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New Thermal and Oxidative Radical Cyclization Methodology and Application to the Total Synthesis of Bridged Diketopiperazine Alkaloids

PhD Thesis

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Declaration

This work was carried out in years 2010-2012 and 2014-2016 at the IOCB AS CR, v.v.i. I declare that I have done the Ph.D. thesis independently noting all used resources. I also declare that I did not use this work to get the same or another university degree.

Prague 15th March 2016 .....

Tynchtyk Amatov

Acknowledgement

At the end of this journey it is the best opportunity I have to thank and express my deepest gratitude to all those whom I met and who helped me on the way to finishing this thesis.

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Abstract

This thesis describes the development of new thermal and oxidative radical cyclization methodologies and their application to the total syntheses of alkaloids, particularly to bridged diketopiperazine (DKP) alkaloids.

A practical solvent free approach to diverse DKPs and quinazolines is described. The methodology proceeds by thermal silica gel mediated deprotection of the Boc protecting group and intramolecular condensation of the resulting free dipeptides and tripeptides. It was applied to the total syntheses of alkaloids glyantrypine and ardeemin.

A major part of the thesis concerns with the discovery and applications of novel diketopiperazine derived alkoxyamines. Their propensity to undergo facile thermal C–O bond homolysis to generate captodative DKP radicals and persistent TEMPO radical allowed using them as radical surrogates. The methodology takes advantage of the persistent radical effect (PRE).

The methodology based on PRE was applied in an asymmetric approach to the alkaloid asperparaline C. An asymmetric synthesis of a very advanced precursor to asperparaline C, 8-oxoasperparaline C, was accomplished in 11 steps and 15% overall yield. The key steps of the synthesis include a direct oxidative cyclization of DKPs, regioselective furan dearomatization with singlet oxygen and a reductive radical spirocyclization. The PRE-based methodology was also applied as a conceptually new approach to diverse bridged DKPs. DKPs with widely variable ring sizes were efficiently synthesized. A formal synthesis of antibiotic bicyclomycin was achieved using this methodology.

The DKP derived alkoxyamines displayed some unusual features. An unusual *trans*/*cis* isomerization at the anomeric center was discovered and its kinetics were determined by ^{1}H NMR spectroscopy. The kinetics of the PRE mediated radical cyclizations were also investigated by ^{1}H NMR spectroscopy. These studies provided deep insight into the mechanisms operating in these PRE mediated transformations.

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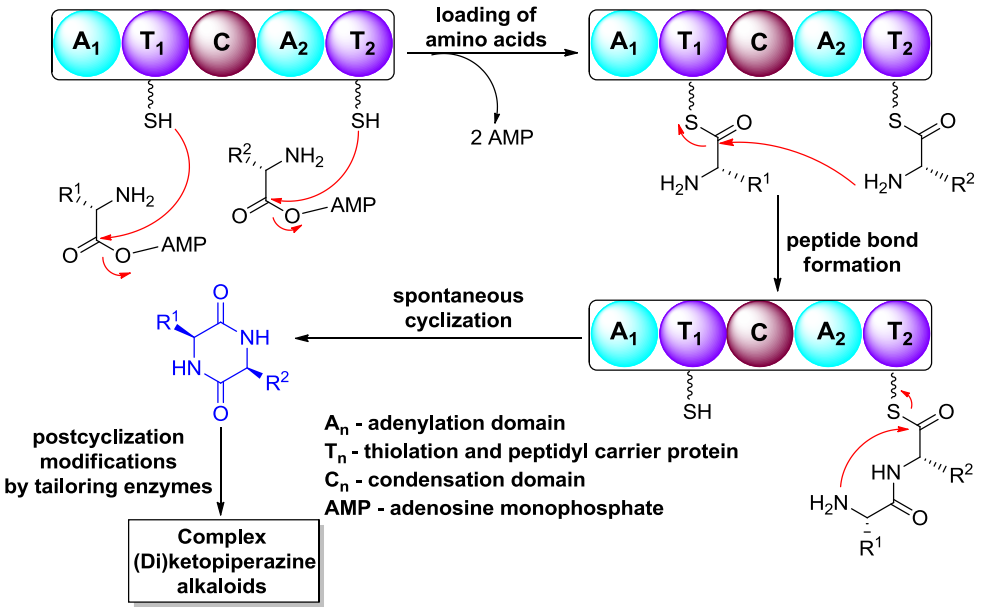
1. Introduction

1.1. Bridged diketopiperazine alkaloids

2,5-Diketopiperazines (DKPs)[1] are the smallest cyclic peptides and very common secondary metabolites that are produced by various microorganisms such as bacteria, fungi, yeasts, lichens and various different marine organisms like sponges, sea stars, tunicates and algae.[2] The DKP unit is present in a vast number of secondary metabolites having complex architectures. The constrained structure of DKPs makes them an attractive naturally occurring privileged scaffold in medicinal chemistry.[3]

1.1.1. Biosynthesis of diketopiperazines

Despite their widespread occurrence in Nature the biosynthesis of DKPs is not well studied. It is believed that in fungi and bacteria DKPs are produced by nonribosomal peptide biosynthesis pathways (Scheme 1.1).[4] Multifunctional nonribosomal peptide synthetases (NRPS) responsible for biosynthesis of myriads of oligopeptide secondary metabolites are also involved in the biosynthesis of DKPs. NPRS are large enzymes consisting of an assembly line of modules, which comprise of semiautonomous domains having catalytic or carrier functions.



Scheme 1.1. Biosynthesis of DKPs by nonribosomal peptide synthetases (NRPS). Adapted from Ref. 4e.

The domains in the modules work in a tandem fashion. The biosynthesis starts by recognition and activation of amino acids by the adenylation (A_n) domain followed by subsequent loading of the activated (adenylated) amino acids by the thiolation domain (T_n). A follow up conversion into thioester bound dipeptide by the condensation domain (C_n) ensues. Spontaneous DKP formation occurs after dipeptide formation by NRPS because of the labile nature of the thioester bond.

A very rare type of DKP biosynthesis independent of NRPS has been discovered recently as well, wherein enzymes, which were named cyclodipeptide synthases (CDPS), use aminoacyl-tRNAs as substrates to catalyze the biosynthesis of DKPs.[5] These enzymes are much smaller in size compared to NRPSs. A crystal structure of AlbC, a CDPS from *Streptomyces noursei* has been reported recently.[6]

The released DKPs are taken up by the tailoring enzymes, genes for which are usually clustered with the NRPS and CDPS coding genes. They convert DKPs to more complex and diverse families of secondary metabolites by further transformations such as methylations, prenylations, oxidative or reductive modifications or by combinations of all. Complex structures arise as a result of cascade transformations, such as cycloadditions or rearrangements, triggered by these post-cyclization modifications.

1.1.2. Biosynthesis and diversity of bridged DKP alkaloids

Bridged alkaloids, containing a central diazabicyclo[*n*.2.2]alkane ring system ($n \geq 2$), which are derived from DKP scaffolds by connecting positions 3 and 6, constitute an ever-growing class of secondary metabolites. Exceptional diversity is observed among these alkaloids because of different bridge *types* and *sizes* (Figure 1.1.). Members of the superfamily of prenylated indole alkaloids ($n = 2$) such as brevianamide A (**1.1**) are the most common bridged DKP alkaloids in Nature.[7] Metacyclophane type azonazine[8] (**1.2**) ($n = 6$) and mycocyclosin (**1.3**) ($n = 8$)[9] are metabolites formed by oxidative coupling of aromatic side chains of the involved amino acids tyrosine and tryptophan and have larger bridges. The unusual antibiotic bicyclomycin[10] (**1.4**) and cottoquinazoline D (**1.5**) are examples of rarely encountered bridged DKP alkaloids with heteroatom bridges. The latter has the DKP unit condensed with an anthranilic acid to form a quinazoline ring system.[11] Epipolythiodioxopiperazines (ETP),[12] such as gliotoxin (**1.6**), bear bridges consisting of only sulfur atoms.

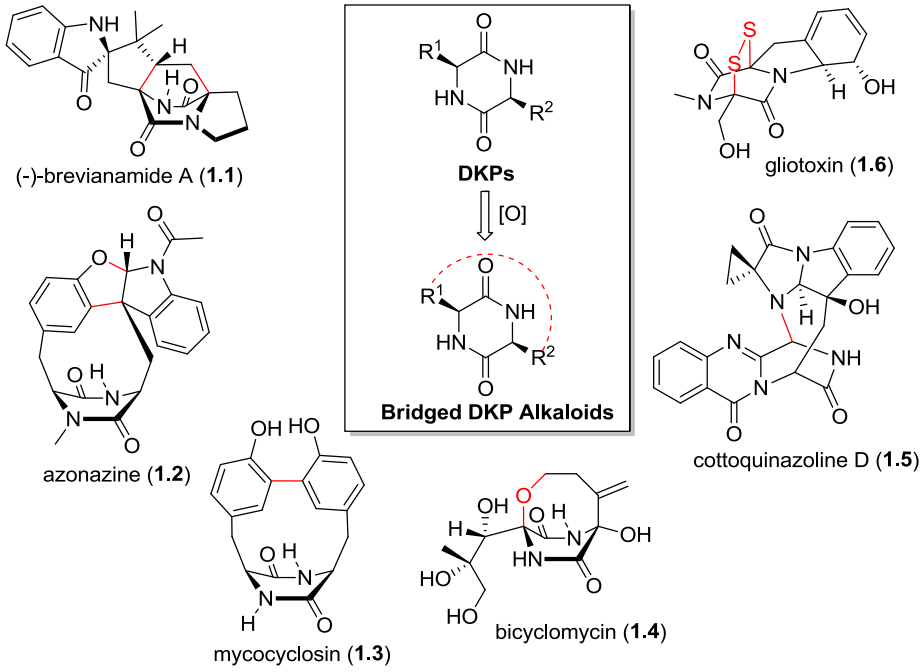
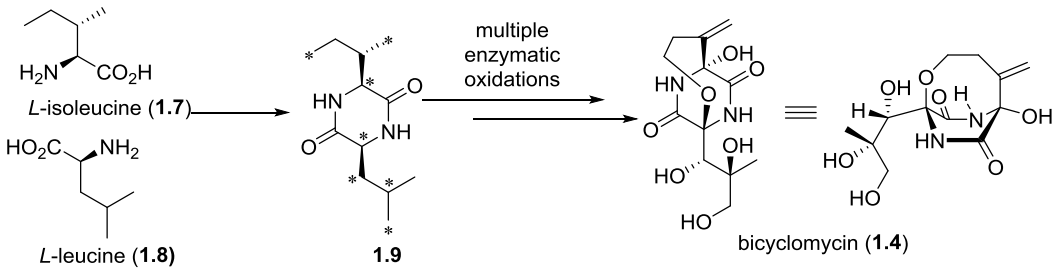


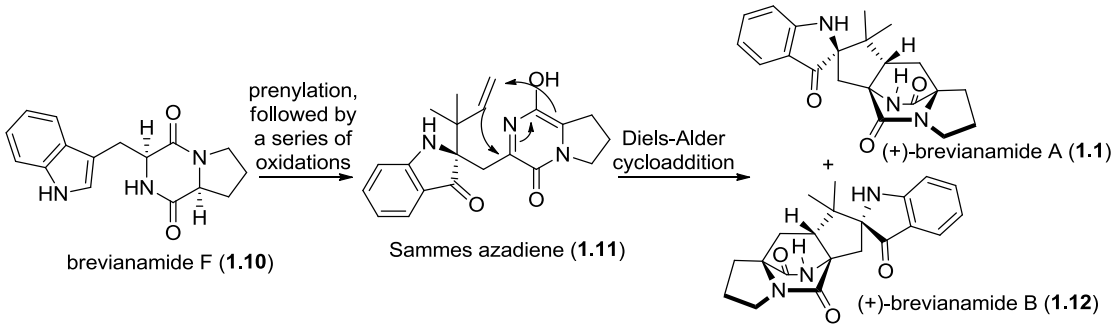
Figure 1.1. Diversity of bridged DKP alkaloids.

Nature extensively uses both the flavin adenine dinucleotide (FAD)-dependent or flavin mononucleotide (FMN)-dependent enzymes (flavoenzymes)[13] and heme iron oxygenases such as cytochrome P450 for oxidative modifications of DKPs. These enzymes can either directly bridge the subtituents and side chains attached to positions 3 and 6 or oxygenate the DKPs generating reactive intermediates such as aminals, (acyl)imines or (acyl)iminium species that undergo cyclizations and cycloadditions. For instance, bicyclomycin (**1.4**), an antibiotic of commercial importance, is formed biosynthetically from *L*-isoleucine (**1.7**) and *L*-leucine (**1.8**) via the intermediacy of DKP **1.9**. Subsequently, impressively selective sequences of enzymatic oxidations at all starred carbon atoms take place (Scheme 1.2.). However, little is known about the timing of the modifications after DKP **1.9**.[14]



Scheme 1.2. Biosynthesis of bicyclomycin.

For the pseudo-enantiomorphic brevianamides A (**1.1**) and B (**1.12**), Sammes and Porter suggested a biosynthetic Diels-Alder reaction as a possible way of formation already in 1970 (Scheme 1.3).[15] Brevianamide A (**1.1**) is the major pseudo-enantiomorph, which arises from the lower energy rotamer of Sammes azadiene (**1.11**) as supported by *ab initio* calculations.[16]



Scheme 1.3. Sammes' biosynthetic Diels-Alder reaction proposal for brevianamides A and B.

Since the isolation of brevianamides A (**1.1**) and B (**1.12**) by Birch from the culture extracts of *Penicillum brevicompactum* in 1969,[17] nearly 70 secondary metabolites, containing the diazabicyclo[2.2.2]octane core structure, were isolated from both terrestrial and marine fungi over the years. This superfamily of alkaloids comprises subfamilies such as paraherquamides, stephacidins, marcfortines, malbranchemides, notoamides, taichunamides and asperparalines.[18] Paraherquamides, marcfortines, malbrancheamides, asperparalines and chrysogenamide A have the carbonyl group derived from the tryprophan unit reduced to methylene group. Hence, they are monoketopiperazine alkaloids. The unusual spirosuccinimide fragment of asperparalines (**1.24-27**),[19] is believed to form by oxidative indole degradation of indole.[20] A further stage of diversity and complexity within the family is achieved by dimerization as in stephacidin B (**1.29**)[21] and the waikialoids A (**1.30**) and B (**1.31**).[22]

The bridged bicyclic motif can have two stereochemical configurations with respect to the relative configuration of the C6-H proton (stephacidin A numbering) of the bicyclic core in relation to the bridging secondary lactam (Figure 1.3). Brevianamides A/B (**1.1**/**1.12**), versicolamide B (**1.13**), chrysogenamide A (**1.14**) and taichunamides (**1.15**-**1.18**) are the only members of the family having *anti*-configuration at the bridging bicycle, all other known members display the more common *syn*-configuration.

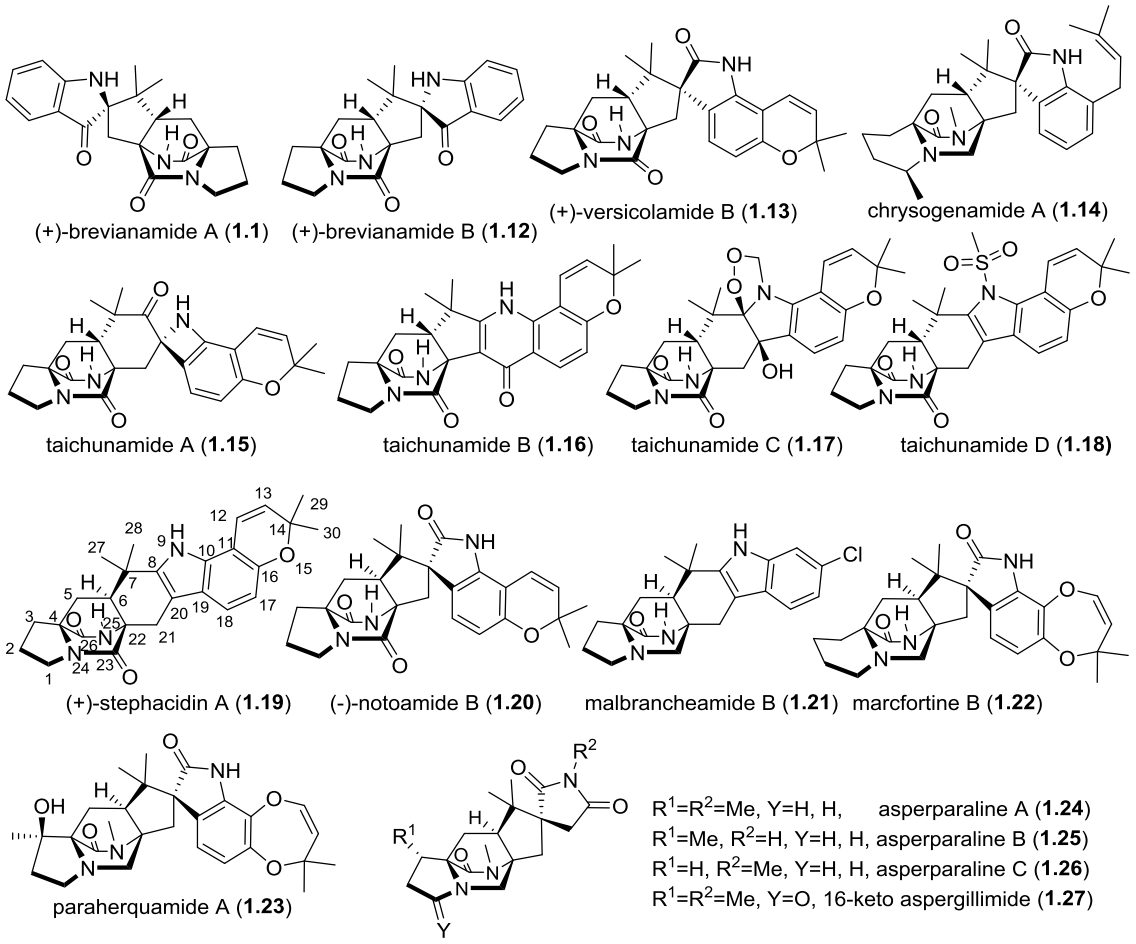
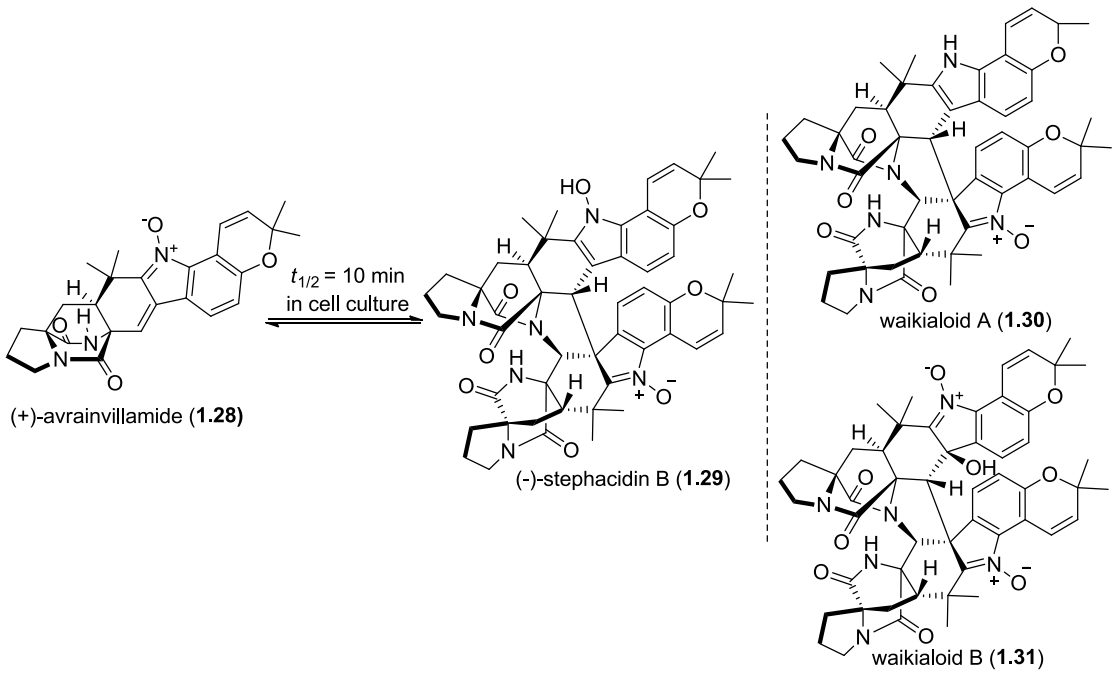


Figure 1.2. Representative alkaloids containing the diazabicyclo[2.2.2]octane ring system.



Scheme 1.4. Dimeric alkaloids containing the diazabicyclo[2.2.2]octane ring system.

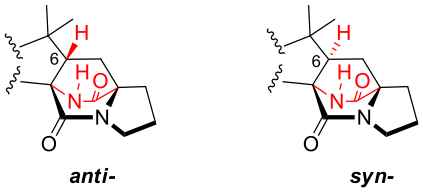


Figure 1.3. *anti*- and *syn*-Configurations of the diazabicyclo[2.2.2]octane core.

The structural diversity within the family results in a variety of bioactivities exhibited by these alkaloids such as insecticidal, cytotoxic, anthelmintic, and antibacterial properties. The dimeric stephacidin B (**1.29**) shows strong antitumor activity. The antiproliferative activity exhibited by **1.29** is believed to be associated with its monomeric form avrainvillamide (**1.28**) whose unusual vinyl nitrone moiety can be attacked by thiol groups of biomolecules.[23] The asperparalines show strong paralytic activities against insects and recent studies aimed at elucidating their mechanism of action showed that asperparaline A strongly and selectively blocks insect nicotinic acetylcholine receptor (nAChR).[24]

1.2. Synthetic approaches to prenylated indole alkaloids containing the diazabicyclo[2.2.2]octane core structure

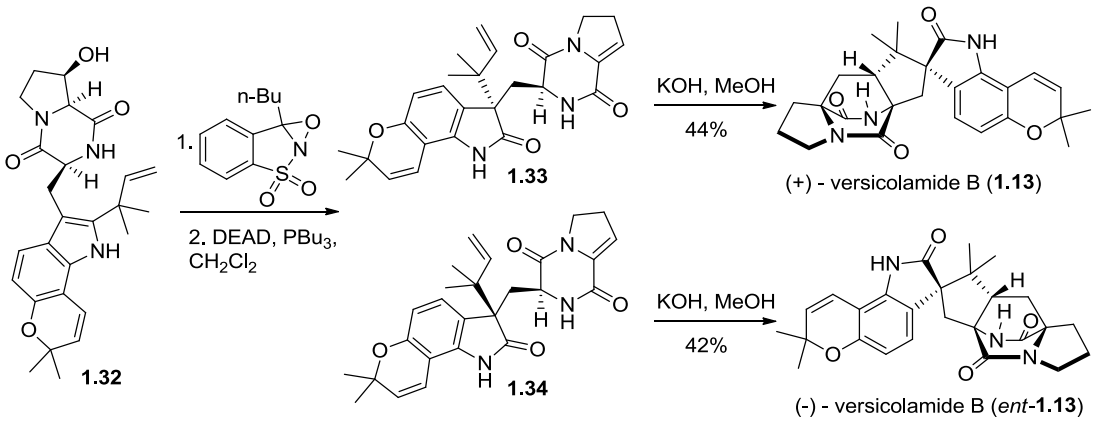
Prenylated indole alkaloids containing the diazabicyclo[2.2.2]octane core structure attracted significant interest from synthetic chemists, especially in the last decade. A plethora of methods and approaches employing various reactive intermediates and strategies is a testament to the importance of these natural products. Several reviews appeared over the years that thoroughly discuss the approaches to bridged prenylated indole alkaloids.[25] In the following sections previous approaches to these alkaloids will be shortly reviewed.

1.2.1. Cycloaddition approaches

Guided by Sammes' biogenetic proposal, Williams and co-workers achieved the total syntheses of a number of alkaloids with both *anti*- and *syn*-bicycle configuration applying the biomimetic Diels-Alder cycloaddition.[26] Liebscher[27] and recently Scheerer[28] and Qin[29] also reported analogous [4+2]-cycloadditions to synthesize structures containing the diazabicyclo[2.2.2]octane motif.

Because the synthesis of Sammes azadiene type precursors in enantiomerically pure form proved to be difficult, only racemic syntheses were initially accomplished. However, an

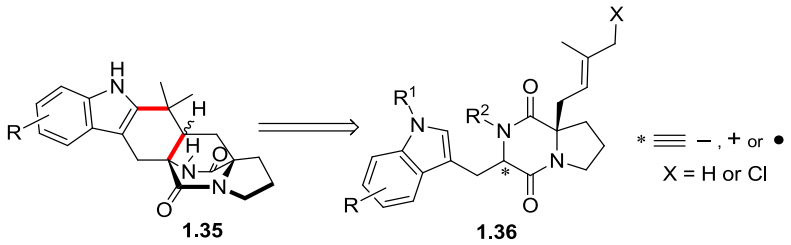
asymmetric access was recently elaborated by Williams in an elegant synthesis of both enantiomers of versicolamide B (**1.13**) starting from a common precursor.[24] DKP **1.32** was oxidized to a separable mixture of oxindoles (not shown) which were dehydrated under Mitsunobu-type conditions to give unsaturated DKPs **1.33** and **1.34**. Each of these unsaturated DKPs was individually treated with methanolic KOH to generate Sammes type azadienes *in situ* (not shown) by tautomerization of **1.33** and **1.34**, which subsequently underwent cycloaddition to enantiomerically pure versicolamides **1.13** and *ent*-**1.13**.



Scheme 1.5. Enantiodivergent biomimetic synthesis of versicolamide B (**1.13**).

1.2.2. Approaches employing reactive α-carbonyl intermediates

The majority of approaches to prenylated indole alkaloids containing the diazabicyclo[2.2.2]octane core structure employed reactive α–carbonyl DKP intermediates such as **1.36** according to the disconnection shown in Scheme 1.5.

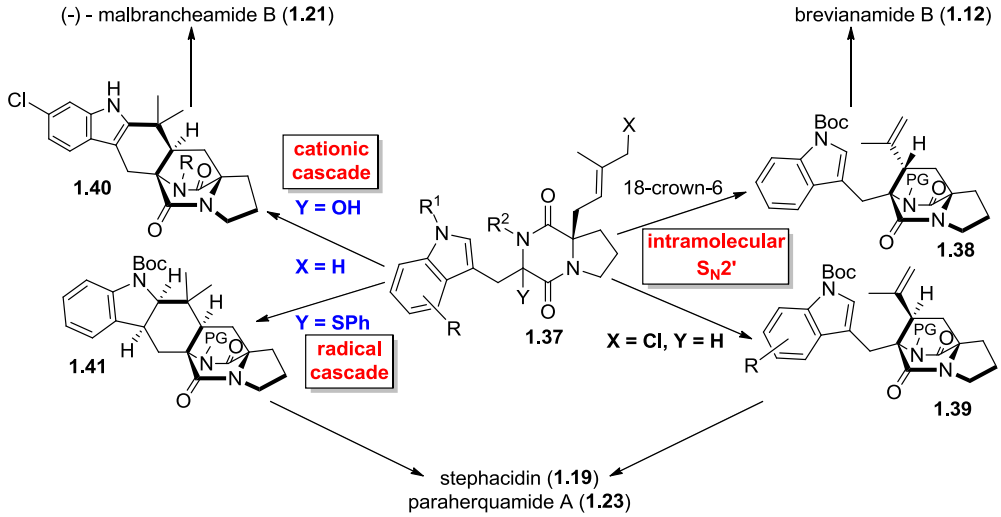


Scheme 1.5. The most common disconnection for the diazabicyclo[2.2.2]octane ring system.

Over the years Williams' lab performed a significant amount of both synthetic and biosynthetic studies, which helped to understand the biogenetic origins of these alkaloids in

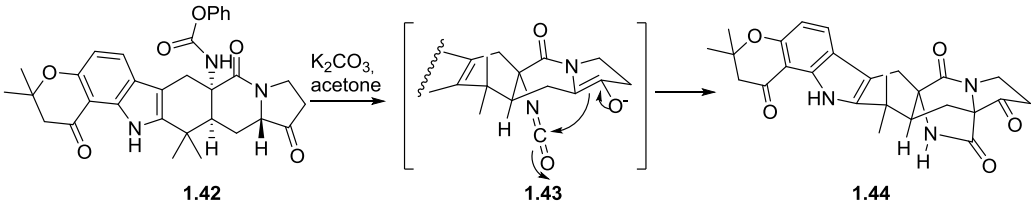
more detail (Scheme 1.6). They developed intramolecular S_N2' cyclizations to rapidly access complex bridged core structures from simple DKPs.[30] Moreover, both the *anti*- and *syn*-configurations of bicyclic **1.38** and **1.39** were accessible in a stereocontrolled manner depending on the presence or absence of 18-crown-6 as an additive. On this basis, total syntheses of brevianamide B (**1.12**)[31] as well as paraherquamides[32,33] and stephacidins A (**1.19**) and B (**1.29**)[34] were achieved.

An elegant asymmetric synthesis of (–)-malbrancheamide B (**1.21**) employing a cationic cyclization of hemiaminal **1.37**, (X=H, Y=OH), mediated by TMSOTf, was developed recently by Simpkins et. al.[35] Complementary to this, Simpkins and co-workers also reported a radical cascade, which gives polycyclic indolines related to the stephacidins from α-sulfenylated DKPs **1.37** (X = H, Y = SPh).[36]



Scheme 1.6. Approaches employing reactive α-carbonyl intermediates.

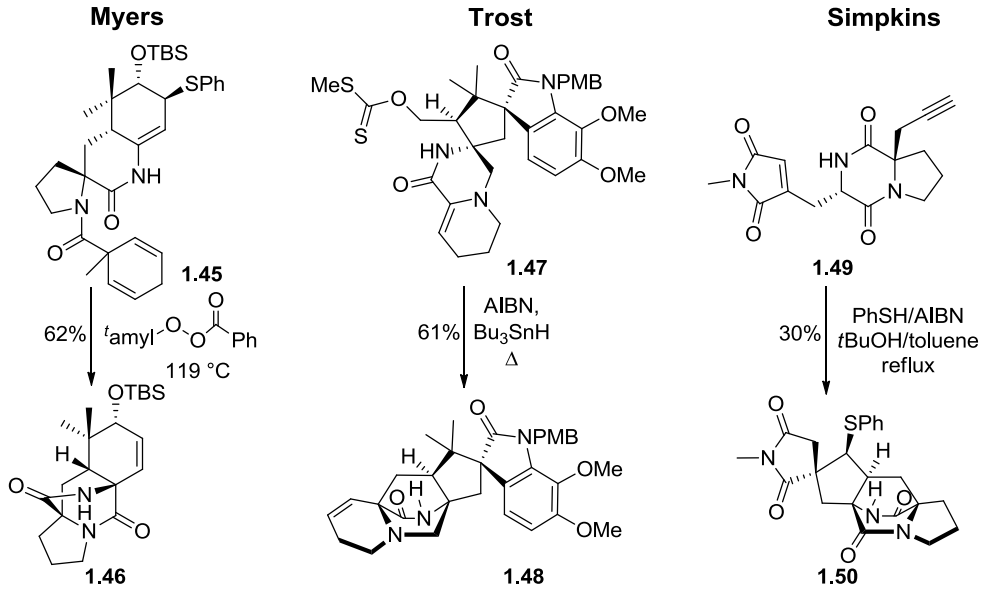
Finally, Sarpong and coworkers used an unusual intramolecular isocyanate capture by an enolate to achieve the synthesis of the central diazabicyclo[2.2.2]octane core in their synthesis of stephacidin A.[37]



Scheme 1.7. A key step in Sarpong's approach to stephacidin A.

1.2.3. Radical approaches

Radicals offer more opportunities in terms of devising less conventional disconnections in synthetic endeavors (Scheme 1.8). For example, a carbamoyl radical was generated from **1.45**, which underwent a 6-exo-trig cyclization to an enamide double bond followed by a β-fragmentation of a thiyl radical as the key step of Myers' synthesis of avrainvillamide (**1.28**) and stephacidin B (**1.29**).[38] A xanthate-transfer/6-exo-trig cyclization starting from **1.47** and concomitant elimination gave access to the core bridged structure **1.48** in Trost's synthesis of marcfortine B (**1.22**).[39]



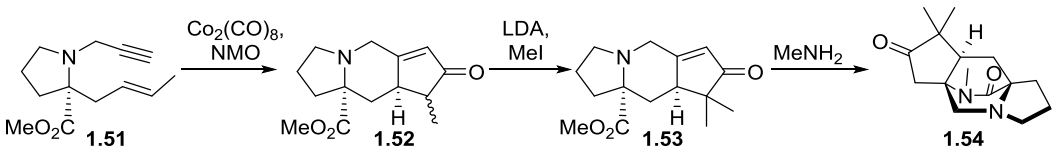
Scheme 1.8. Radical approaches to bridged DKP alkaloids.

Simpkins reported a sophisticated radical cascade transformation to **1.50**, having the complete cyclic structure of the asperparalines in one step, albeit in low yield.[40] An impressive sequence of transformations was initiated by thiyl radical addition to the terminal alkyne functionality of **1.49** generating a vinyl radical that underwent 1,6-hydrogen atom transfer followed by 6-exo-trig and 5-exo-trig cyclizations affording spirotetracycle **1.50**.

1.2.4. Miscellaneous Approaches

Tanimori et al. approached the tricyclic core of asperparalines by using an intramolecular Pauson-Khand reaction as the key step (Scheme 1.9). A tandem Michael

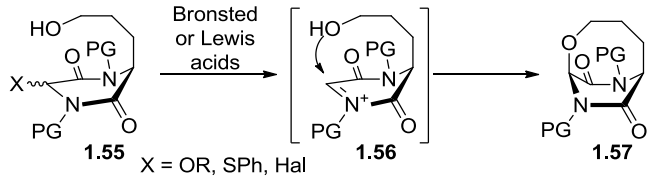
addition/lactamization using methylamine furnished an advanced intermediate **1.54**. However, no further progress en route to the target molecules was reported.



Scheme 1.9. Tanimori's approach to asperparalines.

1.2.5. Approaches to bicyclomycin

Numerous groups were involved in the total synthesis of bicyclomycin in the 1980s which resulted in three independent total syntheses and one formal synthesis.[10] Central to all is an intramolecular capture of *N*-acyliminium type intermediates such as **1.56** (Scheme 1.10).

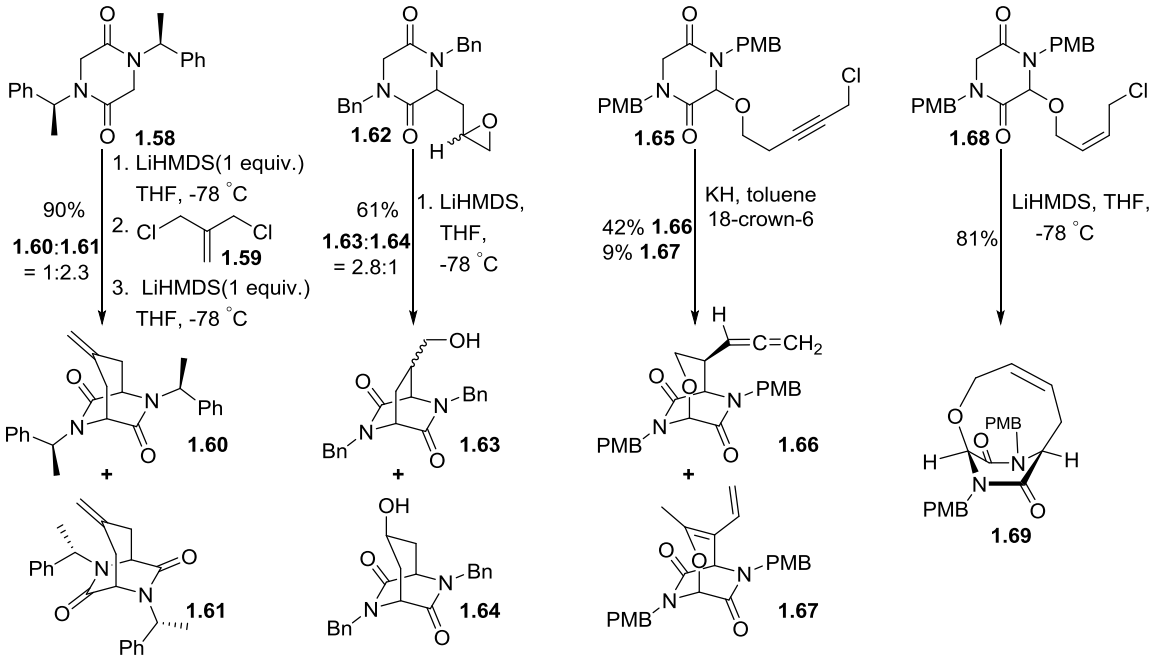


Scheme 1.10. Previous approaches to the bicyclomycin core.

1.3. Synthesis of non-natural bridged DKPs

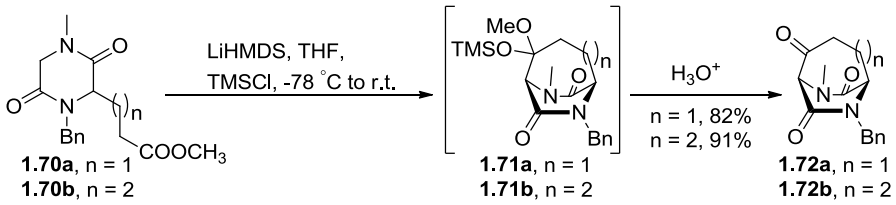
The concept of conformational constraint is an important tool in medicinal chemistry to probe enzyme binding active sites as well as the "active conformations" of drug-like molecules. This concept allows mapping the 3D space involved in drug-enzyme interactions. Rationally designed conformationally constrained molecules have an entropic advantage over flexible, unconstrained molecules and show often enhanced binding affinities to target enzymes. The most common approach of conferring conformational restrictions to molecules is to "lock" the desired conformation within cyclic structures. DKPs are already constrained because of to their cyclic nature and are regarded as privileged structures in drug design. Additional constraints can be conferred to DKP side chains by bridging them "above" the planar DKP ring system.

Porzi and Sandri applied a one-pot two-step alkylation of chiral DKP **1.58** with 2-chloromethyl-3-chloropropene (**1.59**) to synthesize diazabicyclo[3.2.2]nonanes **1.60** and **1.61** in a 1:2.3 ratio,[41] which were shown to be potent α-glucosidase inhibitors.[42] Williams also reported the intramolecular epoxide opening of **1.62** which gave poor selectivity of endo/exo epoxide opening.[43] In a follow up publication, an interesting reactivity of DKPs **1.65** and **1.68** was reported.[44] Whereas **1.65** underwent an unusual rearrangement to a cumulene intermediate, from which diazabicyclo[3.2.2]nonanes **1.66** and **1.67** were formed, **1.68** produced diazabicyclo[5.2.2]undecane **1.69** in high yields (Scheme 1.11).



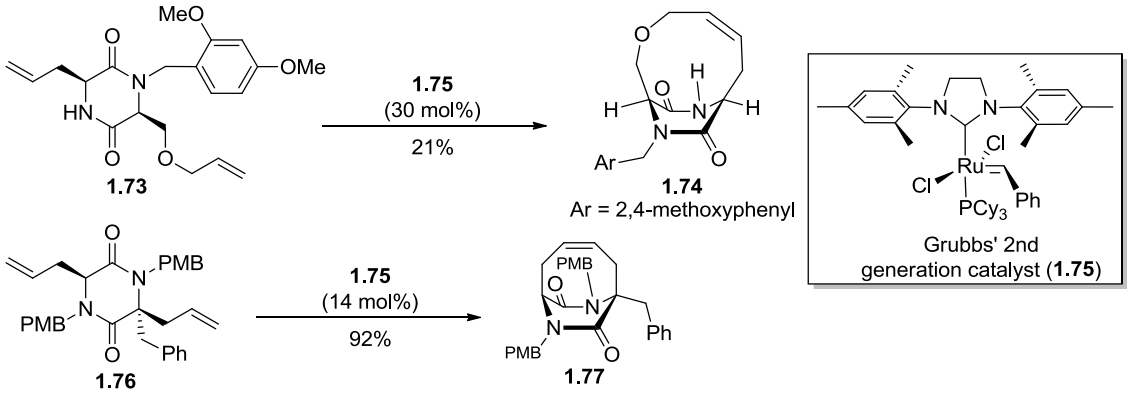
Scheme 1.11. Enolate alkylation approaches to bridged DKPs.

Wünsch and co-workers, in search for conformationally constrained σ receptor ligands, developed an approach to both the diazabicyclo[3.2.2] and diazabicyclo[4.2.2] ring systems (Scheme 1.12). They applied an intramolecular Dieckmann-type cyclization of DKPs **1.70a,b** with propanoate and butanoate side chains, respectively. The reaction proceeds via mixed acetals **1.71a,b** which can be isolated. Aqueous acidic hydrolysis produced bridged ketones **1.72a,b**.[45]



Scheme 1.12. Dieckmann condensation approach to bridged DKPs.

Ring closing metathesis (RCM) using Grubbs' 2nd generation catalyst (**1.75**) allowed Jacobson to access oxygen bridged DKP **1.74** with the diazabicyclo[6.2.2]hexadecane ring system from **1.73**, albeit in low yield.[46] Simpkins reported the synthesis of bridged DKP **1.77** also using **1.75** as a catalyst (Scheme 1.13).[35b]

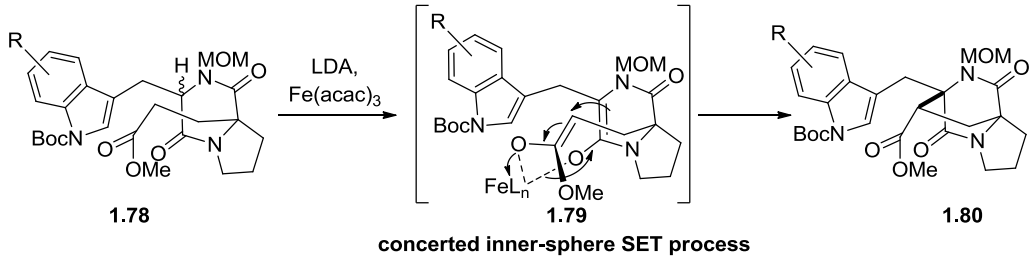


Scheme 1.13. RCM approaches to bridged DKPs.

1.4. Single electron transfer (SET) oxidation of metal enolates in total synthesis

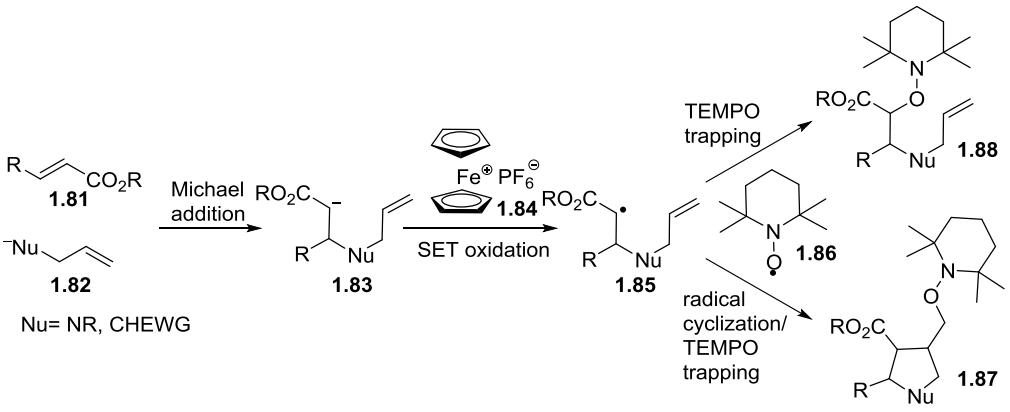
Functionalization of α-CH position of carbonyl compounds is at the heart of organic chemistry. Conventional routes to achieve α-CH functionalization of carbonyl compounds utilize polar reactions of metal enolates or enamines with suitable electrophiles. On the other hand, the electron-rich nature of enolates, enols and enol-derivatives, such as enamines and silyl enol ethers, open up opportunities for oxidative transformations via SET-oxidation of enolates to α-carbonyl radicals and cation-radicals and enable complementary transformations or processes, which are impossible via polar pathways. Oxidative transformations of metal-enolates, enols and enol-derivatives gained significant importance in recent years in the area of complex molecule synthesis.

The most common applications of oxidative enolate chemistry in target oriented synthesis employ intramolecular oxidative enolate coupling reactions as exemplified by Baran's synthesis of stephacidin A (Scheme 1.14).[47] However, these reactions most likely proceed via concerted inner-sphere SET processes via Fe(III)-bridged enolates such as **1.79** since the use of outer-sphere SET oxidants like ferrocenium salts led to low yields or no reaction. Thus, such processes are less likely to involve free radicals. When ferrocenium salts are used as SET oxidants, the major reaction is dimerization of α-carbonyl radicals. This method, introduced by Jahn and coworkers,[48] is also frequently used in natural products total synthesis.



Scheme 1.14. Intramolecular oxidative enolate coupling

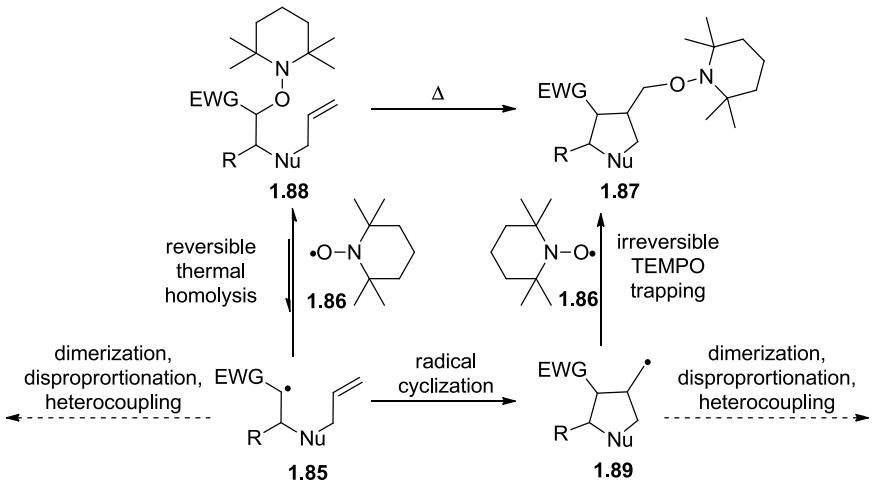
Over the years the Jahn group has developed efficient and practical tandem transformations that extended the scope of oxidative enolate chemistry beyond the oxidative coupling and dimerization of enolates (Scheme 1.15). For example, conjugate addition of suitable nucleophiles **1.82** to Michael acceptors **1.81**, followed by SET oxidation of the resulting enolates **1.83** using ferrocenium hexafluorophosphate salt **1.84** to α-carbonyl radicals **1.85** in the presence of persistent radical TEMPO (**1.86**) lead to rapid generation of molecular complexity as a result of 5-exo-trig radical cyclization followed by TEMPO trapping of the cyclic radicals. Alternatively, direct trapping of α-carbonyl radicals **1.85** lead to α-oxygenation giving access to β-amino α-hydroxy acid derivatives, if **1.82** are lithium amides. A variety of highly functionalized pyrrolidines and cyclopentanes can be achieved in a single reaction from simple starting materials.[49] Such redox switching of intermediates allow design of novel heterointermediate reaction sequences and constitute an unconventional version of the *umpolung* principle.



Scheme 1.15. Tandem heterointermediate reaction sequences developed in the Jahn group.

1.5. The persistent radical effect

The uncyclized ialkoxyamines **1.88** can in principle be converted into cyclic products **1.87** by thermal homolysis of the C-O bond (Scheme 1.16). This is possible because of the low bond dissociation energies (BDE) of the C-O bond in alkoxyamines, which leads to facile reversible homolysis, when R is a good radical stabilizing group, and most importantly, due to the persistent radical effect (PRE).[50] The PRE is a powerful principle that governs the selective cross-coupling of two different radical species that are produced at equal rates, if one is transient and the other persistent.

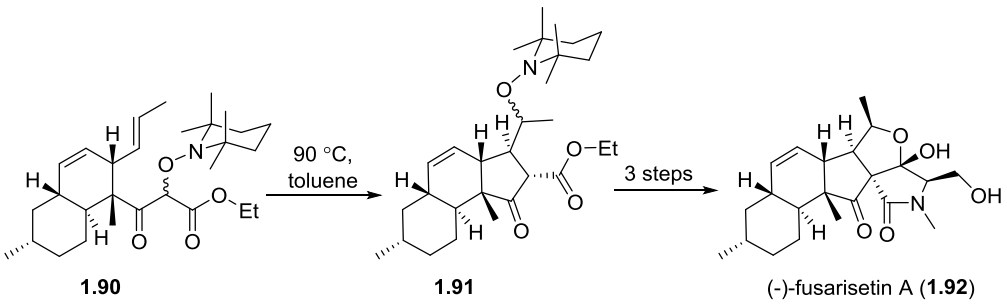


Scheme 1.16. Mechanism of the PRE mediated cyclizations.

According to this principle, the transient radicals **1.85** and **1.89** will selectively couple with the persistent radical TEMPO (**1.86**) because of the high rate constant. This process

results for **1.85** reformation of **1.88**, thus it is a degenerate process. Alternatively, irreversible 5-exo-trig cyclization leads to radical **1.89** which couples with TEMPO to give product **1.87**. The PRE operates on a concentration effect whereupon even a small extent of radical quenching processes such as dimerization, disproportionation and heterocoupling of transient radicals lead to the buildup of the persistent radical concentration and because of this small excess of persistent radical all undesired pathways will be suppressed by cross-coupling with the persistent radical.

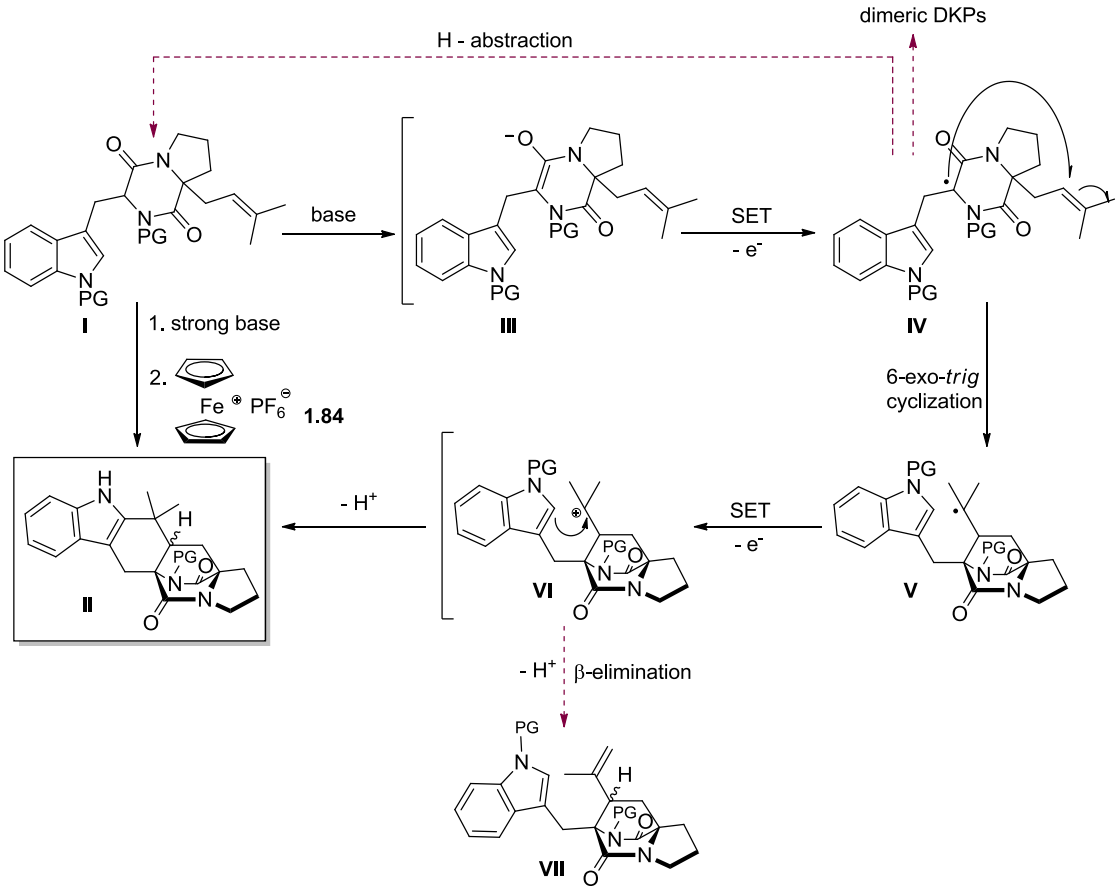
The PRE has found significant applications in polymer research and alkoxyamines are frequently used as initiators in living radical polymerizations.[51] However, synthetic chemists neglected the potential of alkoxyamines in designing novel radical transformations based on PRE until Studer's seminal studies a decade ago.[52] The first application of the PRE as a key step in total synthesis was only recently reported by Theodorakis and co-workers, who used a 5-exo-trig cyclization toward fusarisetin A (**1.92**).[53]



Scheme 1.17. Application of PRE in the total synthesis of fusarisetin A (**1.92**).

Aims of the work: hypotheses and analysis of potential problems

The overview of approaches to bridged (di)ketopiperazine alkaloids, demonstrates that cyclization reactions were employed by most researchers. Moreover, all of them proceed via homointermediate cyclizations, i.e. only one type of reactive species is involved, such as only radicals, or cations or anions. In line with long-standing interests of the Jahn laboratory in the development of heterointermediate reaction sequences it was decided to test the possibility of a heterointermediate approach to these alkaloids (Scheme 2.1).



Scheme A.1. Heterointermediate reaction sequences toward prenylated indole alkaloids containing the diazabicyclo[2.2.2]octane core structure and some potential pitfalls (dashed arrows).

SET oxidation mediated by ferrocenium hexafluorophosphate (**1.84**) would enable a redox switch from the DKP enolate **III** to a DKP radical **IV**, which was expected to undergo 6-exo-*trig* cyclization to the pendant alkene unit generating bridged tertiary radical **V**. This

intermediate may be further oxidized to tertiary carbocation **VI** followed by intramolecular nucleophilic attack of the indole ring in the final stage to give **II**.

It was envisioned that if successful, this approach would allow a rapid access to various members of bridged prenylated indole alkaloids without functionalizing the α-position of DKPs as in Simpkins' approaches or without the need to install chlorinated prenyl side chains as in Williams' approaches. Thus, the initial aim of this project was to develop a new methodology towards these alkaloids.

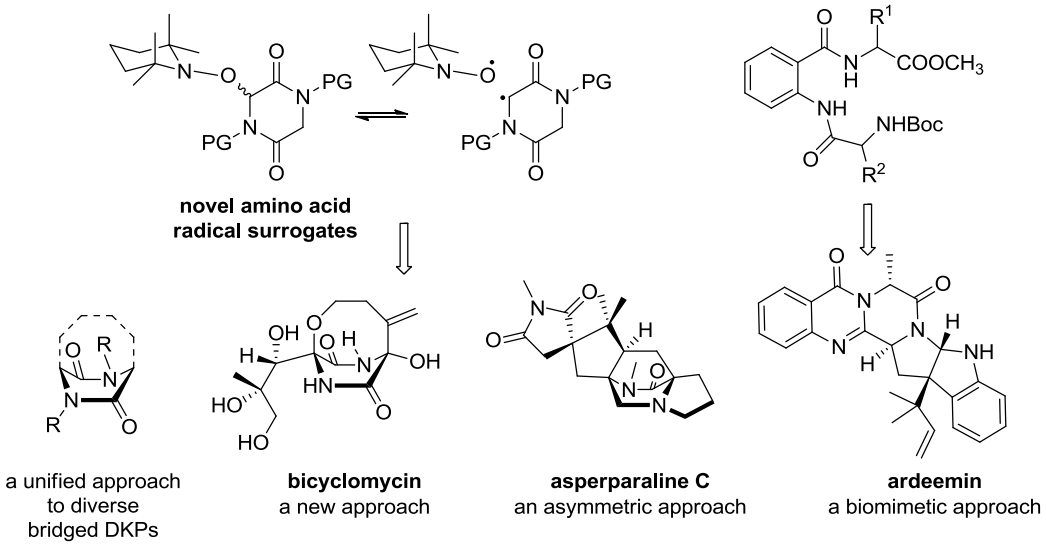
However, analysis of the proposed approach reveals some problems that may hamper the possibility of achieving the goal. Problems or difficulties might arise from the inherent reactivities of the involved intermediates or unfavorable energetics of some key transformations. For example, dimerization and H-atom abstraction may be main side reactions of radical species if the radical cyclization is too slow and β-elimination of carbocations can terminate the reaction sequence prematurely giving compounds **VII**. While the energetics of 6-exo-*trig* radical cyclization is difficult to predict, it was hoped that, provided radical generation is possible the cyclization will take place readily. The low temperature conditions under which the radical has to be generated might be problematic if the radical cyclization is slow.

Apart from Baran's works, no studies concerning the SET oxidation of DKP enolates were known at the outset of this project in 2010.[1] Being aware of these challenges, the initial aims of this work were:

1) To develop efficient synthesis of advanced DKP intermediates and model compounds to study the projected oxidative cyclizations of DKP enolates;
2) To study oxidative enolate chemistry of DKPs using the methodologies developed in the Jahn group;
3) If successful, to develop new approaches to bridged DKP alkaloids containing the diazabicyclo[2.2.2]octane core structure;
4) To apply the developed methodology in the synthesis of selected alkaloids;
5) To study the possibility of extending the developed methodologies for the synthesis of non-natural highly three dimensional conformationally constrained bridged DKPs and bicyclomycin type architectures (bicyclo[*n*.2.2]piperazinediones, *n*>2).

[1] Only in 2013, when this work was in an advanced stage, Simpkins reported a single example of oxidative cyclization of a DKP enolate using $CuCl_2$ as an oxidant which delivered a bridged product but the double cyclization product was not observed: N. S. Simpkins, I. Pavlakos, M. D. Weller, L. Male *Org. Biomol. Chem.* **2013**, *11*, 4957–4970.

If direct oxidative radical cyclyzations would fail because of the aforementioned potential problems, it was envisaged that the persistent radical effect mediated cyclizations as an alternative approach. However, alkoxyamines derived from DKPs or other amino acid derivatives were unprecedented in the literature at the outset of this work. The lack of precedence was taken as an opportunity to explore and develop new approaches to alkaloids such as asperparaline C, bicyclomycin and non-natural bridged DKP scaffolds. During the synthetic studies biomimetic approaches to other peptide alkaloids such as ardeemin could also be explored (Scheme 2.2).



Scheme A.2. Envisioned target molecules.

2. A practical approach to DKPs and quinazolines and initial studies to achieve oxidative radical cyclizations

2.1. Synthesis of building blocks and dipeptides

In order to test the proposed approach, it was necessary to prepare suitably protected DKPs of type **2.1a** and **2.1b** with pendant allyl and prenyl side chains, respectively. Various approaches to DKPs exist in the literature.[1,54] Based on previous syntheses of such DKPs by Baran,[47] it was envisioned that a one-step thermal removal of the Boc-group from dipeptides **2.2** and spontaneous lactamization under the thermal conditions would give access to *N*-unprotected DKPs **2.3**.

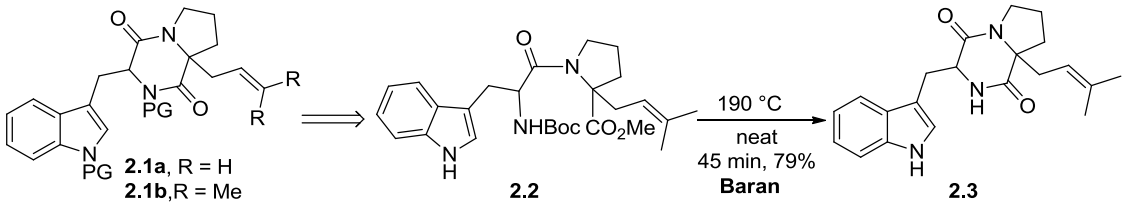
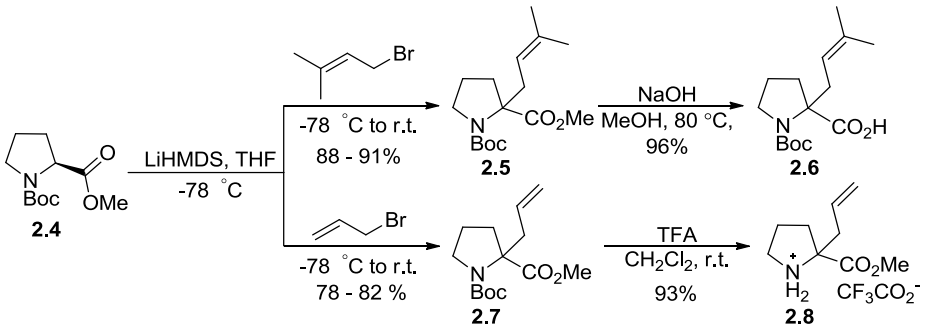


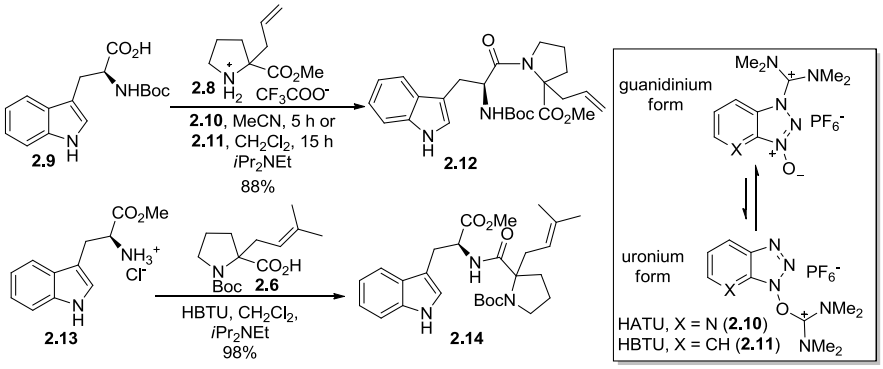
Figure 2.1. DKPs required for initial studies and Baran's synthesis of DKP **2.3**.

Known prenylated and allylated proline derivatives **2.5** and **2.7** were prepared by reported methods.[47] A racemic approach was initially pursued because of its convenience in model studies and methodology development. Because the acid cleavage of Boc group in **2.5** led to an unprotected pyrrolidine (not shown) with unsatisfactory purity it was decided to saponify **2.5** to a carboxylic acid **2.6**. Acidic deprotection of **2.7** gave an easy to handle salt **2.8** as a colorless solid.



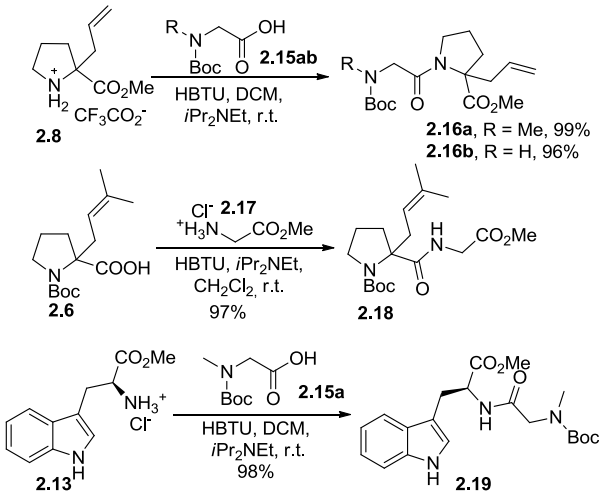
Scheme 2.1. Synthesis of proline building blocks **2.6** and **2.8**.

With efficient syntheses of prenylated and allylated proline building blocks **2.6** and **2.8** secured, peptide coupling with Boc-protected tryptophan **2.9** was tried. Initial attempts with carbodiimide coupling reagents were unsuccessful. It was found that guanidinium/uronium[55] peptide coupling reagents such as HATU (**2.10**) and HBTU (**2.11**) furnished the desired dipeptides in high yields. While the reactions with **2.10** are much faster, it is rather expensive. Consequently, **2.11** was a good alternative, which allowed carrying out peptide coupling with the same efficiency in acceptable time. Similarly, peptide coupling of **2.6** with **2.13** gave the desired dipeptide **2.14** in essentially quantitative yields.



Scheme 2.2. Efficient peptide couplings with **2.10** and **2.11** and equilibrium between the two forms of the coupling agents.

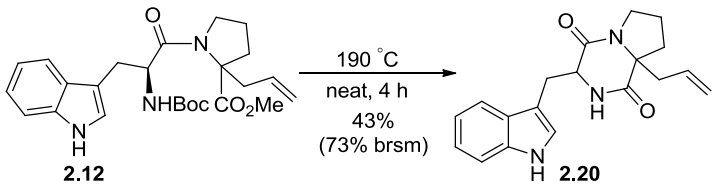
The scope of peptide coupling with **2.11** was wide, giving high yields of the dipeptides in all cases (Scheme 2.3). Amino acids or peptides having both primary and secondary amine as well as hindered carboxylic acid functionalities react equally well.



Scheme 2.3. Efficient peptide couplings with HBTU.

2.2. A practical solvent-free approach to DKPs and quinazolines and total syntheses of glyantrypine and ardeemin

Having established a reliable route to *N*-Boc protected dipeptides, a thermal one step deprotection/lactamization procedure reported by Baran and co-workers (see Scheme 2.1.) was tried.[47] Upon heating neat dipeptide **2.12** at 190 °C as reported, very slow conversion was observed in contrast to very fast and high yielding DKP synthesis as claimed by Baran. The desired DKP **2.20** was isolated in only 43% yield along with 30% recovered starting material after 4 h of heating at 190 °C (Scheme 2.4).



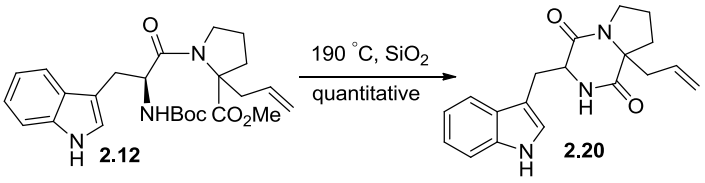
Scheme 2.4. Synthesis of DKP **2.20** by heating neat dipeptide.

Although the overall yield was 73% based on recovered starting material, this was not practical. Repeating this reaction by increasing the reaction time up to 8 h did not result in improvement of the conversion. Moreover, because of decompositions during the prolonged heating, the purity of the isolated product diminished.

Because of the irreproducibility of this key reaction in the synthesis of model compounds other procedures that claimed to achieve this type of transformations in one step were also attempted, but without much success. Heating of suspensions of Boc-dipeptides in deionized water in autoclave at 130 °C resulted in only trace amounts of DKP products.[56] Microwave irradiation of an acetonitrile solution of **2.12** at 130 ° according to Williams gave 68% isolated DKP **2.20** but was not convenient for reaction scale-up.[34]

The irreproducibility of Baran's method led to speculations that trace amounts of acidic impurities might be responsible for the reported fast and high yielding transformation. The first and most obvious candidate for this role was silica gel particles that might have contaminated their products. Silica gel, owing to its unique properties, is able to catalyze or mediate many organic transformations. Especially, solvent-free reactions, where only adsorption and if necessary heating are required to achieve important transformations, make the processes more environmentally friendly and less costly.[57] Whereas a few papers reported

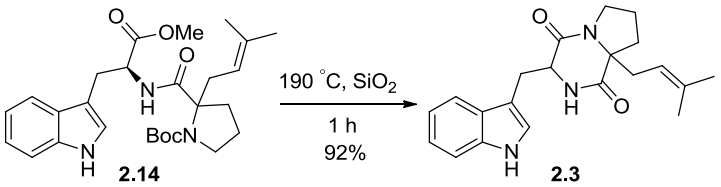
the Boc deprotection by (Lewis) acidic salts supported on silica gel,[58] only one paper reported the use of silica gel in a DKP synthesis under microwave irradiation conditions.[59] Encouraged by this precedence, conventional heating of **2.12** at 190 °C with a small amount of silica gel furnished the desired DKP **2.20** in essentially quantitative yield within 1 h as a separable 1:1 *cis*/*trans* mixture.



Scheme 2.5. Synthesis of DKP **2.20** in the presence of silica gel.

After some optimization it was found that the best yields and cleanest products were formed when Boc-protected dipeptides were adsorbed on an excess silica gel, evaporated to dryness and heated with vigorous stirring to 190 °C under Ar atmosphere for 1-1.5 h. To prevent volatiles from condensing back to the reaction medium the flasks were equipped with a reflux condenser filled with water (no water running). After 1 h, the reaction mixtures were cooled, transferred to a column and the products were eluted with appropriate solvents.

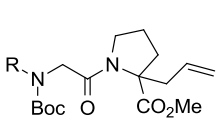
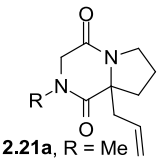
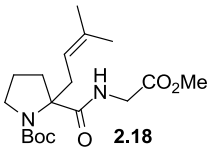
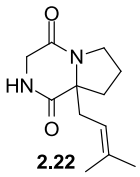
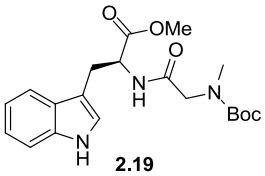
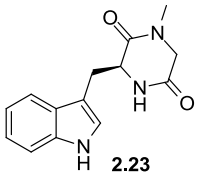
Dipeptide **2.14** with the *N*-Boc-α-prenyl proline unit also gave DKP **2.3** in high yield as a 1:1 mixture of *cis*- and *trans*-isomers, which can be separated for characterization purposes.



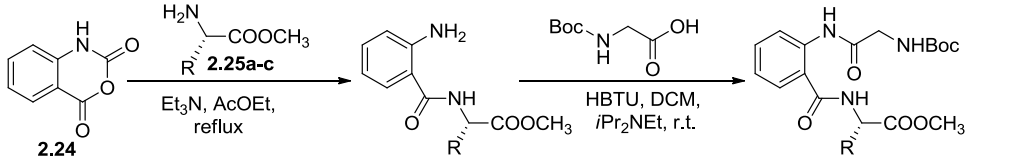
Scheme 2.6. Synthesis of DKP **2.3** in the presence of silica gel.

This protocol could be easily scaled up to gram amounts and some other simpler model substrates, were also synthesized (Table 2.1). It is also suitable for the synthesis of optically pure DKPs such as **2.23** which had a specific rotation that matched the absolute value of the opposite enantiomer which was reported in the literature ($[\alpha]^{20}_{589}$: +125.3 (*c* 0.107, MeOH); *lit.* $[\alpha]_D^{28.4}$: –133.5 (*c* 0.49, MeOH)).[60]

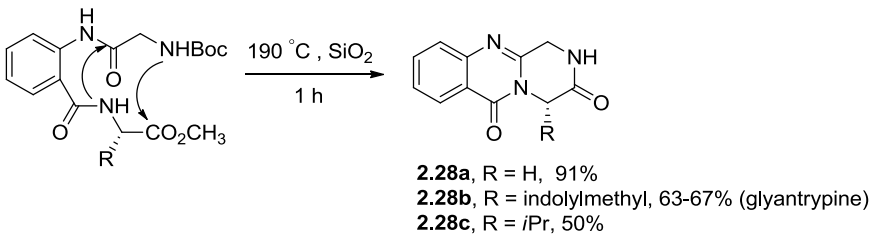
Table 2.1. Efficient silica gel mediated syntheses of various DKPs.

Entry	Dipeptide	DKP	Yield, %
1	 **2.16a-b**	 **2.21a**, R = Me **2.21b**, R = H	94, R = Me 98, R = H
2	 **2.18**	 **2.22**	99
3	 **2.19**	 **2.23**	83

Interested in the possibility of this protocol beyond the synthesis of DKPs, anthranilate derived tripeptides **2.27a-c** were prepared in two steps from isatoic anhydride and amino acid methyl esters **2.25a-c** and Boc-glycine according to literature procedures.[61] After condensation of amino acid methyl esters with isatoic anhydride, dipeptides **2.26a-c** were efficiently converted to tripeptides **2.27a-c** under standard HBTU promoted peptide coupling conditions.



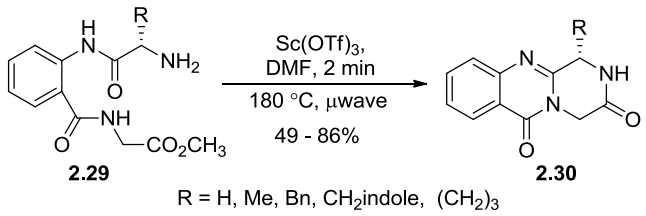
Scheme 2.7. Synthesis of anthranilate derived tripeptides **2.27a-c**.



Scheme 2.8. Silica gel mediated double cyclization of tripeptides **2.28a-c**.

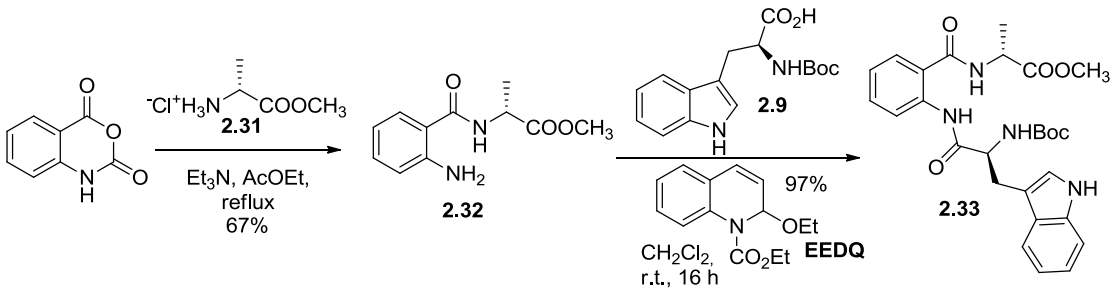
Double cyclization reaction to access quinazolines **2.28** was attempted. The desired transformation took place when the tripeptides **2.27a-c**, adsorbed on silica gel, were heated to 190 °C and quinazolinones **2.28a-c** were obtained in good yields The basic quinazoline **2.28a** was obtained in 91% yield. The natural product (+)–glyantrypine (**2.28b**) was formed in highest yield of 67% and a near-gram amount was obtained in a single batch. Importantly, no racemization took place and **2.28b** was obtained with a specific rotation $[\alpha]^{20}_{D}$ = +547 (*c* 0.12, $CHCl_3$) after recrystallization from methanol in accordance with the literature data, for which absolute values in the range of 522-541 were reported for both enantiomers.[62] Glyantrypine is thought to be a biogenetic precursor for many bridged quinazoline alkaloids. Few syntheses of glyantrypine were reported in the literature. They all delivered small amounts of glyantrypine in at least 4 steps. Compared to those, our synthesis allows access to near gram amounts of this important natural product. The valine derived tripeptide **2.27c** cyclized in 50% moderate yield.

Only few similar direct double dehydrative cylizations are known in the literature. Chu and co-workers reported that at high temperatures in the presence of Lewis acids under microwave irradiation conditions similar tripeptides **2.29** delivered quinazolines **2.30** without loss of optical activity in 49-86% yields. Scandium(III) triflate was identified as the best mediator of this transformation (Scheme 2.9). However, Taylor recently applied Chu's conditions in the synthesis of the quinazoline alkaloids and observed complete racemization of products.[61]



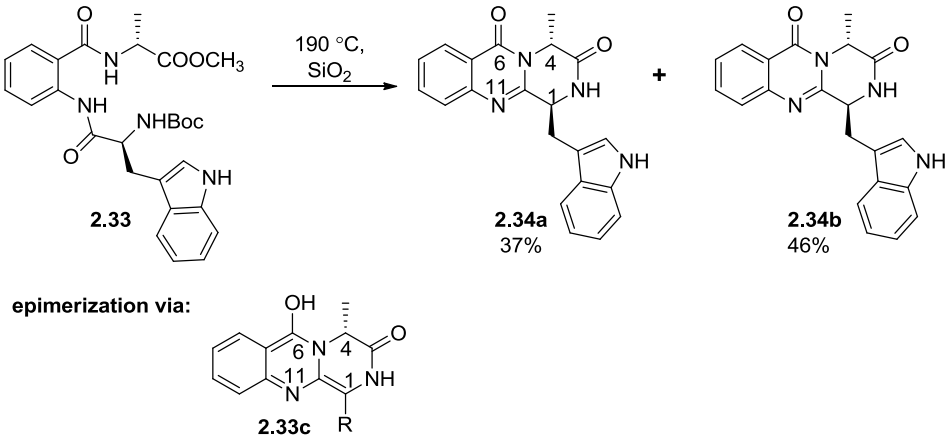
Scheme 2.9. Chu's $Sc(OTf)_3$ mediated double cyclization of anthranilate derived tripeptides.

Next, the tripeptide **2.33** was prepared from *D*-alanine methyl ester (**2.31**), isatoic anhydride and Boc-protected *L*-tryptophan **2.9** with the aim of its cyclization (Scheme 2.10). In this case, 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline (EEDQ) was found to be a very efficient and convenient peptide coupling agent.[63]



Scheme 2.10. Synthesis of the tripeptide **2.33**.

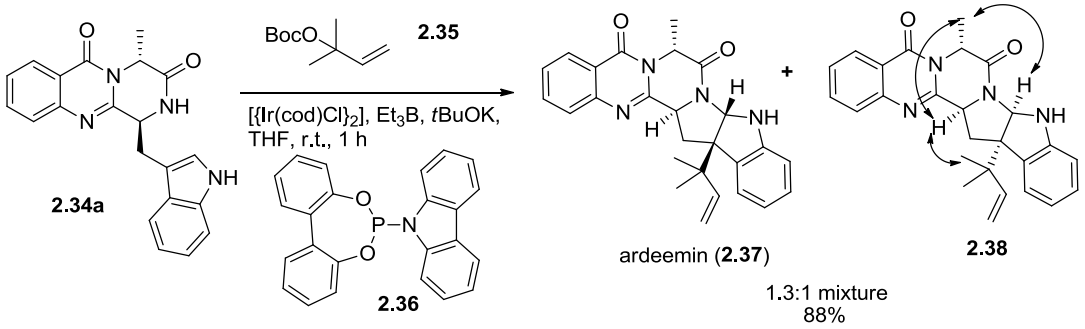
The double cyclization worked as expected but significant epimerization at the tryptophan stereocenter was observed and the chromatographically separable *trans*- and epimeric *cis*-diastereomers **2.34a-b** were obtained in 37% and 46%, respectively (Scheme 2.11). This result reveals the lability of the C1-stereocenter towards epimerization under the reaction conditions, which may be due to the strongly conjugated C6-benzene-N11-C1 system leading to facile enolization via intermediate such as **2.34c**. Note that in the previous examples **2.28a-c** the obtained quinazolines lack substituents at C1-position. Indeed, epimerizations were reported in the literature during the synthesis of quinazoline alkaloids and even during the isolation of these metabolites from natural sources.[64]



Scheme 2.11. Epimerization at C-1 via intermediate **2.34c**.

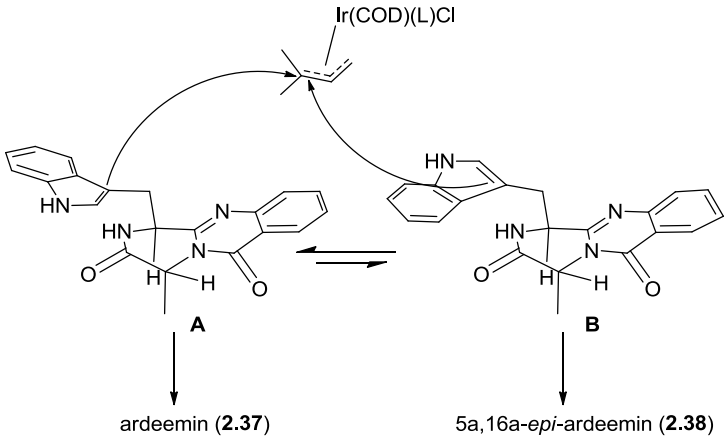
The *trans*-isomer **2.34a** was converted to anti multidrug resistance agent ardeemin (**2.37**) and its diastereomer **2.38** in a single step using a recently reported iridium-catalyzed reverse prenylation method (Scheme 2.12).[65] This approach represents a biomimetic synthesis of ardeemin because it was recently shown that **2.37** is biosynthesized in *Aspergillus fischeri*

by reverse prenylation of **2.34a** by the prenyl transferase enzyme ArdB.[66] The stereochemistry of 5a,16a-*epi*-ardeemin **2.38** was assigned based on the observed NOEs.



Scheme 2.12. Biomimetic synthesis of ardeemin and observed NOEs in **2.38**.

The lack of higher diastereoselectivity for ardeemin was disappointing. It can be rationalized by invoking two low energy conformers **A** and **B**, which rapidly interconvert around the Ar-CH_2 bond. Apparently, both conformers **A** and **B** of **2.34a** are equally reactive via transition states, which do not differ much in energy. The only solution to improve the diastereoselectivity might be tuning the structure of the ligand because lowering the temperature did not lead to significant improvements in diastereoselectivity (max. 1.7:1) and the conversions were low.

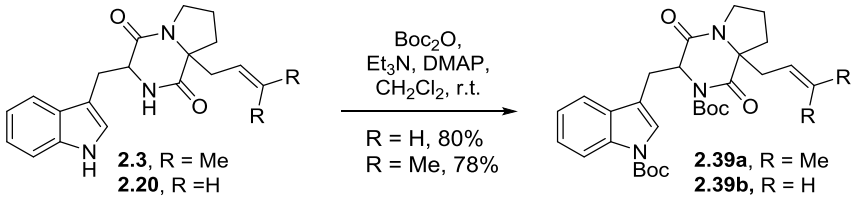


Scheme 2.13. Mechanism and rationalization of the low diastereoselectivity of prenylation.

2.3. Attempts to implement the 1st generation approach

With an efficient, reproducible and practical synthesis of complex DKPs developed, the stage was set to probe the original SET-induced cyclization proposal. This approach requires protection of the nitrogen-atoms of DKP. Initially the Boc group was chosen because

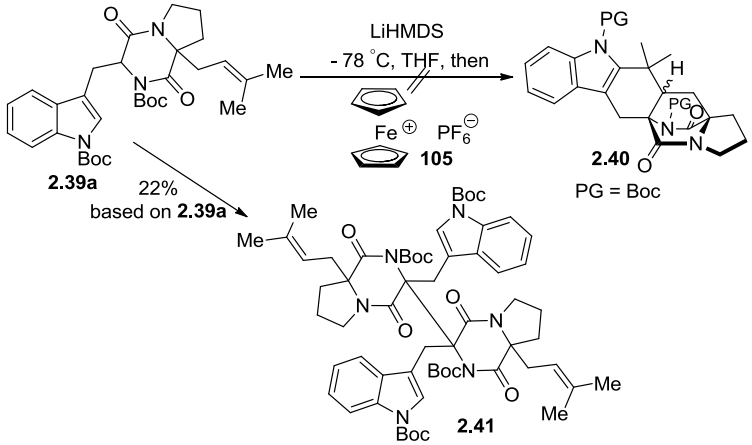
of the ease of introduction and removal based on literature precedence (Scheme 2.14).[40b] Efficient protection of both nitrogen atoms of the DKP and indole rings took place upon treatment of DKPs **2.3** and **2.20** with Boc_2O in the presence of DMAP.



Scheme 2.14. Protection of indole and DKP nitrogen atoms of **2.3** and **2.20** with Boc group.

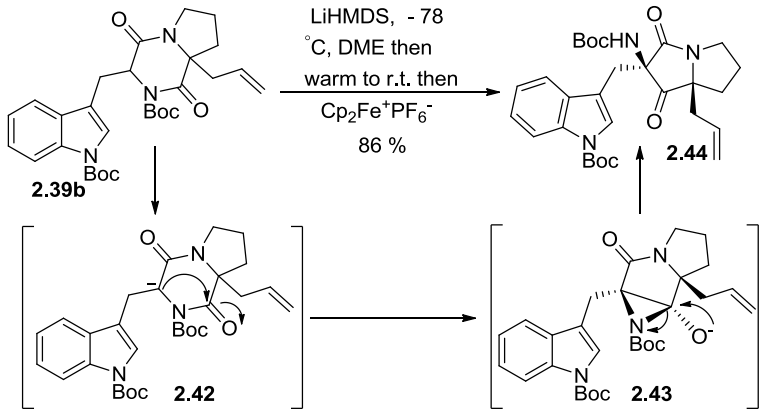
The DKPs of type **2.3**, **2.20** and **2.39ab** were always used as mixtures of *cis*- and *trans*-diastereomers since one of the stereocenters is anyway destroyed during the subsequent enolate formation. The diastereomers were separated only for characterization purposes. They will be drawn without depiction of the configuration of the stereocenters when used as a mixture of diastereomers throughout the text.

DKP **2.39a** was deprotonated with LiHMDS at -78 °C and the SET oxidant $Cp_2Fe^+PF_6^-$ was added to the reaction mixture at this temperature (Scheme 2.15). However, upon work-up and chromatographic purification of the reaction mixture the starting material was recovered in 50% yield and no cyclization products were obtained. The only new compound that was formed was assigned the dimeric structure **2.41** based on ^{13}C NMR and mass-spectra. The yield of this compound was only 22% but interestingly only one diastereomer was formed. The relative configurations of the stereocenters were not possible to determine.



Scheme 2.15. Initial attempt to implement the direct oxidative cyclization.

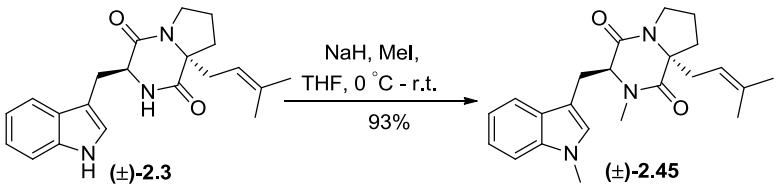
This outcome shows the validity of the concerns discussed in the aim of the work. While the yield of the dimer **2.41** was low it hinted to the fact that the radical cyclization must be slow compared to dimerization and/or hydrogen abstraction from the solvent. However, this initial experiment gave confidence that the initial enolate oxidation is possible. Based on this result, the enolate oxidation was carried out at room temperature. It was hoped that the radical cyclization will compete to a larger extent with dimerization at the higher temperature. Therefore, DKP **2.39b** with the allyl side chain was deprotonated with LiHMDS at -78 °C and the reaction mixture was warmed to room temperature before the oxidant was added. Unexpectedly, a new product was formed in 86% yield which was isomeric to the starting material (Scheme 2.16). The pyrrolidine-2,4-dione structure **2.44** was assigned based on ^{1}H, ^{13}C and 2D NMR spectroscopy and the relative configuration was assigned based on NOE experiments. Under these conditions a Chan-type rearrangement took place, which resulted in the contraction of the DKP ring via aziridine-type intermediate **2.43**, before the oxidant was added. Repeating this reaction at -30 °C also resulted in Chan-rearrangement with 52% yield. A literature search revealed that this type of ring contraction is typical for Boc-protected DKPs upon deprotonation at higher temperatures.[67] This can be rationalized because of the electron withdrawing nature of carbamate protecting groups, which renders the amide carbonyl group electrophilic enough toward intramolecular attack of enolate.



Scheme 2.16. Chan-rearrangement of DKP **2.39b**.

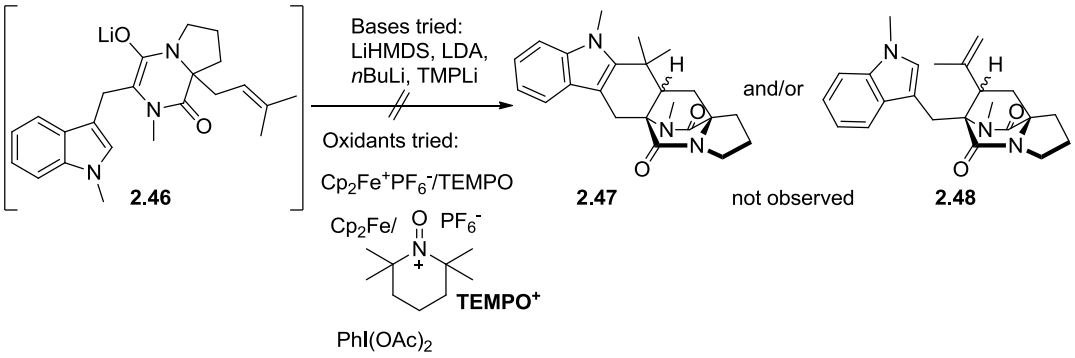
These unsuccessful results prompted a change of the protecting group. To avoid complication of the spectra, methylation of the *N*-atoms was performed instead of benzyl protecting groups at this stage (Scheme 2.17). Numerous experiments were carried out with

dimethylated model DKP **2.45** by varying the parameters like bases, oxidants and oxidation temperatures (Scheme 2.18).



Scheme 2.17. Double methylation of indole and DKP nitrogens of **2.3**.

For example, apart from standard LiHMDS and LDA, *n*BuLi and TMPLi were also used as bases. Different oxidation conditions were also tried, such as: 1) addition of enolate solution to the suspension of ferrocenium hexafluorophosphate in THF; 2) addition of the oxidant to the hot solution of enolate at 80 °C; 3) oxidation in the presence of TEMPO; 4) oxidation with a catalytic amount of ferrocene in the presence of $TEMPO^{+}$; 5) hypervalent iodine oxidant like $PhI(OAc)_2$.[68] In most cases no reaction took place or decomposition was observed along with trace amounts of dimerization products as judged by the disappearance of the α-methine proton in the product mixtures. After numerous fruitless efforts all the experiments with model compound **2.45** were terminated.

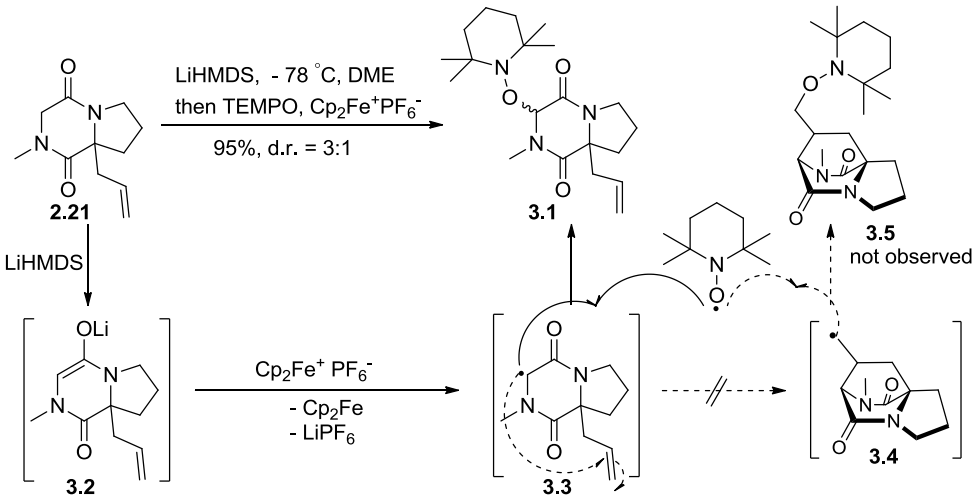


Scheme 2.18. Attempts to promote oxidative enolate cyclization of **2.46**.

3. A PRE mediated approach to diazabicyclo[2.2.2]octanes

3.1. A second generation approach using the persistent radical effect

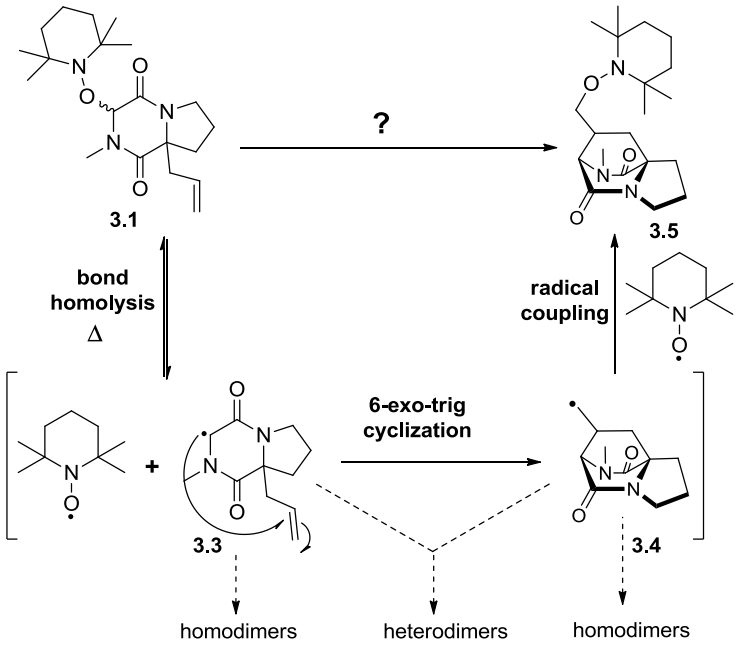
In parallel with the indole side-chain containing model compounds (Chapter 2.3), oxidative cyclization studies with less complex DKP **2.21** were carried out. Although no cyclization was achieved, its oxidation in the presence of TEMPO gave hemiaminal ether type alkoxyamine **3.1** in high yield as a stable colorless solid after chromatography (Scheme 3.1). Compound **3.1** was formed in a ca 3:1 diastereomeric ratio. The high yield of the isolated product is a testament to the efficient formation of the DKP radical **3.3** by SET oxidation of enolate **3.2** followed by a fast coupling of **3.3** with the persistent TEMPO radical before the cyclization to a bridged system **3.4** could take place. As such, the cyclization step was the bottleneck in the original proposal, the rate and energetics of which were overestimated, especially *under the low temperature conditions for radical generation*. Realization of this fact points to a potential solution: *generation of DKP radical **3.3** at higher temperatures that favor the bridge-forming 6-exo-trig radical cyclization should result in the desired cyclization.*



Scheme 3.1. Synthesis of unusual DKP-derived alkoxyamine **3.1** and mechanism of its formation.

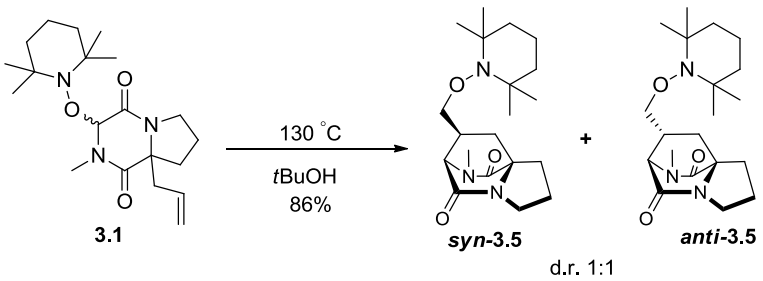
As described in the introduction (Chapter 1.5) and inspired by works of Studer,[54] the possibility of regenerating the transient, but captodatively stabilized DKP radical **3.3** and persistent TEMPO radical by *thermal homolysis* of C-O bond in **3.1** was investigated

(Scheme 3.2.). Thermally generated DKP radical **3.3** can either be trapped by TEMPO to reform the starting compound **3.1** or undergo irreversible bridge-forming 6-exo-trig cyclization to bicyclic radical **3.4**, which after coupling with TEMPO affords the desired diazabicyclo[2.2.2]octane **3.5**. An initial accumulation of persistent TEMPO radical caused by homo- and/or heterodimerization as well as H-abstraction reactions of transient radicals **3.3**/**3.4** steers the reaction to follow a single pathway leading to the desired bicyclic compound (Cf. Chapter 1.5).



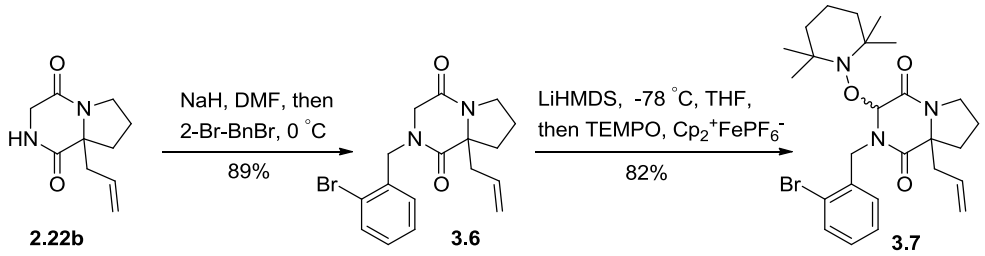
Scheme 3.2. A 2nd generation approach to diazabicyclo[2.2.2]octane ring system.

Upon heating a 0.02 M solution of alkoxyamine **3.1** in degassed *t*BuOH at 130 °C in a sealed tube for 1.5 h, an inseparable 1:1 mixture of diastereomeric bicyclic products **3.5** were indeed obtained in high yield (Scheme 3.3).



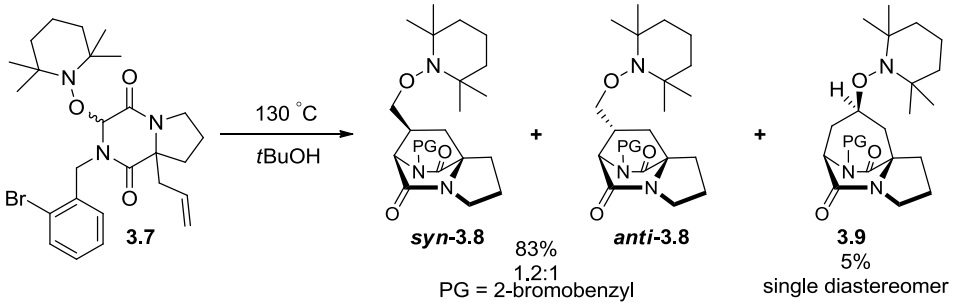
Scheme 3.3. Thermal cycloisomerization of alkoxyamine **3.1**.

Protection of the *N*-atom of **2.22b** with a 2-bromobenzyl group, followed by oxidative alkoxyamination of **3.6** under similar conditions gave alkoxyamine **3.7** (Scheme 3.4).



Scheme 3.4. Syntheses of 2-bromobenzyl protected alkoxyamine **3.7**.

Heating **3.7** under similar conditions led to thermal cycloisomerization with 1.2:1 diastereoselectivity for the 6-exo-trig cyclization (Scheme 3.5). The bicyclic compounds **3.8**, were obtained as an inseparable mixture. However, they crystallized as a mixture diastereomers, which allowed proving their structures by X-ray (Figure 3.1a). Both diastereomers are present in the unit cell.



Scheme 3.5. Cyclization of alkoxyamine **3.7**.

Because even crystallization did not allow separation, the assignment of the NMR signals was only possible by NOE experiments on the mixture of compounds. An NOE was observed between the benzylic protons and the C6-H atom (stephacidin numbering, see Chapter 1) in the major ***syn*-3.8**, while it was not observed in the minor ***anti*-3.7**. A small amount of 7-endo-trig cyclization product **3.9** was also formed, which was isolated as a single diastereomer, whose configuration was also assigned based on NOE experiments (Figure 3.2b).

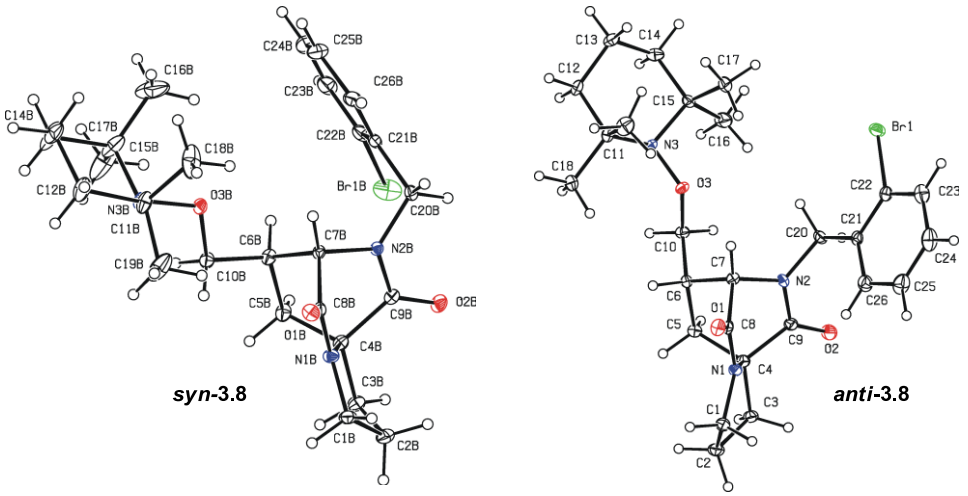


Figure 3.1. X-ray crystallographic structures of ***syn*-3.8** and ***anti*-3.8** in the unit cell of the single crystal. Thermal ellipsoids are drawn at the 30% probability level.

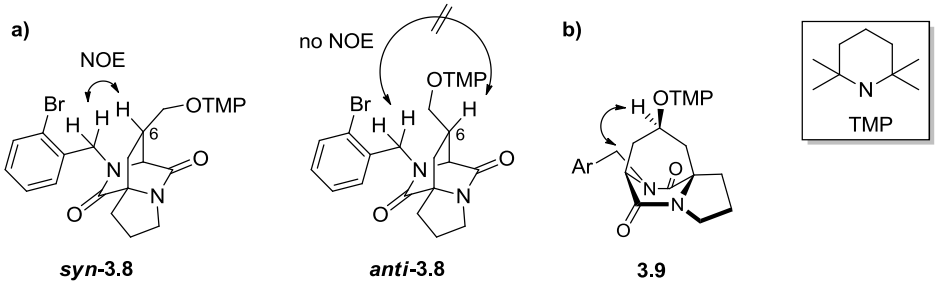
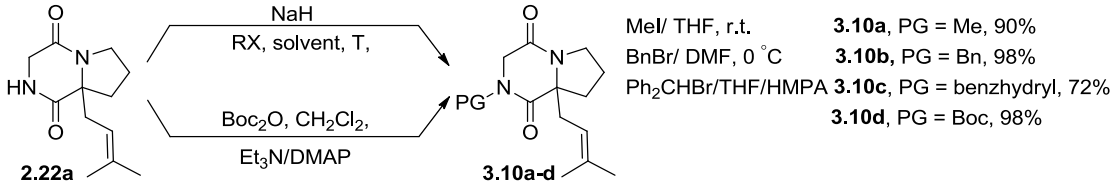


Figure 3.2. a) NOE experiment on the mixture of ***syn*-3.8** and ***anti*-3.8**; b) an NOE observed in **3.9**.

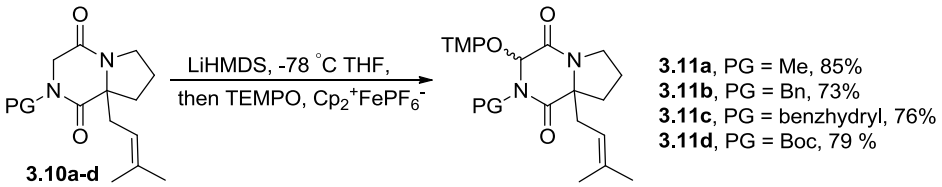
3.2. Thermal cyclizations of prenylated alkoxyamines

DKPs **3.10a-d** bearing a prenyl side chain and different protecting groups were synthesized from **2.22a** to probe analogous thermal cyclizations. Different conditions were identified as optimal for the introduction of different types of protecting groups. While DMF is a standard solvent for deprotonation of amides and benzylation, THF was better for methylation to prevent methylation of the α-carbon. Only trace amounts of benzhydryl protected DKP **3.10c** were formed in DMF even after prolonged heating at 100 °C, presumably because of the reaction of DMF with bromodiphenylmethane. Only if the reaction was carried out in THF in the presence of HMPA, desired **3.10c** was obtained in 72% yield.[69] The Boc group was introduced in a similar way as in Scheme 2.14.



Scheme 3.6. Introduction of different protecting groups to DKP **2.22a**.

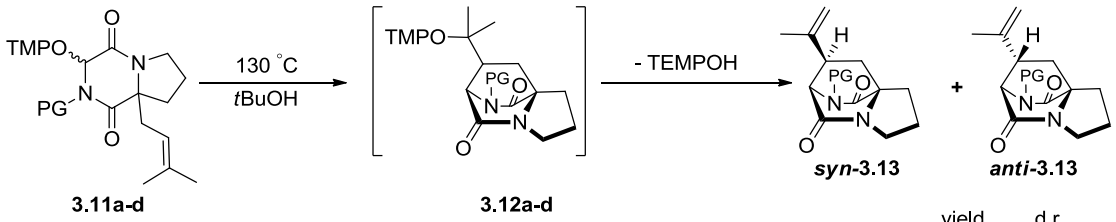
Synthesis of cyclization substrates **3.11a-d** proceeded uneventfully under the standard oxidative TEMPO oxygenation conditions (Scheme 3.7). Based on the experience with Boc-protected DKPs, which were found to undergo Chan-rearrangement (*cf* Chapter 2), oxidation of the enolate derived from **3.10d** was carried out strictly at -78 °C and the alkoxyamine **3.11d** was obtained without rearrangement.



Scheme 3.7. Synthesis of alkoxyamines **3.11a-d** with different protecting groups.

Synthesis of **3.11c**, bearing the bulky benzhydryl group deserves a special mention. When the ferrocenium salt and TEMPO were added to the enolate solution at -78 °C no decoloration of the heterogeneous mixture was observed, which serves usually as an indicator of oxidation because of the consumption of blue-colored ferrocenium salt. However, upon warming the mixture to 0 °C rapid decoloration took place, but the product **3.11c** was isolated in only 31% yield. Further optimization by carrying out the oxidation at -20 °C allowed preparation of **3.11c** in 76% isolated yield. Interestingly, for almost all DKP TEMPO adducts **3.1**, **3.7**, **3.11a-d** described so far, the less polar diastereomers were not stable and quickly isomerized to the more polar diastereomer in $CDCl_3$ and even in benzene-d_6, which did not allow proper NMR characterization of the more labile isomers. The bulky benzhydryl-protected **3.11c** was in contrast formed as an unassigned stable single diastereomer. Only for Boc-protected compound **3.11d** both diastereomers were stable and fully characterizable, which indicates the importance of electronic effects for stabilization of these hemiaminal type alkoxyamines. The structure of ***trans*-3.11d** was confirmed by X-ray crystallography (see Chapter 6).

Thermal cyclizations of alkoxyamines **3.11a-d** furnished propenyl group containing products **3.13a-d** instead of products **3.12a-d** containing TEMPO unit. The formation of diazabicyclo[2.2.2]octanes **3.13a-d** as a result of elimination of TEMPOH is known from the literature, where alkoxyamines, in which TEMPO fragment is attached to *t*-butyl-type fragments, are unstable and easily undergo TEMPOH elimination.[70] A clear influence of the bulkiness of the protecting groups on the diastereoselectivity was observed. In the case of *N*-Me containing alkoxyamine **3.11a** the reaction is not diastereoselective, while *N*-benzyl group induced 3:1 diastereoselectivity and the diastereomers ***syn*-3.13b** and ***anti*-3.13b** could be separated. Interestingly, little diastereoselectivity in favor of the *anti*-diastereomer was observed in the case of *N*-Boc protected substrate **3.11d**. Remarkably, the bulkiest benzhydryl group in **3.11c** induced a 17:1 diastereoselectivity in favor of the desired diastereomer ***syn*-3.13c**. The structures of both ***syn*-3.13c** and ***anti*-3.13d** were confirmed by X-ray crystallography (Figure 3.3).



	PG	yield %	d.r. *syn*:*anti*
a	Me	88	1:1
b	Bn	90	3:1
c	**benzhydryl**	**82**	**17:1**
d	Boc	73	1:1.3

Scheme 3.8. Thermal cyclizations of alkoxyamines **3.11a-d**.

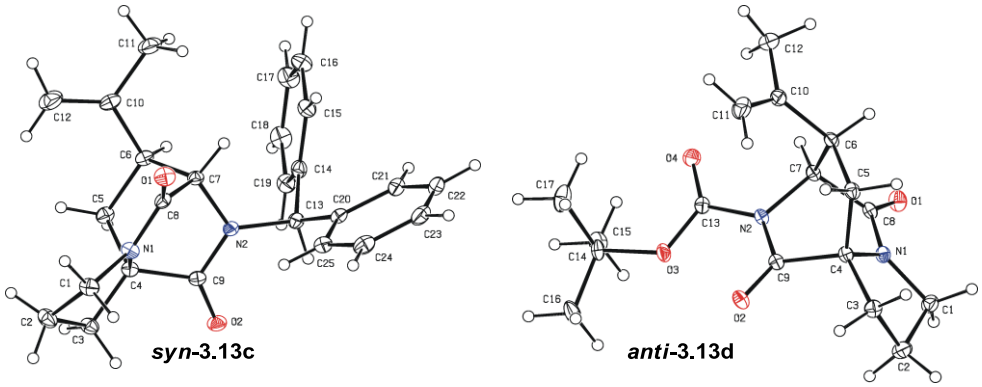
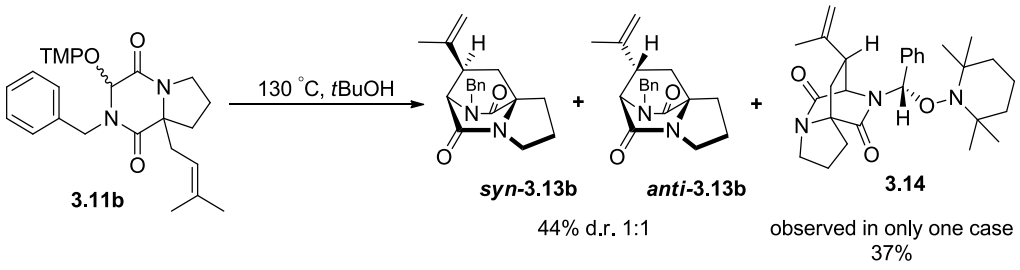


Figure 3.3. X-ray structures of bicyclic compound ***syn*-3.13c** and ***anti*-3.13d**. Thermal ellipsoids are drawn at the 30% probability level.

An unexpected product **3.14** was obtained in one and **only** one instance from thermal cyclization of alkoxyamine **3.11b** in 37% yield (Scheme 3.9). The structure of this product, having the piperidinyloxy group located at the benzylic position, was unambiguously confirmed by X-ray (Figure 3.4). A similar compound stemming from ***anti*-3.13b** was not isolated.



Scheme 3.9. Unexpected formation of an unusual product **3.14**.

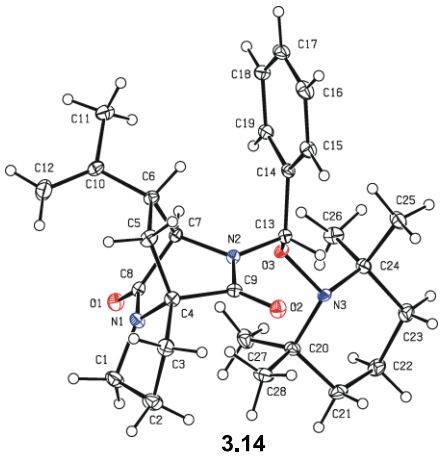
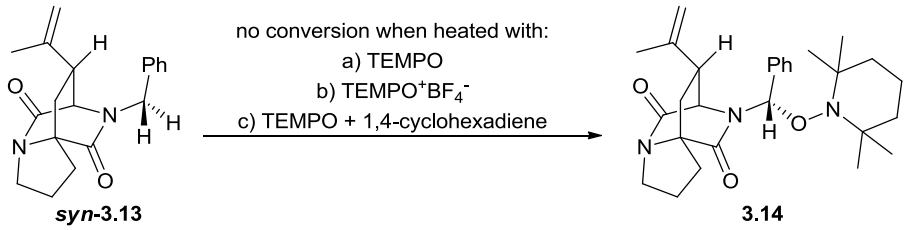


Figure 3.4. X-ray structure of the unexpected "abnormal" product **3.14**. Thermal ellipsoids are drawn at the 30% probability level.

It is known that benzylic positions of aromatic compounds are reactive toward TEMPO at high temperatures.[71] The mechanism of this process is not clear, since TEMPO does not have strong hydrogen-atom abstracting capabilities compared to phtalimide *N*-oxyl radical (PINO) and other O-centered radicals.[72] To shine light on the formation of **3.14** the "normal" product ***syn*-3.13b** was subjected to heating in the presence of excess TEMPO (Scheme 3.10). However, no sign of product **3.14** was observed. Hypothesizing that the oxidized form of TEMPO might be responsible for the formation of the product **3.14**, bicyclic

compound ***syn*-3.13b** was also heated in the presence of the oxoammonium salt $TEMPO^{+}BF_4^{-}$. Again no transformation to product ***syn*-3.13b** was observed; ***syn*-3.13b** remained unchanged and the oxoammonium salt decomposed. As a last attempt, TEMPO and ***syn*-3.13b** were heated in the presence of 1,4-cyclohexadiene which would generate TEMPOH in situ that may somehow lead to product **3.14**. Not surprisingly nothing happened to ***syn*-3.13b**. At this stage, attempts to elucidate the mechanism of formation of product **3.14** were terminated.



Scheme 3.10. Attempted conversion of "***syn*-3.13b** to the product **3.14**.

In conclusion, a second generation approach to diazabicyclo[2.2.2]octane core structures of alkaloids was developed taking advantage of the PRE. The cyclizations are very efficient and the diastereoselectivity can be improved by tuning the steric bulk of the protecting group at the nitrogen atom.

4. Evolution of a synthetic strategy for a total synthesis of asperparaline C

4.1. Introduction and strategies to asperparalines

The asperparalines, comprising asperparalines A, B, C and ketoaspergillimide (**1.24-1.27**), are structurally distinct members of bridged DKP alkaloids containing the central diazabicyclo[2.2.2]octane ring system. They bear a spiro-succinimide unit instead of indole or spiro-oxindole fragments.

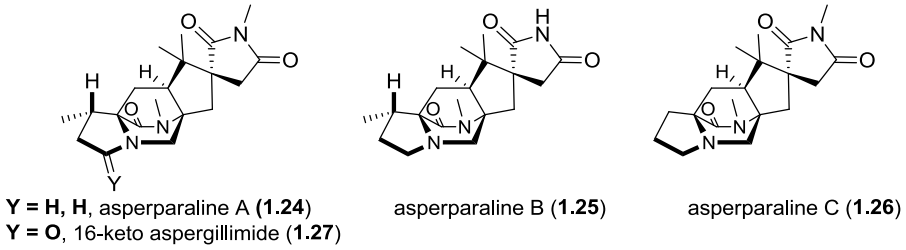
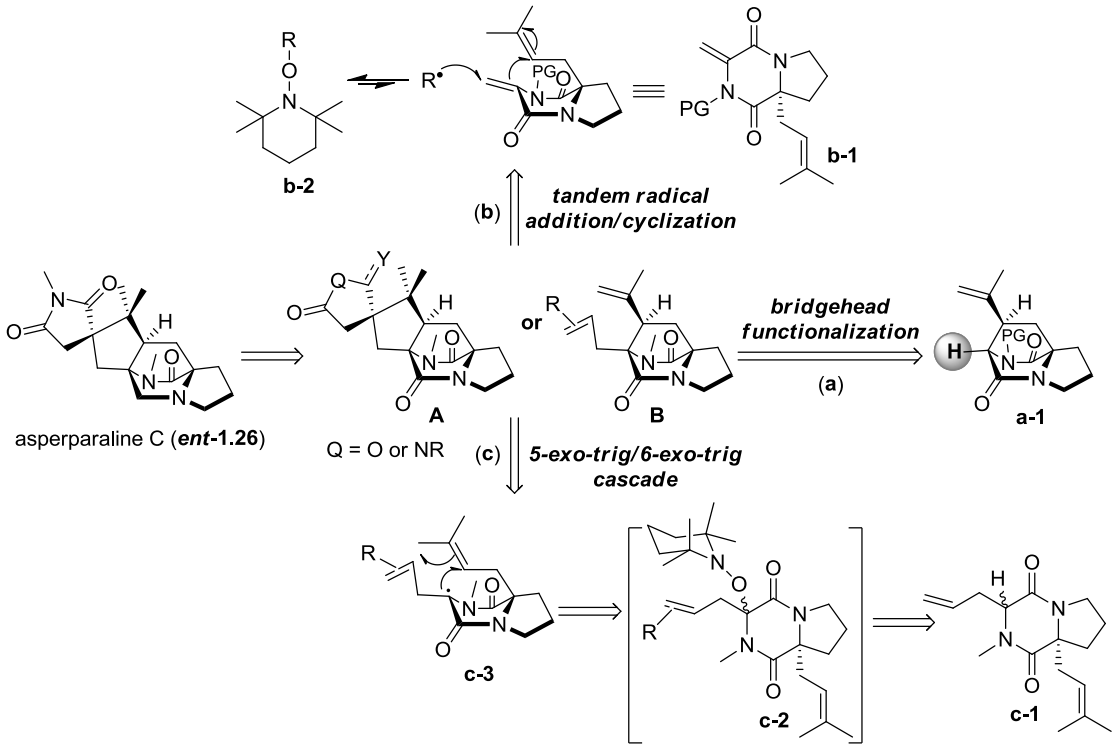


Figure 4.1. Members of the asperparaline family.

Despite that asperparalines were isolated almost twenty years ago and several studies towards their synthesis from leading laboratories were reported, they elude total synthesis. Although the structure of asperparaline A (**1.24**) was determined by X-ray crystallography, its absolute configuration was not assigned. Challenges associated with their synthesis and the ambiguity concerning their absolute configuration were seen as an opportunity to apply the PRE-mediated cyclization process to their synthesis. Asperparaline C was chosen as the main target, since it is the simplest member within the family.

A proposal towards any complex target molecule has to be flexible enough to allow changing the strategy without having to significantly remodify the synthesis of key building blocks. Three main strategies were identified as a means to rapidly access advanced intermediates such as **A** and **B** (Scheme 4.1). In a most straightforward approach (**a**), functionalization of the bridgehead C-H group of bicyclic intermediates such as **a-1** was envisioned. If successful, this strategy would allow developing a modular synthesis of advanced intermediates such as **B** from already synthesized **3.13a-d**. Alternatively, intermediates such as **B** can also be approached convergently, where the PRE-mediated methodology is extended to an inter- and intramolecular tandem process in approach (**b**).

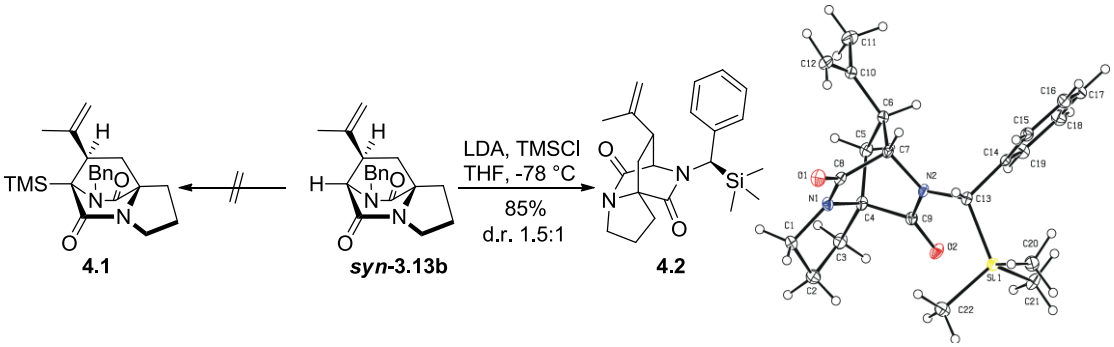
Radical **R·**, thermally generated by the homolysis of a suitable alkoxyamine such as **b-2** in the presence of an unsaturated DKP **b-1**, can attack the terminal double bond of **b-1**. Subsequent 6-exo-trig cyclization/TEMPO-trapping/TEMPOH elimination processes would also provide bridgehead functionalized advanced intermediates **B**. Finally, alkoxyamines such as **c-2** are viable precursors for thermal cyclization according to approach (**c**). The direct construction of all rings by a 6-exo-trig/5-exo-trig cascade process makes this approach very tempting.



Scheme 4.1. Three complementary approaches to asperparaline C.

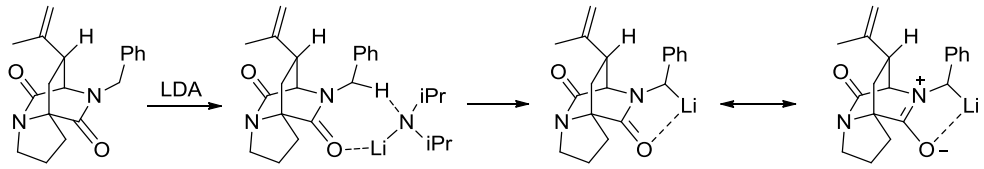
4.2. Bridgehead C-H functionalization approach.

To test the feasibility of approach (**a**), functionalization of the bridgehead position of bicyclic compound ***syn*-3.13b** was investigated. Upon reacting ***syn*-3.13b** with LDA in the presence of TMSCl product **4.1**, which would form by silylation of bridgehead enolate, was not observed but efficient silylation of the benzylic position took place giving **4.2** as a 1.5:1 mixture of diastereomers (Scheme 4.2). Repeating this experiment in the presence of 2.2 equivalents of LDA gave the same monotrimethylsilylated products but bis(trimethylsilyl) products were not observed.



Scheme 4.2. An attempted bridgehead silylation of ***syn*-3.12b** and X-ray structure of actual product **4.2**. Thermal ellipsoids are drawn at the 30% probability level.

The structure of the major diastereomer of **4.2** was proven by X-ray crystallography. Apparently, the benzylic position is significantly more acidic than the bridgehead position. Deprotonation of the bridgehead position is additionally disfavored because an anti-Bredt enolate would be generated. Deprotonation seems to be governed by the well-known complex-induced proximity effect (CIPE) discovered by Beak and others (Scheme 4.3).[73] Initial complexation of the lithium ion to the carbonyl group of the proline unit positions the LDA in close proximity to the benzylic hydrogen atoms as in **4.3**. A facile deprotonation ensues, giving the dipole-stabilized benzylic carbanion **4.4**. Such reactivity was also observed by Williams in their synthetic studies towards brevianamide B.[32b] Therefore, this approach was not studied further.

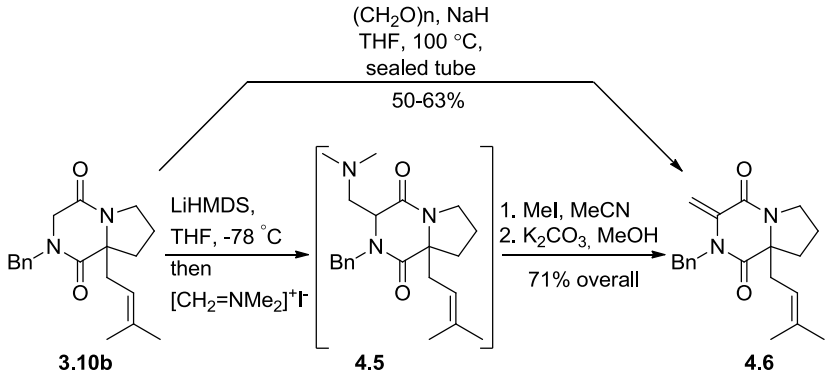


Scheme 4.3. Complex-induced proximity effect enabled benzylic deprotonation of ***syn*-3.13b**.

4.3. Tandem radical addition/6-exo-trig cyclization approach

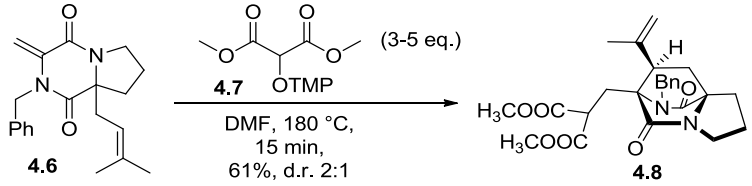
Unsaturated DKP **4.6** was synthesized by direct condensation of racemic DKP **3.10b** with paraformaldehyde in 50-63% yield (Scheme 4.4). Alternatively, **4.6** was obtained by a two-step one pot reaction using Eschenmoser's salt via intermediate **4.5**, which was not isolated and directly quaternized with methyl iodide followed by elimination of

trimethylamine under basic conditions. By this way, **4.6** was obtained in 71% yield. Despite that the single operation method using paraformaldehyde is operationally more convenient, the three-step/one-pot procedure is more preferred from the safety standpoint and with respect to overall yield.



Scheme 4.4. Synthesis of DKP **4.6**.

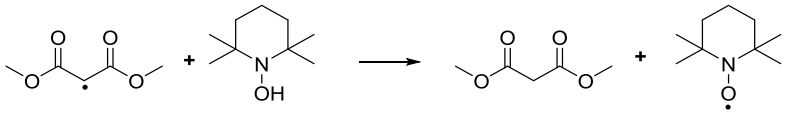
With radical acceptor **4.6** in hand, the feasibility approach (**b**), described in Scheme 4.1, was put to the test using the known dimethyl malonate derived alkoxyamine **4.7** (Scheme 4.5).[54b] Indeed, after some experimentation and optimization, the desired transformation took place with 61% isolated yield of the expected product **4.8** when **4.6** and excess alkoxyamine **4.7** were heated in a microwave reactor at 180 °C for 15 min, albeit with a rather low 2:1 diastereoselectivity.



Scheme 4.5. A tandem radical addition/cyclization approach.

It is important to note that, under conventional heating conditions in a sealed tube at 130 °C or at higher temperatures little conversion was observed even after several hours. Heating under microwave conditions at 180 °C for prolonged times led to byproducts arising from decarboxylation of **4.8** and the overall combined yield of nondecarboxylated and decarboxylated products was within ca 11%. Another critical point is that at least three

equivalents of the malonate-derived alkoxyamine **4.7** have to be used. If smaller amounts of **4.7** were used, DKP **4.6** was not fully consumed and yields were low. The generated malonate radical might be partially consumed by reaction with the conformed TEMPOH, stemming from thermal elimination, to give dimethyl malonate and TEMPO radical (Scheme 4.6). Hydrogen abstraction from the solvent can also contribute to unproductive consumption of **4.7**.



Scheme 4.6. Quenching of the dimethylmalonate radical with TEMPOH.

Despite its attractiveness, there are some practical limitations of this approach. The first and most important is the low diastereoselectivity of the product, which is a consequence of the high reaction temperature. Moreover, the diastereomers of **4.8** are inseparable hampering further advancement of material.

4.4. Direct cyclization of DKPs by oxidative *in situ* generation of alkoxyamines

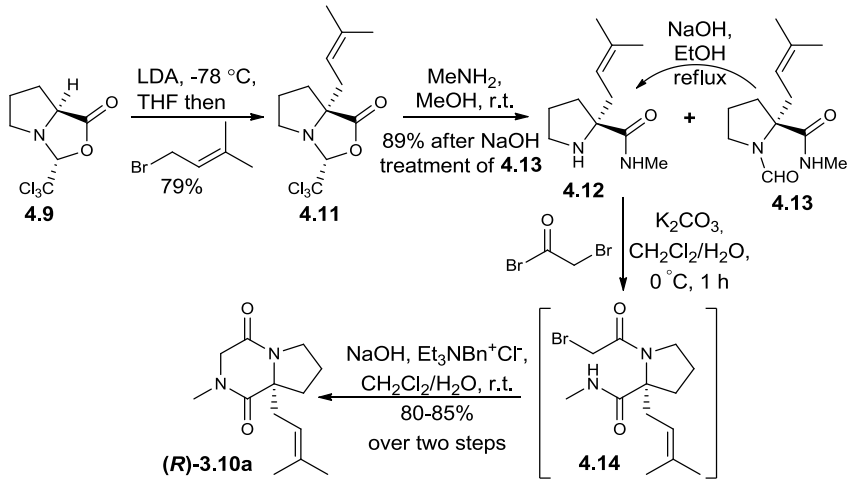
To investigate approach (**c**) toward ***ent*-1.26** an asymmetric synthesis of DKP (***R*)-3.10a** was developed. Seebach's principle of self-regeneration of stereocenters (SRS)[74] was used to introduce the asymmetric quaternary carbon center using **4.9** (Scheme 4.7). Oxazolidinone **4.9** is a more modern, chloral hydrate derived version of Seebach's original oxazolidinone **4.10**, which is derived from pivaldehyde and proline.[75] Additional advantages of using chloral hydrate over the pivaldehyde are short reaction times for condensation of chloral with proline (7-9 h vs. 3-7 days) and use of a small excess of chloral hydrate (1.2. equiv. chloral hydrate vs. 6-7 equiv. pivaldehyde). Finally, compared to **4.10**, **4.9** is air- and moisture-stable easy-to-handle crystalline solid with long shelf life.

4.9
commercially available
easy synthesis on large scales
bench stable crystalline solid

4.10
expensive pivaldehyde used in large excess
long reaction times
moisture sensitive oil

Figure 4.2. Comparison of oxazolidinones **4.9** and **4.10**.

Thus, **4.9** was synthesized on gram scale using the reported method.[76] Prenylation of the enolate derived from **4.9** gave ozaxolidinone **4.11** in high yield as a single diastereomer (Scheme 4.7). Prenylated oxazolidinone **4.11** can be directly used as a crude compound, because of partial decomposition during chromatography, and has to be eluted quickly to minimize loss of the product. Purification by column chromatography for characterization purposes gave **4.11** in 79% yield.

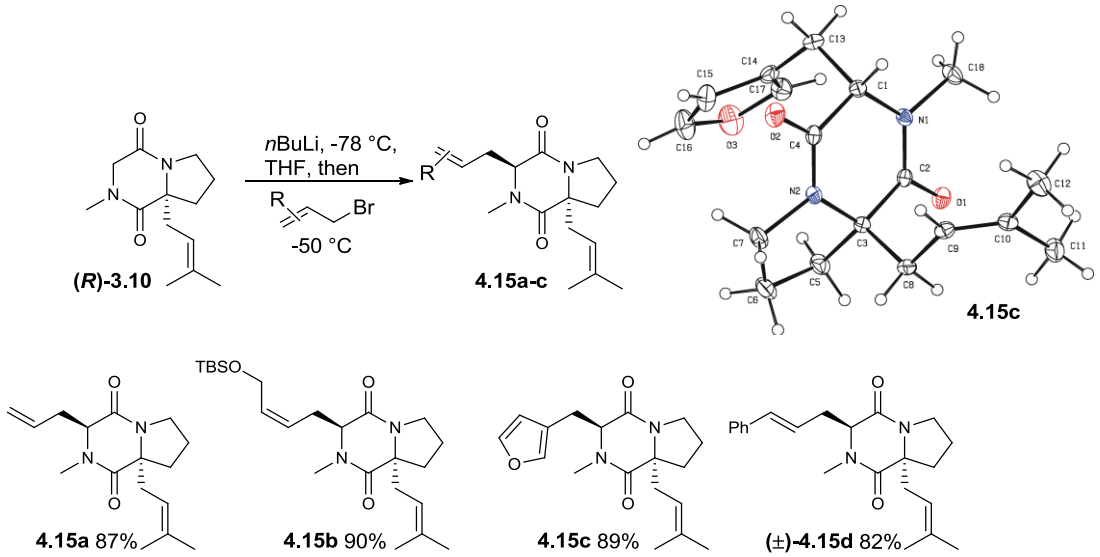


Scheme 4.7. Prenylation of chiral oxazolizidnone **4.10** and conversion to **(*R*)-3.10**.

When **4.11** was reacted with 2 M methylamine solution in methanol a poorly separable mixture of desired pyrrolidine **4.12** and the *N*-formyl pyrrolidine side product **4.13** was obtained. Occasionally, methyl ester side products were also observed in up to 27% isolated yield. Heating the reaction mixture in a sealed tube after consumption of **4.11** ensured that no methyl esters remained. The fractions contaminated with formyl pyrrolidine **4.13** were deformylated by refluxing with NaOH in ethanol. Pyrrolidine **4.12** was converted to DKP **(*R*)-3.10** by a two-step/one-pot protocol via bromoacetamide **4.14**, which was cyclized to **(*R*)-3.10** without isolation under phase-transfer catalysis conditions.

With chiral DKP **(*R*)-3.10** in hand, DKPs **4.15a-c** were obtained by enolate alkylation using commercial or known bromides (Scheme 4.8). Alkylations were highly diastereoselective giving only *trans*-diastereomers when the temperature was carefully controlled at -50 °C. If the temperature was raised to room temperature or even to -20 °C, small amounts of the more polar *cis*-diastereomers and even dialkylated products were isolated. The structure and configuration of **4.15c** was confirmed unambiguously by X-ray

crystallography and the configurations of **4.15a** and **4.15b** were assigned by analogy. Racemic **4.15d** was also obtained by analogous alkylation of **(±)-3.10** with cinnamyl bromide.



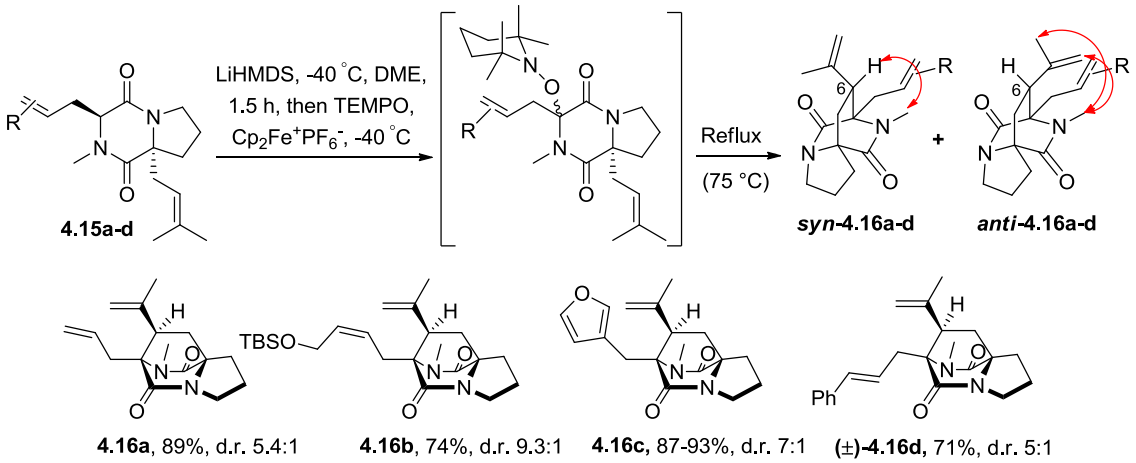
Scheme 4.8. Diastereoselective alkylations of (***R*)-3.10** and **(±)-3.10**, and X-ray crystal structure of **4.15c**. Thermal ellipsoids are drawn at the 30% probability level.

Initial attempts to isolate the alkoxyamine intermediates such as **c-2** in Scheme 4.1 were not successful. Under the standard alkoxyamination conditions only the complex mixtures of products were obtained in which the TEMPOH elimination products predominated along with dimerization products and the recovered starting materials. It was hypothesized that the instability of such alkoxyamines might be because of their low bond dissociation energies (BDE) and that they might undergo homolysis at temperatures close to ambient temperature during the isolation process. It was proposed that, generating alkoxyamines **c-2** under the standard oxidative alkoxyamination conditions at low temperatures and subsequent heating may directly lead to bicyclic products.

Therefore, DKPs **4.15a-d** were deprotonated with LiHMDS, TEMPO was added and the enolate was oxidized by portionwise addition of $Cp_2Fe^+PF_6^-$ at -40 °C in DME. After stirring for about 10 min the cooling bath was removed and the reaction mixture was equipped with a reflux condenser and immersed to a heating bath preheated to 100 ºC and refluxed for 1.5 h. Evaporation to dryness after cooling the reaction mixture to r.t and purification by column chromatography revealed that monocyclization products **4.16a-d** were

formed in good yields and most importantly in 5.4:1, 9.3:1, 7:1 and 5:1 diastereomeric ratios for products **4.16a**, **4.16b, 4.16c** and **(±)-4.16d**, respectively (Scheme 4.9).

The major products showed an NOE-contact between the *N*-CH_3 group and the allylic hydrogen atom at position 6 and the minor diastereomers showed NOE contacts between the exo-methylene as well as methyl groups of the propenyl group with the *N*-CH_3 group. Therefore, the configuration of the major products was assigned as the desired ***syn*-4.16a-d** and the minor diastereomer as ***anti*-4.16a-d**. Although products originating from double cyclization were not observed, this result was a significant progress compared to the previous tandem radical addition/cyclization approach. Specifically, the pronounced cyclization diastereoselectivity in this approach is very important.

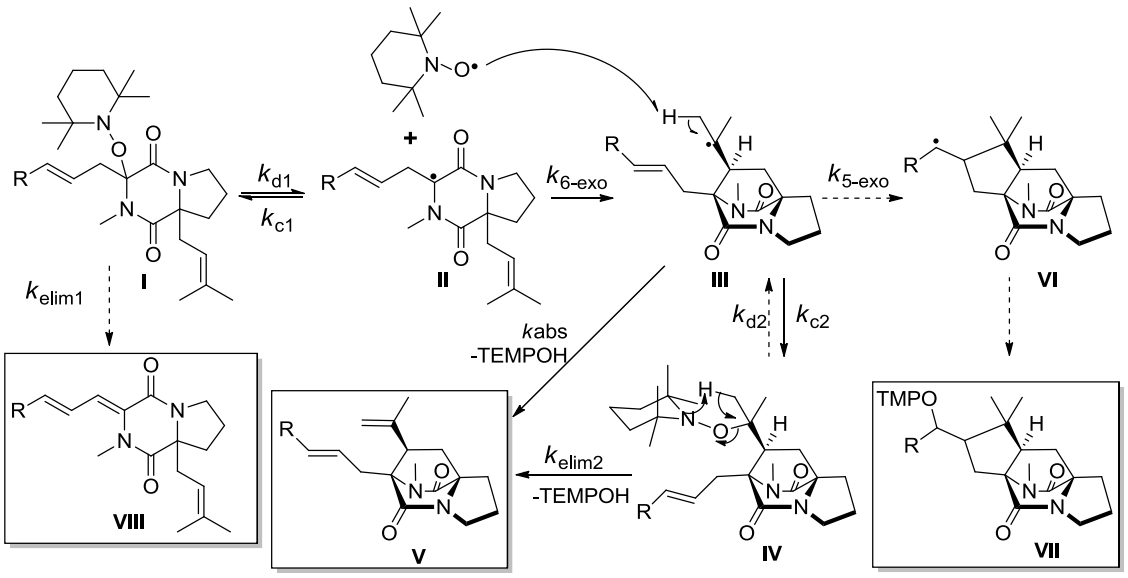


Scheme 4.9. Diastereoselective oxidative cyclizations of **4.15a-d** to bridged DKPs **4.16a-d**.

Importantly, 2.2 equivalents of LiHMDS had to be used to ensure full conversion of the starting material. When 1-1.2 equivalent of base was used yields did not exceed 50%. This is important not only to ensure higher yields of the cyclized products but also because the uncyclized DKPs **4.15a-d** are usually poorly separable from the bicyclic products. As a consequence, more than two equivalents of the SET oxidant $Cp_2Fe^{+}PF_6^{-}$ has to be used.

The fact that double cyclization did not take place in all of the studied examples seemed to be surprising, especially when considering that the second cyclization should be fast because it is a 5-exo-trig process. To explain this the relative rate constants of major competing processes, have to be analyzed which are involved under the reaction conditions (Scheme 4.10). The most critical are the rate constants for 5-exo trig cyclization ($k_{5\text{-exo}}$), for coupling of bicyclic tertiary radical **III** with TEMPO (k_{c2}), for the reverse of the latter process (k_{d2}), the rate of competing nonradical elimination process (k_{elim2}) and direct hydrogen atom

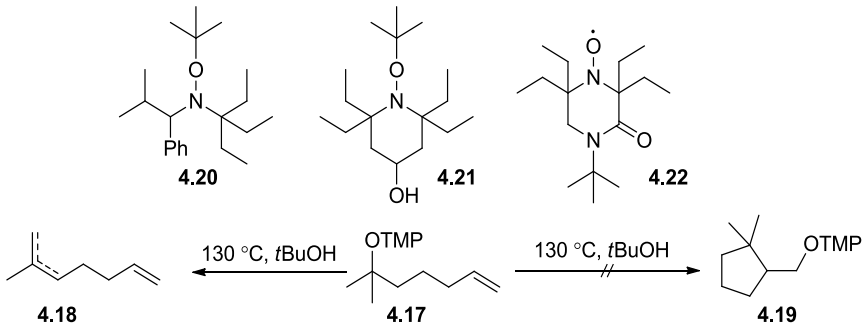
abstraction from **III** by TEMPO (k_{abs}). Additionally, the rate constants for homolysis (k_{c1}) and elimination (k_{elim1}) of TEMPOH from the initially generated alkoxyamine **I** determine the ratio of elimination products **VIII** and bicyclic product **V**. The rate constants for typical 5-exo-trig cyclizations are known to be in the order of 10^5 s^{-1}. Typical rate constants for cross-coupling of various radicals with TEMPO were measured by Ingold by a time-resolved laser flash photolysis,[77] and amount to $1.2x10^9$ $M^{-1}s^{-1}$ for $CH_3(CH_2)_7CH_2$·, $7.6xl0^8$ $M^{-1}s^{-1}$ for $(CH_3)_3C$·, $4.9x10^8$ $M^{-1}s^{-1}$ for $C_6H_5CH_2$·, $1.2x10^8$ $M^{-1}s^{-1}$ for $C_6H_5C(CH_3)_2$· and $4.6x10^7$ $M^{-1}s^{-1}$ for $(C_6H_5)_2CCH_3$·. The homolytic dissociation of tertiary alkoxyamines to tertiary alkyl radicals and TEMPO, is not facile and instead elimination via nonradical pathway often leads to alkenes as has been also observed in the previous chapter. An alternative mechanism involving direct hydrogen atom abstraction from a tertiary radical by TEMPO was also proposed in the literature and evidence for both mechanisms were presented, and this process is an ongoing discussion in literature.[72]



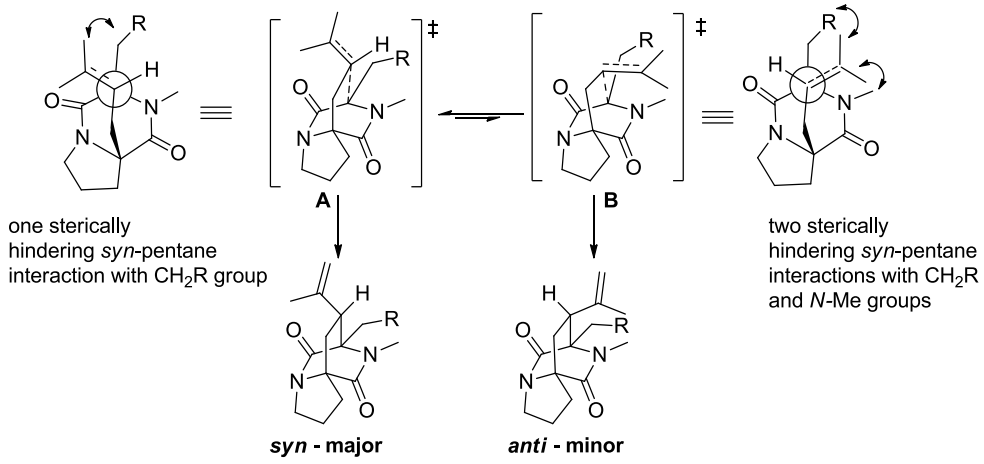
Scheme 4.10. Mechanistic picture of the radical cyclization.

Thus, judging from these literature data, relationships between the key rate constants contributing to exclusive formation of monocyclization product **V** over **VII** and **VIII** are as follows: $k_{c2}>>k_{5\text{-exo}}$ and $k_{elim2}>>k_{d2}$ and $k_{d1}>>k_{elim1}$. As such, very fast and irreversible trapping of the tertiary radical formed by 6-exo-trig cyclization by TEMPO and subsequent elimination of TEMPOH via a nonradical pathway precludes the second 5-exo cyclization. Qualitative analysis of the key steps and their relative rates help to explain the reaction

outcome. This is in line with literature precedent, where in preparative cyclizations, homolysis of *tert*-alkyl alkoxyamines was only possible when more hindered alkoxyamines such as **4.20** or **4.21** develpped by Studer were used.[54g] TEMPO-derived tertiary alkoxyamine **4.17** furnished only the elimination products **4.18** and no cyclization to **4.29** took place (Scheme 4.11).[78] As a means to overcome the dominance of k_{c2} over $k_{5\text{-exo}}$ and in a hope for achieving direct double cyclizations, the oxidative cyclization of **4.15a** in the presence of highly hindered nitroxide **4.22**, kindly provided by Studer, was also tried. However, again only monocyclization product **4.16a** was obtained in a lower 53% yield and nitroxide **4.22** was recovered almost quantitatively.



Scheme 4.11. Known alkoxyamines and a hindered nitroxide **4.22** provided by Studer.

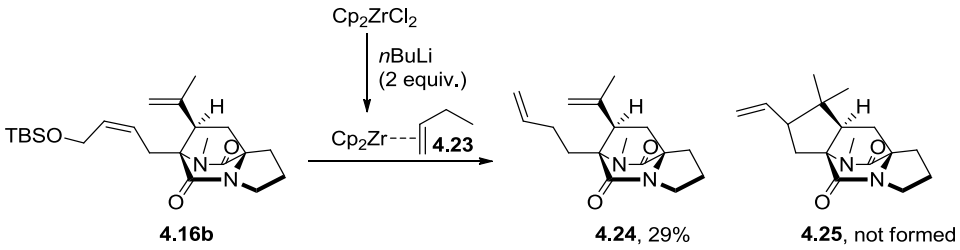


Scheme 4.12. Origin of stereoselectivity in the radical cyclizations of substituted DKPs.

Analysis of the transition states for cyclizations of **4.15a-d** reveals that in the transition state **A**, leading to the major *syn*-diastereomer, the developing isopropyl radical is in a *gauche* or *syn*-pentane interaction with the CH_2R and C=O groups (Scheme 4.12). In

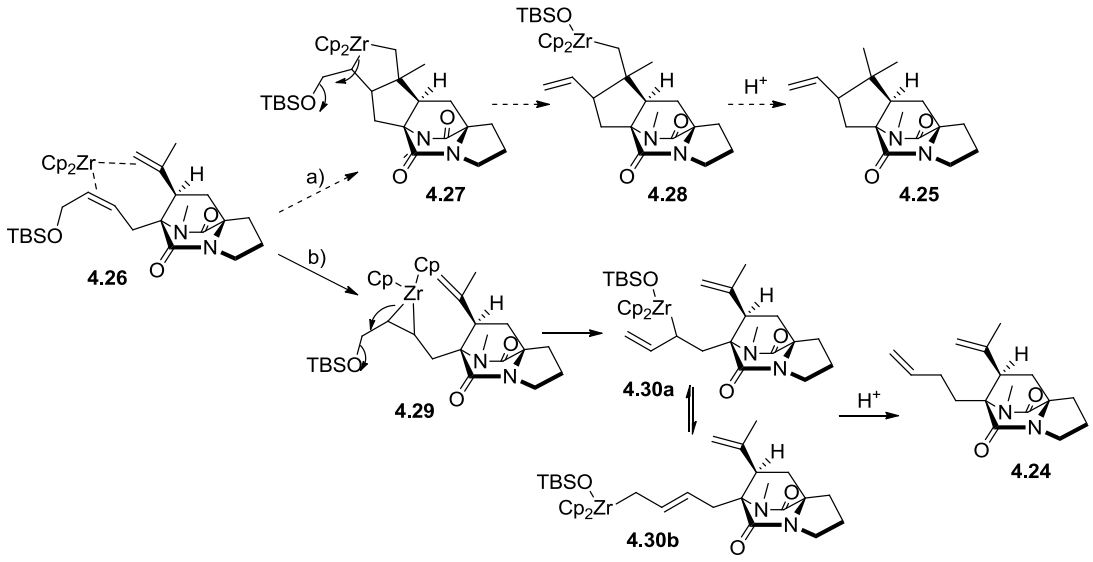
transition state **B**, leading to the undesired and minor *anti*-diastereomer, the incipient isopropyl radical is in a double *syn*-pentane interaction with the CH_2R and the *N*-Me groups. The difference in the relative steric bulk of the C=O and *N*-Me groups makes transition state **A** earlier and determines the outcome of the cyclization in favor of the desired *syn*-diastereomer.[79]

Having accomplished successful and diastereoselective cyclizations of substituted DKPs **4.15a-d**, it was necessary to solve the problem of second. Numerous transition-metal catalyzed or mediated cyclizations and cycloisomerizations of α,ω-dienes to cyclopentanes are known.[80] However, many of these reactions are highly dependent on the substitution pattern of the alkene units and not many examples of 1,1-disubstituted alkenes in such reactions were reported. Nevertheless, a zirconocene mediated cyclization of **4.16b** was attempted (Scheme 4.13). However, when **4.16b** was added to an *in situ* generated solution of Negishi's reagent **4.23**, noncyclized product **4.24** was obtained in 29% yield after stirring at ambient temperature for 6 h. The expected cyclized product **4.25** was not detected.



Scheme 4.13. Attempted zirconocene mediated cyclization of **4.16b**.

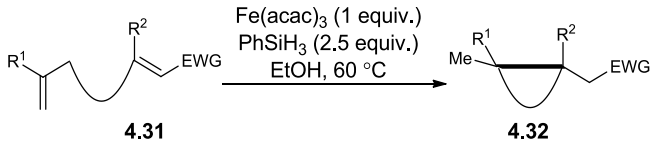
Mechanistically this outcome can be explained as depicted in Scheme 4.14. Because of the hindered 1,1-disubstituted propenyl unit, the desired metallacyclization pathway to **4.27**, from which **4.25** would form via the intermediacy of **4.28** is too slow (pathway a, dashed arrows). Preferential coordination to the less substituted alkene unit takes place (pathway b) which is in equilibrium with the zirconacyclopropane tautomer **4.29.** This can undergo a E1cB-type elimination of OTBS group generating allylic zirconocene intermediate **4.30a**, which can be in a metallotropic equilibrium with the linear form **4.30b**. Acidic quenching leads to homoallyl substituted product **4.24**.



Scheme 4.14. Mechanism of **4.24** formation.

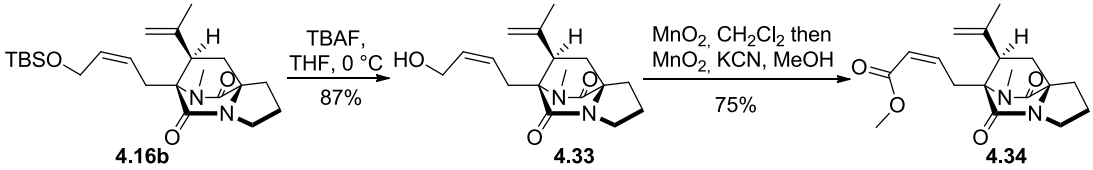
4.5. Reductive radical cyclizations and synthesis of 8-oxoasperparaline C

Recently Baran and coworkers reported $Fe(acac)_3/PhSiH_3$ mediated reductive radical cyclizations of compounds such as **4.31**,[81] having both electron-rich and electron-deficient alkenes, inspired by seminal studies by Mukaiyama (Scheme 4.15).[82] The reaction could also be performed using substoichiometric amounts of $Fe(acac)_3$.



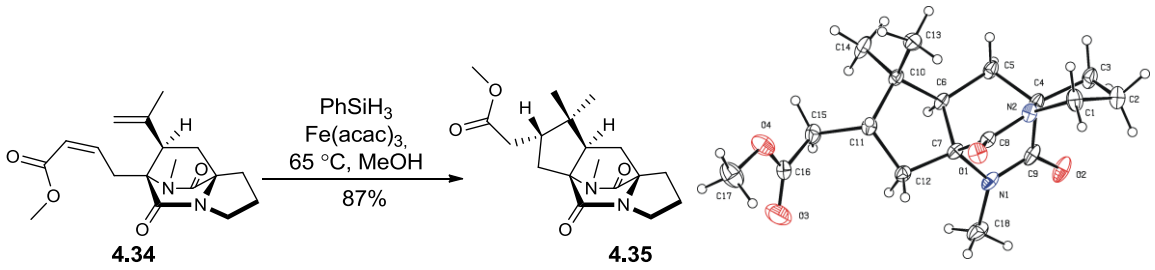
Scheme 4.15. $Fe(acac)_3/PhSiH_3$ mediated reductive cyclizations.

Inspired by these reports, bicyclic compound **4.16b** was deprotected to allylic alcohol **4.33** in 87% yield, which was converted to unsaturated methyl ester **4.34** by deprotection and sequential oxidation using MnO_2 (Scheme 4.16).

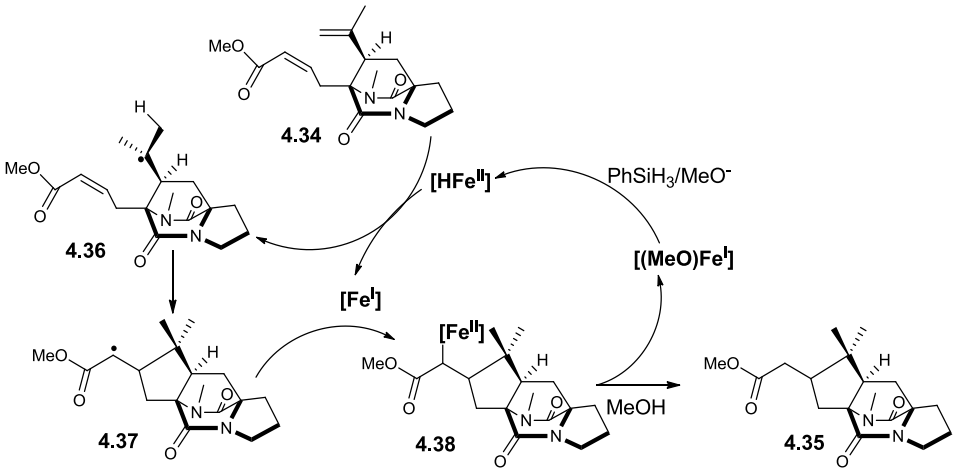


Scheme 4.16. Synthesis of a model substrate **4.34** for reductive radical cyclization.

The cyclization of **4.34** was performed under stoichiometric conditions reported by Baran and proceeded in high yield giving product **4.35** as a single diastereomer (Scheme 4.17). This compound was crystallized from AcOEt/hexane and the configuration at the newly formed stereocenter was unambiguously assigned by X-ray crystallographic analysis.



Scheme 4.17. Reductive cyclization of **4.34** and X-ray structure of **4.35**. Thermal ellipsoids are drawn at the 30% probability level.

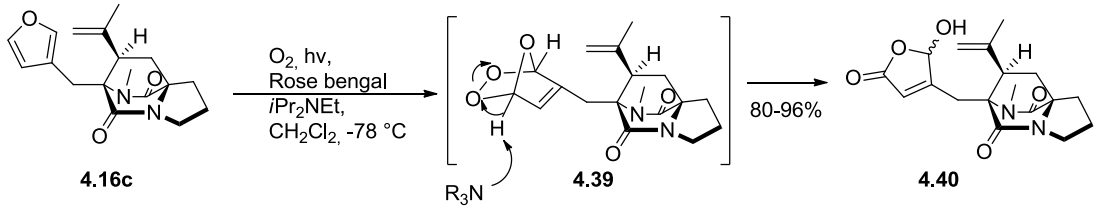


Scheme 4.18. Catalytic cycle and proposed mechanism for reductive radical cyclization of **4.34**.

The mechanism of this transformation remains ambiguous. Because Baran's original mechanistic rationalization did not make sence from thermodynamic consideration, Studer and Curran recently suggested a different mechanism involving $[HFe^{III}]^{-}/[Fe^{II}]^{-}/[Fe^{II}]$ species in a review article.[83] However, their mechanism also suffers from similar contradictions with the thermodynamics of the redox processes. It seems more rational to invoke a $[HFe^{II}]/[Fe^{I}]$ couple for this transformation that would account for all factual data known in the literature (Scheme 4.18). The reaction presumably proceeds by H-atom transfer (HAT) from a transient *in situ* generated hydrido complex $[HFe^{II}]$ to the electron-rich alkene in **4.35** to generate nucleophilic tertiary radical **4.36** and a 5-exo-trig cyclization to the electron-deficient alkene

ensues. The resulting α-carbonyl radical **4.37** presumably couples with the [Fe^{I}] species to give a Fe(II) enolate species such as **4.38**. Hydrolysis of this enlate intermediate would result in product 4.35 and the iron alkoxide from which the crucial hydrido complex [HFe^{II}] can be regenerated by hydride transfer from phenylsilane.

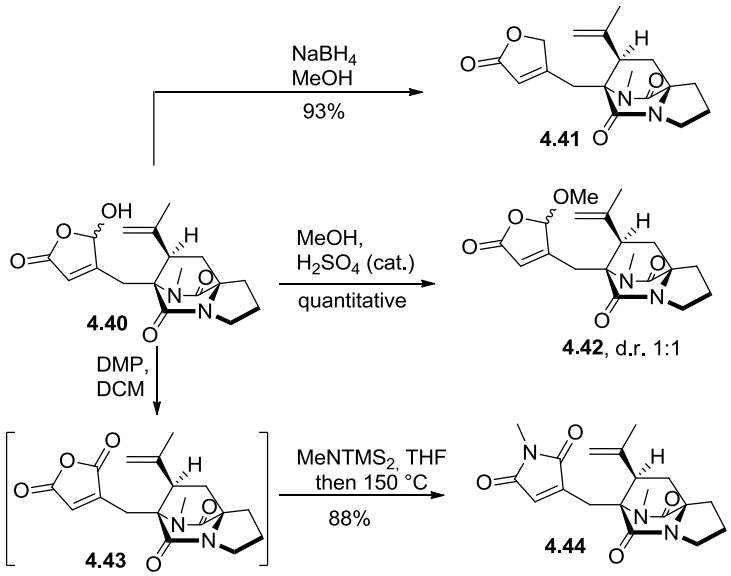
Based on this result, the furan ring in **4.16c** was subjected to oxidative dearomatization via a hetero-Diels-Alder reaction with singlet oxygen as a means to accessing more relevant intermediates en route to asperparaline C (Scheme 4.19). Performing the singlet oxygen mediated dearomatization in the presence of Hünig's base led to highly regioselective opening of the endoperoxide intermediate **4.39** as a result of deprotonation at the less hindered position. The γ-hydroxybutenolide **4.40** was obtained typically in >80% yields as ca 2:1 epimeric mixture at the hemiacetal center. The only drawback of this protocol was the difficulty of removing Rose bengal derived impurities. Because of its high polarity **4.40** had to be eluted with polar solvent systems (typically with 100% AcOEt) and was always obtained as a pale red foam because of contamination by Rose bengal or its decomposition products. Nevertheless, after the subsequent steps the impurities could be easily separated.



Scheme 4.19. Furan dearomatization with singlet oxygen.

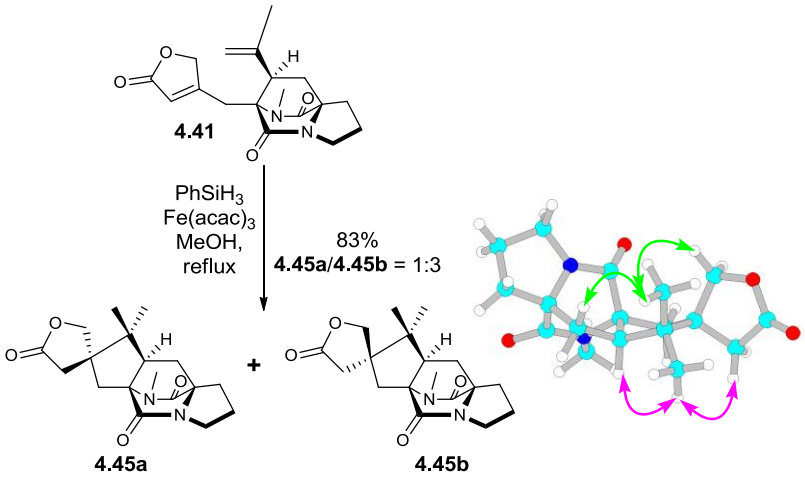
The γ-hydroxybutenolide **4.40** was converted to model cyclization substrates (Scheme 4.20). Treating **4.40** with $NaBH_4$ in MeOH gave butenolide **4.41** in high yield, while in the presence of catalytic concentrated H_2SO_4, γ-methoxybutenolide **4.42** was obtained quantitatively as an inseparable 1:1 mixture of epimers. No change in the ratio of epimers took place upon heating this mixture with catalytic H_2SO_4 in methanol which indicates the lack of thermodynamic preference for one epimer. Oxidation of **4.40** with Dess-Martin periodinane (DMP) gave unstable maleic anhydride intermediate **4.43**, which when treated immediately with heptamethyldisilazane in THF, and then heated at 150 °C for 5 min gave **4.44** in 88% yield. However, this procedure was not reproducible and due to unsuitability of **4.44** in subsequent studies (*vide infra*) this route was not further optimized. Using

methylamine and heating the maleamic acid intermediate with acetic anhydride gave **4.44** in only 12% yield.



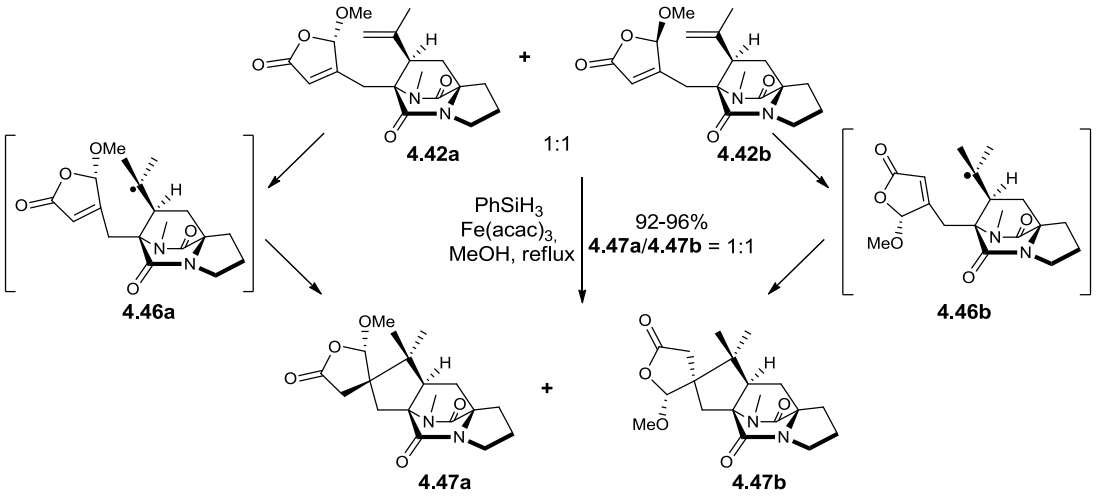
Scheme 4.20. Conversion of γ-hydroxybutenolide **4.40** to cyclization precursors.

The butenolide substrate **4.41** underwent a very efficient cyclization giving an inseparable 3:1 mixture of diastereomers **4.45a** and **4.45b** at the newly generated spiro center in high yield (Scheme 4.21). NOE analysis of this mixture revealed that the desired diastereomer **4.45a** with the correct configuration at the spiro center was the minor product. Nevertheless, this result demonstrated the feasibility of the challenging spirocyclization that generates a C-C bond with two contiguous quaternary carbon atoms.



Scheme 4.21. Reductive spirocyclization of butenolide **4.41** and a 3D-model showing the observed NOE contacts in **4.45b**.

Cyclization of γ-methoxybutenolide **4.42**, which was used as an inseparable 1:1 mixture of epimers **4.42a** and **4.42b**, gave products **4.47a** and **4.47b** as an inseparable 1:1 mixture in 92-96% yield when carried out at 70-100 mg scales (Scheme 4.22). It seems that each of the epimers **4.42a** and **4.42b** stereoselectively cyclized to **4.47a** and **4.47b** via transition states **4.46a** and **4.46b**, respectively. Hence, the methoxy group at the acetal stereocenter effectively controls the approach of the tertiary radical from the opposite face.



Scheme 4.22. Efficient spirocyclization of γ-methoxybutenolide **4.42**.

Although **4.47a** and **4.47b** were inseparable by column chromatography, the undesired diastereomer **4.47b** was poorly soluble in ethyl acetate. Crystallization of **4.47b** allowed unambiguous prove of its structure and configuration by X-ray crystallography (Figure 4.3).

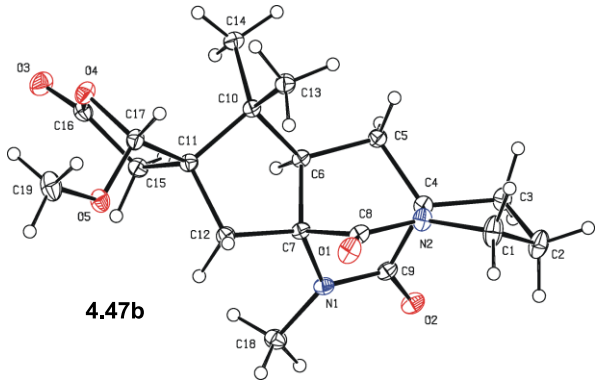
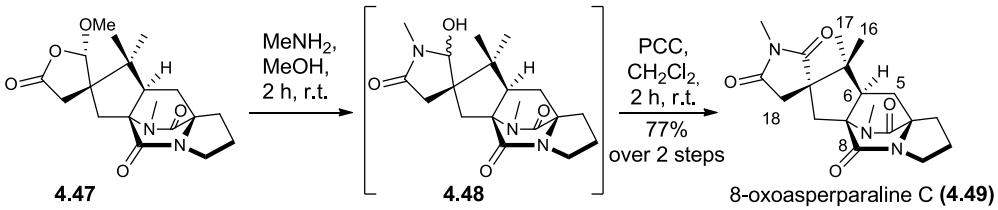


Figure 4.3. X-ray crystal structure of **4.47b**. Thermal ellipsoids are drawn at the 30% probability level.

Pure undesired **4.47b** was obtained by repeated fractional crystallization of a 1:1 mixture of **4.47a** and **4.47b**, and the mother liquor was enriched in **4.47a** (**4.47a**/**4.47b**, 5-5.5:1). Further crystallization attempts did not lead to improvement of the ratio in favor of **4.47a**. This mixture was subjected to a two-step reaction sequence, by treating with five equivalents of a 2 M methanolic methylamine solution for 2 h and subsequent oxidation of the hydroxy lactam intermediate **4.48** by PCC, which gave spirosuccinimide **4.49** in 77% yield (Scheme 4.23). Compound **4.49** differs from asperparaline C only in the oxidation state of the C-8 atom, which is fully reduced in asperparaline C and can be named as 8-oxoasperparaline C.



Scheme 4.23. Synthesis of 8-oxoasperparaline C (**4.49**).

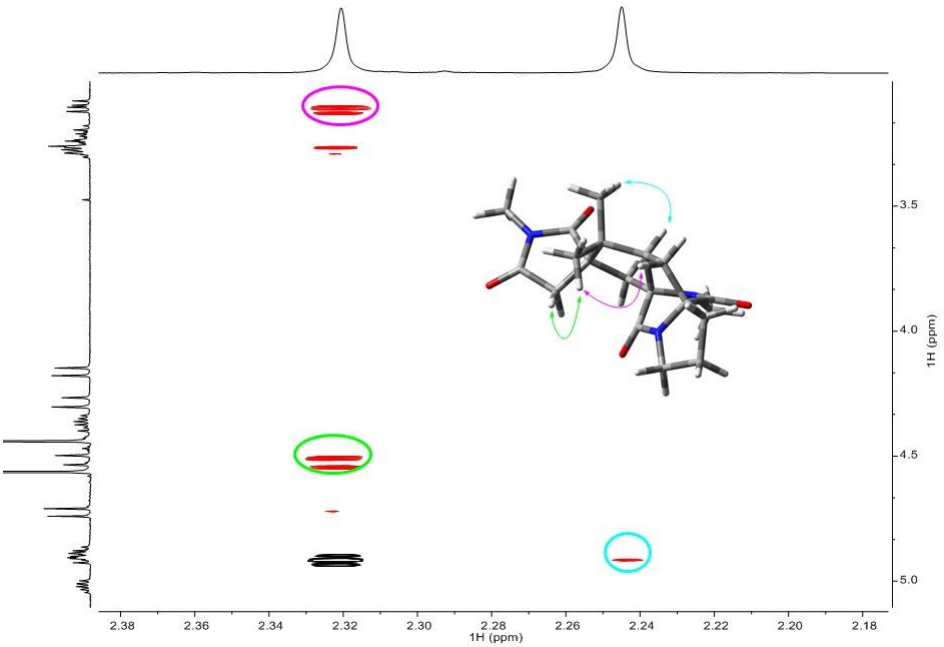
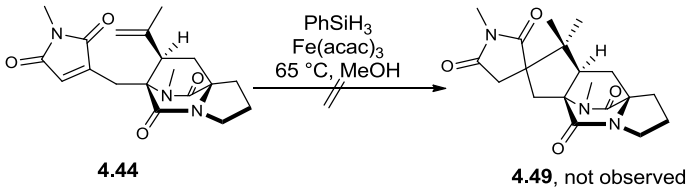


Figure 4.4. NOE analysis of **4.49** in C_5D_5N.

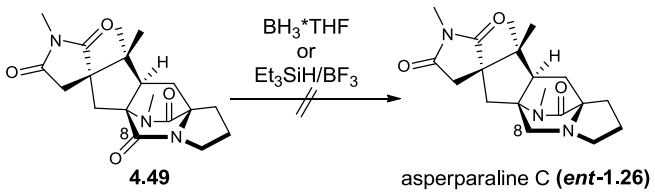
The stereochemistry of **4.49** was confirmed by ROESY analysis which was possible because the geminal methyl groups were well resolved in C_5D_5N and could be differentiated (Figure 4.4). C-16 methyl, group which is in *syn*-relationship with the methylene groups of the succinimide (C-18) as well as the bridging methylene group (C-5) showed NOE contacts with both of these groups while the C-17 methyl group showed only an NOE contact to the C-6 hydrogen atom.

The maleimide **4.44** did not afford the expected spirosuccinimide **4.49** and instead a 2:1 mixture of compounds was formed (Scheme 4.24). Their structure safely assigned. Instead of geminal methyl groups, two sets of isopropyl methyl groups were visible and the maleimide unit also seemed to have been reduced.



Scheme 4.24. Attempted unsuccessful cyclization of maleimide **4.44**.

With a method to 8-oxoasperparaline C (**4.49**) developed, a few attempts chemoselectivrly to reduce the C-8 amide carbonyl group were undertaken (Scheme 4.25). Based on its ^{13}C NMR chemical shift of 168.8 ppm in $CDCl_3$, which is more upfield shifted compared to all other amide carbonyl signals (172.3, 175.7, 182.5 ppm), it was assumed that the C-8 carbonyl group is the most Lewis basic site and using Lewis acidic reducing agents or activation by Lewis acids might lead to chemoselective reduction of this amide group. However, neither BH_3*THF nor Et_3SiH/BF_3 were capable to promote reduction of any of the carbonyl groups at room temperature and **4.49** was recovered essentially quantitatively.



Scheme 4.25. Initial attempts to chemoselectively reduce C-8 amide in **4.49**.

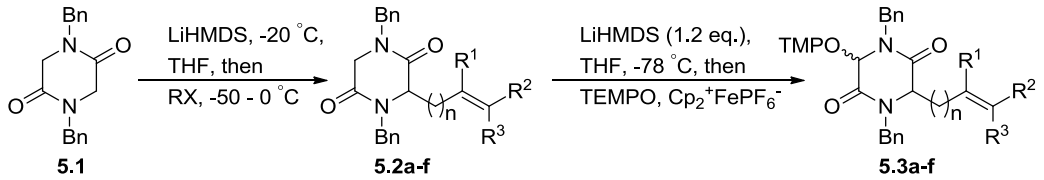
In conclusion, an eleven-step asymmetric approach to 8-oxoasperparaline C (**4.49**) was developed starting from cheap *L*-proline (ca 15% overall yield). The key steps are the PRE-mediated efficient cyclization of in situ generated DKP-derived alkoxyamines to construct the diazabicyclo[2.2.2]octane core, singlet oxygen-mediated furan dearomatization and a reductive spirocyclization. Initial experiments to chemoselectively reduce the C-8 carbonyl function in **4.49** were unsuccessful and further studies are ongoing. Alternatively, reduction of intermediate **4.16c** before the dearomatization and spirocyclization will be studied.

5. Synthesis of diverse bridged DKPs by using the persistent radical effect

5.1. Synthesis of diverse carbon-bridged DKPs

Non-natural bioactive bridged DKPs were also discovered as important bioactive scaffolds. Given the importance of non-natural and natural bridged DKPs and the recent growth of interest in three-dimensional heterocyclic architectures in medicinal chemistry (see Chapter 1), methods allowing rapid access to diverse bridged DKP motives are highly desired. With the discovery of stable alkoxyamines during initial studies and demonstration of their use as radical surrogates, a methodology for the synthesis of diverse non-natural bridged DKPs based on the PRE was developed.

Alkoxyamines **5.3a-f** were synthesized in two steps from 1,4-dibenzylpiperazine-2,5-dione **5.1** by monoalkylation[42b] followed by oxidative alkoxyamine formation under standard conditions (Scheme 5.1). This efficient two step desymmetrization of **5.1** allowed access to a number of substrates and facilitated studying the scope and limitations of the new method.



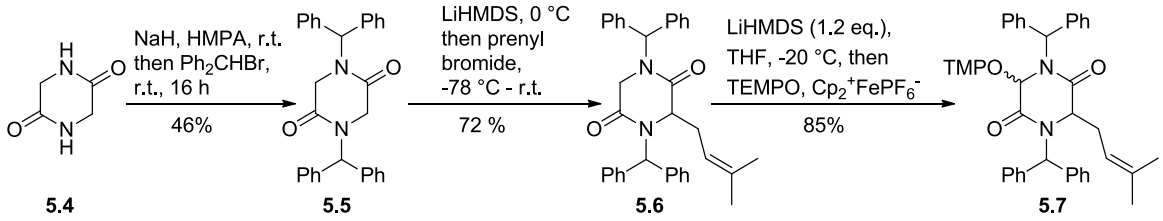
5.1 **5.2a-f** **5.3a-f**

	RX	n	R^1, R^2, R^3	Yield, % 5.2a-f	Yield, % 5.3a-f	d.r.
a	allyl bromide	1	$R^1 = R^2 = R^3 = H$	76	86	4.8:1
b	prenyl bromide	1	$R^1 = H$, $R^2 = R^3 = Me$	73	81	3.2:1
c	cinnamyl bromide	1	$R^1 = R^3 = H$, $R^2 = Ph$	75	93	4.5:1
d	methallyl chloride	1	$R^1 = Me$, $R^2 = R^3 = H$	84	74	1:1
e	α-methylcinnamyl chloride	1	$R^1 = Me$, $R^2 = Ph$, $R^3 = H$	52	90	2.7:1
f	homoallyl bromide	2	$R^1 = R^2 = R^3 = H$	51	82	1.3:1

Scheme 5.1. Two-step desymmetrization approach to DKP derived alkoxyamines **5.3a-f**.

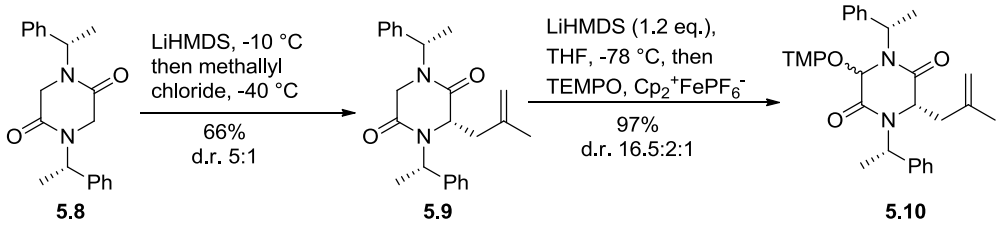
To probe the influence of steric bulk of substituents at the nitrogen atoms, a prenylated DKP alkoxyamine **5.7** with a benzhydryl protecting group was synthesized (Scheme 5.2). Glycine anhydride **5.4** was doubly alkylated with bromodiphenylmethane and

DKP **5.5** was prenylated to give DKP **5.6**. Subsequantly, alkoxyamine **5.7** was obtained as a single diastereomer of unassigned configuration.



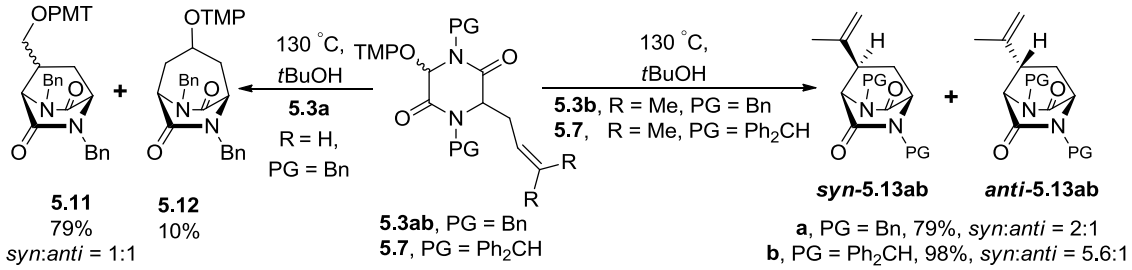
Scheme 5.2. Synthesis of a dibenzhydryl protected alkoxyamine **5.7**.

Additionally, known chiral DKP **5.8**[84] was also converted to alkoxyamine **5.10** by sequential alkylation with methallyl chloride, which gave a 5:1 mixture of inseparable **5.9** diastereomers, followed by standard oxidative alkoxyamination (Scheme 5.3).



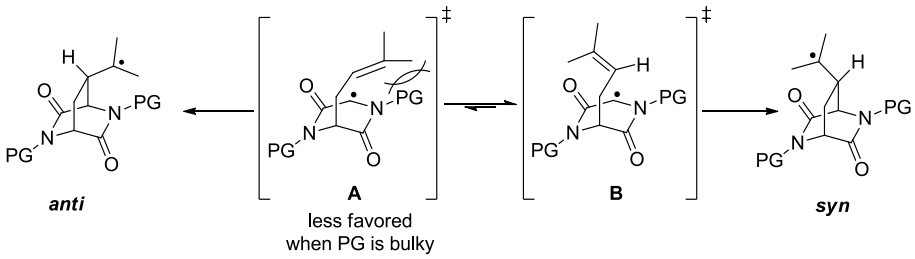
Scheme 5.3. Synthesis of a chiral substrate **5.10**.

Efficient cyclizations took place upon heating *t*BuOH solutions of **5.3a** and **5.3b** under standard conditions (Scheme 5.4). The allylated substrate **5.3a** underwent cycloisomerization giving **5.11** as an inseparable 1:1 mixture of diastereomers. Approximately 10% of the 7-endo-trig cyclization product **5.12** was also formed. Carrying out the reaction in pure water or DMSO as alternative solvents resulted in essentially the same yields and diastereoselectivities. The prenylated alkoxyamine **5.3b** afforded an inseparable mixture of diastereomeric products ***syn*-5.13a** and ***anti*-5.13a** in a 2:1 ratio. The diastereoselectivity of the benzhydryl-protected **5.7** was much more pronounced and a 5.6:1 mixture of ***syn*-5.13b** and ***anti*-5.13b** was obtained.



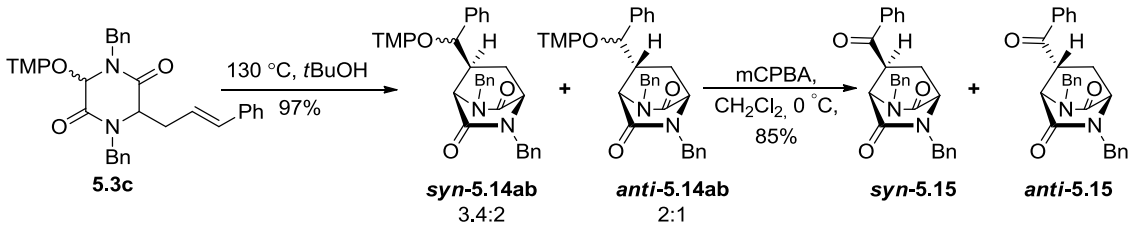
Scheme 5.4. Thermal cyclization of substrates **5.3ab** and **5.7**.

The following mechanistic rationale can be suggested to explain the difference in diastereoselectivities between **5.3b** and **5.7** (Scheme 5.5). In transition state **A**, leading to the *anti*-diastereomer, steric interaction between the protecting group and the methyl groups at the cyclizing alkene group are significantly pronounced. The bigger the sizes of the protecting group the more destabilized the *anti*-transition state **A** becomes.



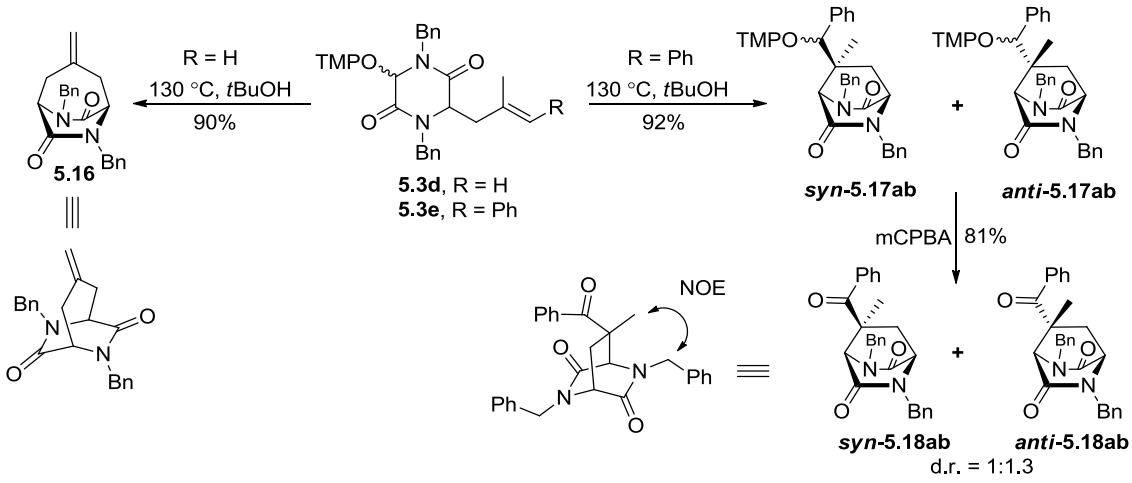
Scheme 5.5. Mechanistic rationale for the diastereoselectivies of cyclization reactions.

The cinnamyl DKP derived alkoxyamine **5.3c** also cyclized very efficiently. However, an inseparable mixture of all four possible diastereomers was formed (Scheme 5.6). Analysis of the crude mixture by NOE suggested that the *syn*:*anti* diastereoselectivity at the bridging atom was 1.8:1. This result was confirmed by a one-step oxidative conversion of the benzylic alkoxyamine, resulting in ketones ***syn*-5.15** and ***anti*-5.15** with essentially the same ratio.



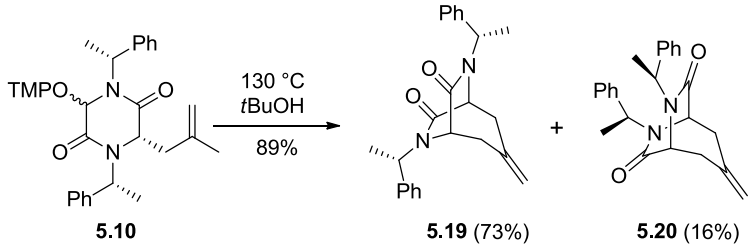
Scheme 5.6. Thermal cycloisomerization of the cinnamyl DKP derived alkoxyamine **5.3c**.

Cyclizations of DKP alkoxyamines bearing 1,1-disubstituted alkene groups were investigated. Methallyl DKP substrate **5.3d** (R = H) exclusively underwent 7-endo-trig cyclization to give the diazabicyclo[3.2.2]nonane product **5.16**, after TEMPOH elimination. On the other hand, the α-methylcinnamyl DKP substrate **5.3e** (R = Ph) provide a mixture of four 6-exo-trig cyclization products **5.17**. The diastereoselectivity at the bridging quaternary center was determined to be 1:1.3 in favor of the *anti*-diastereomer.



Scheme 5.7. Radical cyclizations to 1,1-disubstituted alkene units.

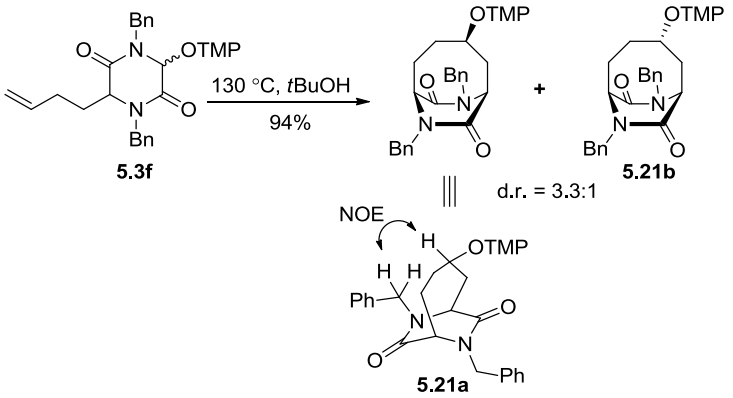
The chiral DKP derived alkoxyamine **5.10** also cyclized efficiently to give a mixture of diazabicyclo[3.2.2]nonanes **5.19** and **5.20** in 73% and 16%, respectively (Scheme 5.8). The 4.6:1 ratio of products is close to the initial 5:1 ratio in **5.9** which was set at the alkylation step (see Scheme 5.3).



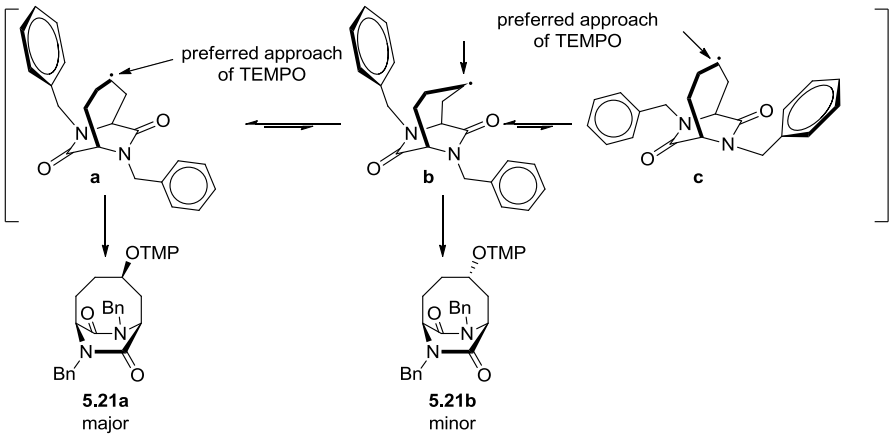
Scheme 5.8. Cyclization of a chiral alkoxyamine **5.10**.

Exclusive 8-endo-trig radical cyclization, giving the diazabicyclo[4.2.2]decane ring system, took place when the substrate with a homoallyl acceptor **5.3f** was heated under standard conditions (Scheme 5.9). This outcome is significant in light of the difficulties of

making medium sized rings. Moreover, a reasonable diastereoselectivity was found in favor of product **5.21a**, where the TEMPO unit points away from the closest *N*-Bn group, in the major diastereomer. The stereochemistry of **5.21a** was assigned based on the observed NOE between the CH_2 protons of the benzyl group and the methine C-H to which the TEMPO-fragment is attached.



Scheme 5.9. Efficient formation of the diazabicyclo[4.2.2]decane ring system.

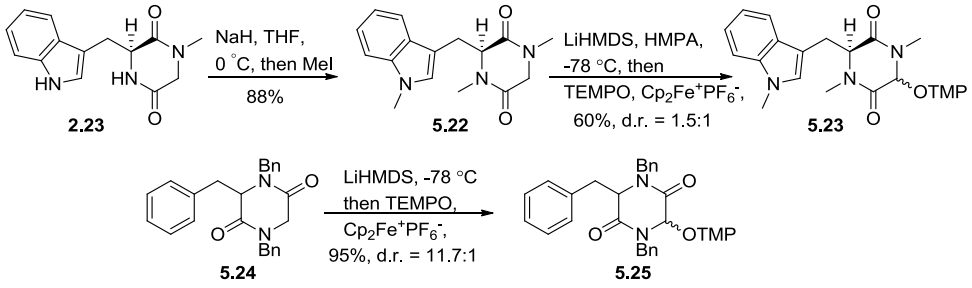


Scheme 5.10. Rationalization of the observed diastereoselectivity in the formation of **5.21ab**.

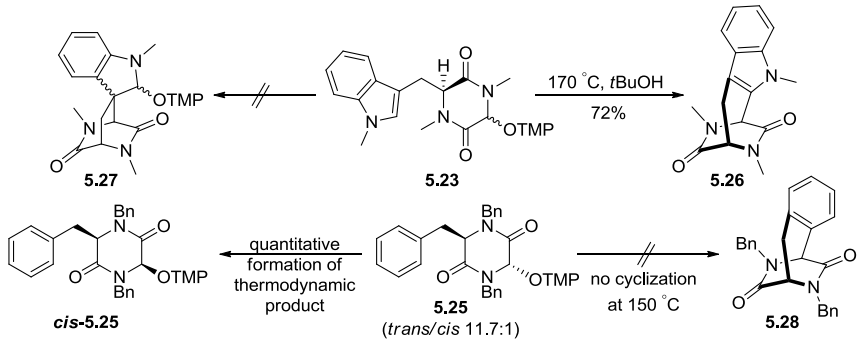
This result can again be rationalized by involving the role of protecting groups on nitrogen atoms of the DKP ring (Scheme 5.10). In conformer **a** the phenyl ring of the protecting group effectively blocks one face of the radical, which leads to the observed major product **5.21a**. On the other hand, due to the same phenyl ring, the bent conformer of the 8-membered ring **b** can be populated to some extent. From bent conformer **b**, the attack of TEMPO-radical from the convex face, resuls in formation of the minor diastereomer **5.21b**.

Alternatively, a conformer of type **c** can also preferentially couple with TEMPO in favor of **5.21b**.

To further explore the scope and limitations of the methodology, it was studied whether aromatic rings can also serve as radical acceptors (Scheme 5.11). For this, alkoxyamines **5.23** and **5.25** were prepared, in which the indole unit and phenyl ring were present instead of the alkene groups. Alkoxyamine **5.23** was synthesized from a chiral DKP **2.23** (see Chapter 2) by double methylation and oxidative alkoxyamination. DKP **5.24** was obtained as a byproduct during the synthesis of **5.1**.



Scheme 5.11. Synthesis of substrates with aromatic rings as radical acceptors.

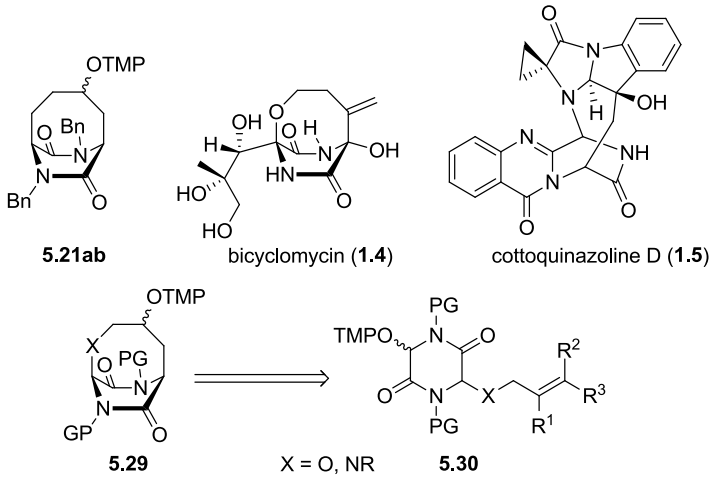


Scheme 5.12. Radical cyclization onto indole ring and an unexpected isomerization of ***trans*-5.25** to ***cis*-5.25**.

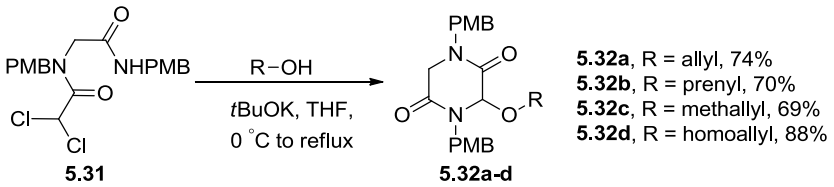
The cyclization to indole unit was sluggish under standard conditions at 130 °C (Scheme 5.12). However, upon increasing the temperature to 170 °C, cyclization took place in an endo-fashion to give **5.26**. Spiro-products, which could have formed via an exo-mode, were not detected. On the other hand, the cyclization of **5.25** to **5.28** failed even when heating to 150 °C for prolonged time; and **5.25** decomposed at 170 °C. Instead, an 11.7:1 ***trans*-5.25**/***cis*-5.25** diastereomeric mixture quantitatively converted to ***cis*-5.25**. This unexpected outcome shows that the *cis*-form of these alkoxyamines is the thermodynamic product. The kinetic features of this unusual *trans*-*cis* isomerization will be discussed in the next chapter.

5.2. Synthesis of heteroatom-bridged DKPs

The diazabicyclo[4.2.2]decane **5.21ab**, which formed by an efficient 8-endo-trig radical cyclization, resembles the core structure of bicyclomycin (**1.4**), except that in bicyclomycin the four-membered bridge incorporates an oxygen atom (Scheme 5.13). Moreover, a related nitrogen bridged diazabicyclo[4.2.2]decane ring system is also present in cottoquinazoline D (**1.5**). The ease and efficiency of formation of the diazabicyclo[4.2.2]decane motif of **5.21ab** suggests that the core bridged substructures **5.29** of bicyclomycin and even cottoquinazolines may also be formed using the methodology developed in the previous section, provided that DKP alkoxyamines of type **5.30** can be easily accessed.



Scheme 5.13. Radical disconnection towards heteroatom bridged DKPs **5.29**.

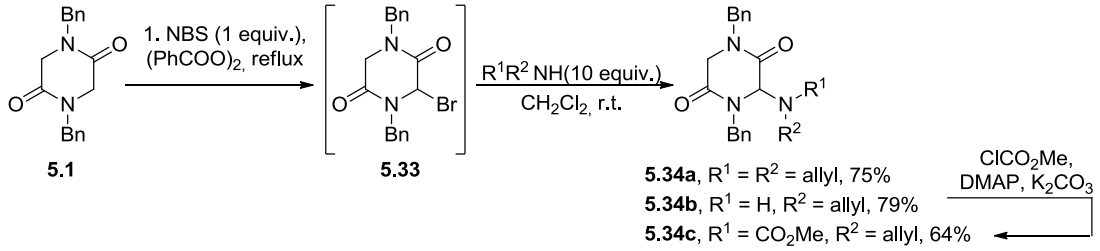


Scheme 5.14. Synthesis of alkoxy-substituted DKPs **5.32a-d**.

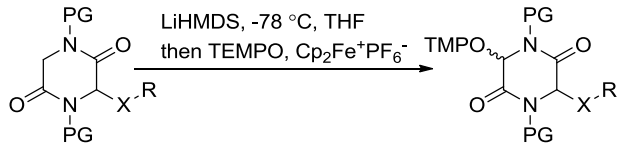
A series of alkoxy-substituted DKPs **5.32a-d** were synthesized from known glycinamide dichloroacetamide **5.31** and excess alcohols in the presence of potassium *tert*-

butoxide according to Williams' method in high yields using allyl, prenyl, methallyl and homoallyl alcohols (Scheme 5.14).[45]

This method did not work for nitrogen analogs, when **5.31** was treated with lithium diallylamide. However, it is known, that DKPs are easily halogenated under Wohl-Ziegler bromination conditions.[85] This property was exploited to introduce sulfur and nitrogen atoms into the DKP unit by treating the labile α-bromo DKPs with sodium thiolates[86] and sodium amides,[87] respectively. In our hands, the generation of metal amides from amines was not required. Bromination of **5.1** with one equivalent of NBS in the presence of a catalytic amount of benzoyl peroxide, followed by filtration and evaporation gave crude monobromo DKP **5.33**. It was immediately dissolved in DCM and treated with excess allylamines to give the desired DKP aminals **5.34ab**. The NH-group of **5.34b** was protected with methyl chloroformate to give DKP **5.34c**.



Scheme 5.15. Synthesis of DKP aminals.



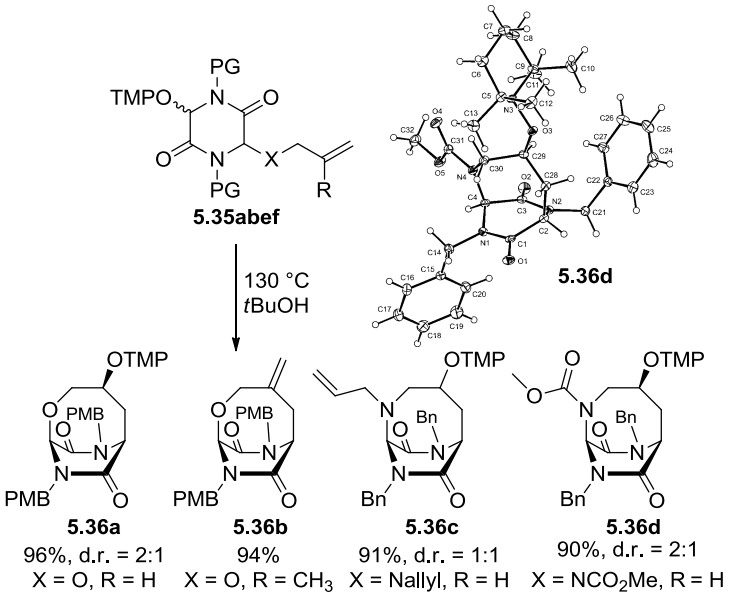
	X	PG	R	Yield, %
a	O	PMB	allyl	90
b	O	PMB	methallyl	91
c	O	PMB	prenyl	91
d	O	PMB	homoallyl	92
e	NAllyl	Bn	allyl	93
f	NCO_2Me	Bn	allyl	81

Scheme 5.16. Synthesis of alkoxyamines **5.35a-f** en route to heteroatom bridged DKPs.

With these starting materials in hand, the corresponding alkoxyamines **5.35a-f** were synthesized under standard oxidative conditions in high yields (Scheme 5.16).

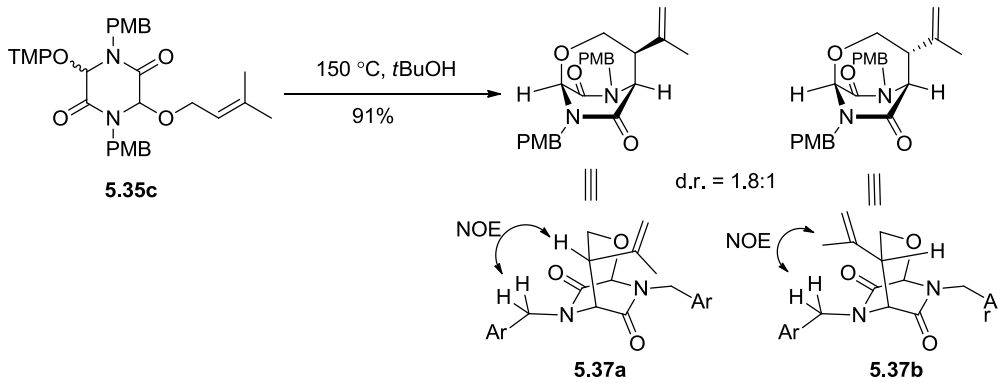
When the alkene side chain in **5.35** was terminal only 8-endo-trig cyclizations took place producing diazabicyclo[4.2.2]decanes **5.36a-d** in yields exceeding 90% in all cases (Scheme 5.17). Substrate **5.35b** delivered the TEMPOH eliminated product **5.36b** as

expected. It seems that the nature of the heteroatom and the substituents at the nitrogen atom influenced the diastereoselectivity to some extent. For example, simple allyloxy substrate **5.35a** gave 2:1 mixture of inseparable diastereomers (only the major diastereomer is shown). Diallylamino substrate **5.35e** gave a 1:1 mixture of inseparable diastereomers of **5.36c**, whereas the methyl carbamate protected analog **5.35f** induced a 2:1 diastereoselectivity. In the latter case, the diastereomers were separable by chromatography and the major diastereomer **5.36d** was analyzed by X-ray crystallography. The TEMPO unit is pointing away from the closest *N*-Bn protecting group similarly to **5.21a** (Scheme 5.9).



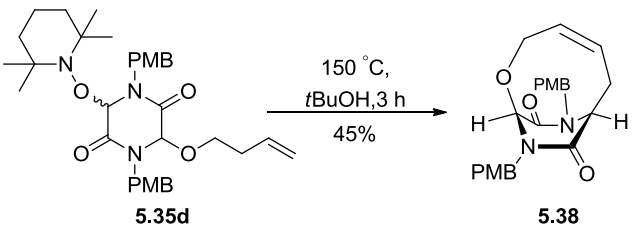
Scheme 5.17. Synthesis of *O*- and *N*-bridged diazabicyclo[4.2.2]decane ring systems and an X-ray structure of **5.36d**. Thermal ellipsoids are drawn at the 30% probability level.

In contrast, the substrate with a prenyloxy substituent **5.35c** cyclized exclusively via a 7-exo-trig pathway with 1.8:1 diastereoselectivity, furnishing the TEMPOH eliminated products **5.37ab** (Scheme 5.18). The configuration of the major diastereomer **5.37a**, in which the propenyl group is *anti*-to the closest *N*-PMB protecting group, was determined by NOE difference spectroscopy. The minor diastereomer **5.37b** showed an NOE contact between the benzylic methylene protons and the protons of the propenyl group



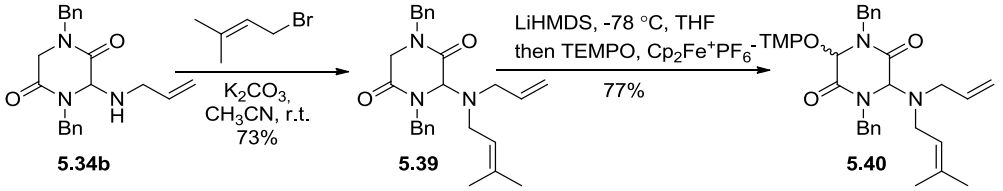
Scheme 5.18. 7-exo-trig cyclization of substrate **5.35c** bearing prenyloxy side chain.

When the homoallyloxy substrate **5.35d** was subjected to the standard cyclization conditions, no cyclization was observed at 130 °C even after prolonged time, but small amounts of dimerization products seemed to form. When the temperature was increased to 150 °C the diazabicyclo[5.2.2]undecane **5.38** was obtained in 45% yield (Scheme 5.19). Interestingly, this compound did not contain the TEMPO fragment. Presumably, elimination of TEMPOH took place either because of higher temperature or facile relief of transannular strains in the 9-membered ring.



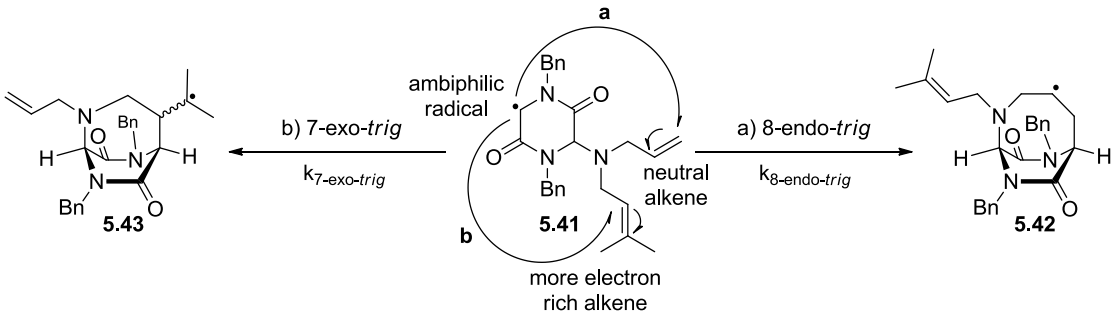
Scheme 5.19. 9-*endo*-trig radical cyclization.

The selective 8-endo cyclization modes observed in the cases of allyloxy and allylamino substituted alkoxyamines **5.35abef** which cyclize only via 8-endo-trig mode vs. the exclusive 7-exo cyclization of the prenyloxy substituted substrate **5.35c** is easy to explain considering steric factors. To gain insight in the relative rates of bridge forming 8-endo-trig and 7-exo-trig radical cyclizations, substrate **5.40** bearing both allyl and prenyl side chains at the same atom was synthesized taking advantage of the additional valency at the nitrogen atom (Scheme 5.20). The synthesis was achieved by *N*-prenylation of **5.34b** followed by standard oxidative alkoxyamination of resulting DKP **5.39**.



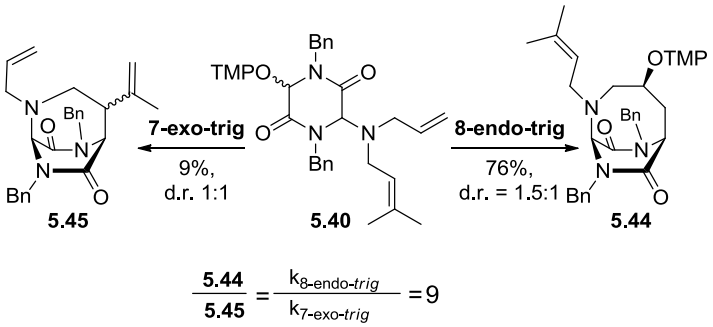
Scheme 5.20. Synthesis of designed substrate **5.40** having both allyl- and prenyl-side chains.

Intuitively the transition state leading to the 7-*exo*-trig cyclization product should be more strained and higher in energy and thus this pathway should be slower (Scheme 5.21). From the perspective of electronic factors, the electron rich prenyl group should be a better radical acceptor for the ambiphilic DKP radical rather than the allyl group. Since both cyclization modes are irreversible this is a kinetically controlled process and allows the determination of relative rates of these otherwise rare processes. The product ratio directly reflects the ratio of the rate constants of the cyclization modes because the cyclization step is obviously the rate limiting step after the homolysis step. For the 7-*exo*-trig cyclization there will be two diastereomeric transition states but if the product yield and the diastereoselectivity of this mode are low it can be assumed that they are close in energy.



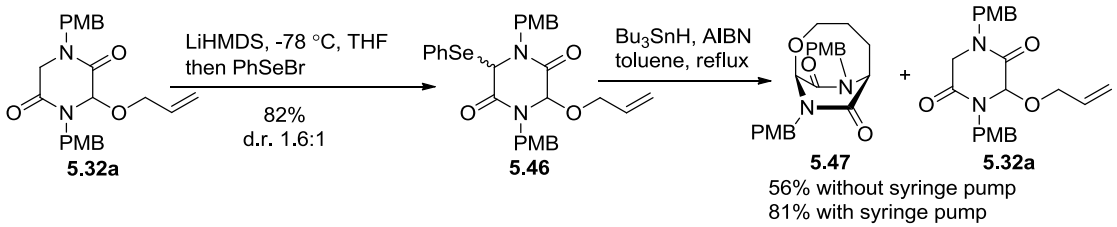
Scheme 5.21. Evaluation of the 7-exo and 8-endo cyclization modes.

Indeed, a clean cyclization took place and the 8-endo:7-exo product ratio was determined to be 9:1 by ^{1}H NMR spectroscopy of the crude products mixture (Scheme 5.22). After separation by chromatography, the 8-endo product was obtained in 76% and the 7-exo-products in 9% yields, respectively. The 8.44:1 ratio essentially matches the ratio determined by crude product NMR analysis. In conclusion, this example shows that in these systems, the 8-endo-trig cyclization reactions are considerably faster than the 7-exo-trig cyclizations. The exo-mode should be only possible when the terminal unit of the alkene is sterically blocked.



Scheme 5.22. Result of the cyclization of substrate **5.40**.

The 8-endo-trig cyclization of unstable phenylselenide **5.46**, synthesized from **5.32a**, was studied under conventional tributyltin hydride mediated conditions for comparison with the PRE methodology (Scheme 5.23). The desired cyclization product **5.47** was obtained in 56% yield under mix-and-heat conditions together with 40% of premature radical reduction product **5.32a**. Slow addition of a Bu_3SnH solution in toluene by syringe pump was necessary to increase the yield of the cyclization product **5.47** to 81%. These results clearly demonstrate the advantage of the PRE-mediated methodology, which is simple to perform, tin-free and atom-economic, since it retains the alkoxyamine functionality in the product.

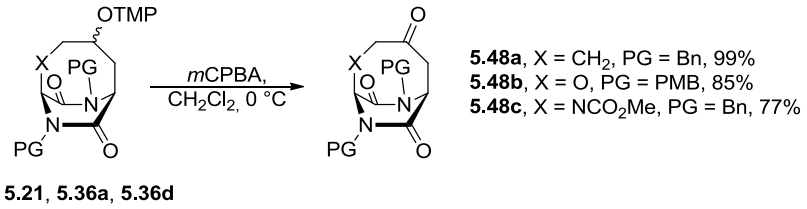


Scheme 5.23. A conventional 8-endo-trig cyclization.

5.3. Further derivatization of bridged DKPs

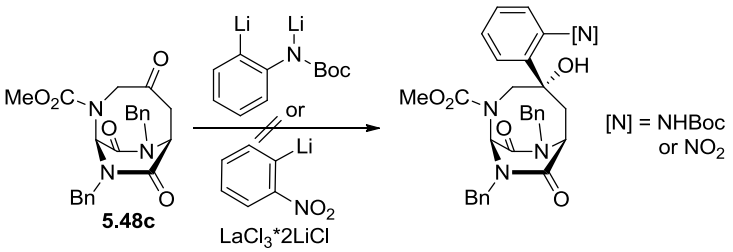
The TEMPO unit can be removed or deprotected oxidatively or reductively leading to carbonyl compounds or alcohols, respectively. The oxidative deprotection leads to the removal of the stereocenter and this was applied in the indirect determination of the diastereoselectivities of 6-exo-trig cyclizations (see Schemes 5.6 and 5.7). Additionally, the diazabicyclo[4.2.2]octane products **5.21**, **5.36a** and **5.36d** were also oxidatively converted to ketones **5.48a-c** upon treating with *m*CPBA in high yields (Scheme 5.24). It is important to carefully monitor the progress of reaction and to quench immediately upon full consumption

of the alkoxyamines. Otherwise, the ketone products can further undergo Baeyer-Villiger oxidation to esters.



Scheme 5.24. Oxidative removal of TEMPO-fragment.

With compound **5.48c** few nucleophilic addition attempts to the ketone functional group were tried as a model study towards cottoquinazoline D (Scheme 5.25). These experiments were not successful, leading to decomposition in the case of dilithiated Boc-aniline or recovery of the starting material using of *o*-lithiated nitrobenzene in the presence of lanthanum trichloride bis(lithium chloride) complex.[88]



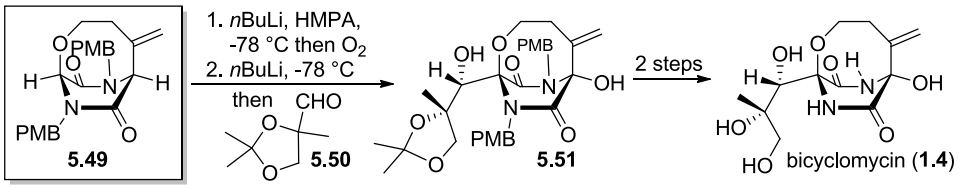
Scheme 5.25. Attempted nucleophilic addition to **5.48c**.

The reductive deprotection of TEMPO unit was successfully applied in the formal synthesis of bicyclomycin, which will be described in the following section.

5.4. A formal synthesis of bicyclomycin

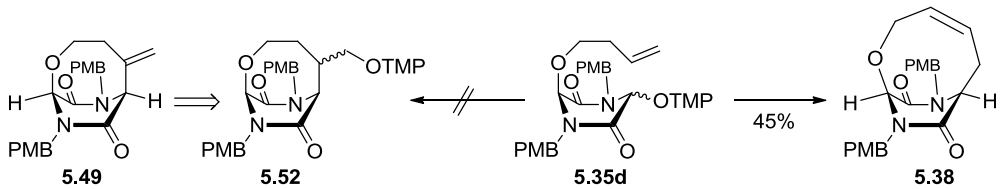
In order to apply the developed methodology to the synthesis of bicyclomycin (**1.4**), the central bridged DKP intermediate **5.49** from Williams' total synthesis was targeted (Scheme 5.26).[85] Intermediate **5.49** can be converted to bicyclomycin in just four steps by sequential functionalization of the bridgehead positions via "anti-Bredt enolates". First, **5.49** was deprotonated at the bridgehead position next to the exo-methylene group and the enolate was oxygenated by molecular oxygen. Next, the other bridgehead position at the bridging

oxygen atom was deprotonated and the resulting bridgehead carbanion was reacted with racemic aldehyde **5.50** giving an advanced intermediate **5.51** as a single diastereomer. Removal of the *p*-methoxybenzyl protecting groups in two steps gave racemic **1.4**. When an optically active aldehyde **(*S*)-5.50** (83% ee) was used, optically active (+)-bicyclomycin was obtained with 78% ee.[85]



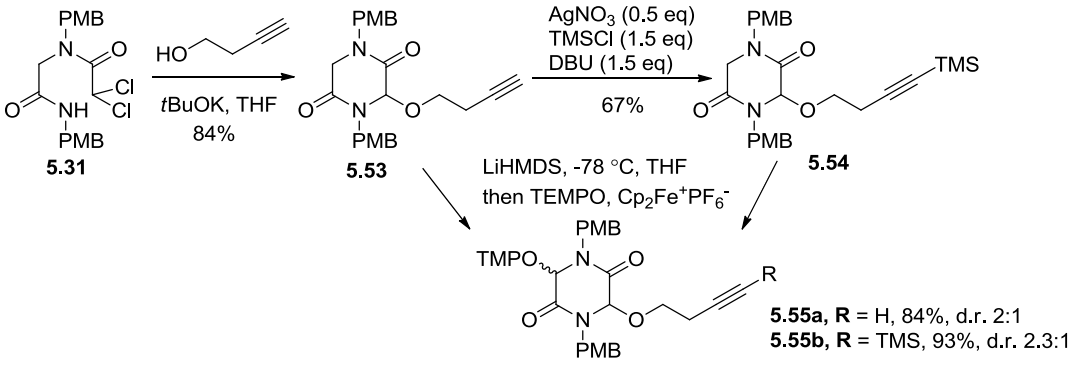
Scheme 5.26. Final steps in Williams' synthesis of bicyclomycin (**1.4**).

Initially, it was envisaged that an 8-exo-trig cyclization of **5.35d** would lead to bridged DKP **5.52** which could then be converted to the targeted compound **5.49** by reductive removal of TMP group followed by elimination of a water molecule (Scheme 5.27). However, as discussed above, no 8-exo-trig cyclization products were observed when **5.35d** was thermally cyclized, but an unexpected 9-endo-trig cyclization/TEMPOH elimination product **5.38** was obtained in moderate yield (see Scheme 5.19).



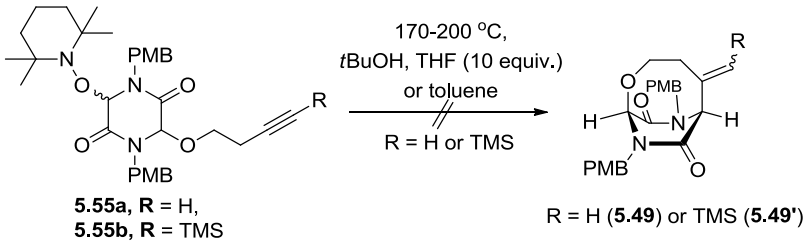
Scheme 5.27. Initial failed strategy towards **5.49**.

Hence, a cyclization to a pendent alkyne group generating a vinyl radical, which would abstract a hydrogen atom from additives or the solvent, was envisaged. Homopropargyloxy substituted DKP **5.53** required for this proposal was synthesized similarly to the previous substrates starting from **5.31** and homopropargylic alcohol (Scheme 5.28). The TMS-protecting group was introduced under silver mediated conditions to give a silylated alkyne **5.54**. Both DKPs **5.53** and **5.54** were converted to alkoxyamines **5.55ab** under standard conditions.[89]



Scheme 5.28. Synthesis of substrates with alkyne acceptors.

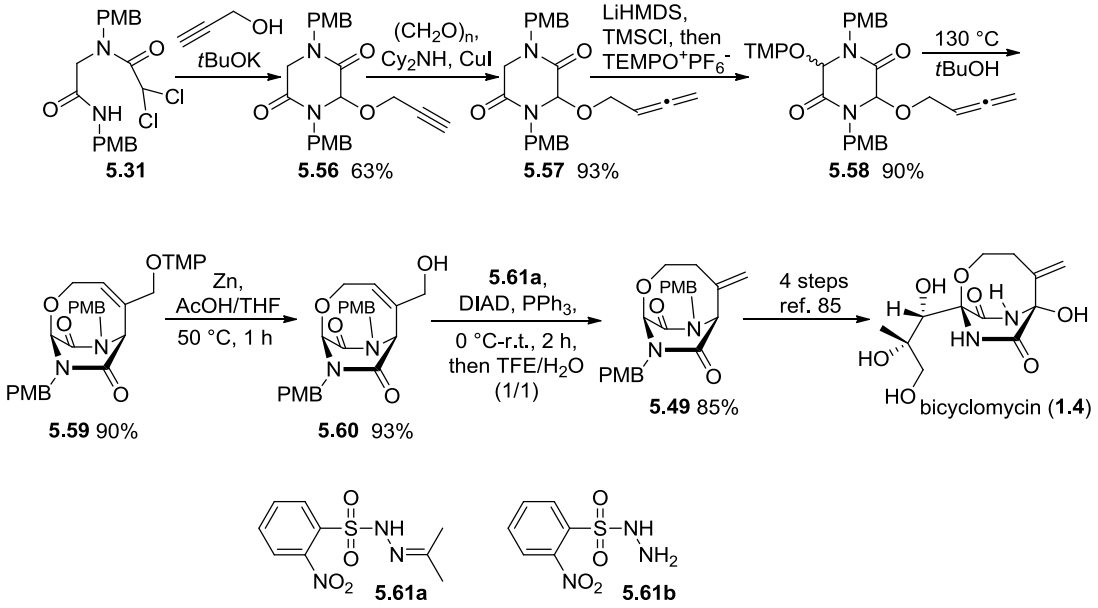
When **5.55a** and **5.55b** were heated at standard 130 °C no cyclization was observed and the starting materials were recovered (Scheme 5.29). Initially 10-15 equivalents of THF were added as H-atom source and the temperature was subsequently increased to 170 °C and 200 °C. In all cases complete conversion of the starting material to intractable complex mixtures took place. Using toluene both as a solvent and as a hydrogen atom source did not lead to any improvement.



Scheme 5.29. Attempted cyclizations to an alkyne group.

A precursor with a so far unused allene group as the radical acceptor was designed (Scheme 5.30). The required alkoxyamine **5.58** was obtained in three steps from **5.31** via oxygenative cyclization to **5.56** under basic conditions, Crabbe homologation[90] to **5.57** and enolate oxygenation under internal quench conditions,[91] because an unexpected fast rearrangement of the enolate takes place under standard oxidative alkoxyamination conditions (*vide infra*). The key radical cycloisomerization of **5.58** took place very efficiently providing bridged DKP **5.59** with an internal double bond. Reductive removal of the tetramethylpiperidinyl unit with zinc in acetic acid afforded allylic alcohol **5.60**. It is important to mention that the sensitive hemiaminal functionality at the bridgehead position

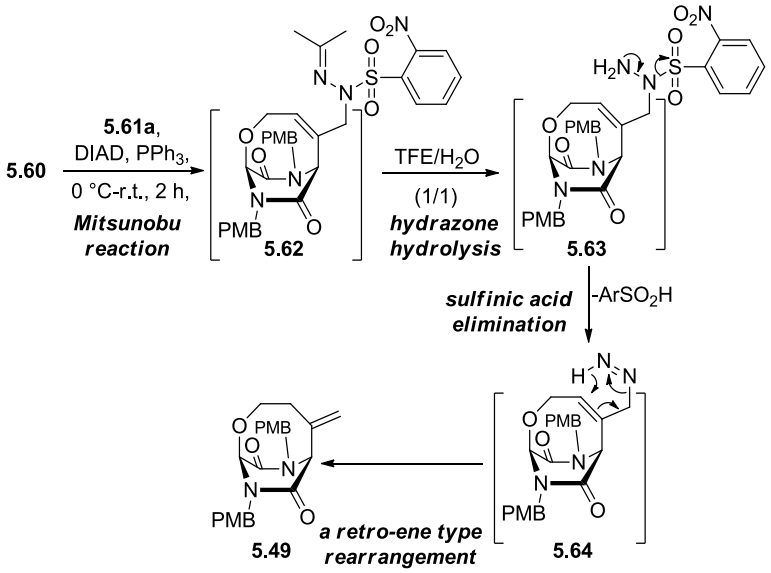
survived the acidic and reductive conditions. A reductive transposition of the internal double bond to the *exo*-position under the conditions developed by Movassaghi[92] furnished Williams' central intermediate **5.49** in 6 steps and 38% overall yield.



Scheme 5.30. Formal synthesis of bicyclomycin (**1.4**).

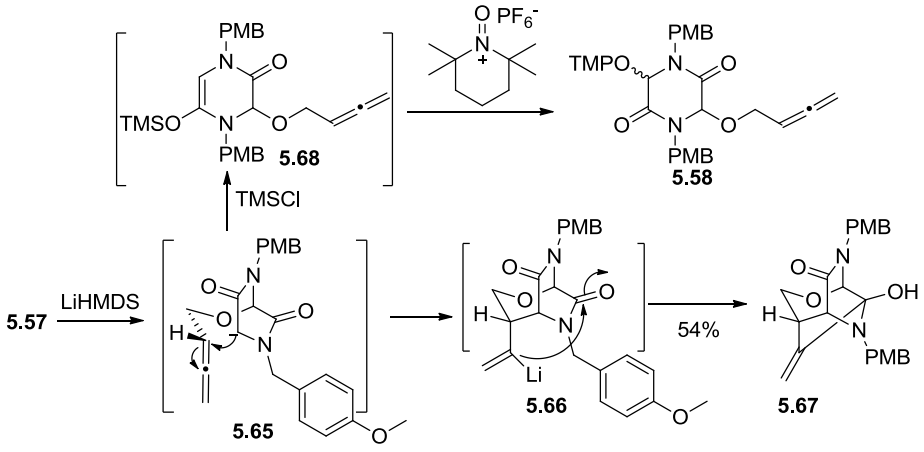
Using hydrazone **5.61a** is critical for the success of the last step as the hydrazide **5.61b** is sensitive to reaction conditions and decomposes in the presence of triphenylphosphine. Additionally, the use of DIAD over DEAD is very important for obtaining pure product **5.49** because the byproduct of DEAD reduction $(NHCO_2Et)_2$ was inseparable from **5.49** by any means.

The mechanism of this last step deserves discussion (Scheme 5.31). First, a Mitsunobu reaction takes place to substitute the hydroxyl group with the hydrazone **5.61a** giving intermediate **5.62**. Upon full consumption of allylic alcohol **5.60**, the reaction mixture was quenched with a 1:1 TFE/H_2O mixture which leads to hydrolysis of the hydrazone **5.62** to a labile hydrazide **5.63**, which decomposes to diazene intermediate **5.64** by elimination of sulfinic acid. The diazene intermediate subsequently undergoes a retro-ene type rearrangement with an intramolecular delivery of a hydrogen atom to the allylic position and transposition of the internal double bond to the exo-position by extrusion of molecular nitrogen (Scheme 5.31).



Scheme 5.31. Mechanism of reductive allylic transposition.

A facile and unexpected cyclization of enolate **5.65** generated from allene **5.57** caused serious troubles and necessitated modification of the alkoxyamination protocol (Scheme 5.32). Under the standard alkoxyamination conditions only low yields of the desired alkoxyamine **5.58** were obtained even when the oxidation was carried out immediately after addition of base. Almost no **5.58** formed when the reaction mixture was allowed to stir for longer times after the deprotonation step. In all cases a mixture of polar compounds formed, from which the major component **5.67** was isolated in a relatively pure form by careful chromatography. Apparently, an unusually facile attack of the DKP enolate at the allene unit center in 7-exo fashion took place. The resulting bridged vinyllithium intermediate **5.66** attacks the *syn*-oriented amide group in a 5-exo-trig fashion. The fast cyclization of enolate **5.65** was prevented by internal quench in the presence of TMSCl generating silyl ketene aminal **5.68**, which was then subsequently oxygenated with 2,2,6,6-tetramethyl-*N*-oxopiperidinium hexafluorophosphate ($TEMPO^+PF_6^-$) to give the desired alkoxyamine **5.58**.



Scheme 5.32. Possible mechanism for the rearrangement of enolate **5.65**.

In conclusion, a conceptually new approach to diverse bridged diketopiperazines has been developed by introducing a novel class of amino acid derived alkoxyamines as radical surrogates and taking advantage of an inherently atomeconomic cyclization that makes use of the PRE. This method provides efficient and practical access to diverse medium-ring bridged DKPs. Importantly, the reaction times are short compared to previously reported simple cyclizations, which can be attributed to facile homolysis of the C–O bond to give captodatively stabilized DKP radicals. The potential of the methodology was demonstrated in a formal total synthesis of the antibiotic bicyclomycin.

6. Features of DKP derived alkoxyamines

6.1. An unusual *trans*-*cis* isomerization of alkoxyamines and kinetic studies.

Alkoxyamines, a family of compounds having general structure $R^1R^2NO–R^1$, have found extensive application as initiators in controlled free radical polymerization.[93] The nitroxide mediated polymerization (NMP) technique, which is a transition metal free process,[94] has become an attractive alternative to atom transfer radical polymerizations (ATRP), and RAFT polymerizations. Apart from their application in polymer chemistry, alkoxyamines provide opportunities for performing green and safe tin-free radical reactions as demonstrated in the previous chapters. Moreover, alkoxyamines can be activated by external stimuli such as change in pH-, temperature, light or other physico-chemical triggering processes allowing the design of functional smart materials and molecules for new applications in material science, biology and medicine.[95]

Numerous studies into the factors influencing the homolysis of the C–ON bond in alkoxyamines have shown in recent years that both the structure of the nitroxide part as well as the alkyl radical fragment effect their propensity to homolysis.[96] Hydrogen-bonding, polar and steric effects strongly affect the homolytic C–ON bond cleavage and nitroxides having diverse structures and functional groups were designed and studied by Studer and others in recent years.[97] Marque and colleagues facilitated the homolytic bond cleavage by chemical processes such as hydrogen-bonding or modifying the alkyl unit of alkoxyamines.[98] Thus, the development of novel types of nitroxides and alkoxyamines and studying their properties is essential for the development of more efficient, selective initiators and mediators of radical polymerizations and also for other potential applications.

The TEMPO-adducts of DKPs introduced in this work, constitute an interesting and unprecedented class of amino acid derived hemiaminal type alkoxyamines. They were found to be very stable compounds towards silica gel chromatography and long-term storage. In most cases the diastereoselectivity is not high during the synthesis of these compounds. This is explained by extremely high rate constants (k_c) for coupling of transient DKP radicals with the persistent TEMPO radical, which is usually in the range of 10^5-10^9 M^{-1} s^{-1} depending on the stability of the transient radical.[79] The more stable the generated transient radical is the smaller the value of k_c is. Still, preference towards the *trans*-diastereomers is observed in many cases under the kinetic conditions employed for their synthesis.

As mentioned in the previous chapter, an attempted cyclization of an inseparable 11:1 mixture of ***trans/cis*-5.25** at 150 °C did not lead to radical cyclization to the aromatic ring. Upon checking the ^{1}H NMR-spectrum of the evaporated reaction mixture only peaks corresponding to *one* diastereomer were found, and they belonged to the minor diastereomer in the original mixture, i.e. complete and clean isomerization of the *trans*-diastereomer to the *cis*-diastereomer took place. This was proven by crystallization of the resulting product and X-ray crystallographic characterization unambiguously established the product to have the *cis* relative stereochemistry and proved it as the thermodynamic product (*vide infra*). The isomerization of ***trans*-5.25** was monitored by ^{1}H NMR spectroscopy at three different temperatures in DMSO-d_6 (Figures 6.1-6.3). Interestingly no line broadening is observed, which means that an increase in the concentration of the persistent radical TEMPO is marginal during the isomerization process, i.e. dimerization of the DKP radical is negligible.

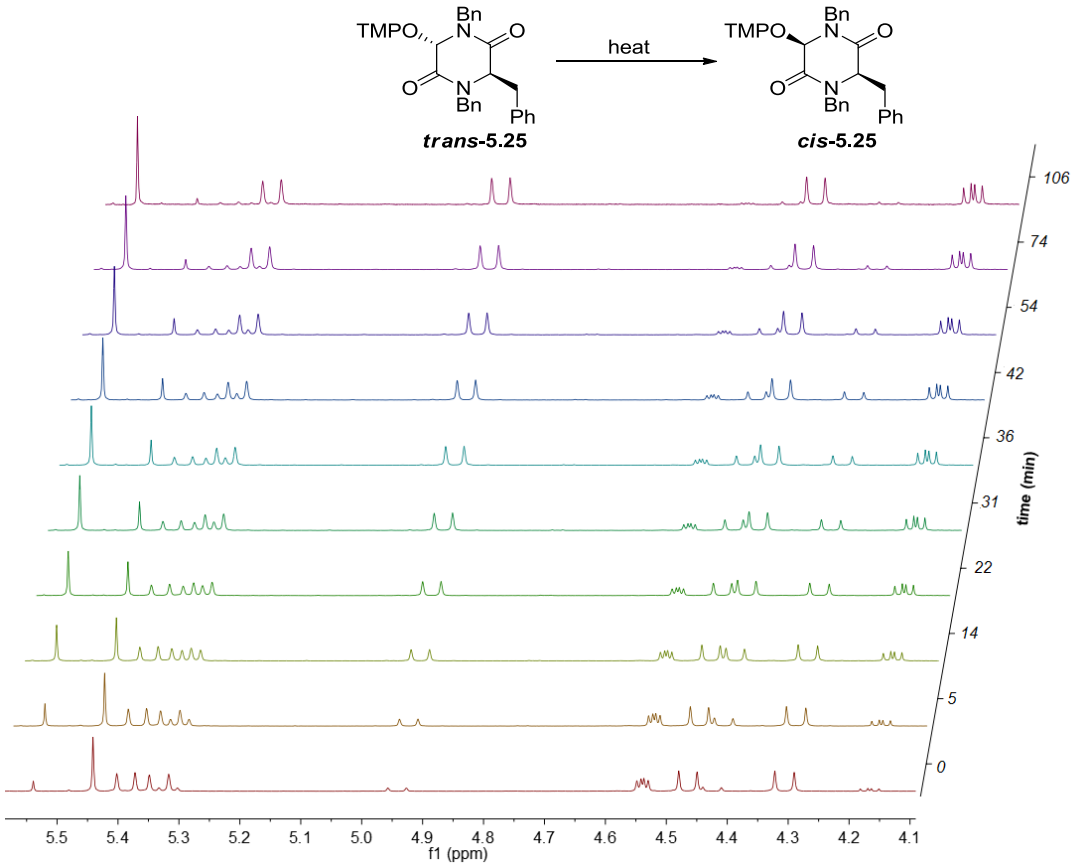


Figure 6.1. ^{1}H NMR monitoring of isomerization of ***trans*-5.25** to ***cis*-5.25** at 80 ºC.

The experimental data for the conversion of ***trans*-5.25** fit to first-order kinetics (Figures 6.2-6.3). The half-life of ***trans*-5.25** is significantly decreased upon increasing the

temperature and at 85 ºC it equals to only 17 min. The activation parameters $\Delta H^{\ddagger}$ = 130.73 kJ/mol (31.3 kcal/mol) and $\Delta S^{\ddagger}$ = 58.4 J/(K*mol) (14.0 cal/(K*mol)) for the overall transformation were obtained using the Eyring equation (Figure 6.4). This translates into an activation energy of E_a = 133.67 kJ/mol (32 kcal/mol) for the overall transformation, taking 80 ºC as the average temperature over the range of measurements. The Arrhenius plot (ln(*k*) vs 1/T) gives the same value of E_a.

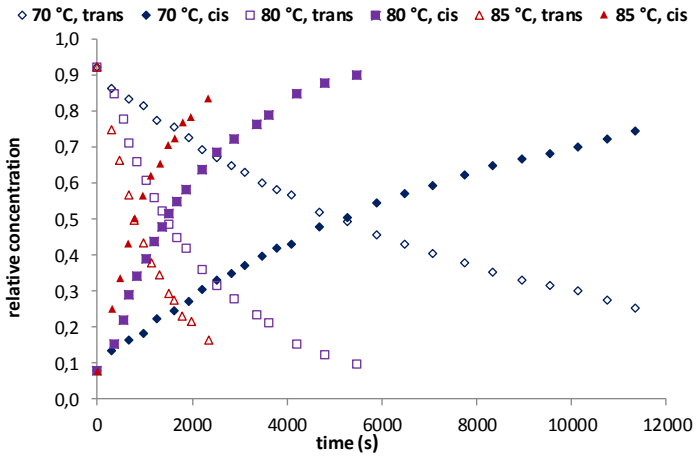


Figure 6.2. Kinetic traces for the isomerization of ***trans*-5.25** to ***cis*-5.25**.

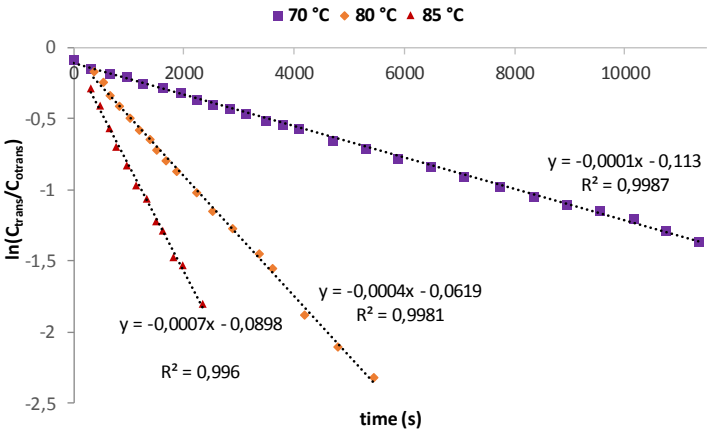


Figure 6.3. First order plot for the isomerization of ***trans*-5.25** to ***cis*-5.25**.

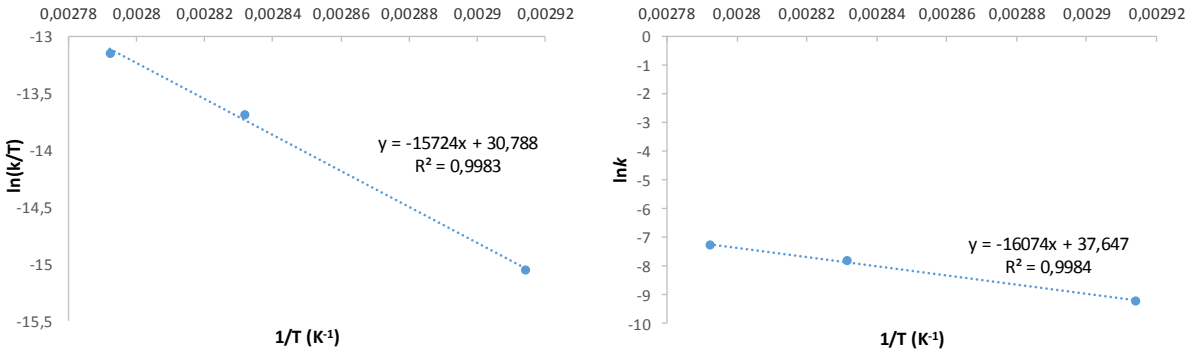


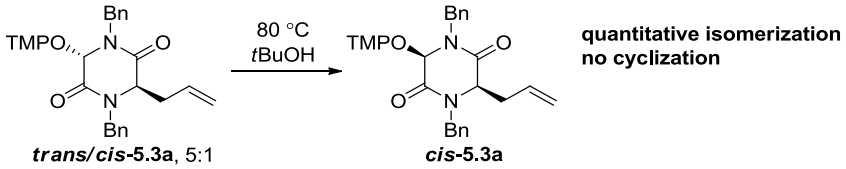
Figure 6.4. Eyring and Arrhenius plots for isomerization of ***trans*-5.25** to ***cis*-5.25**.

The Gibbs activation energy $\Delta G^{\ddagger}$ at three temperatures were also determined (Table 6.1). The observed rate constants for the overall isomerization process k_{obs}, which should be approximately equal to the C-O bond homolysis rate constants (k_d(*trans*)) of ***trans*-5.25**, were calculated and are in the range of 1-7x10^{-4} s^{-1} in the 70-85 °C temperature range, because the homolysis of ***trans*-5.25** is the rate determining step.

Table 6.1. Kinetic data obtained for isomerization of ***trans*-5.25** to ***cis*-5.25**.

T (K)	k_{obs} (s^{-1})	$\Delta G^{\ddagger}$ (kcal/mol)	$t_{1/2}$ (min)
343.15	1.00x10^{-4}	26.50	116
353.15	4.00x10^{-4}	26.34	29
358.15	7.00x10^{-4}	26.27	17

A similar isomerization was discovered during a temperature screening to find optimum conditions for the cyclization reaction of **5.3a** (Scheme 6.1). Upon heating ***trans*-5.3a**, contaminated with small amounts of ***cis*-5.3a** (ca 5:1), in *t*BuOH for 2 h at 80 ºC, no cyclization was observed. However, again complete and clean isomerization of the *trans*-diastereomer to the *cis*-diastereomer was found upon checking the ^{1}H NMR-spectrum of the evaporated reaction mixture. The structure of the thermodynamic product ***cis*-5.3a** was also proven with the help of X-ray crystallography.



Scheme 6.1. Thermal isomerization of ***trans*-5.3a** to ***cis*-5.3a**.

No observable cyclization of ***trans*-5.3a** took place when it was heated in the 75-85 ºC temperature range which allowed carrying out kinetic experiments for the isomerization process (Figures 6.5-6.7). Clean and quantitative isomerization to ***cis*-5.3a** occurs and the experimental data fit first order kinetics. The isomerization in this case is about three times faster. The half-life of ***trans*-5.3a** is 6 min at 85 ºC compared to 17 min for ***trans*-5.25** at the same temperature. The isomerization rate constants k_{obs} are markedly higher and the

isomerization is 2.5-3 times faster for ***trans*-5.3a** compared to ***trans*-5.25** (Table 6.2). The activation parameters also differ and are lower: $\Delta H^{\ddagger}$ = 122.10 kJ/mol (29.21 kcal/mol) and $\Delta S^{\ddagger}$ = 41.80 J/(K*mol) (10.00 cal/(K*mol)), E_a = 125.04 kJ/mol (30 kcal/mol.

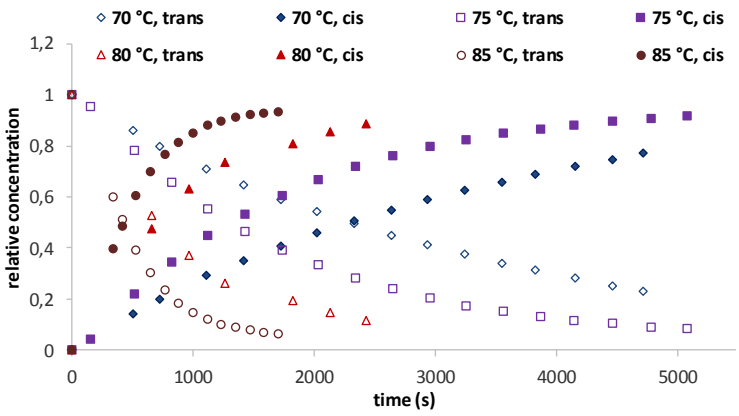


Figure 6.5. Kinetic traces for the isomerization of ***trans*-5.3a** to ***cis*-5.3a**.

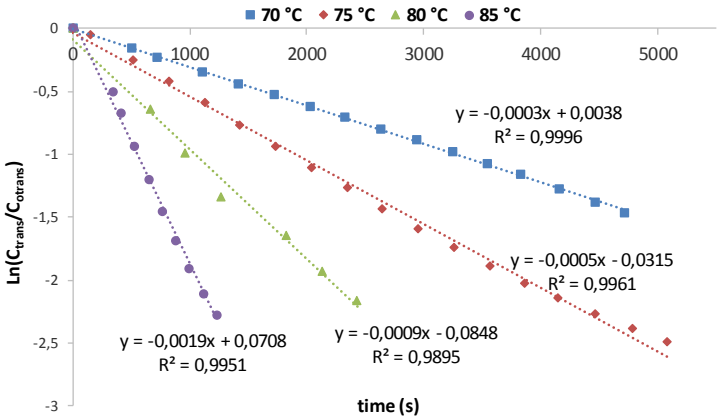


Figure 6.6. First order plot for the isomerization of ***trans*-5.3a** to ***cis*-5.3a**.

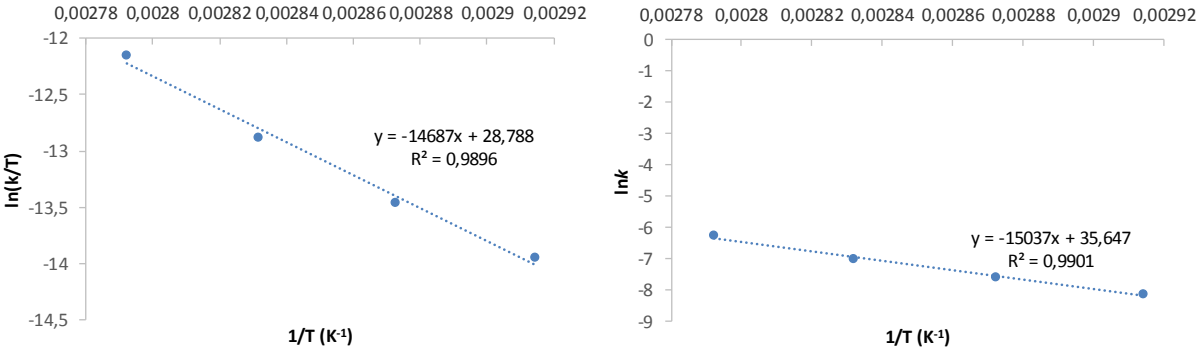


Figure 6.7. Eyring and Arrhenius plots for isomerization of ***trans*-5.3a** to ***cis*-5.3a**.

Table 6.2. Kinetic data obtained for isomerization of ***trans*-5.3a** to ***cis*-5.3a**.

T (K)	$k_{obs}(s^{-1})$	$\Delta G^{\ddagger}$ (kcal/mol)	$t_{1/2}$ (min)
343.15	$3.00x10^{-4}$	25.78	39
348.15	$5.00x10^{-4}$	25.73	23
353.15	$9.00x10^{-4}$	25.68	13
358.15	$1.90x10^{-3}$	25.63	6

The thermal isomerization of diastereomeric alkoxyamines is a well-known phenomenon. Marque and Ananchenko studied thermal isomerizations of few diastereomeric acyclic TEMPO-(**6.1a-b**) and SG1-based (**6.2a-b**) alkoxyamines (Figure 6.8).[99] However, little to no diastereomeric preference was observed upon thermolysis of these compounds. Only **6.2b** equilibrated to a 6:1 mixture when a 1:1 diastereomeric mixture or individual diastereomers were heated. Marque's results revealed that differences in homolysis rate constants k_d between the different diastereomers are the main reason for diastereomeric excess in the quasi-equilibrium. A very interesting *cis-trans* isomerization of alkoxyamines **6.3** derived from a styrene-dimer, which were detected in the course of NMP of styrene, was mentioned in a review as unpublished results of the authors.[100] Georges studied the diastereomeric alkoxyamines **6.4**, which mimic the products of the first monomer addition step in styrene polymerization.[101] They also did not observe significant diastereomeric excess upon thermolysis of individually separated **(*R*,*R*)/(*S*,*S*)-6.4** or **(*R*,*S*/*S*,*R*)** diastereomers. Both diastereomers equilibrated to a 2.1:1 mixture in favor of **(*R*,*R*)/(*S*,*S*)-6.4**. The closest examples of thermal diastereomeric equilibration of alkoxyamines to our system in that they are both cyclic and anomeric alkoxyamines were reported recently by Crich.[102] They studied the influence of protecting groups at the *N*- and *O*-atoms on the anomeric equilibrium using the sialic acid derived alkoxyamines such as **6.4a-b**. However, again no complete preference to one diastereomer was observed and at best 7:1 ratio of α/β-anomers could be achieved.

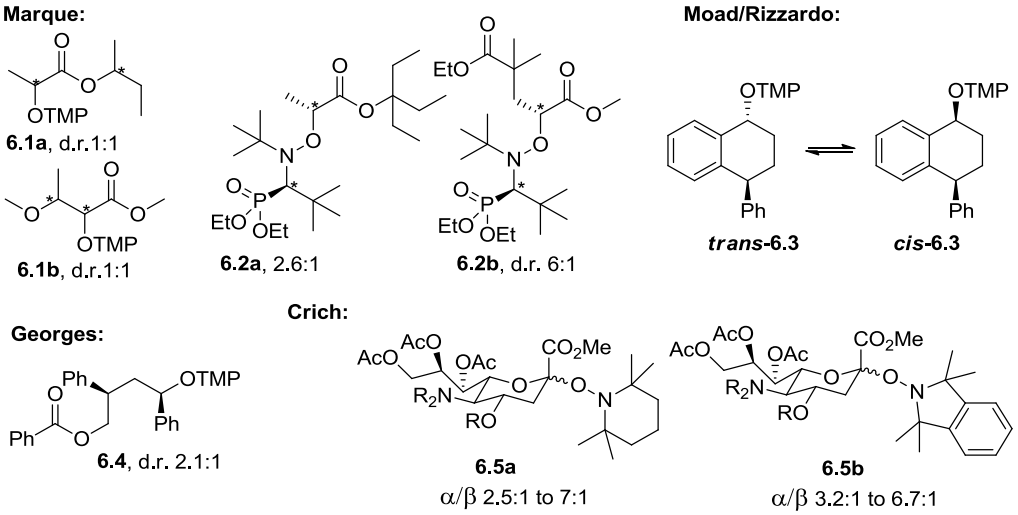


Figure 6.8. Diastereomeric alkoxyamines studied by other authors.

The significance of our system is that essentially complete preference for the *cis*-diastereomer is found under controlled conditions. In other words, the thermodynamic product is most probably not undergoing bond homolysis or its homolysis is 2-3 orders of magnitude slower compared to the homolysis of the *trans*-diastereomer, i.e. $k_{c(trans)} \geq k_{c(cis)} >> k_{d(trans)} >> k_{d(cis)}$ (Scheme 6.2). Assuming that the homolysis of the *cis*-diastereomer is negligible in the temperature range for isomerization studies (70-85 ºC), the rate determining step is the homolysis of ***trans*-6.6** to give transient DKP radical **6.7** and the persistent TEMPO radical.

The kinetic analysis of the mechanism depicted in Scheme 6.2, ignoring the dimerization pathways and assuming that homolysis of the *cis* diastereomer is negligible in the 70-85 °C temperature range, reveals interesting relationship between the k_{obs} and k_d.

$$Rate = -d[\boldsymbol{trans}\text{-}\mathbf{6.6}]/dt = d[\boldsymbol{cis}-\mathbf{6.6}]/dt = k_{c(cis)}[\mathbf{6.7}][\text{TEMPO}] \quad (1)$$

Applying steady state approximation (SSA) for [**6.7**]:

$$\frac{d\ \mathbf{6.7}}{dt} = k_{d\ trans}\ \ \boldsymbol{trans}\text{-}\mathbf{6.6} - k_{c\ trans}\ \ \mathbf{6.7}\ \ \text{TEMPO} - k_{c\ cis}\ \ \mathbf{6.7}\ \ \text{TEMPO} = 0 \quad (2)$$

From which $[\mathbf{6.7}][\text{TEMPO}] = \frac{k_{d(trans)}[\boldsymbol{trans}-\mathbf{6.6}]}{k_{c(trans)}+k_{c(cis)}}$ (3)

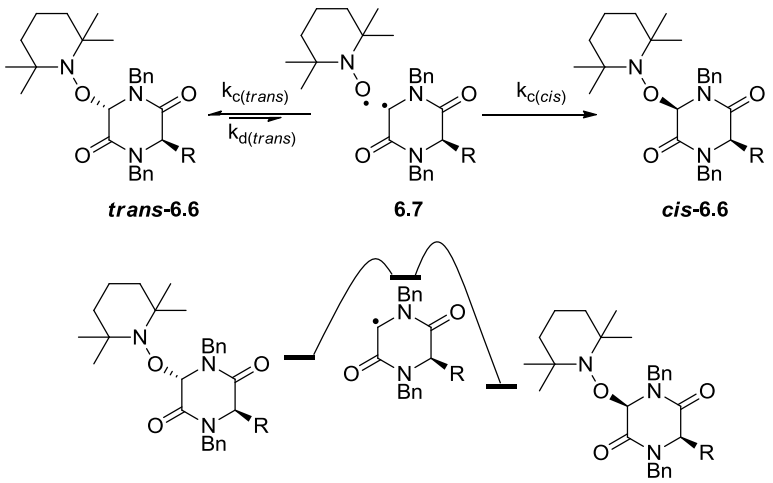
Inserting (3) into rate equation (1) gives:

$$\frac{d\ \boldsymbol{cis}-\mathbf{6.6}}{dt} = \frac{k_{d\ trans}\ k_{c\ cis}}{k_{c\ trans}+k_{c\ cis}}\ \ \boldsymbol{trans}\text{-}\mathbf{6.6} = k_{obs}\ \boldsymbol{trans}\text{-}\mathbf{6.6} \quad (4)$$

Where $k_{obs} = \frac{k_{\mathrm{d}\ trans}\ k_{\mathrm{c}\ cis}}{k_{\mathrm{c}\ trans} + k_{\mathrm{c}\ cis}}$ (5)

If $k_{\mathrm{c}\ trans} << k_{\mathrm{c}\ cis}$ then $k_{obs} \sim k_{\mathrm{d}\ trans}$ and if $k_{\mathrm{c}\ trans} \sim k_{\mathrm{c}\ cis}$ then $k_{\mathrm{d}\ trans} \sim 2k_{obs}$ Generally, if $k_{\mathrm{c}\ trans} = nk_{\mathrm{c}\ cis}$ then $k_{\mathrm{d}\ trans} \sim (n+1)k_{obs}$.

The faster isomerization of allyl-substituted alkoxyamine ***trans*-5.3a** compared to the benzyl-substituted alkoxyamine ***trans*-5.25** can not only be traced to the fact that $k_{\mathrm{d}(\textit{trans}\text{-}5.3)} > k_{\mathrm{d}(\textit{trans}\text{-}5.25)}$, but also because $k_{c(\textit{cis}\text{-}5.3)} > k_{c(\textit{cis}\text{-}5.25)}$. In the irreversible *cis*-coupling of TEMPO with the DKP radical intermediate **6.7**, TEMPO will couple faster when R = allyl than when R = benzyl because the allyl group is less bulky (Scheme 6.2).



Scheme 6.2. Mechanism of the thermal *trans-cis* isomerization and reaction diagram for homolysis and radical recombination of DKP-alkoxyamines.

6.2. Solid state and solution phase structural studies

Many of the DKP derived alkoxyamines are crystalline solids, which allowed to unambiguously prove their structures by X-ray crystallography when the separation of the diastereoisomers was possible (Figure 6.9). The X-ray structures for both ***cis*-5.3a** and ***trans*-5.3a** were determined by crystallization of pure samples. For the alkoxyamine **5.25** only the *cis*-diastereomer was characterized by X-ray crystallography. Additionally, X-ray structures for ***trans*-5.3c** and even the proline derived alkoxyamine ***trans*-3.11d** were obtained. An interesting feature common to all structures is that the TEMPO fragment always occupies a pseudoaxial position despite being a sterically demanding substituent (Figure 6.9). This observation prompts to propose an anomeric effect as an explanation of the observed tendency.

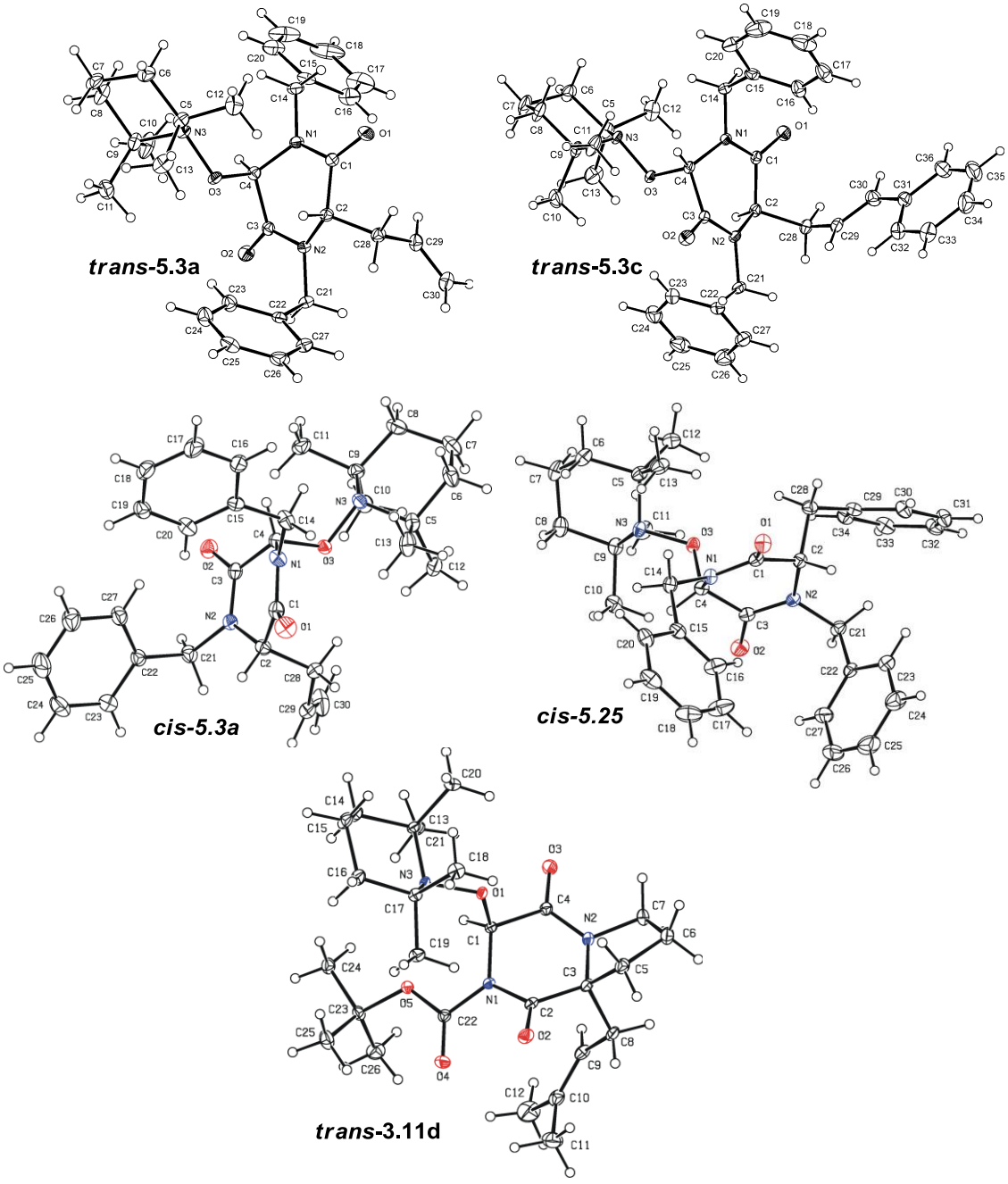


Figure 6.9. X-ray crystal structures of DKP-derived alkoxyamines ***trans*-5.3a**, ***cis*-5.3a**, ***cis*-5.25**, ***trans*-5.3c** and ***trans*-3.11d**. Thermal ellipsoids are drawn at the 30% probability level.

In ***trans*-5.3a** and ***trans*-5.3c**, the allyl and cinnamyl groups occupy a pseudoequatorial position, whereas the TEMPO fragment occupies the pseudoaxial position. In the X-ray structures of the ***cis*-5.3a** and ***cis*-5.25** both the TEMPO fragment and the allyl/benzyl groups at the α-position are in a pseudoaxial position and do not reveal special stabilizing interactions. This does not rule out the presence of stabilizing stereoelectronic

effects in the *cis*-configuration. For example, a relatively close C-H···O contact between the *O*-atom of TEMPO and the CH_2-groups of the substituents is present in both ***cis*-5.3a** and ***cis*-5.25**, with distances 2.45 and 2.67 Å, respectively. However, it is difficult to attribute these observations to unconventional C-H···O hydrogen bonding. Additionally, conformational steric strain might be the reason why the *trans*-diastereomers are less stable. This is supported by the fact that even a simple MM2 optimization suggests that the ***cis*-5.25** and ***cis*-5.3a** are more stable than ***trans*-5.25** and ***trans*-5.3a** by 5.2 kcal/mol and 9.1 kcal/mol, respectively. More detailed quantum-chemical calculations must help to understand the preference for the *cis*-configurations in the future.

To determine whether the pseudoaxial preference of the TEMPO fragment is also present in solution, NOE experiments were carried out with both ***cis*-5.3a**/***trans*-5.3a** and ***cis*-5.25**/***trans*-5.25** pairs (Figure 6.10). Indeed, strong NOE contacts can be seen between the TEMPO methyl groups and the CH_2-groups of the allyl and benzyl groups of ***cis*-5.3a** and ***trans*-5.25**, respectively. These observations suggest that even in the solution, the diaxial conformation seems to be strongly preferred for the *cis*-diastereomers.

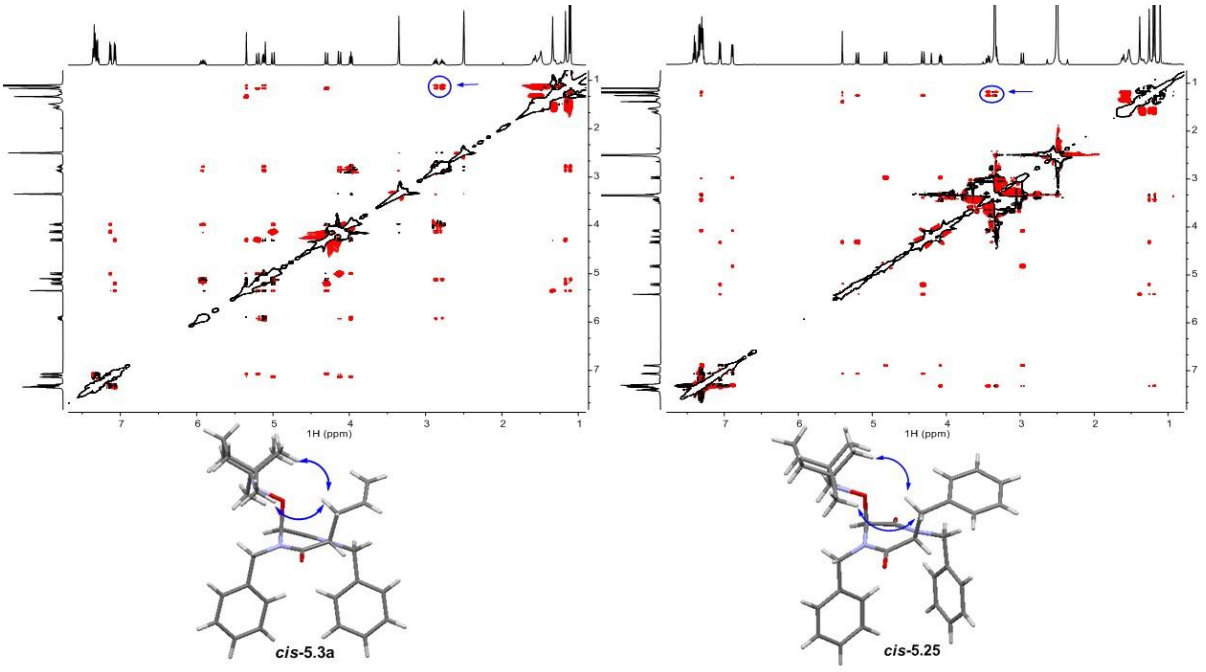


Figure 6.10. NOE contacts between CH_{3TEMPO} and CH_2R groups in ***cis*-5.3a** and ***cis*-5.25**.

In a solution of ***trans*-5.3a** in DMSO-d_6, a weak NOE contact between the TEMPO methyl groups and the nonamomeric αCH proton is observed (Figure 6.11). This observation goes along with the solid state structure in which the allyl group occupies a pseudoequatorial

position and the TEMPO fragment is in a pseudoaxial arrangement. However, no such NOE was observed in a solution of ***trans*-5.25**.

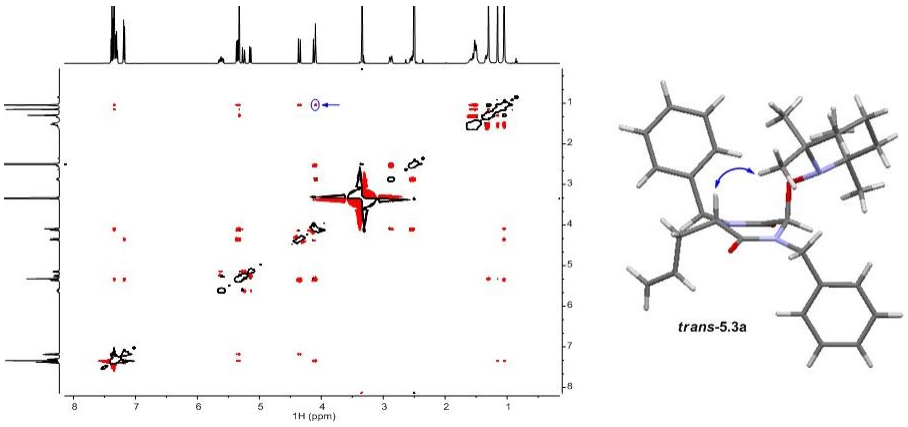
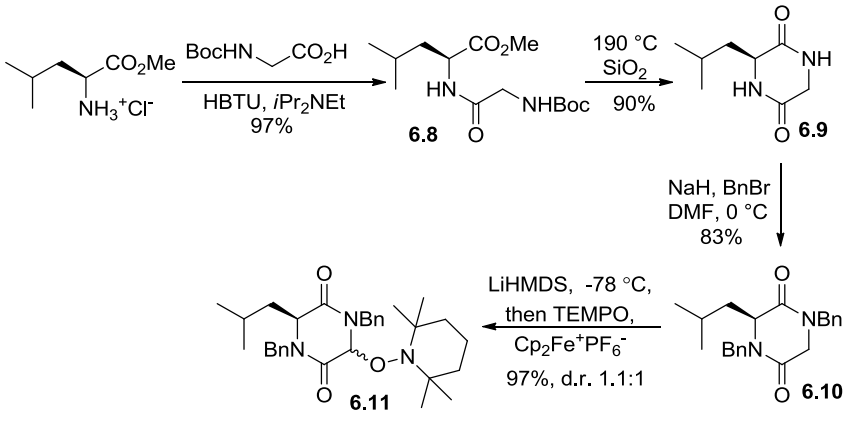


Figure 6.11. An NOE contact between the nonanomeric αCH proton and CH_{3TEMPO} in ***trans*-5.3a**.

An alkoxyamine **6.11** with an isobutyl side chain was synthesized for comparison from DKP **6.10** (Scheme 6.3). DKP **6.10** was synthesized from valine methyl ester hydrochloride by peptide coupling to Boc glycine and silica gel mediated thermal cyclization to DKP **6.9** followed by dibenzylation of nitrogen atoms. Under the standard oxidative alkoxyamination conditions, i.e. under kinetic conditions, an essentially 1:1 mixture of *cis*- and *trans*-diastereomers were formed.



Scheme 6.3. Synthesis of alkoxyamine **6.11** with an isobutyl side chain.

Upon heating a *t*BuOH solution of this diastereomeric mixture at 130 °C, a clean and quantitative conversion to a single diastereomer took place (Figure 6.12). The ^{1}H NMR signals of the thermodynamic product corresponded to the signals of the major component in the original 1.1:1 mixture.

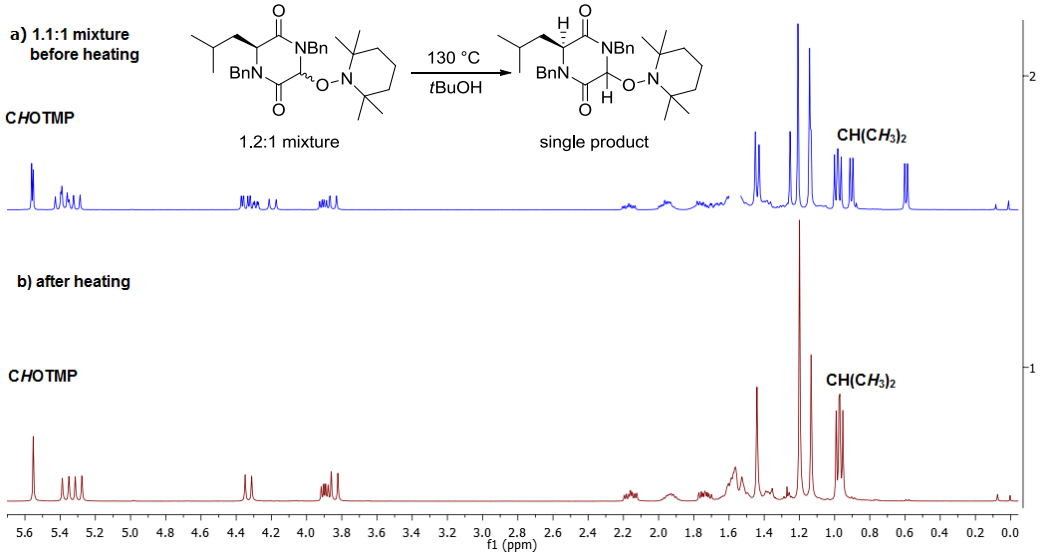


Figure 6.12. Comparison of the ^{1}H NMR spectrum of **6.10** before and after heating.

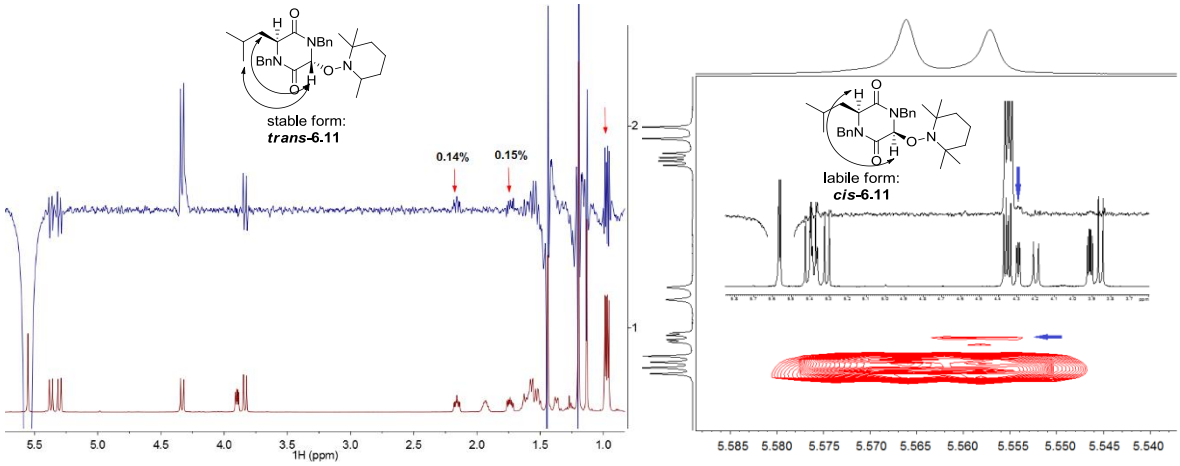


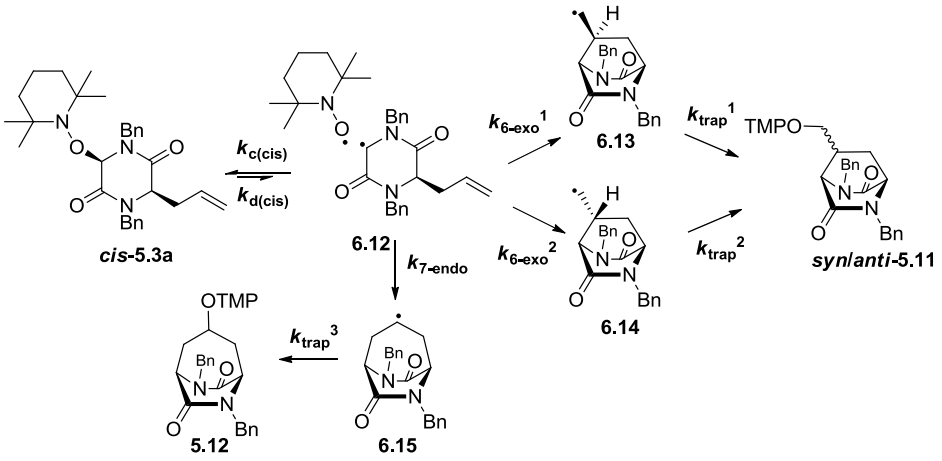
Figure 6.13. The NOE contacts observed in the stable and labile isomers of **6. 11**.

The product could not be crystallized and NOE-experiments were carried out to assign the configuration at the anomeric position of the thermodynamic product (Figure 6.13). Instead of NOE between the nonanomeric and anomeric αCH protons in the thermodynamic product, the presence of which would speak for *cis*-configuration, a weak but clearly visible NOE interaction between the anomeric αCH and the CH_2 protons of the isobutyl side-chain

was observed. This indicated that the thermodynamic product has the *trans*-configuration. When the NOE-experiments were done on the original 1.1:1 mixture, the labile component which underwent thermal isomerization showed an NOE between the two αCH hydrogen atoms. Thus, based on these evidences, a reversal of the thermodynamic stability from *cis*- to *trans*-diastereomer was found when the aliphatic isobutyl side chain was present in the DKP.

6.3. ^{1}H NMR monitoring of the PRE mediated cyclization

During the preparative synthesis at 130 °C, **5.3a** efficiently cyclizes to give an essentially a 1:1 mixture of inseparable ***syn*/*anti*-5.11** in 79% as a result of 6-exo-trig radical cyclization. In addition, the 7-endo-trig cyclization product **5.12** was also isolated in 10% yield (*cf* Chapter 5.1 and Scheme 6.4).



Scheme 6.4. A detailed mechanism of cycloisomerization of ***cis*-5.3a** to bridged DKPs ***syn*/*anti*-5.11** and **5.12**

Having proven that isomerization from *trans*- to *cis*-form occurs before radical cyclization, the cycloisomerization process was also monitored by heating a solution of pure ***cis*-5.3a** at 90 °C, 100 °C, 110 °C and 115 °C in DMSO-d_6 (Figure 6.14). A clean decay of the signals corresponding to ***cis*-5.3a** and appearance of signals corresponding to the cyclization products ***syn*/*anti*-5.11** and **5.12** was observed over time (Figures 6.14-6.15). The 6-exo-trig cyclization products **5.11** were not formed at equal rates and almost 2.3:1 mixture of *syn*/*anti*-products **5.11** was formed at 90 °C but the reaction was too slow and did not reach completion even after 5 h. Upon increasing the temperature, a small but measurable erosion of the diastereoselectivity was observed. At 100 °C, the ratio of the 6-exo-trig

cyclization products **5.11** at the end point was *ca* 2:1, at 110 °C, 1.9:1; and at 115 °C 1.7:1. It appears that increasing the temperature leads to $k_{6\text{-exo}}{}^{1} \sim k_{6\text{-exo}}{}^{2}$. The ratio of ***syn*/*anti*-5.11** products to 7-endo-trig product **5.12** was 8:1 and almost did not change with time, which virtually matches the isolated ratios.

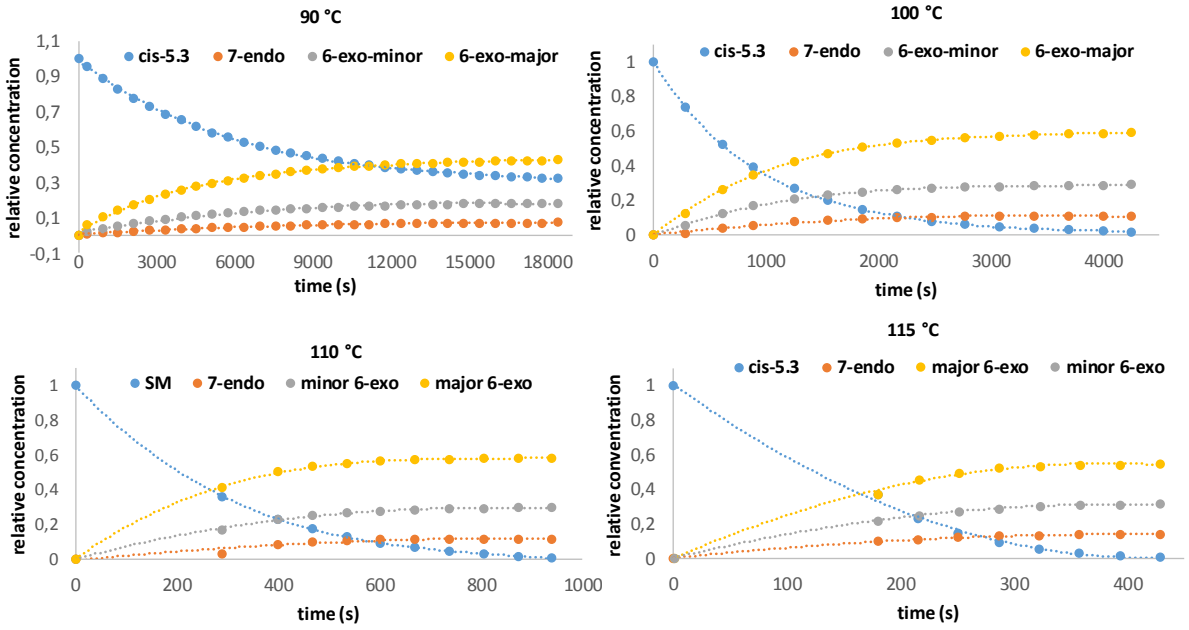


Figure 6.14. Kinetic traces for cycloisomerization of ***cis*-5.3** to bridged DKPs.

The rate constants for the consumption of ***cis*-5.3a** were 9.00×10^{-5} s^{-1}, 1.00×10^{-3} s^{-1}, 4.40×10^{-3} s^{-1} and 1.54×10^{-2} s^{-1} at 90 °C, 100 °C, 110 °C and 115 °C, respectively (Figures 6.14-6.15). A dramatic 11 times increase in conversion rate upon raising the temperature from 90 °C to 100 °C is indicative of a very slow homolytic cleavage of ***cis*-5.3a** at 90 °C, which is obviously the rate determining step of the cycloisomerization process. Hence, the rate constants obtained for the conversion of ***cis*-5.3a** can be used as an estimate for the k_d values for ***cis*-5.3a**. The activation parameters for the overall transformation were determined as: $\Delta H^{\ddagger}$ = 229.34 kJ/mol (54.87 kcal/mol) and $\Delta S^{\ddagger}$ = 308.36 J/(K*mol) (73.77 cal/(K*mol)), E_a = 232.46 kJ/mol (55.61 kcal/mol). The half-life of ***cis*-5.3a** is also significantly reduced upon increasing the temperature and at 115 °C it amounts less than a minute (Table 6.3).

The significant difference in the activation entropies $\Delta S^{\ddagger}$ of the *trans*/*cis* isomerization from ***trans*-5.3a** to ***cis*-5.3a** (10 cal/(K*mol)) compared to the cycloisomerization process of ***cis*-5.3a** to bridged DKPs **5.11**-**5.12** (73.77 cal/(K*mol)) is striking. Such a large difference can be rationalized by generation of a freely diffusing persistent and transient radicals so that

a radical cyclization can occur, whereas in the isomerization process a rapid rebound mechanism in the solvent cage may be largely operating. These data are consistent with the mechanism, that a slow homolysis followed by a rapid radical cyclization and a followed by fast radical trapping of the bicyclic radical intermediates.

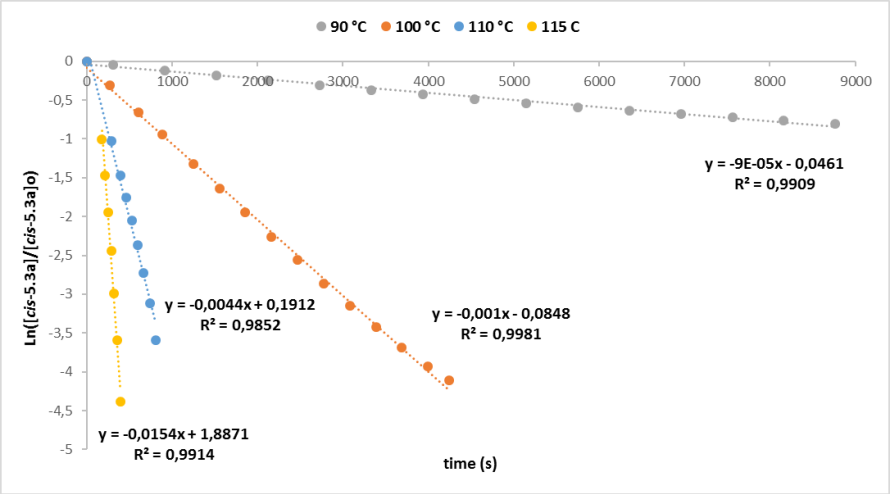


Figure 6.15. Kinetics of consumption of ***cis*-5.3a** at 90 °C, 100 °C, 110 °C and 115 °C.

Table 6.3. Kinetic data for the cycloisomerization of ***cis*-5.3a** to bridged DKPs **5.11-5.12**.

T (K)	k_{obs} (s^{-1})	$\Delta G^{\ddagger}$ (kcal/mol)	$t_{1/2}$ (min)
363.15	9.00×10^{-5}	28.10	128
373.15	1.00×10^{-3}	27.34	12
383.15	4.40×10^{-3}	26.60	2.6
388.15	1.54×10^{-2}	26.24	0.75

Because the cycloisomerization is a complex process with three competing cyclization pathways, extraction of the absolute rate constants for individual cyclization steps was not possible. A kinetic analysis of the mechanism depicted in Scheme 6.4 was attempted to find the rate laws for each pathway, which revealed interesting relationships between the rate constants of the elementary steps. The overall sum of the rates of competing cyclizations should equal the rate of consumption of ***cis*-5.3a**:

$$Rate = -\frac{d\ \textbf{\textit{cis}}\textbf{–5.3a}}{dt} = k_{\mathrm{d}\ cis}\ \ \textbf{\textit{cis}}\textbf{–5.3a}\ \ - k_{\mathrm{c}\ cis}\ \ \textbf{6.12}\ \ \mathrm{TEMPO} \qquad (6)$$

Applying SSA for the transient radical intermediate **6.12**:

$$\frac{d\ \mathbf{6.12}}{dt} = k_{\mathrm{d}\ cis}\ \ \boldsymbol{cis}\mathbf{-5.3a}\ - k_{\mathrm{c}\ cis}\ \ \mathbf{6.12}\ \ \mathrm{TEMPO}\ - k_{6-\mathrm{exo}^1}\ \mathbf{6.12}\ - k_{6-\mathrm{exo}^2}\ \mathbf{6.12}\ - k_{7-\mathrm{endo}}\ \mathbf{6.12}\ = 0 \quad (7)$$

From which the SSA concentration of **6.12** can be derived as

$$\mathbf{6.12}\ = \frac{k_{\mathrm{d}\ cis}\ \ \boldsymbol{cis}\mathbf{-5.3a}}{k_{\mathrm{c}\ cis}\ \ \mathrm{TEMPO}\ + k_{6-\mathrm{exo}^1} + k_{6-\mathrm{exo}^2} + k_{7-\mathrm{endo}}} = \frac{k_{\mathrm{d}\ cis}\ \ \boldsymbol{cis}\mathbf{-5.3a}}{k_{\mathrm{c}\ cis}\ \ \mathrm{TEMPO}\ + k_{cycl}} \quad (8)$$

Where $k_{cycl} = k_{6-\mathrm{exo}^1} + k_{6-\mathrm{exo}^2} + k_{7-\mathrm{endo}}$ is the sum of the rate constants for three competing cyclization pathways. Inserting the expression (8) into equation (6) gives:

$$\frac{d\ \boldsymbol{cis}\mathbf{-5.3a}}{dt} = \frac{k_{\mathrm{d}\ cis}\ k_{cycl}}{k_{\mathrm{c}\ cis}\ \ \mathrm{TEMPO}\ + k_{cycl}}\ \ \boldsymbol{cis} - \mathbf{5.3a}\ = -k_{obs}\ \boldsymbol{cis} - \mathbf{5.3a} \quad (9)$$

And the observed rate constant for conversion of ***cis*-5.3a** equals

$$k_{obs} = \frac{k_{\mathrm{d}\ cis}\ k_{cycl}}{k_{\mathrm{c}\ cis}\ \ \mathrm{TEMPO}\ + k_{cycl}} \quad (10)$$

Concentration of TEMPO has to be very small ($\leq 10^{-5}$ M) and constant for the PRE to be operative. This was shown both theoretically and experimentally by Fischer.[103] Because of this $k_{\mathrm{c}\ cis}\ \ \mathrm{TEMPO}\ \ll k_{cycl}$ and $\boldsymbol{k_{obs} \sim k_{\mathrm{d}\ cis}}$ which is in accordance with the mechanism that is proposed in Scheme 6.4.

The rate laws for the competing irreversible cyclization pathways can also be derived using the expression (8) obtained above:

$$\frac{d\ \boldsymbol{syn}\mathbf{-5.11}}{dt} = k_{6-\mathrm{exo}^1}\ \mathbf{6.12}\ = \frac{k_{6-\mathrm{exo}^1} k_{\mathrm{d}\ cis}\ \ \boldsymbol{cis}\mathbf{-5.3a}}{k_{\mathrm{c}\ cis}\ \ \mathrm{TEMPO}\ + k_{cycl}} \sim \frac{k_{6-\mathrm{exo}^1} k_{\mathrm{d}\ cis}\ \ \boldsymbol{cis}\mathbf{-5.3a}}{k_{cycl}} \quad (11)$$

$$\frac{d\ \boldsymbol{anti}\mathbf{-5.11}}{dt} = k_{6-\mathrm{exo}^2}\ \mathbf{6.12}\ \sim \frac{k_{6-\mathrm{exo}^2} k_{\mathrm{d}\ cis}\ \ \boldsymbol{cis}\mathbf{-5.3a}}{k_{cycl}} \quad (12)$$

$$\frac{d\ \mathbf{5.12}}{dt} = k_{7-\mathrm{endo}}\ \mathbf{6.12}\ \sim \frac{k_{7-\mathrm{endo}} k_{\mathrm{d}\ cis}\ \ \boldsymbol{cis}\mathbf{-5.3a}}{k_{cycl}} \quad (13)$$

In conclusion, from the available experimental data the absolute values for $k_{6\text{-exo}}{}^1$, $k_{6\text{-exo}}{}^2$ and $k_{7\text{-endo}}$ could not be extracted. In the future, experiments should be designed that can help measuring absolute rate constants for radical cyclizations taking advantage of the PRE using labile alkoxyamines. Currently used practical methods rely on competitive kinetic methods using Bu_3SnH and other reagents or using radical clocks.[104] The potential of using the PRE for kinetic purposes has been overlooked. This is mainly because all of the PRE

mediated cyclization reactions reported before required impractically long reaction times under the conventional heating conditions (10-24 h). Thus, the results described in this Chapter can be regarded as a groundwork towards such goals. Additionally, future work should also be directed towards applying the alkoxyamine isomerization reactions in the design of smart molecules.

7. Summary

A synthetic proposal towards bridged DKP alkaloids, which was based on limited knowledge led to the development of several methodologies along the way to achieve the initial goal. Almost every obstacle, which was encountered resulted in the development of practical solutions and new discoveries. Initial hurdles in the synthesis of simple DKP building blocks, because of the difficulty in reproducing reported methods, emerged into a new silica gel mediated DKP synthesis methodology. Moreover, this methodology was further applied to quinazoline alkaloids glyantrypine (**2.28b**) and potent anti-multidrug resistant agent ardeemin (**2.37**) by intramolecular double cyclization of anthranilate derived tripeptides **2.27b** and **2.33**. Iridium catalyzed reverse prenylation was used as the final step that mimics the final stage in the biosynthesis of ardeemin.

With an access to DKP building blocks secured, the oxidative cyclization proposal was probed. Studies on the initially proposed oxidative radical cyclization of monocyclic DKPs to bridged DKPs led to the discovery of a novel class of DKP alkoxyamines. This unprecedented class of alkoxyamines allowed developing a conceptually novel approach to diverse bridged DKP motives. The method takes advantage of the persistent radical effect and represents a green, tin-free radical cyclization approach using DKP alkoxyamines as radical surrogates. Both carbon and heteroatom bridged DKPs were synthesized. Various cyclization modes are possible in a controlled manner depending on the substitution pattern and tether lengths of the pendent alkene units. This method enables synthesis of the core structures of bridged DKP alkaloids and was applied to a formal synthesis of the antibiotic bicyclomycin (**1.4**). An advanced intermediate **5.49** from Williams' synthesis of bicyclomycin was accessed in 6 steps with an overall 38% yield. An unexpected enolate cyclization to an allene group was encountered giving unprecedented polycyclic motif such as **5.67**. This problem was overcome by carrying out the deprotonation under the internal quench conditions in the presence of TMSCl. The key steps in the developed approach to bicyclomycin are a radical cyclization to an allene group in **5.58** and a reductive allylic transposition of the internal double bond in bridged allylic alcohol **5.60**.

Considerable progress towards the total synthesis of asperparaline C has been made. The asymmetric approach to asperparaline C also relied on the PRE, wherein unstable quaternary DKP alkoxyamines were generated *in situ* at low temperatures and cyclized further to bridged DKPs by heating the reaction mixture. Importantly, these cyclizations were very efficient and diastereoselective. The diazabicyclo[2.2.2]octanes **4.16a-d** were obtained

in 5-10:1 diastereoselectivities from **4.15a-d**. The high diastereoselectivity is controlled by differential *syn*-pentane interactions in the transition state. The oxidative cyclizations did not lead to direct double cyclization and two approaches to achieve the second cyclization were evaluated. The first and unsuccessful zirconium mediated approach led to fast deoxygenation of substrate **4.16b** to **4.24** thus preventing further cyclization. The solution of the second cyclization was found by employing a reductive radical cyclization mediated by $Fe(acac)_3/PhSiH_3$. The cyclization was very efficient when an unsaturated ester **4.34** and butenolide derivatives **4.41-4.42** were used and unsuccessful when a maleic imide **4.44** was used. The cyclization of **4.34** was highly diastereoselective, but the spirocyclizations using butenolides **4.41** and **4.42** were less diastereoselective. Cyclization of **4.41** gave an inseparable mixture of spirocyclic lactones in 3:1 ratio on favor of the product having undesired configuration at the spiro center. Cyclization of **4.42** which was used as an inseparable 1:1 epimeric mixture was controlled by the methoxy group at the acetal center and gave 1:1 mixture of undesired and desired spiro-products. The undesired spiro product **4.47b** was successfully separated by repeated crystallization, which allowed obtaining almost pure samples of the desired spiro compound **4.47a**. Compound **4.47a** was converted to **4.49** in a one pot two-step transformation by methylamine opening of the lactone ring followed by oxidation of the intermediate hydroxylactam using PCC. Spiro succinimide **4.49** can be named as 8-oxoasperparaline C because it differs from asperparaline C only regarding the oxidation state of the C-8 atom. Initial experiments to chemoselectively reduce the C-8 amide group were not successful. 8-Oxoasperparaline C (**4.49**) was synthesized in 11 steps from *L*-proline in ca 15% overall yield.

Many of the bridged DKP products as well as DKP alkoxyamines were characterized by X-ray crystallography. It was found that the TEMPO unit shows preference for a pseudoaxial position in the solid state structures. The same seems to be true in the solution as supported by NOE analysis. An interesting *trans*- to *cis*- isomerization of DKP alkoxyamines was discovered during the studies. The kinetics of this isomerization was studied by ^{1}H NMR spectroscopic monitoring and the activation parameters as well as rate constants and half-lives of alkoxyamines ***trans*-5.3a** and ***trans*-5.25** were determined. The structures of the thermodynamically more stable alkoxyamines were unambiguously proven by X-ray crystallography. An isobutyl side chain containing alkoxyamine **6.11** was also synthesized and also underwent isomerization to a single diastereomer upon thermolysis of the 1:1 diastereomeric mixture. In this case, the alkoxyamines were not possible to crystallize and based on the NOE data, a reversal of thermodynamic preference took place. Finally, having

proven that a *trans*/*cis* isomerization occurs before the radical cyclization, kinetics of the cycloisomerization of ***cis*-5.3a** was also studied by ^{1}H NMR spectroscopic monitoring of cyclization. A weak but clear dependence of the diastereoselectivity of the 6-exo-trig cyclization was noticed. While it was possible to determine the rate of conversion of ***cis*-5.3a**, extraction of absolute rate constants for each competing cyclization pathways proved to be difficult.

8. Experimental part

8.1. General experimental conditions

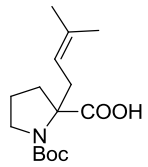
All reactions were conducted in flame or oven dried glassware under a nitrogen or argon atmosphere. Solvents and additives were dried prior to use according to standard procedures: THF, Et_2O and DME were freshly distilled over Na or K with Ph_2CO added. MeOH was dried with Mg, distilled and stored over 4Å molecular sieves. Toluene was freshly distilled with Na. CH_2Cl_2, *i*Pr_2NH, HMDS and HMPA were distilled from CaH_2 and kept over 4Å molecular sieves. *tert*-Butyl alcohol for thermal cyclizations was used as purchased from Sigma Aldrich. TLC plates POLYGRAM SIL G/UV254 (MachereyNagel) were used for monitoring reactions. Flash column chromatographic separations were performed on silica gel 60 (Fluka, 230-400 mesh). IR spectra were taken on a Bruker ALPHA FT-IR spectrometer as neat samples using an ATR device. ^1H and ^{13}C NMR spectra were recorded on Bruker Avance 500 and 400 at 500.0 and 400.1 MHz for ^1H NMR or 125.7 and 100.6 MHz for ^{13}C NMR, respectively. Proton chemical shifts are expressed in ppm (δ scale) downfield from tetramethylsilane and are referenced to this standard. Carbon chemical shifts are expressed in ppm (δ scale) downfield from tetramethylsilane and are referenced to carbon resonance of the NMR solvent ($CDCl_3$ 77.23, DMSO-d_6 39.52). Data are represented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, br = broad signal), coupling constants (*J*) in Hz, integration, assignment. The connectivity was determined by ^1H- ^1H COSY and HMBC experiments. Relative configurations were determined by NOE or NOESY experiments. ^{13}C NMR assignments were obtained from APT and HSQC experiments. EI mass spectra were recorded on a Waters GCT Premier spectrometer at 70 eV. ESI+ mass spectra were obtained on a Thermo Fisher Scientific LCQ Fleet spectrometer, sample concentration approx. 1 μg/mL, spray voltage pos. mode: 3.3 kV. HRMS spectra were measured on a Waters Q-Tof micro spectrometer, resolution: 100000. Combustion analyses were performed at the Microanalytical Laboratories of the IOCB ASCR Prague.

X-Ray crystallographic analyses were performed by Dr. Ivana Císařová at the Department of Inorganic Chemistry, Faculty of Science, Charles University in Prague. X-Ray crystallographic data are described separately in Appendix A.

Synthesis and characterization of compounds **2.19**, **2.23**, **5.2a-f**, **5.3a-f**, **5.4-5.12**, ***syn*/*anti*-5.13ab-5.14ab**, ***syn*/*anti*-5.15**, **5.16**, ***syn*/*anti*-5.17ab-5.18ab**, **5.19**, **5.20**, **5.21ab**, **5.22-5.23**, **5.26**, **5.32a-d**, **5.34a-c**, **5.35a-f**, **5.36a-d**, **5.37a-b**, **5.38-5.40**, **5.44-5.47**, **5.49** and **5.56-5.60** were published and are not repeated here.[105]

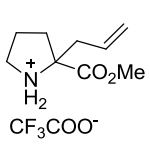
8.2. Procedures and analytical data

1-(*tert*-Butoxycarbonyl)-2-(3-methylbut-2-en-1-yl)pyrrolidine-2-carboxylic acid (2.6):



NaOH (24 mL, 45.7 mmol, 2 M) was added to a solution of **2.5**[47c] (1.50 g, 5.05 mmol) in MeOH (24 mL) and the reaction mixture was stirred at 80 °C for 3.5 h. It was quenched with water (20 mL) and extracted with Et_2O. Citric acid (50 mL, 20% solution) was added to the aqueous layer and extraction with Et_2O was repeated three times. The combined organic layers were washed with water, dried over $MgSO_4$, filtered and evaporated to give 1.37 g (96%) **2.6** as a colorless solid, as a 1.5:1 rotameric mixture. **m.p.** 110-111 °C; $\mathbf{R_f}$ = 0.5 (CH_2Cl_2/MeOH, 10:1); **IR**: ν[cm^{-1}] 3500-2500 (br.), 2974, 2928, 2878, 1737, 1697, 1447, 1389, 1164, 1135, 852, 771, 731; **MS ESI+ *m/z*, (%)**: 328 (51), 306 (100, $[M+Na]^+$), 250 (35, [M+Na-isobutylene]$^+$), 228 (9, [M+H-isobutylene]$^+$), 206 (52, [M+Na-isobutylene-CO_2]$^+$); **HRMS ESI+ *m/z***: ($[M+Na]^+$): Calcd. for $C_{15}H_{25}NO_4Na$: 306.1681; Found: 306.1674; **Anal. Calcd. for** $C_{15}H_{25}NO_4$ (283.37): C, 63.58; H, 8.89; N, 4.94; Found: C, 63.76; H, 8.93; N, 4.72; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 1.41 (s, 3.6H, $C(CH_3)_3$), 1.47 (s, 5.4H, $C(CH_3)_3$), 1.63 (s, 3H, $=CCH_3$), 1.71 (s, 3H, $=CCH_3$), 1.71-1.82 (m, 2H, $NCH_2C\underline{H}_2CH_2$), 1.79-1.96 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 1.98-2.19 (m, 0.5H, $NCH_2CH_2C\underline{H}_2$), 2.49-2.58 (m, 0.5H, $NCH_2CH_2C\underline{H}_2$), 2.57-2.66 (m, 0.4H, $C\underline{H}_2CH=$), 2.66-2.86 (m, 1.6H, $C\underline{H}_2CH=$), 3.22-3.41 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.44-3.57 (m, 0.6H, $NC\underline{H}_2CH_2CH_2$), 3.64-3.75 (m, 0.4H, $NC\underline{H}_2CH_2CH_2$), 4.96 (t, J = 7.3 Hz, 0.6H, $CH_2C\underline{H}=$), 5.07 (t, J = 6.8 Hz, 0.4H, $CH_2C\underline{H}=$), 10.75 (br. s, 1H, $COO\underline{H}$); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 18.3 (q, $=C\underline{C}H_3$), 22.9 (t, $NCH_2\underline{C}H_2CH_2$), 26.3 (q, $=C\underline{C}H_3$), 28.55/28.61 (q, $C(\underline{C}H_3)_3$), 32.7/33.2 (t, $\underline{C}H_2CH=$), 34.9/37.4 (t, $NCH_2CH_2\underline{C}H_2$), 48.8/49.7 (t, $N\underline{C}H_2CH_2CH_2$), 67.9/70.5 (s, C_{Pro}), 80.7/82.0 (s, $\underline{C}(CH_3)_3$), 117.5/118.8 (d, $CH_2\underline{C}H=$), 135.4/136.4 (s, $=\underline{C}(CH_3)_2$), 157.1 (s, $C=O_{Boc}$), 175.7/181.0 (s, $\underline{C}OOH$).

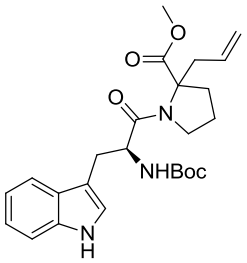
2-Allyl-2-(methoxycarbonyl)pyrrolidin-1-ium 2,2,2-trifluoroacetate (2.8):



Trifluoroacetic acid (4.6 mL, 62 mmol) was added to a solution of **2.7**[106] (1.66 g, 6.2 mmol) in CH_2Cl_2 (9 mL) and the reaction mixture was stirred until TLC indicated complete consumption of the starting material (ca 1.5 h). The reaction mixture was evaporated and the resulting oil was suspended in a 3:1 hexane/Et_2O mixture (7 mL) and shaken (or sonicated). The solvents were separated from the oil by decantation. After repeating this operation a few times, the oil solidified to a colorless powder, which was washed one more time with a 3:1 hexane/Et_2O mixture and dried to give

1.44 g of product. The combined hexane/Et_2O washings were evaporated and additional 225 mg of product was obtained by an analogous operation. The total yield was 1.67 g (95%). **m.p.** 87-88 °C; **IR**: ν[cm^{-1}] 3100-2200 (br.), 1750, 1672, 1591, 1422, 1227, 1184, 1166, 1121, 1035, 1001, 933, 828, 797, 718, 683; **MS ESI+ *m/z*, (%)**: 170 (100, $[M+H\text{-}TFA]^+$), 128 (5, $[M+H\text{-propene-}TFA]^+$); **HRMS ESI+ *m/z***: Calcd. for $C_9H_{16}NO_2^+$: 170.1176; Found: 170.1175; **Anal. Calcd. for** $C_{11}H_{16}F_3NO_4$ (283.25): C, 46.65; H, 5.69; N, 4.95; Found: C, 46.40; H, 5.59; N, 4.76; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 1.86-2.03 (m, 1H, $NCH_2C\underline{H}_2CH_2$), 2.07-2.21 (m, 2H, $NCH_2C\underline{H}_2C\underline{H}_2$), 2.38-2.50 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 2.71-2.91 (m, 2H, $C\underline{H}_2CH$=), 3.38-3.58 (m, 2H, $NC\underline{H}_2CH_2CH_2$), 3.81 (s, 3H, OCH_3), 5.13-5.27 (m, 2H, $=CH_2$), 5.72 (ddt, *J* = 17.3, 10.1, 7.3 Hz, 1H, $CH_2C\underline{H}$=), 9.95 (br. s, 2H, NH_2^+); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 22.8 (t, $NCH_2\underline{C}H_2CH_2$), 32.4 (t, $NCH_2CH_2\underline{C}H_2$), 39.5 (t, $\underline{C}H_2CH$=), 45.7 (t, $N\underline{C}H_2CH_2CH_2$), 53.7 (q, OCH_3), 72.7 (s, C_{Pro}), 121.5 (t, $=CH_2$), 130.2 (d, $CH_2\underline{C}H$=), 162.5 (q, $J_{C\text{-}F}$ = 35.1 Hz, $CF_3\underline{C}OO^-$), 170.6 (s, $\underline{C}OOCH_3$). The CF_3 group can't be seen.

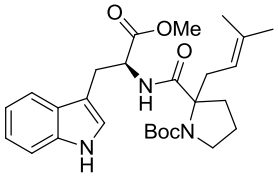
Methyl 2-allyl-1-((*S*)-2-((*tert*-butoxycarbonyl)amino)-3-(1*H*-indol-3-yl)propanoyl)pyrrolidine-2-carboxylate (2.12):



Ethyldiisopropylamine (1.04 mL, 6 mmol) was added dropwise to a suspension of TFA salt **2.8** (500 mg, 1.77 mmol), N_α-Boc-*L*-tryptophane (512 mg, 1.68 mmol) and HBTU (828 mg, 2.18 mmol) in dry CH_2Cl_2 (9 mL) under Ar at r.t. and the reaction mixture was stirred for 24 h. The reaction mixture was washed with saturated NH_4Cl solution and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was adsorbed at silica gel and purified by flash chromatography (hexane/EtOAc, 3:1 gradient to 1:1) to give 670 mg (88%) **2.12** as an inseparable 1:1 mixture of diastereomers, as colorless foam. Because of complex ^{1}H and ^{13}C NMR of the diastereomeric and rotameric mixture, only the diastereomer, which crystallized, was characterized by ^{13}C NMR. **m. p.** 165-167 °C; **R_f** = 0.3 (hexane/EtOAc, 1:1); **IR**: ν[cm^{-1}] 3335, 2978, 1738, 1703, 1638, 1499, 1436, 1366, 1339, 1268, 1245, 1211, 1167, 1124, 1011, 914, 740; **MS ESI+ *m/z*, (%)**: 933 (15, $[2M+Na]^+$), 575 (6), 515 (6), 478 (77, $[M+Na]^+$), 456 (100, $[M+H]^+$), 400 (5, $[M+H\text{-isobutylene}]^+$); **HRMS ESI+ *m/z***: ($[M+H]^+$): Calcd. for $C_{25}H_{34}O_5N_3$: 456.2493; Found: 456.2493; **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 23.8/23.9 (t, $NCH_2\underline{C}H_2CH_2$), 28.3/29.4 (t, $ArCH_2$), 28.49/28.52 (q, $C(\underline{C}H_3)_3$), 34.9/35.3 (t, $NCH_2CH_2\underline{C}H_2$), 37.85/37.93 (t, $\underline{C}H_2CH$=), 48.7/48.9 (t, $N\underline{C}H_2CH_2CH_2$), 52.4 (q, 2C, OCH_3),

52.7/52.8 (d, αCH), 68.4/68.6 (s, C_{Pro}), 79.7/79.8 (s, $\underline{C}(CH_3)_3$), 110.5/110.7 (s, $C_{ind\text{-}3}$), 111.3 (d, 2C, CH_{Ar}), 118.80/119.0 (d, CH_{Ar}), 118.84/119.3 (t, $=CH_2$), 119.7/119.8 (d, CH_{Ar}), 122.1/122.2 (d, CH_{Ar}), 123.2/123.6 (d, CH_{Ar}), 127.8/127.9 (s, C_{Ar}), 133.4/133.5 (d, $CH_2\underline{C}H=$), 136.3/136.4 (s, $\underline{C}_{Ar}NH$), 155.57/155.64 (s, $C=O_{Boc}$), 170.87/171.00 (s, C=O), 174.12/174.14 (s, $\underline{C}O_2Me$).

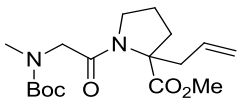
***1-(tert*-Butyloxycarbonyl)-*N*-(((*S*)-3-(1*H*-indol-3-yl)-1-methoxy-1-oxopropan-2-yl)-2-(3-methylbut-2-en-1-yl)pyrrolidine-2-carboxamide (2.14):**



Ethyldiisopropylamine (1.25 mL, 7.2 mmol) was added dropwise to a suspension of carboxylic acid **2.6** (500 mg, 1.764 mmol), *L*-Trp-OMe*HCl (472 mg, 1.853 mmol) and HBTU (800 mg, 2.3 mmol) in dry CH_2Cl_2 (5 mL) under Ar at r.t. and the reaction mixture was stirred for 24 h. The reaction mixture was washed with saturated NH_4Cl solution and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was adsorbed at silica gel and purified by flash chromatography (hexane/EtOAc, 3:1) to give 710 mg (83%) **2.14** as an inseparable 1:1 mixture of diastereomers, as a colorless foam which converts to a colorless gum while standing under air in an open flask. $\mathbf{R_f}$ = 0.5 (hexane/EtOAc, 1:1); **IR**: ν[cm^{-1}] 3318, 2974, 2931, 2878, 1743, 1669, 1505, 1456, 1437, 1389, 1366, 1251, 1208, 1166, 1134, 1105, 1010, 918, 852, 739; **MS ESI+ *m/z*, (%)**: 989 (8, $[2M+Na]^+$), 542 (8), 506 (23, $[M+Na]^+$), 484 (100, $[M+H]^+$), 432 (11, [M+Na–isobutylene–$H_2O]^+$), 288 (6); **HRMS ESI+ *m/z***: ($[M+H]^+$): Calcd. for $C_{27}H_{38}N_3O_5$: 484.2811; Found: 484.2812; **^{1}H NMR (400 MHz, 80 °C, DMSO-d_6)**: δ = 1.31 (s, 9H, $C(CH_3)_3$), 1.34 (s, 9H, $C(CH_3)_3$), 1.43-1.51 (m, 1H, $NCH_2C\underline{H}_2CH_2$), 1.52-1.71 (m, 5H, $NCH_2C\underline{H}_2C\underline{H}_2$), 1.59 (s, 6H, $=CCH_3$), 1.67 (s, 6H, $=CCH_3$), 1.74-1.86 (m, 2H, $NCH_2CH_2C\underline{H}_2$), 1.87-2.09 (m, 2H, NH_{amide}), 2.55-2.64 (m, 2H, $C\underline{H}_2CH=$), 2.67-2.78 (m, 2H, $C\underline{H}_2CH=$), 3.03-3.27 (m, 6H, $ArCH_2$, $NC\underline{H}_2CH_2CH_2$), 3.38-3.52 (m, 2H, $NC\underline{H}_2CH_2CH_2$), 3.48 (s, 3H, OCH_3), 3.60 (s, 3H, OCH_3), 4.56-4.67 (m, 2H, αCH), 4.90-4.99 (m, 2H, $CH_2C\underline{H}=$), 6.96-7.02 (m, 2H, CH_{Ar}), 7.04-7.08 (m, 2H, CH_{Ar}), 7.08-7.13 (m, 2H, CH_{Ar}), 7.32-7.37 (m, 2H, CH_{Ar}), 7.47-7.53 (m, 2H, CH_{Ar}), 10.65 (s, 1H, NH_{ind}), 10.68 (s, 1H, NH_{ind}); **^{13}C NMR (126 MHz, 80 °C, DMSO-d_6)**: δ = 17.5 (q, 2C, $=C\underline{C}H_3$), 21.2 (t, $NCH_2\underline{C}H_2CH_2$), 21.3 (t, $NCH_2\underline{C}H_2CH_2$), 25.4 (q, 2C, $=C\underline{C}H_3$), 26.7 (t, $ArCH_2$), 26.8 (t, $ArCH_2$), 27.6 (q, $C(\underline{C}H_3)_3$), 27.7 (q, $C(\underline{C}H_3)_3$), 32.1 (t, 2C, $\underline{C}H_2CH=$ as determined by HSQC, since the resonance is not visible at 80 °C), 35.6 (t, 2C, $NCH_2CH_2\underline{C}H_2$ s determined by HSQC, since the resonance is not visible at 80 °C), 48.30 (t, $N\underline{C}H_2CH_2CH_2$), 48.33 (t, $N\underline{C}H_2CH_2CH_2$), 51.2 (q, OCH_3), 51.3 (q, OCH_3), 52.8 (d, αCH),

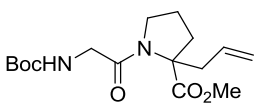
52.9 (d, αCH), 78.5 (s, <u>C</u>$(CH_3)_3$), 78.6 (s, <u>C</u>$(CH_3)_3$), 109.0 (s, $C_{ind\text{-}3}$), 109.1 (s, $C_{ind\text{-}3}$), 111.0 (d, CH_{Ar}), 111.1 (d, CH_{Ar}), 117.46 (d, CH_{Ar}), 117.54 (d, CH_{Ar}), 118.0 (d, CH_{Ar}), 118.1 (d, CH_{Ar}), 118.70 (d, CH_2<u>C</u>H=), 118.74 (d, CH_2<u>C</u>H=), 120.60 (d, CH_{Ar}), 120.64 (d, CH_{Ar}), 123.2 (d, 2C, CH_{Ar}), 126.9 (s, C_{Ar}), 127.0 (s, C_{Ar}), 133.4 (s, <u>C</u>$_{Ar}$NH), 133.5 (s, <u>C</u>$_{Ar}$NH), 135.97 (s, =<u>C</u>$(CH_3)_2$), 135.99 (s, =<u>C</u>$(CH_3)_2$), 171.7 (s, 2C, <u>C</u>O_2Me). CONH and C=O_{Boc} are not visible at 80 °C.

Methyl 2-allyl-1-(2-((*tert*-butoxycarbonyl)(methyl)amino)acetyl)pyrrolidine-2-carboxylate (2.16a):



Ethyldiisopropylamine (2.1 mL, 12.0 mmol) was added dropwise to a suspension of *N*-Boc-sarcosine (645 mg, 3.41 mmol), TFA salt **2.8** (840 mg, 2.97 mmol) and HBTU (1.50 g, 3.86 mmol) in dry CH_2Cl_2 (15 mL) under Ar at r.t. and the reaction mixture was stirred for 24 h. It was quenched with saturated NH_4Cl solution and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was adsorbed at silica gel and purified by flash chromatography (hexane/AcOEt 2:1, gradient to 1:1) to give 1.01 g (99%) dipeptide **2.16a** as a colorless oil as a 3:1 rotameric mixture. $\mathbf{R_f}$ = 0.3 (hexane/AcOEt, 1:1); **IR**: ν[cm^{-1}] 2975, 1738, 1697, 1660, 1419, 1390, 1365, 1240, 1167, 889; **MS ESI+ *m/z*, (%)**: 400 (12), 379 (21, $[M+K]^+$), 363 (67, $[M+Na]^+$), 341 (25, $[M+H]^+$), 285 (18, [M+H-isobutylene]$^+$), 241 (100, [M+H-isobutylene-CO_2]$^+$); **HRMS ESI+ *m/z***: ($[M+H]^+$): Calcd. for $C_{17}H_{29}N_2O$: 341.2076; Found: 341.2071; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 1.43/1.44 (s, 9H, $C(CH_3)_3$), 1.88–2.11 (m, 4H, $NCH_2C\underline{H}_2C\underline{H}_2$), 2.61 (dd, *J* = 14.1, 8.1 Hz, 1H, $C\underline{H}_2CH$=), 2.90 (s, 3H, NCH_3), 3.09-3.22 (m, 1H, $C\underline{H}_2CH$=), 3.42 (td, *J* = 14.1, 7.4 Hz, 1H, $NC\underline{H}_2CH_2CH_2$), 3.55-3.65 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.68 (s, 3H, OCH_3), 3.86-3.90 (m, 1.5H, NCH_2CO), 4.05-4.13 (m, 0.5H, NCH_2CO), 5.04-5.15 (m, 2H, $=CH_2$), 5.68 (m, 1H, $CH_2C\underline{H}$=); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 24.1 (t, $NCH_2\underline{C}H_2CH_2$), 28.5 (q, $C(\underline{C}H_3)_3$), 35.1 (t, $NCH_2CH_2\underline{C}H_2$), 35.7 (q, NCH_3), 38.0 (t, $\underline{C}H_2CH$=), 48.0/48.1 (t, $N\underline{C}H_2CH_2CH_2$), 51.3/52.0 (t, $N\underline{C}H_2C$=O), 52.5 (q, OCH_3), 68.9 (s, C_{Pro}), 80.0 (s, $\underline{C}(CH_3)_3$), 119.3 (t, $=CH_2$), 133.6 (d, $CH_2\underline{C}H$=), 156.3 (s, C=O), 167.6 (s, C=O), 174.3 (s, $\underline{C}O_2$Me).

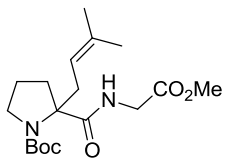
Methyl 2-allyl-1-((*tert*-butoxycarbonyl)glycyl)pyrrolidine-2-carboxylate (2.16b):



Ethyldiisopropylamine (3.51 mL, 20.1 mmol) was added dropwise to a suspension of *N*-Boc glycine (1.53 g, 8.72 mmol), TFA salt **2.8** (1.90 g, 6.71 mmol) and HBTU (3.31 g, 8.72 mmol) in dry CH_2Cl_2 (15 mL) under Ar at r.t. and the reaction mixture was stirred for 24 h. It was quenched with saturated NH_4Cl solution and

extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was adsorbed at silica gel and purified by flash chromatography (hexane/AcOEt 2:1, gradient to 1:1) to give 2.1 g (96%) dipeptide **2.16b** as a colorless oil. $\mathbf{R_f}$ = 0.3 (hexane/AcOEt, 1:1); **IR**: ν[cm^{-1}] 3426, 2986, 1743, 1718, 1658, 1504, 1433, 1370, 1247, 1217, 1166, 1125, 1054, 1027, 1006, 921, 869, 782, 744, 682, 588, 560; **MS ESI+ *m/z*, (%)**: 773 (3), 675 (100, $[2M+Na]^+$), 653 (3, $[2M+H]^+$), 349 (69, $[M+Na]^+$), 327 (9, $[M+H]^+$), 271 (4, [M+H-isobutylene]$^+$); **HRMS ESI+ *m/z***: ($[M+Na]^+$): Calcd. for $C_{16}H_{26}O_5N_2Na$: 349.1734; Found: 349.1735; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 1.42 (s, 9H, $C(CH_3)_3$), 1.89-2.14 (m, 4H, $NCH_2C\underline{H}_2C\underline{H}_2$), 2.63 (dd, *J* = 14.1, 8.0 Hz, 1H, $C\underline{H}_2CH$=), 3.13 (ddd, *J* = 14.3, 6.7, 1.7 Hz, 1H, $C\underline{H}_2CH$=), 3.35-3.45 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.54-3.64 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.70 (s, 3H, OCH_3), 3.89 (d, *J* = 3.6 Hz, 2H, $NHC\underline{H}_2$), 5.05-5.14 (m, 2H, $=CH_2$), 5.43 (br. s, 1H, NH), 5.57-5.71 (m, 1H, $CH_2C\underline{H}$=); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 23.9 (t, $NCH_2\underline{C}H_2CH_2$), 28.5 (q, $C(\underline{C}H_3)_3$), 35.2 (t, $NCH_2CH_2\underline{C}H_2$), 37.9 (t, $\underline{C}H_2CH$=), 43.5 (t, $NHCH_2$), 47.8 (t, $N\underline{C}H_2CH_2CH_2$), 52.7 (q, OCH_3), 69.0 (s, C_{Pro}), 79.7 (s, $\underline{C}(CH_3)_3$), 119.6 (t, $=CH_2$), 133.1 (d, $CH_2\underline{C}H$=), 155.9 (s, $C{=}O_{Boc}$), 167.1 ($N_{Pro}C{=}O$), 174.0 (s, $\underline{C}O_2Me$).

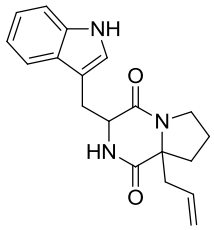
***1-(tert*-Butyloxycarbonyl)-*N*-(2-methoxy-2-oxoethyl)-2-(3-methylbut-2-en-1-yl)pyrrolidine-2-carboxamide (2.18):**



Ethyldiisopropylamine (1.6 mL, 9.24 mmol) was added dropwise to a suspension of GlyOMe*HCl (350 mg, 2.77 mmol), carboxylic acid **2.6** (655 mg, 2.31 mmol) and HBTU (1.14 g, 3.00 mmol) in dry CH_2Cl_2 (13 mL) under Ar at r.t. and the reaction mixture was stirred for 24 h. It was quenched with saturated NH_4Cl solution and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was adsorbed at silica gel and purified by flash chromatography (hexane/AcOEt, 3:1, gradient to 1:1) to give 796 mg (97%) dipeptide **2.18** as a colorless solid. **m.p.** 86-88 °C; $\mathbf{R_f}$ = 0.3 (hexane/AcOEt, 1:1); **IR**: ν[cm^{-1}] 3100, 2920, 2851, 1748, 1664, 1445, 1241, 1228, 1199, 1127, 1075, 861, 820, 781, 739, 677, 558, 531; **MS ESI+ *m/z*, (%)**: 377 (45, $[M+Na]^+$), 355 (29, $[M+H]^+$), 299 (23, [M+H-isobutylene]$^+$), 255 (100, [M+H–isobutylene–CO_2]$^+$); **HRMS ESI+ *m/z***: ($[M+H]^+$): Calcd. for $C_{18}H_{31}N_2O_5$: 355.2223; Found: 355.2226; **Anal. Calcd. for** $C_{18}H_{30}N_2O_5$ (354.45): C, 61.00; H, 8.53; N, 7.90; Found: C, 61.25; H, 8.64; N, 7.83; **^{1}H NMR (400 MHz, DMSO-d_6, <u>120 °C</u>)**: δ = 1.40 (s, 9H, $C(CH_3)_3$), 1.63 (s, 3H, $=CCH_3$), 1.71 (s, 3H, $=CCH_3$), 1.68-1.82 (m, 2H, $NCH_2C\underline{H}_2CH_2$), 1.93 (ddd, *J* = 12.7, 8.5, 7.8 Hz, 1H,

$NCH_2CH_2C\underline{H}_2$), 2.11 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 2.64 (dd, *J* = 14.8, 7.9 Hz, 1H, $C\underline{H}_2CH$=), 2.80 (dd, *J* = 14.6, 6.4 Hz, 1H, $C\underline{H}_2CH$=), 3.27 (dt, *J* = 10.4, 7.7 Hz, 1H, $NC\underline{H}_2CH_2CH_2$), 3.56-3.61 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.65 (s, 3H, OCH_3), 3.81 (dd, *J* = 17.1, 5.7 Hz, 1H, $NHC\underline{H}_2$), 3.90 (dd, *J* = 17.1, 5.9 Hz, 1H, $NHC\underline{H}_2$), 5.02-5.07 (m, 1H, $CH_2C\underline{H}$=), 7.54 (br. s, 1H, NH); **^{13}C NMR (101 MHz, DMSO-d$_6$, 120 °C)**: δ = 17.2 (q, =$C\underline{C}H_3$), 21.1 (t, $NCH_2\underline{C}H_2CH_2$), 25.1 (q, =$C\underline{C}H_3$), 27.5 (q, $C(\underline{C}H_3)_3$), 31.8 (t, $\underline{C}H_2CH$=), 35.9 (t, $NCH_2CH_2\underline{C}H_2$), 40.6 (t, $NHCH_2$), 48.0 (t, $N\underline{C}H_2CH_2CH_2$), 50.7 (q, OCH_3), 68.1 (s, C_{Pro}), 78.3 (s, $\underline{C}(CH_3)_3$), 118.8 (d, $CH_2\underline{C}H$=), 133.0 (s, =$\underline{C}(CH_3)_2$), 152.6 (s, C=O_{Boc}), 169.5 (s, NHC=O), 173.8 (s, $\underline{C}O_2Me$).

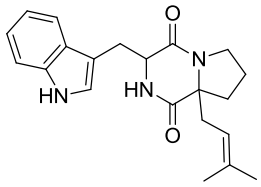
3-((1*H*-Indol-3-yl)methyl)-8a-allylhexahydropyrrolo[1,2-a]pyrazine-1,4-dione (**2.20):**



Dipeptide **2.12** (140 mg, 0.31 mmol) was dissolved in CH_2Cl_2 (5 mL) and silica gel (300 mg) was added. The suspension was evaporated to dryness and heated with vigorous stirring under Ar at 190 °C for 1 h. The solid reaction mixture was transferred to a short packed silica gel column and the product was eluted with 100% AcOEt to give 41 mg less polar *trans*-diastereomer, 26 mg more polar *cis*-diastereomer and 32 mg mixture of two diastereomers. The overall yield and d.r. were 99 mg (99%) and 1:1, respectively. **m.p. (*trans*)** 173-175 ºC (dec.); **R_f(*trans*)** = 0.2; **R_f(*cis*)** = 0.1 (AcOEt); **IR**: ν[cm^{-1}] 3258, 2926, 1669, 1638, 1455, 1334, 1102, 923, 801, 742; **MS ESI+ *m/z*, (%)**: 669 (67, $[2M+Na]^+$), 647 (49, $[2M+H]^+$), 435 (14), 346 (42, $[M+Na]^+$), 324 (100, $[M+H]^+$), 282 (4, [M+H-propene]$^+$), 230 (3), 130 (5, $[ArCH_2]^+$); **HRMS ESI+ *m/z***: ($[M+H]^+$): Calcd. for $C_{19}H_{22}N_3O_2$: 324.1707; Found: 324.1706; **^{1}H NMR (400 MHz, $CDCl_3$)**: *trans*-diastereomer: δ = 1.91-2.00 (m, 2H, $NCH_2C\underline{H}_2CH_2$), 2.08-2.14 (m, 2H, $NCH_2CH_2C\underline{H}_2$), 2.41 (ddt, *J* = 13.9, 7.6, 1.1 Hz, 1H, $C\underline{H}_2CH$=), 2.50 (ddt, *J* = 13.9, 7.6, 1.0 Hz, 1H, $C\underline{H}_2CH$=), 2.89 (dd, *J* = 14.9, 10.9 Hz, 1H, $ArCH_2$), 3.49-3.59 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.78 (ddd, *J* = 15.0, 3.7, 1.0 Hz, 1H, $ArCH_2$), 3.86 (dt, *J* = 12.4, 8.3 Hz, 1H, $NC\underline{H}_2CH_2CH_2$), 4.41 (dd, *J* = 10.9, 3.6 Hz, 1H, αCH), 5.10-5.19 (m, 2H, $=CH_2$), 5.72 (m, 1H, $CH_2C\underline{H}$=), 5.78 (br. s, 1H, NH_{DKP}), 7.07 (br. s, 1H, CH_{ind-2}), 7.15 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, CH_{Ar}), 7.24 (ddd, *J* = 8.2, 7.2, 1.3 Hz, 1H, CH_{Ar}), 7.39 (d, *J* = 8.1 Hz, 1H, CH_{Ar}), 7.59 (d, *J* = 7.9 Hz, 1H, CH_{Ar}), 8.43 (br. s, 1H, NH_{ind}); **^{13}C NMR (101 MHz, $CDCl_3$)**: *trans*-diastereomer: δ = 20.5 (t, $NCH_2\underline{C}H_2CH_2$), 28.2 (t, $ArCH_2$), 34.2 (t, $NCH_2CH_2\underline{C}H_2$), 41.7 (t, $\underline{C}H_2CH$=), 45.2 (t, $N\underline{C}H_2CH_2CH_2$), 54.7 (d, αCH), 68.2 (s, C_{Pro}), 110.1 (s, C_{ind-3}), 111.8 (d, CH_{Ar}), 118.7 (d, CH_{Ar}), 120.18 (d, CH_{Ar}), 121.0 (t, $=CH_2$), 122.9 (d, CH_{Ar}), 123.7 (d, CH_{Ar}), 126.9 (s, C_{Ar}), 131.3 (d, $CH_2\underline{C}H$=), 136.9 (s, $\underline{C}_{Ar}NH$), 165.6 (s, C=O_{Trp}), 171.1 (s, C=O_{Pro}).

^{1}H NMR (400 MHz, $CDCl_3$): *cis*-diastereomer: δ = 1.91-2.01 (m, 3H, $NCH_2C\underline{H}_2C\underline{H}_2$), 2.15-2.23 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 2.27 (dd, *J* = 13.8, 7.2 Hz, 1H, $C\underline{H}_2CH$=), 2.44 (dd, *J* = 13.8, 7.8 Hz, 1H, $C\underline{H}_2CH$=), 3.13 (dd, *J* = 14.3, 10.6 Hz, 1H, $ArCH_2$), 3.37-3.50 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.57 (dd, *J* = 14.3, 3.1 Hz, 1H, $ArCH_2$), 3.96-4.07 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 4.24 (dt, *J* = 10.6, 3.1 Hz, 1H, αCH), 5.13 (dd, *J* = 17.0, 1.6 Hz, 1H, $=CH_2$), 5.19-5.25 (m, 1H, $=CH_2$), 5.77 (dddd, *J* = 17.1, 10.1, 7.8, 7.1 Hz, 1H, $CH_2C\underline{H}$=), 6.12 (br. s, 1H, NH_{DKP}), 7.07 (d, *J* = 2.3 Hz, 1H, $CH_{ind\text{-}2}$), 7.13 (ddd, *J* = 8.0, 7.1, 1.1 Hz, 1H, CH_{Ar}), 7.20 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H, CH_{Ar}), 7.38 (d, *J* = 8.1 Hz, 1H, CH_{Ar}), 7.64 (d, *J* = 7.9 Hz, 1H, CH_{Ar}), 8.40 (br. s, 1H, NH_{ind}); **^{13}C NMR (101 MHz, $CDCl_3$)**: *cis*-diastereomer: δ = 19.6 (t, $NCH_2\underline{C}H_2CH_2$), 32.0 (t, $ArCH_2$), 34.6 (t, $NCH_2CH_2\underline{C}H_2$), 42.4 (t, $\underline{C}H_2CH$=), 44.9 (t, $N\underline{C}H_2CH_2CH_2$), 58.3 (d, αCH), 67.4 (s, C_{Pro}), 110.3 (s, $C_{ind\text{-}3}$), 111.6 (d, CH_{Ar}), 118.9 (d, CH_{Ar}), 120.15 (d, CH_{Ar}), 120.5 (t, $=CH_2$), 122.7 (d, CH_{Ar}), 123.6 (d, CH_{Ar}), 127.1 (s, C_{Ar}), 132.2 (d, $CH_2\underline{C}H$=), 136.6 (s, $\underline{C}_{Ar}NH$), 165.2 (s, $C{=}O_{Trp}$), 170.0 (s, $C{=}O_{Pro}$).

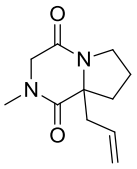
3-((1*H*-indol-3-yl)methyl)-8a-(3-methylbut-2-en-1-yl)hexahydropyrrolo[1,2-a]pyrazine-1,4-dione (2.3):



Dipeptide **2.14** (700 mg, 1.45 mmol) was dissolved in CH_2Cl_2 (5 mL) and silica gel (2 g) was added. The suspension was evaporated to dryness and heated with vigorous stirring under Ar at 190 °C for 1 h. The solid reaction mixture was transferred to a short packed silica gel column and the product was eluted with 100% AcOEt to give 172 mg less polar *trans*-diastereomer (assigned by comparison to the known compound and confirmed by NOE) as a beige powder, 265 mg of 2.3:1 *trans*/*cis* mixture and 30 mg more polar *cis*-diastereomer. The overall yield was 467 mg (92%). **m.p.(*trans*)** 182-184 ºC; **R_f(*trans*)** = 0.4; **R_f(*cis*)** = 0.2 (AcOEt); **IR**: ν[cm^{-1}] 3262, 2968, 1661, 1619, 1448, 1331, 1101, 908, 730, 647, 616; **MS ESI+ *m/z*, (%)**: 725 (21, $[2M+Na]^+$), 374 (100, $[M+Na]^+$), 352 (29, $([M+H]^+$); **HRMS ESI+ *m/z***: ($[M+Na]^+$): Calcd. for $C_{21}H_{25}O_2N_3Na$: 374.1839; Found: 374.1837; **^{1}H NMR (400 MHz, $CDCl_3$)**: *trans*-diastereomer: δ = 1.56 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 1.93-2.04 (m, 2H, $NCH_2C\underline{H}_2CH_2$), 2.05-2.16 (m, 2H, $NCH_2CH_2C\underline{H}_2$), 2.40 (dd, *J* = 14.1, 8.2 Hz, 1H, $C\underline{H}_2CH$=), 2.48 (dd, *J* = 14.2, 7.7 Hz, 1H, $C\underline{H}_2CH$=), 2.85 (dd, *J* = 14.8, 11.2 Hz, 1H, $ArCH_2$), 3.55 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.73-3.88 (m, 2H, $NC\underline{H}_2CH_2CH_2$, $ArCH_2$), 4.39 (dd, *J* = 11.1, 3.5 Hz, 1H, αCH), 5.09 (t, *J* = 7.9 Hz, 1H, $CH_2C\underline{H}$=), 5.75 (br. s, 1H, NH_{DKP}), 7.04 (s, 1H, $CH_{ind\text{-}2}$), 7.12 (ddd, *J* = 8.0, 7.1, 1.0 Hz, 1H, CH_{Ar}), 7.22 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1H, CH_{Ar}), 7.38 (d, *J* = 8.2 Hz, 1H, CH_{Ar}), 7.57 (d, *J* = 7.9 Hz, 1H, CH_{Ar}), 8.52 (s, 1H, NH_{ind});

^{13}C NMR (101 MHz, $CDCl_3$): *trans*-diastereomer: δ = 17.9 (q, CH_3), 20.7 (t, $NCH_2\underline{C}H_2CH_2$), 26.2 (q, CH_3), 28.4 (t, $ArCH_2$), 34.8 (t, $NCH_2CH_2\underline{C}H_2$), 36.3 (t, $\underline{C}H_2CH$=), 45.3 (t, $N\underline{C}H_2CH_2CH_2$), 54.7 (d, αCH), 68.7 (s, C_{Pro}), 110.2 (s, $C_{ind\text{-}3}$), 111.8 (d, CH_{Ar}), 117.4 (d, $CH_2\underline{C}H$=), 118.7 (d, CH_{Ar}), 120.1 (d, CH_{Ar}), 122.9 (d, CH_{Ar}), 123.6 (d, CH_{Ar}), 126.8 (s, C_{Ar}), 137.0 (s, $\underline{C}_{Ar}NH$), 137.9 (s, =$\underline{C}(CH_3)_2$), 165.7 (s, C=O_{Trp}), 171.7 (s, C=O_{Pro}). **^{1}H NMR (400 MHz, $CDCl_3$)**: *cis*-diastereomer: δ = 1.67 (s, 3H, CH_3), 1.79 (s, 3H, CH_3), 1.91-2.05 (m, 3H, $NCH_2C\underline{H}_2C\underline{H}_2$), 2.15-2.24 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 2.38 (dd, *J* = 14.3, 7.6 Hz, 1H, $C\underline{H}_2CH$=), 2.58 (dd, *J* = 14.4, 8.1 Hz, 1H, $C\underline{H}_2CH$=), 2.99 (dd, *J* = 14.2, 11.4 Hz, 1H, $ArCH_2$), 3.39-3.50 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.61 (dd, *J* = 14.2, 2.8 Hz, 1H, $ArCH_2$), 3.97-4.04 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 4.16 (dt, *J* = 11.4, 2.9 Hz, 1H, αCH), 5.22 (t, *J* = 7.8 Hz, 1H, $CH_2C\underline{H}$=), 5.95 (d, *J* = 2.4 Hz, 1H, NH_{DKP}), 7.00 (d, *J* = 1.6 Hz, 1H, $CH_{ind\text{-}2}$), 7.10 (t, *J* = 7.5 Hz, 1H, CH_{Ar}), 7.19 (t, *J* = 7.1 Hz, 1H, CH_{Ar}), 7.36 (d, *J* = 8.1 Hz, 1H, CH_{Ar}), 7.61 (d, *J* = 7.9 Hz, 1H, CH_{Ar}), 8.78 (br. s, 1H, NH_{ind}); **^{13}C NMR (101 MHz, $CDCl_3$)**: *cis*-diastereomer: δ = 18.2 (q, CH_3), 19.8 (t, $NCH_2\underline{C}H_2CH_2$), 26.5 (q, CH_3), 32.0 (t, $ArCH_2$), 35.4 (t, $NCH_2CH_2\underline{C}H_2$), 36.4 (t, $\underline{C}H_2CH$=), 44.9 (t, $N\underline{C}H_2CH_2CH_2$), 58.2 (d, αCH), 68.0 (s, C_{Pro}), 110.4 (s, $C_{ind\text{-}3}$), 111.7 (d, CH_{Ar}), 118.3 (d, $CH_2\underline{C}H$=), 118.8 (d, CH_{Ar}), 120.0 (d, CH_{Ar}), 122.6 (d, CH_{Ar}), 123.5 (d, CH_{Ar}), 127.0 (s, C_{Ar}), 136.8 (s, $\underline{C}_{Ar}NH$), 137.3 (s, =$\underline{C}(CH_3)_2$), 165.1 (s, C=O_{Trp}), 170.2 (s, C=O_{Pro}).

8-Allyl-2-methylhexahydropyrrolo[1,2-a]pyrazine-1,4-dione (2.21a):



Dipeptide **2.16a** (318 mg, 0.93 mmol) was dissolved in CH_2Cl_2 (5 mL) and silica gel (1 g) was added. The suspension was evaporated to dryness and heated under Ar at 190 °C with vigorous stirring for 1 h. The solid reaction mixture was transferred to a short packed silica gel column and the product was eluted with 100% AcOEt, gradient to 1:1 AcOEt/acetone to give 182 mg (94%) **2.21a** as a colorless solid. **m.p.** 41-42 °C; $\mathbf{R_f}$ = 0.3 (acetone/AcOEt, 1:1); **IR**: *v*[cm^{-1}] 2978, 1651, 1449, 908, 724, 646; **MS ESI+ *m/z*, (%)**: 439 (21, $[2M+Na]^+$), 231 (100, $[M+Na]^+$), 209 (18, $[M+H]^+$), 195 (3), 181 (5); **HRMS ESI+ *m/z***: ($[M+Na]^+$): Calcd. for $C_{11}H_{16}N_2O_2Na$: 209.1285; Found: 209.1284; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 1.97 (m, 2H, $NCH_2C\underline{H}_2CH_2$), 2.14 (m, 2H, $NCH_2CH_2C\underline{H}_2$), 2.38 (dd, *J* = 13.7, 7.6 Hz, 1H, $C\underline{H}_2CH$=), 2.53 (dd, *J* = 13.7, 7.6 Hz, 1H, $C\underline{H}_2CH$=), 2.95 (s, 3H, NCH_3), 3.48 (ddd, *J* = 12.8, 8.1, 5.4 Hz, 1H, $NC\underline{H}_2CH_2CH_2$), 3.74 (d, *J* = 17.1 Hz, 1H, $CH_3NC\underline{H}_2$), 3.82 (dt, *J* = 12.3, 8.4 Hz, 1H, $NC\underline{H}_2CH_2CH_2$), 4.15 (d, *J* = 17.1 Hz, 1H, $CH_3NC\underline{H}_2$), 5.06-5.23 (m, 2H, $=CH_2$), 5.71 (ddt, *J* = 17.3, 9.6, 7.5 Hz, 1H, $CH_2C\underline{H}$=); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 20.5 (t, $NCH_2\underline{C}H_2CH_2$), 33.6 (q, NCH_3), 35.0

(t, $NCH_2CH_2\underline{C}H_2$), 42.4 (t, $\underline{C}H_2CH$=), 45.0 (t, $N\underline{C}H_2CH_2CH_2$), 53.7 (t, $CH_3N\underline{C}H_2$), 67.9 (s, C_{Pro}), 120.9 (t, $=CH_2$), 131.5 (d, $CH_2\underline{C}H$=), 162.9 (s, C=O), 169.2 (s, C=O).

8a-Allylhexahydropyrrolo[1,2-a]pyrazine-1,4-dione (2.21b):

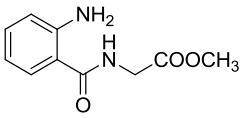
Dipeptide **2.16b** (2.1 g, 6.43 mmol) was dissolved in CH_2Cl_2 (15 mL) and silica gel (4 g) was added. The suspension was evaporated to dryness and heated under Ar at 190 °C with vigorous stirring for 1 h. The solid was transferred to a short packed silica gel column and the product was eluted with 100% AcOEt, gradient to 1:2 AcOEt/acetone to give 1.23 g (98%) **2.21b** as a colorless solid. **m.p.** 144-146 °C; **R_f** = 0.4 (acetone/AcOEt, 1:2); **IR**: *ν*[cm^{-1}] 3256, 2987, 1661, 1453, 1331, 1312, 1213, 1112, 1013, 931, 767, 592; **MS ESI+ *m/z*, (%)**: 315 (4), 217 (65, $[M+Na]^+$), 195 (100, $[M+H]^+$), 155 (6, $[M+H\text{-propyne}]^+$), 136 (8), 119 (6), 100 (4); **HRMS ESI+ *m/z***: ($[M+Na]^+$): Cald. for $C_{10}H_{14}O_2N_2Na$: 217.0948; Found: 217.0948; **Anal. Calcd. For** $C_{10}H_{14}N_2O_2$ (194.23): C, 61.84; H, 7.27; N, 14.42; Found: C, 61.45; H, 7.36; N, 14.14; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 1.90-2.06 (m, 2H, $NCH_2C\underline{H}_2CH_2$), 2.11-2.22 (m, 2H, $NCH_2CH_2C\underline{H}_2$), 2.42 (dd, *J* = 13.8, 7.6 Hz, 1H, $C\underline{H}_2CH$=), 2.54 (ddt, *J* = 13.8, 7.5 Hz, 1H, $C\underline{H}_2CH$=), 3.44-3.55 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.77-3.90 (m, 2H, $NC\underline{H}_2CH_2CH_2$, $NHC\underline{H}_2$), 4.10 (d, *J* = 17.1 Hz, 1H, $NHC\underline{H}_2$), 5.14-5.23 (m, 2H, $=CH_2$), 5.79 (ddt, *J* = 17.2, 9.7, 7.5 Hz, 1H, $CH_2C\underline{H}$=), 6.97 (br. s, 1H, NH); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 20.3 (t, $NCH_2\underline{C}H_2CH_2$), 34.3 (t, $NCH_2CH_2\underline{C}H_2$), 41.9 (t, $\underline{C}H_2CH$=), 45.1 (t, $N\underline{C}H_2CH_2CH_2$), 46.7 (t, $NHCH_2$), 67.5 (s, C_{Pro}), 121.2 (t, $=CH_2$), 131.2 (d, $CH_2\underline{C}H$=), 163.6 (s, C=O), 171.9 (s, C=O).

8a-(3-Methylbut-2-en-1-yl)hexahydropyrrolo[1,2-a]pyrazine-1,4-dione (2.22):

Dipeptide **2.18** (1.06 g, 2.98 mmol) was dissolved in CH_2Cl_2 (10 mL) and silica gel (2 g) was added. The suspension was evaporated to dryness and heated with vigorous stirring under Ar at 190 °C for 1 h. The solid reaction mixture was transferred to a short packed silica gel column and the product was eluted with 100% AcOEt, gradient to 2:1 AcOEt/acetone to give 661 mg (99%) **2.22** as a colorless viscous oil. **R_f** = 0.3 (acetone/AcOEt, 1:3); **IR**: *ν*[cm^{-1}] 3237, 1638, 1441, 1323, 1301, 1107, 762; **MS ESI+ *m/z*, (%)**: 245 (20, $[M+Na]^+$), 223 (100, $[M+H]^+$), 153 (10, $[M\text{-prenyl}]^+$); **HRMS ESI+ *m/z***: ($[M+H]^+$): Calcd. for $C_{12}H_{18}N_2O_2$: 223.1441; Found: 223.1440; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 1.58 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 1.91-2.06 (m, 2H, $NCH_2C\underline{H}_2CH_2$), 2.09-2.16 (m, 2H, $NCH_2CH_2C\underline{H}_2$), 2.39 (dd, *J* = 14.2, 8.3 Hz, 1H, $C\underline{H}_2CH$=), 2.49 (dd, *J* = 14.2, 7.7 Hz, 1H, $C\underline{H}_2CH$=), 3.43-3.53 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.72-3.85 (m,

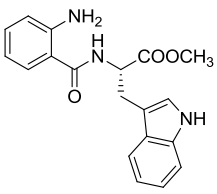
2H, NHC$\underline{H}_2$, NC$\underline{H}_2$CH$_2$CH$_2$), 3.98 (d, *J* = 17.0 Hz, 1H, NHC$\underline{H}_2$), 5.13 (t, *J* = 8.0 Hz, 1H, CH$_2$C$\underline{H}$=), 7.25 (br. s, 1H, NH); **^{13}C NMR (101 MHz, CDCl$_3$)**: δ = 17.9 (q, CH$_3$), 20.4 (t, NCH$_2$$\underline{C}H_2CH_2$), 26.2 (q, CH$_3$), 34.7 (t, NCH$_2CH_2$$\underline{C}H_2$), 36.4 (t, $\underline{C}$H$_2$CH=), 45.2 (t, N$\underline{C}$H$_2$CH$_2$CH$_2$), 46.7 (t, NH$\underline{C}$H$_2$), 67.9 (s, C$_{Pro}$), 117.1 (d, CH$_2$$\underline{C}$H=), 138.1 (s, =$\underline{C}$(CH$_3$)$_2$), 163.6 (s, NC=O), 172.5 (s, NHC=O).

Methyl 2-(2-aminobenzamido)acetate (2.26a):



Triethylamine (9.5 mL, 68.04 mmol) was added to a suspension of isatoic anhydride (3 g, 18.40 mmol) and glycine methyl ester hydrochloride (2.3 g, 18.40 mmol) in AcOEt (100 mL) and the reaction mixture was refluxed for 2.5 h. The precipitates were filtered, washed with AcOEt and the filtrates were evaporated. The residue was purified by column chromatography (SiO$_2$, hexane/AcOEt, 3:1, gradient to 1:1) to give 1.82 g (48%) **2.26a** as a colorless solid. **m.p.** 73-74 °C; **R$_f$** = 0.3 (hexane/AcOEt, 1:1); **IR**: ν[cm^{-1}] 3472, 3364, 3041, 2962, 1747, 1644, 1621, 1589, 1529, 1496, 1443, 1413, 1375, 1327, 1304, 1269, 1217, 1177, 1165, 1038, 1010, 978, 856, 754, 716, 666, 527; **MS ESI+ *m/z*, (%)**: 439 (18, [2M+Na]$^+$), 350 (11), 257 (6), 231 (100, [M+Na]$^+$), 209 (5, [M+H]$^+$); **HRMS ESI+ *m/z***: ([M+Na]$^+$): Calcd. for C$_{10}$H$_{12}$O$_3$N$_2$Na: 231.0740; Found: 231.0740; **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 3.80 (s, 3H, CH$_3$), 4.20 (d, *J* = 5.2 Hz, 2H, NHC$\underline{H}_2$), 5.51 (br. s, 2H, NH$_2$), 6.59 (br. s, 1H, NHCO), 6.63-6.73 (m, 2H, CH$_{Ar}$), 7.22 (ddd, *J* = 8.2, 7.2, 1.5 Hz, 1H, CH$_{Ar}$), 7.41 (dd, *J* = 7.8, 1.5 Hz, 1H, CH$_{Ar}$); **^{13}C NMR (101 MHz, CDCl$_3$)**: δ = 41.6 (t, NH$\underline{C}$H$_2$), 52.6 (q, OCH$_3$), 115.3 (s, $\underline{C}_{Ar}$C=O), 116.9 (d, CH$_{Ar}$), 117.5 (d, CH$_{Ar}$), 127.7 (d, CH$_{Ar}$), 132.8 (d, CH$_{Ar}$), 148.9 (s, $\underline{C}_{Ar}$NH$_2$), 169.5 (s, NHC=O), 170.9 (s, $\underline{C}$O$_2$Me). All data are in agreement with the reported data.[62a]

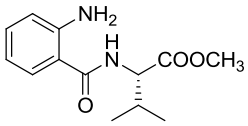
(*S*)-Methyl 2-(2-aminobenzamido)-3-(1*H*-indol-3-yl)propanoate (2.26b):



Compound **2.26b** was synthesized according to the literature and obtained in 82% yield. **m.p.** 132-133 °C; **R$_f$** = 0.2 (hexane/AcOEt, 1:1); **[α]$^{20}_{589}$**: +65.9 (*c* 0.998, CHCl$_3$); **IR**: ν[cm^{-1}] 3386, 3021, 2960, 2860, 1788, 1739, 1643, 1589, 1558, 1517, 1443, 1361, 1259, 1219, 1164, 1100, 1014, 984, 893, 855, 793, 748, 708, 686, 668, 644, 583, 524; **MS EI+ *m/z*, (%)**: 337 (37, [M]$^+$), 201 (58, [M-anthranilamide]$^+$), 170 (8, [M-anthranilamide-MeO]$^+$), 130 (100, [ArCH$_2$]$^+$), 120 (24, [anthranilamide-NH$_2$]$^+$), 103 (5), 92 (9, [C$_6$H$_6$N]$^+$); **HRMS EI+ *m/z***: ([M]$^+$): Calcd. for C$_{19}$H$_{19}$N$_3$O$_3$: 337.1426; Found: 337.1430; **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 3.42 (dd, *J* = 5.4

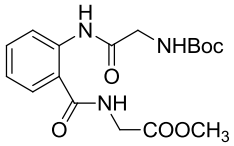
Hz, 1H, $ArCH_2$), 3.43 (d, *J* = 5.4 Hz, 1H, $ArCH_2$), 3.72 (s, 3H, OCH_3), 5.08 (dt, *J* = 7.5, 5.4 Hz, 1H, αCH), 5.50 (br. s, 2H, NH_2), 6.57 (ddd, *J* = 7.9, 7.2, 1.0 Hz, 1H, CH_{Ar}), 6.63 (br. d, *J* = 7.5 Hz, 1H, NHCO), 6.67 (dd, *J* = 8.6, 1.2 Hz, 1H, CH_{Ar}), 7.00 (d, *J* = 2.4 Hz, 1H, CHN_{ind-2}), 7.10 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H, CH_{Ar}), 7.14-7.22 (m, 3H, CH_{Ar}), 7.34 (dt, *J* = 8.1, 0.9 Hz, 1H, CH_{Ar}), 7.56 (dd, *J* = 7.9, 1.1 Hz, 1H, CH_{Ar}), 8.20 (br. s, 1H, NH_{ind}); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 27.9 (t, $ArCH_2$), 52.7 (q, OCH_3), 53.3 (d, αCH), 110.2 (s, C_{ind-3}), 111.5 (d, CH_{Ar}), 115.6 (s, C_{Ar}), 117.1 (d, CH_{Ar}), 117.6 (d, CH_{Ar}), 118.8 (d, CH_{Ar}), 119.9 (d, CH_{Ar}), 122.5 (d, CH_{Ar}), 123.1 (d, CH_{Ar}), 127.5 (s, C_{Ar}), 127.7 (d, CH_{Ar}), 132.8 (d, CH_{Ar}), 136.3 (s, C_{Ar}), 148.6 (s, C_{Ar}), 169.0 (s, NHC=O), 172.8 (s, $\underline{C}O_2Me$). All data are in agreement with the reported data.[107]

(*S*)-Methyl 2-(2-aminobenzamido)-3-methylbutanoate (2.26c):



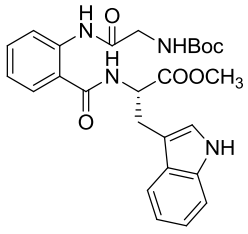
Triethylamine (1.9 mL, 13.50 mmol) was added to a suspension of isatoic anhydride (2 g, 12.26 mmol) and *L*-valine methylester hydrochloride (2.1 g, 12.26 mmol) in AcOEt (120 mL) and the reaction mixture was refluxed for 5 h. The precipitates were filtered, washed with AcOEt and the filtrates were evaporated. The residue was purified by column chromatography (SiO_2, hexane/AcOEt, 3:1, gradient to 1:1) to give 1.73 g (57%) **2.26c** as a colorless solid. **m.p.** 78-80 °C; $\mathbf{R_f}$ = 0.4 (hexane/AcOEt, 2:1); **$[\alpha]^{20}_{589}$**: +5.7 (*c* 2.0, $CHCl_3$); **IR**: ν[cm^{-1}] 3477, 3366, 2975, 1741, 1648, 1621, 1590, 1562, 1522, 1493, 1471, 1441, 1456, 1396, 1377, 1362, 1317, 1271, 1213, 1188, 1162, 753, 652, 598, 531; **MS ESI+ *m/z*, (%)**: 523 (3, $[2M+Na]^+$), 273 (100, $[M+Na]^+$), 251 (8, $[M+H]^+$); **HRMS ESI+ *m/z***: ($[M+Na]^+$): Calcd. for $C_{13}H_{18}O_3N_2Na$: 273.1211; Found: 273.1209; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 0.98 (d, *J* = 6.9 Hz, 3H, $CH(C\underline{H}_3)_2$), 1.01 (d, *J* = 6.9 Hz, 3H, $CH(C\underline{H}_3)_2$), 2.25 (dsept, *J* = 6.9, 4.9 Hz, 1H, $C\underline{H}(CH_3)_2$), 3.77 (s, 3H, OCH_3), 4.72 (dd, *J* = 8.6, 5.0 Hz, 1H, αCH), 5.47 (br. s, 2H, NH_2), 6.54 (d, *J* = 8.6 Hz, 1H, αCHN$\underline{H}$), 6.63-6.71 (m, 2H, CH_{Ar}), 7.22 (ddd, *J* = 8.2, 7.2, 1.5 Hz, 1H, CH_{Ar}), 7.41 (dd, *J* = 8.1, 1.5 Hz, 1H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 18.2 (q, $CH(\underline{C}H_3)_2$), 19.2 (q, $CH(\underline{C}H_3)_2$), 31.7 (d, $\underline{C}H(CH_3)_2$), 52.4 (q, OCH_3), 57.3 (d, αCH), 115.9 (s, $\underline{C}_{Ar}C$=O), 116.9 (d, CH_{Ar}), 117.5 (d, CH_{Ar}), 127.6 (d, CH_{Ar}), 132.8 (d, CH_{Ar}), 149.0 (s, $\underline{C}_{Ar}NH_2$), 169.2 (s, Ar$\underline{C}$=O), 172.9 (s, $\underline{C}O_2Me$).

Methyl 2-(2-(2-((*tert*-butoxycarbonyl)amino)acetamido)benzamido)acetate (2.27a):



Ethyldiisopropylamine (1.14 mL, 6.54 mmol) was added to a suspension of *N*-Boc-glycine (687 mg, 3.92 mmol), **2.26a** (680 mg, 3.27 mmol) and HBTU (1.61 g, 4.25 mmol) in dry CH_2Cl_2 (20 mL) and the reaction mixture was stirred for 24 h. It was quenched with saturated NH_4Cl solution and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and filtered. Evaporation followed by purification of the residue by column chromatography (SiO_2, hexane/AcOEt, 2:1, gradient to 1:2) gave 1.05 g (94%) **2.27a** as a colorless solid. **m.p.** 96-98 °C; $\mathbf{R_f}$ = 0.3 (hexane/AcOEt, 1:2); **IR**: ν[cm^{-1}] 3349, 2978, 1746, 1691, 1650, 1600, 1587, 1513, 1447, 1406, 1367, 1323, 1276, 1249, 1206, 1161, 1051, 1030, 1006, 973, 939, 918, 862, 755, 731, 650, 560, 514; **MS ESI+ *m/z*, (%)**: 753 (5, $[2M+Na]^+$), 545 (8), 425 (15), 388 (100, $[M+Na]^+$), 310 (5, $[M+H\text{-isobutylene}]^+$), 288 (10, $[M+Na\text{-}CO_2\text{-isobutylene}]^+$), 221 (4); **HRMS ESI+ *m/z***: ($[M+Na]^+$): Calcd. for $C_{17}H_{23}N_3O_6Na$: 388.1479; Found: 388.1479; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 1.46 (br. s, 9H, $C(CH_3)_3$), 3.79 (s, 3H, OCH_3), 3.87-4.06 (m, 2H, $C\underline{H}_2NHBoc$), 4.16 (d, *J* = 5.1 Hz, 2H, $C\underline{H}_2CO_2Me$), 5.29 (br. s, 1H, NHBoc), 6.98 (t, *J* = 4.7 Hz, 1H, $N\underline{H}CH_2CO_2Me$), 7.07 (td, *J* = 7.7, 1.2 Hz, 1H, CH_{Ar}), 7.45 (t, *J* = 7.7 Hz, 1H, CH_{Ar}), 7.55 (dd, *J* = 7.9, 1.5 Hz, 1H, CH_{Ar}), 8.54 (d, *J* = 8.4 Hz, 1H, CH_{Ar}), 11.33 (s, 1H, ArNH); **^{13}C NMR (101 MHz, $CDCl_3$)**: 28.5 (q, $C(\underline{C}H_3)_3$), 41.7 (t, $\underline{C}H_2CO_2Me$), 45.4 (t, $\underline{C}H_2NHBoc$), 52.8 (q, OCH_3), 80.3 (s, $\underline{C}(CH_3)_3$), 120.0 (s, $\underline{C}_{Ar}C=O$), 121.7 (d, CH_{Ar}), 123.4 (d, CH_{Ar}), 127.1 (d, CH_{Ar}), 133.1 (d, CH_{Ar}), 139.2 (s, $\underline{C}_{Ar}NH$), 156.1 (s, $C=O_{Boc}$), 168.6 (s, ArC=O), 168.9 (s, $ArNH\underline{C}=O$), 170.4 (s, $\underline{C}O_2Me$).

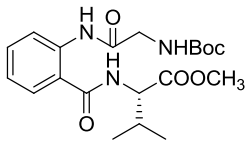
(*S*)-Methyl 2-(2-(2-((*tert*-butoxycarbonyl)amino)acetamido)benzamido)-3-(1*H*-indol-3-yl)propanoate (2.27b):



Ethyldiisopropylamine (1.04 mL, 5.93 mmol) was added to a suspension of *N*-Boc-glycine (623 mg, 3.56 mmol), **2.26b** (1.0 g, 2.96 mmol) and HBTU (1.46 g, 3.85 mmol) in dry CH_2Cl_2 (30 mL) and the reaction mixture was stirred for 24 h. It was quenched with saturated NH_4Cl solution and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and filtered. Evaporation followed by purification of the residue by column chromatography (SiO_2, hexane/AcOEt, 1:1, gradient to 1:2) gave 1.34 g (92%) **2.27b** as a colorless solid. **m.p.** 74-76 °C; $\mathbf{R_f}$ = 0.3 (hexane/AcOEt, 2:1); $\mathbf{[\alpha]^{20}_{589}}$: +43.6 (*c* 0.252, $CHCl_3$); **IR**: ν[cm^{-1}] 3335, 3058, 2978, 2928, 1694, 1649, 1600, 1587, 1513, 1448, 1393, 1367, 1277, 1250, 1214, 1166, 1099, 1052, 1030, 1011, 964, 940, 910, 861, 736, 650, 556, 515; **MS ESI+ *m/z*, (%)**: 1011 (4, $[2M+Na]^+$), 554 (29), 517 (100, $[M+Na]^+$), 439

(8, [M+H-isobutylene]$^+$), 395 (4, [M+H-CO_2-isobutylene]$^+$); **HRMS ESI+ *m/z***: ([M+Na]$^+$): Calcd. for $C_{26}H_{30}O_6N_4Na$: 517.2060; Found: 517.2061; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 1.50 (s, 9H, $C(CH_3)_3$), 3.33 (dd, *J* = 14.9, 6.4 Hz, 1H, $ArCH_2$), 3.46 (dd, *J* = 14.9, 4.9 Hz, 1H, $ArCH_2$), 3.77 (s, 3H, OCH_3), 3.84-4.01 (m, 2H, CH_2NHBoc), 5.08 (ddd, *J* = 7.9, 6.2, 5.0 Hz, 1H, $CHCO_2Me$), 5.20 (br. s, 1H, NHBoc), 6.73 (d, *J* = 7.9 Hz, 1H, NHTrp), 6.92-7.03 (m, 2H, CH_{Ar}), 7.08 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H, CH_{Ar}), 7.17 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H, CH_{Ar}), 7.29 (dd, *J* = 7.9, 1.6 Hz, 1H, CH_{Ar}), 7.35 (dt, *J* = 8.2, 0.9 Hz, 1H, CH_{Ar}), 7.38-7.45 (m, 1H, CH_{Ar}), 7.52 (d, *J* = 7.9 Hz, 1H, CH_{Ar}), 8.51 (d, *J* = 8.7 Hz, 1H, CH_{Ar}), 8.55 (br. s, 1H, NH_{indole}), 11.13 (br. s, 1H, ArNH); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 28.1 (t, $ArCH_2$), 28.6 (q, $C(CH_3)_3$), 42.3 (t, CH_2NHBoc), 52.8 (q, OCH_3), 53.4 (d, $CHCO_2Me$), 80.4 (s, $C(CH_3)_3$), 109.9 (s, $C_{ind\text{-}3}$), 111.6 (d, CH_{Ar}), 118.6 (d, CH_{Ar}), 119.9 (d, CH_{Ar}), 120.6 (s, C_{Ar}), 121.7 (d, CH_{Ar}), 122.5 (d, CH_{Ar}), 123.1 (d, CH_{Ar}), 123.3 (d, CH_{Ar}), 126.9 (d, CH_{Ar}), 127.7 (s, C_{ind}), 132.9 (d, CH_{Ar}), 136.4 (s, $C_{ind}NH$), 139.0 (s, $C_{Ar}NH$), 156.2 (s, $C{=}O_{Boc}$), 168.38 (s, C=O), 168.43 (s, C=O), 172.4 (s, CO_2Me).

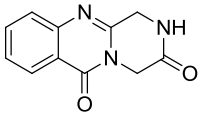
(*S*)-Methyl 2-(2-(2-((*tert*-butoxycarbonyl)amino)acetamido)benzamido)-3-methylbutanoate (2.27c):



Ethyldiisopropylamine (840 μL, 4.8 mmol) was added to a suspension of Boc-glycine (841 mg, 4.8 mmol), **2.26a** (1.0 g, 4.0 mmol) and HBTU (1.82 g, 4.8 mmol) in dry CH_2Cl_2 (40 mL) and the reaction mixture was stirred for 24 h. It was quenched with saturated NH_4Cl solution and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and filtered. Evaporation followed by purification of the residue by column chromatography (SiO_2, hexane/AcOEt, 5:1, gradient to 1:1) gave 1.34 g (82%) **2.27c** as a colorless solid. **m.p.** 127-129 °C; **R_f** = 0.2 (hexane/AcOEt, 2:1); **$[\alpha]^{20}_{589}$**: +16.7 (*c* 0.3, $CHCl_3$); **IR**: ν[cm^{-1}] 3336, 2980, 1701, 1653, 1605, 1592, 1519, 1452, 1411, 1397, 1371, 1278, 1254, 1212, 1166, 1055, 1033, 967, 943, 922, 865, 824, 759, 734, 650, 592, 517; **MS ESI+ *m/z*, (%)**: 430 (100, [M+Na]$^+$), 374 (7, [M+Na-isobutylene]$^+$), 330 (22, [M+Na-CO_2-isobutylene]$^+$); **HRMS ESI+ *m/z***: ([M+Na]$^+$): Calcd. for $C_{20}H_{29}N_3O_6Na$: 430.1949; Found: 430.1948; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 0.98 (d, *J* = 6.7 Hz, 3H, $CH(CH_3)_2$), 1.00 (d, *J* = 6.8 Hz, 3H, $CH(CH_3)_2$), 1.47 (s, 9H, $C(CH_3)_3$), 2.27 (dsept, *J* = 6.9, 4.9 Hz, 1H, $CH(CH_3)_2$), 3.78 (s, 3H, OCH_3), 3.97 (d, *J* = 6.2 Hz, 2H, CH_2NH), 4.69 (dd, *J* = 8.4, 4.8 Hz, 1H, αCH), 5.23 (br. s, 1H, CH_2NH), 6.74 (d, *J* = 8.5 Hz, 1H, αCHNH), 7.11 (td, *J* = 7.6, 1.2 Hz, 1H, CH_{Ar}), 7.47 (ddd, *J* = 8.5, 7.5, 1.5 Hz, 1H, CH_{Ar}), 7.55 (dd, *J* = 8.0, 1.5 Hz, 1H, CH_{Ar}), 8.59 (dd, *J* = 8.6, 1.2 Hz, 1H, CH_{Ar}), 11.32 (s, 1H,

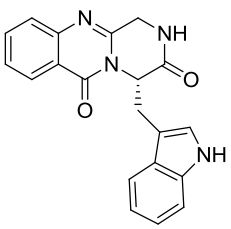
ArNH); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 18.0 (q, CH(<u>C</u>H_3)$_2$), 19.0 (q, CH(<u>C</u>H_3)$_2$), 28.3 (q, C(<u>C</u>H_3)$_3$), 31.5 (d, <u>C</u>H(CH$_3$)$_2$), 45.2 (t, <u>C</u>H_2NH), 52.4 (q, OCH$_3$), 57.4 (d, αCH), 80.0 (s, <u>C</u>(CH$_3$)$_3$), 120.1 (s, <u>C</u>$_{Ar}$C=O), 121.5 (d, CH$_{Ar}$), 123.1 (d, CH$_{Ar}$), 126.6 (d, CH$_{Ar}$), 132.9 (d, CH$_{Ar}$), 139.1 (s, C$_{Ar}$NH), 155.8 (s, C=O$_{Boc}$), 168.3 (s, C=O), 168.5 (s, C=O), 172.2 (s, <u>C</u>O_2Me).

1*H*-Pyrazino[2,1-b]quinazoline-3,6(2*H*,4*H*)-dione (2.28a):



Tripeptide **2.26a** (880 mg, 2.41 mmol) was dissolved in CH_2Cl_2 (5 mL) and silica gel (2 g) was added. The suspension was evaporated to dryness and heated under Ar at 190 °C with vigorous stirring for 1 h. The solid was transferred to a short packed silica gel column and the product was eluted with CH_2Cl_2/MeOH, 20:1, gradient to 10:1 to give 473 mg (91%) **2.27a** as a brownish solid. **R_f** = 0.2 (CH_2Cl_2/MeOH, 10:1); **MS EI+ *m/z*, (%)**: 215 (100, $[M]^+$), 186 (27, $[M\text{-}CH_2\text{=}NH]^+$), 160 (12, $[M\text{-}CH_2\text{=}NH\text{-}CN]^+$), 144 (14, $[M\text{-}CH_2\text{=}NH\text{-}CH_2CO]^+$), 130 (8), 116 (6, $[M\text{-}CH_2\text{=}NH\text{-}CH_2CO\text{-}CO]^+$), 102 (7), 90 (4, $[C_7H_6N]^+$), 76 (5, [benzyne]$^+$); **HRMS EI+ *m/z***: ($[M]^+$): Calcd. for $C_{11}H_9N_3O_2$: 215.0695; Found: 215.0697; **^{1}H NMR (400 MHz, DMSO-d_6)**: δ = 4.43 (d, *J* = 2.7 Hz, 2H, C<u>H</u>$_2$NH), 4.53 (s, 2H, CH_2C=O), 7.54 (ddd, *J* = 8.1, 7.2, 1.2 Hz, 1H, CH$_{Ar}$), 7.64 (ddd, *J* = 8.2, 1.2, 0.6 Hz, 1H, CH$_{Ar}$), 7.84 (ddd, *J* = 8.2, 7.1, 1.6 Hz, 1H, CH$_{Ar}$), 8.14 (ddd, *J* = 8.0, 1.6, 0.6 Hz, 1H, CH$_{Ar}$), 8.60 (br. s, 1H, NH); **^{13}C NMR (101 MHz, DMSO-d_6)**: δ = 44.69 (t, <u>C</u>H_2NH), 44.74 (t, <u>C</u>H_2C=O), 119.7 (s, <u>C</u>$_{Ar}$CO), 126.2 (d, CH$_{Ar}$), 126.75 (d, CH$_{Ar}$), 126.78 (d, CH$_{Ar}$), 134.7 (d, CH$_{Ar}$), 147.1 (s, <u>C</u>$_{Ar}$N), 150.1 (s, C=N), 159.8 (s, ArC=O), 166.0 (s, NHC=O). All data are in agreement with the reported data.[62a]

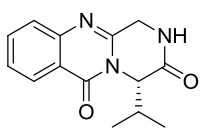
Glyantrypine (2.28b):



Tripeptide **2.26a** (2.06 g, 4.17 mmol) was dissolved in CH_2Cl_2 (10 mL) and silica gel (5 g) was added. The suspension was evaporated to dryness and heated under Ar at 190 °C with vigorous stirring for 1 h. The solid was transferred to a short packed silica gel column and the product was eluted with AcOEt to give 900 mg (63%) glyantrypine (**2.27b)** as a crystalline colorless solid. **m.p.** 159-161 °C; **R_f** = 0.3 (AcOEt); **$[\alpha]^{20}_{589}$**: +547 (*c* 0.123, $CHCl_3$); **IR**: ν[cm^{-1}] 3294, 3070, 1685, 1609, 1575, 1498, 1478, 1414, 1339, 1299, 1256, 1238, 1152, 1114, 805, 774, 744, 701; **MS ESI+ *m/z*, (%)**: 1400 (4), 1055 (39, $[3M+Na]^+$), 779 (4), 727 (9), 711 (100, $[2M+Na]^+$), 689 (24, $[2M+H]^+$), 435 (5), 367 (47, $[M+Na]^+$), 345 (50, $[M+H]^+$); **HRMS ESI+ *m/z***: ($[M+Na]^+$): Calcd. for $C_{20}H_{16}O_2N_4Na$: 367.1166; Found:

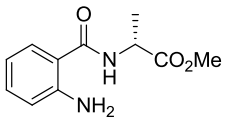
367.1167; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 2.82 (d, *J* = 16.9 Hz, 1H, C<u>H</u>$_2$NH), 3.63 (dd, *J* = 15.0, 5.3 Hz, 1H, ArC<u>H</u>$_2$), 3.72 (dd, *J* = 15.0, 2.9 Hz, 1H, ArC<u>H</u>$_2$), 3.82 (dd, *J* = 16.8, 4.2 Hz, 1H, C<u>H</u>$_2$NH), 5.62 (dd, *J* = 5.3, 3.0 Hz, 1H, αCH), 6.37 (d, *J* = 4.3 Hz, 1H, N<u>H</u>C=O), 6.68 (d, *J* = 2.4 Hz, 1H, CH_{Ar}), 6.91 (ddd, *J* = 8.1, 7.1, 1.0 Hz, 1H, CH_{Ar}), 7.11 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H, CH_{Ar}), 7.28 (dt, *J* = 8.2, 0.9 Hz, 1H, CH_{Ar}), 7.39 (d, *J* = 8.0 Hz, 1H, CH_{Ar}), 7.51-7.57 (m, 2H, CH_{Ar}), 7.75-7.81 (m, 1H, CH_{Ar}), 8.35 (br. s, 1H, NH_{indole}), 8.36-8.40 (m, 1H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 27.4 (t, ArCH_2), 44.8 (t, NHCH_2), 57.0 (d, αCH), 109.3 (s, C_{ind-3}), 111.4 (d, CH_{Ar}), 118.7 (d, CH_{Ar}), 120.3 (d, CH_{Ar}), 120.4 (s, C_{Ar}), 122.9 (d, CH_{Ar}), 123.8 (d, CH_{Ar}), 126.8 (d, CH_{Ar}), 127.2 (d, CH_{Ar}), 127.38 (d, CH_{Ar}), 127.40 (s, C_{Ar}), 135.2 (d, CH_{Ar}), 136.2 (s, C_{Ar}), 147.1 (s, C_{Ar}), 148.7 (s, C=N), 160.7 (s, ArC=O), 169.4 (s, NH<u>C</u>=O). All data are in agreement with the reported data.[108]

(*S*)-4-Isopropyl-1H-pyrazino[2,1-b]quinazoline-3,6(2*H*,4*H*)-dione (2.28c):



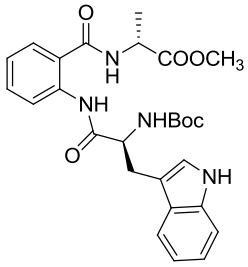
Tripeptide **2.26a** (460 mg, 1.13 mmol) was dissolved in CH_2Cl_2 (5 mL) and silica gel (1.2 g) was added. The suspension was evaporated to dryness and heated under Ar at 190 °C with vigorous stirring for 1 h. The solid was transferred to a short packed silica gel column and the product was eluted with CH_2Cl_2/MeOH, 40:1, gradient to 20:1, to give 145 mg (50%) **2.27c** as a colorless solid. **m.p.** 203-205 °C; **R_f** = 0.3 (CH_2Cl_2/MeOH, 20:1); **$[\alpha]^{20}_{589}$**: +147.0 (*c* 0.221, $CHCl_3$); **IR**: ν[cm^{-1}] 3222, 2977, 1682, 1612, 1574, 1475, 1411, 1376, 1337, 1295, 1250, 1177, 1150, 1102, 1078, 1027, 922, 880, 831, 774, 733, 698, 650, 603, 563, 507; **MS ESI+ *m/z*, (%)**: 794 (4, $[3M+Na]^+$), 537 (79, $[2M+Na]^+$), 378 (7), 302 (15), 280 (100, $[M+Na]^+$), 258 (6, $[M+H]^+$); **HRMS ESI+ *m/z***: ($[M+Na]^+$): Calcd. for $C_{14}H_{15}O_2N_3Na$: 280.1057; Found: 280.1058; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 1.08 (d, *J* = 6.8 Hz, 1H, CH_3), 1.16 (d, *J* = 6.8 Hz, 1H, CH_3), 2.30 (m, 1H, C<u>H</u>(CH_3)$_2$), 4.45 (dd, *J* = 17.2, 5.2 Hz, 1H, CH_2), 4.71 (d, *J* = 17.2 Hz, 1H, CH_2), 5.26 (dd, *J* = 7.9, 1.3 Hz, 1H, αCH), 7.49 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H, CH_{Ar}), 7.56 (br. d, *J* = 5.1 Hz, 1H, NH), 7.62 (d, *J* = 8.2 Hz, 1H, CH_{Ar}), 7.76 (ddd, *J* = 8.5, 7.1, 1.6 Hz, 1H, CH_{Ar}), 8.28 (dd, *J* = 8.0, 1.5 Hz, 1H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 19.0 (q, CH_3), 20.1 (q, CH_3), 32.0 (d, <u>C</u>H(CH_3)$_2$), 45.7 (t, CH_2), 61.0 (d, αCH), 120.5 (s, <u>C</u>$_{Ar}$C=O), 127.1 (d, CH_{Ar}), 127.36 (d, CH_{Ar}), 127.42 (d, CH_{Ar}), 135.0 (d, CH_{Ar}), 147.2 (s, <u>C</u>$_{Ar}$N), 148.5 (s, C=N), 161.0 (s, ArC=O), 169.1 (s, NH<u>C</u>=O).

(*R*)-Methyl 2-(2-aminobenzamido)propanoate (2.32):



Triethylamine (5.2 mL, 36.7 mmol) was added to a suspension of isatoic anhydride (3 g, 18.4 mmol) and *D*-alanine methyl ester hydrochloride (2.57 g, 18.4 mmol) in AcOEt (120 mL) and the reaction mixture was refluxed for 5 h. The precipitates were filtered, washed with AcOEt and the filtrates were evaporated. The residue was purified by column chromatography (SiO_2, hexane/AcOEt, 3:1, gradient to 1:1) to give 2.74 g (69%) **2.32** as a beige crystalline solid. **m.p.** 90-91 °C; $\mathbf{R_f}$ = 0.3 (hexane/AcOEt, 2:1); $\mathbf{[\alpha]^{20}_{589}}$: −4.0 (*c* 0.52, $CHCl_3$); **IR**: ν[cm^{-1}] 3476, 3364, 3001, 2962, 1739, 1640, 1620, 1587, 1523, 1494, 1455, 1383, 1357, 1312, 1262, 1217, 1163, 1053, 984, 922, 886, 854, 816, 752, 709, 666, 528; **MS ESI+ *m/z*, (%)**: 907 (5), 685 (14), 493 (3), 467 (4, $[2M+Na]^+$), 364 (18), 245 (100, $[M+Na]^+$); **HRMS ESI+ *m/z***: ($[M+Na]^+$): Calcd. for $C_{11}H_{14}O_3N_2Na$: 245.0897; Found: 245.0896; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 1.49 (d, *J* = 7.2 Hz, 3H, CHC<u>H</u>$_3$), 3.77 (s, 3H, OCH_3), 4.73 (quint, *J* = 7.2 Hz, 1H, αCH), 4.92-5.59 (br. s, 2H, NH_2), 6.59-6.75 (m, 3H, CH_{Ar}, NHCO), 7.20 (ddd, *J* = 8.4, 7.2, 1.5 Hz, 1H, CH_{Ar}), 7.39 (dd, *J* = 7.9, 1.5 Hz, 1H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 18.7 (q, CH<u>C</u>H$_3$), 48.3 (d, αCH), 52.7 (q, OCH_3), 115.5 (s, <u>C</u>$_{Ar}$CO), 116.9 (d, CH_{Ar}), 117.5 (d, CH_{Ar}), 127.6 (d, CH_{Ar}), 132.7 (d, CH_{Ar}), 148.9 (s, <u>C</u>$_{Ar}$N), 168.9 (s, Ar<u>C</u>=O), 173.9 (s, <u>C</u>O_2Me).

(*R*)-Methyl 2-(2-((S)-2-((*tert*-butoxycarbonyl)amino)-3-(1*H*-indol-3-yl)propanamido)benzamido)propanoate (2.33):

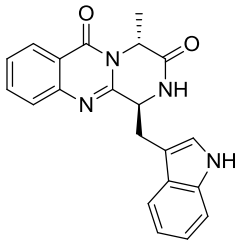


N_α-Boc-*L*-tryptophan (4.05 g, 13.32 mmol) was dissolved in dry CH_2Cl_2 (60 mL), EEDQ (3.57 g, 14.42 mmol) was added and the reaction mixture was stirred for 5 min at r.t. Dipeptide **2.32** (2.47 g, 11.10 mmol) dissolved in CH_2Cl_2 (40 mL) was added dropwise and the reaction mixture was stirred for 24 h. Evaporation of the solvent and purification of the residue by column chromatography (SiO_2, hexane/AcOEt, 3:1, gradient to 1:1) gave 5.48 g (97%) tripeptide **2.33** as a colorless foam. $\mathbf{R_f}$ = 0.2 (hexane/AcOEt, 1:1); $\mathbf{[\alpha]^{20}_{589}}$: −48.7 (*c* 1.00, $CHCl_3$); **IR**: ν[cm^{-1}] 3349, 3070, 2989, 1698, 1651, 1522, 1450, 1357, 1302, 1256, 1221, 1171, 1103, 1056, 985, 913, 858, 738, 649, 562, 530; **MS ESI+ *m/z*, (%)**: 1547 (9, $[3M+Na]^+$), 1039 (100, $[2M+Na]^+$), 531 (78, $[M+Na]^+$), 509 (7, $[M+H]^+$), 227 (4); **HRMS ESI+ *m/z***: ($[M+Na]^+$): Calcd. for $C_{27}H_{32}N_4O_6Na$: 531.2220; Found: 531.2221; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 1.43 (br. s, 9H, C(C<u>H</u>$_3$)$_3$), 1.47 (d, *J* = 7.2 Hz, 3H, CHC<u>H</u>$_3$), 3.35 (br. d, *J* = 5.8 Hz, 2H, $ArCH_2$), 3.77 (s, 3H, OCH_3), 4.56-4.70 (m, 2H, αCH_{Ala}, αCH_{Trp}), 5.22 (br. d, *J* = 6.2 Hz, 1H, N<u>H</u>Boc), 6.80 (d, *J* = 7.1 Hz, 1H, NH_{Ala}), 6.96-7.16 (m, 4H, CH_{Ar}), 7.28 (d, *J* = 8.1 Hz, 1H, CH_{Ar}), 7.41-7.54 (m, 2H,

CH_{Ar}), 7.60 (d, *J* = 7.9 Hz, 1H, CH_{Ar}), 8.23 (br. s, 1H, NH_{ind}), 8.58 (d, *J* = 8.4 Hz, 1H, CH_{Ar}), 11.38 (s, 1H, ArNH); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 18.6 (q, $CH\underline{C}H_3$), 28.2 (t, $ArCH_2$), 28.5 (q, $C(\underline{C}H_3)_3$), 48.6 (d, αCH_{Ala}), 52.9 (q, OCH_3), 56.4 (br. d, αCH_{Trp}), 80.1 (s, $\underline{C}(CH_3)_3$), 110.5 (s, $C_{ind\text{-}3}$), 111.2 (d, CH_{Ar}), 119.1 (d, CH_{Ar}), 119.7 (d, CH_{Ar}), 120.1 (s, $\underline{C}_{Ar}C{=}O$), 121.7 (d, CH_{Ar}), 122.2 (d, CH_{Ar}), 123.2 (d, CH_{Ar}), 123.3 (d, CH_{Ar}), 126.9 (d, CH_{Ar}), 128.1 (s, C_{ind}), 133.0 (d, CH_{Ar}), 136.3 (s, $\underline{C}_{ind}NH$), 139.4 (s, $\underline{C}_{Ar}NH$), 155.6 (s, $C{=}O_{Boc}$), 168.1 (s, $ArC{=}O$), 171.1 (s, $C{=}O_{Trp}$), 173.6 (s, $\underline{C}O_2Me$).

(1*S*,4*R*)-1-((1*H*-Indol-3-yl)methyl)-4-methyl-1*H*-pyrazino[2,1-*b*]quinazoline-3,6(2*H*,4*H*)-dione (2.34a):

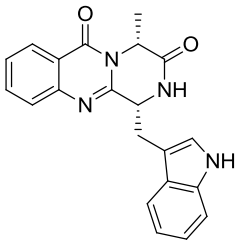
Tripeptide **2.33** (1.0 g, 1.13 mmol) was dissolved in CH_2Cl_2 (15 mL) and silica gel (2 g) was added. The suspension was evaporated to dryness and heated under Ar at 190 °C with vigorous stirring for 1 h. The solid was transferred to a short packed silica gel column and the product was eluted with CH_2Cl_2/MeOH, 60:1, gradient to 30:1, to give 259 mg (37%) **2.34a** as a pale yellow solid and 322 mg (46%) **2.34b** as a beige solid. The overall yield was 83%.



m.p. 220-225 °C (dec. without melting); $\mathbf{R_f}$ = 0.7 (AcOEt); $\mathbf{[\alpha]^{20}_{589}}$: −116.4 (*c* 0.134, $CHCl_3$); **IR**: ν[cm^{-1}] 3352, 2933, 1685, 1609, 1450, 1398, 1324, 1248, 1179, 1099, 913, 775, 739, 700, 654, 548, 517; **MS ESI+ *m/z*, (%)**: 1097 (6, $[3M+Na]^+$), 739 (20, $[2M+Na]^+$), 717 (5, $[2M+H]^+$), 381 (33, $[M+Na]^+$), 359 (100, $[M+H]^+$); **HRMS ESI+ *m/z***: ($[M+H]^+$): Calcd. for $C_{21}H_{20}N_4O_2$: 359.1508; Found: 359.1504; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 1.59 (d, *J* = 7.3 Hz, 3H, $CHC\underline{H}_3$), 3.18 (dd, *J* = 15.0, 10.6 Hz, 1H, $ArCH_2$), 4.27 (ddd, *J* = 15.1, 3.7, 1.1 Hz, 1H, $ArCH_2$), 4.91 (dd, *J* = 10.5, 3.7 Hz, 1H, αCH_{Trp}), 5.45 (qd, *J* = 7.2, 1.0 Hz, 1H, αCH_{Ala}), 5.95 (br. s, 1H, NHCO), 7.15-7.23 (m, 2H, CH_{Ar}), 7.27-7.31 (m, 1H, CH_{Ar}), 7.45 (dt, *J* = 8.2, 0.9 Hz, 1H, CH_{Ar}), 7.54 (ddd, *J* = 8.2, 6.7, 1.6 Hz, 1H, CH_{Ar}), 7.66 (dd, *J* = 7.9, 1.0 Hz, 1H, CH_{Ar}), 7.76-7.85 (m, 2H, CH_{Ar}), 8.25 (br. s, 1H, NH_{ind}), 8.32 (ddd, *J* = 8.1, 1.5, 0.7 Hz, 1H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 17.2 (q, $CH\underline{C}H_3$), 28.5 (t, $ArCH_2$), 52.5 (d, αCH_{Ala}), 52.6 (d, αCH_{Trp}), 109.8 (s, $C_{ind\text{-}3}$), 111.9 (d, CH_{Ar}), 118.6 (d, CH_{Ar}), 120.5 (d, CH_{Ar}), 120.8 (s, C_{Ar}), 123.3 (d, CH_{Ar}), 123.8 (d, CH_{Ar}), 127.0 (s, C_{Ar}), 127.1 (d, CH_{Ar}), 127.6 (d, CH_{Ar}), 127.8 (d, CH_{Ar}), 135.0 (d, CH_{Ar}), 137.0 (s, C_{Ar}), 147.2 (s, C_{Ar}), 150.2 (s, C=N), 160.6 (s, $ArC{=}O$), 169.2 (s, $NH\underline{C}{=}O$).

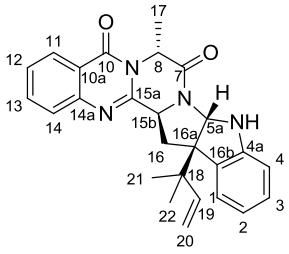
(1*R*,4*R*)-1-((1*H*-Indol-3-yl)methyl)-4-methyl-1*H*-pyrazino[2,1-*b*]quinazoline-3,6(2*H*,4*H*)-dione (2.34b):

m.p. 200-205 °C (dec. without melting); $\mathbf{R_f}$ = 0.4 (AcOEt); $\mathbf{[\alpha]^{20}_{589}}$: −100.7 (*c* 0.132, $CHCl_3$); **IR**: ν[cm^{-1}] 3294, 3072, 2934, 1677, 1601, 1573, 1499, 1478, 1460, 1437, 1412, 1337, 1306, 1252, 1235, 1181, 1133, 1098, 1014, 912, 880, 773, 737, 702, 649, 601; **MS ESI+ *m/z*, (%)**: 1097 (5, $[3M+Na]^+$), 739 (13, $[2M+Na]^+$), 485 (4), 463 (10), 437 (22), 423 (54), 381 (27, $[M+Na]^+$), 359 (100, $[M+H]^+$); **HRMS ESI+ *m/z***: ($[M+H]^+$): Calcd. for $C_{21}H_{20}N_4O_2$: 359.1508; Found: 359.1503;



^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.52 (d, *J* = 7.1 Hz, 1H, CHC<u>H</u>$_3$), 3.28 (dd, *J* = 14.3, 10.0 Hz, 1H, $ArCH_2$), 3.63 (ddd, *J* = 14.4, 3.6, 0.9 Hz, 1H, $ArCH_2$), 4.83 (dt, *J* = 10.0, 3.6 Hz, 1H, αCH_{Trp}), 5.21 (q, *J* = 7.1 Hz, 1H, αCH_{Ala}), 6.32 (d, *J* = 3.7 Hz, 1H, NHCO), 7.02-7.14 (m, 2H, CH_{Ar}), 7.18 (ddd, *J* = 8.2, 7.1, 1.2 Hz, 1H, CH_{Ar}), 7.36 (d, *J* = 8.2 Hz, 1H, CH_{Ar}), 7.49 (ddd, *J* = 8.2, 7.0, 1.3 Hz, 1H, CH_{Ar}), 7.59 (d, *J* = 7.9 Hz, 1H, CH_{Ar}), 7.71-7.77 (m, 1H, CH_{Ar}), 7.80 (ddd, *J* = 8.4, 7.0, 1.5 Hz, 1H, CH_{Ar}), 8.24-8.32 (m, 2H, NH_{ind}, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 19.3 (q, CH<u>C</u>H$_3$), 34.9 (t, $ArCH_2$), 52.1 (d, αCH_{Ala}), 57.5 (d, αCH_{Trp}), 109.7 (s, $C_{ind\text{-}3}$), 111.7 (d, CH_{Ar}), 118.8 (d, CH_{Ar}), 120.4 (d, CH_{Ar}), 120.5 (s, C_{Ar}), 122.9 (d, CH_{Ar}), 123.9 (d, CH_{Ar}), 127.1 (d, CH_{Ar}), 127.17 (s, C_{Ar}), 127.23 (d, CH_{Ar}), 127.3 (d, CH_{Ar}), 135.0 (d, CH_{Ar}), 136.6 (s, C_{Ar}), 147.5 (s, C_{Ar}), 150.4 (s, C=N), 160.7 (s, ArC=O), 168.8 (s, NH<u>C</u>=O).

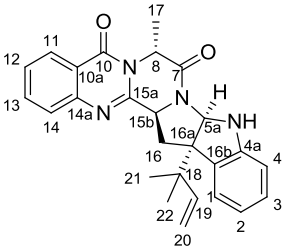
Ardeemin (2.37):



A flame dried Schlenk flask was charged with **2.34a** (60 mg, 0.17 mmol), *t*BuOK (21 mg, 0.19 mmol) and dry THF (1 mL). Triethylborane (190 µL, 0.19 mmol, 1 M solution in THF) was added at r.t. and the reaction mixture was stirred for 40 min at r.t. In a separate flask [{Ir(cod)Cl}$_2$] (0.9 mg, 1.7 µmol) and phosphoramidite **2.36** (1 mg, 2.6 µmol) were dissolved in THF (1 mL) and stirred for 10 min before addition to the reaction mixture. After the catalyst was added, neat *tert*-butyl (2-methylbut-3-en-2-yl) carbonate **2.35** (44 mg, 0.23 mmol) was added and the reaction mixture was stirred for 1 h. It was quenched with saturated NH_4Cl solution, extracted with CH_2Cl_2 and the combined organic layers were dried over $MgSO_4$. Filtration, evaporation and purification of the residue by column chromatography (SiO_2, hexane/AcOEt, 10:1, gradient to 1:1) gave 33 mg (45% or 52% brsm) ardeemin (**2.37**), 19 mg (26%) 5a,16a-*epi*-ardeemin

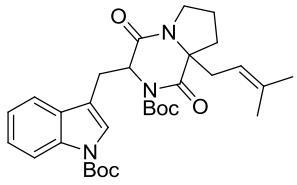
(**2.38**) and 8 mg recovered starting material **2.34a**. $\mathbf{R_f}$(ardeemin) = 0.57 (hexane/AcOEt, 1:1); $\mathbf{R_f}$(5a,16a-*epi*-ardeemin) = 0.51 (hexane/AcOEt, 1:1); $\mathbf{[\alpha]^{20}_{589}}$ (ardeemin): −215.0 (*c* 0.100, $CHCl_3$); **MS ESI+ *m/z*, (%)**: 1728 (54), 1317 (7, $[3M+K]^+$), 1301 (47, $[3M+Na]^+$), 1088 (6), 973 (16), 943 (11), 875 (46, $[2M+Na]^+$), 853 (34, $[2M+H]^+$), 548 (15), 449 (100, $[M+Na]^+$), 427 (96, $[M+H]^+$); **HRMS ESI+ *m/z***: ($[M+Na]^+$): Calcd. for $C_{26}H_{26}N_4O_2Na$: 449.1948; Found: 449.1949; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 1.04 (s, 3H, C-21), 1.18 (s, 3H, C-22), 1.49 (d, *J* = 7.2 Hz, 3H, H-17), 2.75 (dd, *J* = 13.2, 10.8 Hz, 1H, H-16), 2.93 (dd, *J* = 12.8, 6.5 Hz, 1H, H-16), 4.52 (dd, *J* = 10.5, 6.2 Hz, 1H, H-15b), 5.11 (dd, *J* = 17.2, 1.1 Hz, 1H, H-20), 5.12 (dd, *J* = 11.0, 1.1 Hz, 1H, H-20), 5.45 (q, *J* = 7.2 Hz, 1H, H-8), 5.60 (s, 1H, H-5a), 6.03 (dd, *J* = 17.2, 11.0 Hz, 1H, H-19), 6.65 (d, *J* = 7.6 Hz, 1H, H-4), 6.80 (t, *J* = 7.6 Hz, 1H, H-2), 7.14 (t, *J* = 8.0 Hz, 1H, H-3), 7.26 (dd, *J* = 7.5, 1.3 Hz, H-1), 7.49 (t, *J* = 8.0 Hz, 1H, H-12), 7.67 (d, *J* = 7.6 Hz, 1H, H-14), 7.76 (t, *J* = 8.4 Hz, 1H, H-13), 8.26 (d, *J* = 7.6 Hz, 1H, H-11); **^{13}C NMR (100 MHz, $CDCl_3$)**: δ = 17.1 (q, C-17), 22.8 (q, C-21), 23.0 (q, C-22), 38.3 (t, C-16), 41.2 (s, C-18), 53.4 (d, C-8), 57.3 (d, C-15b), 62.0 (s, C-16a), 78.0 (d, C-5a), 109.5 (d, C-4), 114.8 (t, C-20), 119.1 (d, C-2), 120.8 (s, C-10a), 125.3 (d, C-1), 127.1 (d, C-11), 127.5 (d, 2C, C-12, C-14), 129.2 (s, C-16b), 129.3 (d, C-3), 134.9 (d, C-13), 143.7 (d, C-19), 147.3 (s, C-14a), 149.9 (s, C-4a), 151.0 (s, C-15a), 160.2 (s, C-10), 166.8 (s, C-7). All data are in agreement with the reported data.[109]

<u>5a,16a-*epi*-ardeemin (2.38):</u>



^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.06 (s, 1H, H-21), 1.23 (s, 1H, H-22), 1.61 (d, *J* = 7.3 Hz, 3H, H-17), 2.91 (dd, *J* = 14.0, 8.7 Hz, 1H, H-16), 3.16 (dd, *J* = 14.0, 8.6 Hz, 1H, H-16), 4.72 (t, *J* = 8.6 Hz, 1H, H-15b), 5.19 (dd, *J* = 17.4, 1.1 Hz, 1H, H-20), 5.22 (dd, *J* = 10.7, 1.1 Hz, 1H, H-20), 5.44 (q, *J* = 7.3 Hz, 1H, H-8), 5.55 (s, 1H, H-5a), 6.03 (dd, *J* = 17.4, 10.8 Hz, 1H, H-19), 6.54 (d, *J* = 7.8 Hz, 1H, H-4), 6.70 (td, *J* = 7.5, 1.1 Hz, 1H, H-2), 7.02 (m, 1H, H-3), 7.23 (dd, *J* = 7.6, 1.4 Hz, 1H, H-1), 7.45 (ddd, *J* = 8.1, 7.1, 1.2 Hz, 1H, H-12), 7.60 (d, *J* = 7.9 Hz, 1H, H-14), 7.71 (ddd, *J* = 8.3, 7.1, 1.5 Hz, 1H, H-13), 8.21 (m, 1H, H-11); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 16.5 (q, C-17), 22.7 (q, C-21), 22.9 (q, C-22), 38.7 (t, C-16), 42.0 (s, C-18), 53.6 (d, C-8), 56.9 (d, C-15b), 62.3 (s, C-16a), 80.0 (d, C-5a), 109.3 (d, C-4), 115.1 (t, C-20), 118.9 (d, C-2), 120.7 (s, C-10a), 125.8 (d, C-1), 127.1 (d, C-11), 127.3 (d, C-14), 127.5 (d, C-12), 128.7 (d, C-3), 131.7 (s, C-16b), 134.8 (d, C-13), 143.8 (d, C-19), 147.1 (s, C-14a), 148.5 (s, C-4a), 150.9 (s, C-15a), 160.2 (s, C-10), 168.3 (s, C-7).

***tert*-Butyl 3-((1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl)methyl)-8a-(3-methylbut-2-en-1-yl)-1,4-dioxohexahydropyrrolo[1,2-*a*]pyrazine-2(1*H*)-carboxylate (2.39a):**

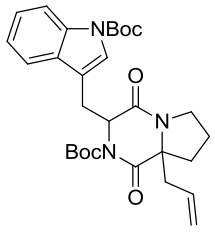


DKP **2.3** (107 mg, 0.31 mmol, diastereomeric mixture) was dissolved in dry DCM (6 mL) under Ar, Et_3N (85 μL, 0.61 mmol) followed by DMAP (80 mg, 0.61 mmol) were added at 0 °C and the reaction mixture was stirred for 5 min. Boc_2O (431 μL, 1.83 mmol) was added via syringe in one portion, the cooling bath was removed and the reaction mixture was stirred at r.t. for 15 h. Water was added and the reaction mixture was extracted with AcOEt, washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography (SiO_2, hexane/AcOEt, 10:1, gradient to 3:1) to give 67 mg less polar *trans*-diastereomer as a colorless solid and 65 mg of more polar *cis*-diastereomer as a colorless foam. The overall yield was 132 mg (78%). **m.p. (*trans*)** 107-109 ºC; **R_f(*trans*)** = 0.7; **R_f(*cis*)** = 0.4 (hexane/AcOEt, 1:1); **IR**: ν[cm^{-1}]2978, 2932, 1773, 1728, 1656, 1453, 1367, 1332, 1254, 1147, 1083, 1017, 913, 850, 766, 729, 646, 593; **MS ESI+ *m/z*, (%)**: 574 (98, $[M+Na]^+$), 474 (74, $[M+Na\text{-}CO_2\text{-isobutylene}]^+$), 418 (49, $[M+Na\text{-}CO_2\text{-}2isobutylene]^+$), 374 (100, $[M+Na\text{-}2CO_2\text{-}2isobutylene]^+$), 352 (7, $[M+H\text{-}2CO_2\text{-}2isobutylene]^+$); **HRMS ESI+ *m/z***: ($[M+Na]^+$): Calcd. for $C_{31}H_{41}N_3O_6$: 574.2893; Found: 574.2887;

^{1}H NMR (400 MHz, $CDCl_3$): *trans*-diastereomer: δ = 0.52-0.62 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 1.31-1.33 (m, 2H, $NCH_2C\underline{H}_2CH_2$), 1.51 (s, 3H, $=CCH_3$), 1.57 (s, 9H, $C(CH_3)_3$), 1.60-1.68 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 1.64 (s, 9H, $C(CH_3)_3$), 1.66 (s, 3H, $=CCH_3$), 2.18 (dd, *J* = 14.3, 7.3 Hz, 1H, $C\underline{H}_2CH=$), 2.29 (dd, *J* = 14.2, 8.5 Hz, 1H, $C\underline{H}_2CH=$), 3.16-3.26 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.46 (dd, *J* = 14.5, 5.0 Hz, 1H, $ArCH_2$), 3.55 (dd, *J* = 14.5, 2.0 Hz, 1H, $ArCH_2$), 3.57-3.66 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 4.83 (dd, *J* = 4.8, 2.4 Hz, 1H, αCH), 4.93 (t, *J* = 7.9 Hz, 1H, $CH_2C\underline{H}=$), 7.16-7.22 (m, 1H, CH_{Ar}), 7.22-7.30 (m, 2H, CH_{Ar}), 7.48 (d, *J* = 7.8 Hz, 1H, CH_{Ar}), 8.08 (d, *J* = 8.3 Hz, 1H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: *trans*-diastereomer: δ = 18.1 (q, $=C\underline{C}H_3$), 19.4 (t, $NCH_2\underline{C}H_2CH_2$), 26.2 (q, $=C\underline{C}H_3$), 28.3 (q, $C(\underline{C}H_3)_3$), 28.4 (q, $C(\underline{C}H_3)_3$), 29.3 (t, $ArCH_2$), 33.8 (t, $NCH_2CH_2\underline{C}H_2$), 37.8 (t, $\underline{C}H_2CH=$), 44.4 (t, $N\underline{C}H_2CH_2CH_2$), 60.4 (d, αCH), 69.3 (s, C_{Pro}), 83.77 (s, $\underline{C}(CH_3)_3$), 83.81 (s, $\underline{C}(CH_3)_3$), 114.3 (s, C_{Ar}), 115.2 (d, CH_{Ar}), 116.7 (d, $CH_2\underline{C}H=$), 119.9 (d, CH_{Ar}), 122.7 (d, CH_{Ar}), 124.8 (d, CH_{Ar}), 126.1 (d, CH_{Ar}), 130.6 (s, C_{Ar}), 135.4 (s, C_{Ar}), 137.5 (s, $=\underline{C}(CH_3)_2$), 149.6 (s, $C=O_{Boc}$), 151.2 (s, $C=O_{Boc}$), 164.2 (s, C=O), 169.2 (s, C=O). All data for the *trans*-diastereomer are in agreement with the reported data.[37] **^{1}H NMR (400 MHz, $CDCl_3$)**: *cis*-diastereomer: δ = 1.26 (s, 9H, $C(CH_3)_3$),

1.59 (s, 3H, =CCH$_3$), 1.65 (s, 9H, C(CH$_3$)$_3$), 1.71 (s, 3H, =CCH$_3$), 1.86-1.95 (m, 2H, NCH$_2$CH$_2$CH$_2$), 2.03 (td, *J* = 12.1, 8.4 Hz, 1H, NCH$_2$CH$_2$CH$_2$), 2.13-2.23 (m, 2H, CH$_2$CH=, NCH$_2$CH$_2$CH$_2$), 2.34 (dd, *J* = 14.6, 8.1 Hz, 1H, CH$_2$CH=), 3.31 (dd, *J* = 14.7, 7.4 Hz, 1H, ArCH$_2$), 3.35-3.44 (m, 2H, NCH$_2$CH$_2$CH$_2$, ArCH$_2$), 3.91 (dt, *J* = 12.4, 8.5 Hz, 1H, NCH$_2$CH$_2$CH$_2$), 5.03-5.12 (m, 2H, CH$_2$CH=, αCH), 7.21-7.33 (m, 2H, CH$_{Ar}$), 7.42 (s, 1H, CH$_{ind-2}$), 7.64 (d, *J* = 7.4 Hz, 1H, CH$_{Ar}$), 8.10 (d, *J* = 7.4 Hz, 1H, CH$_{Ar}$); **^{13}C NMR (101 MHz, CDCl$_3$)**: *cis*-diastereomer: δ = 18.1 (q, =CCH$_3$), 20.3 (t, NCH$_2$CH$_2$CH$_2$), 26.2 (q, =CCH$_3$), 27.6 (q, C(CH$_3$)$_3$), 28.4 (q, C(CH$_3$)$_3$), 30.8 (t, ArCH$_2$), 35.3 (t, NCH$_2$CH$_2$CH$_2$), 36.6 (t, CH$_2$CH=), 45.5 (t, NCH$_2$CH$_2$CH$_2$), 60.7 (d, αCH), 69.1 (s, C$_{Pro}$), 83.7 (s, C(CH$_3$)$_3$), 84.3 (s, C(CH$_3$)$_3$), 115.4 (d, CH$_{Ar}$), 115.5 (s, C$_{ind-3}$), 117.6 (d, CH$_2$CH=), 119.4 (d, CH$_{Ar}$), 122.9 (d, CH$_{Ar}$), 124.78 (d, CH$_{Ar}$), 124.82 (d, CH$_{Ar}$), 130.5 (s, C$_{Ar}$), 135.6 (s, C$_{Ar}$), 136.7 (s, =C(CH$_3$)$_2$), 149.6 (s, C=O$_{Boc}$), 151.1 (s, C=O$_{Boc}$), 164.7 (s, C=O), 169.4 (s, C=O).

***tert*-Butyl 8a-allyl-3-((1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl)methyl)-1,4-dioxohexahydropyrrolo[1,2-*a*]pyrazine-2(1*H*)-carboxylate (2.39b):**

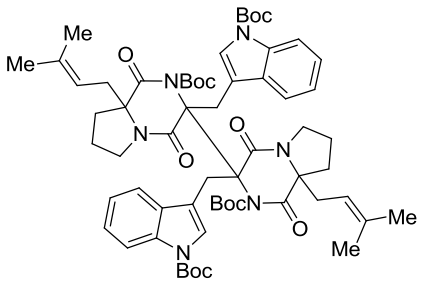


DKP **2.20** (180 mg, 0.56 mmol, diastereomeric mixture) was dissolved in dry DCM (8 mL) under Ar, Et$_3$N (160 μL, 1.11 mmol) followed by DMAP (136 mg, 1.11 mmol) were added at 0 °C and the reaction mixture was stirred for 5 min. Boc$_2$O (740 μL, 3.34 mmol) was added via syringe in one portion, the cooling bath was removed and the reaction mixture was stirred at r.t for 15 h. Water was added and the reaction mixture was extracted with AcOEt. The combined organic layers were washed with brine, dried over MgSO$_4$, filtered and concentrated. The residue was purified by column chromatography (SiO$_2$, hexane/AcOEt, 10:1, gradient to 3:1) to give 166 mg less polar *trans*-diastereomer as a colorless foam, 55 mg mixture of two diastereomers and 13 mg of more polar *cis*-diastereomer. The overall yield was 234 mg (78%). **R$_f$**(*trans*) = 0.3; **R$_f$**(*cis*) = 0.2 (hexane/AcOEt, 2:1); **IR**: ν[cm^{-1}] 2979, 2933, 1727, 1660, 1456, 1368, 1293, 1270, 1256, 1227, 1155, 1082, 1018, 982, 923, 855, 770, 750, 638; **MS ESI+ *m/z*, (%)**: 1069 (8, [2M+Na]$^+$), 583 (100), 546 (93, [M+Na]$^+$), 446 (35, [M+Na-isobutylene-CO$_2$]$^+$), 368 (37, [M+H-2isobutylene-CO$_2$]$^+$), 324 (13, [M+H-2isobutylene-2CO$_2$]$^+$), 209 (8), 195 (13, [M+H-2isobutylene-2CO$_2$-ArCH$_2$]$^+$); **HRMS ESI+ *m/z***: ([M+Na]$^+$): Calcd. for C$_{29}$H$_{37}$O$_6$N$_3$Na: 546.2575; Found: 546.2574; **^{1}H NMR (400 MHz, CDCl$_3$)**: *trans*-diastereomer: δ = 0.35-0.49 (m, 1H, NCH$_2$CH$_2$CH$_2$), 1.08-1.20 (m, 1H, NCH$_2$CH$_2$CH$_2$), 1.46-1.72 (m, 2H, NCH$_2$CH$_2$CH$_2$), 1.55 (s, 9H, C(CH$_3$)$_3$), 1.63 (s, 9H,

$C(CH_3)_3$), 2.17-2.30 (m, 2H, $C\underline{H}_2CH$=), 3.12-3.23 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.43-3.59 (m, 2H, $ArCH_2$), 3.62-3.73 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 4.86 (dd, *J* = 4.8, 2.7 Hz, 1H, αCH), 5.01 (dd, *J* = 17.1, 1.7 Hz, 1H, $=CH_2$), 5.08 (dd, *J* = 10.1, 1.8 Hz, 1H, $=CH_2$), 5.55 (ddt, *J* = 17.5, 10.1, 7.4 Hz, 1H, $CH_2C\underline{H}$=), 7.18 (td, *J* = 7.6, 1.1 Hz, 1H, CH_{Ar}), 7.23 (br. s, 1H, $CH_{ind\text{-}2}$), 7.27 (ddd, *J* = 8.3, 7.1, 1.3 Hz, 1H, CH_{Ar}), 7.47 (d, *J* = 7.7 Hz, 1H, CH_{Ar}), 8.08 (d, *J* = 8.2 Hz, 1H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: *trans*-diastereomer: δ = 19.1 (t, $NCH_2\underline{C}H_2CH_2$), 28.2 (q, $C(\underline{C}H_3)_3$), 28.3 (q, $C(\underline{C}H_3)_3$), 29.3 (t, $ArCH_2$), 33.3 (t, $NCH_2CH_2\underline{C}H_2$), 43.2 (t, $\underline{C}H_2CH$=), 44.1 (t, $N\underline{C}H_2CH_2CH_2$), 60.5 (d, αCH), 69.1 (s, C_{Pro}), 83.80 (s, $\underline{C}(CH_3)_3$), 83.83 (s, $\underline{C}(CH_3)_3$), 114.1 (s, $C_{ind\text{-}3}$), 115.2 (d, CH_{Ar}), 119.9 (d, CH_{Ar}), 120.5 (t, $=CH_2$), 122.6 (d, CH_{Ar}), 124.8 (d, CH_{Ar}), 126.3 (d, CH_{Ar}), 130.5 (s, C_{Ar}), 130.8 (d, $\underline{C}H=CH_2$), 135.4 (s, $\underline{C}_{Ar}$NBoc), 149.5 (s, $C=O_{Boc}$), 151.3 (s, $C=O_{Boc}$), 164.2 (s, C=O), 168.9 (s, C=O).

^{1}H NMR (400 MHz, $CDCl_3$): *cis*-diastereomer: δ = 1.34 (s, 9H, $C(CH_3)_3$), 1.65 (s, 9H, $C(CH_3)_3$), 1.80-2.07 (m, 4H, $NCH_2C\underline{H}_2C\underline{H}_2$, $C\underline{H}_2CH$=), 2.11 (dd, *J* = 14.1, 7.7 Hz, 1H, $C\underline{H}_2CH$=), 2.20 (ddd, *J* = 12.9, 6.8, 2.6 Hz, 1H, $NCH_2CH_2C\underline{H}_2$), 3.28-3.42 (m, 3H, $ArCH_2$, $NC\underline{H}_2CH_2CH_2$), 3.79-3.94 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 4.96 (dd, *J* = 17.0, 1.6 Hz, 1H, $=CH_2$), 5.04-5.12 (m, 2H, αCH, $=CH_2$), 5.63 (ddt, *J* = 17.3, 10.1, 7.3 Hz, 1H, $CH_2C\underline{H}$=), 7.25 (td, *J* = 7.5, 1.1 Hz, 1H, CH_{Ar}), 7.31 (ddd, *J* = 8.3, 7.2, 1.4 Hz, 1H, CH_{Ar}), 7.44 (s, 1H, $CH_{ind\text{-}2}$), 7.63 (dt, *J* = 7.7, 0.9 Hz, 1H, CH_{Ar}), 8.10 (d, *J* = 8.1 Hz, 1H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: *cis*-diastereomer: δ = 20.0 (t, $NCH_2\underline{C}H_2CH_2$), 27.8 (q, $C(\underline{C}H_3)_3$), 28.4 (q, $C(\underline{C}H_3)_3$), 30.1 (t, $ArCH_2$), 34.5 (t, $NCH_2CH_2\underline{C}H_2$), 42.6 (t, $\underline{C}H_2CH$=), 45.5 (t, $N\underline{C}H_2CH_2CH_2$), 60.9 (d, αCH), 68.3 (s, C_{Pro}), 83.9 (s, $\underline{C}(CH_3)_3$), 84.5 (s, $\underline{C}(CH_3)_3$), 115.3 (s, $C_{ind\text{-}3}$), 115.5 (d, CH_{Ar}), 119.5 (d, CH_{Ar}), 119.9 (t, $=CH_2$), 123.1 (d, CH_{Ar}), 125.0 (d, CH_{Ar}), 125.1 (d, $CH_{ind\text{-}2}$), 130.6 (s, C_{Ar}), 131.5 (d, $CH_2\underline{C}H$=), 135.6 (s, $\underline{C}_{Ar}$NBoc), 149.7 (s, $C=O_{Boc}$), 151.2 (s, $C=O_{Boc}$), 164.6 (s, C=O), 168.9 (s, C=O).

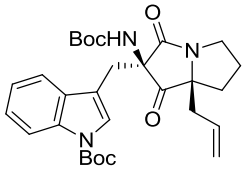
di-*tert*-Butyl 3,3'-bis((1-(*tert*-butoxycarbonyl)-1*H*-indol-3-yl)methyl)-8a,8'a-bis(3-methylbut-2-en-1-yl)-1,1',4,4'-tetraoxododecahydro-[3,3'-bipyrrolo[1,2-*a*]pyrazine]-2,2'(1*H*,1'*H*)-dicarboxylate (2.41):



Dry Schlenk flask was charged with HMDS (100 µL, 0.48 mmol) under Ar followed by THF (0.5 mL). The solution was cooled to -78°C and *n*BuLi (313 µL, 0.48 mmol, 1.6 M in hexanes) was added dropwise and stirred at -78°C for 20 min. A solution of DKP **2.39a** (205 mg, 0.372 mmol) in THF (3 mL) was added dropwise over 7 min

and stirring was continued for 30 min. $Cp_2Fe^+PF_6^-$ (260 mg, 0.80 mmol) was added in small portions until decoloration stopped and the blue color persisted and the reaction mixture was stirred at -78°C for 1 h. The reaction mixture was quenched with saturated NH_4Cl and diluted with Et_2O and filtered through a pad of silica gel and concentrated. The residue was purified by column chromatography (hexane/AcOEt, 6:1 gradient to 1:1) to give 45 mg (22%) dimer **2.41** as a colorless foam and 100 mg recoverd **2.39a** (50%). $\mathbf{R_f}$ = 0.6 (hexane/AcOEt, 2:1); **IR**: *v*[cm^{-1}] 2926, 1732, 1648, 1455, 1365, 1308, 1273, 1253, 1154, 1081, 1054, 1017, 985, 910, 856, 794, 749, 732, 512; **MS ESI+ *m/z*, (%)**:1161 (65), 1123 (100, $[M+Na]^+$), 1001 (28, $[M+H-CO_2$-isobutylene$]^+$), 723 (17, $[M+Na-4CO_2$-4isobuthylene$]^+$), 574 (43, [M+Na-arylideneDKP]$^+$), 550 (5, $[DKP_{monomer}-H]^+$); **HRMS ESI+ *m/z*,** ($[M+Na]^+$): Calcd. for $C_{62}H_{80}N_6O_{12}$: 1123.5726; Found: 1123.5728; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 1.22-1.30 (m, 2H, C<u>H</u>$_2$CH=), 1.50 (s, 18H, C(C<u>H</u>$_3$)$_3$), 1.40-1.47 (m, 2H, C<u>H</u>$_2$CH=), 1.48-1.58 (m, 2H, NCH$_2$C<u>H</u>$_2$CH$_2$), 1.53 (s, 6H, =CC<u>H</u>$_3$), 1.62 (s, 18H, C(C<u>H</u>$_3$)$_3$), 1.63 (s, 6H, =CC<u>H</u>$_3$), 1.70-1.81 (m, 2H, NCH$_2$C<u>H</u>$_2$CH$_2$), 1.93 (dd, *J* = 12.8, 7.2 Hz, 2H, NCH$_2$CH$_2$C<u>H</u>$_2$), 2.22 (td, *J* = 12.2, 9.1 Hz, 2H, NCH$_2$CH$_2$C<u>H</u>$_2$), 2.91 (ddd, *J* = 12.4, 9.7, 2.7 Hz, 2H, NC<u>H</u>$_2$CH$_2$CH$_2$), 3.50 (dt, *J* = 12.3, 9.0 Hz, 2H, NC<u>H</u>$_2$CH$_2$CH$_2$), 3.78 (d, *J* = 13.9 Hz, 2H, ArCH$_2$), 4.62 (t, *J* = 6.8 Hz, 2H, CH$_2$C<u>H</u>=), 5.29 (d, *J* = 14.2 Hz, 1H, ArCH$_2$), 7.16 (ddd, *J* = 8.2, 7.2, 1.2 Hz, 2H), 7.21-7.26 (m, 2H, CH$_{Ar}$), 7.56 (s, 2H, CH$_{Ar}$), 7.68 (d, *J* = 7.6 Hz, 2H, CH$_{Ar}$), 8.10 (d, *J* = 8.4 Hz, 2H, CH$_{Ar}$); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 17.9 (q, =C<u>C</u>H$_3$), 20.1 (t, NCH$_2$<u>C</u>H$_2$CH$_2$), 25.9 (q, =C<u>C</u>H$_3$), 28.3 (q, C(<u>C</u>H$_3$)$_3$), 28.4 (q, C(<u>C</u>H$_3$)$_3$), 28.6 (t, ArCH$_2$), 30.5 (t, NCH$_2$CH$_2$<u>C</u>H$_2$), 34.9 (t, <u>C</u>H$_2$=CH), 46.7 (t, N<u>C</u>H$_2$CH$_2$CH$_2$), 70.2 (s, C$_{Pro}$), 78.7 (s, ArCH$_2$<u>C</u>), 82.7 (s, <u>C</u>(CH$_3$)$_3$), 83.6 (s, <u>C</u>(CH$_3$)$_3$), 114.9 (d, CH$_{Ar}$), 115.7 (s, C$_{Ar}$), 118.4 (d, CH$_2$<u>C</u>H=), 121.4 (d, CH$_{Ar}$), 122.4 (d, CH$_{Ar}$), 124.3 (d, CH$_{Ar}$), 127.2 (d, CH$_{Ar}$), 131.2 (s, C$_{Ar}$), 133.7 (s, =<u>C</u>CH$_3$), 135.5 (s, C$_{Ar}$), 149.8 (s, C=O$_{Boc}$), 153.4 (s, C=O$_{Boc}$), 169.7 (s, C=O), 172.9 (s, C=O).

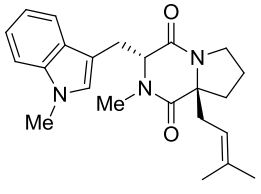
***tert*-Butyl 3-(((2*R**,7a*S**)-7a-Allyl-2-((*tert*-butoxycarbonyl)amino)-1,3-dioxohexahydro-1*H*-pyrrolizin-2-yl)methyl)-1*H*-indole-1-carboxylate (2.44):**



*n*BuLi (263 µL, 0.42 mmol, 1.6 M in hexanes) was added dropwise to a solution of HMDS (87 µL, 0.42 mmol) in DME (1 mL) at -78 ºC and the reaction mixture was stirred for 30 min. A solution of **2.39b** (110 mg, 0.21 mmol) in DME (2 mL) was added dropwise at -78 ºC, stirring was continued for 15 min and the cooling bath was removed to reach to r.t. over 1 h. $Cp_2Fe^+PF_6^-$ (ca 280 mg, 0.84 mmol) was added until the blue color of the oxidant persisted. The reaction

mixture was stired for 30 min and quenched by a few drops of saturated NH_4Cl solution, diluted with Et_2O and filtered through a silica gel pad which was washed with AcOEt. The filtrates were preadsorbed on silica gel and evaporated to dryness. Puurification by column chromatography (SiO_2, hexane/AcOEt, 5:1, gradient to 2:1) gave 95 mg (86%) **2.44** as a pale yellow powder. **m.p.** 175-176 ºC (decomposition with foaming); $\mathbf{R_f}$ = 0.4 (hexane/EtOAc 2:1); **IR**: ν[cm^{-1}] 3335, 2979, 1769, 1734, 1688, 1519, 1452, 1366, 1337, 1308, 1272, 1257, 1231, 1154, 1090, 1022, 913, 768, 731; **MS ESI+ *m/z*, (%)**: 583 (35), 546 (100, $[M+Na]^+$), 524 (13, $[M+H]^+$), 490 (7, [M+Na-isobutylene]$^+$), 468 (20, [M+H-isobutylene]$^+$); **HRMS ESI+ *m/z***: ($[M+Na]^+$): Calcd. for $C_{29}H_{37}N_3O_6Na$: 546.2580; Found: 546.2576; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 0.02 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 0.96 (m, 1H, $NCH_2C\underline{H}_2CH_2$), 1.41 (br. s, 10H, $C(CH_3)_3$, $NCH_2CH_2C\underline{H}_2$), 1.65 (br. s, 10H, $C(CH_3)_3$, $NCH_2C\underline{H}_2CH_2$), 2.44 (dd, *J* = 13.7, 8.0 Hz, 1H, $C\underline{H}_2CH$=), 2.72 (dd, *J* = 13.7, 6.8 Hz, 1H, $C\underline{H}_2CH$=), 3.02-3.16 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.09 (d, *J* = 13.1 Hz, 1H, $ArCH_2$), 3.29 (d, *J* = 13.2 Hz, 1H, $ArCH_2$), 3.65 (ddd, *J* = 12.0, 9.6, 5.3 Hz, 1H, $NC\underline{H}_2CH_2CH_2$), 5.01-5.09 (m, 2H, $=CH_2$), 5.18 (br. s, 1H, N<u>H</u>Boc), 5.83 (m, 1H, $CH_2C\underline{H}$=), 7.20-7.27 (m, 1H, CH_{Ar}), 7.30 (ddd, *J* = 8.3, 7.2, 1.3 Hz, 1H, CH_{Ar}), 7.40 (s, 1H, $CH_{ind\text{-}2}$), 7.55 (d, *J* = 7.7 Hz, 1H, CH_{Ar}), 8.07 (d, *J* = 8.1 Hz, 1H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 24.0 (t, $NCH_2\underline{C}H_2CH_2$), 27.6 (t, $NCH_2CH_2\underline{C}H_2$), 28.40 (q, $C(\underline{C}H_3)_3$), 28.42 (q, $C(\underline{C}H_3)_3$), 31.0 (t, $ArCH_2$), 40.4 (t, $\underline{C}H_2CH$=), 42.5 (t, $N\underline{C}H_2CH_2CH_2$), 65.2 (s, O=C<u>C</u>C=O), 74.4 (s, C_{Pro}), 81.3 (s, $\underline{C}(CH_3)_3$), 84.4 (s, $\underline{C}(CH_3)_3$), 112.0 (s, $C_{ind\text{-}3}$), 115.2 (d, CH_{Ar}), 119.3 (t, $=CH_2$), 119.8 (d, CH_{Ar}), 123.2 (d, CH_{Ar}), 125.2 (d, CH_{Ar}), 126.6 (d, $CH_{ind\text{-}2}$), 129.9 (s, C_{Ar}), 133.0 (d, $\underline{C}H=CH_2$), 135.1 (s, $\underline{C}_{Ar}$NBoc), 149.4 (s, NHC=O), 153.9 (s, $N_{ind}C$=O), 171.4 (s, $C=O_{Trp}$), 209.9 (s, $C=O_{keto}$).

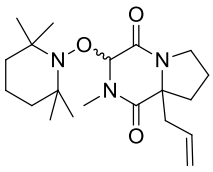
(3*R,8a*S**)-2-Methyl-3-((1-methyl-1*H*-indol-3-yl)methyl)-8a-(3-methylbut-2-en-1-yl)hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (2.45):**



NaH (56 mg, 1.4 mmol, 60% in mineral oil) was added to a solution of ***cis*-2.3** (120 mg, 0.34 mmol) in dry THF (7 mL) under Ar at 0 °C and the reaction mixture was stirred for 30 min. Neat MeI (130 μL, 2.1 mmol) was added dropwise and stirring was continued at r.t. for 4 h. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered and evaporated to give a yellow residue, which was adsorbed at silica gel and purified by column chromatography (hexane/AcOEt, 1:2) affording 153 mg (86%) **2.45** as a colorless foam. $\mathbf{R_f}$ = 0.3 (hexane/EtOAc, 1:2); **IR**: ν[cm^{-1}] 2927, 1647, 1451, 1401, 1377, 1332, 741; **MS ESI+**

m/z*, (%)**: 418 (20, $[M+K]^+$), 402 (100, [M+Na]), 380 (50, $[M+H]^+$); **HRMS ESI+ *m/z: ($[M+H]^+$): Calcd. for $C_{23}H_{30}N_3O_2$: 380.2333; Found: 380.2332; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 0.51 (dt, *J* = 12.2, 10.1 Hz, 1H, $NCH_2CH_2C\underline{H}_2$), 0.75-0.85 (m, 1H, $NCH_2C\underline{H}_2CH_2$), 1.42-1.54 (m, 1H, $NCH_2C\underline{H}_2CH_2$), 1.49 (s, 3H, $=CCH_3$), 1.60-1.68 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 1.64 (s, 3H, $=CCH_3$), 2.08 (dd, *J* = 7.8, 14.0 Hz, 1H, $C\underline{H}_2CH=$), 2.33 (dd, *J* = 14.1, 7.7 Hz, 1H, $C\underline{H}_2CH=$), 2.99-3.07 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.02 (s, 3H, $N_{ind}CH_3$), 3.21 (dd, *J* = 14.9, 4.5 Hz, 1H, $ArCH_2$), 3.34 (ddd, *J* = 12.2, 9.8, 5.9 Hz, 1H, $NC\underline{H}_2CH_2CH_2$), 3.62 (dd, *J* = 14.8, 2.5 Hz, 1H, $ArCH_2$), 3.67 (s, 3H, $N_{DKP}CH_3$), 4.11 (dd, *J* = 4.3, 2.6 Hz, 1H, αCH), 4.84 (t, *J* = 7.8 Hz, 1H, $CH_2C\underline{H}=$), 6.68 (s, 1H, $CH_{ind\text{-}2}$), 7.05 (ddd, *J* = 8.0, 6.7, 1.4 Hz, 1H, CH_{Ar}), 7.13-7.20 (m, 2H, CH_{Ar}), 7.59 (d, *J* = 8.0 Hz, 1H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 18.0 (q, $=C\underline{C}H_3$), 19.3 (t, $NCH_2\underline{C}H_2CH_2$), 26.1 (q, $=C\underline{C}H_3$), 27.4 (t, $ArCH_2$), 32.3 (q, $N_{ind}CH_3$), 32.7 (q, $N_{DKP}CH_3$), 34.2 (t, $C\underline{H}_2CH=$), 36.7 (t, $NCH_2CH_2\underline{C}H_2$), 43.9 (t, $N\underline{C}H_2CH_2CH_2$), 63.0 (d, αCH), 67.7 (s, C_{Pro}), 107.3 (s, $C_{ind\text{-}3}$), 108.9 (d, CH_{Ar}), 117.3 (d, $CH_2\underline{C}H=$), 119.1 (d, CH_{Ar}), 119.9 (d, CH_{Ar}), 121.9 (d, CH_{Ar}), 128.0 (s, C_{Ar}), 128.1 (d, $CH_{ind\text{-}2}$), 136.7 (s, $\underline{C}_{Ar}NCH_3$), 137.1 (s, $=\underline{C}(CH_3)_2$), 164.1 (s, C=O), 169.1 (s, C=O).

8a-Allyl-2-methyl-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)hexahydropyrrolo[1,2-a]pyrazine-1,4-dione (3.1):

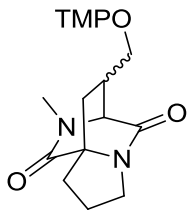


A solution of HMDS (190 µL, 0.913 mmol) in dry DME (1.5 mL) was cooled to -78 °C, *n*BuLi (570 µL, 0.913 mmol, 1.6 M in hexane) was added dropwise and the solution was stirred at -78 °C for 30 min. A solution of **2.21a** (95 mg, 0.456 mmol) in DME (3 mL) was added dropwise. The flask containing the starting material was washed with additional DME (1 mL), which was added to the reaction mixture and stirring was continued at -78 °C for 35 min. TEMPO (86 mg, 0.553 mmol) was added followed by portionwise addition of $Cp_2Fe^+PF_6^-$ (ca 350 mg, 1.05 mmol) until the blue color persisted. The reaction mixture was stirred at -78 °C to -40 °C for 1 h. The reaction mixture was quenched by the addition of a drop of saturated NH_4Cl solution and filtered through pad of silica gel, which was washed with AcOEt. The filtrate was adsorbed on a small amount of silica gel and purified by column chromatography (hexane/AcOEt, 5:1, gradient to 1:1) to give 30 mg less polar diastereomer as a colorless gum, 84 mg more polar diastereomer as a colorless powder, and 43 mg mixture of two diastereomers. The overall yield was 157 mg (95%). Since the less polar diastereomer very rapidly isomerizes to the more polar diastereomer in $CDCl_3$ it was not fully characterized. $\mathbf{R}_f$ (less polar) = 0.6; $\mathbf{R}_f$ (more polar) = 0.3 (hexane/EtOAc, 1:1); **IR**: ν[cm^{-1}]

2977, 1665, 1458, 1400, 1379, 1364, 1339, 1284, 1236, 1183, 1132, 1063, 1008, 978, 955, 905, 846, 738, 559; **MS ESI+ *m/z*, (%)**: 386 (100, $[M+Na]^+$), 364 (79, $[M+H]^+$), 356 (10), 230 (59, $[M+Na\text{-}TEMPO]^+$), 207 (17, $[M\text{-}TEMPO]^+$); **HRMS ESI+ *m/z*,** ($[M+H]^+$): Calcd. for $C_{20}H_{34}N_3O_3$: 364.2600; Found: 364.2594; **^{1}H NMR (400 MHz, C_6D_6)**: less polar diastereomer (detectable resonances): δ = 1.03 (s, 3H, CH_{3TEMPO}), 1.17 (s, 3H, CH_{3TEMPO}), 1.21 (s, 3H, CH_{3TEMPO}), 1.36 (s, 3H, CH_{3TEMPO}), 1.78-1.93 (m, 2H, $NCH_2C\underline{H}_2C\underline{H}_2$), 1.99 (dd, *J* = 13.5, 7.2 Hz, 1H, $C\underline{H}_2CH$=), 2.63 (dd, *J* = 13.4, 7.4 Hz, 1H, $C\underline{H}_2CH$=), 2.82-2.97 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 3.02 (s, 3H, NCH_3), 3.42-3.60 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.88-4.05 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 4.93-5.09 (m, 2H, $=CH_2$), 5.34 (s, 1H, CHOTMP), 5.50-5.67 (m, 1H, CH_2CH=).

^{1}H NMR (400 MHz, $CDCl_3$): more polar diastereomer: δ = 1.07 (s, 3H, CH_{3TEMPO}), 1.15 (s, 6H, CH_{3TEMPO}), 1.32 (m, 1H, CH_{2TEMPO}), 1.42-1.54 (m, 5H, CH_{2TEMPO}), 1.45 (s, 3H, CH_{3TEMPO}), 1.87-1.98 (m, 2H, $NCH_2C\underline{H}_2CH_2$), 2.02-2.11 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 2.29 (ddd, *J* = 12.8, 6.7, 2.9 Hz, 1H, $NCH_2CH_2C\underline{H}_2$), 2.65 (ddt, *J* = 14.0, 8.2, 1.2 Hz, 1H, $C\underline{H}_2CH$=), 2.85 (ddd, *J* = 14.2, 6.7, 1.5 Hz, 1H, $C\underline{H}_2CH$=), 3.14 (s, 3H, NCH_3), 3.48 (ddd, *J* = 12.3, 8.6, 3.9 Hz, 1H, $NC\underline{H}_2CH_2CH_2$), 3.72 (dt, *J* = 12.2, 8.5 Hz, 1H, $NC\underline{H}_2CH_2CH_2$), 5.11-5.19 (m, 2H, $=CH_2$), 5.38 (s, 1H, CHOTMP), 5.76-5.93 (m, 1H, $CH_2C\underline{H}$=); **^{13}C NMR (101 MHz, $CDCl_3$)**: more polar diastereomer: δ = 17.1 (t, CH_{2TEMPO}), 20.2 (q, CH_{3TEMPO}), 20.79 (q, CH_{3TEMPO}), 20.82 (t, $NCH_2\underline{C}H_2CH_2$), 32.9 (q, CH_{3TEMPO}), 33.51 (t, $NCH_2CH_2\underline{C}H_2$), 33.54 (q, CH_{3TEMPO}), 36.3 (q, NCH_3), 40.9 (t, CH_{2TEMPO}), 41.0 (t, CH_{2TEMPO}), 43.4 (t, $\underline{C}H_2CH$=), 45.8 (t, $N\underline{C}H_2CH_2CH_2$), 60.5 (s, C_{TEMPO}), 62.2 (s, C_{TEMPO}), 67.8 (s, C_{Pro}), 93.5 (d, $\underline{C}$HOTMP), 119.5 (t, $=CH_2$), 132.3 (d, $CH_2\underline{C}H$=), 162.0 (s, C=O), 172.0 (s, C=O).

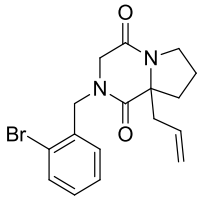
10-Methyl-7-(((2,2,6,6-tetramethylpiperidin-1-yl)oxy)methyl)tetrahydro-1*H*-6,8a-(epiminomethano)indolizine-5,9(6*H*)-dione (3.5):



A 0.02 M solution of alkoxyamine **3.1** (42 mg, 0.12 mmol) in *t*BuOH (6 mL) was degassed in a Carius tube by three freeze-pump-thaw cycles. The reaction vessel was sealed and immersed to an oil bath preheated at 130 °C and stirred at this temperature for 1 h. The solvent was evaporated under reduced pressure and purification of the residue by column chromatography (hexane/AcOEt 1:1) gave 36 mg (86%) **3.5** as an inseparable 1:1 mixture of diastereomers as a colorless gum. $\mathbf{R_f}$ = 0.2 (hexane/EtOAc 1:1); **IR**: *ν*[cm^{-1}] 2928, 1682, 1426, 1397, 1062, 922, 730, 646, 540; **MS ESI+ *m/z*, (%)**: 749 (11, $[2M+Na]^+$), 402 (5), 386 (19, $[M+Na]^+$), 364 (100, $[M+H]^+$), 356 (12), 246 (7, $[M+Na\text{-}TMP]^+$), 230 (59, $[M+Na\text{-}TEMPO]^+$), 207 (17,

[M-TEMPO]$^+$); **HRMS ESI+ *m/z,*** ([M+H]$^+$): Calcd. for $C_{20}H_{34}N_3O_3$: 364.2600; Found: 364.2595; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 0.98-1.17 (m, 24H, CH_{3TEMPO}), 1.18-1.34 (m, 5H, CH_{2TEMPO}, $CH_{2bridge}$), 1.34-1.52 (m, 9H, CH_{2TEMPO}, $CH_{2bridge}$), 1.71-1.81 (m, 2H, $NCH_2CH_2C\underline{H}_2$), 1.88-2.13 (m, 6H, $NCH_2C\underline{H}_2CH_2$, $CH_{2bridge}$), 2.45-2.61 (m, 2H, CH_{bridge}), 2.68-2.78 (m, 2H, $NCH_2CH_2C\underline{H}_2$), 3.00 (s, 3H, NCH_3), 3.06 (s, 3H, NCH_3), 3.37-3.52 (m, 4H, $NC\underline{H}_2CH_2CH_2$), 3.59-3.71 (m, 4H, $C\underline{H}_2OTMP$), 3.92 (d, *J* = 3.3 Hz, 1H, $CH_{bridgehead}$), 4.03 (d, *J* = 1.4 Hz, 1H, $CH_{bridgehead}$); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 17.15 (t, CH_{2TEMPO}), 17.18 (t, CH_{2TEMPO}), 20.19 (q, CH_{3TEMPO}), 20.21 (q, CH_{3TEMPO}), 20.3 (q, 2C, CH_{3TEMPO}), 24.70 (t, $NCH_2\underline{C}H_2CH_2$), 24.74 (t, $NCH_2\underline{C}H_2CH_2$), 29.4 (t, $NCH_2CH_2\underline{C}H_2$), 29.6 (t, $NCH_2CH_2\underline{C}H_2$), 32.3 (q, NCH_3), 32.9 (q, CH_{3TEMPO}), 33.1 (q, CH_{3TEMPO}), 33.3 (q, CH_{3TEMPO}), 33.6 (t, $CH_{2bridge}$), 33.7 (q, CH_{3TEMPO}), 33.8 (q, NCH_3), 34.1 (t, $CH_{2bridge}$), 36.8 (d, CH_{bridge}), 38.1 (d, CH_{bridge}), 39.75 (t, CH_{2TEMPO}), 39.84 (t, 2C, CH_{2TEMPO}), 39.9 (t, CH_{2TEMPO}), 43.80 (t, $N\underline{C}H_2CH_2CH_2$), 43.82 (t, $N\underline{C}H_2CH_2CH_2$), 60.0 (s, C_{TEMPO}), 60.1 (s, C_{TEMPO}), 64.1 (d, $CH_{bridgehead}$), 65.1 (d, $CH_{bridgehead}$), 67.1 (s, C_{Pro}), 67.2 (s, C_{Pro}), 76.5 (t, $\underline{C}H_2OTMP$), 77.1 (t, $\underline{C}H_2OTMP$), 166.6 (s, C=O), 168.4 (s, C=O), 171.2 (s, C=O), 171.5 (s, C=O).

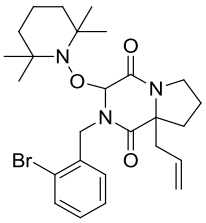
8-Allyl-2-(2-bromobenzyl)hexahydropyrrolo[1,2-a]pyrazine-1,4-dione (3.6):



DKP **2.22b** (630 mg, 3.24 mmol) was dissolved in dry DMF (32 mL) under Ar and the solution was cooled to 0 °C. NaH (170 mg, 4.22 mmol, 60% suspension in mineral oil) was added and stirring was continued at 0 °C for 40 min. Neat 2-bromobenzyl bromide (1.06 g, 4.22 mmol) was added dropwise and the reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, filtered and concentrated. The residue was adsorbed at silica gel and purified by column chromatography (hexane/AcOEt, 1:1, gradient to 100% AcOEt) to give 1.05 g (89%) **3.6** as a colorless oil, which solidified upon standing in air during a few days to give a colorless solid. **m.p.** 83-84 °C; **R_f** = 0.3 (hexane/AcOEt, 1:5); **IR:** *ν*[cm^{-1}] 2979, 1652, 1569, 1437, 1330, 1283, 1226, 1204, 1180, 1046, 1025, 1000, 926, 747, 660, 605, 590, 520; **MS ESI+ *m/z*, (%)**:387/385 (97/100, [M+Na]$^+$), 365/363 (8/10, [M+H]$^+$), 337/335 (3/4, [M+H-CO]$^+$); **HRMS ESI+ *m/z***: ([M+H]$^+$): Calcd. for $C_{17}H_{20}{}^{79}BrN_2O_2$: 363.0703; Found: 363.0705; **Anal. Calcd. for** $C_{17}H_{19}BrN_2O_2$ (363.26): C, 56.21; H, 5.27; N, 7.71; Br, 22.00; Found: C, 56.19; H, 5.35; N, 7.50; Br, 21.83; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 1.91-2.07 (m, 2H, $NCH_2C\underline{H}_2CH_2$), 2.13-2.28 (m, 2H, $NCH_2CH_2C\underline{H}_2$), 2.43 (dd, *J* = 13.8, 7.4 Hz, 1H, $C\underline{H}_2CH$=), 2.57 (dd, *J* = 13.8,

7.4 Hz, 1H, C$\underline{H}_2$CH=), 3.49 (m, 1H, NC$\underline{H}_2$CH$_2$CH$_2$), 3.75 (d, *J* = 17.2 Hz, 1H, BnNC$\underline{H}_2$), 3.83 (m, 1H, NC$\underline{H}_2$CH$_2$CH$_2$), 4.01 (d, *J* = 17.2 Hz, 1H, BnNC$\underline{H}_2$), 4.69 (d, *J* = 14.9 Hz, 1H, ArCH$_2$), 4.79 (d, *J* = 14.9 Hz, 1H, CH$_2$Ar), 5.09-5.18 (m, 2H, =CH$_2$), 5.72 (ddt, *J* = 17.4, 10.0, 7.5 Hz, 1H, CH$_2$C$\underline{H}$=), 7.11-7.20 (m, 1H, CH$_{Ar}$), 7.23-7.31 (m, 2H, CH$_{Ar}$), 7.55 (d, *J* = 7.9 Hz, 1H, CH$_{Ar}$); **^{13}C NMR (101 MHz, CDCl$_3$)**: δ = 20.4 (t, NCH$_2$$\underline{C}H_2CH_2$), 34.8 (t, NCH$_2CH_2$$\underline{C}H_2$), 42.1 (t, $\underline{C}$H$_2$CH=), 45.1 (t, N$\underline{C}$H$_2$CH$_2$CH$_2$), 49.1 (t, ArCH$_2$), 51.2 (t, BnN$\underline{C}$H$_2$), 67.7 (s, C$_{Pro}$), 121.1 (t, =CH$_2$), 124.1 (s, =$\underline{C}$Br), 128.0 (d, CH$_{Ar}$), 129.8 (d, CH$_{Ar}$), 130.4 (d, CH$_{Ar}$), 131.2 (d, CH$_2$$\underline{C}$H=), 133.2 (d, CH$_{Ar}$), 134.8 (s, C$_{Ar}$), 162.3 (s, C=O), 169.2 (s, C=O).

8-Allyl-2-(2-bromobenzyl)-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)hexahydropyrrolo[1,2-a]pyrazine-1,4-dione (3.7):

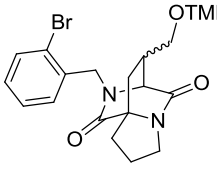


A solution of HMDS (460 µL, 2.204 mmol) in THF (5 mL) was cooled to -78 °C, *n*BuLi (1 mL, 1.65 mmol, 1.6 M in hexane) was added and the solution was stirred for 30 min. DKP **3.6** (400 mg, 1.1 mmol) dissolved in dry THF (10 mL) was added dropwise via cannula. After addition of all **3.6** the yellow reaction mixture completely solidified. Upon warming by removing the cooling bath it turned into a viscous solution, which did not solidify upon cooling back, but vigorous stirring was necessary to ensure mixing. Additional THF (5 mL) was added and stirring at -78 °C was continued for 30 min. TEMPO (215 mg, 1.4 mmol) was added followed by portionwise addition of $Cp_2Fe^+PF_6^-$ (ca 1.1 g, 3.31 mmol) with vigorous stirring at -78 °C until the color of the ferrocenium salt persisted. After 30 min the reaction mixture was quenched with a drop of saturated NH_4Cl solution and filtered through a plug of silica gel, which was washed a few times with AcOEt. Silica gel was added to the filtrate, which was evaporated to dryness and purified by column chromatography (hexane/AcOEt, 10:1, gradient to 2:1) to give 62 mg of less polar diastereomer as a pale yellow honey, 182 mg more polar diastereomer as a colorless solid and 223 mg colorless solid, which consisted mainly of less polar diastereomer with traces of the more polar diastereomer. Since the less polar diastereomer very rapidly isomerizes to the more polar diastereomer in $CDCl_3$ only detectable resonances are provided. The overall yield was 467 mg (82%). **m.p.** (*more polar*) 161-163 °C; **R_f** (less polar) = 0.4; **R_f** (more polar) = 0.3 (hexane/AcOEt, 2:1); **IR**: *ν*[cm^{-1}] 2933, 1673, 1441, 1378, 1364, 1334, 1259, 1232, 1210, 1180, 1151, 1131, 1046, 1024, 1008, 976, 954, 908, 876, 813, 750, 730; **MS ESI+ *m/z*, (%)**: 1061/1059/1057 (18/32/15

$[2M+Na]^+$), 905/903/901 (9/15/7, $[2M+Na\text{-}TEMPO]^+$), 749/747/745 (4/7/4, $[2M+Na\text{-}2TEMPO]^+$), 542/540 (96/100, $[M+Na]^+$), 520/518 (64/65, $[M+H]^+$), 401/399 (19/18, $[M+Na\text{-}TMPH]^+$), 386/384 (44/45, $[M+Na\text{-}TEMPO]^+$), 364/361 (35/33, $[M+H\text{-}TEMPO]^+$), 335/333 (15/15, $[M\text{-}TEMPO\text{-}CO]^+$), 323 (7); **HRMS ESI+ *m/z,*** ($[M+H]^+$): Calcd. for $C_{26}H_{37}{}^{79}BrN_2O_5$: 518.2013; Found: 518.2013; **Anal. Calcd. For** $C_{26}H_{36}BrN_3O_3$ (518.50): C, 60.23; H, 7.00; N, 8.10; Br, 15.41; Found: C, 60.40; H, 7.11; N, 7.84; Br, 15.12; **^{1}H NMR (400 MHz, $CDCl_3$)**: less polar diastereomer (detectable resonances from a 7.4:1 more polar/less polar mixture): δ = 1.06 (s, 3H, CH_{3TEMPO}), 1.14 (s, 3H, CH_{3TEMPO}), 1.22 (s, 3H, CH_{3TEMPO}), 1.34 (s, 3H, CH_{3TEMPO}), 2.21-2.33 (m, 2H, $NCH_2C\underline{H}_2CH_2$), 2.50 (dd, *J* = 13.7, 7.5 Hz, 1H, $C\underline{H}_2CH$=), 2.59-2.68 (m, 2H, $C\underline{H}_2CH$=, $NCH_2CH_2C\underline{H}_2$), 3.26-3.37 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 3.66-3.74 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.96-4.07 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 4.82 (d, *J* = 15.7 Hz, 1H, $ArCH_2$), 4.87-4.96 (m, 2H, $=CH_2$), 5.35 (d, *J* = 15.8 Hz, 1H, $ArCH_2$), 5.66 (s, 1H, C<u>H</u>OTMP), 7.37 (dd, *J* = 7.7, 1.7 Hz, 1H, CH_{Ar}).

^{1}H NMR (101 MHz, $CDCl_3$): more polar diastereomer: δ = 1.11 (s, 3H, CH_{3TEMPO}), 1.16 (s, 3H, CH_{3TEMPO}), 1.26 (s, 3H, CH_{3TEMPO}), 1.31-1.41 (m, 1H, CH_{2TEMPO}), 1.36 (s, 3H, CH_{3TEMPO}), 1.43-1.66 (m, 5H, CH_{2TEMPO}), 1.86-2.03 (m, 2H, $NCH_2C\underline{H}_2CH_2$), 2.02-2.13 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 2.36 (ddd, *J* = 12.1, 6.3, 2.5 Hz, 1H, $NCH_2CH_2C\underline{H}_2$), 2.73 (dd, *J* = 14.0, 8.2 Hz, 1H, $C\underline{H}_2CH$=), 2.92 (dd, *J* = 14.0, 6.6 Hz, 1H, $C\underline{H}_2CH$=), 3.51 (ddd, *J* = 3.9, 8.6, 12.5 Hz, 1H, $NC\underline{H}_2CH_2CH_2$), 3.80 (dt, *J* = 12.1, 8.3 Hz, 1H, $NC\underline{H}_2CH_2CH_2$), 4.67 (d, *J* = 15.7 Hz, 1H, $ArCH_2$), 5.15-5.23 (m, 2H, $=CH_2$), 5.28 (d, *J* = 15.7 Hz, 1H, $ArCH_2$), 5.47 (s, 1H, C<u>H</u>OTMP), 5.84-5.98 (m, 1H, $CH_2C\underline{H}$=), 7.02 (d, *J* = 7.6 Hz, 1H, CH_{Ar}), 7.12 (td, *J* = 7.7, 1.6 Hz, 1H, CH_{Ar}), 7.24 (td, *J* = 7.5, 1.2 Hz, 1H, CH_{Ar}), 7.54 (dd, 1.1, 8.1 Hz, 1H, CH_{Ar}); **^{13}C NMR (400 MHz, $CDCl_3$)**: more polar diastereomer: δ = 17.1 (t, CH_{2TEMPO}), 20.2 (t, $NCH_2\underline{C}H_2CH_2$), 20.7 (q, CH_{3TEMPO}), 20.9 (q, CH_{3TEMPO}), 33.1 (q, CH_{3TEMPO}), 33.3 (q, CH_{3TEMPO}), 33.8 (t, $NCH_2CH_2\underline{C}H_2$), 40.8 (t, CH_{2TEMPO}), 41.1 (t, CH_{2TEMPO}), 43.1 (t, $\underline{C}H_2CH$=), 45.6 (t, $N\underline{C}H_2CH_2CH_2$), 51.1 (t, $ArCH_2$), 60.5 (s, C_{TEMPO}), 62.3 (s, C_{TEMPO}), 67.8 (s, C_{Pro}), 90.8 (d, <u>C</u>HOTMP), 119.6 (t, $=CH_2$), 123.5 (s, =CBr), 127.9 (d, CH_{Ar}), 129.0 (d, CH_{Ar}), 129.3 (d, CH_{Ar}), 132.2 (d, $CH_2\underline{C}H$=), 133.3 (d, CH_{Ar}), 135.7 (s, C_{Ar}), 161.6 (s, C=O), 172.1 (s, C=O).

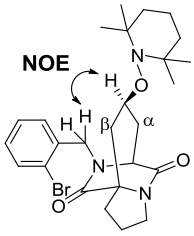
10-(2-Bromobenzyl)-7-(((2,2,6,6-tetramethylpiperidin-1-yl)oxy)methyl)tetrahydro-1*H*-6,8a-(epiminomethano)indolizine-5,9(6*H*)-dione (**3.8**):



A 0.02 M solution of **3.7** (310 mg, 0.60 mmol) in *t*BuOH (30 mL) was degassed in a Carius tube by three freeze-pump-thaw cycles. The

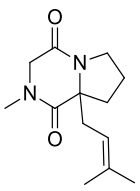
reaction vessel was sealed and immersed to an oil bath preheated at 130 °C and stirred for 1 h. The solvent was evaporated under reduced pressure and the residue was purified by column chromatography (hexane/AcOEt 2:1, gradient to 1:2) to yield 256 mg (83%) **3.8** as an inseparable 1:1 mixture of diastereomers and 15 mg (5%) **3.9** resulting from a 7-endo-trig cyclization. $\mathbf{R_f}$**(3.9)** = 0.6; $\mathbf{R_f}$**(3.8)** = 0.3 (hexane/AcOEt, 1:2); **IR**: ν[cm^{-1}] 2930, 1687, 1470, 1417, 1374, 1359, 1262, 1244, 1210, 1133, 1046, 1028, 993, 956, 873, 752, 731, 657, 606, 523; **MS ESI+ *m/z*, (%)**: 558/556 (8/7, $[M+K]^+$), 542/540 (95/100, $[M+Na]^+$), 520/518 (85/86, $[M+H]^+$), 396/394 (15/16, [M+H-(2,6-dimethylhepta-2,5-diene)]$^+$), 321 (5), 217 (13), 173 (4); **HRMS ESI+ *m/z*,** ($[M+H]^+$): Calcd. for $C_{26}H_{37}{}^{79}BrO_3N_3$: 518.2013; Found: 518.2013; **Anal. Calcd. For** $C_{26}H_{36}BrN_3O_3$ (518.50): C, 60.23; H, 7.00; N, 8.10; Br, 15.41; Found: C, 60.49; H, 7.09; N, 7.88; Br, 15.39; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 0.95 (s, 3H, CH_{3TEMPO}), 0.97 (s, 3H, CH_{3TEMPO}), 1.05 (s, 6H, CH_{3TEMPO}), 1.08 (s, 3H, CH_{3TEMPO}), 1.09 (s, 3H, CH_{3TEMPO}), 1.11 (s, 3H, CH_{3TEMPO}), 1.16 (s, 3H, CH_{3TEMPO}), 1.23-1.68 (m, 14H, CH_{2TEMPO}, $CH_{2bridge}$), 1.73-1.88 (m, 2H, $NCH_2CH_2C\underline{H}_2$), 1.94-2.12 (m, 6H, $CH_{2bridge}$, $NCH_2C\underline{H}_2CH_2$, $NCH_2C\underline{H}_2CH_2$), 2.22 (m, 1H, CH_{bridge}), 2.51-2.62 (m, 1H, CH_{bridge}), 2.74-2.88 (m, 2H, $NCH_2CH_2C\underline{H}_2$), 3.38-3.58 (m, 6H, CH_2OTMP, $NC\underline{H}_2CH_2CH_2$), 3.62-3.72 (m, 2H, $C\underline{H}_2$OTMP), 4.07 (d, *J* = 1.6 Hz, 1H, $CH_{bridgehead}$), 4.08 (d, *J* = 3.3 Hz, 1H, $CH_{bridgehead}$), 4.32 (d, *J* = 15.5 Hz, 1H, $ArCH_2$), 4.45 (d, *J* = 14.7 Hz, 1H, $ArCH_2$), 4.95 (d, *J* = 14.7 Hz, 1H, $ArCH_2$), 5.18 (d, *J* = 15.5 Hz, 1H, $ArCH_2$), 7.11-7.20 (m, 3H, CH_{Ar}), 7.24-7.33 (m, 2H, CH_{Ar}), 7.34-7.38 (m, 1H, CH_{Ar}), 7.56 (m, *J* = 8.0 Hz, 2H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 17.20 (t, CH_{2TEMPO}), 17.22 (t, CH_{2TEMPO}), 20.16 (q, CH_{3TEMPO}), 20.22 (q, CH_{3TEMPO}), 20.3 (q, CH_{3TEMPO}), 20.6 (q, CH_{3TEMPO}), 24.8 (t, 2C, $NCH_2\underline{C}H_2CH_2$), 29.6 (t, $NCH_2CH_2\underline{C}H_2$), 29.7 (t, $NCH_2CH_2\underline{C}H_2$), 33.0 (q, CH_{3TEMPO}), 33.1 (q, CH_{3TEMPO}), 33.3 (q, CH_{3TEMPO}), 33.8 (q, CH_{3TEMPO}), 33.9 (t, $CH_{2bridge}$), 34.0 (t, $CH_{2bridge}$), 36.9 (d, CH_{bridge}), 38.6 (d, CH_{bridge}), 39.7 (t, CH_{2TEMPO}), 39.8 (t, CH_{2TEMPO}), 39.9 (t, 2C, CH_{2TEMPO}), 43.9 (t, $N\underline{C}H_2CH_2CH_2$), 44.0 (t, $N\underline{C}H_2CH_2CH_2$), 48.7 (t, $ArCH_2$), 49.9 (t, $ArCH_2$), 60.0 (s, C_{TEMPO}), 60.07 (s, 2C, C_{TEMPO}), 60.09 (s, C_{TEMPO}), 62.4 (d, $CH_{bridgehead}$), 62.5 (d, $CH_{bridgehead}$), 67.3 (s, 2C, C_{Pro}), 76.9 (t, $\underline{C}H_2$OTMP), 77.1 (t, $\underline{C}H_2$OTMP), 123.5 (s, =CBr), 124.2 (s, =CBr), 128.09 (d, CH_{Ar}), 128.13 (d, CH_{Ar}), 129.71 (d, CH_{Ar}), 129.73 (d, CH_{Ar}), 130.0 (d, CH_{Ar}), 131.5 (d, CH_{Ar}), 133.38 (d, CH_{Ar}), 133.41 (d, CH_{Ar}), 135.5 (s, C_{Ar}), 135.6 (s, C_{Ar}), 166.6 (s, C=O), 168.1 (s, C=O), 171.2 (s, C=O), 171.3 (s, C=O).

(6*S,8*S**,9a*S**)-11-(2-Bromobenzyl)-8-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)hexahydro-1*H*,5*H*-6,9a-(epiminomethano)pyrrolo[1,2-a]azepine-5,10-dione (3.9):**



R_f = 0.6 (hexane/AcOEt, 1:2); **IR**: ν[cm^{-1}] 2929, 1681, 1436, 1375, 1360, 1245, 1229, 1181, 1132, 1027, 991, 974, 751; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 0.97 (s, 3H, CH_{3TEMPO}), 1.02 (s, 3H, CH_{3TEMPO}), 1.04 (s, 3H, CH_{3TEMPO}), 1.06 (s, 3H, CH_{3TEMPO}), 1.18-1.56 (m, 6H, CH_{2TEMPO}), 1.70 (m, 2H, $\alpha C\underline{H}_{2bridge}$, $\beta C\underline{H}_{2bridge}$), 1.80-2.05 (m, 3H, $NCH_2C\underline{H}_2C\underline{H}_2$), 2.34-2.46 (m, 2H, $\alpha C\underline{H}_{2bridge}$, $\beta C\underline{H}_{2bridge}$), 2.72-2.86 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 3.42-3.49 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.66 (ddd, *J* = 11.2, 7.2, 5.7 Hz, 1H, $NC\underline{H}_2CH_2CH_2$), 3.75-3.91 (br. m, 1H, C<u>H</u>OTMP), 4.07 (dd, *J* = 6.8, 1.2 Hz, 1H, $CH_{bridgehead}$), 4.65 (d, *J* = 15.0 Hz, 1H, $ArCH_2$), 4.77 (d, *J* = 15.0 Hz, 1H, $ArCH_2$), 7.15 (td, *J* = 1.5, 7.8 Hz, 1H, CH_{Ar}), 7.26-7.30 (m, 1H, CH_{Ar}), 7.37 (dd, *J* = 7.6, 1.3 Hz, 1H, CH_{Ar}), 7.55 (d, *J* = 7.9 Hz, 1H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 17.2 (t, CH_{2TEMPO}), 20.3 (q, 2C, CH_{3TEMPO}), 23.2 (t, $NCH_2\underline{C}H_2CH_2$), 30.1 (t, $\alpha\underline{C}H_{2bridge}$), 34.2 (q, 2C, CH_{3TEMPO}), 35.2 (t, $NCH_2CH_2\underline{C}H_2$), 40.2 (t, 2C, CH_{2TEMPO}), 40.8 (t, $\beta C\underline{H}_{2bridge}$), 45.1 (t, $N\underline{C}H_2CH_2CH_2$), 48.9 (t, $ArCH_2$), 59.3 (d, $CH_{bridgehead}$), 60.6 (s, 2C, C_{TEMPO}), 65.4 (s, C_{Pro}), 77.6 (d, <u>C</u>HOTMP), 124.1 (s, =CBr), 128.4 (d, CH_{Ar}), 129.8 (d, CH_{Ar}), 131.2 (d, CH_{Ar}), 133.3 (d, CH_{Ar}), 135.6 (s, C_{Ar}), 168.3 (s, C=O), 170.3 (s, C=O).

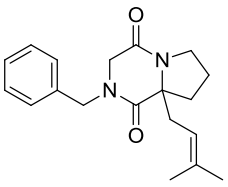
2-Methyl-8a-(3-methylbut-2-en-1-yl)hexahydropyrrolo[1,2-a]pyrazine-1,4-dione (3.10a):



A solution of **2.22** (310 mg, 1.40 mmol) in dry THF (14 mL) was cooled to 0 °C, NaH (70 mg, 1.75 mmol, 60% suspension in mineral oil) was added and the reaction mixture was stirred at 0 °C for 40 min. Methyl iodide (115 µL, 1.83 mmol) was added dropwise and the reaction mixture was stirred at 0 °C for 2 h. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$. After filtration the filtrates were concentrated, the residue was adsorbed on silica and purified by column chromatography (acetone/AcOEt, 1:2, gradient to 1:1) to give 296 mg (90%) **3.10a** as a colorless oil. **R_f** = 0.2 (acetone/AcOEt, 1:2); **IR**: ν[cm^{-1}] 2926, 1644, 1442, 1401, 1379, 1333, 1306, 1279, 1244, 1211, 1155, 1113, 1073, 1011, 877, 839, 750, 640, 595, 520; **MS ESI+ *m/z*, (%)**: 275 (7, $[M+K]^+$), 259 (100, $[M+Na]^+$), 237 (38, $[M+H]^+$), 167 (9, [M-prenyl]$^+$); **HRMS ESI+ *m/z***: ($[M+H]^+$): Calcd. for $C_{13}H_{21}N_2O_2^+$: 237.1598; Found: 237.1598; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 1.58 (s, 3H, $=CCH_3$), 1.69 (s, 3H, $=CCH_3$), 1.89-2.05 (m, 2H, $NCH_2C\underline{H}_2CH_2$), 2.06-2.24 (m, 2H, $NCH_2CH_2C\underline{H}_2$), 2.38 (dd, *J* = 14.1, 8.2 Hz, 1H, $C\underline{H}_2CH=$), 2.52 (dd, *J* = 14.1, 7.8 Hz, 1H, $C\underline{H}_2CH=$), 2.94 (s, 3H, NCH_3), 3.50 (ddd, *J* = 12.8,

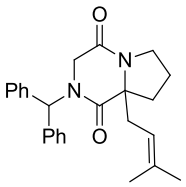
8.8, 4.4 Hz, 1H, NC$\underline{H}_2$CH$_2$CH$_2$), 3.72 (d, *J* = 17.0 Hz, 1H, CH$_3$NC$\underline{H}_2$), 3.80 (dt, *J* = 12.3, 8.5 Hz, 1H, NC$\underline{H}_2$CH$_2$CH$_2$), 4.04 (d, *J* = 17.0 Hz, 1H, CH$_3$NC$\underline{H}_2$), 5.06 (t, *J* = 8.0 Hz, 1H, CH$_2$C$\underline{H}$=); **^{13}C NMR (101 MHz, CDCl$_3$)**: δ = 17.9 (q, =C$\underline{C}$H$_3$), 20.6 (t, NCH$_2\underline{C}$H$_2$CH$_2$), 26.2 (q, =C$\underline{C}$H$_3$), 33.6 (q, NCH$_3$), 35.3 (t, NCH$_2$CH$_2\underline{C}$H$_2$), 36.8 (t, $\underline{C}$H$_2$CH=), 45.1 (t, N$\underline{C}$H$_2$CH$_2$CH$_2$), 53.7 (t, CH$_3$N$\underline{C}$H$_2$), 68.3 (s, C$_{Pro}$), 117.3 (d, CH$_2\underline{C}$H=), 137.9 (s, =$\underline{C}$(CH$_3$)$_2$), 162.8 (s, C=O), 169.6 (s, C=O).

2-Benzyl-8a-(3-methylbut-2-en-1-yl)hexahydropyrrolo[1,2-a]pyrazine-1,4-dione (3.10b):



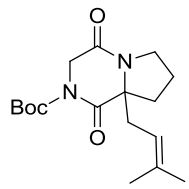
A solution of **2.22** (800 mg, 3.60 mmol) in dry DMF (36 mL) was cooled to 0 °C, NaH (190 mg, 4.68 mmol, 60% suspension in mineral oil) was added and stirring was continued at 0 °C for 40 min. Benzyl bromide (560 μL, 4.68 mmol) was added dropwise and the reaction mixture was stirred at 0 °C for 3 h. The reaction mixture was quenched with saturated NH$_4$Cl solution, extracted with AcOEt. The combined organic layers were dried over anhydrous MgSO$_4$, filtered and evaporated. The residue was purified by column chromatography (100% AcOEt) to give 1.10 g (98%) as a colorless oil, which solidified upon standing for a few days to give **3.10b** as a colorless crystalline solid. **m.p.** 81-83 °C; **R$_f$** = 0.3 (AcOEt); **IR**: *ν*[cm^{-1}] 2892, 1650, 1444, 1378, 1356, 1329, 1300, 1281, 1245, 736, 701, 648; **MS ESI+ *m/z*, (%)**: 335 (8, [M+Na]$^+$), 313 (100, [M+H]$^+$), 243 (3, [M-prenyl]$^+$); **HRMS ESI+ *m/z***: ([M+H]+): Calcd. for C$_{19}$H$_{25}$N$_2$O$_2$: 313.1911; Found: 313.1911; **Anal. Calcd. For** C$_{19}$H$_{24}$N$_2$O$_2$ (312.41): C, 73.05; H, 7.74; N, 8.97; Found: C, 73.20; H, 7.81; N, 8.84; **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 1.48 (s, 3H, CH$_3$), 1.51 (s, 3H, CH$_3$), 1.92-2.08 (m, 2H, NCH$_2$C$\underline{H}_2$CH$_2$), 2.12-2.26 (m, 2H, NCH$_2$CH$_2$C$\underline{H}_2$), 2.39 (dd, *J* = 14.1, 8.4 Hz, 1H, C$\underline{H}_2$CH=), 2.52 (dd, *J* = 14.1, 7.6 Hz, 1H, C$\underline{H}_2$CH=), 3.42-3.51 (m, 1H, NC$\underline{H}_2$CH$_2$CH$_2$), 3.66 (d, *J* = 17.1 Hz, 1H, BnNC$\underline{H}_2$), 3.74-3.82 (m, 1H, NC$\underline{H}_2$CH$_2$CH$_2$), 3.85 (d, *J* = 17.1 Hz, 1H, BnNC$\underline{H}_2$), 4.23 (d, *J* = 14.2 Hz, 1H, PhC$\underline{H}_2$), 4.87 (d, *J* = 14.2 Hz, 1H, PhC$\underline{H}_2$), 4.91-4.96 (m, 1H, CH$_2$C$\underline{H}$=), 7.21-7.41 (m, 5H, CH$_{Ar}$); **^{13}C NMR (101 MHz, CDCl$_3$)**: δ = 17.9 (q, CH$_3$), 20.6 (t, NCH$_2\underline{C}$H$_2$CH$_2$), 26.1 (q, CH$_3$), 35.5 (t, NCH$_2$CH$_2\underline{C}$H$_2$), 37.1 (t, $\underline{C}$H$_2$CH=), 45.1 (t, N$\underline{C}$H$_2$CH$_2$CH$_2$), 50.1 (t, Ph$\underline{C}$H$_2$), 51.2 (t, BnN$\underline{C}$H$_2$), 68.4 (s, C$_{Pro}$), 117.2 (d, CH$_2\underline{C}$H=), 128.2 (d, CH$_{Ar}$), 128.9 (d, CH$_{Ar}$), 129.1 (d, CH$_{Ar}$), 135.7 (s, =$\underline{C}$(CH$_3$)$_2$), 137.8 (s, C$_{Ar}$), 163.0 (s, C=O), 169.5 (s, C=O).

2-Benzhydryl-8-(3-methylbut-2-en-1-yl)hexahydropyrrolo[1,2-a]pyrazine-1,4-dione (3.10c):



DKP **2.22** (400 mg, 1.81 mmol) was dissolved in dry THF (20 mL) and HMPA (2 mL, 10.86 mmol) was added, followed by NaH (91 mg, 2.26 mmol, 60% suspension in mineral oil). The solution was stirred at r.t. for 30 min before the addition of bromodiphenylmethane (1.3 g, 5.43 mmol). The reaction mixture was stirred overnight, quenched with saturated NH_4Cl solution, and extracted with CH_2Cl_2. The combined organic layers were dried over anhydrous $MgSO_4$, filtered, and concentrated. The crude product was purified by flash column chromatography on silica gel (hexane/AcOEt, 3:1, gradient to 1:2) to give 505 mg (72%) **3.10c** as a colorless solid. **m.p.** 111-113 °C; $\mathbf{R_f}$ = 0.4 (hexane/AcOEt, 1:2); **IR**: ν[cm^{-1}] 2928, 1658, 1507, 1445, 1418, 1377, 1327, 1287, 1252, 1187, 1162, 1078, 1031, 921, 873, 845, 730, 710, 610, 554; **MS ESI+ *m/z*, (%)**: 799 (14, $[2M+Na]^+$), 411 (100, $[M+Na]^+$), 389 (23, $[M+H]^+$), 167 (6, [benzhydryl]$^+$); **HRMS ESI+ *m/z***: ($[M+H]^+$): Calcd. for $C_{25}H_{29}N_2O_2$: 389.2224; Found: 389.2223; **Anal. Calcd. For** $C_{25}H_{28}N_2O_2$ (388.51): C, 77.29; H, 7.26; N, 7.21; Found: C, 77.37; H, 7.25; N, 7.01; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 1.38 (s, 3H, CH_3), 1.49 (s, 3H, CH_3), 1.96-2.12 (m, 2H, $NCH_2C\underline{H}_2CH_2$), 2.15-2.31 (m, 2H, $NCH_2CH_2C\underline{H}_2$), 2.42 (dd, *J* = 14.0, 8.5 Hz, 1H, $C\underline{H}_2CH$=), 2.54 (dd, *J* = 14.0, 7.6 Hz, 1H, $C\underline{H}_2CH$=), 3.47-3.54 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.55 (d, *J* = 17.2 Hz, 1H, $Ph_2CHNC\underline{H}_2$), 3.73 (d, *J* = 17.1 Hz, 1H, $Ph_2CHNC\underline{H}_2$), 3.91 (dt, *J* = 12.3, 8.5 Hz, 1H, $NC\underline{H}_2CH_2CH_2$), 4.87 (t, *J* = 8.0 Hz, 1H, $CH_2C\underline{H}$=), 7.09 (d, *J* = 7.3 Hz, 2H, CH_{Ar}), 7.13 (s, 1H, $Ph_2C\underline{H}$), 7.22-7.41 (m, 8H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 17.9 (q, CH_3), 20.6 (t, $NCH_2\underline{C}H_2CH_2$), 25.8 (q, CH_3), 36.1 (t, $NCH_2CH_2\underline{C}H_2$), 36.9 (t, $\underline{C}H_2CH$=), 44.9 (t, $N\underline{C}H_2CH_2CH_2$), 48.4 (t, $Ph_2CHN\underline{C}H_2$), 59.7 (d, $Ph_2\underline{C}H$), 68.6 (s, C_{Pro}), 117.2 (d, $CH_2\underline{C}H$=), 127.5 (d, CH_{Ar}), 127.7 (d, CH_{Ar}), 128.5 (d, CH_{Ar}), 128.9 (d, 2C, CH_{Ar}), 130.0 (d, CH_{Ar}), 137.3 (s, =$\underline{C}(CH_3)_2$), 137.83 (s, C_{Ar}), 137.85 (s, C_{Ar}), 163.4 (s, C=O), 170.1 (s, C=O).

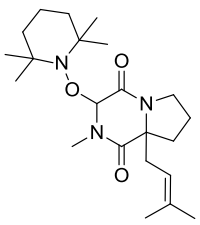
***tert*-Butyl 8a-(3-methylbut-2-en-1-yl)-1,4-dioxohexahydropyrrolo[1,2-a]pyrazine-2(1*H*)-carboxylate (3.10d)**:



DKP **2.22** (495 mg, 2.23 mmol) was dissolved in dry DCM (20 mL) under Ar and cooled to 0 °C. Triethylamine (776 μL, 5.57 mmol) was added followed by DMAP (272 mg, 2.228 mmol). After 10 min neat Boc_2O (1.28 mL, 5.57 mmol) was added and stirring was continued at 0 °C for 1 h and at room temperature for 5 h. The reaction mixture was quenched with water and extracted with

AcOEt. The extracts were dried over anhydrous $MgSO_4$, filtered and evaporated. The crude product was purified by column chromatography (hexane/AcOEt, 3:1, gradient to 1:2) to give 700 mg (98%) **3.10d** as a pale yellow oil. $\mathbf{R_f}$ = 0.4 (hexane/EtOAc, 1:2); **IR**: ν[cm^{-1}] 2978, 1777, 1723, 1655, 1439, 1368, 1289, 1255, 1148, 1055, 1018, 947, 919, 850, 778, 593; **MS ESI+ *m/z*, (%)**: 735 (5), 623 (9), 413 (37), 345 (100, $[M+Na]^+$), 279 (16), 245 (15, [M+Na-isobutylene-CO_2]$^+$); **HRMS ESI+ *m/z***: ($[M+Na]^+$): Calcd. for $C_{17}H_{26}N_2O_4Na$: 345.1784; Found: 345.1785; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 1.51 (s, 9H, C(C$\underline{H}_3$)$_3$), 1.57 (s, 3H, =CCH_3), 1.69 (s, 3H, =CCH_3), 1.95 (m, 2H, NCH_2C$\underline{H}_2$CH_2), 2.15 (ddd, *J* = 13.2, 6.7, 3.7 Hz, 1H, NCH_2CH_2C$\underline{H}_2$), 2.25 (dt, *J* = 13.1, 9.7 Hz, 1H, NCH_2CH_2C$\underline{H}_2$), 2.41 (dd, *J* = 14.3, 7.9 Hz, 1H, C$\underline{H}_2$CH=), 2.52 (dd, *J* = 14.3, 7.9 Hz, 1H, C$\underline{H}_2$CH=), 3.45-3.53 (m, 1H, NC$\underline{H}_2$CH_2CH_2), 3.73 (dt, *J* = 12.2, 8.3 Hz, 1H, NC$\underline{H}_2$CH_2CH_2), 4.14 (d, *J* = 17.3 Hz, 1H, BocNC$\underline{H}_2$), 4.42 (d, *J* = 17.3 Hz, 1H, BocNC$\underline{H}_2$), 5.09 (t, *J* = 7.9 Hz, 1H, CH_2C$\underline{H}$=); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 17.9 (q, =C$\underline{C}H_3$), 20.9 (t, NC$H_2$$\underline{C}$$H_2CH_2$), 26.2 (q, =C$\underline{C}H_3$), 28.1 (q, C($\underline{C}H_3$)$_3$), 35.1 (t, $\underline{C}H_2$CH=), 36.5 (t, NCH_2C$H_2$$\underline{C}$$H_2$), 45.5 (t, N$\underline{C}H_2CH_2CH_2$), 50.1 (t, BocN$\underline{C}H_2$), 69.5 (s, C_{Pro}), 84.5 (s, $\underline{C}$(CH_3)$_3$), 116.7 (d, C$H_2$$\underline{C}$H=), 138.2 (s, =$\underline{C}$($CH_3$)$_2$), 150.6 (s, N$\underline{C}O_2$C($CH_3$)$_3$), 162.8 (s, C=$O_{Gly}$), 169.7 (s, C=$O_{Pro}$).

2-Methyl-8a-(3-methylbut-2-en-1-yl)-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)hexahydropyrrolo[1,2-a]pyrazine-1,4-dione (3.11a):

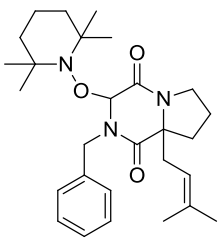


A solution of HMDS (410 µL, 2.10 mmol) in dry THF (3 mL) was cooled to -78 °C, *n*BuLi (900 µL, 1.43 mmol, 1.6 M in hexane) was added dropwise and the solution was stirred at -78 °C for 30 min. A solution of **3.10a** (308 mg, 1.30 mmol) in THF (8 mL) was added dropwise. The flask containing the starting material was washed with additional THF (2 mL), which was added to the reaction mixture and stirring was continued at -78 °C for 30 min. TEMPO (243 mg, 1.56 mmol) was added followed by portionwise addition of $Cp_2Fe^+PF_6^-$ (ca 500 mg, 1.51 mmol) until a blue color persisted. The reaction mixture was stirred at -78 °C for 30 min, quenched by the addition of a drop of saturated NH_4Cl solution and filtered through pad of silica gel, which was washed with AcOEt. The filtrate was adsorbed at a small amount of silica gel and purified by column chromatography (hexane/AcOEt, 5:1, gradient to 1:1) to give 344 mg of a mixture of diastereomers and 90 mg of more polar diastereomer as a colorless solid. The overall yield was 434 mg (85%). Since the less polar diastereomer very rapidly isomerizes to the more polar diastereomer in $CDCl_3$ only detectable resonances are

provided. $\mathbf{R_f}$ = 0.3 (hexane/AcOEt, 1:1); **IR**: ν[cm^{-1}] 2932, 1673, 1444, 1397, 1378, 1363, 1333, 1283, 1240, 1209, 1183, 1132, 1066, 1007, 976, 955, 907, 876, 813, 765; **MS ESI+ *m/z*, (%)**: 1076 (3), 805 (26, $[2M+Na]^+$), 649 (32, $[2M+Na\text{-}TEMPO]^+$), 508 (2, $[2M+Na\text{-}TEMPO\text{-}TMPH]^+$), 493 (6, $[2M+Na\text{-}2TEMPO]^+$), 430 (22, $[M+K]^+$), 414 (100, $[M+Na]^+$), 392 (26, $[M+H]^+$), 273 (19, $[M+Na\text{-}TMPH]^+$), 258 (27, $[M+Na\text{-}TEMPO]^+$), 180 (14, $[TEMPOH+Na]^+$); **HRMS ESI+ *m/z*,** ($[M+H]^+$): Calcd. for $C_{22}H_{38}O_3N_3$: 392.2908; Found: 392.2908; **^{1}H NMR (400 MHz, $CDCl_3$)**: less polar diastereomer (detectable resonances): δ = 2.47-2.52 (m, 2H, $C\underline{H}_2CH$=), 3.19 (s, 3H, NCH_3), 3.81-3.90 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 4.80 (t, J = 8.8 Hz, 1H, $CH_2C\underline{H}$=).

^{1}H NMR (400 MHz, $CDCl_3$): more polar diastereomer: δ = 1.07 (s, 3H, CH_{3TEMPO}), 1.14 (s, 3H, CH_{3TEMPO}), 1.16 (s, 3H, CH_{3TEMPO}), 1.29-1.37 (m, 1H, CH_{2TEMPO}), 1.41-1.58 (m, 5H, CH_{2TEMPO}), 1.46 (s, 3H, CH_{3TEMPO}), 1.66 (s, 3H, $=CCH_3$), 1.73 (s, 3H, $=CCH_3$), 1.83-1.99 (m, 2H, $NCH_2C\underline{H}_2CH_2$), 1.99-2.13 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 2.22 (ddd, J = 12.8, 7.0, 2.7 Hz, 1H, $NCH_2CH_2C\underline{H}_2$), 2.67 (dd, J = 14.5, 6.1 Hz, 2H, $C\underline{H}_2CH$=), 2.75 (dd, J = 14.4, 8.6 Hz, 1H, $C\underline{H}_2CH$=), 3.15 (s, 3H, NCH_3), 3.46 (ddd, J = 12.3, 8.8, 3.8 Hz, 1H, $NC\underline{H}_2CH_2CH_2$), 3.70 (dt, J = 12.1, 8.5 Hz, 1H, $NC\underline{H}_2CH_2CH_2$), 5.23 (m, 1H, $CH_2C\underline{H}$=), 5.40 (s, 1H, CHOTMP); **^{13}C NMR (101 MHz, $CDCl_3$)**: more polar diastereomer: δ = 17.1 (t, CH_{2TEMPO}), 18.2 (q, $=C\underline{C}H_3$), 20.2 (q, CH_{3TEMPO}), 20.9 (q, CH_{3TEMPO}), 21.1 (t, $NCH_2\underline{C}H_2CH_2$), 26.2 (q, $=C\underline{C}H_3$), 32.7 (q, CH_{3TEMPO}), 33.5 (q, CH_{3TEMPO}), 33.6 (t, $NCH_2CH_2\underline{C}H_2$), 36.3 (q, NCH_3), 37.8 (t, $\underline{C}H_2CH$=), 40.8 (t, CH_{2TEMPO}), 40.9 (t, CH_{2TEMPO}), 46.0 (t, $N\underline{C}H_2CH_2CH_2$), 60.3 (s, C_{TEMPO}), 62.2 (s, C_{TEMPO}), 68.5 (s, C_{Pro}), 93.4 (d, $\underline{C}$HOTMP), 118.0 (d, $CH_2\underline{C}H$=), 136.0 (s, $=\underline{C}(CH_3)_2$), 161.9 (s, C=O), 172.5 (s, C=O).

2-Benzyl-8a-(3-methylbut-2-en-1-yl)-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)hexahydropyrrolo[1,2-a]pyrazine-1,4-dione (3.11b):

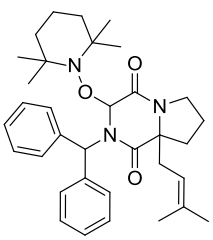


A solution of diisopropylamine (330 µL, 2.30 mmol) in dry THF (5 mL) was cooled to -78 °C and *n*BuLi (970 µL, 1.5 mmol) was added dropwise. The solution was stirred for 30 min and **3.10b** (360 mg, 1.15 mmol) dissolved in THF (10 mL) was added at -78 °C. After stirring for 40 min, TEMPO (216 mg, 1.4 mmol) was added followed by portionwise addition of $Cp_2Fe^+PF_6^-$ until the blue color of the oxidant persisted (ca 590 mg, 1.72 mmol). Stirring was continued for 30 min, the reaction mixture was quenched with a drop of NH_4Cl solution and filtered through a pad of silica gel which was washed with AcOEt. The filtrates were evaporated and the residue was purified by column chromatography (hexane/AcOEt, 15:1,

gradient to 5:1) to give 45 mg less polar diastereomer, 90 mg more polar diastereomer and 260 mg of a mixture of diastereomers. The overall yield was 395 mg (73%). The less polar diastereomer very quickly isomerizes to the more polar diastereomer in $CDCl_3$ and was not characterized by NMR. $\mathbf{R_f}$ = 0.5; $\mathbf{R_f}$ = 0.4 (hexane/EtOAc 3:1); **MS ESI+ *m/z*, (%)**: 623 (68, $[2M+H-2TEMPO]^+$), 468 (100, $[M+H]^+$), 327 (9, $[M+H-TMPH]^+$); **HRMS ESI+ *m/z*,** ($[M+H]^+$): Calcd. for $C_{28}H_{42}N_3O_3$: 468.3221; Found: 468.3213; **^{1}H NMR (400 MHz, $CDCl_3$)**: less polar diastereomer (detectable resonances from a 1:2 more polar/less polar mixture): δ = 1.07 (s, 3H, CH_{3TEMPO}), 1.16 (s, 3H, CH_{3TEMPO}), 1.19 (s, 3H, CH_{3TEMPO}), 1.31 (s, 3H, CH_{3TEMPO}), 1.54 (s, 3H, $=CCH_3$), 1.55 (s, 3H, $=CCH_3$), 2.30-2.37 (m, 1H, $C\underline{H}_2CH=$), 2.71-2.79 (m, 1H, $C\underline{H}_2CH=$), 3.22-3.37 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 4.00-4.13 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 4.61 (d, *J* = 14.8 Hz, 1H, $ArCH_2$), 4.77 (t, *J* = 7.1 Hz, 1H, $CH_2C\underline{H}=$), 5.47 (s, 1H, CHOTMP), 5.53 (d, *J* = 14.8 Hz, 1H, $ArCH_2$).

^{1}H NMR (400 MHz, $CDCl_3$): more polar diastereomer: δ = 1.12 (s, 3H, CH_{3TEMPO}), 1.19 (s, 3H, CH_{3TEMPO}), 1.25 (s, 3H, CH_{3TEMPO}), 1.45 (s, 3H, CH_{3TEMPO}), 1.48-1.65 (m, 6H, CH_{2TEMPO}), 1.70 (s, 3H, $=CCH_3$), 1.76 (s, 3H, $=CCH_3$), 1.82-2.01 (m, 2H, $NCH_2C\underline{H}_2CH_2$), 2.01-2.15 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 2.22-2.35 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 2.72 (dd, *J* = 14.5, 6.2 Hz, 1H, $C\underline{H}_2CH=$), 2.84 (dd, *J* = 14.5, 8.7 Hz, 1H, $C\underline{H}_2CH=$), 3.37-3.52 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.65-3.78 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 4.42 (d, *J* = 14.8 Hz, 1H, $PhCH_2$), 5.31 (t, *J* = 7.5 Hz, 1H, $CH_2C\underline{H}=$), 5.38 (d, *J* = 14.8 Hz, 1H, $PhCH_2$), 5.54 (s, 1H, CHOTMP), 7.14-7.36 (m, 5H, CH_{Ar}); **^{13}C NMR (400 MHz, $CDCl_3$)**: more polar diastereomer: δ = 16.1 (t, CH_{2TEMPO}), 17.0 (q, $=C\underline{C}H_3$), 19.1 (q, CH_{3TEMPO}), 19.80 (t, $NCH_2\underline{C}H_2CH_2$), 19.82 (q, CH_{3TEMPO}), 25.1 (q, $=C\underline{C}H_3$), 31.6 (q, CH_{3TEMPO}), 32.4 (q, CH_{3TEMPO}), 32.7 (t, $NCH_2CH_2\underline{C}H_2$), 36.5 (t, $\underline{C}H_2CH=$), 39.7 (t, CH_{2TEMPO}), 39.8 (t, CH_{2TEMPO}), 44.6 (t, $N\underline{C}H_2CH_2CH_2$), 49.8 (t, $PhCH_2$), 59.2 (s, C_{TEMPO}), 61.1 (s, C_{TEMPO}), 67.3 (s, C_{Pro}), 89.3 (d, $\underline{C}$HOTMP), 116.8 (d, $CH_2\underline{C}H=$), 126.59 (d, CH_{Ar}), 126.64 (d, CH_{Ar}), 127.8 (d, CH_{Ar}), 134.8 (s, C_{Ar}), 136.0 (s, $=\underline{C}(CH_3)_2$), 160.2 (s, C=O), 171.1 (s, C=O).

2-Benzhydryl-8a-(3-methylbut-2-en-1-yl)-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)hexahydropyrrolo[1,2-a]pyrazine-1,4-dione (3.11c):



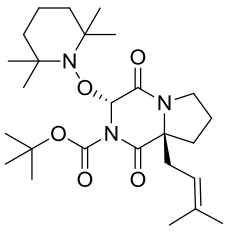
A solution of HMDS (245 μL, 4 mmol) in THF (3 mL) was cooled to -78 °C. *n*BuLi (630 μL, 1.00 mmol, 1.6 M in hexane) was added and the reaction mixture was stirred at this temperature for 30 min. A solution of **3.10c** (300 mg, 0.772 mmol) in THF (7 mL) was added dropwise. The reaction mixture was warmed to -20 °C over 1 h. TEMPO (156 mg, 1.00

mmol) was added followed by portionwise addition of $Cp_2Fe^+PF_6^-$ (385 mg, 1.16 mmol) until the color of the oxidant persisted. The reaction mixture was stirred at -20 °C to 0 °C for 1 h, diluted with Et_2O and quenched with a few drops of saturated NH_4Cl solution. The reaction mixture was filtered through a pad of silica gel, which was washed with AcOEt. The filtrates were evaporated and the residue was purified by column chromatography (hexane/AcOEt, 5:1 gradient to 2:1) to give 340 mg (76%) **3.11c** as a low melting colorless foam as a single diastereomer, whose configuration was not assigned. *Note: The oxidation at -78 °C resulted in poor yield, presumably because of inefficient deprotonation at this temperature.* $\mathbf{R_f}$ = 0.3 (hexane/AcOEt, 3:1); **IR**: *ν*[cm^{-1}] 2931, 1675, 1541, 1507, 1496, 1453, 1420, 1377, 1363, 1313, 1261, 1237, 1185, 1160, 1132, 1081, 1004, 973, 953, 910, 874, 822, 741, 700, 601, 564; **MS ESI+ *m/z*, (%)**: 1110 (4), 953 (9, $[2M+Na\text{-}TEMPO]^+$), 566 (12, $[M+Na]^+$), 544 (100, $[M+H]^+$), 447 (21, [M+H-(5,5-dimethyl-1-pyrroline)]$^+$), 410 (55, $[M+Na\text{-}TEMPO]^+$), 388 (58, $[M+H\text{-}TEMPO]^+$), 319 (68, [M+H-TEMPO-prenyl]$^+$), 167 (29, [benzhydryl]$^+$), 158 (35, $[TEMPOH+H]^+$); **HRMS ESI+ *m/z*,** ($[M+Na]^+$): Calcd. for $C_{34}H_{45}N_3O_3Na$: 566.3353; Found: 566.3352; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 0.80 (s, 3H, CH_{3TEMPO}), 1.03 (s, 3H, CH_{3TEMPO}), 1.06 (s, 3H, CH_{3TEMPO}), 1.15-1.35 (m, 4H, CH_{2TEMPO}), 1.26 (s, 3H, CH_{3TEMPO}), 1.39-1.55 (m, 2H, CH_{2TEMPO}), 1.65 (s, 3H, $=CCH_3$), 1.69 (s, 3H, $=CCH_3$), 1.73-1.85 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 1.84-1.99 (m, 2H, $NCH_2C\underline{H}_2CH_2$), 2.14 (ddd, *J* = 12.8, 6.5, 2.0 Hz, 1H, $NCH_2CH_2C\underline{H}_2$), 2.73-2.91 (m, 2H, $C\underline{H}_2CH=$), 3.44 (ddd, *J* = 12.3, 8.8, 3.6 Hz, 1H, $NC\underline{H}_2CH_2CH_2$), 3.87 (dt, *J* = 12.1, 8.6 Hz, 1H, $NC\underline{H}_2CH_2CH_2$), 5.22 (t, *J* = 7.4 Hz, 1H, $CH_2C\underline{H}=$), 5.55 (s, 1H, C<u>H</u>OTMP), 6.18 (s, 1H, $Ph_2C\underline{H}$), 7.08-7.42 (m, 10H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$):** δ = 17.0 (t, CH_{2TEMPO}), 18.1 (q, $=C\underline{C}H_3$), 20.6 (q, CH_{3TEMPO}), 20.8 (q, CH_{3TEMPO}), 21.1 (t, $NCH_2\underline{C}H_2CH_2$), 26.1 (q, $=C\underline{C}H_3$), 31.9 (q, CH_{3TEMPO}), 33.2 (q, CH_{3TEMPO}), 34.2 (t, $NCH_2CH_2\underline{C}H_2$), 36.8 (t, $\underline{C}H_2CH=$), 40.4 (t, CH_{2TEMPO}), 40.7 (t, CH_{2TEMPO}), 45.4 (t, $N\underline{C}H_2CH_2CH_2$), 60.4 (s, C_{TEMPO}), 61.1 (s, C_{TEMPO}), 66.9 (d, $Ph_2\underline{C}H$), 69.3 (s, C_{Pro}), 89.1 (d, <u>C</u>HOTMP), 118.3 (d, $CH_2\underline{C}H=$), 126.4 (d, CH_{Ar}), 126.8 (d, CH_{Ar}), 128.0 (d, CH_{Ar}), 128.4 (d, CH_{Ar}), 128.7 (d, CH_{Ar}), 131.1 (d, CH_{Ar}), 136.4 (s, C_{Ar}), 137.8 (s, C_{Ar}), 141.8 (s, $=\underline{C}(CH_3)_2$), 162.8 (s, C=O), 172.7 (s, C=O).

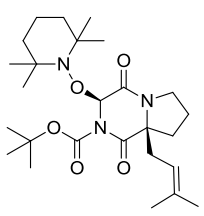
***tert*-Butyl 8a-(3-methylbut-2-en-1-yl)-1,4-dioxo-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)hexahydropyrrolo[1,2-a]pyrazine-2(1*H*)-carboxylate (3.11d):**

A solution of HMDS (840 μL, 4 mmol) in THF (5 mL) was cooled to -78 °C. *n*BuLi (1.8 mL, 2.58 mmol, 1.45 M in hexane) was added and the mixture was stirred at this temperature for 30 min. DKP **3.10d** (640 mg, 2.00 mmol) dissolved in THF (15 mL) was added dropwise.

The reaction mixture was stirred at -78 °C for 20 min, TEMPO (403 mg, 2.58 mmol) was added followed by portionwise addition of $Cp_2Fe^+PF_6^-$ (1.32 g, 3.97 mmol) until the color of the oxidant persisted. The reaction mixture was stirred at -78 °C for 1 h, diluted with Et_2O and quenched by a few drops of saturated NH_4Cl solution. The reaction mixture was filtered through a pad of silica gel, which was washed with AcOEt. The filtrates were preadsorbed at silica gel, evaporated to dryness and the products were isolated by column chromatography (hexane/AcOEt, 10:1 gradient to 2:1) to give 448 mg *trans*-diastereomer as a colorless solid and 300 mg *cis*-isomer as a gummy colorless foam. The overall yield was 748 mg (79%). The structure of the *trans*-diastereomer was proved by X-ray crystallography. *Note: It is important to keep the temperature at -78 °C since at higher temperatures a Chan-type rearrangement of the enolate occurs.* **m.p.** (*trans*) 123-124 °C; $\mathbf{R_f}$(*trans*) = 0.3, (hexane/AcOEt, 5:1); $\mathbf{R_f}$(*cis*) = 0.4 (hexane/AcOEt, 3:1); **IR**: ν[cm^{-1}] 3000, 2931, 1778, 1736, 1678, 1453, 1394, 1366, 1279, 1246, 1146, 1061, 1016, 983, 954, 907, 875, 851, 813, 776, 730, 674, 646, 572; **MS ESI+ *m/z*, (%)**: 500 (7, $[M+Na]^+$), 478 (33, $[M+H]^+$), 378 (100, $[M+H\text{-}CO_2\text{-isobutylene}]^+$), 344 (23, $[M+Na\text{-TEMPO}]^+$), 244 (9, $[M+Na\text{-TEMPO-}CO_2\text{-isobutylene}]^+$), 175 (7, $[M+Na\text{-TEMPO-}CO_2\text{-isobutylene-prenyl}]^+$); **HRMS ESI+ *m/z***: ($[M+H]^+$): Calcd. for $C_{26}H_{44}N_3O_5$: 478.3281; Found: 478.3276; **Anal. Calcd. for** $C_{26}H_{43}N_3O_5$ (477.65): C, 65.38; H, 9.07; N, 8.80; Found: C, 65.35; H, 9.21; N, 8.55;



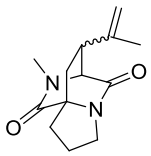
^{1}H NMR (400 MHz, $CDCl_3$): *trans*-diastereomer: δ = 0.94 (s, 3H, CH_{3TEMPO}), 1.07 (s, 3H, CH_{3TEMPO}), 1.08 (s, 3H, CH_{3TEMPO}), 1.34-1.55 (m, 6H, CH_{2TEMPO}), 1.50 (s, 3H, CH_{3TEMPO}), 1.52 (s, 9H, $C(CH_3)_3$), 1.57 (s, 3H, $=CCH_3$), 1.63 (s, 3H, $=CCH_3$), 1.91-2.06 (m, 3H, $NCH_2C\underline{H}_2C\underline{H}_2$), 2.11-2.22 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 2.38 (dd, *J* = 14.2, 6.6 Hz, 1H, $C\underline{H}_2CH=$), 2.55 (dd, *J* = 14.2, 8.8 Hz, 1H, $C\underline{H}_2CH=$), 3.31-3.38 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.97-4.13 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 4.96 (t, *J* = 7.7 Hz, 1H, $CH_2C\underline{H}=$), 6.25 (s, 1H, CHOTMP); **^{13}C NMR (101 MHz, $CDCl_3$)**: *trans*-diastereomer: δ = 16.6 (t, CH_{2TEMPO}), 17.6 (q, $=C\underline{C}H_3$), 19.6 (q, CH_{3TEMPO}), 19.75 (q, CH_{3TEMPO}), 19.80 (t, $NCH_2\underline{C}H_2CH_2$), 25.6 (q, $=C\underline{C}H_3$), 27.6 (q, $C(\underline{C}H_3)_3$), 32.1 (q, CH_{3TEMPO}), 32.9 (q, CH_{3TEMPO}), 33.3 (t, $NCH_2CH_2\underline{C}H_2$), 36.8 (t, $\underline{C}H_2CH=$), 40.3 (t, 2C, CH_{2TEMPO}), 43.5 (t, $N\underline{C}H_2CH_2CH_2$), 59.2 (s, C_{TEMPO}), 61.4 (s, C_{TEMPO}), 70.1 (s, C_{Pro}), 82.9 (s, $\underline{C}(CH_3)_3$), 85.6 (d, $\underline{C}$HOTMP), 115.7 (d, $CH_2\underline{C}H=$), 136.8 (s, $=\underline{C}(CH_3)_2$), 147.3 (s, $C=O_{Boc}$), 161.0 (s, $C=O_{Gly}$), 171.2 (s, $C=O_{Pro}$).



^{1}H NMR (400 MHz, $CDCl_3$): *cis*-diastereomer: δ = 1.01 (s, 3H, CH_{3TEMPO}), 1.07 (s, 3H, CH_{3TEMPO}), 1.12 (s, 3H, CH_{3TEMPO}), 1.36-1.61 (m,

6H, CH_{2TEMPO}), 1.51 (s, 3H, CH_{3TEMPO}), 1.54 (s, 9H, $C(CH_3)_3$), 1.65 (s, 3H, $=CCH_3$), 1.71 (s, 3H, $=CCH_3$), 1.83-2.02 (m, 2H, $NCH_2C\underline{H}_2CH_2$), 2.11 (dt, *J* = 13.2, 9.9 Hz, 1H, $NCH_2CH_2C\underline{H}_2$), 2.28 (ddd, *J* = 13.1, 7.4, 2.7 Hz, 1H, $NCH_2CH_2C\underline{H}_2$), 2.69 (dd, *J* = 14.4, 6.3 Hz, 1H, $C\underline{H}_2CH=$), 2.84 (dd, *J* = 14.4, 8.9 Hz, 1H, $C\underline{H}_2CH=$), 3.39-3.46 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.72 (dt, *J* = 12.2, 8.5 Hz, 1H, $NC\underline{H}_2CH_2CH_2$), 5.25 (t, *J* = 7.6 Hz, 1H, $CH_2C\underline{H}=$), 6.37 (s, 1H, CHOTMP); **^{13}C NMR (101 MHz, $CDCl_3$)**: *cis*-diastereomer: δ = 17.2 (t, CH_{2TEMPO}), 18.2 (q, $=C\underline{C}H_3$), 20.3 (q, 2C, CH_{3TEMPO}), 21.1 (t, $NCH_2\underline{C}H_2CH_2$), 26.2 (q, $=C\underline{C}H_3$), 28.2 (q, $C(\underline{C}H_3)_3$), 32.8 (q, CH_{3TEMPO}), 33.5 (q, CH_{3TEMPO}), 35.1 (t, $NCH_2CH_2\underline{C}H_2$), 38.1 (t, $\underline{C}H_2CH=$), 40.8 (t, CH_{2TEMPO}), 40.9 (t, CH_{2TEMPO}), 45.9 (t, $N\underline{C}H_2CH_2CH_2$), 59.6 (s, C_{TEMPO}), 62.1 (s, C_{TEMPO}), 70.1 (s, C_{Pro}), 84.3 (s, $\underline{C}(CH_3)_3$), 88.7 (d, CHOTMP), 117.7 (d, $CH_2\underline{C}H=$), 136.5 (s, $=\underline{C}(CH_3)_2$), 150.1 (s, $C=O_{Boc}$), 161.6 (s, $C=O_{Gly}$), 172.8 (s, $C=O_{Pro}$).

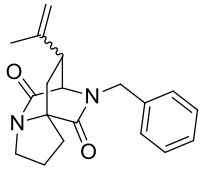
10-Methyl-7-(prop-1-en-2-yl)tetrahydro-1*H*-6,8a-(epiminomethano)indolizine-5,9(6*H*)-dione (3.13a):



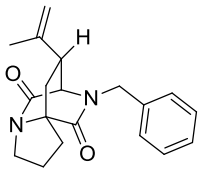
A 0.02 M solution of alkoxyamine **3.11a** (200 mg, 0.51 mmol) in *t*BuOH (26 mL) was degassed in a Carius tube by three freeze-pump-thaw cycles. The reaction vessel was sealed and immersed to an oil bath preheated at 130 °C and stirred at this temperature for 1h. The solvent was evaporated under reduced pressure and purification of the residue by column chromatography (100% AcOEt, gradient to 3:1 AcOEt/acetone) gave 106 mg (88%) **3.13a** as an inseparable 1:1 mixture of diastereomers as a colorless solid. $\mathbf{R_f}$ = 0.3 (AcOEt); **IR**: ν[cm^{-1}] 2970, 1673, 1427, 1396, 1338, 1299, 1232, 1071, 1006, 898, 774, 705, 579, 544; **MS ESI+ *m/z*, (%)**: 491 (30, $[2M+Na]^+$), 257 (100, $[M+Na]^+$), 235 (23, $[M+H]^+$), 217 (14), 167 (8); **HRMS ESI+ *m/z*,** ($[M+H]^+$): Calcd. for $C_{13}H_{19}N_2O_2$: 235.1441; Found: 235.1441; **Anal. Calcd. For** $C_{13}H_{18}N_2O_2$ (234.30): C, 66.64; H, 7.74; N, 11.96; Found: C, 66.61; H, 7.84; N, 11.70; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 1.76 (s, 3H, $=CCH_3$), 1.73-1.82 (m, 3H, $NCH_2CH_2C\underline{H}_2$, $CH_{2bridge}$), 1.79 (s, 3H, $=CCH_3$), 1.87 (dd, *J* = 13.6, 5.0 Hz, 1H, $CH_{2bridge}$), 1.90-1.99 (m, 4H, $NCH_2C\underline{H}_2CH_2$), 2.02 (dd, *J* = 13.6, 10.0 Hz, 1H, $CH_{2bridge}$), 2.13 (dd, *J* = 13.3, 10.2 Hz, 1H, $CH_{2bridge}$), 2.69-2.78 (m, 3H, $NCH_2CH_2C\underline{H}_2$, CH_{bridge}), 2.78-2.84 (m, 1H, CH_{bridge}), 2.90 (s, 3H, NCH_3), 2.97 (s, 3H, NCH_3), 3.35-3.42 (m, 3H, $NC\underline{H}_2CH_2CH_2$), 3.43-3.50 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.82-3.85 (m, 2H, $CH_{bridgehead}$), 4.73 (s, 1H, $=CH_2$), 4.85 (s, 1H, $=CH_2$), 4.87 (s, 1H, $=CH_2$), 4.93 (s, 1H, $=CH_2$); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 22.2 (q, $=C\underline{C}H_3$), 22.9 (q, $=C\underline{C}H_3$), 24.6 (t, $NCH_2\underline{C}H_2CH_2$), 24.7 (t, $NCH_2\underline{C}H_2CH_2$), 29.3 (t, $NCH_2CH_2\underline{C}H_2$), 29.6 (t, $NCH_2CH_2\underline{C}H_2$), 32.2 (q, NCH_3), 34.1 (q, NCH_3), 35.1 (t, $CH_{2bridge}$), 35.9 (t, $CH_{2bridge}$), 43.6 (d, CH_{bridge}), 43.7

(t, N<u>C</u>$H_2CH_2CH_2$), 43.9 (t, N<u>C</u>$H_2CH_2CH_2$), 45.0 (d, CH_{bridge}), 66.2 (d, $CH_{bridgehead}$), 66.4 (d, $CH_{bridgehead}$), 66.9 (s, C_{Pro}), 67.7 (s, C_{Pro}), 112.7 (t, $=CH_2$), 112.9 (t, $=CH_2$), 142.8 (s, =<u>C</u>CH_3), 143.1 (s, =<u>C</u>CH_3), 166.8 (s, C=O), 168.0 (s, C=O), 171.0 (s, C=O), 171.4 (s, C=O).

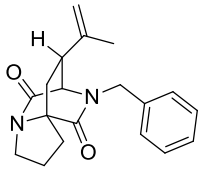
10-Benzyl-7-(prop-1-en-2-yl)tetrahydro-1*H*-6,8a-(epiminomethano)indolizine-5,9(6*H*)-dione (**3.13**):



A 0.02 M solution of alkoxyamine **3.11b** (180 mg, 0.40 mmol) in *t*BuOH (20 mL) was degassed in a Carius tube by three freeze-pump-thaw cycles. The reaction vessel was sealed and immersed to an oil bath preheated at 130 °C and stirred at this temperature for 1 h. The solvent was evaporated under reduced pressure and purification of the residue by column chromatography (hexane/AcOEt 1:1) gave 28 mg almost pure ***syn*-3.13b** and 80 mg 2:1 mixture of *syn*:*anti* diastereomers. The overall yield was 108 mg (90%) as a 3:1 ***syn*-3.13b**/***anti*-3.13b** as determined by ^{1}H NMR spectroscopy of the crude mixture. $\mathbf{R_f}$ = 0.3 (***syn*-3.13b**), $\mathbf{R_f}$ = 0.2 (***anti*-3.13b**) (hexane/*i*PrOH, 7:1); **IR**: ν[cm^{-1}] 2975, 2931, 2869, 1738, 1454, 1375, 1361, 1186, 1133, 1098, 1043, 1028, 992, 922, 737, 698; **MS ESI+ *m/z*, (%)**: 675 (11), 349 (45, $[M+K]^+$), 333 (50, $[M+Na]^+$), 311 (100, $[M+H]^+$), 283 (71, $[M+H-CO]^+$), 241 (4, $[M+H\text{-isoprene}]^+$); **HRMS ESI+ *m/z*,** ($[M+H]^+$): Calcd. for $C_{19}H_{23}N_2O_2$: 311.1754; Found: 311.1754;



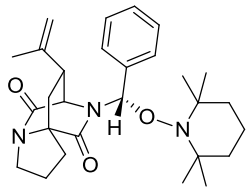
^{1}H NMR (400 MHz, $CDCl_3$): ***syn*-3.13b**: δ = 1.54 (s, 3H, CH_3), 1.72-1.84 (m, 2H, $CH_{2bridge}$, $NCH_2CH_2C\underline{H}_2$), 1.92-2.02 (m, 2H, $NCH_2C\underline{H}_2CH_2$), 2.07 (dd, *J* = 13.4, 10.2 Hz, 1H, $CH_{2bridge}$), 2.34-2.41 (m, 1H, CH_{bridge}), 2.78 (dt, *J* = 13.2, 6.6 Hz, 1H, $NCH_2CH_2C\underline{H}_2$), 3.39 (dt, *J* = 11.4, 7.1 Hz, 1H, N<u>C</u>$H_2CH_2CH_2$), 3.47 (dt, *J* = 11.5, 6.5 Hz, 1H, N<u>C</u>$H_2CH_2CH_2$), 3.87 (d, *J* = 3.2 Hz, 1H, $CH_{bridgehead}$), 4.19 (d, *J* = 14.6 Hz, 1H, $PhCH_2$), 4.67 (s, 1H, $=CH_2$), 4.77 (m, 1H, $=CH_2$), 4.85 (d, *J* = 14.6 Hz, 1H, $PhCH_2$), 7.17-7.36 (m, 5H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: ***syn*-3.13b**: δ = 22.1 (q, CH_3), 24.71 (t, $NCH_2\underline{C}H_2CH_2$), 29.7 (t, $NCH_2CH_2\underline{C}H_2$), 35.7 (t, $CH_{2bridge}$), 43.9 (t, N<u>C</u>$H_2CH_2CH_2$), 45.4 (d, CH_{bridge}), 48.8 (t, $PhCH_2$), 63.9 (d, CH_{bridge}), 67.3 (s, C_{Pro}), 112.6 (t, $=CH_2$), 128.3 (d, CH_{Ar}), 128.5 (d, CH_{Ar}), 129.1 (d, CH_{Ar}), 136.2 (s, C_{Ar}), 142.9 (s, =<u>C</u>CH_3), 166.6 (s, C=O), 171.2 (s, C=O).



^{1}H NMR (400 MHz, $CDCl_3$): ***anti*-3.13b**: δ = 1.65 (s, 3H, CH_3), 1.72-1.87 (m, 2H, $CH_{2bridge}$, $NCH_2CH_2C\underline{H}_2$), 1.89-2.02 (m, 4H, $CH_{2bridge}$, $NCH_2C\underline{H}_2C\underline{H}_2$), 2.66-2.72 (m, 1H, CH_{bridge}), 3.32-3.51 (m, 2H, N<u>C</u>$H_2CH_2CH_2$), 3.86 (d, *J* = 1.5 Hz, 1H, $CH_{bridgehead}$), 3.98 (d, *J* = 15.0 Hz, 1H, $PhCH_2$), 4.71 (s, 1H, $=CH_2$), 4.85 (m, 1H, $=CH_2$), 4.88 (d, *J* = 15.0 Hz, 1H, $PhCH_2$),

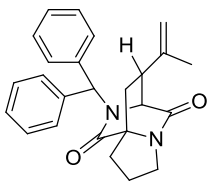
7.08-7.33 (m, 5H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: ***anti*-3.13b**: δ = 23.0 (q, CH_3), 24.74 (t, $NCH_2\underline{C}H_2CH_2$), 29.4 (t, $NCH_2CH_2\underline{C}H_2$), 34.9 (t, $CH_{2bridge}$), 43.6 (d, CH_{bridge}), 43.8 (t, $N\underline{C}H_2CH_2CH_2$), 50.3 (t, $PhCH_2$), 63.8 (d, $CH_{bridgehead}$), 67.6 (s, C_{Pro}), 113.3 (t, $=CH_2$), 128.1 (d, CH_{Ar}), 128.4 (d, CH_{Ar}), 128.9 (d, CH_{Ar}), 136.1 (s, C_{Ar}), 142.4 (s, $=\underline{C}CH_3$), 168.1 (s, C=O), 171.1 (s, C=O).

(6*R,7*R**,8a*R**)-10-((*S*)-Phenyl((2,2,6,6-tetramethylpiperidin-1-yl)oxy)methyl)-7-(prop-1-en-2-yl)tetrahydro-1*H*-6,8a-(epiminomethano)indolizine-5,9(6*H*)-dione (3.14):**



m.p. 160-162 °C; **R_f** = 0.6 (hexane/EtOAc, 1:2); **IR**: ν[cm^{-1}] 2932, 1693, 1491, 1451, 1408, 1378, 1363, 1294, 1232, 1198, 1150, 1133, 1079, 1036, 989, 957, 915, 705; **MS ESI+ *m/z*, (%)**: 488 (78, $[M+Na]^+$), 466 (100, $[M+H]^+$), 348 (12, $[M+Na\text{-}TMP]^+$), 332 (73, $[M+Na\text{-}TEMPO]^+$), 309 (10, $[M\text{-}TEMPO]^+$), 281 (35, $[M\text{-}TEMPO\text{-}CO]^+$), 171 (3); **HRMS ESI+ *m/z*,** ($[M+H]^+$): Calcd. for $C_{28}H_{39}N_3O_3$: 466.3064; Found: 466.3063; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 0.87 (s, 3H, CH_{3TEMPO}), 0.96 (s, 3H, CH_{3TEMPO}), 1.12 (s, 3H, CH_{3TEMPO}), 1.16 (s, 3H, CH_{3TEMPO}), 1.23-1.32 (m, 1H, CH_{2TEMPO}), 1.37 (s, 3H, $=CCH_3$), 1.38-1.59 (m, 5H, CH_{2TEMPO}), 1.62-1.69 (m, 1H, CH_{bridge}), 1.69-2.04 (m, 5H, $CH_{2bridge}$, $NCH_2C\underline{H}_2C\underline{H}_2$), 2.81 (ddd, *J* = 12.7, 6.9, 5.4 Hz, 1H, $NCH_2CH_2C\underline{H}_2$), 3.31-3.49 (m, 2H, $NC\underline{H}_2CH_2CH_2$), 4.05 (d, *J* = 3.0 Hz, 1H, $CH_{bridgehead}$), 4.51 (s, 1H, $=CH_2$), 4.73 (s, 1H, $=CH_2$), 6.81 (s, 1H, $PhC\underline{H}OTMP$), 7.26-7.60 (m, 5H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 17.2 (t, CH_{2TEMPO}), 20.6 (q, 2C, CH_{3TEMPO}), 22.0 (q, $=C\underline{C}H_3$), 24.8 (t, $NCH_2\underline{C}H_2CH_2$), 29.8 (t, $NCH_2CH_2\underline{C}H_2$), 32.4 (q, CH_{3TEMPO}), 33.4 (q, CH_{3TEMPO}), 35.5 (t, $CH_{2bridge}$), 40.4 (t, CH_{2TEMPO}), 40.5 (t, CH_{2TEMPO}), 44.0 (t, $N\underline{C}H_2CH_2CH_2$), 45.2 (d, CH_{bridge}), 59.8 (d, $CH_{bridgehead}$), 60.9 (s, 2C, C_{TEMPO} as determined by HMBC, since the resonance is not visible), 67.6 (s, C_{Pro}), 88.8 (d, $Ph\underline{C}HOTMP$), 112.5 (t, $=CH_2$), 126.3 (d, CH_{Ar}), 128.4 (d, CH_{Ar}), 128.8 (d, CH_{Ar}), 139.1 (s, C_{Ar}), 142.8 (s, $=\underline{C}CH_3$), 166.1 (s, C=O), 170.1 (s, C=O).

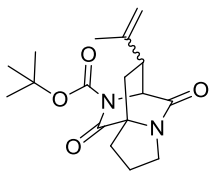
10-Benzhydryl-7-(prop-1-en-2-yl)tetrahydro-1*H*-6,8a-(epiminomethano)indolizine-5,9(6*H*)-dione (3.13c):



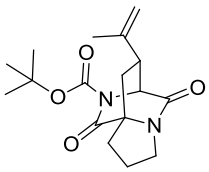
A 0.02 M solution of alkoxyamine **3.11c** (385 mg, 0.71 mmol) in *t*BuOH (36 mL) was degassed in a Carius tube by three freeze-pump-thaw cycles. The reaction vessel was sealed and immersed to an oil bath preheated at 130 °C and stirred at this temperature for 1 h. The solvent was evaporated under reduced pressure and purification of the residue by column chromatography

(hexane/AcOEt, 1:1 gradient to 2:1) gave 226 mg (82%) ***syn*-3.13d** and 13 mg *anti*-diastereomer with inseparable impurities (5%). **m.p.** 139-141 °C; $\mathbf{R_f}$ = 0.2 (hexane/EtOAc, 1:2); **IR** ν[cm^{-1}] 2972, 1682, 1495, 1408, 1377, 1338, 1208, 1145, 1078, 1031, 1003, 903, 787, 732, 702, 609, 588, 530; **MS ESI+ *m/z*, (%)**: 795 (8, $[2M+Na]^+$), 446 (4), 425 (11), 409 (100, $[M+Na]^+$), 387 (36, $[M+H]^+$); **HRMS ESI+ *m/z*,** ($[M+Na]^+$): Calcd. for $C_{25}H_{26}N_2O_2Na$: 409.1887; Found: 409.1887; **Anal. Calcd. For** $C_{25}H_{26}N_2O_2$: C, 77.69; H, 6.78; N, 7.25; Found: C, 77.39; H, 6.79; N 6.99; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 1.39 (s, 3H, CH_3), 1.82-1.94 (m, 2H, $CH_{2bridge}$, $NCH_2CH_2C\underline{H}_2$), 1.96-2.10 (m, 4H, $CH_{2bridge}$, $NCH_2C\underline{H}_2CH_2$, CH_{bridge}), 2.84 (dt, *J* = 13.1, 7.0 Hz, 1H, $NCH_2CH_2C\underline{H}_2$), 3.48-3.62 (m, 2H, $NC\underline{H}_2CH_2CH_2$), 4.06 (d, *J* = 2.9 Hz, 1H, $CH_{bridgehead}$), 4.57 (s, 1H, $=CH_2$), 4.78 (s, 1H, $=CH_2$), 6.86 (s, 1H, Ph_2CH), 7.19-7.41 (m, 10H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 22.1 (q, CH_3), 24.6 (t, $NCH_2\underline{C}H_2CH_2$), 29.8 (t, $NCH_2CH_2\underline{C}H_2$), 35.4 (t, $CH_{2bridge}$), 44.0 (t, $N\underline{C}H_2CH_2CH_2$), 45.0 (d, CH_{bridge}), 60.2 (d, Ph_2CH), 61.8 (d, $CH_{bridgehead}$), 67.6 (s, C_{Pro}), 112.6 (t, $=CH_2$), 127.4 (d, CH_{Ar}), 127.6 (d, CH_{Ar}), 128.7 (d, CH_{Ar}), 128.9 (d, CH_{Ar}), 129.1 (d, CH_{Ar}), 129.9 (d, CH_{Ar}), 138.3 (s, C_{Ar}), 139.1 (s, C_{Ar}), 142.7 (s, $=\underline{C}CH_3$), 166.5 (s, C=O), 171.4 (s, C=O).

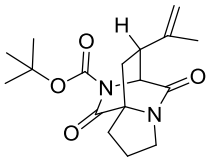
(6*S,7*R**,8a*S**)-*tert*-Butyl 5,9-dioxo-7-(prop-1-en-2-yl)hexahydro-1*H*-6,8a-(epiminomethano)indolizine-10-carboxylate (3.13d):**



A 0.02 M solution of alkoxyamine **3.11d** (230 mg, 0.48 mmol) in *t*BuOH (24 mL) was degassed in a Carius tube by three freeze-pump-thaw cycles. The reaction vessel was sealed and immersed to an oil bath preheated at 130 °C and stirred at this temperature for 1 h. The solvent was evaporated under reduced pressure and purification of the residue by column chromatography (hexane/AcOEt, 1:1, gradient to 1:2) gave 45 mg less polar diastereomer ***syn*-3.13d** as a colorless oil, 32 mg of a 1:4 *syn*/*anti* mixture and 41 mg more polar diastereomer ***anti*-3.13d** as a colorless solid. The overall yield was 118 mg (73%). The diastereoselectivity of the cyclization was measured to be *syn*:*anti*=1:1.3 by ^{1}H NMR measurement spectroscopy of the crude mixture. **m.p.** 158-160 °C (***anti*-3.13d**); $\mathbf{R_f}$ = 0.5 (***syn*-3.13d**), $\mathbf{R_f}$ = 0.3 (***anti*-3.13d**) (hexane/EtOAc 1:2); **IR**: ν[cm^{-1}] 2980, 1738, 1716, 1689, 1647, 1432, 1395, 1359, 1313, 1287, 1256, 1141, 1010, 899, 845, 781, 749, 706, 591; **MS ESI+ *m/z*, (%)**: 663 (6, $[2M+Na]^+$), 343 (53, $[M+Na]^+$), 243 (100, $[M+Na\text{-isobutylene-}CO_2]^+$), 175 (16, $[M+Na\text{-isobutylene-isoprene-}CO_2]^+$); **HRMS ESI+ *m/z*,** ($[M+Na]^+$): Calcd. for $C_{17}H_{24}N_2O_4Na$: 343.1628; Found: 343.1628;

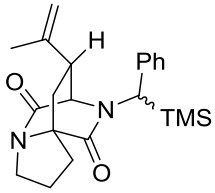


^{1}H NMR (400 MHz, $CDCl_3$): ***anti*-3.13d**: δ = 1.47 (s, 9H, $C(CH_3)_3$), 1.76-1.86 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 1.83 (s, 3H, $=CCH_3$), 1.93-2.09 (m, 4H, $CH_{2bridge}$, $NCH_2C\underline{H}_2CH_2$), 2.76-2.84 (m, H, CH_{bridge}, $NCH_2CH_2C\underline{H}_2$), 3.40-3.51 (m, 2H, $NC\underline{H}_2CH_2CH_2$), 4.76 (s, 1H, $=CH_2$), 4.94 (s, 1H, $=CH_2$), 4.95 (d, *J* = 1.4 Hz, 1H, $CH_{bridgehead}$); **^{13}C NMR (101 MHz, $CDCl_3$)**: ***anti*-3.13d**: δ = 23.0 (q, $=C\underline{C}H_3$), 24.5 (t, $NCH_2\underline{C}H_2CH_2$), 28.1 (q, $C(\underline{C}H_3)_3$), 29.5 (t, $NCH_2CH_2\underline{C}H_2$), 34.3 (t, $\underline{C}H_{2bridge}$), 42.8 (d, $\underline{C}H_{bridge}$), 44.0 (t, $N\underline{C}H_2CH_2CH_2$), 60.7 (d, $\underline{C}H_{bridgehead}$), 68.8 (s, C_{Pro}), 84.2 (s, $\underline{C}(CH_3)_3$), 112.8 (t, $=CH_2$), 142.3 (s, $=\underline{C}CH_3$), 148.4 (s, $C=O_{Boc}$), 166.9 (s, C=O), 169.1 (s, C=O).



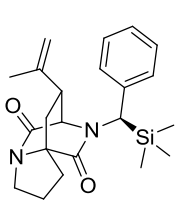
^{1}H NMR (400 MHz, $CDCl_3$): ***syn*-3.13d**: δ = 1.51 (s, 9H, $C(C\underline{H}_3)_3$), 1.79 (s, 3H, $=CCH_3$), 1.81-1.87 (m, 1H, $CH_{2bridge}$), 1.90-2.04 (m, 3H, $NCH_2C\underline{H}_2C\underline{H}_2$), 2.24 (dd, *J* = 13.6, 10.2 Hz, 1H, $CH_{2bridge}$), 2.74-2.81 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 2.83-2.89 (m, 1H, CH_{bridge}), 3.38-3.48 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.51-3.57 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 4.83 (s, 1H, $=CH_2$), 4.94 (s, 1H, $=CH_2$), 4.97 (d, *J* = 2.9 Hz, 1H, $CH_{bridgehead}$); **^{13}C NMR (101 MHz, $CDCl_3$)**: ***syn*-3.13d**: δ = 22.2 (q, $=C\underline{C}H_3$), 24.4 (t, $NCH_2\underline{C}H_2CH_2$), 28.1 (q, $C(\underline{C}H_3)_3$), 29.8 (t, $NCH_2CH_2\underline{C}H_2$), 35.1 (t, $\underline{C}H_{2bridge}$), 44.1 (t, $N\underline{C}H_2CH_2CH_2$), 44.6 (d, $\underline{C}H_{bridge}$), 61.2 (d, $\underline{C}H_{bridgehead}$), 68.2 (s, C_{Pro}), 84.6 (s, $\underline{C}(CH_3)_3$), 113.1 (t, $=CH_2$), 142.8 (s, $=\underline{C}CH_3$), 149.5 (s, $C=O_{Boc}$), 165.6 (s, C=O), 169.1 (s, C=O).

10-(Phenyl(trimethylsilyl)methyl)-7-(prop-1-en-2-yl)tetrahydro-1*H*-6,8a-(epiminomethano)indolizine-5,9(6*H*)-dione (4.2):

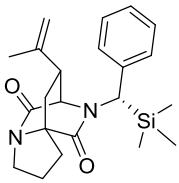


TMSCl (250 µL, 1.93 mmol) in THF (1 mL) was added to a freshly prepared LDA solution prepared by addition of *n*BuLi (140 µL, 0.223 mmol, 1.6 M solution in hexanes) to *i*Pr_2NH (40 µL, 0.28 mmol) in THF (0.5 mL) at -78 °C. Bridged DKP ***syn*-3.13b** (60 mg, 0.193 mmol) in THF (1 mL) was added and the reaction mixture was stirred at -78 °C for 30 min. The reaction mixture was quenched with Et_3N (3 mL) followed by addition of saturated $NaHCO_3$ solution and water. Extraction with AcOEt, drying the combined organic layers over $MgSO_4$, filtration and evaporation gave almost pure crude product as a colorless solid. Purification by column chromatography (hexane/AcOEt, 3:1, gradient to 1:1) gave 24 mg pure less polar diastereomer as a colorless crystalline solid and 39 mg of a mixture of more polar and less polar diastereomers (2.3:1). Overall yield was 63 mg (85%). The diastereomeric ratio was determined to be 1.54:1 by ^{1}H NMR spectroscopy of the crude product. **m.p.** (major): 178-

179 °C; $\mathbf{R_f}$ = 0.52 (major), $\mathbf{R_f}$ = 0.45 (minor), (hexane/EtOAc, 1:1); **IR**: ν[cm^{-1}] 2952, 1677, 1649, 1599, 1491, 1424, 1376, 1338, 1242, 1199, 1175, 1133, 1121, 905, 864, 840, 752, 703, 684; **MS ESI+ *m/z*, (%)**: 477 (5), 421 (4, $[M+K]^+$), 405 (100, $[M+Na]^+$), 383 (11, $[M+H]^+$), 355 (6, $[M+H-CO]^+$); **HRMS ESI+ *m/z*,** ($[M+H]^+$): Calcd. for $C_{22}H_{31}N_2O_2Si$: 383.2149; Found: 383.2149;

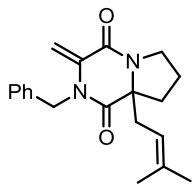


^{1}H NMR (400 MHz, $CDCl_3$): major diastereomer: δ = 0.04 (s, 9H, $Si(CH_3)_3$), 1.55 (s, 3H, $=CCH_3$), 1.71-1.88 (m, 2H, $CH_{2bridge}$, $NCH_2CH_2C\underline{H}_2$), 1.91-2.08 (m, 2H, $NCH_2C\underline{H}_2CH_2$), 2.16 (dd, *J* = 13.3, 10.3 Hz, 1H, $CH_{2bridge}$), 2.41-2.49 (m, 1H, CH_{bridge}), 2.81 (ddd, *J* = 12.7, 6.9, 5.5 Hz, 1H, $NCH_2CH_2C\underline{H}_2$), 3.36-3.45 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.50-3.59 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.71 (s, 1H, $PhC\underline{H}Si$), 3.93 (d, *J* = 3.2 Hz, 1H, $CH_{bridgehead}$), 4.69 (s, 1H, $=CH_2$), 4.79 (s, 1H, $=CH_2$), 7.11-7.16 (m, 2H, CH_{Ar}), 7.17-7.22 (m, 1H, CH_{Ar}), 7.24-7.31 (m, 2H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$):** major diastereomer: δ = −0.98 (q, $Si(\underline{C}H_3)_3$), 22.10 (q, $=C\underline{C}H_3$), 24.8 (t, $NCH_2C\underline{H}_2CH_2$), 30.0 (t, $NCH_2CH_2\underline{C}H_2$), 35.57 (t, $CH_{2bridge}$), 43.9 (t, $N\underline{C}H_2CH_2CH_2$), 46.2 (d, CH_{bridge}), 59.7 (d, $Ph\underline{C}HSi$), 67.7 (s, C_{Pro}), 68.8 (d, $CH_{bridgehead}$), 112.4 (t, $=\underline{C}H_2$), 126.8 (d, CH_{Ar}), 127.7 (d, CH_{Ar}), 128.7 (d, CH_{Ar}), 140.2 (s, C_{Ar}), 143.3 (s, $=\underline{C}CH_3$), 167.2 (s, C=O), 171.8 (s, C=O).



^{1}H NMR (400 MHz, $CDCl_3$): minor diastereomer: δ = 0.12 (s, 9H, $Si(CH_3)_3$), 1.64 (s, 3H, $=CCH_3$), 1.75-1.87 (m, 2H, $CH_{2bridge}$, $NCH_2CH_2C\underline{H}_2$), 1.91-2.21 (m, 2H, $NCH_2C\underline{H}_2CH_2$), 2.08 (dd, *J* = 13.3, 10.2 Hz, 1H, $CH_{2bridge}$), 2.46-2.53 (m, 1H, CH_{bridge}), 2.76-2.86 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 3.33-3.58 (m, 2H, $NC\underline{H}_2CH_2CH_2$), 3.96 (d, *J* = 3.1 Hz, 1H, $CH_{bridgehead}$), 4.37 (s, 1H, $PhC\underline{H}Si$), 4.73 (s, 1H, $=CH_2$), 4.83 (s, 1H, $=CH_2$), 7.11-7.30 (m, 5H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: minor diastereomer: δ = −1.3 (q, $Si(\underline{C}H_3)_3$), 22.12 (q, $=C\underline{C}H_3$), 24.9 (t, $NCH_2C\underline{H}_2CH_2$), 30.0 (t, $CH_{2bridge}$), 35.62 (t, $NCH_2CH_2\underline{C}H_2$), 43.9 (t, $N\underline{C}H_2CH_2CH_2$), 45.6 (d, CH_{bridge}), 54.9 (d, $Ph\underline{C}HSi$), 65.5 (d, $CH_{bridgehead}$), 67.2 (s, C_{Pro}), 112.7 (t, $=\underline{C}H_2$), 127.2 (d, CH_{Ar}), 128.8 (d, CH_{Ar}), 128.9 (d, CH_{Ar}), 138.9 (s, C_{Ar}), 143.1 (s, $=\underline{C}CH_3$), 166.7 (s, C=O), 171.0 (s, C=O).

2-Benzyl-8a-(3-methylbut-2-en-1-yl)-3-methylenehexahydropyrrolo[1,2-a]pyrazine-1,4-dione (4.6):

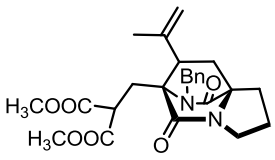


Method A:Paraformaldehyde (863 mg, 29 mmol) and NaH (240 mg, 6.0 mmol, 60% dispersion in mineral oil) were added to a solution of **3.10** (300 mg, 0.96 mmol) in THF (20 mL) under Ar. The reaction vessel was sealed, immersed to a bath preheated to 100 °C and stirred at this temperature for 1.5 h. The reaction mixture was cooled to room temperature, and carefully unsealed (*Caution! High pressure and toxicity!*), poured into an excess saturated NH_4Cl solution and diluted with water. The reaction mixture was extracted with AcOEt and the combined organic layers were dried over $MgSO_4$, filtered and evaporated. The crude reaction mixture was purified by flash chromatography (hexane/AcOEt, 2:1, gradient to 1:2) to afford 195 mg (63%) **4.6** as a pale yellow viscous oil.

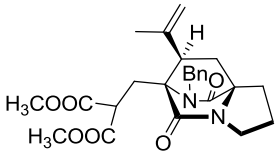
Method B: *n*BuLi (1.3 mL, 2.1 mmol, 1.6 M in hexanes) was added to a solution of **3.10** (540 mg, 1.73 mmol) in THF (20 mL) at -78 °C. The reaction mixture was stirred at -78 °C for 40 min and solid Eschenmoser's salt (650 mg, 3.46 mmol) was added in one portion. Stirring was continued for 1.5 h, during which the temperature was raised to -40 °C. The reaction mixture was quenched with saturated NH_4Cl solution. The mixture was extracted with CH_2Cl_2, the combined organic layers were dried over $MgSO_4$ and filtered. The filtrate was evaporated, redissolved in anhydrous MeCN (20 mL) and MeI (400 μL, 6.42 mmol) was added. The reaction mixture was stirred at r.t. for 3 h and the acetonitrile was evaporated. The residue was redissolved in anhydrous MeOH (20 mL), K_2CO_3 (720 mg, 5.2 mmol) was added and stirring was continued at r.t. for 5 h. The reaction mixture was filtered, evaporated and the residue was purified by column chromatography (hexane/AcOEt, 2:1, gradient to 1:2) to give 400 mg (71%) **4.6** as pale yellow viscous oil. $\mathbf{R_f}$ = 0.6 (hexane/EtOAc, 1:2); **IR**: ν[cm^{-1}] 2950, 1675, 1609, 1497, 1450, 1383, 1349, 1328, 1271, 1234, 1216, 1157, 1128, 1091, 1078, 1030, 991, 966, 931, 876, 778, 737, 700, 669; **MS ESI+ *m/z*, (%)**: 365 (75), 347 (100, $[M+Na]^+$), 325 (5, $[M+H]^+$), 257 (4, $[M+H\text{-isoprene}]^+$); **HRMS ESI+ *m/z*,** ($[M+H]^+$): Calcd. for $C_{20}H_{25}N_2O_2$: 325.1910; Found: 325.1911; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 1.53 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 1.96-2.11 (m, 2H, $NCH_2C\underline{H}_2CH_2$), 2.21-2.31 (m, 2H, $NCH_2CH_2C\underline{H}_2$), 2.43 (dd, *J* = 14.2, 7.9 Hz, 1H, $C\underline{H}_2CH$=), 2.55 (dd, *J* = 14.2, 7.8 Hz, 1H, $C\underline{H}_2CH$=), 3.53-3.63 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.84 (dt, *J* = 12.7, 8.5 Hz, 1H, $NC\underline{H}_2CH_2CH_2$), 4.71 (d, *J* = 15.6 Hz, 1H, $PhC\underline{H}_2$), 4.83 (d, *J* = 1.4 Hz, 1H, $=CH_2$), 4.95-5.02 (m, 1H, $CH_2C\underline{H}$=), 5.10 (d, *J* = 15.6 Hz, 1H, $PhC\underline{H}_2$), 5.64 (d, *J* = 1.4 Hz, 1H, $=CH_2$), 7.17-7.33 (m, 5H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 17.9 (q, CH_3), 20.3 (t, $NCH_2\underline{C}H_2CH_2$), 26.1

(q, CH_3), 35.0 (t, $\underline{C}H_2CH$=), 37.7 (t, $NCH_2CH_2\underline{C}H_2$), 45.3 (t, $N\underline{C}H_2CH_2CH_2$), 47.4 (t, $Ph\underline{C}H_2$), 68.3 (s, C_{Pro}), 102.5 (t, $=CH_2$), 117.0 (d, $CH_2\underline{C}H$=), 127.2 (d, CH_{Ar}), 127.5 (d, CH_{Ar}), 128.8 (d, CH_{Ar}), 136.2 (s, C_{Ar}), 138.1 (s, $=\underline{C}(CH_3)_2$), 138.7 (s, $\underline{C}=CH_2$), 157.9 (s, $C=O_{Dha}$), 168.8 (s, $C=O_{Pro}$).

Dimethyl 2-(((6*S,7*R**,8a*S**)-10-benzyl-5,9-dioxo-7-(prop-1-en-2-yl)hexahydro-1H-6,8a-(epiminomethano)indolizin-6-yl)methyl)malonate and dimethyl 2-(((6*S**,7*S**,8a*S**)-10-benzyl-5,9-dioxo-7-(prop-1-en-2-yl)hexahydro-1H-6,8a-(epiminomethano)indolizin-6-yl)methyl)malonate (4.8):**

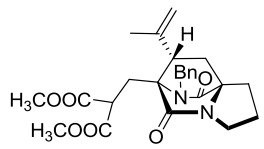


A microwave tube was charged with alkoxyamine **4.7** (886 mg, 3.1 mmol) under Ar. A solution of methyleneDKP **4.6** (200 mg, 0.62 mmol) in 7 mL freshly degassed DMF was added, the tube was sealed and irradiated in a microwave reactor at 150 W power at 180 °C for 15 min. The reaction mixture was evaporated to dryness and the residue was purified by column chromatography (hexane/AcOEt, 2:1, gradient to 1:2) to give 170 mg (61%) **4.8** as beige foam as a 2:1 mixture of diastereomers. Pure samples of both diastereomers were obtained by fractional crystallization from AcOEt/hexane for characterization. $\mathbf{R_f}$ = 0.4 (hexane/AcOEt, 1:2); **IR**: ν[cm^{-1}] 2953, 1749, 1733, 1686, 1496, 1435, 1393, 1356, 1276, 1213, 1156, 1107, 1078, 1032, 903, 798, 730, 702, 601, 540; **MS ESI+ *m/z*, (%)**: 477 (100, $[M+Na]^+$), 445 (10, $[M+Na\text{-}MeOH]^+$), 409 (8, $[M+Na\text{-isoprene}]^+$), 391 (4, $[M+H\text{-}2MeOH]^+$), 349 (8); **HRMS ESI+ *m/z*,** ($[M+Na]^+$): Calcd. for $C_{25}H_{30}N_2O_6Na$: 477.1993; Found: 477.1996;



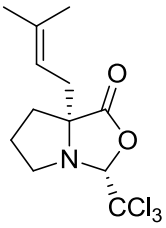
^{1}H NMR (400 MHz, $CDCl_3$): major diastereomer: δ = 1.57 (s, 3H, $=CCH_3$), 1.75 (dd, *J* = 13.5, 5.5 Hz, 1H, $CH_{2bridge}$), 1.86 (dt, *J* = 13.2, 7.4 Hz, 1H, $NCH_2CH_2C\underline{H}_2$), 1.95-2.08 (m, 2H, $NCH_2C\underline{H}_2CH_2$), 2.17 (dd, *J* = 13.5, 10.4 Hz, 1H, $CH_{2bridge}$), 2.51-2.62 (m, 2H, CH_{bridge}, $C\underline{H}_2CH(CO_2Me)$), 2.80-2.92 (m, 2H, $C\underline{H}_2CH(CO_2Me)_2$, $NCH_2CH_2C\underline{H}_2$), 3.44-3.53 (m, 2H, $C\underline{H}(CO_2Me)_2$, $NC\underline{H}_2CH_2CH_2$), 3.56-3.70 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.69 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 4.36 (d, *J* = 16.2 Hz, 1H, $PhC\underline{H}_2$), 4.62 (s, 1H, $=CH_2$), 4.81 (s, 1H, $=CH_2$), 4.98 (d, *J* = 16.2 Hz, 1H, $PhC\underline{H}_2$), 7.16-7.34 (m, 5H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: major diastereomer: δ = 18.4 (q, $=C\underline{C}H_3$), 24.50 (t, $NCH_2\underline{C}H_2CH_2$), 28.4 (t, $\underline{C}H_2CH(CO_2Me)_2$), 30.0 (t, $NCH_2CH_2\underline{C}H_2$), 36.4 (t, $CH_{2bridge}$), 44.6 (t, $N\underline{C}H_2CH_2CH_2$), 45.2 (t, $Ph\underline{C}H_2$), 48.9 (d, $\underline{C}H(CO_2Me)_2$), 52.9 (q, OCH_3), 53.2 (q, OCH_3), 53.4 (d, CH_{bridge}), 66.1 (s, C_{Pro}), 69.3 (s, $C_{bridgehead}$), 116.9 (t, $=\underline{C}H_2$), 127.1 (d, CH_{Ar}), 127.7 (d, CH_{Ar}), 128.9 (d,

CH_{Ar}), 137.8 (s, C_{Ar}), 142.8 (s, =$\underline{C}CH_3$), 167.4 (s, C=O), 170.0 (s, C=O), 170.5 (s, C=O), 173.6 (s, C=O);



^{1}H NMR (400 MHz, $CDCl_3$): minor diastereomer: δ = 1.70 (s, 3H, =CCH_3), 1.77-1.92 (m, 2H, $CH_{2bridge}$, $NCH_2CH_2C\underline{H}_2$), 1.96-2.06 (m, 2H, $NCH_2C\underline{H}_2CH_2$), 2.19 (dd, *J* = 13.6, 10.5 Hz, 1H, $CH_{2bridge}$), 2.56 (dd, *J* = 15.4, 4.9 Hz, 1H, $C\underline{H}_2CH(CO_2Me)_2$), 2.77-2.92 (m, 3H, $NCH_2CH_2C\underline{H}_2$, CH_{bridge}, $C\underline{H}_2CH(CO_2Me)_2$), 3.34 (t, *J* = 4.7 Hz, 1H, $C\underline{H}(CO_2Me)_2$), 3.53 (t, *J* = 6.8 Hz, 2H, $NC\underline{H}_2CH_2CH_2$), 3.59 (s, 3H, OCH_3), 3.70 (s, 3H, OCH_3), 4.26 (d, *J* = 16.6 Hz, 1H, $PhC\underline{H}_2$), 4.82 (s, 1H, =CH_2), 4.97 (s, 1H, =CH_2), 5.15 (d, *J* = 16.6 Hz, 1H, $PhC\underline{H}_2$), 6.97 (d, *J* = 7.3 Hz, 2H, CH_{Ar}), 7.17-7.23 (m, 1H, CH_{Ar}), 7.24-7.31 (m, 2H, CH_{Ar}); **^{13}C NMR (126 MHz, $CDCl_3$)**: minor diastereomer: δ = 19.9 (q, =$C\underline{C}H_3$), 24.5 (t, $NCH_2\underline{C}H_2CH_2$), 28.1 (t, $\underline{C}H_2CH(CO_2Me)$), 29.9 (t, $NCH_2CH_2\underline{C}H_2$), 36.1 (t, $CH_{2bridge}$), 44.51 (t, $N\underline{C}H_2CH_2CH_2$), 45.9 (t, $Ph\underline{C}H_2$), 48.4 (d, $\underline{C}H(CO_2Me)$, 48.8 (d, CH_{bridge}), 53.06 (q, OCH_3), 53.07 (q, OCH_3), 66.2 (s, C_{Pro}), 68.7 (s, $C_{bridgehead}$), 117.4 (t, =$\underline{C}H_2$), 126.0 (d, CH_{Ar}), 127.4 (d, CH_{Ar}), 129.0 (d, CH_{Ar}), 137.2 (s, C_{Ar}), 142.2 (s, =$\underline{C}CH_3$), 168.9 (s, C=O), 169.6 (s, C=O), 170.4 (s, C=O), 172.6 (s, C=O).

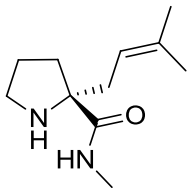
(3*R*,7a*R*)-7a-(3-Methylbut-2-en-1-yl)-3-(trichloromethyl)tetrahydropyrrolo[1,2-*c*]oxazol-1(3*H*)-one (4.11):



A flame-dried, 250 mL Schlenk flask was charged with *N*,*N*-diisopropylamine (3.4 mL, 24.3 mmol) and THF (47 mL) under an Ar atmosphere and cooled to -78 °C. *n*BuLi (15 mL, 24.3 mmol, 1.6M in hexanes) was added and the reaction mixture was stirred at -78 °C for 30 min. In a separate 100-mL round-bottomed flask equipped with a magnetic stirbar under argon, **4.9** (4.25 g, 17.38 mmol) was dissolved in THF (35 mL). This solution was added via cannula to the LDA solution at -78 °C. The resulting brown solution was stirred at -78 °C for 30 min and prenyl bromide (2.9 mL, 24.3 mmol) was added in a single portion. The reaction mixture was warmed to -40 °C over 1 h, where it was maintained for additional 30 min. The reaction mixture was poured into a separatory funnel containing 50 mL of water. The aqueous solution was extracted three times with chloroform. The combined organic layers were dried over $MgSO_4$, filtered and concentrated to give a brown oil, which was pure enough for the next stage. In one experiment, the crude product was purified by column chromatography (hexane/AcOEt, 15:1, gradient to 7:1) to give 4.3 g (79%) **4.11** as pale yellow oil. $\mathbf{R_f}$ = 0.5 (hexane/AcOEt, 5:1); $\mathbf{[\alpha]^{20}_{589}}$: +31.5 (*c* 1.586, $CHCl_3$); **IR**: ν[cm^{-1}] 2914,

1796, 1449, 1377, 1353, 1322, 1276, 1249, 1190, 1130, 1101, 1076, 1019, 983, 945, 920, 900, 835, 799, 744, 687, 654, 641, 608, 570, 544, 512; **MS ESI+ *m/z*, (%)**: 616/615/614/613/612/611 (4/9/10/27/7/25, $[2M+Na-HCl]^+$), 340/338/336/334 (4/32/97/100, $[M+Na]^+$), 318/316/314/312 (3/9/5/5, $[M+H]^+$), 280/278/276 (1/13/20, $[M+H-HCl]^+$), 252/250/248 (8/15/27, $[M+H-CO-HCl]^+$), 216/214 (5/15, $M+H-CO-2HCl]^+$), 184 (8), 178 (2); **HRMS ESI+ *m/z*,** ($[M+H]^+$): Calcd. for $C_{12}H_{17}{}^{35}Cl_3NO_2$: 312.0319; Found: 312.0320; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 1.55-1.69 (m, 1H, $NCH_2C\underline{H}_2CH_2$), 1.64 (s, 3H, CH_3), 1.73 (s, 3H, CH_3), 1.83-1.90 (m, 1H, $NCH_2C\underline{H}_2CH_2$), 1.90-1.99 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 2.05-2.14 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 2.50 (dd, *J* = 14.4, 6.6 Hz, 1H, $C\underline{H}_2CH$=), 2.58 (dd, *J* = 14.4, 8.4 Hz, 1H, $C\underline{H}_2CH$=), 3.10-3.26 (m, 2H, $NC\underline{H}_2CH_2CH_2$), 4.95 (s, 1H, NCHO), 5.24 (ddt, *J* = 8.2, 6.2, 1.5 Hz, 1H, $CH_2C\underline{H}$=); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 18.3 (q, CH_3), 25.5 (t, $NCH_2\underline{C}H_2CH_2$), 26.2 (q, CH_3), 35.5 (t, $NCH_2CH_2\underline{C}H_2$), 35.9 (t, $\underline{C}H_2CH$=), 58.5 (t, $N\underline{C}H_2CH_2CH_2$), 72.3 (s, C_{Pro}), 102.5 (s, CCl_3), 102.6 (d, NCHO), 117.9 (d, $CH_2\underline{C}H$=), 136.4 (s, =$\underline{C}CH_3$), 176.6 (s, C=O).

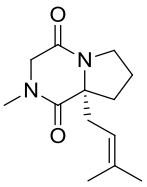
(*R*)-*N*-Methyl-2-(3-methylbut-2-en-1-yl)pyrrolidine-2-carboxamide (4.12):



Crude **4.11** (10.5 g, ca 33.6 mmol) was dissolved in $MeNH_2$ solution (100 mL, 200 mmol, 2 M in MeOH) at r.t. and the reaction mixture was stirred overnight. The reaction mixture was transferred to a sealed tube and heated to 80 °C for 2 h to ensure that the methyl ester byproduct does not remain. Evaporation of the reaction mixture followed by purification of the residue by column chromatography (Et_2O with 1% Et_3N, gradient to hexane/*i*PrOH, 10:1) gave 3.97 g (60%) amine **4.12** and 2.1 g amine contaminated with the *N*-formyl byproduct **4.13** (ca 3.5:1). This mixture was converted to the pure amine by refluxing with NaOH solution (950 mg, 23.8 mmol in 5 mL H_2O) in EtOH (15 mL) for 5 h followed by evaporation of ethanol and extraction of the inhomogeneous mixture with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and evaporated to give 1.9 g (29%) amine. The overall yield was 5.87 g (89%). **R_f** = 0.2 (Et_2O/Et_3N, 99:1); **IR**: *ν*[cm^{-1}] 3345, 2927, 1656, 1523, 1455, 1412, 1381, 1277, 1202, 1164, 1105, 1041, 991, 849, 786, 750, 664; **$[\alpha]^{20}_{589}$**: −11.2 (*c* 1.025, $CHCl_3$); **MS EI+ *m/z*, (%)**: 197 (100, $[M+H]^+$), 138 (68, $[M+H-MeNH_2-CO]^+$), 127 (14, M-prenyl]$^+$); **HRMS EI+ *m/z*,** ($[M+H]^+$): Calcd. for $C_{11}H_{21}N_2O$: 197.1647; Found: 197.1654; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 1.62 (s, 3H, =CCH_3), 1.64-1.78 (m, 4H, $NCH_2C\underline{H}_2C\underline{H}_2$, NH_{Pro}), 1.71 (s, 3H, =CCH_3), 2.08-2.17 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 2.31 (dd, *J* = 14.5, 8.3 Hz, 1H, $C\underline{H}_2CH$=), 2.62 (dd, *J* = 14.5, 6.6 Hz, 1H, $C\underline{H}_2CH$=), 2.76-2.86 (m, 1H, $NC\underline{H}_2CH_2CH_2$),

2.79 (d, *J* = 5.0 Hz, 3H, NCH_3), 2.95-3.05 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 5.03 (ddt, *J* = 8.3, 6.8, 1.5 Hz, 1H, $CH_2C\underline{H}$=), 7.88 (br. s, 1H, N<u>H</u>Me); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 18.2 (q, =C<u>C</u>H_3), 26.1 (q, =C<u>C</u>H_3), 26.2 (q, NCH_3), 26.6 (t, $NCH_2\underline{C}H_2CH_2$), 36.0 (t, $NCH_2CH_2\underline{C}H_2$), 36.8 (t, <u>C</u>$H_2$CH=), 47.3 (t, N<u>C</u>$H_2CH_2CH_2$), 69.6 (s, C_{Pro}), 119.2 (d, $CH_2\underline{C}H$=), 135.9 (s, =<u>C</u>CH_3), 177.8 (s, C=O).

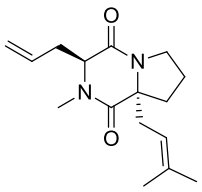
(*R*)-2-Methyl-8a-(3-methylbut-2-en-1-yl)hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione ((*R*)-3.10):



Amine **4.12** (1.11 g, 5.66 mmol) was dissolved in dichloromethane (20 mL), a 0.5 M K_2CO_3 solution (12 mL, 6.22 mmol) was added and the mixture was cooled to 0 °C. Bromoacetyl bromide (541 µL, 6.23 mmol) was added in one portion to the vigorously biphasic solution. The reaction mixture was stirred until the starting material disappeared as indicated by TLC (ca. 1 h). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were evaporated and the residue was redissolved in CH_2Cl_2 (20 mL). A 50% NaOH solution (2.0 mL, 25 mmol) was added followed by benzyl(triethyl)ammonium chloride (20 mg, 1.4 mol%) and the reaction mixture was vigorously stirred for 15 h. More catalyst (20 mg) was added every 3-4 h to accelerate the conversion. The mixture was diluted with water and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and evaporated. Purification of the residue by column chromatography (100% AcOEt, gradient to AcOEt/acetone 3:1) gave 1.1 g (82%) **(*R*)-3.10** as a colorless oil. $\mathbf{R_f}$ = 0.2 (acetone/AcOEt, 1:2); **$[\alpha]^{20}_{589}$**: −77 (*c* 1.040, $CHCl_3$); **IR**: *ν*[cm^{-1}] 2926, 1644, 1442, 1401, 1379, 1333, 1306, 1279, 1244, 1211, 1155, 1113, 1073, 1011, 877, 839, 750, 640, 595, 520; **MS ESI+ *m/z*, (%)**: 275 (7, $[M+K]^+$), 259 (100, $[M+Na]^+$), 237 (38, $[M+H]^+$), 167 (9, [M-prenyl]$^+$); **HRMS ESI+ *m/z*,** ($[M+H]^+$): Calcd. for $C_{13}H_{21}N_2O_2$: 237.1598; Found: 237.1598; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 1.58 (s, 3H, =CCH_3), 1.69 (s, 3H, =CCH_3), 1.89-2.05 (m, 2H, $NCH_2C\underline{H}_2CH_2$), 2.06-2.24 (m, 2H, $NCH_2CH_2C\underline{H}_2$), 2.38 (dd, *J* = 14.1, 8.2 Hz, 1H, C<u>H</u>$_2$CH=), 2.52 (dd, *J* = 14.1, 7.8 Hz, 1H, C<u>H</u>$_2$CH=), 2.94 (s, 3H, NCH_3), 3.50 (ddd, *J* = 12.8, 8.8, 4.4 Hz, 1H, $NC\underline{H}_2CH_2CH_2$), 3.72 (d, *J* = 17.0 Hz, 1H, $CH_3NC\underline{H}_2$), 3.80 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 4.04 (d, *J* = 17.0 Hz, 1H, $CH_3NC\underline{H}_2$), 5.06 (t, *J* = 8.0 Hz, 1H, $CH_2C\underline{H}$=); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 17.9 (q, =C<u>C</u>H_3), 20.6 (t, $NCH_2\underline{C}H_2CH_2$), 26.2 (q, =C<u>C</u>$H_3$), 33.6 (q, NCH_3), 35.3 (t, $NCH_2CH_2\underline{C}H_2$), 36.8 (t, <u>C</u>$H_2$CH=), 45.1 (t, N<u>C</u>$H_2CH_2CH_2$), 53.7 (t, $CH_3N\underline{C}H_2$), 68.3 (s, C_{Pro}), 117.3 (d, $CH_2\underline{C}H$=), 137.9 (s, =<u>C</u>CH_3), 162.8 (s, C=O), 169.6 (s, C=O).

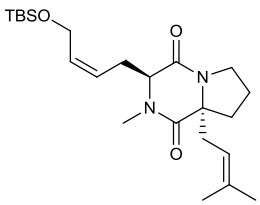
General procedure A: Representative procedure for the alkylation of **(±)-3.10** or **(*R*)-3.10**: **(±)-3-Cinnamyl-2-methyl-8a-(3-methylbut-2-en-1-yl)hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione ((±)-4.15d):** DKP **3.10a** (300 mg, 1.27 mmol) was dissolved in dry THF (14 mL) and cooled to -78 °C. *n*BuLi (900 µL, 1.4 mmol, 1.6 M in hexane) was added dropwise and the resulting pale yellow turbid solution was stirred at -78 °C for 1 h. Cinnamyl bromide (350 mg, 1.52 mmol) was added, the temperature was raised to -50 °C and the mixture was stirred for 1.5 h. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography at silica gel (hexane/AcOEt, 3:1, gradient to 1:1) to give 367 mg (82%) **(±)-4.15d** as a colorless oil. $\mathbf{R_f}$ = 0.3 (hexane/AcOEt, 1:1); **IR**: *v*[cm^{-1}] 2940, 1656, 1453, 1402, 1334, 1303, 1217, 1075, 972, 748, 697, 639; **MS ESI+ *m/z*, (%)**: 727 (3, $[2M+Na]^+$), 391 (14, $[M+K]^+$), 375 (100, $[M+Na]^+$), 353 (14, $[M+H]^+$), 273 (6); **HRMS ESI+ *m/z*,** ($[M+H]^+$): Calcd. for $C_{22}H_{29}N_2O_2$: 353.2224; Found: 353.2226; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 1.57 (s, 3H, $=CCH_3$), 1.69 (s, 3H, $=CCH_3$), 1.76-1.88 (m, 1H, $NCH_2C\underline{H}_2CH_2$), 1.87-2.01 (m, 2H, $NCH_2C\underline{H}_2CH_2$, $NCH_2CH_2C\underline{H}_2$), 2.07-2.19 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 2.33 (dd, *J* = 14.0, 8.1 Hz, 1H, $C\underline{H}_2CH=C(CH_3)_2$), 2.51 (dd, *J* = 14.0, 7.9 Hz, 1H, $C\underline{H}_2CH=C(CH_3)_2$), 2.78 (dddd, *J* = 14.6, 7.3, 4.7, 1.3 Hz, 1H, $C\underline{H}_2CH=CHPh$), 3.02 (m, 3H, NCH_3), 3.13 (dddd, *J* = 14.6, 7.2, 2.7, 1.4 Hz, 1H, $C\underline{H}_2CH=CHPh$), 3.40-3.52 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.77-3.88 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 4.03 (dd, *J* = 4.7, 2.7 Hz, 1H, αCH), 4.98 (t, *J* = 8.0 Hz, 1H, $C\underline{H}=C(CH_3)_2$), 5.88 (dt, *J* = 15.8, 7.3 Hz, 1H, $C\underline{H}=CHPh$), 6.48 (d, *J* = 15.9 Hz, 1H, $CH=C\underline{H}Ph$), 7.15-7.33 (m, 5H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 18.0 (q, $=C\underline{C}H_3$), 20.1 (t, $NCH_2\underline{C}H_2CH_2$), 26.3 (q, $=C\underline{C}H_3$), 31.8 (q, NCH_3), 34.1 (t, $\underline{C}H_2CH=CHPh$), 35.6 (d, $NCH_2CH_2\underline{C}H_2$), 37.0 (d, $\underline{C}H_2CH=C(CH_3)_2$), 44.6 (t, $N\underline{C}H_2CH_2CH_2$), 62.2 (d, α$\underline{C}$H), 67.9 (s, C_{Pro}), 117.3 (d, $\underline{C}H=C(CH_3)_2$), 122.7 (d, $\underline{C}H=CHPh$), 126.3 (d, CH_{Ar}), 127.7 (d, CH_{Ar}), 128.7 (d, CH_{Ar}), 134.7 (d, $CH=\underline{C}HPh$), 137.1 (s, C_{Ar}), 137.9 (s, $=\underline{C}(CH_3)_2$), 163.8 (s, C=O), 169.7 (s, C=O).

(3*S*,8a*R*)-3-Allyl-2-methyl-8a-(3-methylbut-2-en-1-yl)hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (4.15a):



Prepared according to general procedure A from 390 mg (1.65 mmol) **(*R*)-3.10** using allyl bromide. Purification of the crude product by column chromatography (hexane/AcOEt, 1:1, gradient to 1:2) gave 397 mg (87%) product **4.15a** as a colorless oil. $\mathbf{R_f}$ = 0.3 (hexane/AcOEt, 1:2); $\mathbf{[\alpha]^{20}_{589}}$: −57.9 (*c* 0.993, $CHCl_3$); **IR**: *ν*[cm^{-1}] 2983, 2939, 1654, 1448, 1401, 1334, 1304, 1241, 1218, 1158, 1119, 1075, 999, 923, 851, 712, 655, 570; **MS EI+ *m/z*, (%)**: 277 (100, $[M+H]^+$), 251 (13), 235 (8, $[M\text{-allyl}]^+$), 207 (54, $[M\text{-prenyl}]^+$), 182 (4), 179 (8, $[M\text{-prenyl-ethylene}]^+$), 110 (5); **HRMS EI+ *m/z*,** ($[M+H]^+$): Calcd. for $C_{16}H_{25}N_2O_2$: 277.1916; Found: 277.1915; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 1.56 (s, 3H, $=CCH_3$), 1.67 (s, 3H, $=CCH_3$), 1.90-2.11 (m, 3H, $NCH_2C\underline{H}_2C\underline{H}_2$), 2.13-2.22 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 2.34 (dd, *J* = 14.0, 8.1 Hz, 1H, $C\underline{H}_2CH=C(CH_3)_2$), 2.51 (dd, *J* = 14.0, 7.9 Hz, 1H, $C\underline{H}_2CH=C(CH_3)_2$), 2.60 (dddt, *J* = 14.8, 7.9, 4.8, 1.0 Hz, 1H, $C\underline{H}_2CH=CH_2$), 2.94 (s, 3H, NCH_3), 3.01 (dddt, *J* = 14.8, 5.9, 2.8, 1.4 Hz, 1H, $C\underline{H}_2CH=CH_2$), 3.43-3.53 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.77-3.88 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.94 (dd, *J* = 4.8, 2.8 Hz, 1H, αCH), 4.96 (m, 1H, $C\underline{H}=C(CH_3)_2$), 5.04-5.18 (m, 2H, $=CH_2$), 5.43-5.56 (m, 1H, $C\underline{H}=CH_2$); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 18.0 (q, $=C\underline{C}H_3$), 20.1 (t, $NCH_2\underline{C}H_2CH_2$), 26.3 (q, $=C\underline{C}H_3$), 31.5 (q, NCH_3), 34.7 (t, $\underline{C}H_2CH=CH_2$), 35.7 (t, $NCH_2CH_2\underline{C}H_2$), 37.0 (t, $\underline{C}H_2CH=C(CH_3)_2$), 44.7 (t, $N\underline{C}H_2CH_2CH_2$), 61.7 (d, αCH), 67.9 (s, C_{Pro}), 117.3 (d, $\underline{C}H=C(CH_3)_2$), 119.7 (t, $=CH_2$), 131.5 (d, $\underline{C}H=CH_2$), 137.9 (s, $=\underline{C}(CH_3)_2$), 163.8 (s, C=O), 169.8 (s, C=O).

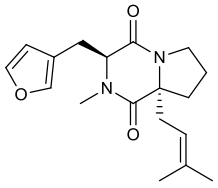
(*3S*,8a*R*)-3-((*Z*)-4-((*tert*-Butyldimethylsilyl)oxy)but-2-en-1-yl)-2-methyl-8a-(3-methylbut-2-en-1-yl)hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (4.15b):



Prepared according to general procedure A from 960 mg (4.1 mmol) **(*R*)-3.10** using (*Z*)-((4-bromobut-2-en-1-yl)oxy)(*tert*-butyl)dimethylsilane.[110] Purification of the crude product by column chromatography (hexane/AcOEt, 3:1, gradient to 1:1) gave 1.52 g (90%) product **4.15b** as a colorless oil. $\mathbf{R_f}$ = 0.5 (hexane/AcOEt, 1:1); $\mathbf{[\alpha]^{20}_{589}}$: −2.9 (*c* 1.0, $CHCl_3$); **IR**: *ν*[cm^{-1}] 2964, 2938, 2865, 1658, 1453, 1401, 1365, 1328, 1304, 1256, 1217, 1078, 1010, 986, 942, 839, 779, 719, 669, 571, 522; **MS ESI+ *m/z*, (%)**: 443 (100, $[M+Na]^+$), 421 (1, $[M+H]^+$), 289 (8, $[M+H\text{-TBSOH}]^+$), 207 (2); **HRMS ESI+ *m/z***: ($[M+Na]^+$): Calcd. for $C_{23}H_{40}O_3N_2SiNa$: 443.2700; Found: 443.2700; **Anal. Calcd. for** $C_{23}H_{40}N_2O_3Si$ (420.28): C, 65.57; H, 9.58; N, 6.66; Found: C, 65.30; H, 9.72; N, 6.43; **^{1}H**

NMR (400 MHz, $CDCl_3$): δ = 0.06 (s, 6H, $Si(CH_3)_2$), 0.88 (s, 9H, $C(CH_3)_3$) 1.56 (s, 3H, $=CCH_3$), 1.67 (s, 3H, $=CCH_3$), 1.91-2.12 (m, 3H, $NCH_2CH_2C\underline{H}_2$, $NCH_2C\underline{H}_2CH_2$), 2.14-2.23 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 2.34 (dd, *J* = 13.9, 8.2 Hz, 1H, $C\underline{H}_2CH=C(CH_3)_2$), 2.51 (dd, *J* = 13.9, 7.9 Hz, 1H, $C\underline{H}_2CH=C(CH_3)_2$), 2.61-2.71 (m, 1H, $=CHC\underline{H}_2CH_\alpha$), 2.93 (s, 3H, NCH_3), 2.96-3.05 (m, 1H, $=CHC\underline{H}_2CH_\alpha$), 3.42-3.51 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.71-3.86 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.95 (dd, *J* = 4.9, 2.7 Hz, 1H, αCH), 4.18 (ddd, *J* = 13.4, 5.6, 1.6 Hz, 1H, CH_2OTBS), 4.26 (ddd, *J* = 13.4, 6.6, 1.6 Hz, 1H, CH_2OTBS), 4.92-5.01 (m, 1H, $C\underline{H}=C(CH_3)_2$), 5.04-5.14 (m, 1H, $=C\underline{H}CH_2CH_\alpha$), 5.56-5.66 (m, 1H, $=C\underline{H}CH_2OTBS$); **^{13}C NMR (101 MHz, $CDCl_3$)**: -5.0 (q, $Si(CH_3)_2$), 18.0 (q, $=C\underline{C}H_3$), 18.5 (s, $\underline{C}(CH_3)_3$), 20.1 (t, $NCH_2\underline{C}H_2CH_2$), 26.1 (q, $C(\underline{C}H_3)_3$), 26.3 (q, $=C\underline{C}H_3$), 28.7 (t, $=CH\underline{C}H_2CH_\alpha$), 31.4 (q, NCH_3), 35.7 (t, $NCH_2CH_2\underline{C}H_2$), 37.0 (t, $\underline{C}H_2CH=C(CH_3)_2$), 44.7 (t, $N\underline{C}H_2CH_2CH_2$), 59.8 (t, CH_2OTBS), 61.4 (d, αCH), 67.9 (s, C_{Pro}), 117.3 (d, $\underline{C}H=C(CH_3)_2$), 122.8 (d, $=\underline{C}HCH_2CH_\alpha$), 134.1 (d, $=\underline{C}HCH_2OTBS$), 138.0 (s, $=\underline{C}(CH_3)_2$), 163.9 (s, C=O), 169.9 (s, C=O).

(3*S*,8a*R*)-3-(3-Furylmethyl)-2-methyl-8a-(3-methylbut-2-en-1-yl)hexahydropyrrolo[1,2-*a*]pyrazine-1,4-dione (4.15c):

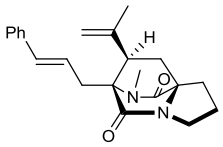


Prepared according to general procedure A from 266 mg (1.13 mmol) **(*R*)-3.10** using 3-(bromomethyl)furan[111]. Purification of the crude product by column chromatography (hexane/AcOEt, 2:1, gradient to 1:1) gave 320 mg (89%) product **4.15c** as a colorless crystalline solid. **m.p.** 116-118 °C; **R_f** = 0.2 (hexane/AcOEt, 1:1); **$[\alpha]^{20}_{589}$**: −20.5 (*c* 0.999, $CHCl_3$); **IR**: *ν*[cm^{-1}] 3132, 2992, 2972, 2924, 1651, 1505, 1462, 1411, 1388, 1344, 1313, 1287, 1255, 1221, 1182, 1157, 1118, 1080, 1060, 1026, 995, 975, 875, 818, 783, 731, 678, 650, 604, 554, 515; **MS ESI+ *m/z*, (%)**: 655 (15, $[2M+Na]^+$), 339 (100, $[M+Na]^+$), 317 (15, $[M+H]^+$), 261 (7), 235 (4, $[M\text{-}FurCH_2]^+$); **HRMS ESI+ *m/z***: ($[M+Na]^+$): Calcd. for $C_{18}H_{24}O_3N_2Na$: 339.1679; Found: 339.1679; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 1.46-1.55 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 1.54 (s, 3H, $=CCH_3$), 1.67 (s, 3H, $=CCH_3$), 1.69-1.81 (m, 1H, $NCH_2C\underline{H}_2CH_2$), 1.81-1.95 (m, 1H, $NCH_2C\underline{H}_2CH_2$), 2.00 (ddd, *J* = 12.3, 8.0, 1.7 Hz, 1H, $NCH_2CH_2C\underline{H}_2$), 2.26 (dd, *J* = 14.0, 8.1 Hz, 1H, $C\underline{H}_2CH=$), 2.45 (dd, *J* = 14.0, 7.8 Hz, 1H, $C\underline{H}_2CH=$), 2.95 (dd, *J* = 14.8, 4.4 Hz, 1H, $ArCH_2$), 2.99 (s, 3H, NCH_3), 3.33 (dd, *J* = 14.9, 2.6 Hz, 1H, $ArCH_2$), 3.25-3.41 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.66-3.75 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 4.04 (ddt, *J* = 4.3, 2.7, 0.8 Hz, 1H, αCH), 4.91 (tq, *J* = 7.9, 1.4 Hz, 1H, $CH_2C\underline{H}=$), 6.12 (dd, *J* = 1.8, 0.9 Hz, 1H, CH_{Ar}), 7.16 (dd, *J* = 1.6, 0.8 Hz, 1H, CH_{Ar}), 7.28 (t, *J* = 1.7 Hz, 1H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 18.1 (q, $=C\underline{C}H_3$), 19.9 (t,

$NCH_2\underline{C}H_2CH_2$), 26.3 (q, =$C\underline{C}H_3$), 26.8 (t, $ArCH_2$), 32.1 (q, NCH_3), 35.0 (t, $NCH_2CH_2\underline{C}H_2$), 36.9 (t, $\underline{C}H_2CH$=), 44.4 (t, $N\underline{C}H_2CH_2CH_2$), 62.6 (d, αCH), 67.8 (s, C_{Pro}), 111.5 (d, CH_{Ar}), 117.1 (d, $CH_2\underline{C}H$=), 117.9 (s, C_{Ar}), 137.9 (s, =$\underline{C}(CH_3)_2$), 141.0 (d, CH_{Ar}), 143.0 (d, CH_{Ar}), 163.6 (s, C=O), 169.2 (s, C=O).

General procedure B: Representative procedure for the cyclization of **(±)-4.15d**:

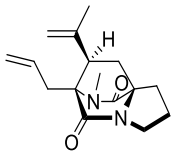
(6*R,7*R**,8a*R**)-6-Cinnamyl-10-methyl-7-(prop-1-en-2-yl)tetrahydro-1*H*-6,8a-(epiminomethano)indolizine-5,9(6*H*)-dione ((±)-4.16d):**



*n*BuLi (330 μL, 0.53 mmol, 1.6 M in hexane) was added to a solution of HMDS (126 μL, 0.60 mmol) in dry DME (2 mL) at -78 °C and the solution was stirred for 15 min. DKP **(±)-4.15d** (85 mg, 0.24 mmol) in DME (3 mL) was added, the temperature was gradually raised to -40 °C and stirrring was continued at this temperature for 1.5 h. TEMPO (45 mg, 0.3 mmol) was added to the reaction mixture followed by portionwise addition of $Cp_2Fe^+PF_6^-$ until the color of the oxidant persisted (ca 200 mg, 0.60 mmol) and stirring was continued for 10 min. The cooling bath was removed, the reaction flask was equipped with a reflux condenser and immersed to an oil bath preheated to 100 °C and refluxed for 1.5 h. The reaction mixture was cooled to r.t., evaporated to dryness and the residue was purified by column chromatography (hexane/AcOEt, 1:1, gradient to 1:2) to give 60 mg (71%) **4.16d** as an inseparable 5:1 mixture of diastereomers as a colorless oil. $\mathbf{R_f}$ = 0.2 (hexane/AcOEt, 1:1); **IR**: *ν*[cm^{-1}] 2940, 1680, 1500, 1433, 1384, 1268, 1203, 1066, 969, 909, 846, 731, 697, 648, 560, 538; **MS ESI+ *m/z*, (%)**: 723 (5, $[2M+Na]^+$), 427 (4), 373 (100, $[M+Na]^+$), 351 (16, $[M+H]^+$), 283 (4, $[M+H\text{-isoprene}]^+$); **HRMS ESI+ *m/z*,** ($[M+H]^+$): Calcd. for $C_{22}H_{27}N_2O_2$: 351.2067; Found: 351.2069; **^{1}H NMR (400 MHz, $CDCl_3$)**: major diastereomer: δ = 1.67 (s, 3H, =CCH_3), 1.74 (dd, *J* = 13.4, 5.7 Hz, 1H, $CH_{2bridge}$), 1.78-1.84 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 1.95-2.04 (m, 2H, $NCH_2C\underline{H}_2CH_2$), 2.19 (dd, *J* = 13.4, 10.4 Hz, 1H, $CH_{2bridge}$), 2.75-2.85 (m, 2H, $NCH_2CH_2C\underline{H}_2$, $C\underline{H}_2CH$=), 2.90 (dd, *J* = 10.3, 5.6 Hz, 1H, CH_{bridge}), 3.00 (s, 3H, NCH_3), 3.03 (ddd, *J* = 16.7, 5.4, 1.6 Hz, 1H, $C\underline{H}_2CH$=), 3.46-3.54 (m, 1H, $N\underline{C}H_2CH_2CH_2$), 3.55-3.61 (m, 1H, $N\underline{C}H_2CH_2CH_2$), 4.87 (br. s, 1H, =$CH_2$), 4.88-4.90 (m, 1H, =$CH_2$), 6.42-6.51 (m, 1H, $CH_2C\underline{H}$=), 6.53 (d, *J* = 16.5 Hz, 1H, =$C\underline{H}$Ph), 7.16-7.37 (m, 5H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: major diastereomer: δ = 19.0 (q, =$C\underline{C}H_3$), 24.4 (t, $NCH_2\underline{C}H_2CH_2$), 28.7 (q, NCH_3), 29.91 (t, $NCH_2CH_2\underline{C}H_2$), 33.3 (t, $\underline{C}H_2CH$=), 36.64 (t, $CH_{2bridge}$), 44.4 (t, $N\underline{C}H_2CH_2CH_2$), 50.9 (d, CH_{bridge}), 65.9 (s, C_{Pro}), 67.1 (s, $C_{bridgehead}$), 116.2 (t, =CH_2), 125.2 (d, $CH_2\underline{C}H$=), 126.2 (d, CH_{Ar}), 127.5 (d, CH_{Ar}), 128.7 (d, CH_{Ar}), 133.9 (d, =$\underline{C}$HPh), 137.3 (s, C_{Ar}), 143.1 (s, =$\underline{C}CH_3$), 168.1 (s, $N_{Pro}C$=O), 173.1 (s, $CH_3N\underline{C}$=O).

^{1}H NMR (400 MHz, $CDCl_3$): minor diastereomer (detectable resonances): δ = 1.68 (s, 3H, $=CCH_3$), 2.12 (d, *J* = 13.5, 10.4 Hz, 1H, $CH_{2bridge}$), 2.95 (s, 3H, NCH_3), 4.76 (br. s, 1H, $=CH_2$), 4.96 (m, 1H, $=CH_2$). **^{13}C NMR (101 MHz, $CDCl_3$)**: minor diastereomer: δ = 20.7 (q, $=C\underline{C}H_3$), 24.4 (t, $NCH_2\underline{C}H_2CH_2$), 29.0 (q, NCH_3), 29.85 (t, $NCH_2CH_2\underline{C}H_2$), 33.6 (t, $\underline{C}H_2CH=$), 36.56 (t, $CH_{2bridge}$), 44.2 (t, $N\underline{C}H_2CH_2CH_2$), 47.9 (d, CH_{bridge}), 66.1 (s, C_{Pro}), 66.8 (s, $C_{bridgehead}$), 116.5 (t, $=CH_2$), 125.1 (d, $CH_2\underline{C}H=$), 126.3 (d, CH_{Ar}), 127.4 (d, CH_{Ar}), 128.6 (d, CH_{Ar}), 134.2 (d, $=\underline{C}HPh$), 137.4 (s, C_{Ar}), 142.5 (s, $=\underline{C}CH_3$), 169.2 (s, $N_{Pro}C=O$), 172.3 (s, $CH_3N\underline{C}=O$).

(6*R*,7*R*,8a*R*)-6-Allyl-10-methyl-7-(prop-1-en-2-yl)tetrahydro-1*H*-6,8a-(epiminomethano)indolizine-5,9(6*H*)-dione (4.16a):

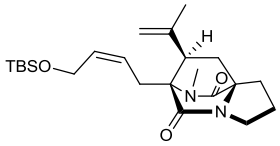


Prepared according to general procedure B from 100 mg (0.362 mmol) **4.15a**. Purification of the crude product by column chromatography (hexane/AcOEt, 1:1, gradient to 1:2) gave 88 mg (89%) **4.16a** as an inseparable 5.4:1 mixture of diastereomers as a colorless oil. $\mathbf{R_f}$ = 0.3 (hexane/AcOEt, 1:2); **IR**: *ν*[cm^{-1}] 2965, 1680, 1431, 1382, 1343, 1233, 1205, 1136, 1063, 999, 911, 845, 775, 733, 705, 647, 587, 562; **MS ESI+ *m/z*, (%)**: 571 (73, $[2M+Na]^+$), 465 (6), 454 (11), 432 (49), 395 (7), 297 (100, $[M+Na]^+$), 275 (22, $[M+H]^+$); **HRMS ESI+ *m/z***: ($[M+Na]^+$): Calcd. for $C_{23}H_{38}O_3N_2Na$: 297.1574; Found: 297.1574; **^{1}H NMR (400 MHz, $CDCl_3$)**: major diastereomer: δ = 1.64 (dd, *J* = 1.3, 0.6 Hz, 3H, $=CCH_3$), 1.71 (dd, *J* = 13.4, 5.6 Hz, 1H, $CH_{2bridge}$), 1.74-1.84 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 1.90-2.04 (m, 2H, $NCH_2C\underline{H}_2CH_2$), 2.17 (dd, *J* = 13.4, 10.4 Hz, 1H, $CH_{2bridge}$), 2.63 (ddt, *J* = 16.9, 7.1, 1.6 Hz, 1H, $C\underline{H}_2CH=$), 2.71-2.87 (m, 3H, $NCH_2CH_2C\underline{H}_2$, $C\underline{H}_2CH=$, CH_{bridge}), 2.95 (s, 3H, NCH_3), 3.42-3.59 (m, 2H, $NC\underline{H}_2CH_2CH_2$), 4.82 (d, *J* = 0.8 Hz, 1H, $C\underline{H}_2=CCH_3$), 4.85 (t, *J* = 1.5 Hz, 1H, $C\underline{H}_2=CCH_3$), 5.15-5.24 (m, 2H, $CH=C\underline{H}_2$), 6.07 (dddd, *J* = 17.4, 10.4, 7.1, 5.9 Hz, 1H, $C\underline{H}=CH_2$); **^{13}C NMR (101 MHz, $CDCl_3$)**: major diastereomer: δ = 19.0 (q, $=C\underline{C}H_3$), 24.4 (t, $NCH_2\underline{C}H_2CH$), 28.7 (q, NCH_3), 29.93 (t, $NCH_2CH_2\underline{C}H_2$), 33.8 (t, $\underline{C}H_2CH=$), 36.6 (t, $CH_{2bridge}$), 44.3 (t, $N\underline{C}H_2CH_2CH_2$), 50.7 (d, CH_{bridge}), 65.9 (s, C_{Pro}), 66.8 (s, $C_{bridgehead}$), 116.2 (t, $C=\underline{C}H_2$), 119.0 (t, $CH=\underline{C}H_2$), 133.6 (d, $CH_2\underline{C}H=$), 143.0 (s, $=\underline{C}CH_3$), 168.1 (s, $N_{Pro}C=O$), 173.1 (s, $CH_3N\underline{C}=O$).

^{1}H NMR (400 MHz, $CDCl_3$): minor diastereomer (detectable resonances): δ = 1.65 (dd, *J* = 1.5, 0.8 Hz, 3H, $=CCH_3$), 2.12 (dd, *J* = 13.5, 10.4 Hz, 1H, $CH_{2bridge}$), 2.91 (s, 3H, NCH_3), 4.75 (br. s, 1H, $C\underline{H}_2=CCH_3$), 4.92-4.94 (m, 1H, $C\underline{H}_2=CCH_3$), 5.11-5.17 (m, 2H, $CH=C\underline{H}_2$), 6.10-6.21 (m, 1H, $C\underline{H}=CH_2$); **^{13}C NMR (101 MHz, $CDCl_3$)**: minor diastereomer (detectable resonances): δ = 20.8 (q, $=C\underline{C}H_3$), 24.8 (t, $NCH_2\underline{C}H_2CH$), 29.1 (q, NCH_3), 29.86 (t,

$NCH_2CH_2\underline{C}H_2$), 34.2 (t, $\underline{C}H_2CH$=), 44.2 (t, $N\underline{C}H_2CH_2CH_2$), 48.0 (d, CH_{bridge}), 66.1 (s, C_{Pro}), 66.7 (s, $C_{bridgehead}$), 116.5 (t, C=$\underline{C}H_2$), 133.5 (d, $CH_2\underline{C}H$=), 142.4 (s, =$\underline{C}CH_3$), 169.1 (s, $N_{Pro}C$=O), 172.4 (s, $CH_3N\underline{C}$=O).

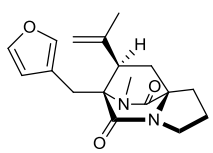
(6*R*,7*R*,8a*R*)-6-((*Z*)-4-((*tert*-Butyldimethylsilyl)oxy)but-2-en-1-yl)-10-methyl-7-(prop-1-en-2-yl)tetrahydro-1*H*-6,8a-(epiminomethano)indolizine-5,9(6*H*)-dione (4.16b):



Prepared according to general procedure B from 550 mg (1.31 mmol) **4.15b**. Purification of the crude product by column chromatography (hexane/AcOEt, 5:1, gradient to 1:1) gave 403 mg (74%) **4.16b** as an inseparable 9.3:1 mixture of diastereomers as a colorless oil. $\mathbf{R_f}$ = 0.2 (hexane/AcOEt, 1:1); **IR**: *v*[cm^{-1}] 2963, 2936, 2864, 1687, 1436, 1384, 1344, 1257, 1205, 1083, 1010, 942, 903, 838, 778, 725, 667, 563, 511; **MS ESI+ *m/z*, (%)**: 481 (6), 457 (14, $[M+K]^+$), 441 (100, $[M+Na]^+$), 419 (10, $[M+H]^+$), 287 (5, $[M+H\text{-}TBSOH]^+$); **HRMS ESI+ *m/z***: ($[M+Na]^+$): Calcd. for $C_{23}H_{38}O_3N_2Na$: 441.2544; Found: 441.2543; **^{1}H NMR (400 MHz, $CDCl_3$)**: major diastereomer: δ = 0.07 (s, 6H, $Si(CH_3)_2$), 0.89 (s, 9H, $C(CH_3)_3$), 1.64 (s, 3H, =CCH_3), 1.70-1.87 (m, 2H, $CH_{2bridge}$, $NCH_2CH_2C\underline{H}_2$), 1.92-2.05 (m, 2H, $NCH_2C\underline{H}_2CH_2$), 2.19 (dd, *J* = 13.4, 10.4 Hz, 1H, $CH_{2bridge}$), 2.57-2.67 (m, 1H, =$CHC\underline{H}_2$), 2.73-2.85 (m, 2H, $NCH_2CH_2C\underline{H}_2$, =$CHC\underline{H}_2$), 2.87-2.92 (m, 1H, CH_{bridge}), 2.93 (s, 3H, NCH_3), 3.43-3.61 (m, 2H, $NC\underline{H}_2CH_2CH_2$), 4.19-4.33 (m, 2H, OCH_2), 4.82 (s, 1H, =CH_2), 4.86 (s, 1H, =CH_2), 5.61-5.74 (m, 2H, CH=CH); **^{13}C NMR (101 MHz, $CDCl_3$)**: major diastereomer: δ = -5.2 (q, $Si(CH_3)_2$), 18.3 (s, $\underline{C}(CH_3)_3$), 18.9 (q, =$C\underline{C}H_3$), 24.3 (t, $NCH_2\underline{C}H_2CH_2$), 25.9 (q, $C(\underline{C}H_3)_3$), 27.4 (t, =$CH\underline{C}H_2$), 28.4 (q, NCH_3), 29.8 (t, $NCH_2CH_2\underline{C}H_2$), 36.3 (t, $CH_{2bridge}$), 44.2 (t, $N\underline{C}H_2CH_2CH_2$), 50.3 (d, CH_{bridge}), 59.7 (t, OCH_2), 65.8 (s, $C_{bridgehead}$), 66.9 (s, $C_{bridgehead}$), 116.2 (t, =CH_2), 124.7 (d, =$\underline{C}HCH_2$OTBS), 132.0 (d, =$\underline{C}HCH_2C_\alpha$), 142.7 (s, =$\underline{C}CH_3$), 168.0 (s, $N_{Pro}C$=O), 173.0 (s, $CH_3N\underline{C}$=O).

^{1}H NMR (400 MHz, $CDCl_3$): minor diastereomer (detectable resonances): δ = 1.67 (s, 3H, =CCH_3), 2.92 (s, 3H, NCH_3), 4.77 (s, 1H, =CH_2), 4.95 (s, 1H, =CH_2).

(6*R*,7*R*,8a*R*)-6-(Furan-3-ylmethyl)-10-methyl-7-(prop-1-en-2-yl)tetrahydro-1*H*-6,8a-(epiminomethano)indolizine-5,9(6*H*)-dione (4.16c):

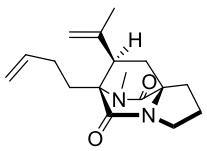


Prepared according to general procedure B from 340 mg (1.08 mmol) **4.15c**. Purification of the crude product by column chromatography (hexane/AcOEt, 1:1, gradient to 1:2) two times gave 315 mg (93%) **4.16c** as an inseparable 7:1 mixture of diastereomers as a pale yellow honey. $\mathbf{R_f}$ = 0.3

(hexane/AcOEt, 1:2); **IR**: ν[cm^{-1}] 2961, 1679, 1506, 1437, 1421, 1382, 1344, 1283, 1204, 1164, 1069, 1027, 907, 876, 789, 733, 693, 603, 562; **MS ESI+ *m/z*, (%)**: 337 (100, $[M+Na]^+$), 247 (4, $[M+H\text{-isoprene}]^+$); **HRMS ESI+ *m/z***: ($[M+Na]^+$): Calcd. for $C_{18}H_{22}O_3N_2Na$: 337.1523; Found: 337.1523; **^{1}H NMR (400 MHz, $CDCl_3$)**: major diastereomer: δ = 1.63 (s, 3H, $=CCH_3$), 1.75 (dd, *J* = 13.4, 5.6 Hz, 1H, $CH_{2bridge}$), 1.84 (dd, *J* = 13.2, 7.1 Hz, 1H, $NCH_2CH_2C\underline{H}_2$), 1.95-2.06 (m, 2H, $NCH_2C\underline{H}_2CH_2$), 2.17 (dd, *J* = 13.4, 10.3 Hz, 1H, $CH_{2bridge}$), 2.75-2.84 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 2.84-2.91 (m, 1H, CH_{bridge}), 2.85 (s, 3H, NCH_3), 2.90 (d, *J* = 17.1 Hz, 1H, $ArCH_2$), 3.25 (dd, *J* = 16.9, 1.2 Hz, 1H, $ArCH_2$), 3.55 (td, *J* = 6.7, 2.0 Hz, 2H, $NC\underline{H}_2CH_2CH_2$), 4.76 (br. s, 1H, $=CH_2$), 4.84 (m, 1H, $=CH_2$), 6.33 (dd, *J* = 1.7, 1.0 Hz, 1H, CH_{Ar}), 7.31-7.34 (m, 2H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: major diastereomer: δ = 19.0 (q, 3H, CH_3), 24.18 (t, $NCH_2\underline{C}H_2CH_2$), 26.0 (t, $ArCH_2$), 28.9 (q, NCH_3), 29.7 (t, $NCH_2CH_2\underline{C}H_2$), 36.6 (t, $CH_{2bridge}$), 44.23 (t, $N\underline{C}H_2CH_2CH_2$), 51.0 (d, CH_{bridge}), 65.8 (s, C_{Pro}), 68.0 (s, $C_{bridgehead}$), 112.5 (d, CH_{Ar}), 116.0 (t, $=CH_2$), 119.4 (s, C_{Ar}), 141.2 (d, CH_{Ar}), 142.2 (d, CH_{Ar}), 142.8 (s, $=\underline{C}CH_3$), 167.6 (s, $N_{Pro}C=O$), 173.4 (s, $CH_3N\underline{C}=O$).

^{1}H NMR (400 MHz, $CDCl_3$): minor diastereomer (detectable resonances): 1.61 (s, 3H, $=CCH_3$), 2.66 (dd, *J* = 10.7, 5.1 Hz, 1H, CH_{bridge}), 2.90 (s, 3H, NCH_3), 3.00 (dd, *J* = 14.8, 0.7 Hz, 1H, $ArCH_2$), 3.16 (dd, *J* = 14.8, 0.9 Hz, 1H, $ArCH_2$), 3.44-3.51 (m, 2H, $NC\underline{H}_2CH_2CH_2$), 4.63 (br. s, 1H, $=CH_2$), 4.89-4.92 (m, 1H, $=CH_2$), 6.41 (dd, *J* = 1.8, 0.8 Hz, 1H, CH_{Ar}), 7.29 (t, *J* = 1.7 Hz, 1H, CH_{Ar}), 7.37 (dd, *J* = 1.7, 0.9 Hz, 1H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: minor diastereomer: δ = 21.0 (q, $=C\underline{C}H_3$), 24.18 (t, $NCH_2\underline{C}H_2CH_2$), 24.22 (t, $NCH_2\underline{C}H_2CH_2$), 25.2 (t, $ArCH_2$), 28.9 (q, NCH_3), 36.7 (t, $CH_{2bridge}$), 44.19 (t, $N\underline{C}H_2CH_2CH_2$), 46.7 (d, CH_{bridge}), 66.0 (s, C_{Pro}), 67.7 (s, $C_{bridgehead}$), 113.5 (d, CH_{Ar}), 115.6 (t, $=CH_2$), 118.5 (s, C_{Ar}), 141.7 (d, CH_{Ar}), 142.6 (d, CH_{Ar}), 142.7 (s, $=\underline{C}CH_3$), 169.2 (s, $N_{Pro}C=O$), 172.3 (s, $N_{Pro}C=O$).

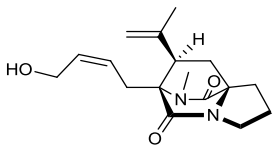
(6*R*,7*R*,8a*R*)-6-(But-3-en-1-yl)-10-methyl-7-(prop-1-en-2-yl)tetrahydro-1*H*-6,8a-(epiminomethano)indolizine-5,9(6*H*)-dione (4.24):



Cp_2ZrCl_2 (37 mg, 0.13 mmol) was dissolved in dry THF (1 mL) under Ar in a flame-dried Schlenk flask and the solution was cooled to -78 °C. *n*BuLi (163 µL, 0.26 mmol, 1.6 M in hexane) was added dropwise and the reaction mixture was stirred at -78 °C for 1 h. **4.16b** (50 mg, 0.12 mmol) in THF (1.5 mL) was added and after stirring for 5 min the cooling bath was removed. The reaction mixture was warmed to ambient temperature and stirred at r. t for 5 h. It was

quenched with saturated NH_4Cl solution and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography (hexane/AcOEt, 1:1, gradient to 1:2) to give 10 mg (29 %) **4.24** as a pale yellow oil. $\mathbf{R_f}$ = 0.3 (hexane/AcOEt, 1:2); **IR**: *ν*[cm^{-1}] 2953, 1682, 1419, 1383, 1252, 1206, 1102, 1063, 1009, 909, 838, 733, 564, 422; **MS ESI+ *m/z*, (%)**: 599 (28, $[2M+Na]^+$), 583 (7), 311 (100, $[M+Na]^+$), 289 (32, $[M+H]^+$); **HRMS ESI+ *m/z***: ($[M+Na]^+$): Calcd. for $C_{17}H_{24}O_2N_2Na$: 311.1730; Found: 311.1731; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 1.66 (dd, *J* = 1.5, 0.8 Hz, 3H, $=CCH_3$), 1.70 (dd, *J* = 13.4, 5.7 Hz, 1H, $CH_{2bridge}$), 1.78-1.84 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 1.86-1.94 (m, 1H, $C\underline{H}_2CH_2CH=$), 1.95-2.03 (m, 2H, $NCH_2C\underline{H}_2CH_2$), 2.03-2.13 (m, 1H, $C\underline{H}_2CH_2CH=$), 2.18 (dd, *J* = 13.5, 10.4 Hz, 1H, $CH_{2bridge}$), 2.19-2.29 (m, 1H, $CH_2C\underline{H}_2CH=$), 2.42-2.54 (m, 1H, $CH_2C\underline{H}_2CH=$), 2.76-2.84 (m, 2H, $NCH_2CH_2C\underline{H}_2$, CH_{bridge}), 2.95 (s, 3H, NCH_3), 3.41-3.58 (m, 2H, $NC\underline{H}_2CH_2CH_2$), 4.83 (br. s, 1H, $C\underline{H}_2=CCH_3$), 4.86 (t, *J* = 1.5 Hz, 1H, $C\underline{H}_2=CCH_3$), 4.97-5.11 (m, 2H, $CH=C\underline{H}_2$), 5.86 (ddt, *J* = 16.8, 10.2, 6.4 Hz, 1H, $C\underline{H}=CH_2$); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 19.0 (q, $=C\underline{C}H_3$), 24.5 (t, $NCH_2\underline{C}H_2CH_2$), 28.3 (t, $CH_2\underline{C}H_2CH=$), 28.5 (t, $\underline{C}H_2CH_2CH=$), 28.7 (q, NCH_3), 30.0 (t, $NCH_2CH_2\underline{C}H_2$), 36.8 (t, $CH_{2bridge}$), 44.4 (t, $N\underline{C}H_2CH_2CH_2$), 50.7 (d, CH_{bridge}), 65.9 (s, C_{Pro}), 67.7 (s, $C_{bridgehead}$), 115.1 (t, $\underline{C}H_2=CCH_3$), 115.9 (t, $CH=\underline{C}H_2$), 137.9 (d, $\underline{C}H=CH_2$), 143.5 (t, $=\underline{C}CH_3$), 168.4 (s, $N_{Pro}C=O$), 173.6 (s, $CH_3N\underline{C}=O$).

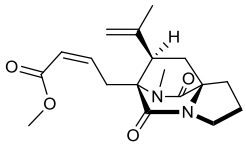
(6*R*,7*R*,8a*R*)-6-((*Z*)-4-Hydroxybut-2-en-1-yl)-10-methyl-7-(prop-1-en-2-yl)tetrahydro-1*H*-6,8a-(epiminomethano)indolizine-5,9(6*H*)-dione (4.33):



4.16b (131 mg, 0.313 mmol) was dissolved in dry THF (5 mL) under Ar and the solution was cooled to 0 °C. TBAF (1 mL, 1.0 mmol, 1 M in THF) was added and the reaction mixture was stirred for 1 h. The reaction mixture was quenched with saturated NH_4Cl solution and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography (100% AcOEt) to give 83 mg (87%) alcohol **4.33** contaminated with traces of the *anti*-diastereomer (ca 20:1) as a colorless heavy oil. $\mathbf{R_f}$ = 0.2 (AcOEt); **IR**: *ν*[cm^{-1}] 3448, 2934, 1671, 1438, 1385, 1344, 1252, 1204, 1104, 1021, 907, 732, 632, 563; **MS ESI+ *m/z*, (%)**: 631 (3, $[2M+Na]^+$), 343 (6, $[M+K]^+$), 327 (100, $[M+Na]^+$), 287 (3, $[M+H-H_2O]^+$); **HRMS ESI+ *m/z***: ($[M+Na]^+$): Calcd. for $C_{17}H_{24}O_3N_2Na$: 327.1679; Found: 327.1680; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 1.64 (s, 3H, $=CCH_3$), 1.74 (dd, *J* = 13.5, 5.7 Hz, 1H, $CH_{2bridge}$), 1.82 (dt, *J* = 13.1, 7.5 Hz, 1H, $NCH_2CH_2C\underline{H}_2$), 1.91-2.09 (m, 3H, OH, $NCH_2C\underline{H}_2CH_2$), 2.17 (dd, *J* = 13.5, 10.3 Hz, 1H, $CH_{2bridge}$), 2.55 (dd, *J* = 16.7, 5.5 Hz, 1H,

=CHC$\underline{H}_2$), 2.76-2.93 (m, 3H, CH_{bridge}, =CHC$\underline{H}_2$, $NCH_2CH_2C\underline{H}_2$), 2.95 (s, 3H, NCH_3), 3.42-3.64 (m, 2H, $NC\underline{H}_2CH_2CH_2$), 4.19 (dd, *J* = 12.9, 5.9 Hz, 1H, $C\underline{H}_2OH$), 4.29 (dd, *J* = 12.9, 6.2 Hz, 1H, $C\underline{H}_2OH$), 4.83 (s, 1H, $=CH_2$), 4.87 (s, 1H, $=CH_2$), 5.68-5.85 (m, 2H, CH=CH); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 19.0 (q, =C$\underline{C}H_3$), 24.5 (t, $NCH_2\underline{C}H_2CH_2$), 27.7 (t, =CH$\underline{C}H_2$), 28.6 (q, NCH_3), 29.9 (t, $NCH_2CH_2\underline{C}H_2$), 36.6 (t, $CH_{2bridge}$), 44.5 (t, $N\underline{C}H_2CH_2CH_2$), 51.0 (d, CH_{bridge}), 58.8 (t, CH_2OH), 65.9 (s, C_{Pro}), 67.2 (s, $C_{bridgehead}$), 116.5 (t, $=CH_2$), 126.6 (d, =$\underline{C}HCH_2OH$), 131.4 (d, =$\underline{C}HCH_2C$), 142.9 (s, =$\underline{C}CH_3$), 168.0 (s, $N_{Pro}C$=O), 173.2 (s, $CH_3N\underline{C}$=O).

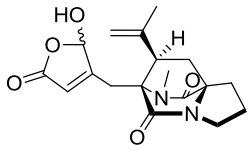
(*Z*)-Methyl 4-((6*R*,7*R*,8a*R*)-10-methyl-5,9-dioxo-7-(prop-1-en-2-yl)hexahydro-1*H*-6,8a-(epiminomethano)indolizin-6-yl)but-2-enoate (4.34):



Alcohol **4.33** (165 mg, 0.5 mmol) was dissolved in CH_2Cl_2 (5 mL) in a brown round bottom flask, which was additionally covered with aluminum foil. MnO_2 (700 mg, 8 mmol) was added and the reaction mixture was stirred overnight at r.t for 15 h. The reaction mixture was quickly filtered through a pad of Celite in the dark, which was thoroughly washed with AcOEt. The filtrates were evaporated and the residue was redissolved in CH_2Cl_2 (5 mL) in a brown round bottom flask. KCN (530 mg, 8.2 mmol), methanol (4 mL), glacial acetic acid (400 μL, 7.2 mmol) and MnO_2 (700 mg, 8 mmol) were subsequently added, the reaction flask was covered by aluminum foil and stirred for 20 h. The reaction mixture was filtered through a pad of Celite, which was thoroughly washed with AcOEt. The filtrates were evaporated and the residue was purified by column chromatography (hexane/AcOEt, 1:2 gradient to 1:5) to give 135 mg (75%) ester **4.34** as a colorless gum. The addition order of reagents may be important for the reproducibility of the second stage as judged by some precedence in the literature.[112] **R_f** = 0.6 (AcOEt); **IR**: *ν*[cm^{-1}] 2961, 1723, 1684, 1648, 1441, 1384, 1344, 1240, 1179, 1062, 1009, 907, 815, 735, 588, 560, 513; **$[\alpha]^{20}_{589}$**: −1.7 (*c* 0.998, $CHCl_3$); **MS ESI+ *m/z*, (%)**: 687 (3, $[2M+Na]^+$), 371 (2, $[M+K]^+$), 355 (100, $[M+Na]^+$), 333 (9, $[M+H]^+$), 301 (5, $[M+H-CH_3OH]^+$), 287 (2); **HRMS ESI+ *m/z***: ($[M+Na]^+$): Calcd. for $C_{18}H_{24}O_4N_2Na$: 355.1628; Found: 355.1629; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 1.66 (s, 3H, $=CCH_3$), 1.74-1.88 (m, 2H, $NCH_2CH_2C\underline{H}_2$, $CH_{2bridge}$), 1.94-2.07 (m, 2H, $NCH_2C\underline{H}_2CH_2$), 2.16 (dd, *J* = 13.5, 10.3 Hz, 1H, $CH_{2bridge}$), 2.74-2.85 (m, 2H, CH_{bridge}, $NCH_2CH_2C\underline{H}_2$), 2.87 (s, 3H, NCH_3), 3.18 (ddd, *J* = 18.8, 4.6, 2.7 Hz, 1H, =CHC$\underline{H}_2$), 3.44 (ddd, *J* = 18.9, 7.7, 1.9 Hz, 1H, =CHC$\underline{H}_2$), 3.49-3.60 (m, 2H, $NC\underline{H}_2CH_2CH_2$), 3.72 (s, 3H, OCH_3), 4.87 (br. s, 1H, $=CH_2$), 4.91 (br. s, 1H, $=CH_2$), 5.90 (ddd, *J* = 11.6, 2.7, 1.9 Hz, 1H, O=CC$\underline{H}$=CH), 6.62 (ddd, *J* = 11.5, 7.6, 4.6 Hz, 1H, O=CCH=C$\underline{H}$); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 19.2 (q, =C$\underline{C}H_3$), 24.4 (t,

$NCH_2\underline{C}H_2CH_2$), 28.2 (q, NCH_3), 29.9 (t, $NCH_2CH_2\underline{C}H_2$), 30.3 (t, $=CH\underline{C}H_2$), 36.9 (t, $CH_{2bridge}$), 44.4 (t, $N\underline{C}H_2CH_2CH_2$), 51.4 (d, CH_{bridge}), 51.7 (q, OCH_3), 65.9 (s, C_{Pro}), 67.6 (s, $C_{bridgehead}$), 116.8 (t, $=CH_2$), 120.3 (d, $O=C\underline{C}H=CH$), 142.6 (s, $=\underline{C}CH_3$), 146.7 (d, $O=CCH=\underline{C}H$), 167.0 (s, $O\underline{C}=O$), 167.3 (s, $N_{Pro}C=O$), 173.2 (s, $CH_3N\underline{C}=O$).

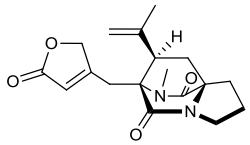
(6*R*,7*R*,8a*R*)-6-((2-Hydroxy-5-oxo-2,5-dihydrofuran-3-yl)methyl)-10-methyl-7-(prop-1-en-2-yl)tetrahydro-1*H*-6,8a-(epiminomethano)indolizine-5,9(6*H*)-dione (4.40):



Furan **4.16c** (195 mg, 0.62 mmol) was dissolved in dry CH_2Cl_2 (50 mL) in a Schlenk flask. Rose bengal (30 mg, 0.03 mmol) and iPr$_2$NEt (216 µL, 1.24 mmol) were added. The reaction mixture was connected to an oxygen inlet and oxygen gas was bubbled through the solution for 20 min at -78 °C before it was irradiated with a tungsten flood light, until full consumption of furan was reached as indicated by TLC, at -78 °C under constant bubbling of oxygen gas for 2 h. The light was turned off, the reaction mixture was quenched by an excess saturated oxalic acid solution, stirred at r.t. for 30 min and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography (hexane/AcOEt, gradient to 100% AcOEt) to give 207 mg (96%) γ-hydroxybutenolide **4.40** as a pale red foam as an inseparable 2:1 epimeric mixture contaminated with Rose Bengal residues which was directly used in the next step. When a larger amount of iPr$_2$NEt was used and temperature was not carefully controlled, small amounts of more polar components were observed, which could be the regioisomeric hydroxybutenolide (not analyzed). $\mathbf{R_f}$ = 0.3 (AcOEt); **IR**: ν[cm^{-1}] 3291 (br.), 2957, 1761, 1675, 1442, 1390, 1342, 1288, 1255, 1193, 1136, 1066, 1003, 956, 914, 868, 732, 649, 557; **MS ESI+ *m/z*, (%)**: 1407 (2, $[4M+Na]^+$), 1083 (7), 1061 (18, $[3M+Na]^+$), 888 (4), 813 (3), 737 (6), 715 (47, $[2M+Na]^+$), 650 (4), 467 (4), 369 (100, $[M+Na]^+$); **HRMS ESI+ *m/z***: ($[M+Na]^+$): Calcd. for $C_{18}H_{22}N_2O_5Na$: 369.1421; Found: 369.1422; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 1.63 (s, 3H, $=CCH_3$), 1.64 (s, 3H, $=CCH_3$*), 1.78-1.85 (m, 2H, $CH_{2bridge}$, $CH_{2bridge}$*), 1.85-1.94 (m, 2H, $NCH_2CH_2C\underline{H}_2$, $NCH_2CH_2C\underline{H}_2$*), 2.00-2.10 (m, 4H, $NCH_2C\underline{H}_2CH_2$, $NCH_2C\underline{H}_2CH_2$*), 2.12-2.20 (m, 2H, $CH_{2bridge}$, $CH_{2bridge}$*), 2.65 (dd, J = 18.2, 2.1 Hz, 1H, $=CCH_2$), 2.77-2.87 (m, 5H, $NCH_2CH_2C\underline{H}_2$, $NCH_2CH_2C\underline{H}_2$*, CH_{bridge}, CH_{bridge}*, $=CCH_2$*), 2.91 (s, 3H, NCH_3*), 2.98-3.06 (m, 1H, $=CCH_2$*), 3.01 (s, 3H, NCH_3), 3.07 (dd, J = 18.2, 1.1 Hz, 1H, $=CCH_2$), 3.49-3.61 (m, 4H, $NC\underline{H}_2CH_2CH_2$, $NC\underline{H}_2CH_2CH_2$*), 4.87 (s, 1H, $=CH_2$), 4.89 (s, 1H, $=CH_2$*), 4.95 (s, 1H, $=CH_2$*), 4.97 (s, 1H, $=CH_2$), 5.83 (br. s, 1H,

=CH*), 5.85 (br. s, 1H, =CH), 5.96 (br. s, 1H, C<u>H</u>OH), 6.08 (br. s, 1H, C<u>H</u>OH*); **^{13}C NMR (101 MHz, $CDCl_3$)**: (ca 2:1 mixture of epimers): δ = 18.7 (q, =CCH_3), 18.9 (q, =CCH_3*), 24.2 (t, $NCH_2\underline{C}H_2CH_2$), 24.3 (t, $NCH_2\underline{C}H_2CH_2$*), 27.0 (t, =$CCH_2$), 28.8 (t, =$CCH_2$*), 29.0 (q, NCH_3*), 29.4 (q, NCH_3), 29.6 (t, $NCH_2CH_2\underline{C}H_2$), 29.7 (t, $NCH_2CH_2\underline{C}H_2$*), 36.75 (t, $CH_{2bridge}$*), 36.83 (t, $CH_{2bridge}$), 44.7 (t, $N\underline{C}H_2CH_2CH_2$*), 44.9 (t, $N\underline{C}H_2CH_2CH_2$), 51.3 (d, CH_{bridge}), 51.8 (d, CH_{bridge}*), 66.2 (s, 2C, C_{Pro}, C*$_{Pro}$), 68.0 (s, $C_{bridgehead}$*), 69.6 (s, $C_{bridgehead}$), 99.3 (d, CHOH*), 100.5 (d, CHOH), 117.7 (t, =CH_2*), 118.1 (t, =CH_2), 119.8 (d, =<u>C</u>HC=O), 120.2 (d, =<u>C</u>HC=O*), 141.5 (s, =<u>C</u>CH_3), 141.8 (s, =<u>C</u>CH_3*), 163.8 (s, =<u>C</u>CHOH), 164.1 (s, =<u>C</u>CHOH*), 166.2 (s, $N_{Pro}C$=O*), 166.5 (s, $N_{Pro}C$=O), 170.8 (s, $CH_3N\underline{C}$=O), 170.9 (s, $CH_3N\underline{C}$=O*), 173.7 (s, COO*), 173.8 (s, COO). Resonances of the minor epimer are marked by an *.

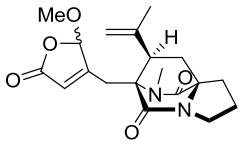
(6*R*,7*R*,8a*R*)-10-Methyl-6-((5-oxo-2,5-dihydrofuran-3-yl)methyl)-7-(prop-1-en-2-yl)tetrahydro-1*H*-6,8a-(epiminomethano)indolizine-5,9(6*H*)-dione (4.41):



γ-Hydroxybutenolide **4.40** (60 mg, 0.173 mmol) was dissolved under Ar in dry methanol (2 mL) and the solution was cooled to 0 ºC. $NaBH_4$ (26 mg, 0.7 mmol) was added in small portions and the reaction mixture was stirred until conversion of was complete as indicated by TLC (ca 15 min). The reaction mixture was quenched carefully with 10% HCl solution (5 mL), stirred for 5 min and extracted with chloroform. The combined organic layers were dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography (100% AcOEt) to give 53 mg (93%) butenolide **4.41** as a colorless solid as a 10:1 mixture of diastereomers. **R_f** = 0.3 (AcOEt); **IR**: *ν*[cm^{-1}] 2959, 1786, 1752, 1687, 1645, 1440, 1383, 1259, 1206, 1180, 1125, 1035, 899, 733; **MS ESI+ *m/z*, (%)**: 1013 (30, $[3M+Na]^+$), 781 (15), 683 (81, $[2M+Na]^+$), 451 (6), 353 (100, $[M+Na]^+$), 331 (42, $[M+H]^+$); **HRMS ESI+ *m/z***: ($[M+Na]^+$): $C_{18}H_{22}O_4N_2Na$: 353.1472; Found: 353.1474; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 1.64 (dd, *J* = 1.5, 0.8 Hz, 3H, =CCH_3), 1.78-1.93 (m, 2H, $NCH_2CH_2C\underline{H}_2$, $CH_{2bridge}$), 1.99-2.10 (m, 2H, $NCH_2C\underline{H}_2CH_2$), 2.16 (dd, *J* = 13.6, 10.2 Hz, 1H, $CH_{2bridge}$), 2.77-2.87 (m, 3H, =$CC\underline{H}_2$, CH_{bridge}, $NCH_2CH_2C\underline{H}_2$), 2.89 (s, NCH_3), 3.16 (ddt, *J* = 18.0, 2.0, 1.0 Hz, 1H, =$CC\underline{H}_2$), 3.56 (t, *J* = 6.9 Hz, 2H, $NC\underline{H}_2CH_2CH_2$), 4.73-4.97 (m, 4H, OCH_2, =CH_2), 5.96 (qd, *J* = 1.9, 1.1 Hz, 1H, =CH); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 18.6 (q, =$C\underline{C}H_3$), 24.4 (t, $NCH_2\underline{C}H_2CH_2$), 29.0 (q, NCH_3), 29.8 (t, $NCH_2CH_2\underline{C}H_2$), 30.5 (t, =$C\underline{C}H_2$), 36.5 (t, $CH_{2bridge}$), 44.6 (t, $N\underline{C}H_2CH_2CH_2$), 52.0 (d, CH_{bridge}), 66.2 (s, C_{Pro}), 67.6 (s, $C_{bridgehead}$), 74.2 (t, OCH_2), 117.6 (t,

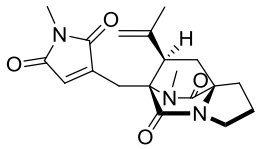
=CH_2), 119.1 (d, C=<u>C</u>H), 142.0 (s, =<u>C</u>CH_3), 165.7 (s, <u>C</u>=CH), 166.4 (s, N_{Pro}C=O), 173.5 (s, CH_3N<u>C</u>=O), 173.6 (s, OC=O).

(6*R*,7*R*,8a*R*)-6-((2-Methoxy-5-oxo-2,5-dihydrofuran-3-yl)methyl)-10-methyl-7-(prop-1-en-2-yl)tetrahydro-1*H*-6,8a-(epiminomethano)indolizine-5,9(6*H*)-dione (4.42):



γ-Hydroxybutenolide **4.40** (200 mg, 0.58 mmol) was dissolved in dry methanol (5 mL), three drops of concentrated sulfuric acid were added with a Pasteur pipette and the reaction mixture was stirred at r.t for 15 h. The reaction mixture was quenched carefully by addition of an excess saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and evaporated to give 208 mg (99%) essentially pure **4.42** as a 1:1 mixture of epimers. $\mathbf{R_f}$ = 0.6 (AcOEt); **IR**: *ν*[cm^{-1}] 2941, 1766, 1730, 1683, 1439, 1379, 1342, 1252, 1206, 1181, 1120, 1070, 959, 905, 732, 648, 589, 557; **MS ESI+ *m/z*, (%)**: 1103 (2, $[3M+Na]^+$), 841 (5), 743 (47, $[2M+Na]^+$), 495 (5), 481 (13), 429 (26), 383 (100, $[M+Na]^+$), 361 (19, $[M+H]^+$); **HRMS ESI+ *m/z***: ($[M+Na]^+$): Calcd. for $C_{19}H_{24}N_2O_5Na$: 383.1577; Found: 383.1578; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 1.63 (dd, *J* = 1.5, 0.7 Hz, 3H, =CCH_3), 1.64 (dd, *J* = 1.5, 0.7 Hz, 3H, =CCH_3), 1.76-1.92 (m, 4H, $NCH_2CH_2C\underline{H}_2$, $CH_{2bridge}$), 1.98-2.09 (m, 4H, $NCH_2C\underline{H}_2CH_2$), 2.10-2.22 (m, 2H, $CH_{2bridge}$), 2.60-2.71 (m, 2H, =CCH_2), 2.74-2.89 (m, 3H, CH_{bridge}, $2NCH_2CH_2C\underline{H}_2$), 2.83 (s, 3H, NCH_3), 2.87 (s, 3H, NCH_3), 2.89-2.98 (m, 2H, CH_{bridge}, =CCH_2), 3.15 (dd, *J* = 19.5, 2.3 Hz, 1H, =CCH_2), 3.53 (s, 3H, OCH_3), 3.54-3.60 (m, 4H, $NC\underline{H}_2CH_2CH_2$), 3.64 (s, 3H, OCH_3), 4.81 (s, 1H, =CH_2), 4.87 (s, 1H, =CH_2), 4.90 (t, *J* = 1.5 Hz, 1H, =CH_2), 4.94 (t, *J* = 1.5 Hz, 1H, =CH_2), 5.68 (s, C<u>H</u>OCH_3), 5.73 (s, C<u>H</u>OCH_3), 5.85 (s, =CH), 5.97 (s, =CH); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 18.5 (q, =C<u>C</u>H_3), 18.8 (q, =C<u>C</u>H_3), 24.3 (t, $NCH_2\underline{C}H_2CH_2$), 24.4 (t, $NCH_2\underline{C}H_2CH_2$), 28.8 (t, =C<u>C</u>$H_2$), 28.9 (q, NCH_3), 29.16 (q, NCH_3), 29.22 (t, =C<u>C</u>H_2), 29.7 (t, $NCH_2CH_2\underline{C}H_2$), 29.8 (t, $NCH_2CH_2\underline{C}H_2$), 36.2 (t, $CH_{2bridge}$), 36.9 (t, $CH_{2bridge}$), 44.5 (t, N<u>C</u>$H_2CH_2CH_2$), 44.6 (t, N<u>C</u>$H_2CH_2CH_2$), 51.3 (q, OCH_3), 51.8 (q, OCH_3), 56.5 (d, CH_{bridge}), 58.3 (d, CH_{bridge}), 66.09 (s, C_{Pro}), 66.11 (s, C_{Pro}), 67.1 (s, $C_{bridgehead}$), 67.9 (s, $C_{bridgehead}$), 105.06 (d, <u>C</u>HOCH_3), 105.09 (d, <u>C</u>HOCH_3), 117.48 (t, =CH_2), 117.52 (t, =CH_2), 120.6 (d, =<u>C</u>HC=O), 121.2 (d, =<u>C</u>HC=O), 141.9 (s, =<u>C</u>CH_3), 142.1 (s, =<u>C</u>CH_3), 162.0 (s, <u>C</u>=CH), 162.2 (s, <u>C</u>=CH), 165.9 (s, N_{Pro}C=O), 166.7 (s, N_{Pro}C=O), 170.2 (s, CH_3N<u>C</u>=O), 170.5 (s, CH_3N<u>C</u>=O), 173.1 (s, OC=O), 173.7 (s, OC=O).

(6*R*,7*R*,8a*R*)-10-Methyl-6-((1-methyl-2,5-dioxo-2,5-dihydro-1*H*-pyrrol-3-yl)methyl)-7-(prop-1-en-2-yl)tetrahydro-1*H*-6,8a-(epiminomethano)indolizine-5,9(6*H*)-dione (4.44):



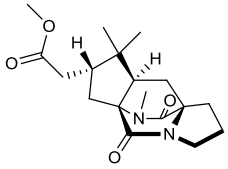
γ-Hydroxybutenolide **4.40** (135 mg, 0.4 mmol) was dissolved in CH_2Cl_2 (3 mL), DMP (215 mg, 0.51 mmol) was added and the reaction mixture was stirred at r.t for 4 h. The reaction mixture was quenched by addition of a 1:1 saturated aqueous $NaHCO_3/Na_2S_2O_3$ mixture (5 mL). The biphasic solution was stirred for 5 min and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and evaporated. The residue was quickly purified by column chromatography (hexane/AcOEt, 1:1, gradient to 1:3) to give 121 mg (90%) sensitive maleic anhydride **4.43** as a colorless foam which was immediately used in the next step. (**^{1}H NMR (400 MHz, $CDCl_3$)**: maleic anhydride: δ = 1.64 (br. s, 3H, $=CCH_3$), 1.83 (dd, *J* = 13.5, 5.9 Hz, 1H, $CH_{2bridge}$), 1.85-1.93 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 1.99-2.09 (m, 2H, $NCH_2C\underline{H}_2CH_2$), 2.17 (dd, *J* = 13.6, 10.2 Hz, 1H, $CH_{2bridge}$), 2.77-2.89 (m, 3H, $NCH_2CH_2C\underline{H}_2$, CH_{bridge}, $=CH_2$), 2.82 (s, 3H, NCH_3), 3.18 (dd, *J* = 18.4, 2.3 Hz, 1H, $=CCH_2$), 3.57 (t, *J* = 6.8 Hz, 2H, $NC\underline{H}_2CH_2CH_2$), 4.90 (s, 1H, $=CH_2$), 4.96 (t, *J* = 1.5 Hz, 1H, $=CH_2$), 6.85 (dd, *J* = 2.3, 1.4 Hz, 1H, =CH); **^{13}C NMR (101 MHz, $CDCl_3$)**: maleic anhydride: δ = 18.6 (q, $=CCH_3$), 24.3 (t, $NCH_2\underline{C}H_2CH_2$), 26.7 (t, $=C\underline{C}H_2$), 28.9 (q, NCH_3), 29.7 (t, $NCH_2CH_2\underline{C}H_2$), 36.6 (t, $CH_{2bridge}$), 44.7 (t, $N\underline{C}H_2CH_2CH_2$), 52.2 (d, CH_{bridge}), 66.2 (s, C_{Pro}), 68.5 (s, $C_{bridgehead}$), 118.2 (t, $=CH_2$), 131.8 (d, $=\underline{C}HC=O$), 141.5 (s, $=\underline{C}CH_3$), 148.2 (s, $CH=\underline{C}C=O$), 163.8 (s, CO_{MA}), 165.9 (s, $N_{Pro}C=O$), 166.6 (s, CO_{MA}), 173.2 (s, $CH_3N\underline{C}=O$)).

Maleic anhydride **4.43** (50 mg, 0.15 mmol) was dissolved in THF (2 mL) and heptamethyldisilazane (66 µL, 0.3 mmol) was added at r.t. under Ar. The reaction mixture was stirred for 2 h and then evaporated to dryness to give a beige foam. The residue was further dried under high vacuum for 15 min and was heated under Ar at 150 °C for 5 min. It was cooled to r.t. and purified by column chromatography (hexane/AcOEt, 1:2, gradient to 1:3) to give 46 mg (88%) maleic imide **4.44**. **R_f** = 0.2 (hexane/AcOEt, 1:3); **IR**: *ν*[cm^{-1}] 2936, 1708, 1687, 1447, 1388, 1265, 1206, 1125, 1059, 997, 919, 734, 648, 558; **MS ESI+ *m/z*, (%)**: 737 (4, $[2M+Na]^+$), 380 (100, $[M+Na]^+$), 358 (10, $[M+H]^+$), 290 (4, $[M+H\text{-isoprene}]^+$); **HRMS ESI+ *m/z***: ($[M+Na]^+$): Calcd. for $C_{19}H_{23}O_4N_3Na$: 380.1581; Found: 380.1582; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 1.63 (dd, *J* = 1.3, 0.7 Hz, 3H, $=CCH_3$), 1.79 (dd, *J* = 13.3, 6.0 Hz, 1H, $CH_{2bridge}$), 1.85 (dt, *J* = 13.3, 7.5 Hz, 1H, $NCH_2CH_2C\underline{H}_2$), 1.99-2.05 (m, 2H, $NCH_2C\underline{H}_2CH_2$), 2.27 (dd, *J* = 13.3, 10.3 Hz, 1H, $CH_{2bridge}$), 2.79 (s, 3H, $N_{DKP}CH_3$), 2.80-2.86 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 2.98 (dd, *J* = 10.4, 6.0 Hz, 1H, CH_{bridge}), 3.08 (s, 3H, $N_{imide}CH_3$),

3.13 (dd, J = 22.2, 2.4 Hz, 1H, =C$\underline{H}_2$), 3.49-3.62 (m, 2H, NC$\underline{H}_2$CH$_2$CH$_2$), 3.73 (dd, J = 22.0, 2.4 Hz, 1H, =C$\underline{H}_2$), 4.87-4.97 (m, 2H, =CH$_2$), 6.91 (t, J = 2.5 Hz, 1H, =CH); **^{13}C NMR (101 MHz, CDCl$_3$)**: δ = 19.7 (q, =C$\underline{C}$H$_3$), 24.3 (t, NCH$_2$$\underline{C}H_2CH_2$), 25.2 (q, N$_{imide}CH_3$), 29.5 (q, N$_{DKP}CH_3$), 30.0 (t, NCH$_2CH_2$$\underline{C}H_2$), 34.4 (t, =C$\underline{C}H_2$), 37.0 (t, CH$_{2bridge}$), 44.9 (t, N$\underline{C}H_2CH_2CH_2$), 51.3 (d, CH$_{bridge}$), 65.9 (s, C$_{Pro}$), 67.1 (s, C$_{bridgehead}$), 116.8 (t, =CH$_2$), 127.4 (d, =CH), 135.1 (s, CH=$\underline{C}$), 142.1 (s, =$\underline{C}$CH$_3$), 164.5 (s, N$_{Pro}$C=O), 169.8 (s, C=O$_{imide}$), 172.8 (s, C=O$_{imide}$), 173.8 (s, CH$_3$N$\underline{C}$=O).

General procedure C: Representative procedure for the cyclization of **4.34**:

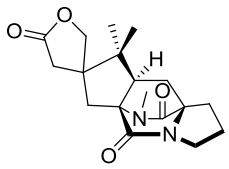
Methyl 2-((5a*R*,7*R*,8a*R*,9a*R*)-8,8,11-trimethyl-5,10-dioxooctahydro-1*H*-5a,9a-(epiminomethano)cyclopenta[*f*]indolizin-7-yl)acetate (4.35):



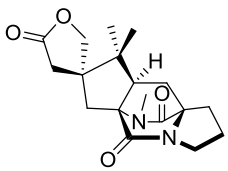
Unsaturated ester **4.34** (70 mg, 0.21 mmol) was dissolved in dry methanol (5 mL) under Ar and Fe(acac)$_3$ (80 mg, 0.21 mmol) was added. PhSiH$_3$ (75 μL, 0.53 mmol) was added to the brown suspension at r.t. Vigorous gas evolution was observed. The reaction mixture was immersed to an oil bath preheated to 65 °C and refluxed for 1.5 h. The reaction mixture was evaporated to dryness and the residue was purified by column chromatography eluting first with hexane/AcOEt (1:2) until the yellow-orange colors were washed out and subsequently with 100% AcOEt to give 61 mg (87%) crystalline **4.35** as a single diastereomer. The product does not stain well in most common staining solutions, such as KMnO$_4$ or anisaldehyde. Cerium ammonium molybdate (CAM) was identified as the best staining solution for all fully cyclized compounds. Suitable crystals for X-ray crystallographic analysis were grown by diffusion of hexane into a saturated AcOEt solution of **4.35**. **m.p.** 119-121 °C; **R$_f$** = 0.3 (AcOEt); **[α]$^{20}_{589}$**: +32.0 (*c* 0.1, CH$_3$OH); **IR**: ν[cm^{-1}] 2963, 2885, 1739, 1682, 1443, 1422, 1383, 1342, 1276, 1207, 1164, 1075, 996, 842; **MS ESI+ *m/z*, (%)**: 691 (1, [2M+Na]$^+$), 357 (100, [M+Na]$^+$), 335 (2, [M+H]$^+$); **HRMS ESI+ *m/z***: ([M+Na]$^+$): Calcd. for C$_{18}$H$_{26}$O$_4$N$_2$Na: 357.1785; Found: 357.1785; **^{1}H NMR (400 MHz, CDCl$_3$)**: δ = 0.85 (s, 3H, C(CH$_3$)$_2$), 0.90 (s, 3H, C(CH$_3$)$_2$), 1.53 (dd, J = 11.6, 10.4 Hz, 1H, CH$_{2cyclopentane}$), 1.71-1.84 (m, 2H, CH$_{2bridge}$, NCH$_2$C$\underline{H}_2$CH$_2$), 1.89-2.06 (m, 3H, CH$_{2bridge}$, NCH$_2$C$\underline{H}_2$CH$_2$, NCH$_2$CH$_2$C$\underline{H}_2$), 2.17 (dd, J = 10.4, 7.1 Hz, 1H, CH$_{bridge}$), 2.32 (dd, J = 14.9, 8.7 Hz, 1H, C$\underline{H}_2$CO$_2$Me), 2.50 (dd, J = 14.9, 6.6 Hz, 1H, C$\underline{H}_2$CO$_2$Me), 2.59 (ddt, J = 10.5, 8.6, 6.8 Hz, 1H, C$\underline{H}$CH$_2$CO$_2$Me), 2.69 (dd, J = 11.6, 7.0 Hz, 1H, CH$_{2cyclopentane}$), 2.79 (ddd, J = 12.7, 7.1, 5.3 Hz, 1H, NCH$_2$CH$_2$C$\underline{H}_2$), 2.87 (s, 3H, NCH$_3$), 3.42 (dt, J = 11.4, 7.4 Hz, 1H, NC$\underline{H}_2$CH$_2$CH$_2$), 3.53 (ddd, J = 11.3, 7.5, 5.0

Hz, 1H, NC<u>H</u>$_2$CH$_2$CH$_2$), 3.72 (s, 3H, OCH$_3$); **^{13}C NMR (101 MHz, CDCl$_3$)**: δ = 24.9 (t, NCH$_2$<u>C</u>H$_2$CH$_2$), 26.4 (q, C(<u>C</u>H$_3$)$_2$), 26.5 (q, C(<u>C</u>H$_3$)$_2$), 28.1 (q, NCH$_3$), 30.3 (t, NCH$_2$CH$_2$<u>C</u>H$_2$), 31.4 (t, CH$_{2bridge}$), 32.0 (t, CH$_{2cyclopentane}$), 37.0 (t, <u>C</u>H$_2$CO$_2$Me), 38.4 (s, <u>C</u>(CH$_3$)$_2$), 43.9 (t, N<u>C</u>H$_2$CH$_2$CH$_2$), 44.4 (d, <u>C</u>HCH$_2$CO$_2$Me), 51.9 (q, OCH$_3$), 57.7 (d, CH$_{bridge}$), 68.3 (s, C$_{Pro}$), 68.9 (s, C$_{bridgehead}$), 168.5 (s, N$_{Pro}$C=O), 172.5 (s, CH$_3$N<u>C</u>=O), 173.3 (s, <u>C</u>O$_2$Me).

(3'*S*,5a*R*,8a*R*,9a*R*)-8,8,11-Trimethyltetrahydro-2'*H*-spiro[5a,9a-(epiminomethano)cyclopenta[*f*]indolizine-7,3'-furan]-5,5',10(1*H*,4'*H*,6*H*,8*H*)-trione (4.45b) and (3'*R*,5a*R*,8a*R*,9a*R*)-8,8,11-trimethyltetrahydro-2'*H*-spiro[5a,9a-(epiminomethano)cyclopenta[*f*]indolizine-7,3'-furan]-5,5',10(1*H*,4'*H*,6*H*,8*H*)-trione (4.45a):

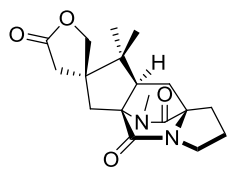


Prepared according to general procedure C from 40 mg (0.12 mmol) butenolide **4.41**. Purification of the crude product by column chromatography (hexane/AcOEt, 1:2, gradient to 100% AcOEt) gave 33 mg (83%) **4.45ab** as an inseparable 3:1 mixture of diastereomers as a colorless solid. **R$_f$** = 0.2 (AcOEt); **IR**: *ν*[cm^{-1}] 2966, 2892, 1782, 1684, 1431, 1385, 1342, 1273, 1181, 1097, 1060, 1011, 919, 734; **MS ESI+ *m/z*, (%)**: 1019 (6, [3M+Na]$^+$), 753 (10), 687 (32, [2M+Na]$^+$), 453 (14), 355 (100, [M+Na]$^+$), 333 (24, [M+H]$^+$); **HRMS ESI+ *m/z***: ([M+Na]$^+$): Calcd. for C$_{18}$H$_{24}$N$_2$O$_4$: 355.1628; Found: 355.1628;



minor diastereomer

^{1}H NMR (400 MHz, CDCl$_3$): minor diastereomer **4.45a** (detectable resonances): δ = 0.79 (s, 3H, C(CH$_3$)$_2$), 0.95 (s, 3H, C(CH$_3$)$_2$), 2.20 (d, *J* = 15.1 Hz, 1H, CH$_{2cyclopentane}$), 2.50 (d, *J* = 17.2 Hz, 1H, CH$_2$C=O), 2.56 (d, *J* = 17.2 Hz, 1H, CH$_2$C=O), 2.89 (s, 3H, NCH$_3$), 3.05 (d, *J* = 15.1 Hz, 1H, CH$_{2cyclopentane}$), 4.09 (d, *J* = 9.0 Hz, 1H, OCH$_2$), 4.35 (d, *J* = 8.9 Hz, 1H, OCH$_2$); **^{13}C NMR (101 MHz, CDCl$_3$)**: minor diastereomer **4.45a**: δ 19.3 (s, C(<u>C</u>H$_3$)$_2$), 23.5 (s, C(<u>C</u>H$_3$)$_2$), 24.9 (t, NCH$_2$<u>C</u>H$_2$CH$_2$), 25.1 (t, NCH$_2$<u>C</u>H$_2$CH$_2$), 28.4 (q, NCH$_3$), 30.8 (t, CH$_{2bridge}$), 35.2 (t, CH$_{2cyclopentane}$), 37.2 (t, <u>C</u>H$_2$C=O), 41.8 (s, <u>C</u>(CH$_3$)$_2$), 44.1 (t, N<u>C</u>H$_2$CH$_2$CH$_2$), 55.1 (s, C$_{spiro}$), 58.0 (d, CH$_{bridge}$), 68.13 (s, C$_{Pro}$), 69.0 (s, C$_{bridgehead}$), 77.0 (t, OCH$_2$), 168.5 (s, N$_{Pro}$C=O), 172.4 (s, CH$_3$N<u>C</u>=O), 175.5 (s, OC=O).

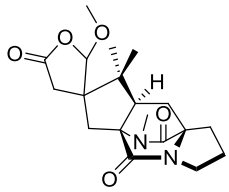


major diastereomer

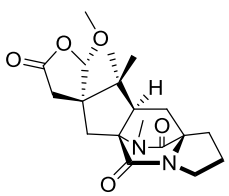
^{1}H NMR (400 MHz, CDCl$_3$): major diastereomer **4.45b**: δ = 0.78 (s, 3H, C(CH$_3$)$_2$), 0.97 (s, 3H, C(CH$_3$)$_2$), 1.70 (dd, *J* = 12.9, 7.9 Hz, 1H, CH$_{2bridge}$), 1.83 (dd, *J* = 12.9, 8.6 Hz, 1H, CH$_{2bridge}$), 1.91-2.07 (m, 3H, NCH$_2$C<u>H</u>$_2$C<u>H</u>$_2$), 2.05 (d, *J* = 14.9 Hz, 1H, CH$_{2cyclopentane}$), 2.26-2.33 (m, 1H, CH$_{bridge}$), 2.33 (d, *J* = 16.5 Hz, 1H, CH$_2$C=O), 2.69 (d, *J* = 16.5 Hz, 1H, CH$_2$C=O), 2.82

(ddd, *J* = 12.5, 7.1, 4.8 Hz, 1H, $NCH_2CH_2C\underline{H}_2$), 2.88 (s, 3H, NCH_3), 3.16 (d, *J* = 14.9 Hz, 1H, $CH_{2cyclopentane}$), 3.37-3.47 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.51-3.60 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 4.20 (d, *J* = 9.2 Hz, 1H, OCH_2), 4.31 (d, *J* = 9.2 Hz, 1H, OCH_2); **^{13}C NMR (101 MHz, $CDCl_3$)**: major diastereomer **4.45b**: δ = 17.4 (q, $C(\underline{C}H_3)_2$), 24.6 (q, $C(\underline{C}H_3)_2$), 24.9 (t, $NCH_2\underline{C}H_2CH_2$), 28.4 (q, NCH_3), 30.3 (t, $NCH_2CH_2\underline{C}H_2$), 30.4 (t, $CH_{2bridge}$), 36.1 (t, $CH_{2cyclopentane}$), 40.9 (t, $\underline{C}H_2C{=}O$), 41.7 (s, $\underline{C}(CH_3)_2$), 44.3 (t, $N\underline{C}H_2CH_2CH_2$), 54.7 (s, C_{spiro}), 58.1 (d, CH_{bridge}), 68.09 (s, C_{Pro}), 69.1 (s, $C_{bridgehead}$), 75.1 (t, OCH_2), 168.6 (s, $N_{Pro}C{=}O$), 172.3 (s, $CH_3N\underline{C}{=}O$), 176.0 (s, $OC{=}O$).

(2'*R*,3'*S*,5a*R*,8a*R*,9a*R*)-2'-Methoxy-8,8,11-trimethyltetrahydro-2'*H*-spiro[5a,9a-(epiminomethano)cyclopenta[*f*]indolizine-7,3'-furan]-5,5',10(1*H*,4'*H*,6*H*,8*H*)-trionen (4.47b) and (2'S,3'R,5aR,8aR,9aR)-2'-methoxy-8,8,11-trimethyltetrahydro-2'H-spiro[5a,9a-(epiminomethano)cyclopenta[f]indolizine-7,3'-furan]-5,5',10(1*H*,4'*H*,6*H*,8*H*)-trione (4.47a):

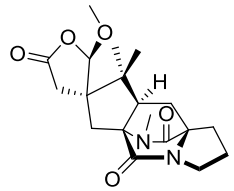


Prepared according to general procedure C from 110 mg (0.31 mmol) methoxybutenolide **4.42**. Purification of the crude product by column chromatography (hexane/AcOEt, 1:2, gradient to 100% AcOEt) gave 103 mg (92%) **4.47ab** as an inseparable 1:1 mixture of diastereomers as a colorless solid. The undesired diastereomer **4.47b** was not very soluble in AcOEt and repeated crystallization from AcOEt (or washing with cold AcOEt) gave 40 mg crystalline undesired diastereomer and 60 mg of a 5.5:1 mixture enriched in the desired diastereomer **4.47a**. **m.p.** (**4.47b**) > 250 °C (at ~257 °C crystal became dark without changing crystallinity, does not melt to 267 °C); $\mathbf{R}_f$ = 0.2 (AcOEt); **IR**: *ν*[cm^{-1}] 2962, 1788, 1731, 1680, 1430, 1384, 1272, 1209, 1143, 1111, 942, 914, 797, 733, 649; **MS ESI+ *m/z*, (%)**: 1109 (2, $[3M+Na]^+$), 815 (6), 747 (52, $[2M+Na]^+$), 453 (7), 431 (14), 385 (100, $[M+Na]^+$), 363 (12, $[M+H]^+$); **HRMS ESI+ *m/z***: ($[M+Na]^+$): Calcd. for $C_{19}H_{26}O_5N_2Na$: 385.1734; Found: 385.1734;



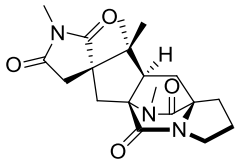
^{1}H NMR (400 MHz, $CDCl_3$): diastereomer **4.47a**: δ = 0.71 (s, 3H, $C(CH_3)_2$), 0.90 (s, 3H, $C(CH_3)_2$), 1.61 (dd, *J* = 12.8, 8.2 Hz, 1H, $CH_{2bridge}$), 1.70-1.83 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 1.90-2.04 (m, 3H, $NCH_2C\underline{H}_2CH_2$, $CH_{2bridge}$), 2.43 (dd, *J* = 10.1, 8.2 Hz, 1H, CH_{bridge}), 2.53 (br. s, 2H, $CH_2C{=}O$), 2.66 (d, *J* = 15.2 Hz, 1H, $CH_{2cyclopentane}$), 2.72-2.81 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 2.78 (d, *J* = 15.0 Hz, 1H, $CH_{2cyclopentane}$), 2.88 (s, 3H, NCH_3), 3.33-3.41 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.45-3.54 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.56 (s, 3H, OCH_3), 5.23 (s, 1H, $C\underline{H}OCH_3$); **^{13}C NMR (101 MHz, $CDCl_3$)**: diastereomer **4.47a**: δ = 19.1 (q, $C(\underline{C}H_3)_2$), 23.1 (q, $C(\underline{C}H_3)_2$), 24.8 (t, $NCH_2\underline{C}H_2CH_2$), 27.8 (q, NCH_3), 28.1 (t, $CH_{2cyclopentane}$), 30.2 (t,

$NCH_2CH_2\underline{C}H_2$), 30.7 (t, $CH_{2bridge}$), 38.0 (t, $CH_2C{=}O$), 41.5 (s, $\underline{C}(CH_3)_2$), 44.1 (t, $N\underline{C}H_2CH_2CH_2$), 57.1 (d, CH_{bridge}), 58.0 (q, OCH_3), 58.2 (s, C_{spiro}), 68.1 (s, C_{Pro}), 69.1 (s, $C_{bridgehead}$), 108.0 (d, $\underline{C}HOCH_3$), 168.8 (s, $N_{Pro}C{=}O$), 172.2 (s, $CH_3N\underline{C}{=}O$), 172.6 (s, $O\underline{C}{=}O$).



^{1}H NMR (400 MHz, $CDCl_3$): diastereomer **4.47b**: δ = 0.87 (s, 3H, $C(CH_3)_2$), 0.89 (s, 3H, $C(CH_3)_2$), 1.67 (dd, *J* = 12.8, 8.2 Hz, 1H, $CH_{2bridge}$), 1.82 (ddd, *J* = 13.0, 8.7, 7.4 Hz, 1H, $NCH_2CH_2C\underline{H}_2$), 1.90 (d, *J* = 15.9 Hz, 1H, $CH_{2cyclopentane}$), 1.91-2.08 (m, 3H, $CH_{2bridge}$, $NCH_2C\underline{H}_2CH_2$), 2.26 (dd, *J* = 10.0, 8.2 Hz, 1H, CH_{bridge}), 2.61 (d, *J* = 17.1 Hz, 1H, $C\underline{H}_2C{=}O$), 2.72 (d, *J* = 17.1 Hz, 1H, $C\underline{H}_2C{=}O$), 2.78-2.85 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 2.87 (s, 3H, NCH_3), 3.39-3.47 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.47 (d, *J* = 15.9 Hz, 1H, $CH_{2cyclopentane}$), 3.51-3.59 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.55 (s, 3H, OCH_3), 5.27 (s, 1H, $C\underline{H}OCH_3$); **^{13}C NMR (101 MHz, $CDCl_3$)**: diastereomer **4.47b**: δ = 18.5 (q, $C(\underline{C}H_3)_2$), 22.8 (q, $C(\underline{C}H_3)_2$), 24.9 (t, $NCH_2\underline{C}H_2CH_2$), 28.1 (q, NCH_3), 30.2 (t, $CH_{2cyclopentane}$), 30.3 (t, $NCH_2CH_2\underline{C}H_2$), 30.5 (t, $CH_{2bridge}$), 39.7 (t, $\underline{C}H_2C{=}O$), 42.6 (s, $\underline{C}(CH_3)_2$), 44.3 (t, $N\underline{C}H_2CH_2CH_2$), 57.3 (d, CH_{bridge}), 57.4 (q, OCH_3), 57.8 (s, C_{spiro}), 68.2 (s, C_{Pro}), 68.4 (s, $C_{bridgehead}$), 107.7 (d, $\underline{C}HOCH_3$), 168.6 (s, $N_{Pro}C{=}O$), 172.5 (s, $CH_3N\underline{C}{=}O$), 175.3 (s, $O\underline{C}{=}O$).

(3'*R*,5a*R*,8a*R*,9a*R*)-1',8,8,11-Tetramethyltetrahydrospiro[5a,9a-(epiminomethano)cyclopenta[*f*]indolizine-7,3'-pyrrolidine]-2',5,5',10(1*H*,6*H*,8*H*)-tetraone (4.49):

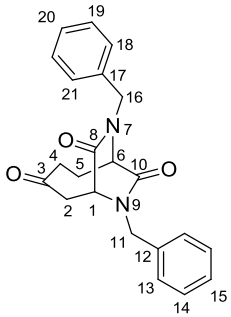


The spiro γ-methoxybutenolide **4.47a** (60 mg, 0.17 mmol, enriched to > 5.5:1 ratio) was dissolved in methanol (2 mL) and $MeNH_2$ (415 µL, 0.85 mmol, 2 M in MeOH) was added at r.t. under Ar. The reaction mixture was stirred for 2 h, evaporated to dryness and the residue was dried at high-vacuum for 15 min. It was dissolved in dichloromethane (3 mL), PCC (110 mg, 0.51 mmol) was added and the reaction mixture was stirred at r.t. for 2 h. The reaction mixture was filtered through a pad of Celite, which was thoroughly washed with AcOEt. The filtrates were evaporated to dryness and the residue was purified by column chromatography eluting with AcOEt to give 46 mg (77%) **4.49** as a colorless solid. **m.p**. 223 °C (dec. without melting); **$[\alpha]^{20}_{589}$**: +47.7 (*c* 0.109, $CHCl_3$); **IR**: *ν*[cm^{-1}] 2963, 1778, 1687, 1438, 1383, 1288, 1197, 1146, 1117, 1013, 983, 924, 813, 734, 699, 648; **MS ESI+ *m/z*, (%)**: 741 (25, $[2M+Na]^+$), 480 (9), 422 (4), 417 (7), 382 (100, $[M+Na]^+$), 360 (24, $[M+H]^+$), 304 (3); **HRMS ESI+ *m/z***: ($[M+Na]^+$): Calcd. for $C_{19}H_{25}N_3O_4Na$: 382.1737; Found: 382.1737; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 0.81 (s, 3H, $C(CH_3)_2$), 0.82 (s, 3H, $C(CH_3)_2$), 1.66 (dd, *J* =

12.6, 8.3 Hz, 1H, $CH_{2bridge}$), 1.76-1.89 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 1.90-2.11 (m, 3H, $NCH_2C\underline{H}_2CH_2$, $CH_{2bridge}$), 2.55 (d, *J* = 15.1 Hz, 1H, $CH_{2cyclopentane}$), 2.69 (d, *J* = 18.8 Hz, 1H, $CH_2C{=}O$), 2.78-2.90 (m, 1H, $NCH_2CH_2C\underline{H}_2$), 2.90 (d, *J* = 18.9 Hz, 1H, $CH_2C{=}O$), 2.77 (s, 3H, $N_{imide}CH_3$), 2.99 (s, 3H, $N_{DKP}CH_3$), 3.04 (d, *J* = 15.1 Hz, 1H, $CH_{2cyclopentane}$), 3.32 (dd, *J* = 10.2, 8.3 Hz, 1H, CH_{bridge}), 3.38-3.49 (m, 1H, $NC\underline{H}_2CH_2CH_2$), 3.49-3.63 (m, 1H, $NC\underline{H}_2CH_2CH_2$); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 18.8 (q, $C(\underline{C}H_3)_2$), 22.4 (q, $C(\underline{C}H_3)_2$), 24.9 (t, $NCH_2\underline{C}H_2CH_2$), 25.0 (q, $N_{imide}CH_3$), 28.2 (q, $N_{DKP}CH_3$), 30.3 (t, $NCH_2CH_2\underline{C}H_2$), 31.0 (t, $CH_{2bridge}$), 33.1 (t, $CH_{2cyclopentane}$), 37.9 (t, $\underline{C}H_2C{=}O$), 44.3 (t, $N\underline{C}H_2CH_2CH_2$), 44.9 (s, $\underline{C}(CH_3)_2$), 55.6 (d, CH_{bridge}), 58.3 (s, C_{spiro}), 68.3 (s, C_{Pro}), 69.8 (s, $C_{bridgehead}$), 168.8 (s, $N_{Pro}C{=}O$), 172.3 ($CH_3N\underline{C}{=}O$), 175.7 (s, $CH_2\underline{C}{=}O$), 182.5 (s, $C_{spiro}\underline{C}{=}O$).

7,9-Dibenzyl-7,9-diazabicyclo[4.2.2]decane-3,8,10-trione (5.48a):

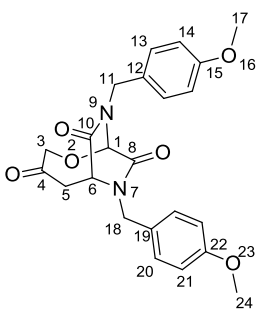
Bicyclic **5.21** (125 mg, 0.25 mmol), consisting of a 3:1 mixture of diastereomers, was dissolved in dichloromethane (25 mL) and the reaction mixture was cooled to 0 °C. *m*CPBA (80 mg, ca 0.28 mmol) was added to the reaction mixture and stirred until the starting material was consumed during ca 20 min as indicated by TLC. The reaction mixture was quenched with saturated $Na_2S_2O_3$ solution and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography (hexane/AcOEt, 1:2) to give 90 mg (99%) ketone **5.48a** as a colorless solid. **m.p.** 123-125 °C; **R_f** = 0.3 (hexane/EtOAc, 1:2); **IR**: *ν*[cm^{-1}] 2930, 1708, 1660, 1496, 1463, 1450, 1358, 1311, 1269, 1229, 1209, 1161, 1122, 1107, 1075, 1029, 970, 912, 821, 723, 698, 657, 593, 516; **MS ESI+ *m/z*, (%)**: 401 (7, $[M+K]^+$), 385 (100, $[M+Na]^+$), 363 (6, $[M+H]^+$); **HRMS ESI+ *m/z*,** ($[M+Na]^+$): Calcd. for $C_{22}H_{22}O_3N_2Na$: 385.1523; Found: 385.1522; **Anal. Calcd. for** $C_{22}H_{22}O_3N_2$ (362.42): C, 72.91; H, 6.12; N, 7.37; Found: C, 72.80; H, 6.32; N, 7.43;



^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.88-1.96 (m, 1H, H-5), 2.02-2.12 (m, 1H, H-5'), 2.32 (dddd, *J* = 12.1, 6.3, 4.3, 1.3 Hz, 1H, H-4), 2.42 (ddd, *J* = 12.0, 10.9, 4.7 Hz, 1H, H-4'), 2.88 (ddd, *J* = 13.6, 6.1, 1.0 Hz, 1H, H-2), 3.08 (ddd, *J* = 13.6, 2.5, 0.5 Hz, 1H, H-2'), 4.08 (d, *J* = 14.9 Hz, 1H, $PhCH_2$), 4.18 (dd, *J* = 6.1, 2.1 Hz, 1H, H-6), 4.20 (dd, *J* = 6.1, 2.5 Hz, 1H, H-1), 4.29 (d, *J* = 14.7 Hz, 1H, $PhCH_2$), 4.92 (d, *J* = 14.7 Hz, 1H, $PhCH_2$), 5.08 (d, *J* = 14.9 Hz, 1H, $PhCH_2$), 7.17-7.41 (m, 10H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 27.2 (t, C-5), 37.2 (t, C-4), 47.4 (t, $PhCH_2$), 48.4 (t, $PhCH_2$), 50.1 (t, C-2), 56.2 (d, C-1), 59.1 (d, C-6), 128.55 (d, CH_{Ar}), 128.59 (d, CH_{Ar}), 128.65 (d, 2C, CH_{Ar}), 129.27 (d,

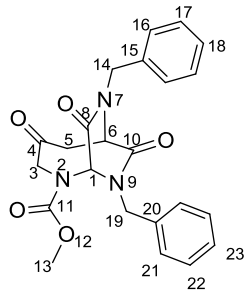
CH_{Ar}), 129.31 (d CH_{Ar}), 135.1 (s, C_{Ar}), 136.2 (s, C_{Ar}), 167.1 (s, 2C, C-8, C-10), 207.0 (s, C-3).

7,9-Bis(4-methoxybenzyl)-2-oxa-7,9-diazabicyclo[4.2.2]decane-4,8,10-trione (5.48b):



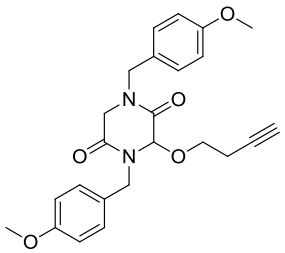
5.36a (513 mg, 0.91 mmol), consisting of a 2:1 mixture of diastereomers, was dissolved in dichloromethane (91 mL) and the reaction mixture was cooled to 0 °C. *m*CPBA (287 mg, ca 1.00 mmol) was added to the reaction mixture and stirring was continued until the starting material was consumed during ca 15 min as indicated by TLC. The reaction mixture was quenched with saturated $Na_2S_2O_3$ solution and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography (hexane/AcOEt, 1:1) to give 327 mg (85%) ketone **5.48b** as a colorless crystalline solid. **m.p.** 153-155 °C; $\mathbf{R_f}$ = 0.2 (hexane/EtOAc, 1:1); **IR**: *v*[cm^{-1}] 2931, 1674, 1611, 1585, 1511, 1457, 1421, 1357, 1303, 1243, 1170, 1096, 1062, 1030, 974, 915, 885, 808, 768, 733, 623, 571, 517; **MS ESI+ *m/z*, (%)**: 935 (7), 871 (3, $[2M+Na]^+$), 479 (100, $[M+Na+MeOH]^+$), 447 (77, $[M+Na]^+$); **HRMS ESI+ *m/z*,** ($[M+Na]^+$): Calcd. for $C_{23}H_{24}N_2O_6Na$: 447.1527; Found: 447.1526; **Anal. Calcd. for** $C_{23}H_{24}N_2O_6$ (424.45): C, 65.08; H, 5.70; N, 6.60; Found: C, 64.64; H, 5.54; N, 6.60; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 2.87 (dd, *J* = 14.8, 7.0 Hz, 1H, H-5), 3.08 (dd, *J* = 15.0, 2.8 Hz, 1H, H-5'), 3.81 (s, 3H, OCH_3), 3.81 (s, 3H, OCH_3), 3.89 (d, *J* = 14.8 Hz, 1H, H-3), 3.97 (d, *J* = 14.6 Hz, 1H, H-3'), 4.20 (dd, *J* = 7.0, 2.8 Hz, 1H, H-6), 4.23 (d, *J* = 14.6 Hz, 1H, $ArCH_2$), 4.27 (d, *J* = 14.5 Hz, 1H, $ArCH_2$), 4.81 (d, *J* = 14.6 Hz, 1H, $ArCH_2$), 4.88 (d, *J* = 14.5 Hz, 1H, $ArCH_2$), 5.31 (s, 1H, H-1), 6.86-6.89 (m, 4H, CH_{Ar}), 7.15-7.21 (m, 4H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 47.2 (t, C-5), 47.6 (t, $ArCH_2$), 48.4 (t, $ArCH_2$), 55.2 (d, C-6), 55.4 (q, OCH_3), 55.5 (q, OCH_3), 69.8 (t, C-3), 84.6 (d, C-1), 114.5 (d, C-14 or C-21), 114.8 (d, C-14 or C-21), 126.4 (s, C-12 or C-19), 126.7 (s, C-12 or C-19), 130.1 (d, C-13 or C-20), 130.3 (d, C-13 or C-20), 159.8 (s, C-15 or C-22), 160.0 (s, C-15 or C-22), 162.4 (s, C-10), 168.8 (s, C-8), 204.3 (s, C-4).

Methyl 7,9-dibenzyl-4,8,10-trioxo-2,7,9-triazabicyclo[4.2.2]decane-2-carboxylate (5.48c):



Bicyclic **5.36d** (281 mg, 0.50 mmol) was dissolved in dichloromethane (53 mL) and the reaction mixture was cooled to 0 °C. *m*CPBA (150 mg, ca 0.55 mmol) was added to the reaction mixture and stirring was continued until the starting material was consumed during ca 15 min as indicated by TLC. The reaction mixture was quenched with saturated $Na_2S_2O_3$ solution and extracted three times with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography (hexane/AcOEt, 1:1, gradient to 1:2) to give 162 mg (77%) ketone **5.48c** as a colorless crystalline solid. **m.p.** 58-60 °C; $\mathbf{R_f}$ = 0.3 (hexane/EtOAc, 1:1); **IR**: *ν*[cm^{-1}] 2955, 1711, 1673, 1440, 1386, 1260, 1149, 959, 911, 725, 699; **MS ESI+ *m/z*, (%)**: 476 (100, $[M+Na+MeOH]^+$), 444 (58, $[M+Na]^+$); **HRMS ESI+ *m/z*,** ($[M+Na]^+$): Calcd. for $C_{23}H_{23}N_3O_5Na$: 444.1530; Found: 444.1528; **Anal. Calcd. for** $C_{23}H_{23}N_3O_5$ (421.45): C, 65.55; H, 5.50; N, 9.97; Found: C, 65.31; H, 5.80; N, 9.55; **^{1}H NMR (500 MHz, DMSO-d_6, 100 °C)**: δ = 3.01 (dd, *J* = 14.3, 3.3 Hz, 1H, H-5), 3.17 (dd, *J* = 14.3, 5.4 Hz, 1H, H-5'), 3.70 (s, 3H, H-13), 3.95 (s, 2H, H-3), 4.29 (d, *J* = 15.0 Hz, 1H, $PhCH_2$), 4.30 (d, *J* = 14.9 Hz, 1H, $PhCH_2$), 4.36 (dd, *J* = 5.4, 3.3 Hz, 1H, H-6), 4.87 (d, *J* = 15.0 Hz, 1H, $PhCH_2$), 4.93 (d, *J* = 14.9 Hz, 1H, $PhCH_2$), 5.95 (s, 1H, H-1), 7.21-7.24 (m, 2H, $CH_{Ar\text{-}para}$), 7.27-7.39 (m, 8H, CH_{Ar}); **^{13}C NMR (125 MHz, DMSO-d_6, 100 °C)**: δ = 46.8 (t, $ArCH_2$), 47.1 (t, $ArCH_2$), 47.5 (t, C-5), 49.3 (t, C-3), 53.1 (q, C-13), 55.8 (d, C-6), 68.1 (d, C-1), 127.31 (d, $CH_{Ar\text{-}para}$), 127.34 (d, $CH_{Ar\text{-}para}$), 127.4 (d, CH_{Ar}), 127.5 (d, CH_{Ar}), 128.1 (d, CH_{Ar}), 128.2 (d, CH_{Ar}), 135.1 (s, C-15 or C-20), 135.3 (s, C-15 or C-20), 154.6 (s, C-11 – almost invisible), 161.3 (s, C-10), 166.6 (s, C-8), 202.5 (s, C-4).

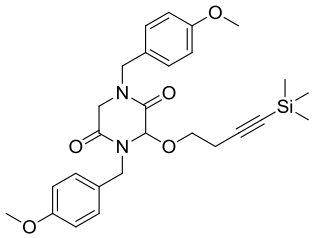
31,4-Bis(4-methoxybenzyl)-(but-3-yn-1-yloxy)-piperazine-2,5-dione (5.53):



A solution of dichloroacetamide **5.31**[45] (450 mg, 1.06 mmol) in THF (3 mL) was added dropwise to a stirred solution of homopropargyl alcohol (830 μL, 11 mmol) and potassium *tert*-butoxide (261 mg, 2.33 mmol) in THF (6 mL) at 0 °C over 10 min. The cooling bath was removed after 10 min and the mixture was refluxed for 2 h. The reaction mixture was cooled to room temperature, diluted with water and extracted with AcOEt. The combined organic layers were dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography (silica gel, hexane/AcOEt, 2:1, gradient to 1:1) to afford 377 mg (84%) **5.51** as a colorless oil, which solidified after sometime. **m.p.** 94-

96 °C; $\mathbf{R_f}$ = 0.14 (hexane/EtOAc, 2:1); **IR**: ν[cm^{-1}] 3283, 2934, 2837, 1672, 1612, 1585, 1559, 1513, 1459, 1421, 1357, 1303, 1246, 1175, 1095, 1077, 1055, 1033, 957, 824, 765, 638, 579, 518; **MS ESI+ *m/z*, (%)**: 461 (4, $[M+K]^+$), 445 (100, $[M+Na]^+$); **HRMS ESI+ *m/z*,** ($[M+Na]^+$): Calcd. for $C_{24}H_{26}N_2O_5Na$: 445.1734; Found: 445.1731; **Anal. Calcd. for** $C_{24}H_{26}N_2O_5$ (422.47): C, 68.23; H, 6.20; N, 6.63; Found: C, 68.28; H, 6.19; N, 6.47; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 2.00 (t, *J* = 2.6 Hz, 1H, ≡CH), 2.43 (td, *J* = 6.5, 2.6 Hz, 2H, CH_2C≡), 3.61 (dt, *J* = 9.3, 6.7 Hz, 1H, OCH_2), 3.78 (d, *J* = 17.5 Hz, 1H, CH_2C=O), 3.78-3.81 (m, 1H, OCH_2), 3.79 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.03 (d, *J* = 17.5 Hz, 1H, CH_2C=O), 4.16 (d, *J* = 14.6 Hz, 1H, $ArCH_2$), 4.33 (d, *J* = 14.5 Hz, 1H, $ArCH_2$), 4.66 (d, *J* = 14.5 Hz, 1H, $ArCH_2$), 4.74 (s, 1H, NCHO), 5.10 (d, *J* = 14.6 Hz, 1H, $ArCH_2$), 6.86 (m, 4H, CH_{Ar}), 7.15 (d, *J* = 8.7 Hz, 2H, CH_{Ar}), 7.20 (d, *J* = 8.6 Hz, 2H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 19.9 (t, $\underline{C}H_2C$≡), 46.8 (t, $ArCH_2$), 48.9 (t, $ArCH_2$), 49.1 (t, $\underline{C}H_2C$=O), 55.49 (q, OCH_3), 55.50 (q, OCH_3), 67.3 (t, OCH_2), 69.9 (d, ≡CH), 81.0 (s, $CH_2\underline{C}$≡), 84.3 (d, NCHO), 114.5 (d, CH_{Ar}), 114.6 (d, CH_{Ar}), 127.1 (s, C_{Ar}), 127.5 (s, C_{Ar}), 129.9 (d, CH_{Ar}), 130.3 (d, CH_{Ar}), 159.69 (s, C_{Ar}), 159.72 (s, C_{Ar}), 162.6 (s, C=O), 165.7 (s, C=O).

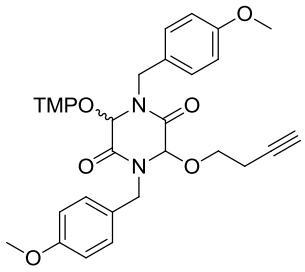
1,4-Bis(4-methoxybenzyl)-3-((4-(trimethylsilyl)but-3-yn-1-yl)oxy)piperazine-2,5-dione (5.54):



Alkyne **5.53** (555 mg, 1.31 mmol) and DBU (492 µL, 1.97 mmol) were added to a stirred suspension of silver nitrate (112 mg, 0.7 mmol) in dichloromethane (7 mL). The reaction mixture was heated to 40 °C, TMSCl (417 µL, 3.3 mmol) was added and refluxed for 8 h. The reaction mixture was cooled to ambient temperature, diluted with AcOEt and quenched with saturated $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with AcOEt. The combined organic layers were washed with saturated $Na_2S_2O_3$ solution, dried over $MgSO_4$, filtered and evaporated. Purification of the residue by column chromatography (hexane/AcOEt, 2:1) gave 445 mg (67%) **5.54** as a colorless oil. $\mathbf{R_f}$ = 0.6 (hexane/EtOAc, 1:1); **IR**: ν[cm^{-1}] 2957, 2837, 2178, 1673, 1613, 1585, 1513, 1460, 1421, 1356, 1303, 1246, 1174, 1095, 1035, 959, 908, 842, 761, 700, 639, 576, 518; **MS ESI+ *m/z*, (%)**: 533 (7, $[M+K]^+$), 517 (100, $[M+Na]^+$); **HRMS ESI+ *m/z*,** ($[M+Na]^+$): Calcd. for $C_{27}H_{34}N_2O_5SiNa$: 517.2129; Found: 517.2128; **Anal. Calcd. for** $C_{27}H_{34}N_2O_5Si$ (494.65): C, 65.56; H, 6.93; N, 5.66; Found: C, 65.30; H, 7.05; N, 5.45; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 0.14 (s, 9H, $Si(CH_3)_3$), 2.41-2.56 (m, 2H, CH_2C≡), 3.60 (dt, *J* = 9.2, 7.0 Hz, 1H, OCH_2), 3.77-3.82 (m, 1H, OCH_2), 3.80 (d, *J* = 17.6

Hz, 1H, CH_2C=O), 3.795 (s, 3H, OCH_3), 3.802 (s, 3Hz, OCH_3), 4.02 (d, *J* = 17.6 Hz, 1H, CH_2C=O), 4.14 (d, *J* = 14.5 Hz, 1H, $ArCH_2$), 4.37 (d, *J* = 14.5 Hz, 1H, $ArCH_2$), 4.62 (d, *J* = 14.4 Hz, 1H, $ArCH_2$), 4.72 (s, 1H, NCHO), 5.15 (d, *J* = 14.5 Hz, 1H, $ArCH_2$), 6.86 (d, *J* = 8.8 Hz, 2H, CH_{Ar}), 6.87 (d, *J* = 8.8 Hz, 2H, CH_{Ar}), 7.15 (d, *J* = 8.8 Hz, 2H, CH_{Ar}), 7.22 (d, *J* = 8.7 Hz, 2H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 0.2 (q, $Si(CH_3)_3$), 21.3 (t, $\underline{C}H_2C\equiv$), 46.6 (t, $ArCH_2$), 48.9 (t, $ArCH_2$), 49.1 (t, $\underline{C}H_2C$=O), 55.50 (q, OCH_3), 55.52 (q, OCH_3), 67.4 (t, OCH_2), 84.0 (d, NCHO), 86.5 (s, $\equiv\underline{C}Si(CH_3)_3$), 103.4 (s, $CH_2\underline{C}\equiv$), 114.5 (d, CH_{Ar}), 114.6 (d, CH_{Ar}), 127.1 (s, C_{Ar}), 127.4 (s, C_{Ar}), 129.9 (d, CH_{Ar}), 130.4 (d, CH_{Ar}), 159.73 (s, C_{Ar}), 159.74 (s, C_{Ar}), 162.5 (s, C=O), 165.5 (s, C=O).

1,4-Bis(4-methoxybenzyl)-3-(but-3-yn-1-yloxy)-6-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)piperazine-2,5-dione (5.55a):

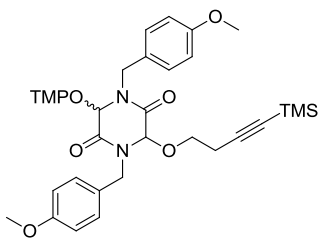


A freshly prepared solution of LiHMDS (0.94 mmol) in THF (3 mL) was cannulated dropwise to a solution of **5.53** (330 mg, 0.78 mmol) in THF (4 mL) at −78 °C and the mixture was stirred at this temperature for 30 min. TEMPO (160 mg, 1.03 mmol) was added followed by portionwise addition of $Cp_2Fe^+PF_6^-$ until a blue color persisted (overall ca 390 mg, 1.20 mmol). After 30 min, the reaction mixture was quenched with a drop of saturated NH_4Cl solution and filtered through a short pad of silica, which was washed with AcOEt. The filtrates were concentrated under reduced pressure and the residue was purified by column chromatography (silica gel, hexane/AcOEt, 10:1, gradient to 2:1) to give 377 mg (84%) **5.55a** as pale yellow foam as an inseparable 2:1 mixture of *cis*/*trans* diastereomers. **R_f** = 0.5 (hexane/EtOAc, 2:1); **IR**: *ν*[cm^{-1}] 3000, 1782, 1743, 1716, 1614, 1420, 1388, 1311, 1198, 1178, 1148, 1123, 934, 906, 752, 734, 615, 558, 520; **MS ESI+ *m/z*, (%)**: 600 (14, $[M+Na]^+$), 578 (100, $[M+H]^+$), 481 (7, [M+H-(5,5-dimethyl-1-pyrroline)]$^+$), 444 (10, [M+Na-TEMPO]$^+$), 422 (30, [M+H-TEMPO]$^+$), 352 (11, [M+H-TEMPO-homopropargyl alcohol]$^+$), 323 (11, [M+Na-TEMPO-PMB]$^+$), 158 (9, [TEMPOH+H]$^+$); **HRMS ESI+ *m/z*,** ($[M+H]^+$): Calcd. for $C_{33}H_{44}N_3O_6$: 578.3230; Found: 578.3229; **Anal. Calcd. for** $C_{33}H_{44}N_3O_6$ (577.71): C, 68.61; H, 7.50; N, 7.27; Found: C, 68.42; H, 7.62; N, 6.87; **^{1}H NMR (400 MHz, $CDCl_3$)**: major diastereomer: δ = 0.98 (s, 3H, CH_{3TEMPO}), 1.05 (s, 3H, CH_{3TEMPO}), 1.20 (s, 3H, CH_{3TEMPO}), 1.34-1.39 (m, 1H, CH_{2TEMPO}), 1.38 (s, 3H, CH_{3TEMPO}), 1.45-1.65 (m, 5H, CH_{2TEMPO}), 2.04 (t, *J* = 2.7 Hz, 1H, ≡CH), 2.56 (td, *J* = 6.7, 2.6 Hz, 2H, $CH_2C\equiv$), 3.47 (dt, *J* = 8.6, 6.7 Hz, 1H, OCH_2), 3.786 (s,

3H, OCH_3), 3.792 (br. s, 3H, OCH_3), 3.83 (dt, *J* = 8.6, 6.7 Hz, 1H, OCH_2), 4.19 (d, *J* = 14.4 Hz, 1H, $ArCH_2$), 4.28 (d, *J* = 14.6 Hz, 1H, $ArCH_2$), 4.72 (s, 1H, $C\underline{H}OCH_2$), 5.34 (d, *J* = 14.4 Hz, 1H, $ArCH_2$), 5.39 (d, *J* = 14.4 Hz, 1H, $ArCH_2$), 5.41 (s, 1H, CHOTMP), 6.81-6.86 (m, 4H, CH_{Ar}), 7.14 (d, *J* = 8.7 Hz, 2H, CH_{Ar}), 7.30 (d, *J* = 8.4 Hz, 2H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: major diastereomer: δ = 17.16 (t, CH_{2TEMPO}), 19.84 (t, $\underline{C}H_2C{\equiv}$), 20.2 (q, CH_{3TEMPO}), 20.4 (q, CH_{3TEMPO}), 33.1 (q, CH_{3TEMPO}), 33.63 (q, CH_{3TEMPO}), 40.5 (t, 2C, CH_{2TEMPO}), 43.9 (t, $ArCH_2$), 50.1 (t, $ArCH_2$), 55.38 (q, 2C, OCH_3), 60.48 (s, C_{TEMPO}), 62.3 (s, C_{TEMPO}), 67.0 (t, OCH_2), 69.9 (d, ≡CH), 81.1 (s, $CH_2\underline{C}{\equiv}$), 81.2 (d, $\underline{C}HOCH_2$), 87.8 (d, CHOTMP), 114.1 (d, CH_{Ar}), 114.5 (d, CH_{Ar}), 127.58 (s, C_{Ar}), 128.3 (s, C_{Ar}), 129.35 (d, CH_{Ar}), 129.43 (d, CH_{Ar}), 159.2 (s, C_{Ar}), 159.42 (s, C_{Ar}), 162.5 (s, C=O), 166.5 (s, C=O).

^{1}H NMR (400 MHz, $CDCl_3$): minor diastereomer: δ = 1.11 (s, 3H, CH_{3TEMPO}), 1.18 (s, 3H, CH_{3TEMPO}), 1.18 (s, 3H, CH_{3TEMPO}), 1.34-1.38 (m, 1H, CH_{2TEMPO}), 1.36 (s, 3H, CH_{3TEMPO}), 1.45-1.65 (m, 5H, CH_{2TEMPO}), 1.99 (t, *J* = 2.7 Hz, 1H, ≡CH), 2.44-2.51 (m, 2H, $CH_2C{\equiv}$), 3.70 (dt, *J* = 9.2, 7.3 Hz, 1H, OCH_2), 3.792 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 3.90 (ddd, *J* = 9.3, 7.0, 6.5 Hz, 1H, OCH_2), 4.17 (d, *J* = 14.8 Hz, 1H, $ArCH_2$), 4.34 (d, *J* = 14.7 Hz, 1H, $ArCH_2$), 4.86 (s, 1H, $C\underline{H}OCH_2$), 5.05 (d, *J* = 14.9 Hz, 1H $ArCH_2$), 5.28 (d, *J* = 14.7 Hz, 1H, $ArCH_2$), 5.44 (s, 1H, CHOTMP), 6.81-6.86 (m, 4H, CH_{Ar}), 7.08 (d, *J* = 8.7 Hz, 2H, CH_{Ar}), 7.13 (d, *J* = 8.8 Hz, 2H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: minor diastereomer: δ = 17.20 (t, CH_{2TEMPO}), 19.79 (t, $\underline{C}H_2C{\equiv}$), 20.2 (q, CH_{3TEMPO}), 20.6 (q, CH_{3TEMPO}), 32.4 (q, CH_{3TEMPO}), 33.57 (q, CH_{3TEMPO}), 40.59 (t, CH_{2TEMPO}), 40.62 (t, CH_{2TEMPO}), 47.3 (t, $ArCH_2$), 50.0 (t, $ArCH_2$), 55.38 (q, OCH_3), 55.42 (q, OCH_3), 60.52 (s, C_{TEMPO}), 62.1 (s, C_{TEMPO}), 68.3 (t, OCH_2), 69.8 (d, ≡CH), 80.8 (s, $CH_2\underline{C}{\equiv}$), 84.9 (d, $\underline{C}HOCH_2$), 87.3 (d, CHOTMP), 114.36 (d, CH_{Ar}), 114.39 (d, CH_{Ar}), 127.62 (s, C_{Ar}), 128.5 (s, C_{Ar}), 129.2 (d, CH_{Ar}), 129.7 (d, CH_{Ar}), 159.36 (s, C_{Ar}), 159.5 (s, C_{Ar}), 163.5 (s, C=O), 164.7 (s, C=O).

1,4-Bis(4-methoxybenzyl)-3-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)-6-((4-(trimethylsilyl)but-3-yn-1-yl)oxy)piperazine-2,5-dione (5.55b):



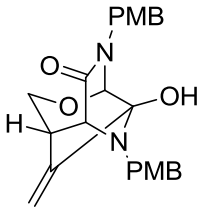
A freshly prepared solution of LiHMDS (1.34 mmol) in THF (3 mL) was cannulated dropwise to a solution of **5.54** (555 mg, 1.12 mmol) in THF (8 mL) at −78 °C and the mixture was stirred at this temperature for 30 min. TEMPO (228 mg, 1.46 mmol) was added followed by portionwise addition of $Cp_2Fe^+PF_6^-$ until the blue color persisted (overall ca 560 mg, 1.70 mmol). After 30 min the reaction mixture was quenched with a drop of saturated NH_4Cl solution and filtered through a short pad of silica,

which was washed with AcOEt. The filtrates were concentrated under reduced pressure and the residue was purified by column chromatography (silica gel, hexane/AcOEt, 20:1, gradient to 5:1) to give 128 mg less polar diastereomer contaminated with more polar diastereomer (5:1 ratio) and 553 mg ca 1:1 mixture of diastereomers as a white foam. The overall yield was 681 mg (93%). $\mathbf{R_f}$ (less polar) = 0.4; $\mathbf{R_f}$ (more polar) = 0.3 (hexane/EtOAc, 5:1); **IR**: ν[cm^{-1}] 2935, 2178, 1684, 1612, 1586, 1512, 1458, 1441, 1419, 1377, 1362, 1335, 1302, 1245, 1210, 1175, 1131, 1095, 1080, 1033, 974, 956, 909, 878, 840, 782, 759, 731, 640, 622, 577, 516; **MS ESI+ *m/z*, (%)**: 1321 (3, $[2M+Na]^+$), 712 (5), 688 (13, $[M+K]^+$), 672 (100, $[M+Na]^+$), 650 (87, $[M+H]^+$), 553 (5), 532 (13, $[M+K\text{-}TEMPO]^+$), 516 (85, $[M+Na\text{-}TEMPO]^+$); **HRMS ESI+ *m/z*,** ($[M+Na]^+$): Calcd. for $C_{36}H_{51}N_3O_6SiNa$: 672.3439; Found: 672.3421; **^{1}H NMR (400 MHz, $CDCl_3$)**: less polar diastereomer: δ = 0.153 (s, 9H, $Si(CH_3)_3$), 0.97 (s, 3H, CH_{3TEMPO}), 1.04 (s, 3H, CH_{3TEMPO}), 1.20 (s, 3H, CH_{3TEMPO}), 1.39 (s, 3H, CH_{3TEMPO}), 1.45-1.67 (m, 6H, CH_{2TEMPO}), 2.63 (td, *J* = 6.7, 2.5 Hz, 2H, $CH_2C{\equiv}$), 3.49 (dd, *J* = 14.9, 6.9 Hz, 1H, OCH_2), 3.77-3.88 (m, 1H, OCH_2), 3.79 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.25 (d, *J* = 14.8 Hz, 1H, $ArCH_2$), 4.28 (d, *J* = 15.5 Hz, 1H, $ArCH_2$), 4.82 (s, 1H, $C\underline{H}OCH_2$), 5.34 (d, *J* = 14.8 Hz, 1H, $ArCH_2$), 5.39 (d, *J* = 15.5 Hz, 1H, $ArCH_2$), 5.41 (s, 1H, CHOTMP), 6.79-6.91 (m, 4H, CH_{Ar}), 7.14 (d, *J* = 8.5 Hz, 2H, CH_{Ar}), 7.35 (d, *J* = 8.5 Hz, 2H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: less polar diastereomer: δ = 0.08 (q, $Si(CH_3)_3$), 17.10 (t, CH_{2TEMPO}), 20.13 (q, CH_{3TEMPO}), 20.3 (q, CH_{3TEMPO}), 21.13 (t, $\underline{C}H_2C{\equiv}$), 33.1 (q, CH_{3TEMPO}), 33.6 (q, CH_{3TEMPO}), 40.4 (t, 2C, CH_{2TEMPO}), 43.9 (t, $ArCH_2$), 50.1 (t, $ArCH_2$), 55.33 (s, 2C, OCH_3), 60.4 (s, C_{TEMPO}), 62.3 (s, C_{TEMPO}), 66.7 (t, OCH_2), 80.9 (d, $\underline{C}HOCH_2$), 86.3 (s, ≡CTMS), 87.6 (d, CHOTMP), 103.7 (s, $CH_2\underline{C}{\equiv}$), 114.0 (d, CH_{Ar}), 114.4 (d, CH_{Ar}), 127.63 (s, C_{Ar}), 128.3 (s, C_{Ar}), 129.3 (d, CH_{Ar}), 129.73 (d, CH_{Ar}), 159.2 (s, C_{Ar}), 159.36 (s, C_{Ar}), 162.4 (s, C=O), 166.4 (s, C=O).

^{1}H NMR (400 MHz, $CDCl_3$): more polar diastereomer (detectable signals): δ = 0.151 (s, 9H, $Si(CH_3)_3$), 1.11 (s, 3H, CH_{3TEMPO}), 1.18 (s, 6H, CH_{3TEMPO}), 1.36 (s, 3H, CH_{3TEMPO}), 2.42-2.58 (m, 2H, $CH_2C{\equiv}$), 3.64-3.72 (m, 1H, OCH_2), 3.78 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.82-3.93 (m, 1H, OCH_2), 4.14 (d, *J* = 14.7 Hz, 1H, $ArCH_2$), 4.33 (d, *J* = 14.7 Hz, 1H, $ArCH_2$), 4.70 (s, 1H, $C\underline{H}OCH_2$), 5.06 (d, *J* = 14.7 Hz, 1H, $ArCH_2$), 5.28 (d, *J* = 14.7 Hz, 1H, $ArCH_2$), 5.43 (s, 1H, CHOTMP); **^{13}C NMR** (101 MHz, $CDCl_3$): more polar diastereomer: δ = 0.09 (q, $Si(CH_3)_3$), 17.14 (t, CH_{2TEMPO}), 20.12 (q, CH_{3TEMPO}), 20.5 (q, CH_{3TEMPO}), 21.07 (t, $\underline{C}H_2C{\equiv}$), 32.4 (q, CH_{3TEMPO}), 33.5 (q, CH_{3TEMPO}), 40.5 (t, CH_{2TEMPO}), 40.6 (t, CH_{2TEMPO}), 47.2 (t, $ArCH_2$), 49.9 (t, $ArCH_2$), 55.31 (s, 2C, OCH_3), 60.5 (s, C_{TEMPO}), 62.1 (s, C_{TEMPO}), 68.4 (t,

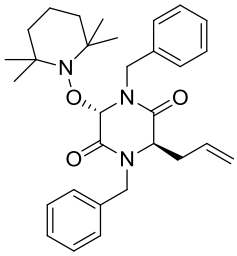
OCH_2), 84.7 (d, <u>C</u>HOCH_2), 86.2 (s, ≡CTMS), 87.2 (d, CHOTMP), 102.9 (s, CH_2<u>C</u>≡), 114.31 (d, CH_{Ar}), 114.33 (d, CH_{Ar}), 127.55 (s, C_{Ar}), 128.5 (s, C_{Ar}), 129.2 (d, CH_{Ar}), 129.70 (d, CH_{Ar}), 159.3 (s, C_{Ar}), 159.45 (s, C_{Ar}), 163.5 (s, C=O), 164.6 (s, C=O).

(1*S,6*R**)-2,5-Bis(4-methoxybenzyl)-1-hydroxy-10-methylene-7-oxa-2,5-diazatricyclo[4.4.0.0^{3,9}]decan-4-one (5.67):**



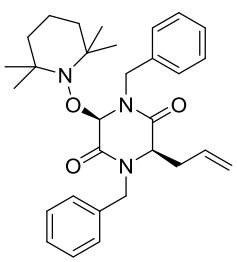
A freshly prepared solution of LiHMDS (1.18 mmol) in THF (8 mL) was added dropwise to a solution of allene **5.57**[104] (500 mg, 1.18 mmol) in THF (10 mL) at −78 °C and the mixture was stirred at this temperature for 40 min. TEMPO (240 mg, 1.54 mmol) was added followed by portionwise addition of $Cp_2Fe^+PF_6^-$ until the blue color persisted. A very small amount of $Cp_2Fe^+PF_6^-$ sufficed to achieve persistent blue color compared to the calculated amount. The rest of $Cp_2Fe^+PF_6^-$ was added (overall ca 510 mg, 1.54 mmol) and the reaction mixture was stirred for 30 min. The reaction mixture was quenched with a drop of saturated NH_4Cl solution, filtered through a short pad of silica, which was washed with AcOEt, and the filtrates were concentrated under reduced pressure. The residue was purified by column chromatography (hexane/AcOEt, 10:1, gradient to 1:2) to give 45 mg (6%) alkoxyamine **5.58**, 140 mg complex mixture of unidentified polar products and 272 mg (54%) **5.67** contaminated with small amounts of unidentified component. $\mathbf{R_f}$ = 0.1 (hexane/AcOEt, 2:1); **IR**: ν[cm^{-1}] 3332 (br.), 2957, 2845, 1648, 1618, 1591, 1517, 1464, 1365, 1307, 1250, 1204, 1180, 1150, 1038, 1013, 956, 918, 826, 777, 741, 674, 597, 572, 520; **MS ESI+ *m/z*, (%)**: 845 (3, $[2M+H]^+$), 461 (7, $[M+K]^+$), 445 (22, $[M+Na]^+$), 423 (100, $[M+H]^+$); **HRMS ESI+ *m/z*,** ($[M+H]^+$): Calcd. for $C_{24}H_{27}N_2O_5$: 423.1915; Found: 423.1916; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 3.02 (dd, *J* = 7.8, 2.4 Hz, 1H, OCH_2C<u>H</u>), 3.37 (d, *J* = 13.0 Hz, 1H, $ArCH_2$), 3.73-3.90 (m, 2H, OCH_2, OH), 3.77 (s, 3H, OCH_3), 3.79 (s, 3H, OCH_3), 3.84 (d, *J* = 13.5 Hz, 1H, $ArCH_2$), 3.87 (d, *J* = 14.3 Hz, 1H, $ArCH_2$), 3.95 (br. s, 1H, NC<u>H</u>CO), 4.43 (dd, *J* = 8.8, 7.8 Hz, 1H, OCH_2), 4.93 (s, 1H, OCHN), 4.98 (dd, *J* = 2.0, 0.9 Hz, 1H, =CH_2), 5.19 (d, *J* = 14.3 Hz, 1H, $ArCH_2$), 5.24 (dd, *J* = 2.3, 0.9 Hz, 1H, =CH_2), 6.82 (d, *J* = 8.6 Hz, 2H, CH_{Ar}), 6.86 (d, *J* = 8.6 Hz, 2H, CH_{Ar}), 7.13 (d, *J* = 8.6 Hz, 2H, CH_{Ar}), 7.34 (d, *J* = 8.6 Hz, 2H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 44.8 (t, Ar<u>C</u>H_2), 48.0 (t, Ar<u>C</u>H_2), 51.2 (d, OCH_2<u>C</u>H), 55.5 (q, 2C, OCH_3), 67.7 (d, N<u>C</u>HCO), 72.5 (t, OCH_2), 87.5 (d, OCHN), 99.2 (s, NC(OH)), 111.2 (t, =CH_2), 114.2 (d, CH_{Ar}), 114.3 (d, CH_{Ar}), 128.5 (s, C_{Ar}), 129.3 (s, C_{Ar}), 130.3 (d, CH_{Ar}), 130.7 (d, CH_{Ar}), 145.4 (s, <u>C</u>=CH_2), 159.2 (s, C_{Ar}), 159.4 (s, C_{Ar}), 167.9 (s, C=O).

(3*R,6*S**)-3-Allyl-1,4-dibenzyl-6-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)piperazine-2,5-dione (5.3a)**:



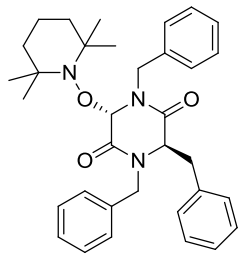
A freshly prepared solution of LiHMDS (0.540 mmol) in THF (2 mL) was cannulated dropwise to a solution of 1,4-dibenzyl-3-allylpiperazine-2,5-dione **5.1** (150 mg, 0.45 mmol) in THF (4 mL) at −78 °C and the mixture was stirred at this temperature for 30 min. TEMPO (91 mg, 0.584 mmol) was added followed by portionwise addition of $Cp_2Fe^+PF_6^-$ until the blue color persisted (overall ca 185 mg, 0.56 mmol). After 30 min the reaction mixture was quenched by a drop of saturated NH_4Cl solution, and filtered through a short pad of silica, which was washed with AcOEt, and the filtrates were concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/AcOEt, 20:1, gradient to 5:1) to give 140 mg pure *trans*-diastereomer as a colorless solid and 50 mg of a ca 2:1 mixture of *cis*/*trans* diastereomers. Overall yield 190 mg (86%). The *trans*-diastereomer was crystallized from hexane/AcOEt for X-ray crystallographic characterization. **m.p.** (***trans*-5.3a**) 120-121 °C; $\mathbf{R_f}$ = 0.5 (hexane/AcOEt, 5:1); **IR**: *ν*[cm^{-1}] 2933, 1677, 1496, 1454, 1422, 1377, 1306, 1260, 1164, 1131, 1029, 1004, 972, 827, 730, 698; **MS ESI+ *m/z*, (%)**: 490 (100, $[M+H]^+$), 356 (17, $[M+Na\text{-}TEMPO]^+$), 333 (54, $[M\text{-}TEMPO]^+$); **HRMS ESI+ *m/z***: ($[M+H]^+$): Calcd. for $C_{30}H_{40}N_3O_3$: 490.3064; Found: 490.3061; **Anal. Calcd. for** $C_{30}H_{39}N_3O_3$ (489.66): C, 73.59; H, 8.03; N, 8.58; Found: C, 73.70; H, 8.10; N, 8.34; **^{1}H NMR (400 MHz, $CDCl_3$)**: ***trans*-5.3a**: δ = 1.11 (s, 3H, CH_{3TEMPO}), 1.13 (s, 3H, CH_{3TEMPO}), 1.26 (s, 3H, CH_{3TEMPO}), 1.34-1.47 (m, 1H, CH_{2TEMPO}), 1.43 (s, 3H, CH_{3TEMPO}), 1.48-1.72 (m, 5H, CH_{2TEMPO}), 2.57 (ddd, *J* = 15.7, 7.7, 5.0 Hz, 1H, $C\underline{H}_2CH$=), 3.05 (ddd, *J* = 15.7, 5.0, 2.9 Hz, 1H, $C\underline{H}_2CH$=), 4.03 (d, *J* = 15.8 Hz, 1H, $ArCH_2$), 4.17 (dd, *J* = 4.8, 3.0 Hz, 1H, $CH_2C\underline{H}N$), 4.39 (d, *J* = 15.0 Hz, 1H, $ArCH_2$), 5.17 (d, *J* = 10.3 Hz, 1H, $=CH_2$), 5.22 (dd, *J* = 17.3, 1.1 Hz, 1H, $=CH_2$), 5.53 (s, 1H, CHOTMP), 5.54 (d, *J* = 14.9 Hz, 1H, $ArCH_2$), 5.64-5.76 (m, 1H, $CH_2C\underline{H}$=), 5.65 (d, *J* = 15.6 Hz, 1H, $ArCH_2$), 7.21-7.38 (m, 10H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: ***trans*-5.3a**: δ = 17.3 (t, CH_{2TEMPO}), 20.3 (q, CH_{3TEMPO}), 20.5 (q, CH_{3TEMPO}), 32.2 (t, $\underline{C}H_2CH$=), 33.2 (q, CH_{3TEMPO}), 33.8 (q, CH_{3TEMPO}), 40.6 (t, CH_{2TEMPO}), 40.7 (t, CH_{2TEMPO}), 45.4 (t, $ArCH_2$), 51.2 (t, $ArCH_2$), 56.4 (d, $CH_2\underline{C}HN$), 60.6 (s, C_{TEMPO}), 62.4 (s, C_{TEMPO}), 88.5 (d, CHOTMP), 119.06 (t, $=CH_2$), 127.2 (d, CH_{Ar}), 127.76 (d, CH_{Ar}), 127.84 (d, CH_{Ar}), 127.9 (d, CH_{Ar}), 129.02 (d, CH_{Ar}), 129.04 (d, CH_{Ar}), 132.9 (d, $CH_2\underline{C}H$=), 135.7 (s, C_{Ar}), 136.8 (s, C_{Ar}), 164.5 (s, C=O), 168.1 (s, C=O).

(3*R,6*R**)-3-Allyl-1,4-dibenzyl-6-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)piperazine-2,5-dione (*cis*-5.3a):**



A solution of alkoxyamine **5.3a** (215 mg, 0.44 mmol), consisting of ca 4:1 *trans*/*cis* diastereomeric mixture, in *t*BuOH (22 mL) was degassed by three freeze-pump-thaw cycles. The reaction vessel was sealed and immersed to an oil bath preheated at 80 °C and stirred at this temperature for 2 h. The solvent was evaporated to dryness and the residue was dried at high-vacuum for 1 h to give 203 mg (94%) ***cis*-5.25** as a colorless crystalline solid. **m.p. (*cis*-5.3a)** 109-110 °C; **^{1}H NMR (400 MHz, $CDCl_3$)**: ***cis*-5.3a**: δ = 1.14 (s, 3H, CH_{3TEMPO}), 1.21 (s, 3H, CH_{3TEMPO}), 1.22 (s, 3H, CH_{3TEMPO}), 1.45 (s, 3H, CH_{3TEMPO}), 1.48-1.68 (m, 6H, CH_{2TEMPO}), 2.82-2.96 (m, 2H, $C\underline{H}_2CH$=), 3.92 (d, *J* = 15.1 Hz, 1H, $ArCH_2$), 3.93 (dd, *J* = 8.0, 7.0 Hz, 1H, $CH_2C\underline{H}N$), 4.33 (d, *J* = 14.9 Hz, 1H, $ArCH_2$), 5.17-5.26 (m, 2H, $=CH_2$), 5.31 (d, *J* = 15.1 Hz, 1H, $ArCH_2$), 5.37 (d, *J* = 14.9 Hz, 1H, $ArCH_2$), 5.55 (s, 1H, CHOTMP), 5.93 (ddt, *J* = 16.9, 10.1, 7.2 Hz, $CH_2C\underline{H}$=), 7.06-7.15 (m, 4H, CH_{Ar}), 7.24-7.33 (m, 6H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: ***cis*-5.3a**: δ = 17.2 (t, CH_{2TEMPO}), 20.2 (q, CH_{3TEMPO}), 21.1 (q, CH_{3TEMPO}), 33.1 (q, CH_{3TEMPO}), 33.6 (q, CH_{3TEMPO}), 39.7 (t, $\underline{C}H_2CH$=), 40.9 (t, CH_{2TEMPO}), 41.1 (t, CH_{2TEMPO}), 48.7 (t, $ArCH_2$), 51.1 (t, $ArCH_2$), 60.5 (s, C_{TEMPO}), 60.7 (d, $CH_2\underline{C}HN$), 62.5 (s, C_{TEMPO}), 89.4 (d, CHOTMP), 119.14 (t, $=CH_2$), 127.7 (d, CH_{Ar}), 127.99 (d, CH_{Ar}), 128.01 (d, CH_{Ar}), 128.2 (d, CH_{Ar}), 128.9 (d, CH_{Ar}), 129.1 (d, CH_{Ar}), 133.7 (d, $CH_2\underline{C}H$=), 136.1 (s, C_{Ar}), 136.9 (s, C_{Ar}), 163.1 (s, C=O), 169.1 (s, C=O).

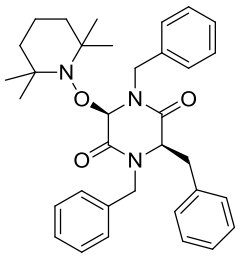
(3*R,6*S**)-1,3,4-Tribenzyl-6-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)piperazine-2,5-dione (*trans*-5.25):**



A freshly prepared solution of LiHMDS (1.56 mmol) in THF (6 mL) was cannulated dropwise to a solution of 1,3,4-tribenzylpiperazine-2,5-dione **5.24**[113] (500 mg, 1.3 mmol) in THF (14 mL) at −78 °C and the mixture was stirred at this temperature for 30 min. TEMPO (244 mg, 1.56 mmol) was added followed by portionwise addition of $Cp_2Fe^+PF_6^-$ until the blue color persisted (overall ca 645 mg, 1.95 mmol). After 30 min the reaction mixture was quenched by a drop of saturated NH_4Cl solution, filtered through a short pad of silica, which was washed with AcOEt, and the filtrates were concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, hexane/AcOEt, 10:1, gradient to 3:1) to give 665 mg (95%) **5.25** as an inseparable 11.7:1 *trans/cis* mixture as a colorless solid. $\mathbf{R}_f$ = 0.7 (hexane/AcOEt, 3:1); **IR**: *ν*[cm^{-1}] 2974, 1680, 1497, 1455, 1431,

1377, 1363, 1308, 1260, 1207, 1163, 1132, 1077, 1029, 1005, 973, 954, 909, 876, 823, 732, 697, 604, 503; **MS ESI+ *m/z*, (%)**: 945 (5, $[2M+Na-TEMPO]^+$), 789 (11, $[2M+Na-2TEMPO]^+$), 540 (100, $[M+H]^+$), 443 (89, $[M+H-(5,5\text{-dimethyl-1-pyrroline})]^+$), 384 (96, $[M+H-TEMPO]^+$), 355 (23), 293 (17, $[M+H-TEMPO\text{-benzyl}]^+$), 236 (11), 158 (4, $[TEMPOH+H]^+$); **HRMS ESI+ *m/z***: ($[M+Na]^+$): Calcd. for $C_{34}H_{41}N_3O_3Na$: 562.3040; Found: 562.3042; **^{1}H NMR (400 MHz, $CDCl_3$)**: ***trans*-5.25**: δ = 1.12 (s, 3H, CH_{3TEMPO}), 1.13 (s, 3H, CH_{3TEMPO}), 1.25 (s, 3H, CH_{3TEMPO}), 1.42 (s, 3H, CH_{3TEMPO}), 1.50-1.68 (m, 6H, CH_{2TEMPO}), 3.21 (dd, *J* = 16.0, 5.4 Hz, 1H, C<u>H</u>$_2$CHN), 3.59 (dd, *J* = 16.1, 3.3 Hz, 1H, C<u>H</u>$_2$CHN), 3.99 (d, *J* = 15.8 Hz, 1H, $ArCH_2$), 4.40 (d, *J* = 14.8 Hz, 1H, $ArCH_2$), 4.44 (dd, *J* = 5.4, 3.5 Hz, 1H, CH_2C<u>H</u>N), 5.47 (d, *J* = 14.8 Hz, 1H, $ArCH_2$), 5.54 (d, *J* = 16.2 Hz, 1H, $ArCH_2$), 5.55 (s, 1H, CHOTMP), 7.01-7.08 (m, 3H, CH_{Ar}), 7.15-7.22 (m, 3H, CH_{Ar}), 7.24-7.37 (m, 9H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: ***trans*-5.25**: δ = 17.2 (t, CH_{2TEMPO}), 20.3 (q, CH_{3TEMPO}), 20.5 (q, CH_{3TEMPO}), 33.16 (t, Ar<u>C</u>H$_2$CHN), 33.20 (q, CH_{3TEMPO}), 33.7 (q, CH_{3TEMPO}), 40.58 (t, CH_{2TEMPO}), 40.61 (t, CH_{2TEMPO}), 45.8 (t, $ArCH_2N$), 51.2 (t, $ArCH_2N$), 57.2 (d, CH_2<u>C</u>HN), 60.6 (s, C_{TEMPO}), 62.4 (s, C_{TEMPO}), 88.5 (d, CHOTMP), 126.7 (d, CH_{Ar}), 127.1 (d, CH_{Ar}), 127.78 (d, CH_{Ar}), 127.83 (d, CH_{Ar}), 128.0 (d, CH_{Ar}) 128.7 (d, CH_{Ar}), 128.88 (d, CH_{Ar}), 128.93 (d, CH_{Ar}), 129.1 (d, CH_{Ar}), 135.7 (s, C_{Ar}), 136.3 (s, C_{Ar}), 136.6 (s, C_{Ar}), 164.1 (s, C=O), 168.2 (s, C=O).

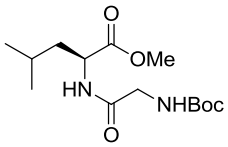
(3*R,6*R**)-1,3,4-Tribenzyl-6-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)piperazine-2,5-dione** (***cis*-5.25**):



A solution of alkoxyamine **5.25** (100 mg, 0.19 mmol), consisting of 11.7:1 *trans*/*cis* diastereomeric mixture, in *t*BuOH (9 mL) was degassed by three freeze-pump-thaw cycles. The reaction vessel was sealed and immersed to an oil bath preheated at 130 °C and stirred at this temperature for 1.5 h. The solvent was evaporated to dryness and the residue was dried at high-vacuum for 1 h to give 100 mg (99%) ***cis*-5.25** as a colorless solid. **m.p.** (***cis*-5.25**) 153-155 °C; **^{1}H NMR (400 MHz, $CDCl_3$)**: ***cis*-5.25**: δ = 1.22 (s, 3H, CH_{3TEMPO}), 1.29 (s, 3H, CH_{3TEMPO}), 1.30 (s, 3H, CH_{3TEMPO}), 1.37-1.45 (m, 1H, CH_{2TEMPO}), 1.50 (s, 3H, CH_{3TEMPO}), 1.53-1.67 (m, 5H, CH_{2TEMPO}), 2.53 (d, *J* = 15.0 Hz, 1H, $ArCH_2N$), 3.45 (dd, *J* = 13.3, 4.3 Hz, 1H, C<u>H</u>$_2$CHN), 3.53 (dd, *J* = 13.2, 10.9 Hz, 1H, C<u>H</u>$_2$CHN), 4.08 (dd, *J* = 11.0, 4.3 Hz, 1H, $ArCH_2$C<u>H</u>N), 4.35 (d, *J* = 14.9 Hz, 1H, $ArCH_2N$), 5.04 (d, *J* = 15.0 Hz, 1H, $ArCH_2N$), 5.41 (d, *J* = 14.9 Hz, 1H, $ArCH_2N$), 5.60 (s, 1H, CHOTMP), 6.78 (dd, *J* = 7.2, 2.2 Hz, 2H, CH_{Ar}), 7.10-7.14 (m, 2H, CH_{Ar}), 7.16-7.43 (m, 11H, CH_{Ar}); **^{13}C NMR (101**

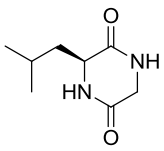
MHz, $CDCl_3$): ***cis*-5.25**: δ = 17.0 (t, CH_{2TEMPO}), 20.1 (q, CH_{3TEMPO}), 21.0 (q, CH_{3TEMPO}), 31.3 (q, CH_{3TEMPO}), 33.0 (q, CH_{3TEMPO}), 40.8 (t, CH_{2TEMPO}), 40.9 (t, CH_{2TEMPO}), 41.6 (t, Ar$\underline{C}H_2$CH), 48.5 (t, ArCH_2N), 51.0 (t, ArCH_2N), 60.4 (s, C_{TEMPO}), 62.3 (d, Ar$CH_2C\underline{H}$N), 62.4 (s, C_{TEMPO}), 89.7 (d, CHOTMP), 127.52 (d, 2C, CH_{Ar}), 127.53 (d, CH_{Ar}), 127.85 (d, CH_{Ar}), 127.89 (d, CH_{Ar}), 128.8 (d, CH_{Ar}), 128.9 (d, CH_{Ar}), 129.2 (d, CH_{Ar}), 129.4 (d, CH_{Ar}), 135.7 (s, C_{Ar}), 136.7 (s, C_{Ar}), 137.3 (s, C_{Ar}), 163.0 (s, C=O), 169.3 (s, C=O).

(*S*)-Methyl 2-(2-((*tert*-butoxycarbonyl)amino)acetamido)-4-methylpentanoate (6.8):



Ethyldiisopropylamine (2.9 mL, 16.63 mmol) was added dropwise to a suspension of *L*-leucine methyl ester hydrochloride (1.00 g, 5.51 mmol), *N*-Boc glycine (1.11 g, 6.33 mmol) and HBTU (2.1 g, 6.61 mmol) in dry CH_2Cl_2 (55 mL) under Ar at r.t. and the reaction mixture was stirred for 24 h. It was washed with saturated NH_4Cl solution and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The resulting residue was adsorbed at silica gel and purified by flash chromatography (hexane/EtOAc, 2:1 gradient to 1:1) to give 1.61 g (97%) **6.8** as pale yellow oil. $\mathbf{R_f}$ = 0.4 (hexane/AcOEt, 1:1); $\mathbf{[\alpha]^{20}_{589}}$: -31.0 (*c* 0.1, CH_3OH); **IR**: ν[cm^{-1}] 3323, 2968, 1748, 1724, 1671, 1526, 1476, 1458, 1443, 1395, 1371, 1279, 1251, 1210, 1159, 1054, 1030, 989, 949, 868, 784, 643, 543; **MS ESI+ *m/z*, (%)**: 627 (19, $[2M+Na]^+$), 347 (4), 341 (9, $[M+K]^+$), 325 (100, $[M+Na]^+$), 303 (4, $[M+H]^+$), 247 (9, [M+H-isobutylene]$^+$), 203 (7, [M+H-isobutylene-CO_2]$^+$); **HRMS ESI+ *m/z***: ($[M+Na]^+$): Calcd. for $C_{14}H_{26}O_5N_2Na$: 325.1734; Found: 325.1735; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 0.91 (d, *J* = 6.3 Hz, 3H, $CH(C\underline{H}_3)_2$), 0.92 (d, *J* = 6.0 Hz, 3H, $CH(C\underline{H}_3)_2$), 1.44 (s, 9H, $C(CH_3)_3$), 1.49-1.59 (m, 1H, $C\underline{H}_2$*i*Pr), 1.59-1.69 (m, 2H, $C\underline{H}(CH_3)_2$, $C\underline{H}_2$*i*Pr), 3.71 (s, 3H, OCH_3), 3.77 (dd, *J* = 16.9, 5.2 Hz, 1H, $C\underline{H}_2$NH), 3.84 (dd, *J* = 16.8, 4.7 Hz, 1H, $C\underline{H}_2$NH), 4.62 (td, *J* = 8.5, 4.4 Hz, 1H, $CH_2C\underline{H}$NH), 5.24 (br. s, 1H, $CH_2N\underline{H}$), 6.60 (d, *J* = 7.2 Hz, 1H, $CH_2CHN\underline{H}$); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 22.0 (q, $CH(\underline{C}H_3)_2$), 23.0 (q, $CH(\underline{C}H_3)_2$), 25.0 (d, $\underline{C}H(CH_3)_2$), 28.5 (q, $C(\underline{C}H_3)_3$), 41.7 (t, CH_2*i*Pr), 44.5 (t, CH_2NH), 50.8 (d, $CH_2\underline{C}$HNH), 52.5 (q, OCH_3), 80.5 (s, $\underline{C}(CH_3)_3$), 156.3 (s, $C{=}O_{Boc}$), 169.5 (s, NHC=O), 173.5 (s, $\underline{C}O_2$Me).

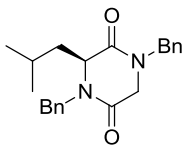
(*S*)-3-Isobutylpiperazine-2,5-dione (6.9):



Dipeptide **6.8** (1.55 g, 5.13 mmol) was dissolved in CH_2Cl_2 (15 mL) and silica gel (2 g) was added. The suspension was evaporated to dryness and heated with vigorous stirring under Ar at 190 °C for 1 h. The solid reaction mixture was transferred to a short packed silica gel column and the product was eluted with CH_2Cl_2/MeOH (10:1, gradient to 5:1) to give 783 mg (90%) **6.9** as a colorless solid. **m.p.**

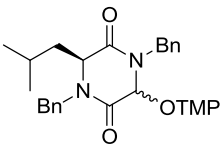
251-253 °C; $\mathbf{R_f}$ = 0.2 (acetone/AcOEt, 1:1); **[α]$^{20}_{589}$**: +10.5 (*c* 1.00, CH_3OH); **MS ESI+ *m/z*, (%)**: 431 (9), 363 (100, $[2M+Na]^+$), 329 (6), 291 (8), 261 (30), 207 (4), 193 (86, $[M+Na]^+$), 171 (4, $[M+H]^+$); **HRMS ESI+ *m/z***: ($[M+Na]^+$): Calcd. for $C_8H_{14}O_2N_2Na$: 193.0948; Found: 193.0945; **^{1}H NMR (400 MHz, CD_3OD)**: δ = 0.96 (d, *J* = 6.6 Hz, 3H, $CH(C\underline{H}_3)_2$), 0.98 (d, *J* = 6.7 Hz, 3H, $CH(C\underline{H}_3)_2$), 1.62-1.74 (m, 2H, CH_2*i*Pr), 1.83 (m, 1H, $C\underline{H}(CH_3)_2$), 3.83 (dd, *J* = 17.8, 0.9 Hz, 1H, $C\underline{H}_2NH$), 3.86-3.93 (m, 1H, $CH_2C\underline{H}NH$), 4.01 (dd, *J* = 17.8, 0.9 Hz, 1H, $C\underline{H}_2NH$); **^{13}C NMR (101 MHz, CD_3OD)**: δ = 22.1 (q, $CH(\underline{C}H_3)_2$), 23.4 (q, $CH(\underline{C}H_3)_2$), 25.3 (d, $\underline{C}H(CH_3)_2$), 43.8 (t, CH_2*i*Pr), 45.3 (t, CH_2NH), 54.8 (d, $CH_2\underline{C}HNH$), 168.9 (s, C=O), 171.6 (s, C=O).

(*S*)-1,4-Dibenzyl-3-isobutylpiperazine-2,5-dione (6.10):



DKP **6.9** (700 mg, 4.11 mmol) was dissolved in dry DMF (20 mL) under Ar and the solution was cooled to 0 °C. NaH (378 mg, 9.45 mmol, 60% dispersion in mineral oil) was added and the reaction mixture was stirred at 0 °C for 30 min. Benzyl bromide (1.2 mL, 10.30 mmol) was added dropwise and stirring at 0 °C was continued for 4 h. The reaction mixture was carefully quenched by NH_4Cl solution and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and evaporated. The residue was purified by column chromatography (hexane/AcOEt, 2:1, gradient to 1:1) to give 1.2 g (83%) **6.10** as a colorless oil. $\mathbf{R_f}$ = 0.3 (hexane/AcOEt, 1:1); **[α]$^{20}_{589}$**: +0.3 (*c* 1.00, $CHCl_3$); **IR**: ν[cm^{-1}] 3040, 2966, 2879, 1666, 1500, 1471, 1457, 1392, 1360, 1319, 1271, 1211, 1175, 1075, 1032, 951, 825, 728, 701, 601; **MS ESI+ *m/z*, (%)**: 1073 (6, $[3M+Na]^+$), 723 (96, $[2M+Na]^+$), 701 (19, $[2M+H]^+$), 471 (4), 389 (5), 373 (100, $[M+Na]^+$), 351 (59, $[M+H]^+$); **HRMS ESI+ *m/z***: ($[M+Na]^+$): Calcd. for $C_{22}H_{26}N_2O_2Na$: 373.1887; Found: 373.1888; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 0.91 (d, *J* = 6.7 Hz, 3H, $CH(C\underline{H}_3)_2$), 0.92 (d, *J* = 6.5 Hz, 3H, $CH(C\underline{H}_3)_2$), 1.53 (ddd, *J* = 13.9, 9.0, 4.9 Hz, 1H, $C\underline{H}_2$*i*Pr), 1.65 (ddd, *J* = 14.0, 9.0, 5.0 Hz, 1H, $C\underline{H}_2$*i*Pr), 1.73-1.86 (m, 1H, $C\underline{H}(CH_3)_2$), 3.84 (d, *J* = 17.4 Hz, 1H, αCH_2), 3.90 (dd, *J* = 9.0, 4.9 Hz, 1H, $CH_2C\underline{H}N$), 3.95 (d, *J* = 14.9 Hz, 1H, $ArCH_2$), 3.96 (d, *J* = 17.4 Hz, 1H, αCH_2), 4.37 (d, *J* = 14.5 Hz, 1H, $ArCH_2$), 4.78 (d, *J* = 14.5 Hz, 1H, $ArCH_2$), 5.24 (d, *J* = 14.9 Hz, 1H, $ArCH_2$), 7.19-7.25 (m, 4H, CH_{Ar}), 7.27-7.40 (m, 6H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 22.1 (q, $CH(\underline{C}H_3)_2$), 23.4 (q, $CH(\underline{C}H_3)_2$), 24.7 (d, $\underline{C}H(CH_3)_2$), 41.1 (t, $\underline{C}H_2$*i*Pr), 47.8 (t, $ArCH_2$), 49.5 (t, αCH_2), 49.6 (t, $ArCH_2$), 58.3 (d, $CH_2C\underline{H}N$), 128.27 (d, CH_{Ar}), 128.30 (d, CH_{Ar}), 128.4 (d, 2C, CH_{Ar}), 129.1 (d, 2C, CH_{Ar}), 135.6 (s, C_{Ar}), 135.8 (s, C_{Ar}), 164.8 (s, C=O), 166.9 (s, C=O).

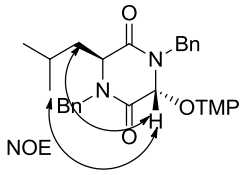
(3*S*)-1,4-Dibenzyl-3-isobutyl-6-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)piperazine-2,5-dione (6.11):



A freshly prepared solution of LiHMDS (1.03 mmol) in THF (2 mL) was cannulated dropwise to a solution of (*S*)-1,4-dibenzyl-3-isobutylpiperazine-2,5-dione (300 mg, 0.86 mmol) in THF (8 mL) at −78 °C and the mixture was stirred at this temperature for 30 min. TEMPO (161 mg, 1.03 mmol) was added followed by portionwise addition of $Cp_2Fe^+PF_6^-$ until the blue color persisted (overall ca 370 mg, 1.12 mmol). After 30 min the reaction mixture was quenched by a drop of saturated NH_4Cl solution, filtered through a short pad of silica, which was washed with AcOEt, and the filtrates were concentrated under reduced pressure. The residue was purified by column chromatography (silica gel, 100% hexane, gradient to 5:1 hexane/AcOEt) to give inseparable mixture of TEMPO and the product as orange oil. Keeping this mixture at high-vacuum for several hours at 45 °C gave 420 mg (97%) **6.11** as a pale yellow gum as an inseparable 1.1:1 mixture of diastereomers. $\mathbf{R_f}$ = 0.6 (hexane/AcOEt, 1:1); **IR**: ν[cm^{-1}] 2950, 2880, 1679, 1457, 1368, 1307, 1265, 1212, 1174, 1135, 1077, 1025, 981, 957, 910, 879, 822, 728, 699, 631, 604, 508; **MS ESI+ *m/z*, (%)**: 1033 (9, $[2M+Na]^+$), 612 (4), 565 (23), 528 (44, $[M+Na]^+$), 506 (100, $[M+H]^+$), 372 (3, $[M+Na\text{-}TEMPO]^+$), 228 (7); **HRMS ESI+ *m/z***: ($[M+H]^+$): Calcd. for $C_{31}H_{43}N_3O_3$: 506.3377; Found: 506.3378; **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 0.58 (d, *J* = 6.5 Hz, 3H, $CH(C\underline{H}_3)_2$), 0.89 (d, *J* = 6.6 Hz, 3H, $CH(C\underline{H}_3)_2$), 0.96 (d, *J* = 6.6 Hz, 3H, $CH(C\underline{H}_3)_2$), 0.98 (d, *J* = 6.5 Hz, 3H, $CH(C\underline{H}_3)_2$), 1.12 (s, 3H, CH_{3TEMPO}), 1.13 (s, 6H, CH_{3TEMPO}), 1.20 (s, 6H, CH_{3TEMPO}), 1.24 (s, 3H, CH_{3TEMPO}), 1.42 (s, 3H, CH_{3TEMPO}), 1.44 (s, 3H, CH_{3TEMPO}), 1.27-1.47 (m, 3H, CH_{2TEMPO}), 1.48-1.84 (m, 11H, CH_{2TEMPO}, $2C\underline{H}_2$*i*Pr), 1.86-2.01 (m, 3H, $C\underline{H}_2$*i*Pr, $2C\underline{H}(CH_3)_2$), 2.16 (ddd, *J* = 13.4, 10.0, 4.6 Hz, 1H, $C\underline{H}_2$*i*Pr), 3.84 (d, *J* = 14.9 Hz, 1H, $ArCH_2$), 3.89 (dd, *J* = 10.0, 5.6 Hz, 1H, $CH_2C\underline{H}N$), 4.18 (d, *J* = 15.9 Hz, 1H, $ArCH_2$), 4.28 (dd, *J* = 8.5, 2.9 Hz, 1H, $CH_2C\underline{H}N$), 4.33 (d, *J* = 14.9 Hz, 1H, $ArCH_2$), 4.34 (d, *J* = 14.9 Hz, 1H, $ArCH_2$), 5.29 (d, *J* = 14.9 Hz, 1H, $ArCH_2$), 5.32-5.43 (m, 3H, $ArCH_2$), 5.54 (s, 1H, CHOTMP), 5.55 (s, 1H, CHOTMP), 7.07-7.16 (m, 5H, CH_{Ar}), 7.18-7.35 (m, 15H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 16.6 (t, CH_{2TEMPO}), 16.7 (t, CH_{2TEMPO}), 19.6 (q, CH_{3TEMPO}), 19.7 (q, CH_{3TEMPO}), 19.9 (q, CH_{3TEMPO}), 20.4 (q, CH_{3TEMPO}), 21.0 (q, $CH(\underline{C}H_3)_2$), 21.2 (q, $CH(\underline{C}H_3)_2$), 22.5 (q, $CH(\underline{C}H_3)_2$), 23.0 (q, $CH(\underline{C}H_3)_2$), 24.2 (d, $\underline{C}H(CH_3)_2$), 25.2 (d, $\underline{C}H(CH_3)_2$), 32.3 (q, CH_{3TEMPO}), 32.8 (q, CH_{3TEMPO}), 33.0 (q, CH_{3TEMPO}), 33.1 (q, CH_{3TEMPO}), 35.1 (t, $\underline{C}H_2$*i*Pr), 40.0 (t, CH_{2TEMPO}), 40.1 (t, CH_{2TEMPO}), 40.3 (t, CH_{2TEMPO}), 40.4 (t, CH_{2TEMPO}), 42.9 (t, $\underline{C}H_2$*i*Pr), 44.9 (t, $ArCH_2$), 47.3 (t,

$ArCH_2$), 50.5 (t, $ArCH_2$), 50.8 (t, $ArCH_2$), 54.9 (d, $CH_2\underline{C}HN$), 58.0 (d, $CH_2\underline{C}HN$), 59.8 (s, C_{TEMPO}), 59.9 (s, C_{TEMPO}), 61.8 (s, C_{TEMPO}), 61.9 (s, C_{TEMPO}), 88.8 (d, CHOTMP), 89.0 (d, CHOTMP), 126.3 (d, CH_{Ar}), 127.0 (d, CH_{Ar}), 127.1 (d, CH_{Ar}), 127.4 (d, CH_{Ar}), 127.5 (d, 3C, CH_{Ar}), 127.6 (d, CH_{Ar}), 128.42 (d, CH_{Ar}), 128.44 (d, CH_{Ar}), 128.48 (d, CH_{Ar}), 128.52 (d, CH_{Ar}), 135.5 (s, C_{Ar}), 135.8 (s, C_{Ar}), 136.3 (s, C_{Ar}), 136.4 (s, C_{Ar}), 162.4 (s, C=O), 164.6 (s, C=O), 168.8 (s, C=O), 169.2 (s, C=O).

(3*S*,6*R*)-1,4-Dibenzyl-3-isobutyl-6-((2,2,6,6-tetramethylpiperidin-1-yl)oxy)piperazine-2,5-dione (*trans*-6.11):



A solution of alkoxyamine **6.11** (40 mg, 0.08 mmol), consisting of 1.1:1 *cis/trans* diastereomeric mixture, in *t*BuOH (4 mL) was degassed by three freeze-pump-thaw cycles. The reaction vessel was sealed and immersed to an oil bath preheated at 90 °C and stirred at this temperature for 2 h. The solvent was evaporated to dryness and the residue was dried at high-vacuum for 1 h to give 40 mg (99%) ***trans*-6.11** as a colorless foam. **^{1}H NMR (400 MHz, $CDCl_3$)**: δ = 0.96 (d, *J* = 6.7 Hz, 3H, $CH(C\underline{H}_3)_2$), 0.98 (d, *J* = 6.5 Hz, 3H, $CH(C\underline{H}_3)_2$), 1.13 (s, 3H, CH_{3TEMPO}), 1.20 (s, 6H, CH_{3TEMPO}), 1.32-1.42 (m, 1H, CH_{2TEMPO}), 1.44 (s, 3H, CH_{3TEMPO}), 1.47-1.67 (m, 5H, CH_{2TEMPO}), 1.74 (ddd, *J* = 13.5, 9.7, 5.7 Hz, 1H, $C\underline{H}_2$*i*Pr), 1.86-2.01 (m, 1H, $C\underline{H}(CH_3)_2$), 2.16 (ddd, *J* = 13.6, 10.0, 4.7 Hz, 1H, $C\underline{H}_2$*i*Pr), 3.84 (d, *J* = 15.0 Hz, 1H, $ArCH_2$), 3.90 (dd, *J* = 10.0, 5.7 Hz, 1H, $CH_2C\underline{H}N$), 4.33 (d, *J* = 14.9 Hz, 1H, $ArCH_2$), 5.30 (d, *J* = 15.0 Hz, 1H, $ArCH_2$), 5.37 (d, *J* = 14.9 Hz, 1H, $ArCH_2$), 5.55 (s, 1H, CHOTMP), 7.07-7.17 (m, 4H, CH_{Ar}), 7.20-7.34 (m, 6H, CH_{Ar}); **^{13}C NMR (101 MHz, $CDCl_3$)**: δ = 17.2 (t, CH_{2TEMPO}), 20.2 (q, CH_{3TEMPO}), 20.9 (q, CH_{3TEMPO}), 21.8 (q, $CH(\underline{C}H_3)_2$), 23.1 (q, $CH(\underline{C}H_3)_2$), 24.7 (d, $\underline{C}H(CH_3)_2$), 32.8 (q, CH_{3TEMPO}), 33.6 (q, CH_{3TEMPO}), 40.8 (t, CH_{2TEMPO}), 40.9 (t, CH_{2TEMPO}), 43.5 (t, $\underline{C}H_2$*i*Pr), 47.8 (t, $ArCH_2$), 51.1 (t, $ArCH_2$), 58.6 (d, $CH_2\underline{C}HN$), 60.4 (s, C_{TEMPO}), 62.4 (s, C_{TEMPO}), 89.4 (d, CHOTMP), 127.7 (d, CH_{Ar}), 127.9 (d, CH_{Ar}), 128.0 (d, CH_{Ar}), 128.2 (d, CH_{Ar}), 129.0 (d, CH_{Ar}), 129.1 (d, CH_{Ar}), 136.1 (s, C_{Ar}), 137.0 (s, C_{Ar}), 163.0 (s, C=O), 169.4 (s, C=O).

Experimental data of kinetic studies

^{1}H NMR spectroscopic monitoring of trans/cis isomerization.

Kinetic experiments to determine the isomerization rate constants were conducted by monitoring the conversion at indicated temperatures by dissolving ***trans*-5.25** (*trans/cis*, 11.7:1) or ***trans*-5.3a** (5 mg) in DMSO-d_6 (0.5 mL). For isomerization of ***trans*-5.25** the decay of ***trans*-5.25** was measured by integration of the resonance for nonanomeric αCH proton at δ = 4.45 (dd, *J* = 5.9, 3.5 Hz, 1H, $CH_2C\underline{H}CO$) and the accumulation of ***cis*-5.25** was measured by integration of the benzylic signal at δ = 4.85 (d, *J* = 15.1 Hz, 1H, $PhC\underline{H}_2$) ppm. For isomerization of ***trans*-5.3a** the decay of ***trans*-5.3a** was measured by integration of the resonance for vinylic proton at δ = 5.59-5.68 ppm (m, 1H, $C\underline{H}=CH_2$) and the accumulation of ***cis*-5.25** was measured by integration of the vinylic signal at δ = 5.86-5.96 (m, 1H, $C\underline{H}=CH_2$) ppm. In principle, integration of any other nonoverlapping resonance can be used for measurements.

Table S1. Kinetic trace for isomerization of ***trans*-5.25** to ***cis*-5.25** at 70 °C, 80 °C and 90 °C

70 °C:				**80 °C:**				**90 °C:**			
Entry	**Time [s]**	**Trans-5.25**	**Cis-5.25**	**Entry**	**Time [s]**	**Trans-5.25**	**Cis-5.25**	**Entry**	**Time [s]**	**Trans-5.25**	**Cis-5.25 [%]**
1	0	0.92	0.08	1	0	0.92	0.08	1	0	0.92	0.08
2	300	0.86	0.14	2	360	0.85	0.15	2	300	0.75	0.25
3	660	0.84	0.16	3	540	0.78	0.22	3	480	0.66	0.34
4	960	0.82	0.18	4	660	0.71	0.29	4	660	0.57	0.43
5	1260	0.78	0.22	5	840	0.66	0.34	5	780	0.50	0.50
6	1620	0.75	0.25	6	1020	0.61	0.39	6	960	0.44	0.56
7	1920	0.73	0.27	7	1200	0.56	0.44	7	1140	0.38	0.62
8	2220	0.69	0.31	8	1380	0.52	0.48	8	1320	0.34	0.66
9	2520	0.67	0.33	9	1500	0.48	0.52	9	1500	0.29	0.71
10	2820	0.65	0.35	10	1680	0.45	0.55	10	1620	0.28	0.72
11	3120	0.63	0.37	11	1860	0.42	0.58	11	1800	0.23	0.77
12	3480	0.60	0.40	12	2220	0.36	0.64	12	1980	0.22	0.78
13	3780	0.58	0.42	13	2520	0.32	0.68	13	2340	0.17	0.83
14	4080	0.57	0.43	14	2880	0.28	0.72				
15	4680	0.52	0.48	15	3360	0.23	0.77				
16	5280	0.49	0.51	16	3600	0.21	0.79				
17	5880	0.46	0.54	17	4200	0.15	0.85				
18	6480	0.43	0.57	18	4800	0.12	0.88				
19	7080	0.41	0.59	19	5460	0.10	0.90				
20	7740	0.38	0.62								
21	8340	0.35	0.65								
22	8940	0.33	0.67								
23	9540	0.32	0.68								
24	10140	0.30	0.70								
25	10740	0.28	0.72								
26	11340	0.25	0.75								

^{1}H NMR spectroscopic monitoring of cycloisomerization of *cis*-5.3a.

Table S2. Kinetic trace for isomerization of ***trans*-5.3a** at 70 °C and 75 °C.

70 °C:				**75 °C:**			
Entry	**Time [s]**	**Trans-5.3a**	**Cis-5.3a**	**Entry**	**Time [s]**	**Trans-5.3a**	**Cis-5.3a**
1	0	1.00	0.00	1	0	1.00	0.00
2	503	0.86	0.14	2	152	0.96	0.04
3	724	0.80	0.20	3	516	0.78	0.22
4	1112	0.71	0.29	4	820	0.66	0.34
5	1417	0.65	0.35	5	1125	0.55	0.45
6	1721	0.59	0.41	6	1430	0.47	0.53
7	2026	0.54	0.46	7	1734	0.39	0.61
8	2331	0.49	0.51	8	2039	0.33	0.67
9	2635	0.45	0.55	9	2344	0.28	0.72
10	2940	0.41	0.59	10	2649	0.24	0.76
11	3245	0.38	0.62	11	2953	0.20	0.80
12	3550	0.34	0.66	12	3258	0.18	0.82
13	3825	0.31	0.69	13	3563	0.15	0.85
14	4159	0.28	0.72	14	3867	0.13	0.87
15	4464	0.25	0.75	15	4143	0.12	0.88
16	4715	0.23	0.77	16	4466	0.10	0.90
				17	4782	0.09	0.91
				18	5086	0.08	0.92

Table S3. Kinetic trace for isomerization of ***trans*-5.3a** at 80 °C and 85 °C.

80 °C:				**85 °C:**			
Entry	**Time [s]**	**Trans-5.3a**	**Cis-5.3a**	**Entry**	**Time [s]**	**Trans-5.3a**	**Cis-5.3a**
1	0	1.00	0.00	1	0	1	0
2	658	0.53	0.47	2	342	0.60	0.40
3	962	0.37	0.63	3	411	0.51	0.49
4	1267	0.26	0.74	4	528	0.39	0.61
5	1826	0.19	0.81	5	646	0.30	0.70
6	2130	0.15	0.85	6	764	0.23	0.77
7	2434	0.12	0.88	7	881	0.18	0.82
				8	999	0.15	0.85
				9	1117	0.12	0.88
				10	1234	0.10	0.90
				11	1352	0.09	0.91
				12	1470	0.08	0.92
				13	1587	0.07	0.93

^{1}H NMR spectroscopic monitoring of cycloisomerization of *cis*-5.3a

Kinetic experiments to monitor cycloisomerization of ***cis*-5.3a** to bicyclic DKPs were carried out by dissolving pure ***cis*-5.3a** (5 mg), prepared by preparative thermal isomerization, in DMSO-d_6 (0.5 mL). The decay rate of ***cis*-5.3a** was measured by integration of the vinylic resonance at δ = 5.86-5.96 (m, 1H, C<u>H</u>=CH_2) or by integration of the anomeric CH resonance at δ = (s, 5.40, CHOTMP). For measuring the accumulation of the bicyclic products the following resonances were used: 6-exo-major, δ = 2.22-2.32 (m, 1H, CH_{bridge}); 6-exo-minor, δ = 3.63 (dd, *J* = 9.8, 6.8 Hz, 1H, C<u>H</u>$_2$OTMP); 7-endo, δ = 3.71-3.77 (m, 1H, C<u>H</u>OTMP).

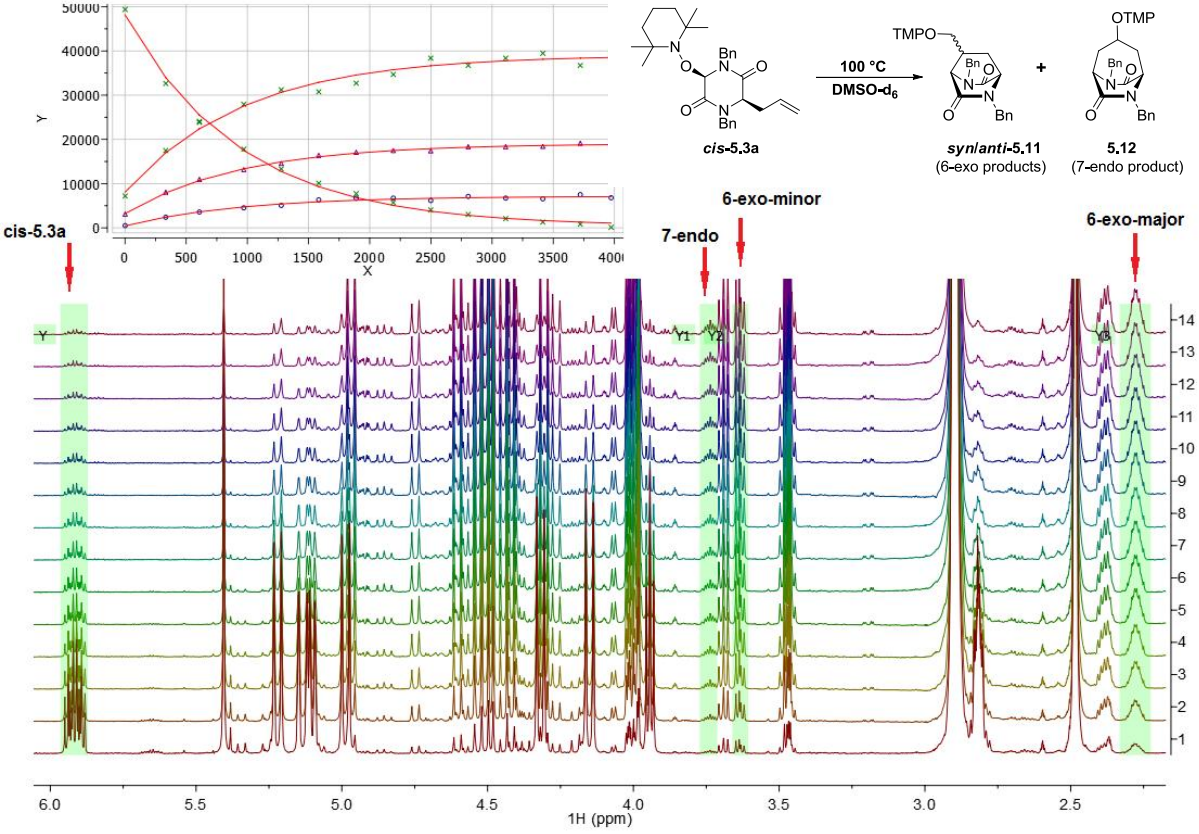


Figure S1. Monitoring of cycloisomerization of cis-5.3a at 100 °C.

Table S4. Kinetic trace for cycloisomerization of ***cis*-5.3a** at 90 °C.

Entry	Time [s]	cis-5.3a	6-exo major	6-exo minor	7-endo
1	0	1.000	0.000	0.000	0.000
2	312	0.953	0.059	0.019	0.006
3	916	0.888	0.102	0.037	0.012
4	1520	0.830	0.140	0.053	0.018
5	2124	0.778	0.174	0.068	0.023

6	2728	0.730	0.205	0.081	0.028
7	3332	0.687	0.231	0.092	0.032
8	3936	0.651	0.253	0.102	0.036
9	4540	0.614	0.275	0.111	0.039
10	5144	0.582	0.294	0.120	0.043
11	5748	0.554	0.310	0.127	0.046
12	6352	0.528	0.324	0.134	0.048
13	6956	0.505	0.337	0.139	0.051
14	7560	0.484	0.348	0.145	0.053
15	8164	0.465	0.358	0.149	0.055
16	8768	0.448	0.367	0.154	0.057
17	9372	0.433	0.375	0.157	0.059
18	9976	0.419	0.382	0.161	0.060
19	10580	0.406	0.388	0.164	0.061
20	11184	0.395	0.393	0.166	0.063
21	11788	0.385	0.398	0.169	0.064
22	12392	0.375	0.402	0.171	0.065
23	12996	0.367	0.406	0.173	0.066
24	13600	0.360	0.409	0.174	0.067
25	14204	0.353	0.412	0.176	0.068
26	14808	0.347	0.415	0.177	0.068
27	15412	0.341	0.417	0.179	0.069
28	16016	0.336	0.419	0.180	0.070
29	16620	0.332	0.421	0.181	0.070
30	17224	0.328	0.422	0.181	0.071
31	17828	0.324	0.424	0.182	0.071
32	18432	0.321	0.425	0.183	0.071

Table S5. Kinetic trace for cycloisomerization of ***cis*-5.3a** at 100 °C.

Entry	**Time [s]**	**cis-5.3a**	**6-exo major**	**6-exo minor**	**7-endo**
1	0	1.000	0.000	0.000	0.000
2	276	0.736	0.123	0.049	0.007
3	610	0.518	0.260	0.121	0.037
4	883	0.390	0.342	0.163	0.055
5	1248	0.267	0.421	0.204	0.072
6	1554	0.194	0.468	0.228	0.083
7	1859	0.142	0.503	0.245	0.090
8	2165	0.104	0.528	0.258	0.095
9	2470	0.077	0.546	0.267	0.099
10	2776	0.057	0.560	0.274	0.102
11	3081	0.043	0.570	0.278	0.104
12	3387	0.033	0.577	0.282	0.105
13	3692	0.025	0.582	0.284	0.106
14	3998	0.020	0.586	0.286	0.107

Table S6. Kinetic trace for cycloisomerization of ***cis*-5.3a** at 110 °C.

Entry	Time [s]	cis-5.3a	6-exo major	6-exo minor	7-endo
1	0	1.000	0.000	0.000	0.000
2	289	0.359	0.413	0.168	0.028
3	400	0.230	0.502	0.230	0.085
4	467	0.173	0.531	0.252	0.099
5	535	0.128	0.551	0.267	0.107
6	602	0.093	0.563	0.277	0.111
7	670	0.066	0.571	0.284	0.114
8	738	0.044	0.577	0.289	0.115
9	805	0.028	0.580	0.292	0.116
10	873	0.014	0.582	0.295	0.116
11	940	0.004	0.584	0.296	0.116

Table S7. Kinetic trace for cycloisomerization of ***cis*-5.3a** at 115 °C.

Entry	Time [s]	cis-5.3a	6-exo major	6-exo minor	7-endo
1	0	1.000	0.000	0.000	0.000
2	180	0.367	0.371	0.218	0.097
3	216	0.230	0.455	0.251	0.109
4	251	0.144	0.498	0.273	0.118
5	287	0.087	0.521	0.289	0.125
6	323	0.050	0.533	0.299	0.130
7	358	0.028	0.539	0.306	0.134
8	394	0.013	0.543	0.311	0.138
9	429	0.003	0.544	0.315	0.140

9. APPENDIX A: X-Ray crystallographic data

Single-crystal X-ray diffraction data for all compounds were obtained on a Bruker Apex II CCD diffractometer applying monochromatic Mo *K*α radiation (λ = 0.71073 Å) at 150 K. The structures were solved by direct methods and refined by full-matrix least squares based on F_2.[114] The hydrogen atoms were fixed into idealized positions (riding model) and assigned temperature factors $H_{iso}(H) = 1.2\ Ueq$(pivot atom). The crystallographic data are summarized in Tables S1-S3. Crystallographic data (excluding structure factors) for structures ***syn*-3.13c** (CCDC 1457047), ***anti*-13d** (CCDC 1457045), **3.14** (CCDC 1457042), ***syn/anti*-3.8** (CCDC 1457046), **4.2** (CCDC 1457044), **4.15c** (CCDC 1457050), **4.35** (CCDC 1457049), **4.47b** (CCDC 1457040), **5.36d** (CCDC 1063461), ***trans*-5.3a** (CCDC 1063459), ***cis*-5.3a** (CCDC 1457042), ***trans*-5.3c** (CCDC 1063460), ***cis*-5.25** (CCDC 1457048)and ***trans*-3.11d** (CCDC 1457041)have been deposited at the Cambridge Crystallographic Data Centre with their respective CCDC numbers given in parentheses. Copies of the data can be obtained, free of charge by application to the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

Table A1: Crystal data, data collection, and refinement parameters for ***syn*-3.13c, *anti*-13d** and **3.14**.

Compound	***syn*-3.13c**	***anti*-13d**	**3.14**
CCDC	1457047	1457045	1457042
Formula	$C_{25}H_{26}N_2O_2$	$C_{17}H_{24}N_2O_4$	$C_{28}H_{39}N_3O_3$
M.w.	386.48	320.38	465.62
Crystal system	Monoclinic	Monoclinic	Monoclinic
Space group	$P2_1/c$	$P2_1/c$	$P2_1/c$
a [Å]	9.7653 (3)	15.2632 (5)	12.9272 (5)
b [Å]	17.8474 (5)	9.7840 (4)	12.8825 (4)
c [Å]	23.2056 (6)	11.4973 (4)	15.4316 (6)
α [°]			
β [°]	96.592 (1)	105.730 (1)	90.646 (1)
γ [°]			
Z	8	4	4
V [Å^3]	4017.7 (2)	1652.65 (10)	2569.73 (16)
D_x [g cm^{-3}]	1.278	1.288	1.204
Crystal size [mm]	0.62×0.34×0.32	0.45×0.45×0.20	0.73×0.40×0.27
Crystal color, shape	colorless, prism	colorless, cube	colorless, prism
μ [mm^{-1}]	0.08	0.09	0.08
T_{min}, T_{max}	0.951, 0.975	0.960, 0.982	0.945, 0.979
Measured reflections	65706	17113	43615
Independent diffractions (R_{int} [a])	9224, (0.026)	3790, (0.026)	5903, (0.026)
Observed diffract. [I>2σ(I)]	7484	3064	4850
No. of parameters	525	212	312
R[b]	0.040	0.039	0.037
wR(F^2) for all data	0.103	0.101	0.097
GOF[c]	1.01	1.04	1.03
Residual electron density [e/Å^3]	0.28, -0.23	0.34, -0.21	0.34, -0.20

[a] $R_{int} = \Sigma \left| F_o^2 - F_{o,mean}^2 \right| / \Sigma F_o^2$; [b] $R(F) = \Sigma \left| \left| F_o \right| - \left| F_c \right| \right| / \Sigma \left| F_o \right|$; $wR(F^2) = [\Sigma(w(F_o^2 - F_c^2)^2)/(\Sigma w(F_o^2)^2)]^{½}$;
[c] $GOF = [\Sigma(w(F_o^2 - F_c^2)^2)/(N_{diffrs} - N_{params})]^{½}$

Table A2: Crystal data, data collection, and refinement parameters for ***syn/anti*-3.8**, **4.2** and **4.15c**.

Compound	***syn/anti*-3.8**	**4.2**	**4.15c**
CCDC	1457046	1457044	1457050
Formula	$C_{26}H_{36}BrN_3O_3$	$C_{22}H_{30}N_2O_2Si$	$C_{18}H_{24}N_2O_3$
M.w.	518.49	382.57	316.39
Crystal system	Triclinic	Triclinic	Orthorhombic
Space group	$P\bar{1}$	$P\bar{1}$	$P2_12_12_1$
a [Å]	11.4500 (6)	8.8175 (4)	8.6924 (2)
b [Å]	11.8832 (7)	10.0555 (5)	9.2483 (2)
c [Å]	20.1352 (12)	12.4834 (6)	21.1651 (5)
α [°]	104.616 (2)	87.061 (2)	
β [°]	106.078 (2)	71.539 (2)	
γ [°]	94.343 (2)	84.094 (2)	
Z	4	2	4
V [Å^3]	2515.9 (2)	1044.10 (9)	1701.46 (7)
D_x [g cm^{-3}]	1.369	1.217	1.235
Crystal size [mm]	0.56×0.51×0.28	0.54×0.36×0.24	0.61×0.54×0.41
Crystal color, shape	colorless, prism	colorless, prism	colorless, prism
μ [mm^{-1}]	1.67	0.13	0.08
T_{min}, T_{max}	0.454, 0.653	0.932, 0.969	0.950, 0.966
Measured reflections	50168	12964	12587
Independent diffractions (R_{int} [a])	10986, (0.034)	4785, (0.020)	3906, (0.017)
Observed diffract. [I>2σ(I)]	8493	3874	3714
No. of parameters	603	248	211
R[b]	0.035	0.037	0.032
wR(F^2) for all data	0.076	0.094	0.085
GOF[c]	1.02	1.03	1.04
Residual electron density [e/Å^3]	1.01, -1.01	0.28, -0.24	0.24, -0.17

[a] $R_{int} = \Sigma|F_o^2 - F_{o,mean}^2|/\Sigma F_o^2$; [b] $R(F) = \Sigma||F_o| - |F_c||/\Sigma|F_o|$; $wR(F^2) = [\Sigma(w(F_o^2 - F_c^2)^2)/(\Sigma w(F_o^2)^2)]^{½}$;
[c] $GOF = [\Sigma(w(F_o^2 - F_c^2)^2)/(N_{diffrs} - N_{params})]^{½}$

Table A3: Crystal data, data collection, and refinement parameters for **4.35**, **4.47b** and **5.36d**.

Compound	**4.35**	**4.47b**	**5.36d**
CCDC	1457049	1457040	1063461
Formula	$C_{18}H_{26}N_2O_4$	$C_{19}H_{26}N_2O_5$	$C_{32}H_{42}N_4O_5$
M.w.	334.41	362.42	562.70
Crystal system	Trigonal,	Monoclinic	Triclinic
Space group	$P3_1$	$P2_1$	$P\bar{1}$
a [Å]	9.4759 (7) Å	6.6697 (3)	11.5773 (3)
b [Å]		12.9985 (5)	11.9927 (3)
c [Å]	16.7019 (11)	10.5140 (4)	12.0903 (3)
α [°]			91.448 (1)
β [°]		92.171 (1)	105.301 (1)
γ [°]			112.082 (1)
Z	3	2	2
V [Å^3]	1298.78 (16)	910.87 (6)	1485.76 (6)
D_x [g cm^{-3}]	1.283	1.321	1.258
Crystal size [mm]	0.60×0.51×0.28	0.20×0.17×0.06	0.45×0.21×0.14
Crystal color, shape	colorless, prism	colorless, bar	colorless, prism
μ [mm^{-1}]	0.09	0.79	0.09
T_{min}, T_{max}	0.948, 0.975	0.860, 0.951	0.962, 0.988
Measured reflections	13253	14827	22099
Independent diffractions (R_{int} [a])	3972, (0.019)	3560, (0.034)	6820, (0.028)
Observed diffract. [I>2σ(I)]	3757	3407	5036
No. of parameters	221	239	375
R[b]	0.035	0.032	0.042
wR(F^2) for all data	0.096	0.079	0.102
GOF[c]	1.05	1.05	1.03
Residual electron density [e/Å^3]	0.21, -0.14	0.16, -0.15	0.27, −0.21

[a] $R_{int} = \Sigma \left| F_o^2 - F_{o,mean}^2 \right| / \Sigma F_o^2$; [b] $R(F) = \Sigma \left| \left| F_o \right| - \left| F_c \right| \right| / \Sigma \left| F_o \right|$; $wR(F^2) = [\Sigma(w(F_o^2 - F_c^2)^2)/(\Sigma w(F_o^2)^2)]^{½}$; [c] $GOF = [\Sigma(w(F_o^2 - F_c^2)^2)/(N_{diffrs} - N_{params})]^{½}$

Table A4: Crystal data, data collection, and refinement parameters for ***trans*-5.3a, *cis*-5.3a** and ***trans*-5.3c**

Compound	***trans*-5.3a**	***cis*-5.3a**	***trans*-5.3c**
CCDC	1063459	1457042	1063460
Formula	$C_{30}H_{39}N_3O_3$	$C_{30}H_{39}N_3O_3$	$C_{36}H_{43}N_3O_3$
M.w.	489.64	489.64	565.73
Crystal system	Monoclinic	Orthorhombic	Monoclinic
Space group	$P2_1/c$	$P2_12_12_1$	$P2_1/c$
a [Å]	15.9520 (7)	11.7840 (3)	11.0440 (4)
b [Å]	10.8850 (4)	12.9269 (3)	11.5088 (5)
c [Å]	15.8910 (6)	17.8355 (4)	25.6679 (11)
α [°]			
β [°]	103.833 (2)		99.302 (1)
γ [°]			
Z	4	4	4
V [Å^3]	2679.25 (18)	2716.89 (11)	3219.6 (2)
D_x [g cm^{-3}]	1.214	1.197	1.167
Crystal size [mm]	0.47×0.43×0.23	0.81×0.57×0.25	1.03×0.67×0.46
Crystal color, shape	colourless, prism	colourless, plate	colourless, cube
μ [mm^{-1}]	0.08	0.08	0.07
T_{min}, T_{max}	0.964, 0.983	0.940, 0.981	0.927, 0.967
Measured reflections	35092	21221	20544
Independent diffractions (R_{int} [a])	6137, (0.041)	6244 (0.023)	7370, (0.027)
Observed diffract. [I>2σ(I)]	4239	5518	5727
No. of parameters	329	329	383
R[b]	0.047	0.037	0.047
wR(F^2) for all data	0.117	0.085	0.111
GOF[c]	1.01	1.03	1.02
Residual electron density [e/Å^3]	0.32, −0.37	0.14, -0.16	0.27, −0.19

[a] $R_{int} = \Sigma \left| F_o^2 - F_{o,mean}^2 \right| / \Sigma F_o^2$; [b] $R(F) = \Sigma \left| \left| F_o \right| - \left| F_c \right| \right| / \Sigma \left| F_o \right|$; $wR(F^2) = [\Sigma(w(F_o^2 - F_c^2)^2)/(\Sigma w(F_o^2)^2)]^{½}$; [c] $GOF = [\Sigma(w(F_o^2 - F_c^2)^2)/(N_{diffrs} - N_{params})]^{½}$

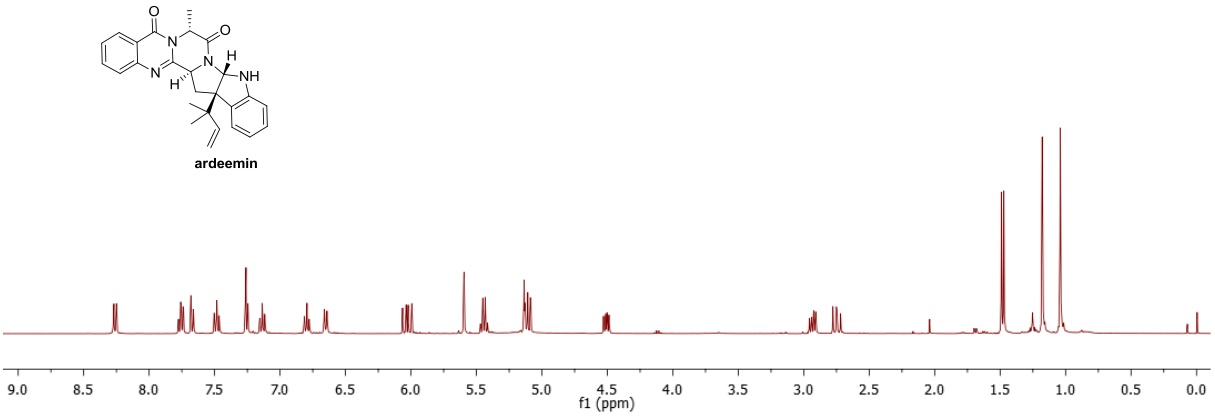
Table A5: Crystal data, data collection, and refinement parameters for ***cis*-5.25** and ***trans*-3.11d**

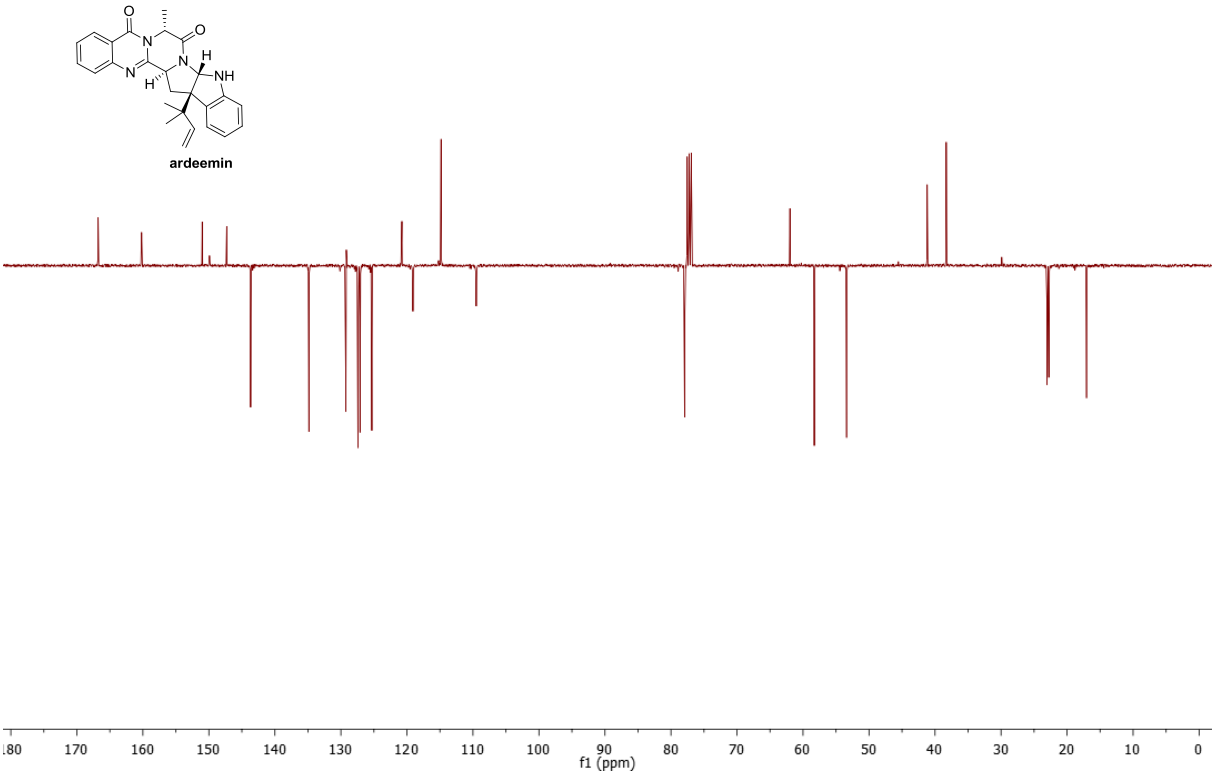
Compound	***cis*-5.25**	***trans*-3.11d**
CCDC	1457048	1457041
Formula	$C_{34}H_{41}N_3O_3$	$C_{26}H_{43}N_3O_5$
M.w.	539.70	477.63
Crystal system	Monoclinic	Monoclinic
Space group	*C*2/*c*	$P2_1/c$
a [Å]	17.7879 (5)	10.6707 (3)
b [Å]	12.5245 (4)	13.1169 (3)
c [Å]	29.8358 (11)	18.8958 (5)
α [°]		
β [°]	104.219 (1)	95.719 (1)
γ [°]		
Z	8	4
V [Å^3]	6443.3 (4)	2631.61 (12)
D_x [g cm^{-3}]	1.113	1.206
Crystal size [mm]	0.86×0.30×0.15	0.51×0.43×0.33
Crystal color, shape	colorless, bar	colorless, prism
μ [mm^{-1}]	0.07	0.08
T_{min}, T_{max}	0.942, 0.990	0.959, 0.973
Measured reflections	25450	31198
Independent diffractions *(R_{int} [a])*	7012 (0.024)	6026 (0.026)
Observed diffract. [I>2σ(I)]	5316	4825
No. of parameters	365	316
R[b]	0.042	0.037
wR(F^2) for all data	0.101	0.096
GOF[c]	1.05	1.02
Residual electron density [e/Å^3]	0.20, -0.19	0.33, -0.22

[a] $R_{int} = \Sigma \left| F_o^2 - F_{o,mean}^2 \right| / \Sigma F_o^2$; [b] $R(F) = \Sigma \left| \left| F_o \right| - \left| F_c \right| \right| / \Sigma \left| F_o \right|$; $wR(F^2) = [\Sigma(w(F_o^2 - F_c^2)^2)/(\Sigma w(F_o^2)^2)]^{½}$; [c] $GOF = [\Sigma(w(F_o^2 - F_c^2)^2)/(N_{diffrs} - N_{params})]^{½}$

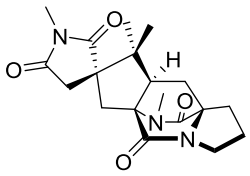
10. APPENDIX B: Copies of selected NMR spectra

10.1. ^{1}H and ^{13}C NMR of ardeemin

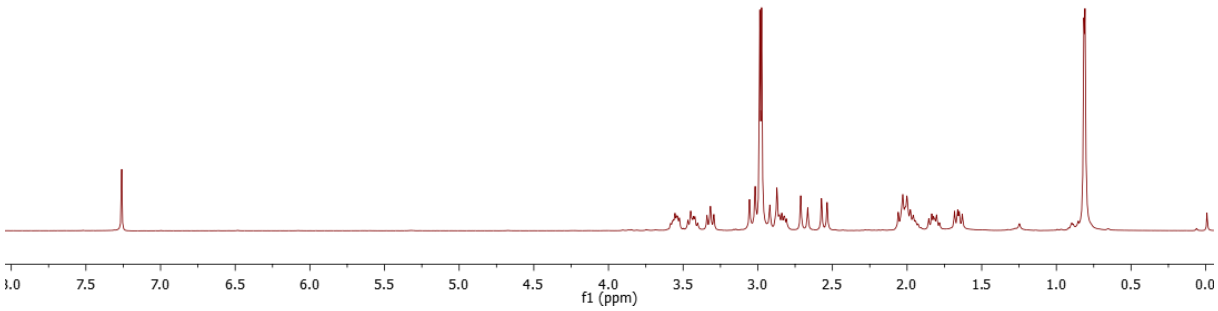


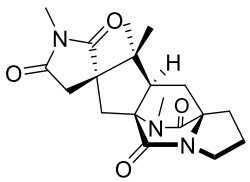


10.2. ^{1}H and ^{13}C NMR of 8-oxoasperparaline C in $CDCl_3$.



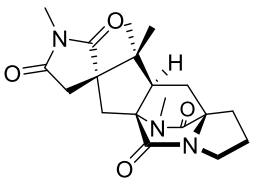
8-oxoasperparaline C



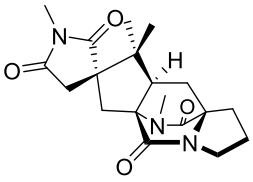


8-oxoasperparaline C

10.3. ^{1}H and ^{13}C NMR of 8-oxoasperparaline C in C_5D_5N.

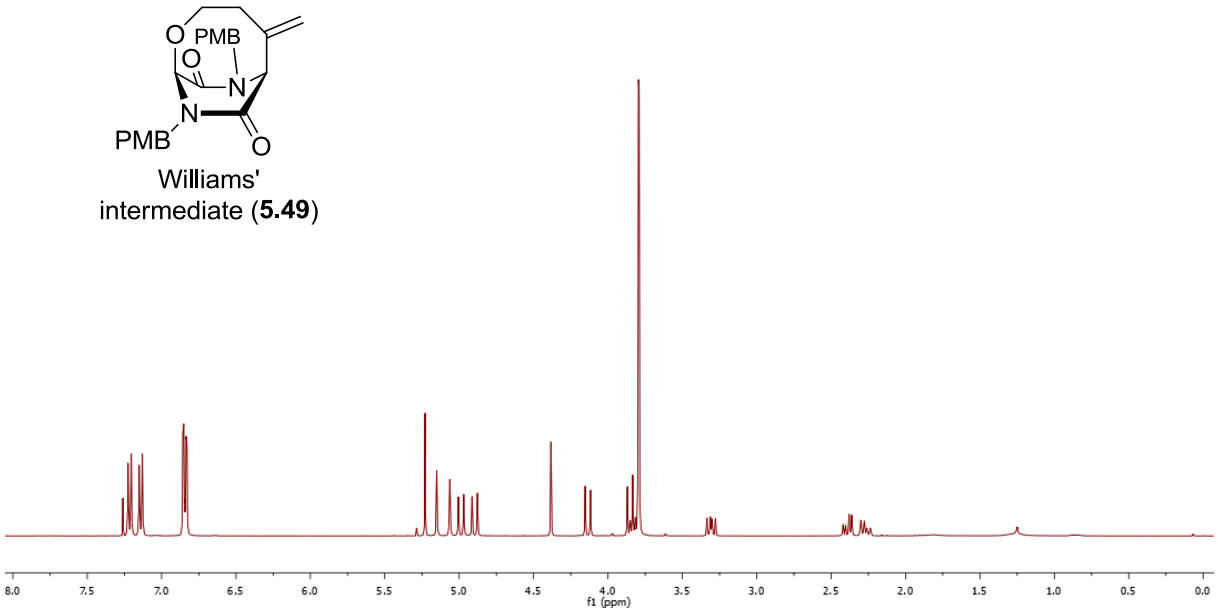


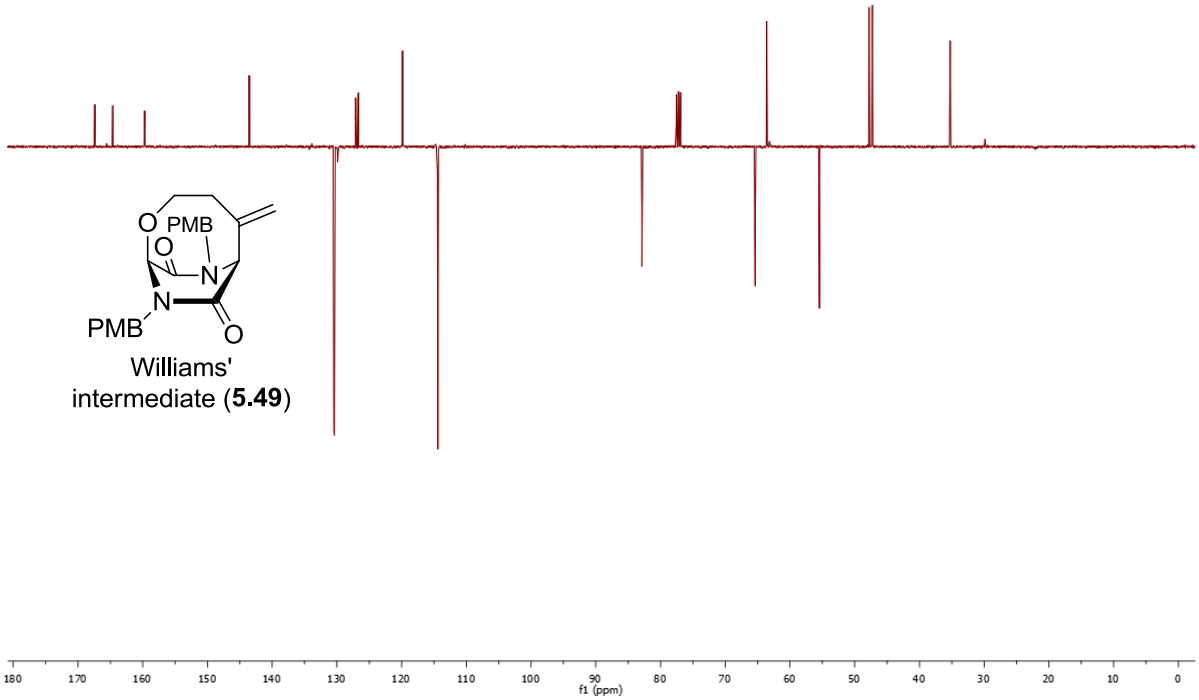
8-oxoasperparaline C



8-oxoasperparaline C

10.4. ^{1}H and ^{13}C NMR of precursor to bicyclomycin.





11. Abbreviations

AIBN	1,1'-Azobis(isobutyronitrile)
AMP	Adenosine monophosphate
BDE	Bond dissociation energy
brsm	Based on recovered starting material
DKP	Diketopiperazine
CDPS	Cyclodipeptide synthase
CAM	Cerium(IV) ammonium molybdate
CNS	Central nervous system
*m*CPBA	3-Chloroperbenzoic acid
CSA	Camphorsulfonic acid
DIPEA	*N*,*N*-Diisopropyl-ethylamine, Hünig's base
DMAP	4-Dimethylaminopyridine
DMP	Dess-Martin periodinane
FAD	Flavine adenine dinucleotide
FMN	Flavine mononucleotide
FGI	Functional group interconversion
HATU	1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate
HBTU	2-(1*H*-Benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate
nAChR	Nicotinic acetylcholine receptor
NMP	Nitroxide mediated polymerization
NRPS	Nonribosomal peptide synthetases
NOE	Nuclear Overhauser effect
PG	Protecting group
PIDA	(Bis(acetoxy)iodo)benzene
PINO	Phtalimide *N*-oxyl radical
PPTS	Pyridinium *p*-toluenesulfonate
PRE	Persistent radical effect
quant.	Quantitative
RAFT	Reversible addition-fragmentation chain transfer
RCM	Ring closing metathesis
ROESY	Rotating-frame nuclear Overhauser effect spectroscopy
r.t.	Room temperature
SET	Single electron transfer
SSA	Steady-state approaximation
TBAF	Tetrabutylammonium fluoride
TEMPO	(2,2,6,6-Tetramethylpiperidin-1-yl)oxyl
TFA	Trifluoroacetic acid
TFE	Trifluoroethanol
TMP	2,2,6,6-Tetramethylpiperidin-1-yl

Common abbreviations are adapted from *The ACS Style guide*.[115]

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13. PUBLICATIONS AND SCIENTIFIC PRESENTATIONS

Publications

1. T. Amatov, R. Pohl, I. Cisařová, U. Jahn, Synthesis of Bridged Diketopiperazine by Using the Persistent Radical Effect and a Formal Synthesis of Bicyclomycin. *Angew. Chem. Int. Ed.* **2015**, *54*, 12153–12157.
2. T. Amatov, U. Jahn, Gliotoxin: Nature's Way of Making the Epidithio Bridge. *Angew. Chem. Int. Ed.* **2014**, *53*, 3312–3314.
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4. I. V. Yampolsky, A. A. Kislukhin, T. T. Amatov, D. Shcherbo, V. K. Potapov, S. Lukyanov, K. A. Lukyanov, Synthesis and Properties of the Red Chromophore of the Green-to-Red Photoconvertible Fluorescent Protein Kaede and Its Analogs. *Bioorg. Chem.* **2008**, *36*, 96–104.

Presentations

1. T. Amatov, U. Jahn: A radical approach to asperparaline C. „Liblice-2015", Pokroky v organické, bioorganické a farmaceutické chemii, Olomouc, Czech Republic, November 6–8, 2014. (lecture)
2 T. Amatov, U. Jahn: A radical approach to asperparaline C. 6th French – Czech „Vltava" Chemistry Meeting, August 27–28, 2015, Brno, Czech Republic. (lecture)
3. T. Amatov, U. Jahn: Synthesis of diverse bridged diketopiperazines using the Persistent Radical Effect. EuCheMS Conference on Organic Free Radicals, Praha, Czech Republic, June 29–July 4, 2014. (lecture).
4. T. Amatov, U. Jahn: Radical approaches to bridged diketopiperazine alkaloids: a formal synthesis of bicyclomycin and progress toward asperparaline C. „Liblice-2014", Pokroky v organické, bioorganické a farmaceutické chemii, Lázně Bělohrad, Czech Republic, November 7–9, 2014. (lecture)
5. T. Amatov, U. Jahn: Studies towards biologically active bridged diketopiperazine alkaloids. XIV. Mezioborové setkání mladých biologů, biochemiků a chemiků, Milovy, Czech Republic, May 13–16, 2014. *Chem. Listy* **2014**, *108*, p. 521. (lecture)
6. T. Amatov, R. Pohl, I. Cisařová, U. Jahn: A new approach to diverse bridged diketopiperazines using the persistent radical effect (PRE). „Liblice-2013", Pokroky v organické, bioorganické a farmaceutické chemii. (poster presentation).

7. T. Amatov, U. Jahn: A new approach to diverse bridged diketopiperazines using the persistent radical effect (PRE). 11th International Conference on Free Radicals, Bern, Switzerland, July 1–5. (poster presentation)
8. T. Amatov, F. Rekhroukh, U. Jahn: Synthetic studies towards complex bridged alkaloids. 23rd Conference on Advances in Organic Synthesis, Hradec Králové, Czech Republic, June 26–30, 2011. (poster presentation)
9. T. Amatov, U. Jahn: Synthetic studies towards complex bridged alkaloids containing the diazabicyclo[2.2.2]octane core structure. „Liblice-2010“, Pokroky v organické, bioorganické a farmaceutické chemii, Nymburk, Czech Republic. *Chem. Listy* **2010**, *104*, p. 1068. (poster presentation)