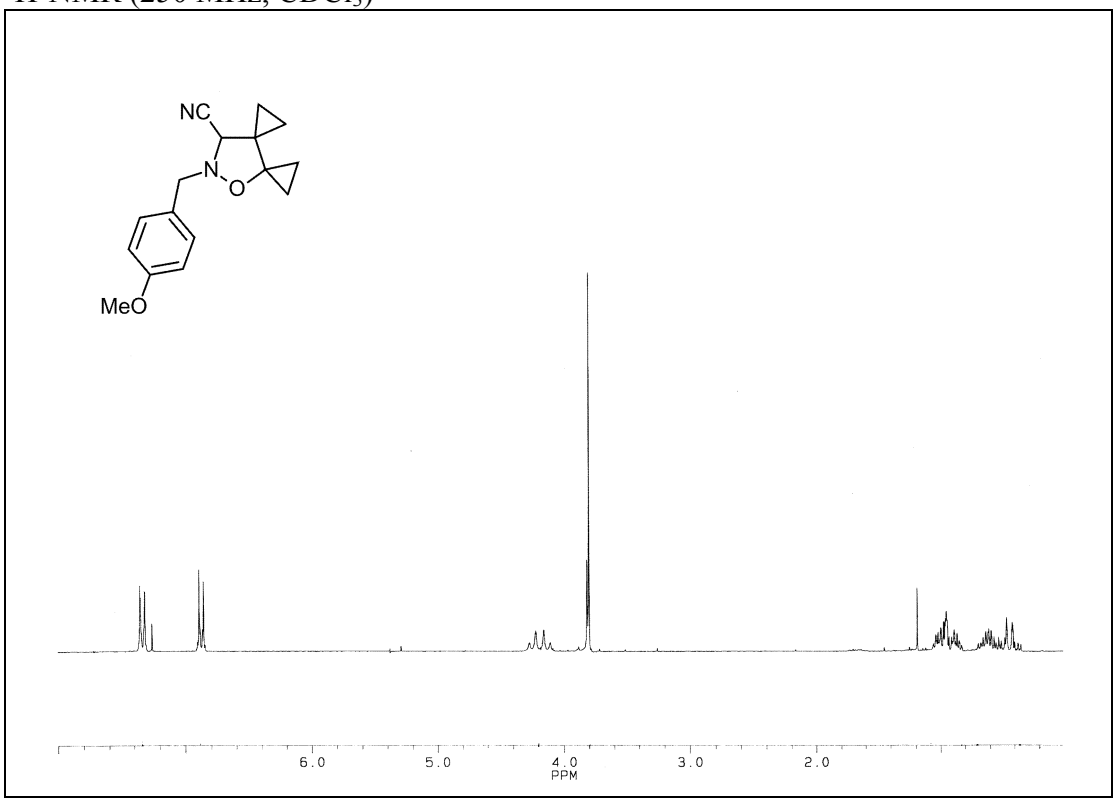
[111] N. N. Schwarz, J. N. Blumberg, *J. Org. Chem*. **1964**, *29*, 1976–1979.

F. Spectral Data

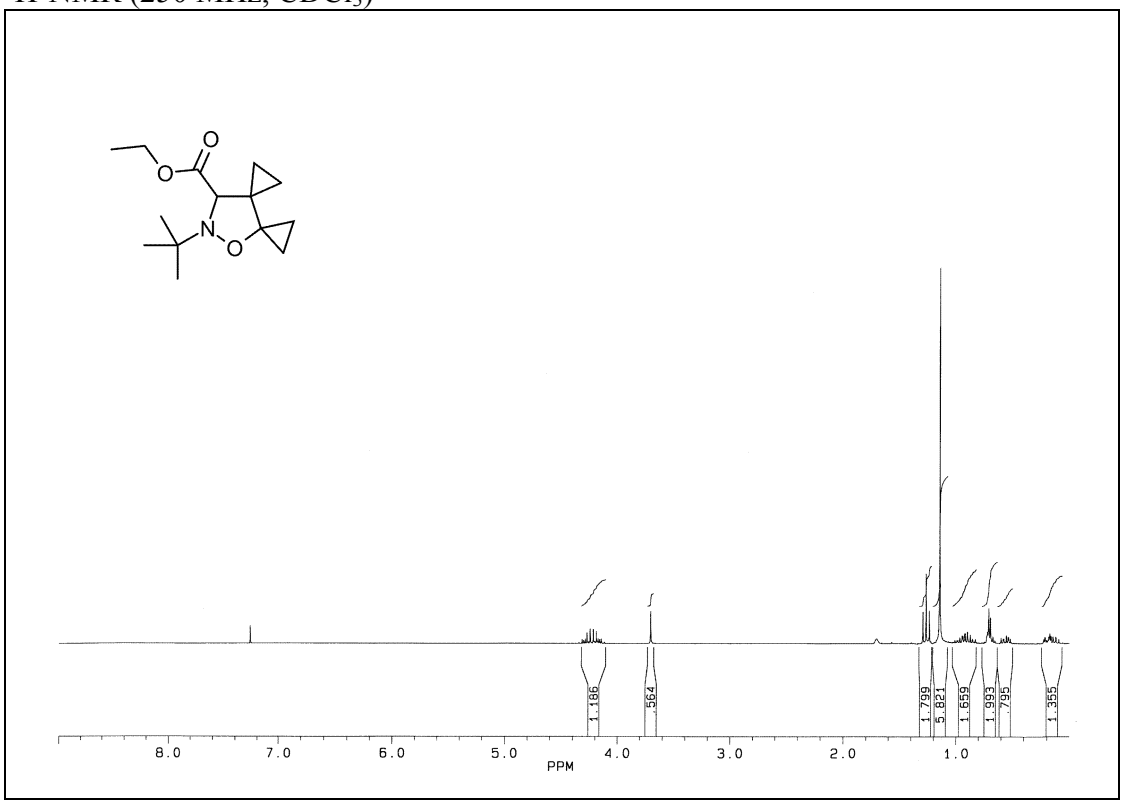
Methyl 8-Benzyl-8-aza-7-oxadispiro[2.0.2.3]nonane-9-carboxylate (47b)
^{1}H-NMR (250 MHz, $CDCl_3$)



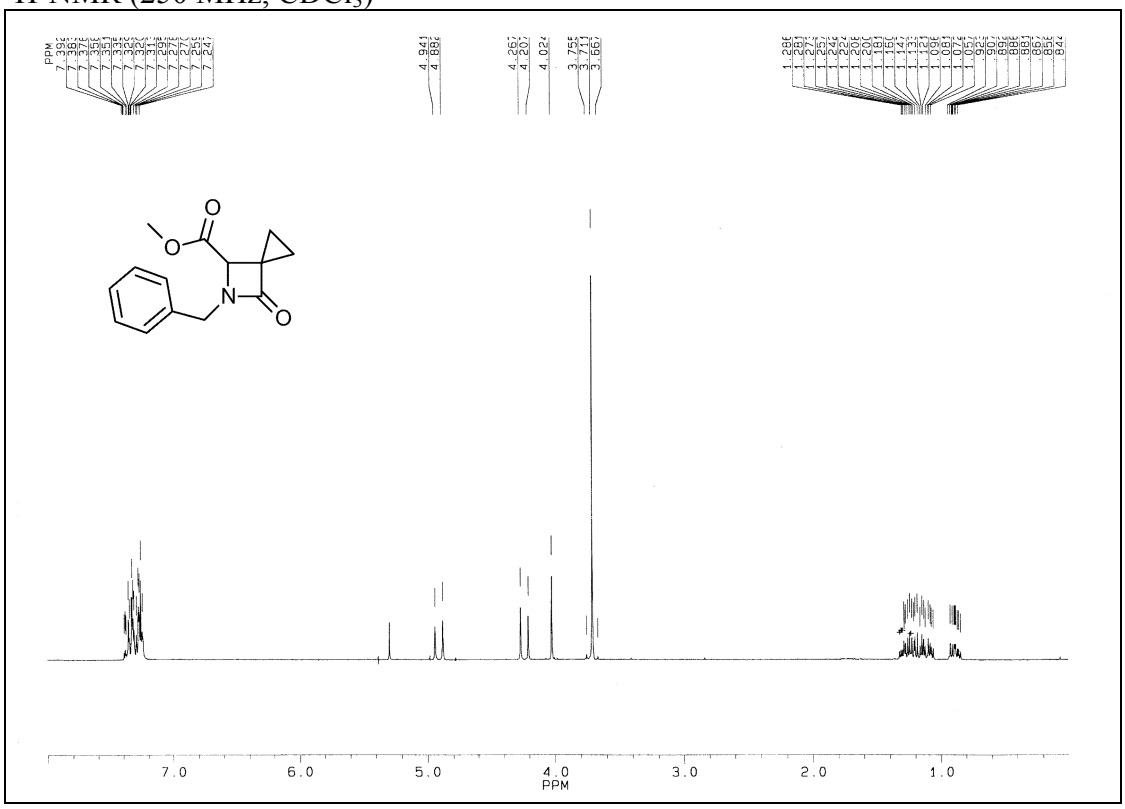
8-Benzyl-9-cyano-8-aza-7-oxadispiro[2.0.2.3]nonane (47d)
^{1}H-NMR (250 MHz, $CDCl_3$)



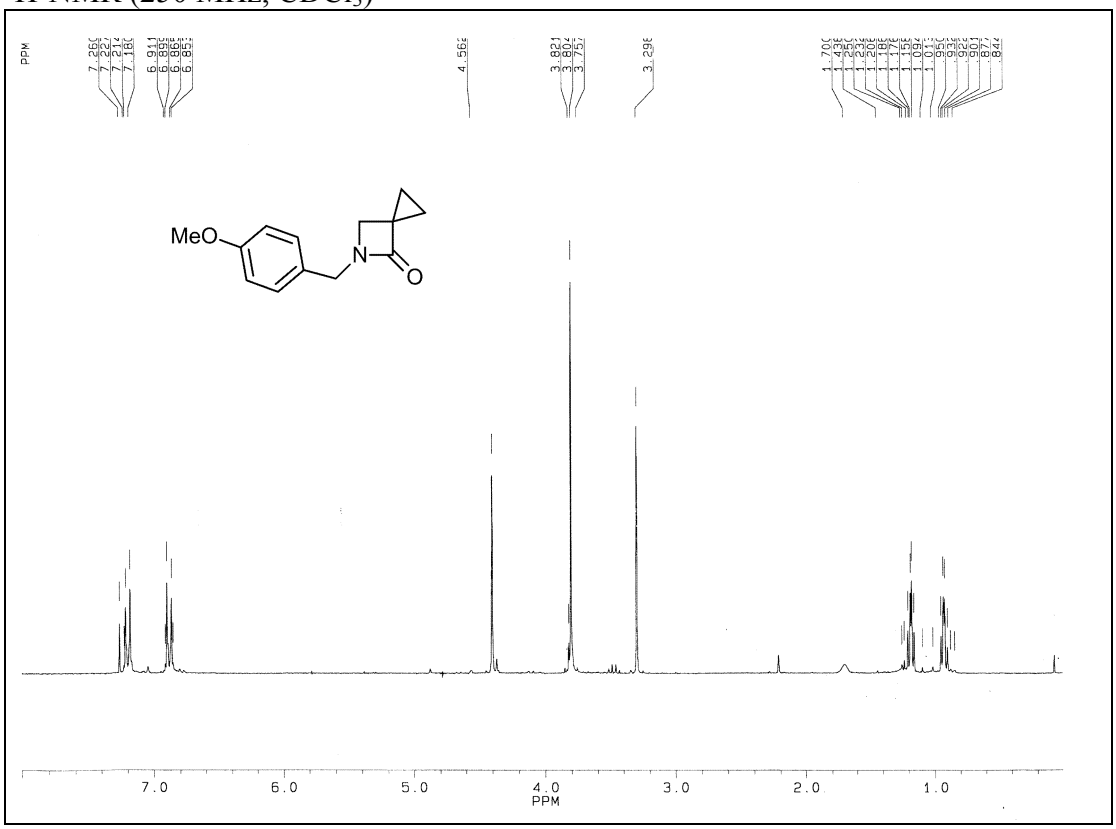
Ethyl 8-*tert*-butyl-7-oxa-8-azadispiro[2.0.2.3]nonane-9-carboxylate (47f-Et)
^{1}H-NMR (250 MHz, $CDCl_3$)



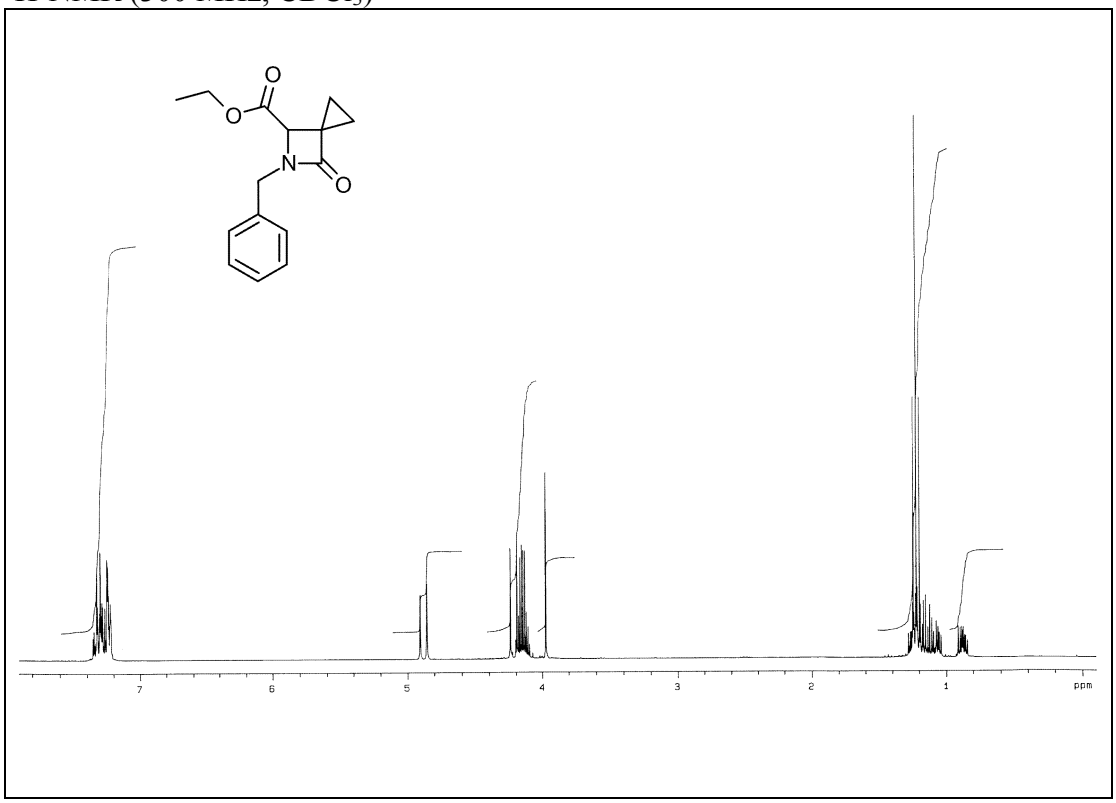
Methyl 5-Benzyl-6-oxo-5-azaspiro[2.3]hexane-4-carboxylate (53b)
^{1}H-NMR (250 MHz, $CDCl_3$)



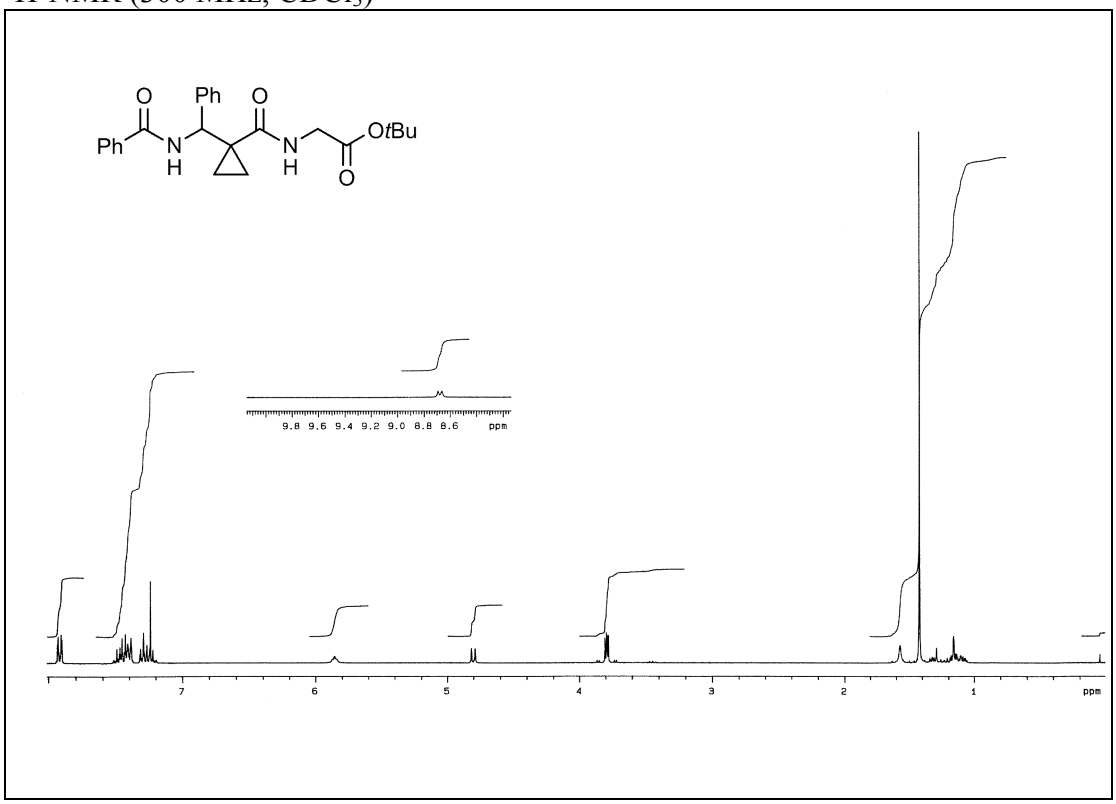
5-(*p*-Methoxybenzyl)-5-azaspiro[2.3]hexan-4-one (53g)
^{1}H-NMR (250 MHz, $CDCl_3$)



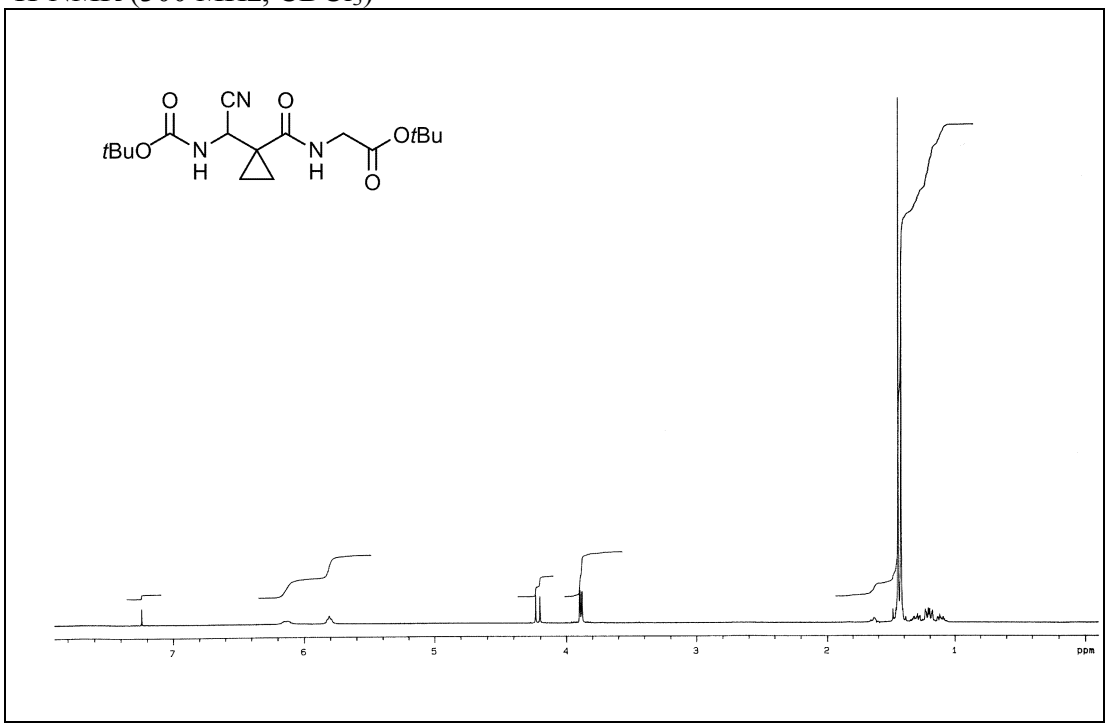
Ethyl 5-benzyl-6-oxo-5-azaspiro[2.3]hexane-4-carboxylate (77c-Et)
^{1}H-NMR (300 MHz, $CDCl_3$)



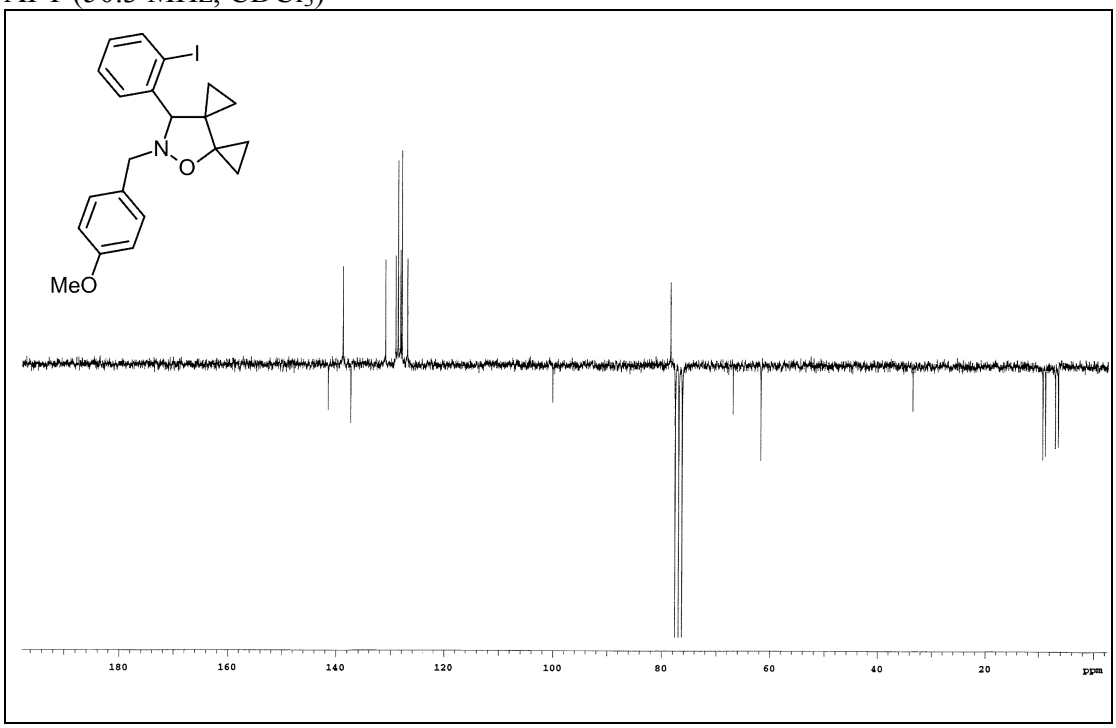
***tert*-Butyl {[1-(Benzoylaminophenylmethyl)cyclopropylcarbonyl]amino}acetate (116)**
^{1}H-NMR (300 MHz, $CDCl_3$)



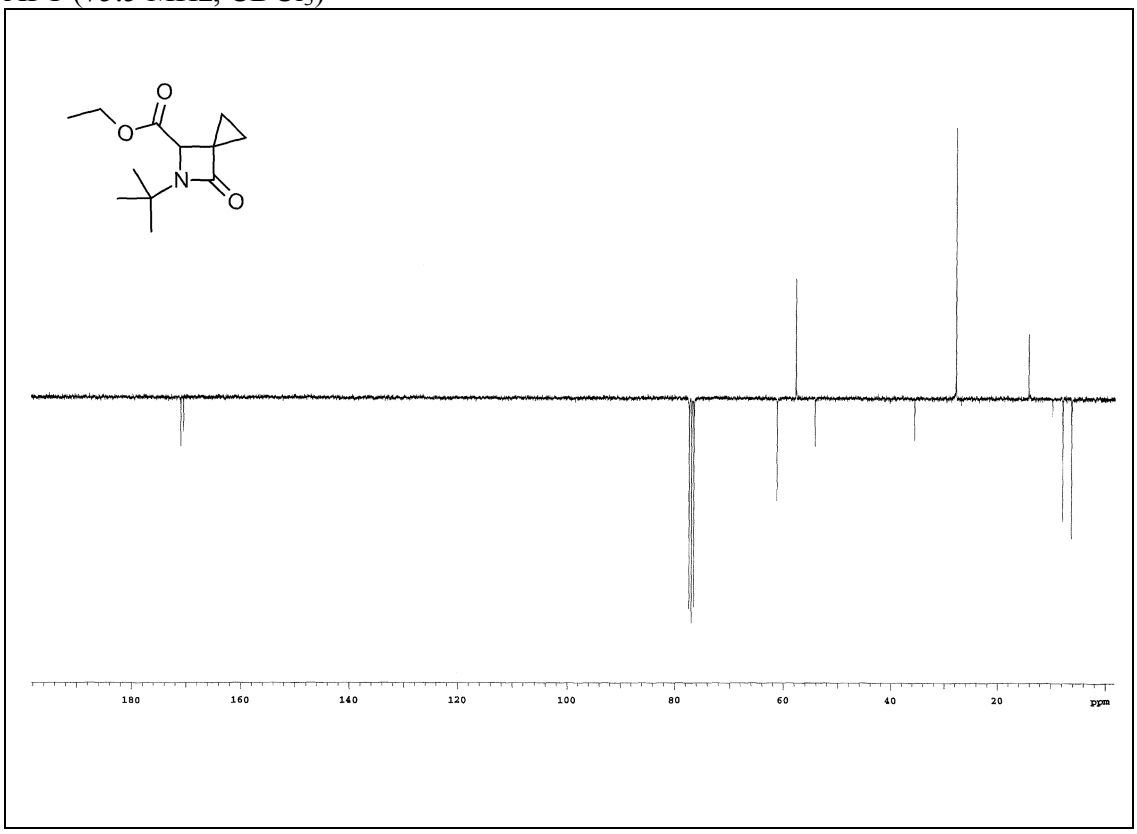
***tert*-Butyl {[1-(*tert*-Butoxycarbonylaminocyanomethyl)cyclopropylcarbonyl]amino}acetate (117)**
^{1}H-NMR (300 MHz, $CDCl_3$)



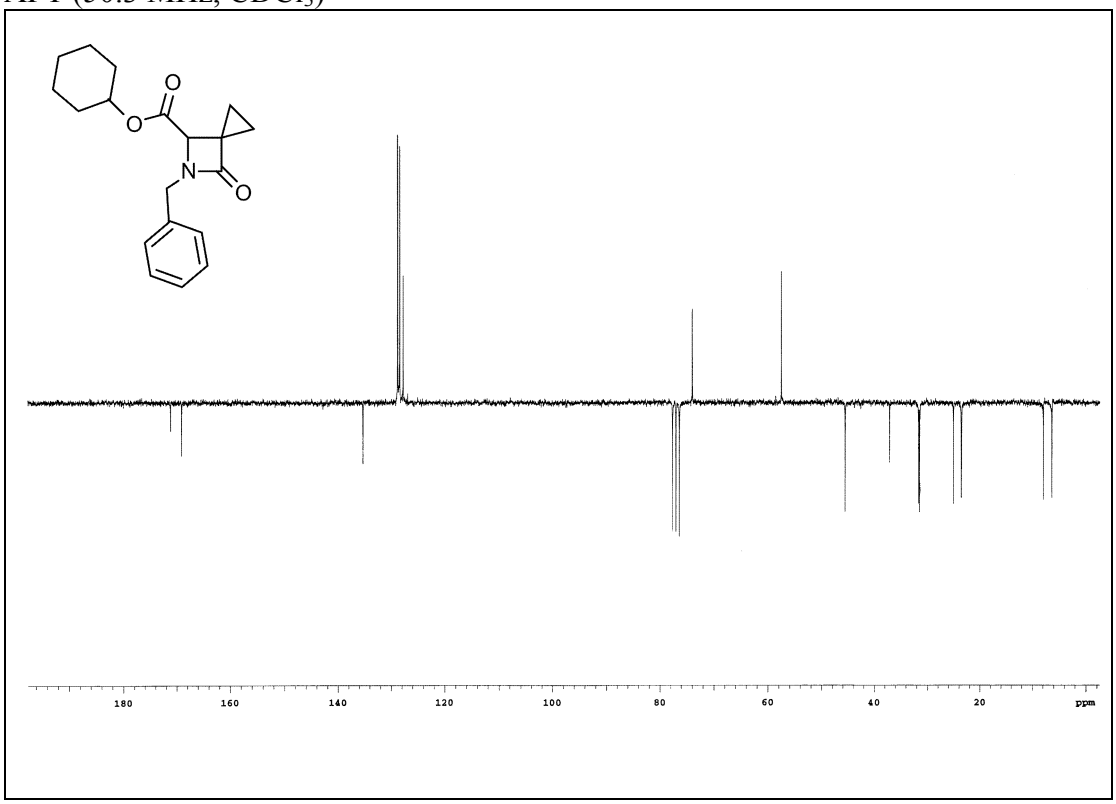
8-(*p*-Methoxybenzyl)-9-(2-iodophenyl)-7-oxa-8-azadispiro[2.0.2.3]nonane (47f)
APT (50.3 MHz, $CDCl_3$)



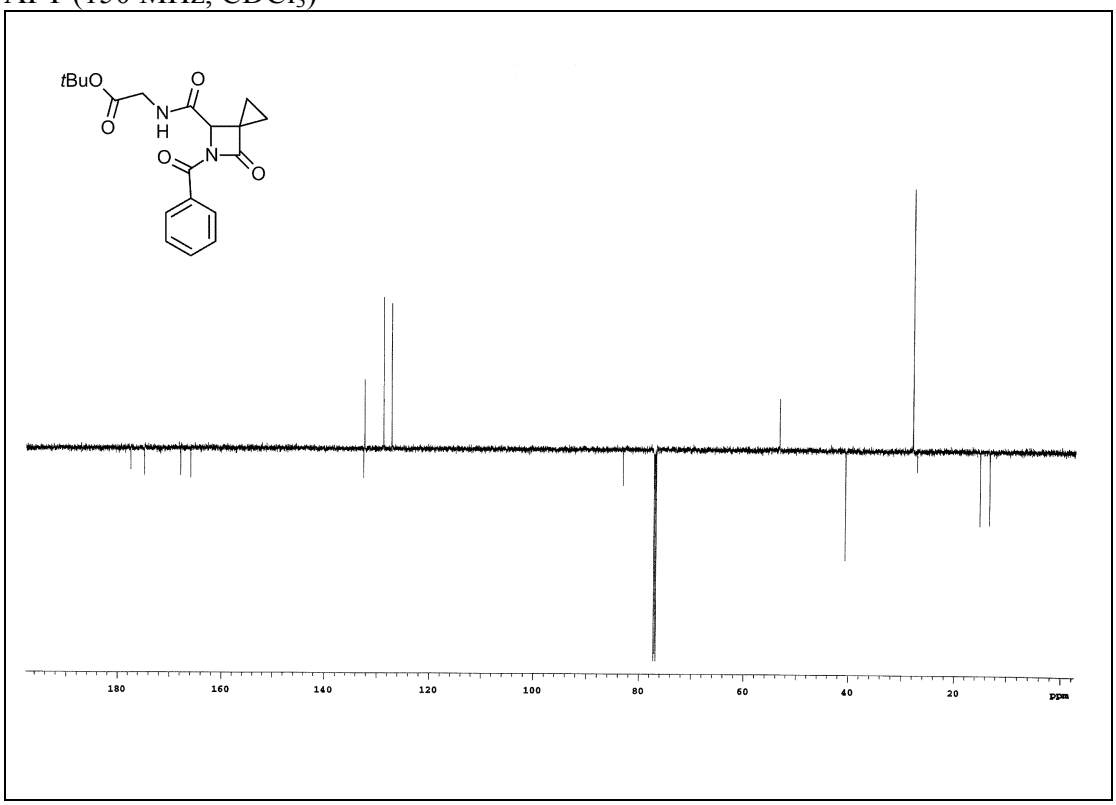
Ethyl 5-*tert*-butyl-6-oxo-5-azaspiro[2.3]hexane-4-carboxylate (77f-Et)
APT (75.5 MHz, $CDCl_3$)



Cyclohexyl 5-benzyl-6-oxo-5-azaspiro[2.3]hexane-4-carboxylate (77c-cHex)
APT (50.3 MHz, $CDCl_3$)

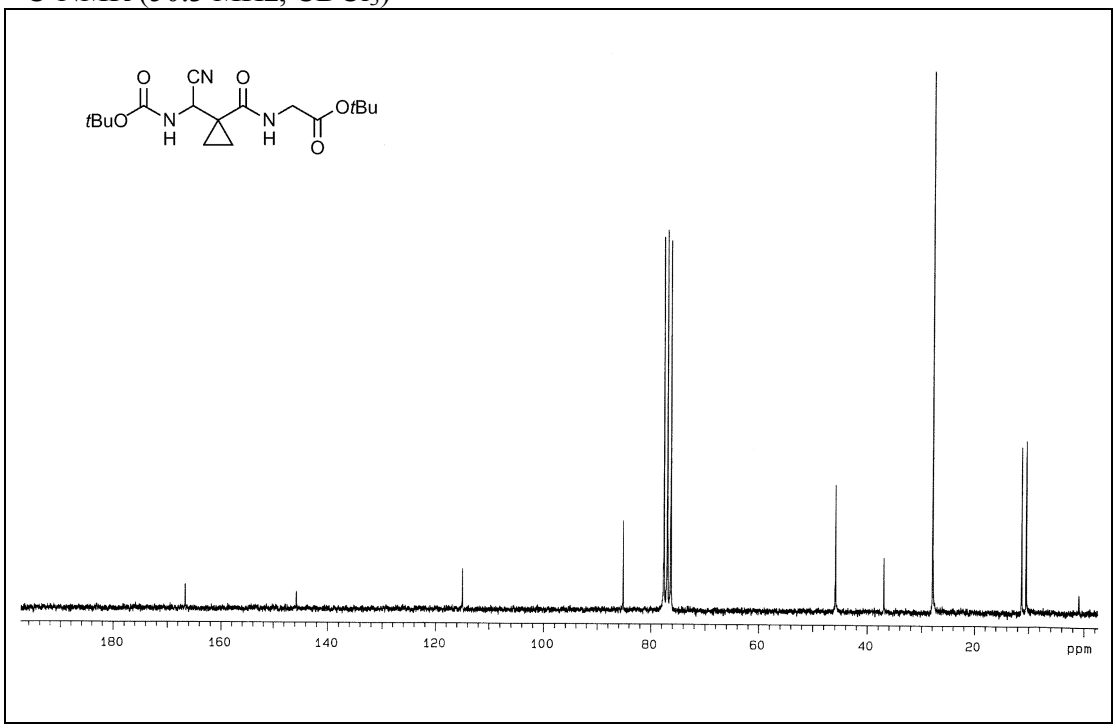


***tert*-Butyl [(5-Benzoyl-6-oxo-5-azaspiro[2.3]hexane-4-carbonyl)amino]acetate (114)**
APT (150 MHz, $CDCl_3$)



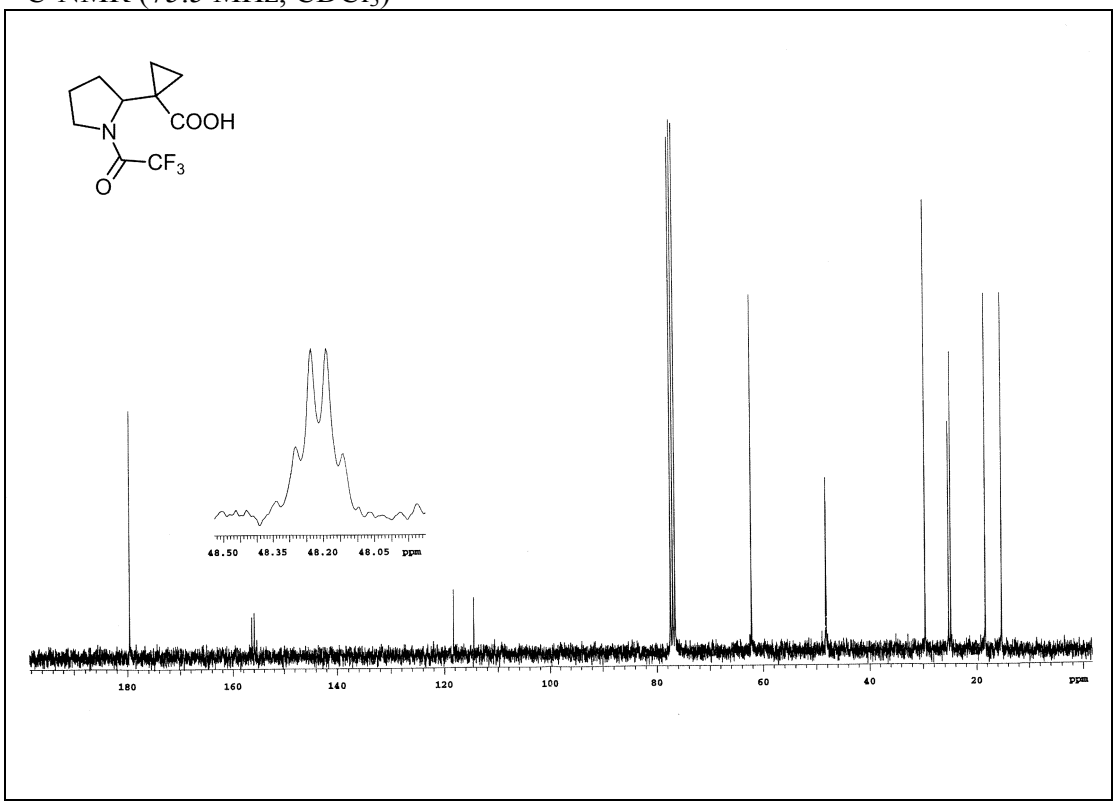
***tert*-Butyl {[1-(*tert*-Butoxycarbonylaminocyanomethyl)cyclopropylcarbonyl]amino}acetate (117)**

^{13}C-NMR (50.3 MHz, $CDCl_3$)



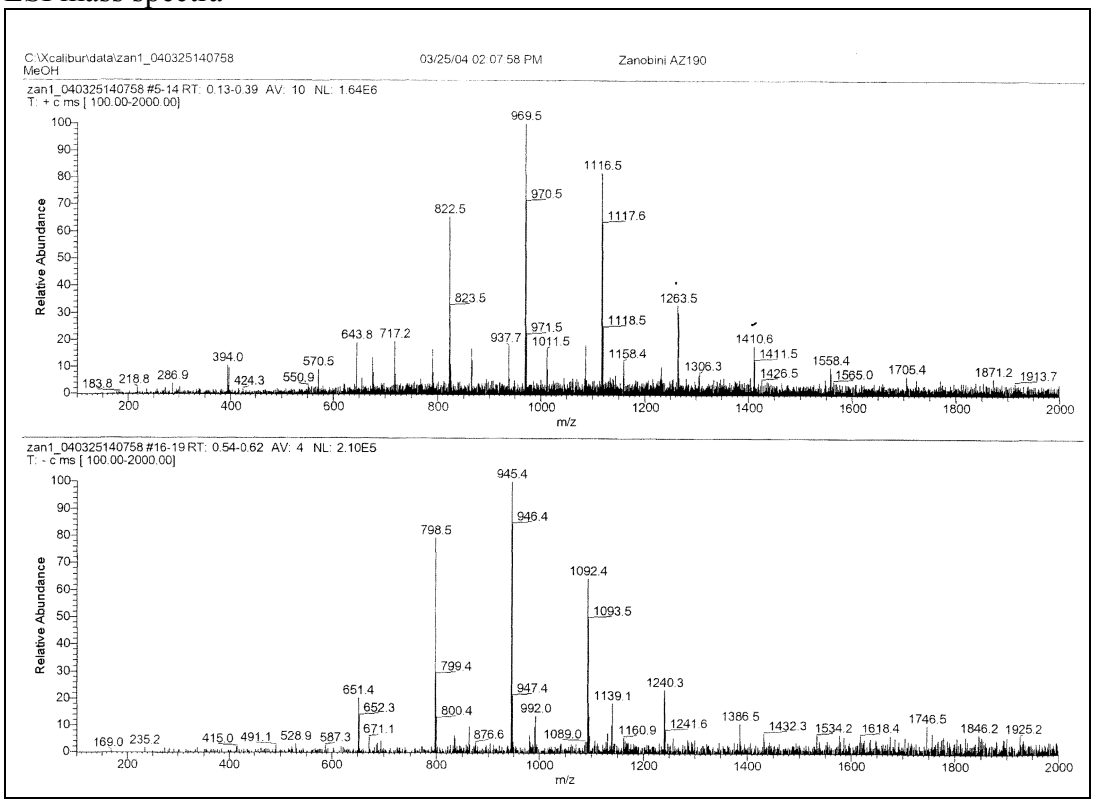
1-[1-(2,2,2-Trifluoroacetyl)-pyrrolidin-2-yl]-cyclopropane carboxylic acid (72)

^{13}C-NMR (75.5 MHz, $CDCl_3$)



Poly(3-Phenyl-2-azetidinone) (154)

ESI mass spectra



G. Crystal Structural Data

1. 8-Benzyl-9-phenyl-8-aza-7-oxadispiro[2.0.2.3]nonane (47a)

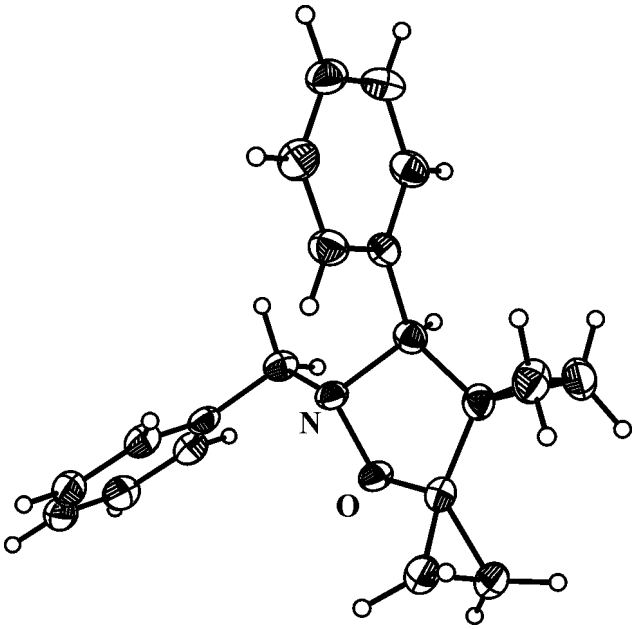


Table 1.1. Crystal data and structure refinement.

Empirical Formula	$C_{20}H_{21}NO$
Formula weight, g/mol	291.38
Crystal systesm	monoclinic
Space group	P21/n
Unit cell dimensions	
a, Å	9.2097(7)
b, Å	5.6716(3)
c, Å	30.290(2)
α, °	90
β, °	94.307(6)
γ, °	90
Volume, $Å^3$	1577.70(19)
Z	4
Calculated density, Mg/m^3	1.227
Absorption coefficient, mm^{-1}	0.075
F(000)	624

Θ-Range, °	1.35 to 23.25
Observed Reflections	1979
Reflections collected/ unique [Rint]	7117/2237 [0.0327]
Data/Restraints/Parameter	2237 / 0 / 199
Goof F^2	1.040
R_1, wR_2 values [I>2σ(I)]	0.0310, 0.0738
R_1, wR_2 values (all data)	0.0367, 0.0768
Largest diff. peak and hole, e · $Å^{-3}$	0.183 and –0.136

Tabelle 1.2. Atomic coordinates and equivalent isotropic displacement parameters (Å2). U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
O(7)	0.1661(1)	0.3274(2)	0.1504(1)	0.0244(2)
N(8)	0.0253(1)	0.3141(2)	0.1235(1)	0.0225(3)
C(1)	–0.0500(2)	0.2030(3)	0.2415(1)	0.0362(4)
C(2)	–0.0888(2)	–0.0184(3)	0.2158(1)	0.0342(4)
C(3)	–0.0080(1)	0.1762(2)	0.1949(1)	0.0254(3)
C(4)	0.2259(1)	–0.0768(2)	0.1775(1)	0.0283(3)
C(5)	0.2785(1)	0.1007(2)	0.2127(1)	0.0286(3)
C(6)	0.1475(1)	0.1511(2)	0.1826(1)	0.0229(3)
C(9)	–0.0777(1)	0.3380(2)	0.1586(1)	0.0245(2)
C(10)	–0.2311(1)	0.2868(2)	0.1404(1)	0.0239(2)
C(11)	–0.3422(1)	0.4436(2)	0.1478(1)	0.0300(2)
C(12)	–0.4834(2)	0.4046(3)	0.1300(1)	0.0335(3)
C(13)	–0.5145(2)	0.2084(3)	0.1041(1)	0.0322(3)
C(14)	–0.4052(1)	0.0493(3)	0.0969(1)	0.0321(3)
C(15)	–0.2644(1)	0.0874(2)	0.1149(1)	0.0294(3)
C(16)	0.0227(1)	0.5206(2)	0.0947(1)	0.0257(3)
C(17)	0.1239(1)	0.4960(2)	0.0582(1)	0.0239(3)
C(18)	0.1196(1)	0.2962(2)	0.0316(1)	0.0276(3)
C(19)	0.2088(2)	0.2783(3)	–0.0031(1)	0.0323(3)
C(20)	0.3029(2)	0.4598(3)	–0.0117(1)	0.0341(4)
C(21)	0.3085(2)	0.6588(3)	0.0146(1)	0.0300(3)
C(22)	0.2196(1)	0.6762(2)	0.0495(1)	0.0228(3)

Tabelle 1.3. Bondlengths [Å] and angles [°].

O(7)-C(6)	141.8(2)	C(4)-C(6)	149.4(2)	C(14)-C(15)	138.6(2)
O(7)-N(8)	147.9(1)	C(4)-C(5)	151.9(2)	C(16)-C(17)	150.4(2)
N(8)-C(16)	146.0(2)	C(5)-C(6)	148.4(2)	C(17)-C(22)	138.8(2)
N(8)-C(9)	148.3(2)	C(9)-C(10)	150.6(2)	C(17)-C(18)	138.9(2)
C(1)-C(3)	150.0(2)	C(10)-C(11)	138.6(2)	C(18)-C(19)	138.6(2)
C(1)-C(2)	150.7(2)	C(10)-C(15)	139.0(2)	C(19)-C(20)	138.3(2)
C(2)-C(3)	149.8(2)	C(11)-C(12)	138.8(2)	C(20)-C(21)	138.1(2)
C(3)-C(6)	151.3(2)	C(12)-C(13)	137.8(2)	C(21)-C(22)	138.9(2)
C(3)-C(9)	153.4(2)	C(13)-C(14)	138.2(2)		

C(6)-O(7)-N(8)	101.32(8)	C(10)-C(9)-C(3)	101.69(10)
C(16)-N(8)-O(7)	105.15(9)	C(11)-C(10)-C(15)	118.58(11)
C(16)-N(8)-C(9)	111.90(10)	C(11)-C(10)-C(9)	118.49(12)
O(7)-N(8)-C(9)	100.55(8)	C(15)-C(10)-C(9)	120.00(12)
C(3)-C(1)-C(2)	59.77(9)	C(10)-C(11)-C(12)	121.48(11)
C(3)-C(2)-C(1)	59.89(9)	C(13)-C(12)-C(11)	121.08(13)
C(2)-C(3)-C(1)	60.35(9)	C(12)-C(13)-C(14)	119.88(13)
C(2)-C(3)-C(6)	122.96(12)	C(13)-C(14)-C(15)	119.68(12)
C(1)-C(3)-C(6)	123.83(11)	C(14)-C(15)-C(10)	120.43(13)
C(2)-C(3)-C(9)	119.31(11)	N(8)-C(16)-C(17)	120.42(10)
C(1)-C(3)-C(9)	103.50(12)	C(22)-C(17)-C(18)	112.45(12)
C(6)-C(3)-C(9)	59.01(10)	C(22)-C(17)-C(16)	118.78(12)
C(6)-C(4)-C(5)	59.66(8)	C(18)-C(17)-C(16)	120.55(12)
C(6)-C(5)-C(4)	115.11(8)	C(19)-C(18)-C(17)	120.62(12)
O(7)-C(6)-C(5)	117.01(10)	C(20)-C(19)-C(18)	120.46(13)
O(7)-C(6)-C(3)	61.33(11)	C(21)-C(20)-C(19)	120.29(13)
C(5)-C(6)-C(3)	105.57(9)	C(20)-C(21)-C(22)	119.76(13)
C(4)-C(6)-C(3)	127.46(10)	C(18)-C(17)-C(16)	119.94(13)
N(8)-C(9)-C(10)	125.50(11)	C(17)-C(22)-C(21)	120.75(13)
N(8)-C(9)-C(13)	110.58(11)		

Tabelle 1.4. Anisotropic displacement parameters (Å2 × 103). The anisotropic displacement factor esponent takes the form: –2π2[h2a*2U11+ ... +2hka*b*U12].

Atom	U11	U22	U33	U23	U13	U12
O(7)	19.1(4)	27.6(5)	26.2(5)	4.6(4)	–1.7(4)	–1.6(4)
N(8)	16.9(5)	26.9(6)	23.5(5)	2.4(5)	–0.9(4)	–0.2(4)

C(1)	32.1(8)	51.7(10)	25.4(7)	–3.6(7)	5.3(6)	–4.9(7)
C(2)	31.9(8)	41.8(9)	28.8(7)	5.8(7)	1.0(6)	–10.5(7)
C(3)	24.9(7)	29.6(8)	21.5(7)	–2.4(6)	0.8(5)	–4.0(6)
C(4)	32.9(7)	26.5(7)	25.1(7)	0.2(6)	–0.9(6)	1.3(6)
C(5)	29.3(7)	30.9(8)	25.0(7)	0.4(6)	–2.4(6)	0.4(6)
C(6)	24.8(7)	23.1(7)	20.6(6)	1.2(5)	0.1(5)	–2.7(5)
C(9)	23.7(7	24.2(7)	25.7(7)	–3.6(6)	3.0(5)	–0.8(5)
C(10)	22.8(7)	25.9(7)	23.5(7)	1.1(6)	4.0(5)	–1.1(6)
C(11)	29.2(7)	26.8(8)	34.6(7)	–4.6(6)	5.9(6)	0.1(6)
C(12)	22.7(7)	35.4(8)	42.8(8)	0.8(7)	5.9(6)	4.6(6)
C(13)	22.0(7)	40.4(9)	33.7(8)	5.8(7)	–0.7(6)	–4.6(6)
C(14)	30.3(8)	32.5(8)	32.9(8)	–5.1(6)	–1.0(6)	–6.3(6)
C(15)	26.2(7)	29.0(8)	33.0(7)	–3.7(6)	2.8(6)	3.1(6)
C(16)	23.7(7)	25.1(7)	28.0(7)	3.5(6)	–1.0(5)	2.4(6)
C(17)	21.0(6)	27.2(7)	22.9(6)	6.5(6)	–3.5(5)	3.2(6)
C(18)	26.5(7)	27.5(7)	28.2(7)	5.4(6)	–2.9(6)	–0.9(6)
C(19)	35.0(8)	32.9(8)	26.7(7)	–0.3(6)	–1.4(6)	5.1(7)
C(20)	30.8(8)	43.9(9)	26.8(7)	7.2(7)	3.5(6)	4.8(7)
C(21)	28.4(7)	37.4(8)	34.3(8)	9.9(7)	2.4(6)	–3.9(6)
C(22)	29.7(7)	27.2(7)	29.0(7)	3.0(6)	–3.2(6)	–0.2(6)

Tabelle 1.5. H-Coordinates (× 104) and isotropic displacement parameters (Å2 × 103).

Atom	x	y	z	U(eq)
H(1A)	–1296	3142	2469	43
H(1B)	282	1930	2657	43
H(2A)	–344	–1641	2242	41
H(2B)	–1923	–428	2054	41
H(4A)	2837	–953	1515	34
H(4B)	1790	–2229	1873	34
H(5A)	2639	624	2440	34
H(5B)	3685	1899	2081	34
H(9A)	–735	5039	1698	29
H(11A)	–3213	5799	1653	36
H(12A)	–5585	5130	1356	40
H(13A)	–6106	1827	914	39
H(14A)	–4267	–870	794	38
H(15A)	–1901	–236	1099	35
H(16A)	508	6615	1127	31
H(16B)	–777	5451	815	31
H(18A)	549	1710	372	33
H(19A)	2054	1407	–210	38
H(20A)	3634	4476	–356	41
H(21A)	3731	7838	89	40
H(22A)	2243	8131	677	35

2. Methyl 5-Benzoyl-6-oxo-5-azaspiro[2.3]hexane-4-carboxylate (107b)

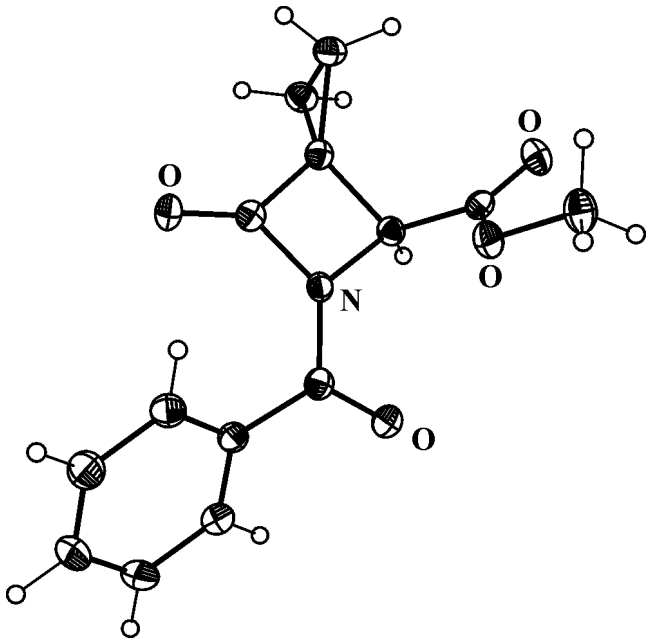


Table 2.1. Crystal data and structure refinement.

Empirical Formula	$C_{14}H_{13}NO_4$
Formula weight, g/mol	259.25
Crystal systesm	monoclinic
Space group	P21/c
Unit cell dimensions	
a, Å	10.7153(6)
b, Å	8.9670(4)
c, Å	13.7210(6)
α, °	90
β, °	109.056(4)
γ, °	90
Volume, $Å^3$	1246.12(10)
Z	4
Calculated density, Mg/m^3	1.382
Absorption coefficient, mm^{-1}	0.102
F(000)	544
Θ-Range, °	2.76 to 24.71
Observed Reflections	1996
Reflections collected/ unique [Rint]	24299/2073 [0.0326]
Data/Restraints/Parameter	2073 / 0 / 173

Goof F^2	1.072
R_1, wR_2 values [I>2σ(I)]	0.0305, 0.0703
R_1, wR_2 values (all data)	0.0316, 0.0709
Largest diff. peak and hole, e · $Å^{-3}$	0.258 and –0.170

Tabelle 2.2. Atomic coordinates and equivalent isotropic displacement parameters (Å2). U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
N(5)	–0.1500(1)	0.4959(1)	0.2862(1)	0.0165(2)
O(7)	–0.0710(1)	0.7293(1)	0.3697(1)	0.0217(2)
O(9)	0.0280(1)	0.1429(1)	0.3635(1)	0.0238(2)
O(10)	–0.1626(1)	0.2286(1)	0.3783(1)	0.0217(2)
O(13)	–0.2897(1)	0.3982(1)	0.1404(1)	0.0254(2)
C(1)	0.1690(1)	0.4701(1)	0.4595(1)	0.0218(3)
C(2)	0.1905(1)	0.5285(1)	0.3638(1)	0.0219(3)
C(3)	0.0527(1)	0.4946(1)	0.3634(1)	0.0176(3)
C(4)	–0.0464(1)	0.3820(2)	0.2958(1)	0.0172(2)
C(6)	–0.0578(1)	0.6030(1)	0.3458(1)	0.0172(2)
C(8)	–0.0564(1)	0.2374(1)	0.3490(1)	0.0175(2)
C(11)	–0.1733(1)	0.0932(1)	0.4338(1)	0.0271(3)
C(12)	–0.2634(1)	0.5031(1)	0.1999(1)	0.0184(3)
C(14)	–0.3478(1)	0.6387(1)	0.1838(1)	0.0194(3)
C(15)	–0.4202(1)	0.6751(1)	0.0821(1)	0.0252(3)
C(16)	–0.5040(1)	0.7969(2)	0.0613(1)	0.0323(3)
C(17	–0.5181(1)	0.8811(2)	0.1418(1)	0.0341(3)
C(18)	–0.4485(1)	0.8443(2)	0.2428(1)	0.0300(3)
C(19)	–0.3624(1)	0.7241(1)	0.2641(1)	0.0228(3)

Tabelle 2.3. Bondlengths [Å] and angles [°].

N(5)-C(12)	139.4(2)	O(13)-C(12)(1)	121.6(2)	C(12)-C(14)	148.8(2)
N(5)-C(6)	142.9(2)	C(1)-C(2)(2)	150.0(2)	C(14)-C(19)	139.3(2)
N(5)-C(4)	148.2(1)	C(1)-C(3)(2)	150.6(2)	C(14)-C(15)	139.6(2)
O(7)-C(6)	120.0(1)	C(2)-C(3)(2)	150.7(2)	C(15)-C(16)	138.4(2)
O(9)-C(8)	120.7(1)	C(3)-C(6)(2)	148.9(2)	C(16)-C(17)	138.6(2)
O(10)-C(8)	132.7(1)	C(3)-C(4)(2)	153.7(2)	C(17)-C(18)	138.3(2)
O(10)-C(11)	145.8(1)	C(4)-C(8)(2)	150.9(2)	C(18)-C(19)	138.7(2)

C(12)-N(5)-C(6)	134.70(9)	O(7)-C(6)-C(3)	136.92(11)
C(12)-N(5)-C(4)	121.83(9)	N(5)-C(6)-C(3)	91.03(9)
C(6)-N(5)-C(4)	93.12(8)	O(9)-C(8)-O(10)	125.35(10)
C(8)-O(10)-C(11)	115.44(9)	O(9)-C(8)-C(4)	121.01(10)
C(2)-C(1)-C(3)	60.15(7)	O(10)-C(8)-C(4)	113.63(9)
C(1)-C(2)-C(3)	60.12(7)	O(13)-C(12)-N(5)	118.70(10)
C(6)-C(3)-C(1)	128.58(10)	O(13)-C(12)-C(14)	122.42(10)
C(6)-C(3)-C(2)	126.51(10)	N(5)-C(12)-C(14)	118.87(11)
C(1)-C(3)-C(2)	59.73(8)	C(19)-C(14)-C(15)	119.59(10)
C(6)-C(3)-C(4)	88.60(8)	C(19)-C(14)-C(12)	123.46(10)
C(1)-C(3)-C(4)	130.09(10)	C(15)-C(14)-C(12)	116.86(12)
C(2)-C(3)-C(4)	128.16(10)	C(16)-C(15)-C(14)	120.11(12)
N(5)-C(4)-C(8)	117.76(9)	C(15)-C(16)-C(17)	119.90(12)
N(5)-C(4)-C(3)	87.19(8)	C(18)-C(17)-C(16)	120.36(12)
C(8)-C(4)-C(3)	114.59(9)	C(17)-C(18)-C(19)	120.06(12)
O(7)-C(6)-N(5)	132.05(11)	C(18)-C(19)-C(14)	119.95(12)

Tabelle 2.4. Anisotropic displacement parameters (Å2 × 103). The anisotropic displacement factor esponent takes the form: –2π2[h2a*2U11+ ... +2hka*b*U12].

Atom	U11	U22	U33	U23	U13	U12
N(5)	18.3(5)	13.4(5)	17.8(5)	0.1(4)	5.8(4)	0.9(4)
O(7)	24.9(4)	15.6(4)	26.0(4)	–2.9(3)	10.1(3)	–0.9(3)
O(9)	27.4(5)	19.1(4)	26.3(5)	2.6(3)	10.5(4)	6.1(4)
O(10)	23.8(4)	17.4(4)	26.0(4)	3.6(3)	11.1(3)	1.0(3)
O(13)	27.9(5)	20.5(5)	23.7(4)	–4.7(4)	2.8(4)	0.3(4)
C(1)	21.1(6)	23.5(6)	18.7(6)	0.4(5)	3.6(5)	1.0(5)
C(2)	17.9(6)	24.0(6)	23.7(6)	1.8(5)	6.7(5)	0.5(5)
C(3)	19.6(6)	16.7(6)	17.4(5)	0.1(4)	7.1(5)	–0.3(4)

C(4)	17.9(5)	16.5(6)	17.5(5)	–0.6(4)	6.4(4)	1.9(4)
C(6)	19.9(6)	17.8(6)	15.8(5)	1.4(4)	8.2(4)	–2.0(4)
C(8)	19.9(6)	16.8(6)	14.9(5)	–3.8(4)	4.2(4)	–0.6(5)
C(11)	32.6(7)	20.5(6)	31.5(7)	5.5(5)	14.9(6)	–2.5(5)
C(12)	20.2(6)	17.3(6)	19.1(6)	1.1(5)	8.2(5)	–2.1(5)
C(14)	15.7(5)	17.9(6)	23.9(6)	1.3(5)	5.6(5)	–2.3(4)
C(15)	23.3(6)	23.1(6)	25.3(6)	–1.4(5)	2.7(5)	–1.8(5)
C(16)	25.4(7)	28.9(7)	32.5(7)	4.0(6)	–4.4(5)	2.4(5)
C(17)	20.8(6)	25.9(7)	48.7(8)	–2.1(6)	2.1(6)	7.1(5)
C(18)	22.2(6)	29.0(7)	38.5(7)	–6.7(6)	9.6(6)	2.8(5)
C(19)	18.7(6)	24.4(6)	25.6(6)	–0.1(5)	7.5(5)	–0.5(5)

Tabelle 2.5. H-Coordinates (× 104) and isotropic displacement parameters (Å2 × 103).

Atom	x	y	z	U(eq)
H(1A)	1811	5403	5176	26
H(1B)	1956	3660	4801	26
H(2A)	2304	4602	3255	26
H(2B)	2159	6345	3630	26
H(4A)	–310	3645	2286	21
H(11A)	–2577	932	4473	41
H(11B)	–1006	894	4994	41
H(11C)	–1690	58	3921	41
H(15A)	–4119	6160	270	30
H(16A)	–5518	8228	–80	39
H(17A)	–5760	9645	1274	41
H(18A)	–4597	9015	2977	36
H(19A)	–3134	7000	3335	27

3. tert-butyl (2S,2'R)-2-{[1-(tert-butoxycarbonylamino-cyanomethyl)cyclopropylcarbonyl]amino}-3-phenylpropionate [(2S,2'R)-118]

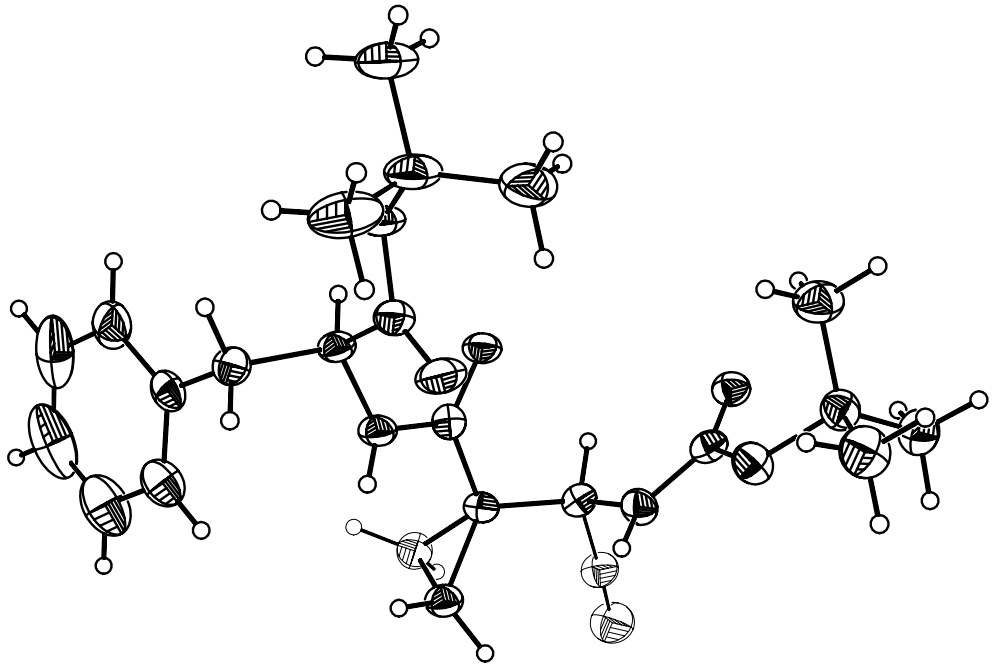


Table 3.1. Crystal data and structure refinement.

Empirical Formula	$C_{24}H_{33}N_3O_5$
Formula weight, g/mol	443.53
Crystal systesm	monoclinic
Space group	P21
Unit cell dimensions	
a, Å	11.905(5)
b, Å	9.2517(16)
c, Å	23.371(6)
α, °	90
β, °	92.25(3)
γ, °	90
Volume, $Å^3$	2572.1(13)
Z	4
Calculated density, Mg/m^3	1.145
Absorption coefficient, mm^{-1}	0.081
F(000)	952
Θ-Range, °	1.71 to 24.84
Observed Reflections	6613
Reflections collected/ unique [Rint]	21983/8604 [0.0594]

Data/Restraints/Parameter	8604 / 1 / 597
Goof F^2	0.994
R_1, wR_2 values [I>2σ(I)]	0.0457, 0.0935
R_1, wR_2 values (all data)	0.0679, 0.1011
Largest diff. peak and hole, e · $Å^{-3}$	0.247 and –0.225

Tabelle 3.2. Atomic coordinates and equivalent isotropic displacement parameters (Å2). U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

Atom	x	y	z	U(eq)
C(1)	0.2926(2)	1.2484(3)	0.5953(1)	0.0373(7)
C(2)	0.4022(2)	1.2023(3)	0.6268(1)	0.0322(6)
C(3)	0.4131(2)	1.2750(3)	0.6855(1)	0.0370(7)
C(4)	0.5185(2)	1.2283(3)	0.7195(1)	0.0335(6)
C(5)	0.5137(3)	1.1194(3)	0.7605(1)	0.0434(8)
C(6)	0.6112(3)	1.0745(3)	0.7908(1)	0.0543(9)
C(7)	0.7134(3)	1.1356(4)	0.7801(2)	0.0552(9)
C(8)	0.7195(3)	1.2428(4)	0.7400(1)	0.0488(8)
C(9)	0.6223(2)	1.2898(3)	0.7099(1)	0.0388(7)
O(10)	0.2077(2)	1.1678(3)	0.6111(1)	0.0597(7)
C(11)	0.0914(3)	1.1904(4)	0.5850(2)	0.0586(10)
C(121)	0.0338(7)	1.0405(9)	0.5996(4)	0.054(3)
C(131)	0.0458(9)	1.3029(14)	0.6050(4)	0.068(3)
C(141)	0.0951(7)	1.1828(11)	0.5153(4)	0.043(2)
C(122)	0.0212(6)	1.1078(9)	0.6276(4)	0.060(3)
C(132)	0.0532(7)	1.3629(10)	0.5981(3)	0.054(2)
C(142)	0.0853(9)	1.1515(12)	0.5302(5)	0.066(3)
O(15)	0.2866(2)	1.3436(2)	0.5604(1)	0.0557(6)
N(1‘)	0.4961(2)	1.2397(3)	0.5920(1)	0.0301(5)

Tabelle 3.3. Bondlengths [Å] and angles [°].

C(1)-O(15)	120.1(4)	C(3‘)-C(6‘)	151.7(4)	C(22)-C(23)	135.9(6)
C(1)-O(10)	132.0(4)	C(3‘)-C(4‘)	152.3(4)	C(23)-C(24)	137.3(5)
C(1)-C(2)	153.3(4)	C(4‘)-C(5‘)	149.5(5)	O(25)-C(26)	135.9(3)
C(2)-N(1‘)	145.1(3)	C(6‘)-N(7‘)	145.8(4)	C(26)-C(28)	137.3(5)
C(2)-C(3)	152.7(4)	C(6‘)-C(15‘)	148.5(5)	C(26)-C(27)	149.6(5)
C(3)-C(4)	152.2(4)	N(7‘)-C(8‘)	134.9(4)	C(26)-C(29)	151.3(4)
C(4)-C(9)	138.7(4)	C(8‘)-O(17‘)	121.8(3)	N(18‘)-C(19‘)	151.2(3)
C(4)-C(5)	139.3(4)	C(8‘)-O(9‘)	134.0(3)	C(19‘)-O(31‘)	151.8(3)

C(5)-C(6)	139.9(5)	O(9‘)-C(10‘)	149.0(4)	C(19‘)-C(20‘)	134.9(4)
C(6)-C(7)	137.4(5)	C(10‘)-C(13‘)	150.4(5)	C(20‘)-C(21‘)	122.4(4)
C(7)-C(8)	136.8(4)	C(10‘)-C(12‘)	151.2(4)	C(20‘)-C(22‘)	151.2(4)
C(8)-C(9)	140.0(4)	C(10‘)-C(11‘)	152.5(4)	C(20‘)-C(23‘)	150.4(3)
O(10)-C(11)	150.5(4)	C(15‘)-N(16‘)	114.8(4)	C(21‘)-C(22‘)	151.8(4)
C(11)-C(131)	127.1(12)	C(16)-O(30)	119.7(3)	C(23‘)-N(24‘)	152.3(3)
C(11)-C(142)	133.0(10)	C(16)-O(25)	133.7(3)	C(23‘)-C(32‘)	149.4(4)
C(11)-C(122)	152.9(8)	C(16)-C(17)	153.1(4)	N(24‘)-C(25‘)	134.3(3)
C(11)-C(121)	159.0(9)	C(17)-N(18‘)	145.7(3)	C(25‘)-O(34‘)	122.2(3)
C(11)-C(141)	163.4(10)	C(17)-C(18)	153.7(4)	C(25‘)-O(26‘)	134.4(3)
C(11)-C(132)	169.0(10)	C(18)-C(19)	149.9(4)	O(26‘)-C(27‘)	147.3(3)
N(1‘)-C(2‘)	133.5(4)	C(19)-C(20)	138.8(4)	C(27‘)-C(28‘)	150.9(4)
C(2‘)-O(14‘)	123.8(3)	C(19)-C(24)	140.3(4)	C(27‘)-C(30‘)	151.2(4)
C(2‘)-C(3‘)	149.9(4)	C(20)-C(21)	140.5(5)	C(27‘)-C(29‘)	152.5(4)
C(3‘)-C(5‘)	150.1(4)	C(21)-C(22)	139.3(6)	C(32‘)-N(33‘)	114.8(4)

O(15)-C(1)-O(10)	125.3(3)	O(14‘)-C(2‘)-C(3‘)	120.4(6)
O(15)-C(1)-C(2)	123.9(3)	N(1‘)-C(2‘)-C(3‘)	117.7(6)
O(10)-C(1)-C(2)	110.8(3)	C(2‘)-C(3‘)-C(5‘)	122.4(6)
N(1‘)-C(2)-C(3)	111.0(2)	C(2‘)-C(3‘)-C(6‘)	111.0(6)
N(1‘)-C(2)-C(1)	108.9(2)	C(5‘)-C(3‘)-C(6‘)	119.2(6)
C(3)-C(2)-C(1)	110.5(2)	C(2‘)-C(3‘)-C(4‘)	116.3(6)
C(4)-C(3)-C(2)	112.5(2)	C(5‘)-C(3‘)-C(4‘)	59.2(6)
C(9)-C(4)-C(5)	118.0(3)	C(6‘)-C(3‘)-C(4‘)	119.8(6)
C(9)-C(4)-C(3)	121.4(2)	C(5‘)-C(4‘)-C(3‘)	56.66(6)
C(5)-C(4)-C(3)	120.6(3)	C(4‘)-C(5‘)-C(3‘)	61.11(6)
C(4)-C(5)-C(6)	120.5(3)	N(7‘)-C(6‘)-C(15‘)	110.8(6)
C(7)-C(6)-C(5)	120.6(3)	N(7‘)-C(6‘)-C(3‘)	110.2(6)
C(8)-C(7)-C(6)	119.6(3)	C(15‘)-C(6‘)-C(3‘)	111.1(6)
C(7)-C(8)-C(9)	120.3(3)	C(8‘)-N(7‘)-C(6‘)	121.3(3)
C(4)-C(9)-C(8)	121.0(3)	O(17‘)-C(8‘)-N(7‘)	124.1(3)
C(1)-O(10)-C(11)	120.8(2)	O(9‘)-C(8‘)-N(7‘)	110.0(2)
C(131)-C(11)-C(142)	124.6(7)	C(8‘)-O(9‘)-C(10‘)	121.3(2)
C(131)-C(11)-O(10)	111.4(6)	O(9‘)-C(10‘)-C(13‘)	110.6(2)
C(142)-C(11)-O(10)	111.5(5)	O(9‘)-C(10‘)-C(12‘)	109.7(3)
C(131)-C(11)-C(122)	85.3(6)	C(13‘)-C(10‘)-C(12‘)	113.5(3)
C(142)-C(11)-C(122)	118.8(6)	O(9‘)-C(10‘)-C(11‘)	100.9(2)
O(10)-C(11)-C(122)	100.7(3)	C(13‘)-C(10‘)-C(11‘)	110.5(3)

C(131)-C(11)-C(121)	116.2(6)	C(12‘)-C(10‘)-C(11‘)	111.0(3)
C(142)-C(11)-C(121)	87.9(6)	N(16‘)-C(15‘)-C(6‘)	178.7(4)
O(10)-C(11)-C(121)	101.0(4)	O(30)-C(16)-O(25)	126.8(3)
C(122)-C(11)-C(121)	34.2(3)	O(30)-C(16)-C(17)	123.4(2)
C(131)-C(11)-C(141)	115.5(6)	O(25)-C(16)-C(17)	109.7(2)
C(142)-C(11)-C(141)	14.0(6)	N(18‘)-C(17)-C(16)	110.1(2)
O(10)-C(11)-C(141)	109.7(4)	N(18‘)-C(17)-C(18)	110.4(2)
C(122)-C(11)-C(141)	131.6(5)	C(16)-C(17)-C(18)	107.2(2)
C(121)-C(11)-C(141)	101.9(5)	C(19)-C(18)-C(17)	115.4(2)
C(131)-C(11)-C(132)	16.0(6)	C(20)-C(19)-C(24)	118.0(3)
C(142)-C(11)-C(132)	115.1(6)	C(20)-C(19)-C(18)	121.8(3)
O(10)-C(11)-C(132)	107.9(4)	C(24)-C(19)-C(18)	120.2(3)
C(122)-C(11)-C(132)	101.3(5)	C(19)-C(20)-C(21)	120.1(4)
C(121)-C(11)-C(132)	131.6(5)	C(22)-C(21)-C(20)	119.8(3)
C(141)-C(11)-C(132)	103.8(5)	C(23)-C(22)-C(21)	120.3(3)
C(2‘)-N(1‘)-C(2)	121.2(3)	C(22)-C(23)-C(24)	120.0(4)
O(14‘)-C(2‘)-N(1‘)	121.9(3)	C(23)-C(24)-C(19)	121.8(3)
C(16)-O(25)-C(26)	110.6(3)	C(22‘)-C(21‘)-C(20‘)	60.83(17)
O(25)-C(26)-C(28)	113.8(3)	C(21‘)-C(22‘)-C(20‘)	59.93(16)
O(25)-C(26)-C(27)	101.0(2)	N(24‘)-C(23‘)-C(32‘)	111.0(2)
C(28)-C(26)-C(27)	111.0(3)	N(24‘)-C(23‘)-C(20‘)	109.3(2)
O(25)-C(26)-C(29)	111.2(3)	C(32‘)-C(23‘)-C(20‘)	110.4(2)
C(28)-C(26)-C(29)	120.3(2)	C(25‘)-N(24‘)-C(23‘)	122.2(2)
C(27)-C(26)-C(29)	122.7(2)	O(34‘)-C(25‘)-N(24‘)	125.4(2)
C(19‘)-N(18‘)-C(17)	120.3(2)	O(34‘)-C(25‘)-O(26‘)	125.5(2)
O(31‘)-C(19‘)-N(18‘)	122.7(2)	N(24‘)-C(25‘)-O(26‘)	109.0(2)
O(31‘)-C(19‘)-C(20‘)	120.4(2)	C(25‘)-O(26‘)-C(27‘)	122.3(2)
N(18‘)-C(19‘)-C(20‘)	116.9(2)	O(26‘)-C(27‘)-C(28‘)	102.0(2)
C(21‘)-C(20‘)-C(19‘)	122.4(2)	O(26‘)-C(27‘)-C(30‘)	109.7(2)
C(21‘)-C(20‘)-C(22‘)	59.24(17)	C(28‘)-C(27‘)-C(30‘)	111.3(2)
C(19‘)-C(20‘)-C(22‘)	116.0(2)	O(26‘)-C(27‘)-C(29‘)	110.5(2)
C(21‘)-C(20‘)-C(23‘)	117.9(2)	C(28‘)-C(27‘)-C(29‘)	110.2(2)
C(19‘)-C(20‘)-C(23‘)	111.5(2)	C(30‘)-C(27‘)-C(29‘)	112.7(2)
C(22‘)-C(20‘)-C(23‘)	120.7(2)	N(33‘)-C(32‘)-C(23‘)	177.7(3)

Tabelle 3.4. Anisotropic displacement parameters (Å2 × 103). The anisotropic displacement factor esponent takes the form: –2π2[h2a*2U11+ ... +2hka*b*U12].

Atom	U11	U22	U33	U23	U13	U12
C(1)	26.3(15)	38.2(17)	47.1(17)	1.7(15)	–3.4(12)	–3.9(13)
C(2)	20.6(14)	35.7(16)	40.4(15)	3.9(12)	0.9(11)	–4.4(12)
C(3)	30.1(16)	41.7(17)	39.4(16)	1.4(14)	3.8(12)	–4.0(13)
C(4)	39.9(17)	30.5(14)	29.9(14)	1.0(12)	0(12)	–2.9(13)
C(5)	60(2)	37.5(17)	33.5(16)	1.0(13)	6.7(15)	–9.3(15)
C(6)	91(3)	36.4(18)	34.7(17)	9.9(14)	–9.8(18)	–1.6(18)
C(7)	61(2)	51(2)	52(2)	7.2(17)	–26.6(17)	1.9(18)
C(8)	45.8(19)	52.1(19)	46.8(18)	9.3(16)	–19.1(14)	–5.7(16)
C(9)	43.5(18)	37.0(16)	35.0(15)	8.8(13)	–9.2(13)	–5.9(14)
O(10)	19.7(11)	82.5(17)	76.0(16)	43.5(14)	–10.1(11)	–13.6(11)
C(11)	23.2(17)	77(3)	75(2)	34(2)	–8.5(16)	–11.1(17)
O(15)	33.8(12)	50.1(13)	82.3(16)	25.4(13)	–11.4(11)	–9.4(10)
N(1‘)	27.1(13)	25.6(13)	37.5(13)	–2.1(11)	–1.0(10)	–6.5(10)
C(2‘)	26.5(15)	26.6(14)	32.1(14)	4.6(12)	–10.6(11)	2.9(12)
C(3‘)	24.6(14)	32.2(15)	33.1(15)	1.4(12)	–3.5(12)	2.1(11)
C(4‘)	23.0(16)	78(2)	39.3(17)	5.0(16)	–6.6(13)	–1.9(16)
C(5‘)	35.0(17)	49.1(18)	44.0(17)	–5.1(14)	3.9(14)	–13.0(14)
C(6‘)	33.7(16)	32.8(15)	34.6(15)	0.9(12)	–2.2(12)	8.4(12)
N(7‘)	51.2(17)	27.9(14)	39.3(14)	–5.4(12)	–18.3(12)	11.3(12)
C(8‘)	44.5(18)	34.9(17)	29.8(15)	0.4(13)	–5.9(13)	12.7(14)
O(9‘)	51.5(13)	33.5(11)	46.5(12)	–7.9(9)	–19.3(10)	15.5(10)
C(10‘)	43.5(18)	43.0(17)	42.8(16)	–2.3(15)	–17.8(14)	14.3(15)
C(11‘)	69(3)	59(2)	69(2)	–8.5(19)	–30.2(19)	35(2)
C(12‘)	63(2)	49.3(19)	38.2(17)	2.7(15)	–11.5(15)	6.9(16)
C(13‘)	47(2)	62(2)	55(2)	2.0(17)	–8.5(17)	14.4(17)
C(14‘)	37.5(12)	29.9(11)	47.2(12)	–2.6(9)	–6.1(9)	–6.7(9)
C(15‘)	55(2)	49.2(19)	36.4(17)	6.4(14)	0.2(17)	15.7(16)
N(16‘)	66(2)	83(2)	57.2(18)	20.3(17)	20.5(17)	16.3(19)
O(17‘)	44.0(12)	30.1(11)	37.8(11)	–5.5(9)	–10.4(9)	9.0(9)
C(16)	30.7(16)	27.9(15)	36.8(16)	6.6(12)	2.9(12)	4.3(12)
C(17)	18.3(13)	27.6(13)	37.1(15)	7.8(12)	0.2(11)	2.7(11)
C(18)	21.5(15)	32.3(15)	37.6(16)	5.5(12)	1.5(11)	–2.7(11)
C(19)	32.4(15)	29.1(14)	32.8(14)	6.7(14)	6.0(12)	–7.5(12)
C(20)	60(2)	31.9(16)	57(2)	7.1(2)	25.5(17)	1.1(15)
C(21)	11.0(4)	42(2)	71(3)	–18(2)	57(3)	–26(2)

C(22)	11.2(4)	75(3)	39(2)	–6(19)	11(2)	–48(3)
C(23)	77(3)	71(3)	37.6(19)	2.5(14)	–5.8(18)	–22(2)
C(24)	47(2)	40.1(16)	37.3(17)	3.1(8)	–0.9(14)	–9.3(15)
O(25)	30.8(10)	34.0(10)	33.3(10)	1.9(14)	–7.3(8)	13.2(8)
C(26)	49(2)	46.0(18)	35.8(16)	–4.0(14)	–16.2(13)	21.9(15)
C(27)	95(3)	85(3)	31.5(17)	1.9(18)	–2.7(18)	53(2)
C(28)	51(2)	46.6(19)	68(2)	–15.1(17)	–28.2(17)	11.6(16)
C(29)	57(2)	48.5(19)	45.2(18)	–5.7(15)	–17.4(15)	26.6(16)
O(30)	41.4(13)	38.1(12)	41.3(11)	–1.9(9)	–4.4(9)	17.6(10)
N(18‘)	20.3(12)	25.6(12)	37.5(13)	8.1(10)	–0.4(9)	1.0(10)
C(19‘)	23.2(14)	25.6(14)	23.5(13)	–1.9(11)	–0.7(10)	–2.8(11)
C(20‘)	22.4(13)	21.1(12)	27.0(13)	1.8(11)	–2.4(10)	–0.6(10)
C(21‘)	24.1(14)	29.4(14)	35.1(14)	4.2(12)	–1.0(11)	2.8(12)
C(22‘)	27.4(15)	41.2(16)	26.0(14)	–0.4(12)	–2.6(11)	1.8(12)
C(23‘)	20.7(13)	21.8(13)	30.1(14)	–3.0(11)	0.1(10)	–2.0(10)
N(24‘)	33.5(13)	21.3(12)	30.6(13)	1.4(10)	3.7(10)	–3.3(10)
C(25‘)	20.9(13)	24.6(14)	33.7(15)	–1.1(12)	0.9(10)	2.0(11)
O(26‘)	43.8(12)	28.6(10)	28.6(10)	–2.3(8)	–0.3(8)	–3.0(9)
C(27‘)	31.6(16)	37.3(16)	28.8(15)	–0.9(12)	–0.6(12)	0.8(12)
C(28‘)	53(2)	43.6(18)	41.3(18)	–7.0(14)	–3.7(15)	–3.4(15)
C(29‘)	41.9(18)	45.5(18)	42.8(17)	–2.1(14)	–9.1(14)	7.2(15)
C(30‘)	42.2(18)	39.8(17)	38.5(16)	–3.1(13)	5.6(13)	–1.4(14)
O(31‘)	27.2(10)	23.9(10)	39.0(10)	7.9(8)	1.5(8)	3.3(8)
C(32‘)	23.3(16)	30.0(14)	39.0(15)	0.8(12)	0.5(12)	–3.0(12)
N(33‘)	29.3(15)	48.6(16)	56.9(16)	7.1(13)	–0.1(12)	–3.1(12)
O(34‘)	30.8(10)	25.0(10)	34.4(10)	1.5(8)	0.9(8)	1.0(8)

Tabelle 3.5. H-Coordinates (× 104) and isotropic displacement parameters (Å2 × 103).

Atom	x	y	z	U(eq)
H(2A)	4011	10951	6323	39
H(3A)	4147	13812	6802	44
H(3B)	3463	12511	7075	44
H(5A)	4437	10753	7679	52
H(6A)	6067	10010	8190	65
H(7A)	7795	11037	8005	66
H(8A)	7900	12855	7325	59
H(9A)	6275	13650	6824	47
H(12A)	354	10269	6412	82

H(12B)	748	9615	5819	82
H(12C)	–444	10408	5847	82
H(13A)	802	13891	5887	102
H(13B)	569	13042	6468	102
H(13C)	–349	13021	5949	102
H(14A)	185	11897	4986	65
H(14B)	1288	10910	5040	65
H(14C)	1403	12632	5015	65
H(12D)	256	11569	6647	89
H(12E)	502	10091	6319	89
H(12F)	–573	11044	6133	89
H(13D)	–266	13757	5875	81
H(13E)	982	14288	5755	81
H(13F)	659	13842	6389	81
H(14D)	71	11567	5157	100
H(14E)	1130	10523	5265	100
H(14F)	1316	12168	5080	100
H(1‘N)	516(2)	1321(3)	5929(11)	27(8)
H(4‘A)	7420	11517	5881	57
H(4‘B)	8035	11437	5251	57
H(5‘A)	7327	13821	5016	51
H(5‘B)	6713	13900	5644	51
H(6‘A)	5912	10530	4516	41
H(7‘N)	518(3)	1321(4)	4359(14)	50(11)
H(11A)	1742	13975	3682	100
H(11B)	1439	13700	3018	100
H(11C)	2556	14568	3206	100
H(12A)	3621	11111	2793	76
H(12B)	3713	12802	2659	76
H(12C)	2596	11933	2471	76
H(13A)	2430	10266	3576	82
H(13B)	1329	11037	3305	82
H(13C)	1760	11414	3945	82
H(17A)	2564	7965	9475	33
H(18A)	3240	10777	9082	37
H(18B)	4080	9443	9168	37
H(20A)	4240	7673	8409	59
H(21A)	3905	7119	7433	87
H(22C)	2547	8413	6892	90

H(23C)	1521	10209	7314	75
H(24B)	1834	10757	8272	50
H(27A)	3248	10242	11255	106
H(27B)	4245	9582	11653	106
H(27C)	3307	8538	11369	106
H(28A)	4559	11385	10587	84
H(28B)	5461	10416	10272	84
H(28C)	5654	10812	10936	84
H(29D)	4827	7093	10973	76
H(29E)	5821	8167	11172	76
H(29F)	5625	7774	10509	76
H(18N)	124(3)	1038(4)	9280(13)	43(9)
H(21A)	–1605	11107	9123	36
H(21B)	–247	11203	8977	36
H(22A)	–393	8921	8478	38
H(22B)	–1752	8824	8625	38
H(23A)	–1404	7706	9914	29
H(24N)	–120(2)	1049(3)	10263(12)	33(8)
H(28A)	–1155	11889	12019	69
H(28B)	132	11460	11940	69
H(28C)	–459	11086	12525	69
H(29A)	680	8907	11865	66
H(29B)	–258	7670	11813	66
H(29C)	21	8429	12418	66
H(30A)	–2626	10062	11970	60
H(30B)	–2043	9152	12483	60
H(30C)	–2325	8394	11879	60

Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited as supplementary publication no. CCDC-240722 (**47a**), CCDC-240723 (**107b**) and CCDC-240724 [(2*S*,2'*R*)-**118**] 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).

Aknowledgments

I would like to thank Professor A. de Meijere for giving me the possibility to spend the years of my Ph.D. in his group, for the helpful discussions and explanations about the drawing up of publications.

For my participation at the academic activities I thank Professors W. Knepel, J. Magull and the Göttingen University.

I am very grateful to Mr. Machinek for the measurements of the NMR spectra. I thank Dr. Frauendorf and Mrs. Udvarnoki for the measurement of the mass spectra and Mr. Hambloch for the measurements of the elemental analyses. I am very grateful to Mr. D. Vidovic for the measurement of the X-Ray structures. I also thank very much the group of Professor Buback, for the attempts of carachterization of my polymers and for the helpful discussions. I wish to thank the group of Prof. Tietze for the introduction to the use of the microwave system.

I am very grateful to Dr. Sergej I. Kozhukov for his help in the drawing up of my first paper and for the help in the lab, during the preparation of my starting materials.

For his indefatigable help in the lab, and for the precious suggestions about the use of computers I am very grateful to Heiko. I thank a lot Farina for her untiring corrections in my first indipendent scientific works and for every time she helped me to menage in the life in a foreign country.

I thank Anna, Surya, Martina and particularly Farina and Marco for the correction of this work. I would like to thank all the members of the group of Prof. de Meijere, especially Anna, Daniel, Vesta, Boris, Surja, Viktor, Dr. Andrej S., Dr. Belov, Takuja, Baris, André and Shamil. A special thank to my collegues in the administrations of our NMR: Mario and Hans.

I thank Mrs. G. Keil Knepel and Mr. Carsten Rauch and expecially Mr. Stefan Besshausen for helping me in any problem.

I thank Farina, Anna, Martina, Marco, Heiko and Jochen for their friendship. I really thank Hans, for his help in all the difficult periods I had in chemistry or in life and also for a lot of shared fun.

I wish to thank expecially my mother and Andrea, who, although faraway, have always been close to me with support and trust.

Publications List

1. S. Cicchi, J. Revuelta, A. Zanobini, M. Betti, A. Brandi *Synlett* **2003**, *15*, 2305–2308. "Domino palladium(II)-mediated rearrangement-oxidative cyclization of β-aminocyclopropanols"

2. A. Zanobini, M. Gensini, J. Magull, D. Vidović, S. I. Kozhushkov, A. Brandi, A. de Meijere, *Eur. J. Org. Chem.* **2004**, 4158–4166.

   Part 102 in the series "Cyclopropyl Building Blocks for Organic Synthesis"

   "A Convenient New Synthesis of 3-Substituted β-Lactams Formally Derived from 1-(Aminomethyl)cyclopropanecarboxylic Acids"

3. A. Zanobini, A. Brandi, A. de Meijere, *Chem. Eur. J.* **2005**, submitted.

   Part 122 in the series "Cyclopropyl Building Blocks for Organic Synthesis"

   "A New Three-Component Cascade Reaction to Yield 3-Spirocyclopropanated 2-Azetidinones"

Lectures

1. "Microwave-assisted one-pot approach to 3-spirocyclopropanated monocyclic β-lactams", A. Zanobini, A. de Meijere, Fourth International Youth Conference on Organic Synthesis, June 27–30, 2005, St. Petersburg, Russia.

Poster presentations

1. "Azaanaloghi di Illudine: eterocicli spirociclopropanici alchilanti del DNA", S. Cicchi, A. Zanobini, A. Brandi, XXI Congresso Nazionale della Societá Italiana di Chemioterapia, December 2–5, 2001, Firenze, Italia.

Lebenslauf

Ich wurde am 25. April 1977 als eiziges Kind von Pietro Zanobini und Elena Boccoli in Florenz, Italien, geboren.
Von September 1983 bis Juni 1988 besuchte ich die Grundschule „La Quiete. Istituto delle Montalve“ und von September 1988 bis Juni 1991 die Mittelschule in dem selbem Institut, in Florenz, Italien. Anschließend wechselte ich auf das humanistische Liceo Ginnasio Statale Niccoló Forteguerri in Pistoia, das ich von September 1991 bis Juni 1994 besuchte. Von September 1994 bis Juli 1996 besuchte ich das humanistische Liceo Ginnasio Statale Galileo in Florenz, wo ich im Juli 1996 das Abitur bestand. Zum Wintersemester 1996/97 nahm ich das Studium der Chemie an der Universitá degli studi di Firenze auf. Unter der wissenschaftlichen Anleitung von Prof. Dr. Alberto Brandi fertigte ich von Oktober 2001 bis Juli 2002 meine Diplomarbeit mit dem Thema „Reattivitá di Derivati Ciclopropanici con Pd(II). Sintesi di Composti Tetraidro e Diidropiridonici“ an. Am 23. Juli 2002 wurde mir den akademische Grad Diplom-Chemikerin zuerkannt. Seit Oktober 2002 arbeite ich im Arbeitskreis von Prof. Dr. Armin de Meijere an meiner Dissertation zum Thema „Synthesis of New Spirocyclopropanated β-Lactams and Their Application as Building Blocks for β-Amino Acids Peptides“. In der Zeit von Oktober 2003 bis Juni 2005 wurde ich mehrfach mit der Betreuung des organisch-chemischen Praktikums, zweimal mit der Betreuung der Übungen zur Vorlesung „Experimentalchemie II, Organische Chemie“, beauftragt. Im Sommersemester 2005 absolvierte ich erfolgreich einen Kurs der „Allgemeinen und systematischen Pharmakologie und Toxikologie“.
Ich besitze die italienische Staatsangehörigkeit.