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XXI CICLO

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DIVERSITY-ORIENTED SYNTHESIS OF PEPTIDOMIMETIC SCAFFOLDS FROM SUGARS AND AMINO ACIDS DERIVATIVES

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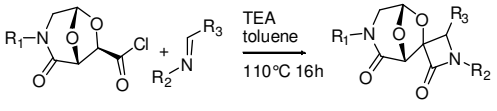
SUMMARY

PART III - Experimental Section

Abstract

The creation of new molecules useful for therapeutic applications is necessary for the screening of large compound libraries, in order to identify molecular structures to be selected as new lead compounds for biological targets. Diversity-Oriented Synthesis (DOS) concept has been placed as new paradigm for the improvement of molecular diversity in the same synthetic process, which combines the generation of a functionalized precursor with further synthetic elaborations, in order to obtain diverse cyclic molecule and variably decorated.
The aim of this thesis is to apply the principles of the DOS to obtain densely functionalized molecular scaffolds from simple building blocks like sugars and amino acids derivatives.
The investigation of the structural diversification of BTAa scaffolds, synthesized from tartaric acid and amino acids derivatives, has led to a new class of spiro-β-lactams *via* Staudinger reaction, useful for medicinal chemistry[a] (Scheme 1). The reactivity of L-Ascorbic acid derivatives with Glycine acetale, to give a new α-amino acid bicyclic scaffold, Proline analogue,[b] has been then explored (Figure 1).



Scheme 1

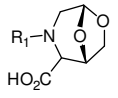
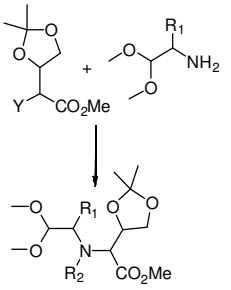


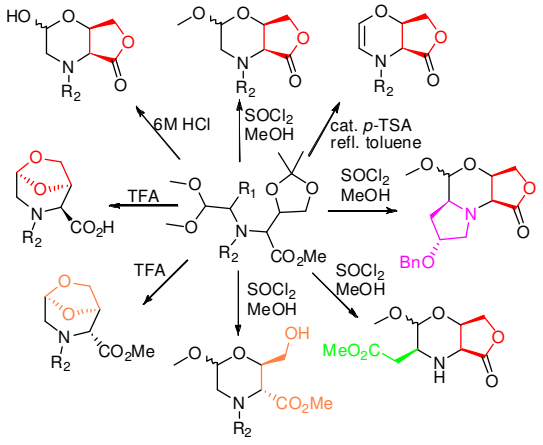
Figure 1

Secondary cyclic amino acids and in particular morpholine ring have an important role in medicinal chemistry. We moved towards a DOS approach to generate morpholine scaffolds starting from enantiopure compounds like L-Ascorbic acid and amino acids derivatives (Scheme 2). The acyclic densely functionalized template gave the 1st generation of morpholine scaffolds in which is included the Proline bicyclic analogue of above (Scheme 3).

[a] A . Trabocchi, C. Lalli, F. Guarna, A. Guarna *Eur. J. Org. Chem.* **2007**, *16*, 4594-4599.
[b] C. Lalli, A. Trabocchi, F. Guarna, C. Mannino, A. Guarna *Synthesis* **2006**, *18*, 3122.

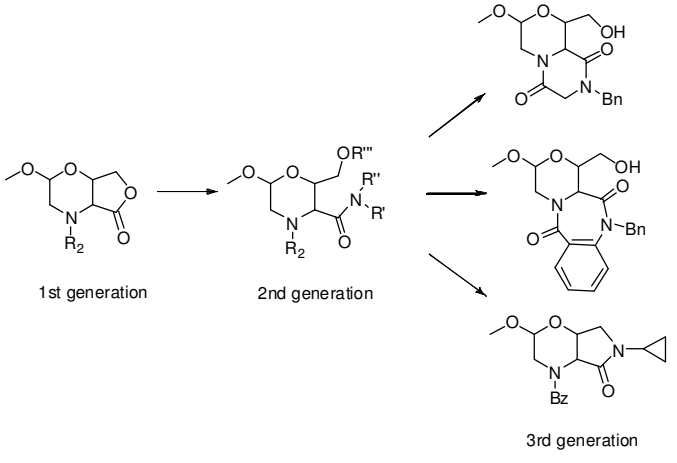


Scheme 2



Scheme 3

Lactone aminolysis using $LiNTf_2$ as catalyst (see below) gave the 2nd generation. Functional-group-pairing reactions allowed to obtain molecules of 3rd generation[c] (Scheme 4).

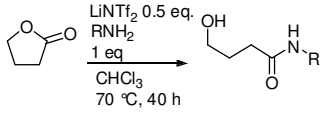


Scheme 4

During the development of the 2nd generation we were interested in finding an efficient method for synthesizing molecules through the aminolysis of lactones.

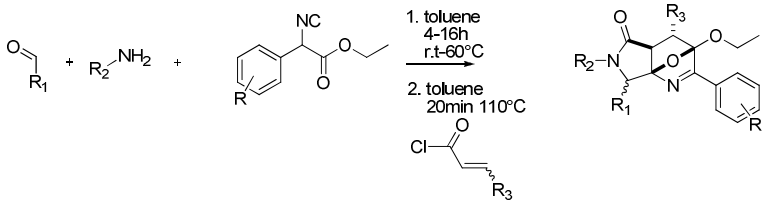
[c] A. Guarna, A. Trabocchi, G. Menchi, C. Lalli, F. Sladojevich, N. Cini Heterocyclic compounds containing the morpholine nucleus their preparation and use. **WO2008/129004, October 30th 2008**.

In this contest an aminolysis of lactones process, $LiNTf_2$-catalyzed,[d] with stoichiometric quantities of amine, was developed (Scheme 5).



Scheme 5

Multicomponent reactions are another powerful process to obtain diversity and complexity in a rapid way. They allow to combine in only one synthetic operation at least three elements to give densely functionalized products. In the context of a collaboration program with Dr. Jieping Zhu from ICSN, CNRS of Gif-sur-Yvette (France), a new four-component reaction has been developed for the synthesis of heterocyclic scaffolds oxa-bridged, with four points of diversity, useful for medicinal chemistry (Scheme 6).



Scheme 6

[d] C. Lalli, A. Trabocchi, G. Menchi, A. Guarna *Synlett* **2008**, *2*, 189-192.

PART I

Introduction

Chapter 1

Peptidomimetics and Diversity-Oriented Synthesis

The creation of new molecules useful for therapeutic applications is necessary for the screening of large compound libraries, in order to identify molecular structures to be successively selected as new lead compounds with respect to biological targets. Modern methods for stereoselective organic synthesis have increased the efficiency with which small molecules can be prepared.[1] During last years organic synthesis has taken advantage of solid-phase synthetic techniques,[2] as demonstrated by the high number of papers and patents in the field. Solid phase organic synthesis increases dramatically the diversity and number of small molecules available for medical and biological applications and it has provided to synthesize not only single target compounds but also collections of structurally differentiated compounds. Differently decorated heterocyclic compounds and functionalizable with reactive groups for immobilization on solid supports are very useful for this new kind of synthetic strategy. During last decade, drug discovery focused on the generation of combinatorial libraries of *ad hoc* designed molecules. Unfortunately, most common synthetic methods in combinatorial chemistry are based on the generation of libraries through simple functionalization of a given molecule, often of cyclic or polycyclic nature, thus limiting the achievement of molecules carriers of high molecular diversity within the same synthetic process. More recently the concept of Diversity-Oriented Synthesis[3] has been placed as a new paradigm for the improvement of molecular diversity in the same synthetic process, which combines the generation of a densely functionalized

[1] P. S. Farmer in *Drug Design* (Ed.: E. J. Ariens), Academic Press, New York, **1980**, 119–143

[2] (a) R. B. Merrifield, *J. Am. Chem. Soc.* **1963**, *85*, 2149. (b) C. C. Leznoff and J. Y. Wong, *Can. J. Chem.* **1972**, *50*, 2892. (c) F. Camps, J. Castells, M. J. Ferrando, J. Font, *Tetrahedron Lett.* **1971**, *12*, 1713. (d) F. Camps, J. Castells, J. Pi, *An. Quim.* **1974**, *70*, 848. (e) A. Patchornik and M. A. Kraus, *J. Am. Chem. Soc.* **1970**, *92*, 7857. (f) J. I. Crowley and H. Rapoport, *J. Am. Chem. Soc.* **1970**, *92*, 6363. (g) V. Yedida and C. C. Leznoff, *Can. J. Chem.* **1980**, *58*, 1140.

[3] Schreiber, S.L. *Science* **2000**, *287*, 1964-1968.

precursor with further synthetic elaborations, in order to obtain a large array both of diverse cyclic molecules and variably decorated with functional groups.

1.1. Peptidomimetics

During the last three decades a huge number of biologically active peptides has been discovered and characterized. As a consequence of interaction with their membrane-bound receptors, these peptides acting as hormones, neurotransmitters and neuromodulators influence cell-cell communication and control a series of vital functions such as metabolism, immune defense, digestion, respiration, behavior. Many physiological processes are governed by protein-protein interactions, thus peptides are of special interest as targets in drug discovery and in the biomedical field, and the number of native and modified peptides used as therapeutics is ever increasing. Many bioactive peptides have been prepared in large scale and tested both in pharmacology and clinic, thus allowing the development of new therapies for a variety of pathologies. However, the use of peptides as therapeutics is limited due to several factors:[4] low metabolic stability towards proteolysis, poor absorption after oral ingestion, rapid excretion, undesired effects caused by potential interaction of relatively flexible peptides with several receptors. Besides all these drawbacks, biomedical research is now oriented towards the development of *peptidomimetics*.[5] In this approach peptides and proteins are considered as leads for the discovery of other classes of compounds, more than potential therapeutics.

Peptidomimetics are small molecules having the same structural or functional features of the native peptides, such that they bind to enzymes or receptors with higher affinity than starting peptide. During last years peptidomimetics have shown great interest both in organic and medicinal chemistry. They are more selective and efficient than native peptides, they show greater oral bioavailability and biological activity is prolonged due to lower enzymatic degradation.[6]

The discovery of new peptidomimetics is crucial, as peptides are not 'optimal drugs' due to low metabolic stability, low oral bioavailability, high flexibility resulting in poor selectivity and difficulty in reaching the target.

[4] A. Giannis, T. Kolter, *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1244-1267.

[5] J. Gante, *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 1699-1720.

[6] (a) R.M.J. Liskamp *Recl. Trav. Chim.* Pays-Bas **1994**, *113*, 1. (b) G.L. Olson, D. R. Bolin, M. P. Bonner, M. Bös, C. M. Cook, D. C. Fry, B. J. Graves, M. Hatada, D. E. Hill, M. Kahn, V. S. Madison, V.K. Rusiecki, R. Sarabu, J Sepinwall, G. P. Vincent, M. E. Voss *J. Med. Chem.* **1993**, *36*, 3039-3049.

The generation of peptidomimetics is basically focused on the knowledge of electronic and conformational features of the native peptide and its receptor or active site of an enzyme. Peptidomimetics may be subdivided into three classes depending on their structural and functional characteristics:

1. Structural mimetics or type I mimetics: these compounds show an analogy of a local topography with the native substrate, and they carry all the functionalities responsible of the interaction with an enzyme or a receptor in a well-defined spatial orientation.
2. Functional mimetics or type II mimetics: in these molecules the analogy with the native compound is based on the interaction with the target receptor or enzyme, without apparent structural analogies.
3. Structural-functional mimetics or type III mimetics: an example is a scaffold having a structure different from the substrate, in which all the functional groups needed for biological interactions are mounted in a well-defined spatial orientation.

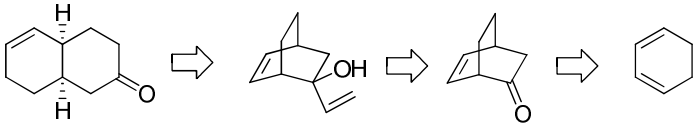
1.2. From Target-Oriented Synthesis (TOS) to Diversity-Oriented Synthesis (DOS)

Synthetic organic chemistry aims to gain access to small molecules for medical and biological applications using three general approaches.

The first approach uses Target-Oriented Synthesis (TOS). Target-oriented synthesis has a long history in organic chemistry. The targets are natural products or drugs. Natural compounds can be identified in screens of extract mixtures, isolated, and then structurally characterized. Once the structure has been identified, it can become a target for chemical synthesis. Beginning in 1960s, a systematic method to plan syntheses of target molecules, named retrosynthetic analysis, was devised.[7] Synthetic pathways in TOS are linear and convergent, and they are planned in the reverse-synthetic direction by using retrosynthetic planning, which aims to move in the direction of complex → simple (Figure 1.1).

[7] (a) E. J. Corey, X.-M. Cheng *The Logic of Chemical Synthesis* (Wiley, New York, **1989**). (b) E. J. Corey *Angew. Chem.* **1991**, *103*, 469. (c) E. J. Corey *Angew. Chem. Int. Ed. Engl.* **1991**, *30*, 455 (Nobel Lecture). (d) E. J. Corey *Pure. Appl. Chem.* **1967**, *14*, 19. (e) E. J. Corey, W. T. Wipke *Science* **1969**, *166*, 178. (f) E. J. Corey *Q. Rev. Chem. Soc.* **1971**, *25*, 455.

Retrosynthetic analysis has been used in the synthetic planning of many target compounds of value in medicine and biology. It is also used in solid phase synthesis, in particular in the synthesis of 'focused libraries'.[8]



Target complex

Starting Material simple

Figure 1.1. Beginning with a complex target the analysis leads to the identification of simple starting materials.[9]

The second approach uses either combinatorial chemistry. The instrument of combinatorial chemistry is the solid phase synthesis and it has become largely used only in recent years.[10] Solid phase syntheses have been performed in parallel, so similar reactions are performed, but the structures of the building blocks in key fragment-coupling steps are varied. Solid phase, parallel synthesis is an example of what is commonly referred to as combinatorial synthesis and is most commonly used to synthesize a focused library. A second variation of solid phase synthesis is the split-and-pool strategy of synthesis.[11] The aim in medicinal and combinatorial chemistry is to access diversity to some degree, and usually involves synthesizing analogues of a given target structure. This can be accomplished efficiently using a solid-phase synthesis approach to append different sets of building blocks to a common molecular skeleton.[12] If this common skeleton contains multiple reactive sites with potential for orthogonal functionalization, the powerful technique of split-pool synthesis can be used to access all possible combinations of building blocks efficiently.

The third approach uses Diversity-Oriented Synthesis (DOS). Diversity-Oriented Synthesis is not aimed at one particular target, and retrosynthetic analysis can therefore not be applied directly. It is instead

[8] (a) P. H. H. Hermkens, H. C. J. Ottenheijm, D. Rees *Tetrahedron* **1996**, *52*, 4527. (b) R. E. Dolle, K. H. Nelson Jr. *J. Combinatorial Chem.* **1999**, *1*, 235.
[9] D. A. Evans, J. V. Nelson *J. Am. Chem. Soc.* **1980**, *102*, 774.
[10] (a) B. A. Bunin, J. A. Ellman *J. Am. Chem. Soc.* **1992**, *114*, 10997. (b) R. J. Simon *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **1992**, *89*, 9367. (c) S. H. DeWitt *et al.*, *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 6909.
[11] (a) R. A. Houghten *et al.*, *Nature* **1991**, *354*, 84. (b) K. S. Lam *et al.*, *Nature* **1991**, *354*, 82.
[12] (a) R. E. Dolle, *J. Comb. Chem.* **2000**, *2*, 383. (b) R. E. Dolle *J. Comb. Chem.* **2001**, *3*, 477. (c) R. E. Dolle *J. Comb. Chem.* **2002**, *4*, 369.

aimed at a collection of many compounds having structural complexity and diversity. In DOS, where the structural complexity of the individual compounds and the structural diversity of the overall collection are maximized, synthesis pathways are branched and divergent, and they are planned in the forward-synthetic direction by using forward-synthetic analysis (Figure 1.2).

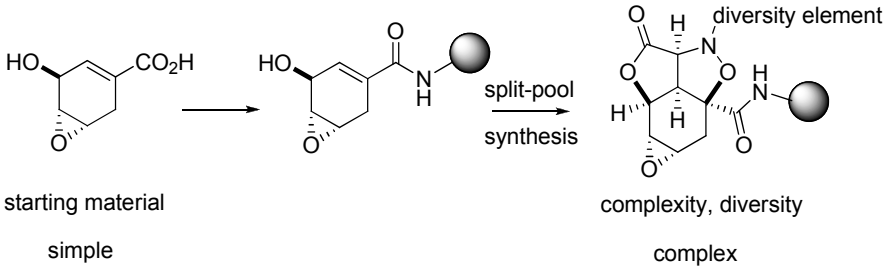


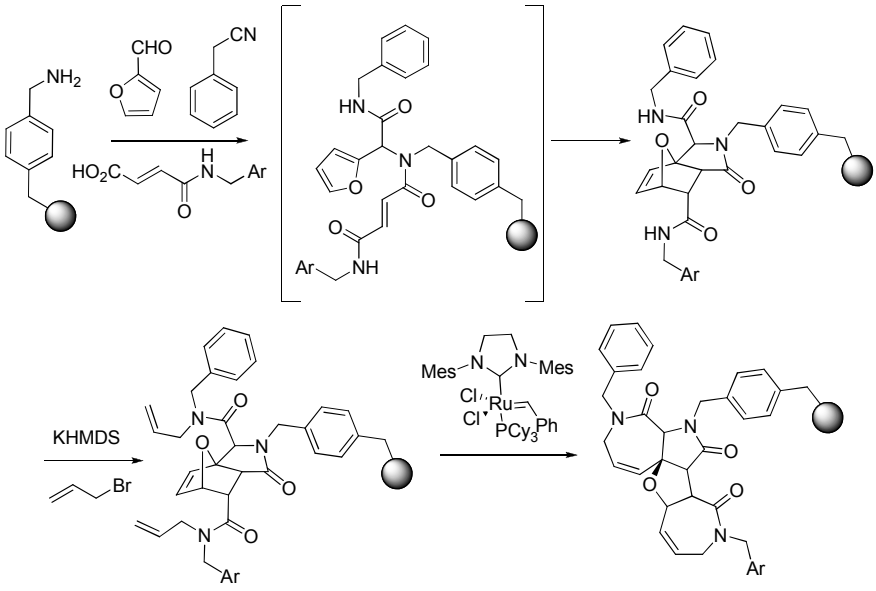
Figure 1.2. Beginning with a simple building block, the analysis provides a synthetic pathway leading to a large collection of structurally complex and diverse compounds.[13]

1.3. Diversity-Oriented Synthesis (DOS): principles

Forward-synthetic planning aims to move in the direction of simple and similar → complex and diverse. Complexity is important because many biological processes are critically dependent on protein-protein interactions, and many small molecules are able to disrupt these interactions. The basic subunit of forward-synthetic planning is the transformation of a collection of substrates into a collection of products by performing a number of chemical reactions together in the forward-synthetic direction. The key element is the chemical reactivity common to a collection of compounds that makes them all potential substrates for the same reaction. When a diversity-oriented synthesis is planned, complexity-generating reactions are most valuable for accessing complexity in an efficient manner. Moreover, identification of pairwise relationships, where the product of one complexity-generating reaction is the substrate for another, can lead to highly complex products with just a few synthetic steps (3-5 steps). An

[13] D. S. Tan, M. A. Foley, M. D. Shair, S. L. Schreiber *J. Am. Chem. Soc.* **1998**, *120*, 8565.

example of the application of these concepts is reported in Scheme 1.1.[14] The Ugi four-component coupling reaction can be used to assemble a complex product from simple starting materials in a single step. If those simple starting materials are selected to include both a diene and a dienophile, then the product of this first complexity-generating reaction is a substrate for another, namely an intramolecular Diels–Alder reaction. After bisallylation an additional complexity-generating reaction, namely a ring-opening/ring-closing metathesis can generate a highly complex polycyclic molecular skeleton.



Scheme 1.1. Three-step synthesis of a complex polycyclic ring system using complexity-generating reactions.

In DOS, where there is not a target structure, the problem of diversity is subdivided into three diversity elements: appendages, stereochemistry and molecular skeletons.[15]

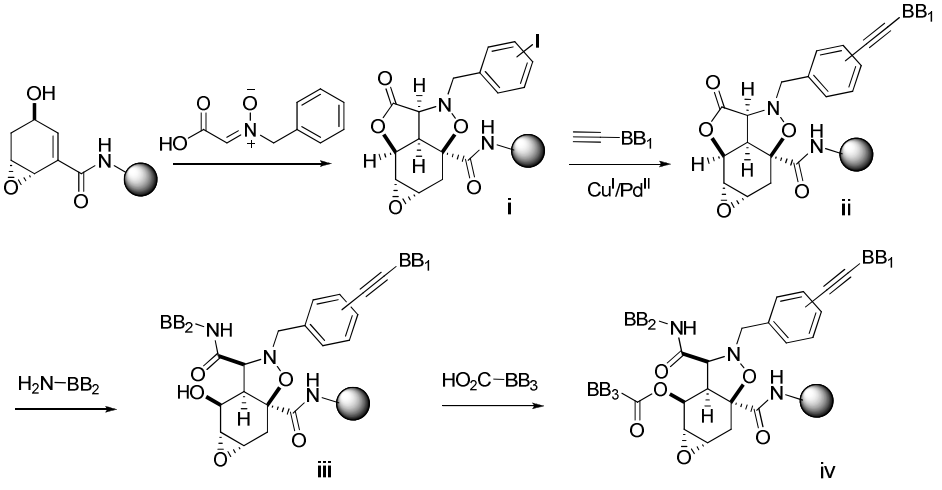
- Appendage Diversity

The simplest diversity-generating process involves the use of coupling reactions to attach different appendages to a common molecular skeleton. It's a complexity-generating reaction to yield a single, complex molecular skeleton having several attachment points followed by a series of diversity-generating appending processes to attach all possible combinations of building blocks to this common skeleton. This one-synthesis/one-skeleton

[14] (a) K. Paulvannan, *Tetrahedron Lett.* **1999**, *40*, 1851. (b) D. Lee, J.K. Sello, S. L. Schreiber, *Org. Lett.* **2000**, *2*, 709.
[15] S. L. Schreiber, M. D. Burke *Angew. Chem. Int. Ed.* **2004**, *43*, 46-58.

approach is general and capable of generating hundreds, thousands, or even millions of distinct small molecules in just three to five steps.

An interesting example is a complexity-generating, consecutive transesterification–cycloaddition reaction used to generate, in one step, the tetracyclic skeleton (i) with suitable functional groups for further elaboration through a series of diversity-generating appending processes.[13] A Sonogashira coupling reaction was first used to append a diverse collection of alkyne building blocks (BB_1) to the iodoaryl moiety of (i) to generate the collection of more diverse products (ii). These products have a common electrophilic lactone moiety so they are substrates for another appending process, an amine-mediated lactone-opening reaction that generated a collection of new products (iii). They all share a common nucleophilic secondary hydroxy group, thus making them all substrates for a third appending process, the coupling with a collection of carboxylic acid building blocks (BB_3). This generate the complete matrix of building blocks (iv) in a highly efficient manner (Scheme 1.2).



Scheme 1.2. Complexity-generating synthesis of compounds derived from Shikimic Acid.

- Stereochemical Diversity

Stereochemical diversity increases the number of relative orientations of potential macromolecule-interacting elements in small molecules. It can best be achieved by using stereospecific reactions that proceed with enantio- or diastereoselectivity. Since diversity-generating processes involve the transformation of a collection of substrates into a collection of products, it is critical that the processes used to generate new stereogenic

centers are both selective and general.[16] The collective transformation of chiral substrates into products having increased stereochemical diversity requires powerful reagents that can override substrate bias and deliver diastereomeric products with very high selectivity.[17]

- Skeletal Diversity

There are two different strategies for planning DOS pathways that generate skeletal diversity.

The first strategy, using different reagents, transform a common substrate with the potential for diverse reactivity into a collection of products having distinct molecular skeletons (Figure 1.3 A).[18]

In the second strategy diverse skeletons of small molecules can be accessed by transforming a collection of substrates having different appendages that pre-encode skeletal information (called σ elements) into a collection of products having distinct molecular skeletons using common reaction conditions (Figure 1.3 B).[19]

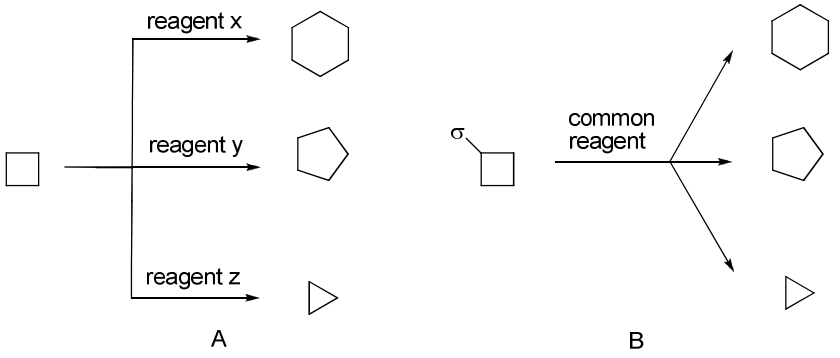


Figure 1.3 A and B. Two general approaches for planning synthesis pathways that generate skeletal diversity.

[16] (a) W. S. Knowles, M. J. Sabacky *Chem. Commun.* **1968**, 1445. (b) T. P. Dang, H. B. Kagan *Chem. Commun.* **1971**, 481. (c) W. S. Knowles, M. J. Sabacky, B. D. Vineyard, D. J. Weinkauff *J. Am. Chem. Soc.* **1975**, *97*, 2567.

[17] (a) K. B. Sharpless *Chem. Scr.* **1985**, *25*, 71. (b) S. Masamune, W. Choy, J. S. Petersen, L. R. Sita *Angew. Chem.* **1985**, *97*, 1. (c) S. Masamune, W. Choy, J. S. Petersen, L. R. Sita *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 1. (d) S. Y. Ko, A.W. M. Lee, S. Masamune, L. A. Reed III, K. B. Sharpless, F. J. Walker *Science* **1983**, *220*, 949.

[18] D. Lee, J. Sello, S. L. Schreiber *J. Am. Chem. Soc.* **1999**, *121*, 10648.

[19] M. D. Burke, E. M. Berger, S. L. Schreiber *Science* **2003**, *302*, 613.

1.4. The Build/Couple/Pair (B/C/P) strategy

Some recent efforts in diversity synthesis provide a systematic and general process for obtaining a dense matrix of stereochemically and skeletally diverse products in a small number of synthetic transformations. This three-phase strategy is called Build/Couple/Pair (B/C/P):[20]

- Build: asymmetric synthesis of chiral building blocks containing orthogonal sets of functionality for subsequent coupling and pairing steps; this process when combined with the 'Couple' phase provides the basis for stereochemical diversity.
- Couple: intermolecular coupling reactions without stereochemical consequences or with complete control of all possible stereochemical outcomes.
- Pair: intramolecular coupling reactions that join pairwise combinations of functional groups incorporated in the 'build' phase (what Porco and co-workers have termed functional-group-pairing reactions[21]); this process provides the basis for skeletal diversity (Figure 1.4).

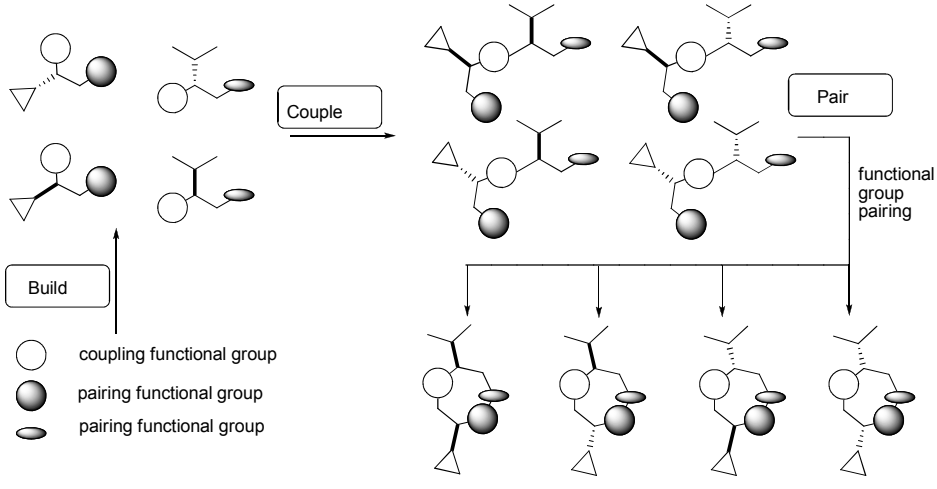


Figure 1.4. Generation of stereochemical diversity with the Build/Couple/Pair strategy.

In the build phase building blocks are synthesized. Chiral building blocks can be prepared by using either enantio- and diastereoselective reactions or compounds from the 'chiral pool'. Chiral building blocks ideally are

[20] T. E. Nielsen; S. L. Schreiber *Angew. Chem. Int. Ed.* **2008**, *47*, 48-56.
[21] E. Comer, E. Rohan, L. Deng, J. A. Porco *Org. Lett.* **2007**, *9*, 2123 – 2126.

synthesized in every possible stereoisomeric form. To minimize the number of synthetic steps, functional groups needed for subsequent coupling and pairing reactions should be embedded within these building blocks, although, additional steps have been performed immediately after the coupling process.
In the couple phase intermolecular coupling reactions are performed, which join the building blocks and result in compounds with a dense array of functional groups that can undergo intramolecular reactions in distinct pairwise combinations.
In the pair phase intramolecular coupling reactions are performed and compounds with diverse skeletons are obtained. For this purpose, the power of modern synthesis, especially the functional group preferences of different transition metals, can be exploited to achieve a dense combinatorial matrix of functional group pairings in the cyclization reactions.[22] Functional groups used in the subsequent pairing reactions should be strategically positioned so as to allow as many ring-closing modes as possible. Selective coupling of pairs of functional groups ('chemoselectivity') in functional-group-pairing reactions may be achieved by several different strategies. Three categories of functional group couplings are:
1) polar/polar (amine/ester to form a lactam);
2) nonpolar/nonpolar (alkene/alkene ring-closing metathesis to generate a cycloalkene);
3) polar/nonpolar (alcohol/alkyne cycloacetalization enabled by alkynophilic metal activation).
In conclusion the B/C/P strategy will yield small molecules with increased probability of success in the discovery, optimization, and manufacturing phases of drug-discovery research. Public databases that provide access to the results of these researchs are expected to provide the means to evaluate the performance of compounds from different origins, including from pathways by the B/C/P strategy.

[22] (a) N. Kumagai,G. Muncipinto, S. L. Schreiber *Angew. Chem.* **2006**, *118*, 3717 – 3720. (b) N. Kumagai,G. Muncipinto, S. L. Schreiber *Angew. Chem. Int. Ed.* **2006**, *45*, 3635 – 3638.

Chapter 2

Aim of this thesis work

2.1. BTAa, BTS and BTKa: previous works

During last years our interest in the development of heterocycles and constrained amino acids for peptidomimetic chemistry has focused on developing heterocyclic scaffolds using amino acids and sugars derivatives as building blocks.[23] In particular has been developed a new class of 3-aza-6,8-dioxabicyclo[3.2.1]octane scaffolds named **B**icycles from **T**artaric acid and **A**mino **a**cids (**BTAa**). As reported in the first paper about BTAa,[24] they satisfy all the requirements needed for the development of peptidomimetics:

- easy synthetic procedures in few steps, starting from commercially available compounds in both enantiomeric forms
- stereochemical control in every step
- high number of functions for molecular diversity

Successively the synthesis of a BTS scaffold has been achieved, in which a polar group is present in position 4, as a consequence of the use of serine as amino acid.[25]

A new sub-class of BTAa, developed more recently, presents as a common feature an aromatic substituent in position 5. These new compounds, named **B**icycles from **T**artaric acid and **K**eto-**a**mine (**BTKa**), are obtained from the condensation of tartaric acid derivatives and aromatic amino ketones.[26] In this case the possibility of expanding the diversification is

[23] For an account, see: A. Trabocchi, G. Menchi, F. Guarna, F. Machetti, D. Scarpi, A. Guarna *Synlett* **2006**, *3*, 331-353.
[24] A. Guarna, A. Guidi, F. Machetti, G. Menchi, E. G. Occhiato, D. Scarpi, S. Sisi, A. Trabocchi *J. Org. Chem.* **1999**, *64*, 7347-7364.
[25] N. Cini, F. Machetti, G. Menchi, E. G. Occhiato, A. Guarna *Eur. J. Org. Chem.* **2002**, 873-880.
[26] A. Guarna, I. Bucelli, F. Machetti, G. Menchi, E. G. Occhiato, D. Scarpi, A. Trabocchi *Tetrahedron* **2002**, *58*, 9865–9870.

given by the high number of aromatic amino ketones, commercially available or easy to obtain.

Recently, we moved from tartaric acid to sugars as building blocks for new versatile scaffolds with complete control of the stereochemistry. In particular, it was possible to generate new enantiopure bicyclic amino acids, such as γ- or δ-amino acids as reverse turn inducers by use of erythrose derivatives, and bicyclic Proline mimetics starting from Serine and Glyceraldehyde derivatives as reported for the synthesis of α-,[27] β-[28] and γ/δ -amino acids[29] as well as tricyclic scaffolds containing the 4-hydroxyproline nucleus[30] and [4.2.1]- and [5.2.1]-sized heterocyclic analogues[31] (Figure 2.1).

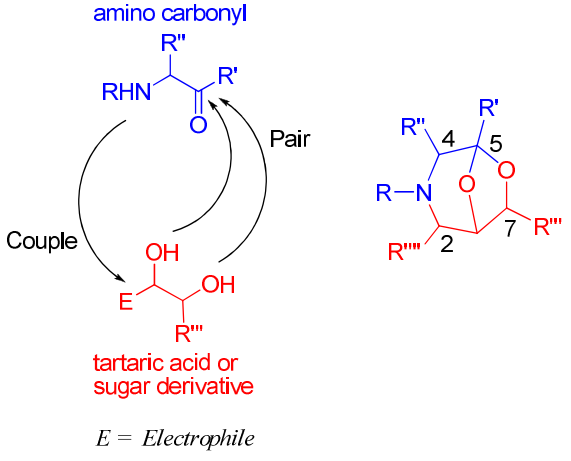


Figure 2.1. New class of 3-aza-6,8-dioxabicyclo[3.2.1]octane scaffolds from amino acids and tartaric acid or sugars derivatives.

The keys steps in the synthesis of such BTAa are a coupling of the building blocks obtained from the chiral pool, namely an amidation, to give a densely functionalized acyclic template and an intramolecular transacetalization to give the biclyclic scaffold. In this approach the two building blocks react with all their functionalities to give the bicyclic structure. Further manipulations on the R group can lead to structural diversification, so to new structures.

Now, what happens if we change approach? Can we imagine just to allow only one cyclization, to obtain a morpholine ring? In this new approach not all the functionalities would be already implicated in the cycle so that there

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[30] A. Trabocchi, M. Rolla, G. Menchi, A. Guarna *Tetrahedron Lett.* **2005**, *46*, 7813–7816.

[31] (a) D. Scarpi, D. Stranges, A. Trabocchi, A. Guarna *Tetrahedron* **2006**, *7*, 1575–1582. (b) D. Scarpi, D. Stranges, L. Cecchi, A. Guarna *Tetrahedron* **2004**, *60*, 2583–2591.

would be space for a more vast investigation of the molecular diversification. In particular it would be possible to operate, according to the principles of the Diversity-Oriented Synthesis, a skeletal diversification obtained with a differentiating pairing process.

2.2. Topics discussed in this thesis work

Nowadays there is an ever-increasing need for versatile scaffolds to be applied in peptidomimetic design. The attempt to satisfy this demand produced the previous work and as consequence this thesis work.
How to prepare collections of molecules with molecular diversity in a rapid and efficient way? In this thesis work we will demonstrate that DOS chemistry is a powerful concept for the development of new highly diverse chemical entities.
Starting from the background we first explored the structural diversification, so we tried to obtain new structures from known ones: the investigation of the diversification of BTAa scaffolds has led to a new class of spiro-β-lactams useful for medicinal chemistry.
We explored the reactivity of L-Ascorbic acid derivatives with amino acids to give a new α-amino acid bicyclic scaffold, Proline analogue, as consequence of the previous works involving the coupling of amino acids and sugars derivatives. This new scaffold results in a structure 'BTAa-like', but in this case the couple phase consists in a nucleophylic substitution S_N2 to give the densely functionalized acyclic template, that undergoes intramolecular transacetalization to give the biclyclic scaffold.
Then we moved towards a DOS approach to generate morpholine scaffolds starting from the same starting materials, just operating in different reaction conditions (pair phase). In the first generation of morpholine compounds is also included the bicyclic Proline analogue of above. During the development of the second generation of these heterocycles for chemical diversity, we were interested in finding an easy and efficient method to synthesize molecules through the aminolysis of lactones, and in particular we were interested in achieving the reaction using stoichiometric quantities of reactants. In this contest a work about aminolysis lactones $LiNTf_2$-catalyzed is placed. The second generation has been submitted to further manipulation and a third generation of complex bi- and tricyclic molecules has been obtained.
Multicomponent reactions are another powerful process to obtain diversity and complexity in a rapid way. They allow to combine in only one synthetic operation at least three elements to give highly functionalized products. In

the context of a collaboration program with Dr. Jieping Zhu from ICSN, CNRS of Gif-sur-Yvette (France), a new four-component reaction for the synthesis of heterocyclic scaffolds useful for medicinal chemistry was developed.
In summary, in this Ph.D. thesis the following topics will be discussed:

- Diastereoselective synthesis of highly constrained spiro-β-lactams *via* Staudinger reaction using an unsymmetrical bicyclic (BTAa) ketene. The spiro-β-lactams formation is commonly used for constraining the torsion angles for the development of constrained β-turn mimetics.
- Synthesis of an α-amino acid from L-Ascorbic acid, considered as bicyclic mimetic of Proline, particularly suited for peptidomimetic chemistry on solid-phase.
- Diversity-oriented synthesis of morpholine based scaffolds from L-Ascorbic acid and amino acids, to give a 1st, 2nd and 3rd generation of complex bi- and tricyclic molecules.
- $LiNTf_2$-catalyzed aminolysis of lactones with stoichiometric quantities of amines, specifically, as a part of the program towards the development of heterocycles for chemical diversity.
- Development of a novel multicomponent reaction with functionalized α-isocyanoacetates to give highly functionalized oxa-bridged heterocycles.

The applications of such heterocycles are in the field of medicinal and peptidomimetic chemistry. BTAa, BTS and BTKa have been proved to be dipeptide isosteres when inserted in peptide chains and they have been used as reverse turn inducers; the bicyclic mimetic of Proline could be applied in the same field. Morpholine scaffolds have been incorporated in polypeptides. Spiro-β-lactams have antiviral and antibacterial properties, they have been subjected to biological evaluation as antibiotics and β-lactamase inhibitors. Finally the oxa-bridged heterocycles should find applications in a large number of fields for the synthesis of libraries of medicinally important heterocycles of this type.

PART II

Diversity-Oriented Synthesis of heterocyclic scaffolds

Chapter

3

Diastereoselective synthesis of highly constrained Spiro-β-Lactams *via* Staudinger Reaction using an unsymmetrical bicyclic ketene*

Control of the topological arrangement of the residues that constitute the pharmacophore in peptidomimetics is accomplished by the use of molecular scaffolds.[63] Organic chemistry uses modern synthetic techniques to make structurally diverse scaffolds to use as peptidomimetic templates, including cyclic, polycyclic and spiro compounds varying in ring size and in their level of functionalization. In particular, lactam or bicyclic lactam formation is commonly used for constraining the torsion angles for the synthesis of peptidomimetics,[64] and β-lactams have been extensively used as synthetic intermediates in organic synthesis (the β-lactam synthon

* Trabocchi, A.; Lalli, C.; Guarna, F.; Guarna, A. *Eur. J. Org. Chem.* **2007**, *16*, 4594-4599.

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method),[65] thus providing a very useful route to a number of α- and β-amino acid derivatives and peptides. The application of spiro-β-lactams in peptidomimetic chemistry is well-documented, and relevant examples include the development of constrained β-turn mimetics.[66] Spiro-β-lactams have also received attention in medicinal chemistry owing to their antiviral and antibacterial properties,[67] as well as recognized activity as cholesterol absorption inhibitors.[68] Among the strategies developed for the construction of β-lactams,[69] the reaction of acyl chlorides with imines (known as the Staudinger reaction)[70] constitutes one of the most popular procedures. Also, several syntheses of spiro-β-lactams have been described in the literature,[71] and in recent years many researchers have accomplished the synthesis of spiro-β-lactams through cycloaddition reactions employing different ketenes and imines.[72]

In recent years, our interest in the development of heterocycles and constrained amino acids for peptidomimetic chemistry has focused on the

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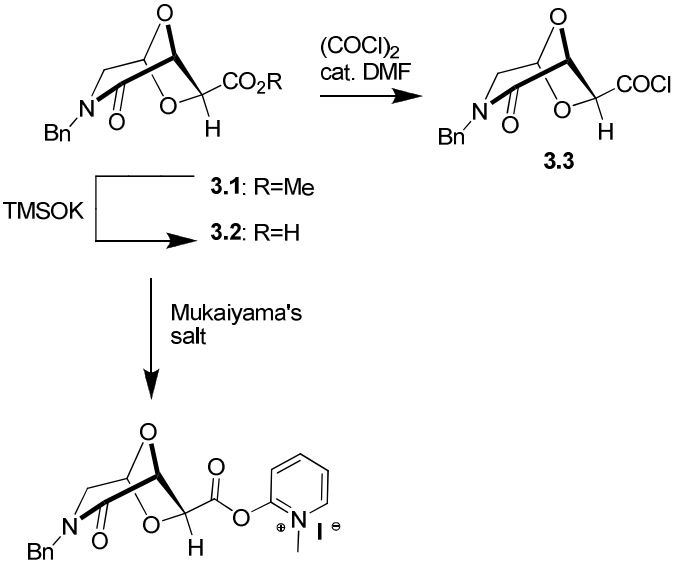
[72] (a) B. Alcaide, P. Almendros, R. Rodriguez-Acebes, *Chem. Eur. J.* **2005**, *11*, 5708–5712. (b) B. Alcaide, P. Almendros, T. M. Campo, R. Rodriguez-Acebes, *Tetrahedron Lett.* **2004**, *45*, 6429–6431. (c) G. Cremonesi, P. D. Croce, C. L. Rosa, *Tetrahedron* **2004**, *60*, 93–97. (d) A. Macias, E. Alonso, C. del Pozo, A. Venturini, J. Gonzalez, *J. Org. Chem.* **2004**, *69*, 7004–7012. (e) A. Macias, E. Alonso, C. del Pozo, J. Gonzalez, *Tetrahedron Lett.* **2004**, *45*, 4657–4660. (f) E. Alonso, C. del Pozo, J. Gonzalez, *J. Chem. Soc. Perkin Trans. 1* **2002**, 571–576. (g) P. D. Croce, C. L. Rosa, *Tetrahedron: Asymmetry* **1999**, *10*, 1193–1199. (h) J. C. Sheehan, E. Chacko, Y. S. Lo, D. R. Ponzi, E. Sato, *J. Org. Chem.* **1978**, *43*, 4856–4859.

synthesis of bicyclic 3-aza-6,8-dioxabicyclo[3.2.1]octane scaffolds as γ/δ-amino acids.[23] We were interested in further exploring the skeletal diversity of such constrained scaffolds by generating polycyclic spiro compounds through the Staudinger reaction with different types of imines. Our aim was to generate compounds possessing diverse scaffolds to which different functional groups could be fixed in a stereodefined 3D topological arrangement.

Derivatives **3.2** and **3.3**, obtained from bicyclic Bn-BTG(O)-OMe **3.1** (BTG: Bicycles from Tartaric acid and Glycin derivatives), were used to assess the yield and selectivity resulting from the reaction of the corresponding BTAa-derived ketene with selected imines (Table 3.1). Ketenes are commonly generated from acyl chlorides, and the use of Mukaiyama's salt for in situ generation of the reactive species, even in solid-phase chemistry, has also been reported.[73,74] Both methodologies were thus explored to verify the reactivity of the unsymmetrical bicyclic ketene at the 7-position of the scaffold with respect to the imine at different temperatures and with different solvent systems (Scheme 3.1).



Scheme 3.1. Methodologies explored for the formation of the ketene: from acyl chloride and from Mukaiyama's salt.

Hydrolysis of **3.1** with potassium trimethylsilanolate (TMSOK) in anhydrous THF furnished corresponding carboxylic acid **3.2** in quantitative yield (Scheme 3.1). Activation of the carboxylic function of the BTG

[73] (a) S. Matsui, Y. Hashimoto, K. Saigo, *Synthesis* **1998**, 1161–1166. (b) G. I. Georg, P. M. Mashava, X. Guan, *Tetrahedron Lett.* **1991**, *32*, 581–584. (c) R. L. Funk, M. M. Abelman, K. M. Jellison, *Synlett* **1989**, 36–37. (d) S. G. Amin, R. D. Glazer, M. S. Manhas, *Synthesis* **1979**, 210–213.
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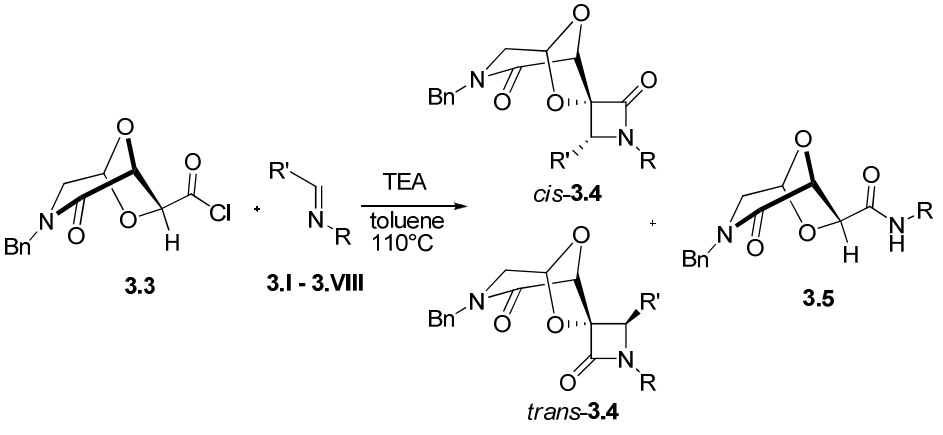
scaffold by means of Mukaiyama's salt, followed by reaction of either imine **3.I** or **3.VII** (see Table 3.1) in anhydrous CH_2Cl_2, resulted in the formation of corresponding amides **3.5**. This was a consequence of the hydrolysis of the iminium salt that resulted from the condensation of the activated acid with the corresponding imine (Scheme 3.2).
Replacement of CH_2Cl_2 with toluene as the solvent and a change in the order of addition of the reagents to the reaction mixture resulted in the same amide byproducts. The effect of temperature was also investigated, but no improvement in the reactivity was obtained in refluxing chloroform or toluene solutions of the reactive Mukaiyama's adduct with imine **3.I** (Table 3.1). Thus, the use of Mukaiyama's salt with bicyclic carboxylic acid **3.2** could not lead to the preferential formation of the corresponding spiro-β-lactam after conrotatory ring closure, because hydrolysis of the intermediate *N*-acyl iminium species was favoured under all the conditions tested, leading to amide byproducts **3.5**.



Scheme 3.2. Spiro-β-lactams are obtained when a solution of acyl chloride in toluene is added to a refluxing toluene solution of the imine. The amide **3.5** is also obtained in some cases, and it is the only product starting from the Mukaiyama's salt.

Therefore, more reactive acyl chloride derivative **3.3** was used to obtain title spiro-β-lactams **3.4**. The addition of preformed acyl chloride **3.3** to a refluxing CH_2Cl_2 solution of the imine and triethylamine (TEA) resulted in poor conversion to spiro-β-lactam **3.4** after a reaction time of 18 h. However, spiro-β-lactam **3.4** was obtained after a reaction time of 24 h by adding a solution of acyl chloride **3.3** in toluene to a refluxing toluene solution of the imine and TEA (method 1) (Scheme 3.2). When the reaction was conducted at lower temperatures, the reverse approach was used, which consisted of the preformation of the ketene by allowing the acyl chloride to react with TEA, followed by the addition of the imine species (method 2). The reaction was explored with imines derived from α-

amino esters, benzylamine and aromatic amines and gave different results in terms of yield and diastereoselectivity, as shown in Table 3.1.

Entry	Imine	R'	R	Product	Yield(%)	*cis*/*trans*
1	**3.I**	Ph	$CH(CH_2Ph)CO_2Me$	**3.6**	33	1.4:1
2	**3.II**	Ph	CH_2Ph	**3.7**	66	1:1.2
3	**3.III**	Ph	*p*-CH_3Ph	**3.8**	14	15:1
4	**3.IV**	Ph	*p*-NO_2Ph	**3.9**	-	-
5	**3.V**	Ph	*p*-OMePh	**3.10**	39	10:1
6	**3.VI**	*p*-NO_2Ph	*p*-CH_3Ph	**3.11**	24	20:1
7	**3.VII**	*p*-OMePh	*p*-CH_3Ph	**3.12**	59	>50:1
8	**3.VIII**	*p*-BrPh	*p*-CH_3Ph	**3.13**	33	7:1

Table 3.1. Selected examples of spiro-β-lactams **3.4** with general formulas as in Scheme 3.2: reactions were all conducted in toluene at 110°C by using method 1.

The nucleophilicity of the amine derivatives comprising the imine proved to influence the yield, as the conversion proceeded in the order benzyl > amino ester ≈ aryl. In particular, substitution on the aniline ring influenced the reactivity, as *p*-NO_2-aryl-*N*-substituted imine **3.IV** (Table 3.1, entry 4) failed to react with the bicyclic ketene, probably as a result of the unfavourable electronic effects in the Staudinger reaction, whereas *p*-OMe-aryl-*N*-substitution (Table 3.1, entry 5) gave the highest yield of the benzaldehyde-derived aryl imines (Table 3.1, entries 3–5). Also the nature of the aromatic aldehyde-derived moiety agreed with the hypothesis that an electron-rich imine could improve the yield of the corresponding spiro-β-lactam, as *p*-NO_2-aryl-*C*-substitution gave **3.11** in 24% yield, whereas *p*-OMe-aryl-*C*-substitution yielded corresponding spiro compound **3.12** in 59% yield (Table 3.1, entries 6 and 7, respectively).

In the latter case (Table 3.1, entry 7), the order of addition of the reagents proved to influence the ratio of **3.4**/**3.5** as a consequence of the hydrolysis of the intermediate iminium species. Specifically, method 1 proved to give the spiro-β-lactam even at 60°C, whereas method 2, consisting of the preformation of the ketene followed by imine addition, resulted in a 1:1 mixture of spiro-β-lactam **3.4**/amide byproduct **3.5** (Scheme 3.2). In terms of stereoselectivity, imine **3.I** (derived from benzaldehyde and phenylalanine methyl ester; Table 3.1, entry 1) gave a mixture of two compounds as a result of poor diastereoselectivity, as did imine **3.II** (derived from benzylamine; Table 3.1, entry 2). However, aromatic imines **3.III–3.VIII** gave in all cases a major stereoisomer. Spiro-β-lactam formation by using benzylamine-derived imine **3.II** (Table 3.1,

entry 2) was further investigated as a function of the reaction temperature. In this case, method 2, involving preformation of the ketene, was found to be crucial for achieving corresponding spiro compound **3.7**. Interestingly, we observed an effect of the temperature on the diastereomeric ratio, as shown in Table 3.2.

Entry	Temperature (°C)	Yield (%)	*cis*/*trans*
1	0	22	2.7:1
2	20	14	2.2:1
3	60	24	1:1
4	80	19	1.1:1
5	110	66	1:1.2

Table 3.2. Effect of the temperature on the diastereoisomeric ratio of spiro-β-lactams **3.7** as in Table 3.1, entry 2: reactions were all conducted by using method 2.

Specifically, when moving from 110 to 0°C we observed a slight increase in the stereoselectivity and a shift towards the preferential formation of one of the two diastereoisomers (Figure 3.1).

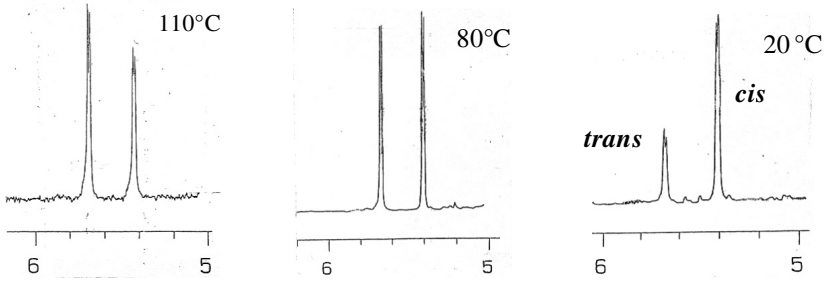


Figure 3.1. ^{1}H NMR signal of 5-H of compound **3.7** resulting from the reaction of **3.3** with imine **3.II**. The reactions were carried out at 110°C, 80°C and 20°C.

The structure of the two stereoisomers was assigned by NOESY experiments of the mixture resulting from the reaction at 20°C (Table 3.2, entry 2). In the major stereoisomer, a strong NOE signal was observed between 1-H of the bicyclic compound and 4'-H of the azetidine ring,

which suggests that spiro-β-lactam **3.7** with the general structure of *cis*-**3.4** as in Scheme 3.2 was obtained as the major compound at temperatures below 60°C. X-ray and NMR spectroscopic analysis of compound **3.12** revealed information about the structure of the major diastereoisomer. NOESY experiments agreed with the X-ray crystal structure of **3.12** as shown in Figure 3.2,[75] as demonstrated by a NOE crosspeak between 4'-H of the azetidine ring and 1-H of the bicyclic scaffold, and also by a weak NOE crosspeak between the CH_2 protons at N-3 and the 4'-*p*-OMePh hydrogen atoms (Figure 3.3).

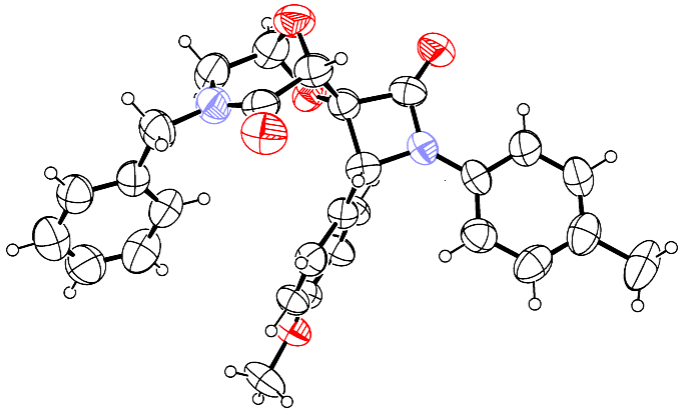


Figure 3.2. X-ray structure of compound **3.12** with thermal ellipsoids at 50% probability. For table see experimental section chapter 8.3.

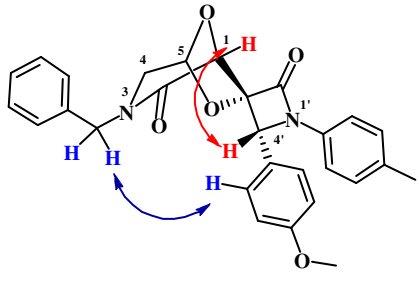


Figure 3.3. Selected NOE contacts for compound **3.12**.

The mechanism of the reaction is widely thought to involve nucleophilic attack of the imine on the ketene species to give a zwitterionic intermediate, which undergoes a subsequent conrotatory ring closure to generate the spiro-β-lactam species. In agreement with similar substrates

[75] CCDC-641203 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

reported in the literature,[41(f)] diastereoisomer *cis*-**3.12** (Scheme 3.2) would thus have resulted from initial attack of the imine species on the bicyclic ketene in the *anti* orientation with respect to the O-6 oxygen atom of the scaffold, followed by a preferential outward conrotatory ring closure of the O-6 substituent favoured by a torquoelectronic effect (Figure 3.4).

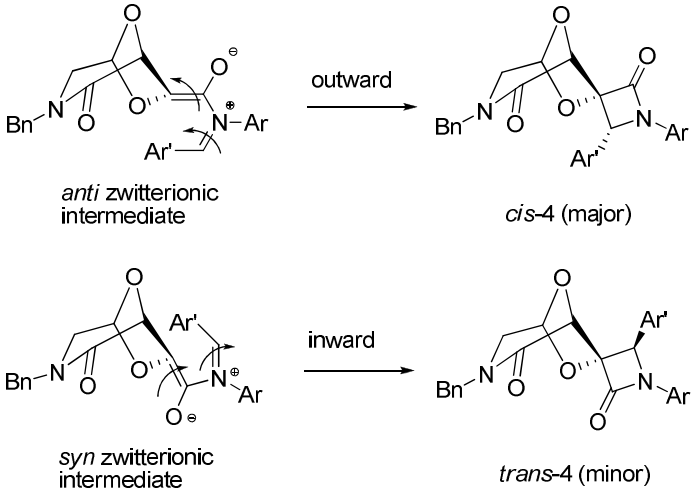


Figure 3.4. Proposed mechanism for the stepwise Staudinger reaction.

This effect has been demonstrated to be very pronounced for ketenes bearing a heteroatom adjacent to the carbon–carbon double bond,[41(f)] thus agreeing with the high stereoselectivity observed in our compounds derived from aromatic imines. The minor stereoisomer could result from *syn* attack of the imine species to give the *trans* compound as shown in Figure 3.4. This hypothesis is supported by the absence of NOESY peaks either between 4'-H of the azetidine ring and 1-H of the bicyclic scaffold, thus excluding the other possible *cis* stereoisomer, or between the CH_2 protons at N-3 and the 4'-aryl hydrogen atoms, thus excluding the other possible *trans* structure. The loss of stereoselectivity in the case of benzyl- and phenylalanine-derived imines may take account of the higher conformational freedom due to the lack of conjugation within the imine with respect to the aromatic ones.

In conclusion the synthesis of highly constrained spiro-β-lactams from a bicyclic ketene was achieved by the Staudinger reaction. The outcome of the reaction indicated that the aromatic imines are best choice for the generation of a new molecular architecture bearing aromatic functional groups, as in this case the reaction proceeded with high stereoselectivity to produce the corresponding *cis* spiro-β-lactams as the major compounds. Both aliphatic- and amino acid derived imines provided mixtures of *cis*- and *trans* spiro-β-lactams in variable amounts. Given the potential structural diversity of the ketene bicyclic scaffold,[23] this method is of interest for the generation of densely functionalized molecular scaffolds having restricted conformational freedom and a stereodefined 3D topological array of the substituents. Optimized reaction conditions may be applied for the subsequent generation of polycyclic spiro-β-lactams as peptidomimetics for biomedical research.

Chapter 4

Bicyclic Proline analogue from L-Ascorbic acid*

Nowadays there is an ever-increasing need for versatile scaffolds, including new amino acid templates, to be applied in peptidomimetic design.[45] Among the various approaches for mimicking peptide structures,[46] numerous mimetics and analogues of Proline have been developed and applied in the synthesis of biologically active compounds,[47] expecially with the aim of modulating the *cis/trans* isomerism of acyl-proline bonds, and producing proline-like reverse turn inducers.[48]

Since the development of first examples of 3-aza-6,8-dioxabicyclo[3.2.1]octane-based scaffolds (BTAa, see Figure 4.1), functionalities have been introduced at positions 3, 4, 5 and 7,[23] whereas position 2 remained largely unexplored, occupied only by C=O, C=S, or CH_2 groups. In particular, the possibility of generating scaffolds with differently positioned carboxy groups (Figure 4.1, A-C) has been recently

* C. Lalli, A. Trabocchi, F. Guarna, C. Mannino, A. Guarna Synthesis **2006**, 18, 3122–3126.

[45] A. Trabocchi, F. Guarna, A. Guarna *Curr. Org. Chem.* **2005**, *9*, 1127.

[46] See for example: S. Hanessian, G. McNaughton-Smith, H. -G. Lombart, W. D. Lubell *Tetrahedron* **1997**, *53*, 12789.

[47] (a) D. Damour, F. Herman, R. Labaudinière, G. Pantel, M. Vuilhorgne, S. Mignani *Tetrahedron* **1999**, *55*, 10135. (b) Q. Wang, M. –E. Tran Huu Dau, N. A. Sasaki, P. Potier *Tetrahedron* **2001**, *57*, 6455. (c) L. Demange, J. Cluzeau, A. Ménez, C. Dugave *Tetrahedron Lett.* **2001**, *42*, 651. (d) M. V. Gorichko, O. O. Grygorenko, I. V. Komarov *Tetrahedron Lett.* **2002**, *43*, 9411. (e) A. Dahlgren, J. Bråualt, I. Kuaenström, I. Nilsson, D. Musil, B. Samuelsson *Bioorg. Med. Chem.* **2002**, *10*, 1567. (f) X. J. Wang, S. A. Hart, B. Xu, M. D. Mason, J. R. Goodell, F. A. Etzkorn *J. Org. Chem.* **2003**, *68*, 2343. (g) I. O. Donkor, R. Korukonda, T. L. Huang, L. Le Cour Jr *Bioorg. Med. Chem. Lett.* **2003**, *13*, 783. (h) G. Jeannotte, W. D. Lubell *J. Org. Chem.* **2004**, *69*, 4656. (i) Y. –T. Liu, J. K. Wong, M. Tao, R. Osterman, M. Sannigrahi, V. M. Girijavallabhan, A. K. Saksena *Tetrahedron Lett.* **2004**, *45*, 6097.

[48] (a) K. Kym, J. P. Germanas *J. Org. Chem.* **1997**, *62*, 2847. (b) L. Halab, W. D. Lubell *J. Org. Chem.* **1999**, *64*, 3312. (c) L. Halab, W. D. Lubell *J. Am. Chem. Soc.* **2002**, *124*, 2474. (d) T. K. Chakraborty, A. Ghosh, S. K. Kumar, A. C. Kunwar *J. Org. Chem.* **2003**, *68*, 6459. (e) W. –J. Zhang, A. Berglund, J. L. –F. Kao, J. –P. Couty, M. C. Gershengorn, G. R. Marshall *J. Am. Chem. Soc.* **2003**, *125*, 1221. (f) S. Chierici, M. Jourdan, M. Figuet, P. Dumy *Org. Biomol. Chem.* **2004**, *2*, 2437.

pursued, in order to expand the scope of peptidomimetic chemistry within this class of bicyclic scaffolds. For this approach new synthetic strategies have been necessary, using different building blocks from the chiral pool.[27]

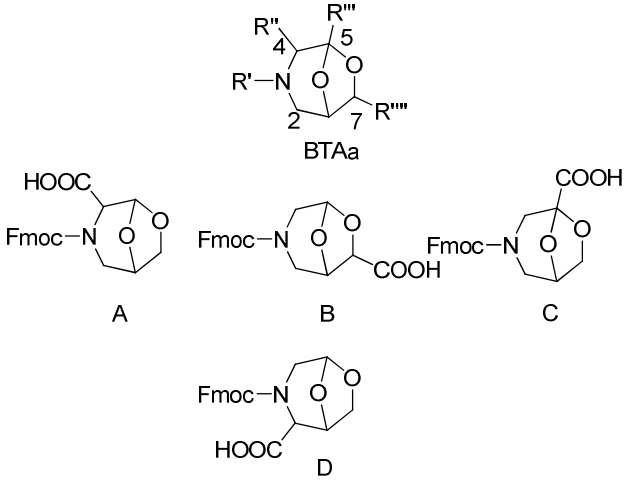


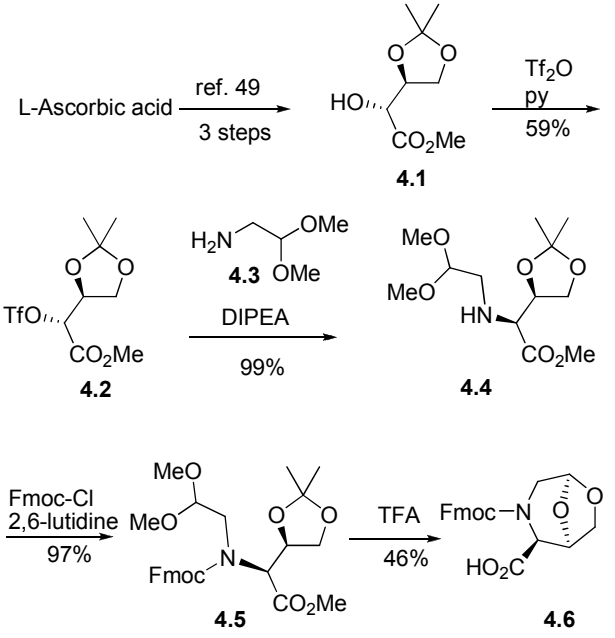
Figure 4.1. General formula of BTAa scaffolds (*top*) and isomeric bicyclic amino acids A-D, with A and D as proline mimetics.

Recently, we moved from tartaric acid to sugars as building blocks for new versatile scaffolds in enantiopure form with complete control of the stereochemistry.[27] In particular, it was possible to generate new enantiopure bicyclic amino acids, such as γ- or δ-amino acids as reverse turn inducers by use of erythrose derivatives,[27(b)] and bicyclic proline mimetics starting from Serine and Glyceraldehyde derivatives.[27(a)] We reasoned that starting from L-Ascorbic acid derivative **4.1** (Scheme 4.1), we could afford a new set of scaffolds bearing a substituent at position 2 (Figure 4.1, D). L-Ascorbic acid has appeared in literature as a valuable source of chiral building blocks for the preparation of enantiopure β-lactams[49] and L-hexoses.[50] Moreover, the use of such an inexpensive starting material is an advantage in multigram-scale organic synthesis.

Thus, starting from triflate **4.2**, obtained from the protected L-Ascorbic acid derivative **4.1**[49,51] compound **4.4** was obtained in 99% yield by nucleophilic substitution with aminoacetaldehyde dimethylacetal **4.3** at room temperature and overnight stirring (Scheme 4.1). Further protection as Fmoc-urethane **4.5**, wich was obteined with 9-fluorenylmethyl chloroformate in 1,4-dioxane as solvent, whereas *N*-(9-fluorenylmethoxycarbonyloxy)succinimide did not yield any product. Then, Fmoc-derivative **4.5** was subjected to acid cyclization at 0°C, according to reported procedures,[27] to afford the methyl ester of scaffold **4.6**.

[49] C. C. Wei, S. De Bernardo, J. P. Tengi, J. Borgese, M. Weigele *J. Org. Chem.* **1985**, *50*, 3462.
[50] L. Ermolenko, A. Sasaki *J. Org. Chem.* **2006**, *71*, 693.
[51] A. Tanaka, K. Yamashita *Synthesis* **1987**, 570.

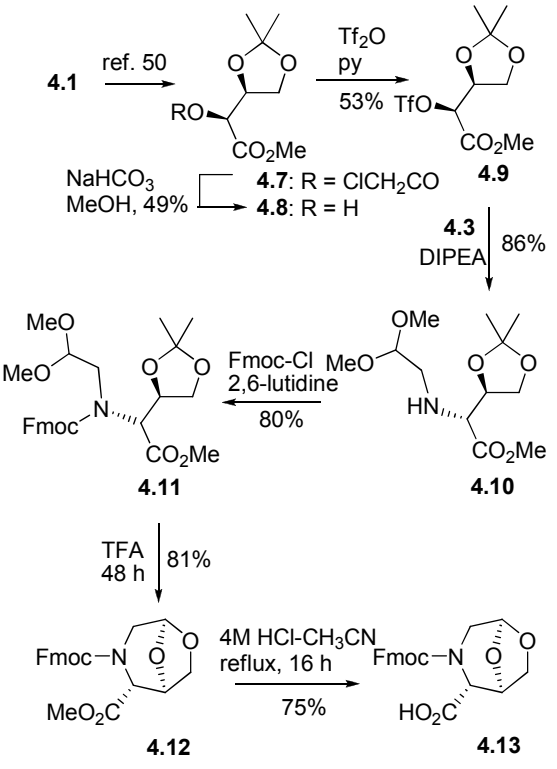
Surprisingly, the corresponding carboxylic acid **4.6** was obtained as major product by concomitant deprotection of the carbomethoxy group, and the conversion to acid **4.6** went to completion when the reaction was conducted at 25°C. Since the preparation of 4-*endo*-carboxylic scaffolds proved to be problematic and low yielding, as previously reported (see Figure 4.1, structure A),[27(a)] the facile synthesis of **4.6**, with the carboxylic group in *endo* position, provides a more complete collection of bicyclic amino acids for application in peptidomimetic chemistry.



Scheme 4.1. Synthesis of a bicyclic α-amino acid with an *endo*-carboxy group from L-Ascorbic acid.

Formal inversion of the configuration at the C-2 stereocenter of compound **4.6** gives **4.13**, the corresponding diastereomer of **4.6**, carrying the carboxy group in 2-*exo* position (Scheme 4.2). Thus, treatment of L-Ascorbic acid derivative **4.1** with chloroacetic acid and triphenylphosphine, as previously reported,[50] produced the corresponding ester-derivative **4.7** with inversion of configuration at C-2 (Scheme 4.2). Subsequent hydrolysis with sodium hydrogen carbonate in place of triethylamine gave **4.8**, the stereoisomer of **4.1**, which was converted to the corresponding triflate derivative **4.9** in 53% yield. The reaction of triflate **4.9** with acetal **4.3** gave adduct **4.10**, a diastereoisomer of **4.4**, with inversion of configuration at C-2. Successively, Fmoc protection by the same procedure used to prepare **4.5** yielded **4.11**, which was subsequently cyclized by treatment with trifluoroacetic acid. Interestingly, in this case, the reaction provided the bicyclic scaffold as methyl ester derivative **4.12** (Scheme 4.2), since the

concomitant hydrolysis failed to occur, probably because of the axial orientation of the carbomethoxy group. This led to the hypothesis that the facile hydrolysis to give compound **4.12** might occur through the urethane carbonyl group providing anchimeric assistance to the equatorial carbomethoxy group. Compound **4.12** could be obtained in excellent yield when the cyclization time was prolonged from 16 hours (35% yield) to 48 hours (81% yield).



Scheme 4.2. Synthesis of a bicyclic α-amino acid with an *exo*-carboxy group from L-Ascorbic acid.

Hydrolysis of **4.12** proved to be problematic, and different methods were tried. Specifically, basic hydrolysis with lithium hydroxide did not yield α-amino acid **4.13** in significant amounts, and partial Fmoc-deprotection of **4.12** was observed. Hydrolysis with a dioxane-water system at room temperature for 48 hours gave **4.13** with 19% conversion, and a similar result (17%) was achieved when ester **4.12** was treated with 4 M aqueous hydrogen chloride in acetonitrile. However, when ester **4.12** was refluxed in the same aqueous hydrogen chloride-acetonitrile system for 16 hours, acid **4.13** was obtained in satisfactory yield (75%) (Scheme 4.2).

In conclusion, a new bicyclic α-amino acid was synthesized in a three-steps procedure starting from an L-Ascorbic acid derivative, producing amino acid derivative **4.6** directly after acid cyclization. In addition, inversion of configuration at the carbon atom bearing the triflate group of the L-Ascorbic acid derivative allowed the synthesis the corresponding diastereomeric bicyclic amino acid **4.13**, wich has the carboxy group in the 2-*exo* configuration. These two new bicyclic Proline analogues may thus find application in peptidomimetic research, and, in particular, are suited for solid-phase organic and peptide synthesis by the Fmoc-protocol.

Chapter

5

Diversity-Oriented Synthesis of Morpholine-based scaffolds*

In the field of medicinal chemistry the synthesis of cyclic amino acids have attracted considerable interest, particularly for the peptidomimetic applications.[5] Secondary cyclic amino acids have been extensively used in biomedical research, and their insertion in biologically active peptides has been documented in the course of the years. In particular, the morpholine ring is found in numerous bioactive molecules, such as inhibitors of TACE,[52] of MMP and TNF, and within the structure of the potent VLA-4 antagonist.[53] Moreover, morpholine has been successfully inserted in the heterocyclic structure of tricyclic benzodiazepines,[54] of 6-methylidene-penem as β-lactamase inhibitors[55] of β-carbolines as IKK-2 inhibitors, of 6,8-fused bicyclic peptidomimetics as interleukin-1β converting enzyme inhibitors,[56] and in the structure of benzoxazepines as stimulators of AMPA receptor, which demonstrates the high interest in the biomedical field towards this heterocycle and the molecules containing it.

* Guarna, A.; Trabocchi, A.; Menchi, G.; Lalli, C.; Sladojevich, F.; Cini, N. Heterocyclic compounds containing the morpholine nucleus their preparation and use. **WO2008/129004, October 30th 2008.**

[52] J. I. Levin, J. M. Chen, L. M. Laakso, M. Du, X. Du, A. M. Venkatesan, V. Sandanayaka, A. Zask, J. Xu, W. Xu, Y. Zhang, J. S. Skotnicki *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4345-4349.

[53] J. Chiba, N. Machinaga, T. Takashi, A. Ejima, G. Takayama, M. Yokoyama, A. Nakayama, J. J. Baldwin, E. McDonald, K. W. Saionz, R. Swanson, Z. Hussain, A. Wong *Bioorg. Med. Chem. Lett.* **2005**, *15*, 41-45.

[54] J. M. Matthews, A. B. Dyatkin, M. Evangelisto, D. A. Gauthier, L. R. Hecker, W. J. Hoekstra, F. Liu, B. L. Poulter, K. L. Sorgi, B. E. Maryanoff *Tetrahedron: Asymmetry* **2004**, *15*, 1259-1267.

[55] A. M. Venkatesan, A. Agarwal, T. Abe, H. Ushirogochi, I. Yamamura, M. Ado, T. Tsuyoshi, O. Dos Santos, Y. Gu, F. -W. Sum, Z. Li, G. Francisco, Y. –I. Lin, P. J. Petersen, Y. Yang, T. Kumagai, W. J. Weiss, D. M. Shlaes, J. R. Knox, T. S. Mansour *J. Med. Chem.* **2006**, *49*, 4623-4637.

[56] S. V. O'Neil, Y. Wang, M. C. Laufersweiler, K. A. Oppong, D. L. Soper, J. A. Wos, C. D. Ellis, M.W. Baize, G. K. Bosch, A. N. Fancher, W. Lu, M. K. Suchanek, R. L. Wang, B. De, T. P. Demuth *Bioorg. Med. Chem. Lett.* **2005**, *15*, 5434-5438.

The scope of this project is to obtain morpholine scaffolds from simple building blocks like sugars and amino acids derivatives according with the principles of the Diversity-Oriented Synthesis (Figure 5.1).

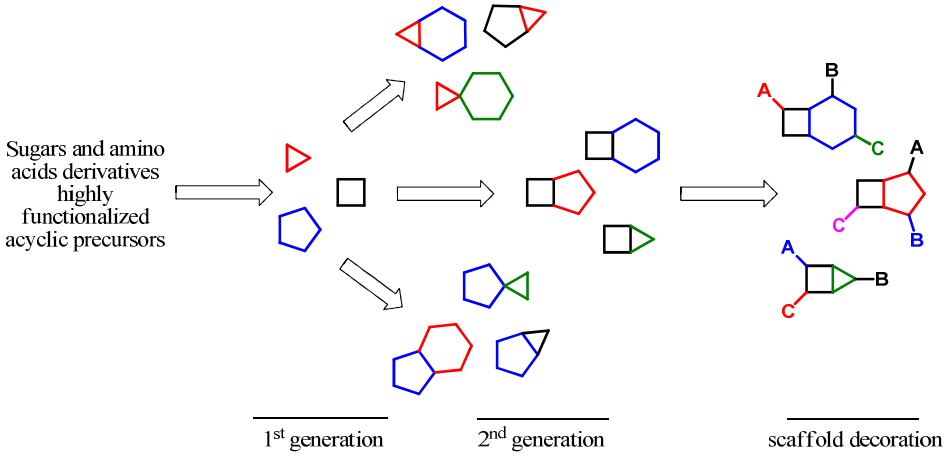
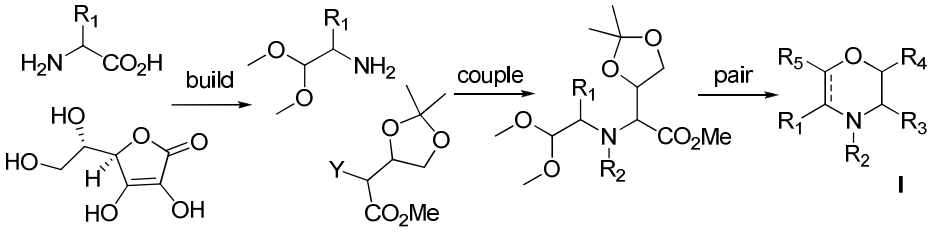


Figure 5.1. *'Diversity-oriented synthesis involves the deliberate, simultaneous and efficient synthesis of more than one target compound in a diversity-driven approach to answer a complex problem' (David R. Spring)*[57]

5.1. Heterocyclic compounds containing morpholine nucleus

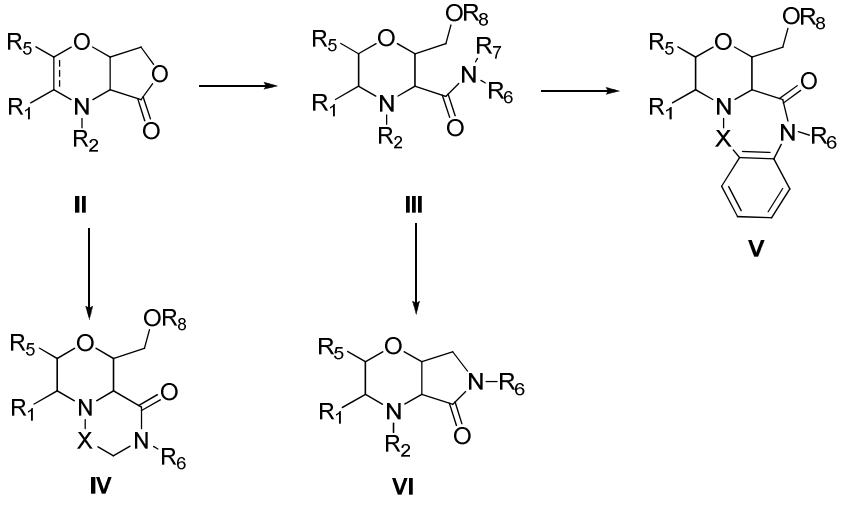
Our attention is focused on the generation of morpholine-based heterocyclic scaffolds, using building blocks selected from the chiral pool, taking into account the existence of two functionalities acting as nucleophile and electrophile. The compounds of general formula **I** can be achieved from a two steps synthetic process using precursors easily obtainable as enantiopure compounds (Scheme 5.1). In particular the building blocks taken into account are amino acids and the L-Ascorbic acid derivatives, this already described in Chapter 4.

[57] D. R. Spring *Org. Biomol. Chem.* **2003**, *1*, 3867.



Scheme 5.1. Two-steps synthetic process for the synthesis of morpholine scaffolds.

Such new type of compounds, cyclic or bicyclic in structure, can be successively functionalized in different positions and transformed in other compounds containing the morpholine ring through subsequent reactions, as known in literature, thus functioning as core structure for the generation of a wide array of new compounds with high level of molecular diversity (Scheme 5.2).



Scheme 5.2. Structures obtained by manipulations of the morpholine core.

We are interested in α-amino aldehydes derived from natural amino acids as nucleophiles, and L-Ascorbic acid-derived protected threonate derivative as electrophile. In the build phase the amino acids and sugar derivatives are obtained from natural products. In particular the amino acids derivatives are synthesized by reduction of the carboxylic group to aldehyde and successively protection as dimethylacetals **A**. The sugar moiety is the threonate derivative **B**, obtained as reported[49,50] from L-Ascorbic acid in three steps (see Chapter 4) (Figure 5.2). While for the amino acid moiety we have taken into account only natural amino acids of L-serie, in the case of

the L-Ascorbic acid derivatives we have synthesized two diastereoisomers (a*R*,b*S*) and (a*S*,b*S*) respectively (see Chapter 4) (Figure 5.2).

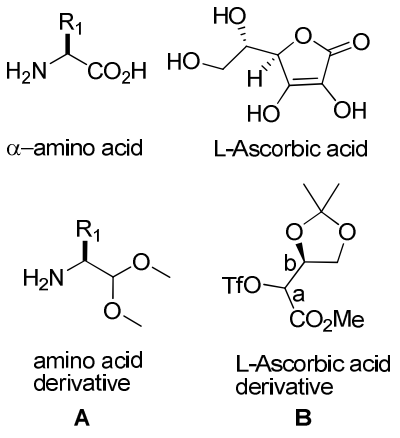


Figure 5.2. Selected building blocks for the coupling step.

In the coupling phase we allowed the electrophile **B** bearing the hydroxyl group to react with the nucleophile **A** bearing the amine. Building block **B** was coupled with α-amino acid-derived **A** *via* S_N2 to give the corresponding adduct **C** as the highly functionalized acyclic precursor (Figure 5.3).

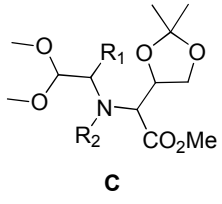
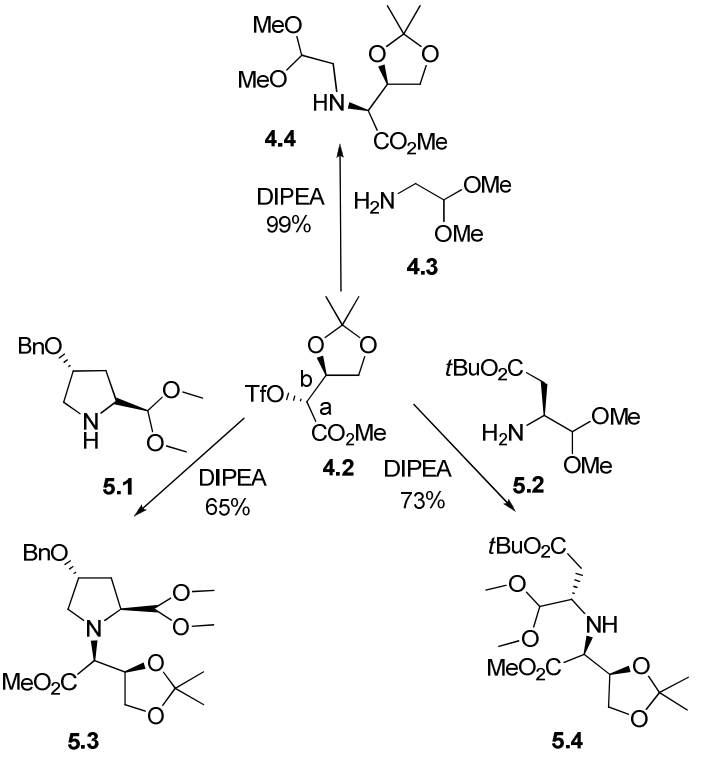


Figure 5.3. Acyclic precursor for the cyclization step.

Compound **B** with (a*R*,b*S*) configuration (molecule **4.2** see Chapter 4) has been coupled by nucleophilic substitution with:

- the Glycine derived aminoacetaldehyde dimethylacetal **4.3** to give the acyclic precursor **4.4** (see Chapter 4)[58] (Scheme 5.3).
- the 4-OH-Proline-derived acetal precursor **5.1** to give the acyclic precursor **5.3** (Scheme 5.3).
- the Asp-(O*t*-Bu)-derived acetal precursor **5.2** to give the acyclic precursor **5.4** (Scheme 5.3).

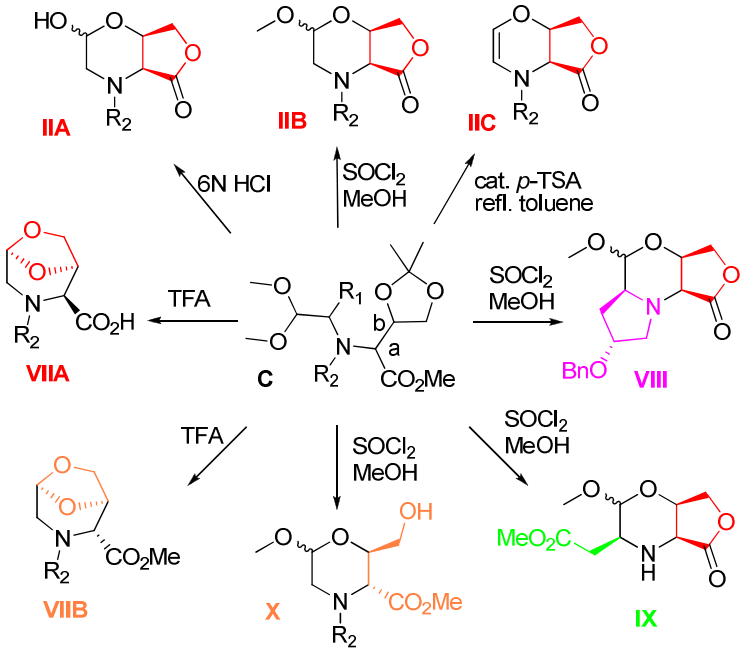
[58] C. Lalli, A. Trabocchi, F. Guarna, C. Mannino, A. Guarna Synthesis **2006**, 18, 3122–3126.



Scheme 5.3. Selected acyclic precursors for the cyclization step obtained with: Glycine derived aminoacetaldehyde dimethylacetal, 4-OH-Proline-derived acetal, Asp-(O*t*-Bu)-derived acetal.

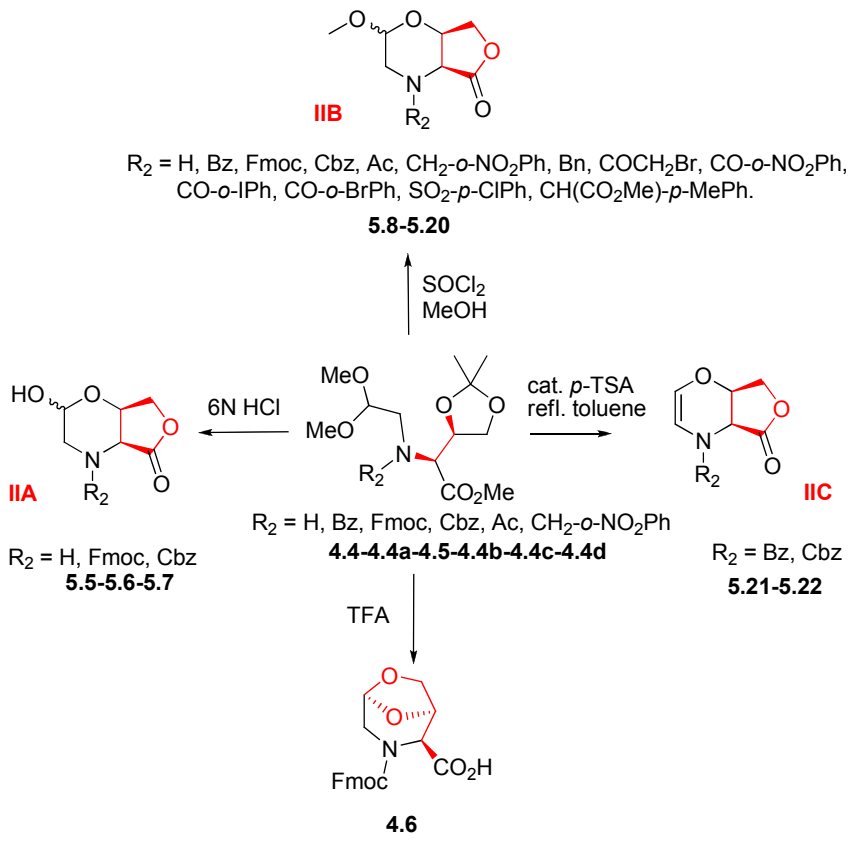
5.1.1. 1st generation scaffolds

Intramolecular reactions provide the cyclization of intermediate **C** to the morpholine scaffold to give the first degree of skeletal diversity around the morpholine nucleus (Scheme 5.4).



Scheme 5.4. 1st generation scaffolds: general structures.

The intermediate **4.4** could be derivatized at the nitrogen atom and cyclized, or could be directly cyclized and then functionalized at the nitrogen atom, to give hemiacetal **IIA** or acetal **IIB** with 6M HCl at 80°C or $SOCl_2$ in MeOH respectively (Scheme 5.5). Acylation of the nitrogen atom of the acyclic precursor, followed by cyclization in refluxing toluene with a catalytic amount of *p*-TSA resulted in the bicyclic oxazine **IIC**, due to the contemporaneous cyclization and elimination of a molecule of MeOH (Scheme 5.5). Finally the cyclization in TFA gives the bicyclic scaffold **4.6** (see chapter 4)[58] (Scheme 5.5).



Scheme 5.5. 1st generation derived from the coupling of compound **B** with (a*R*,b*S*) configuration, with Gly derivative.

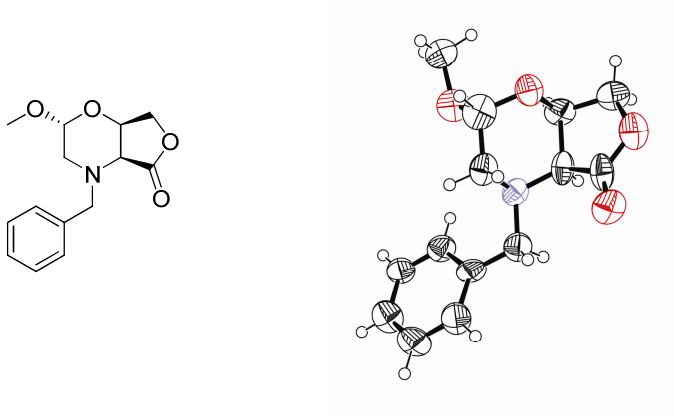
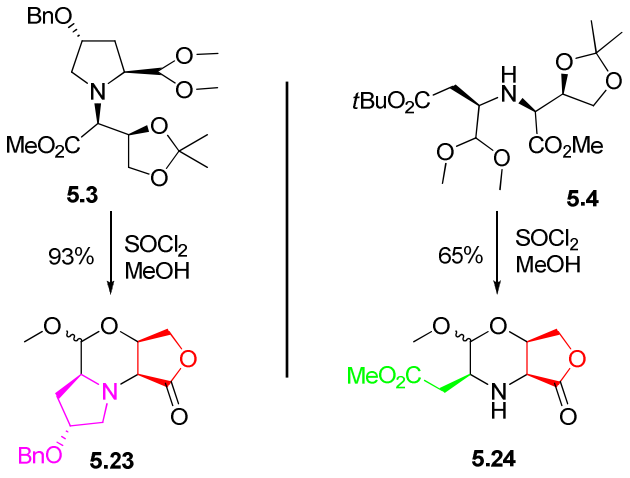


Figure 5.4. X-ray structure of compound **5.14** (**IIB** with R=Bn) with thermal ellipsoids at 50% probability. For Tables see experimental section chapter 8.5.

The cyclization of **5.3** and **5.4** with $SOCl_2$ in MeOH resulted respectively in the tricyclic compound **5.23** and in the bicyclic molecule **5.24**, having the side chain group as a methyl ester (Scheme 5.6).



Scheme 5.6. 1st generation scaffolds: morpholine-lactones derived from 4-OH-Pro and Asp-(O*t*-Bu).

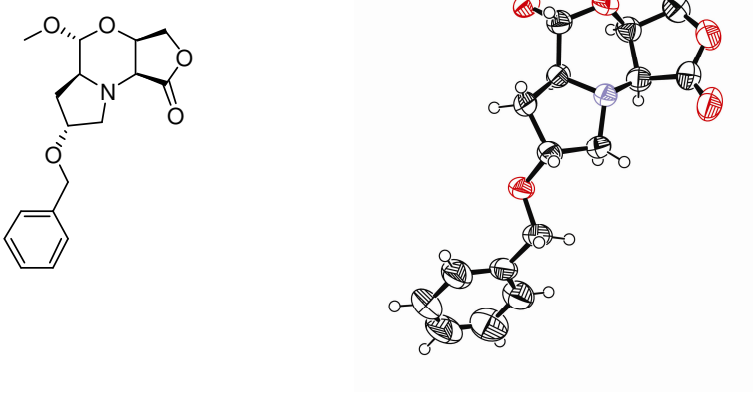
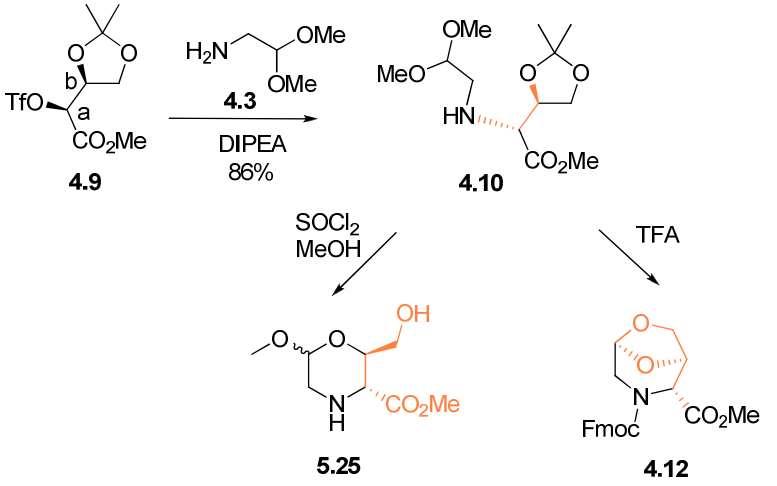


Figure 5.5. X-ray structure of compound **5.23** with thermal ellipsoids at 50% probability. For Tables see experimental section chapter 8.5.

Investigation by X-ray crystallography analysis of compounds **5.14** and **5.23** revealed the propensity of α anomer to crystallize.

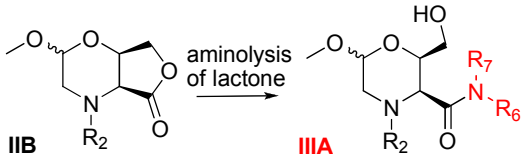
Interestingly, by using building block **B** with (a*S*,b*S*) configuration (molecule **4.9** see Chapter 4) for the coupling with Glycine derived aminoacetaldehyde dimethylacetal **4.3**, different 1st generation scaffolds were achieved (Scheme 5.7). Compound **5.25** was obtained upon treatment of **4.10** with $SOCl_2$ in MeOH, whereas reaction of the *N*-protected acyclic adduct in pure TFA resulted in the corresponding bicyclic scaffold **4.12**, as also previously reported for the compound **4.6** (see chapter 4)[58] (Scheme 5.7).



Scheme 5.7. Different 1st generation derived from the coupling of compound **B** with inversion of configuration at C-2, (a*S*,b*S*) configuration, with Gly derivative.

5.1.2. 2nd generation scaffolds

Lactone aminolysis of molecules of structure **IIB** with different amines using $LiNTf_2$ as catalyst[59] (see chapter 5), gave 2nd generation compounds of structure **IIIA** (Scheme 5.8).



Scheme 5.8. 2nd generation scaffolds: aminolysis of morpholine-lactones.

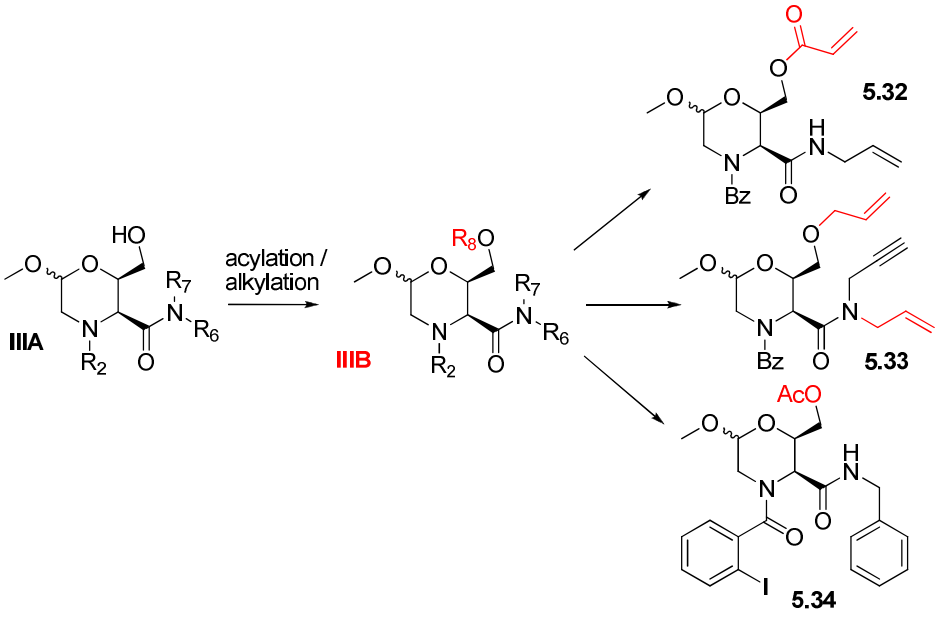
The results obtained for the aminolysis of the morpholine-lactones are reported in Table 5.1.

Entry	R_2	R_6	R_7	Yield(%)	Compound
1	Bz	H	CH_2Ph	93	**5.26**
2	Bz	H	$CH_2CH{=}CH_2$	97	**5.27**
3	Bz	H	$CH_2C{\equiv}CH$	93	**5.28**
4	Bz	H	$-CHCH_2CH_2$	86	**5.29**
5	Bz	$-CH_2(CH_2)_3CH_2-$		85	**5.30**
6	CO-*o*-IPh	H	CH_2Ph	97	**5.31**

Table 5.1. Aminolysis of the morpholine-lactones.

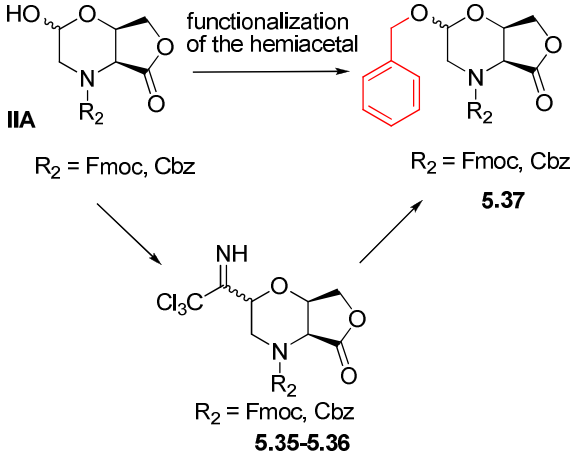
The morpholine core could be further decorated, in fact the common nucleophilic hydroxy group makes the structures obtained, substrates for a third appending process, the alkylation at the hydroxyl group or the acylation with a collection of carboxylic acid building blocks, to give structures **IIIB** (Scheme 5.9).

[59] C. Lalli, A. Trabocchi, G. Menchi, A. Guarna *Synlett* **2008**, *2*, 189-192.



Scheme 5.9. Further manipulations: scaffold decoration.

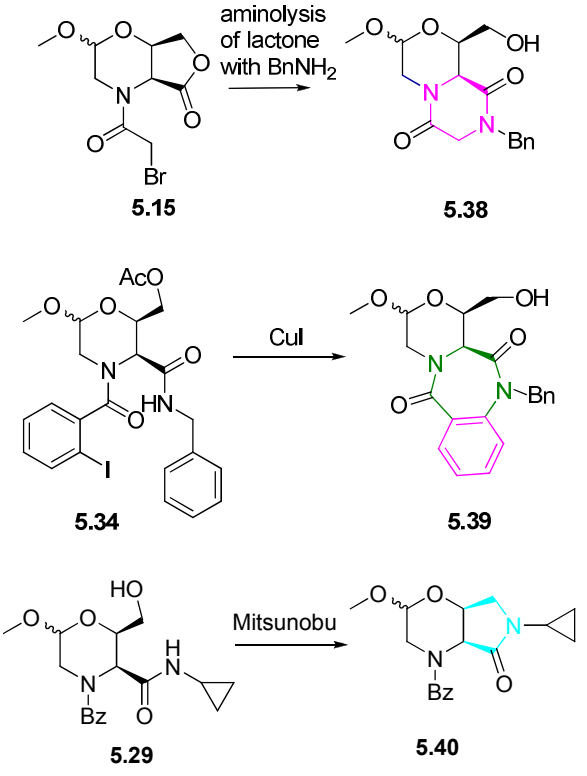
The possibility of a different 2nd generation from the hemiacetal **IIA** was also explored and the corresponding benzyl derivatives through trichloroacetimidate intermediates were obtained (Scheme 5.10). This kind of reactivity demonstrates the possibility of loading on resin of these morpholine structures, that are suited for solid-phase organic and peptide synthesis by the Fmoc-protocol.



Scheme 5.10. 2nd generation scaffolds: manipulation of the morpholine-hemiacetal.

5.1.3. 3rd generation scaffolds

The 3rd generation is obtained by manipulation of the 2nd one, in particular the processes involved are again intramolecular reactions that provide other cycles to be closed.
When **IIB** was acylated with $BrCH_2COBr$, aminolysis with benzylamine gave directly **5.38** (Scheme 5.11); acylation with *o*-I-benzoyl chloride provided the intermediate for Cu-catalyzed cyclization to give tricyclic **5.39** (Scheme 5.11) and Mitsunobu reaction gave tricyclic lactam **5.40** (Scheme 5.11).



Scheme 5.11. Further cyclizations: 3rd generation.

5.1.4. Summary of the structures

The structures reported in Figure 5.6 are obtained with the strategy discussed (see experimental section chapter 8.5).

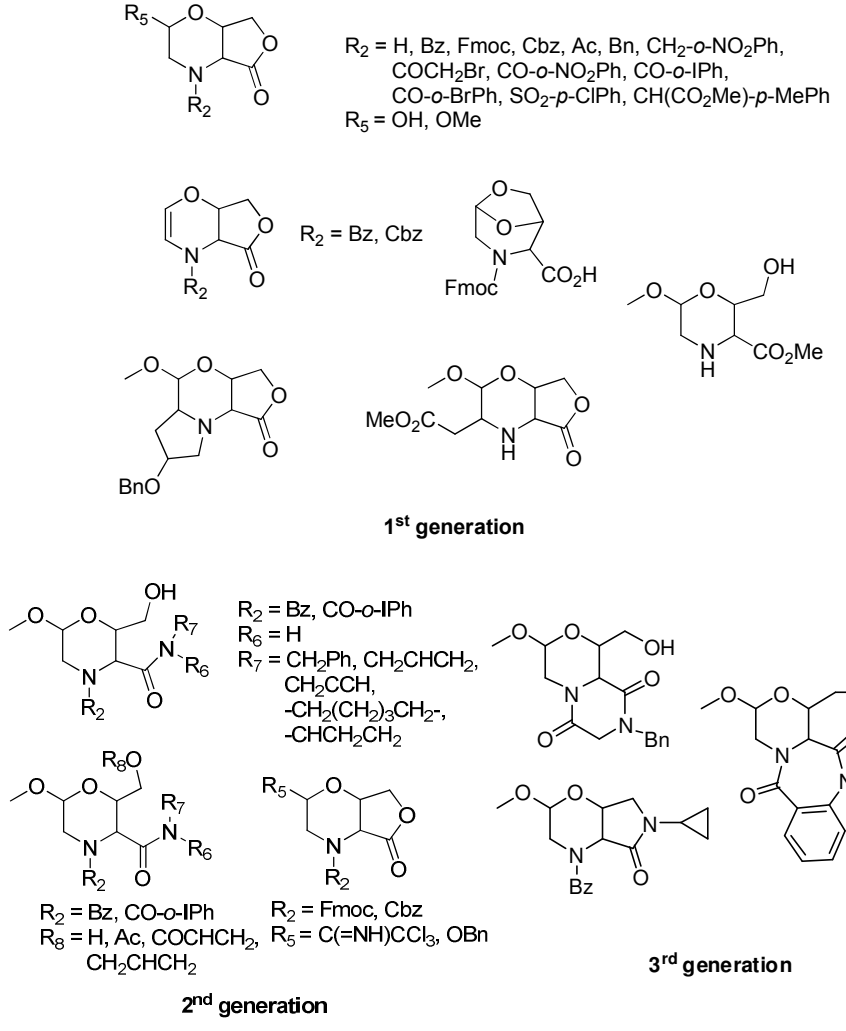


Figure 5.6. Morpholine-based scaffolds obtained with complexity-generating synthesis.

In conclusion DOS chemistry is a powerful concept for the development of new highly diverse chemical entities. We applied this approach in the generation of morpholine-containing molecular scaffolds for peptidomimetic chemistry by using bifunctional building blocks deriving from α-amino acids and L-Ascorbic acid in a pairwise approach, followed by subsequent generation of complex bi- and tricyclic molecules.

Chapter 6

LiNTf$_2$-Catalyzed aminolysis of lactones with stoichiometric quantities of amines*

Lactone aminolysis is a common transformation which allows direct conversion to the corresponding amides, and it is a highly attractive transformation in modern organic synthesis, although it generally requires harsh conditions,[60] which are limiting factors expecially in scale-up procedures. Moreover, excess of amine is generally used to guarantee proper conversion and reaction rate, making the direct aminolysis not feasible especially when the amines are not readily available.[61] Several methods have been reported in the literature for facilitating the reaction of lactones with amines,[62] and the use of the Weinreb reagents coming from the reaction of trimethylaluminium with an amine, or the use of 2-hydroxypyridine have been considered as being the most popular.[63] Recently, Shimizu reported on the use of Me_2AlCl–HN(OMe)Me as an

* C. Lalli, A. Trabocchi, G. Menchi, A. Guarna Synlett **2008**, 2, 189-192.

[60] M. J. Robins, S. Sarker, M. Xie, W. Zhang, M. A. Peterson *Tetrahedron Lett*. **1996**, *37*, 3921–3924

[61] (a) J. H. Musser, P. F. VonVoightlander, J. Szmuszkovicz *Heterocycles* **1986**, *24*, 155–159. (b)G. Blay, L. Cardona, B. Garcia, C. L. Garcia, J. Pedro *Tetrahedron Lett*. **1994**, *35*, 931–934.

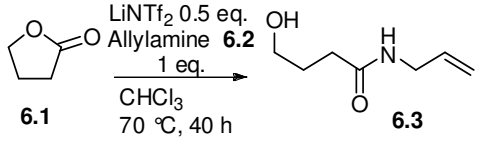
[62] (a) A. Basha, M. Lipton, S. M. Weinreb *Tetrahedron Lett*. **1977**, 4171–4174. (b) J. I. Levin, E. Turos, S. M. Weinreb *Synth. Commun*. **1982**, *12*, 989–993. (c) M. F. Lipton, A. Basha, S. M. Weinreb *Org. Synth*. **1979**, *59*, 49. (d) D. R. Sidler, T. C. Lovelace, J. M. McNamara, P. J. Reider *J. Org. Chem*. **1994**, *59*, 1231–1233. (e) W. M. Liu, D. D. Xu, O. Repic, T. J. Blacklock *Tetrahedron Lett*. **2001**, *42*, 2439–2441. (f) J. M. Williams, R. B. Jobson, N. Yasuda, G. Marchesini, U. H. Dolling, E. J. J. Grabowski *Tetrahedron Lett*. **1995**, *36*, 5461– 5464. (g) K. Iseki, D. Asada, Y. Kuroki *J. Fluorine Chem*. **1999**, *97*, 85–89.

[63] See for example: (a) Jr. J. Rebek, R. Beerli *Tetrahedron Lett*. **1995**, *36*, 1813–1816. (b) M. Shibasaki, S. Nakamura *Tetrahedron Lett*. **1994**, *35*, 4145–4148. (c) D. A. Evans, S. W. Kaldor, T. K. Jones, J. Clardy, T. J. Stout *J. Am. Chem. Soc*. **1990**, *112*, 7001–7031. (d) R. S. Garigipati, D. M. Tschaen, S. M. Weinreb *J. Am. Chem. Soc*. **1985**, *107*, 7790–7792.

efficient amidating agent.[64] As lactone aminolysis is commonly carried out in multi-step synthesis, there is an interest for versatile activators which could be of great benefit, expecially where stoichiometric amounts of valuable building blocks have to be used.

Recently, Cossy and coworkers reported the application of $LiNTf_2$ as an efficient activator towards regioselective ring opening of epoxides with a variety of nucleophiles including amines.[65] This process was adopted by our group as a tool to synthesize intermediate compounds in the gram scale.[28] We reasoned that a similar effect could exist with respect to oxygen atoms of lactones, as a consequence of activation of the carbonyl group towards nucleophilic aminolysis, thus opening the route towards a general and facile method for the ring opening of lactones of different ring size with amines belonging to different classes.

Specifically, as a part of a program towards the development of heterocycles carrying of chemical diversity, we were interested in finding an easy and efficient method for synthesizing molecules through the aminolysis of lactones,[66] and in particular we were interested in achieving the reaction using stoichiometric quantities of the reactants (see chapter 5). After the initial observation that the addition of sub-stoichiometric quantities of $LiNTf_2$ could catalyze the aminolysis of γ-butyrolactone **6.1**, we started investigating the best conditions to achieve optimal conversion using allylamine **6.2** (Scheme 6.1), specifically by tuning the solvent and the temperature, and monitoring the reaction time until completion.



Scheme 6.1. Model reaction with γ-butyrolactone and allylamine.

Among the three main solvent systems tested, namely THF, EtOH and chloroform, the corresponding control experiments were also carried out at refluxing temperatures, to have reference data about the yields without $LiNTf_2$ (Table 6.1, entries 1-4, respectively). Reactions conducted in EtOH at 80°C in a sealed vial showed a 43% and 62% yield after 17 and 40 h, respectively (Table 6.1), whereas THF and chloroform produced the title amido alcohol in 37% and 52% yield, respectively. Addition of $LiNTf_2$ in THF did not yield any improvement (entry 5), as the reaction outcome dropped to 12%, indicating this solvent is not compatible with the lithium

[64] (a) T. Shimizu, K. Osako, T. Nakata *Tetrahedron Lett.* **1997**, 38, 2685–2688. (b) N. Murakami, T. Nakajima, M. Kobayashi *Tetrahedron Lett.* **2001**, *42*, 1941–1943.

[65] J. Cossy, V. Bellosta, C. Hamoir, J. –R. Desmurs *Tetrahedron Lett.* **2002**, *43*, 7083–7086.

[66] A. Guarna, A. Trabocchi, G. Menchi, C. Lalli, F. Sladojevich, N. Cini Heterocyclic compounds containing the morpholine nucleus their preparation and use. **WO2008/129004, October 30th 2008**.

salt-catalyzed aminolysis. The reaction in EtOH and in the presence of $LiNTf_2$ indicated a small effect of the catalyst, as a similar yield as the control experiment was achieved at lower temperature (Table 6.1, entry 6 compared to entry 2). We next turned our attention to halogenated solvents, as these were reported being the systems of choice in the aminolysis of epoxides,[65] probably due to their low coordinating effect towards the catalyst, thus resulting in a lower interference in the process. Dichloromethane was tested at different temperatures (entries 7-9), giving at 40°C yields similar to EtOH, with no additional improvement by prolonging the reaction time from 17 to 72 h (entries 8-9). Also, the addition of 10% 1,1,1,3,3,3-hexafluoroisopropanol produced the same result as of pure dichloromethane, indicating no beneficial effect to the reaction (entry 10). These preliminary experiments suggested the solvent to play a role in the reaction, and that an aprotic solvent with a high polar character might allow the lithium salt to work optimally in activating the carbonyl group towards the ring opening aminolysis. In fact, chloroform showed a marked improvement with respect to dichloromethane, as when the reaction was carried out at refluxing temperature, the yield was raised to 83% (entry 12). Finally, the best conditions were achieved by prolonged reaction of γ-butyrolactone and allylamine in stoichiometric amounts in chloroform at 85°C for 40 h, giving a clean product in quantitative yield (entry 13). Further attempts to lower both the temperature and the catalyst load resulted in lower yield (entry 14-16). Whenever incomplete reaction was observed, the crude mixture contained only the starting material and the title product, without significant amount of degraded material.

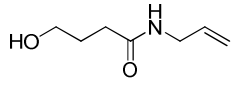
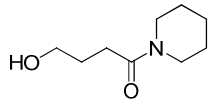
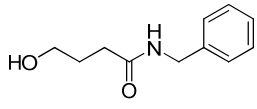
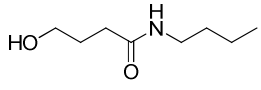
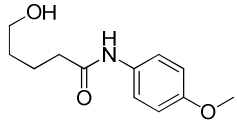
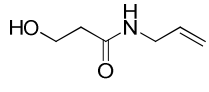
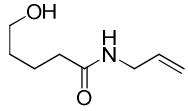
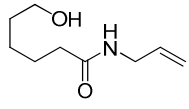
Entry	Solvent	T(°C)	t(h)	$LiNTf_2$(eq)	Yield(%)
1	THF	85[a]	24	0	37
2	EtOH	95[a]	17	0	43
3	EtOH	95[a]	40	0	62
4	$CHCl_3$	85[a]	40	0	52
5	THF	50	17	0.5	12
6	EtOH	50	17	0.5	62
7	CH_2Cl_2	20	17	0.5	33
8	CH_2Cl_2	40	17	0.5	58
9	CH_2Cl_2	40	72	0.5	60
10	CH_2Cl_2-HFIP(9:1)	20	17	0.5	38
11	$ClCH_2CH_2Cl$	20	17	0.5	48
12	$CHCl_3$	85[a]	17	0.5	83
13	**$CHCl_3$**	**85[a]**	**40**	**0.5**	**99**
14	$CHCl_3$	20	17	0.5	43
15	$CHCl_3$	85[a]	40	0.2	62
16	$CHCl_3$	85[a]	40	0.1	60

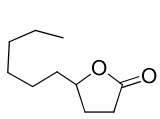
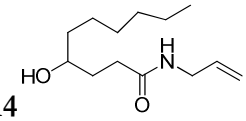
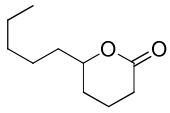
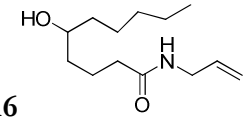
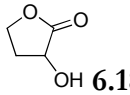
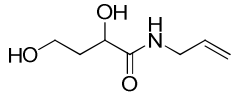
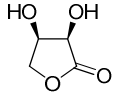
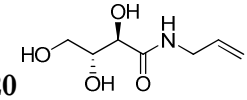
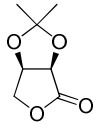
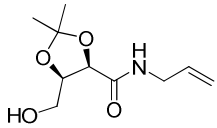
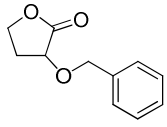
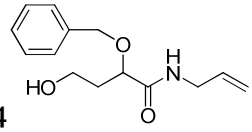
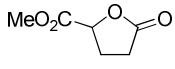
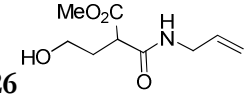
[a] Oil-bath temperature corresponding to reflux condition in the sealed vial.

Table 6.1. Aminolysis of γ-butyrolactone with 1 eq of allylamine in a sealed vial.

As a hypothesized mechanism relating to the activating role of $LiNTf_2$ towards lactone aminolysis, the coordinating effect of the lactone carbonyl group was considered. Thus, the interaction of the strong electron withrawing lithium salt with the C=O bond would increase the electrophilic character of the carbonyl carbon atom towards nucleophilic addition of the amine, resulting in higher yield to the corresponding hydroxy amide.
We next investigated the generality of the process by performing the reaction with lactones varying in ring-size and in substitution pattern, and also using amines of different steric and nucleophilic character. Ring-opening of γ-butyrolactone was explored with secondary amines, and while piperidine gave quantitative yield, the bulky diisopropylamine did not yield any product, suggesting the relevance of steric hindrance (Table 6.2, entries 2-3). Also, the nucleophilic character of the amine influenced the reaction conversion, as benzylamine and butylamine gave 100% yield, whereas aromatic *p*-anisidine gave the adduct in only 11% yield and the corresponding lactam resulting from subsequent cyclization of the hydroxy amide in 12% yield (entry 6).
Surveying ring size of lactones indicated 4-6 membered rings to proceed in almost quantitative yields (entries 7-8), and also ε-caprolactone reacted under these conditions to furnish the corresponding product in 53% yield

(Table 6.2, entry 9). The presence of unprotected functional groups, and in particular of hydroxylic functions, proved to influence negatively the outcome of the reaction (entries 12-13), probably by interfering with the lithium salt. In particular, unprotected erythronolactone **6.20** failed to react, giving the adduct in only 6% yield (entry 13), whereas the corresponding isopropylidene derivative **6.22**, having the two hydroxyls embedded in the dioxolane ring, reacted cleanly to produce the adduct in 93% yield (entry 14). Similarly, α-benzyloxy-γ-butyrolactone **6.24** reacted quantitatively (entry 15), compared to the corresponding unprotected α-hydroxy-γ-butyrolactone **6.18**, which furnished the amido alcohol in 46% yield (entry 12), thus corroborating the importance of having protic functional groups protected. In all cases, the amides resulting from aminolysis of the corresponding lactones where easily purified by standard flash chromatography.

Entry	Amine	Lactone	Product	Yield(%)
1	allylamine **6.2**	 **6.1**	 **6.3**	99
2	piperidine	**6.1**	 **6.4**	100
3	diisopropyl-amine	**6.1**	-	-
4	benzylamine	**6.1**	 **6.5**	100
5	butylamine	**6.1**	 **6.6**	99
6	*p*-methoxy-aniline	**6.1**	 **6.7**	11[a]
7	**6.2**	 **6.8**	 **6.9**	100
8	**6.2**	 **6.10**	 **6.11**	95
9	**6.2**	 **6.12**	 **6.13**	53

10	**6.2**		**6.14**		**6.15**	80
11	**6.2**		**6.16**		**6.17**	64
12	**6.2**		**6.18**		**6.19**	46
13	**6.2**		**6.20**		**6.21**	6
14	**6.2**		**6.22**		**6.23**	93
15	**6.2**		**6.24**		**6.25**	99
16	**6.2**		**6.26**		**6.27**	80

[a] The corresponding butyrolactam **6.7bis** was also obtained in 12% yield.

Table 6.2. Various Lactones and Amines tested.

Finally, preliminary investigations indicated this catalytic system to work with even more inactivated carboxylic esters, as the amidation of Boc-Ala-OMe with allylamine in the presence of 0.5 eq of $LiNTf_2$ under standard conditions furnished the corresponding Boc-alanine allylamide in 52%, whereas only starting reagents were obtained in the corresponding control experiment without the lithium salt. Similar results were obtained for the synthesis of protected hydroxamic acids from lactones, as the reaction of γ-butyrolactone with *O*-benzylhydroxylamine resulted in 45% yields under standard conditions compared to 0% of the control experiment, thus indicating the possibility of preparing *N*-hydroxamic acids from lactones by this method.

In conclusion, we report a mild and effective method for the aminolysis of lactones with stoichiometric quantities of amines, which consists on the use of $LiNTf_2$ as an activator of the carbonyl function of the lactone. The method was developed using chloroform as solvent, and the generality of the reaction was demonstrated with selected amines and lactones, indicating the importance of avoiding steric hindrance and of the protection of protic functional groups for optimal conversions. The method was also tested for the reaction of an allylamine with the methyl ester of Boc-alanine, and for the lactone aminolysis of γ-butyrolactone with protected hydroxylamine, indicating the possibility of a more general application of $LiNTf_2$-catalyzed reactions on lactones and esters.

Chapter

7

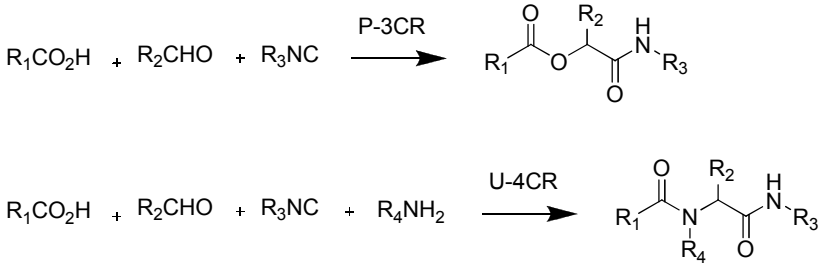
Modulating the reactivity of α-Isocyanoacetates: novel Four-Component Reaction for heterocyclic scaffolds synthesis

The reactions involving more than two reagents in a one-pot process to give a product incorporating the majority of the atoms of the reactants are called MultiComponent Reactions (MCRs). The MCRs are powerful processes to give molecular complexity and to generate more than two chemical bonds, with the advantage of selectivity, convergence and atom economy. The starting materials are generally commercially available or simple to synthesize. The synthesis of α-amino acid *via* α-aminonitrile developed by Strecker in 1850 is considered the first multicomponent reaction.[67] Then the synthesis of heterocycles were developed by Hantzsch[68] and a lot of examples are known in literature until the first four-component reaction to give access to natural products.[69]

The most employed MCR involves an isonitrile (IMCR, Isocyanide-based MultiComponent Reaction) and this is due to the particular reactivity of the isonitrile able to react with the nucleophiles and the electrophiles. The first multicomponent reaction involving an isonitrile was developed by Passerini in 1921,[70] then Ugi described the most important four-component reaction

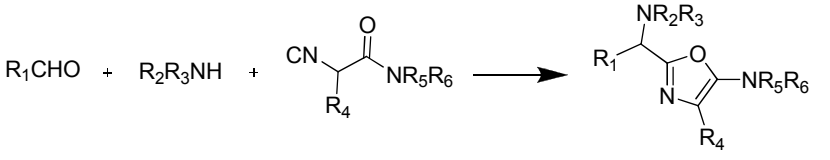
[67] (a) A. Strecker *Justus Liebig Ann. Chem.* **1850**, *75*, 27. (b) A. Strecker *Justus Liebig Ann. Chem.* **1850**, *91*, 349.
[68] (a) A. Hantzsch *Justus Liebig Ann. Chem.* **1882**, *215*, 1. (b) A. Hantzsch *Ber.Dtsch. Chem. Ges.* **1890**, *23*, 1474.
[69] (a) H. T. Bucherer, W. Steiner *J. Prakt. Chem.* **1934**, *140*, 24.
[70] (a) M. Passerini *Gazz. Chim. Ital.* **1921**, *51*, 126. (b) M. Passerini *Gazz. Chim. Ital.* **1921**, *51*, 181. (c) M. Passerini *Gazz. Chim. Ital.* **1922**, *52*, 432.

involving an amine, an aldehyde, a carboxylic acid and an isonitrile[71] (Scheme 7.1).



Scheme 7.1. The three-component Passerini reaction (P-3CR) and the four-component Ugi reaction (U-4CR) involving isonitriles.

Recently a new multicomponent synthesis of 5-aminooxazoles has been reported using an aldehyde, an amine and an α-isocyanoacetamide[72] (Scheme 7.2).



Scheme 7.2. Three-component synthesis of 5-aminooxazoles with an α-isocyanoacetamide.

As has been demonstrated the interesting property of these isonitriles consists in the acidity of the α-proton, due to electron-withdrawing group in α position like an ester or a nitrile. The chemistry of methyl α-isocyanoacetate[73] was investigated thoroughly in the 1970s, mainly by the research groups of Schllkopf and Matsumoto.[74,75,76] By taking advantage of

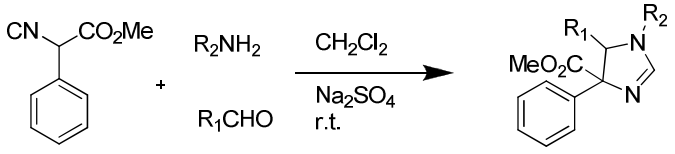
[71] (a) I. Ugi, R. Meyer *Angew. Chem.* **1958**, *70*, 702. (b) I. Ugi, R. Meyer *Chem. Ber.* **1960**, 93, 239. (c) I. Ugi, R. Meyer *Angew. Chem.* **1959**, *71*, 386. (d) I. Ugi, C. Steinbruckner *Angew. Chem.* **1960**, *72*, 267.

[72] (a) X. Sun, P. Janvier, G. Zhao, H. Bienayme, J. Zhu *J. Org. Chem.* **2001**, *3*, 877. (b) X. Sun, P. Janvier, G. Zhao, H. Bienayme, J. Zhu *J. Am. Chem. Soc.* **2002**, *124*, 2560.

[73] (a) D. Hoppe *Angew. Chem.* **1974**, *86*, 878–893. (b) D. Hoppe *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 789–804. (c) U. Schllkopf *Angew. Chem.* **1977**, *89*, 351–360. (d) U. Schllkopf *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 339–348. (c) S. Marcaccini, T. Torroba *Org. Prep. Proced. Int.* **1993**, *25*, 141–208.

[74]For selected examples of metal-mediated C-H activation of α-isocyanoacetates for the synthesis of heterocycles, see: (a) T. Saegusa, Y. Ito, H. Kinoshita, S. Tomita *J. Org. Chem.* **1971**, *36*, 3316–3323. (b) H. Takaya, S. Kojima, S. Murahashi *Org. Lett.* **2001**, *3*, 421–424. (c) Y. Ito, M. Sawamura, T. Hayashi *J. Am. Chem. Soc.* **1986**, *108*, 6405–6406. (d) A. Tongi, S. D. Pastor *J. Org. Chem.* **1990**, *55*, 1649–1664. (e) T. Hayashi, E. Kishi, V. A. Soloshonok, Y. Uozumi *Tetrahedron Lett.* **1996**, *37*, 4969–4972. (f) Y.-R. Lin, X.-T. Zhou, L.-X. Dai, J. Sun *J. Org. Chem.* **1997**, *62*, 1799–1803. (g) R. Grigg, M. I. Lansdell, M. Thornton-Pett *Tetrahedron* **1999**, *55*, 2025–2044. (h) S. Kamijo, C. Kanazawa, Y. Yamamoto *J. Am. Chem. Soc.* **2005**, *127*, 9260–9266. (i) C. Kanazawa, S. Kamijo, Y. Yamamoto *J. Am. Chem. Soc.* **2006**, *128*, 10662–10663.

the higher acidity of the α-phenyl-α-isocyanoacetate, Orru and co-workers recently developed an elegant three-component synthesis of imidazolines (Scheme 7.3).[75]



Scheme 7.3. Three-component synthesis of imidazolines described by Orru and co-workers.

The presence of the phenyl group is essential for this one-pot process. The phenyl group was thought to render the α CH position acidic enough to be deprotonated by a weak base. In general, the exploitation of the nucleophilicity of the α carbon atom and the electrophilicity of the divalent carbon atom of the isocyanide for the effective construction of C-C and C-N bonds characterized the known chemistry of α-isocyanoacetates.[73-76]
In connection with some project developed in Zhu group aimed at the development of novel multicomponent reactions[77,78] with functionalized isocyanides as a key component,[79,80,81] they became interested in the reactivity profile of hitherto unknown methyl α-(*p*-nitrophenyl)-α-isocyanoacetate (Scheme 7.4). The nitro group is strategically incorporated into the phenyl ring to render the α C-H bond even more acidic, so that it can be deprotonated by weaker bases. Whereas the ready formation of the carbanion is the key consideration in the development of the three-component reaction described by Orru and co-workers, we expected that

[75] (a) R. S. Bon, C. Hong, M. J. Bouma, R. F. Schmitz, F. J. J. De Kanter, M. Lutz, A. L. Spek, R. V. A. Orru *Org. Lett.* **2003**, *5*, 3759–3762. (b) R. S. Bon, B. Van Vliet, N. E. Sprenkels, R. F. Schmitz, F. J. J. De Kanter, C. V. Stevens, M. Swart, F. M. Bickelhaupt, M. B. Groen, R. V. A. Orru *J. Org. Chem.* **2005**, *70*, 3542–3553.

[76] For an alternative reaction pathway, see: M. Suzuki, K.-I. Nunami, T. Moriya, K. Matsumoto, N. Yoneda *J. Org. Chem.* **1978**, *43*, 4933–4935.

[77] For recent reviews, see: (a) C. Hulme, V. Gore *Curr. Med. Chem.* **2003**, *10*, 51–80. (b) R. V. A. Orru, M. De Greef *Synthesis* **2003**, 1471–1499. (c) A. Jacobi vonWangelin, H. Neumann, D. Gordes, S. Klaus, D. StrJbing, M. Beller *Chem. Eur. J.* **2003**, *9*, 4286–4294. (d) V. Nair, C. Rajesh, A. U. Vinod, S. Bindu, A. R. Sreekanth, J. S. Mathen, L. Balagopal *Acc. Chem. Res.* **2003**, *36*, 899–907. (e) J. Zhu *Eur. J. Org. Chem.* **2003**, 1133–1144. (f) G. Balme, E. Bossharth, N. Monteiro *Eur. J. Org. Chem.* **2003**, 4101–4111. (g) C. Simon, T. Constantieux, J. Rodriguez *Eur. J. Org. Chem.* **2004**, 4957–4980. (h) P. Tempest *Curr. Opin. Drug Discovery Dev.* **2005**, *8*, 776–788. (i) A. D mling *Chem. Rev.* **2006**, *106*, 17–89.

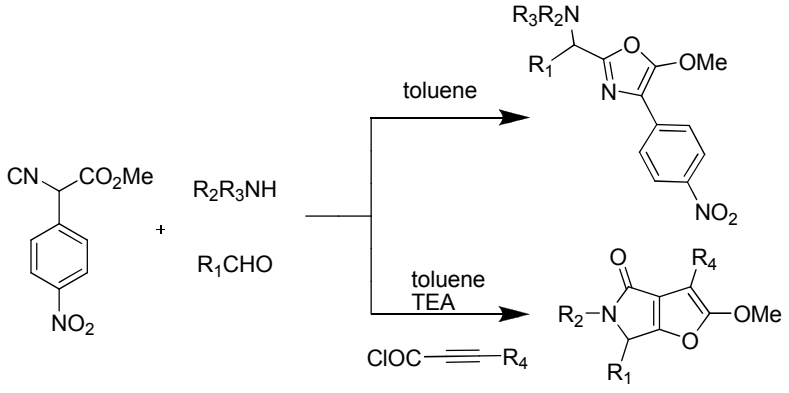
[78] For a monograph, see: Multicomponent Reactions (Eds.: J. Zhu, H. BienaymK), *Wiley-VCH*, Weinheim, **2005**.

[79] For α-isocyanoacetamide, see: (a) X. Sun, P. Janvier, G. Zhao, H. BienaymK, J. Zhu *Org. Lett.* **2001**, *3*, 877–880. (b) P. Janvier, X. Sun, H. BienaymK, J. Zhu *J. Am. Chem. Soc.* **2002**, *124*, 2560–2567. (c) P. Janvier, M. Bois-Choussy, H. BienaymK, J. Zhu *Angew. Chem.* **2003**, *115*, 835–838. (d) P. Janvier, M. Bois-Choussy, H. BienaymK, J. Zhu *Angew. Chem. Int. Ed.* **2003**, *42*, 811–814.

[80] For *ortho*-isocyanobenzamide, see: D. Bonne, M. Dekhane, J. Zhu *Org. Lett.* **2005**, *7*, 5285–5288.

[81] For α-isocyanoacetic acid, see: (a) D. Bonne, M. Dekhane, J. Zhu *Org. Lett.* **2004**, *6*, 4771–4774. (b) D. Bonne, M. Dekhane, J. Zhu *J. Am. Chem. Soc.* **2005**, *127*, 6926–6927.

the carbanion derived from the isocyanoacetate would display decreased nucleophilicity, as it is highly stabilized. Consequently, its reaction with a polar double bond, such as that of an imine, would be initiated by the nucleophilicity of the divalent carbon atom of the isocyanide and lead to different heterocycles.[82,83] The development of a three-component synthesis of 5-methoxyoxazoles and a four-component synthesis of furopyrrolones on the basis of the unique reactivity of methyl α-(*p*-nitrophenyl)-α-isocyanoacetate has been reported[84] (Scheme 7.4).



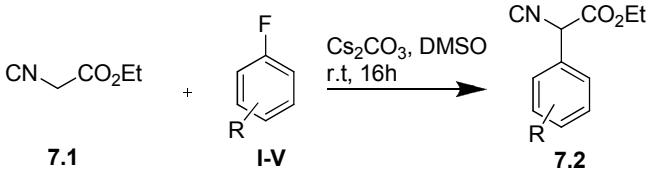
Scheme 7.4. Multicomponent synthesis of 5-methoxyoxazoles and furopyrrolones.

[82] (a) A. D mling, I. Ugi *Angew. Chem.* **2000**, *112*, 3300–3344. (b) A. D mling, I. Ugi *Angew. Chem. Int. Ed.* **2000**, *39*, 3168–3210.

[83] For recent innovative development of Ugi-type reactions, see: (a) L. El KaLm, L. Grimaud, J. Oble *Angew. Chem.* **2005**, *117*, 8175–8178 *Angew. Chem. Int. Ed.* **2005**, *44*, 7961–7964. (b) L. El KaLm, M. Gizolme, L. Grimaud, J. Oble *Org. Lett.* **2006**, *8*, 4019–4021. (c) G. B. Giovenzana, G. C. Tron, S. D. Paola, I. G. Menegotto, T. Pirali *Angew. Chem.* **2006**, *118*, 1117–1120. (d) G. B. Giovenzana, G. C. Tron, S. D. Paola, I. G. Menegotto, T. Pirali *Angew. Chem. Int. Ed.* **2006**, *45*, 1099–1102.

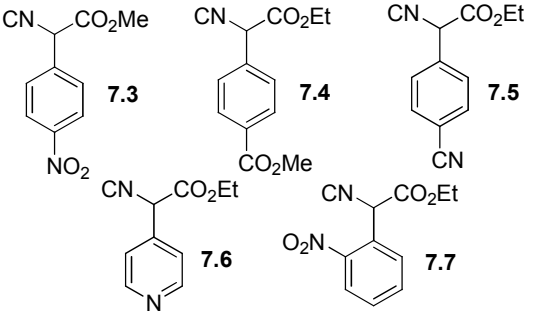
[84] D. Bonne, M. Dekhane, J. Zhu *Angew. Chem.Int. Ed.* **2007**, *46*, 2485.

This work proposes the three-component synthesis of 5-ethoxyoxazoles and the four-component synthesis of heterocycles oxa-bridged.
Compounds **7.2** were synthesized readily by a nucleophilic substitution reaction (S_NAr) between the commercially available α-isocyanoacetate **7.1** and fluoro derivatives **I-V** under basic conditions, in a different way Zhu and co-workers[85] previously developed for the monoalkylation of **7.1** (Scheme 7.5).



Scheme 7.5. Synthesis of ethyl α-isocyanoacetates **7.2** by a nucleophilic substitution reaction (S_NAr) between **7.1** and fluoro derivatives **I-V** under basic conditions.

The isonitriles synthesized are reported in Figure 7.1, the yields are good (53-72%) as shown in Table 7.1.

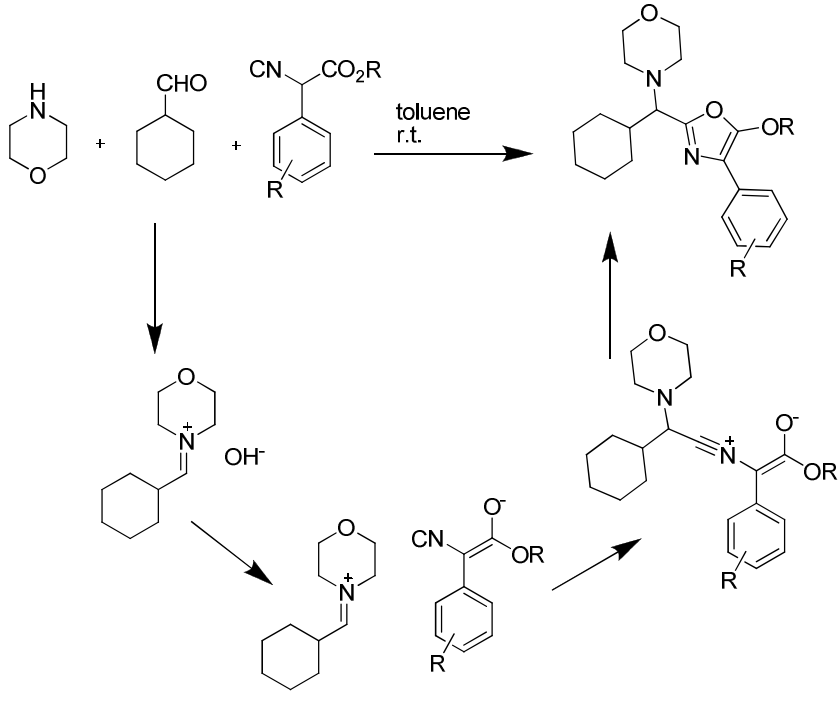


Entry	Alkylating	Yield(%)	Product
1	1-F-4-NO_2benzene **(I)**	63	**7.3**
3	Me-4-F-benzoate **(II)**	58	**7.4**
4	4-F-benzonitrile **(III)**	53	**7.5**
5	4-F-pyridine **(IV)**	72	**7.6**
6	1-F-2-NO_2benzene **(V)**	66	**7.7**

Figure 7.1 and Table 7.1. α-isocyanoacetates **7.3-7.7** synthesized.

[85] (a) C. Housseman, J. Zhu *Synlett* **2006**, 1777–1779. (b) R. Beugelmans, A. Bigot, J. Zhu *Tetrahedron Lett.* **1994**, *35*, 5649–5652.

Detailed NMR spectroscopic studies indicated that these isocyanates exist as the ester and not in the enol form in common organic solvents. To evaluate the chemical reactivity of these isonitriles it was examined the three-component reaction with morpholine and cyclohexanal and other aldehydes. Condensation of the aldehyde with the amine affords the iminium ion (Scheme 7.6). The addition of the isocyanide to the iminium ion provides the nitrilium intermediate, which undergoes cyclization to afford the 5-ethoxyoxazole[86] (Scheme 7.6).



Scheme 7.6. Three-component synthesis of 5-ethoxyoxazoles: proposed mechanism.

[86] For recent reviews on the chemistry of oxazoles, see: (a) V. S. C. Yeh *Tetrahedron* **2004**, *60*, 11 995–12042. (b) J. Zhong *Nat. Prod. Rep.* **2005**, *22*, 186–229.

In Figure 7.2 are reported the isocyanoacetate, the amines and the aldehydes used for this three-component reaction.

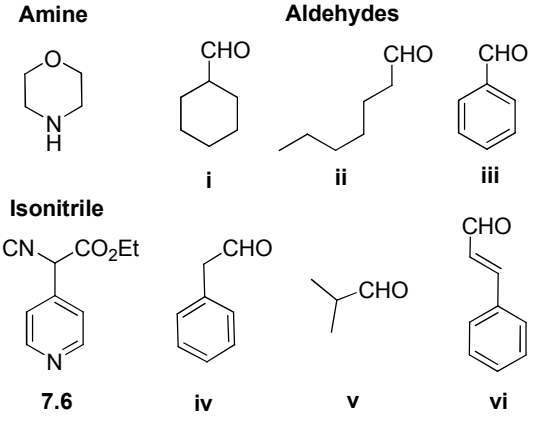
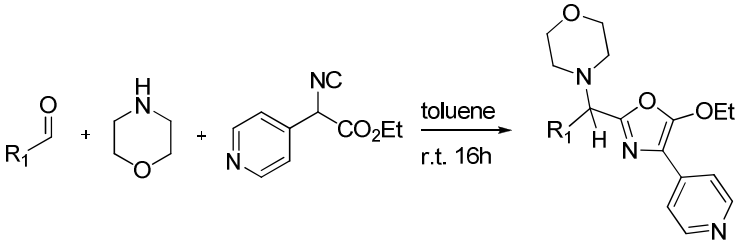


Figure 7.2. Isocyanoacetate, amines and aldehydes used for the three-component reaction for the synthesis of 5-ethoxyoxazole.

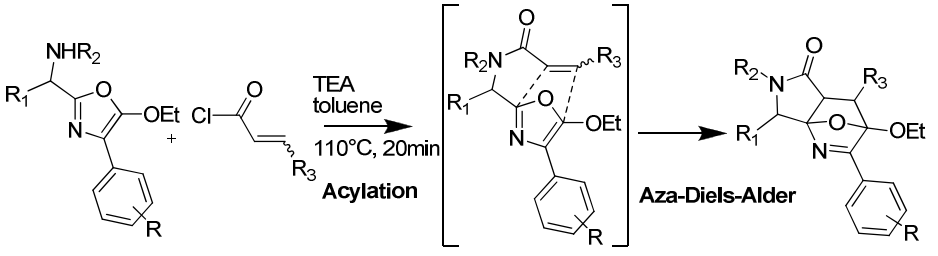
This reaction is performed in toluene at r.t. for 16h (Scheme 7.7) and the yields are in every case good (50-81%) as shown in Table 7.2.



Entry	R_1	Yield (%)	Product
1	Cyclohexyl **(i)**	81	**7.8**
2	Hexyl **(ii)**	54	**7.9**
3	Phenyl **(iii)**	50	**7.10**
4	Benzyl **(iv)**	53	**7.11**
5	Isopropyl **(v)**	61	**7.12**
6	Cinnamyl **(vi)**	54	**7.13**

Scheme 7.7. and Table 7.2. Development of three-component reaction: synthesis of 5-ethoxyoxazole with different aldehydes.

One shortcoming of this three-component reaction is that it provides only one point of diversity, at least three changing also amines and isonitriles. To further illustrate the utility of the α-isocyanoacetates (**7.2**) in the development of novel multicomponent reactions for heterocycle synthesis, the chemical transformation of the 5-ethoxyoxazole was next investigated by taking advantage of the functionalities of the 5-ethoxyoxazoles. 5-ethoxyoxazole is known to be an active diene that readily undergoes Diels–Alder reactions with a range of dienophiles.[87] In literature is reported the cycloaddition of an oxazole with an alkene,[88] for pyridine synthesis *via* oxa-bridged intermediate. The 5-ethoxyoxazole presents a secondary amine that could be acylated with an α,β-insaturated acyl chloride and an azadiene moiety that could be involved in an intramolecular aza-Diels-Alder reaction (Scheme 7.8).



Scheme 7.8. Synthesis of oxa-bridged intermediate from 5-ethoxyoxazoles and α,β-insaturated acyl chlorides *via* intramolecular aza-Diels-Alder reaction.

When a solution of oxazole, TEA and (*E*)-ethyl 4-chloro-4-oxobut-2-enoate in toluene was stirred at 110°C for 20 min, the oxa-bridged intermediate was obtained in a mixture of two saparable diastereoisomers. The stereochemistry can be deduced from the mechanism and from NMR studies. The coupling constant between H_a and H_b for each diastereoisomer is 4.2 Hz like in a *trans* relationship, and the strain of the oxa-bridged imposes a cyclization amide-*exo*, ester-*endo* giving only two of the four possible diastereoisomers (Figure 7.3).

[87] For reviews on the Diels–Alder reaction of oxazoles with alkynes, see: (a) M. Y. Karpeiskii, V. L. FlorentOev *Russ. Chem. Rev.* **1969**, *38*, 540–546. (b) P. A. Jacobi in *Adv. in Heterocyclic Nat. Prod. Syn.*, Vol. *2* (Ed.:W. H. Pearson), **1992**, pp. 251 – 298; for examples of the cycloaddition of 5-aminooxazoles with alkynes, see: (c) P. Janvier, H. BienaymK, J. Zhu *Angew. Chem.* **2002**, *114*, 4467–4470. (d)) P. Janvier, H. BienaymK, J. Zhu *Angew. Chem. Int. Ed.* **2002**, *41*, 4291–4294. (d) A. Fayol, J. Zhu *Angew. Chem.* **2002**, *114*, 3785–3787. (e) A. Fayol, J. Zhu *Angew. Chem. Int. Ed.* **2002**, *41*, 3633–3635.

[88] (a) G. Y. Kondrat'eva *Chem. Abstr.* **1958**, *52*, 6345. (b) M. Karpeiskii *Russ. Chem. Rev.* **1969**, *38*, 540. (c) A. Hassner, B. Fischer *Heterocycles* **1993**, *35*, 1441.

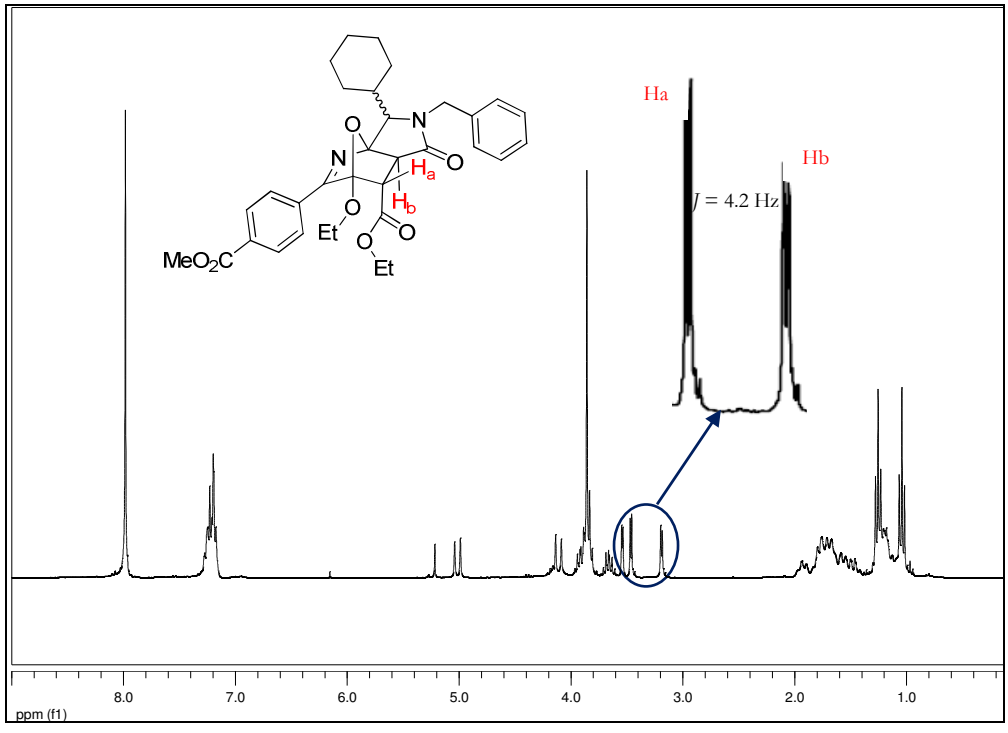


Figure 7.3. ^{1}H NMR of one diastereoisomer of **7.14**.

If the same reaction is performed with (*Z*)-ethyl 4-chloro-4-oxobut-2-enoate a mixture of two diastereoisomers is obtained and the relationship between the two protons H_a and H_b is always *trans*-like, this indicates that the cyclization is again *endo-exo* and not *exo-exo* as expected. This is due to an interaction between the carbonyl of the amide and the CO_2Et group and the consequence is an epimerization of the intermediate *exo-exo* to give the *endo-exo* product (Figure 7.4).

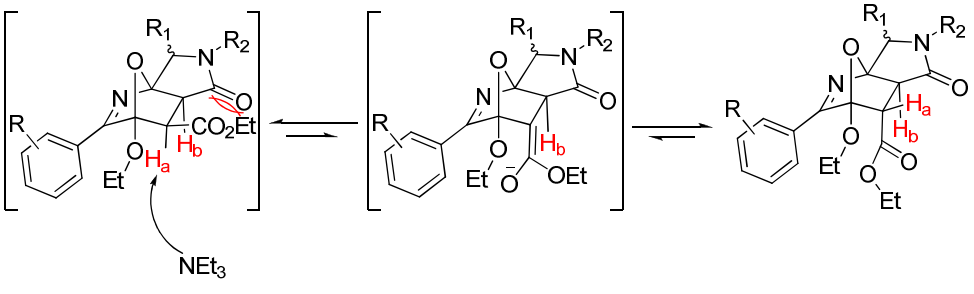


Figure 7.4. Unfavourable interaction in the expected product *exo-exo*: epimerization of this intermediate to give the *endo-exo* product.

The sequence of reactions proposed is one-pot and involves the formation of the 5-ethoxyoxazole and a two domino process involving an acylation and an aza-Diels-Alder reaction with the same yields with respect of the three-component reaction.
The scope of this four-component reaction was examined by using three α-isocyanoacetates, three aldehydes, five primary amines and three α,β-insaturated acyl chlorides (Figure 7.5).

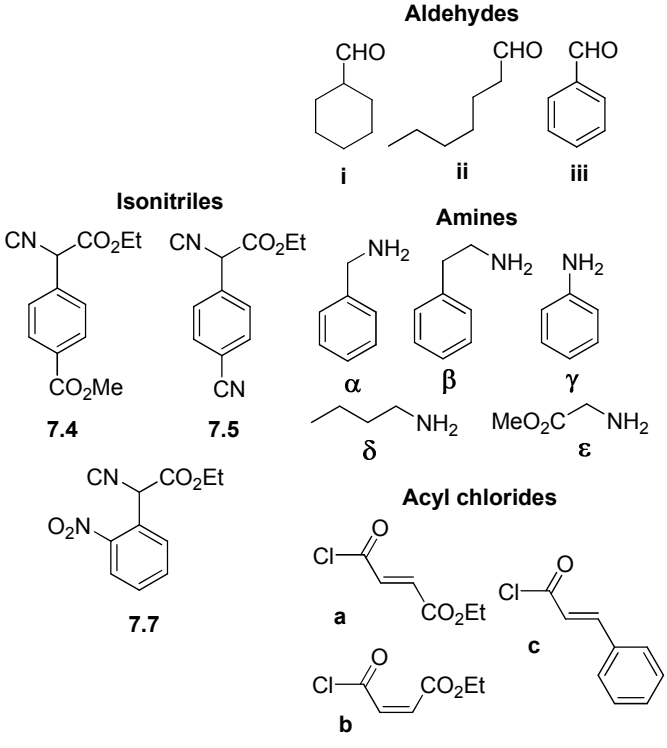
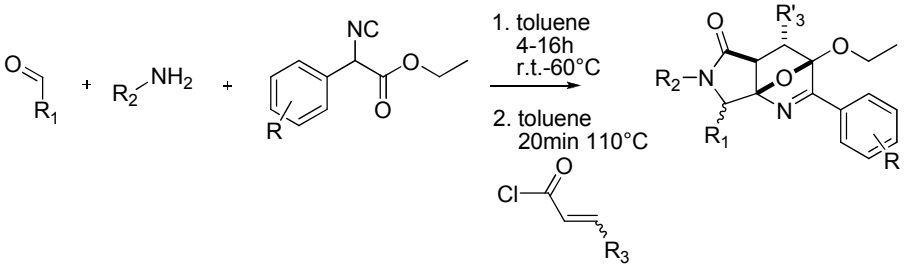


Figure 7.5. Isocyanoacetates, amines, aldehydes and α,β-insaturated acyl chlorides used for the four-component reaction for the synthesis of oxa-bridge heterocycles.

This reaction is performed in toluene at r.t. for 4-16h, depending on the reactivity of the isocyanate (Scheme 7.9), then the acyl chloride is added and the mixture is refluxed 20min; and the yields are in every case good (45-68%) as shown in Table 7.3.



Entry	R	R_1	R_2	R_3	Yield(%)	Mix
1 **(7.14)**	*p*-CO_2Me	Cy	Bn	(Z)-CO_2Et	68	13:1
2 **(7.15)**	*p*-CO_2Me	Ph	Bn	(Z)-CO_2Et	57	1.8:1
3 **(7.16)**	*p*-CO_2Me	Ph	Bn	(E)-CO_2Et	58	1.8:1
4 **(7.17)**	*p*-CO_2Me	eptanal	butyl	(Z)-CO_2Et	65	2:1[a]
5 **(7.18)**	*p*-CO_2Me	Ph	Bn	(E)-Ph	61	2.5:1
6 **(7.19)**	*p*-CN	Cy	Bn	(E)-CO_2Et	54	20:1
7 **(7.20)**	*p*-CN	Cy	Gly	(Z)-CO_2Et	45[b]	6:1
8 **(7.21)**	*o*-NO_2	Cy	Bn	(Z)-CO_2Et	57	>50:1
9 **(7.22)**	*o*-NO_2	Cy	butyl	(E)-CO_2Et	54	>50:1
10**(7.23)**	*o*-NO_2	Cy	butyl	(E)-Ph	65	10:1

[a]separated
[b]conversion incomplete isolated oxazole

Sheme 7.9 and Table 7.3. Development of four-component reaction with functionalized isocyanides with different aldehydes, amines and α,β-insaturated acyl chlorides.

In conclusion a novel four-component reaction is proposed. The investigation of the reactivity of α-isocyanoacetates provide the formation of an oxa-bridged heterocyclic scaffold, highly functionalized, with four points of diversity. This four-component reaction exploites the formation of 5-ethoxyoxazoles that can undergo aza-Diels-Alder reaction in a very diastereoselective way, providing only the amide-*exo*, ester-*endo* product. These kind of new scaffolds should therefore find applications in a large number of fields for the synthesis of libraries of medicinally important heterocycles of this type.[89]

[89] (a) B. H. Lipshutz *Chem. Rev.* **1986**, *86*, 795–819, and references therein. (b) M. Chapdelaine,**WO Patent 2005/100351A1, 2005** [*Chem. Abstr.* **2005**, *143*, 422508].

Conclusions

In this thesis work it has been described about new achievements in the field of development of peptidomimetic scaffolds *via* Diversity-Oriented Synthesis. In particular new synthetic methodologies have been developed and libreries of densely functionalized compounds are obtained for screening, in order to identify molecular structures to be selected as lead compounds for biological targets.

Structural Diversification

In Chapter 3, it has been described about the possibility of obtain structural diversification starting from known structures like BTAa. In particular the synthesis of highly constrained spiro-β-lactams via Staudinger reaction, starting from a bicyclic ketene Bn-BTG(O)-OMe derived, is achieved. The aromatic imines are the best choice for the generation of spiro-β-lactams, in fact in this case the reaction proceeded with high stereoselectivity to produce the corresponding *cis* spiro-β-lactams as major compounds. Both aliphatic- and amino acid derived imines provided mixtures of *cis*- and *trans* spiro-β-lactams. Given the potential structural diversity of the bicyclic ketene, this method is of interest for the generation of densely functionalized molecular scaffolds having restricted conformational freedom. The optimization of the reaction conditions may allow the generation of polycyclic spiro-β-lactams as peptidomimetics for biomedical research.

In Chapter 4, a new strategy for the development of bicyclic analogues of Proline was illustrated, which allowed to obtain Fmoc-amino acids readily available for solid phase synthesis of new modified reverse turn peptides. The use of L-Ascorbic acid and Glycine derivatives was explored to obtain a new α-amino acid bicyclic scaffold. The coupling of the building blocks by S_N2 achieved a densely functionalized acyclic intermediate that undergoes cyclization in the standard conditions (trifluoroacetic acid) providing the scaffold carrying the carboxylic group in 2-*endo* and in 2-*exo* position. The preparation of 4-*endo*-carboxylic scaffolds proved to be problematic and low yielding, as previously reported, so the facile synthesis of this Proline analogue with the carboxylic group in 2-*endo* position, provides a more complete collection of bicyclic amino acids for application in peptidomimetic chemistry. The *exo*-diastereoisomer is more difficult to obtain, the cyclization by treatment with trifluoroacetic acid provided the bicyclic scaffold as methyl ester derivative, probably because of the axial orientation of the carbomethoxy group. This lead to the hypothesis that the facile hydrolysis of the 2-*endo* diastereoisomer might occur through the urethane carbonyl group providing anchimeric assistance to the equatorial carbomethoxy group.

Scaffold generation

In Chapter 5 the DOS approach has been applied to the generation of morpholine-containing molecular scaffolds for peptidomimetic chemistry. The build phase consists in the synthesis of the building blocks from chiral pool: bifunctional building blocks deriving from α-amino acids and L-Ascorbic acid were coupled. The pair phase allowed to obtain morpholine-lactones, a first degree of skeletal diversity around the morpholine nucleus. In this 1st generation of morpholine compounds is included also the bicyclic Proline analogue of above. The aminolysis of the lactones gave a 2nd generation of morpholine scaffolds that then could be further modified to obtain complex bi- and tricyclic molecules (3rd generation) like diketopiperazine, benzodiazepyne and lactam. During the development of this 2nd generation we were interested in finding an easy and efficient method to operate the aminolysis of lactones, and in particular we were interested in achieving the reaction using stoichiometric quantities of reactants. In this contest the studies about aminolysis lactones $LiNTf_2$-catalyzed are placed.

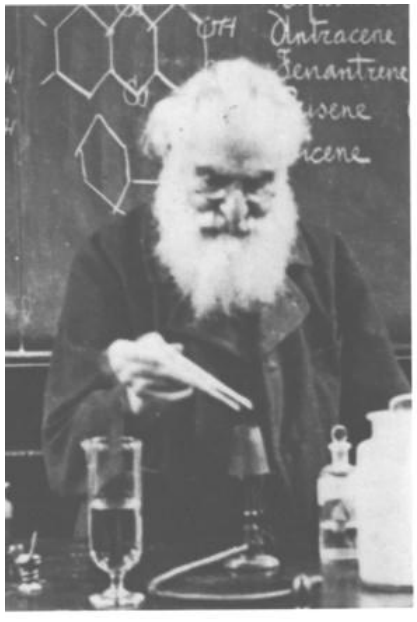
In Chapter 6 is reported a mild method for the aminolysis of lactones with stoichiometric quantities of amines, which consists on the use of $LiNTf_2$ as an activator of the carbonyl function of the lactone. The scope of the reaction has been investigated with selected amines and lactones and the generality of the reaction is demonstrated, except for amines with steric hindrance and lactones presenting non-protected protic functional groups. The method was also tested for the reaction of the methyl ester of Boc-alanine with allylamine, and for the lactone aminolysis of γ-butyrolactone with protected hydroxylamine, indicating the possibility of a more general application of $LiNTf_2$-catalyzed reactions on lactones and esters.

In Chapter 7 the development of a novel multicomponent reaction with α-isocyanoacetates to give highly functionalized oxa-bridged heterocycles is proposed. Multicomponent reactions are a powerful process to obtain diversity and complexity in a rapid way. In the context of a collaboration program with Dr. Jieping Zhu from ICSN, CNRS of Gif-sur-Yvette (France), a new four-component reaction for heterocyclic scaffolds synthesis, useful for medicinal chemistry, was developed. The sequence of reactions proposed is the formation of a 5-ethoxyoxazole starting from α-isocyanoacetates and a two domino process involving an acylation and an aza-Diels-Alder reaction. The scope of this four-component reaction was examined by using three α-isocyanoacetates, three aldehydes, five primary amines and three α,β-insaturated acyl chlorides. Oxa-bridged heterocyclic scaffolds, highly functionalized, with four points of diversity were synthesized. The aza-Diels-Alder reaction is highly diastereoselective, providing only the amide-*exo*, ester-*endo* product. These kind

of new scaffolds should find applications in a large number of fields for the synthesis of libraries of medicinally important heterocycles of this type.

PART III

Experimental Section



Chapter 8

Experimental Section

8.1. General

Melting points are uncorrected. Chromatographic separations were performed on silica gel using flash-column techniques; R_f values refer to TLC carried out on 25-mm silica gel 60 F_{254} plates with the same eluant indicated for column chromatography.

^{1}H and ^{13}C NMR spectra were recorded with a Varian Gemini 200 (and 50.33 MHz, respectively with a Varian Gemini 200) or a Varian Mercury Plus 400 instrument using $CDCl_3$ DMSO or CD_3OD solutions. EI mass spectra were carried out at 70 eV ionizing voltage using a QMD 1000 Carlo Erba Shimadzu spectrometer. IR spectra were recorded with a Perkin Elmer FT-IR-881 spectrophotometer. Elemental analyses were obtained with a Perkin-Elmer 2400/2 C analyzer. A JASCO DIP-370 instrument was used for polarimetric determinations.

THF was distilled from Na/benzophenone. CH_2Cl_2 was distilled from CaH_2. All reactions requiring anhydrous conditions were performed in oven-dried glassware.

8.2. Abbreviations

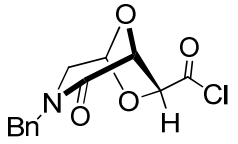
°C	Degrees Celsius
Å	Ångström
Ac	Acetyl
Ar	Aromatic group, not phenyl
Atm	Standard Atmosphere
Bn	Benzyl
Boc	di-tert-butyl dicarbonate
bs	broad signal
Bu	Butyl
C	cyclo / concentration
Cat	catalyst
Cbz	Carboxybenzyl
CH_2Cl_2	Dichloromethane
COSY	COrrelation SpectroscopY
d	doublet
dd	doublet of doublets
DIAD	diisopropyl azodicarboxylate
DMAP	4-dimethylaminopyridine
DMF	dimethylformamide
DMSO	dimethylsulfoxide
EDG	Electron Donating Group
eq	equivalents
ESI	ElectroSpray Ionization
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl Acetate
EtOH	Ethanol
EWG	Electron Withdrawing Group
Fmoc	9H-fluoren-9-yl-methoxycarbonyl
g	gram
h	hour(s)
HPLC	High Performance Liquid Chromatography
Hz	Hertz
i	*iso*
IR	InfraRed
M	molar
m	*meta*
m	multiplet
m/z	mass-to-charge ratio
Me	Methyl
MeOH	Methanol

mg	milligram
MHz	MegaHertz
min	minute
mL	millilitre
µL	microlitre
mmol	millimole
mol	mole
M.p.	melting point
MS	molecular sieves / mass spectrometry
n	normal, straight chain
nm	nanometre
NMR	Nuclear Magnetic Resonance
NOE	Nuclear Overhauser Effect
Nu	nucleophile
o	*ortho*
p	*para*
Ph	Phenyl
Pr	Propyl
ppm	parts per million
q	quartet
quat	quaternary
R	any alkyl group
Ref	reference
r.t.	room temperature
s	singlet
t	triplet (NMR) / tertiary
T	temperature
t-Bu	*tert*-butyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl
p-TSA	*p*-toluene sulfonic acid

8.3. Experimental Section of Chapter 3

Diastereoselective synthesis of spiro-β-lactams

(1*R*,5*S*,7*R*)-3-Benzyl-2-oxo-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-carbonyl Chloride



3.3

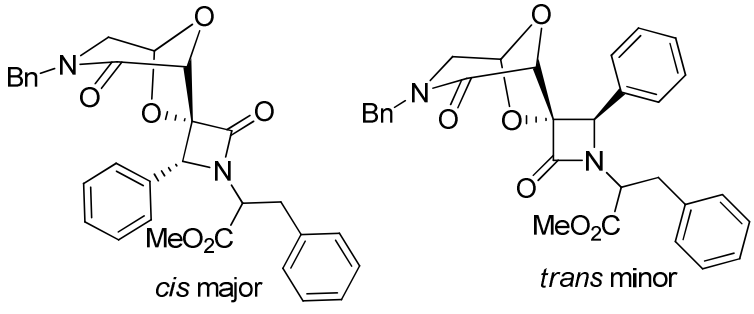
Bn-BTG(O)-OMe **3.1** was dissolved in anhydrous THF to give a 0.1 M solution, and TMSOK (1.5 eq) was added in one portion. After stirring 1.5h at room temperature, the mixture was diluted with EtOAc, washed with 5% $KHSO_4$ and brine and dried with Na_2SO_4. Evaporation of the organic phase gave pure acid **3.2** in 95% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.36–7.18 (m, 5 H, Ph), 5.92 (d, J = 2.2 Hz, 1 H, 5-H), 5.12 (s, 1 H, 1-H), 4.96 (s, 1 H, 7-H), 4.56 (s, 2 H, CH_2-Ph), 3.39 (dd, J = 12.4 Hz, J = 2.4 Hz, 1 H, 4-H), 3.14 (d, J = 12.0 Hz, 1 H, 4-H) ppm. To a solution of acid **3.2** (1 eq) in dry CH_2Cl_2 (0.7 M) was slowly added a solution of oxalyl chloride (5 M, 3 eq) in dry CH_2Cl_2, and a drop of dry DMF was then added. The mixture was stirred at room temperature under a nitrogen atmosphere for 15h, and the solvent was then concentrated in vacuo to give the corresponding acyl chloride **3.3**, which was immediately used in the Staudinger reaction.

General Procedure for the Synthesis of Spiro Compounds 3.6–3.13

(Method 1): A solution of the proper imine (1.1 eq) and dry TEA (1.5 eq) in dry toluene (0.2 M) was heated to reflux under a nitrogen atmosphere; a mixture of Bn-BTG(O)-Cl (250 mg, 0.89 mmol, 1 eq) in dry toluene (0.4 M) was then added. The mixture was stirred at 110°C under a nitrogen atmosphere for 16h, and it was then washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried with Na_2SO_4, filtered and concentrated in vacuo to give a dark oil. The pure products were afforded after purification by flash chromatography (petroleum ether/EtOAc, 1:1).

General Procedure for the Synthesis of Spiro Compound 3.7 (Method 2): A solution of Bn-BTG(O)-Cl (250 mg, 0.89 mmol, 1 eq) and dry TEA (1.5 eq) in dry toluene (0.4 M) was stirred at the desired temperature under a nitrogen atmosphere for 10min, and a solution of imine (1.1 eq) in dry toluene (0.2 M) was then added. The mixture was stirred at the desired temperature under a nitrogen atmosphere for 15h, and it was then washed with saturated aqueous $NaHCO_3$ and brine. The organic layer was dried with Na_2SO_4, filtered and concentrated in vacuo to give a dark oil, which was purified by flash chromatography (petroleum ether/ EtOAc, 1:1).

Methyl 2-((1'*R*,3*R*/*S*,4*R*,5'*S*)-3'-benzyl-2,2'-dioxo-4-phenyl-6',8'-dioxa-3'-azaspiro[azetidine-3,7'-bicyclo[3.2.1]octane]-1-yl)-3-phenylpropanoate

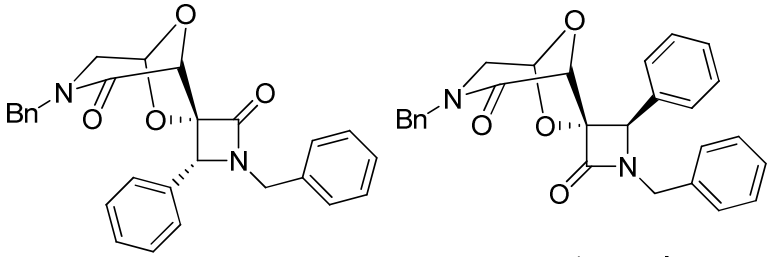


3.6

White solid, 150 mg, 33% yield. ^{1}H NMR (400 MHz, $CDCl_3$) 3:2 mixture of diastereomers A and B: δ = 7.40–7.19 (m, 15 H, Ph, A+B), 5.59 (d, J = 2.4 Hz, 1 H, 5-H, A), 5.32 (d, J = 2.4 Hz, 1 H, 5-H, B), 4.94 (s, 1 H, 1-H, A), 4.89 (d, J = 15.1 Hz, CH_2, A), 4.88 (s, 2 H, 4'-H, A+B), 4.82 (s, 1 H, 1-H, B), 4.74 (d, J = 15.3 Hz, 1 H, CH_2, B), 4.52 (m, 1 H, α-H, B), 4.50 (d, J = 15.3 Hz, 1 H, CH_2, B), 4.05 (m, 1 H, α-H, A), 3.91 (d, J = 14.7 Hz, 1 H, CH_2, A), 3.79 (s, 3 H, OCH_3, B), 3.71 (s, 3 H, O CH_3, A), 3.56 (dd, J = 14.0, J = 11.9 Hz, 1 H, β-H, A), 3.30 (dd, J = 14.0 Hz, J = 4.6 Hz, 1 H, β-H A), 3.18 (m, 2 H, 4-H, B), 3.15 (m, 1 H, β-H, B), 3.13 (dd, J = 12.4 Hz, J = 3.0 Hz, 1 H, 4-H, B), 3.05 (dd, J = 12.7 Hz, J = 2.4 Hz, 1 H, 4-H, A), 3.00 (dd, J = 14.4 Hz, J = 9.6 Hz, 1 H, β-H, B), 2.45 (d, J = 14.0 Hz, 1 H, 4-H, A) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) mixture of diastereomers A and B: δ = 169.2 (s, A), 168.2 (s, B), 164.5 (s, A), 163.3 (s, B), 136.8 (s, A), 136.6 (s, B), 135.3 (s, A), 134.7 (s, B), 134.0 (s, A), 132.7 (s, B), 129.3 (d), 129.2 (d), 128.9 (d), 128.8 (d), 128.7 (d), 128.5 (d), 128.3 (d), 128.2 (d), 127.9 (d), 127.7 (d), 127.6 (d), 127.2 (d), 127.1 (d), 100.5 (d, B), 100.1 (d, A), 92.5 (s, A), 91.9 (s, B), 79.6 (d, A), 76.8 (d, B), 70.9 (d, A), 62.9 (d, B) 58.9 (d), 57.9 (d), 57.1 (d), 52.9 (q), 50.7 (d, A), 50.6 (d, B), 48.6 (d, A), 48.4 (d, B), 36.2 (t,

B), 35.6 (d, A) ppm. MS: *m*/*z* (%) = 512 (3) $[M]^+$, 307 (48), 268 (11), 160 (76), 148 (21), 117 (13), 91 (100). IR ($CDCl_3$): ν = 3072, 2931, 1792, 1743, 1664, 1493, 1458 cm^{-1}.

(1'*R*,3*R*/*S*,4*R*,5'*S*)-1,3'-dibenzyl-4-phenyl-6',8'-dioxa-3'-azaspiro [azetidine-3,7'-bicyclo[3.2.1]octane]-2,2'-dione

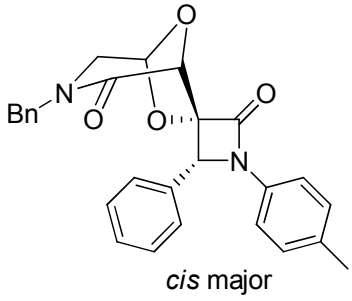


cis major *trans* minor

3.7

White solid, 258 mg, 66% yield. ^1H NMR (400 MHz, $CDCl_3$) mixture of diastereomers A and B: δ = 7.48–7.07 (m, 15 H, Ph, A+B), 5.68 (d, *J* = 2.6 Hz, 1 H, 5-H, B), 5.42 (d, *J* = 2.3 Hz, 1 H, 5-H, A), 4.98 (s, 1 H, 4'-H, B), 4.97 (d, *J* = 14.2 Hz, 1 H, CH_2, A), 4.96 (s, 1 H, 4'-H, A), 4.84 (d, *J* = 15.2 Hz, 1 H, CH_2, A), 4.83 (d, *J* = 14.7 Hz, 1 H, CH_2, B), 4.82 (s, 1 H, 1-H, B), 4.78 (d, *J* = 14.8 Hz, 1 H, CH_2, B), 4.55 (s, 1 H, 1-H, A), 4.45 (d, *J* = 14.8 Hz, 1 H, CH_2, A), 3.99 (d, *J* = 14.8 Hz, 1 H, CH_2, B), 3.97 (d, *J* = 14.7 Hz, 1 H, CH_2, B), 3.94 (d, *J* = 14.7 Hz, 1 H, CH_2, A), 3.22 (dd, *J* = 12.5 Hz, *J* = 2.4 Hz, 1 H, 4-H, A), 3.18 (dd, *J* = 12.5 Hz, *J* = 2.7 Hz, 1 H, 4-H, B), 3.10 (dd, *J* = 12.5 Hz, *J* = 2.3 Hz, 1 H, 4-H, A), 2.54 (d, *J* = 12.3 Hz, 1 H, 4-H, B) ppm. ^{13}C NMR (50 MHz, $CDCl_3$) mixture of diastereomers A and B: δ = 166.8 (s, B), 164.6 (s, B), 164.5 (s, A), 163.6 (s, A), 135.3 (s, A), 134.7 (s, B), 134.4 (s, B), 134.3 (s, A), 133.8 (s, B), 132.8 (s, A), 128.9 (d), 128.8 (d), 128.7 (d), 128.6 (d), 128.5 (d), 128.4 (d), 128.3 (d), 128.2 (d), 128.0 (d), 127.8 (d), 127.7 (d), 127.6 (d), 100.6 (d, B), 100.1 (d, A), 93.2 (s, B), 92.6 (s, A), 79.5 (d, A), 76.7 (d, B), 68.1 (d, B), 62.3 (d, A), 50.8 (t, A), 50.5 (t, B), 48.6 (t, A), 48.4 (t, B), 44.6 (t, 2 C) ppm. MS: *m*/*z* (%) = 440 (7) $[M]^+$, 307 (63), 292 (17), 216 (15), 160 (75), 148 (27), 132 (22), 91 (100), 65 (25). IR ($CDCl_3$): ν = 3055, 2923, 1767, 1676, 1496, 1455 cm^{-1}.

(1'*R*,3*R*,4*R*,5'*S*)-3'-benzyl-4-phenyl-1-*p*-tolyl-6',8'-dioxa-3'-azaspiro [azetidine-3,7'-bicyclo[3.2.1]octane]-2,2'-dione

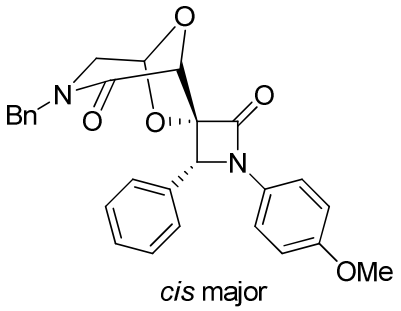


cis major

3.8

Yellow solid, 55 mg, 14% yield. M.p. 86–89°C. $[\alpha]^{25}_{D}$ = –84.44 (*c* = 0.7, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.33–7.03 (m, 14 H, Ph), 5.70 (d, *J* = 2.6 Hz, 1 H, 5-H), 5.40 (s, 1 H, PhCHN), 5.09 (s, 1 H, 1-H), 5.04 (d, *J* = 14.6 Hz, 1 H, CH_2Ph), 4.03 (d, *J* = 14.3 Hz, 1 H, CH_2Ph), 3.41 (dd, *J* = 12.4 Hz, *J* = 2.6 Hz, 1 H, 4-H), 2.64 (d, *J* = 12.4 Hz, 1 H, 4-H), 2.23 (s, 3 H, CH_3) ppm. ^{13}C NMR ($CDCl_3$): δ = 164.6 (s, C=O), 163.7 (s, C=O), 134.6 (s, Ph), 134.5 (s, Ph), 133.9 (s, Ph), 132.9 (s, Ph), 129.5 (d, 2 C, Ph), 128.9 (d, 2 C, Ph), 128.8 (d, Ph), 128.6 (d, 2 C, Ph), 128.5 (d, 2 C, Ph), 128.1 (d, Ph), 127.2 (d, 2 C, Ph), 117.7 (d, Ph), 100.1 (d, C-5), 92.2 (s, C-7), 76.9 (d, PhCHN), 62.5 (d, C-1), 50.9 (t, C-4), 48.9 (t, CH_2Ph), 21.1 (q, CH_3) ppm. MS: *m*/*z* (%) = 440 (8) $[M]^+$, 307 (19), 195 (41), 160 (51), 91 (100), 65 (18). IR ($CDCl_3$): ν = 3067, 2928, 1760, 1673 cm^{-1}. $C_{27}H_{24}N_2O_4$ (440.5): calcd. C 73.62, H 5.49, N 6.36; found C 73.59, H 5.48, N 6.34.

(1'*R*,3*R*,4*R*,5'*S*)-3'-benzyl-1-(4-methoxyphenyl)-4-phenyl-6',8'-dioxa-3'-azaspiro[azetidine-3,7'-bicyclo[3.2.1]octane]-2,2'-dione

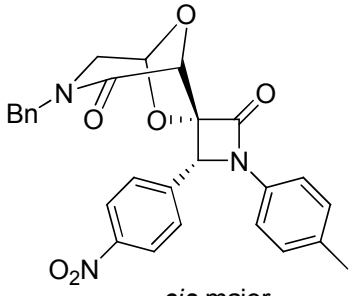


cis major

3.10

Yellow solid, 158 mg, 39% yield. M.p. 94–97°C. $[\alpha]^{25}_{D}$ = –124.98 (*c* = 0.8, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.23 (m, 12 H, Ph), 6.85–6.81 (m, 2 H, Ph), 5.75 (d, *J* = 2.6 Hz, 1 H, 5-H), 5.41 (s, 1 H, PhCHN), 5.12 (s, 1 H, 1-H), 5.08 (d, *J* = 14.6 Hz, 1 H, CH_2Ph), 4.05 (d, *J* = 14.7 Hz, 1 H, CH_2Ph), 3.78 (s, 3 H, OCH_3), 3.30 (dd, *J* = 12.1, *J* = 2.6 Hz, 1 H, 4-H), 2.67 (d, *J* = 12.1 Hz, 1 H, 4-H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 164.7 (s, C=O), 163.4 (s, C=O), 156.5 (s, Ph), 134.6 (s, Ph), 132.9 (s, Ph), 129.9 (s, Ph), 128.9 (d, Ph), 128.6 (d, Ph), 128.5 (d, Ph), 128.0 (d, Ph), 127.2 (d, Ph), 119.0 (d, Ph), 114.3 (d, Ph), 100.1 (d, C-5), 92.3 (s, C-7), 76.9 (d, PhCHN), 62.6 (d, C-1), 55.5 (q, OCH_3), 50.9 (t, C-4), 48.9 (t, CH_2Ph) ppm. MS: *m*/*z* (%) = 456 (25) $[M]^+$, 307 (23), 211 (66), 196 (33), 160 (75), 148 (18), 91 (100), 77 (17), 65 (13). IR ($CDCl_3$): ν = 3081, 2921, 1758, 1672, 1513 cm^{-1}. $C_{27}H_{24}N_2O_5$ (456.5): calcd. C 71.04, H 5.30, N 6.14; found C 71.06, H 5.32, N 6.13.

(1'*R*,2*R*,3*R*,5'*S*)-3'-benzyl-2-(4-nitrophenyl)-1-*p*-tolyl-6',8'-dioxa-3'-azaspiro[azetidine-3,7'-bicyclo[3.2.1]octane]-2',4-dione

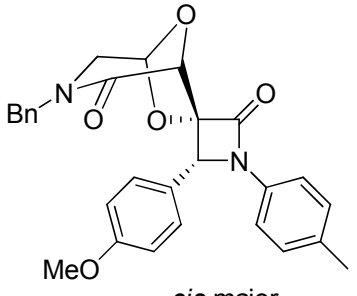


cis major

3.11

Yellow solid, 104 mg, 24% yield. M.p. 97–100°C. $[\alpha]^{25}_{D}$ = –121.72 (c = 0.95, CH_2Cl_2). ^{1}H NMR (200 MHz, CDCl3): δ = 8.08 (d, J = 8.4 Hz, 2 H, Ar), 7.42–7.05 (m, 11 H, Ph), 5.74 (d, J = 2.20 Hz, 1 H, 5-H), 5.46 (s, 1 H, PhCHN), 5.11 (s, 1 H, 1-H), 4.81 (d, J = 14.3 Hz, 1 H, CH_2Ph), 4.25 (d, J = 14.3 Hz, 1 H, CH_2Ph), 3.35 (dd, J = 12.1, J = 2.6 Hz, 1 H, 4-H), 2.74 (d, J = 12.4 Hz, 1 H, 4-H), 2.28 (s, 3 H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 164.5 (s, C=O), 163.8 (s, C=O), 148.0 (s, Ph), 140.5 (s, Ph), 135.0 (s, Ph), 134.5 (s, Ph), 133.5 (s, Ph), 129.8 (d, Ph), 129.0 (d, Ph), 128.9 (d, Ph), 128.4 (d, Ph), 128.0 (d, Ph), 123.9 (d, Ph), 117.5 (d, Ph), 100.4 (d, C-5), 92.4 (s, C-7), 76.9 (d, PhCHN), 61.5 (d, C-1), 51.0 (t, C-4), 49.2 (t, CH_2Ph), 21.1 (q, CH_3) ppm. MS: m/z (%) = 485 (5) $[M]^+$, 352 (13), 261 (23), 240 (30), 148 (32), 91 (100), 65 (15). IR ($CDCl_3$): ν = 3053, 2947, 1765, 1673, 1525 cm^{-1}. $C_{27}H_{23}N_3O_6$ (485.5): calcd. C 66.80, H 4.78, N 8.66; found C 66.83, H 4.80, N 8.69.

(1'*R*,2*R*,3*R*,5'*S*)-3'-benzyl-2-(4-methoxyphenyl)-1-*p*-tolyl-6',8'-dioxa-3'-azaspiro[azetidine-3,7'-bicyclo[3.2.1]octane]-2',4-dione



cis major

3.12

Yellow solid, 247 mg, 59% yield. M.p. 99–101°C. $[\alpha]^{25}_{D}$ = –103.63 (c = 0.95, CH_2Cl_2). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34–7.02 (m, 11 H, Ph), 6.85–6.80 (m, 2 H, Ph), 5.72 (d, J = 2.6 Hz, 1 H, 5-H), 5.34 (s, 1 H, PhCHN), 5.07 (s, 1 H, 1-H), 4.98 (d, J = 14.6 Hz, 1 H, CH_2Ph), 4.05 (d, J = 14.6 Hz, 1 H, CH_2Ph), 3.79 (s, 3 H, OCH_3), 3.26 (dd, J = 12.4 Hz, J = 2.6 Hz, 1 H, 4-H), 2.68 (d, J = 12.4 Hz, 1 H, 4-H), 2.26 (s, 3 H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 164.6 (s, C=O), 163.9 (s, C=O), 159.8 (s, Ph), 134.8 (s, Ph), 134.3 (s, Ph), 134.1 (s, Ph), 129.6 (d, Ph), 128.9 (d, Ph), 128.6 (d, Ph), 128.0 (d, Ph), 124.7 (s, Ph), 117.7 (d, Ph), 114.1 (d, Ph), 100.2 (d, C-5), 92.2 (s, C-7), 76.9 (d, PhCHN), 62.2 (d, C-1), 55.3 (q, OCH_3), 50.9 (t, C-4), 48.9 (t, CH_2Ph), 21.2 (q, CH_3) ppm. MS: m/z (%) = 470 (7) $[M]^+$, 337 (74), 225 (54), 190 (73), 161 (22), 91 (100), 65 (24). IR ($CDCl_3$): ν = 3063, 2926, 1759, 1671, 1515 cm^{-1}. $C_{28}H_{26}N_2O_5$ (470.5): calcd. C 71.47, H 5.57, N 5.95; found C 71.47, H 5.55, N 5.96.

Crystallographic data are reported.

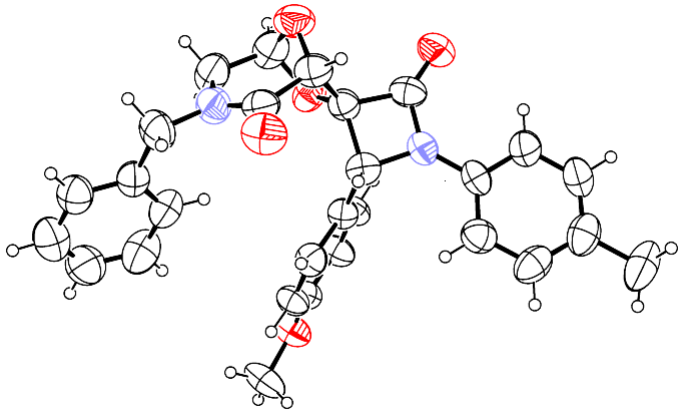


Table 1. Crystal data and structure refinement for 12.

Identification code	12
Empirical formula	C28 H26 N2 O5
Formula weight	470.51
Temperature	293(2) K
Wavelength	0.71069 A
Crystal system, space group	Orthorhombic, P 21 21 21
Unit cell dimensions	a=6.770(1)A alpha=90.00(1)deg. b=18.915(3)A beta=90.00(1)deg. c=19.146(2)A gamma=90.00(1)deg.
Volume	2451.7(6) A^3
Z, Calculated density	4, 1.275 Mg/m^3
Absorption coefficient	0.088 mm^-1
F(000)	992
Crystal size	? x ? x ? mm
Theta range for data collection	4.27 to 22.45 deg.
Limiting indices	-7<=h<=7, -20<=k<=20, -19<=l<=20
Reflections collected/unique	6552/3019[R(int)=0.0443]
Completeness to theta = 22.45	97.4 %
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	3019/0/316

Goodness-of-fit on F^2 0.731

Final R indices[I>2sigma(I)] R1=0.0401,wR2=0.0661

R indices (all data) R1 = 0.1180,wR2=0.0844

Absolute structure parameter 0.7(16)

Largest diff. peak and hole 0.119 and -0.131 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic
displacement parameters (A^2 x 10^3) for 12.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
N(1)	3739(7)	8936(2)	1545(3)	73(1)
N(2)	4760(7)	9887(3)	3944(3)	89(2)
O(1)	8068(5)	6392(2)	3137(2)	90(1)
O(2)	2240(5)	8927(2)	3096(2)	82(1)
O(3)	423(5)	9324(2)	1597(2)	99(1)
O(4)	1370(6)	10087(2)	3213(2)	103(1)
O(5)	6441(5)	10450(2)	3088(2)	107(1)
C(1)	4949(8)	8991(3)	2183(3)	71(2)
C(2)	3095(8)	9318(3)	2539(3)	70(1)
C(3)	8518(7)	7653(3)	2930(2)	71(2)
C(4)	5775(8)	8307(3)	2445(2)	62(1)
C(5)	4701(7)	7692(3)	2454(3)	75(2)
C(6)	7426(8)	7042(3)	2922(3)	70(2)
C(7)	7689(8)	8276(3)	2693(2)	72(2)
C(8)	5503(8)	7059(3)	2679(3)	78(2)
C(9)	4930(9)	10156(3)	3303(4)	80(2)
C(10)	2043(9)	9206(3)	1836(3)	80(2)
C(11)	3161(9)	10063(3)	2826(3)	83(2)
C(12)	4230(11)	8710(3)	863(4)	74(2)
C(13)	6125(10)	8501(3)	709(4)	86(2)
C(14)	2943(10)	9546(3)	4185(3)	100(2)
C(15)	7274(9)	9415(4)	4794(4)	79(2)
C(16)	5168(14)	8294(3)	-501(4)	96(2)
C(17)	3295(12)	8496(3)	-318(4)	97(2)
C(18)	6570(10)	8280(3)	30(4)	95(2)
C(19)	2817(9)	8714(3)	356(4)	92(2)
C(20)	7260(8)	8748(5)	4506(3)	96(2)
C(21)	10098(7)	6313(3)	3342(3)	116(2)
C(22)	1526(9)	9447(4)	3582(4)	98(2)
C(23)	8353(10)	9528(4)	5391(4)	95(2)
C(24)	6245(8)	10033(3)	4476(3)	102(2)
C(25)	9428(11)	9003(6)	5697(4)	122(2)
C(26)	5678(9)	8053(3)	-1235(3)	137(2)
C(27)	8305(13)	8208(4)	4823(4)	120(2)
C(28)	9347(11)	8352(5)	5411(5)	121(2)

Table 3. Bond lengths [A] and angles [deg] for 12.

N(1)-C(10)	1.375(6)
N(1)-C(12)	1.413(6)
N(1)-C(1)	1.475(5)
N(2)-C(9)	1.333(6)
N(2)-C(24)	1.458(6)
N(2)-C(14)	1.464(6)
O(1)-C(6)	1.367(5)
O(1)-C(21)	1.437(4)
O(2)-C(2)	1.420(5)
O(2)-C(22)	1.438(6)
O(3)-C(10)	1.208(5)
O(4)-C(22)	1.406(6)
O(4)-C(11)	1.422(5)
O(5)-C(9)	1.235(6)
C(1)-C(4)	1.496(6)
C(1)-C(2)	1.556(6)
C(1)-H(1)	0.9800
C(2)-C(11)	1.514(6)
C(2)-C(10)	1.538(7)
C(3)-C(6)	1.372(6)
C(3)-C(7)	1.381(5)
C(3)-H(3)	0.9300
C(4)-C(5)	1.371(6)
C(4)-C(7)	1.381(6)
C(5)-C(8)	1.384(5)
C(5)-H(5)	0.9300
C(6)-C(8)	1.383(6)
C(7)-H(7)	0.9300
C(8)-H(8)	0.9300
C(9)-C(11)	1.516(7)
C(11)-H(11)	0.9800
C(12)-C(19)	1.363(6)
C(12)-C(13)	1.375(6)
C(13)-C(18)	1.399(6)
C(13)-H(13)	0.9300
C(14)-C(22)	1.512(6)
C(14)-H(14A)	0.9700
C(14)-H(14B)	0.9700
C(15)-C(23)	1.374(6)
C(15)-C(20)	1.377(6)
C(15)-C(24)	1.491(6)
C(16)-C(17)	1.370(7)
C(16)-C(18)	1.391(7)
C(16)-C(26)	1.516(7)
C(17)-C(19)	1.394(7)
C(17)-H(17)	0.9300
C(18)-H(18)	0.9300
C(19)-H(19)	0.9300
C(20)-C(27)	1.382(7)
C(20)-H(20)	0.9300
C(21)-H(21A)	0.9600
C(21)-H(21B)	0.9600
C(21)-H(21C)	0.9600
C(22)-H(22)	0.9800
C(23)-C(25)	1.363(7)

C(23)-H(23)	0.9300
C(24)-H(24A)	0.9700
C(24)-H(24B)	0.9700
C(25)-C(28)	1.349(7)
C(25)-H(25)	0.9300
C(26)-H(26A)	0.9600
C(26)-H(26B)	0.9600
C(26)-H(26C)	0.9600
C(27)-C(28)	1.357(7)
C(27)-H(27)	0.9300
C(28)-H(28)	0.9300
C(10)-N(1)-C(12)	133.1(5)
C(10)-N(1)-C(1)	95.9(5)
C(12)-N(1)-C(1)	131.0(5)
C(9)-N(2)-C(24)	120.8(5)
C(9)-N(2)-C(14)	122.0(5)
C(24)-N(2)-C(14)	116.3(5)
C(6)-O(1)-C(21)	118.7(4)
C(2)-O(2)-C(22)	105.5(4)
C(22)-O(4)-C(11)	99.9(4)
N(1)-C(1)-C(4)	115.1(4)
N(1)-C(1)-C(2)	86.7(4)
C(4)-C(1)-C(2)	120.0(5)
N(1)-C(1)-H(1)	111.0
C(4)-C(1)-H(1)	111.0
C(2)-C(1)-H(1)	111.0
O(2)-C(2)-C(11)	103.0(4)
O(2)-C(2)-C(10)	113.4(4)
C(11)-C(2)-C(10)	117.3(5)
O(2)-C(2)-C(1)	116.7(5)
C(11)-C(2)-C(1)	120.4(5)
C(10)-C(2)-C(1)	86.3(4)
C(6)-C(3)-C(7)	119.7(4)
C(6)-C(3)-H(3)	120.2
C(7)-C(3)-H(3)	120.2
C(5)-C(4)-C(7)	117.2(5)
C(5)-C(4)-C(1)	122.6(5)
C(7)-C(4)-C(1)	120.2(5)
C(4)-C(5)-C(8)	122.0(4)
C(4)-C(5)-H(5)	119.0
C(8)-C(5)-H(5)	119.0
O(1)-C(6)-C(3)	125.7(5)
O(1)-C(6)-C(8)	114.9(5)
C(3)-C(6)-C(8)	119.4(5)
C(4)-C(7)-C(3)	122.1(5)
C(4)-C(7)-H(7)	119.0
C(3)-C(7)-H(7)	119.0
C(6)-C(8)-C(5)	119.6(4)
C(6)-C(8)-H(8)	120.2
C(5)-C(8)-H(8)	120.2
O(5)-C(9)-N(2)	123.3(6)
O(5)-C(9)-C(11)	120.4(7)
N(2)-C(9)-C(11)	116.2(6)
O(3)-C(10)-N(1)	132.3(6)
O(3)-C(10)-C(2)	136.6(6)
N(1)-C(10)-C(2)	91.1(5)
O(4)-C(11)-C(2)	101.1(4)
O(4)-C(11)-C(9)	110.9(4)
C(2)-C(11)-C(9)	110.4(5)

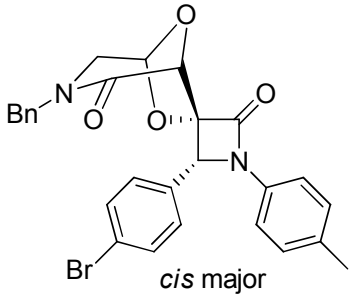
O(4)-C(11)-H(11)	111.3
C(2)-C(11)-H(11)	111.3
C(9)-C(11)-H(11)	111.3
C(19)-C(12)-C(13)	120.2(6)
C(19)-C(12)-N(1)	119.4(6)
C(13)-C(12)-N(1)	120.4(6)
C(12)-C(13)-C(18)	119.2(6)
C(12)-C(13)-H(13)	120.4
C(18)-C(13)-H(13)	120.4
N(2)-C(14)-C(22)	110.3(4)
N(2)-C(14)-H(14A)	109.6
C(22)-C(14)-H(14A)	109.6
N(2)-C(14)-H(14B)	109.6
C(22)-C(14)-H(14B)	109.6
H(14A)-C(14)-H(14B)	108.1
C(23)-C(15)-C(20)	118.7(6)
C(23)-C(15)-C(24)	117.8(7)
C(20)-C(15)-C(24)	123.5(7)
C(17)-C(16)-C(18)	116.8(6)
C(17)-C(16)-C(26)	122.1(8)
C(18)-C(16)-C(26)	121.1(7)
C(16)-C(17)-C(19)	122.3(6)
C(16)-C(17)-H(17)	118.9
C(19)-C(17)-H(17)	118.9
C(16)-C(18)-C(13)	121.8(6)
C(16)-C(18)-H(18)	119.1
C(13)-C(18)-H(18)	119.1
C(12)-C(19)-C(17)	119.7(6)
C(12)-C(19)-H(19)	120.1
C(17)-C(19)-H(19)	120.1
C(15)-C(20)-C(27)	119.8(6)
C(15)-C(20)-H(20)	120.1
C(27)-C(20)-H(20)	120.1
O(1)-C(21)-H(21A)	109.5
O(1)-C(21)-H(21B)	109.5
H(21A)-C(21)-H(21B)	109.5
O(1)-C(21)-H(21C)	109.5
H(21A)-C(21)-H(21C)	109.5
H(21B)-C(21)-H(21C)	109.5
O(4)-C(22)-O(2)	106.7(5)
O(4)-C(22)-C(14)	108.9(5)
O(2)-C(22)-C(14)	111.5(5)
O(4)-C(22)-H(22)	109.9
O(2)-C(22)-H(22)	109.9
C(14)-C(22)-H(22)	109.9
C(25)-C(23)-C(15)	121.8(7)
C(25)-C(23)-H(23)	119.1
C(15)-C(23)-H(23)	119.1
N(2)-C(24)-C(15)	117.3(5)
N(2)-C(24)-H(24A)	108.0
C(15)-C(24)-H(24A)	108.0
N(2)-C(24)-H(24B)	108.0
C(15)-C(24)-H(24B)	108.0
H(24A)-C(24)-H(24B)	107.2
C(28)-C(25)-C(23)	118.0(7)
C(28)-C(25)-H(25)	121.0
C(23)-C(25)-H(25)	121.0
C(16)-C(26)-H(26A)	109.5
C(16)-C(26)-H(26B)	109.5

H(26A)-C(26)-H(26B)	109.5
C(16)-C(26)-H(26C)	109.5
H(26A)-C(26)-H(26C)	109.5
H(26B)-C(26)-H(26C)	109.5
C(28)-C(27)-C(20)	118.9(8)
C(28)-C(27)-H(27)	120.5
C(20)-C(27)-H(27)	120.5
C(25)-C(28)-C(27)	122.7(8)
C(25)-C(28)-H(28)	118.6
C(27)-C(28)-H(28)	118.6

Table 4. Anisotropic displacement parameters (A^2x10^3) for 12. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
N(1)	77(4)	71(3)	70(4)	8(3)	-11(3)	0(3)
N(2)	75(4)	101(4)	92(4)	-9(3)	-5(4)	-11(3)
O(1)	77(2)	78(3)	116(3)	13(2)	-18(2)	2(2)
O(2)	80(2)	86(3)	79(2)	-11(2)	14(2)	-12(2)
O(3)	72(2)	115(3)	109(3)	-3(2)	-16(3)	9(2)
O(4)	69(3)	113(3)	128(4)	-25(3)	-2(3)	6(2)
O(5)	88(3)	91(3)	141(4)	0(2)	0(3)	-25(2)
C(1)	72(4)	55(3)	85(4)	3(3)	6(4)	-6(3)
C(2)	61(4)	78(4)	72(4)	2(4)	0(4)	-5(3)
C(3)	53(3)	74(4)	87(4)	0(4)	-12(3)	-5(4)
C(4)	53(4)	66(4)	67(4)	1(3)	2(3)	-14(3)
C(5)	48(3)	92(4)	86(4)	7(4)	-8(3)	-6(4)
C(6)	61(4)	74(4)	75(4)	-3(3)	-5(3)	5(4)
C(7)	74(4)	64(4)	77(4)	-7(3)	-1(3)	-11(3)
C(8)	63(4)	63(4)	107(5)	4(4)	-16(4)	-11(3)
C(9)	65(5)	73(4)	103(5)	-18(4)	1(5)	2(3)
C(10)	62(4)	77(4)	101(6)	-1(4)	-1(5)	0(3)
C(11)	70(4)	80(4)	100(5)	-3(3)	6(4)	-6(4)
C(12)	79(5)	74(4)	70(5)	15(4)	-18(5)	-1(4)
C(13)	84(5)	84(4)	88(5)	10(4)	0(4)	4(4)
C(14)	95(5)	118(5)	88(5)	-20(4)	10(5)	-14(4)
C(15)	76(4)	87(5)	73(5)	1(4)	2(4)	-11(4)
C(16)	131(7)	84(5)	72(6)	8(4)	14(6)	-12(5)
C(17)	106(6)	115(5)	70(5)	7(4)	-20(5)	0(4)
C(18)	115(6)	81(4)	90(5)	8(4)	32(6)	3(4)
C(19)	106(5)	98(5)	74(4)	4(4)	-4(5)	14(4)
C(20)	117(5)	94(5)	76(4)	-14(5)	10(4)	0(5)
C(21)	85(4)	108(5)	154(5)	22(4)	-49(4)	16(3)
C(22)	65(4)	128(6)	101(5)	-20(5)	17(4)	-31(4)
C(23)	94(5)	100(6)	91(5)	-2(5)	0(4)	-12(5)
C(24)	105(4)	89(5)	110(5)	-18(4)	-37(4)	-8(4)
C(25)	118(6)	137(7)	110(6)	-2(7)	-22(5)	-15(6)
C(26)	204(7)	131(5)	77(4)	-16(4)	30(5)	-1(5)
C(27)	164(7)	100(6)	96(6)	0(5)	17(5)	-3(6)
C(28)	135(6)	120(8)	106(6)	26(6)	-4(6)	24(6)

(1'*R*,2*R*,3*R*,5'*S*)-3'-benzyl-2-(4-bromophenyl)-1-*p*-tolyl-6',8'-dioxa-3'-azaspiro[azetidine-3,7'-bicyclo[3.2.1]octane]-2',4-dione



cis major

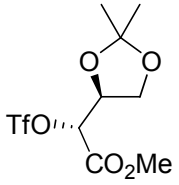
3.13

Yellow solid, 152 mg, 33% yield. M.p. 96–99°C. $[\alpha]^{25}_{D}$ = –123.02 (c = 0.95, CH_2Cl_2). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.42–7.16 (m, 9 H, Ph), 7.05–6.99 (m, 4 H, Ph), 5.68 (d, J = 2.6 Hz, 1 H, 5-H), 5.37 (s, 1 H, PhCHN), 5.09 (s, 1 H, 1-H), 4.87 (d, J = 14.6 Hz, 1 H, CH_2Ph), 4.14 (d, J = 13.2 Hz, 1 H, CH_2Ph), 3.26 (dd, J = 12.4 Hz, J = 2.6 Hz, 1 H, 4-H), 2.69 (d, J = 12.1 Hz, 1 H, 4-H), 2.25 (s, 3 H, CH_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 164.5 (s, C=O), 163.5 (s, C=O), 134.7 (s, Ph), 134.6 (s, Ph), 133.8 (s, Ph), 132.1 (s, Ph), 131.8 (d, Ph), 129.7 (d, Ph), 129.0 (d, Ph), 128.9 (d, Ph), 128.7 (d, Ph), 128.1 (d, Ph), 122.8 (s, Ph), 117.6 (d, Ph), 100.3 (d, C-5), 92.2 (s, C-7), 76.9 (d, PhCHN), 61.9 (d, C-1), 50.9 (t, C-4), 48.9 (t, CH_2Ph), 21.2 (q, CH_3) ppm. MS: m/z (%) = 520 (5) $[M + 1]^+$, 518 (5) $[M – 1]^+$, 387 (13), 385 (13), 275 (22), 273 (22), 240 (15), 238 (15). IR ($CDCl_3$): ν = 3054, 2991, 1762, 1672, 1515, 1488 cm^{-1}. $C_{27}H_{23}BrN_2O_4$ (519.4): calcd. C 62.44, H 4.46, N 5.39; found C 62.41, H 4.44, N 5.39.

8.4. Experimental Section of Chapter 4

Bicyclic Proline analogue from L-Ascorbic acid

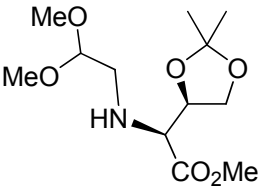
Methyl (*R*)-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl](trifluoromethansulfonyloxy)acetate



4.2

A solution of **4.1** (5.00 g, 26.3 mmol) in dry CH_2Cl_2 (45.5 mL) was cooled at -10°C, and precooled dry pyridine (4.50 mL) was added under a nitrogen atmosphere. Then a solution of Tf_2O (7.30 mL, 34.2 mmol) in dry CH_2Cl_2 (13.6 mL) was added over 30 min, and the mixture was stirred at r.t. for 30min. After the organic phase had been washed with a satured $NaHCO_3$ solution (3×50 mL), the organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo to give a dark oil. Flash chromatography (petroleum ether/EtOAc, 2:1) afforded **4.2** as a white solid; yield: 4.98 g, (59%). M.p. 51-54°C. $[\alpha]^{25}_D$ = +38.8 (c = 0.8, CH_2Cl_2). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 5.04 (d, *J* = 5.5 Hz, 1 H, TfOCH), 4.56-4.52 (m, 1 H, ring H-4), 4.18 (dd, *J* = 9.4 Hz, *J* = 6.7 Hz, 1 H, CH_2), 4.06 (dd, *J* = 9.4 Hz, *J* = 4.7 Hz, 1 H, CH_2), 3.88 (s, 3 H, OCH_3), 1.45 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 165.1 (s, C=O), 121.5 (s, CF_3), 111.1 (s, [$C(CH_3)_2$], 82.6 (d, TfOCH), 74.1 (d, ring C-4), 65.4 (t, CH_2), 53.5 (q, OCH_3), 25.9 (q, CH_3), 25.0 (q, CH_3) ppm. MS: *m*/*z* (%): 322 (8) $[M]^+$, 69 (100), 55 (77). IR ($CDCl_3$): ν = 3052, 2986, 1733, 1265 cm^{-1}. $C_9H_{13}F_3O_7S$ (322.03): calcd. C 33.54, H 4.07; found C 33.46, H 3.99.

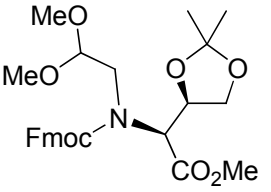
Methyl (*S*)-[(2,2-Dimethoxyethyl)amino][(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]acetate



4.4

A solution of **4.2** (1.30 g, 4.01 mmol) in dry CH_2Cl_2 (20 mL) was cooled to 0°C, and then a solution of 2,2-dimethoxyethanamine (**4.3**) (0.50 mL, 4.81 mmol) and DIPEA (1.40 mL, 8.02 mmol) in dry CH_2Cl_2 (20 mL) was added under a nitrogen atmosphere. The mixture was stirred at r.t. for 15h, and then it was extracted with a satured $NaHCO_3$ solution (3×40 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo to give a dark oil. Flash chromatography (petroleum ether/EtOAc, 3:1) afforded pure **4.4** as a yellow oil; yield: 1.11 g, (99%). $[\alpha]^{25}_D$ = +15.6 (c = 0.9, CH_2Cl_2). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.41 [(t, *J* = 4.8 Hz, 1 H, $(CH_3)_2CHCH_2NH$)], 4.18-4.13 (m, 1 H, ring H-4), 4.07-4.00 (m, 2 H, ring CH_2), 3.76 (s, 3 H, CO_2CH_3), 3.35 (s, 3 H, OCH_3), 3.34 (s, 3 H, OCH_3), 3.27 (d, *J* = 7.3 Hz, 1 H, $CHNH$), 2.76 (dd, *J* = 12.1 Hz, *J* = 6.3 Hz, 1 H, CH_2NH), 2.63 (dd, *J* = 12.1 Hz, *J* = 4.6 Hz, 1 H, CH_2NH), 1.72 (br, 1 H, NH), 1.41 (s, 3 H, CH_3), 1.31 (s, 3 H, CH_3) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 173.3 (s, C=O), 109.7 (s), 103.5 [d, $CH(OCH_3)_2$], 76.8 [d, $CHOC(CH_3)_2$], 67.1 (t, CH_2NH), 64.4 (d, $CHCO_2CH_3$), 53.9 (q, OCH_3), 53.2 (q, OCH_3), 51.9 (q, OCH_3), 49.5 (t, ring CH_2), 26.7 (q, CH_3), 25.3 (q, CH_3) ppm. MS: *m/z* (%): 277 (4) $[M]^+$, 177 (79), 144 (100), 75 (96). IR ($CDCl_3$): ν = 2991, 2955, 2836, 1733, 1250, 1219 cm^{-1}. $C_{12}H_{23}NO_6$ (277.15): calcd. C 51.97, H 8.36, N 5.05; found C 51.84, H 8.40, N 5.12.

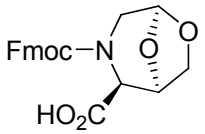
Methyl (*S*)-[(2,2-Dimethoxyethyl)(9*H*-fluoren-9-ylmethoxy carbonyl)amino][(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]acetate



4.5

To a solution of **4.4** (616 mg, 2.22 mmol) in dioxane (44 mL) at 0°C and under a nitrogen atmosphere, were added FmocCl (863 mg, 3.33 mmol) and 2,6-lutidine (388 μL, 3.33 mmol). The mixture was stirred at r.t. for 15h. The solution was then concentrated in vacuo, the crude dissolved in CH_2Cl_2 (20 mL), and the solution was washed with 5% citric acid solution (3×20 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo to give a coulorless oil. Flash chromatography (petroleum ether/EtOAc, 5:1) afforded **4.5** as a colorless oil; yield: 1.07 g, (97%). $[\alpha]^{25}_D$ = -48.1 (c = 1.45, CH_2Cl_2). ^{1}H-NMR (400 MHz, $CDCl_3$) mixture of rotamers: δ = 7.68 (d, *J* = 5.4 Hz, 2 H, Ar), 7.51 (d, *J* = 3.9 Hz, 2 H, Ar), 7.33-7.22 (m, 4 H, Ar), 4.61 (m, 2 H), 3.62 (s, 3 H, OCH_3), 4.56-3.02 (m, 14 H), 1.28 (s, 3 H, CH_3), 1.25 (s, 3 H, CH_3) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) mixture of rotamers: δ = 169.7 (s), 156.1 and 155.9 (s), 143.5 (s, 2 C), 141.4 and 141.3 (s, 2 C), 127.7 (d, 2 C), 127.1 (d, 2 C), 124.8 and 124.5 (d, 2 C), 120.1 and 119.9 (d, 2 C), 110.1 and 109.9 (s), 103.4 and 102.9 (d), 74.9 and 74.6 (d), 67.2 and 66.6 (d), 66.1 (q), 62.2 and 61.9 (d), 55.3 and 55.1 (t), 54.4 and 54.1 (t), 52.2 (q, 2 C), 49.6 (d), 47.4 and 47.1 (t), 26.8 and 25.4 (q), 26.6 and 25.4 (q) ppm. MS: *m*/*z* (%): 499 (0.3) $[M]^+$, 178 (99), 75 (100). IR ($CDCl_3$): ν = 2958, 1794, 1709 cm^{-1}. $C_{27}H_{33}NO_8$ (499.22): calcd. C 64.92, H 6.66, N 2.80; found C 64.91, H 6.62, N 2.75.

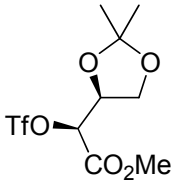
(1*R*,2*S*,5*S*)-3-(9fluorenylmethoxycarbonyl)-6,8-dioxa-3-azabicyclo[3.2.1]octane-2-*endo*-carboxylic Acid



4.6

Compound **4.5** (1.02 g, 2.00 mmol) was dissolved in TFA (4.20 mL), and then the solution was stirred at 25°C overnight. The solution was then concentrated in vacuo to give a dark oil. Flash chromatography (CH_2Cl_2/MeOH, 20:1, buffered with 0.1% TFA) afforded **4.6** as a white solid; yield: 0.351 g, (46%). M.p. 198-201°C. $[\alpha]^{25}_D$ = -78.1 (c = 1, CH_2Cl_2-1% TFA). ^{1}H-NMR (400 MHz, $CDCl_3$) 2:1 mixture of rotamers: δ = 7.69 (d, *J* = 7.1 Hz, 2 H, Ar), 7.50 (d, *J* = 7.8 Hz, 2 H, Ar), 7.33-7.22 (m, 4 H, Ar), 5.16 (s, 2/3 H, H-5, rot A), 5.11 (d, *J* = 2.7 Hz, 1/3 H, H-5, rot B), 4.68-4.21 (m, 7 H), 3.95 (d, *J* = 13.4 Hz, 1/3 H, H-4, rot B), 3.85 (d, *J* = 13.6 Hz, 2/3 H, H-4, rot A), 3.06 (d, *J* = 13.6 Hz, 2/3 H, H-4, rot A), 2.99 (d, *J* = 13.4 Hz, 1/3 H, H-4, rot B) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) mixture of rotamers: δ = 173.0 (s, O-C=O), 158.6 (s, N-C=O), 143.2 (s, 2 C, Ar), 141.0 (s, 2 C, Ar), 127.9 (d, 2 C, Ar), 127.4 and 127.3 (d, 2 C, Ar), 124.9 (d, 2 C, Ar), 120.1 and 119.8 (d, 2 C, Ar), 88.7 and 88.6 (d, C-5), 72.2 and 71.2 (t, C-7), 70.9 and 69.8 (t), 65.4 and 65.0 (d, C-1), 53.9 and 53.8 (d, C-2), 47.0 and 46.7 (d), 44.4 and 43.7 (t, C-4) ppm. MS: *m*/*z* (%): 381 (1.3) $[M]^+$, 178 (100). IR ($CDCl_3$): ν = 3691, 2958, 1794, 1602 cm^{-1}. $C_{21}H_{19}NO_6$ (381.12): calcd. C 66.13, H 5.02, N 3.67; found C 65.94, H 4.94, N 3.55.

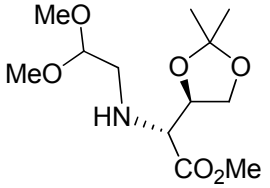
Methyl (*S*)-[(*S*)-2,2-Dimethyl-1,3-dioxolan-4-yl](trifluoromethan sulfonyloxy)acetate



4.9

A solution of **4.8** (150 mg, 0-79 mmol) in dry CH_2Cl_2 (1.4 mL) was cooled to -10°C, precooled dry pyridine (4.50 mL) was added under a nitrogen atmosphere, followed by the addition of a solution of Tf_2O (219 µL, 1.02 mmol) in dry CH_2Cl_2 (0.4 mL) over 30min. The mixture was stirred at r.t. for 30 min and the neutralized with a satured $NaHCO_3$ solution. The organic layer was separated, dried (Na_2SO_4), filtered and concentrated in vacuo to give a dark oil. Flash chromatography (petroleum ether/EtOAc, 2:1) afforded **4.9** as a yellow oil; yield: 136 mg, (53%). ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 5.24 (d, *J* = 3.6 Hz, 1 H, TfOCH), 4.58-4.50 (m, 1 H, ring H-4), 4.10-3.94 (m, 2 H, ring CH_2), 3.84 (s, 3 H, OCH_3), 1.43 (s, 3 H, CH_3), 1.34 (s, 3 H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 165.0 (s, C=O), 121.5 (s, CF_3), 110.9 (s, [*C*$(CH_3)_2$], 81.0 (d, TfOCH), 74.0 (d, ring C-4), 65.4 (t, CH_2), 53.5 (q, OCH_3), 25.8 (q, CH_3), 24.9 (q, CH_3) ppm. MS: *m*/*z* (%): 322 (3) $[M]^+$, 75 (100), 55 (62).

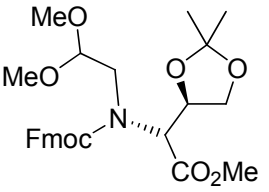
Methyl (*R*)-[(2,2-Dimethoxyethyl)amino][(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]acetate



4.10

A solution of **4.9** (136 mg, 0.42 mmol) in dry CH_2Cl_2 (2.1 mL) was cooled to 0°C, and then a solution of 2,2-dimethoxyethanamine (**4.3**) (56 μL, 0.51 mmol) and DIPEA (144 μL, 0.84 mmol) in dry CH_2Cl_2 (2.1 mL) was added under a nitrogen atmosphere. The mixture was stirred at r.t. for 15h, and then neutralized with a satured $NaHCO_3$ solution. The organic layer was separated, dried (Na_2SO_4), filtered and concentrated in vacuo to give a dark oil. Flash chromatography (petroleum ether/EtOAc, 3:1) afforded pure **4.10** as a colourless oil; yield: 101 mg, (86%). $[\alpha]^{25}_D$ = +19.3 (c = 0.7, CH_2Cl_2). ^{1}H-NMR (200 MHz, $CDCl_3$): δ = 4.41 [(t, *J* = 5.4 Hz, 1 H, $(CH_3)_2CHCH_2NH$)], 4.23 (q, *J* = 6.5 Hz, 1 H, ring H-4), 4.01-3.86 (m, 2 H, ring CH_2), 3.71 (s, 3 H, CO_2CH_3), 3.31 (s, 7 H, OCH_3, C*H*NH), 2.80 (dd, *J* = 12.1 Hz, *J* = 5.9 Hz, 1 H, CH_2NH), 2.57 (dd, *J* = 12.4 Hz, *J* = 5.1 Hz, 1 H, CH_2NH), 1.36 (s, 3 H, CH_3), 1.29 (s, 3 H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$): δ = 172.7 (s, C=O), 109.6 (s), 103.9 [d, *C*H$(OCH_3)_2$], 76.2 [d, *C*HOC$(CH_3)_2$], 66.4 (t, CH_2NH), 62.9 (d, *C*HCO_2CH_3), 54.0 (q, OCH_3), 53.2 (q, OCH_3), 52.1 (q, OCH_3), 49.5 (t, ring CH_2), 26.5 (q, CH_3), 25.4 (q, CH_3) ppm. MS: *m*/*z* (%): 277 (6) $[M]^+$, 177 (75), 144 (89), 75 (100). IR ($CDCl_3$): ν = 2990, 2954, 2834, 1739, 1271, 1261 cm^{-1}. $C_{12}H_{23}NO_6$ (277.15): calcd. C 51.97, H 8.36, N 5.05; found C 52.10, H 8.55, N 5.14.

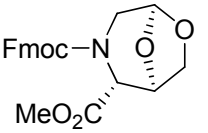
Methyl (*R*)-[(2,2-Dimethoxyethyl)(9*H*-fluoren-9-ylmethoxy carbonyl)amino][(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]acetate



4.11

To a solution of **4.10** (136 mg, 0.29 mmol) in dioxane (5.8 mL) at 0°C and under a nitrogen atmosphere, were added FmocCl (122 mg, 0.43 mmol) and 2,6-lutidine (50 μL, 0.43 mmol). The mixture was stirred at r.t. for 15h. The solution was then concentrated in vacuo, the crude dissolved in CH_2Cl_2 and the solution was washed with 5% citric acid solution (3×10 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo to give a clear oil. Flash chromatography (petroleum ether/EtOAc, 5:1) afforded **4.11** as a colorless oil; yield: 115 mg, (80%). $[\alpha]^{25}_D$ = +48.4 (c = 0.95, CH_2Cl_2). ^{1}H-NMR (200 MHz, $CDCl_3$) mixture of rotamers: δ = 7.81-7.74 (m, 2 H, Ar), 7.63-7.53 (m, 2 H, Ar), 7.44-7.31 (m, 4 H, Ar), 4.77-3.55 (m, 10 H), 3.68 (s, 3 H, OCH_3), 3.37 and 3.32 (s, 6 H, OCH_3), 1.41 (s, 3 H, CH_3), 1.36 (s, 3 H, CH_3) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) mixture of rotamers: δ = 169.4 and 168.7 (s), 155.5 and 155.3 (s), 143.7 and 143.6 (s, 2 C), 141.6 and 141.3 (s, 2 C), 127.6 and 127.0 (d, 2 C), 124.8 (d, 2 C), 124.3 and 124.1 (d, 2 C), 120.1 and 119.9 (d, 2 C), 108.9 and 108.6 (s), 104.4 and 104.3 (d), 73.6 and 73.5 (d), 68.6 and 68.5 (d), 67.1 (q), 65.0 and 64.5 (d), 55.8 and 55.6 (t), 55.5 and 55.4 (t), 52.3 and 51.9 (q), 51.8 and 51.3 (q), 47.4 and 47.1 (t), 26.8 and 26.7 (q), 25.2 and 25.1 (q) ppm. MS: *m*/*z* (%): 499 (0.3) $[M]^+$, 178 (100), 75 (60). IR ($CDCl_3$): ν = 2988, 1739, 1701, 1261, 1066 cm^{-1}. $C_{27}H_{33}NO_8$ (499.22): calcd. C 64.92, H 6.66, N 2.80; found C 64.90, H 6.51, N 2.70.

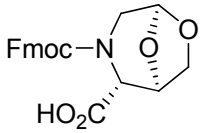
Methyl (1*R*,2*R*,5*S*)-3-(9fluorenylmethoxycarbonyl)-6,8-dioxa-3-azabicyclo[3.2.1]octane-2-*exo*-carboxylate



4.12

Compound **4.11** (226 mg, 0.45 mmol) was dissolved in TFA (950 μL), and then the solution was stirred at 25°C for 48h. The solution was then concentrated in vacuo to give a dark oil. Flash chromatography (CH_2Cl_2/MeOH, 20:1, buffered with 0.1% TFA) afforded **4.12** as a white solid; yield: 145 mg, (81%). M.p. 56-59°C. $[\alpha]^{25}_D$ = +48.5 (c = 0.35, CH_2Cl_2-1% TFA). ^{1}H-NMR (400 MHz, $CDCl_3$) 3:2 mixture of rotamers: δ = 7.69 (m, 2 H, Ar), 7.51 and 7.41 (m, 2 H, Ar), 7.36-7.21 (m, 4 H, Ar), 5.45 (s, 1 H, H-5), 4.92 (d, *J* = 3.9 Hz, 3/5 H, H-1, rot A), 4.78 (d, *J* = 3.9 Hz, 2/5 H, H-1, rot B) 4.52-3.64 (m, 7 H), 3.74 and 3.64 (s, 3 H, OCH_3), 3.30 (d, *J* = 12.5 Hz, 3/5 H, H-4, rot A), 3.14 (d, *J* = 13.0 Hz, 2/5 H, H-4, rot B) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) mixture of rotamers: δ = 168.9 (s, O-C=O), 156.6 (s, N-C=O), 143.5 (s, 2 C, Ar), 141.2 (s, 2 C, Ar), 127.7 and 127.0 (d, 2 C, Ar), 124.9 (d, 2 C, Ar), 124.6 and 124.5 (d, 2 C, Ar), 120.0 (d, 2 C, Ar), 98.9 and 98.4 (d, C-5), 72.7 and 72.3 (d, C-1), 68.2 and 67.7 (t), 67.3 (t, C-7), 59.5 and 58.9 (d, C-2), 52.8 (q), 47.5 and 47.2 (t, C-4), 47.3 (d) ppm. MS: *m*/*z* (%): 395 (0.7) $[M]^+$, 336 (2), 178 (100), 165 (14), 89 (7), 55 (8). IR ($CDCl_3$): ν = 2927, 1752, 1708, 1269 cm^{-1}. $C_{22}H_{21}NO_6$ (395.14): calcd. C 66.83, H 5.35, N 3.54; found C 66.34, H 5.30, N 3.46.

(1*R*,2*R*,5*S*)-3-(9fluorenylmethoxycarbonyl)-6,8-dioxa-3-azabicyclo [3.2.1]octane-2-*exo*-carboxylic Acid



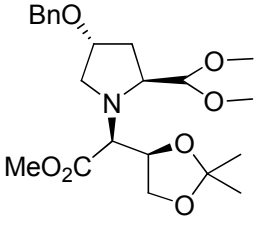
4.13

A solution of **4.12** (55 mg, 0.14 mmol) in MeCN (2 mL) and 4M HCl (3 mL) was refluxed for 16h and then the solvent was evaporated in vacuo. The white solid was treated with Et_2O (10 mL), and the solution was filtered and evaporated. This gave a yellow solid which was purified by flash chromatography (CH_2Cl_2/MeOH, 20:1, buffered with 0.1% TFA) to give **4.13** as a white solid; yield: 40 g, (75%). M.p. 86-88°C. $[\alpha]^{25}_D$ = +62.9 (c = 0.5, CH_2Cl_2). ^{1}H-NMR (200 MHz, $CDCl_3$) 3:2 mixture of rotamers: δ = 10.34 (br, 1 H, COOH), 7.75 (m, 2 H, Ar), 7.70-7.27 (m, 6 H, Ar), 5.55 and 5.53 (s, 1 H, H-5), 5.04 (d, *J* = 4.6 Hz, 3/5 H, H-1, rot A), 4.86 (m, 2/5 H, H-1, rot B), 4.66-3.67 (m, 7 H), 3.36 (d, *J* = 12.8 Hz, 3/5 H, H-4, rot A), 3.19 (d, *J* = 13.0 Hz, 2/5 H, H-4, rot B) ppm. ^{13}C-NMR (50 MHz, $CDCl_3$) mixture of rotamers: δ = 173.5 and 173.3 (s, O-C=O), 156.5 and 155.4 (s, N-C=O), 143.2 (s, 2 C, Ar), 140.9 (s, 2 C, Ar), 128.4 (d, 2 C, Ar), 127.5 (d, 2 C, Ar), 124.7 and 124.3 (d, 2 C, Ar), 119.7 (d, 2 C, Ar), 98.6 and 98.0 (d, C-5), 72.3 and 71.8 (d, C-1), 67.9 (t), 67.3 and 66.9 (t, C-7), 58.7 and 58.4 (d, C-2), 47.1 and 46.7 (t, C-4), 46.8 (d) ppm. MS: *m*/*z* (%): 381 (0.3) $[M]^+$, 178 (100). IR ($CDCl_3$): ν = 3066, 2960, 2900, 1709, 1451, 1413 cm^{-1}. $C_{21}H_{19}NO_6$ (381.12): calcd. C 66.13, H 5.02, N 3.67; found C 66.05, H 4.92, N 3.65.

8.5. Experimental Section of Chapter 5

Morpholine-based scaffolds

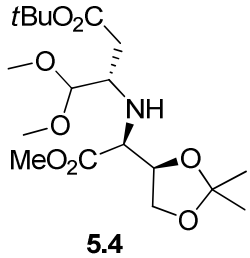
(*R*)-methyl-2-[(2*S*,4*R*)-4-(benzyloxy)-2-(dimethoxyethyl)pyrrolidin-1-yl]-2-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]acetate



5.3

A solution of **4.2** (see Chapter 8.4) (743 mg, 2.30 mmol) in dry CH_2Cl_2 (15 mL) was cooled to 0°C, and then a solution of (2*R*,4*R*)-4-(benzyloxy)-2-(dimethoxymethyl)pyrrolidine (**5.1**) (579 mg, 2.30 mmol) and DIPEA (0.79 mL, 4.61 mmol) in dry CH_2Cl_2 (10 mL) was added under a nitrogen atmosphere. The mixture was stirred at r.t. for 15h, and then it was extracted with a satured $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo to give a dark oil. Flash chromatography (petroleum ether/EtOAc, 3:1) afforded pure **5.3** as a yellow oil; yield: 654 mg, (65%). ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.31-7.23 (m, 5H, Ar), 4.52-4.36 (m, 3 H, CH_2Ph and $CH(OMe)_2$), 4.11-4.01 (m, 3 H, ring H-4, CHOBn and CHN), 3.94-3.74 (m, 2 H, ring CH_2 and CHN ring Pro), 3.60 (s, 3 H, CO_2CH_3), 3.56-3.47 (m, 1 H, CH_2 ring Pro), 3.41 (s, 3 H, OCH_3), 3.35 (s, 3 H, OCH_3), 3.07-2.97 (m, 1 H, CH_2 ring Pro), 1.99-1.95 (m, 1 H, CH_2 ring Pro), 1.81-1.75 (m, 1 H, CH_2 ring Pro), 1.38 (s, 3 H, CH_3), 1.35 (s, 3 H, CH_3) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 170.7 (C=O), 138.2 (Ar), 128.2 (2 C, Ar), 127.5 (2 C, Ar), 127.4 (1 C, Ar), 109.6 (s), 108.3 ($CH(OCH_3)_2$), 76.4 ($CHOC(CH_3)_2$), 74.8 (CH_2Ph), 70.9 (CHOBn), 67.1 (CH_2NH), 65.3 ($CHCH(OCH_3)_2$), 60.5 ($CHCO_2CH_3$), 54.5 (OCH_3), 53.5 (OCH_3), 52.5 (ring CH_2), 51.3 (OCH_3), 33.7 (CH_2 ring Pro), 27.0 (CH_3), 25.8 (CH_3) ppm. MS: *m*/*z* (%): 423 (4) $[M]^+$, 170 (68), 137 (27), 128 (29), 111 (100), 95 (24), 84 (42), 75 (29), 60 (43), 57 (30).

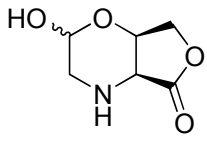
(*R*)-*tert*-butyl-3-[(*R*)-1-[(*R*)-2,2-dimethyl-1,3-dioxolan-4-yl]-2-methoxy-2-oxoethylamino]-4,4-dimethoxybutanoate



5.4

A solution of **4.2** (see Chapter 8.4) (1.13 g, 3.12 mmol) in dry CH_2Cl_2 (20 mL) was cooled to 0°C under a nitrogen atmosphere, then a solution of (*S*)-*tert*-butyl-3-amino-4,4'-dimethoxybutanoate **5.2** (770 mg, 3.52 mmol) and DIPEA (1.20 mL, 7.63 mmol) in dry CH_2Cl_2 (15 mL) were added. The mixture was stirred at room temperature for 15h, then it was extracted with a saturated $NaHCO_3$ solution. The organic layer was dried (Na_2SO_4), filtered and concentrated in vacuo to give a dark oil. Flash chromatography afforded pure **5.4** as a yellow oil (1.00 g, 73%). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 4.17 (d, 1 H), 4.12-4.07 (m, 1 H), 3.99 (d, 2 H), 3.73 (s, 3 H), 3.48 (d, 1 H), 3.38 (s, 3 H), 3.36 (s, 3 H), 3.18-3.09 (m, 1 H), 2.45 (dd, 1 H), 2.23 (dd, 1 H), 2.03 (br, 1 H), 1.43 (s, 9 H), 1.40 (s, 3 H), 1.30 (s, 3 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.4 (s, 1 C), 170.8 (s, 1 C), 109.4 (s, 1 C), 106.8 (d, 1 C), 80.4 (s, 1C), 77.1 (d, 1 C), 66.9 (t, 1 C), 62.1 (d, 1 C), 55.2 (q, 3 C), 51.8 (d, 1 C), 33.6 (t, 1 C), 28.1 (q, 3 C), 26.7 (q, 1 C), 25.2 (q, 1 C) ppm. MS: *m*/*z* (%): 392 (1) $[M+1]^+$, 316 (26), 260 (50), 203 (15), 202 (100), 101 (12), 75 (31), 71 (11), 57 (39).

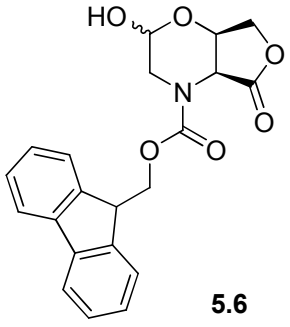
(5*R*/*S*,3a*S*,7a*R*)-5-Hydroxy-hexahydro-2,4-dioxa-7-aza-inden-1-one



5.5

Compound **4.4** (see Chapter 8.4) (1 eq) is dissolved in HCl 6N (3.5 mL/mmol). The mixture is left for 2h at 80°C under a nitrogen atmosphere. Successively, the mixture is concentrated and filtered on a weakly basic resin, giving compound **5.5** as a yellow oil. ^{1}H NMR (200 MHz, D_2O): mixture of epimers δ = 5.19 (s, 1 H), 4.77-4.74 (m, 1 H), 4.52-4.48 (m, 1 H), 4.42-4.39 (m, 1 H minor), 4.37-4.34 (m, 1 H major), 4.25-4.23 (d, 1 H major), 4.19-4.17 (d, 1 H minor), 3.04-2.81 (m, 2 H). ^{13}C NMR (50 MHz, D_2O): mixture of epimers δ = 170.7 and 170.2 (s, 1 C), 86.6 and 86.9 (d, 1 C), 72.4 and 70.5 (t, 1 C), 64.5 (d, 1 C), 52.3 and 51.5 (d, 1 C), 43.3 and 43.0 (t, 1 C). MS: *m*/*z* (%): 159 (6) $[M]^+$, 142 (10), 135 (13), 114 (17), 99 (19), 85 (39), 74 (46), 71 (30), 68 (39), 59 (98), 54 (100), 52 (25).

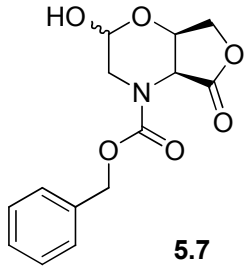
(5*R*/*S*,3a*S*,7a*R*)-5-hydroxy-7-fluorenylmethoxycarbonyl-hexahydro-2,4-dioxa-7-aza-inden-1-one



5.6

To a solution of **5.5** (1 eq) and 2,6-lutidine (2.5 eq) in dioxane (20 mL/mmol) Fmoc-Cl (1.5 eq) is added at 0°C. The mixture is allowed to reach room temperature and is left overnight stirring under a nitrogen atmosphere. Successively, the mixture is concentrated, dissolved in EtOAc and washed with 5% citric acid and brine. The organic phase is dried (Na_2SO_4) and concentrated. Compound **5.6** is isolated by flash chromatography (petroleum ether/EtOAc, 1:2). White solid, yield: 58%. ^{1}H NMR (200 MHz, DMSO): mixture of epimers and rotamers δ = 7.68-7.61 (m, 2 H), 7.58-7.45 (m, 2 H), 7.32-7.14 (m, 4 H), 5.11 (s, 1 H major), 5.05 (d, 1 H minor), 4.81 (d, 1 H minor), 4.72-4.55 (m, 1 H major), 4.47-4.23 (m, 6 H), 4.00-3.81 (m, 1 H), 2.97 (dd, 1 H major), 2.79-2.42 (m, 1 H minor). ^{13}C NMR (50 MHz, DMSO): mixture of epimers and rotamers δ = 171.9 (s, 1 C), 155.4 and 154.7 (s, 1 C), 143.0 and 142.9 (s, 2 C), 140.4 (s, 2 C), 127.1 (d, 2 C), 126.5 (d, 2 C), 124.5 (d, 2 C), 119.3 (d, 2 C), 91.0 (d, 1 C minor), 88.1 and 87.8 (d, 1 C major), 70.5 and 70.1 (t, 1 C), 67.8 (t, 1 C), 64.1 and 63.8 (d, 1 C), 55.3 and 52.8 (d, 1 C), 46.4 (d, 1 C), 44.6 and 43.9 (t, 1 C). MS: *m*/*z* (%): 381 (1) $[M]^+$, 179 (23), 178 (100), 166 (9), 165 (18), 89 (4), 76 (3), 63 (3), 54 (9).

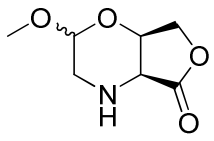
(5*R*/*S*,3a*S*,7a*R*)-5-hydroxy-7-carbobenzyloxy-hexahydro-2,4-dioxa-7-aza-inden-1-one



5.7

To a solution of **5.5** (1 eq) and $NaHCO_3$ (2 eq) in H_2O-EtOAc (1.7 mL/mmol-2 mL/mmol) benzylchloroformate (1 eq) is added at 0°C. The mixture is allowed to reach room temperature and is left overnight stirring under a nitrogen atmosphere. Successively, the mixture is washed with 1N HCl and brine. The organic phase is dried (Na_2SO_4) and concentrated. Compound **5.7** is isolated by flash chromatography (petroleum ether/EtOAc, 1:2). White solid, yield: 53%. ^{1}H NMR (200 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 7.31 (s, 5 H), 5.15 (s, 2 H major), 5.12 (s, 2 H minor), 4.90-4.64 (m, 2 H), 4.30-4.23 (m, 3 H), 4.03-3.87 (m, 1 H), 3.03-2.88 (m, 1 H major), 2.75-2.56 (m, 1 H minor). ^{13}C NMR (50 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 172.8 and 172.5 (s, 1 C), 156.3 and 155.8 (s, 1 C), 135.7 and 135.5 (s, 1 C), 128.5 (d, 1 C), 128.3 (d, 1 C), 128.1 (d, 1 C), 127.9 (d, 1 C), 127.7 (d, 1 C), 91.8 and 91.4 (d, 1 C minor), 88.9 and 88.5 (d, 1 C major), 71.2 and 70.7 (t, 1 C), 68.3 (t, 1 C), 64.9 and 64.5 (d, 1 C), 53.9 (d, 1 C minor), 53.4 and 52.8 (d, 1 C, major), 45.9 and 45.4 (t, 1 C minor), 44.7 and 44.1 (t, 1 C major). MS: *m*/*z* (%): 294 (1) $[M]^+$, 293 (5), 132 (8), 92 (9), 91 (100), 65 (13).

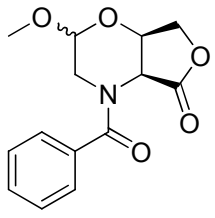
(5*R*/*S*,3a*S*,7a*R*)-5-methoxy-hexahydro-2,4-dioxa-7-aza-inden-1-one



5.8

Compound **4.4** (see Chapter 8.4) (1 eq) is added to a solution of $SOCl_2$ (2.5 eq) in MeOH (5 mL/mmol). The mixture is refluxed for 4h under a nitrogen atmosphere. Successively the mixture is concentrated and filtered on a weakly basic resin giving quantitatively compound **5.8** as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): mixture of epimers δ = 4.43-4.28 (m, 3 H), 3.76-3.70 (m, 2 H), 3.45 (s, 3 H major),3.40 (s, 3 H minor), 2.94-2.76 (m, 2 H), 2.44 (br, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): mixture of epimers δ = 174.8 (s, 1 C), 95.8 (d, 1 C), 70.8 (t, 1 C), 65.3 (d, 1 C), 55.6 (q, 1 C), 54.8 (d, 1 C), 44.4 (t, 1 C). MS: *m*/*z* (%): 173 (17) $[M]^+$, 115 (10), 113 (12), 85 (59), 67 (16), 58 (100).

(5*R*/*S*,3a*S*,7a*R*)-7-benzoyl-5-methoxy-hexahydro-2,4-dioxa-7-aza-inden-1-one

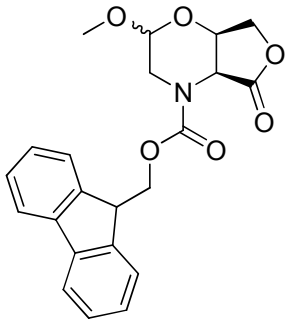


5.9

To a solution of compound **4.4** (see Chapter 8.4) (1 eq) and DIPEA (1.2 eq) in anhydrous THF (1.8 mL/mmol), benzoyl chloride (1 eq) is added at 0°C. The mixture is allowed to reach room temperature and is left overnight stirring under a nitrogen atmosphere. Successively the mixture is concentrated, diluted with EtOAc, and washed with water and brine. The organic phase is dried (Na_2SO_4) and concentrated. Compound **4.4**, functionalized at the nitrogen atom with Bz group (**4.4a**), is isolated by flash chromatography (petroleum ether/EtOAc, 1:1). Colourless oil, yield: 99%. ^{1}H NMR (200 MHz, $CDCl_3$): mixture of rotamers δ = 7.50-7.41 (m, 5 H), 4.79 (br, 1 H), 4.47 (br, 2 H), 4.12-3.96 (m, 2 H), 3.74 (s, 3 H), 3.46-3.43 (m, 2 H), 3.33 (s, 3 H), 3.23 (s, 3 H), 1.32 (s, 6 H). MS: *m*/*z* (%): 381 (1) $[M]^+$, 366 (5), 249 (16), 144 (3), 105 (55), 101 (11), 77 (33), 75 (100), 58 (15).

A solution of compound **4.4a** and $SOCl_2$ (1.5 eq) in MeOH (10 mL/mmol) is overnight stirred at room temperature under a nitrogen atmosphere. Successively, the mixture is concentrated and purified by flash chromatography (petroleum ether/EtOAc, 1:1), thus giving product **5.9** as a white solid, yield: 66%. ^{1}H NMR (400 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 7.60-7.53 (m, 2 H), 7.47-7.42 (m, 3 H), 5.68 (d, 1 H), 4.66-4.28 (m, 4 H), 3.67 (d, 1 H major), 3.46 (s, 3 H minor), 3.41 (s, 3 H major), 3.30 (d, 1 H major), 2.99 (d, 1 H minor). ^{13}C NMR (50 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 171.9 and 171.7 (s, 2 C), 133.5 and 133.3 (s, 1 C), 130.3 and 130.1 (d, 1 C), 128.4 and 128.2 (d, 2 C), 127.2 and 126.9 (d, 2 C), 95.3 and 94.7 (d, 1 C), 70.8 and 70.5 (t, 1 C), 65.3 and 64.9 (d, 1 C), 56.5 and 56.1 (q, 1 C), 51.3 (d, 1 C), 47.2 (t, 1 C). MS: *m*/*z* (%): 277 (7) $[M]^+$, 216 (7), 118 (10), 105 (100), 85 (15), 77 (52), 71 (24), 69 (18), 57 (63), 55 (19), 51 (24).

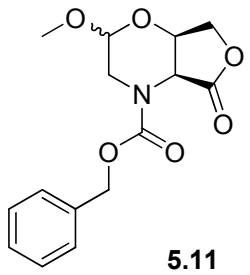
(4a*S*,7a*R*)-(9*H*-fluoren-9-yl)methyl-2-methoxy-5-oxotetrahydro-2*H*-furo[3,4-*b*][1,4]oxazine-4(3*H*)-carboxylate



5.10

Compound **4.4** is functionalized at the nitrogen atom with Fmoc group to give **4.5** (see Chapter 8.4). A solution of **4.5** and $SOCl_2$ (1.5 eq) in MeOH (10 mL/mmol) is overnight stirred at room temperature under a nitrogen atmosphere. Successively, the mixture is concentrated and purified by flash chromatography (petroleum ether/EtOAc, 1:1), giving product **5.10** as a white solid, yield: 86%. ^{1}H NMR (400 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 7.77-7.73 (m, 2 H, Ar), 7.61-7.56 (m, 2 H, Ar), 7.41-7.37 (m, 2 H, Ar), 7.32-7.25 (m, 2 H, Ar), 5.12 (d, *J* = 5.4 Hz, 1 H, $CHOCH_3$), 4.68-4.30 (m, 7 H), 4.05-3.99 (m, 1 H), 3.45 (s, 3 H, OCH_3 major), 3.41 (s, 3 H, OCH_3 minor), 3.17 (dd, *J* = 14.0 Hz, *J* = 2.4 Hz, 1 H, major) ppm. ^{13}C-NMR (100 MHz, $CDCl_3$) mixture of rotamers: δ = 169.7 (s), 155.8 (s), 143.5 (s, 2 C), 141.2 (s, 2 C), 127.7 (d, 2 C), 127.2 and 127.0 (d, 2 C), 125.2 and 125.1 (d, 2 C), 119.9 and 119.8 (d, 2 C), 109.9 (s), 95.6 and 95.1 (d), 70.6 (t), 68.4 (t), 65.0 and 64.5 (q), 55.3 and 55.1 (d), 532 and 53.1 (d), 46.9 (d), 43.9 and 43.1 (t) ppm.

(5*R*/*S*,3a*S*,7a*R*)-7-carbobenzyloxy-5-methoxy-hexahydro-2,4-dioxa-7-aza-inden-1-one

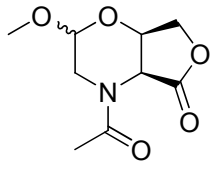


5.11

To a solution of **4.4** (see Chapter 8.4) (1 eq) and $NaHCO_3$ (2 eq) in H_2O-EtOAc (1.7 mL/mmol - 2 mL/mmol) Cbz-Cl (1 eq) is added at 0°C. The mixture is allowed to reach room temperature and is left overnight stirring under a nitrogen atmosphere. Successively, the mixture is washed with aqueous 1N HCl and brine. The organic phase is dried (Na_2SO_4) and concentrated. Compound **4.4**, functionalized at the nitrogen atom with Cbz group (**4.4b**), is obtained after flash chromatography (petroleum ether/EtOAc, 1:1) as a colourless oil, yield: 80%. ^{1}H NMR (200 MHz, $CDCl_3$): mixture of rotamers δ = 7.35-7.21 (m, 5 H), 5.18-5.14 (m, 1 H), 4.70-4.42 (m, 3 H), 4.04-3.85 (m, 2 H), 3.73-3.56 (m, 4 H), 3.60 (s, 3 H), 3.41-3.27 (m, 6 H), 1.39 (s, 3 H), 1.35 (s, 3 H). MS: *m*/*z* (%): 412 (1) $[M]^+$, 279 (8), 162 (11), 101 (10), 91 (36), 75 (100), 65 (4).

A solution of **4.4b** and $SOCl_2$ (1.5 eq) in MeOH (10 mL/mmol) is overnight stirred at room temperature under a nitrogen atmosphere. Successively, the mixture is concentrated and purified by flash chromatography (petroleum ether/EtOAc, 1:1), giving product **5.11** as a white solid, yield: 99%. ^{1}H NMR (200 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 7.36 (s, 5 H), 5.21 (s, 2 H), 4.85-4.60 (m, 2 H), 4.48-4.36 (m, 3 H), 4.08-3.94 (m, 1 H), 3.44 and 3.41 (s, 3 H), 3.14-2.99 (m, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 172.3 (s, 1 C), 155.9 and 155.3 (s, 1 C), 135.9 (s, 1 C), 128.5 (d, 2 C), 128.1 (d, 2 C), 127.7 (d, 1 C), 95.7 and 95.2 (d, 1 C), 71.2 (t, 1 C), 68.2 (t, 1 C), 65.3 and 65.0 (d, 1 C), 55.7 (q, 1 C), 53.9 and 53.4 (d, 1 C), 44.1 and 43.4 (t, 1 C). MS: *m*/*z* (%): 307 (10) $[M]^+$, 132 (13), 91 (100), 65 (15), 58 (13).

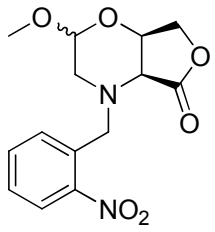
(5*R*/*S*,3a*S*,7a*R*)-5-methoxy-7-acetyl-hexahydro-2,4-dioxa-7-aza-inden-1-one



5.12

To a solution of **4.4** (see Chapter 8.4) (1 eq) and DIPEA (3.5 eq) in anhydrous CH_2Cl_2 (2 mL/mmol) Ac_2O (3 eq) and DMAP (0.1 eq) are added. The mixture is left overnight stirring under a nitrogen atmosphere. Successively the mixture is washed with H_2O/ice and 1M $KHSO_4$. The organic phase is dried (Na_2SO_4) and concentrated. Compound **4.4**, functionalized at the nitrogen atom with Ac group (**4.4c**), is isolated by flash chromatography (petroleum ether/EtOAc, 1:1) as a colourless oil; yield: 95%. ^{1}H NMR (200 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 4.78-4.71 (m, 1 H), 4.52 (t, 1 H), 4.34 (d, 1 H), 4.08-4.01 (d, 1 H), 3.88-3.80 (m, 1 H), 3.73 (s, 3 H), 3.55 (d, 1 H), 3.46 (s, 3 H), 3.44 (s, 3 H), 3.36 (d, 1 H), 2,16 (s, 3 H), 1.39 (s, 3 H), 1.34 (s, 3 H).
A solution of **4.4c** and $SOCl_2$ (1.5 eq) in MeOH (10 mL/mmol) is overnight stirred at room temperature under a nitrogen atmosphere. Successively the mixture is concentrated and purified by flash chromatography (petroleum ether/EtOAc, 1:1) thus giving product **5.12** as a yellow oil; yield: 72%. ^{1}H NMR (200 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 5.55 (d, 1 H), 4.65 (s, 1 H), 4.43-4.24 (m, 3 H), 3.64 (d, 1 H), 3.36 (s, 3 H), 3.28 (dd, 1 H), 2.16 (s, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 172.3 (s, 1 C), 171.7 (s, 1 C), 95.3 and 94.6 (d, 1 C), 70.7 (t, 1 C), 65.3 and 64.3 (d, 1 C), 55.2 and 55.0 (q, 1 C), 51.0 (d, 1 C), 46.1 (t, 1 C), 20.3 (q, 1 C). MS: *m*/*z* (%): 215 (14) $[M]^+$, 142 (29), 140 (10), 84 (56), 68 (15), 58 (100), 53 (18).

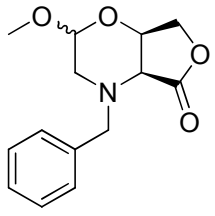
(5*R*/*S*,3a*S*,7a*R*)-5-methoxy-7-(2-nitrobenzyl)-hexahydro-2,4-dioxa-7-aza-inden-1-one



5.13

To a solution of **4.4** (see Chapter 8.4) (1 eq) and 2-nitrobenzaldehyde (1 eq) in THF (0.2M), $NaBH(OAc)_3$ (1.3 eq) is added in small portions. The mixture is left overnight stirring at room temperature, then it is concentrated, diluted with EtOAc, and washed with water and brine. The organic phase is dried (Na_2SO_4) and concentrated. Compound **4.4**, functionalized at the nitrogen atom with CH_2-*o*-NO_2Ph group (**4.4d**), is obtained after flash chromatography (petroleum ether/EtOAc, 1:1) as a colourless oil, yield: 40%. ^{1}H NMR (200 MHz, $CDCl_3$): mixture of epimers δ = 8.14 (d, 1 H), 7.78-7.62 (m, 2 H), 7.49-7.38 (m, 2 H), 4.96 (s, 2 H), 4.38-4.29 (m, 1 H), 4.11-3.98 (m, 1 H), 3.77 (s, 3 H), 3.24 (s, 3 H), 3.19 (s, 3 H), 2.91-2.57 (m, 2 H), 1.24 (s, 6 H).
A solution of **4.4d** and $SOCl_2$ (1.5 eq) in MeOH (10 mL/mmol) overnight stirred at room temperature and under a nitrogen atmosphere. Successively, the mixture is concentrated and purified through flash chromatography (petroleum ether/EtOAc, 1:1), thus giving compound **5.13** as a yellow oil, yield: 43%. ^{1}H NMR (200 MHz, $CDCl_3$): mixture of epimers δ = 7.88-7.38 (m, 4 H), 4.62 (m, 1 H), 4.60 (d, *J* = 15.4 Hz, 1 H), 4.5 (m, 1 H), 4.32 (d, *J* = 15.4 Hz, 1 H), 4.35 (d, *J* = 8 Hz, 1 H), 4.25 (s, 2 H), 3.59 (d, *J* = 4.0 Hz, 1 H), 3.38 (s, 3 H), 2.83 (dd, *J* = 12.5 Hz, *J* = 2.5 Hz, 1 H), 2.60 (d, *J* = 12.5 Hz, 1 H).

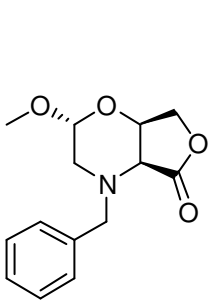
(5*R*/*S*,3a*S*,7a*R*)-7-benzyl-5-methoxy-hexahydro-2,4-dioxa-7-aza-inden-1-one



5.14

To a solution of **5.8** (1 eq) and benzaldehyde (1 eq) in THF (5 mL/mmol) $NaBH(OAc)_3$ (1.3 eq) is added in small portions. The mixture is left overnight stirring at room temperature, then is concentrated, diluted with EtOAc and washed with H_2O and brine. The organic phase is dried (Na_2SO_4) and concentrated. Compound **5.14** is isolated by flash chromatography (petroleum ether/EtOAc, 2:1). White solid, yield: 45%. ^{1}H NMR (200 MHz, $CDCl_3$): mixture of epimers δ = 7.45-7.29 (m, 5 H), 4.68 (s, 1 H), 4.49-4.26 (m, 2 H), 4.24 (s, 2 H), 4.11 (d, 1 H), 3.56 (d, 1 H major), 3.51 (d, 1 H minor), 3.48 (s, 3 H minor), 3.43 (s, 3 H major), 2.94-2.77 (m, 2 H major), 2.60-2.50 (m, 2 H minor). ^{13}C NMR (50 MHz, $CDCl_3$): mixture of epimers δ = 173.8 (s, 1 C), 136.9 (s, 1 C), 129.1 (d, 2 C), 128.3 (d, 1 C), 127.6 (d, 1 C), 127.4 (d, 1 C), 99.5 and 97.2 (d, 1 C), 70.7 and 70.4 (t, 1 C), 66.4 (d, 1 C), 58.3 and 57.3 (q, 1 C), 57.8 (t, 1 C), 55.7 (d, 1 C), 51.4 and 50.3 (t, 1 C). MS: *m*/*z* (%): 263 (5) $[M]^+$, 205 (8), 174 (7), 133 (13), 91 (100), 65 (95), 58 (33), 51 (66).

Crystallographic data are reported: only one diastereoisomer crystallizes.



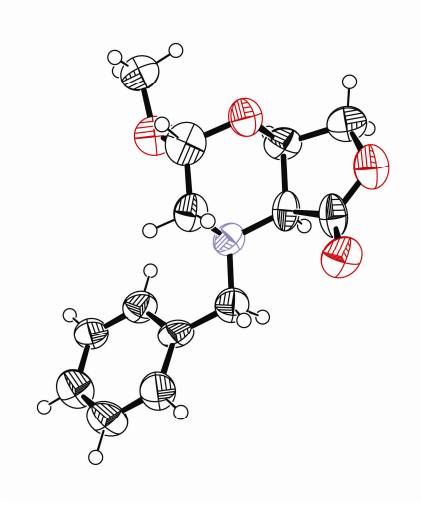


Table 1. Crystal data and structure refinement for exp_229.

Identification code	exp_229
Empirical formula	C14 H17 N O4
Formula weight	263.29
Temperature	293(2) K
Wavelength	1.54178 A
Crystal system, space group	Orthorhombic, P 21 21 21
Unit cell dimensions	a = 5.418(1)A alpha = 90 deg. b = 8.842(1)A beta = 90 deg. c = 27.603(3)A gamma = 90 deg.
Volume	1322.3(3) A^3
Z, Calculated density	4, 1.322 Mg/m^3
Absorption coefficient	0.804 mm^-1
F(000)	560
Crystal size	? x ? x ? mm
Theta range for data collection	5.25 to 62.12 deg.
Limiting indices	-6<=h<=5, -9<=k<=9, -31<=l<=28
Reflections collected/unique	5242 / 1853 [R(int) = 0.0880]
Completeness to theta=62.12	97.4 %
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	1853 / 0 / 172

Goodness-of-fit on F^2	1.069
Final R indices[I>2sigma(I)]	R1 = 0.1004, wR2 = 0.2395
R indices (all data)	R1 = 0.1495, wR2 = 0.2639
Absolute structure parameter	-0.9(10)
Largest diff. peak and hole	0.364 and -0.308 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for exp_229.
U(eq) is defined as one third of the trace of the Orthogonalized Uij tensor.

	x	y	z
		U(eq)	
N(1)	7619(11)	-1131(7)	1018(2)	50(2)
O(1)	7426(11)	1877(6)	682(2)	60(2)
O(2)	8719(10)	214(7)	-202(2)	71(2)
O(3)	5612(10)	1593(7)	1439(2)	72(2)
O(4)	11210(10)	-1377(7)	177(2)	69(2)
C(1)	6031(14)	765(9)	436(3)	56(2)
C(2)	8255(14)	-3191(9)	1602(3)	54(2)
C(3)	9253(16)	-720(11)	167(3)	62(2)
C(4)	6120(15)	-2779(9)	1878(3)	59(2)
C(5)	6309(15)	973(9)	-98(3)	64(2)
C(6)	9463(15)	-4780(11)	2285(3)	71(3)
C(7)	8551(16)	-2660(10)	1103(3)	59(2)
C(8)	8989(15)	66(9)	1253(3)	59(2)
C(9)	7335(15)	-4358(11)	2541(3)	72(3)
C(10)	9865(17)	-4198(11)	1824(3)	69(3)
C(11)	7113(15)	-797(10)	523(3)	55(2)
C(12)	7758(16)	1599(11)	1184(3)	69(3)
C(13)	5722(16)	-3334(10)	2341(3)	62(2)
C(14)	4500(20)	3092(10)	1455(3)	82(3)

Table 3. Bond lengths [A] and angles [deg] for exp_229.

N(1)-C(11)	1.426(9)
N(1)-C(8)	1.446(9)
N(1)-C(7)	1.462(10)
O(1)-C(1)	1.414(9)
O(1)-C(12)	1.419(10)
O(2)-C(3)	1.341(10)
O(2)-C(5)	1.495(10)
O(3)-C(12)	1.359(10)
O(3)-C(14)	1.457(9)
O(4)-C(3)	1.209(9)
C(1)-C(5)	1.492(10)
C(1)-C(11)	1.520(11)
C(2)-C(10)	1.388(11)
C(2)-C(4)	1.433(11)
C(2)-C(7)	1.464(11)
C(3)-C(11)	1.521(11)
C(4)-C(13)	1.385(11)
C(6)-C(10)	1.391(11)
C(6)-C(9)	1.402(11)
C(8)-C(12)	1.523(11)
C(9)-C(13)	1.374(11)

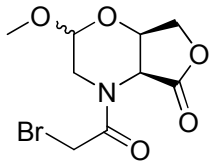
C(11)-N(1)-C(8)	112.1(6)
C(11)-N(1)-C(7)	114.3(6)
C(8)-N(1)-C(7)	115.3(6)
C(1)-O(1)-C(12)	114.6(6)
C(3)-O(2)-C(5)	108.6(6)
C(12)-O(3)-C(14)	111.5(7)
O(1)-C(1)-C(5)	109.5(7)
O(1)-C(1)-C(11)	110.5(6)
C(5)-C(1)-C(11)	103.2(7)
C(10)-C(2)-C(4)	115.8(8)
C(10)-C(2)-C(7)	123.5(8)
C(4)-C(2)-C(7)	120.5(7)
O(4)-C(3)-O(2)	120.2(7)
O(4)-C(3)-C(11)	129.2(9)
O(2)-C(3)-C(11)	110.6(8)
C(13)-C(4)-C(2)	121.8(8)
C(1)-C(5)-O(2)	102.9(6)
C(10)-C(6)-C(9)	119.4(9)
N(1)-C(7)-C(2)	114.2(7)
N(1)-C(8)-C(12)	111.7(7)
C(13)-C(9)-C(6)	119.7(9)
C(2)-C(10)-C(6)	122.8(9)
N(1)-C(11)-C(1)	114.5(7)
N(1)-C(11)-C(3)	118.8(7)
C(1)-C(11)-C(3)	98.7(7)
O(3)-C(12)-O(1)	113.5(7)
O(3)-C(12)-C(8)	107.8(8)
O(1)-C(12)-C(8)	109.4(7)
C(9)-C(13)-C(4)	120.3(8)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for exp_229.
The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
N(1)	39(4)	58(4)	54(4)	-4(3)	14(3)	1(4)
O(1)	54(3)	71(4)	56(4)	2(3)	5(3)	-4(3)
O(2)	51(3)	100(5)	61(4)	-3(4)	4(3)	-8(4)
O(3)	53(4)	78(5)	86(4)	1(4)	3(3)	-6(4)
O(4)	33(3)	92(4)	84(4)	-10(4)	5(3)	10(3)
C(1)	27(4)	67(6)	75(6)	4(5)	6(4)	20(5)
C(2)	37(5)	55(5)	70(6)	-3(4)	0(4)	18(4)
C(3)	51(6)	96(7)	40(5)	-4(5)	8(4)	-6(5)
C(4)	46(5)	64(6)	68(6)	-4(5)	-3(4)	11(5)
C(5)	43(5)	68(6)	81(7)	1(5)	-5(5)	6(5)
C(6)	38(5)	92(7)	83(7)	12(6)	-9(5)	14(5)
C(7)	47(5)	70(6)	61(6)	-4(5)	-2(4)	11(4)
C(8)	46(5)	72(6)	59(5)	-6(5)	4(4)	0(5)
C(9)	47(5)	95(7)	73(6)	8(5)	1(5)	3(6)
C(10)	52(5)	89(7)	65(6)	-3(5)	-1(5)	12(5)
C(11)	48(5)	76(6)	42(5)	-9(4)	10(4)	-12(5)
C(12)	42(5)	81(7)	84(7)	-3(5)	6(5)	-18(6)
C(13)	49(5)	70(6)	65(6)	-1(5)	1(4)	17(5)
C(14)	96(8)	69(7)	80(7)	-6(5)	2(6)	18(6)

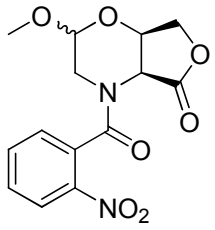
(5*R*/*S*,3a*S*,7a*R*)-7-(2-Bromo-acetyl)-5-methoxy-hexahydro-2,4-dioxa-7-aza-inden-1-one



5.15

To a solution of **5.8** (1 eq) and TEA (1 eq) in anhydrous CH_2Cl_2 (1 mL/mmol) bromoacetyl bromide (1 eq) is added dropwise at 0°C. The mixture is allowed to reach room temperature and is left 30min stirring under a nitrogen atmosphere. Successively the mixture is diluted with H_2O, washed with 1N HCl and brine. The organic phase is dried (Na_2SO_4) and concentrated. Compound **5.15** is isolated by flash chromatography (petroleum ether/EtOAc, 1:1). White solid, yield: 55%. ^{1}H NMR (200 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 5.44 (d, 1 H major), 5.34 (d, 1 H, minor), 4.74-4.22 (m, 5 H), 3.93 (d, 1 H major), 3.90 (d, 1 H minor), 3.67 (d, 1 H major), 3.48 (d, 1 H minor), 3.39 (s, 3 H), 3.33 (dd, 1 H major), 2.81 (dd, 1 H minor). ^{13}C NMR (50 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 172.1 (s, 1 C), 167.1 (s, 1 C), 95.8 and 94.8 (d, 1 C), 70.8 and 70.7 (t, 1 C), 65.7 and 64.8 (d, 1 C), 55.5 (q, 1 C), 51.6 (d, 1 C), 46.6 (t, 1 C), 25.7 and 25.4 (t, 1 C). MS: *m*/*z* (%): 294 (2) $[M]^+$, 293 (13) $[M-1]^+$, 214 (32), 172 (25), 170 (11), 154 (17), 142 (22), 122 (11), 120 (12), 113 (25), 112 (20), 68 (15), 57 (100), 54 (31).

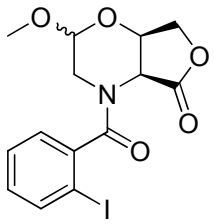
(5*R*/*S*,3a*S*,7a*R*)-7-(2-nitrobenzoyl)-5-methoxy-hexahydro-2,4-dioxa-7-aza-inden-1-one



5.16

To a solution of **5.8** (1 eq) and TEA (1.5 eq) in anhydrous CH_2Cl_2 (2.5 mL/mmol) a solution of 2-nitrobenzoyl chloride (1.2 eq) in anhydrous CH_2Cl_2 (2.5 mL/mmol) is added at 0°C. The mixture is allowed to reach room temperature and is left overnight stirring under a nitrogen atmosphere. Successively the mixture is washed with $NaHCO_3$, 1N HCl and brine. The organic phase is dried (Na_2SO_4) and concentrated. Compound **5.16** is isolated by flash chromatography (petroleum ether/EtOAc, 1:2). White solid, yield: 83%.^{1}H NMR (200 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 8.15 (d, 1 H major), 8.07 (d, 1 H minor), 7.74-7.47 (m, 3 H), 5.59 (d, 1 H), 4.79 (s, 1 H minor), 4.63-4.23 (m, 4 H), 4.35 (d, 1 H), 3.39 (s, 3 H minor), 3.35 (s, 3 H major), 3.24-3.18 (m, 1 H major), 2.96 (dd, 1 H minor). ^{13}C NMR (50 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 173.9 (s, 1 C), 167.7 (s, 1 C), 134.8 (s, 1 C), 134.5 and 134.2 (d, 1 C), 130.4 (d, 1 C), 128.7 (d, 1 C), 124.7 (d, 1 C), 116.1 (d, 1 C), 95.6 and 94.8 (d, 1 C), 70.9 (t, 1 C), 65.5 and 65.0 (d, 1 C), 56.5 and 55.6 (q, 1 C), 51.4 (d, 1 C), 46.8 (t, 1 C). MS: *m*/*z* (%): 322 (2) $[M]^+$, 292 (7), 232 (51), 215 (24), 151 (20), 150 (100), 133 (20), 104 (17), 84 (13), 76 (34), 68 (11), 58 (73), 51 (66).

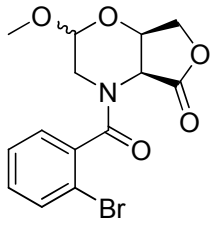
(5*R*/*S*,3a*S*,7a*R*)-7-(2-iodobenzoyl)-5-methoxy-hexahydro-2,4-dioxa-7-aza-inden-1-one



5.17

To a solution of **5.8** (1 eq) and TEA (1.5 eq) in anhydrous CH_2Cl_2 (2.5 mL/mmol) a solution of 2-iodobenzoyl chloride (1.2 eq) in anhydrous CH_2Cl_2 (2.5 mL/mmol) is added at 0°C. The mixture is allowed to reach room temperature and is left overnight stirring under a nitrogen atmosphere. Successively the mixture is washed with $NaHCO_3$, 1N HCl and brine. The organic phase is dried (Na_2SO_4) and concentrated. Compound **5.17** is isolated by flash chromatography (petroleum ether/EtOAc, 1:1). White solid, yield: 61%. ^{1}H NMR (200 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 7.80-7.64 (m, 1 H), 7.38-7.21 (m, 2 H), 7.11-7.01 (m, 1 H), 5.61 (d, 1 H major), 5.52 (d, 1 H minor), 4.78 (s, 1 H minor), 4.54-4.25 (m, 4 H), 4.08-3.98 (m, 1 H), 3.38 (s, 3 H minor), 3.32 (s, 3 H major), 3.22-3.15 (m, 1 H major), 2.91-2.59 (m, 1 H minor). ^{13}C NMR (50 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 171.4 (s, 1 C), 170.6 and 170.3 (s, 1 C), 142.2 (s, 1 C), 139.2 (d, 1 C), 130.8 and 130.6 (d, 2 C), 128.5 and 128.2 (d, 1 C), 128.0 and 127.6 (d, 1 C), 95.8 and 95.2 (d, 1 C), 70.9 (t, 1 C), 65.8 and 65.2 (d, 1 C), 56.2 and 55.4 (q, 1 C), 51.2 (d, 1 C), 47.5 and 46.5 (t, 1 C). MS: *m*/*z* (%): 403 (26) $[M]^+$, 276 (18), 230 (100), 202 (17), 105 (16), 76 (25), 49 (14).

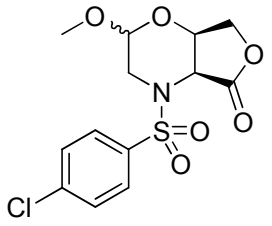
(5*R*/*S*,3a*S*,7a*R*)-7-(2-bromobenzoyl)-5-methoxy-hexahydro-2,4-dioxa-7-aza-inden-1-one



5.18

To a solution of **5.8** (1 eq) and TEA (1.5 eq) in anhydrous CH_2Cl_2 (2.5 mL/mmol) a solution of 2-bromobenzoyl chloride (1.2 eq) in anhydrous CH_2Cl_2 (2.5 mL/mmol) is added at 0°C. The mixture is allowed to reach room temperature and is left overnight stirring under a nitrogen atmosphere. Successively the mixture is washed with $NaHCO_3$, 1N HCl and brine. The organic phase is dried (Na_2SO_4) and concentrated. Compound **5.18** is isolated by flash chromatography (petroleum ether/EtOAc, 1:1). White solid, yield: 79%. ^{1}H NMR (200 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 7.59-7.52 (m, 1 H), 7.44-7.19 (m ,3 H), 5.66 (d, 1 H major), 5.55 (d, 1 H minor), 4.78 (s, 1 H minor), 4.57-4.28 (m ,4 H), 4.13-4.09 (m, 1 H), 3.41 (s, 3 H minor), 3.34 (s, 3 H major), 3.26-3.18 (m, 1 H major), 2.92 (dd, 1 H minor). ^{13}C NMR (50 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 170.9 (s, 1 C), 169.3 and 168.9 (s, 1 C), 135.8 (s, 1 C), 133.4 and 132.8 (d, 1 C), 130.9 and 130.7 (d, 2 C), 128.8 (d, 1 C), 127.9 and 127.4 (d, 1 C), 95.7 and 95.2 (d, 1 C), 70.8 (t, 1 C), 65.4 and 65.2 (d, 1 C), 56.1 and 55.5 (q, 1 C), 51.2 and 50.9 (d, 1 C), 47.3 and 46.3 (t, 1 C). MS: *m*/*z* (%): 355 (26) $[M-1]^+$, 184 (100), 182 (85), 154 (20), 99 (37), 76 (28), 58 (70), 54 (63), 50 (30).

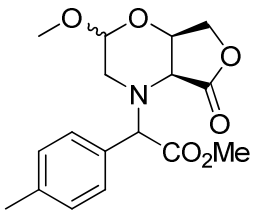
(5*R*/*S*,3a*S*,7a*R*)-7-(4-chlorobenzenesulfonyl)-5-methoxy-hexahydro-2,4-dioxa-7-aza-inden-1-one



5.19

To a solution of **5.8** (1 eq), TEA (2.5 eq) and DMAP (0.2 eq) in anhydrous CH_2Cl_2 (10 mL/mmol) 4-chlorobenzenesulfonyl chloride (2 eq) is added at 0°C. The mixture is allowed to reach room temperature and is left overnight stirring under a nitrogen atmosphere. Successively the mixture is washed with $NaHCO_3$, 1N HCl and brine. The organic phase is dried (Na_2SO_4) and concentrated. Compound **5.19** is isolated by flash chromatography (petroleum ether/EtOAc, 1:1). White solid, yield: 87%. ^{1}H NMR (200 MHz, $CDCl_3$): mixture of epimers δ = 7.96 (d, 2 H minor), 7.82 (d, 2 H major), 7.58 (d, 2 H minor), 7.45 (d, 2 H major), 4.86 (d, 1 H), 4.61 (s, 1 H minor), 4.51-4.28 (m, 4 H), 3.64 (d, 1 H), 3.44 (s, 3 H minor), 3.30 (s, 3 H major), 2.99 (dd, 1 H major), 2.57 (dd, 1 H minor). ^{13}C NMR (50 MHz, $CDCl_3$): mixture of epimers δ = 171.2 (s, 1 C), 139.3 (s, 1 C), 137.9 (s, 1 C), 129.3 and 129.2 (d, 2 C), 129.0 and 128.4 (d, 2 C), 94.7 (d, 1 C), 70.8 and 70.7 (t, 1 C), 64.9 (d, 1 C), 55.6 and 55.4 (q, 1 C), 54.6 and 54.2 (d, 1 C), 44.8 and 44.3 (t, 1 C).

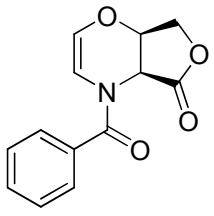
(5*R*/*S*,3a*S*,7a*R*)-7-(carbomethoxy-4-tolylmethyl)-5-methoxy-hexahydro-2,4-dioxa-7-aza-inden-1-one



5.20

A solution of **5.8** (1 eq), p-tolylboronic acid (1 eq) and glyoxylic acid (1 eq) in EtOH (3.5 mL/mmol) is left overnight stirring at room temperature, then is concentrated. The crude acid was dissolved in $MeOH/CH_2Cl_2$ (5 mL/mmol-5mL/mmol) and was added $TMSCHN_2$ (2M in Et_2O) dropwise. The mixture is left 2h stirring at room temperature successively is concentrated. Compound **5.20** is isolated by flash chromatography (petroleum ether/EtOAc, 3:2). White solid, yield: 65%. ^1H NMR (200 MHz, $CDCl_3$): mixture of epimers δ = 7.48 (d, 2 H), 7.16 (d, 2 H), 5.16 (s, 1 H), 4.68 (s, 1 H), 4.47 (s, 1 H), 4.15 (s, 2 H), 3.67 (s, 3 H), 3.48 (s, 3 H), 3.42 (d, 1 H), 2.99-2.81 (m, 2 H), 2.32 (s, 3 H).

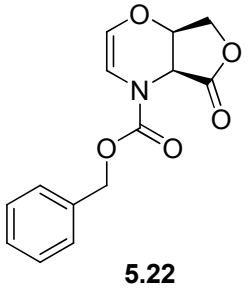
(4a*S*,7a*R*)-4-benzoyl-7,7a-dihydro-4*H*-furo[3,4-*b*][1,4]oxazin-5(4a*H*)-one



5.21

A mixture of **4.4a** (see molecule **5.9**) (1 eq) and *p*-toluenesulfonic acid (0.1 eq) in toluene (10 mL/mmol) is refluxed (110°C) for 3h in presence of 4Å molecular sieves. Successively, the mixture is filtered over $NaHCO_3$, and purified by flash chromatography (petroleum ether/EtOAc, 3:2), giving compound **5.21** as a white solid, yield: 20%. ^{1}H NMR (200 MHz, $CDCl_3$): mixture of rotamers δ = 7.61-7.58 (m, 2 H), 7.50-7.41 (m, 3 H), 6.04 (s, 1 H), 5.86 (s, 1 H), 5.71 (s, 1 H), 4.59-4.50 (m, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): mixture of rotamers δ = 186.8 (s, 1 C), 158.1 (s, 1 C), 133.3 (s, 1 C) 131. (d, 2 C), 128.6 (d, 2 C), 128.2 (d, 1 C), 106.1 (d, 1 C), 101.0 (d, 1 C), 71.0 (t, 1 C), 70.1 (d, 1 C), 51.8 (d, 1 C). MS: *m*/*z* (%): 245 (8) $[M]^+$, 105 (100), 77 (57), 51 (24).

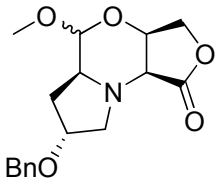
(4a*S*,7a*R*)-benzyl-5-oxo-4a,5,7,7a-tetrahydro-4*H*-furo[3,4-*b*][1,4]oxazine-4-carboxylate



5.22

A mixture of **4.4b** (see molecule **5.11**) (1 eq) and *p*-toluenesulfonic acid (0.1 eq) in toluene (10 ml/mmol) is refluxed (110°C) for 3h in presence of 4Å molecular sieves. Successively the mixture is filtered on $NaHCO_3$ and purified by flash chromatography (petroleum ether/EtOAc, 3:2) giving compound **5.22** as a white solid yield: 23%. ^{1}H NMR (200 MHz, $CDCl_3$): mixture of rotamers δ = 7.37 (s, 5 H minor), 7.34 (s, 5 H major), 6.46 (d, 1 H minor), 6.30 (d, 1 H major), 6.02 (d, 1 H minor), 5.89 (d, 1 H major), 5.24 (d, 2 H minor), 5.18 (d, 2 H major), 5.09-4.47 (m, 2 H), 4.40 (d, 2 H major), 4.35 (d, 2 H minor). ^{13}C NMR (100 MHz, $CDCl_3$): mixture of rotamers δ = 185.7 (s, 1 C), 158.3 (s, 1 C), 129.3 (1 C), 128.5 (1 C), 128.4 (1 C), 128.2 (1 C), 127.9 (1 C), 104.3 and 104.1 (d, 1 C), 95.5 and 95.2 (d, 1 C), 71.0 and 70.9 (1 C), 68.9 and 68.6 (1 C), 65.1 and 64.8 (1 C), 53.5 and 53.7 (1 C). MS: *m*/*z* (%): 275 (2) $[M]^+$, 231 (7), 91 (100), 65 (16).

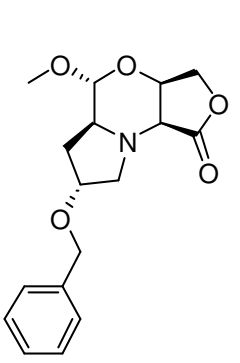
(3a*R*, 5a*S*, 7*R*, 9a*S*)-7-(benzyloxy)-5-methoxyoctahydro-1*H*-furo[3,4-*b*]pyrrolo[1,2-*d*] [1,4]oxazin-1-one



5.23

Compound **5.3** (1 eq) is added to a solution of $SOCl_2$ (2.5 eq) in MeOH (5 mL/mmol). The mixture is refluxed for 4h under a nitrogen atmosphere. Successively the mixture is concentrated and filtered on a weakly basic resin giving compound **5.23** as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36-7.25 (m, 5 H, Ar), 4.65-4.62 (m, 1 H, C*H*CH_2O), 4.56 (d, *J* = 6.8 Hz, 1 H, C*H*OCH_3), 4.47 (q, *J* = 11.6 Hz, 2 H, CH_2Ph), 4.39 (d, *J* = 3.6 Hz, 2 H, CH_2O), 4.25-4.20 (m, 1 H, CHOBn), 4.01 (dd, *J* = 6.4 Hz, *J* = 3.6 Hz, 1 H, CH_2N), 3.43 (s, 3 H, OCH_3), 3.26 (d, *J* = 6.0 Hz, 1 H, CHC=O), 2.73-2.67 (m, 1 H, C*H*$CHOCH_3$), 2.49 (dd, *J* = 4.8 Hz, *J* = 6.5 Hz, 1 H, CH_2N), 2.14 (ddd, *J* = 13.2 Hz, *J* = 6.0 Hz, *J* = 1.6 Hz, 1 H, CH_2CHOBn), 1.78-1.70 (m, 1 H, CH_2CHOBn) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): mixture of epimers δ = 174.7 (C=O), 137.9 (C, Ar), 128.4 (CH, 3 C, Ar), 127.6 (CH, 2 C, Ar), 104.3 (*C*$HOCH_3$), 76.8 (CHOBn), 71.2 (CH_2Ph), 70.5 (CH_2O), 67.2 (*C*HCH_2O), 61.6 (*C*HC=O), 60.2 (*C*$HCHOCH_3$), 59.3 (CH_2N), 55.6 (OCH_3), 35.2 (*C*H_2CHOBn) ppm.

Crystallographic data are reported: only one diastereoisomer crystallizes.



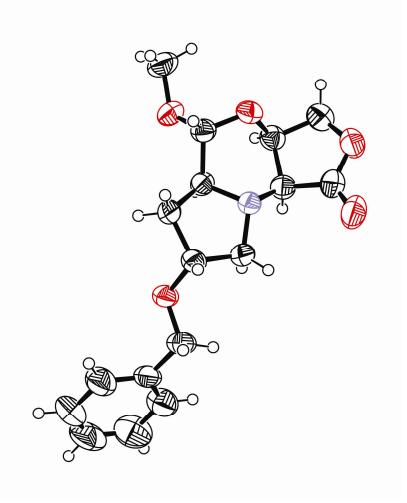


Table 1. Crystal data and structure refinement for new.

Identification code	new
Empirical formula	C34 H42 N2 O10
Formula weight	638.70
Temperature	293(2) K
Wavelength	1.54178 A
Crystal system,space group	Monoclinic, C 2
Unit cell dimensions	a = 25.827(1)A alpha=90deg. b = 4.624(1)A beta=135.374(2)deg. c = 19.232(1)A gamma=90deg.
Volume	1613.4(4) A^3
Z, Calculated density	2, 1.315 Mg/m^3
Absorption coefficient	0.802 mm^-1
F(000)	680
Crystal size	? x ? x ? mm
Theta range for data collection	4.60 to 71.12 deg.
Limiting indices	-30<=h<=27, -5<=k<=4, -23<=l<=22
Reflections collected/unique	3473/2151 [R(int) = 0.0173]
Completeness to theta=71.12	93.2 %
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2151 / 1 / 208

Goodness-of-fit on F^2 1.058

Final R indices[I>2sigma(I)] R1 = 0.0355, wR2 = 0.0854

R indices (all data) R1 = 0.0469, wR2 = 0.0911

Absolute structure parameter -0.1(3)

Largest diff. peak and hole 0.115 and -0.141 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic
displacement parameters (A^2 x 10^3) for new.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
N(1)	1823(1)	10307(4)	10705(1)	47(1)
O(1)	2267(1)	11781(4)	12365(1)	56(1)
O(2)	3683(1)	11194(5)	12850(1)	71(1)
O(3)	3277(1)	8503(6)	11587(1)	86(1)
O(4)	1135(1)	13948(4)	11548(1)	59(1)
O(5)	159(1)	10104(4)	8177(1)	55(1)
C(1)	2472(1)	12155(6)	11328(2)	53(1)
C(2)	2585(1)	13574(6)	12148(2)	55(1)
C(3)	3416(1)	13507(7)	13031(2)	67(1)
C(4)	3167(1)	10388(7)	11891(2)	61(1)
C(5)	1488(1)	11607(6)	11565(1)	51(1)
C(6)	1240(1)	11594(6)	10574(1)	49(1)
C(7)	576(1)	9749(6)	9761(1)	55(1)
C(8)	700(1)	8783(6)	9126(1)	52(1)
C(9)	1482(1)	9808(6)	9699(1)	58(1)
C(10)	164(1)	8955(8)	7495(2)	70(1)
C(11)	-465(1)	10247(6)	6498(1)	58(1)
C(12)	-1184(1)	9717(9)	5988(2)	82(1)
C(13)	-1759(2)	10939(11)	5075(2)	103(1)
C(14)	-1614(2)	12636(9)	4658(2)	100(1)
C(15)	-903(2)	13178(9)	5151(2)	103(1)
C(16)	-333(2)	12017(8)	6070(2)	80(1)
C(17)	1236(2)	14068(8)	12378(2)	78(1)

Table 3. Bond lengths [A] and angles [deg] for new.

N(1)-C(1)	1.454(3)
N(1)-C(9)	1.465(2)
N(1)-C(6)	1.465(2)
O(1)-C(5)	1.421(3)
O(1)-C(2)	1.423(3)
O(2)-C(4)	1.348(3)
O(2)-C(3)	1.444(3)
O(3)-C(4)	1.192(3)
O(4)-C(5)	1.400(3)
O(4)-C(17)	1.424(2)
O(5)-C(8)	1.422(2)
O(5)-C(10)	1.425(3)
C(1)-C(4)	1.514(3)
C(1)-C(2)	1.532(3)
C(2)-C(3)	1.517(3)
C(5)-C(6)	1.519(3)
C(6)-C(7)	1.516(3)
C(7)-C(8)	1.536(3)
C(8)-C(9)	1.533(3)
C(10)-C(11)	1.496(3)
C(11)-C(16)	1.363(4)
C(11)-C(12)	1.372(4)
C(12)-C(13)	1.377(4)
C(13)-C(14)	1.351(5)
C(14)-C(15)	1.362(5)
C(15)-C(16)	1.369(4)
C(1)-N(1)-C(9)	115.98(16)
C(1)-N(1)-C(6)	110.13(18)
C(9)-N(1)-C(6)	104.93(15)
C(5)-O(1)-C(2)	112.57(16)
C(4)-O(2)-C(3)	110.90(19)
C(5)-O(4)-C(17)	114.0(2)
C(8)-O(5)-C(10)	112.09(18)
N(1)-C(1)-C(4)	110.9(2)
N(1)-C(1)-C(2)	111.29(17)
C(4)-C(1)-C(2)	103.47(18)
O(1)-C(2)-C(3)	108.12(19)
O(1)-C(2)-C(1)	109.0(2)
C(3)-C(2)-C(1)	103.04(18)
O(2)-C(3)-C(2)	106.4(2)
O(3)-C(4)-O(2)	121.6(2)
O(3)-C(4)-C(1)	128.2(2)
O(2)-C(4)-C(1)	110.2(2)
O(4)-C(5)-O(1)	112.2(2)
O(4)-C(5)-C(6)	106.73(18)
O(1)-C(5)-C(6)	111.47(16)
N(1)-C(6)-C(7)	102.72(18)
N(1)-C(6)-C(5)	108.81(16)
C(7)-C(6)-C(5)	116.87(18)
C(6)-C(7)-C(8)	105.02(17)
O(5)-C(8)-C(9)	112.28(19)
O(5)-C(8)-C(7)	108.92(17)
C(9)-C(8)-C(7)	104.62(17)
N(1)-C(9)-C(8)	104.22(15)
O(5)-C(10)-C(11)	108.6(2)

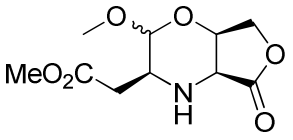
C(16)-C(11)-C(12)	117.9(2)
C(16)-C(11)-C(10)	120.3(2)
C(12)-C(11)-C(10)	121.8(3)
C(11)-C(12)-C(13)	121.4(3)
C(14)-C(13)-C(12)	119.5(3)
C(13)-C(14)-C(15)	120.0(3)
C(14)-C(15)-C(16)	120.3(3)
C(11)-C(16)-C(15)	120.9(3)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for new.
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
N(1)	47(1)	53(1)	42(1)	5(1)	32(1)	7(1)
O(1)	56(1)	66(1)	43(1)	6(1)	34(1)	2(1)
O(2)	51(1)	80(1)	62(1)	2(1)	34(1)	7(1)
O(3)	62(1)	107(2)	90(1)	-16(1)	54(1)	6(1)
O(4)	68(1)	64(1)	65(1)	-3(1)	53(1)	3(1)
O(5)	56(1)	67(1)	39(1)	6(1)	32(1)	14(1)
C(1)	55(1)	58(2)	50(1)	8(1)	39(1)	4(1)
C(2)	57(1)	52(1)	53(1)	5(1)	38(1)	5(1)
C(3)	61(1)	68(2)	58(1)	-3(1)	38(1)	-3(1)
C(4)	52(1)	70(2)	64(1)	-2(1)	42(1)	-3(1)
C(5)	55(1)	54(1)	48(1)	3(1)	38(1)	2(1)
C(6)	53(1)	53(1)	48(1)	14(1)	38(1)	14(1)
C(7)	46(1)	75(2)	45(1)	12(1)	33(1)	15(1)
C(8)	51(1)	60(2)	41(1)	9(1)	31(1)	13(1)
C(9)	54(1)	79(2)	47(1)	7(1)	38(1)	13(1)
C(10)	71(2)	89(2)	45(1)	2(1)	40(1)	19(2)
C(11)	61(1)	65(2)	41(1)	-5(1)	35(1)	2(1)
C(12)	69(2)	111(3)	55(1)	6(2)	40(1)	-8(2)
C(13)	62(2)	152(4)	53(2)	-5(2)	26(1)	2(2)
C(14)	98(2)	109(3)	48(1)	16(2)	36(2)	25(2)
C(15)	119(3)	98(3)	80(2)	24(2)	67(2)	5(2)
C(16)	78(2)	88(2)	64(2)	0(2)	47(1)	-7(2)
C(17)	82(2)	103(2)	72(2)	-28(2)	63(1)	-21(2)

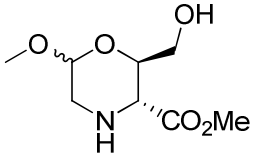
(5*R*/*S*,3a*S*,7a*R*)-6-carbomethoxymethyl-5-methoxy-hexahydro-2,4-dioxa-7-aza-inden-1-one



5.24

Compound **5.4** (1 eq) is added to a solution of $SOCl_2$ (2.5 eq) in MeOH (5 mL/mmol). The mixture is refluxed for 4h under a nitrogen atmosphere. Successively the mixture is concentrated and filtered on a weakly basic resin giving compound **5.24** as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): mixture of epimers δ = 4.49-4.13 (m, 3 H), 3.64 (s, 3 H minor), 3.59 (m, 3 H major), 3.53-3.41 (m, 3 H), 3.35 (s, 3 H major), 3.33 (s, 3 H minor), 3.16-3.02 (m, 1 H), 2.57-2.32 (m 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): mixture of epimers δ = 176.5 and 173.1 (s, 1 C), 172.1 and 171.6 (s, 1 C), 106.6 (d, 1 C), 98.9 (d, 1 C), 71.8 (d, 1 C), 70.8 (t, 1 C), 64.7 and 62.9 (d, 1 C), 63.8 and 62.7 (t, 1 C), 55.4 and 55.9 (q, 1 C), 52.5 and 52.2 (q, 1 C). MS: *m*/*z* (%): 246 (12) $[M+1]^+$, 245 (7) $[M]^+$, 234 (25), 214 (21), 202 (46), 186 (12), 172 (17), 170 (24), 158 (20), 154 (18), 130 (21), 112 (14), 85 (100), 75 (90), 71 (74), 55 (22).

(2*R*,3*R*)- methyl-2-(hydroxymethyl)-6-methoxymorpholine-3-carboxylate



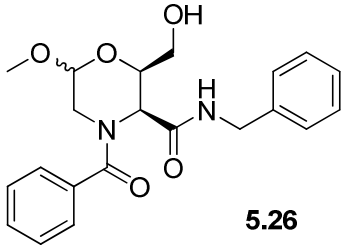
5.25

Compound **4.10** (see Chapter 8.4) (1 eq) is added to a solution of $SOCl_2$ (2.5 eq) in MeOH (5 mL/mmol). The mixture is refluxed for 4h under a nitrogen atmosphere. Successively the mixture is concentrated and filtered on a weakly basic resin giving quantitatively compound **5.25** as a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$): mixture of epimers δ = 4.52 (s, 1 H), 3.79-3.71 (m, 3 H), 3.72 (s, 3 H, OCH_3), 3.66-3.61 (m, 3 H), 3.48-3.42 (m, 2 H), 3.37 (s, 3 H, OCH_3), 2.91 (br, 1 H).

General Procedure for the Synthesis of Compounds of general formula III A 5.26-5.31.

To a solution of **IIB** (1 eq) and and amine (1 eq) in dry $CHCl_3$ (0.5 ml/mmol) was added under a nitrogen atmosphere $LiNTf_2$ (0.5 eq). The mixture was stirred in sealed vial at 85°C (oil bath) for 40h, then it was washed with a sat. $NaHCO_3$ solution, and the organic phase was dried (Na_2SO_4), filtered and concentrated, and purified by flash chromatography (petroleum ether/EtOAc, 1:1), thus giving product **IIIA**.

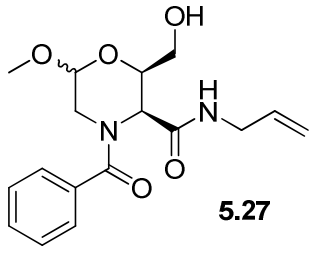
Benzyl-(5*R*/*S*,3a*S*,7a*R*)-4-benzoyl-2-hydroxymethyl-6-methoxy-morpholin-3-carboxamide



5.26

Compound **5.9** reacted with benzylamine thus giving product **5.26** as a white solid, yield: 93%. ^{1}H NMR (400 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 7.50-7.28 (m, 10 H), 7.01 (br, 1 H), 5.15 (d, 1 H), 4.70 (s, 1 H), 4.49 (dq, 2 H), 4.36-4.32 (m, 1 H), 4.03 (dd, 1 H), 3.84 (br, 1 H), 3.71 (dd, 2 H) 3.41 (s, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 172.3 (s, 1 C), 168.0 (s, 1 C), 137.9 (s, 1 C), 134.1 (s, 1 C), 130.3 (d, 1 C), 128.6 (d, 2 C), 128.4 (d, 2 C), 127.7 (d, 2 C), 127.6 (d, 2 C), 127.3 (d, 1 C), 95.7 (d, 1 C), 68.2 (d, 1 C), 61.9 (t, 1 C), 54.9 (q, 1 C), 53.3 (d, 1 C), 48.0 (t, 1 C), 43.5 (t, 1 C). MS: *m*/*z* (%): 384 (1) $[M]^+$, 352 (60), 250 (53), 219 (15), 128 (22), 104 (100), 91 (54), 77 (74), 67 (12), 58 (14), 51 (23).

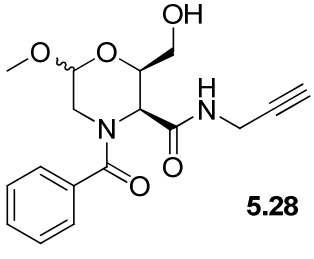
Allyl-(5*R*/*S*,3a*S*,7a*R*)-4-benzoyl-2-hydroxymethyl-6-methoxy-morfolin-3-carboxamide



5.27

Compound **5.9** reacted with allylamine thus giving product **5.27** as a white solid, yield: 97%. ^{1}H NMR (400 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 7.53-7.49 (m, 2 H), 7.42-7.39 (m, 3 H), 6.83 (br, 1 H), 5.88-5.81 (m, 1 H), 5.25-5.14 (m, 3 H), 4.70 (s, 1 H major), 4.61 (s, 1 H minor), 4.33 (q, 1 H), 4.03-3.75 (m, 7 H) 3.75 (s), 3.41 (s, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 172.2 (s, 1 C), 168.0 (s, 1 C), 134.2 (s, 1 C), 133.6 (d, 1 C), 130.3 (d, 2 C), 128.4 (d, 2 C) 127.7 (d, 1 C), 116.4 (t, 1 C), 95.7 (d, 1 C), 68.1 (d, 1 C), 61.8 (t, 1 C), 54.9 (q, 1 C), 53.2 (d, 1 C), 48.0 and 47.6 (t, 1 C), 41.9 (t, 1 C). MS: *m*/*z* (%): 334 (1) $[M]^+$, 302 (44), 250 (32), 128 (15), 106 (16), 105 (100), 96 (14), 77 (60), 58 (13), 51 (16).

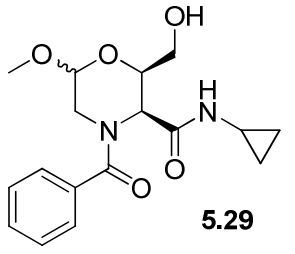
Propargyl-(5*R*/*S*,3a*S*,7a*R*)-4-benzoyl-2-hydroxymethyl-6-methoxy-morfolin-3-carboxamide



5.28

Compound **5.9** reacted with propargylamine thus giving product **5.28** as a yellow solid, yield: 93%. ^{1}H NMR (400 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 7.56-7.52 (m, 2 H), 7.41-7.38 (m, 3 H), 7.15 (br, 1 H), 5.18 (d, 1 H), 4.69 (s, 1 H), 4.61 (s, 1 H), 4.34 (q, 1 H), 4.14-4.04 (m, 2 H), 4.00-3.96 (m, 1 H), 3.84-3.69 (m, 3 H), 3.50 (s, 3 H minor), 3.40 (s, 3 H major), 2.23 (s, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 172.1 (s, 1 C), 167.7 (s, 1 C), 133.9 (s, 1 C), 130.0 (d, 1 C), 128.4 and 128.2 (d, 2 C), 127.4 and 126.8 (d, 2 C), 95.4 (d, 1 C), 71.2 (t, 1 C), 67.7 (d, 1 C), 61.2 (s, 1 C), 54.5 (q, 1 C), 52.5 (d, 1 C), 47.7 (t, 1 C), 28.7 (t, 1 C). MS: *m*/*z* (%): 332 (1) $[M]^+$, 300 (19), 250 (19), 127 (11), 105 (100), 77 (62), 57 (18), 51 (14).

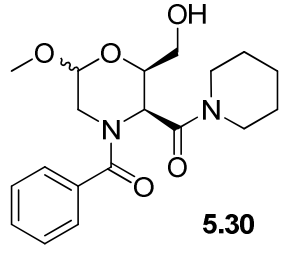
Cyclopropyl-(5*R*/*S*,3a*S*,7a*R*)-4-benzoyl-2-hydroxymethyl-6-methoxy-morfolin-3-carboxamide



5.29

Compound **5.9** reacted with cyclopropylamine thus giving product **5.29** as a white solid, yield: 86%. ^{1}H NMR (400 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 7.56-7.52 (m, 2 H), 7.41-7.38 (m, 3 H), 7.21 (br, 1 H), 5.16 (d, 1 H), 4.67 (d, 1 H), 4.33 (q, 1 H), 3.98 (dd, 1 H), 3.87-3.82 (m, 1 H), 3.67-3.64 (m, 2 H), 3.37 (s, 3 H), 2.78 (m, 1 H), 0.88 (d, 2 H), 0.49 (d, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 172.2 (s, 1 C), 169.5 (s, 1 C), 134.3 (s, 1 C), 130.3 (d, 1 C), 128.4 (d, 2 C), 127.6 (d, 2 C), 95.7 (d, 1 C), 68.1 (d, 1 C), 61.7 (t, 1 C), 54.9 (q, 1 C), 52.9 (d, 1 C), 48.1 (t, 1 C), 22.7 (d, 1 C), 6.6 (t, 1 C), 6.4 (t, 1 C). MS: *m*/*z* (%): 334 (1) $[M]^+$, 302 (2), 105 (100), 85 (14), 77 (60), 71 (25), 69 (19), 58 (21), 57 (87), 56 (26), 55 (24), 51 (19).

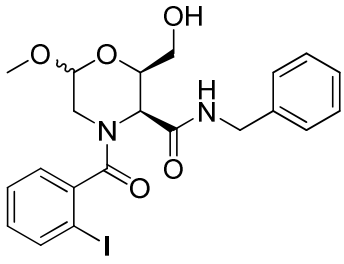
Piperidinyl-(5*R*/*S*,3a*S*,7a*R*)-4-benzoyl-2-hydroxymethyl-6-methoxy-morfolin-3-carboxamide



5.30

Compound **5.9** reacted with piperidine thus giving product **5.30** as a yellow solid, yield: 85%. ^{1}H NMR (400 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 7.56-7.52 (m, 2 H), 7.41-7.38 (m, 3 H), 5.56 (d, 1 H), 4.69 (d, 1 H), 4.31 (q, 1 H), 4.02 (dd, 1 H), 3.87-3.64 (m, 5 H), 3.55-3.48 (m, 2 H), 3.36 (s, 3 H), 2.60-2.56 (m, 1 H), 1.64 (m, 6 H). ^{13}C NMR (50 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 171.7 (s, 1 C), 167.0 (s, 1 C), 134.8 (s, 1 C), 129.9 (d, 1 C), 128.3 (d, 2 C), 127.5 (d, 2 C), 95.8 (d, 1 C), 68.5 (d, 1 C), 62.5 (t, 1 C), 54.7 (q, 1 C), 48.2 (d, 1 C), 47.2 (t, 1 C), 43.3 (t, 1 C), 26.9 (t, 1 C), 25.9 (t, 1 C), 24.7 (t, 1 C). MS: *m*/*z* (%): 362 (1) $[M]^+$, 330 (15), 250 (15), 128 (14), 105 (100), 84 (27), 77 (53), 69 (18), 56 (19), 51 (12).

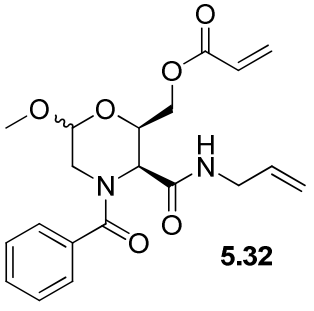
(2*R*/3*S*)-*N*-benzyl-2-hydroxymethyl-4-(2-iodobenzoyl)-6-methoxymorpholine-3-carboxamide



5.31

Compound **5.17** reacted with benzylamine thus giving product **5.31** as a white solid, yield: 97%. ^{1}H NMR (200 MHz, $CDCl_3$): mix of epimers and rotamers δ = 7.70 (d, 1 H), 7.42-7.35 (m, 2 H), 7.28 (s, 5 H), 7.09-7.03 (m, 2 H), 5.36 (d, 1 H major), 5.18 (d, 1 H minor), 4.60 (s, 1 H), 4.51 (t, 2 H), 4.32-4.25 (m, 1 H), 4.01-3.83 (m, 2 H), 3.63-3.38 (m, 1 H), 3.31 (s, 3 H) 3.26-3.19 (m, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): mix of epimers and rotamers δ = 170.9 and 170.7 (s, 1 C), 167.4 and 167.2 (s, 1 C), 141.1 and 140.9 (s, 1 C), 139.5 and 138.8 (d, 1C), 138.0 (s, 1 C), 137.5 (s, 1 C), 130.6 (d, 1 C), 128.6 (d, 2 C), 128.4 (d, 2 C), 128.2 (d, 1 C), 127.5 (d, 1 C), 127.2 and 126.9 (d, 1 C), 96.2 and 95.5 (d, 1 C), 68.6 and 67.8 (d, 1 C), 62.1 and 61.2 (t, 1 C), 56.2 and 54.8 (q, 1 C), 53.4 and 53.0 (d, 1 C), 48.0 and 46.9 (t, 1 C), 43.8 and 43.5 (t, 1 C). MS: *m*/*z* (%): 511 (1) $[M+1]^+$, 478 (48), 376 (11), 230 (100), 202 (13), 104 (22), 91 (43), 75 (13).

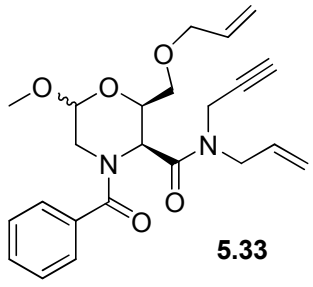
Allyl-(5*R*/*S*,3a*S*,7a*R*)-4-benzoyl-2-acryloyloxy-6-methoxy-morfolin-3-carboxamide



5.32

To a solution of **5.27** (1 eq) and TEA (1 eq) in anhydrous CH_2Cl_2 (5 mL/mmol) acryloyl chloride (1.1 eq) is added at 0°C. The mixture is allowed to reach room temperature and left overnight stirring, then a saturated $NaHCO_3$ solution is added. The organic phase is washed with 1N HCl, a saturated $NaHCO_3$ solution and brine, and successively dried (Na_2SO_4), filtered and concentrated. Compound **5.32** is obtained after flash chromatography (petroleum ether/EtOAc, 1:1) as a colourless oil, yield: 78%. ^{1}H NMR (400 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 7.56-7.55 (m, 2 H), 7.46-7.40 (m, 3 H), 6.68 (br, 1 H), 6.45 (d, 1 H), 6.16 (dd, 1 H), 5.87 (d, 1 H), 5.83-5.79 (m, 1 H), 5.19-5.11 (m, 3 H), 4.70-4.62 (m, 2 H), 4.55-4.41 (m, 2 H), 3.92-3.87 (m, 2 H), 3.77 (d, 1 H), 3.62 (d, 1 H), 3.41 (s, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 172.0 (s, 1 C), 167.0 (s, 1 C), 165.3 (s, 1 C), 137.1 (d, 1 C), 133.4 (d, 1 C), 133.6 (s, 1 C), 131.1 (t, 1 C), 130.2 (d, 1 C), 128.1 (d, 2 C), 127.7 (d, 2 C), 115.9 (t, 1 C), 95.1 (d, 1 C), 66.1 (d, 1 C), 63.8 (t, 1 C), 54.4 (q, 1 C), 52.6 (d, 1 C), 47.2 (t, 1 C), 41.2 (t, 1 C). MS: *m*/*z* (%): 388 (1) $[M]^+$, 356 (18), 232 (23), 106 (13), 105 (100), 96 (10), 77 (51), 58 (11), 57 (22), 55 (33).

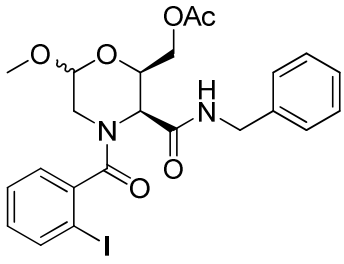
(5*R*/*S*,3a*S*,7a*R*)-2-allyloxymethyl-4-benzoyl-6-methoxy-morpholine-3-carboxylic acid allyl-prop-2-ynyl-amide



5.33

To a solution of **5.28** (1 eq) in anhydrous THF (10 ml/mmol) TBAI (0.01 eq) and allyl bromide (1 eq) were added. Then NaH (60% suspension in mineral oil; 20 mg, 3 eq) was added at 0°C. The mixture was allowed to reach room temperature and left overnight stirring, then washed with ice/water and exctracted with EtOAc. The organic phase is dried (Na_2SO_4), filtered and concentrated. Compound **5.33** is obtained after flash chromatography (petroleum ether/EtOAc, 1:1) as a colourless oil, yield: 88%. ^{1}H NMR (400 MHz, $CDCl_3$): mix of epimers and rotamers δ = 7.50-7.38 (m, 5 H), 5.96- 5.75 (m, 2 H), 5.62 (d, 1 H major), 5.50 (d, 1 H minor), 5.30-5.15 (m, 4 H), 4.66 (m, 1 H), 4.53-4.42 (m, 2 H), 4.24-3.92 (m, 6 H), 3.72-3.57 (m, 3 H), 3.37 (s, 3 H, minor), 3.35 (s, 3 H, major), 2.28 (s, 1 H minor), 2.20 (s, 1 H major). ^{13}C NMR (50 MHz, $CDCl_3$): mix of epimers and rotamers δ = 171.4 (s, 1 C), 168.0 and 167.5 (s, 1 C), 134.9 (s, 1 C), 134.4 and 134.2 (d, 1 C), 133.0 and 132.1 (d, 1 C), 129.9 (d, 1 C), 128.3 (d, 2 C), 127.5 (d, 2 C), 118.4 and 118.0 (t, 1 C), 117.2 and 116.5 (t, 1 C), 95.6 (d, 1 C), 73.0 and 72.4 (t, 1 C), 69.9 and 69.8 (t, 1 C), 67.5 and 67.0 (d, 1 C), 54.7 (q, 1 C), 50.1 and 49.8 (t, 1 C), 48.7 and 48.5 (d, 1 C), 47.7 and 47.4 (t, 1 C), 36.9 (s, 1 C) 33.8 (t, 1 C). MS: *m*/*z* (%): 412 (1) $[M]^+$, 380 (35), 318 (19), 290 (50), 232 (21), 105 (100), 77 (45).

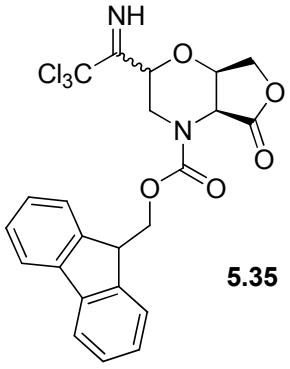
[(2*R*,3*S*)-3-(benzylcarbomoyl)-4-(2-iodobenzoyl)-6-methoxymorpholin-2-yl]methyl acetate



5.34

To a solution of **5.31** (1 eq) in anhydrous CH_2Cl_2 (2 mL/mmol) Ac_2O (3 eq) and DMAP (0.1 eq) are added. The mixture is left overnight stirring under a nitrogen atmosphere. Successively, the mixture is washed with H_2O/ice and 1M $KHSO_4$. The organic phase is dried (Na_2SO_4) and concentrated, giving compound **5.34** after flash chromatography (petroleum ether/EtOAc, 1:1) as colourless oil, yield: 95%. ^{1}H NMR (200 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 7.71 (d, 1 H), 7.44-7.36 (m, 2 H), 7.30 (s, 5 H), 7.14-7.04 (m, 1 H), 6.85 (br, 1 H), 5.32 (d, 1 H major), 5.21 (d, 1 H minor), 4.75-4.33 (m, 6 H), 3.55-3.40 (m, 1 H), 3.34 (s, 3 H) 3.27-3.20 (m, 1 H), 2.08 (s, 3 H). ^{13}C NMR (50 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 170.7 and 170.3 (s, 1 C), 166.2 (s, 1 C), 140.2 (s, 1 C), 139.0 and 138.7 (d, 1 C), 137.6 (s, 2 C), 130.6 (d, 1 C), 128.6 (d, 2 C), 128.4 (d, 2 C), 128.0 (d, 2 C), 127.5 and 127.2 (d, 1 C), 95.3 (d, 1 C), 66.9 (d, 1 C), 64.3 (t, 1 C), 54.6 (q, 1 C), 52.6 and 52.4 (d, 1 C), 46.7 (t, 1 C), 43.7 (t, 1 C), 20.9 (q, 1 C). MS: m/z (%): 553 (1) $[M+1]^+$, 520 (24), 358 (18), 333 (18), 230 (100), 202 (17), 105 (16), 104 (42), 90 (74), 76 (30), 75 (31), 68 (20), 64 (15), 58 (15), 50 (11).

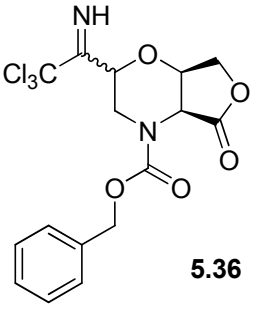
(3a*S*,5*R*/*S*,7a*R*)-7-fluorenylmethoxycarbonyl-5-trichloroacetimido-hexahydro-2,4-dioxa-7-aza-inden-1-one



5.35

To a solution of **5.6** (1 eq) in anhydrous CH_2Cl_2 (5 mL/mmol) trichloroacetonitrile (2 eq) is added dropwise and DBU (0.1 eq) at 0°C. The mixture is allowed to reach room temperature and is left 2h stirring under a nitrogen atmosphere. Successively the mixture is diluted with Et_2O and washed with H_2O and brine. The organic phase is dried (Na_2SO_4) and concentrated. Compound **5.35** is isolated by flash chromatography (petroleum ether/EtOAc, 1:2). White solid, yield: 38%. ^{1}H NMR (200 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 8.65 (d, 1 H), 7.76 (d, 2 H), 7.55 (d, 2 H), 7.43-7.29 (m, 4 H), 6.21 (d, 1 H), 5.25 (d, 1 H), 4.87-4.23 (m, 7 H), 3.35-3.14 (m, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 171.3 (s, 1 C), 160.1 (s, 1 C) 155.6 (s, 1 C), 143.3 (s, 2 C), 141.1 (s, 2 C), 127.8 (d, 2 C), 127.1 (d, 2 C), 124.8 (d, 2 C), 120.0 (d, 2 C), 92.2 (d, 1 C), 77.1 (s, 1 C), 70.5 (t, 1 C), 68.8 (t, 1 C), 67.0 and 66.6 (d, 1 C), 53.6 and 53.1 (d, 1 C), 47.1 (d, 1 C), 42.7 and 42.0 (t, 1 C). MS: *m*/*z* (%): 526 (1) $[M]^+$, 179 (37), 178 (100), 165 (8), 152 (3), 89 (3), 81 (1), 68 (2), 53 (3).

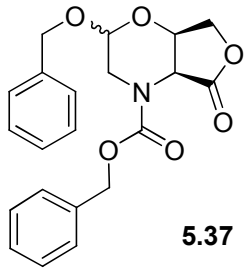
(3a*S*,5*R*/*S*,7a*R*)-7-carbobenzyloxy-5-trichloroacetimido-hexahydro-2,4-dioxa-7-aza-inden-1-one



5.36

To a solution of **5.7** (1 eq) in anhydrous CH_2Cl_2 (5 mL/mmol) trichloroacetonitrile (2 eq) is added dropwise and DBU (0.1 eq) at 0°C. The mixture is allowed to reach room temperature and is left 2h stirring under a nitrogen atmosphere. Successively the mixture is diluted with Et_2O and washed with H_2O and brine. The organic phase is dried (Na_2SO_4) and concentrated. Compound **5.36** is isolated by flash chromatography (petroleum ether/EtOAc, 1:2). White solid, yield: 46%. ^{1}H NMR (200 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 8.65 (d, 1 H), 7.33-7.31 (m, 5 H), 6.18 (d, 1 H), 5.24-4.99 (m, 3 H major and minor), 4.73-4.67 (m, 1 H), 4.42-4.24 (m, 3 H major and minor), 3.29-3.11 (m, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 171.4 (1 C), 160.1 (1 C), 155.5 (1 C), 135.5 (1 C), 128.5 (2 C), 128.3 (1 C), 128.0 (1 C), 127.9 (1 C), 92.4 and 92.1 (1 C), 77.1 (s, 1 C), 70.5 (1 C), 68.4 (1 C), 67.0 and 66.7 (1 C), 53.6 and 53.2 (1 C), 42.8 and 42.1 (1 C). MS: *m*/*z* (%): 436 (1) $[M]^+$, 275 (3), 232 (15), 231 (15), 169 (11), 141 (5), 132 (11), 92 (13), 91 (100), 82 (3), 65 (17), 51 (4).

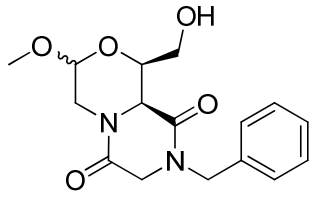
(3a*S*,5*R*/*S*,7a*R*)-5-benzyloxy-7-carbobenzyloxy-hexahydro-2,4-dioxa-7-aza-inden-1-one



5.37

To a solution of **5.36** (1 eq) and benzyl alcohol (1 eq) in anhydrous CH_2Cl_2-Cyclohexane (2.2 mL/mmol-4.4 mL/mmol) $BF_3{\cdot}2Et_2O$ (0.1 eq) is added dropwise at 0°C. The mixture is allowed to reach room temperature and is left 2h stirring under a nitrogen atmosphere. Successively the mixture is concentrated, dissolved in EtOAc and washed with $NaHCO_3$ and brine. The organic phase is dried (Na_2SO_4) and concentrated. Compound **5.37** is isolated by flash chromatography (petroleum ether/EtOAc, 1:1). White solid, yield: 93%. ^{1}H NMR (200 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 7.34-7.31 (m, 10 H), 5.29-5.12 (m, 3 H), 4.89-4.31 (m, 6 H), 4.08-3.97 (m, 1 H), 3.16-2.98 (m, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 171.9 and 171.6 (1 C), 155.8 and 155.0 (1 C), 136.3 and 136.2 (1 C), 135.6 and 135.4 (1 C), 128.2 (2 C), 127.9 (2 C), 127.8 (2 C), 127.7 (1 C), 127.6 (1 C), 127.4 (1 C), 127.3 (1 C), 93.1 and 92.7 (1 C), 70.4 and 70.3 (1 C), 69.1 and 69.0 (1 C), 67.9 and 67.8 (1 C), 65.0 and 64.6 (1 C), 53.3 and 53.0 (1 C), 43.8 and 43.1 (1 C). MS: *m*/*z* (%): 383 (1) $[M]^+$, 248 (5), 186 (11), 142 (6), 107 (1), 92 (8), 91 (100), 77 (2), 65 (8), 51 (3).

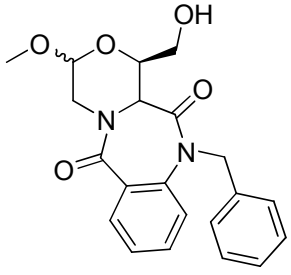
(1*S*,3*R*/*S*,10*R*)-8-Benzyl-1-hydroxymethyl-3-methoxy-hexahydro-pyrazino[2,1-c][1,4]oxazine-6,9-dione



5.38

To a solution of **5.15** (1 eq) and and benzylamine (1 eq) in dry $CHCl_3$ (0.5 ml/mmol) was added under a nitrogen atmosphere $LiNTf_2$ (0.5 eq). The mixture was stirred in sealed vial at 85°C (oil bath) for 40h, then it was washed with a sat. $NaHCO_3$ solution, and the organic phase was dried (Na_2SO_4), filtered and concentrated, and purified by flash chromatography (petroleum ether/EtOAc, 1:1), thus giving product **5.38** as a white solid, yield: 59%. ^{1}H NMR (200 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 7.38-7.31 (m, 5 H), 4.84 (t, 1 H), 4.73 (d, 1 H), 4.59 (d, 1 H), 4.51-4.32 (m, 3 H), 3.98-3.77 (m, 4 H), 3.52 (s, 3 H minor), 3.48 (s, 3 H major), 2.89 (dd, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 162.7 and 162.9 (s, 2 C), 134.6 (s, 1 C), 128.8 (d, 2C), 128.4 and 128.2 (s, 2 C), 128.1 (s, 1 C), 94.9 (d, 1 C), 72.7 (d, 1 C), 61.7 (t, 1 C), 56.2 (q, 1 C), 55.7 (d, 1 C), 49.3 (t, 1 C), 49.0 (t, 1 C), 45.2 (t, 1 C). MS: *m*/*z* (%): 306 (1) $[M]^+$, 288 (12), 260 (27), 120 (8), 91 (81), 65 (11), 58 (100), 56 (10).

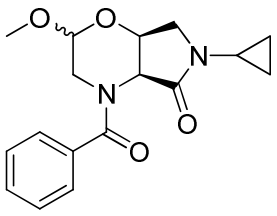
(1*S*,3*R*/*S*,11a*R*)-10-Benzyl-1-hydroxymethyl-3-methoxy-1,3,4,11a-tetrahydro-10H-2-oxa-4a,10-diaza-dibenzo[a,d]cycloheptene-5,11-dione



5.39

A solution of **5.34** (1 eq) in anhydrous DMSO (50 mL/mmol) was added under argon to a solution of K_2CO_3 (2 eq), CuI (0.1 eq) and sarcosine (0.2 eq) in anhydrous DMSO. The mixture is left overnight stirring at 110°C, successively the mixture is diluted with EtOAc washed with NH_4Cl and brine. The organic phase is dried (Na_2SO_4) concentrated and purified by flash chromatography (petroleum ether/EtOAc, 1:1), thus giving product **5.39** as a yellow oil, yield: 30%. ^{1}H NMR (400 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 7.86-7.07 (m, 9 H), 5.55 (d, J = 4.0 Hz, 1 H, major), 5.16 (d, J = 4.0 Hz, 1 H, minor), 4.78-4.31 (m, 4 H, CH_2Ph, CH_2OH), 4.02-3.99 (m, 1 H major), 3.93-3.90 (m, 1 H, minor), 3.60 (t, J = 6.0 Hz, 1 H), 3.43 (s, 3 H, OCH_3 major) and 3.41 (s, 3 H, OCH_3 major), 3.36 (s, 3 H, OCH_3 minor), 3.35-3.13 (m, 2 H).

(2*R*/*S*,4a*R*,7a*R*)-4-Benzoyl-6-cyclopropyl-2-methoxy-hexahydro-pyrrolo[3,4-b][1,4]oxazin-5-one



5.40

To a solution of **5.29** (1 eq) in anhydrous toluene (10 mL/mmol), triphenylphosphine (1 eq) were added. To this stirred solution diisopropyl azodicarboxylate (1 eq) was added dropwise. The resulting yellow solution is left overnight stirring at room temperature, successively the mixture is concentrated. Compound **5.40** is isolated by flash chromatography (petroleum ether/EtOAc, 1:1). Yellow solid, yield: 58%. ^{1}H NMR (400 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 7.65-7.29 (m, 5 H major and minor), 5.7 (d, 1 H, $CHOCH_3$, minor), 5.60 (d, 1 H, $CHOCH_3$, major), 4.74-4.07 (m, 4 H, CH_2NBz, CHCO, C*H*CHCO), 3.61-3.51 (m, 1H, CH_2NCyclopropyl), 3.42 (s, 3 H minor), 3.36 (s, 3 H major), 3.30 (br, 1 H, CH cyclopropyl), 3.10-3.01 (m, 1H, CH_2NCyclopropyl) 0.73-0.58 (m, 4 H, CH_2 cyclopropyl). ^{13}C NMR (100 MHz, $CDCl_3$): mixture of epimers and rotamers δ = 171.9, 167.4, 134.7, 131.9 (minor), 129.9, 129.8 (minor), 128.3, 128.2, 127.9 (minor), 125.8, 96.1 (minor), 95.4, 71.7, 71.3 (minor), 66.4, 65.8 (minor), 56.7, 55.2 and 55.0 (minor), 51.3, 46.5, 40.5, 29.3, 7.81 and 7.60, 7.46 and 7.24. MS: *m*/*z* (%): 316 (2) $[M]^+$, 315 (5), 255 (13), 204 (9), 151 (24), 105 (100), 77 (72), 70 (20), 68 (12), 58 (29), 54 (11), 51 (25).

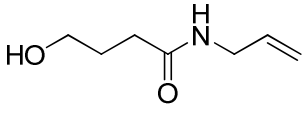
8.6. Experimental Section of Chapter 6

$LiNTf_2$-catalyzed aminolysis of lactones

General Procedure for the aminolysis of lactones

To a solution of lactone (1 eq) and amine (1 eq) in dry $CHCl_3$ (0.5 ml/mmol) was added under a nitrogen atmosphere $LiNTf_2$ (0.5 eq). The mixture was stirred in sealed vial at 85°C (oil bath) for 40h, then it was washed with a sat. $NaHCO_3$ solution, and the organic phase was evaporated to give the title products.

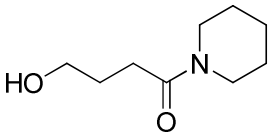
_N_-allyl-4-hydroxybutanamide



6.3

White solid 99% yield. M.p. 78-81°C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.62 (br, 1 H, NH), 6.03-5.73 (m, 1 H, =CH), 5.23-5.04 (m, 2 H, $=CH_2$), 4.02 (br, 1 H, OH), 3.88 (t, *J* = 5.5 Hz, 2 H), 3.72 (t, *J* = 5.5 Hz, 2 H), 2.40 (t, *J* = 6.2 Hz, 2 H), 1.96-1.79 (m, 2 H) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 178.2 (s, 1 C, C=O), 137.1 (d, 1 C, =CH), 119.4 (t, 1 C, $=CH_2$), 65.1 (t, 1 C, CH_2), 45.4 (t, 1 C, CH_2), 36.4 (t, 1 C, CH_2), 31.5 (t, 1 C, CH_2) ppm. MS: *m*/*z* (%) = 143 (1) $[M]^+$, 99 (28), 84 (10), 69 (14), 57 (100). $C_7H_{13}NO_2$ (143.09): calcd. C 58.72, H 9.15, N 9.78; found C 58.70, H 9.14, N 9.76.

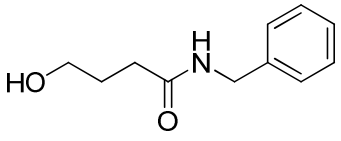
4-hydroxy-1-(piperidin-1-yl)butan-1-one



6.4

Yellow oil 100% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 3.70-3.63 (m, 2 H), 3.55-3.51 (m, 2 H), 3.43-3.41 (m, 2 H), 3.15 (br, 1 H, OH), 2.50 (t, *J* = 6.6 Hz, 2 H), 1.93-1.80 (m, 2 H), 1.60-1.55 (m, 6 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.4 (s, 1 C, C=O), 61.1 (t, 1 C, CH_2), 46.3 (t, 1 C, CH_2), 44.6 (t, 1 C, CH_2), 42.3 (t, 1 C, CH_2), 29.7 (t, 1 C, CH_2), 27.6 (t, 1 C, CH_2), 25.8 (t, 1 C, CH_2), 21.9 (t, 1 C, CH_2). MS: *m*/*z* (%) = 171 (1) $[M]^+$, 127 (14), 86 (27), 85 (47), 84 (100), 70 (15), 69 (67) 57 (47), 56 (67), 55 (20). $C_9H_{17}NO_2$ (171.13): calcd. C 63.13, H 10.01, N 8.18; found C 63.13, H 10.03, N 8.21.

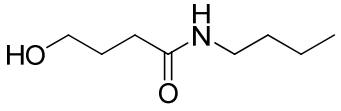
***N*-benzyl-4-hydroxybutanamide**



6.5

Yellow solid 100% yield. M.p. 55-57°C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.36-7.21 (m, 5 H, Ar), 6.42 (br, 1 H, NH), 4.36 (d, *J* = 5.9 Hz, 2 H), 3.81 (br, 1 H, OH), 3.61 (t, *J* = 5.9 Hz, 2 H), 2.32 (t, *J* = 5.9 Hz, 2 H), 1.87-1.75 (m, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.9 (s, 1 C, C=O), 137.9 (s, 1 C, Ar), 128.6 (d, 1 C, Ar), 128.2 (d, 1 C, Ar), 128.1 (d, 1 C, Ar), 127.1 (d, 1 C, Ar), 126.9 (d, 1 C, Ar), 61.2 (t, 1 C, CH_2), 43.1 (t, 1 C, CH_2), 32.8 (t, 1 C, CH_2), 28.0 (t, 1 C, CH_2). MS: *m*/*z* (%) = 193 (37) $[M]^+$, 162 (13), 149 (45), 148 (16), 107 (29), 106 (100), 103 (17), 92 (14), 91 (98), 79 (15), 77 (17), 68 (12), 65 (25), 51 (16). $C_{11}H_{15}NO_2$ (193.11): calcd. C 68.37, H 7.82, N 7.25; found C 68.38, H 7.82, N 7.27.

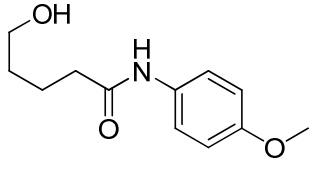
_N_-butyl-4-hydroxybutanamide



6.6

Yellow oil 99% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.54 (br, 1 H, NH), 3.60 (td, *J* = 5.9, 1.5 Hz, 2 H), 3.16 (q, *J* = 5.5 Hz 2 H), 2.29 (t, *J* = 6.6 Hz, 2 H), 1.86-1.73 (m, 2 H), 1.50-1.21 (m, 4 H), 0.87 (t, *J* = 6.9 Hz, 3 H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.6 (s, 1 C, C=O), 61.4 (t, 1 C, CH_2), 39.1 (t, 1 C, CH_2), 33.2 (t, 1 C, CH_2), 31.1 (t, 1 C, CH_2), 28.1 (t, 1 C, CH_2), 19.7 (t, 1 C, CH_2), 13.4 (q, 1 C, CH_3). MS: *m*/*z* (%) = 159 (5) $[M]^+$, 129 (16), 117 (43), 115 (67), 100 (47), 87 (77), 86 (34), 73 (100), 69 (45), 58 (44), 57 (86). $C_8H_{17}NO_2$ (159.13): calcd. C 60.35, H 10.76, N 8.80; found C 60.37, H 10.77, N 8.80.

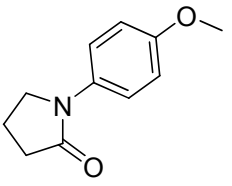
4-hydroxy-_N_-(4-methoxyphenyl)butanamide



6.7

Brown solid 11% yield. M.p. 90-93°C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 8.8 Hz, 3 H, Ar and NH), 6.85 (d, *J* = 6.8 Hz, 2 H, Ar), 3.79 (s, 3 H, OCH_3), 3.76-3.73 (m, 2 H), 2.52 (t, *J* = 6.6 Hz, 2 H), 2.04-1.91 (m, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 171.9 (s, 1 C, C=O), 155.9 (s, 1 C, Ar), 130.8 (s, 1 C, Ar), 121.7 (d, 1 C, Ar), 121.6 (d, 1 C, Ar), 113.7 (d, 2 C, Ar), 61.4 (t, 1 C, CH_2), 55.1 (q, 1 C, OCH_3), 33.8 (t, 1 C, CH_2), 27.9 (t, 1 C, CH_2). MS: *m*/*z* (%) = 209 (17) $[M]^+$, 123 (100), 108 (80), 80 (14), 52 (13). $C_{11}H_{15}NO_3$ (209.11): calcd. C 63.14, H 7.23, N 6.69; found C 63.12, H 7.23, N 6.67.

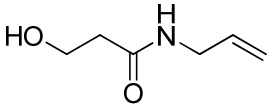
1-(4-methoxyphenyl)pyrrolidin-2-one



6.7bis

Brown solid 12% yield. M.p. 99-102°C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.47-7.41 (m, 2 H, Ar), 6.89-6.83 (m, 2 H, Ar), 3.80-3.69 (m, 2 H), 3.75 (s, 3 H, OCH_3), 2.53 (t, *J* = 8.1 Hz, 2 H), 2.16-2.05 (m, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.5 (s, 1 C, C=O), 156.1 (s, 1 C, Ar), 132.3 (s, 1 C, Ar), 121.4 (d, 1 C, Ar), 121.1 (d, 1 C, Ar), 113.6 (d, 2 C, Ar), 55.1 (q, 1 C, OCH_3), 48.8 (t, 1 C, CH_2), 32.2 (t, 1 C, CH_2), 17.6 (t, 1 C, CH_2). MS: *m*/*z* (%) = 191 (51) $[M]^+$, 190 (16), , 176 (12), 149 (25), 136 (100), 134 (11), 123 (61), 122 (11), 121 (13), 108 (39), 99 (12), 92 (10), 80 (14), 77 (16), 69 (29), 62 (16), 60 (45), 57 (29), 55 (36), 52 (19). $C_{11}H_{13}NO_2$ (191.09): calcd. C 69.09, H 6.85, N 7.32; found C 69.08, H 6.86, N 7.32.

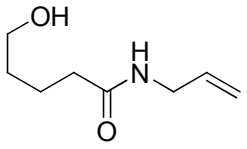
***N*-allyl-3-hydroxypropanamide**



6.9

Yellow solid 100% yield. M.p. 89-91°C. ^{1}H NMR (200 MHz, CD_3OD): δ = 7.61 (br, 1 H, NH), 5.96-5.73 (m, 1 H, =CH), 5.27-5.08 (m, 2 H, $=CH_2$), 3.85 (t, *J* = 5.5 Hz, 1 H), 3.31 (d, *J* = 6.2 Hz, 1 H), 2.97-2.85 (m, 2 H), 2.43 (t, *J* = 5.5 Hz, 2 H). ^{13}C NMR (50 MHz, CD_3OD): δ = 174.2 (s, 1 C, C=O), 132.9 (d, 1 C, =CH), 116.1 (t, 1 C, $=CH_2$), 42.7 (t, 1 C, CH_2), 29.9 (t, 1 C, CH_2), 20.1 (t, 1 C, CH_2), 21.6 (t, 1 C, CH_2). MS: *m*/*z* (%) = 129 (1) $[M]^+$, 127 (10), 98 (18), 84 (22), 70 (66), 69 (66), 68 (36), 58 (24), 57 (41), 56 (100), 55 (30). $C_6H_{11}NO_2$ (129.08): calcd. C 55.80, H 8.58, N 10.84; found C 55.80, H 8.56, N 10.83.

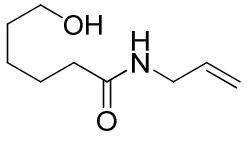
***N*-allyl-5-hydroxypentanamide**



6.11

Yellow oil 95% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.93-5.74 (m, 2 H, =CH and NH), 5.22-5.10 (m, 2 H, $=CH_2$), 3.85 (t, *J* = 5.9 Hz, 2 H), 3.64 (t, *J* = 5.9 Hz, 2 H), 2.43 (br, 1 H, OH), 2.26 (t, *J* = 6.9 Hz, 2 H), 1.82-1.56 (m, 4 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.8 (s, 1 C, C=O), 133.5 (d, 1 C, =CH), 115.6 (t, 1 C, $=CH_2$), 61.1 (t, 1 C, CH_2), 41.5 (t, 1 C, CH_2), 35.4 (t, 1 C, CH_2), 31.3 (t, 1 C, CH_2), 21.6 (t, 1 C, CH_2). MS: *m*/*z* (%) = 157 (2) $[M]^+$, 98 (10), 84 (21), 83 (11), 70 (33), 69 (13), 68 (15), 58 (23), 57 (100), 56 (94), 55 (82). $C_8H_{15}NO_2$ (157.11): calcd. C 61.12, H 9.62, N 8.91; found C 61.13, H 9.64, N 8.93.

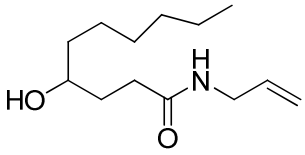
***N*-allyl-6-hydroxyhexanamide**



6.13

Yellow oil 53% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.91-5.72 (m, 2 H, =CH and NH), 5.29-5.09 (m, 2 H, $=CH_2$), 4.05 (br, 1 H, OH), 3.86 (t, *J* = 5.5 Hz, 2 H), 3.63 (t, *J* = 6.2 Hz, 2 H), 2.21 (t, *J* = 7.3 Hz, 2 H), 1.73-1.51 (m, 4 H), 1.45-1.34 (m, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.4 (s, 1 C, C=O), 133.8 (d, 1 C, =CH), 115.6 (t, 1 C, $=CH_2$), 61.7 (t, 1 C, CH_2), 41.5 (t, 1 C, CH_2), 36.0 (t, 1 C, CH_2), 31.8 (t, 1 C, CH_2), 25.1 (t, 1 C, CH_2), 25.0 (t, 1 C, CH_2). MS: *m*/*z* (%) = 171 (3) $[M]^+$, 99 (40), 98 (18), 84 (16), 69 (38), 68 (11), 57 (100), 56 (83), 55 (87). $C_9H_{17}NO_2$ (171.13): calcd. C 63.13, H 10.01, N 8.18; found C 63.13, H 9.99, N 8.17.

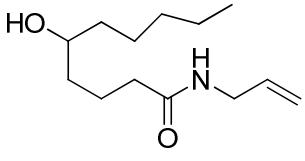
_N_-allyl-4-hydroxydecanamide



6.15

White solid 80% yield. M.p. 65-67°C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.93-5.73 (m, 2 H, =CH and NH), 5.22-5.10 (m, 2 H, $=CH_2$), 3.87 (t, *J* = 5.9 Hz, 2 H), 3.62 (d, *J* = 5.9 Hz, 1 H), 2.75 (br, 1 H, OH), 2.37 (t, *J* = 6.9 Hz, 2 H), 1.94-1.57 (m, 2 H), 1.42-1.27 (m, 10 H), 0.87 (t, *J* = 6.9 Hz, 3 H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.8 (s, 1 C, C=O), 133.8 (d, 1 C, =CH), 115.5 (t, 1 C, $=CH_2$), 70.6 (d, 1 C, CH), 41.5 (t, 1 C, CH_2), 37.3 (t, 1 C, CH_2), 32.6 (t, 2 C, CH_2), 31.5 (t, 1 C, CH_2), 29.0 (t, 1 C, CH_2), 25.4 (t, 1 C, CH_2), 22.3 (t, 1 C, CH_2), 13.7 (q, 1 C, CH_3). MS: *m*/*z* (%) = 227 (1) $[M]^+$, 142 (30), 99 (57), 97 (26), 85 (15), 84 (15), 69 (13), 58 (60), 57 (100), 56 (43), 54 (39). $C_{13}H_{25}NO_2$ (227.19): calcd. C 68.68, H 11.08, N 6.16; found C 68.66, H 10.09, N 6.14.

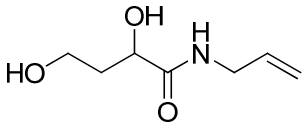
_N_-allyl-5-hydroxydecanamide



6.17

White solid 64% yield. M.p. 63-65°C. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 5.93-5.74 (m, 1 H, =CH), 5.61 (br, 1 H, NH), 5.22-5.10 (m, 2 H, $=CH_2$), 3.89 (t, *J* = 5.9 Hz, 2 H), 3.62-3.49 (m, 1 H), 2.24 (t, *J* = 6.9 Hz, 2 H), 1.84-1.69 (m, 4 H), 1.53-1.29 (m, 10 H), 0.91-0.85 (m, 3 H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 173.3 (s, 1 C, C=O), 133.9 (d, 1 C, =CH), 115.3 (t, 1 C, $=CH_2$), 70.5 (d, 1 C, CH), 41.4 (t, 1 C, CH_2), 37.1 (t, 1 C, CH_2), 36.2 (t, 1 C, CH_2), 35.7 (t, 1 C, CH_2) 31.6 (t, 1 C, CH_2), 25.1 (t, 1 C, CH_2), 22.3 (t, 1 C, CH_2), 21.5 (t, 1 C, CH_2), 13.7 (q, 1 C, CH_3). MS: *m*/*z* (%) = 209 (2) $[M - H_2O]^+$, 156 (21), 99 (69), 98 (20), 84 (18), 71 (12), 69 (17), 58 (73), 57 (100), 56 (45), 55 (46) $C_{13}H_{25}NO_2$ (227.19): calcd. C 68.68, H 11.08, N 6.16; found C 68.69, H 10.09, N 6.15.

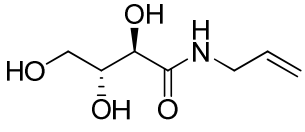
N-allyl-2,4-dihydroxybutanamide



6.19

Yellow oil 46% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.35 (br, 1 H, NH), 5.88-5.69 (m, 1 H, =CH), 5.19-5.06 (m, 2 H, $=CH_2$), 4.24 (dd, *J* = 8.4, 3.3 Hz, 1 H), 3.85-3.72 (m, 4 H), 2.09-1.94 (m, 1 H), 1.81-1.65 (m, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 174.9 (s, 1 C, C=O), 133.2 (d, 1 C, =CH), 115.9 (t, 1 C, $=CH_2$), 69.4 (d, 1 C, CH), 58.6 (t, 1 C, CH_2), 41.1 (t, 1 C, CH_2), 36.3 (t, 1 C, CH_2). MS: *m*/*z* (%) = 159 (4) $[M]^+$, 115 (59), 114 (25), 85 (25), 84 (24), 75 (26), 58 (69), 57 (100), 56 (53), 55 (13). $C_7H_{13}NO_3$ (159.09): calcd. C 52.82, H 8.23, N 8.80; found C 52.81, H 8.24, N 8.82.

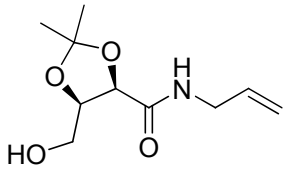
(2*R*,3*R*)-*N*-allyl-2,3,4-trihydroxybutanamide



6.21

White solid 6% yield. M.p. 73-76°C. ^{1}H NMR (200 MHz, CD_3OD): δ = 6.83 (br, 1 H, NH), 5.94-5.75 (m, 1 H, =CH), 5.26-5.06 (m, 2 H, $=CH_2$), 4.12 (d, *J* = 4.8 Hz, 1 H), 3.89-3.82 (m, 3 H), 3.63 (d, *J* = 5.1 Hz, 2 H). ^{13}C NMR (50 MHz, CD_3OD): δ = 172.9 (s, 1 C, C=O), 132.9 (d, 1 C, =CH), 115.9 (t, 1 C, $=CH_2$), 72.5 (d, 1 C, CH), 71.5 (d, 1 C, CH), 62.0 (t, 1 C, CH_2), 41.0 (t, 1 C, CH_2). MS: *m*/*z* (%) = 175 (1) $[M]^+$, 144 (11), 115 (31), 114 (13), 84 (22), 74 (73), 73 (14), 69 (10), 61 (26), 60 (11), 58 (29), 57 (43), 56 (100), 55 (20). $C_7H_{13}NO_4$ (175.08): calcd. C 47.99, H 7.48, N 8.00; found C 48.00, H 7.48, N 8.02.

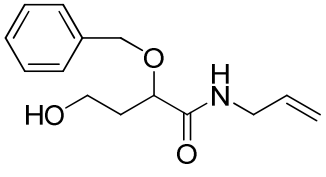
(4*R*,5*R*)-*N*-allyl-5-(hydroxymethyl)-2,2-dimethyl-1,3-dioxolane-4-carboxamide



6.23

Yellow oil 93% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.86 (br, 1 H, NH), 5.93-5.74 (m, 1 H, =CH), 5.24-5.14 (m, 2 H, $=CH_2$), 4.67-4.49 (m, 2 H), 3.97-3.87 (m, 1 H), 3.82-3.75 (m, 1 H), 3.64-3.55 (m, 2 H), 1.54 (s, 3 H, CH_3), 1.39 (s, 3 H, CH_3). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 169.9 (s, 1 C, C=O), 132.8 (d, 1 C, =CH), 116.1 (t, 1 C, $=CH_2$), 109.7 (s, 1 C, C_{quat}), 76.9 (d, 1 C, CH), 75.8 (d, 1 C, CH), 60.7 (t, 1 C, CH_2), 40.8 (t, 1 C, CH_2), 26.3 (q, 1 C, CH_3), 23.8 (q, 1 C, CH_3). MS: *m*/*z* (%) = 215 (1) $[M]^+$, 131 (16), 115 (11), 59 (100), 57 (22), 56 (21), 55 (13). $C_{10}H_{17}NO_4$ (215.12): calcd. C 55.80, H 7.96, N 6.51; found C 55.79, H 7.96, N 6.50.

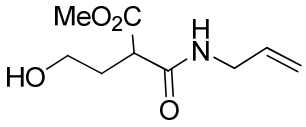
***N*-allyl-2-(benzyloxy)-4-hydroxybutanamide**



6.25

Brown oil 99% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.37-7.34 (m, 5 H, Ar), 6.82 (br, 1 H, NH), 5.91-5.72 (m, 1 H, =CH), 5.21-5.11 (m, 2 H, $=CH_2$), 4.58 (s, 2 H, CH_2-Ph), 4.07 (t, *J* = 6.2 Hz, 1 H), 3.89 (t, *J* = 5.9 Hz, 2 H), 3.74 (t, *J* = 5.9 Hz, 2 H), 2.84 (br, 1 H, OH) 2.10-1.96 (m, 2 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 172.5 (s, 1 C, C=O), 136.5 (s, 1 C, Ar), 133.4 (d, 1 C, =CH), 128.3 (d, 2 C, Ar), 127.9 (d, 1 C, Ar), 127.7 (d, 2 C, Ar), 116.1 (t, 1 C, $=CH_2$), 78.0 (d, 1 C, CH), 72.7 (t, 1 C, CH_2), 58.8 (t, 1 C, CH_2), 41.0 (t, 1 C, CH_2), 35.4 (t, 1 C, CH_2). MS: *m*/*z* (%) = 143 (13) $[M - PhCH_2O]^+$, 112 (12), 92 (23), 91 (100), 75 (11), 65 (16), 57 (10), 55 (8). $C_{14}H_{19}NO_3$ (249.14): calcd. C 67.45, H 7.68, N 5.62; found C 67.43, H 7.69, N 5.61.

Methyl-2-(allylcarbamoyl)-4-hydroxybutanoate



6.27

Yellow oil 80% yield. ^{1}H NMR (200 MHz, $CDCl_3$): δ = 6.08 (br, 1 H, NH), 5.90-5.70 (m, 1 H, =CH), 5.20-5.08 (m, 2 H, $=CH_2$), 4.26-4.20 (m, 1 H), 3.84 (t, *J* = 5.9 Hz, 2 H), 3.75 (s, 3 H, OCH_3), 2.41-2.10 (m, 3 H), 2.02-1.84 (m, 1 H). ^{13}C NMR (50 MHz, $CDCl_3$): δ = 175.1 (s, 1 C, C=O), 173.3 (s, 1 C, C=O), 133.2 (d, 1 C, =CH), 115.8 (t, 1 C, $=CH_2$), 69.5 (d, 1 C, CH), 52.1 (q, 1 C, OCH_3), 41.6 (t, 1 C, CH_2), 31.4 (t, 1 C, CH_2), 29.3 (t, 1 C, CH_2). MS: *m*/*z* (%) = 201 (1) $[M]^+$, 142 (10), 113 (8), 99 (10), 85 (45), 58 (52), 57 (100), 56 (55), 55 (14). $C_9H_{15}NO_4$ (201.10): calcd. C 53.72, H 7.51, N 6.96; found C 53.72, H 7.50, N 6.98.

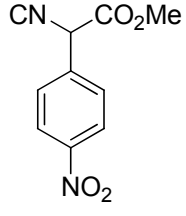
8.7. Experimental Section of Chapter 7

Novel four-component reaction for heterocyclic scaffolds synthesis

General Procedure for the synthesis of isocyanoacetate

To a solution of ethyl isocyanoacetate **7.1** (1 eq) in dry DMSO (0.2 M) was added Cs_2CO_3 (1.5 eq) and the mixture was stirred 10min at room temperature under an argon atmosphere. Then fluoro derivative (1-fluoro-4-nitrobenzene **I**, methyl-4-fluoro-benzoate **II**, 4-fluorobenzonitrile **III**, 4-fluoropyridine HCl **IV**, 1-fluoro-2-nitrobenzene **V**) (1.05 eq) was added and stirring was continued for 16h at room temperature. The mixture was washed with water extracted with EtOAc, then the organic layer was dried with Na_2SO_4, filtered and concentrated in vacuo. The crude was purified by column chromatography on silica gel (heptanes/EtOAc, 2:1) to give the desired compound.

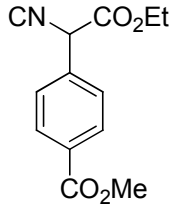
Methyl 2-isocyano-2-(4-nitrophenyl)acetate



7.3

Yellow solid, yield: 63%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.85 (3H, s, OCH_3), 5.53 (1H, s, CH), 7.72 (2H, d, J = 5.1 Hz, Ar-H), 8.32 (2H, d, J = 5.1 Hz, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 53.4 (CH), 54.3 (CH_3), 124.4 (2 × CH), 127.8 (2 × CH), 137.9 (C), 148.7 (C), 163.6 (C), 164.8 (C) ppm. MS: m/z (ES$^+$) 221 [M+H]$^+$. IR (neat): ν = 2957, 2149, 1753, 1523, 1347, 1212 cm^{-1}.

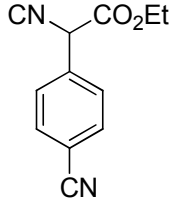
Methyl 4-(2-ethoxy-1-isocyano-2-oxoethyl)benzoate



7.4

Yellow solid, yield: 58%. M.p. 65-67°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (3H, t, J = 7.1 Hz, CH_3), 3.94 (3H, s, OCH_3), 4.25 (2H, q, J = 7.1 Hz, CH_2), 5.43 (1H, s, CH), 7.58 (2H, d, J = 8.4 Hz, Ar-H), 8.11 (2H, d, J = 8.4 Hz, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8 (CH_3), 52.4 (CH_3), 60.1 (CH), 63.4 (CH_2), 126.7 (2 × CH), 130.3 (2 × CH), 131.3 (C), 136.2 (C), 162.2 (C), 164.9 (C), 166.1 (C) ppm. MS: m/z (ES^+) 248 $[M+H]^+$. IR (neat): ν = 2993, 2152, 1754, 1708, 1271, 1210, 1190, 1112, 1013, 753 cm^{-1}.

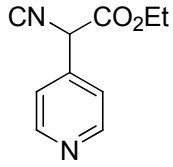
Ethyl 2-(4-cyanophenyl)-2-isocyanoacetate



7.5

Yellow oil, yield: 53%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.25 (3H, t, J = 7.2 Hz, CH_3), 4.24 (2H, q, J = 7.2 Hz, CH_2), 5.45 (1H, s, CH), 7.63 (2H, d, J = 8.4 Hz, Ar-H), 7.73 (2H, d, J = 8.4 Hz, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8 (CH_3), 59.9 (CH), 63.6 (CH_2), 113.6 (C), 117.9 (C), 127.5 (2 × CH), 132.9 (2 × CH), 136.5 (C), 162.8 (C), 164.4 (C) ppm. MS: m/z (ES^+) 215 $[M+H]^+$. IR (neat): ν = 2983, 2359, 2230, 2147, 1746, 1725, 1697, 1263, 1205, 1018, 697 cm^{-1}.

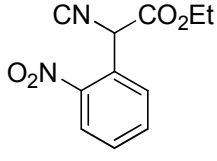
Ethyl 2-isocyano-2-(pyridin-4-yl)acetate



7.6

Purple solid, yield: 72%. The crude was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.31 (3H, t, J = 7.0 Hz, CH_3), 4.30 (2H, q, J = 7.0 Hz, CH_2), 5.40 (1H, s, CH), 7.46 (2H, d, J = 5.8 Hz, Ar-H), 8.73 (2H, d, J = 5.8 Hz, Ar-H) ppm.

Ethyl 2-isocyano-2-(2-nitrophenyl)acetate



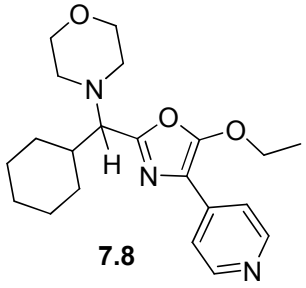
7.7

Yellow oil, yield: 66%. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.22 (3H, t, J = 7.2 Hz, CH_3), 4.20 (2H, q, J = 7.2 Hz, CH_2), 6.31 (1H, s, CH), 7.57 (1H, td, J = 8.4 Hz, J = 1.5 Hz, Ar-H), 7.72 (1H, td, J = 8.1 Hz, J = 1.5 Hz, Ar-H), 7.80 (1H, dd, J = 8.1 Hz, J = 1.5 Hz, Ar-H), 8.11 (1H, dd, J = 8.1 Hz, J = 1.5 Hz, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8 (CH_3), 57.4 (CH), 63.7 (CH_2), 125.7 (CH), 127.3 (C), 129.1 (CH), 130.5 (CH), 134.4 (CH), 147.8 (C), 158.9 (C), 164.0 (C) ppm. MS: m/z (ES^+) 235 $[M+H]^+$. IR (neat): ν = 2985, 2147, 1725, 1643, 1525, 1346, 1199, 1016 cm^{-1}.

General Procedure for the three-component synthesis of 5-ethoxyoxazoles

To a solution of morpholine (1 eq) in dry toluene (1 M) was added the aldehyde (**i-vi**) (1 eq) and the mixture was stirred 10min at room temperature under an argon atmosphere. Ethyl-2-isocyano-2-(pyridin-4-yl)acetate **7.6** (1 eq) was then added and stirring was continued for 16h at 60°C. The solvent was removed in vacuo. The crude was purified by column chromatography on silica gel (EtOAc) to give the desired compound.

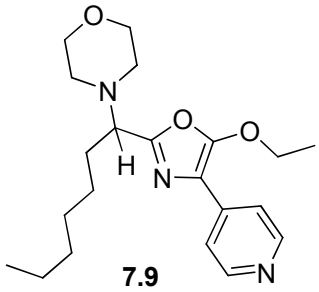
4-(Cyclohexyl(5-ethoxy-4-(pyridin-4-yl)oxazol-2-yl)methyl) morpholine



7.8

yellow oil, 81% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.86-0.97 (2H, m, CH_2), 1.14-1.37 (4H, m, 2 × CH_2), 1.42 (3H, t, J = 6.9 Hz, $OCH_2C\underline{H}_3$), 1.63-1.93 (4H, m, 2 × CH_2), 2.01-2.05 (1H, m, C<u>H</u>CHN), 2.36-2.55 (4H, m, 2 × CH_2N), 3.25 (1H, d, J = 10.5 Hz, CHN), 3.58-3.78 (4H, m, 2 × CH_2O), 4.34 (2H, q, J = 6.9 Hz, $OC\underline{H}_2CH_3$), 7.62 (2H, d, J = 6.0 Hz, Ar-H), 8.48 (2H, d, J = 6.0 Hz, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.1 ($OCH_2\underline{C}H_3$), 25.9 (CH_2), 26.6 (CH_2), 30.2 (2 × CH_2), 30.5 (CH_2), 36.6 (CH), 49.9 (2 × CH_2N), 67.3 (2 × CH_2O), 68.5 (CHN), 69.4 ($O\underline{C}H_2CH_3$), 111.7 (C), 119.1 (2 × CH), 139.5 (C), 149.4 (2 × CH), 153.4 (C), 155.7 (C) ppm. MS: m/z (ES^+) 372 $[M+H]^+$. IR (neat): ν = 2922, 2849, 1631, 1602, 1114, 1028, 1005, 829 cm^{-1}.

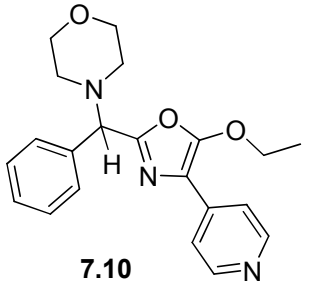
4-(1-(5-ethoxy-4-(pyridin-4-yl)oxazol-2-yl)heptyl)morpholine



7.9

yellow oil, 54% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.82-0.78 (3H, m, CH_3), 1.18-1.25 (8H, m, 4 × CH_2), 1.43 (3H, t, J = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.77-1.86 (2H, m, $C\underline{H}_2CHN$), 2.43-2.59 (4H, m, 2 × CH_2N), 3.54 (1H, t, J = 6.9 Hz, CHN), 3.61-3.66 (4H, m, 2 × CH_2O), 4.37 (2H, q, J = 7.2 Hz, $OC\underline{H}_2CH_3$), 7.63 (2H, d, J = 6.3 Hz, Ar-H), 8.49 (2H, d, J = 6.3 Hz, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.0 (CH_3), 15.1 ($OCH_2\underline{C}H_3$), 22.5 (CH_2), 26.2 (CH_2), 29.0 (CH_2), 29.7 ($\underline{C}H_2CHN$), 31.6 (CH_2), 50.0 (2 × CH_2N), 63.1 (CHN), 67.2 (2 × CH_2O), 69.4 ($O\underline{C}H_2CH_3$), 119.1 (2 × CH), 128.5 (C), 139.6 (C), 149.3 (2 × CH), 153.9 (C), 155.7 (C) ppm. MS: m/z (ES^+) 374 $[M+H]^+$. IR (neat): ν = 2924, 2853, 1631, 1602, 1188, 1114, 1029, 830 cm^{-1}.

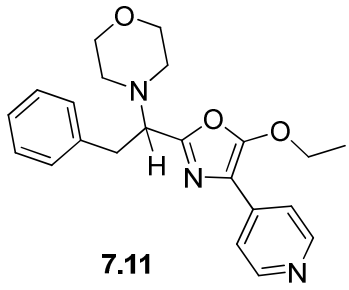
4-((5-ethoxy-4-(pyridin-4-yl)oxazol-2-yl)(phenyl)methyl)morpholine



7.10

yellow oil, 50% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39 (3H, t, J = 6.9 Hz, $OCH_2C\underline{H}_3$), 2.32-2.50 (4H, m, 2 × CH_2N), 3.66 (4H, m, 2 × CH_2O), 4.34 (2H, q, J = 6.9 Hz, $OC\underline{H}_2CH_3$), 4.46 (1H, s, CHN), 7.24-7.31 (3H, m, Ar-H), 7.46 (2H, d, J = 6.6 Hz, Ar-H), 7.62 (2H, d, J = 5.4 Hz, Ar-H), 8.47 (2H, d, J = 5.4 Hz, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.0 ($OCH_2\underline{C}H_3$), 51.8 (2 × CH_2N), 66.9 (2 × CH_2O), 69.4 ($O\underline{C}H_2CH_3$), 69.5 (CHN), 112.0 (C), 119.0 (2 × CH), 128.3 (C), 128.6 (3 × CH), 128.7 (2 × CH), 136.5 (C), 149.1 (2 × CH), 152.8 (C), 156.7 (C) ppm. MS: m/z (ES^+) 366 $[M+H]^+$. IR (neat): ν = 2958, 2853, 2358, 1622, 1601, 1185, 1113, 1029, 1003, 829, 698 cm^{-1}.

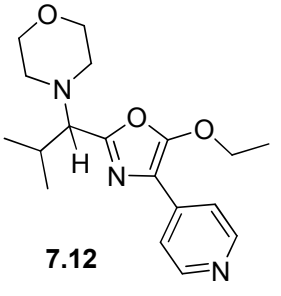
4-(1-(5-ethoxy-4-(pyridin-4-yl)oxazol-2-yl)-2-phenylethyl) morpholine



7.11

yellow oil, 53% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.37 (3H, t, J = 6.9 Hz, $OCH_2C\underline{H}_3$), 2.49-2.69 (4H, m, 2 × CH_2N), 3.11-3.27 (2H, m, CH_2Ph), 3.63-3.67 (4H, m, 2 × CH_2O), 3.81 (1H, dd, J = 5.7 Hz, J = 3.6 Hz, CHN), 4.29 (2H, q, J = 6.9 Hz, $OC\underline{H}_2CH_3$), 7.09-7.16 (5H, m, Ar-H), 7.61 (2H, d, J = 6.3 Hz, Ar-H), 8.48 (2H, d, J = 5.7 Hz, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.1 ($OCH_2\underline{C}H_3$), 36.1 (CH_2Ph), 50.1 (2 × CH_2N), 64.9 (CHN), 67.1 (2 × CH_2O), 69.5 ($O\underline{C}H_2CH_3$), 119.1 (2 × CH), 126.5 (C), 128.3 (3 × CH), 129.1 (2 × CH), 138.6 (CH), 140.1 (C) 149.2 (2 × CH) 151.9 (C), 156.2 (C) ppm. MS: m/z (ES^+) 380 $[M+H]^+$. IR (neat): ν = 2957, 2852, 2359, 1625, 1602, 1186, 1112, 1028, 997, 830, 699 cm^{-1}.

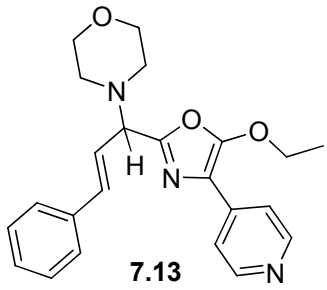
4-(1-(5-ethoxy-4-(pyridin-4-yl)oxazol-2-yl)-2-methylpropyl) morpholine



7.12

yellow oil, 61% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.79 (3H, d, J = 6.3 Hz, CH_3), 1.01 (3H, d, J = 6.3 Hz, CH_3), 1.43 (3H, t, J = 7.2 Hz, $OCH_2C\underline{H}_3$), 2.15-2.24 (1H, m, $C\underline{H}(CH_3)_2$), 2.36-2.55 (4H, m, 2 × CH_2N), 3.12 (1H, d, J = 10.5 Hz, CHN), 3.60-3.66 (4H, m, 2 × CH_2O), 4.36 (2H, q, J = 7.2 Hz, $OC\underline{H}_2CH_3$), 7.64 (2H, d, J = 6.3 Hz, Ar-H), 8.49 (2H, d, J = 6.3 Hz, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.1 ($OCH_2\underline{C}H_3$), 19.8 (CH_3), 19.9 (CH_3), 27.4 ($\underline{C}H(CH_3)_2$), 50.0 (2 × CH_2N), 67.3 (2 × CH_2O), 69.4 ($O\underline{C}H_2CH_3$), 69.7 (CHN), 109.8 (C), 119.1 (2 × CH), 127.7 (C), 149.2 (2 × CH), 153.2 (C), 157.6 (C) ppm. MS: m/z (ES^+) 332 $[M+H]^+$. IR (neat): ν = 2959, 2852, 1604, 1529, 1187, 1113, 1011, 830 cm^{-1}.

(*E*)4-(1-(5-ethoxy-4-(pyridin-4-yl)oxazol-2-yl)-3-phenylallyl) morpholine



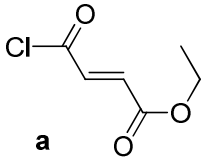
7.13

yellow oil, 54% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.43 (3H, t, *J* = 6.9 Hz, $OCH_2C\underline{H}_3$), 2.42-2.65 (4H, m, 2 × CH_2N), 3.67-3.70 (4H, m, 2 × CH_2O), 4.12 (1H, d, *J* = 8.4 Hz, CHN), 4.40 (2H, q, *J* = 6.9 Hz, $OC\underline{H}_2CH_3$), 6.33 (1H, d, *J* = 15.9 Hz, *J* = 8.4 Hz, C<u>H</u>CHN), 6.63 (1H, d, *J* = 15.9 Hz, CHPh), 7.20-7.35 (5H, m, Ar-H), 7.65 (2H, d, *J* = 6.0 Hz, Ar-H), 8.49 (2H, d, *J* = 6.0 Hz, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.1 ($OCH_2\underline{C}H_3$), 51.3 (2 × CH_2N), 66.9 (2 × CH_2O), 67.1 (CHN), 69.7 ($O\underline{C}H_2CH_3$), 98.4 (<u>C</u>HCHN), 119.1 (2 × CH), 124.4 (C), 126.6 (3 × CH), 128.3 (C), 128.7 (2 × CH), 135.1 (CHPh), 135.2 (C) 149.0 (2 × CH) 151.7 (C), 154.3 (C) ppm. MS: m/z (ES^+) 392 $[M+H]^+$. IR (neat): ν = 2959, 2853, 2359, 1633, 1602, 1185, 1112, 1028, 830, 697 cm^{-1}.

General Procedure for the synthesis of acyl chloride

To a solution of carboxylic acid (1 eq) in dry CH_2Cl_2 (0.32 M) oxalyl chloride (1.2 eq) and one drop of DMF were added. The reaction mixture was stirred for 1h at room temperature. The excess of reagent and solvent were distilled off and the acyl chloride was used without further purification.

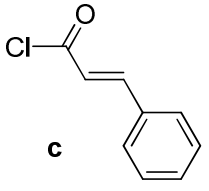
(*E*)-ethyl 4-chloro-4-oxobut-2-enoate



a

78% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.36 (3H, t, J = 7.2 Hz, CH_3), 4.32 (2H, q, J = 7.2 Hz, CH_2), 7.01 (2H, d, J = 3.6 Hz, CH=CH), ppm.

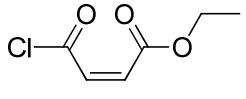
Cinnamoyl chloride



c

81% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.68 (1H, d, J = 15.6 Hz, CH), 7.49-7.46 (3H, m, Ar-H), 7.60 (2H, d, J = 6.3 Hz, Ar-H), 7.85 (1H, d, J = 15.6 Hz, CH), ppm.

(*Z*)-ethyl 4-chloro-4-oxobut-2-enoate

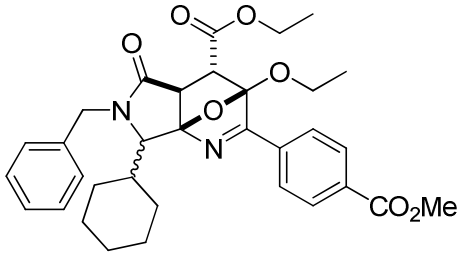


b

A solution of maleic anhydride (1 eq) in ethanol (0.77 M), was heated for 1h to reflux. The solvent was distilled and the residue was dissolved in CH_2Cl_2 (0.32 M), then oxalyl chloride (1.2 eq) and one drop of DMF were added. The reaction mixture was stirred for 1h at room temperature. The excess of reagent and solvent were distilled off and the (Z)-ethyl-4-chloro-4-oxobut-2-enoate was used without further purification (80% yield).
^{1}H NMR (300 MHz, Acetone-d_6): δ = 1.33 (t, J = 7.2 Hz, 3 H, CH_3), 4.2 (q, J = 7.2 Hz, 2 H, CH_2), 6.41 (d, J = 11.4 Hz, 1 H, CH), 6.88 (d, J = 11.4 Hz, 1 H, CH) ppm.

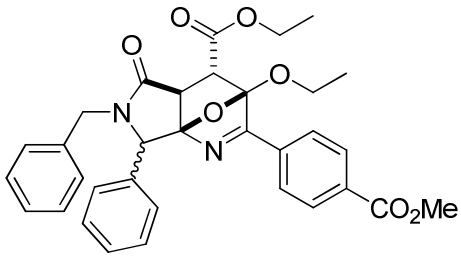
General Procedure for the four-component synthesis with methyl 4-(2-ethoxy-1-isocyano-2-oxoethyl)benzoate 7.4

To a solution of amine (1 eq) in dry toluene (1 M) was added the aldehyde (1 eq) and the mixture was stirred 10min at room temperature under an argon atmosphere. Methyl 4-(2-ethoxy-1-isocyano-2-oxoethyl)benzoate (1 eq) was then added and stirring was continued for 7h at r.t, then the mixture was cooled at 0°C and TEA (5 eq) followed by a solution of acyl chloride (2.2 eq) in dry toluene (0.15M) were added. The reaction was allowed to warm up to room temperature and then it was heated to reflux for 20 min. The solvent was removed in vacuo. The crude was purified by column chromatography on silica gel (heptanes/EtOAc, 1:2) to give the desired compound.



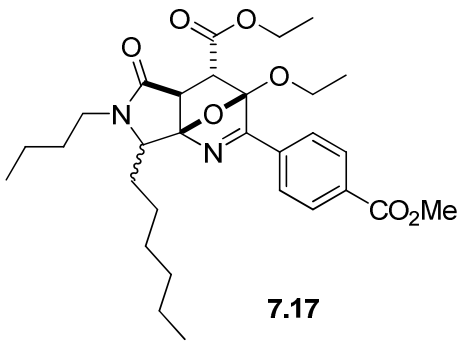
7.14

yellow solid, 68% yield, 13:1 mixture of diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.04 (3H, t, J = 7.2 Hz, $COCH_2C\underline{H}_3$), 1.29-1.32 (2H, m, CH_2), 1.35 (3H, t, J = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.74-1.98 (8H, m, 4 × CH_2), 2.02-2.04 (1H, m, C<u>H</u>CHN), 3.28 (1H, d, J = 4.2 Hz, C<u>H</u>CHCO$_2$Et), 3.55 (1H, d, J = 4.2 Hz, CHC<u>H</u>CO$_2$Et), 3.63 (1H, d, J = 3.6 Hz, CHN), 3.72-3.77 (1H, m, $OC\underline{H}_2CH_3$), 3.92-3.96 (2H, m, $COC\underline{H}_2CH_3$), 3.95 (3H, s, OCH_3), 3.97-4.04 (1H, m, $OC\underline{H}_2CH_3$), 4.19 (1H, d, J = 15.3 Hz, CH_2Ph), 5.10 (1H, d, J = 15.3 Hz, CH_2Ph), 7.27-7.34 (5H, m, Ar-H), 8.07 (4H, br, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9 ($COCH_2\underline{C}H_3$), 15.2 ($OCH_2\underline{C}H_3$), 26.3 (CH_2), 26.5 (CH_2), 26.7 (CH_2), 27.6 (CH_2), 28.4 (CH_2), 38.8 (<u>C</u>HCHN), 45.5 (CH_2Ph), 46.2 (CH<u>C</u>HCO$_2$Et), 52.3 (OCH_3), 53.7 (<u>C</u>HCHCO$_2$Et), 61.2 ($CO\underline{C}H_2CH_3$), 63.7 ($O\underline{C}H_2CH_3$), 64.1 (CHN), 99.7 (C), 113.6 (C), 127.6 (3 × CH), 127.9 (2 × CH), 128.6 (2 × CH), 129.5 (2 × CH), 132.5 (C), 134.5 (C), 135.9 (C), 166.4 (C), 168.5 (C), 171.5 (C), 172.0 (C) ppm. MS: m/z (ES$^+$) 597 [M+Na]$^+$. IR (neat): ν = 2928, 2854, 1723, 1693, 1272, 1180, 1104, 1018, 699 cm^{-1}.



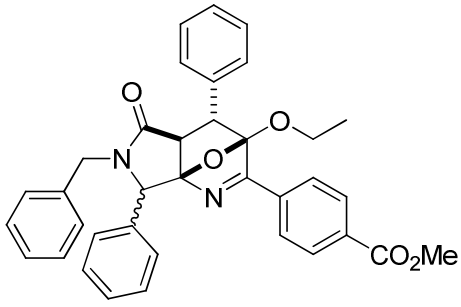
7.15-7.16

With (*E*)-ethyl 4-chloro-4-oxobut-2-enoate (1.8:1) and (*Z*)-ethyl 4-chloro-4-oxobut-2-enoate (1.8:1)
yellow oil, 58% yield, 1.8:1 mixture of diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.04-1.15 (3H, m, $COCH_2C\underline{H}_3$ major and minor), 1.27 (3H, t, J = 7.2 Hz, $OCH_2C\underline{H}_3$ minor), 1.36 (3H, t, J = 6.9 Hz, $OCH_2C\underline{H}_3$ major), 3.31 (1H, d, J = 4.2 Hz, C<u>H</u>CHCO$_2$Et minor), 3.36 (1H, d, J = 3.9 Hz, C<u>H</u>CHCO$_2$Et major), 3.51 (1H, d, J = 14.7 Hz, CH_2Ph minor), 3.56-3.59 (2H, m, CHC<u>H</u>CO$_2$Et and $O\underline{H}_2CH_3$), 3.66-3.72 (2H, $CO\underline{H}_2CH_3$), 3.78-3.80 (1H, m, CH_2Ph major), 3.82 (3H, s, OCH_3), 3.92-3.98 (1H, m, $O\underline{H}_2CH_3$), 4.75 (1H, s, CHN), 5.13-5.23 (2H, m, CH_2Ph major and minor), 6.90-6.91 (1H, m, Ar-H, minor), 7.11 (2H, d, J = 6.0 Hz, Ar-H, major and minor), 7.18-7.24 (6H, m, Ar-H major and minor), 7.30-7.31 (2H, m, Ar-H major and minor), 7.38-7.41 (2H, m, Ar-H major and minor), 7.83-7.95 (5H, m, Ar-H major and minor) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8 ($COCH_2\underline{C}H_3$ minor), 13.9 ($COCH_2\underline{C}H_3$ major), 15.1 ($OCH_2\underline{C}H_3$ minor), 15.2 ($OCH_2\underline{C}H_3$ major), 44.2 (CH_2Ph minor), 44.7 (CH_2Ph major), 46.0 (CH<u>C</u>HCO$_2$Et minor), 46.1 (CH<u>C</u>HCO$_2$Et major), 52.1 (<u>C</u>HCHCO$_2$Et major), 52.3 (OCH_3), 54.0 (<u>C</u>HCHCO$_2$Et minor), 61.6 ($CO\underline{C}H_2CH_3$), 63.4 (CHN minor), 63.5 (CHN major), 63.9 ($O\underline{C}H_2CH_3$ major), 64.0 ($O\underline{C}H_2CH_3$ minor), 99.3 (C minor), 99.7 (C major), 114.3 (C major), 114.5 (C minor), 127.4 (CH), 127.6 (CH), 127.7 (CH), 127.8 (CH), 128.0 (CH), 128.4 (CH), 128.5 (CH), 128.7 (CH), 128.8 (CH), 129.0 (CH), 129.4 (CH), 129.5 (CH), 131.6 (C minor), 132.6 (C major), 132.7 (C minor), 133.6 (C major), 134.2 (C major), 135.3 (C major), 135.5 (C minor), 166.2 (C minor), 166.3 (C major), 168.1 (C minor), 168.2 (C major), 171.4 (C minor), 171.5 (C major), 172.0 (C major), 172.5 (C minor) ppm. MS: m/z (ES$^+$) 591 [M+Na]$^+$. IR (neat): ν = 2981, 1722, 1697, 1273, 1181, 1108, 1018, 729, 698 cm^{-1}.



7.17

65% yield, 2:1 mixture of separated diastereomers.
Major, white solid
M.p. 86-89°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.94-0.98 (6H, m, 2 × CH_3), 1.10 (3H, t, *J* = 7.2 Hz, $COCH_2C\underline{H}_3$), 1.33 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.35-1.39 (6H, m, 3 × CH_2), 1.54-1.61 (6H, m, 3 × CH_2), 1.90-2.11 (2H, m, $NCHC\underline{H}_2$), 2.97-3.06 (1H, m, NCH_2), 3.21 (1H, d, *J* = 4.2 Hz, $C\underline{H}CHCO_2Et$), 3.48 (1H, d, *J* = 4.2 Hz, $CHC\underline{H}CO_2Et$), 3.66-3.77 (2H, m, NCH_2 and $OC\underline{H}_2CH_3$), 3.83-3.86 (1H, m, CHN), 3.88-3.93 (2H, m, $COC\underline{H}_2CH_3$), 3.95 (3H, s, OCH_3), 3.97-4.07 (1H, m, $OC\underline{H}_2CH_3$), 8.07 (4H, br Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.7 (CH_3), 13.8 (CH_3), 14.0 ($COCH_2\underline{C}H_3$), 15.2 ($OCH_2\underline{C}H_3$), 19.9 (CH_2), 22.5 (CH_2), 25.1 (CH_2), 29.2 ($NCH\underline{C}H_2$), 29.3 (2 × CH_2), 31.6 (CH_2), 41.0 (CH_2N), 45.7 ($\underline{C}HCHCO_2Et$), 52.3 (OCH_3), 52.7 ($CH\underline{C}HCO_2Et$), 59.9 (CHN), 61.5 ($CO\underline{C}H_2CH_3$), 63.7 ($O\underline{C}H_2CH_3$), 99.7 (C), 114.1 (C), 127.6 (2 × CH), 129.5 (2 × CH), 134.6 (C), 166.4 (C), 168.5 (C), 170.8 (C), 170.9 (C), 182.3 (C) ppm.
Minor, colourless oil
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.78-0.82 (3H, m, CH_3), 0.88 (3H, t, *J* = 7.2 Hz, CH_3), 0.96 (3H, t, *J* = 7.2 Hz, $COCH_2C\underline{H}_3$), 1.18-1.22 (6H, m, 3 × CH_2), 1.26 (3H, t, *J* = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.53-1.54 (6H, m, 3 × CH_2), 1.73-1.84 (2H, m, $NCHC\underline{H}_2$), 2.84-2.93 (1H, m, NCH_2), 3.13 (1H, d, *J* = 4.5 Hz, $C\underline{H}CHCO_2Et$), 3.41 (1H, d, *J* = 4.5 Hz, $CHC\underline{H}CO_2Et$), 3.66-3.83 (4H, m, $OC\underline{H}_2CH_3$, $COC\underline{H}_2CH_3$ and NCH_2), 3.87 (3H, s, OCH_3), 3.94-3.97 (1H, m, $OC\underline{H}_2CH_3$), 4.32 (1H, dd, *J* = 3.9 Hz, *J* = 10.8 Hz, CHN), 8.07 (4H,br, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8 (2 × CH_3), 14.0 ($COCH_2\underline{C}H_3$), 15.2 ($OCH_2\underline{C}H_3$), 20.0 (CH_2), 22.5 (CH_2), 24.8 (CH_2), 27.4 ($NCH\underline{C}H_2$), 29.3 (CH_2), 29.4 (CH_2), 31.5 (CH_2), 39.3 (CH_2N), 44.5 ($\underline{C}HCHCO_2Et$), 52.4 (OCH_3), 53.4 ($CH\underline{C}HCO_2Et$), 58.4 (CHN), 61.5 ($CO\underline{C}H_2CH_3$), 63.7 ($O\underline{C}H_2CH_3$), 99.5 (C), 114.4 (C), 127.5 (2 × CH), 129.6 (2 × CH), 132.6 (C), 134.5 (C), 166.3 (C), 168.3 (C), 170.7 (C), 171.2 (C) ppm.
MS: *m/z* (ES^+) 565 $[M+Na]^+$. IR (neat): ν = 2928, 2858, 1725, 1692, 1273, 1183, 1108, 1032, 1015, 980, 958, 927 cm^{-1}.

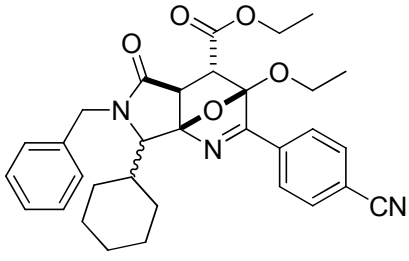


7.18

yellow solid, 61% yield, 2.5:1 mixture of diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13 (3H, t, J = 6.9 Hz, $OCH_2C\underline{H}_3$ minor), 1.21 (3H, t, J = 6.9 Hz, $OCH_2C\underline{H}_3$ major), 3.34 (1H, d, J = 3.9 Hz, C<u>H</u>CHPh minor), 3.36-3.37 (1H, m, $OC\underline{H}_2CH_3$ minor), 3.40 (1H, d, J = 3.9 Hz, C<u>H</u>CHPh major), 3.45-3.50 (1H, m, $OC\underline{H}_2CH_3$ major), 3.64 (1H, d, J = 14.7 Hz, CH_2Ph minor), 3.64-3.70 (1H, m, $OC\underline{H}_2CH_3$ minor), 3.81-3.85 (2H, m, CH_2Ph major and $OC\underline{H}_2CH_3$ major), 3.86 (3H, s, OCH_3), 3.96 (2H, d, J = 3.9 Hz, CHC<u>H</u>Ph major and minor), 4.91 (1H, s, CHN), 5.25-5.38 (2H, m, CH_2Ph major and minor), 7.05-7.10 (8H, m, Ar-H major and minor), 7.20 (2H, d, J = 8.1 Hz, Ar-H major), 7.26-7.41 (13H, m, Ar-H major and minor), 7.48-7.53 (4H, m, Ar-H major and minor), 7.70-7.76 (3H, m, Ar-H major) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.1 ($OCH_2\underline{C}H_3$ minor), 15.2 ($OCH_2\underline{C}H_3$ major), 44.2 (CH_2Ph minor), 44.7 (CH_2Ph major), 48.1 (CHC<u>H</u>Ph minor), 48.3 (CHC<u>H</u>Ph major), 52.2 (OCH_3), 53.4 (C<u>H</u>CHPh major), 55.4 (C<u>H</u>CHPh minor), 63.6 (CHN), 64.0 ($O\underline{C}H_2CH_3$ major), 64.1 ($O\underline{C}H_2CH_3$ minor), 99.4 (C minor), 100.0 (C major), 116.1 (C major), 116.3 (C minor), 127.0 (CH), 127.1 (CH), 127.5 (CH), 127.7 (CH), 128.0 (CH), 128.2 (CH), 128.3 (CH), 128.6 (CH), 128.7 (CH), 128.8 (CH), 128.9 (CH), 129.1 (CH), 129.7 (CH), 131.9 (C major), 132.0 (C minor), 134.0 (C), 134.4 (C minor), 134.6 (C major), 134.8 (C minor), 135.0 (C major), 135.6 (C major), 135.8 (C minor), 166.2 (C minor), 166.3 (C major), 172.3 (C minor), 172.5 (C major), 174.9 (C major), 175.0 (C minor) ppm. MS: m/z (ES^+) 595 $[M+Na]^+$. IR (neat): ν = 2949, 1697, 1273, 1109, 729, 696 cm^{-1}.

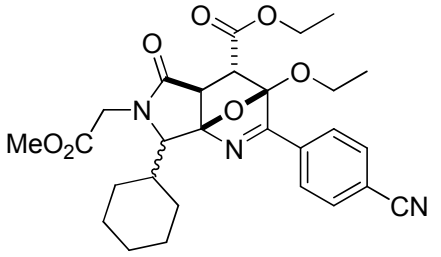
General Procedure for the four-component synthesis with ethyl 2-(4-cyanophenyl)-2-isocyanoacetate 7.5

To a solution of amine (1 eq) in dry toluene (1 M) was added the aldehyde (1 eq) and the mixture was stirred 10min at room temperature under an argon atmosphere. Ethyl 2-(4-cyanophenyl)-2-isocyanoacetate (1 eq) was then added and stirring was continued for 4h at r.t, then the mixture was cooled at 0°C and TEA (5 eq) followed by a solution of acyl chloride (2.2 eq) in dry toluene (0.15M) were added. The reaction was allowed to warm up to room temperature and then it was heated to reflux for 20 min. The solvent was removed in vacuo. The crude was purified by column chromatography on silica gel (heptanes/EtOAc, 1:2) to give the desired compound.



7.19

yellow oil, 54% yield, 20:1 mixture of diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.05 (3H, t, J = 7.2 Hz, $COCH_2C\underline{H}_3$), 1.18 (2H, m, CH_2), 1.27 (3H, t, J = 6.9 Hz, $OCH_2C\underline{H}_3$), 1.40-1.81 (8H, m, 4 × CH_2), 1.81-1.97 (1H, m, C<u>H</u>CHN), 3.16 (1H, d, J = 4.2 Hz, C<u>H</u>CHCO$_2$Et), 3.48 (1H, d, J = 4.2 Hz, CHC<u>H</u>CO$_2$Et), 3.54 (1H, d, J = 3.3 Hz, CHN), 3.62-3.72 (1H, m, $OC\underline{H}_2CH_3$), 3.86 (2H, q, J = 7.2 Hz, $COC\underline{H}_2CH_3$), 3.91-3.99 (1H, m, $OC\underline{H}_2CH_3$), 4.11 (1H, d, J = 15.3 Hz, CH_2Ph), 5.02 (1H, d, J = 15.3 Hz, CH_2Ph), 7.17-7.28 (5H, m, Ar-H), 7.62 (2H, d, J = 8.4 Hz, Ar-H), 8.04 (2H, d, J = 8.4 Hz, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9 ($COCH_2\underline{C}H_3$), 15.2 ($OCH_2\underline{C}H_3$), 26.4 (CH_2), 26.7 (CH_2), 27.6 (CH_2), 28.4 (CH_2), 29.2 (CH_2), 38.8 (<u>C</u>HCHN), 45.5 (CH_2Ph), 45.8 (CH<u>C</u>HCO$_2$Et), 53.7 (<u>C</u>HCHCO$_2$Et), 61.7 ($CO\underline{C}H_2CH_3$), 63.6 ($O\underline{C}H_2CH_3$), 64.1 (CHN), 99.8 (C), 113.4 (C), 114.9 (C), 118.2 (C), 127.6 (CH), 127.9 (2 × CH), 128.3 (2 × CH), 128.6 (2 × CH), 132.1 (2 × CH), 134.5 (C), 135.8 (C), 168.6 (C), 171.0 (C), 171.7 (C) ppm. MS: m/z (ES$^+$) 564 [M+Na]$^+$. IR (neat): ν = 2928, 2854, 2229, 1731, 1693, 1272, 1181, 1041, 699 cm^{-1}.

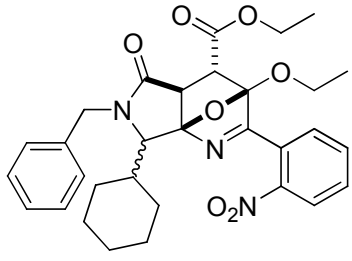


7.20

yellow solid, 45% yield, 6:1 mixture of diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.97 (3H, t, *J* = 7.2 Hz, $COCH_2C\underline{H}_3$ minor), 1.04 (3H, t, *J* = 7.2 Hz, $COCH_2C\underline{H}_3$ major), 1.18 (2H, m, CH_2), 1.26 (3H, t, *J* = 6.9 Hz, $OCH_2C\underline{H}_3$), 1.42-1.89 (8H, m, 4 × CH_2), 1.93-1.97 (1H, m, C<u>H</u>CHN), 3.12 (1H, d, *J* = 4.2 Hz, C<u>H</u>CHCO$_2$Et major), 3.19 (1H, d, *J* = 4.5 Hz, C<u>H</u>CHCO$_2$Et minor), 3.39 (1H, d, *J* = 4.5 Hz, CHC<u>H</u>CO$_2$Et minor), 3.43 (1H, d, *J* = 4.2 Hz, CHC<u>H</u>CO$_2$Et major), 3.54 (1H, d, *J* = 18.0 Hz, NCH_2 minor), 3.68-3.71 (1H, m, $OC\underline{H}_2CH_3$), 3.71 (3H, s, OCH_3), 3.75 (1H, d, *J* = 3.3 Hz, CHN), 3.85 (2H, q, *J* = 7.2 Hz, $COC\underline{H}_2CH_3$), 3.92-4.02 (2H, m, $OC\underline{H}_2CH_3$ and NCH_2 major), 4.19 (1H, d, *J* = 17.4 Hz, NCH_2 major), 4.70 (1H, d, *J* = 18.0 Hz, NCH_2 minor), 7.63 (2H, d, *J* = 8.4 Hz, Ar-H), 8.06 (2H, d, *J* = 8.4 Hz, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.9 ($OCH_2\underline{C}H_3$), 15.1 ($COCH_2\underline{C}H_3$), 26.3 (CH_2), 26.5 (CH_2 minor), 26.6 (CH_2), 27.5 (CH_2), 28.2 (CH_2), 29.2 (CH_2 minor), 29.3 (CH_2), 29.7 (CH_2 minor), 31.7 (CH_2 minor), 39.1 (<u>C</u>HCHN), 41.9 (NCH_2 minor), 44.0 (NCH_2 major), 44.6 (CH<u>C</u>HCO$_2$Et minor), 45.6 (CH<u>C</u>HCO$_2$Et major), 52.3 (OCH_3 major), 52.4 (OCH_3 minor), 53.1 (<u>C</u>HCHCO$_2$Et major), 53.9 (<u>C</u>HCHCO$_2$Et minor), 61.7 ($O\underline{C}H_2CH_3$), 63.6 ($CO\underline{C}H_2CH_3$), 66.4 (CHN), 99.6 (C), 113.4 (C), 114.7 (C), 118.2 (C), 128.3 (2 × CH), 132.1 (2 × CH), 134.5 (C), 168.4 (C), 168.6 (C), 171.1 (C), 171.8 (C) ppm. MS: *m*/*z* (ES$^+$) 546 [M+Na]$^+$. IR (neat): ν = 2928, 2853, 2229, 1733, 1701, 1275, 1205, 1179, 1017, 845 cm^{-1}.

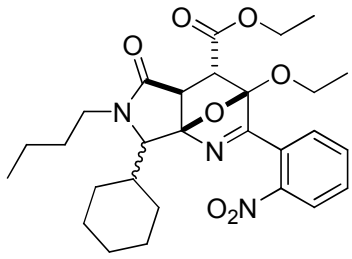
General Procedure for the four-component synthesis with ethyl 2-isocyano-2-(2-nitrophenyl)acetate 7.7

To a solution of amine (1 eq) in dry toluene (1 M) was added the aldehyde (1 eq) and the mixture was stirred 10min at room temperature under an argon atmosphere. Ethyl 2-isocyano-2-(2-nitrophenyl)acetate (1 eq) was then added and stirring was continued for 1h at r.t, then the mixture was cooled at 0°C and TEA (5 eq) followed by a solution of acyl chloride (2.2 eq) in dry toluene (0.15M) were added. The reaction was allowed to warm up to room temperature and then it was heated to reflux for 20 min. The solvent was removed in vacuo. The crude was purified by column chromatography on silica gel (heptanes/EtOAc, 1:2) to give the desired compound.



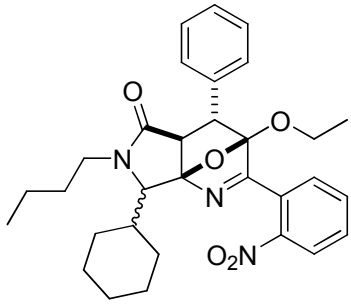
7.21

White solid, 57% yield. M.p. 82-84°C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.91 (3H, t, *J* = 7.2 Hz, $COCH_2C\underline{H}_3$), 1.18-1.19 (2H, m, CH_2), 1.20 (3H, t, *J* = 6.9 Hz, $OCH_2C\underline{H}_3$), 1.39-1.73 (8H, m, 4 × CH_2), 1.85-1.94 (1H, m, C<u>H</u>CHN), 3.21 (1H, d, *J* = 4.2 Hz, C<u>H</u>CHCO$_2$Et), 3.43 (1H, d, *J* = 4.2 Hz, CHC<u>H</u>CO$_2$Et), 3.61 (1H, d, *J* = 3.3 Hz, CHN), 3.67-3.72 (1H, m, $OC\underline{H}_2CH_3$), 3.78-3.82 (2H, m, $COC\underline{H}_2CH_3$), 3.88-3.93 (1H, m, $OC\underline{H}_2CH_3$), 4.09 (1H, d, *J* = 15.3 Hz, CH_2Ph), 4.99 (1H, d, *J* = 15.3 Hz, CH_2Ph), 7.16-7.28 (5H, m, Ar-H), 7.47-7.56 (2H, m, Ar-H), 7.63-7.70 (2H, m, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.7 ($COCH_2\underline{C}H_3$), 14.9 ($OCH_2\underline{C}H_3$), 26.1 (CH_2), 26.5 (CH_2), 26.6 (CH_2), 27.3 (CH_2), 28.0 (CH_2), 38.7 (<u>C</u>HCHN), 44.3 (CHC<u>H</u>CO$_2$Et), 45.4 (CH_2Ph), 52.9 (C<u>H</u>CHCO$_2$Et), 61.4 ($CO\underline{C}H_2CH_3$), 63.0 ($O\underline{C}H_2CH_3$), 64.2 (CHN), 100.1 (C), 112.9 (C), 123.6 (CH), 124.5 (C), 127.5 (CH), 127.9 (2 × CH), 128.6 (2 × CH), 130.9 (CH), 131.4 (CH), 131.7 (CH), 135.8 (C), 149.7 (C), 168.4 (C), 170.4 (C), 171.7 (C) ppm. MS: *m*/*z* (ES$^+$) 584 [M+Na]$^+$. IR (neat): ν = 2926, 2853, 1730, 1692, 1536, 1357, 1280, 1181, 1030, 699 cm^{-1}.



7.22

yellow oil, 54% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.84-0.92 (6H, m, CH_3 and $COCH_2C\underline{H}_3$), 1.17-1.27 (9H, m, $OCH_2C\underline{H}_3$ and 3 × CH_2), 1.34-1.50 (4H, m, 2 × CH_2), 1.50-1.78 (4H, m, 2 × CH_2), 1.91-1.97 (1H, m, C<u>H</u>CHN), 2.91-3.00 (1H, m, NCH_2), 3.13 (1H, d, *J* = 4.2 Hz, C<u>H</u>CHCO$_2$Et), 3.35 (1H, d, *J* = 4.2 Hz, CHC<u>H</u>CO$_2$Et), 3.63-3.80 (5H, m, CHN, $COC\underline{H}_2CH_3$, $OC\underline{H}_2CH_3$ and NCH_2), 3.87-3.92 (1H, m, $OC\underline{H}_2CH_3$), 7.50-7.53 (2H, m, Ar-H), 7.70-7.72 (2H, m, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.7 (CH_3), 14.8 ($COCH_2\underline{C}H_3$), 19.9 ($OCH_2\underline{C}H_3$), 26.2 (CH_2), 26.6 (2 × CH_2), 26.7 (CH_2), 27.3 (CH_2), 28.1 (CH_2), 29.0 (CH_2), 38.9 (<u>C</u>HCHN), 41.5 (NCH_2), 44.2 (CH<u>C</u>HCO$_2$Et), 53.0 (<u>C</u>HCHCO$_2$Et), 61.3 ($CO\underline{C}H_2CH_3$), 62.9 (CHN), 64.5 ($O\underline{C}H_2CH_3$), 100.2 (C), 112.9 (C), 123.6 (CH), 124.5 (C), 130.9 (CH), 131.4 (CH), 131.7 (CH), 149.8 (C), 168.5 (C), 170.5 (C), 171.3 (C) ppm. MS: m/z (ES$^+$) 550 [M+Na]$^+$. IR (neat): ν = 2926, 2853, 1731, 1693, 1536, 1356, 1280, 1181, 1030, 699 cm^{-1}.



7.23

yellow solid, 65% yield, 10:1 mixture of diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.88 (3H, t, J = 7.2 Hz, CH_3), 1.11 (3H, t, J = 7.2 Hz, $OCH_2C\underline{H}_3$), 1.18-1.78 (14H, m, 7 × CH_2), 1.93-1.97 (1H, m, C<u>H</u>CHN), 2.93-2.98 (1H, m, NCH_2), 3.01 (1H, d, J = 4.5 Hz, C<u>H</u>CHPh), 3.44-3.54 (1H, m, $OC\underline{H}_2CH_3$), 3.59-3.65 (1H, m, NCH_2), 3.67-3.69 (1H, m, CHN and CHC<u>H</u>Ph), 3.79-3.89 (1H, m, $OC\underline{H}_2CH_3$), 6.27 (1H, dd, J = 7.8 Hz, J = 0.9 Hz, Ar-H), 6.94-7.00 (3H, m, Ar-H), 7.06-7.08 (3H, m, Ar-H), 7.29 (1H, td, J = 7.8 Hz, J = 0.9 Hz, Ar-H), 7.42 (1H, dd, J = 7.8 Hz, J = 0.9 Hz, Ar-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.8 (CH_3), 15.2 ($OCH_2\underline{C}H_3$), 19.9 (CH_2), 26.2 (CH_2), 26.5 (CH_2), 26.8 (CH_2), 26.9 (CH_2), 28.3 (CH_2), 29.1 (CH_2) 38.8 (<u>C</u>HCHN), 41.3 (NCH_2), 47.9 (CH<u>C</u>HPh), 54.6 (<u>C</u>HCHPh), 63.9 ($O\underline{C}H_2CH_3$), 64.7 (CHN), 100.1 (C), 115.4 (C), 123.0 (CH), 123.8 (C), 127.6 (2 × CH), 128.4 (3 × CH), 129.6 (CH), 130.2 (CH), 130.8 (CH), 135.1 (C), 149.4 (C), 170.7 (C), 172.0 (C) ppm. MS: m/z (ES^+) 554 $[M+Na]^+$. IR (neat): ν = 2929, 2854, 1681, 1537, 1370, 1260, 1036, 848, 777, 701 cm^{-1}.

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