SYNTHESIS OF CYCLIC HYDRAZINES
AND α-HYDRAZINO ACID DERIVATIVES
VIA N-ACYLHYDRAZONIUM IONS

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Synthesis of Cyclic Hydrazines
and α-Hydrazino Acid Derivatives
via N-Acylhydrazonium Ions

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door

Floris Petrus Johannes Theodorus Rutjes

geboren te Heiloo
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Co-promotor: Dr. H. Hiemstra

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aan Hans en Elly
aan Miranda
There is no finish line...
VOORWOORD

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ABBREVIATIONS

[α] specific rotation
Ac acetyl
Ala alanine
Alloc allyloxycarbonyl
Anal. analysis
APT attached proton test
Ar aryl
Bn benzyl
Boc tert-butoxycarbonyl
bp boiling point
Bu butyl
f-Bu tert-butyl
Bz benzoyl
calcd calculated
CBz benzylxycarbonyl
DBAD di-ierr-butyl azodicarboxylate
DBMP 2,6-di-tert-butyl-4-methylpyridine
DBU 1,8-diazabicyclo[5.4.0]undec-7-ene
DEAD diethyl azodicarboxylate
DIBAL-H diisobutylaluminum hydride
DMAP 4-(dimethylamino)pyridine
DMF N,N-dimethylformamide
DMPU 1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone
EI electron impact (in mass spectrometry)
Et ethyl
FMOC fluorenyl methoxycarbonyl
Gly glycine
HMPA hexamethylphosphoric triamide
HRMS high resolution mass spectrum
LDA lithium diisopropylamide
Me methyl
MOM methoxymethyl
mp melting point (range)
MS mass spectrometry
m/z mass to charge ratio (in mass spectroscopy)
NBS N-bromosuccinimide

NOE nuclear Overhauser effect
PFP pentafluorophenyl
Ph phenyl
Pr propyl
i-Pr isopropyl
pTSA para-toluene sulfonic acid monohydrate
Rf retention factor (in chromatography)
THF tetrahydrofuran
TLC thin layer chromatography
TMS trimethylsilyl, tetramethylsilane
CHAPTER 1
APPLICATIONS OF ORGANIC HYDRAZINE DERIVATIVES

1.1 INTRODUCTION

Hydrazine (N₂H₄) is an inorganic compound which is conveniently handled in its hydrated form (N₂H₄·H₂O). Hydrazine (pKₐ 7.95) is a weaker base than ammonia (pKₐ 9.24), but unlike amines, its basicity is lowered when alkyl substituents are introduced (Table 1.1).¹ The basicity is further decreased if the steric bulk on the nitrogen atoms is increased, e.g. tri- and tetraalkylhydrazines with groups larger than butyl are nearly non-basic. Introduction of electron-withdrawing or electron-delocalizing substituents at nitrogen will also cause a substantial lowering of the pKₐ.

Table 1.1

<table>
<thead>
<tr>
<th>Hydrazine</th>
<th>pKₐ of the protonated hydrazine</th>
</tr>
</thead>
<tbody>
<tr>
<td>N₂H₄</td>
<td>7.95</td>
</tr>
<tr>
<td>CH₃NHNH₂</td>
<td>7.85</td>
</tr>
<tr>
<td>CH₃NHNHCH₃</td>
<td>7.49</td>
</tr>
<tr>
<td>(CH₃)₂NNH₂</td>
<td>7.12</td>
</tr>
<tr>
<td>(CH₃)₂NNHCH₃</td>
<td>6.58</td>
</tr>
<tr>
<td>(CH₃)₂NN(CH₃)₂</td>
<td>6.10</td>
</tr>
</tbody>
</table>

Despite their relatively low basicity, hydrazine and its derivatives display a strong nucleophilic character and react more vigorously with alkylating agents and carbonyl compounds than amines. This phenomenon, known as the α-effect,² is more generally observed in compounds that possess two adjacent heteroatoms with unshared electron pairs. One of the possible explanations for this effect is based on the repulsion between the adjacent lone pairs, causing a raised ground state energy. In the transition state, this repulsion between the two lone pair orbitals is decreased, as one of the lone pairs becomes involved in bond formation with the electrophilic reagent. The α-effect is substantial for substitution at a carbonyl or at unsaturated carbon atoms, but is generally smaller or absent for substitution at saturated carbon atoms.

Hydrazine derivatives can occur in several oxidation states. Examples are the conjugated system 1, the hydrazone 2, the azo compound 3 or the saturated tetrasubstituted hydrazine 4.
Chapter 1

This thesis will mainly deal with synthesis and reactions of linear and cyclic tetrasubstituted hydrazine derivatives 4.

1.2 CONFORMATIONS OF HYDRAZINES

Compounds with adjacent heteroatoms are likely to adopt a conformation in which the lone pair orbitals on the heteroatoms are nearly perpendicular to each other (the dihedral angle $\theta \sim 90^\circ$, Scheme 1.1). This ‘gauche-effect’, as it is called, is rationalized by two principal factors: repulsion between the lone pair orbitals and attractive lone pair-adjacent bonding pair interactions.

Because of the relatively short N-N bond of cyclic hydrazines and the resultant large overlap between the lone pair orbitals, large torsional effects are observed. These effects cause that hydrazines form an attractive object for studies on conformational equilibria and the influence of the dihedral angle on the conformation of the hydrazines.

Scheme 1.1

The conformation of a cyclic hydrazine is a result of both steric and electronic interactions. As an example, 1,2-dimethylhexahydropyridazine exists only in the $5_{ee}$ and $5_{ae}$ conformation, while the $5_{aa}$ conformation is not found (Scheme 1.1). The $5_{ee}$ conformation is electronically destabilized ($\theta \sim 180^\circ$), but has the methyl groups in a favorable equatorial position. The $5_{ae}$ conformation is electronically more favored ($\theta \sim 60^\circ$), but has unfavorable 1,3-diaxial Me$_2$H interactions. If these diaxial interactions are reduced by introduction of a double bond, the $ee$ conformation is no longer observed so that tetrahydropyridazine 6 exists only in the $6_{ae}$ conformation.

Conformational changes at the nitrogens (inversion at nitrogen and rotation around the N-N bond) are also influenced by steric and electronic factors. Carbonyl substituents on the nitrogen atoms cause them to flatten completely if the lone pair orbitals can be perpendicular to each other, which is the most favored conformation (7).
Applications of organic hydrazine derivatives

If this is not possible, substantial deformation of the nitrogens from planarity can occur. For example, the average bond angle at nitrogen ($\alpha(\text{av})$) in 8 $\alpha(\text{av}) = 119.5^\circ$, whereas in the strained system 9 $\alpha(\text{av}) = 115.8^\circ$.7

Like tetraalkylhydrazines, tetrasubstituted $N,N'$-diacylhydrazines also show a high rotational barrier around the N-N bond.7,8 The origin of this barrier is partly steric, as rotation around the N-CO bond is necessary to force the acyl groups past the alkyl groups. But it also has been shown that compared to the tetraalkylhydrazines the electronic component of this barrier is increased which is explained by a rehybridization of the nitrogen lone pair orbitals to essentially pure p character, causing a larger overlap between these orbitals.

In order to study inversion at the nitrogen atoms,6 rotation around the N-N bond,7,8 conformations,9,10 and $pK_a$ values11 of hydrazines as well as other physical aspects of molecules containing an N-N moiety, numerous cyclic hydrazines have been synthesized and studied with various techniques like NMR,12 crystallography, cyclic voltammetry,13 and photoelectron spectroscopy.14

1.3 AZAANALOGS OF PHYSIOLOGICALLY ACTIVE COMPOUNDS

In the past, many attempts have been undertaken to influence the potency of biologically active substances by synthesizing analogs of these compounds. Main targets in increasing the potency of these compounds are the manipulation of receptor and enzyme interactions and also the extension of duration of action of these compounds by inhibiting the generally fast enzymatic degradation. Some examples will be given to illustrate the potency of hydrazines in the synthesis of analogs of physiologically active compounds.

1.3.1 AZAPEPTIDES

Peptide analogs have been synthesized by either modification of the side chain or of the backbone structure of the amino acids, in such a way that the original structure and conformation of the peptide are largely preserved.

One compound class which looks promising as peptide analogs consists of the so-called azapeptides11,14

\[
\begin{align*}
\text{10} & \quad \text{11}
\end{align*}
\]

Compared with ordinary peptides 10, the $\alpha$-CH group in one or more amino acid residues is replaced by a nitrogen atom. One advantage of these compounds is the unproblematic synthetic
accessibility which enables any amino acid to be exchanged, irrespective of its position in the original peptide. Analogs of various amino acids have been reported, which include more complex amino acids such as tyrosine,\(^\text{15}\) tryptophan,\(^\text{15}\) asparagine,\(^\text{16}\) ornithine,\(^\text{17}\) proline,\(^\text{18}\) glutamic acid,\(^\text{19}\) and pyroglutamic acid.\(^\text{15}\)

Several decades ago, the first stepwise synthesis of such chain molecules was described,\(^\text{20}\) while Hess \textit{et al.} reported the first natural product analog of this type namely [Azaval\(^3\)]-angiotensin II (12).\(^\text{21}\) Through these studies, an impetus was given to further research directed at the synthesis of natural product analogs of biological interest.

\[
\begin{array}{cccccccccccc}
1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 \\
\text{Asp-Arg-Azaval-Tyr-Val-His-Pro-Phe} & \\
\end{array}
\]

12

From a purely structural point of view, the CH/N exchange does not cause a major change in the conformation of a peptide as atomic distances, bond angles, and side chains remain the same. On the other hand, the chirality at the \(\alpha\)-center is lost and the area of planarity is extended.\(^\text{16}\) This causes a change of conformational freedom, allowing the side chains to take up a conformation somewhere between the D- and L-conformation of the original amino acid.

Measurements have confirmed that the acidity of the NH function attached to the \(\alpha\)-N atom is higher than in normal amino acids.\(^\text{22}\) This higher acidity favors hydrogen bonding, but prevents protonation at physiological pH.\(^\text{23}\) Thus, the modified 'local' configuration and the higher NH acidity will affect absorption, transport, enzyme/receptor binding and metabolic stability of the analog of a biologically active substance in the organism.

The physiological effects of local changes also strongly depend on other interactions in the peptide. Formation of H-bonds and the presence of Van der Waals and charge-transfer interactions in other parts of the molecule can largely 'restore' the shape of the original molecule.\(^\text{24}\) Of course, this will be more likely for larger than for smaller peptides.

The biological importance of the azapeptides will be demonstrated with only a few examples; many azaanalogs have been reported in various fields of action with promising inhibiting or stimulating effects.\(^\text{14d}\) Some noteworthy results were found with azaanalogs of the decapeptide hormone luliberin (LHRH) (13).

\[
\begin{array}{cccccccccccc}
1 & 2 & 3 & 4 & 5 & 6 & 7 & 8 & 9 & 10 \\
\text{Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly-NH\_2} & \\
\end{array}
\]

13

It proved to be possible to prepare strong agonists with an ovulation-inducing effect, as well as antagonists causing total ovulation inhibition. The agonistic analogs with [Azagly\(^6\)], [Azagly\(^10\)] and [Azaala\(^6\)] residues were many times more active than luliberin itself.\(^\text{14d}\) If the [Azagly\(^10\)] analog was substituted in the 6-position with the lipophilic amino acid 3-(2-
naphthyl)-D-alanine, it was shown to be 100-230 times more active than luliberin.\textsuperscript{25} Furthermore, [D-Ser(r-Bu)\textsuperscript{6}, Azagly\textsuperscript{10}]-LHRH was introduced into the pharma market as a drug for treating carcinoma of the prostate.\textsuperscript{26}

1.3.2 \(\alpha\)-HYDRAZINO ACIDS

In addition to \(N\)-alkylated \(\alpha\)-amino acids\textsuperscript{27} and \(N\)-hydroxy-\(\alpha\)-amino acids\textsuperscript{28} another class of analogs of \(\alpha\)-amino acids \textsuperscript{14} consists of the so-called \(\alpha\)-hydrazino acids \textsuperscript{15}, in which the amino function is replaced by a hydrazino function. As a result of their strong resemblance to the corresponding \(\alpha\)-amino acids, \(\alpha\)-hydrazino acids are potential inhibitors of certain amino acid metabolizing enzymes, especially ammonia lyases\textsuperscript{29} and pyridoxal phosphate dependent proteins.\textsuperscript{30} Other hydrazino acids possess antibiotic activity or produce interesting physiological effects.\textsuperscript{31}

\[
\begin{align*}
14 & \quad H_2N_{\text{R}}\text{O}H \\
15 & \quad H_2\text{NN}_{\text{R}}\text{O}H
\end{align*}
\]

Syntheses of these compounds have been achieved by reduction of \(\alpha\)-diazo esters,\textsuperscript{32} nitrosation and reduction of amino acids,\textsuperscript{33} Hofmann rearrangement of \(\alpha\)-ureido acids\textsuperscript{34} and treatment of \(\alpha\)-halocarboxylic acids with hydrazine.\textsuperscript{35} However, these methods often suffer from low yields and loss of optical purity. Some new methods have been introduced, which are based on amination of silyl enol ethers and lithium enolates with azodicarboxylates.\textsuperscript{31,36} More recently, \(\alpha\)-hydrazino acids were prepared by reaction of \(r\)-butyl carbazate with \(2-\{((4\text{-nitrobenzene})sulfonyl)oxy\}(2\text{-nosyloxy})\) esters and \(2\text{-triflyloxy}\) esters in high yields.\textsuperscript{37}

\[
\text{L-156,602 (16)}
\]

\(\alpha\)-Hydrazino acids also occur in nature, although infrequently. Examples are hexa- or
tetrahydropyridazine-3-carboxylic acids (piperazic acids), which are incorporated in larger molecules. One of them is the cyclic hexadepsipeptide antibiotic L-156,602 (16),\textsuperscript{38} which was isolated from cultures of Streptomyces sp. MA6348.\textsuperscript{39} In this molecule two of such piperazic acid moieties are present in the large ring. These piperazic acid residues have also been used as a building block in analogs of A.C.E. inhibitors.\textsuperscript{40}

\[
\text{(-)-negamycin (22)}
\]

A linear naturally occurring α-hydrazino acid is (+)-negamycin (22),\textsuperscript{41} an antibiotic that was isolated from cultures of the Streptomyces purpeofuscus. Several total syntheses of this molecule have been published.\textsuperscript{42}

1.3.3 β-LACTAM TYPE ANTIBACTERIALS

β-Lactam antibiotics act by binding to and inhibiting the action of various transpeptidase/carboxypeptidase enzymes (the penicillin-binding proteins (PBPs)) which are involved in the synthesis of bacterial cell wall peptidoglycan. A ‘fit’ at the active site of the enzyme and a reactive β-lactam ring are both necessary for acylation and inhibition of these enzymes. While searching for new classes of antibiotics,\textsuperscript{43} many compounds were tested in which the β-lactam ring system was replaced by a chemically activated γ-lactam ring system. Among these substances were the bicyclic pyrazolidinone LY 186826 (23)\textsuperscript{44} and the tetrahydropyridazinone 24.\textsuperscript{45}

These bicyclic pyrazolidinones were the first non-β-lactam containing compounds that were reported to bind to the PBPs. Especially, LY 186826 (23) showed a very strong activity in inhibiting bacterial cell wall synthesis, which is even larger than that of several penicillins and cephalosporins.\textsuperscript{44} The homologous bicyclic tetrahydropyridazinone 24 was also expected to be sufficiently reactive to exhibit antibacterial activity. However, no activity was found in the tests, which was explained, after various modeling experiments, by the presence of too much steric bulk of the tetrahydropyridazinone ring, which hinders good binding to the PBPs.
1.3.4 β-TURN MIMICS

Several conformationally restricted nonpeptide mimetics were designed by Kahn et al. in order to investigate the relationship between peptide structure and function. Among these systems, both 26 and 27 were synthesized as a mimetic of a type I β-turn (25).46,47

![Molecular structures of 25, 26, and 27](image)

Stimulated by molecular modeling experiments of the interactions between inhibitors and the enzyme HIV-1 protease, both systems 26 and 2748 were connected to a peptide chain and tested for their activity in inhibiting HIV-1 protease.49 This enzyme is essential for viral replication and thus represents an ideal target for antiviral therapy. The β-turn mimetics 26 and 27 proved to exhibit moderate to good activity against HIV-1 protease and might therefore serve as lead compounds for the development of more potent HIV-1 inhibitors.

1.4 N-N-BONDS AS A TOOL IN ORGANIC CHEMISTRY

Hydrazines possess, compared with C-C bonds, relatively weak N-N bonds which are easily oxidized to N-N double bonds, cleaved or which rearrange to the corresponding amides or medium-sized lactams. Therefore, a hydrazine moiety in a molecule can serve as a versatile tool for further transformations. Some applications of these possibilities will be illustrated.

1.4.1 CLEAVAGE OF N-N BONDS

Reductive cleavage of N-N bonds in hydrazines has been achieved by various methods such as hydrogenation,50 reduction with diborane,51 electroreduction52 and reduction with Raney nickel53 and dissolving metals.54 This approach is not often used, but can be a suitable method for the synthesis of cyclic amines and lactams that are less easily accessible via other sequences.

In general, it appears that the ease of the reduction is strongly related to the structure of the hydrazine that is involved. The ease of the reduction can be enhanced by relief of strain in the system, but also by substitution of the hydrazine with one or more acyl functions.55
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This concept has been applied in the synthesis of some natural products like saxitoxin,\textsuperscript{56} celacinnine\textsuperscript{57} and glidobactin antibiotics.\textsuperscript{58} An example of the reduction with a dissolving metal is the reaction of the bicyclic hydrazine 28 with Na in NH\textsubscript{3} to give the nine-membered azalactam 29 (eq 1.1), which is a key intermediate in the synthesis of the alkaloid celacinnine.\textsuperscript{57}

1.4.2 THE 3,4-DIAZA-[3,3]-SIGMATROPIC REARRANGEMENT

The 3,4-diaza-[3,3]-sigmatropic rearrangement has often been applied in synthetic organic chemistry.\textsuperscript{59} Both aromatic and aliphatic versions of this reaction are known. An important example of the aromatic rearrangement is found in the Fisher indole synthesis (eq 1.2), in which the first step, the conversion of an enylhydrazine 30 to a diimine 31, is believed to proceed via such a rearrangement.\textsuperscript{59,60}

\begin{equation}
R \begin{array}{c}
N \\
Me
\end{array} \begin{array}{c}
N \\
Me
\end{array} \rightarrow R \begin{array}{c}
N \end{array} \begin{array}{c}
N \\
Me
\end{array} \rightarrow R \begin{array}{c}
N \end{array} \begin{array}{c}
N \\
Me
\end{array}
\end{equation}

After the sigmatropic shift, the diimide reacts further with loss of methylamine to the indole 32. Aliphatic versions of the rearrangement are also possible, starting from substituted bis(eny1)-hydrazines and leading to the corresponding substituted pyrroles.\textsuperscript{61}

Recently, this methodology was extended to an anionic 3,4-diaza-[3,3]-sigmatropic rearrangement.\textsuperscript{62}

\begin{equation}
\begin{array}{c}
\text{Ph} \\
\text{O}
\end{array} \begin{array}{c}
\text{N} \\
\text{O}
\end{array} \rightarrow \begin{array}{c}
\text{Ph} \\
\text{OLi}
\end{array} \begin{array}{c}
\text{N} \\
\text{OLi}
\end{array} \rightarrow \begin{array}{c}
\text{Ph} \\
\text{OLi}
\end{array} \begin{array}{c}
\text{N} \\
\text{OLi}
\end{array} \rightarrow \begin{array}{c}
\text{Ph} \\
\text{H}
\end{array} \begin{array}{c}
\text{N} \\
\text{H}
\end{array} \begin{array}{c}
\text{Ph} \\
\text{O}
\end{array}
\end{equation}

An interesting example of this anionic sigmatropic shift is shown in eq 1.3. The diacylated pyrazolidine 33 is converted into the dienolate 34 by deprotonation with LDA, which immediately rearranges to the medium-sized ring system 35. Protonation affords the medium-
1.4.3 PHOTOCHEMICAL REARRANGEMENT TO N-AMINO β-LACTAMS

A novel approach for the synthesis of β-lactams from 3-pyrazolidinones was presented by Johnson et al. and further elaborated by White and co-workers. Irradiation of the (substituted) 3-pyrazolidinones 37 afforded in moderate to good yields the N-amino substituted azetidinones 40.

The proposed mechanism for this photochemical rearrangement is shown in eq 1.4.

\[
\begin{align*}
37 & \xrightarrow{\text{hv, } \lambda < 300 \text{ nm}} \text{biradical } 38 \\
& \overset{\text{biradical 38}}{\xrightarrow{\text{bicyclic diaziridinium ion 39}}} \text{azetidinones 40}
\end{align*}
\]

Irradiation of the pyrazolidones 37 with light (\(\lambda < 300 \text{ nm}\)) will give the biradical 38, that reacts via the bicyclic diaziridinium ion 39 to the N-amino-β-lactams 40. The cleavage of the diaziridinium C-N bond is assisted by the presence of the electron-withdrawing acetyl substituent at the nitrogen atom, ensuring that the reverse reaction is not taking place.

1.5 THE REACTIVITY OF (SUBSTITUTED) IMINIUM IONS

Iminium ions 41 and 42 are well-known to react in inter- and intramolecular processes as electrophilic species with various nucleophiles like alkenes, alkynes, arenes, silyl enol ethers, allylsilanes and vinylsilanes. They are, therefore, useful intermediates in the synthesis of numerous azacycles 43 and natural products.

The conjugate base of an iminium ion, *i.e.* an imine or enamine, is a relatively strong base, which facilitates the formation of the iminium ion. Thus, the iminium ion can be generated under almost neutral conditions.

Introduction of electron-withdrawing substituents onto nitrogen renders the imine less basic and thus makes the formation of the iminium ion more difficult. $N$-Acyliminium ions, as an example, can be generated only under acidic conditions. Recently, Seebach and co-workers
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showed that after introduction of a formyl or nitro function on nitrogen the resulting iminium ions were strongly destabilized. By using *ab initio* calculations, they compared the reactivity of an N-formyliminium (45) and an N-nitroiminium ion (46) with an oxycarbenium ion, present in the same molecule (eq 1.5). The formyl group destabilizes the iminium ion, but leaves it still more stable than the oxycarbenium ion, so that product 44 will be formed. The nitro group appears such a strongly electron-withdrawing group that reaction will take place with the opposite regiochemical outcome as a result of the relatively more stable oxycarbenium ion.

The above reasoning leads to the expectation that introduction of an amino function should have a similar effect, as the inductive electron-withdrawing effect of the nitrogen atom will be more important than the mesomeric electron-donating influence. The latter can be visualized by considering the unlikely resonance structure 49 that will be formed by resonance stabilization of the positive charge of the hydrazonium ion 48 (eq 1.6).

Although an enhancement of the reactivity is expected, this type of intermediate has, in contrast with N-oxygen substituted iminium ions, never been used in electrophilic addition reactions. In the literature, some examples are known in which hydrazonium ions are generated. They are obtained as the stable salts 51 and 53 from the corresponding hydrazones 50 and 52 upon alkylation (eq 1.7) or protonation with a strong acid (eq 1.8).

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{E} \\
44 & \quad 1) \text{E}^+ \quad 2) \text{Nuc}^-
\end{align*}
\]

(eq 1.5)

\[
\begin{align*}
\text{Nuc} \quad 45 \quad X = \text{CHO} \\
46 \quad X = \text{NO}_2 \\
47 & \quad 1) \text{E}^+ \quad 2) \text{Nuc}^-
\end{align*}
\]

(eq 1.5)

\[
\begin{align*}
\text{48} & \quad \begin{pmatrix}
\text{N}^+ \\
\text{Y} \\
\text{N}^+ \\
\text{Y}
\end{pmatrix} \\
\text{49} & \quad \begin{pmatrix}
\text{N}^+ \\
\text{Y} \\
\text{N}^+ \\
\text{Y}
\end{pmatrix}
\end{align*}
\]

(eq 1.6)

Although an enhancement of the reactivity is expected, this type of intermediate has, in contrast with N-oxygen substituted iminium ions, never been used in electrophilic addition reactions. In the literature, some examples are known in which hydrazonium ions are generated. They are obtained as the stable salts 51 and 53 from the corresponding hydrazones 50 and 52 upon alkylation (eq 1.7) or protonation with a strong acid (eq 1.8).
Applications of organic hydrazine derivatives

![Equation 1.8](image)

Other derivatives of these hydrazonium structures are the ylide-like intermediates 54 which consist of a hydrazonium part which is both positively and negatively charged. These ylides are stable structures, which serve as useful dipolarophiles in both inter- and intramolecular cycloaddition reactions (eq 1.9) with olefins and acetylenes to give various bicyclic hydrazines. Hydrolysis of these ylides leads to the deprotected hydrazines. It has been shown that nucleophilic addition reactions can be carried out with the anionic part, whereas the iminium part has been used as an electrophile in Grignard addition reactions.

![Equation 1.9](image)

The more reactive equivalents of iminium ions, the N-acyliminium ions, have proven to be extremely useful intermediates in cyclization reactions as they react readily with a variety of nucleophiles. In addition to hydrazonium ions and N-acyliminium ions, N-acylhydrazonium ions such as 56 are expected to be even more destabilized as a result of the combined effect of the two electron-withdrawing substituents. These species might therefore display a high reactivity in intramolecular addition reactions (eq 1.10).

![Equation 1.10](image)

Such a reactivity would make them useful intermediates in the synthesis of cyclic hydrazine derivatives 57. The reactivity of N-acylhydrazonium ions has not been described in the literature.

1.6 NUCLEOPHILES IN INTRAMOLECULAR ADDITION REACTIONS

As stated earlier, numerous nucleophiles have been used in intramolecular additions. Overman et al. compared the reactivity of several π-nucleophiles in intramolecular reactions of
Chapter 1

iminium ions in acetonitrile. For example, in the case of amine 58 (eq 1.11), the unsubstituted (Z)-vinylsilane reacts faster than the substituted (Z)-vinylsilane moiety as is concluded from the ratio of the six-membered tetrahydropyridines 59 and 60.

\[
\text{Me}_3\text{Si}\text{CH}_2\text{C}_6\text{H}_4\text{SO}_2\text{H} + \text{MeCN, 80 °C} \quad \begin{array}{c}
\text{(eq 1.11)}
\end{array}
\]

In this type of reaction, it was found that allylsilanes 61 show the highest reactivity, followed by the substituted olefin 62, which in turn is more reactive than both vinylsilanes 63 and 64. The unsubstituted olefin 68 showed a reactivity which is equal to that of the unsubstituted phenyl group 66 (eq 1.12).

\[
\begin{array}{cccccc}
61 & > & 62 & > & 63 & > & 64 & > & 65 \\
66 & \gg & 67 & \gg & 68 & \\
\end{array} \quad \text{(eq 1.12)}
\]

The high nucleophilicity of allylsilanes\(^\text{76}\), propargylsilanes and vinylsilanes\(^\text{76}\) in this type of cyclization reactions can be explained by invoking the \(\beta\)-effect.\(^\text{77}\) The double or triple bond of the silane is more nucleophilic as the positive charge of the intermediate 70 can be stabilized by the silicon atom. This is only possible if the positive charge develops at the \(\beta\)-position with respect to the silicon atom, so that a strong directive effect is observed as well (eq 1.13). Attack of a nucleophile on silicon then leads to the formation of the olefin 71.

\[
\begin{array}{cccc}
69 & \xrightarrow{\text{E}^+} & 70 & \xrightarrow{\text{Nuc}} & 71 \\
& & + & \text{NucSiMe}_3 & \quad \text{(eq 1.13)}
\end{array}
\]

There is evidence that the conversion shown in eq 1.13 is not a concerted reaction, in which nucleophilic attack at the silicon atom and attack of the olefin are taking place.
simultaneously, but that the whole process occurs in two steps, with the carbocation 73 as an intermediate. The stabilization of the positive charge may occur either via the three-membered ring siliconium ion 72 in which pentavalency of silicon is permitted by its d-orbitals, or by hyperconjugation (74) as shown in eq 1.14.

In both cases, the positive charge is stabilized by the less electronegative silicon atom. In addition to these mesomeric effects, there is also the inductive effect of the more electropositive silicon which assists in stabilizing the positive charge.

Throughout this thesis, several of the above nucleophiles will be subjected to reaction with N-acylhydrazonium ions in order to prepare new cyclic hydrazine derivatives.

1.7 PURPOSE OF THE INVESTIGATION

In this thesis, the reactivity and the usefulness of several types of N-acylhydrazonium ions in the synthesis of cyclic hydrazine derivatives will be discussed.

In Chapter 2, the synthesis of simple hydrazines via cyclizations with N,N'-diacylhydrazonium ions as intermediates will be detailed.

In Chapter 3, attention will be focused on the deprotection of cyclic hydrazines, in which both nitrogens are protected with allyloxycarbonyl functions.

In Chapter 4, endocyclic N-acylhydrazonium ions will be utilized in the synthesis of bridged bicyclic hydrazines.

In Chapter 5, the synthesis of an azadervative of cocaine will be described as well as some studies towards a synthetic route to chiral bridged azabicycles.

In Chapter 6, exocyclic N-acylhydrazonium ions are applied in the synthesis of bicyclic [3.3.0] and [4.3.0] pyrazolidinones. In this way, both simple bicyclic hydrazines and bicyclic α-hydrazino esters were prepared.

In Chapter 7, α-methoxycarbonyl substituted N-acylhydrazonium ions are applied in the synthesis of cyclic α-hydrazino acids.

Parts of this thesis have already been published. 78
Chapter I

Applications of organic hydrazine derivatives


Chapter 1


Applications of organic hydrazine derivatives

CHAPTER 2
SYNTHESIS OF CYCLIC HYDRAZINE DERIVATIVES VIA
N,N'-DIACYLHYDRAZONIUM INTERMEDIATES

2.1 INTRODUCTION

Substituted cyclic hydrazine derivatives of type 1 are known compounds which have been synthesized via several methods. Among these methods, one of the most important reactions for the synthesis of six-membered rings is the hetero Diels-Alder reaction of azo diesters with 1,3-dienes. Methods for the synthesis of other rings include: dialkylation of hydrazo 1,2-diesters with α,ω-dihalides, α,ω-dimesylates or α,ω-ditosylates, and reductive condensation of hydrazines with α,ω-dialdehydes. In this Chapter, attention will be focused on a novel approach for the synthesis of this type of compound, which will lead to a larger choice of cyclic hydrazines of different ring sizes and with various substitution patterns. The outline of the method is given in eq 2.1 in retrosynthetic form.

The cyclic hydrazines are formed by an intramolecular attack of the internal nucleophile at the electrophilic 1,2-diacylhydrazonium ion 2. The hydrazonium ions 2 are generated from the precursors under the influence of a Lewis or a Brønsted acid. These precursors, in turn, are obtained upon alkylation of the azodicarboxylates 4 with a nucleophilic side chain and a methoxymethyl function.

Compared with the well-investigated N-acyliminium ions, the N,N'-diacylhydrazonium ions bear an extra electron-withdrawing substituent i.e. an amide function. This substituent will have an extra destabilizing effect on the positive charge, thus resulting in relatively difficult formation and a more electrophilic character of the hydrazonium ions relative to the corresponding iminium ions.
Chapter 2

It might be somewhat naive to expect that this increased electrophilicity will lead to a higher reactivity. It is important to take into account that in this type of intermediate, there is an sp²-center at the α-position relative to the iminium part, which might influence the transition state of the cyclization reaction. Furthermore, the amide function is a reasonably good leaving group, which might cause cleavage of the relatively weak N-N bond prior to formation of the hydrazonium ion. Another problem could be that the more severe conditions which are required for formation of the intermediates, will give rise to side reactions or decomposition.

2.2 SYNTHESIS OF THE AZO ESTERS

An example of the synthesis of azo esters is presented in eq 2.2. Generally, hydrazine hydrate is easily 1,2-diacylated with a chloroformate to give the corresponding hydrazo 1,2-diester 7, which can be further oxidized to the azoester 8. Several methods are known for this oxidation, but in the case of the diallylhydrazo ester 7, only treatment with Pb(OAc)₄ in cold CH₂Cl₂ gave a satisfying result. Other azodicarboxylates (dimethyl, diethyl, diisopropyl or di-tert-butyl) are all commercially available.

\[
\begin{align*}
\text{H₂NNH₂H₂O} & \xrightarrow{\text{K₂CO₃ (1 equiv) \text{EtOH/H₂O, 0 °C}}} \text{Alloc-NH} \text{Alloc-NH} \xrightarrow{\text{Pb(OAc)₄ (1 equiv) \text{CH₂Cl₂, 0 °C}}} \text{Alloc-N, Alloc-N} \\
& \text{eq 2.2}
\end{align*}
\]

2.3 SYNTHESIS OF THE HYDRAZIDES

Monoalkylated hydrazo esters 9 can be synthesized via different methods, such as ene reactions of olefins with azodicarboxylates and 1,4-additions to azodicarboxylates. By using the latter route, alkyl- and aryllithium compounds, lithium enolates (eq 2.3) and silyl enol ethers have been aminated via a 1,4-addition. However, only one example of an addition of a Grignard reagent to azo esters is known.

\[
\begin{align*}
\text{R}^1\text{MgX} & \xrightarrow{-78 °C \rightarrow \text{rt}} \text{R}^1\text{N-CO₂R} \\
& \text{eq 2.3}
\end{align*}
\]

Although in that procedure the reaction was carried out at 0 °C, it was found that better results were obtained if the addition was performed at -78 °C by slowly adding the Grignard reagent to a slurry of the azo ester 4 in ether or THF (eq 2.3).
Table 2.1. Addition reactions to azodicarboxylates.

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>alkylating agent</th>
<th>hydrazide (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF</td>
<td></td>
<td>( \text{RO}_2\text{C} - \text{N} - \text{O}_n )</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>( \text{Cl} )</td>
<td>n = 1: 10 ( R = \text{Me} ) (25%)</td>
</tr>
<tr>
<td>3</td>
<td>ether</td>
<td>( \text{Br} )</td>
<td>n = 2: 11 ( R = t)-Bu (40%)</td>
</tr>
<tr>
<td>4</td>
<td>ether</td>
<td>( \text{Br} )</td>
<td>12 ( R = \text{Me} ) (51%)</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>( \text{Cl} )</td>
<td>n = 3: 13 ( R = \text{Me} ) (53%)</td>
</tr>
<tr>
<td>6</td>
<td>ether</td>
<td></td>
<td>Me(\text{O}_2\text{C} - \text{N} - \text{H} )</td>
</tr>
<tr>
<td>7</td>
<td>ether</td>
<td>( \text{Cl} )</td>
<td>14 (70%)</td>
</tr>
<tr>
<td>8</td>
<td>ether</td>
<td>( \text{Br} )</td>
<td>15 (38%)</td>
</tr>
</tbody>
</table>
| 9     | ether   | Me\(\text{Si} - \text{Cl} \) | 16 \( R = \text{Me} \) (79%)
| 10    | THF     | Me\(\text{Si} - \text{Cl} \) | 17 \( R = i\)-Pr (65%)
| 11    | THF     | Me\(\text{Si} - \text{Cl} \) | 18 (28%)
| 12    | THF     | Me\(\text{Si} - \text{Cl} \) | 19 (28%)
| 13    | DMF     | Me\(\text{Si} - \text{Cl} \) | 20 (28%)
| 14    | neat    | Me\(\text{Si} - \text{Cl} \) | 21 \( R = \text{Me} \) (64%)
| 15    | neat    | Me\(\text{Si} - \text{Cl} \) | 22 \( R = \text{Et} \) (63%)
| 16    | neat    | Me\(\text{Si} - \text{Cl} \) | 23 \( R = \text{allyl} \) (55%)
| 17    | neat    | Me\(\text{Si} - \text{Cl} \) | 24 (37%)
| 18    | neat    | Me\(\text{Si} - \text{Cl} \) | 25 (37%)
| 19    | neat    | Me\(\text{Si} - \text{Cl} \) | 26 (82%)
Chapter 2

The results of these addition reactions are summarized in Table 2.1. The choice of alkenyl halides and azodicarboxylates was primarily aimed at determining the scope of this method. The iodides 18\(^1\) and 24\(^2\) were prepared from the corresponding alcohols\(^2\) via the mesylates, whereas bromide 20 was prepared from the alcohol\(^2\) via the tosylate.\(^2\)

The addition reaction usually proceeded in moderate to good yields, although in some cases (entries 6 and 9) rather low yields were obtained. These latter unsatisfactory results could be partly explained by incomplete conversion of the halides into the corresponding Grignard reagents, which was concluded from the amount of unreacted magnesium that was recovered after the reaction. The results in the Table also show that variation of the protective groups does not lead to significant changes in the yield of the addition reaction.

It appeared that hydrazide 25 could not be prepared via a Grignard addition. This is probably due to a rearrangement of the Grignard reagent. The compound was eventually synthesized by a simple alkylation of the hydrazo ester 7 (NaH (1.1 equiv), DMF, 0 °C → rt) with the suitable iodide 24.

In order to obtain the vinylsilane 27, another route was chosen.\(^3\) If dimethyl azodicarboxylate was heated in allyltrimethylsilane (1 equiv), an ene reaction occurred (eq 2.4) to produce a 1:1.5 mixture of (E-) and (Z)-isomers in almost quantitative yield (according to \(^1\)H NMR data of the crude product). After distillation, the pure (E)/(Z)-mixture was obtained in 82% yield.

2.4 LEWIS ACID-MEDIATED CYCLIZATION REACTIONS

The cyclization precursors 28-38 could be obtained in a straightforward manner upon deprotonation with NaH and subsequent alkylation with chloromethyl methyl ether in DMF. In this way, a C\(_1\) unit with a good leaving group was introduced. These alkylations proceeded in fair yields, as summarized in Table 2.2. Under these conditions hydrazide 21 was found to give a considerable amount of the desilylated product. After treatment of the crude mixture with CsF/n-Bu\(_4\)NF in THF, 36 was obtained in 49% yield.

From the same Table, it is evident that the yields of the cyclization reactions vary. At first, some attempts were made to cyclize the di-tert-butoxycarbonyl precursor 29. This would lead to cyclic hydrazines protected with tert-butoxycarbonyl functions, which can be removed under relatively mild acidic conditions. This acid-lability, however, seriously thwarted the cyclization reactions.

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Table 2.2. Lewis acid-mediated cyclizations.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cyclization precursor (yield)</th>
<th>Lewis acid</th>
<th>Cyclization product(s) (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{RO}<em>2\text{C}</em>\text{N}<em>\text{O}</em>\text{Me} )</td>
<td>( \text{TiCl}_4 )</td>
<td>( \text{RO}<em>2\text{C}</em>\text{N}_\text{Cl} )</td>
</tr>
<tr>
<td>2</td>
<td>( n = 1: \text{R} = \text{Me} ) (90%)</td>
<td>( \text{TiCl}_4 )</td>
<td>( n = 1: \text{R} = \text{Me} ) (32%)</td>
</tr>
<tr>
<td>3</td>
<td>( n = 2: \text{R} = \text{t-Bu} ) (95%)</td>
<td>( \text{TiCl}_4 )</td>
<td>( n = 2: \text{R} = \text{Me} ) (80%)</td>
</tr>
<tr>
<td>4</td>
<td>( n = 3: \text{R} = \text{Me} ) (89%)</td>
<td>( \text{TiCl}_4 )</td>
<td>( n = 3: \text{R} = \text{Me} ) (15%)</td>
</tr>
<tr>
<td>5</td>
<td>( \text{Me}<em>2\text{OC}</em>\text{N}<em>\text{O}</em>\text{Me} ) (87%)</td>
<td>( \text{TiCl}_4 )</td>
<td>( \text{Me}<em>2\text{OC}</em>\text{N}_\text{Me} ) (54%)</td>
</tr>
<tr>
<td>6</td>
<td>( \text{Me}<em>2\text{OC}</em>\text{N}_\text{Me} ) (91%)</td>
<td>( \text{TiCl}_4 )</td>
<td>( \text{Me}<em>2\text{OC}</em>\text{N}_\text{Me} ) (54%)</td>
</tr>
<tr>
<td>7</td>
<td>( \text{Me}<em>2\text{OC}</em>\text{N}_\text{Me} ) (98%)</td>
<td>( \text{TiCl}_4 )</td>
<td>( \text{Me}<em>2\text{OC}</em>\text{N}_\text{Me} ) (54%)</td>
</tr>
<tr>
<td>8</td>
<td>( \text{Me}<em>2\text{OC}</em>\text{N}_\text{Me} ) (91%)</td>
<td>( \text{BF}_2\text{OEt}_2 )</td>
<td>( \text{Me}<em>2\text{OC}</em>\text{N}_\text{Me} ) (54%)</td>
</tr>
<tr>
<td>9</td>
<td>( \text{Me}<em>2\text{OC}</em>\text{N}_\text{Me} ) (49%)</td>
<td>( \text{TiCl}_4 )</td>
<td>( \text{Me}<em>2\text{OC}</em>\text{N}_\text{Me} ) (54%)</td>
</tr>
<tr>
<td>10</td>
<td>( \text{Me}<em>2\text{OC}</em>\text{N}_\text{Me} ) (43%)</td>
<td>( \text{BF}_2\text{OEt}_2 )</td>
<td>( \text{Me}<em>2\text{OC}</em>\text{N}_\text{Me} ) (54%)</td>
</tr>
<tr>
<td>11</td>
<td>( \text{Me}<em>2\text{OC}</em>\text{N}_\text{Me} ) (82%)</td>
<td>( \text{BF}_2\text{OEt}_2 )</td>
<td>( \text{Me}<em>2\text{OC}</em>\text{N}_\text{Me} ) (54%)</td>
</tr>
</tbody>
</table>

\( \text{a}) \) Yield after desilylation (CsF (2 equiv), \( \text{n-Bu}_4\text{NF} \) (0.1 equiv), THF. \( \text{b}) \) Obtained as an inseparable mixture of 4 diastereomers.
Under the influence of Lewis acid (TiCl₄ or SnCl₄ (2 equiv), -78 °C → rt) no cyclization occurred, and loss of the tert-butyl groups was observed. Reaction at lower temperature (TiCl₄ (2 equiv), -78 °C) or with a milder Lewis acid (BF₃·OEt₂ (2 equiv), 0 °C → rt) only afforded starting material.

Treatment of methallyl precursor 32 with SnCl₄ (2 equiv, -78 °C → rt) led to a small amount of cyclization product 42, together with unreacted 32, whereas TiCl₄ (2 equiv, -78 °C → rt) led to complete formation of 42. Therefore, all cyclizations were carried out with TiCl₄ (except for entries 8, 10 and 11).

It is remarkable that there is a large yield difference in the formation of the six- and seven-membered rings 39 and 40, respectively (entries 1 and 3). As this type of cyclization reaction is comparable to the corresponding iminium and N-acyliminium ion cyclizations, the reaction is likely to occur via the chair-like transition state 51, similar to its iminium analog 50. The observed difference in yield is probably due to the two adjacent carbamate functions. Conformational studies indicate that 1,2-diacylated hydrazines prefer a conformation in which both nitrogen lone pair orbitals are perpendicular to each other (θ = 90°). Such an electronic effect implies that the transition state 51 is relatively strained as a result of the smaller dihedral angle (θ = 60°) between the carbamates. In addition to this effect, the transition state 51 will be even more strained by the presence of an additional angle of ca. 120° in the molecule compared with 50. These effects will be smaller in the conformationally less strained transition state 52 of the seven-membered ring. Another (steric) reason for favoring the latter transition state might be that the allylic 1,3-strain between the two carbamate functions is reduced compared with 51.

On the other hand, despite the longer chain, the eight-membered ring 41 was formed in low yield. This result is in agreement with the usually observed more difficult formation of medium-sized rings. The (Z)-hexenyl precursor 33 led to an inseparable mixture of diastereomers of six- and seven-membered rings 43 and 44 (entry 6) which could not be further characterized because of the complex NMR spectra (for spectral data and proof, see: Section 2.9). Consistent with the proposed transition state, formation of the seven-membered ring is more likely to occur, but ¹H NMR data show that the six-membered ring is formed as well.

Slightly higher yields were obtained in the synthesis of six-membered rings, if more activated nucleophiles were used such as the methallyl precursor 32 and the allylsilane 35. Upon treatment of 35 with TiCl₄ (2 equiv, 20 min at -78 °C) only protodesilylation was observed, resulting in formation of precursor 31. The protodesilylation is probably a result of the presence of traces of HCl in the TiCl₄-solution. Therefore, BF₃·OEt₂ was used to cyclize the
Synthesis of cyclic hydrazine derivatives

allylsilane 35, the propargylsilane 37 and the vinylsilane 38. Cyclization of the propargylsilane 37 led to the five-membered allene 48 in reasonable yield.

\[ \text{(eq 2.5)} \]

The differences in yields of the various six-membered ring products are also remarkable. Both the phthalazide 45 and the tetrahydropyridazine 49 are obtained in significant higher yields than the other six-membered rings. This behavior might be explained by the conformation of the final products. They will adopt a half-chair conformation\(^{27}\) (eq 2.5) in which the strain between the carbamates is decreased compared with a normal chair conformation. This more stable conformation of the final products might already be felt in the transition state 53, thus giving rise to higher yields.

2.5 CHLORIDE AS A LEAVING GROUP

In order to improve the yield of the cyclization products in entries 1, 4 and 6 (Table 2.2), the precursors 28, 31 and 33 were activated by substitution of the methoxy group by a better leaving group in the form of a chlorine atom.\(^{28}\) Variation of the leaving group will affect the equilibrium between the precursor and the corresponding hydrazonium ion.

<table>
<thead>
<tr>
<th>Table 2.3. Chloride as a leaving group.</th>
</tr>
</thead>
<tbody>
<tr>
<td>entry</td>
</tr>
<tr>
<td>-------</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

\(a)\) PC\(_3\) (1.5 equiv), CC\(_4\), 0° C (yield after filtration and concentration in vacuo)
Chapter 2

A better leaving group will lead to an increased concentration of the hydrazonium ion and hence will result in a higher cyclization rate. Treatment of the methoxy compounds 28, 31 and 33 with PCl₅ afforded the corresponding chlorides 56-58 in good yields (Table 2.3). These chlorides were reacted with TiCl₄ (2 equiv, -78 °C → rt) thereby providing the cyclization products as summarized in Table 2.3.

Formation of the 6-membered ring 39 was indeed improved, but in the other cases side products were also obtained. Formation of the eight-membered ring 41 was accompanied by formation of the pyrrolopyrazole 59, which is formed in a transannular reaction of one of the nitrogen atoms with the electrophilic carbon ring atom (eq 2.6). This bicyclic product was not found upon cyclization of the methoxy precursor 31.

\[
\begin{align*}
41 & \rightarrow \text{Cl} \quad \begin{array}{c}
\text{MeO}_2\text{C} \\quad \text{Cl} \\
\text{Me}_2\text{C} \quad \text{MeO}_2\text{C} \\
\end{array} \rightarrow 59 \\
(\text{eq.} \, 2.6)
\end{align*}
\]

Cyclization of the (Z)-hexenyl precursor 33 led to the formation of a mixture of six- and seven-membered rings 43 and 44 in addition to the elimination product 60. The latter product has the (Z)-configuration as concluded from the ¹H NMR spectrum (J_{CH=CH} = 15.2 Hz).

2.6 CYCLIZATIONS WITH FORMIC ACID

<table>
<thead>
<tr>
<th>Table 2.4. HCOOH cyclizations.</th>
</tr>
</thead>
<tbody>
<tr>
<td>entry</td>
</tr>
<tr>
<td>-------</td>
</tr>
</tbody>
</table>
| 1     | MeO₂C\begin{array}{c}
\text{N} \\
\text{OMe}
\end{array} & 40 °C, 18 h | MeO₂C\begin{array}{c}
\text{N} \\
\text{OCHO}
\end{array} |
| 2     | MeO₂C\begin{array}{c}
\text{N} \\
\text{OMe}
\end{array} & 40 °C, 42 h | MeO₂C\begin{array}{c}
\text{N} \\
\text{CHO}
\end{array} |
| 3     | MeO₂C\begin{array}{c}
\text{N} \\
\text{OR}
\end{array} R = Me, R₁ = H, R₂ = Me | 40 °C, 42 h | 62 R = Me (83%) |
| 4     | MeO₂C\begin{array}{c}
\text{N} \\
\text{OR}
\end{array} R = Et, R₁ = H:SiMe₃ 1:1, R₂ = CH₂CH₂OMe | 40 °C, 42 h | 64 R = Et (64%) |
| 5     | MeO₂C\begin{array}{c}
\text{N} \\
\text{OR}
\end{array} R = allyl, R₁ = H:SiMe₃ 1:1, R₂ = CH₂CH₂OMe | 40 °C, 42 h | 66 R = allyl (53%) |

a) yield after introduction of the 2-(ethoxymethoxy)methyl function and cyclization.
Several precursors were also subjected to Brønsted acid conditions in order to be cyclized. They were dissolved in neat formic acid and as stirring at room temperature did not lead to any cyclization product, reactions were performed at 40 °C (Table 2.4). The hydrazide 30 afforded in high yield the seven-membered formate 61 after 18 h, while for the acetylenes 36, 63 and 65 (entries 2-4) even longer reaction times were required (42 h). The use of the 2-(ethoxymethoxy)methyl group gave slightly lower yields than the methoxymethyl group. The crude mixtures 63 and 65 of silylated and desilylated acetylenes afforded the corresponding ketones 64 and 66 after hydrolysis of the intermediate enol formates 67 to the enols 68 (eq 2.7).

\[ \text{RO}_2\text{C} \cdots \text{N} \cdots \text{OCHO} \quad \text{H}_2\text{O} \quad \text{RO}_2\text{C} \cdots \text{N} \cdots \text{OH} \quad \text{RO}_2\text{C} \cdots \text{N} \cdots \text{O} \quad (\text{eq 2.7}) \]

Literature examples show that precursors for the cyclization reactions can also be generated in situ starting from the monoalkylated hydrazides by treating these with formaldehyde\textsuperscript{30} or 1,3,5-trioxane\textsuperscript{31} under acidic conditions. Results of the application of these methods are summarized in Table 2.5. Surprisingly, the allyl precursor 10 did not give cyclization under these conditions, despite the formation of the cyclization precursor 70. On the other hand, the more easily formed seven-membered ring 61 was obtained in a reasonable yield.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Hydrazide</th>
<th>Conditions</th>
<th>Product (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeO\textsubscript{2}C \cdots \text{N} \cdots (\text{H}_2\text{O}) \text{n}</td>
<td>1,3,5-trioxane (1.3 equiv), 70 °C</td>
<td>70 (46%)</td>
</tr>
<tr>
<td>2</td>
<td>MeO\textsubscript{2}C \cdots \text{N} \cdots \text{H}</td>
<td>1,3,5-trioxane (1.3 equiv), 40 °C</td>
<td>61 (55%)</td>
</tr>
<tr>
<td>3</td>
<td>16 R = Me</td>
<td>1,3,5-trioxane (1.3 equiv), 70 °C</td>
<td>45 R = Me (93%)</td>
</tr>
<tr>
<td>4</td>
<td>16</td>
<td>(CH\textsubscript{2}O) \text{n} (1.5 equiv), 70 °C</td>
<td>45 R = Me (74%)</td>
</tr>
<tr>
<td>5</td>
<td>17 R = i-Pr</td>
<td>1,3,5-trioxane (1.3 equiv), 90 °C</td>
<td>71 R = i-Pr (64%)</td>
</tr>
<tr>
<td>6</td>
<td>17</td>
<td>(CH\textsubscript{2}O) \text{n} (1.5 equiv), 60 °C</td>
<td>71 R = i-Pr (64%)</td>
</tr>
</tbody>
</table>

The less nucleophilic acetylenes did not cyclize under these conditions. The benzyl precursors 16 and 17 easily gave cyclization under several conditions. Slightly lower yields
were obtained for the more hindered di(isopropoxycarbonyl) substituted hydrazines.

These results are in agreement with those that were found starting from the methoxymethylated precursors. Apparently, formic acid is a less suitable acid for the generation of this type of hydrazonium ions, so that cyclization is less likely to occur. Under these circumstances only the favored seven-membered rings and phthalazides are obtained in reasonable yields.

2.7 ATTEMPTS TO INTRODUCE A GLYOXYLATE MOIETY

Introduction of a methoxymethyl function in hydrazides like 16 leads, after cyclization, to cyclic hydrazine systems, which bear no substituents at the α-position. Introduction of a methoxycarbonyl group at this α-position would lead to α-amino acid type compounds, in which an amino function is attached to the nitrogen atom. Considering the biological importance of amino acids in general and the extensive interest in analogs, it would be interesting to study the synthesis of this compound class.

Several attempts were made to synthesize precursors, which bear both a methoxycarbonyl function and a leaving group at the α-position. Possible routes to obtain these products from 16 include condensation reactions with methyl glyoxylate, and alkylations with methyl chloromethoxyacetate or methyl chloro(phenylthio)acetate under Lewis acidic and basic conditions. Unfortunately, neither of these methods were successful (for positive results with methyl glyoxylate, see: Sections 6.3 and 7.3). Attempts to introduce a bromine atom in hydrazide 58 at the α-position via a radical mechanism (NBS, CCl₄) only led to debenzylation, probably via hydrolysis of the intermediate hydrazonium ion after bromination at the benzylic position.

Precursor 72 was prepared in order to investigate whether a thiophenyl function could be introduced with a strong base (LDA, 2 equiv) and PhSSPh (1 equiv). In this case, 2 equiv of base were used as the enolate anion of the desired product is more stable than that of the starting material and therefore could give dialkylation. Surprisingly, sulphenylation did not take place, but instead the rearranged product 73 was obtained (eq 2.8). Variation of temperature or base could not prevent the formation of this rearranged product as is shown in Table 2.6.
**Synthesis of cyclic hydrazine derivatives**

Table 2.6. Entry base (equiv) PhSSPh (equiv) T (°C) solvent produces) (yield)

<table>
<thead>
<tr>
<th>entry</th>
<th>base (equiv)</th>
<th>PhSSPh (equiv)</th>
<th>T (°C)</th>
<th>solvent</th>
<th>product(s)</th>
<th>(yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LDA (2)</td>
<td>1.1</td>
<td>-78 → rt</td>
<td>THF</td>
<td>73</td>
<td>41%</td>
</tr>
<tr>
<td>2</td>
<td>NaH (2)</td>
<td>1.1</td>
<td>-78 → rt</td>
<td>THF</td>
<td>73</td>
<td>20%</td>
</tr>
<tr>
<td>3</td>
<td>LDA (2)</td>
<td>1.1</td>
<td>-115</td>
<td>THF/hexane</td>
<td>73 (8%) + 72 (58%)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>LDA (1)</td>
<td>0</td>
<td>-78 → rt</td>
<td>THF</td>
<td>73</td>
<td>59%</td>
</tr>
</tbody>
</table>

Similar rearrangements of hydrazides have been reported in literature.[37] The enolate anion 74 attacks the β-nitrogen atom, while the other nitrogen serves as a leaving group (eq 2.9). The nucleophilicity of the enolate anion and the stabilization of the negative charge in the rearranged product are believed to be important factors which are involved in this reaction. If the reaction was carried out without PhSSPh and only one equiv of LDA (entry 4), the rearranged product 73 was obtained in a reasonable yield.

![Reaction Diagram](image)

2.8 CLEAVAGE OF THE N-N-BONDS

Various examples are known in which cleavage of the N-N-bond is useful for the preparation of linear or cyclic diamines.[38] Reductive methods are most often used such as lithium or sodium in NH$_3$ or LiAlH$_4$. Cyclic products 45 and 77 (the keto function was protected as a dioxolane) were subjected to these conditions (Li (4 equiv), NH$_3$, -78 °C → rt) to give the ring opened diamides 76 and 78. Remarkably, debenzylation is not encountered under these conditions.

Table 2.7. Cleavage of the N-N-bond.

<table>
<thead>
<tr>
<th>entry</th>
<th>hydrazine</th>
<th>diamide (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image" alt="Image" /></td>
<td><img src="image" alt="Image" /></td>
</tr>
<tr>
<td>2</td>
<td><img src="image" alt="Image" /></td>
<td><img src="image" alt="Image" /></td>
</tr>
</tbody>
</table>
Cleavage of the carbamates will lead to primary diamines. The diamide 76 might also be prepared by reduction of 1,2-dicyanobenzene, but the diamide 78 is less accessible via other routes. Cleavage of these types of cyclic hydrazides might therefore be useful in order to obtain functionalized primary diamines.

2.9 NMR DATA AND STRUCTURAL PROOF

The presence of two carbamate functions in almost all of the molecules described in this chapter often caused significant line-broadening and appearance of rotamers in both $^1$H and $^13$C NMR spectra. In particular, the spectra of the methoxymethylated hydrazides and the cyclization products were often difficult to interpret. These rotamers are in the case of the first group a result of hindered rotation around both the N-N and amide bonds and in the latter group only a result of hindered rotation around the amide bonds.$^{25,27}$

Spectra of a typical example are shown in Figure 2.1. In the $^1$H NMR spectrum in CDCl$_3$ and DMSO-$d_6$ all ring protons of pyridazine 46 appear as broad multiplets. On heating the solution to 70 °C in DMSO-$d_6$ the signals of the spectrum considerably sharpened (Fig 2.3). H$_{\text{5ax}}$ appears as a double quartet ($^3J_{\text{de}} = 4.5$ Hz, $^3J_{\text{ax}} = 2J = 12.8$ Hz), while H$_{\text{5eq}}$ appears as a broad doublet ($^2J = 12.0$ Hz). Both H$_{\text{3ax}}$ and H$_{\text{6ax}}$ show a triplet ($^3J_{\text{ax}} = 2J = 12.4$ and 13.1, respectively), whereas H$_{\text{6ax}}$ also shows another small coupling ($^3J_{\text{de}} = 1.5$ Hz). The other ring protons (H$_4$, H$_{\text{3eq}}$ and H$_{\text{6eq}}$) only appear as multiplets. Unfortunately, higher temperatures did not allow complete assignment of the NMR spectra in all cases.

2.10 DISCUSSION

From the results of the cyclizations via the intermediate N,N'-diacylhydrazonium ions compared with those of N-acyliminium ions, a few conclusions can be drawn. Several observations point to the fact that formation of this type of intermediate is indeed more difficult than that of the N-acyliminium ions. For instance, a strong Lewis acid (TiCl$_4$) has to be used with most nucleophiles. Another indication is that at -78 °C the hydrazonium ion is not formed, but that cation formation and cyclization take place at higher temperatures. A similar observation is made with the formic acid cyclizations. The reaction mixture has to be warmed up in order to get a reaction. However, formic acid is less suitable than TiCl$_4$ to induce cyclization. Only if cyclizations with TiCl$_4$ proceed well, formic acid also affords a good result. If the barrier for cyclization is increased (low yields with TiCl$_4$), cyclization with formic acid does not occur, even at higher temperatures.

In contrast with ordinary iminium ion cyclizations, formation of six-membered rings via N,N'-diacylhydrazonium ions is not particularly favorable, unless the final products possess some special features like the phthalazides and the tetrahydropyridazines.
Synthesis of cyclic hydrazine derivatives

Fig. 2.3. 
$^1$H NMR spectrum (250 MHz) of pyridazine 46 in DMSO-$d_6$ at 70 °C.

Fig. 2.2. 
$^1$H NMR spectrum (200 MHz) of pyridazine 46 in DMSO-$d_6$ at 23 °C.

Fig. 2.1. 
$^1$H NMR spectrum (200 MHz) of pyridazine 46 in CDCl$_3$ at 23 °C.
Chapter 2

The remarkably facile formation of seven-membered rings might be a result of a less strained transition state compared with six-membered rings, caused by a more favorable conformation of the adjacent carbamate functions.

In conclusion, it is evident that a variety of cyclic substituted hydrazides can be prepared via this method. The efficient formation of the seven-membered rings is particularly interesting because such products are not readily accessible via other methods.

ACKNOWLEDGEMENT

M. M. Paz is gratefully acknowledged for the synthesis of compound 48.

2.11 EXPERIMENTAL SECTION

General information. All reactions were carried out under an inert atmosphere of dry nitrogen, unless otherwise described. Standard syringe techniques were applied for transfer of Lewis acids and dry solvents. Infrared (IR) spectra were obtained from CHCl$_3$ solutions, unless indicated otherwise, using a Jasco FTIR 2000 spectrophotometer and wavelengths ($\nu$) are reported in cm$^{-1}$. Proton nuclear magnetic resonance ($^1$H NMR) spectra were determined in CDCl$_3$ (unless indicated otherwise) using a JEOL PMX 60 (60 MHz), a Bruker AC 200 (200 MHz), a Bruker WM 250 (250 MHz) or a Bruker AMX 300 (300 MHz) spectrometer. The latter three machines were also used for $^{13}$C NMR (APT) spectra (50, 63 and 75 MHz resp.) in CDCl$_3$ (unless indicated otherwise). Chemical shifts (s) are given in ppm downfield from tetramethylsilane. Mass spectra and accurate mass measurements were carried out using a Varian MAT 711 or a VG Micromass ZAB-2HF instrument. Elemental analyses were performed by Domis u. Kolbe Mikroanalytisches Laboratorium, Miilheim a.d. Ruhr, Germany. $R_f$ values were obtained by using thin-layer chromatography (TLC) on silica gel-coated plastic sheets (Merck silica gel 60$F_{254}$) with the indicated solvents (mixture). Chromatographic purification refers to flash chromatography$^{39}$ using the same solvent as for TLC and Merck silica gel 60 (230-400 mesh) or Janssen Chimica silica gel (0.030-0.075 mm). Melting and boiling points are uncorrected. CH$_2$Cl$_2$ was distilled from P$_2$O$_5$ and stored over MS 4Å under an atmosphere of dry nitrogen. TiCl$_4$ and SnCl$_4$ were distilled and stored under a dry nitrogen atmosphere as a solution in CH$_2$Cl$_2$. BF$_3$-OEt$_2$ was distilled and stored under a dry nitrogen atmosphere. Dry THF and Et$_2$O were distilled from sodium benzophenone ketyl prior to use. Dry DMF$^8$ was distilled from CaH$_2$ and stored over MS 4Å under a dry nitrogen atmosphere.

1,2-Hydrainedicarboxylic acid diallyl ester (7). Allyl chloroformate (63.5 mL, 0.60 mol) was added dropwise to a solution of hydrazine hydrate (14.6 mL, 0.30 mmol) in MeOH (250 mL), while the temperature inside the flask was kept below 5 °C. After one half of the chloroformate had been added, a solution of K$_2$CO$_3$ (41.5 g, 0.30 mol) in water (125 mL) was added dropwise simultaneously. After the addition was complete, the precipitate was washed from the flask with water (125 mL) and the mixture was stirred for another 30 min. Filtration, washing with water (3 x) and drying in vacuo yielded 7 (53.0 g, 265 mmol, 88%) as a white solid, mp 85-86 °C (methanol/water). IR v 3410, 1730. $^1$H NMR (200 MHz) $\delta$ 4.65 (d, J = 5.6 Hz, 4 H, 2 x CH$_2$), 5.30-5.45 (m, 4 H, 2 x CH$_2$), 5.91-6.09 (m, 2 H, 2 x =CH), 6.57 (br s, 2 H, 2 x NH).
Diallyl azodicarboxylate (8). To a well-stirred suspension of hydrazoester 7 (2.00 g, 10.0 mmol) in CH$_2$Cl$_2$ (20 mL) was added Pb(OAc)$_4$ (4.43 g, 10.0 mmol) in portions at 0 °C over a period of 30 min. The resulting mixture was filtered over Celite and the residue was washed with pentane. After concentration of the filtrate in vacuo, the residue was taken up in pentane, filtered over Celite and washed with aq satd K$_2$CO$_3$. The organic layer was dried (MgSO$_4$), filtered and concentrated in vacuo to afford 8 as an orange oil (11.99 g, 61.0 mmol, 86%). IR ν 3090, 1770; $^1$H NMR (200 MHz) δ 4.90 (d, J = 5.9 Hz, 4 H, 2 × CH$_2$), 5.34-5.49 (m, 4 H, 2 × =CH$_2$), 5.90-6.09 (m, 2 H, 2 × =CH).

General procedure A for the synthesis of hydrazides 10-23. Synthesis of the Grignard reagent (unless indicated otherwise): to magnesium chips (excess) and one iodine crystal was added one fifth of a solution of the halide in ether or THF. When the brown color disappeared, the remaining solution was added slowly in such a way that a gentle reflux was maintained. After the addition was complete, the solution was refluxed for another 2 h and allowed to cool to rt. The Grignard reagent was added slowly by syringe to a slurry of the azo ester in THF or ether (0.15 M) at -78 °C. After the addition was complete, the mixture was stirred at -78 °C for 1 h and 3-4 h at rt. It was poured into aq satd NH$_4$Cl and the aq layer was extracted with ether (3 ×). The combined organic layers were dried (MgSO$_4$), filtered and concentrated in vacuo. The pure hydrazide was obtained after flash chromatography or distillation.

1-(2-Propenyl)-1,2-hydrazinedicarboxylic acid dimethyl ester (10). According to the general procedure A, allylmagnesium chloride (15.1 mL of a 2.0 M solution in THF, 30.1 mmol) was added at -78 °C to a well-stirred solution of dimethyl azodicarboxylate (4.01 g, 27.5 mmol) in THF. After work-up and purification by flash chromatography (ethyl acetate/hexane 1:1.5), 10 (1.86 g, 9.88 mmol, 36%) was obtained as a yellowish oil, $R_f$ 0.30. IR ν 3400, 1755, 1710; $^1$H NMR (200 MHz) δ 3.70 (s, 6 H, 2 × CO$_2$CH$_3$), 4.06 (d, J = 5.9 Hz, 2 H, CH$_2$), 5.11-5.20 (m, 2 H, =CH$_2$), 5.69-5.88 (m, 1 H, CH), 6.87 (br s, 1 H, NH).

1-(3-Butenyl)-1,2-hydrazinedicarboxylic acid di-tert-butyl ester (11). 3-Butenylmagnesium bromide was prepared from magnesium chips (0.150 g, 6.17 mmol) and a solution of 4-bromo-l-butene (702 mg, 5.19 mmol) in ether (4 mL). After cooling to rt, the solution was added to a solution of di-tert-butyl azodicarboxylate (1.04 g, 4.52 mmol) in ether (30 mL) according to the general procedure A. The residue was purified by flash chromatography (ethyl acetate/hexane 1:4) to yield 11 as a white solid (1.04 g, 3.64 mmol, 81%), mp 77-78 °C (ethyl acetate/hexane 1:8), $R_f$ 0.35. IR ν 3400, 1745, 1700; $^1$H NMR (200 MHz) δ 1.47 (s, 18 H, 2 × tert-butyl), 2.32 (q, J = 7 Hz, 2 H, CH$_2$CH$_2$-CH), 3.52 (s, J = 5 Hz, 2 H, NCH$_2$), 4.96-5.12 (m, 2 H, CH=C$(CH_3)_2$), 5.68-5.89 (m, J = 7 Hz, 1 H, =CH), 6.28 (br s, 1 H, NH); Anal. Calcd for C$_{14}$H$_{26}$N$_2$O$_4$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.76; H, 9.17; N, 9.72.

1-(3-Butenyl)-1,2-hydrazinedicarboxylic acid dimethyl ester (12). 3-Butenylmagnesium bromide was prepared from magnesium chips (439 g, 18.1 mmol) and 4-bromo-l-butene (2.03 g, 15.1 mmol) in ether (25 mL). The addition reaction was carried out following the general procedure A with dimethyl azodicarboxylate (2.00 g, 13.7 mmol) in THF (100 mL). After work-up and purification by flash chromatography (ethyl acetate/hexane 1:1), 12 (1.41 g, 7.00 mmol, 51 %) was obtained as a light-yellow oil, $R_f$ 0.32. IR ν 3400, 1748, 1705; $^1$H NMR (200 MHz) δ 2.29 (q, J = 7.0 Hz, 2 H, NCH$_2$CH$_2$), 3.53 (s, J = 5 Hz, 2 H, NCH$_2$), 3.70 (s, J = 6 Hz, 2 × CO$_2$CH$_3$), 4.96-5.08 (m, 2 H, =CH$_2$), 5.72 (m, 1 H, =CH), 6.90 (br s, 1 H, NH).

1-(4-Pentenyl)-1,2-hydrazinedicarboxylic acid dimethyl ester (13). 4-Pentenylmagnesium bromide
was prepared from magnesium chips (590 mg, 24.3 mmol) and a solution of 4-bromo-1-pentene (3.05 g, 20.5 mmol) in ether (35 mL). Following the general procedure A, the Grignard reagent was added at -78 °C to a solution of dimethyl azodicarboxylate (2.67 g, 18.3 mmol) in ether. After work-up and purification by flash chromatography (ethyl acetate/hexane 1:2:1), 13 (2.11 g, 9.79 mmol, 53%) was obtained as a colorless oil, Rf 0.35. IR v 3395, 1750, 1705; 1H NMR (200 MHz) δ 1.59-1.77 (m, 2 H, NCH₂CH₃), 2.03 (q, 2 H, J = 7.0 Hz, NCH₂CH₂CH₂), 3.50 (t, J = 7.0 Hz, 2 H, NCH₂), 3.74 (s, 6 H, 2 × CO₂CH₃), 4.94-5.06 (m, 2 H, =CH₂), 5.79 (m, 1 H, =CH), 6.73 (br s, 1 H, NH).

1-(2-Methyl-2-propenyl)-1,2-hydrazinedicarboxylic acid dimethylester (14). Preparation of methallylmagnesium chloride: 40 to magnesium chips (801 mg, 33.0 mmol) and one iodine crystal was added 4 mL of a solution of 3-chloro-2-methyl-1-propene (2.73 g, 30.1 mmol) in THF (20 mL) at 0 °C. When the brown color disappeared, the remaining chloride was added slowly in 30 min. After addition, the mixture was refluxed for 1 h, allowed to cool to rt and added to a solution of dimethyl azodicarboxylate (3.99 g, 27.3 mmol) in THF according to the general procedure A. After work-up and purification by flash chromatography (ethyl acetate/hexane 1.5:1), 14 (3.85 g, 19.1 mmol, 70%) was obtained as a white solid, mp 59-62 °C, Rf 0.31. IR v 3400, 1750, 1715; 1H NMR (200 MHz) δ 1.72 (s, 3 H, CH₃), 3.75 (s, 3 H, CO₂CH₃), 3.76 (s, 3 H, CO₂CH₃), 4.05 (br s, 2 H, NCH₂), 4.82 (br s, 1 H, =CH₂), 4.90 (br s, 1 H, =CH₂), 6.65 (br s, 1 H, NH).

1-((Z)-3-hexenyl)-1,2-hydrazinedicarboxylic acid dimethyl ester (15). The Grignard reagent of 6-bromo-(Z)-3-hexene was prepared from magnesium chips (633 mg, 25.9 mmol) and a solution of 6-bromo-(Z)-3-hexene (3.47 g, 21.3 mmol) in ether (35 mL). It was added to a solution of dimethyl azodicarboxylate (2.83 g, 19.4 mmol) in ether according to the general procedure A. After work-up and purification by flash chromatography (ethyl acetate/hexane 1:1), 15 (1.71 g, 7.45 mmol, 38%) was obtained as a light yellow oil, Rf 0.35. IR v 3400, 1745, 1715; 1H NMR (200 MHz) δ 0.94 (t, J = 7.5 Hz, 3 H, CH₃), 2.03 (quintet, J = 7.2 Hz, 2 H, CH₂CH₃), 2.31 (q, J = 7.1 Hz, 2 H, NCH₂CH₂), 3.51 (t, J = 7.0 Hz, 2 H, NCH₂), 3.74 (s, 6 H, 2 × CO₂CH₃), 5.26 (td, J = 7.2, 10.7 Hz, 1 H, CH₃CH₂CH₂), 5.46 (td, J = 7.1, 10.7 Hz, 1 H, NCH₂CH₂CH₃), 6.73 (br s, 1 H, NH).

1-Benzyl-1,2-hydrazinedicarboxylic acid dimethylester (16). Benzylmagnesium chloride was prepared from magnesium chips (2.00 g, 82.0 mmol) and a solution of benzyl chloride (9.44 g, 75.0 mmol) in ether (50 mL). The mixture was added to a solution of dimethyl azodicarboxylate (9.95 g, 68.0 mmol) in ether according to the general procedure A. After work-up and purification by flash chromatography (ethyl acetate/hexane 1:1), 16 (12.8 g, 53.7 mmol, 79%) was obtained as a white solid, mp 88-93 °C, Rf 0.31. IR v 3400, 1745, 1710; 1H NMR (200 MHz) δ (some signals appear as rotamers) 3.73, 3.78 (s, 6 H, 2 × CO₂CH₃), 4.69 (br s, 2 H, NCH₂Ph), 5.47 (br s, 1 H, NH), 7.31 (s, 5 H, ArH).

1-Benzyl-1,2-hydrazinedicarboxylic acid diisopropyl ester (17). Benzylmagnesium chloride was prepared from magnesium chips (1.46 g, 60.0 mmol) and a solution of benzyl chloride (6.13 g, 54.5 mmol) in ether (50 mL). The mixture was added to a solution of dimethyl azodicarboxylate (10.0 g, 49.5 mmol) in ether following the general procedure A. After work-up and flash chromatography (ethyl acetate/hexane 1:1), 17 (9.46 g, 32.2 mmol, 65%) was obtained as a white crystalline solid, mp 79-81 °C (ethyl acetate/hexane 1:5), Rf 0.40. IR v 3405, 1720, 1700; 1H NMR (200 MHz) δ 1.20-1.27 (m, 12 H, 2 × (CH₃)₂CH), 4.66 (br s, 2 H, NCH₂), 4.88-4.99 (m, 2 H, 2 × (CH₃)₂CH), 6.25 (br s, 1 H, NH), 7.24-7.29 (m, 5 H, ArH).

1-((3-(Trimethylsilyl)-3-(Z)-pentenyl)-1,2-hydrazinedicarboxylic acid dimethylester (19).
Synthesis of cyclic hydrazine derivatives

Grignard reagent of 5-iodo-1-(trimethylsilyl)-(Z)-2-pentene was prepared from magnesium chips (370 mg, 15.0 mmol) and a solution of iodide 18 (1.70 g, 6.31 mmol) in ether (15 mL). The resulting mixture was added slowly to a solution of dimethyl azodicarboxylate (850 mg, 5.80 mmol) in ether following the general procedure A. After work-up and purification by flash chromatography (ethyl acetate:hexane 1:1), 19 (499 mg, 1.75 mmol, 28%) was obtained as a light yellow oil, $R_f 0.40$. IR v 3410, 1750, 1710, 1245, 855; $^1$H NMR (200 MHz) δ 0 (s, 9 H, (CH$_3$)$_3$Si), 1.47 (d, $J = 8.6$ Hz, 2 H, CH$_2$Si), 2.28 (q, $J = 7.1$ Hz, 2 H, CH$_2$CH$_2$CH), 3.52 (t, $J = 6.6$ Hz, 2 H, NCH$_2$), 3.76 (s, 6 H, 2 x CO$_2$CH$_3$), 5.20 (q, $J = 7.2$ Hz, 1 H, =CH$_2$CH), 5.50 (q, $J = 8.6$ Hz, 1 H, =CH(CH$_3$)$_2$), 6.61 (br s, 1 H, NH).

4-Bromo-1-(trimethylsilyl)-1-butyne (20). To a solution of 4-(trimethylsilyl)-3-butyn-1-ol (49.0 g, 0.34 mol) in pyridine (175 mL) was added at 0 °C p-toluenesulfonyl chloride (78.0 g, 0.41 mmol) in portions. The suspension was stirred for 30 min at 0 °C and 2 h at rt. It was poured into an ice water mixture (500 mL) and extracted with ether (5 x 200 mL). The combined ether extracts were washed with 6 N HCl (2 x 200 mL) and aq NaHCO$_3$ (200 mL), dried (MgSO$_4$), filtered and concentrated in vacuo to afford the crude tosylate (87.0 g, 0.29 mmol) as a light yellow solid. The crude tosylate was dissolved in DMF (350 mL), potassium bromide (55.0 g, 0.46 mol) was added and the mixture was stirred at 60 °C for 25 h. After cooling to rt, the mixture was poured into water (2 L) and extracted with pentane (5 x 500 mL). The combined organic layers were dried (MgSO$_4$), filtered and concentrated in vacuo. Distillation of the residue yielded 20 (49.0 g, 0.24 mol, 70%) as a colorless oil, bp 81-82 °C (27 mm). IR v 2170, 1250, 840; $^1$H NMR (200 MHz) δ 0.16 (s, 9 H, (CH$_3$)$_3$Si), 2.77 (t, $J = 7.5$ Hz, 2 H, CH$_2$C=C), 3.42 (t, $J = 7.5$ Hz, 2 H, NCH$_2$), 3.76 (s, 6 H, 2 x CO$_2$CH$_3$), 6.76 (br s, 1 H, NH).

1-[4-(Trimethylsilyl)-3-butynyl]-1,2-hydrazinedicarboxylic acid dimethyl ester (21). The Grignard reagent of 4-bromo-1-(trimethylsilyl)-1-butyne was prepared from magnesium chips (711 mg, 21.9 mmol) and a solution of bromide 20 (4.01 g, 19.5 mmol) in THF (20 mL). The mixture was added to a solution of dimethyl azodicarboxylate (2.59 g, 17.7 mmol) in THF following the general procedure A. After work-up and purification by bulb-to-bulb distillation, 21 (3.08 g, 11.3 mmol, 64%) was obtained as a viscous yellow oil, bp 143-148 °C (0.03 mm), $R_f 0.35$ (ethyl acetate/hexane 2:3). IR v 3405, 2170, 1750, 1715, 1250, 840; $^1$H NMR (200 MHz) δ 0.16 (s, 9 H, (CH$_3$)$_3$Si), 2.52 (t, $J = 6.9$ Hz, 2 H, CH$_2$C=C), 3.68 (t, $J = 6.8$ Hz, 2 H, NCH$_2$), 3.76 (s, 6 H, 2 x CO$_2$CH$_3$), 6.76 (br s, 1 H, NH).

1-[4-(Trimethylsilyl)-3-butynyl]-1,2-hydrazinedicarboxylic acid diethyl ester (22). The Grignard reagent of 4-bromo-1-(trimethylsilyl)-1-butyne was prepared from magnesium chips (3.59 g, 0.14 mol) and a solution of bromide 20 (24.2 g, 0.12 mol) in THF (120 mL). The mixture was added to a solution of diethyl azodicarboxylate (8.38 g, 42.3 mmol) in THF following the general procedure A. After work-up and flash chromatography (ethyl acetate/hexane 1:4), 22 (20.4 g, 69.3 mmol, 65%) was obtained as a viscous yellow oil, bp 145-150 °C (0.03 mm), $R_f 0.35$ (ethyl acetate/hexane 2:3). IR v 3405, 2170, 1745, 1710, 1250, 840; $^1$H NMR (200 MHz) δ 0.12 (s, 9 H, (CH$_3$)$_3$Si), 1.25 (t, $J = 7.1$ Hz, 6 H, 2 x CH$_2$CH$_3$), 2.50 (t, $J = 7.0$ Hz, 2 H, CH$_3$), 3.65 (t, $J = 6.8$ Hz, 2 H, NCH$_2$), 4.17 (q, $J = 7.1$ Hz, 4 H, 2 x CH$_2$CH$_3$), 6.76 (br s, 1 H, NH).

1-[4-(Trimethylsilyl)-3-butynyl]-1,2-hydrazinedicarboxylic acid diallyl ester (23). The Grignard reagent of 4-bromo-1-(trimethylsilyl)-1-butyne was prepared from magnesium chips (1.13 g, 46.5 mmol) and a solution of bromide 20 (9.55 g, 46.5 mmol) in THF (40 mL). The mixture was added to a solution of diallyl azodicarboxylate (8) (8.38 g, 42.3 mmol) in THF following the general procedure A. After work-up and flash chromatography (ethyl acetate/hexane 1:4), 23 (7.63 g, 23.4 mmol, 55%) was obtained as a colorless oil,
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Rf 0.35. IR v 3400, 3080, 1715, 1245, 840; 1H NMR (200 MHz) δ 0.14 (s, 9 H, (CH₃)₃Si), 2.53 (t, J = 6.9 Hz, 2 H, CH₂C=CH), 3.70 (t, J = 6.9 Hz, 2 H, NCH₂), 4.63 (d, J = 5.5 Hz, 4 H, 2 × OCH₂), 5.21-5.36 (m, 4 H, 2 × =CH₂), 5.84-5.97 (m, 2 H, 2 × =CH), 6.80 (br s, 1 H, NH).

1-[4-(Trimethylsilyl)-2-butynyl]-1,2-hydrazone dicarboxylic acid diallyl ester (25). To a suspension of NaH (66.3 mg, 2.75 mmol, the oil was washed from the NaH with pentane) in DMF (5 mL) was added dropwise a solution of 7 (500 mg, 2.50 mmol) in DMF (2 mL). After being stirred at rt for 15 min, the resulting clear solution was added via syringe to a solution of 4-ido-1-(trimethylsilyl)-2-butyne (24) in DMF (5 mL). After being stirred for 30 min at rt, the mixture was poured into aq satd NaCl (25 mL) and extracted with CH₂Cl₂ (3x15 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo. The residue was chromatographed (ethyl acetate/hexane 1:4) to afford 25 as a colorless oil (302 mg, 0.93 mmol, 37%), Rf 0.37. IR v 3400, 3080, 2210, 1745, 1720, 1250, 850; 1H NMR (200 MHz) δ 0.09 (s, 9 H, (CH₃)₃Si), 1.46 (t, J = 2.5 Hz, 2 H, CH₂Si), 4.32 (br s, 2 H, NCH₂), 4.60 (m, 4 H, 2 × CH₂O), 5.19-5.36 (m, 4 H, 2 × =CH₂), 5.81-6.00 (m, 2 H, 2 × =CH), 6.73 (br s, 1 H, NH).

1-[3-(Trimethylsilyl)-2-propenyl]-1,2-hydrazone dicarboxylic acid dimethyl ester (27). A solution of dimethyl azodicarboxylate (3.00 g, 20.5 mmol) in allyltrimethylsilane 26 (2.40 g, 21.0 mmol) was heated at reflux temperature until the orange color disappeared (2.5 h). The resulting solution was distilled to yield 27 (4.35 g, 16.7 mmol, 81%) as a colorless oil, (E)/(Z)-ratio 1.5:1, bp 124-126 °C (0.01 mm). IR v 3410, 1750, 1450, 1260, 1245, 855, 840; (E)-isomer: 1H NMR (200 MHz) δ 0.06 (s, 9 H, (CH₃)₃Si), 3.74 (s, 6 H, 2 × CO₂CH₃), 4.17-4.21 (m, 2 H, NCH₂), 5.78 (d, J = 18.7 Hz, 1 H, CHSi), 6.05 (dt, J = 18.7, 5 Hz, 1 H, CHCH₂), 6.67 (br s, 1 H, NH); 13C NMR (63 MHz) δ -1.5 ((CH₃)₃Si), 51.7 (NCH₂), 52.8 (CO₂CH₃), 133.8, 139.5 (C=C), 156.5 (CO); (Z)-isomer: 1H NMR (200 MHz) δ 0.11 (s, 9 H, (CH₃)₃Si), 3.74 (s, 6 H, 2 × CO₂CH₃), 4.17-4.21 (m, 2 H, NCH₂), 5.75 (d, J = 14.2 Hz, 1 H, CHSi), 6.26 (dt, J = 14.2, 7.1 Hz, 1 H, CHCH₂), 6.67 (br s, 1 H, NH); 13C NMR (63 MHz) δ -0.1 ((CH₃)₃Si), 53.4 (CO₂CH₃), 55.0 (NCH₂), 133.8, 141.4 (C=C), 156.5 (CO); MS (EI, 70 eV) m/z (relative intensity) 260 (M⁺, 2), 254 (14), 213 (30), 186 (87), 170 (52), 89 (100), 73 (58), 59 (76); HRMS calc'd for C₁₀H₂₀N₂O₄Si 260.1192, found 260.1206.

General procedure B for the reactions with chloromethyl methyl ether. Sodium hydride (purchased as a 55% dispersion in oil) was washed prior to use with pentane, removing the pentane by syringe after the sodium hydride had settled. The dry solid was then mixed with DMF and the hydrazide, dissolved in DMF was added dropwise to the suspension at rt. After being stirred for 15 min at rt, the resulting clear solution was cooled to 0 °C and a solution of chloromethyl methyl ether in DMF was added. After being stirred for 15 min at 0 °C and 3 h at rt, the mixture was poured into aq satd NaCl, extracted with 1,1,1-trichloroethane (6 ×), dried (MgSO₄), filtered and concentrated in vacuo. The residue was subjected to flash chromatography to afford the pure hydrazides.

1-(Methoxymethyl)-2-(2-propenyl)-1,2-hydrazone dicarboxylic acid dimethyl ester (28). According to the general procedure B, 10 (508 mg, 2.70 mmol) was deprotonated with NaH (128 mg, 2.93 mmol) and alkylated with chloromethyl methyl ether (300 μL, 4.00 mmol), while all compounds were dissolved in DMF (5 mL). After work-up and flash chromatography (ethyl acetate/hexane 1:1), 28 (567 mg, 2.44 mmol, 90%) was obtained as a light yellow oil, Rf 0.30. IR v 1710; 1H NMR (200 MHz) δ 3.35 (s, 3 H, OCH₃), 3.72 (s, 6 H, 2 × CO₂CH₃), 3.94-4.25 (m, 2 H, NCH₂CH=), 4.64-4.69 (d, J = 11.0 Hz, 1 H, NCHHO), 4.86-5.05 (m, 1 H, NCHHO), 5.12-5.23 (m, 2 H, CH₂), 5.80-6.00 (m, 1 H, =CH).
Synthesis of cyclic hydrazine derivatives

1-(3-Butenyl)-2-(methoxymethyl)-1,2-hydrazinedicarboxylic acid di-tert-butyl ester (29).
According to the general procedure B, 11 (149 mg, 0.521 mmol) was treated with NaH (13.9 mg, 0.577 mmol) and chloromethyl methyl ether (60 μL, 0.79 mmol), all compounds were dissolved in DMF (2 mL). After work-up and flash chromatography (ethyl acetate/hexane 1:4), 29 (163 mg, 0.495 mmol, 95%) was obtained as a yellowish oil, \( R_f 0.40 \). IR \( \nu 1700 \); \( ^1H \) NMR (60 MHz, CDCl₃) \( \delta 1.47 (s, 18 \text{ H}, 2 \times \text{ tert-butyl}), 2.38 (q, \text{ J }= 7 \text{ Hz}, 2 \text{ H}, \text{ OCH}_3), 3.27-3.70 (m, 2 \text{ H}, \text{ NCH}_2CH_2), 4.37-5.17 (m, 4 \text{ H}, \text{ CH}_2O \text{ and } =\text{CH}_2), 5.43-6.13 (m, 1 \text{ H}, =\text{CH}) \).

1-(3-Butenyl)-2-(methoxymethyl)-1,2-hydrazinedicarboxylic acid dimethyl ester (30).
According to the general procedure B, 12 (502 mg, 2.49 mmol) was deprotonated with NaH (65.1 mg, 2.70 mmol) and alkylated with chloromethyl methyl ether (280 μL, 3.70 mmol), all compounds dissolved in DMF (5 mL). After work-up and flash chromatography (ethyl acetate/hexane 1:1), 30 (493 mg, 2.01 mmol, 81%) was obtained as a colorless oil, \( R_f 0.32 \). IR \( \nu 1720, 1700 \); \( ^1H \) NMR (200 MHz) \( \delta 2.39 (q, \text{ J }= 6.9 \text{ Hz}, 2 \text{ H}, \text{ NCH}_2C\text{H}_2), 3.30-3.40 (m, 1 \text{ H}, \text{ NCH} = \text{CH}_2), 3.37 (s, 3 \text{ H}, \text{ OCH}_3), 3.60-3.80 (m, 1 \text{ H}, \text{ NCH} = \text{CH}_2), 3.73 (s, 6 \text{ H}, 2 \times \text{ CO}_2\text{CH}_3), 4.58 (d, \text{ J }= 11.0 \text{ Hz}, 1 \text{ H}, \text{ NCH} = \text{O}), 4.92-5.11 (m, 3 \text{ H}, =\text{CH} \text{ and } =\text{CH}_2), 5.70-5.81 (m, 1 \text{ H}, =\text{CH}) \).

1-(Methoxymethyl)-2-(4-pentenyl)-1,2-hydrazinedicarboxylic acid dimethyl ester (31).
Following the general procedure B, 13 (501 mg, 2.32 mmol) was treated with NaH (61 mg, 2.55 mmol) and chloromethyl methyl ether (260 μL, 3.47 mmol), all compounds dissolved in DMF (5 mL). After work-up and flash chromatography (ethyl acetate/hexane 1:1), 31 (534 mg, 2.05 mmol, 89%) was obtained as a light yellow oil, \( R_f 0.45 \). IR \( \nu 1715, 1690 \); \( ^1H \) NMR (200 MHz) \( \delta 1.76 (s, 3 \text{ H}, \text{ CH}_3), 3.34 (s, 3 \text{ H}, \text{ OCH}_3), 3.71-3.77 (m, 6 \text{ H}, 2 \times \text{ CO}_2\text{CH}_3), 3.81-3.88 (m, 1 \text{ H}, \text{ NCH} = \text{CH}), 4.57-4.67 (m, 1 \text{ H}, \text{ NCH} = \text{O}), 4.93-5.12 (m, 3 \text{ H}, =\text{CH} \text{ and } \text{NCH} = \text{O}), 5.97 (m, 1 \text{ H}, =\text{CH}) \).

1-(Methoxymethyl)-2-(2-methyl-2-propenyl)-1,2-hydrazinedicarboxylic acid dimethyl ester (32). According to the general procedure B, 14 (1.48 g, 7.34 mmol) was deprotonated with NaH (198 mg, 8.23 mmol) and alkylated with chloromethyl methyl ether (850 μL, 11.0 mmol), while all compounds were dissolved in DMF (20 mL). Work-up and purification by flash chromatography (ethyl acetate/hexane 1:1.5) afforded 32 (1.57 g, 6.39 mmol, 87%) as a yellowish oil, \( R_f 0.35 \). IR \( \nu 1700, 1735 \); \( ^1H \) NMR (200 MHz) \( \delta 1.76 (s, 3 \text{ H}, \text{ CH}_3), 3.34 (s, 3 \text{ H}, \text{ OCH}_3), 3.71-3.77 (m, 6 \text{ H}, 2 \times \text{ CO}_2\text{CH}_3), 3.81-3.88 (m, 1 \text{ H}, \text{ NCH} = \text{O}), 4.08-4.37 (m, 1 \text{ H}, \text{ NCH} = \text{CH}), 4.86 (br s, 2 \text{ H}, =\text{CH}_2), 4.66-4.99 (m, 2 \text{ H}, \text{ OCH}_2) \).

1-[(Z)-3-hexenyl]-(methoxymethyl)-1,2-hydrazinedicarboxylic acid dimethyl ester (33).
According to the general procedure B, 15 (509 mg, 2.21 mmol) was deprotonated with NaH (58 mg, 2.39 mmol) and alkylated with chloromethyl methyl ether (250 μL, 3.20 mmol), while all compounds were dissolved in DMF (3 mL). Work-up and purification by flash chromatography (ethyl acetate/hexane 1:1) yielded 33 (551 mg, 2.01 mmol, 91%) as a colorless oil, \( R_f 0.45 \). IR \( \nu 1715, 1690 \); \( ^1H \) NMR (200 MHz) \( \delta 1.76 (s, 3 \text{ H}, \text{ CH}_3), 2.05 (quintes, \text{ J }= 7.5 \text{ Hz}, 2 \text{ H}, \text{ CH}_2\text{CH}_2), 2.39 (q, \text{ J }= 7.1 \text{ Hz}, 2 \text{ H}, \text{ NCH}_2\text{CH}_2), 3.38 (s, 3 \text{ H}, \text{ OCH}_3), 3.74 (s, 6 \text{ H}, 2 \times \text{ CO}_2\text{CH}_3), 3.20-3.80 (m, 2 \text{ H}, \text{ NCH}_2\text{CH}_2), 4.51 (d, \text{ J }= 11.0 \text{ Hz}, 1 \text{ H}, \text{ NCH} = \text{O}), 4.93-5.13 (m, 1 \text{ H}, \text{ NCH} = \text{CH}), 5.26-5.52 (m, 2 \text{ H}, =\text{CH}) \).

1-Benzyl-2-(methoxymethyl)-1,2-hydrazinedicarboxylic acid dimethyl ester (34). Following the general procedure B, 16 (1.50 g, 6.31 mmol) was deprotonated with NaH (167 mg, 6.93 mmol) and alkylated...
with chloromethyl methyl ether (570 μL, 7.56 mmol), while all compounds were dissolved in DMF (12 mL). After work-up and flash chromatography (ethyl acetate/hexane 1:1), 34 (1.74 g, 6.17 mmol, 98%) was obtained as a light yellow oil, \( R_f \) 0.45. \( ^1H \) NMR (200 MHz) \( \delta \) (some signals appear as rotamers) 3.15, 3.30 (s, 3 H, OCH\(_3\)), 3.55, 3.75, 3.80 (s, 6 H, 2 × CO\(_2\)CH\(_3\)), 4.20-5.20 (m, 4 H, NCH\(_2\)Ph and NCH\(_2\)O), 7.32 (s, 5 H, ArH).

1-(Methoxymethyl)-2-[5-(trimethylsilyl)-3-(Z)-pentenyl]-1,2-hydrazinedicarboxylic acid dimethyl ester (35). Following the general procedure B, 19 (285 mg, 1.00 mmol) was treated with NaH (26.5 mg, 1.10 mmol) and chloromethyl methyl ether (91 μL, 1.20 mmol), while all compounds were dissolved in DMF (2 mL). Work-up and flash chromatography (ethyl acetate/hexane 1:1) afforded 35 (245 mg, 0.74 mmol, 74%) as a light yellow oil, \( R_f \) 0.45. \( ^1H \) NMR (200 MHz) \( \delta \) 0.0 (s, 9 H, (CH\(_3\))\(_3\)Si), 1.48 (d, \( J = \) 8.6 Hz, 2 H, CH\(_2\)Si), 2.37 (br s, 2 H, NCH\(_2\)CH\(_2\)), 3.39 (s, 3 H, OCH\(_3\)), 3.25-3.39 (m, 1 H, NCH\(_2\)CH\(_2\)), 3.74 (s, 6 H, 2 × CO\(_2\)CH\(_3\)), 3.71-3.80 (m, 1 H, NCH\(_2\)CH\(_2\)), 4.60 (d, \( J = \) 10.9 Hz, 1 H, NCH\(_2\))O and HC=CH).

1-(3-Butynyl)-2-(methoxymethyl)-1,2-hydrazinedicarboxylic acid dimethyl ester (36). According to the general procedure B, 21 (500 mg, 1.84 mmol) was deprotonated with NaH (49 mg, 2.02 mmol) and alkylated with chloromethyl methyl ether (168 μL, 2.21 mmol), while all compounds were dissolved in DMF (2 mL). After work-up and flash chromatography, an inseparable 1:1 mixture was obtained of silylated- and desilylated hydrazide 3. The mixture (303 mg) was dissolved in THF (10 mL) and treated with CsF (304 mg, 2.0 mmol) and \( n-Bu\)_4NF (0.2 mL of a 1.0 M solution in THF, 0.2 mmol). After being stirred at rt for 15 min, the mixture was poured into aq satd NaCl (25 mL) and extracted with CH\(_2\)Cl\(_2\) (3 x 25 mL), The combined organic layers were dried (MgSO\(_4\)), filtered and concentrated in vacuo. Purification of the crude residue by flash chromatography (ethyl acetate/hexane 1:1) afforded 36 (130 mg, 0.53 mmol, 49%) as a colorless oil, \( R_f \) 0.35. \( ^1H \) NMR (200 MHz) \( \delta \) 1.98 (br s, 1 H, C=CH), 2.56 (br s, 2 H, CH\(_2\)CS), 3.40 (s, 3 H, OCH\(_3\)), 3.53 (m, 1 H, NCH\(_2\)C and 2 x =CHC=CH), 3.75 (s, 6 H, 2 × CO\(_2\)CH\(_3\)), 3.72-3.80 (m, 1 H, NCH\(_2\)CH\(_2\)), 4.61 (d, \( J = \) 10.9 Hz, 1 H, NCH\(_2\)O), 5.08 (m, 1 H, NCH\(_2\))O and HC=CH).

1-(Methoxymethyl)-2-[4-(trimethylsilyl)-2-butynyl]-1,2-hydrazinedicarboxylic acid diallyl ester (37). According to the general procedure B, 25 (280 mg, 0.86 mmol) was deprotonated with NaH (26 mg, 1.08 mmol) and alkylated with chloromethyl methyl ether (95 μL, 1.26 mmol), while all compounds were dissolved in DMF (2 mL). Work-up and purification by flash chromatography (ethyl acetate/hexane 1:3) afforded 37 (157 mg, 0.42 mmol, 43%) as a colorless oil, \( R_f \) 0.32. \( ^1H \) NMR (200 MHz) \( \delta \) 0.02, 0.09 (s, 9 H, (O ^S i)). 3.32 (br s, 3 H, OCH\(_3\)), 3.70, 3.73, 3.74 (s, 6 H, 2 × CO\(_2\)CH\(_3\)), 3.97-4.15 (m, 1 H, NCH\(_2\)C and 2 x =CHCH\(_2\)), 4.87-5.07 (m, 2 H, NCH\(_2\)O), 5.10-5.30 (m, 4 H, 2 x =CH\(_2\)), 5.75-5.95 (m, 2 H, 2 × =CH).

1-(Methoxymethyl)-2-[3-(trimethylsilyl)-2-propenyl]-1,2-hydrazinedicarboxylic acid dimethyl ester (38). According to the general procedure B, 27 (2.00 g, 7.69 mmol) was alkylated with NaH (204 mg, 5.46 mmol) and chloromethyl methyl ether (700 μL, 9.23 mmol), while all compounds were dissolved in DMF (10 mL). Work-up and purification by flash chromatography (ethyl acetate/hexane 1:4) afforded 38 (1.91 g, 6.28 mmol, 82%) as a colorless oil, (\( \Delta /\Delta' \)) (Z)-ratio 1:1.8, \( R_f \) 0.35. \( ^1H \) NMR (200 MHz) \( \delta \) 0.02, 0.09 (s, 9 H, (CH\(_3\))\(_3\)Si), 1.43 (t, \( J = \) 2.5 Hz, 2 H, CH\(_2\)Si), 3.40 (s, 3 H, OCH\(_3\)), 4.10-4.70 (m, 6 H, NCH\(_2\)C and 2 × =CHCH\(_2\)), 4.87-5.07 (m, 2 H, NCH\(_2\)O), 5.10-5.30 (m, 4 H, 2 x =CH\(_2\)), 5.75-5.95 (m, 2 H, 2 × =CH).
Synthesis of cyclic hydrazine derivatives

**General procedure C for the cyclization reactions with TiCl₄.** To a 0.1 M solution of the hydrazide in CH₂Cl₂ was added TiCl₄ (2 equiv, as a solution of TiCl₄ in CH₂Cl₂) at -78 °C by syringe. The mixture was stirred at -78 °C for 15 min and for 3-5 h at rt. The reaction mixture was poured into cold aq satd NaHCO₃ and the resulting suspension was filtered over Celite and extracted with CH₂Cl₂ (3 x). The combined organic layers were dried (MgSO₄) and concentrated in vacuo.

Purification of the residue by flash chromatography afforded the pure cyclization product(s).

4-Chlorotetrahydro-1,2-pyridazinedicarboxylic acid dimethyl ester (39). Following the general procedure C, 28 (205 mg, 0.884 mmol) was cyclized by using TiCl₄ (1.44 mL of a 1.2 M solution, 1.72 mmol). After work-up and purification by flash chromatography (ethyl acetate/hexane 1:1), 39 (67.5 mg, 0.29 mmol, 32%) was obtained as a colorless oil, Rₜ 0.30. IR ν 1715; ¹H NMR (200 MHz) δ 1.70-2.20 (m, 2 H, 2 x H₅), 2.94-3.00 (m, 1 H, HS₅), 3.25-3.47 (m, 1 H, 3.72 (s, 6 H, 2 x CO₂CH₃), 3.70-4.43 (m, 3 H, and H₄); ¹H NMR (250 MHz, C₆D₆, 70 °C) δ 1.25-1.50 (m, 2 H, 2 x H₅), 2.54 (dt, J₁ = 2,12.1 Hz, H₅), 2.81 (t, J₂ = 12.0 Hz, 1 H, M₅), 3.40 (s, 6 H, CO₂CH₃), 3.8-4.0 (m, 2 H, and 4.3-4.4 (m, 1 H, H₄); ¹3C NMR (63 MHz) δ 34.3 (C₅), 50.2, 52.0 (C₃ and C₆), 51.3 (C₄), 53.3, 54.1 (2 x CO₂CH₃); MS (El, 70 eV) m/z (relative intensity) 236 (90, M⁺), 205 (6), 201 (15), 177 (90), 59 (100); HRMS calcd for C₈H₁₃N₂O₄Cl 236.0564, found 236.0567.

5-Chlorotetrahydro-1//-l,2-diazepine-l,2(3//-)dicarboxylic acid dimethyl ester (40). According to the general procedure C, 30 (210 mg, 0.854 mmol) was cyclized by using TiCl₄ (0.81 mL of a 2.1 M solution, 1.71 mmol). After work-up and purification by flash chromatography (ethyl acetate/hexane 1:1) afforded 40 (175 mg, 0.700 mmol, 82%) as a yellowish oil, Rₜ 0.32. IR ν 1720, 1695; ¹H NMR (250 MHz) δ 1.94-2.15 (m, 4 H, 2 x H₄ and 2 x H₆), 3.25-3.40 (m, 2 H, H₃ and H₇), 3.68 (s, 6 H, 2 x CO₂CH₃), 3.90-4.10 (m, 2 H, H₃ and H₇), 4.28-4.35 (m, 1 H, H₅); ¹3C NMR (50 MHz) δ (some signals appear as rotamers) 34.5, 34.7, 36.2, 36.7 (C₄ and C₆), 45.3, 45.5, 45.7 (C₃ and C₇), 53.2 (2 x CO₂CH₃), 58.0 (C₅), 155.4, 155.8 (C(O)); MS (EL, 70 eV) m/z (relative intensity) 250 (65, M⁺), 215 (100), 191 (65), 59 (76); HRMS calcd for C₉H₁₅N₂O₄Cl 250.0721, found 250.0721.

5-Chlorohexahydro-l,2-diazocine-l,2-dicarboxylic acid dimethyl ester (41). Hydrazide 31 (200 mg, 0.770 mmol) was cyclized by using TiCl₄ (0.81 mL of a 2.1 M solution, 1.71 mmol). After work-up and purification by flash chromatography (ethyl acetate/hexane 1:1) afforded 41 (175 mg, 0.700 mmol, 82%) as a yellow oil, Rₜ 0.30. IR ν 1720, 1695; ¹H NMR (200 MHz) δ 1.48-1.80 (m, 2 H, 2 x H₇), 2.07-2.21 (m, 4 H, 2 x H₄ and 2 x H₆), 3.07-3.43 (m, 2 H, H₃ and H₈), 3.72, 3.75, 3.78 (s, 6 H, CO₂CH₃), 3.84-4.18 (m, 2 H, H₃ and H₈), 4.25-4.30 (m, 1 H, H₅); ¹3C NMR (63 MHz) δ (all signals appear as rotamers) 148-180 (m, 2 H, 2 x H₇), 2.07-2.21 (m, 4 H, 2 x H₄ and 2 x H₆), 2.81 (s, 6 H, CO₂CH₃), 3.84-4.18 (m, 2 H, H₃ and H₈), 4.25-4.30 (m, 1 H, H₅); ¹3C NMR (63 MHz) δ (all signals appear as rotamers) 22.4, 22.8 (CH₂), 32.4, 32.7 (CH₂), 35.8, 36.2 (CH₂), 43.5, 43.8 (CH₂), 47.8, 48.5 (CH₂), 53.3, 53.5 (2 x CO₂CH₃), 59.7, 60.0 (CH); MS (EL, 70 eV) m/z (relative intensity) 264 (20, M⁺), 229 (78), 205 (43), 59 (100); HRMS calcd for C₁₀H₁₃N₂O₄Cl 264.0877, found 264.0894.

4-Chlorotetrahydro-4-methyl-1,2-pyridazinedicarboxylic acid dimethyl ester (42). According to
Hash chromatography (ethyl acetate/hexane 1:1) yielded 35 (15 mg) and 46 (57 mg, 0.25 mmol, 54% (after correction)) as a colorless oil, R_f 0.30. IR v 1744, 1705; 1H NMR (250 MHz) δ (some signals appear as rotamers) 1.56 (s, 3 H, CH3), 1.67-1.79 (m, 2 H, 2 x H4), 2.91, 3.06 (d, J = 14 Hz, 1 H, H6g), 3.40-3.44 (m, 1 H, H3g), 3.73, 3.74 (s, 6 H, 2 x CO2CH3), 4.0-4.4 (m, 1 H, H3g). 4.13, 4.32 (dd, J = 14.4, 1.9 Hz, H6g); 13C NMR (50 MHz) δ (some signals appear as rotamers) 29.7, 29.8 (CH3), 38.9 (C5), 53.2, 53.6 (2 x CO2CH3), 55.6, 57.3 (C3 and C6), 66.1, 66.4 (C4), 155.3, 155.7 (2 x C(O)); MS (EI, 70 eV) m/z (relative intensity) 250 (100, M+), 191 (76), 59 (83); HRMS calcd for C9H15N2O4Cl2 250.0720, found 250.0716.

Chapter 2

Cyclization of hydrazide 33. According to the general procedure C, 33 (200 mg, 0.730 mmol) was cyclized with 1,4-dihydro-2,3-phthalazinedicarboxylic acid dimethyl ester (45). Following the general procedure C, 34 (640 mg, 2.27 mmol) was cyclized by using TiCl4 (1.22 mL of a 1.2 M solution, 1.46 mmol). Work-up and purification by flash chromatography (ethyl acetate/hexane 1:1) afforded an inseparable mixture of 4-(1-chloropropyl)tetrahydro-1,2,2-pyridazinedicarboxylic acid dimethyl ester (43) and 5-chloro-4-ethyltetrahydro-1H-1,2-diazepine-1,2(3H)-dicarboxylic acid dimethyl ester (44) (80 mg, 0.285 mmol, 39%) as a colorless oil, R_f 0.30. IR v 1710, 1705; 1H NMR (250 MHz) δ 1.0-1.20 (m, 6 H, 2 x CH2), 1.25-1.30 (m, CH2CH2, NCH2CH2 and CH), 2.40-3.10 (m, NCH), 3.75 (s, CO2CH3), 4.0-4.4 (m, NCH and CHC1); 13C NMR (50 MHz) δ 10.9, 25.6, 27.8, 28.4, 28.5, 29.3, 32.2, 41.3, 43.6, 44.2, 44.0, 50.0, 53.4, 54.9, 66.3, 66.7, 155.6; MS (EI, 70 eV) m/z (relative intensity) 278 (100, M+), 243 (25), 219 (7), 197 (58), 59 (42); HRMS calcd for C11H19N2O4Cl2 278.1027, found 278.1025.

4-Ethenylenedioxy-1,2-pyridazinedicarboxylic acid dimethyl ester (46). To a solution of 35 (153 mg, 0.47 mmol) in CH2Cl2 (5 mL) was added at 0 °C BF3·OEt2 (116 μL, 0.93 mmol). After being stirred at 0 °C for 15 min and at rt for 16 h, the reaction mixture was poured into aq satd NaCl (50 mL) and extracted with CH2Cl2 (3 x 50 mL). The combined organic layers were dried (MgSO4), filtered and concentrated in vacuo. Flash chromatography (ethyl acetate/hexane 1:1) yielded 35 (15 mg) and 46 (57 mg, 0.25 mmol, 54% (after correction)) as a colorless oil, R_f 0.32. IR v 1700, 1710; 1H NMR (200 MHz) δ 1.38-1.60 (m, 1 H, H5g), 1.71-1.87 (m, 1 H, H5g), 2.20-2.40 (m, 1 H, H4), 2.60-2.70 (m, 1 H, H3g), 2.80-3.00 (m, 1 H, H6g), 3.73 (s, 6 H, 2 x CO2CH3), 4.10-4.20 (m, 2 H, H3g and H6g), 5.07 (d, J = 10.8 Hz, 1 H, H6g), 5.10 (d, J = 17.0 Hz, 1 H, =CH2), 5.62 (ddd, J = 6.4, 10.8, 17.0 Hz, 1 H, =CH); 1H NMR (200 MHz, DMSO-d6, 70 °C) δ 1.44 (s, J = 4.5, 12.8 Hz, H8g), 1.76 (d, J = 12.0 Hz, 1 H, H5g), 2.37 (m, 1 H, H4), 2.73 (t, J = 12.4 Hz, 1 H, H3g), 3.00 (dt, J = 1.5, 13.1 Hz, 1 H, H6g), 3.69 (s, 6 H, 2 x CO2CH3), 4.04-4.30 (m, 2 H, H3g and H6g), 5.07 (d, J = 10.0 Hz, 1 H, =CH2), 5.13 (d, J = 16.0 Hz, 1 H, =CH); 13C NMR (50 MHz) δ 29.5 (C5), 38.3 (C4), 44.0, 50.0 (C3 and C6), 53.4 (2 x CO2CH3), 138.1 (=CH), 155.6 (2 x C(O)); MS (EI, 70 eV) m/z (relative intensity) 228 (100, M+), 197 (6), 169 (85), 59 (37); HRMS calcd for C10H16N2O4 228.1110, found 228.1108.
5-Chloro-4,7-dihydro-1H-1,2-diazepine-1,2(3H)-dicharboxylic acid dimethyl ester (47). Following the general procedure C, 36 (111 mg, 0.455 mmol) was cyclized by using TiCl₄ (0.76 mL of a 1.2 M solution, 0.91 mmol). Work-up and purification by flash chromatography yielded 47 (90 mg, 0.40 mmol, 80%) as a colorless oil, Rₜ 0.33. IR ν 1725, 1705; ¹H NMR (200 MHz) δ (some signals appear as rotamers) 1.75-1.95 (m, 1 H, H₆), 2.40-2.60 (m, 1 H, H₆), 2.8-3.0 (m, 1 H, H₇), 3.30-4.20 (m, 2 H, H₇ and H₃), 3.75 (s, 6 H, 2 x CO₂CH₃), 4.5-4.8 (m, 1 H, H₃), 5.72 (t, J = 3 Hz, 1 H, H₅); ¹³C NMR (50 MHz) δ (some signals appear as rotamers) 33.9 (C₆), 44.2 (C₃ and C₇), 53.3 (2 x CO₂CH₃), 123.3 (C₅), 155.4 (2 x C(0)); MS (El, 70 eV) m/z (relative intensity) 248 (14, M⁺), 213 (26), 189 (28), 59 (100).

4-Ethenylidene-1,2-pyrazolidinedicarboxylic acid diallyl ester (48). BF₃·OEt₂ (60 μL, 0.48 mmol) was added at 0 °C to a solution of 37 (88 mg, 0.24 mmol) in CH₂Cl₂ (3 mL). After being stirred at 0 °C for 15 min and 7 h at rt, the solution was poured into aq satd NaCl (5 mL) and extracted with CH₂Cl₂ (4 x 5 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo. The residue was chromatographed (ethyl acetate/hexane 1:6) to yield 48 (38 mg, 0.14 mmol, 60%) as a light yellow oil, Rₜ > 0.33. IR ν 3080, 1965, 1720; ¹H NMR (200 MHz) δ 3.91-4.04 (br m, 2 H, 2 x NC≡CH), 4.58-4.67 (m, 6 H, 2 x NCH₂ and 2 x OCH₂), 4.99 (quintet, J = 4.2 Hz, 2 H, C=C=CH₂), 5.19-5.36 (m, 4 H, 2 x CH=O), 5.81-6.01 (m, 2 H, 2 x =CH); ¹³C NMR (50 MHz) δ 49.3 (2 x NCH₂), 67.1 (2 x OCH₂), 80.9 (CM=CH₂), 97.0 (C=C=CH₂), 118.1 (2 x CH=CH₂), 131.9 (2 x =CH), 156.4 (2 x C(0)), 198.3 (C=C=CH₂).

3,6-Dihydro-1,2-pyridazinedicarboxylic acid dimethyl ester (49). BF₃·OEt₂ (205 μL, 1.64 mmol) was added to a solution of 38 (250 mg, 0.822 mmol) in CH₂Cl₂ (8 mL) at 0 °C. After being stirred at 0 °C for 15 min and 18 h at rt, the solution was poured into aq satd NaCl (50 mL) and extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo. Flash chromatography (ethyl acetate/hexane 1:1) afforded 49 (127 mg, 0.635 mmol, 77%) as a colorless oil, Rₜ > 0.35. IR ν 1700, 1440; ¹H NMR (200 MHz) δ 3.73 (s, 6 H, 2 x CO₂CH₃), 3.81 (br s, 2 H, 2 x NCH₂), 4.35 (br s, 2 H, 2 x NCH₂), 5.75 (br s, 2 H, HC=CH); ¹³C NMR (63 MHz) δ 44.1 (2 x NCH₂), 53.2 (2 x CO₂CH₃), 123.5 (2 x CH), 155.7 (2 x C(0)); MS (El, 70 eV) m/z (relative intensity) 200 (M⁺, 10), 141 (25), 59 (100).

1-(Chloromethyl)-2-(2-propenyl)-1,2-hydrazinedicarboxylic acid dimethyl ester (56). To a solution of 28 (317 mg, 1.36 mmol) in CCl₄ (5 mL) was added PCl₅ (460 mg, 2.18 mmol) and the mixture was stirred at rt for 24 h. The reaction was followed by ¹H NMR. The mixture was concentrated in vacuo and the residue was taken up in hexane (5 mL). After separation of the sticky residue and concentration in vacuo of the organic layer, 56 (198 mg, 0.84 mmol, 62%) was obtained as a light yellow oil, Rₜ 0.40 (ethyl acetate/hexane 1:1). IR ν 1720, 1440; ¹H NMR (200 MHz) δ 3.72 (s, 6 H, 2 x CO₂CH₃), 4.08 (t, J = 7 Hz, 2 H, C≡CH₂), 5.0-6.3 (5 H, NCH₂Cl and CH=CH₂).

1-(Chloromethyl)-2-(4-pentenyl)-1,2-hydrazinedicarboxylic acid dimethyl ester (57). To a solution of 31 (311 mg, 1.20 mmol) in CCl₄ (6 mL) was added PCl₅ (370 mg, 1.80 mmol). After being stirred at rt for 42 h, the mixture was concentrated in vacuo, dissolved in hexane and the residue was separated. After concentration in vacuo of the organic layer, 57 (293 mg, 1.11 mmol, 94%) was obtained as a light yellow oil, IR ν 1720; ¹H NMR (200 MHz) δ 1.79 (m, 2 H, CH₂CH₂CH=), 2.06 (q, J = 7.2 Hz, 2 H, CH₂CH₃), 3.31 (dt, J = 7.2, 12.0 Hz, 1 H, NCH₃), 3.75 (s, 6 H, 2 x CO₂CH₃), 3.76 (d, J = 12 Hz, 1 H, NCH₃), 4.92-5.05 (m, 3 H, NCH₂Cl and =CH₂), 5.69-5.85 (m, 2 H, NCH₂Cl and =CH₂); ¹³C NMR (63 MHz) δ (some signals appear as rotamers) 27.2 (CH₂CH₂CH=), 30.8 (CH₂CH₃=), 50.8 (t, NCH₂CH₂), 53.5, 54.1 (CO₂CH₃), 61.4, 61.5.
1-(Chloromethyl)-2-[(Z)-3-hexenyl]-1,2-hydrazinedicarboxylic acid dimethyl ester (58). To a solution of 33 (200 mg, 0.370 mmol) in CCl₄ (6 mL) was added PVC (230 mg, 1.10 mmol) and the mixture was stirred at rt for 64 h. After concentration in vacuo, taking up the residue in hexane and separation of the remaining residue, the organic layer was concentrated in vacuo to afford 58 (184 mg, 0.66 mmol, 91%) as a light yellow oil. IR v 1730, 1700; ¹H NMR (200 MHz) δ 0.95 (t, J = 7.5 Hz, 3 H, CH₂C₃H₃), 2.06 (quintet, J = 7.3 Hz, 2 H, CH₂CH₃), 2.30-2.50 (m, 2 H, NCH₂C₃H₃), 3.26-3.31 (m, 1 H, NCWHCH₂), 3.77 (s, 6 H, 2 x CO₂CH₃), 3.71-3.85 (m, 1 H, NCH₃CH₂), 4.77-5.80 (m, 4 H, NCH₂C₁ and HC=CH).

Cyclization of chloride 56. According to the general procedure C, 56 (198 mg, 0.837 mmol) was cyclized by using TiCl₄ (1.39 mL of a 1.2 M solution, 1.67 mmol). After work-up and purification by flash chromatography (ethyl acetate/hexane 1:1), 39 (138 mg, 0.58 mmol, 68%) was obtained as a colorless oil, Rf 0.30.

Cyclization of chloride 57. Following the general procedure C, 57 (213 mg, 0.805 mmol) was cyclized by using TiCl₄ (1.34 mL of a 1.2 M solution, 1.61 mmol). Work-up and purification by flash chromatography (ethyl acetate/hexane 1:1) afforded 41 (17 mg, 0.06 mmol, 8%) as a colorless oil, Rf 0.35 and 2,3,3a,4,5,6-hexahydro-1H-1H-pyrrolo[1,2-b]pyrazolecarboxylic acid methyl ester (59) (53 mg, 0.31 mmol, 39%) as a colorless oil, Rf 0.10.

Cyclization of chloride 58. According to the general procedure C, 58 (137 mg, 0.492 mmol) was cyclized by using TiCl₄ (0.81 mL of a 1.2 M solution, 0.98 mmol). After work-up and purification by flash chromatography (ethyl acetate/hexane 1:2) two fractions were obtained containing a mixture of 43 and 44 (27 mg, 0.097 mmol, 20%) as a colorless oil, Rf 0.35, and 4-[1-(E)-propenyl]tetrahydro-1H-1,2-pyrazinedicarboxylic acid dimethyl ester (60) (35 mg, 0.145 mmol, 29%) as a colorless oil, Rf 0.17. ¹H NMR (200 MHz) δ 6.4-6.7 (m, 2 H, H4), 2.0-2.1 (m, 1 H, H5), 4.7-5.0 (m, 1 H, H6), 3.74 (s, 6 H, 2 x CO₂CH₃), 3.90 (s, 6 H, 2 x CO₂CH₃), 5.11 (t, J = 8.0 Hz, 1 H, H5), 7.98 (s, 1 H, CHO); ¹3C NMR (50 MHz) δ 30.9, 31.8, 32.3 (C4 and C6), 44.4, 45.0 (C3 and C7), 53.3 (2 x CO₂CH₃), 71.2 (C5), 155.5, 159.9 (3 x C(O)); MS (EI, 70 eV) m/z (relative intensity) 248 (100, M⁺), 211 (5), 183 (52), 59 (40).

5-(Formyloxy)tetrahydro-1H,1,2-diazepine-1,2(3H)-dicarboxylic acid dimethyl ester (61). A solution of 30 (223 mg, 0.91 mmol) in HCOOH (5 mL) was stirred at 40 °C for 18 h, the mixture was concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexane 2:1) yielded 61 (179 mg, 0.69 mmol, 76%) as a colorless oil, Rf 0.20. IR v 1710, 1695; ¹H NMR (200 MHz) δ 1.40-1.55 (m, 1 H, H5), 1.63-1.66 (m, 1 H, H6), 2.20-2.40 (m, 1 H, H4), 2.60-2.75 (m, 1 H, H3), 2.85-3.05 (m, 1 H, H8), 3.74 (s, 6 H, 2 x CO₂CH₃), 3.90-4.30 (m, 2 H, H7), 5.20 (dd, J = 8.5, 15.2 Hz, 1 H, H6), 5.49 (dt, J = 15.2, 6.3 Hz, 1 H, H5); ¹3C NMR (50 MHz) δ 13.5 (CHO), 20.5 (CH₂), 22.1 (C4), 23.9 (C5), 31.6 (C6), 44.0, 49.5 (C3 and C6), 53.4 (2 x CO₂CH₃), 126.5, 131.0 (CH=CH), 155.7 (2 x C(O)); MS (EI, 70 eV) m/z (relative intensity) 260 (26, M⁺), 229 (4), 215 (36), 201 (6), 155 (100), 59 (87); HRMS calcd for C₁₄H₁₄N₂O₂ 248.1057, found 248.1042.
Synthesis of cyclic hydrazine derivatives

Tetrahydro-5-oxo-1H-1,2-diazepine-1,2(3H)-dicarboxylic acid dimethyl ester (62). A solution of 36 (80 mg, 0.33 mmol) in HCOOH (2 mL) was stirred at 40 °C for 42 h. After addition of water (1 mL) and being stirred at rt for 2 h, the reaction mixture was poured into water (30 mL) and extracted with CH2Cl2 (3 × 25 mL). The combined organic layers were washed withaq satd NaHCO3 (25 mL), dried (MgSO4), filtered and concentrated in vacuo. Purification of the residue by flash chromatography (ethyl acetate/hexane 1:1) afforded 62 (63 mg, 0.27 mmol, 83%) as a colorless oil, Rf 0.20. IR v 1710,1695; 1H NMR (200 MHz) δ 2.51-2.83 (m, 4 H, 2 × H4 and 2 × H6), 3.21-3.38 (m, 2 H, H3 and H7), 3.74 (s, 6 H, 2 × CO2CH3), 4.04-4.27 (m, 2 H, H3 and H7); 13C NMR (50 MHz) δ 42.7 (C4 and C6), 42.9 (C3 and C7), 53.6 (2 × CO2CH3), 208.2 (C5); MS (EI, 70 eV) m/z (relative intensity) 230 (93, M+), 199 (12), 171 (47), 101 (100), 59 (98); HRMS calcd for C9H14N2O5 230.0903, found 230.0906.

Tetrahydro-5-oxo-1H-1,2-diazepine-1,2(3H)-dicarboxylic acid diethyl ester (64). Following the general procedure B, 22 (14.0 g, 47.0 mmol) was deprotonated with NaH (1.23 g, 51 mmol) and alkylated with 2-(ethoxymethoxy)methyl chloride (6.96 mL, 56 mmol), while all compounds were dissolved in DMF (80 mL). After work-up and concentration in vacuo, the alkylated product 65 was obtained as a 2:1 mixture of silylated and desilylated product (2-1). The viscous brown oil was dissolved in HCOOH (500 mL) and stirred at 60 °C for 66 h. After addition of water (250 mL) and being stirred at rt for 5 h, the dark brown solution was extracted with CH2Cl2 (4 × 400 mL). The combined organic layers were washed withaq satd NaHCO3 until the washings had a basic pH, dried (MgSO4), filtered and concentrated in vacuo. Flash chromatography (ethyl acetate/hexane 1:1) afforded 64 (7.76 g, 30.1 mmol, 64%) as a viscous light yellow oil, Rf 0.35. IR v 1725,1705; 1H NMR (200 MHz) δ 1.22 (t, J = 7.0 Hz, 6 H, 2 × CH2CH3), 2.51-2.76 (m, 4 H, 2 × H4 and 2 × H6), 3.21-3.38 (m, 2 H, H3 and H7), 4.13-4.19 (m, 2 H, H3 and H7), 4.16 (q, J = 7.0 Hz, 4 H, 2 × CH2CH3).

Tetrahydro-5-oxo-1H-1,2-diazepine-1,2(3H)-dicarboxylic acid diallyl ester (66). According to the general procedure B, 20 (7.59 g, 23.3 mmol) was treated with NaH (675 mg, 28.0 mmol) and 2-(ethoxymethoxy)methyl chloride (3.77 g, 30.3 mmol), while all compounds were dissolved in DMF (40 mL). After work-up and concentration in vacuo, the alkylated product 65 was obtained as a 2:1 mixture of silylated and desilylated product (2-1). This viscous dark oil was dissolved in HCOOH (300 mL) and stirred at 60 °C for 60 h. The dark brown solution was diluted with water (150 mL) and stirred at rt for 5 h before it was extracted with CH2Cl2 (5 × 150 mL). The combined organic layers were washed withaq satd NaHCO3 until the washings had a basic pH, dried (MgSO4), filtered and concentrated in vacuo. The residue was subjected to flash chromatography (ethyl acetate/hexane 1:1) to give 66 (3.45 g, 12.2 mmol, 53%) as a colorless oil, Rf 0.35. IR v 3080, 1720, 1705; 1H NMR (200 MHz) δ 25.4-3.86 (m, 4 H, 2 × H4 and 2 × H6), 3.19-3.40 (m, 2 H, H3 and H7), 4.05-4.19 (m, 2 × H4, 2 × H6, 2 × H3 and H7), 4.62 (br s, 4 H, 2 × OCH2), 5.17-5.31 (m, 4 H, 2 × =CH2), 5.79-5.98 (m, 2 H, 2 × =CH); 13C NMR (50 MHz) δ 42.6 (C4 and C6), 44.1 (C3 and C7), 67.0 (OCH2), 118.3 (−CH2), 131.9 (−CH), 208.1 (C(O)); MS (EI, 70 eV) m/z (relative intensity) 282 (M+, 35), 197 (37), 153 (67), 41 (100), 17 (100); HRMS calcd for C13H18N2O5 282.1216, found 282.1222.

1-[(Formyloxy)methyl]-2-(2-propenyl)-1,2-hydrazinedicarboxylic acid dimethyl ester (70). To a solution of 10 (314 mg, 1.67 mmol) in HCOOH (10 mL) was added 1,3,5-trioxane (201 mg, 2.22 mmol) and the mixture was stirred at 70 °C for 18 h. Concentration in vacuo and purification by flash chromatography (ethyl acetate/hexane 1:1) afforded 70 (189 mg, 0.77 mmol, 46%) as a colorless oil, Rf 0.50. IR v 1740, 1710; 1H
Cyclization of 12 with 1,3,5-trioxane/HCOOH to 61. To a solution of 12 (313 mg, 1.55 mmol) in HCOOH (5 mL) was added 1,3,5-trioxane (181 mg, 2.0 mmol) and the mixture was stirred at 40 °C for 16 h. Concentration in vacuo and purification by flash chromatography (ethyl acetate/hexane 1:1) yielded 12 (92 mg, 0.45) and 61 (112 mg, 0.431 mmol, 40% (after correction)) as a colorless oil.

Cyclization of 16 with 1,3,5-trioxane/HCOOH to 45. To a solution of 16 (519 mg, 2.18 mmol) in HCOOH (10 mL) was added 1,3,5-trioxane (260 mg, 2.88 mmol) and the mixture was stirred at 80 °C for 20 h. Concentration in vacuo and purification by flash chromatography (ethyl acetate/hexane 1:1) yielded 45 (506 mg, 2.02 mmol, 93%) as a colorless oil.

Cyclization of 16 with (CH₂O)n/HCOOH to 45. To a solution of 16 (810 mg, 3.40 mmol) in HCOOH (10 mL) was added (CH₂O)n (189 mg, 6.3 mmol) and the mixture was stirred at 70 °C for 18 h. Concentration in vacuo and purification by flash chromatography (ethyl acetate/hexane 1:1) afforded 45 (629 mg, 2.52 mmol, 74%) as a light yellow oil.

1.4-Dihydro-2,3-phthalazinedicarboxylic acid diisopropyl ester (71). To a solution of 17 (297 mg, 1.01 mmol) in HCOOH (8 mL) was added 1,3,5-trioxane (118 mg, 1.31 mmol) and the mixture was stirred at 90 °C for 20 h. Concentration in vacuo and purification by flash chromatography (ethyl acetate/hexane 1:1) yielded 71 (198 mg, 0.647 mmol, 64%) as white crystals, mp 97-99 °C, Rf 0.45. IR ν 1700; ¹H NMR (200 MHz) δ 1.25 (d, J = 6.2 Hz, 12 H, 2 × (CH₃)₂CH), 4.37 (d, J = 15.7 Hz, 2 H, 2 × NCH₃), 4.97 (septet, J = 6.2 Hz, 2 H, 2 × (CH₃)₂CH), 5.09 (d, J = 15.7 Hz, 2 H, 2 × NCH₃), 7.20 (m, 4 H, ArH); ¹³C NMR (50 MHz) δ 22.0, 22.1 ((CH₃)₂CH), 45.3 (NCH₃), 70.1 ((CH₃)₂CH), 126.3, 126.8 (ArH), 132.0 (ArC); Anal. Calcd. for C₁₆H₂₂N₂O₄: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.64; H, 7.21; N, 9.04.

Cyclization of 17 with HC(OH)/(CH₂O)n to 71. To a solution of 17 (297 mg, 1.01 mmol) in HCOOH (10 mL) was added (CH₂O)n (45.5 mg, 1.52 mmol) and the mixture was stirred at 60 °C for 20 h. Concentration in vacuo and flash chromatography (ethyl acetate/hexane 1:1) afforded 71 (197 mg, 0.64 mmol, 64%) as a white solid, Rf 0.45.

1-Benzyl-1,2-di(methoxycarbonyl)hydrazineacetic acid ethyl ester (72). According to the general procedure B, 16 (5.01 g, 21.1 mmol) was deprotonated with NaH (557 mg, 23.1 mmol) and alkylated with ethyl chloroacetate (2.66 mL, 25.3 mmol), while all compounds were dissolved in DMF (30 mL). After work-up and flash chromatography (ethyl acetate/hexane 1:6) 72 (6.19 g, 19.1 mmol, 91%) was obtained as a light yellow oil, Rf 0.32. IR ν 1745, 1720, 1705, 695; ¹H NMR (200 MHz) δ 1.18 (d, J = 7.2 Hz, 3 H, CH₃CH₂CH₂), 4.06 (q, J = 7.1 Hz, 2 H, CH₂CH₂), 4.25-4.30 (m, 1 H, NCH₂), 4.54 (d, J = 15.1 Hz, 1 H, NCH₂Ph), 4.88 (d, J = 15.1 Hz, 1 H, NCH₂Ph), 5.0-5.25 (m, 1 H, NCH₂), 7.24-7.39 (m, 5 H, ArH).

Ethyl [N-benzyl-N-(methoxycarbonyl)amino][N-(methoxycarbonyl)amino]acetate (73). LDA was prepared from diisopropylamine (0.27 mL, 1.94 mmol) and n-butyllithium (1.21 mL of a 1.6 M solution in 54
hexane, 1.94 mmol) in THF (5 mL) at 0 °C. PhSSPh (203 mg, 0.93 mmol) was added to this solution and the mixture was added dropwise via syringe to a solution of 72 (300 mg, 0.93 mmol) in THF (10 mL) at -78 °C. After being stirred at -78 °C for 30 min and 1 h at rt, the mixture was poured into aq satd NH₄Cl (20 mL) and extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo. After flash chromatography (ethyl acetate/hexane 1:4), 73 (122 mg, 0.377, 41%) was obtained as a colorless oil, Rf 0.35. IR ν 3410, 1740, 1710, 1690, 690; ¹H NMR (200 MHz) δ (some signals appear as rotamers) 1.17 (t, J = 6.7 Hz, 2 H, CH₂CH₃), 3.67, 3.73 (s, 3 H, CO₂CH₃), 4.10 (q, J = 6.7 Hz, 2 H, CH₂CH₃), 4.50 (d, J = 15.9 Hz, 1 H, NCH₂), 4.80 (d, J = 15.9 Hz, 1 H, NCH₂), 5.36-5.49 (m, 1 H, CH), 6.0, 6.31 (br s, 1 H, NH), 7.30-7.36 (m, 5 H, ArH); ¹³C NMR (200 MHz) δ 164 (2 x C(O)), 151.9, 127.4, 127.9 (ArC), 136.6 (ArC), 156.3, 167.4 (C(O)); MS (EI, 70 eV) m/z (relative intensity) 252.1110, found 252.1149.

5,5-Ethynedioxytetrahydro-1H-1,2-diazepine-1,2(3H)-dicarboxylic acid diethyl ester (77). A solution of 45 (140 mg, 0.551 mmol) in THF (5 mL) was added to a solution of Li (15.3 mg, 2.20 mmol) in anhydrous NH₃ (294 mg, 5.50 mmol) and the ammonia was allowed to evaporate. The residue was dissolved in water (20 mL) and extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were dried (MgSO₄), filtered, concentrated in vacuo and chromatographed (ethyl acetate/hexane 1:4) to yield 77 (500 mg, 1.66 mmol) as a white solid, mp 84-85 °C (ethyl acetate/hexane 1:5), Rf 0.50. IR ν 3440, 1710, 1510; ¹H NMR (200 MHz) δ 1.17 (t, J = 6.7 Hz, 2 H, CH₂CH₃), 1.82 (t, J = 7.1 Hz, 4 H, 2 x CH₂CH₃), 3.67, 3.73 (s, 3 H, CO₂CH₃), 4.06 (q, J = 6.7 Hz, 4 H, 2 x CH₂CH₃), 5.18 (br s, 2 H, 2 x NH); ¹³C NMR (50 MHz) δ 14.4 (2 x CH₂CH₃), 36.0 (2 x CH₂O), 42.5 (2 x NCH₂), 60.4 (2 x CH₂CH₃), 64.2, 65.4 (CH), 127.3, 127.9 (ArH), 136.6 (ArC), 156.3, 164.0 (CH₃), 167.4 (C(O)).
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64.6 (2 x OCH₂), 110.3 (C), 155.5 (2 x C(0)); Anal. Calcd. for C₁₃H₂₄N₂O₆: C, 51.31; H, 7.95; N, 9.20.
Found: C, 51.24; H, 7.86; N, 9.28.

2.12 REFERENCES AND NOTES


Chapter 2

41) For the di-tert-butyl ester, see ref 4a.

CHAPTER 3
DEPROTECTION OF 1,2-DIALLYLOXYCARBONYLHYDRAZINES

3.1 INTRODUCTION

In the previous Chapter, the synthesis of various protected cyclic hydrazine compounds via an intramolecular N,N'-diacylhydrazonium ion cyclization has been described. In this Chapter, a method to obtain the free hydrazines 2 will be discussed, as well as some further reactions with these hydrazines to form the bicyclic products 3 (eq 3.1).

Various procedures are known to cleave methyl and ethyl carbamates, which include basic hydrolysis (e.g., KOH, MeOH) and cleavage with Me$_3$SiH. These methods have also been applied to deprotect hydrazines with good results, but often suffer from formation of side products. This is particularly true for the seven-membered rings, which are easily oxidized (even by air) to the corresponding hydrazones. Several attempts to deprotect some hydrazines of type 1 did not lead to reproducible results upon use of either of these methods.

3.2 THE ALLYLOXYCARBONYL (ALLOC) FUNCTION AS A PROTECTIVE GROUP

The use of allyl and allyloxy carbonyl functions as protective groups is based on the well-known palladium-catalyzed allylic alkylation method. Allyl esters, allyl carbonates and allyl carbamates have been used in various fields of chemistry like β-lactam chemistry and peptide, glycopeptide and oligonucleotide synthesis. Although other methods are known for removal of this protective group, the deprotection is most frequently carried out under relatively mild conditions using a palladium(0) catalyst in the presence of a nucleophile (eq 3.2).

In this reaction, the palladium catalyst will react with the allyloxy carbonyl moiety of the carbamate 4 to form a π-allylpalladium complex, which is attacked by the nucleophile to give the...
free amine 5, the allylated nucleophile and carbon dioxide. Several compounds have been studied as the nucleophile in this process, including potassium 2-ethylhexanoate, morpholine, dimedone, formic acid, and n-butylamine.

### 3.3 DEPROTECTION OF ALLOC PROTECTED HYDRAZINES

As model systems for these deprotection reactions both the ketone 6 and its protected analog 7 were chosen. Deprotection of both compounds upon use of standard conditions (10% Pd(PPh$_3$)$_4$, 0.6 equiv PPh$_3$, excess of the nucleophile, THF, rt) led to rather disappointing results which are summarized in Table 3.1.

<table>
<thead>
<tr>
<th>entry</th>
<th>Alloc compound</th>
<th>nucleophile (equiv)</th>
<th>solvent</th>
<th>products (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Alloc N=O</td>
<td>HCOOH (10)</td>
<td>THF</td>
<td>8 (49%)</td>
</tr>
<tr>
<td>2</td>
<td>Alloc N=O</td>
<td>n-BuNH$_2$ (10)</td>
<td>THF</td>
<td>9 (55%) + 10 (12%)</td>
</tr>
<tr>
<td>3</td>
<td>Alloc N=O</td>
<td>n-BuNH$_2$</td>
<td>n-BuNH$_2$</td>
<td>10 (49%)</td>
</tr>
</tbody>
</table>

Depending on the nucleophile that was used, either diallylhydrazine 8 was formed (entry 1), or a mixture of allylhydrazine 9 and azo compound 10 (entry 2). Formation of the NN double bond was indicated by an absorbance in the UV spectrum at 380 nm. If the reaction, work-up and purification were not carefully carried out under an inert nitrogen atmosphere, oxidation of allylhydrazine 9 to the corresponding allylhydrazone 11 took place rapidly (eq 3.3). Upon using n-BuNH$_2$ as the solvent, N-allylation was not observed and azocompound 10 was the only product that could be detected (entry 3).

\[ \text{Alloc N=O} + \text{HCOOH} \rightarrow \text{Alloc H$_2$N=O} + \text{8 (49%)} \]

These results can be explained by the reaction sequence shown in Scheme 3.1. Pd(PPh$_3$)$_4$ dissociates to react with the allyl carbamate under the formation of the π-allylpalladium complex 13. This intermediate can react with any nucleophile present in the reaction mixture. Either formic acid or n-butylamine can act as a nucleophile, but also a (partly)
Deprotection of 1,2-di(allyloxycarbonyl)hydrazines

deprotected hydrazine which will lead to the formation of N-allylated products. Considering the relatively large amounts of N-allylated products, it can be concluded that these cyclic hydrazines give a very fast reaction with the π-allylpalladium complex. The high reaction rate might be a result of the α-effect, but on the other hand, it could also point to some intramolecular mechanism, in which the first (deprotected) nitrogen atom attacks the complex involving the second nitrogen atom.

Scheme 3.1

Only if a large excess of a different nucleophile was used (n-BuNH₂ as solvent), formation of allylated products could be avoided, but under these conditions the initially formed free hydrazine is further oxidized to the azo compound 10.

N-Allylation as a side reaction has also been reported in the literature and has even been used intentionally. In order to prevent N-allylation, Guibé and co-workers used n-Bu₂SnH, which acts as a very fast hydride-donor. Rapid reaction with the π-allylpalladium complex 13 affords the relatively stable tri-n-butyltin carbamate 14 as an intermediate and propene, which immediately evolves from the reaction mixture (see Scheme 3.1). The tin carbamate 14 is cleaved in situ with a proton donor (water or acetic acid) that is already present.
in the reaction mixture to give the free amine 15, carbon dioxide and a tributyltin salt.

Surprisingly, application of the exact Guibé conditions in the deprotection of hydrazine 7 led to allylhydrazine 9 in a quantitative yield (eq 3.4). The formation of this product can only be explained by assuming a very fast reaction between deprotected hydrazine and the π-allylpalladium complex that is still present in the reaction mixture.

![Diagram](image)

This result made clear that, again, the hydrazine reacts faster with the π-allylpalladium complex than the external nucleophile (the tin hydride) present in the reaction mixture. Therefore a modification of the Guibé method was used in which the intermediate ditin carbamate 17 was generated in the absence of a proton donor. Only after complete reduction of the π-allylpalladium complex with n-Bu3SnH and concomitant conversion of the diallyl carbamate into the ditin carbamate, a proton donor was introduced in order to cleave the ditin carbamate.

![Diagram](image)

An example of this modification is shown in eq 3.5 in which dry HCl(g) was used to cleave the ditin carbamate 17 and to protonate the resulting free hydrazine. In this way, the oxidation-sensitive hydrazine was precipitated from the reaction mixture to afford the more stable HCl-salt 18 in a quantitative yield.16 This salt could be alkylated17 with activated dihalides (1.5 equiv, K2CO3 (5 equiv), NaI (cat), 2-butanone, rt) to afford the bicyclic hydrazines 19 and 20 in rather low yields (eq 3.6).

![Diagram](image)

Remarkably, the ditin carbamate 17 proved to be an interesting intermediate because it could not only be cleaved by a simple proton donor, but also by other electrophilic species such as activated carbonyl groups, to give the corresponding amides or carbamates. Thus, treatment
Deprotection of 1,2-di(allyloxycarbonyl)hydrazines

of the intermediate ditin carbamate 17 with an excess of acetic anhydride gave a quantitative yield of diacetylhydrazine 21 (eq 3.7).

\[
\text{Pd(PPh}_3\text{)}_4 \text{(0.04 equiv), Bu}_3\text{SnH (2.2 equiv), AqO (5 equiv), CH}_2\text{Cl}_2, \text{rt, 10 min} \rightarrow \text{21 (100%)}
\]

(eq 3.7)

In contrast with the deprotection reactions, the electrophile was added together with the palladium catalyst and the \(\text{n-Bu}_3\text{SnH}\), without formation of any \(\text{N}\)-allylated products. Apparently, the ditin carbamate shows a high selectivity towards the activated carbonyl compound and does not give any reaction with the palladium complex present in the reaction mixture. This reaction proved to be more generally applicable and some examples of this acylation with activated carbonyl compounds are shown in Table 3.2.

Table 3.2. Pd-Catalyzed formation of amide bonds.

<table>
<thead>
<tr>
<th>entry</th>
<th>precursor</th>
<th>activated carbonyl compound</th>
<th>equiv</th>
<th>product (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>(\text{1BuO} - \text{CO} - \text{O'Bu})</td>
<td>5</td>
<td>24 (87%)</td>
</tr>
<tr>
<td>2</td>
<td>6</td>
<td>(\text{MeC} - \text{CO})</td>
<td>2.5</td>
<td>25 (62%)*</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
<td>FMOC-Gly-OPFP 22</td>
<td>1</td>
<td>26 (74%)</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>FMOC-L-Ala-OPFP 23</td>
<td>1</td>
<td>27 (46%)</td>
</tr>
</tbody>
</table>

\([a]_D^{27} +6.0 \text{ (c 0.5, CHCl}_3\)

\*After treatment of the crude mixture with HCl/MeOH.
Different from the reaction with acetic anhydride and although in some cases an excess of the electrophile was used (entries 1 and 2), only the monosubstituted products 24 and 25 were formed. This is probably due to steric hindrance of the first introduced substituent, which hinders the introduction of the second substituent.

In entry 1, the Alloc group is replaced by a Boc group in a one-pot procedure. Thus, one protective group is replaced by another protective group, so that this reaction might also be called a 'transprotection'. In this way, the stable compound 24 is obtained, which can also be easily deprotected to give the salt of the free hydrazine upon treatment with acid (HCl/MeOH or HCOOH). The Boc-protected hydrazine is, in contrast with its HCl-salt, a stable compound as the presence of the carbamate function in the molecule suppresses the oxidation to the corresponding hydrazone.

Coupling with succinic anhydride afforded, after concentration of the reaction mixture, the corresponding tributyltin ester. The methyl ester 25 was obtained upon stirring of the crude reaction mixture in an HCl/MeOH solution. The use of the N-protected α-amino acids glycine and alanine, that are activated by a pentafluorophenoxy group (22 and 23, entries 3 and 4) led to the hydrazides 26 and 27 in reasonable yields.

3.4 DISCUSSION

The rapid reaction of tin carbamates with activated carbonyl compounds might be explained by assuming a cyclic transition state 28 (eq 3.8) in which the nucleophilicity of the nitrogen atom is strongly enhanced by cleavage of the Sn-O bond and concomitant formation of carbon dioxide.

\[
\begin{align*}
\text{N} & \quad \text{O} \\
R' & \quad \text{SnBu}_3 \\
\text{R} & \quad \text{O} \\
\text{R} & \quad \text{N} \\
\text{R} & \quad \text{O} \\
& \quad \text{BuSnOR} \\
\end{align*}
\]

(eq 3.8)

It is not very likely that the α-effect is responsible for the increased nucleophilicity of the nitrogen atom in this transprotection reaction. This can be concluded from reactions that were carried out with Alloc-protected α-amino acids 29 and α-amino acids 30 of which the carbonyl groups were activated (eq 3.9). In these cases, the corresponding dipeptides 31 were obtained in high yields. Thus, it has been shown that with this method it is also possible to couple two amino acids under neutral conditions with high efficiency. An interesting aspect of this coupling is that the protected starting material is reacted without an extra deprotection step. Comparison with known dipeptides indicated that the coupling occurred without noticeable racemization.
In conclusion, the deprotection method described herein provides a useful route to deprotected hydrazines. Reaction of an Alloc-protected hydrazine with \( n\text{-Bu}_3\text{SnH} \) and \( \text{Pd(PPh}_3\text{)}_4 \) affords a versatile intermediate, which can be transformed in several ways: (i) it can be directly cleaved with a proton donor to yield the salt of the free hydrazine; (ii) it can be "transprotected" with a different protective group, leading to a stable protected product, that can be deprotected under other conditions; (iii) it can be directly coupled with other activated carbonyl compounds so that in a one-pot procedure the Alloc group is replaced by another substituent under formation of an amide bond. An application of the transprotection method will be detailed in Section 7.5.

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E. C. Roos is kindly acknowledged for stimulating discussions.

**3.5 EXPERIMENTAL SECTION**

**General information.** \( n\text{-Bu}_3\text{SnH} \) was purchased from Aldrich and Merck and used without further purification. As the quality of the \( n\text{-Bu}_3\text{SnH} \) proved to be crucial in the deprotection reactions, a test reaction was run to determine whether further purification was necessary. Distillation of the residue provided \( n\text{-Bu}_3\text{SnH} \) of sufficient quality.\(^{20}\) \( \text{Pd(PPh}_3\text{)}_4 \) was purchased from Aldrich and stored in the absence of light under a dry nitrogen atmosphere. The rotation was measured with a Perkin Elmer 241 polarimeter. For further experimental details, see: Section 2.11.

**5,5-Ethylendioxytetrahydro-1H-1,2-diazepine-1,2(3H)-dicarboxylic acid diallyl ester (7).** To a solution of 6 (5.65 g, 21.9 mmol) in toluene (100 mL) were added ethylene glycol (419 mg, 3.89 mmol) and a catalytic amount of \( \rho\text{TSA} \). The mixture was heated at reflux for 18 h with the use of a Dean Stark trap. After cooling to rt, the solution was concentrated in vacuo. The residue was dissolved in \( \text{CH}_2\text{Cl}_2 \) (50 mL), washed with water (20 mL), dried (\( \text{MgSO}_4 \)), filtered and concentrated in vacuo. Purification by flash chromatography (ethyl acetate/hexane 1:1) afforded 7 (1.16 g, 3.39 mmol, 88%) as a yellowish oil, \( R_f 0.35 \). IR \( v 2990, 2950, 2880, 1720, 1700, 1445, 1405, 1335, 1115, 1040, 990 \); \(^1\text{H NMR} \) (200 MHz) \( \delta 173-2.04 \) (m, 6 H, \( \text{2} \times \text{NCH}_2 \)), \( 3.19-3.48 \) (m, 2 H, \( \text{2} \times \text{NCH}_2 \)), \( 3.63 \) (s, 4 H, \( \text{OCH}_2\text{CH}_2\text{O} \)), \( 4.65 \) (m, 4 H, \( 2 \times \text{CH}_2\text{O} \)), 5.15-
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5.35 (m, 4 H, 2 × CH₂), 5.79-5.91 (m, 2 H, 2 × CH).  

1,2-Di-(2-propenyl)-5-oxohexahydro-1,2-diazepine (8). To a solution of 6 (23 mg, 0.084 mmol) in THF (1 mL) was added PPh₃ (22 mg, 0.084 mmol), HCOOH (38 mg, 0.84 mmol) and Pd(PPh₃)₄ (18 mg, 0.014 mmol). The mixture was stirred at rt for 45 min and concentrated in vacuo. The residue was subjected to flash chromatography (ethyl acetate/hexane 1:4) yielding 8 (15 mg, 0.041 mmol, 49%) as a colorless oil, R_f 0.30. IR ν 2940, 1710, 1410, 1255, 990, 860, 720; ¹H NMR (200 MHz) δ 2.83 (t, J = 6.0 Hz, 2 H, NCH₂), 2.92 (t, J = 6.5 Hz, H(CH₂CH₂), 3.24 (d, J = 6.2 Hz, 2 H, CH₂CH₂), 3.92 (s, 4 H, OCH₂CH₂), 5.09-5.21 (m, 2 H, =CH₂), 5.91-6.02 (m, 2 H, =CH); ¹C NMR (50 MHz) δ 39.6, 40.1 (CH₂CH₂), 50.1 (NCH₂), 64.3 (NCH₂), 65.4 (OCH₂CH₂), 105.5 (C), 117.3 (CH₃), 135.4 (CH), 146.9 (N=CH); MS (EI, 70 eV) m/z (relative intensity) 196 (M⁺, 28), 155 (15), 109 (10), 99 (100), 83 (27), 55 (24); HRMS calcd for C₁₀H₁₆N₂O₂ 196.1212, found 196.1204.

Deprotection of 7 with n-BuNH₂ (10 equiv). To a solution of 7 (67 mg, 0.20 mmol) in THF (2 mL) was added PPh₃ (28 mg, 0.12 mmol), n-BuNH₂ (264 mg, 3.6 mmol) and Pd(PPh₃)₄ (24 mg, 0.020 mmol). The solution was stirred at rt for 2 h, concentrated in vacuo and subjected to flash chromatography (ethyl acetate/hexane 3:1) to afford a mixture of 4,5,6,7-tetrahydro-1H-5,5-ethylenedioxy-1,2-diazepine (10) (10 mg, 0.06 mmol, 12%) as a light yellow oil, R_f 0.50. 9: IR ν 3350, 3070, 2960, 1430, 1170, 1115; ¹H NMR (200 MHz) δ 1.89 (t, J = 6.0 Hz, 2 H, NCH₂), 2.00 (t, J = 6.5 Hz, HNCH₂CH₂), 2.64 (t, J = 6.0 Hz, 2 H, NCH₂), 2.92 (t, J = 6.5 Hz, NCH₂), 3.24 (d, J = 6.2 Hz, 2 H, CH₂CH₂), 3.92 (s, 4 H, OCH₂CH₂), 5.09-5.21 (m, 2 H, =CH₂), 5.83-6.02 (m, 1 H, =CH); ¹C NMR (50 MHz) δ 39.6, 40.1 (CH₂CH₂), 50.1 (NCH₂), 64.3 (NCH₂), 65.4 (OCH₂CH₂), 105.5 (C), 117.3 (CH₃), 135.4 (CH), 146.9 (N=CH); MS (EI, 70 eV) m/z (relative intensity) 196 (M⁺, 28), 155 (15), 109 (10), 99 (100), 83 (27), 55 (24); HRMS calcd for C₁₀H₁₆N₂O₂ 196.1212, found 196.1204.

Reaction of 7 in n-BuNH₂. To a solution of 7 (58 mg, 0.18 mmol) in n-BuNH₂ (2 mL) were added PPh₃ (28 mg, 0.11 mmol) and Pd(PPh₃)₄ (22 mg, 0.018 mmol). The mixture was stirred at rt for 2 h, concentrated in vacuo and purified by flash chromatography (ethyl acetate/hexane 3:1) to yield 10 (14 mg, 0.090 mmol, 49%) as a yellowish oil, R_f 0.50.

General procedure A for the deprotection reactions. To a well-stirred solution of the Alloc-protected compound in CH₂Cl₂ was added Pd(PPh₃)₄ (0.04 equiv), immediately followed by the addition of the whole amount of n-Bu₃SnH (2.2 equiv). Evolution of gas was observed and after being stirred for 15 min, the electrophile was added to the yellow solution. After being stirred for an additional 15 min, the mixture was concentrated in vacuo and the remaining residue was purified by flash chromatography.

General procedure B for the deprotection reactions. To a well-stirred solution of the Alloc-protected hydrazine in the presence of the electrophile in CH₂Cl₂ was added Pd(PPh₃)₄ (0.04 equiv), immediately followed by the addition of the whole amount of n-Bu₃SnH (2.2 equiv). Evolution of gas was observed and after being
stirred at rt for 30 min, the yellow solution was concentrated in vacuo and the remaining residue was subjected to flash chromatography.

**Deprotection of 7 via procedure A.** According to the general procedure A, 7 (50 mg, 0.15 mmol) was treated with water (15 mg, 0.83 mmol), Pd(PPh₃)₄ (7.5 mg, 0.006 mmol) and n-Bu₃SnH (87 µL, 0.33 mmol) in CH₂Cl₂ (2 mL). After flash chromatography (ethyl acetate/hexane 1:1, under a nitrogen atmosphere), 9 (30 mg, 0.15 mmol) was obtained as a yellow oil, which upon standing, was oxidized to hydrazone 11.

5-Oxo-hexahydro-1,2-diazepine·HCl (18). According to the general procedure B, 6 (41 mg, 0.15 mmol) was converted into the ditin carbamate 17 by using Pd(PPh₃)₄ (5 µmol) and a catalytic amount of Nal. The reaction mixture was stirred at rt for 17 h, concentrated in vacuo, taken up in CH₂Cl₂ (10 mL), washed with water (10 mL), dried (MgSO₄), filtered and concentrated in vacuo again. Purification by flash chromatography (CH₂Cl₂/acetone/Et₃N 2:1:0.1) afforded the bicyclic hydrazine 19 (18 mg, 0.11 mmol, 16%) as a light yellow solid. IR (KBr) ν 3400, 2900, 1700, 1430, 1390, 1340, 1240, 1110, 945, 740; ¹H NMR (200 MHz) δ 2.90–2.95 (m, 4 H, 2 × NCH₂), 4.91 (t, J = 2.2 Hz, 2 H, =CH₂); ¹³C NMR (50 MHz) δ 42.6 (2 × CH₂), 112.5, 126.6 (2 × Ar), 132.2 (2 × ArC), 171.8 (2 × C(O)).

**1,5-Diaza-3-methylene-8-oxobicyclo[5.3.0]dodecanec (19).** To a suspension of 18 (85 mg, 0.70 mmol) in 2-butane (2 mL) were added K₂CO₃ (483 mg, 3.5 mol), 3-chloro-2-chloromethyl-1-propane (131 mg, 1.05 mmol) and a catalytic amount of NaI. The reaction mixture was stirred at rt for 17 h, concentrated in vacuo, taken up in CH₂Cl₂ (10 mL), washed with water (10 mL), dried (MgSO₄), filtered and concentrated in vacuo again. Purification by flash chromatography (CH₂Cl₂/acetone/Et₃N 2:1:0.1) afforded the bicyclic hydrazine 19 (18 mg, 0.11 mmol, 16%) as a light yellow oil, IR (KBr) ν 3400, 2900, 1700, 1430, 1390, 1340, 1240, 1110, 945, 740; ¹H NMR (200 MHz) δ 2.90–2.95 (m, 4 H, 2 × NCH₂), 4.91 (t, J = 2.2 Hz, 2 H, =CH₂); ¹³C NMR (50 MHz) δ 42.6 (2 × CH₂), 112.5, 126.6 (2 × Ar), 132.2 (2 × ArC), 171.8 (2 × C(O)).

**Bicyclic hydrazine 20.** To a suspension of 18 (52 mg, 0.34 mmol) in 2-butane (5 mL) were added K₂CO₃ (143 mg, 1.05 mmol), a,a'-dibromo-a-xylo1 (133 mg, 0.51 mmol) and a catalytic amount of NaI. After being stirred at rt for 18 h, the reaction mixture was concentrated in vacuo, taken up in CH₂Cl₂ (15 mL), washed with water (10 mL), dried (MgSO₄), filtered and concentrated in vacuo again. After purification by flash chromatography (CH₂Cl₂/acetone/Et₃N 6:1:0.1), the bicyclic hydrazine 20 (12 mg, 0.055 mmol, 16%) was obtained as a yellowish oil, IR (KBr) ν 2950, 2920, 1700, 1440, 1370, 1305, 1250, 1120, 1005, 890; ¹H NMR (200 MHz) δ 2.67–2.73 (m, 4 H, CH₂), 2.90–2.96 (m, 4 H, 2 × NCH₂), 3.53 (t, J = 2.1 Hz, 4 H, 2 × NCH₂), 4.91 (t, J = 2.2 Hz, 2 H, =CH₂); ¹³C NMR (50 MHz) δ 44.2 (2 × CH₂), 51.0 (NCH₂), 61.7 (NCH₂), 104.1 (=CH₂), 212 [(C(O)].

**1,2-Diacetely-5,5-ethylendioxyhexahydro-1,2-diazepine (21).** Following the general procedure A, 7 (355 mg, 1.10 mmol) was transprotected by using acetic anhydride (561 mg, 5.5 mol), Pd(PPh₃)₄ (54 mg, 0.043 mmol) and n-Bu₃SnH (705 mg, 2.42 mmol) in CH₂Cl₂ (5 mL). After flash chromatography (ethyl acetate), 21 (294 mg, 1.10 mmol, 100%) was obtained as a white solid, mp 56–57 °C (ethyl acetate/hexane 1:1), IR (KBr) ν 3400, 2950, 2880, 1640, 1400, 1350, 1380, 1345, 1240, 1080, 940; ¹H NMR (200 MHz) δ 1.68–1.79 (m, 2 H, 2 × NCH₂CH₂), 1.81–2.05 (m, 2 H, NCH₂CH₂), 2.02 (s, 6 H, 2 × CH₃), 3.03–3.16 (m, 2 H, 2 × NCH₂), 3.93 (s, 4 H, 2 × OCH₃), 4.15–4.31 (m, 2 H, NCH₂); ¹³C NMR (50 MHz) δ 20.0 (2 × CH₂), 34.4 (2 × CCH₂), 43.1 (2 × NCH₂), 64.2 (2 × CH₂O), 108.5 (C), 171.8 (2 × C(O)); MS (EI, 70 eV) m/z (relative abundance):
intensity) 242 (M+, 10), 200 (100), 157 (42), 99 (43), 43 (43); HRMS calcd for C_{11}H_{18}N_{2}O_{4} 242.1267, 242.1272; Anal. Calcd. C, 54.53; H, 7.49; N, 11.56. Found: C, 54.66; H, 7.53; N, 11.51.

5-Oxo-hexahydro-1,2-diazepine-1-carboxylic acid tert-butyl ester (24). According to the general procedure A, 6 (129 mg, 0.457 mmol) was transprotected by using di-tert-butyl dicarbonate (490 mg, 2.25 mmol), Pd(PPh$_3$)$_4$ (23 mg, 0.018 mmol) and n-Bu$_3$SnH (290 mg, 1.00 mmol) in CH$_2$Cl$_2$ (5 mL). After purification by flash chromatography (ethyl acetate/hexane 2:1), 24 (85 mg, 0.40 mmol, 87%) was obtained as a colorless oil, $R_f$ 0.30. IR $\nu$ 2970, 2870, 1670, 1470, 1390, 1240, 1160, 1010, 1080, 940; $^1$H NMR $\delta$ 1.46 (s, 9 H, (CH$_3$)$_3$C), 2.68 (m, 4 H, CH$_2$(O)CH$_2$), 3.04 (m, 2 H, NCH$_2$), 3.67 (m, 2 H, NCH$_2$); $^{13}$C NMR (50 MHz) $\delta$ 28.2 (CH$_3$), 43.5 (NCH$_2$CH$_2$), 44.0 (NCH$_2$CH$_2$), 45.1 (NCH$_2$), 46.5 (NCH$_2$), 81.1 (C), 154.5, 210.4 (C(0)). MS (El, 70 eV) $m/z$ (relative intensity) 213 (M+-1, 12), 158 (M+-56, 100), (M+-100, 28), 86 (28), 57 (100), 41 (100).

Transprotection with succinic anhydride (25). According to the general procedure B, 6 (38 mg, 0.13 mmol) was coupled with succinic anhydride (26 mg, 0.26 mmol) by using Pd(PPh$_3$)$_4$ (7 mg, 0.005 mmol) and n-Bu$_3$SnH (83 mg, 0.28 mmol) in THF (2 mL). After concentration in vacuo, the residue was taken up in 4 mL of a 1.5 N solution of HCl in methanol and stirred at rt for 2 h. After this period, ether (3 mL) was added and a precipitate appeared. After removal of the solvent by syringe and washing with ether (5 x 2 mL), the remaining solid was taken up in aq satd NaHCO$_3$ (10 mL) and extracted with CH$_2$Cl$_2$ (3 x 5 mL). The combined organic layers were dried (MgSO$_4$), filtered, and concentrated in vacuo. Purification of the residue by flash chromatography (ethyl acetate) afforded 25 (18 mg, 0.079 mmol, 62%) as a colorless oil, $R_f$ 0.20. IR $\nu$ 3300, 1745, 1700, 1645; NMR (250 MHz) $\delta$ (some signals appear as rotamers) 2.40-2.70 (m, 8 H, 4 x CH$_2$(O)), 3.03-3.20 (m, 2 H, 2 x NCH$_2$), 3.66, 3.68 (s, 3 H, CO$_2$CH$_3$), 3.80-3.90 (m, 2 H, 2 x NCH$_2$); $^{13}$C NMR (50 MHz) $\delta$ 27.6, 29.0 (2 x CH$_2$(O)), 42.9, 44.3, 47.3, 47.5 (4 x CH$_2$), 51.7 (CO$_2$CH$_3$); MS (El, 70 eV) $m/z$ (relative intensity) 228 (M+, 23), 201 (12), 197 (15), 115 (28).

1-FMOC-Gly-1,2-diaza-5-cycloheptanone (26). According to the general procedure B, 6 (34 mg, 0.12 mmol) was coupled with FMOC-Gly-O-pentafluorophenol (22) (67 mg, 0.14 mmol) by using Pd(PPh$_3$)$_4$ (5 mg, 0.005 mmol) and n-Bu$_3$SnH (77 mg, 0.26 mmol) in CH$_2$Cl$_2$ (2 mL). Flash chromatography (ethyl acetate/hexane 2:1) afforded 26 (35 mg, 0.09 mmol, 74%) as a light yellow oil, $R_f$ 0.20. IR $\nu$ 3420, 2980, 1700, 1660, 1500, 1440, 1260, 800; $^1$H NMR (200 MHz) $\delta$ 2.62-2.82 (m, 4 H, CH$_2$(O)CH$_2$), 3.09-3.12 (m, 2 H, NCH$_2$), 3.83-3.92 (m, 2 H, NCH$_2$C(0) and CH), 4.20-4.26 (m, 3 H, NCH$_2$(O) and CH), 4.37 (d, $J$ = 7.0 Hz, 2 H, CH$_2$O), 5.65 (br s, 1 H, NHC(O)), 7.30-7.77 (m, 8 H, ArH); $^{13}$C NMR $\delta$ 42.6, 42.9, 44.2, 47.1, 47.3, 47.5 (4 x CH$_2$), 51.7 (CO$_2$CH$_3$); MS (El, 70 eV) $m/z$ (relative intensity) 366 (14), 277 (100), 199 (20), 172 (40), 152 (15), 77 (14).

1-FMOC-L-Ala-1,2-diaza-5-cycloheptanone (27). Following the general procedure B, 6 (26 mg, 0.09 mmol) was coupled with FMOC-L-Ala-O-pentafluorophenol (23) (44 mg, 0.09 mmol) by using Pd(PPh$_3$)$_4$ (5 mg, 0.004 mmol) and n-Bu$_3$SnH (59 mg, 0.20 mmol) in CH$_2$Cl$_2$ (2 mL). Flash chromatography (ethyl acetate/hexane 2:1) yielded 27 (12 mg, 0.03 mmol, 33%) as a viscous colorless oil, $R_f$ 0.20, $[\alpha]_D^{27}$ 6.0 (c 0.5, CHCl$_3$). IR $\nu$ 3420, 2980, 1700, 1650, 1500, 1445, 1435, 1400; $^1$H NMR (200 MHz) $\delta$ 1.32 (d, $J$ = 6.8 Hz, 3 H, CH$_3$), 2.65-2.82 (m, 4 H, CH$_2$(O)CH$_2$), 3.17 (m, 2 H, NCH$_2$), 3.70-4.24 (m, 3 H, NCH$_2$ and CHAr), 5.08 (q, $J$ = 7.5 Hz, 1 H, CH$_2$CH$_3$), 5.68 (br s, 1 H, NHC(O)), 7.29-7.77 (m, 8 H, ArH); $^{13}$C NMR (50 MHz) $\delta$ 19.0 (CH$_3$), 42.6, 44.3, 47.2, 47.4 (CH$_2$), 46.9, 47.1 (CH), 66.8 (CH$_2$O), 119.8, 125.1, 127.0, 127.6 (ArH), 141.2, 143.8 (ArC), 156.4, 170.0, 209.1 (C(O)); MS (El, 70 eV) $m/z$ (relative intensity) 238 (M$,^+$ 23), 201 (12), 197 (15), 115 (28).

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Deprotection of 1,2-di(allyloxycarbonyl)hydrazines

141.1, 143.9 (ArC), 156.6, 174.5 (C(O)); MS (El. 70 eV) m/z (relative intensity) 407 (2), 277 (100), 201 (12), 180 (37), 152 (14), 114 (8), 77 (7); HRMS calcd for C_{23}H_{25}N_{3}O_{4} 407.1845, found 407.1853.

3.6 REFERENCES AND NOTES


16) The HCl-salt can be stored for only a few days under an inert atmosphere of dry nitrogen.


18) Müller, E. In Methoden der Organischen Chemie (Houben-Weyl); Müller, E., Ed.; Georg Thieme Verlag: Stuttgart, 1974; Vol. 15/1 and 15/2.


20) For purification methods, see: Klinger, R. J.; Mochida, K.; Kochi, J. K. J. Am. Chem. Soc. 1979, 101,
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6626.
CHAPTER 4
SYNTHESIS OF BRIDGED BICYCLIC HYDRAZINES VIA ENDOCYCLIC 
N-ACYLHYDRAZONIUM INTERMEDIATES

4.1 INTRODUCTION

The synthesis and applications of bridged bicyclic hydrazines with a 1,7-diazabicyclo[2.2.1]heptane or a 1,8-diazabicyclo[3.2.1]octane skeleton such as 5 and 7 respectively, have received scant attention in the literature. The structures with a heptane skeleton are particularly interesting compounds as both the N-chloro and N-methyl substituted molecules have been reported to exhibit very high nitrogen inversion barriers for the bridge nitrogen atom. One method for the preparation of these types of compounds was developed by Oppolzer, who obtained the 1,7-diazabicyclo[2.2.1]heptane 5 via an intramolecular 1,3-dipolar cycloaddition reaction of the intermediate ylide 3 (m = 1, Scheme 4.1). However, the regiochemistry of this cycloaddition reaction proved to be strongly dependent on the length of the olefin side chain as the corresponding pentenyl compound 3 (m = 2) reacted in the opposite way to give the 1,7-diazabicyclo[3.2.1]octane 4.

The regiochemistry could also be influenced by using substituted aldehydes or functionalized alkenyl substituents. If benzaldehyde was used in the condensation reaction, mixtures of stereoisomers were obtained. On the other hand, if the pentenyl group was functionalized with a phenyl moiety (i.e. 6, eq 4.1), the regioselectivity changed completely and the 1,8-diazabicyclo[3.2.1]octane 7 was obtained as a single product.

(eq 4.1)
Another method that provides 1,8-diaza[3.2.1]bicyclooctanes is shown in eq 4.2.6,7 Again, a 1,3-dipolar cycloaddition reaction is the key step in the synthesis of the products. Deprotonation of the tosylate salt 8 affords the stable betaine 9 which reacts intermolecularly with various substituted acetylenes to give the bridged bicyclic hydrazines 10.

From these examples it can be concluded that the existing methods for the preparation of bridged 1,7-diazabicycloheptanes and 1,8-diazabicyclooctanes are rather limited as far as substitution pattern and ring size are concerned. In this Chapter, a novel pathway for the preparation of these compounds will be detailed, which offers the possibility of synthesizing various new functionalized bridged diazabicycles.

A short outline of the method is given in eq 4.3. The key intermediate is the endocyclic \(N\)-acylhydrazonium ion 12, which is converted via an intramolecular attack of the internal nucleophile into the bicyclic product 11. Compared to the \(N,N'\)-diacylhydrazines that are described in Chapter 2, the second nitrogen atom in these types of hydrazines will be less electron-withdrawing, probably resulting in a somewhat more easy formation of the intermediate \(N\)-acylhydrazonium ion. The precursor of the \(N\)-acylhydrazonium ion 12 is readily obtained in a few steps starting from the alkylated 3-pyrazolidinone 13.

### 4.2 SYNTHESIS OF THE PRECURSORS

The starting material, 3-pyrazolidinone 15 could be efficiently obtained by the condensation of hydrazine hydrate with ethyl 3,3-dimethylacrylate (14) in refluxing ethanol (eq 4.4).8 Distillation of the crude residue afforded the pure 3-pyrazolidinone 15 as a colorless oil which solidified upon standing.
Synthesis of bridged bicyclic hydrazines

\[
\text{CO}_2\text{Et} \quad \text{H}_2\text{NNH}_2\text{H}_2\text{O} \text{ (1.05 equiv)} \quad \text{EtOH, reflux, 18 h} \quad \text{NH} \quad \text{NH} \\
14 \quad (\text{eq 4.4}) \quad 15 \quad (95\%) \\
\]

Alkylation of the pyrazolidinone 15\textsuperscript{9,10} with various activated alkenyl halides was expected to give the hydrazines 16, that after alkoxy carbonylation and subsequent reduction of the ring oxo function should yield the precursors 17 for the cyclization reactions (eq 4.5). These different steps will be fully detailed.

\[
\text{NH} \quad \text{NH} \quad \text{N}^\text{R} \quad \text{O} \quad \text{CO}_2\text{R} \\
15 \quad 16 \quad 17 \quad 18 \quad (\text{eq 4.5}) \\
\]

In the alkylation reactions, the different nature of the two nitrogen atoms was very important. The N-1 nitrogen is an amine type nitrogen atom, whereas the N-2 nitrogen is an amide type nitrogen atom. If the pyrazolidinone 15 is treated with alkenyl halides, only the more nucleophilic N-1 atom will give an \textit{S}_2\text{2} reaction. The results of the alkylation of 15 with methallyl chloride (1.05 equiv) under various circumstances are shown in Table 4.1.

Table 4.1. Alkylations with methallyl chloride.

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent\textsuperscript{a}</th>
<th>base</th>
<th>yield\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeCN</td>
<td>Et\textsubscript{3}N</td>
<td>12%</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>Et\textsubscript{3}N</td>
<td>13%</td>
</tr>
<tr>
<td>3</td>
<td>EtOH</td>
<td>Et\textsubscript{3}N</td>
<td>19%</td>
</tr>
<tr>
<td>4</td>
<td>2-butane</td>
<td>Et\textsubscript{3}N</td>
<td>19%</td>
</tr>
<tr>
<td>5</td>
<td>THF</td>
<td>DBU</td>
<td>37%</td>
</tr>
<tr>
<td>6</td>
<td>THF</td>
<td>DBMP</td>
<td>38%</td>
</tr>
<tr>
<td>7</td>
<td>THF</td>
<td>K\textsubscript{2}CO\textsubscript{3}</td>
<td>57%</td>
</tr>
<tr>
<td>8</td>
<td>2-butane</td>
<td>K\textsubscript{2}CO\textsubscript{3}</td>
<td>88%</td>
</tr>
</tbody>
</table>

\textsuperscript{a} reflux temperature, 18 h. \textsuperscript{b} The alkylations were performed in the presence of Lil (cat).

From this Table, it is evident that the choice of the base played an important role in this reaction. The results with Et\textsubscript{3}N were poor (entries 1-4), while DBU and the very hindered DBMP (di-tert-butyl-4-methylpyridine) gave better yields (entries 5 and 6). This is probably due to the fact that the N-1 nitrogen atom is sterically hindered (by the \textit{gem}-dimethyl substituent) so that a competition occurs between alkylation of the pyrazolidinone and the base. If the base
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becomes too hindered, alkylation of the pyrazolidinone is favored. In some cases, the
quaternary ammonium salts could be isolated. Introduction of an inorganic non-nucleophilic
base (i.e. K$_2$CO$_3$, entries 7 and 8) led to a significant increase of the yield.

Generally, the latter reaction conditions (K$_2$CO$_3$, LiI (cat), 2-butanone, reflux) were
found to give fair yields with different alkylation agents as summarized in Table 4.2. The low
yield in the case of propargyl bromide (entry 8) was explained by the formation of a considerable
amount of the dialkylated pyrazolidinone 28 (30%). It was also shown that use of an excess of
the alkylation agent led to the formation of the dialkylated product. For example, if 1.5
equivalent of allyl bromide was added (eq 4.6), 27 was formed in 42% yield.

\[ \text{allyl bromide (1.5 equiv), } \]
\[ \text{LiI (cat), K$_2$CO$_3$ (1.5 equiv) } \]
\[ \text{2-butanone, reflux} \]
\[ \text{15} \rightarrow \text{19 47%} + \text{27 42%} \] (eq 4.6)

The pyrazolidinone 26 was obtained upon alkylation with 4-ido-1-(trimethylsilyl)-2-butyne,\textsuperscript{11}
which was prepared via the corresponding mesylate.\textsuperscript{12}

The alkoxycarbonylation of the hydrazines 19-26 was performed using four different
methods:
A: deprotonation with a strong base (NaH (1.05 equiv), rt) and alkylation with methyl
chloroformate (1.2 equiv, 0 °C → rt) in THF;
B: the same procedure as A with ethyl chloroformate instead of methyl chloroformate;
C: treatment with diethyl dicarbonate (2.0 equiv, rt) in the presence of Et$_3$N (1 equiv) and
DMAP (1 equiv) in CH$_2$Cl$_2$;\textsuperscript{13}
D: deprotonation with LDA (1.1 equiv, -78 °C), followed by methoxycarbonylation with methyl
cyanoformate (2 equiv, -78 °C → rt) in THF.\textsuperscript{14}

The results of the different methods are given in Table 4.2. A disadvantage of the first two
methods is that mixtures of N- and O-alkylated products (entries 7 and 10) or only the O-
alkylated products were obtained (entries 1 and 5).\textsuperscript{15,16} The selectivity of this reaction could not
be influenced by changing the temperature of the reaction. The formation of the O-alkylated
products was indicated by a strong absorbance in the IR spectra at 1630 cm$^{-1}$ as a result of the
presence of the C=N bond.\textsuperscript{15} In the case of entry 7, an unexpected rearrangement occurred, in
which presumably 39 was formed. The assignment of this structure is in full accord with the $^1$H
NMR data, showing a vinyl substituent without further couplings, and an absorbance at 1680
cm$^{-1}$ in the IR spectrum indicating the presence of a 3-pyrazolidinone ring, which is not bearing
a methoxycarbonyl group at the N-2 nitrogen atom. The formation of this product can be
explained via the intermediacy of the ylide-type structure 30 (eq 4.7). An SN$_2$'-reaction of the
negatively charged nitrogen atom with the prenyl substituent will lead to the rearranged hydrazine
39.

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### Table 4.2. Alkylation and alkoxy carbonylation.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Alkylation Product (Yield)</th>
<th>Method</th>
<th>Products (Yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19 (66%)</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>20 (88%)</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>21 (61%) /Z:3:1</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>22 (82%)</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>23 R = H (40%)*</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>24 (80%)</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>25 (83%)</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>26 (68%)</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>27 (74%)</td>
<td>O</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>28 (R = CH₂CH₃)</td>
<td>B</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>29 (81%)</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>30 (75%)</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>31 R = Me (33%)</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>32 R = Et (82%)</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>33 R = Me (57%)</td>
<td>D</td>
<td></td>
</tr>
</tbody>
</table>

a) 28 (R = CH₂CH₃) was also found in 30% yield.
The lack of regioselectivity could be overcome by using the more selective reagent methyl cyanoformate, instead of methyl or ethyl chloroformate (entries 3, 8 and 14).\textsuperscript{17}

The alternative method C, in which the use of a strong base is avoided, afforded also satisfactory results (entries 2, 6, 11 and 12). Although in this reaction, in principle, a base is not required, it proved that the best results were obtained by using stoichiometric amounts of Et\textsubscript{3}N and DMAP.

The reduction of the pyrazolidinone ring was performed under conditions that were also used for the corresponding pyrrolidinones.\textsuperscript{14} Treatment of the hydrazines at -20 °C in ethanol with a large excess of sodium borohydride (6 equiv) and a catalytic amount of H\textsubscript{2}SO\textsubscript{4} afforded the hydroxypyrazolidines, which were directly converted into the corresponding ethoxy-pyrazolidines 45-50 by stirring in ethanol which was acidified with H\textsubscript{2}SO\textsubscript{4}. This last step already indicates the intermediacy of the endocyclic N-acylhydrazonium ion. The reduction steps proceeded in fair yields as can be seen from Table 4.3.

The hydroxypyrazolidines 51 and 52 (entries 13 and 15) were isolated only in the case of the allyl- and propargylsilanes 43 and 44. This was done in order to prevent protodesilylation under the acidic conditions that are required for the hydroxy/ethoxy exchange.

### 4.3 CYCLIZATION REACTIONS WITH LEWIS AND BRØNSTED ACID

The cyclization reactions were performed under standard conditions with the Lewis acid TiCl\textsubscript{4} (2 equiv, CH\textsubscript{2}Cl\textsubscript{2}, -78 °C → rt) and in the case of the silanes 51 and 52 with BF\textsubscript{3}-OEt\textsubscript{2} (2 equiv, CH\textsubscript{2}Cl\textsubscript{2}, 0 °C → rt). For the cyclization reactions in entries 1, 3, 5 and 7 SnCl\textsubscript{4} was also tried as the Lewis acid but gave lower yields. In the cyclizations with Brønsted acid, the best results were obtained by stirring in HCOOH for 18 h at 50 °C. The results are summarized in Table 4.3.

Treatment of 45 with TiCl\textsubscript{4} afforded the bridged hydrazine 53 in a good yield (entry 1). Its stereochemistry was established by using NOE-difference \textsuperscript{1}H NMR techniques on the corresponding free hydrazine 72 (see Section 4.4). Irradiation of the \textit{endo}-Me signal of 72 gave a strong enhancement of the signal of the proton adjacent to the chlorine atom. This is only possible if the six-membered ring is in a chair conformation with the chlorine atom in the equatorial position. This assignment was confirmed by the \textsuperscript{1}H NMR spectrum of 72, in which the signal of the hydrogen atom adjacent to the chlorine atom (4.20 ppm, tt) showed two axial-axial (\textit{J}_{\text{ax}} = 11.1 Hz) and two axial-equatorial couplings (\textit{J}_{\text{ae}} = 6.3 Hz).
<table>
<thead>
<tr>
<th>entry</th>
<th>reduction product (yield)</th>
<th>acid</th>
<th>cyclization product(s) (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>45 (83%)</td>
<td>TiCl₄, HCOOH</td>
<td>53 (95%), 65 (83%)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>46 (75%)</td>
<td>TiCl₄, HCOOH</td>
<td>54 X = Cl (56%), 55 (16%)</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td>56 X = OCHO (34%)</td>
</tr>
<tr>
<td>5</td>
<td>47 (71%) E/Z 3:1</td>
<td>TiCl₄, HCOOH</td>
<td>57 (53%), 66 (91%)</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>48 (44%)</td>
<td>TiCl₄, HCOOH</td>
<td>58 X = Cl (84%), 59 X = OCHO (84%)</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>49 (65%)</td>
<td>TiCl₄, HCOOH</td>
<td>60 (24%), 61 (47%)</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>50 (90%)</td>
<td>TiCl₄, HCOOH</td>
<td>62 (82%), 67 (80%)</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>51 (90%)</td>
<td>BF₃OEt₂, HCOOH</td>
<td>63 (61%), 64 (62%)</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>52 (59%)</td>
<td>BF₃OEt₂, HCOOH</td>
<td>64 (42%)</td>
</tr>
<tr>
<td>16</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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Such a conformation is in agreement with the expected cyclization mechanism for a cationic olefin cyclization\textsuperscript{18} in which the ring closure takes place via a chair-like transition state \textsuperscript{68}, and chloride comes in from the equatorial side (eq 4.8, \( R = H \)).

\[
\begin{align*}
68 + \text{CO}_{2}\text{Et} & \rightarrow \text{Cl}^- \\
\text{RO}_{2}\text{C} & \text{Cl} \quad \text{(eq 4.8)}
\end{align*}
\]

This transition state also explains the stereochemical outcome of the cyclization of the crotyl precursor 47 to 57 (entry 5), in which both substituents occupy the equatorial position. In the transition state of the (E)-precursor, the methyl group is in the equatorial position (68, \( R = \text{Me} \)), while chloride attacks from the equatorial side, thus giving rise to the formation of the \textit{trans}-product 57 as the only product. The (Z)-isomer would lead to a transition state with the methyl group in the axial position, so that cyclization to the \textit{cis}-product would take place. However, this product was not observed in the reaction mixture. The relative configuration of 57 was inferred from the splitting pattern of the \( ^1\text{H} \) NMR signal of the proton adjacent to the chlorine atom (3.76 ppm, \( \text{dt} \)) showing one eq-ax (\( ^3\text{J}_{\text{ax}} = 6.3 \text{ Hz} \)) and two ax-ax couplings (\( ^3\text{J}_{\text{aa}} = 10.8 \text{ Hz} \)).

Cyclization of the methallyl precursor 46 (entry 2) afforded an inseparable mixture of 54 and the elimination product 55. The stereochemistry of the product 54 could not be fully ascertained, but it is most likely that the methyl substituent is equatorial in view of the severe steric interaction between the two endo-methyl groups in the alternative stereoisomer.

\[
\begin{align*}
70 & \rightarrow \text{MeO} & \text{Cl}^- \\
\text{MeO}_{2}\text{C} & \text{Cl} \quad \text{(eq 4.9)}
\end{align*}
\]

At first glance, the formation of these products might look anomalous as attack of chloride occurs from the most hindered bottom side (see 70, eq 4.9). This could be explained by assuming the initial formation of the dioxycarbenium ion 71, in which the positive charge is stabilized by the carbamate function, and a subsequent \( \text{SN}_2 \)-type attack of a nucleophile leading to the product 54 with the assigned conformation. The crowded nature of the product is also reflected in the formation of a relatively large amount of the elimination product 55. As the double bond causes the six-membered ring to flatten, a favorable conformation is obtained in...
Synthesis of bridged bicyclic hydrazines

which the interaction of the substituents with the carbamate function and the endo-methyl group is decreased.

Upon cyclization of precursor 48 with TiCl₄, the 1,7-diazabicyclo[2.2.1]heptane 58 was formed as a single product in high yield (entry 7). The bulky substituent is in the exo-orientation, which was concluded from the splitting pattern of the signal of the bridgehead hydrogen atom (4.43 ppm, d, $J = 4.9$ Hz). The coupling constants of the bridgehead proton with both adjacent endo-protons are zero as a result of dihedral angles of approximately 90°.

The less nucleophilic acetylene 49 cyclized in a rather low yield (entry 9). This can be either a result of the poor nucleophilicity of the acetylene or of the instability of the product 60. The benzyl precursor 50 (entry 11) afforded the corresponding hydrazine 62 in 62% yield. Both silanes 51 and 52 cyclized in reasonable yields to give the elimination products 63 and 64.

In contrast with the Lewis acid cyclizations, the outcome of the HCOOH cyclizations was variable as is evident from the Table. In some cases (entries 2, 6 and 12), the corresponding hydroxypyrazolidines 65-67 were recovered as single products after the reaction. This is somewhat surprising, as during work-up the use of water is avoided. Presumably, the formyloxy group was exchanged during flash chromatography to give the more stable hydroxypyrazolidines. From the formation of the hydroxypyrazolidines it is evident that the N-acylhydrazonium ion was formed, but that cyclization did not take place. For precursor 45, other acidic circumstances were also tried e.g. CF₃CO₂H in CH₂Cl₂, HCOOH at 100 °C or in a sealed tube, HCl in MeOH, and Me₃SiOTf, but none of these conditions proved to be successful.

The cyclization products were obtained in reasonable to good yields only in the cases where cyclization leads to a stabilized carbocation. The stereochemical outcome is similar compared to the Lewis acid cases. These results emphasize that formic acid is less suitable for the cyclization reactions than Lewis acids, which was also observed in the diacylhydrazonium series.

4.4 DEPROTECTION AND FURTHER REACTIONS

The cyclization products 53, 62 and 63 were deprotected to give the free hydrazines 72, 74, and 75, respectively (eqs 4.10 to 4.12). Two methods were applied i.e. hydrolysis under basic conditions (KOH in MeOH) and cleavage with Me₃SiI.
Conversion of the carbamate 63 into the corresponding methylated hydrazine 76 took place in a rather poor yield. An alternative route that provided the N-methyl compound is the reductive methylation of the free hydrazine 72, in which the intermediate iminium ion is reduced with NaBH₃CN leading to the desired compound 73 in a fair yield. ²¹

4.5 NMR DATA AND STRUCTURAL PROOF

The ¹H NMR spectra of the cyclization products show some characteristic signals which immediately point towards the formation of a bridged bicyclic compound. The endo-proton adjacent to the gem-dimethyl function shows a doublet ($2J = 12$ Hz for the bicyclooctanes and $2J = 11$ Hz for the bicycloheptanes, $3J = 0$, $\theta = 90^\circ$), whereas the exo-proton shows a double doublet ($2J = 12$, $3J = 8$ Hz for the bicyclooctanes, $2J = 11$, $3J = 5$ Hz for the bicycloheptanes). Furthermore, the bridgehead proton shows in the case of the bicyclooctanes a multiplet (even at $90^\circ \mathrm{C}$) near 5 ppm and in the case of the bicycloheptanes a doublet ($3J = 5$ Hz) around the same position.

Another phenomenon which is observed in most of the ¹H and ¹³C NMR spectra is the appearance of rotamers, which is a result of a hindered rotation around the amide bond of the carbamate. In some cases, by recording the spectrum at a high temperature the rotation became fast on the NMR timescale so that only one rotamer was observed. This is clearly shown in the spectra of the cyclic hydrazine 53 (Fig 4.1 and 4.2). The spectrum at room temperature (Fig 4.1) shows the characteristic multiplet around 4.5 ppm and rotamers of all signals. Raising the temperature to $90^\circ \mathrm{C}$ in C₇D₈ led to signals of a single rotamer (Fig 4.2), thereby excluding the possibility that the signals belong to a different stereoisomer. Conversion of the carbamate 53 into the free hydrazine 70 led to the same conclusion. Sharp signals of only one isomer were observed (Fig 4.3).
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Fig 4.1.
$^1$H NMR spectrum (250 MHz) of 53 at 23 °C in CDCl$_3$.

Fig 4.2.
$^1$H NMR spectrum (250 MHz) of 53 at 90 °C in C$_7$D$_8$.

Fig 4.3.
$^1$H NMR spectrum (200 MHz) of 72 at 23 °C in CDCl$_3$. 

---

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4.6 CONCLUDING REMARKS

The method described in this Chapter offers an efficient novel route to functionalized bridged bicyclic hydrazines. Compared with the \( N,N' \)-diacylhydrazonium ions described in Chapter 2, it is expected that the formation of the endocyclic \( N \)-acylhydrazonium intermediates will be somewhat easier as a result of the less electron-withdrawing amino function. However, no striking differences were observed in the conditions that were required to form the reactive intermediates. As a Lewis acid, TiCl\(_4\) afforded better results than the milder SnCl\(_4\), except for the silanes where BF\(_3\)OEt\(_2\) was preferred. Cyclization with the Brønsted acid formic acid took only place upon heating at 50 °C. Again, a remarkable difference was observed between the Lewis acid and the formic acid promoted reactions. In the cases of less activated nucleophiles, cyclization did not take place under the protic acid conditions, whereas it did under Lewis acid conditions. Furthermore, it can be concluded that both five- and six-membered rings can be obtained in similar yields.

ACKNOWLEDGEMENT

F. O. H. Pirrung is gratefully acknowledged for his contribution to this Chapter. R. H. Balk is kindly acknowledged for the large scale preparation of 4-(trimethylsilyl)-2-butynol.

4.7 EXPERIMENTAL SECTION

General information. The cyclization products described in this Chapter are numbered according to the structures 53 and 58. For more experimental details, see: Section 2.11.

5,5-dimethyl-3-pyrazolidinone (15).\(^8\) To a solution of ethyl 3,3-dimethylacrylate (14) (80 mL, 0.58 mol) in ethanol (300 mL) was added \( N_2H_2\)H\(_2\)O (37 mL of an 80% solution in H\(_2\)O, 0.61 mol). The mixture was refluxed for 18 h, concentrated in vacuo and the residue was distilled to give 15 (63.2 g, 0.55 mol, 96%) as a viscous colorless oil, which solidified upon standing, bp 100-105 °C (0.1 mbar). IR v 3430, 3220, 1690; \(^1\)H NMR (200 MHz) \( \delta \) 1.27 (s, 6 H, (CH\(_3\))^2), 2.29 (s, 2 H, CH\(_2\)), 4.10 (br s, 1 H, NH), 7.99 (br s, 1 H, NH).
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General procedure for the alkylation reactions. The halide (1.1 equiv), K₂CO₃ (1.5 equiv) and a catalytic amount of Lil were added to a solution of 3-pyrazolidinone 15 in 2-butane. The solution was heated at reflux temperature for 18 h, concentrated in vacuo, taken up in water and extracted with CH₂Cl₂ (3 x). The combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo. The residue was chromatographed to afford the pure alkylation product.

5,5-Dimethyl-1-(2-propenyl)-3-pyrazolidinone (19). According to the general procedure, 3-pyrazolidinone 15 (2.0 g, 17.5 mmol) was alkylated with allyl bromide (1,51 mL, 17.5 mmol), K₂CO₃ (2.67 g, 19.3 mmol) and Lil in 2-butane (80 mL). Work-up and flash chromatography (ethyl acetate) afforded 19 (1.71 g, 11.5 mmol, 66%) as a white solid, mp 40-42 °C, Rf 0.19. IR V 3340, 3400, 3080, 1675; ¹H NMR (200 MHz) δ 1.22 (s, 6 H, (CH₃)₂C), 2.28 (s, 2 H, CCH₂), 3.22 (d, J = 6.4 Hz, 2 H, NCH₂), 5.15 (dd, J = 1.8, 8.1 Hz, 1 H, =CHH), 5.23 (d, J = 2.8 Hz, 1 H, =CH₂), 5.65-5.90 (m, 1 H, =CH), 8.27 (br s, 1 H, NH). Upon use of 1.5 equiv of allyl bromide, 5,5-dimethyl-1,2-di(2-propenyl)-3-pyrazolidinone (27) was also formed, IR v 3080, 1670; ¹H NMR (200 MHz) δ 1.14 (s, 6 H, (CH₃)₂C), 2.23 (s, 2 H, CH₂), 3.37 (d, J = 6.6 Hz, 2 H, CH₂), 3.92 (d, J = 6.6 Hz, 2 H, CH₂), 5.00-5.20 (m, 4 H, 2 × CH₂), 5.60-5.95 (m, 2 × CH₂).

5.5-Dimethyl-1-(2-methyl-2-propenyl)-3-pyrazolidinone (20). 3-Pyrazolidinone 15 (1.00 g, 8.80 mmol) was alkylated (according to the general procedure) with 3-chloro-2-methyl-1-propene (0.91 mL, 9.21 mmol), K₂CO₃ (1.27 g, 9.20 mmol) and Lil in 2-butane (50 mL). After work-up and flash chromatography (ethyl acetate), 20 (1.29 g, 7.69 mmol, 88%) was obtained as a white solid, mp 97.5-98.5 °C (ether), Rf 0.45. IR v 3430, 3400, 3080, 1680; ¹H NMR (200 MHz) δ 1.25 (s, 6 H, (CH₃)₂C), 1.75 (s, 3 H, CH₃), 2.34 (s, 2 H, CCH₂), 3.12 (s, 2 H, NCH₂), 4.92 (m, 2 H, =CH₂), 7.24 (br s, 1 H, NH); Anal. Calcd. for C₉H₁₆N₂O: C, 64.25; H, 9.59; N, 16.65. Found: C, 64.27; H, 9.57; N, 16.56.

1-(2-Butenyl)-5,5-dimethyl-3-pyrazolidinone (21). Following the general procedure, 3-pyrazolidinone 15 (3.02 g, 26.3 mmol) was alkylated by using 4-bromo-2-butene ((E)/(Z) 3.3:1) (2.8 mL, 27.6 mmol), K₂CO₃ (3.82 g, 27.6 mmol) and Lil in 2-butane (100 mL). After work-up and flash chromatography (ethyl acetate), 21 (2.71 g, 16.0 mmol, 62%) was obtained as white crystals, mp 66.5-68 °C, Rf 0.20, (E)/(Z) 3.3:1, IR v 3430, 3190, 1689; (E)-isomer: ¹H NMR (200 MHz) δ 1.29 (s, 6 H, (CH₃)₂C), 1.69 (dt, J = 6.3, 1.0 Hz, 3 H, CH₃), 2.35 (s, 2 H, CCH₂), 3.21 (d, J = 6.5 Hz, 2 H, NCH₂), 5.35-5.55 (m, 1 H, CH₂CH=), 5.60-5.80 (dq, J = 15, 6.3 Hz, CH₂CH=), 7.60 (br s, 1 H, NH). (Z)-isomer: ¹H NMR (200 MHz) δ 1.32 (s, 6 H, (CH₃)₂C), 1.69 (dt, J = 1.0, 6.3 Hz, 3-H, CH₃), 2.38 (s, 2 H, CCH₂), 3.35 (d, J = 6.9 Hz, 2 H, NCH₂), 5.35-5.55 (m, 1 H, CH₂CH=), 5.60-5.80 (m, 1 H, CH₂CH=), 7.60 (br s, 1 H, NH).

5,5-Dimethyl-1-(3-methyl-2-butenyl)-3-pyrazolidinone (22). Following the general procedure, 3-pyrazolidinone 15 (7.61 g, 67.0 mmol) was alkylated by using 4-bromo-2-methyl-2-buten (10.5 g, 70.5 mmol), K₂CO₃ (13.9 g, 0.10 mol) and Lil in 2-butane (400 mL). After work-up and flash chromatography (ethyl acetate), 22 (9.75 g, 53.6 mmol, 80%) was obtained as white crystals, mp 96.5-97 °C (CH₂Cl₂/ether 1:10), Rf 0.30. IR v 3430, 1685; ¹H NMR (200 MHz) δ 1.30 (s, 6 H, CH₃(CH₂)₂C), 1.74 (s, 3 H, CH₃), 2.36 (s, 2 H, CCH₂), 3.30 (d, J = 7.1 Hz, 2 H, NCH₂), 5.20 (s, J = 1.3, 7.1 Hz, =CH), 6.90 (br s, 1 H, NH).

5,5-Dimethyl-1-(2-propynyl)-3-pyrazolidinone (23). Following the general procedure, 3-pyrazolidinone 15 (4.02 g, 35.1 mmol) was alkylated by using 3-bromo-1-propyne (4.11 mL, 36.9 mmol),
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K₂CO₃ (5.11 g, 36.9 mmol) and Lil in 2-butanone (150 mL). Work-up and flash chromatography (ethyl acetate/acetone 1:1) afforded 23 (2.11 g, 13.9 mmol, 40%) as yellow crystals, mp 100-105 °C, Rf 0.54 and 5,5-dimethyl-1,2-di(2-propynyl)-3-pyrazolidinone (28) (2.01 g, 10.5 mmol, 30%) as a dark oil, Rf 0.89.

23: IR v 3430, 3300, 2250, 1690; ¹H NMR (200 MHz) δ 1.32 (s, 6 H, (CH₂)₂C), 2.27 (t, J = 2.4 Hz, 1 H, C=CH), 2.44 (s, 2 H, CCH₂), 3.52 (d, J = 2.4 Hz, 2 H, NCH₂), 8.07 (br s, 1 H, NH). 28: IR v 3300, 2250, 1690; ¹H NMR (200 MHz) δ 1.29 (s, 6 H, (CH₂)₂C), 2.11 (s, 2 H, CCH₂), 2.25 (t, 2 H, 2 x C=CH), 3.45-3.75 (m, 4 H, 2 x NCH₂).

1-Benzyl-5,5-dimethyl-3-pyrazolidinone (24). According to the general procedure, 3-pyrazolidinone 15 (3.02 g, 26.3 mmol) was alkylated by using benzyl chloride (3.03 mL, 26.3 mmol), K₂CO₃ (4.00 g, 29.3 mmol) and Lil in 2-butanone (130 mL). Work-up and flash chromatography (ethyl acetate) afforded 24 (4.30 g, 22.1 mmol, 80%) as white needles, mp 107.5-108.5 °C (hexane), Rf 0.42. IR v 3430, 3400, 1685; ¹H NMR (200 MHz) δ 1.35 (s, 6 H, (O ^C ), 2.39 (s, 2 H, CCH₂), 3.77 (s, 2 H, NCH₂), 6.77 (br s, 1 H, NH), 7.31 (s, 5 H, ArH); Anal. Calcd. for C₁₂H₁₆N₂O: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.52; H, 7.92; N, 13.68.

5,5-Dimethyl-1-{2-[2-(trimethylsilyl)]methyl]-2-propynyl}-3-pyrazolidinone (25). According to the general procedure, 3-pyrazolidinone 15 (2.50 g, 21.5 mmol) was alkylated upon use of 2-chloromethyl-3-(trimethylsilyl)-l-propene (2.90 g, 22.8 mmol), K₂CO₃ (2.73 g, 19.7 mmol) and Lil in 2-butanone (70 mL). Work-up and flash chromatography (ethyl acetate) afforded 25 (3.61 g, 14.8 mmol, 83%) as white crystals, mp 59-61 °C (ether), Rf 0.60. IR v 3440, 3400, 3080, 1690, 1250, 850; ¹H NMR (200 MHz) δ 0.09 (s, 9 H, (CH₃)₃Si), 1.26 (s, 6 H, (CH₂)₂C), 1.61 (d, J = 0.7 Hz, 2 H, CH₂Si), 2.34 (s, 2 H, CCH₂), 3.08 (s, 2 H, NCH₂), 4.72 (d, J = 0.6 Hz, 1 H, =CWH), 4.85 (d, J = 1.9 Hz, 1 H, =CHH), 6.83 (br s, 1 H, NH).

5,5-Dimethyl-1-[4-(trimethylsilyl)-2-butynyl]-3-pyrazolidinone (26). Following the general procedure, 3-pyrazolidinone 15 (2.60 g, 22.8 mmol) was alkylated with 4-iodo-1-(trimethylsilyl)-2-butyne (6.00 g, 23.9 mmol) and K₂CO₃ (3.30 g, 23.9 mmol) in 2-butanone (130 mL). After work-up and flash chromatography (ethyl acetate), 26 (3.70 g, 15.4 mmol, 68 %) was obtained as yellowish crystals, mp 81.5-83.5 °C (ether), Rf 0.65. IR v 3420, 3200, 2220, 1690, 1250, 850; ¹H NMR (200 MHz) δ 0.09 (s, 9 H, (CH₂)₂Si), 1.33 (s, 6 H, (CH₂)₂C), 1.46 (t, J = 2.4 Hz, 2 H, CH₂Si), 2.42 (s, 2 H, CCH₂), 3.52 (t, J = 2.4 Hz, 2 H, NCH₂), 7.70 (br s, 1 H, NH).

General procedure A for the methoxycarbonylation. To a suspension of NaH (obtained from a 55% dispersion in oil by washing with dry pentane) in THF was added dropwise a solution of the hydrazide in THF. After being stirred at rt for 30 min, the resulting clear solution was cooled to 0 °C and a solution of MeO₂CCl in THF was added. Stirring was maintained at 0 °C for 30 min and for 2 h at rt. The reaction mixture was concentrated in vacuo and the residue was taken up in water and extracted with CH₂Cl₂ (3 x). The combined organic layers were dried (MgSO₄), filtered, concentrated in vacuo and purified by flash chromatography to afford the pure product.

General procedure B for the ethoxycarbonylation. See procedure A with EtO₂CCl instead of MeO₂CCl.

General procedure C for the ethoxycarbonylation. To a solution of the hydrazide in CH₂Cl₂ were added Et₃N (1.1 equiv), diethyl dicarbonate (2.1 equiv) and a solution of DMAP (1.1 equiv) in CH₂Cl₂. The light
yellow solution was stirred at rt for 18 h, concentrated \textit{in vacuo} and purified by flash chromatography.

**General procedure D for the methoxycarbonylation.** To a solution of LDA (prepared from diisopropylamine (1.1 equiv) and n-butyllithium (1.1 equiv) at 0 °C) in THF was added at -78 °C a solution of the hydrazide (1 equiv) in THF. After being stirred at -78 °C for 1 h, MeO_2CCN dissolved in THF, was added and the mixture was allowed to warm to rt. After being stirred for 30 min, the mixture was poured into an ice/water mixture and extracted with ether (3 x). The combined organic layers were dried (MgSO_4), filtered and concentrated \textit{in vacuo}.

5.5-Dimethyl-3-[(ethoxycarbonyl)oxy-l-(2-propenyl)-2-pyrazoline (31). According to the general procedure A, 19 (2.00 g, 13.0 mmol) was treated with NaH (680 mg, 15.6 mmol) and MeO_2CCl (3.0 mL, 39 mmol), all compounds dissolved in THF (20 mL). Work-up and flash chromatography (ethyl acetate/hexane 1:1) afforded 31 (920 mg, 4.3 mmol, 33%) as a yellow oil, 

\[ \text{IR} \nu 3080, 1760, 1630; \text{^1H NMR} (200 MHz) 5 1.26 (s, 6 H, \text{(CH}_3}_2\text{C}), 2.73 (s, 2 H, C\text{CH}_2), 3.40 (dd, J = 1.2, 6.1 Hz, 2 H, NCH}_2), 3.81 (s, 3 H, CO_2CH}_3), 5.11 (dd, J = 1.2, 10.7 Hz, 1 H, =C//H), 5.22 (dd, J = 1.2, 17.2 Hz, 1 H, =CH//), 5.85-5.90 (m, 1 H, =CH). \]

5.5-Dimethyl-1-(2-propenyl)-3-pyrazolidinone-2-carboxylic acid ethyl ester (32). According to the general procedure C, a solution of 19 (12.6 g, 82.0 mmol) in CH_2Cl_2 (300 mL) was treated with Et_3N (11.6 mL, 86 mmol), diethyl dicarbonate (24.1 mL, 164 mmol) and a solution of DMAP (10.0 g, 82.0 mmol) in CH_2Cl_2 (30 mL). After concentration \textit{in vacuo} and purification by flash chromatography (ethyl acetate), 32 (11.5 g, 50.9 mmol, 82% (after correction)) was obtained as a colorless oil, 

\[ \text{IR} \nu 3080, 1780, 1730; \text{^1H NMR} (200 MHz) 5 1.23 (s, 6 H, \text{(CH}_3}_2\text{C}), 1.24 (t, J = 7.1 Hz, 3 H, CH}_2\text{CH}_3), 2.43 (s, 2 H, C\text{CH}_2), 3.46 (d, J = 6.9 Hz, 2 H, NCH}_2), 4.22 (q, J = 7.1 Hz, 2 H, CH}_2\text{CH}_3), 5.05-5.13 (m, 2 H, =CH), 5.75-5.90 (m, 1 H, =CH). \]

5.5-Dimethyl-1-(2-propenyl)-3-pyrazolidinone-2-carboxylic acid methyl ester (33). Following the general procedure D, 19 (300 mg, 1.95 mmol) was deprotonated with LDA (prepared from diisopropylamine (0.33 mL, 2.33 mmol) and n-butyllithium (1.4 mL, 2.33 mmol)) and alkylated with MeO_2CCN (350 mg, 4.0 mmol). Work-up and flash chromatography (ethyl acetate) afforded 33 (235 mg, 1.11 mmol, 57%) as a yellow oil, 

\[ \text{IR} \nu 3080, 1785, 1735; \text{^1H NMR} (200 MHz) 5 1.31 (s, 6 H, \text{(CH}_3}_2\text{C}), 2.52 (s, 2 H, C\text{CH}_2), 3.53 (d, J = 6.9 Hz, 2 H, NCH}_2), 3.84 (s, 3 H, CO_2CH}_3), 5.13-5.22 (m, 2 H, =CH), 5.82-6.03 (m, 1 H, =CH). \]

5.5-Dimethyl-1-(2-methyl-2-propenyl)-3-pyrazolidinone-2-carboxylic acid methyl ester (34). According to the general procedure A, 20 (500 mg, 2.98 mmol) was reacted with NaH (79 mg, 3.28 mmol) and MeO_2CCl (0.69 mL, 8.94 mmol) in THF (5 mL). Work-up and flash chromatography (ethyl acetate/hexane 1:1) afforded 34 (497 mg, 2.20 mmol, 74%) as a colorless oil, 

\[ \text{IR} \nu 3080, 1810, 1760; \text{^1H NMR} (200 MHz) 5 1.27 (s, 6 H, \text{(CH}_3}_2\text{C}), 1.84 (s, 3 H, CH}_3), 2.53 (s, 2 H, C\text{CH}_2), 5.34 (s, 3 H, NCH}_2), 3.78 (s, 3 H, CO_2CH}_3), 4.84, 4.86 (s, 2 H, =CH). \]

1-(2-Butenyl)-5,5-dimethyl-3-[(methoxycarbonyl)oxy-l-(2-propenyl)-2-pyrazoline (35). Following the general procedure A, 21 (2.20 g, 13.1 mmol) was treated with NaH (630 mg, 14.4 mmol) and MeO_2CCl (3.04 mL, 39.3 mmol), all compounds were dissolved in THF (30 mL). Work-up and flash chromatography (ethyl acetate/hexane 1:2) afforded 35 (1.40 g, 6.21 mmol, 47%) as a colorless oil, 

\[ \text{IR} \nu 1760, 1630; \text{^1H NMR} (200 MHz) 5 1.26 (s, 6 H, \text{(CH}_3}_2\text{C}), 1.67 (d, J = 4.6 Hz, 3 H, CH}_3), 2.74 (s, 2 H, C\text{CH}_2), 3.33 (dd, J = 1.1, 3.9 Hz, 2 H, NCH}_2), 3.82 (s, 3 H, CO_2CH}_3), 5.55-5.70 (m, 2 H, H=CH), (Z)-isomer: \text{IR} \nu 1760, 1630; \text{^1H NMR} (200 MHz) 5 1.26 (s, 6 H, \text{(CH}_3}_2\text{C}), 1.67 (d, J = 4.6 Hz, 3 H, CH}_3), 2.74 (s, 2 H, C\text{CH}_2), 3.33 (dd, J = 1.1, 3.9 Hz, 2 H, NCH}_2), 3.82 (s, 3 H, CO_2CH}_3), 5.55-5.70 (m, 2 H, H=CH); (E)-isomer: \text{IR} \nu 1760, 1630; \text{^1H NMR} (200 MHz) 5 1.26 (s, 6 H, \text{(CH}_3}_2\text{C}), 1.67 (d, J = 4.6 Hz, 3 H, CH}_3), 2.74 (s, 2 H, C\text{CH}_2), 3.33 (dd, J = 1.1, 3.9 Hz, 2 H, NCH}_2), 3.82 (s, 3 H, CO_2CH}_3), 5.55-5.70 (m, 2 H, H=CH). \]

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NMR (200 MHz) δ 1.28 (s, 6 H, (CH₃)₂C), 1.65 (d, J = 6.1 Hz, 3 H, CH₃), 2.75 (s, 2 H, C(CH₃)₂), 3.45 (dd, J = 1.1, 3.9 Hz, 2 H, NCH₂), 3.82 (s, 3 H, CO₂CH₃), 5.55-5.70 (m, 2 H, H=CH).

1-(2-Butenyl)-5,5-dimethyl-3-pyrazolidinone-2-carboxylic acid ethyl ester (36). Following the general procedure C, a solution of 21 (1.13 g, 6.70 mmol) in CH₂Cl₂ (25 mL) was treated with Et₃N (0.9 mL, 6.7 mmol), diethyl dicarbonate (1.97 mL, 13.4 mmol) and a solution of DMAP (0.82 g, 6.7 mmol) in CH₂Cl₂ (5 mL). Concentration in vacuo and flash chromatography (ethyl acetate) afforded 36 (1.03 g, 4.3 mmol, 64%) as a yellowish oil, Rf 0.76, (E)/(Z)-ratio 3.3:1. IR ν 1780, 1730; (£)-isomer: 1H NMR (200 MHz) δ 1.26 (s, 6 H, (CH₃)₂C), 1.30 (t, J = 7.1 Hz, 3 H, CH₂C), 1.60 (d, J = 6.1 Hz, 3 H, CH₃), 2.50 (s, 2 H, CCH₂), 3.57 (d, J = 5.4 Hz, 2 H, NCH₂), 4.28 (q, J = 7.1 Hz, 2 H, CCH₂), 5.40-5.70 (m, 2 H, H=CH); (Z)-isomer: JH NMR (200 MHz) δ 1.27 (s, 6 H, (CH₃)₂C), 1.30 (t, J = 7.1 Hz, 3 H, CH₂C), 1.56 (d, J = 9.2 Hz, 3 H, CH₃), 2.46 (s, 2 H, CCH₂), 3.43 (d, J = 7.1 Hz, 2 H, NCH₂), 4.28 (q, J = 7.1 Hz, 2 H, CCH₂), 5.40-5.70 (m, 2 H, H=CH).

5.5-Dimethyl-1-(3-methyl-2-butenyl)-3-pyrazolidinone-2-carboxylic acid methyl ester (37) via the general procedure A. 22 (2.02 g, 11.0 mmol) was treated with NaH (380 mg, 15.8 mmol) and MeO₂CCl (2.56 mL, 33.0 mmol) in THF (20 mL). Work-up and flash chromatography (ethyl acetate/hexane 1:1) afforded 37 (635 mg, 2.65 mmol, 24%) as a light yellow oil, Rf 0.27, 5,5-dimethyl[(3-methoxycarbonyl)oxy]-1-(3-methyl-2-butenyl)-2-pyrazoline (38) (486 mg, 2.0 mmol, 18%), as a yellowish oil, Rf 0.75 and 5,5-dimethyl-2-(1,1-dimethyl-2-propenyl)-3-pyrazolidinone-1-carboxylic acid methyl ester (39) (338 mg, 1.4 mmol, 13%) as an orange oil, Rf 0.45. 37: IR ν 3030, 1780, 1730; 1H NMR (250 MHz) δ 1.32 (s, 6 H, (CH₃)₂C), 1.58 (s, 3 H, CH₃), 1.70 (d, J = 7.1 Hz, 3 H, CH₂C), 2.51 (s, 2 H, CCH₂), 3.55 (d, J = 7.6 Hz, 2 H, NCH₂), 3.85 (s, 3 H, CO₂CH₃), 5.20-5.35 (m, 1 H, =CH). 38: IR ν 3030, 1760, 1630; 1H NMR (200 MHz) δ 1.28 (s, 6 H, (CH₃)₂C), 1.65 (s, 3 H, CH₃), 2.27 (d, J = 0.9 Hz, 3 H, CH₃), 2.74 (s, 2 H, CCH₂), 3.37 (d, J = 6.5 Hz, 2 H, NCH₂), 3.83 (s, 3 H, CO₂CH₃), 5.30-5.45 (s, J = 6.5 Hz, 1 H, =CH). 39: IR ν 3030, 1760, 1630; 1H NMR (200 MHz) δ 1.28 (s, 6 H, (CH₃)₂C), 1.65 (s, 3 H, CH₃), 2.27 (d, J = 0.9 Hz, 3 H, CH₃), 2.74 (s, 2 H, CCH₂), 3.37 (d, J = 6.5 Hz, 2 H, NCH₂), 3.83 (s, 3 H, CO₂CH₃), 5.30-5.45 (s, J = 6.5 Hz, 1 H, =CH); 13C NMR (50 MHz) δ 24.3 (2 x CH₃), 26.5 (2 x CH₃), 47.5 (CH₂), 52.9 (CO₂CH₃), 61.6 (NC), 65.1 (NC), 112.5 (=CH₂), 141.5 (=CH), 159.8, 172.5 (C(=O)).

5.5-Dimethyl-1-(3-methyl-2-butenyl)-3-pyrazolidinone-2-carboxylic acid methyl ester (37) via the general procedure D. 22 (25 mg, 0.14 mmol) was alkylated by using LDA (prepared from diisopropylamine (24 mL, 0.17 mmol) and n-butyllithium (105 mL, 0.17 mmol)) and MeO₂CCN (24 mg, 0.28 mmol), all compounds dissolved in THF (1 mL). After work-up and flash chromatography (ethyl acetate/hexane 1:1), 37 (31 mg, 0.13 mmol, 93%) was obtained as a colorless oil, Rf 0.30.

5.5-Dimethyl-1-(3-methyl-2-butenyl)-3-pyrazolidinone-2-carboxylic acid ethyl ester (40). Following the general procedure B, 23 (1.06 g, 7.00 mmol) was treated with NaH (201 mg, 8.36 mmol) and EtO₂CCI (2.0 mL, 21 mmol) in THF (50 mL). Work-up and purification by flash chromatography (ethyl acetate/hexane 1:1) afforded 40 (0.45 g, 3.07 mmol) as a pale yellow oil, Rf 0.41. IR ν 3300, 2105, 1780, 1725; 1H NMR (200 MHz) δ 1.34 (s, J = 7.1 Hz, 3 H, CH₂CH₃), 1.34 (s, 6 H, (CH₃)₂C), 2.30 (s, J = 2.4 Hz, 1 H, C=CH), 2.74 (br s, 2 H, CCH₂), 3.81 (d, J = 1.7 Hz, 2 H, NCH₂), 4.32 (q, J = 7.1 Hz, 2 H, CH₂CH₃).

1-Benzyl-5,5-dimethyl-3-pyrazolidinone-2-carboxylic acid ethyl ester (41) via the general procedure B. 24 (2.03 g, 10.0 mmol) was treated with NaH (550 mg, 12.7 mmol) and EtO₂CCI (2.86 mL, 30
mmol), while all compounds were dissolved in THF (30 mL). Work-up and flash chromatography (ethyl acetate/hexane 2:1) afforded 41 (1.64 g, 5.94 mmol, 59%) as a colorless oil, mp 89-92 °C, Rf 0.54 and 1-benzyl-5,5-dimethyl-1-[(ethoxycarbonyl)oxy]-2-pyrazoline (42) (1.07 g, 3.40 mmol, 39%) as a colorless oil, Rf 0.92. 41: IR v 1780, 1740; *H NMR (200 MHz) δ 1.17 (t, J = 7.1 Hz, 3 H, CH2Cl2), 1.28 (s, 6 H, (CH3)2Si), 2.57 (s, 2 H, CCH3), 4.03 (s, 2 H, NCH2), 4.08 (q, J = 7.1 Hz, 2 H, CH2CH3), 7.25-7.45 (m, 5 H, ArH). 42: IR v 1760, 1635; 1H NMR (200 MHz) δ 1.33 (t, J = 7.1 Hz, 3 H, CH2CH3), 1.34 (s, 6 H, (CH3)2Si), 2.81 (s, 2 H, CCH3), 3.96 (s, 2 H, NCH2), 4.25 (q, 2 H, CH2CH3), 7.15-7.45 (m, 5 H, ArH).

1-Benzyl-5,5-dimethyl-2-carboxylic acid ethyl ester (41) via the general procedure C. A solution of 24 (2.00 g, 9.80 mmol) in CH2Cl2 (40 mL) was treated with Et3N (2.06 mL, 15.3 mmol), diethyl dicarbonate (8.6 mL, 58 mmol) and a solution of DMAP (1.20 g, 9.80 mmol) in CH2Cl2 (4 mL). After being stirred for 66 h, the solution was concentrated in vacuo and purified by flash chromatography (ethyl acetate/hexane 2:1) to yield 41 (1.36 g, 4.90 mmol, 81% (after correction)) as white crystals.

5,5-Dimethyl-1-[(2-trimethylsilyl)methyl]-2-propenyl]-3-pyrazolidinone-2-carboxylic acid ethyl ester (43). Following the general procedure C, a solution of 25 (3.50 g, 14.6 mmol) in CH2Cl2 (60 mL) was treated with Et3N (2.06 mL, 15.3 mmol), diethyl dicarbonate (8.6 mL, 58 mmol) and a solution of DMAP (1.78 g, 14.6 mmol) in CH2Cl2 (10 mL). Concentration in vacuo and purification by flash chromatography (ethyl acetate/hexane 1:2) afforded 25 (900 mg, 3.75 mmol) and 43 (2.11 g, 6.76 mmol, 62% (after correction)) as a colorless oil, Rf 0.38. IR v 3080, 1780, 1740, 1250, 850; 1H NMR (200 MHz) δ 0.0 (s, 9 H, (CH3)2Si), 1.27 (s, 6 H, (CH3)2C), 1.29 (t, J = 7.1 Hz, 3 H, CH2CH3), 1.70 (d, J = 0.5 Hz, 2 H, CH2Si), 2.52 (s, 2 H, CCH3), 3.23 (s, 2 H, NCH2), 4.23 (q, J = 7.1 Hz, 2 H, CH2CH3), 4.68 (s, 1 H, =CH2), 4.83 (t, J = 0.7 Hz, 1 H, =CH2).

5,5-Dimethyl-1-[4-(trimethylsilyl)-2-butynyl]-3-pyrazolidinone-2-carboxylic acid methyl ester (44) via the general procedure A. 26 (412 mg, 1.73 mmol) was treated with NaH (51 mg, 2.1 mmol) and MeO2CCl (0.40 mL, 5.2 mmol) in THF (15 mL). Work-up and purification by flash chromatography (ethyl acetate/hexane 1:1) afforded 44 (317 mg, 1.07 mmol, 62%) as a colorless oil, Rf 0.60. IR v 2250, 1780, 1730, 1250, 850; 1H NMR (200 MHz) δ 0.03 (s, 9 H, (CH3)2Si), 1.33 (s, 6 H, (CH3)2C), 1.39 (t, J = 2.3 Hz, 2 H, CH2Si), 2.73 (br s, 2 H, CCH2), 3.79 (br s, 2 H, NCH2), 3.87 (s, 3 H, CO2CH3).

5,5-Dimethyl-1-[4-(trimethylsilyl)-2-butynyl]-3-pyrazolidinone-2-carboxylic acid methyl ester (44) via the general procedure D. 26 (130 mg, 0.55 mmol) was alkylated upon use of LDA (prepared from diisopropylamine (84 μL, 0.60 mmol) and n-butyllithium (380 μL, 0.61 mmol)) and MeO2CCl (94 mg, 1.10 mmol). Work-up and flash chromatography (ethyl acetate/hexane 1:1) afforded 44 (87 mg, 0.29 mmol, 53%) as a colorless oil, Rf 0.60.

General procedure E for the reduction reactions with NaBH4. A solution of the functionalized pyrazolidinone in ethanol was cooled to -20 °C and NaBH4 (6 equiv) was added in one portion. The solution was stirred at -20 °C while each 10 min 1 drop of a 2 M solution of sulfuric acid in ethanol was added to the mixture. The reaction was monitored by TLC. After complete reduction (2-3 h), the solution was cooled to -78 °C and acidified to pH = 3 with a 2 M H3SO4/CH3OH solution. After being stirred at rt for 4-5 h, the reaction mixture was poured into aq satd NaHCO3 and extracted with CH2Cl2 (3 ×). The combined organic layers were washed with water, dried (K2CO3), filtered and concentrated in vacuo. The residue was chromatographed to yield the pure pyrazolidine.

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5.5-Dimethyl-3-ethoxy-l-(2-propenyl)-2-pyrazolidinecarboxylic acid ethyl ester (45).

According to the general procedure E, 32 (10.0 g, 44.2 mmol) was reduced with NaB\textsubscript{H\textsubscript{4}} (10.0 g, 0.27 mol) in EtOH (500 mL). After work-up and flash chromatography (ethyl acetate/hexane 1:1), 45 (9.36 g, 26.6 mmol, 83%) was obtained as a light yellow oil, \( R_f 0.50 \). IR \( v 3080,1720,1680; \) NMR (200 MHz) \( \delta \)

- 0.95 (s, 3 H, \( \text{CH}_3 \))
- 1.08 (t, \( J = 7.1 \) Hz, 3 H, \( \text{OCH}_2\text{CH}_3 \))
- 1.19 (s, 3 H, \( \text{CH}_3 \))
- 1.26 (s, 3 H, \( \text{CH}_3 \))
- 2.02 (dd, \( J = 4.7, 13.5 \) Hz, 1 H, \( \text{CHCH}_3 \))
- 2.22 (dd, \( J = 6.0, 13.5 \) Hz, 1 H, \( \text{CHCH}_2 \))

5.5-Dimethyl-3-ethoxy-l-(2-methyl-2-propenyl)-2-pyrazolidinecarboxylic acid methyl ester (46).

Following the general procedure E, 34 (465 mg, 2.06 mmol) was reduced with NaB\textsubscript{H\textsubscript{4}} (467 mg, 12.3 mmol) in EtOH (25 mL). After work-up and flash chromatography (ethyl acetate/hexane 1:1), 46 (397 mg, 1.55 mmol, 75%) was obtained as a colorless oil, \( R_f 0.78 \). IR \( v 3070, 1680; \) NMR (200 MHz) \( \delta \)

- 0.99 (s, 3 H, \( \text{CH}_3 \))
- 1.16 (t, \( J = 7.0 \) Hz, 3 H, \( \text{CH}_2\text{CH}_3 \))
- 1.28 (s, 3 H, \( \text{CH}_3 \))
- 1.85 (s, 3 H, \( \text{CH}_3 \))
- 2.07 (dd, \( J = 4.9, 13.5 \) Hz, 1 H, \( \text{CHCH}_3 \))
- 2.27 (dd, \( J = 7.3, 13.4 \) Hz, 1 H, \( \text{CHCH}_2 \))
- 3.38 (s, 2 H, \( \text{NCH}_2 \))
- 3.69 (s, 3 H, \( \text{CO}_2\text{CH}_3 \))
- 4.82 (s, 2 H, \( =\text{CH}_2 \))
- 5.55 (dd, \( J = 5.0, 7.2 \) Hz, 1 H, OCH).

1-(2-Butenyl)-5,5-dimethyl-3-ethoxy-2-pyrazolidinecarboxylic acid ethyl ester (47).

Following the general procedure E, 36 (502 mg, 2.1 mmol) was reduced with NaB\textsubscript{H\textsubscript{4}} (473 mg, 12.6 mmol) in EtOH (25 mL). Work-up and flash chromatography (ethyl acetate) afforded 47 (404 mg, 1.5 mmol, 71%) as a colorless oil, \( (E)/(Z) \)-ratio 3.3:1, \( R_f 0.70 \). IR \( v 1690; \) NMR (200 MHz) \( \delta \)

- 0.98 (s, 3 H, \( \text{CH}_3 \))
- 1.14 (t, \( J = 7.0 \) Hz, 3 H, \( \text{OCH}_2\text{CH}_3 \))
- 1.24 (s, 3 H, \( \text{CH}_3 \))
- 1.29 (s, 3 H, \( \text{CH}_3 \))
- 1.55 (m, 3 H, \( \text{CHCH}_3 \))
- 2.07 (dd, \( J = 4.7, 13.5 \) Hz, 1 H, \( \text{CHCH}_2 \))
- 2.24 (dd, \( J = 7.3, 13.4 \) Hz, 1 H, \( \text{CHCH}_2 \))
- 3.30-3.45 (m, 2 H, \( \text{NCH}_2 \))
- 3.45-3.75 (m, 3 H, \( \text{CHCH}_2 \))
- 4.05-4.40 (m, 2 H, \( \text{CO}_2\text{CH}_2\text{CH}_3 \))

5.5-Dimethyl-3-ethoxy-1-(3-methyl-2-butenyl)-2-pyrazolidinecarboxylic acid methyl ester (48).

Following the general procedure E, 37 (634 mg, 2.35 mmol) was reduced with NaB\textsubscript{H\textsubscript{4}} (620 mg, 16.5 mmol) in EtOH (60 mL). After work-up and flash chromatography (ethyl acetate/hexane 1:1), 48 (318 mg, 1.18 mmol, 44%) was obtained as a colorless oil, \( R_f 0.55 \). IR \( v 3030, 1685; \) NMR (250 MHz) \( \delta \)

- 0.96 (s, 3 H, \( \text{CH}_3 \))
- 1.09 (s, \( J = 7.0 \) Hz, 3 H, \( \text{CH}_2\text{CH}_3 \))
- 1.26 (s, 3 H, \( \text{CH}_3 \))
- 1.64 (s, 3 H, \( \text{CH}_3 \))
- 2.06 (dd, \( J = 5.0, 13.4 \) Hz, 1 H, \( \text{CHCH}_3 \))
- 2.23 (dd, \( J = 7.3, 13.4 \) Hz, 1 H, \( \text{CHCH}_3 \))
- 3.35-3.40 (m, 3 H, \( \text{CHCH}_3 \))
- 3.65-3.65 (m, 3 H, \( \text{NCH}_2 \) and \( \text{CHCH}_2 \))
- 5.27 (br s, 1 H, \( =\text{CH} \))
- 5.51 (dd, \( J = 5.4, 6.8 \) Hz, 1 H, \( \text{OCH} \)).

5.5-Dimethyl-3-ethoxy-1-(2-propynyl)-2-pyrazolidinecarboxylic acid ethyl ester (49).

According to the general procedure E, 40 (1.00 g, 4.50 mmol) was reduced with NaB\textsubscript{H\textsubscript{4}} (1.02 g, 27.0 mmol) in EtOH (50 mL). After work-up and flash chromatography (ethyl acetate/hexane 1:1), 49 (741 mg, 2.92 mmol, 65%) was obtained as a colorless oil, \( R_f 0.56 \). IR \( v 3310, 1690; \) NMR (200 MHz) \( \delta \)

- 0.93 (s, 3 H, \( \text{CH}_3 \))
- 1.07 (s, \( J = 7.1 \) Hz, 3 H, \( \text{OCH}_2\text{CH}_3 \))
- 1.18 (t, \( J = 7.1 \) Hz, 3 H, \( \text{CO}_2\text{CH}_2\text{CH}_3 \))
- 1.22 (s, 3 H, \( \text{CH}_3 \))
- 1.95 (dd, \( J = 4.4, 14.2 \) Hz, 1 H, \( \text{CHCH}_2 \))
- 2.07 (t, \( J = 2.4 \) Hz, 1 H, \( \text{CH} \))
- 2.20 (dd, \( J = 7.2, 13.6 \) Hz, 1 H, \( \text{CHCH}_2 \))
- 3.50-3.70 (m, 2 H, \( \text{OCH}_2\text{CH}_3 \))
- 3.61 (dd, \( J = 2.4, 9.3 \) Hz, 2 H, \( \text{NCH}_2 \))

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Synthesis of bridged bicyclic hydrazines

1-Benzyl-5,5-dimethyl-3-ethoxy-2-pyrazolidinecarboxylic acid ethyl ester (50). Following the general procedure E, 41 (2.00 g, 7.24 mmol) was reduced with NaBH₄ (1.64 g, 43.4 mmol) in EtOH (100 mL). Work-up and flash chromatography (ethyl acetate/hexane 1:4) afforded 50 (2.02 g, 6.53 mmol, 90%) as a colorless oil, Rf 0.43. IR ν 1680; ¹H NMR (200 MHz) δ 0.97 (t, J = 7.0 Hz, 3 H, OCH₂CF₃), 1.01 (s, 3 H, CH₃), 1.19 (t, J = 7.1 Hz, 3 H, CH₂), 2.21 (dd, J = 5.2, 13.4 Hz, 1 H, CHCH₂), 2.32 (dd, J = 7.1, 13.4 Hz, 2 H, OCH₂CH₂), 3.59 (q, J = 7.1 Hz, 2 H, OCH₂CF₃), 3.89 (d, J = 11.7 Hz, 1 H, CH₂), 4.08 (d, J = 11.7 Hz, 1 H, NCH₂), 5.56 (q, J = 7.1 Hz, 2 H, OCH₂CH₂), 7.15-7.45 (m, 5 H, ArH).

5,5-Dimethyl-3-hydroxy-1-{2-{[(trimethylsilyl)methyl]-2-propenyl}-2-pyrazolidinecarboxylic acid ethyl ester (51). Following the general procedure E, 43 (678 mg, 2.17 mmol) was reduced with NaBH₄ (493 mg, 13.0 mmol) in EtOH (25 mL). After being stirred for 2 h at -20 °C, the reaction was quenched with cold aq satd NaHCO₃ (30 mL). After work-up according to the general procedure and flash chromatography (ethyl acetate/hexane 2:2), SI (653 mg, 2.08 mmol, 96%) was obtained as a white solid, mp 66-68 °C (hexane), Rf 0.68. IR ν 3450, 3080, 1725, 1660, 1240, 850; JH NMR (200 MHz) δ 0.07 (s, 9 H, (CH₃)₃Si), 1.05 (s, 3 H, CH₃), 1.26 (s, 3 H, CH₃), 1.63 (d, J = 13.6 Hz, CH₂), 1.84 (d, J = 13.6 Hz, CH₂), 2.07 (dd, J = 5.4, 13.3 Hz, 1 H, CHCH₂), 2.22 (dd, J = 7.2, 13.2 Hz, 1 H, CHCH₂), 3.52 (s, 2 H, NCH₂), 4.05-4.20 (m, 2 H, CH₂), 4.62 (s, 1 H, =CHH), 4.80 (s, 1 H, =CHH), 5.71 (t, J = 5.4 Hz, 1 H, OCH).

5,5-Dimethyl-3"hydroxy-l-[4-(trimethylsilyl)-2-butynyl]-2-pyrazolidinecarboxylic acid methyl ester (52). Following the general procedure E, 44 (315 mg, 1.06 mmol) was reduced with NaBH₄ (241 mg, 6.39 mmol) in EtOH (10 mL). After being stirred at -20 °C for 2 h, the reaction was quenched with cold aq satd NaHCO₃ (30 mL). After work-up according to the general procedure and flash chromatography (ethyl acetate/hexane 3:2) afforded 52 (185 mg, 0.62 mmol, 59%) as a colorless oil, Rf 0.52. IR ν 3500, 2200, 1679, 1250, 850; JH NMR (200 MHz) δ 0.07 (s, 3 H, CH₃), 1.15 (s, 3 H, CH₃), 1.35 (s, 3 H, CH₃), 1.45 (t, J = 2.3 Hz, 2 H, CH₂), 2.18 (br s, 1 H, CHCH₂), 2.41 (dd, J = 7.3, 13.2 Hz, 1 H, CHCH₂), 3.45 (br s, 1 H, CH₂), 3.66 (br s, 2 H, OCH₂), 3.79 (s, 3 H, CO₂CH₂), 5.71 (br s, 1 H, OCH).

General procedure F for the cyclization reactions with TiCl₄. To a 0.1 M solution of the hydrazide in CH₂Cl₂ was added TiCl₄ (2 equiv, as a solution of TiCl₃ in CH₂Cl₂) at -78 °C by a syringe. The mixture was stirred at -78 °C for 15 min and for 5-18 h at rt. The reaction mixture was poured into cold aq satd NaHCO₃ and the resulting suspension was filtered over Celite and extracted with CH₂Cl₂ (3 x). The combined organic layers were dried (MgSO₄) and concentrated in vacuo. Purification of the residue by flash chromatography afforded the pure cyclization product(s).

rel-(3S,5S)-3-Chloro-1,8-diaza-7,7-dimethylbicyclo[3.2.1]octane-8-carboxylic acid ethyl ester (53). According to the general procedure F, 45 (3.00 g, 11.7 mmol) dissolved in CH₂Cl₂ (120 mL) was cyclized with TiCl₄ (19.5 mL of a 1.2 M solution, 33.4 mmol). The mixture was worked-up after being stirred at rt for 18 h and the residue was purified by flash chromatography (ethyl acetate) to afford 53 (2.72 g, 11.1 mmol, 95%) as a yellow oil, Rf 0.76. IR ν 1670; ¹H NMR (200 MHz) δ 1.11, 1.16 (s, 3 H, CH₃), 1.28 (t, J = 7.0 Hz, 3 H, CH₂), 1.41 (s, 3 H, CH₃), 1.65 (br d, 12.9 Hz, 1 H, CH₂), 2.00-2.25 (m, 3 H, H₂ex, and 2 x H₄), 3.05-3.25 (m, 1 H, H₂), 3.40-3.50 (m, 1 H, H₂), 4.10-4.35 (m, 2 H, CH₂), 4.40-4.45, 4.59-4.62 (m, 1 H, H₅); ¹H NMR (250 MHz, CDCl₃, 90 °C) δ 0.94 (s, 3 H, CH₃), 0.96


(s, 3 H, CH₃), 1.06 (t, J = 7.1 Hz, 3 H, CH₂CH₃), 1.17 (d, J = 12.8 Hz, 1 H, H₆endo), 1.65 (dd, J = 8.0, 12.7 Hz, 1 H, H₆exo), 1.79 (ddd, J = 2.8, 6.5, 12.7 Hz, 1 H, H₄), 2.03 (dt, J = 3.0, 10.7 Hz, 1 H, H₄), 3.10-3.20 (m, 2 H, NCH₂), 3.90-4.10 (m, 3 H, CO₂CH₂CH₃ and H3), 4.08-4.38 (m, 1 H, H₅); ¹³C NMR (50 MHz) δ (all signals appear as rotamers) 14.5, 14.7 (CH₃), 22.5, 22.6 (CH₃), 31.1, 31.3 (CH₂), 40.2, 40.4 (C4), 43.9, 44.5 (C6), 49.5 (C5), 54.7, 55.4 (C5), 56.7, 57.5 (C2), 61.2, 61.6 (CH₂CH₃), 64.7, 65.7 (C7), 153.0, 153.7 (C(O)); ¹³C NMR (50 MHz, CDCl₃, 65 °C) δ 15.5 (CH₂CH₃), 22.4 (CH₃), 41.5 (C4), 45.1 (C6), 51.0 (C3), 56.3 (C5), 58.5 (C2), 61.9 (CH₂CH₃), 65.5 (C7), 153.0 (C(O)); MS (El, 70 eV) m/z (relative intensity) 246 (M⁺, 40), 211 (100), 128 (36), 70 (18); HRMS calcd for C₁₁H₁₈N₂O₂ 210.1322, found 210.1322.

rel-(3R,5S)-3-Chloro-1,8-diaza-3,7,7-trimethylbicyclo[3.2.1]octane-8-carboxylic acid methyl ester (54). A solution of 32 (232 mg, 0.91 mmol) in HCOOH (9 mL) was stirred at 50 °C for 18 h. The reaction was worked-up and the residue was chromatographed (ethyl acetate/hexane 1:1) to give an inseparable mixture (153 mg) of 54 (56%) and 1,8-diaza-3,7,7-trimethylbicyclo[3.2.1]oct-2-ene-8-carboxylic acid methyl ester (55) (16%) as a colorless oil, Rf 0.37, 54 (mixture): IR ν 1690; ¹H NMR (250 MHz, CDCl₃, 65 °C) δ 1.20 (dd, J = 12.3, 5.4 Hz, 1 H, H₆endo), 1.52-1.56 (m, 2 H, H₂CH₃), 1.66 (dt, J = 12.2, 7.9 Hz, 1 H, H₆exo), 2.56 (d, J = 15.7 Hz, 1 H, H₄), 3.54 (s, 3 H, CO₂CH₃), 4.46 (br s, 1 H, H₅), 6.04 (s, 1 H, H₇); ¹³C NMR (50 MHz) δ (some signals appear as rotamers) 19.6 (CH₃), 24.2 (CH₂), 29.3 (CH₃), 37.3, 37.6 (C4), 45.5, 46.2 (C6), 52.6 (CO₂CH₃), 53.6 (C5), 73.2 (C7), 124.7 (C3), 134.8 (C2), 154.6 (C(O)); MS (El, 70 eV) m/z (relative intensity) 210 (M⁺, 11), 154 (67), 153 (70), 109 (56), 95 (100); HRMS calcd for C₁₁H₁₈N₂O₂Cl 210.1368, found 210.1368.

rel-(3R,5S)-1,8-Diaza-3-(formyloxy)-3,7,7-trimethylbicyclo[3.2.1]octane-8-carboxylic acid methyl ester (56). A solution of 32 (232 mg, 0.91 mmol) in HCOOH (9 mL) was stirred at 50 °C for 18 h. Concentration in vacuo and flash chromatography (ethyl acetate/hexane 1:1) afforded 56 (85 mg, 0.33 mmol, 37%) as a colorless oil, Rf 0.20 and 55 (65 mg, 0.31 mmol, 34%) as a colorless oil, Rf 0.34. 56: IR ν 1680; ¹H NMR (200 MHz) δ (some signals appear as rotamers) 1.08-1.12 (m, 9 H, 3 x CH₃), 1.90-2.12 (m, 2 H, 2 x H6), 2.33-2.36 (m, 1 H, H4), 2.64 (d, J = 12.8 Hz, 1 H, H₄), 3.56 (d, J = 16.3 Hz, 1 H, H₇); 3.72 (s, 3 H, CO₂CH₃), 3.76 (d, J = 16 Hz, 1 H, H₂), 4.35-4.55 (m, 1 H, H5); ¹³C NMR (50 MHz) δ 25.7 (CH₃), 31.8 (CH₃), 37.0 (CH₃), 40.7 (C6), 41.5 (C4), 52.6 (CO₂CH₃), 52.8 (C5), 63.1 (C2), 65.9 (C7), 66.9 (C3), 155.0 (C(O)); MS (El, 70 eV) m/z (relative intensity) 246 (M⁺, 40), 211 (100), 128 (36), 70 (18); HRMS calcd for C₁₁H₁₈N₂O₂ 210.1368, found 210.1368.

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rel-(3S,4R,5S)-3-Chloro-1,8-diazaoctane-8-carboxylic acid ethyl ester (57). Following the general procedure F, 47 (145 mg, 0.54 mmol) was cyclized with TICl4 (0.92 ml of a 1.2 M solution, 1.11 mmol) in CH2Cl2 (5 ml). Work-up and flash chromatography (ethyl acetate/hexane 2:1) afforded 57 (67 mg, 0.26 mol, 53% (after correction)) as a colorless oil, Rf 0.50. IR ν 3640; δH NMR (200 MHz) δ 1.28 (s, 3 H, CH3), 1.42 (s, 3 H, CH3), 1.72, 1.70 (dd, J = 5.0, 11.3 Hz, 1 H, H5endo), 2.05-2.10 (m, 1 H, H5exo), 2.31, 2.29 (dd, J = 4.2, 11.3 Hz, 1 H, H4), 3.22, 3.17 (CO2CH3), 4.45, 4.51 (d, J = 5.0 Hz, 1 H, H4), 7.86, 7.87 (s, 1 H, OCHO); 13C NMR (125 MHz) δ (all signals appear as rotamers) 14.6, 14.8 (CH2), 23.1, 23.5 (CH3), 23.6, 24.0 (CH3), 30.4, 30.5 (CH3), 46.5, 47.4 (C7), 65.6 (C5), 51.7, 52.1 (C2), 52.4, 52.6 (C3), 53.7, 54.5 (C4), 60.6, 61.4 (CO2CH3), 65.9, 66.6 (C6), 83.4, 83.5 (CO), 135.7, 159.6, 160.0 (C(0)); MS (EI, 70 eV) m/z (relative intensity) 270 (M+, 15), 225 (16), 168 (100), 153 (47), 141 (72), 127 (81), 123 (41), 109 (32), 83 (38), 59 (45), 41 (89); HRMS calcd for C12H21N2O2Cl 260.1292, found 260.1284.

rel-(3R,4S)-1,7-Diaza-6,6-dimethyl-3-[[dimethyl(formyloxy)methyl]bicyclo[2.2.1]heptane-7-carboxylic acid methyl ester (58). A solution of 48 (142 mg, 0.52 mmol) in HCOOH (5 ml) was stirred at 50 °C for 18 h. The reaction mixture was worked-up and purified by flash chromatography (ethyl acetate/hexane 1:1) afforded 58 (50 mg, 0.21 mmol, 84%) as a light yellow oil, Rf 0.37. IR ν 3640; δH NMR (200 MHz) δ 1.25, 1.27 (s, 3 H, CH3), 1.30, 1.32 (s, 3 H, CH3), 1.62, 1.63 (d, J = 6.5 Hz, 3 H, CH3), 2.05, 2.06 (dd, J = 6.3, 10.8 Hz, 1 H, H3), 4.26 (m, 2 H, CH2), 4.35 (m, 1 H, H5); 13C NMR (50 MHz) δ (all signals appear as rotamers) 14.6, 14.8 (CH2), 23.1, 23.5 (CH3), 23.6, 24.0 (CH3), 30.4, 30.5 (CH3), 46.5, 47.4 (C7), 65.6 (C5), 51.7, 52.1 (C2), 52.4, 52.6 (C3), 53.7, 54.5 (C4), 60.6, 61.4 (CO2CH3), 65.9, 66.6 (C6), 83.4, 83.5 (CO), 135.7, 159.6, 160.0 (C(0)); MS (EI, 70 eV) m/z (relative intensity) 260 (M+, 19), 225 (25), 212 (18), 204 (46), 169 (30), 141 (21), 127 (100), 83 (42); HRMS calcd for C12H21N2O2Cl 260.1292, found 260.1292.
solution of 49 (201 mg, 0.79 mmol) in CH₂Cl₂ (8 mL) was treated with TiCl₄ (1.32 mL of a 1.2 M solution, 1.58 mmol) according to the general procedure F. After being stirred at rt for 18 h, the reaction was worked-up and purified by flash chromatography (ethyl acetate/hexane 1:1) to afford 60 (46 mg, 0.19 mmol, 24%) as a yellow oil, Rᶠ 0.69. IR ν 1690; ¹H NMR (200 MHz) δ 1.18 (s, 3 H, CH₃), 1.28 (t, J = 7.0 Hz, 3 H, CH₂CH₂), 1.39 (s, 3 H, CH₃), 1.95-2.10 (m, 2 H, 2 × H6), 3.49 (d, J = 18.1 Hz, 1 H, H2), 3.95 (d, J = 18.2 Hz, 1 H, H2), 4.25 (q, J = 7.1 Hz, 2 H, CH₂CH₂), 4.50-4.75 (m, 1 H, H5), 6.15 (d, J = 5.5 Hz, H4); ¹³C NMR (30 MHz) δ (some signals appear as rotamers) 14.6 (CH₂CH₂), 26.1, 26.3 (CH₂), 32.1 (CH₃), 49.7, 49.8 (C₅), 54.4 (C₅), 61.7 (CH₂CH₂), 61.8, 61.9 (C₂), 67.9 (C₇), 128.8 (C₄), 150.3 (C₃), 153.0 (C(O)); MS (EI, 70 eV) m/z (relative intensity) 244 (M⁺, 90), 208 (61), 187 (39), 152 (37), 143 (38), 121 (57), 115 (100), 80 (84), 65 (22), 58 (33), 41 (33); HRMS calcd for C₁₁H₁₇N₂O₂Cl 244.0979, found 244.0981.

1,8-Diaza-7.7-dimethylbicyclo[3.2.1]octan-3-one-8-carboxylic acid ethyl ester (61). A solution of 49 (134 mg, 0.53 mmol) in HCOOH (5 mL) was stirred at 50 ºC for 20 h. After addition of H₂O (5 mL), the reaction mixture was stirred at 60 ºC for another 6 h and poured into aq satd NaHCO₃ (100 mL). An additional amount of NaHCO₃ was added until the water layer reached pH = 9. After extraction with CH₂Cl₂ (3 × 100 mL), the combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo. Flash chromatography (ethyl acetate/hexane 1:1) afforded 61 (56 mg, 0.25 mmol, 47%) as a light yellow oil, Rᶠ 0.28. IR ν 1720, 1690; ¹H NMR (200 MHz) δ 1.18 (s, 3 H, CH₃), 1.61 (t, J = 6.9 Hz, 3 H, CH₂CH₂), 1.61 (s, 3 H, CH₃), 1.69 (d, J = 12.8 Hz, 1 H, H₆endo), 2.24 (dd, J = 7.8, 12.8 Hz, 1 H, H₆exo), 2.42 (d, J = 16.6 Hz, 1 H, H₄), 2.78 (dd, J = 3.2, 16.3 Hz, 1 H, H₄), 3.63 (s, 2 H, 2 × H₂), 4.28 (q, J = 6.9 Hz, 2 H, CH₂CH₂), 4.75-5.00 (m, 1 H, H₅); ¹³C NMR (50 MHz) δ 14.8 (CH₂CH₂), 24.8 (CH₃), 31.2 (CH₂), 45.9 (C₆), 48.5 (C₄), 54.8 (C₅), 62.3 (CH₂CH₂), 62.9 (C₂), 67.5 (C₇), 154.0 (C(O)), 208.2 (C(O)); MS (EI, 70 eV) m/z (relative intensity) 226 (M⁺, 12), 198 (84), 157 (31), 143 (100), 71 (26); HRMS calcd for C₁₁H₁₇N₂O₂ 226.1305, found 226.1311.

3,4-Benzao-1,8-diaza-7.7-dimethylbicyclo[3.2.1]octane-8-carboxylic acid ethyl ester (62). According to the general procedure F, a solution of 50 (1.04 g, 3.4 mmol) in CH₂Cl₂ (34 mL) was treated with TiCl₄ (5.7 mL of a 1.2 M solution in CH₂Cl₂, 6.8 mmol). After being stirred at rt for 18 h, the reaction mixture was worked-up and the residue was chromatographed (ethyl acetate, then ethyl acetate/hexane 1:2) to afford 62 (508 mg, 1.95 mmol, 64% (after correction)) as a colorless oil, Rᶠ 0.28. IR ν 1690; ¹H NMR (200 MHz) δ (some signals appear as rotamers) 1.17-1.30 (m, 9 H, 3 × CH₃), 1.69 (d, J = 11.8 Hz, 1 H, H₆exo), 2.23 (dd, J = 7.0, 11.9 Hz, 1 H, H₆endo), 4.05-4.25 (m, 3 H, H₂ and CH₂CH₂), 4.46 (d, J = 17.2 Hz, 1 H, H₂), 5.02, 5.16 (d, J = 6.0 Hz, 1 H, H₅), 6.94-7.15 (m, 4 H, 4 × ArH); ¹H NMR (250 MHz, CDCl₃, 65 ºC) δ 0.97 (s, 3 H, CH₃), 1.06 (t, J = 7.1 Hz, 3 H, CH₂CH₂), 1.19 (s, 3 H, CH₃), 1.65 (d, J = 11.8 Hz, 1 H, H₆endo), 2.06 (dd, J = 7.0, 11.8 Hz, 1 H, H₆exo), 3.88 (d, J = 17.6 Hz, 1 H, H₂), 4.09 (q, J = 7.1 Hz, 2 H, CH₂CH₂), 4.48 (d, J = 17.6 Hz, 1 H, H₂), 5.16 (d, J = 6.7 Hz, 1 H, H₅), 6.60-7.00 (m, 4 H, 4 × ArH); ¹³C NMR (50 MHz) δ (some signals appear as rotamers) 14.5 (CH₂CH₂), 25.4 (CH₃), 31.9 (CH₂), 50.9, 51.3 (C₆), 52.7 (C₂), 56.7, 57.2 (C₅), 61.2, 61.5 (CH₂CH₂), 66.0, 66.5 (C₇), 124.1, 125.4, 126.2, 127.1 (ArH), 131.0, 140.0 (ArC), 154.0, 154.5 (C(O)); MS (EI, 70 eV) m/z (relative intensity) 260 (M⁺, 81), 245 (11), 204 (82), 187 (37), 159 (370, 131), 131 (100), 117 (72), 91 (36), 77 (17); HRMS calcd for C₁₅H₁₈N₂O₂ 260.1525, found 260.1529.

1,8-Diaza-7.7-dimethyl-3-methylenebicyclo[3.2.1]octane-8-carboxylic acid ethyl ester (63). To a solution of 51 (101 mg, 0.32 mmol) in CH₂Cl₂ (4 mL) was added BF₃·OEt₂ (79 µL, 0.64 mmol) at 0 ºC. The reaction mixture was stirred at 0 ºC for 15 min and 2 h at rt, poured into aq satd NaCl (40 mL) and extracted
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with \( \text{CH}_2\text{Cl}_2 \) (3 × 40 mL). The combined organic layers were dried (MgSO\(_4\)), filtered and concentrated in vacuo. Purification of the residue by flash chromatography (ethyl acetate/hexane 1:1) afforded 63 (43 mg, 0.19 mmol, 61%) as a colorless oil, \( R_f \) 0.32. IR \( \nu \) 3070, 1690; \(^1\text{H} \) NMR (200 MHz) (all signals appear as rotamers) 1.04, 1.09 (s, 3 H, \( \text{CH}_3 \)), 1.20-1.32 (m, 3 H, \( \text{CH}_2\text{CH}_3 \)), 1.33 (s, 3 H, \( \text{CH}_3 \)), 1.64, 1.66 (d, J = 12.3 Hz, 1 H, \( H_6\text{endo} \)), 1.75-2.15 (m, 2 H, \( H_6\text{exo} \) and \( H_4 \)), 4.41-4.23 (m, 2 H, \( \text{CH}_2\text{CH}_3 \)), 4.47-4.65 (m, 2 H, \( H_5 \)), 4.88, 4.93 (s, 2 H, =\( \text{CH}_2 \)); \(^1\text{C} \) NMR (50 MHz) (some signals appear as rotamers) 14.8 (CH\(_2\text{CH}_3 \)), 22.8 (CH\(_3 \)), 31.4, 31.5 (CH\(_3 \)), 39.4, 39.6 (C\(_6\)), 43.7, 44.3 (C\(_7\)), 54.9, 55.6 (C\(_5\)), 56.5, 57.3 (C\(_2\)), 61.2, 61.3 (CH\(_2\text{CH}_3 \)), 66.5 (C\(_7\)), 113.8, 114.0 (=CH\(_2\)), 140.8, 141.0 (C\(_3\)), 154.5 (C(O)); MS (El, 70 eV) \( m/z \) (relative intensity) 224 (M\(^+\), 93), 209 (24), 168 (38), 151 (100), 137 (42), 109 (32), 95 (25), 81 (17); HRMS calcd for C\(_{12}\)H\(_{20}\)N\(_2\)O\(_2\) 224.1525, found 224.1530.

\( 1,8\)-Diaza-7,7-dimethyl-3-methylenebicyclo[3.2.1]octane-8-carboxylic acid ethyl ester (63). A solution of 51 (2.50 g, 7.97 mmol) in HCOOH (80 mL) was stirred for 18 h at rt. Concentration in vacuo and flash chromatography (ethyl acetate/hexane 1:1) afforded 63 (1.52 g, 6.8 mmol, 85%) as a yellowish oil, \( R_f \) 0.32.

\( 1,7\)-Diaza-5,5-dimethyl-3-ethenylidenebicyclo[2.2.1]heptane-7-carboxylic acid methyl ester (64). To a solution of 52 (109 mg, 0.37 mmol) in CH\(_2\)Cl\(_2\) (4 mL) was added BF\(_3\)OEt\(_2\) (91 \( \mu \)L, 0.74 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min and for 18 h at rt. The resulting orange solution was poured into aq satd NaCl (50 mL) and extracted with CH\(_2\)Cl\(_2\) (3 × 50 mL). The combined organic layers were washed with H\(_2\)O (50 mL), dried (MgSO\(_4\)), filtered and concentrated in vacuo. The residue was chromatographed (ethyl acetate/hexane 1:1) to give 64 (48 mg, 0.23 mmol, 62%) as a colorless oil, \( R_f \) 0.36. IR \( \nu \) 1980, 1960, 1690, 890, 840; \(^1\text{H} \) NMR (200 MHz) 1.23 (s, 3 H, \( \text{CH}_3 \)), 1.24 (s, 3 H, \( \text{CH}_3 \)), 1.51 (d, J = 11.3 Hz, 1 H, \( H_5\text{endo} \)), 1.71 (dd, J = 7.7, 12.1 Hz, 1 H, \( H_5\text{exo} \)), 3.57 (dt, J = 15.1, 4.7 Hz, 1 H, \( H_2 \)), 3.74 (s, 3 H, \( \text{CO}_2\text{CH}_3 \)), 3.81 (dt, J = 15.1, 3.1 Hz, 1 H, H2)), 4.83 (br s, 2 H, =\( \text{CH}_2 \)); \(^1\text{C} \) NMR (50 MHz) (some signals appear as rotamers) 24.9 (CH\(_3 \)), 30.6 (CH\(_3 \)), 46.3 (C\(_5\)), 53.0 (CO\(_2\text{CH}_3 \)), 54.3 (C\(_2\)), 64.9 (C\(_6\)), 65.0 (C\(_4\)), 79.3 (=CH\(_2\)), 100.8 (C=C=CH\(_2\)), 156.0 (C(O)); MS (El, 70 eV) \( m/z \) (relative intensity) 208 (M\(^+\), 82), 193 (15), 152 (100), 141 (74), 125 (30), 107 (16), 97 (20), 70 (8); HRMS calcd for C\(_{11}\)H\(_{16}\)O\(_2\) 208.1212, found 208.1205.

\( 1,7\)-Diaza-5,5-dimethyl-3-ethenylidenebicyclo[2.2.1]heptane-7-carboxylic acid methyl ester (64). To a solution of 52 (96 mg, 0.45 mmol) in HCOOH (5 mL) was stirred at 50 °C for 18 h. Concentration in vacuo and flash chromatography (ethyl acetate/hexane 1:1) afforded 64 (28 mg, 0.13 mmol, 42%) as a colorless oil, \( R_f \) 0.36.

\( 5,5\)-Dimethyl-3-hydroxy-1-(2-propenyl)-2-pyrazolidinecarboxylic acid ethyl ester (65). A solution of 45 (174 mg, 0.74 mmol) in HCOOH (5 mL) was stirred at 50 °C for 18 h. Concentration in vacuo and flash chromatography (ethyl acetate/hexane 1:1) afforded 65 (129 mg, 0.56 mmol, 83%) as a colorless oil, \( R_f \) 0.30. IR \( \nu \) 3410, 3080, 1720, 1675; \(^1\text{H} \) NMR (200 MHz) 0.95 (s, 3 H, \( \text{CH}_3 \)), 1.19 (t, J = 7.0 Hz, 3 H, \( \text{CO}_2\text{CH}_2\text{CH}_3 \)), 1.26 (s, 3 H, \( \text{CH}_3 \)), 2.02 (dd, J = 4.7, 13.5 Hz, 1 H, \( \text{CHCH}_3 \)), 2.22 (dd, J = 6.0, 13.5 Hz, 1 H, \( \text{CHCH}_2\)), 3.30-3.70 (m, 2 H, \( \text{NCH}_2 \)), 3.84 (br s, 1 H, \( \text{OH} \)), 4.15 (q, J = 7.0 Hz, 2 H, \( \text{CO}_2\text{CH}_2\text{CH}_3 \)), 5.01-5.07
1-(2-Butenyl)-5,5-dimethyl-3-hydroxy-2-pyrazolidinecarboxylic acid ethyl ester (66). A solution of 47 (145 mg, 0.54 mmol) in HCOOH (5 mL) was stirred at 50 °C for 18 h. Concentration in vacuo and flash chromatography (ethyl acetate/hexane 2:1) afforded 66 (119 mg, 0.49 mmol, 91%) as a colorless oil, Rf 0.33. IR ν 3580, 3420, 1720, 1670; 1H NMR (200 MHz) δ (mixture) 0.98 (s, 3 H, CH3), 1.24 (t, J = 7.0 Hz, 3 H, CH2CH3), 1.29 (s, 3 H, CH3), 1.50-1.65 (m, 3 H, CH=CH2), 2.07 (dd, J = 4.7, 13.5 Hz, 1 H, CHCH3), 2.24 (dd, J = 7.3, 13.4 Hz, 1 H, CHCH2), 3.30-3.45 (m, 2 H, NCH2), 3.90 (br s, 1 H, OH), 4.05-4.40 (m, 2 H, CO2CH2CH3), 5.45-5.65 (m, 3 H, CH=CH and OCH).

1-Benzyl-5,5-dimethyl-3-hydroxy-2-pyrazolidinecarboxylic acid ethyl ester (67). A solution of 50 (564 mg, 1.84 mmol) in HCOOH (20 mL) was stirred at 50 °C for 18 h. Concentration in vacuo and flash chromatography (ethyl acetate/hexane 2:1) afforded 67 (409 mg, 1.47 mmol, 80%) as a colorless oil, Rf 0.52. IR ν 3400; 1H NMR (200 MHz) δ 1.01 (s, 3 H, CH3), 1.19 (t, J = 7.1 Hz, 3 H, CH2CH3), 1.36 (s, 3 H, CH3), 2.21 (dd, J = 5.2, 13.4 Hz, 1 H, CHCH3), 2.32 (dd, J = 7.1, 13.4 Hz, 1 H, CHCH2), 3.89 (d, J = 11.7 Hz, NCH2), 3.92 (q, J = 7.0 Hz, 2 H, CH2CH3), 4.08 (d, J = 11.7 Hz, 1 H, NCH2), 4.10 (br s, 1 H, OH), 5.56 (dd, J = 5.3, 7.0 Hz, OCH), 7.15-7.45 (m, 5 H, ArH).

rel-(3S,5S)-3-Chloro-1,8-diaza-7,7-dimethylibicyclo[3.2.1]octane (72). To a solution of 53 (65 mg, 0.27 mmol) in MeCN (3 mL) was added MegSil (0.11 mL, 0.80 mmol) and the reaction mixture was stirred at 40 °C for 2 h. The resulting dark brown solution was poured into aq NaHSO3 and extracted with CH2Cl2 (3 x 20 mL). The combined organic layers were dried (MgSO4), filtered, and concentrated in vacuo. The residue was chromatographed (acetone) to yield 72 (37 mg, 0.21 mmol, 79%) as white crystals, mp 44.5-45 °C, Rf 0.35. IR ν 3300; 1H NMR (200 MHz) δ 1.13 (s, 3 H, CH3exo), 1.42 (s, 3 H, CH3endo), 1.67 (d, J = 12.9 Hz, H6endo), 1.89 (dd, 1 H, J = 12.9, 7.6 Hz, H6exo), 2.12 (m, 2 H, H4), 3.20 (dd, J = 11.1, 14.0 Hz, 1 H, H2ax), 3.35 (dd, J = 6.2, 14.0 Hz, 1 H, H2eq), 3.60 (m, 1 H, H3), 3.79 (br s, 1 H, NH), 4.20 (tt, J = 11.1, 6.3 Hz, 1 H, H3); 13C NMR (50 MHz) δ 22.9 (CH3), 31.9 (CH3), 42.2 (C4), 45.3 (C3), 50.9 (C6), 57.7 (C5), 58.1 (C2), 65.6 (C7); MS (El, 70 eV) m/z (relative intensity) 174 (M+, 52), 143 (100), 139 (100), 118 (24), 111 (76), 70 (75), 67 (35), 56 (32), 41 (31); HRMS calcld for C8H15N2Cl 174.0924, found 174.0931.

rel-(3S,5S)-3-Chloro-1,8-diaza-7,7,8-trimethylibicyclo[3.2.1]octane (73). To a solution of 72 (50 mg, 0.33 mmol) in MeCN (1 mL) were added 37% aq formaldehyde (130 |±L, 1.66 mmol) and NaBH4CN (33 mg, 0.53 mmol). After being stirred for 15 min at rt, a few drops of glacial acetic acid were added carefully until the pH was neutral. Stirring was continued for 45 min, while the pH was kept neutral by drop wise addition of glacial acetic acid. The solution was poured into 1 N KOH (10 mL) and extracted with CH2Cl2 (3 x 20 mL). The combined organic layers were washed with H2O (10 mL), dried (K2CO3), filtered, concentrated in vacuo and chromatographed (ethyl acetate/hexane 1:1) to afford 73 (45 mg, 0.27 mmol, 82%) as a colorless oil, Rf 0.40. IR ν 1455, 1260, 900, 635; 1H NMR (200 MHz) δ 1.28 (3 H, CH3), 1.33 (s, 3 H, CH3), 1.56 (d, J = 13.1 Hz, 1 H, H6endo), 1.85-1.90 (m, 1 H, H6exo), 2.10 (dd, J = 12.6, 7.7 Hz, 1 H, H4), 2.23 (dd, J = 13.1, 2.4 Hz, 1 H, H4), 2.68 (s, 3 H, NCH3), 3.00 (dd, J = 6.4, 14.9 Hz, 1 H, H2), 3.25 (dd, J = 11.3, 14.9 Hz, 1 H, H2), 3.50-3.40 (m, 1 H, H5), 4.28 (tt, J = 11.1, 6.8 Hz, 1 H, H3); 13C NMR (63 MHz) δ 22.8 (CH3), 29.5 (C6), 31.0 (CH3), 32.7 (CH3), 42.9 (C4), 47.8 (C3), 52.4 (C2), 58.1 (C5), 73.9 (C7); MS (El, 70 eV) m/z (relative intensity) 188 (M+, 18), 153 (100), 97 (35), 43 (42); HRMS calcld for C9H17N2Cl 188.1081, found 188.1077.
Synthesis of bridged bicyclic hydrazines

3,4-Dibenzo-1,8-diaza-7,7-dimethylenebicyclo[3.2.1]octane (74). A solution of 62 (187 mg, 0.72 mmol) and KOH (160 mg, 2.88 mmol) in MeOH (7 mL) was heated at reflux temperature for 90 h. The resulting mixture was poured into aq satd NH₄Cl (25 mL) and extracted with CH₂Cl₂ (3 x 25 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo. The residue was chromatographed (acetone) to yield 74 (109 mg, 0.58 mmol, 81%) as a yellow oil, Rf 0.13. IR ν 3390, 3060; ¹H NMR (250 MHz) δ 1.25 (s, 3 H, CH₃), 1.27 (s, 3 H, CH₃), 1.95-2.15 (m, 2 H, 2 x H₆), 3.90 (br s, 1 H, NH), 4.07 (d, J = 17.3 Hz, 1 H, H₂), 4.17 (d, J = 6.0 Hz, 1 H, H₅), 4.45 (d, J = 17.3 Hz, 1 H, H₂), 6.85-7.15 (m, 4 H, ArH); ¹³C NMR (50 MHz) δ 26.1 (CH₃), 32.7 (CH₃), 53.1 (C₂ and C₆), 65.6 (C₇), 124.4, 125.4, 125.8, 126.9 (ArH), 132.1, 141.7 (ArC); MS (EI, 70 eV) m/z (relative intensity) 188 (M⁺, 64), 173 (23), 145 (8), 132 (66), 131 (100), 117 (36), 104 (8), 91 (8), 77 (9), 32 (48), 31 (64); HRMS calcd for C₁₂H₁₆N₂ 188.1313, found 188.1320.

1,8-Diaza-7,7-dimethyl-3-methylenebicyclo[3.2.1]octane (75). A solution of 63 (78 mg, 0.35 mmol) and KOH (78 mg, 1.4 mmol) in MeOH (4 mL) was heated at reflux temperature for 90 h. The resulting solution was poured into aq satd NH₄Cl (25 mL) and extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo. Purification of the residue by flash chromatography (acetone) afforded 75 (21.5 mg, 0.14 mmol, 40%) as a colorless oil, Rf 0.10. IR ν 3300, 3060, 895; ¹H NMR (200 MHz) δ 1.11 (s, 3 H, CH₃), 1.38 (s, 3 H, CH₃), 1.66 (d, J = 12.0 Hz, 1 H, H₆endo), 1.80 (dd, J = 0.7, 7.1, 12.4 Hz, 1 H, H₆exo), 2.07 (d, J = 13.3 Hz, 1 H, H₄), 2.68 (d, J = 13.3 Hz, 1 H, H₄), 3.49 (d, J = 15.4 Hz, 1 H, H₂), 3.60-3.80 (m, 2 H, H² and H₅), 3.93 (br s, 1 H, NH), 4.75-4.85 (m, 2 H, =CH₂); ¹³C NMR (63 MHz) δ 23.1 (CH₃), 32.0 (CH₃), 41.0 (C₄), 45.4 (C₆), 57.4 (C₅), 57.7 (C₂), 66.4 (C₇), 112.3 (=CH₂), 142.7 (C₃); MS (EI, 70 eV) m/z (relative intensity) 152 (M⁺, 33), 137 (100), 109 (13), 95 (26), 81 (25), 69 (40), 55 (25), 41 (32); HRMS calcd for C₉H₁₆N₂ 152.1313, found 152.1310.

1,8-Diaza-3-methylene-7,7,8-trimethylbicyclo[3.2.1]octane (76). To a suspension of LiAlH₄ (17 mg, 0.45 mmol) in THF (2 mL) was added dropwise a solution of 63 (51 mg, 0.23 mmol) in THF (2 mL) and the mixture was heated at reflux temperature for 3 h. After cooling to rt, H₂O (53 mL) was added and the resulting suspension was washed with ether (50 mL). The organic layer was dried (MgSO₄), filtered and concentrated in vacuo. Purification of the residue by flash chromatography (ethyl acetate) afforded 76 (9.8 mg, 0.059 mmol, 13%) as a colorless oil, Rf (ethyl acetate) 0.10. IR ν 3060, 890; ¹H NMR (200 MHz) δ 1.27 (s, 3 H, CH₃), 1.32 (s, 3 H, CH₃), 1.62 (d, J = 12.1 Hz, 1 H, H₆endo), 1.89 (d, J = 14.9 Hz, 1 H, H₄), 2.06 (dd, J = 7.4, 12.1 Hz, 1 H, H₆endo), 2.73 (s, 3 H, NCH₃), 2.78 (d, J = 14.9 Hz, 1 H, H₄), 3.25 (d, J = 16.2 Hz, 1 H, H₂), 3.36-3.46 (m, 1 H, H₅), 3.80 (dd, J = 1.0, 16.2 Hz, 1 H, H₂), 4.71-4.84 (m, 2 H, =CH₂); ¹³C NMR (75 MHz) δ 24.6 (CH₃), 32.7 (C₄), 33.0 (CH₃), 35.9 (NCH₃), 45.9 (C₆), 49.1 (C₂), 59.8 (C₅), 63.9 (C₇), 111.3 (=CH₂), 142.6 (C₃); MS (EI, 70 eV) m/z (relative intensity) 166 (M⁺, 57), 151 (95), 125 (26), 111 (17), 95 (27), 83 (100), 82 (90), 61 (25), 43 (37); HRMS calcd for C₁₆H₂₈N₂ 166.1470, found 166.1470.

4.8 REFERENCES AND NOTES

Chapter 4

5.1 INTRODUCTION

During the last century, the tropane alkaloids have been prominent targets for organic synthesis. One of the most important representatives of this group of alkaloids is \((R)-(\pm)-\)
cocaine 1 which is isolated from the leaves of *Erythroxylon coca* and has been a major subject of scientific investigations. It is one of the eight possible stereoisomers of 3-[(benzoyl)oxy]-8-
methyl-8-azabicyclo[3.2.1]octane-2-carboxylic acid methyl ester with both substituents in the exo-position. The different isomers at the 2- and the 3-position are indicated with the prefixes pseudo and allo, respectively. For example, the isomer 2 with both substituents in the endo-position is referred to as allopseudococaine.

\[
\begin{align*}
\text{(R)-cocaine (1)} & \quad \text{(R)-allopseudococaine (2)}
\end{align*}
\]

It is well known that Sigmund Freud was one of the first investigators who studied the effects of cocaine and who in fact proposed its use in the treatment of alcohol and opiate abuse. Even though this error was soon recognized, cocaine has continued to be abused. In both animals and humans, cocaine is one of the most reinforcing drugs known, which is presumably related to its great abuse potential.

Cocaine has many physiological effects. It is a powerful vasoconstrictant and as such has some current use in medicine during nasal or throat surgery where control of bleeding is desired. Cocaine also has very potent effects on the sympathetic nervous system and it is well known to increase heart rate and blood pressure. From the point of view of drug abuse, the most relevant effects of the drug include its ability to produce euphoria and its reinforcing properties. The latter are readily demonstrated in animal models and the euphorigenic effects of cocaine are amply documented in humans.

Over the past ten years, there have been significant advances in understanding the mechanism of action of cocaine. The most important explanation is the so-called 'dopamine hypothesis' which assumes that cocaine binds to the dopamine transporter in such a way that reuptake of dopamine is inhibited, thus resulting in a buildup of dopamine in the synaptic cleft,
leading to a significant potentiation of dopaminergic transmission. This potentiation is responsible for the reinforcing properties of cocaine and probably for its euphorogenic effects as well. Because of the important role of the dopamine transporter in the action of cocaine, the transporter has been the subject of many studies to elucidate the characteristics of the cocaine binding site at the transporter. For this reason, many analogs of cocaine have been synthesized, some of which are shown below.

![Chemical structures](image)

It has been reported that the nitrogen atom can be moved from the 8- to the 6- (3) or the 7-position (4) of the azabicyclic ring system without loss in binding potency. Remarkably, the (+)- and (-)-isomers of 4 showed similar binding potency. A representative of the class of aryl substituted tropane analogs is 5, which shows a high binding affinity at the receptor site.

### 5.2 AZAANALOGS OF TROPANE ALKALOIDS

Regarding the ongoing search for new cocaine analogs, it is interesting that the method described in Chapter 4 provides a route which might lead to compounds that possess an azatropane skeleton, i.e. one of the bridgehead carbon atoms is replaced by a nitrogen atom. Starting from a dimethyl substituted pyrazolidinone, for example the azaanalog 7 of cocaine 6 should be accessible.

![Chemical structures](image)

If the developed sequence is applied to unsubstituted 3-pyrazolidinone, an exact analog of cocaine (8) could be obtained. Thus, a retrosynthesis for 'azacocaine' is presented in Scheme 5.1.

![Scheme 5.1](image)
After transformation of the alkylation product 12 into the cyclization precursor 11, the cyclic compound 10 might be obtained. Cleavage of the dioxenone moiety and subsequent reduction and benzoylation of the $\beta$-ketoester 9 might lead to the final product 8.

In this sequence of reactions, the $\beta$-ketoester 13 is already introduced in the first step in its acetonide form 14. Cleavage of this acetonide to the $\beta$-ketoester is achieved thermally in most cases. It has been shown by Clemens et al. that thermolysis of the dioxenone 14 will lead to the acylketene 15 in a retro Diels-Alder reaction (eq 5.1). The very electrophilic acylketene 15 will react with any nucleophile present in the reaction mixture. If for instance methanol is added during the thermolysis, it will readily react with the intermediate acylketene 15 to give the methyl ester 16.

The successful use of 1,3-dioxen-4-ones for this purpose is illustrated by several recent applications of this moiety in intermolecular addition reactions. An interesting intramolecular variant is shown in eq 5.2, in which thermolysis of the dioxenones 17 and subsequent intramolecular nucleophilic attack of the alcohol at the acylketene 18 leads to the 8-membered $\beta$-ketolactones 19 in very high yields (> 90%).
5.3 CHOICE OF THE STARTING COMPOUND: UNSUBSTITUTED VERSUS MONO- OR DISUBSTITUTED PYRAZOLIDINONES

The application of the unsubstituted 3-pyrazolidinone (24) as the starting material would lead to unsubstituted azatropine systems. While all of the possible substituted pyrazolidinones can be synthesized by a condensation of the appropriate acrylic ester with hydrazine hydrate, this methodology does not work for the pyrazolidinone 24. A convenient synthesis for this pyrazolidinone is shown in eq 5.3. Hydrazine hydrate is reacted with acrylonitrile (20) to give the hydrazinonitrile 21, which is cyclized under the influence of sulfuric acid, affording the stable sulfuric acid-salt of the aminopyrazoline 22.9 Hydrolysis of the enamine and treatment with HCl will give the stable HCl-salt 23.10 The free pyrazolidinone 24 can be obtained after the addition of 1 equiv of NaOMe and filtering off the NaCl.11

In order to study the sequence of reactions as described in Chapter 4 with the pyrazolidinone 24, both the benzyl and the methallyl substituent were chosen as model systems. The results of the different reactions are summarized in Table 5.1.

<table>
<thead>
<tr>
<th>entry</th>
<th>alkylation product (yield)</th>
<th>reduction precursor (yield)</th>
<th>reduction product(s) (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>25 (30%)</td>
<td>27 (40%)</td>
<td>29 (80%)</td>
</tr>
<tr>
<td>2</td>
<td>26 (30%)</td>
<td>28 (26%)</td>
<td>30 (33%)</td>
</tr>
</tbody>
</table>

It is remarkable that the alkylations occur in rather poor yields. The fact the the gem-dimethyl function is absent from the molecule should enhance the nucleophilicity of the N-1 nitrogen atom as the steric hindrance is significantly decreased. Unfortunately, this decrease of
Studies towards the synthesis of azatropine derivatives

steric bulk is probably one of the main reasons for some unwanted side reactions. For example, the alkylation method described in Chapter 4 (alkenyl halide (1 equiv), K$_2$CO$_3$ (1.2 equiv), LiI (cat), 2-butanone) has to be carried out in a different solvent as the pyrazolidinone 24 will immediately condense with 2-butanone to give a mixture of the ylides 32 and 33 (eq 5.4).$^9$

\[
\text{eq 5.4}
\]

An indication of another side reaction which might be responsible for the low yield is given by work of Draheim and co-workers. Alkylation of the monosubstituted pyrazolidinone 36 afforded the desired product 37 together with the ylide 38 (eq 5.6).$^{12}$ A similar product can be formed in the reaction with 24, leading to the very polar ylide 35 (eq 5.5), which will remain in the water layer, thus giving rise to a low yield of the desired alkylation product 34. If there is a gem-dimethyl function present in the five-membered ring, dialkylation at the N-1 nitrogen atom is impossible as a result of steric hindrance. In that case, if an excess of the alkylating agent is used, the second alkyl function will be introduced at the N-2 nitrogen atom (see Chapter 4).

\[
\text{eq 5.5}
\]

The methoxycarbonylation reactions (Table 5.1) were carried out with LDA (1 equiv, -78 °C, THF) and methyl cyanoformate (2 equiv, -78 °C). In the subsequent reduction step, another disadvantage of the unsubstituted 3-pyrazolidinone is encountered. If the reduction is carried out under 'standard conditions' (excess of NaBH$_4$, EtOH, -20 °C) only the ring-opened amide-alcohols 29 and 30 are obtained.

\[
\text{eq 5.7}
\]
As shown in equation 5.7, during the reduction there is an equilibrium between the ring-
closed lactol 39 and the ring-opened aldehyde 40. The latter intermediate can be further reduced
with NaBH₄ to give the alcohol 30. A similar result was obtained if the reductions were carried
out at -78 °C, although in the case of the methallyl substituent a small amount of the desired
ethoxypyrazolidine 31 was also found. Such a ring opening and overreduction were not
observed if the pyrazolidinone ring was substituted with the gem-dimethyl function (see: Section
4.2).

The effect, that alkyl substitution favors the cyclic structure in cases of ring-chain
tautomerism, is an example of the well-known 'gem-dimethyl effect' and was recognized for the
first time by Ingold and Thorpe.¹³ A general explanation for this phenomenon was postulated by
Allinger and Zalkow.¹⁴ They state that the effect is partly a result of a change in enthalpy and
partly of a change in entropy. The effect of alkyl groups on the enthalpy of ring-closure is
interpreted in terms of the change of gauche interactions in going from the reactant to the
product, which is larger in the substituted cases. The loss of entropy upon cyclization is less in
the substituted compound since the substituents restrict the rotation in the acyclic system, thereby
lowering its entropy.

In the case of a similar type of pyrrolidinone (eq 5.8), identical changes in the
equilibrium have been observed by Chiron and Graff.¹⁵ The hydroxylactams 41 exist entirely in
the open form (42) when they are un- or monosubstituted (R = H, R' = H or Me), whereas they
can be found only in the hydroxylactam form when disubstituted (R = R' = Me).

\[
\begin{align*}
\text{41} & \quad \leftrightarrow \quad \text{42} \\
\end{align*}
\]

(eq 5.8)

The corresponding six-membered hydroxylactams show similar behavior. Other factors
that influence the equilibrium are the temperature (the lower the temperature, the more the
equilibrium will shift to the ring-closed form) and the substituent at the nitrogen atom (electron-
withdrawing substituents will stabilize the anion, thus enhancing ring opening).

In order to circumvent the problems with the unsubstituted pyrazolidinone and to avoid
the introduction of the gem-methyl function, an alternative pyrazolidinone was chosen as the
starting material, containing one substituent at the 4-position which should be easily removable
and make ring opening during the reduction less likely to happen. An advantage of such a
starting material is also that it offers the possibility to start from an enantiopure pyrazolidinone
(45, eq 5.9), leading eventually to enantiopure azatropane systems. This strategy bears analogy
with the work that has been carried out with the (S)-malic acid derived succinimide 43. The
stereocenter at the 4-position controls the stereochemistry at the 5-position in the N-acyliminium
ion 44 with moderate to high diastereoselectivity.¹⁶ A similar induction might be expected in the
case of the corresponding $N$-acylhydrazonium ion 46.

\[ \text{AcO} \quad 43 \quad \text{AcO} \]
\[ \text{O} \quad \text{O} \quad \text{+} \quad \text{N} \quad \text{H} \quad \text{CO} \quad \text{R} \]
\[ \text{X} \quad \text{N} \quad \text{H} \quad \text{OR} \]
\[ \text{X} \quad \text{N} \quad \text{H} \quad \text{OR} \]
\[ \text{43} \quad 44 \quad 45 \quad 46 \]

(eq 5.9)

Concerning the substituent X there are several options: X could be an oxygen atom protected with an alkyl or acyl group, or a protected nitrogen atom. The synthesis of such a synthon ($X = \text{OR}$) via a direct reaction of hydrazine with oxirane carboxylic acids ($49 \, R' = \text{H}$, eq 5.10) or oxirane carboxylates ($49 \, R = \text{alkyl}$)\(^\text{17}\) was not successful, although regioselective reactions with substituted oxirane carboxylic acids have been reported with other nucleophiles than hydrazine (e.g. thiophenol, diethylamine)\(^\text{18}\). Furthermore, substituted oxirane carboxylates have been reported to react with hydrazine to give the cyclic systems\(^\text{19}\).

\[ \text{RO} \quad \text{NH} \quad \text{NH} \quad \text{OH} \quad \text{NH} \quad \text{NH} \quad \text{OR'} \]
\[ \text{47} \quad \text{48} \quad \text{49} \]

(eq 5.10)

A possible route to the alternative amino substituted pyrazolidinone has been developed at Eli Lilly & Company (eq 5.11)\(^\text{20}\). The readily available L-serine, protected with a Boc group and a methyl ester (50)\(^\text{21}\) was used as starting material and converted into the corresponding hydrazide by stirring it in the presence of hydrazine hydrate (eq 5.11). It was found that if the hydroxy function was converted into a good leaving group, i.e. a tosylate, the ring closure of the hydrazide gave rise to complete racemization\(^\text{22}\).

\[ \text{OH} \quad \text{H} \quad \text{N} \quad \text{O} \quad \text{H} \quad \text{N} \quad \text{CO} \quad \text{Me} \]
\[ \text{50} \quad 51 \quad \text{52} \]

(eq 5.11)

a) $\text{N}_2\text{H}_4\cdot\text{H}_2\text{O}$ (1 equiv), MeOH, rt. b) $\text{EtSC(O)}\text{CF}_3$ (1.5 equiv), EtOH, rt. c) $\text{PPh}_3$ (1.1 equiv), DEAD (1.1 equiv), THF, rt. d) 1 N NaOH, pH = 12, 1 h.

Only if the cyclization was carried out under Mitsunobu-type conditions, the enantiopure pyrazolidinone 52 could be obtained. In order to perform such a ring closure, the hydrazide had to be activated with a trifluoroacetyl function, which was achieved by treating the hydrazide with $S$-ethyl trifluorothioacetate. Ring closure took place upon treatment with equimolar amounts of
triphenylphosphine and diethyl azodicarboxylate, after which the trifluoroacetyl function was removed by stirring in 1 N NaOH to give 52. In similar ring closure reactions, the Mitsunobu-type reaction was found to be the only reaction that gave satisfactory yields of five- or six-membered cyclic hydrazines.\(^{23,24}\)

In order to investigate the application of this monofunctionalized pyrazolidinone, some model experiments were performed with the racemic CBz-protected 4-aminopyrazolidinone 54. This compound was obtained by a condensation of hydrazine hydrate with the protected dehydroalanine 53.\(^{25}\)

\[
\text{CBzNH} \rightleftharpoons \text{CO}_2\text{Me} \quad \text{H}_2\text{NNH}_2 \cdot \text{H}_2\text{O} 
\text{MeOH} \quad \text{CBzNH} \rightleftharpoons \text{NH} \quad \text{NH} \quad \text{O} 
53 \quad \text{(eq 5.12)}
\]

One of the possible routes for synthesizing this compound is shown in eq 5.13, in which benzyl carbamate 55 is reacted with pyruvic acid under azeotropic removal of water to give the dehydroalanine 56.\(^{26}\) Esterification with diazomethane afforded the appropriate dehydroalanine methyl ester 53.

\[
\text{BnO} \quad \text{NH}_2 
\text{MeCO}_2\text{H} \quad \text{H}_2\text{NNH}_2 \cdot \text{H}_2\text{O} 
\text{trichloroethene Ether, } 0 \degree \text{C} 
\text{CBzNH} \rightleftharpoons \text{CO}_2\text{H} 
\text{CH}_2\text{N}_2 
\text{ether, } 0 \degree \text{C} 
\text{CBzNH} \rightleftharpoons \text{CO}_2\text{Me} 
53 \quad \text{(eq 5.13)}
\]

The results obtained with the pyrazolidinone 54 and the \textit{gem}-dimethyl substituted pyrazolidinone are summarized in Table 5.2. The alkylation of 54 proceeded best (entries 1 and 2), if they were carried out under the conditions described by White et al. (halide (1 equiv), \text{Et}_3\text{N} (1 equiv), \text{LiI} (cat), DMF, rt).\(^{27}\) The chlorinated dioxenone 58 used in this alkylation reaction was obtained by quenching the lithium enolate of the commercially available dioxenone 57 with hexachloroethane (eq 5.14).\(^{28}\)

\[
\text{1) LDA, } -78 \degree \text{C} 
\text{2) Cl}_3\text{CCl}_3, -78 \degree \text{C} 
\text{Cl} 
\text{57} 
\text{Cl} 
\text{58} 
\text{(eq 5.14)}
\]

The relatively low yield (compared with the series described in Section 4.2) of the alkylation product 61 (entry 3) is explained by the thermal instability of the dioxenone moiety. This result was obtained after stirring in acetone at 40 °C for 40 h. Both higher and lower temperatures showed a decrease of the yield of 61.
Studies towards the synthesis of azatropine derivatives

Ethoxycarbonylation of 59 and 60 (entries 1 and 2) was carried out by using diethyl dicarbonate (see: Section 4.2, method C). Although an excess of the dicarbonate was used, only the pyrazolidinone nitrogen atom reacted to give the hydrazines 62 and 63. This is indicated by the different positions at which the NH protons appear in the \(^1\)H NMR spectra. The ring proton is found between 7 and 8 ppm, whereas the carbamate proton appears between 5 and 6 ppm. Compound 61 was deprotonated with NaH and treated with MeO\(_2\)CCN to give the methoxycarbonylated product 64 in a reasonable yield.

Table 5.2. Reactions with substituted 3-pyrazolidinones.

<table>
<thead>
<tr>
<th>entry</th>
<th>alkylation product (yield)</th>
<th>reduction precursor (yield)</th>
<th>reduction product(s) (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>59 (34%)</td>
<td>62 (57%)</td>
<td>65 (58%) ctri 1:5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>66 (8%)</td>
</tr>
<tr>
<td>2</td>
<td>60 (55%)</td>
<td>63 (53%)</td>
<td>67 (24%) ctri 1:4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>68 (38%)</td>
</tr>
<tr>
<td>3</td>
<td>61 (61%)</td>
<td>64 (68%)</td>
<td>69 (68%)</td>
</tr>
</tbody>
</table>

In the subsequent reduction step, ring opening and overreduction took place rapidly if the monosubstituted pyrazolidinones were subjected to 'standard conditions' (NaBH\(_4\) (excess), -20 °C). Small amounts of the desired product 67 could be obtained together with the ring-opened product 68 and starting material 60 if the reaction was performed at -78 °C. Reduction of 63 with DIBAL-H or LiBH\(_4\) in THF did not give satisfactory results either. However, better results were obtained if the reduction was carried out in the presence of a stoechiometric amount of CeCl\(_3\)·7H\(_2\)O at -50 °C. This is explained by the high affinity of the cerous ion for oxygen, thus favoring the ring-closed product in the equilibrium with the open product. Unfortunately, formation of the open-chain products 66 and 68 could not be totally prevented. In accordance with the results presented in Chapter 4, reduction of 64 (entry 3) under 'standard conditions' (NaBH\(_4\) (4 equiv), -20 °C) led to 69 without a trace of the ring-opened product.
5.4 CYCLIZATION REACTIONS

The cyclization precursors 65 and 67 were subjected to various Lewis acid cyclization conditions, but none of them led to the desired products. In the case of the benzyl precursor 65 a remarkable side product was obtained if acetic anhydride was used together with TiCl₄ (eq 5.15). Acetic anhydride was expected to enhance the rate of the reaction via *in situ* formation of the corresponding acetoxyprazolidine, thus leading to a higher concentration of the cationic intermediate.

\[
\begin{align*}
70 & \quad \xrightarrow{\text{TiCl}_4 (5 \text{ equiv}), \text{Ac}_2\text{O} (3 \text{ equiv}), \text{CH}_2\text{Cl}_2, 0 \, ^\circ\text{C} \rightarrow \text{rt}} \quad 71 (46\%) 
\end{align*}
\]

The formation of the acetyl protected carbamate 71 is probably a result of Lewis acid catalyzed debenzylation, followed by immediate reacylation with acetic anhydride. The fact that only the ethoxypyrazolidine 71 was found, suggests that the intermediate hydrazonium ion has not been formed, because otherwise the corresponding acetoxyprazolidine should also have been found.

Reaction of 67 under these conditions led to decomposition of the dioxenone moiety. A completely different result was obtained by treatment of 67 with BF₃·OEt₂ and acetic anhydride (Scheme 5.2). Surprisingly, formation of the intermediate hydrazonium ion 72 did not lead to the desired cyclization product but to the bicyclic oxazolidinone 74, which was the only product that could be detected. This result can be explained by initial stabilization of the *N*-acylhydrazonium ion by the carbamate function giving the stabilized dioxycarbénium ion 73. During the course of the reaction or during work up, the benzyl group is removed and the oxazolidinone 74 is formed.³⁰

Scheme 5.2

\[
\begin{align*}
67 & \quad \xrightarrow{\text{BF}_3\cdot\text{OEt}_2 (5 \text{ equiv}), \text{Ac}_2\text{O} (3 \text{ equiv}), \text{CH}_2\text{Cl}_2, 0 \, ^\circ\text{C} \rightarrow \text{rt}} \quad 72 \\
\left[ \text{Nu} \xrightarrow{\text{Ph}} \right] & \quad \xrightarrow{\text{TiCl}_4 (5 \text{ equiv}), \text{Ac}_2\text{O} (3 \text{ equiv}), \text{CH}_2\text{Cl}_2, 0 \, ^\circ\text{C} \rightarrow \text{rt}} \quad 74 (32\%)
\end{align*}
\]
In contrast with these results, the gem-dimethyl substituted precursor 69 led to the expected cyclization product 76. Although many conditions were tried, cyclization took only place after treatment with BF$_3$·OEt$_2$ (4 equiv). A smaller amount of BF$_3$·OEt$_2$ led to an incomplete conversion of the precursor 69 into the cyclization product 76. The use of TiCl$_4$ and SnCl$_4$ led to decomposition of the dioxenone moiety prior to cyclization.

Formic acid was the only protic acid that led to cyclization. However, at room temperature no reaction took place, whereas at high temperature (100 °C), the cyclization product immediately decarboxylated to give the azatropanone 75 (see compound 59, Chapter 4).

5.5 SYNTHESIS OF AZATROPANE DERIVATIVES

In order to convert the cyclization product 76 into azatropanes two major conversions were to be carried out. The methyl carbamate had to be converted into a methyl function and the dioxenone part had to be deprotected and reduced. It would be advantageous to perform a catalytic hydrogenation of the dioxenone at this stage, as it would immediately give the desired cis-relationship between the two substituents. Various catalysts were tried at different pressures of H$_2$ gas, but the double bond could not be reduced. This might be a result of the very hindered nature of this double bond. At the bottom-side, it is shielded by the ethylene bridge with the gem-dimethyl function and at the top-side the carbamate hinders the approach of a catalyst. If 76 was treated with Na/NH$_3$ the double bond remained unaffected (eq 5.17), but instead the N-N bond was cleaved to give the bicyclic system 77 as a single product in a rather poor yield.

There are several methods to convert a methyl carbamate into the corresponding N-methyl compound. Direct conversion of 76 into the desired product 79 (eq 5.18) by a reduction
with LiAlH₄ led to decomposition of the dioxenone part. A suitable result was obtained if the carbamate 76 was first cleaved with (CH₃)₂SiH to give the free hydrazine 78 (eq 5.18). Conversion into the N-methyl compound with MeI or Me₂SO₄ did not give satisfactory results. Therefore a reductive methylation was carried out, using 37% aq formaldehyde in acetonitrile to give the intermediate iminium ion which was further reduced with NaBH₃CN to the methylated compound 79.

\[
\text{MeO₂C} \quad \text{N} \quad \text{O} \quad \text{O}
\]

\[
\begin{align*}
&\text{76} & \xrightarrow{\text{a}} & \text{78 (98\%)} \\
& & \xrightarrow{\text{b}} & \text{79 (90\%)}
\end{align*}
\]

(eq 5.18)

\(a)\ Me₂SiH (1.2\text{ equiv}), \text{MeCN}, 1 \text{ h, } 40 \circ \text{C.} \quad \(b)\ (i)\ 37\% \text{ aq } \text{H}_2\text{CO} (5 \text{ equiv}), \text{NaBH}_3\text{CN (1.6 equiv), MeCN, rt} \quad (ii)\ \text{AcOH.}

Efforts to reduce the double bond of the dioxenone at this stage by using a catalytic hydrogenation also failed. On the other hand, ring opening of the dioxenone proceeded smoothly and was proven to give the best result if the product 79 was heated in a sealed tube for 10 min at 170 °C in xylenes in the presence of an excess of methanol (eq 5.19). The crude β-ketoester 80 was obtained in a quantitative yield but could not be easily purified. Despite the clear ¹H NMR spectrum, flash chromatography gave a dramatic decrease of the yield. Therefore, crude 80 was treated with benzoyl chloride to afford the azatropane derivative 81 in a reasonable overall yield. Unfortunately, this product could not be reduced to the desired cocaine derivative.

\[
\begin{align*}
\text{MeO₂C} & \quad \text{N} & \quad \text{O} & \quad \text{O} \\
\text{79} & \xrightarrow{\text{CH₃OH (10 equiv), xylenes, 170 °C, sealed tube, 10 min}} & \text{80} & \xleftarrow{\text{PhCOCl (1.2 equiv), Et₃N (1.05 equiv), CH₂Cl₂}} & \text{81 (70\%)}
\end{align*}
\]

(eq 5.19)

The crude β-ketoester 80 was also reduced in the presence of an excess of NaBH₄ at 0 °C to give the ecgonine analog 82 (eq 5.20). In accordance with the outcome of a similar reduction of 2-(carbomethoxy)tropanone at -30 °C carried out by Carroll et al., only one isomer was obtained in which both substituents occupy the endo-position (allopseudo). They also reported that reduction at 0 °C gave a mixture of the pseudo- and the allopseudoisomer. The fact that reduction of 80 seems to be more selective probably is a result of the endo-methyl substituent, which is shielding the bottom side of the molecule, thus preventing an endo-attack from occurring.
Studies towards the synthesis of azatropine derivatives

\[
\begin{align*}
\text{NaBH}_4 \text{ (10 equiv), } & \quad \text{MeOH, 0-5 °C} \\
\text{80} & \quad \text{OH} \\
\text{82} & \quad (73\%) \\
\text{MeO}_2\text{C} & \quad \text{N}^+\text{Me}
\end{align*}
\]

The stereochemistry of 82 was proven by using \(^1\text{H} \) NMR NOE-difference techniques. Irradiation of the proton adjacent to the hydroxy function (H3) showed an enhancement of the signals of all of the H2 and H4 protons, thus confirming its equatorial position. Irradiation of the hydroxyl proton showed a slight enhancement of the signal of the H2 eq proton, but not of the H4 proton, indicating its axial position. The assigned stereochemistry was confirmed by comparison of the coupling constants of the H3 and H4 protons with allopseudococaine \(^{34}\) (H3: \( J = 4.9 \) Hz, whereas for allopseudococaine: \( d, J = 1.1, 4.8 \) Hz; H4: br \( t, J = 4 \) Hz, whereas for allopseudococaine: \( dd, J = 3.1, 4.8 \) Hz).

Attempts to convert this allopseudoecgonine derivative 82 into the benzoyl ester according to literature procedures were not successful.\(^{35}\) A possible explanation might be that the reactivity of the hydroxy function is strongly decreased as a result of the presence of the endo-methyl group.

5.6 CONCLUSIONS

Several conclusions can be drawn from the results described in this Chapter. The unsubstituted 3-pyrazolidinone has been shown to be a troublesome starting compound. Its most important disadvantage is the instability of the corresponding hydroxypyrazolidine which easily gives ring-opening. A similar effect is observed in the monosubstituted systems, although a higher yield of the desired reduction product can be obtained. The use of a protected amino function to induce a stereoselective cyclization seems to be an improper choice as under various conditions cyclization to the desired products failed.

The gem-dimethyl substituted 3-pyrazolidinone has been shown to be a suitable starting material for the synthesis of various azatropine derivatives. A major drawback of this compound is the presence of two methyl functions which makes the resulting compounds somewhat less attractive analogs of the corresponding tropane alkaloids.

ACKNOWLEDGEMENT

F. O. H. Pirrung is kindly acknowledged for the synthesis of compound 69.
Chapter 5

5.7 EXPERIMENTAL SECTION

General information. For experimental details, see: Section 2.11.

1-Benzyl-3-pyrazolidinone (25). A mixture of 3-pyrazolidinone (24) (2.00 g, 23.3 mmol), benzyl chloride (2.1 g, 16.3 mmol), K$_2$CO$_3$ (4.8 g, 35 mmol) and a catalytic amount of LiI in THF (40 mL) was refluxed for 18 h and concentrated in vacuo. The residue was taken up in H$_2$O (100 mL) and extracted with CH$_2$Cl$_2$ (3 x 100 mL). The combined organic layers were dried (MgSO$_4$), filtered, concentrated in vacuo and chromatographed (ethyl acetate) to afford 25 (872 mg, 4.95 mmol, 30%) as a colorless oil, R$_f$ 0.30. IR 3420, 3400, 1660, 1380, 690; $^1$H NMR (200 MHz) 2.50 (t, $J = 8.0$ Hz, 2 H, CH$_2$), 3.33 (t, $J = 7.7$ Hz, 2 H, NCH$_2$), 3.84 (s, 2 H, CH$_2$Ph), 7.32 (s, 5 H, ArH).

1-(2-Methyl-2-propenyl)-3-pyrazolidinone (26). A mixture of 3-pyrazolidinone (24) (500 mg, 5.81 mmol), methallyl chloride (473 mg, 5.23 mmol), K$_2$CO$_3$ (960 mg, 7.00 mmol) and a catalytic amount of LiI in THF (10 mL) and MeOH (5 mL) was refluxed for 18 h and concentrated in vacuo. The residue was taken up in H$_2$O (20 mL) and extracted with CH$_2$Cl$_2$ (3 x 20 mL). The combined organic layers were dried (MgSO$_4$), filtered, concentrated in vacuo and chromatographed (ethyl acetate) to afford 26 (123 mg, 0.88 mmol, 30%) as a colorless oil, R$_f$ 0.20. IR 3410, 3400, 1670, 1440, 1400, 900; $^1$H NMR (200 MHz) 1.78 (s, 3 H, CH$_3$), 2.54 (t, $J = 8.0$ Hz, 2 H, CH$_2$), 3.22 (s, 2 H, NCH$_2$), 3.28 (t, $J = 7.7$ Hz, 2 H, NCH$_2$), 4.94 (br s, 2 H, =CH$_2$), 7.54 (br s, 1 H, NH).

1-Benzyl-3-pyrazolidinone-2-carboxylic acid methyl ester (27). A solution of 25 (500 mg, 2.84 mmol) in THF (5 mL) was deprotonated with LDA (prepared from diisopropylamine (0.44 mL, 3.13 mmol) and n-butyllithium (2.0 mL of a 1.6 M solution in hexane, 3.2 mmol) in THF (10 mL) at 0 °C and treated at that temperature with a solution of Me$_2$CCCN (483 mg, 5.68 mmol) in THF (5 mL). The mixture was stirred at -78 °C for 1 h, allowed to warm to rt, poured into water (50 mL) and extracted with CH$_2$Cl$_2$ (3 x 50 mL). The combined organic layers were dried (MgSO$_4$), filtered, concentrated in vacuo and chromatographed (ethyl acetate/hexane 1:1) to give 27 (263 mg, 1.12 mmol, 40%) as a colorless oil, R$_f$ 0.30. IR 1780, 1735, 1430, 1210, 690; $^1$H NMR (200 MHz) 2.56 (t, $J = 7.5$ Hz, 2 H, CH$_2$), 3.32 (s, 2 H, NCH$_2$), 3.90 (s, 3 H, CO$_2$CH$_3$), 4.04 (s, 2 H, CH$_2$Ph), 7.36 (s, 5 H, ArH).

1-(2-Methyl-2-propenyl)-3-pyrazolidinone-3-carboxylic acid methyl ester (28). A solution of 26 (120 mg, 0.86 mmol) in THF (5 mL) was deprotonated with LDA (prepared from diisopropylamine (0.04 mL, 0.33 mmol) and n-butyllithium (2.0 mL of a 1.6 M solution in hexane, 3.2 mmol) in THF (10 mL) at 0 °C and treated at that temperature with a solution of Me$_2$CCCN (483 mg, 5.68 mmol) in THF (5 mL). The mixture was stirred at -78 °C for 1 h, allowed to warm to rt, poured into water (50 mL) and extracted with CH$_2$Cl$_2$ (3 x 50 mL). The combined organic layers were dried (MgSO$_4$), filtered, concentrated in vacuo and chromatographed (ethyl acetate/hexane 1:1) to give 28 (44.5 mg, 0.22 mmol, 26%) as a colorless oil, R$_f$ 0.40. IR 1780, 1735, 1430, 1310, 1290, 900; $^1$H NMR (200 MHz) 2.56 (t, $J = 7.5$ Hz, 2 H, CH$_2$), 3.32 (s, 2 H, NCH$_2$), 3.90 (s, 3 H, CO$_2$CH$_3$), 4.04 (s, 2 H, CH$_2$Ph), 7.36 (s, 5 H, ArH).

1-Benzyl-1-(3-hydroxypropyl)-2-hydrazinecarboxylic acid methyl ester (29). A solution of 27 (44 mg, 0.19 mmol) in EtOH (2 mL) was treated with NaBH$_4$ (22 mg, 0.58 mmol) at -78 °C and every 10 min with one drop of a 2 M H$_2$SO$_4$/EtOH solution. After 1 h (the reaction was monitored with TLC), the mixture
was acidified to pH = 3 at -78 °C, allowed to warm to rt, poured into aq satd NaHCO₃ (20 mL) and extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were dried (MgSO₄), filtered, concentrated in vacuo and chromatographed (ethyl acetate/hexane 1:1) to give 29 (36.5 mg, 0.15 mmol, 80%) as a colorless oil, Rₜ 0.20.

IR v 3440, 3340, 1720, 1490, 1230; *H NMR (200 MHz) 8 1.75 (quintet, J = 5.5 Hz, 2 H, Oty), 2.87 (br s, 2 H, NCHjO), 3.64 (t, J = 5.3 Hz, 2 H, CH₂OH), 3.74 (s, 3 H, CH₂), 3.93 (s, 2 H, CH₂Ph), 5.72 (br s, 1 H, NH); ¹³C NMR (50 MHz) δ 28.9 (CH₂), 52.1 (C(0)₂CH₃), 55.3 (C(0)₂CH₃), 62.0 (C(0)₂Ph), 127.5, 128.3, 129.2 (ArH), 135.7 (ArC), 157.0 (C(0)).

3-Ethoxy-1-(2-methyl-2-propenyl)-pyrazolidine-2-carboxylic acid methyl ester (31). A solution of 28 (43 mg, 0.21 mmol) in EtOH (2 mL) was treated with NaBH₄ (32 mg, 0.84 mmol) at -78 °C and every 10 min with one drop of a 2 M H₂SO₄ solution. After 1 h (the reaction was monitored with TLC), the mixture was acidified to pH = 3 at -78 °C, allowed to warm to rt after 15 min, poured into aq satd NaHCO₃ (20 mL) and extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were dried (MgSO₄), filtered, concentrated in vacuo and chromatographed (ethyl acetate/hexane 1:1) to give 31 (3 mg, 0.013 mmol, 6%) as a colorless oil, Rₜ 0.65 and l-(3-hydroxypropyl)-l-(2-methyl-2-propenyl)-2-hydrazinecarboxylic acid methyl ester (30) (14 mg, 0.069 mmol, 33%) as a colorless oil, Rₜ 0.25. 31: IR v 1720, 1690, 1440, 1370, 1120, 1090, 900; *H NMR (200 MHz) 8 1.20 (t, J = 7.0 Hz, 3 H, CH₂Cf3), 1.88 (s, 3 H, CH₃), 2.22-2.26 (m, 2 H, CH₂), 2.99-3.24 (m, 3 H, NCH₂ and NCHH), 3.52-3.69 (m, 3 H, NCH₂ and 0 / CH₃), 3.75 (s, 3 H, CO₂CH₃), 4.87 (br s, 2 H, =CH₂), 5.55 (t, J = 5.1 Hz, 1 H, OCH). 30: IR v 3440, 3340, 1720, 1505, 1450, 1255, 900; *H NMR (200 MHz) δ 1.74 (quintet, J = 5.5 Hz, 2 H, CH₂), 1.82 (s, 3 H, CH₃), 2.86 (t, J = 5.5 Hz, 2 H, CH₂), 3.24 (s, 2 H, NCH₂), 3.69 (s, 3 H, CO₂CH₃), 3.79 (t, J = 5.5 Hz, 2 H, CH₂), 4.88 (s, 2 H, =CH₂), 5.53 (br s, 1 H, NH).

2-Propenyl-3-pyrazolidinone (34). A solution of 3-pyrazolidinone (24) (2.16 g, 25.1 mmol), allyl bromide (1.74 mL, 20.1 mmol), Et₃N (2.77 mL, 20.1 mmol) and a catalytic amount of NaI in DMF (25 mL) was stirred at rt for 18 h. Concentration in vacuo and purification of the residue by flash chromatography (ethyl acetate) afforded 34 (571 mg, 4.53 mmol, 18%) as a colorless oil, Rₜ 0.10. IR v 3420, 3080, 1670, 1405, 990, 925; *H NMR (200 MHz) δ 2.16 (t, J = 7.6 Hz, 2 H, CH₂), 2.93 (t, J = 7.1 Hz, 2 H, CH₂), 2.98 (t, J = 6.5 Hz, 2 H, CH₂), 4.86 (d, J = 9.8 Hz, 1 H, =CH₂), 4.91 (d, J = 14.4 Hz, 1 H, =CHH), 5.39-5.56 (m, 1 H, =CH), 8.22 (br s, 1 H, NH).

N-{(Benzzyloxy)carbonyl}dehydroalanine methyl ester (53). To a solution of N-{(benzzyloxy)carbonyl}dehydroalanine 56 (25.1 g, 60.2 mmol) in ether (50 mL) was added at 0 °C diazomethane (prepared from Diazald® (26.8 g) and KOH (6.25 g) in ether (250 mL)) until the yellow color persisted. The solution was concentrated in vacuo to afford 53 (12.9 g, 60.0 mmol, 100%) as a colorless oil. IR v 3405, 1730, 1710, 1630, 1520, 1440, 900, 690; *H NMR δ 3.68 (s, 3 H, CH₂), 5.17 (s, 2 H, =CH₂), 5.17 (s, 2 H, =CH₂), 4.33-4.43 (m, 1 H, =CH), 7.24-7.33 (s, 6 H, ArH and NH).

4-{(Benzzyloxy)carbonylamino}-3-pyrazolidinone (54). A mixture of 53 (12.0 g, 55.8 mmol) and hydrazine hydrate (3.0 mL, 61.8 mmol) in EtOH (150 mL) was heated at reflux temperature for 3 h. The solution was concentrated in vacuo (10% methanol/ethyl acetate) to afford 54 (10.5 g, 44.7 mmol, 80%) as a white solid, mp 154-156 °C (lit.: 155-156°C). IR v 1710, 1680; *H NMR δ 3.22 (br t, J = 11.4 Hz, 1 H, NCH₂), 3.89-3.96 (m, 1 H, NCH₂), 4.33-4.43 (m, 1 H, NCH), 5.09 (s, 2 H, CH₂Ph), 5.51 (br s, 1 H, NH), 7.24-7.33 (s, 6 H, ArH and NH).
1-Benzyl-4-[(benzyloxy)carbonyl]amino]-3-pyrazolidinone (59). A solution of 54 (545 mg, 2.32 mmol) in DMF (3 mL) was treated with benzyl chloride (293 μL, 2.55 mmol), Et3N (386 μL, 2.78 mmol) and a catalytic amount of Lil. The mixture was stirred at rt for 18 h and concentrated in vacuo. The residue was taken up in H2O (50 mL) and extracted with CH2Cl2 (3 × 50 mL). The combined organic layers were dried (MgSO4), filtered, concentrated in vacuo and chromatographed (ethyl acetate) to give 59 (257 mg, 0.79 mmol, 34%) as a colorless oil, Rf 0.40. IR ν 3410, 1710, 1500, 690; 1H NMR (200 MHz) δ 3.05-3.20 (m, 1 H, NCWH), 3.80-3.95 (m, 3 H, CH2Ph and NCH2), 4.48-4.60 (m, 1 H, NCH), 5.09 (s, 2 H, OCH2), 5.28-5.32 (m, 1 H, NH), 7.32 (s, 5 H, ArH), 7.60-7.70 (m, 1 H, NH).

4-[(Benzyloxy)carbonyl]amino]-1-[3,3-dimethyl-5-oxo-2,4-diox-6-enyl)methyl]-3-pyrazolidinone (60). A solution of 54 (2.54 g, 10.8 mmol) in DMF (25 mL) was treated with dioxenone 5828 (2.10 g, 11.9 mmol), Et3N (2.55 mL, 18.3 mmol) and a catalytic amount of Lil. The mixture was stirred at rt for 18 h and concentrated in vacuo. The residue was taken up in H2O (100 mL) and extracted with CH2Cl2 (3 × 100 mL). The combined organic layers were dried (MgSO4), filtered, concentrated in vacuo and chromatographed (ethyl acetate) to give 60 (2.23 g, 5.95 mmol, 55%) as a white solid, which decomposed at 125 °C before melting, Rf 0.40. IR ν 3410, 1710, 1635, 1360, 900, 690; 1H NMR (200 MHz) δ 1.69 (s, 6 H, (CH2)2), 3.21 (t, J = 11.5 Hz, 1 H, NOffl), 3.52 (s, 2 H, NCH2), 3.73-3.82 (m, 1 H, NCH//), 4.50-4.70 (m, 1 H, NCH), 5.10 (s, 2 H, OCH2), 5.50 (s, 1 H, =CH), 5.66 (d, J = 5.4 Hz, 1 H, NH), 7.33 (s, 5 H, ArH), 8.66 (br s, 1 H, NH).

5,5-Dimethyl-1-[3,3-dimethyl-5-oxo-2,4-diox-6-enyl)methyl]-3-pyrazolidinone (61). To a solution of 5,5-dimethyl-3-pyrazolidinone (3.55 g, 31.1 mmol) in acetone (130 mL) were added dioxenone 5828 (5.50 g, 31.2 mmol), K2CO3 (4.7 g, 34 mmol) and a catalytic amount of Lil. After being stirred at 45 °C for 48 h, the mixture was concentrated in vacuo, taken up in H2O (100 mL) and extracted with CH2Cl2 (3 × 100 mL). The combined organic layers were dried (MgSO4), filtered and concentrated in vacuo. The residue was purified by flash chromatography (ethyl acetate) to afford 61 (4.79 g, 18.9 mmol, 61%) as orange crystals, mp 112.5-113 °C (pentane/ether/CH2Cl2 10:10:1), Rf 0.28 (ethyl acetate). IR ν 3420, 1720, 1635, 1385, 1370, 1270, 1010; 1H NMR (200 MHz) δ 1.30 (s, 6 H, (CH2)2), 1.71 (s, 6 H, (CH2)2), 2.36 (s, 2 H, CH2), 3.40 (s, 2 H, NCH2), 5.52 (s, 1 H, =CH), 7.70 (br s, 1 H, NH); 13C NMR (50 MHz) δ 24.9 (4 x CH3), 42.7 (CH2), 54.1 (NCH2), 63.0 (NC), 94.6 (eCH), 107.0 (OCO), 160.6, 167.3, 174.9 (2 x C(O) and =C); MS (EI, 70 eV) m/z (relative intensity) 196 (M+58, 100), 127 (100), 83 (62), 43 (74).

1-Benzyl-4-[(benzyloxy)carbonyl]amino]-3-pyrazolidinone-2-carboxylic acid ethyl ester (62). To a solution of 59 (250 mg, 0.77 mmol) in CH2Cl2 (6 mL) were added diethyl dicarbonate (180 μL, 1.54 mmol), Et3N (117 μL, 0.85 mmol) and DMAP (103 mg, 0.84 mmol) and the mixture was stirred at rt for 18 h. The resulting solution was concentrated in vacuo and purified by flash chromatography (ethyl acetate/hexane 1:1) to afford 62 (173 mg, 0.44 mmol, 57%) as a colorless oil, Rf 0.35. IR ν 3420, 1785, 1710, 1490, 1160, 900, 690; 1H NMR (250 MHz) δ 1.37 (s, J = 7.1 Hz, 3 H, CH2CH2), 3.17 (t, J = 8.1 Hz, 1 H, NCH2), 3.68-3.71 (m, 1 H, NCH2), 4.03 (d, J = 12.6 Hz, 1 H, CH/CH2 = CHPh), 4.07 (d, J = 12.6 Hz, 1 H, CH/CH2 = CHPh), 4.35 (q, J = 7.1 Hz, 2 H, CH2CH2), 4.40-4.50 (m, 1 H, NCH), 5.07 (s, 2 H, OCH2), 5.15 (br d, 1 H, NH), 7.24-7.35 (m, 10 H, ArH).

4-[(Benzyloxy)carbonyl]amino]-1-[3,3-dimethyl-5-oxo-2,4-diox-6-enyl)methyl]-3-pyrazolidinone-2-carboxylic acid ethyl ester (63). To a solution of 60 (2.50 g, 6.67 mmol) in CH2Cl2 (50 mL) were added diethyl dicarbonate (1.55 mL, 13.3 mmol), Et3N (1.85 mL, 13.3 mmol) and DMAP
(814 mg, 6.67 mmol) and the mixture was stirred at rt for 18 h. The resulting solution was concentrated in vacuo and purified by flash chromatography (ethyl acetate/hexane 4:1) to afford 63 (1.57 g, 3.51 mmol, 53%) as a colorless oil. $R_f$ 0.35. IR v 3420, 1785, 1720, 1640, 1500, 1300, 900, 690; $^1$H NMR (200 MHz) δ 1.36 (t, $J = 7.2$ Hz, 3 H, CH$_3$CH$_2$), 1.71 (s, 6 H, (CH$_3$)$_2$CO), 3.38 (t, $J = 12.2$ Hz, 1 H, NCH), 3.73 (s, 2 H, NCH$_2$), 3.70-3.80 (m, 1 H, NCHH), 3.35 (q, $J = 7.1$ Hz, 2 H, CH$_2$CH$_3$), 4.65-4.80 (m, 1 H, NCH), 5.12 (s, 2 H, OCH$_2$), 5.33 (br s, 1 H, NH), 7.34 (s, 5 H, ArH); $^{13}$C NMR (63 MHz) δ 21.8, 25.4 (2 x CH$_3$), 50.8 (NCH), 55.7 (NCH$_2$), 57.9 (NCH$_2$), 63.9 (CH$_2$CH$_3$), 67.6 (CH$_2$Ph), 95.9 (=CH), 107.3 (OCHO), 128.3, 128.5, 128.6 (ArH), 135.7 (ArC), 149.1, 155.0, 160.2, 165.2, 170.0 (4 x C(0) and =C).

5,5-Dimethyl-1-[(3,3-dimethyl-5-oxo-2,4-diox-6-enyl)methy]-3-pyrazolidinone-2-carboxylic acid methyl ester (64). To a suspension of NaH (29 mg, 1.2 mmol) in THF (2 mL) was added dropwise at rt a solution of 61 (303 mg, 1.2 mmol) and the mixture was stirred at rt for 18 h. The resulting solution was concentrated in vacuo and chromatographed (ethyl acetate/hexane 4:1) to afford 63 (1.57 g, 3.51 mmol, 53%) as a colorless oil, $R_f$ 0.35. IR v 3420, 1785, 1720, 1640, 1500, 1300, 900, 690; $^1$H NMR (200 MHz) δ 1.36 (t, $J = 7.2$ Hz, 3 H, CH$_3$CH$_2$), 1.71 (s, 6 H, (CH$_3$)$_2$CO), 3.38 (t, $J = 12.2$ Hz, 1 H, NCH), 3.73 (s, 2 H, NCH$_2$), 3.70-3.80 (m, 1 H, NCHH), 3.35 (q, $J = 7.1$ Hz, 2 H, CH$_2$CH$_3$), 4.65-4.80 (m, 1 H, NCH), 5.12 (s, 2 H, OCH$_2$), 5.33 (br s, 1 H, NH), 7.34 (s, 5 H, ArH); $^{13}$C NMR (63 MHz) δ 21.8, 25.4 (2 x CH$_3$), 50.8 (NCH), 55.7 (NCH$_2$), 57.9 (NCH$_2$), 63.9 (CH$_2$CH$_3$), 67.6 (CH$_2$Ph), 95.9 (=CH), 107.3 (OCHO), 128.3, 128.5, 128.6 (ArH), 135.7 (ArC), 149.1, 155.0, 160.2, 165.2, 170.0 (4 x C(0) and =C).

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reL-(35,4S)-1-[(3,3-Dimethyl-5-oxo-2,4-diox-6-enyl)methyl]-4-[(benzyloxy)carbonyl]-3-ethoxyxyporazolidine-2-carboxylic acid ethyl ester (67). To a solution of 63 (237 mg, 0.19 mmol) in EtOH (2 mL) were added at -78 °C TiCl4 (156 μL of a 1.0 M solution, 0.197 mg, 0.53 mmol). The solution was stirred at -20 °C for 2 h, while every 10 min a drop of a 2 M H2SO4/EtOH solution was added. After being stirred at rt for 30 min, the mixture was poured into aq satd NaHCO3 (50 mL) and extracted with CH2Cl2 (3 × 50 mL). The combined organic layers were dried (MgSO4), filtered, concentrated in vacuo and chromatographed (ethyl acetate/hexane 4:1) to give 67 (60 mg, 0.13 mmol, 24%) as a colorless oil, 1:4 mixture of cis/trans-isomers, Rf 0.45 and 1-2-[(benzyloxy)carbonyl]amino]-3-hydroxypropyl]-1-[(3,3-dimethyl-5-oxo-2,4-diox-6-enyl)methyl]-2-hydrazonecarboxylic acid ethyl ester (68) (90 mg, 0.20 mmol, 38%) as a colorless oil, Rf 0.2. trans-67: IR v 3430, 3350, 1720, 1710, 1635, 1505, 1270, 1240, 900, 690; 1H NMR (200 MHz) δ 8.12 (m, 4 H, CH2Ph), 3.88 (d, J = 14.7 Hz, 1 H, CH=Ph), 3.50-3.75 (m, 2 H, OCH2CH2), 3.22 (AB system, 2 H, NCH2), 3.39 (d, 7 = 14.7 Hz, 1 H, CH2Ph), 3.50-3.75 (m, 2 H, OCH2CH2), 4.30-4.40 (m, 1 H, NCH), 5.08 (s, 2 H, OCH2), 5.23 (br d, J = 7.0 Hz, 1 H, NH), 5.52 (s, 1 H, NCHO), 5.53 (s, 1 H, =CH), 7.33 (s, 5 H, ArH); 13C NMR (63 MHz) δ 14.4, 14.8 (2 × CH2CH2), 24.8, 25.2 ((CH3)2C), 57.4 (NCH2), 61.6 (NCH2), 62.4, 63.5 (2 x CH3), 67.2 (OCH2), 85.3 (NCO), 95.4 (w=CH), 106.9 (OCO), 128.2, 128.3, 128.5 (ArH), 136.0 (ArC), 155.6, 156.0, 160.8 166.4 (3 x C(0) and =C); MS (El, 70 eV) m/z (relative intensity) 342 (M+, 15), 284 (100), 239 (50), 216 (100), 159 (100), 113 (60), 103 (37), 43 (27); HRMS calcd for C16H22N2O6 342.1791, found 342.1801; Anal. Calcd. for C16H22N2O6: C, 55.75; H, 7.68.

reL-(35,4S)-1-Benzyl-4-[(acetylemino)-3-ethoxyxyporazolidine-2-carboxylic acid ethyl ester (71). To a solution of 70 (11 mg, 0.026 mmol) were added at -78 °C TiCl4 (156 μL of a 1.0 M solution, 0.156
mmol) and AC2O (10 μL, 0.103 mmol). The mixture was stirred 10 min at -78 °C and 1 h at rt. The mixture was poured into aq satd NaHCO3 (10 mL) and extracted with CH2Cl2 (3 x 10 mL). The combined organic layers were dried (MgSO4), filtered, concentrated in vacuo and chromatographed (ethyl acetate/hexane 1:1) to afford 71 (4 mg, 0.012 mmol, 46%) as a colorless oil, Rf 0.30. 1H NMR (200 MHz) δ 1.21 (t, J = 7.0 Hz, 3 H, CH2CH3), 1.29 (t, J = 7.0 Hz, 3 H, CH2CH3), 1.92 (s, 3 H, NCH3), 2.99 (d, J = 10.8 Hz, 1 H, NCH2), 3.25 (dd, J = 5.6, 10.8 Hz, 1 H, NCH2), 3.55-3.70 (m, 4 H, CH2Ph and OCH2CH3), 4.10-4.30 (m, 2 H, CH2CH3), 4.46 (s, J = 5.5 Hz, 1 H, NCH), 5.27 (s, 1 H, NCHO), 5.87 (d, J = 5.8 Hz, 1 H, NH), 7.30-7.38 (m, 5 H, ArH); 13C NMR (63 MHz) δ 14.5, 14.9 (2 x CH3), 23.0 (C(0)CH3), 55.1 (NCH), 56.9, 62.1, 63.3, 64.3 (4 x CH2), 91.9 (NCO), 127.7, 128.4, 129.7 (ArH), 136.5 (ArC).

Pyrazoline 74. To a solution of 67 (30 mg, 0.063 mmol) in CH2Cl2 (1 mL) were added at 0 °C BF3·OEt2 (40 μL, 0.31 mmol) and acetic anhydride (18 μL, 0.19 mmol). The mixture was stirred at 0 °C for 15 min and for 3 h at rt and poured into aq satd NaCl (10 mL) and extracted with CH2Cl2 (3 x 20 mL). The combined organic layers were dried (MgSO4), filtered, concentrated in vacuo and purified by flash chromatography (ethyl acetate) to afford 72 (7 mg, 0.020 mmol, 32%) as a colorless oil.

Pyrazoline 75. To a solution of 69 (1.57 g, 4.59 mmol) in CH2Cl2 (50 mL) was added at 0 °C BF3·OEt2 (2.26 mL, 18.4 mmol). The mixture was stirred 10 min at -78 °C and 1 h at rt. The mixture was chilled to 0 °C and poured in vacuo. The residue was chromatographed (ethyl acetate/hexane 1:1) to give 75 (1.44 g, 4.86 mmol, 94%) as a colorless oil that solidified upon standing, mp 106-107 °C (ethyl acetate/hexane), Rf 0.36. 1H NMR δ 1.18 (s, 3 H, CH3), 1.61 (s, 3 H, CH3), 1.69 (dd, J = 12.8 Hz, 1 H, H6endo), 5.72 (s, 1 H, w=CH). 6.27 (br s, 1 H, NH), 6.53 (d, J = 7.0 Hz, OCH); 13C NMR (30 MHz) δ 14.4 (CH2CH3), 24.5 (CH3), 25.5 (CH3), 59.6 (NCH), 59.7 (NCH2), 60.7 (NCH2), 63.2 (CH2CH2O), 89.4 (NCO), 95.2 (=CH), 107.1 (OCO), 152.0, 156.9, 159.6, 166.6 (3 x C(0) and =C); MS (El, 70 eV) m/z (relative intensity) 242 ((M-99), 7), 225 (67), 172 (100), 156 (25), 137 (22), 73 (14).

Pyrazoline 76. To a solution of 69 (77 mg, 0.23 mmol) was stirred in HCOOH (2 mL) at 100 °C for 5 h. Concentration in vacuo and chromatography (ethyl acetate/hexane 1:1) afforded 76 (1.44 g, 4.86 mmol, 94%) as a colorless oil that solidified upon standing, mp 106-107 °C (ethyl acetate/hexane), Rf 0.36. 1H NMR δ 1.18 (s, 3 H, CH3), 1.61 (s, 3 H, CH3), 1.69 (dd, J = 12.8 Hz, 1 H, H6endo), 5.72 (s, 1 H, w=CH). 6.27 (br s, 1 H, NH), 6.53 (d, J = 7.0 Hz, OCH); 13C NMR (30 MHz) δ 14.4 (CH2CH3), 24.5 (CH3), 25.5 (CH3), 59.6 (NCH), 59.7 (NCH2), 60.7 (NCH2), 63.2 (CH2CH2O), 89.4 (NCO), 95.2 (=CH), 107.1 (OCO), 152.0, 156.9, 159.6, 166.6 (3 x C(0) and =C); MS (El, 70 eV) m/z (relative intensity) 242 ((M-99), 7), 225 (67), 172 (100), 156 (25), 137 (22), 73 (14).

Pyrazoline 77. To a solution of 67 (30 mg, 0.063 mmol) in CH2Cl2 (1 mL) were added at 0 °C BF3·OEt2 (40 μL, 0.31 mmol) and acetic anhydride (18 μL, 0.19 mmol). The mixture was stirred at 0 °C for 15 min and for 3 h at rt and poured into aq satd NaCl (10 mL) and extracted with CH2Cl2 (3 x 10 mL). The combined organic layers were dried (MgSO4), filtered, concentrated in vacuo.

Diazepine 77. A solution of 76 (100 mg, 0.34 mmol) in THF (2 mL) was added to a solution of Na (31 mg,
1.35 mmol) in NH₃ (15 mL) at -78 °C. The mixture was stirred at -78 °C for 3 h, quenched by addition of NH₄Cl (182 mg, 3.4 mmol) and the ammonia was allowed to evaporate. The residue was dissolved in H₂O (20 mL) and extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were dried (MgSO₄), filtered, concentrated in vacuo and chromatographed (ethyl acetate/hexane 4:1) to afford 76 (12 mg) and 77 (12 mg, 0.040 mmol, 16% (after correction)) as a white solid, mp 157-159 °C, Rf 0.20. IR ν 3495, 1710, 1640, 1420, 1295, 1110, 1030, 890; ¹H NMR (200 MHz) δ 1.12 (s, 3 H, CH₃), 1.34 (s, 3 H, CH₃), 1.64 (s, 6 H, 2 x CH₃), 1.91 (dd, J = 5.8, 12.2 Hz, 1 H, H6exo), 2.06 (dd, J = 12.2 Hz, 1 H, H6endo), 2.46 (d, J = 18.7 Hz, 1 H, H2), 3.81 (d, J = 18.7 Hz, 1 H, H2), 4.20 (br s, 1 H, NH); 13C NMR (50 MHz) δ 13.9, 23.7, 26.2, 26.5, 32.6 (CH₃), 51.5, 51.6 (C2 and C6), 53.2 (C5), 66.2 (C7), 105.3, 107.2 (OCO and C3), 156.9, 161.1, 168.8 (2 x C(0) and C4); MS (El, 70 eV) m/z (relative intensity) 238 (M⁺, 7), 223 (50), 183 (17), 165 (100), 150 (25), 71 (30), 58 (85).

Hydrazine 78. To a solution of 76 (700 mg, 2.36 mmol) in MeCN (3 mL) was added Me²SiH (403 µL, 2.83 mmol) and the ammonia was allowed to evaporate. The residue was dissolved in H₂O (20 mL) at -78 °C. The mixture was stirred at -78 °C for 15 min at rt, glacial acetic acid was added carefully until the pH was neutral. Stirring was continued for 45 min, while the pH was kept neutral by dropwise addition of glacial acetic acid. The solution was poured into 1 N KOH (40 mL) and extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were dried (K₂CO₃), filtered, concentrated in vacuo and chromatographed (acetone) to afford 78 (350 mg, 2.31 mmol, 98%) as a colorless oil that solidified upon standing, mp 157-159 °C (decomposes before melting), Rf 0.30. IR ν 3495, 1710, 1640, 1295, 1110, 1030, 890; ¹H NMR (200 MHz) δ 6.12 (s, 3 H, CH₃), 1.34 (s, 3 H, CH₃), 1.64 (s, 6 H, 2 x CH₃), 1.91 (dd, J = 5.8, 12.2 Hz, 1 H, H6exo), 2.06 (dd, J = 12.2 Hz, 1 H, H6endo), 3.81 (d, J = 18.7 Hz, 1 H, H2), 4.20 (br s, 1 H, NH); 13C NMR (50 MHz) δ 13.9, 23.7, 26.2, 26.5, 32.6 (CH₃), 51.5, 51.6 (C2 and C6), 53.2 (C5), 66.2 (C7), 105.3, 107.2 (OCO and C3), 155.9, 161.1, 168.8 (2 x C(0) and C4); MS (El, 70 eV) m/z (relative intensity) 298 (M⁺, 7), 223 (50), 183 (17), 165 (100), 150 (25), 71 (30), 58 (85).

N-Methylhydrazine 79. To a solution of 78 (600 mg, 2.52 mmol) in MeCN (6 mL) were added 37% aq formaldehyde (1.01 mL, 12.3 mmol) and NaBH₄CN (253 mg, 4.03 mmol). After being stirred for 15 min at rt, glacial acetic acid was added carefully until the pH was neutral. Stirring was continued for 45 min, while the pH was kept neutral by dropwise addition of glacial acetic acid. The solution was poured into 1 N KOH (40 mL) and extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were dried (K₂CO₃), filtered, concentrated in vacuo and chromatographed (ethyl acetate) to afford 79 (570 mg, 2.26 mmol, 98%) as a colorless oil that solidified upon standing, mp 157-159 °C (decomposes before melting), Rf 0.30. IR ν 3515, 1700, 1640, 1420, 1295, 1110, 1030, 890; ¹H NMR (200 MHz) δ 6.12 (s, 3 H, CH₃), 1.34 (s, 3 H, CH₃), 1.64 (s, 6 H, 2 x CH₃), 1.91 (dd, J = 5.8, 12.2 Hz, 1 H, H6exo), 2.06 (dd, J = 12.2 Hz, 1 H, H6endo), 3.81 (d, J = 18.7 Hz, 1 H, H2), 4.20 (br s, 1 H, NH); 13C NMR (50 MHz) δ 13.9, 23.7, 26.2, 26.5, 32.6 (CH₃), 51.5, 51.6 (C2 and C6), 53.2 (C5), 66.2 (C7), 105.3, 107.2 (OCO and C3), 155.9, 161.1, 168.8 (2 x C(0) and C4); MS (El, 70 eV) m/z (relative intensity) 298 (M⁺, 7), 223 (50), 183 (17), 165 (100), 150 (25), 71 (30), 58 (85).

3-Benzoyloxy-7,7,8-trimethyl-1,8-diazabicyclo[3.2.1]oct-3-ene-4-carboxylic acid methyl ester (81). A solution of 79 (13 mg, 0.052 mmol) and MeOH (18 µL, 0.5 mmol) in xylene (0.5 mL) was heated at 170 °C for 10 min in a sealed tube. The mixture was concentrated in vacuo to afford 3-oxo-7,7,8-trimethyl-1,8-diazabicyclo[3.2.1]octane-4-carboxylic acid methyl ester (80) (10 mg) as a light yellow oil. ¹H NMR (200 MHz) δ 1.27 (s, 3 H, CH₃), 1.35 (s, 3 H, CH₂), 1.86 (d, J = 11.7 Hz, 1 H, H6endo),...
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2.27 (dd, J = 3.8 Hz, 1 H, H4), 3.34 (d, J = 19.2 Hz, 1 H, H2), 3.76 (s, 3 H, NCH3), 3.82 (d, J = 19.2 Hz, 1 H, H2), 3.83 (dd, J = 6.1, 3.8 Hz, 1 H, H5). The crude residue was dissolved in CH2Cl2 (1 mL) and treated with benzoyl chloride (6.5 µL, 0.056 mmol) and Et3N (8 µL, 0.057 mmol) at 0 °C. The mixture was stirred at 0 °C for 10 min and 5 h at rt and concentrated in vacuo.

Flash chromatography (ethyl acetate/hexane 4:1) afforded 81 (12 mg, 0.036 mmol, 70%) as a colorless oil, Rf 0.35.

1HNMR (200 MHz) δ 1.39 (s, 3 H, CH3), 1.45 (s, 3 H, CH3endo), 2.01 (d, J = 11.8 Hz, 1 H, H6exo), 2.30 (dd, J = 6.5, 11.8 Hz, 1 H, H6endo), 2.74 (s, 3 H, NCH3), 3.45 (d, J = 19.7 Hz, 1 H, H2), 3.59 (s, 3 H, CO2CH3), 3.82 (d, J = 19.9 Hz, 1 H, H5), 7.40-7.60 (m, 3 H, ArH), 8.06-8.11 (m, 2 H, ArH); 13C NMR (63 MHz) δ 26.6, 33.1 (2 x CH3), 36.5 (NCH3), 45.6 (C6), 51.2 (C2), 51.7 (C02CH3), 59.7 (C5), 65.3 (C7), 120.0 (C4), 128.6, 129.8, 133.7 (ArH), 128.9 (ArC), 152.0 (C3), 164.0, 164.2 (C(O)); MS (El, 70 eV) m/z (relative intensity) 330 (M+, 20), 169 (20), 105 (100), 77 (21); HRMS calcd for C18H22N2O4 330.1580, found 330.1579.

(3-Hydroxy-7,7,8-trimethyl-1,8-diazabicyclo[3.2.1]octane-4-carboxylic acid methyl ester (82). A solution of 79 (13 mg, 0.052 mmol) and MeOH (18 µL, 0.5 mmol) in xylenes (0.5 mL) was heated at 170 °C for 10 min in a sealed tube and concentrated in vacuo to afford 80 (10 mg) as a light yellow oil. The crude residue was dissolved in MeOH (1 mL) and treated at 0 °C with NaBH4 (12 mg, 0.32 mmol). After being stirred at 0 °C for 3 h, the solution was poured into H2O (5 mL) and extracted with CH2Cl2 (3 x 5 mL). The combined organic layers were dried (MgSO4), filtered, concentrated in vacuo and chromatographed (acetone) to afford 82 (9 mg, 0.038 mmol, 73%) as a colorless oil, Rt 0.30. IR ν 3600, 1705, 1430, 1290, 1060, 900; 1HNMR (200 MHz) δ 1.35 (s, 3 H, CH3exo), 1.51 (s, 3 H, CH3endo), 1.98 (dd, J = 7.8, 12.5 Hz, 1 H, H6exo), 2.26 (d, J = 12.5 Hz, 1 H, H6endo), 2.66 (s, 3 H, NCH3), 3.05 (t, J = 4 Hz, 1 H, H4), 3.12 (d, J = 16.2 Hz, H2), 3.43 (dd, J = 5.3, 16.3 Hz, 1 H, H2), 3.47 (dd, J = 7.6, 2.6 Hz, 1 H, H5), 3.73 (s, 3 H, CO2CH3), 3.79 (br s, 1 H, OH), 4.09 (t, J = 4.9 Hz, 1 H, H3); 13C NMR (63 MHz) δ 24.4, 33.1, 34.9 (3 x CH3), 40.2 (C4), 42.8 (C6), 45.2 (C2), 51.9 (CO2CH3), 58.5 (C5), 62.6 (C3), 63.2 (C7), 174.3 (C(O)); MS (El, 70 eV) m/z (relative intensity) 227 (M+ - 1), 171 (M+ - 57, 36), 122 (25), 105 (100), 77 (37).

5.8 REFERENCES AND NOTES

1) See e.g.: (a) Lounasmaa, M. Alkaloids 1988, 33, 1. (b) Fodor, G.; Dharanipragada, R. Nat. Prod. Reports 1991, 603.

2 For a recent review, see e.g.: Carroll, F. I.; Lewin, A. H.; Boja, J. W.; Kuhar, M. J. J. Med. Chem. 1992, 35, 969.


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30) A similar result was obtained with the corresponding pyrrolidinone: Koot, W. J. Forthcoming Ph.D. Thesis, University of Amsterdam, 1993.
CHAPTER 6
SYNTHESIS OF BICYCLIC PYRAZOLIDINONES
VIA EXOCYCLIC N-ACYLHYDRAZONIUM IONS

6.1 INTRODUCTION

Functionalized bicyclic pyrazolidines have found widespread use in physical and biological applications. Common syntheses of these compound classes include condensations of pyrazolidines and hexahydropyridazines with \( \alpha,\omega \)-dihalides, \( \alpha,\omega \)-diacylhalides or \( \alpha,\omega \)-diesters, \( \alpha,\beta \)-unsaturated aldehydes, \( \alpha,\beta \)-unsaturated esters or \( \alpha,\beta \)-unsaturated acylhalides. Some more recently developed sequences will be detailed in the sequel.

One interesting class of compounds consists of the so-called bimanes, which can be divided in symmetrical (syn-2) and asymmetrical (anti-2) compounds (eq 6.1). In contrast with the trans-isomers, the syn-isomers exhibit a strong fluorescence in solution, thus rendering them very useful in biochemical investigations.

\[
\begin{align*}
1 & \quad \text{K}_2\text{CO}_3 \text{ or } i-\text{Pr}_2\text{NEt} \\
& \quad \text{Cl} \quad \text{H}_3\text{C} \quad \text{N} \quad \text{CH}_3 \\
& \quad \text{H}_3\text{C} \quad \text{C} \quad \text{N} \quad \text{OH}_3 \\
& \quad \text{CH}_3 \quad \text{H}_3\text{C} \\
\end{align*}
\]

The synthesis of bimanes has been described extensively and starts from a suitable pyrazolinone. For example, if 1 is treated with a base, a mixture of symmetrical and asymmetrical bimanes 2 is obtained in a ratio that is strongly dependent of the base that is used. The desired syn-bimane can be obtained in large excess if \( \text{K}_2\text{CO}_3 \) is used.

Comparable saturated pyrazolopyrazoles (e.g. 5) are obtained via the so-called 'criss-cross' cycloaddition reaction of aldazines (condensation products of hydrazine with two identical aldehydes) with acrylic esters, enols or enamines.

\[
\begin{align*}
3 & \quad \text{CO}_2\text{Me} \\
& \quad \text{Ph} \\
\end{align*}
\]

An example is shown in eq 6.2, in which reaction of benzaldazine (3) with one equiv of methyl acrylate affords the dipolar species 4, which will give a cycloaddition reaction with a second
molecule of methyl acrylate to give the diadduct 5. This reaction proceeds with high regioselectivity to the 'trans'-products.

As an application of the 1,3-dipolar cycloaddition reaction, the stable ylide 6, obtained by a condensation of the corresponding pyrazolidinone with formaldehyde, was reacted with several symmetric and asymmetric acetylenes to afford the [3.3.0] pyrazolidinones 7 as shown in eq 6.3.\(^{12}\)

\[
\text{R} = \text{allyl, t-Bu, Me} \\
\text{R'} = \text{H, CO}_2\text{Me, Ph, CH}_2\text{OH}
\]

The antibacterial activity of some of these compounds has already been described in Section 1.3.3. Via a different route various other functionalized [3.3.0] pyrazolidinones could be obtained (Scheme 6.1).\(^{13}\)

Scheme 6.1

The pyrazolidinone 8 was reacted with the phosphonate to give the 1,4-addition product 9. Treatment of 9 in a one-pot procedure with allyloxyal chloride and 2 equiv of i-Pr\(_2\)NEt afforded the bicyclic hydrazine 11 via an intramolecular Wadsworth-Homer-Emmons reaction. The intermediacy of the initial product 10 was proven by treatment of 9 with allyloxyal chloride and only one equiv of i-Pr\(_2\)NEt.

Upon use of a comparable methodology, the corresponding [4.3.0] pyrazolidinones (e.g. 14, Scheme 6.2) could also be synthesized.\(^{14}\) The alkyalted pyrazolidinone 12 afforded after treatment with NaH and the sulfoxide the bicyclic system 13. Elimination of the sulfoxide with DBU led to the desired bicyclic [4.3.0] pyrazolidinone 14.
A novel method for the preparation of both simple and methoxycarbonylated bicyclic [3.3.0] and [4.3.0] pyrazolidinones is presented in this Chapter. A short outline of the method is shown in a retrosynthetic way in eq 6.4.

In contrast with the method described in Chapter 4, exocyclic N-acylhydrazonium ions 16 are the intermediates that are expected to react intramolecularly to give the fused hydrazines 15. Via this method not only the bicyclic hydrazines (15, \( R = H \)) should be accessible, but also the corresponding bicyclic \( \alpha \)-hydrazino acid derivate (15, \( R = \text{CO}_2\text{CH}_3 \)) that are obtained if the precursors 17 contain a one carbon moiety with both a methoxycarbonyl substituent and a good leaving group. The starting compounds for this sequence are the alkylated pyrazolidinones 18 that have been described in Section 4.2.

6.2 SYNTHESIS OF BICYCLIC HYDRAZINES

The precursors 19-22 (Table 6.1) were obtained in a similar way as described in Section 2.4 for the acyclic hydrazines. Upon use of identical conditions (NaH (1.1 equiv), DMF then chloromethyl methyl ether (1.5 equiv), 0 °C \( \rightarrow \) rt), moderate to good yields of the desired products were obtained. Use of other bases or solvents did not lead to more satisfactory results. A side reaction that is probably responsible for the somewhat disappointing yields is reaction at oxygen, which was also encountered in the reactions with methyl chloroformate (see: Section 4.3). The resulting products however, could not be traced after the reaction.

The precursors were subjected to the Lewis acids TiCl\(_4\) (2 equiv, -78 °C \( \rightarrow \) rt) for the non-activated nucleophiles 19 and 20 (entries 1 and 3), and BF\(_3\)·OEt\(_2\) (2 equiv, 0 °C \( \rightarrow \) rt) for both silanes 21 and 22 (entries 5 and 6), while all precursors were treated with formic acid at
differences between different temperatures.

Table 6.1. Cyclizations to bicyclic hydrazines.

<table>
<thead>
<tr>
<th>entry</th>
<th>cyclization precursor (yield)</th>
<th>acid</th>
<th>cyclization product(s) (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td><img src="image1.png" alt="Image" /> 19 (86%)</td>
<td>TiCl₄</td>
<td><img src="image2.png" alt="Image" /> 23 (98%)</td>
</tr>
<tr>
<td>2</td>
<td><img src="image3.png" alt="Image" /> 20 (35%)</td>
<td>HCOOH⁺</td>
<td><img src="image4.png" alt="Image" /> 23 (52%)</td>
</tr>
<tr>
<td>3</td>
<td><img src="image5.png" alt="Image" /> 20 (35%)</td>
<td>TiCl₄</td>
<td><img src="image6.png" alt="Image" /> 24 X = Cl (76%) 25 (17%)</td>
</tr>
<tr>
<td>4</td>
<td><img src="image7.png" alt="Image" /> 20 (35%)</td>
<td>HCOOH⁻</td>
<td><img src="image8.png" alt="Image" /> 26 X = OCHO (96%)</td>
</tr>
<tr>
<td>5</td>
<td><img src="image9.png" alt="Image" /> 21 (53%)</td>
<td>BF₃*OEt₂</td>
<td><img src="image10.png" alt="Image" /> 27 (71%)</td>
</tr>
<tr>
<td>6</td>
<td><img src="image11.png" alt="Image" /> 21 (53%)</td>
<td>HCOOH⁻</td>
<td><img src="image12.png" alt="Image" /> 27 (91%)</td>
</tr>
<tr>
<td>7</td>
<td><img src="image13.png" alt="Image" /> 22 (54%)</td>
<td>BF₃*OEt₂</td>
<td><img src="image14.png" alt="Image" /> 28 (88%)</td>
</tr>
<tr>
<td>8</td>
<td><img src="image15.png" alt="Image" /> 22 (54%)</td>
<td>HCOOH⁻</td>
<td><img src="image16.png" alt="Image" /> 28 (94%)</td>
</tr>
</tbody>
</table>

a) 50 °C, 17 h. b) 25 °C, 17 h. c) 25 °C, 5 h.

The results of these reactions are summarized in Table 6.1. Most of the Lewis acid-promoted cyclizations occurred in good yields to give the expected products. In the case of the prenyl precursor 20 (entry 3) treatment with TiCl₄ did not only give the expected product 24 but also a small amount of the elimination product 25. Surprisingly, this is the thermodynamically less favored product. The formic acid cyclizations gave, without exception, excellent yields of the desired products. In contrast with other type of N-acylhydrazonium ion cyclizations (see
Synthesis of bicyclic pyrazolidinones

Sections 2.6 and 4.3), the formic acid cyclizations provided better yields than the Lewis acid cyclizations. The transition state of the cyclization is visualized in eq 6.5 for the allylsilane 21. The six-membered ring is likely to adopt a chair-like conformation 29, which will react intramolecularly to the bicyclic product 27.

\[
\text{In situ generation of the } N\text{-acylhydrazonium ion, starting from the pyrazolidinone 30 (eq 6.6) led to the phthalazine derivative 23. 1,3,5-Trioxane in HCOOH}^{15} \text{ was used to form the hydrazonium intermediate, which cyclized under rather harsh conditions (80 °C, 18 h) in a reasonable yield.}
\]

\[
\begin{align*}
\text{1,3,5-trioxane (1.5 equiv)} & \quad \text{HCOOH, 80 °C, 18 h} \\
\text{30} & \quad \text{23 (66%)}
\end{align*}
\]

In addition to the precursors shown in Table 6.1, also the allyl- and methally-substituted pyrazolidinones were treated with Lewis and protic acids, but cyclization products were only obtained in very small quantities (< 5%), independent of the acid that was used. Conversion of the methoxy group into a chloride did not give better results either. A possible explanation for this problem will be detailed in Section 6.3.

6.3 SYNTHESIS OF BICYCLIC $\alpha$-HYDRAZINO ACID DERIVATIVES

In analogy with the synthesis of cyclization precursors starting from alcohols\textsuperscript{16} or the corresponding pyrrolidinones,\textsuperscript{17} the $\alpha$-methoxycarbonylated precursors 33 might be accessible via an addition reaction with methyl glyoxylate. The reaction is shown in eq 6.7.
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Condensation of the pyrazolidinone 31 with methyl glyoxylate hydrate\(^\text{18}\) or anhydrous methyl glyoxylate\(^\text{19}\) yielded the corresponding stable hydroxy compounds 32 upon stirring at room temperature. The hydroxy compounds 32 were converted without any further purification into the acetates 33 by treatment with an excess of acetic anhydride (DMAP (cat), pyridine, 18 h). As shown in Table 6.2, all reactions occurred in reasonable to good overall yields.

These results sharply contrast with the outcome of the attempts to add glyoxylate to the acyclic hydrazides under similar circumstances (Section 2.7). This is probably due to the less electronegative amine nitrogen atom in the present case, leaving the amide nitrogen atom sufficiently nucleophilic to react with methyl glyoxylate.

Table 6.2. Cyclizations to bicyclic \(\alpha\)-hydrazino acid derivatives.

<table>
<thead>
<tr>
<th>entry</th>
<th>cyclization precursor (yield)</th>
<th>acid</th>
<th>cyclization product(s) (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{N} - \text{OAc})</td>
<td>TiCl(_4)</td>
<td>38 (68%)</td>
</tr>
<tr>
<td>2</td>
<td>(\text{OAc})</td>
<td>HCOOH(^*)</td>
<td>38 (33%)</td>
</tr>
<tr>
<td>3</td>
<td>(\text{N} - \text{OAc})</td>
<td>TiCl(_4)</td>
<td>39 (X = \text{Cl}) (36%)</td>
</tr>
<tr>
<td>4</td>
<td>(\text{OAc})</td>
<td>HCOOH(^*)</td>
<td>40 (20%)</td>
</tr>
<tr>
<td>5</td>
<td>(\text{OAc})</td>
<td>BF(_3)OE(_2)</td>
<td>42 (69%)</td>
</tr>
<tr>
<td>6</td>
<td>(\text{OAc})</td>
<td>HCOOH(^*)</td>
<td>42 (21%)</td>
</tr>
<tr>
<td>7</td>
<td>(\text{N} - \text{OAc})</td>
<td>BF(_3)OE(_2)</td>
<td>43 (68%)</td>
</tr>
<tr>
<td>8</td>
<td>(\text{OAc})</td>
<td>HCOOH(^*)</td>
<td>43 (54%)</td>
</tr>
</tbody>
</table>

a) 50 °C, 18 h. \(b) 25 \^\circ\) C, 40 h. c) 25 °C, 5 h.
Synthesis of bicyclic pyrazolidinones

The cyclization reactions were carried out under the same conditions as described in Section 6.2 and the results are summarized in Table 6.2. Generally, it can be concluded that the Lewis acid cyclizations give better yields than the formic acid cyclizations. In the case of the prenyl precursor 35 (entries 3 and 4), mixtures of the cis- and trans-products were obtained. This can be rationalized by looking at the possible conformations leading to the transition states (Scheme 6.3). Cyclization can either take place via the boat-like conformation 44 or the chair-like conformation 45. In both cases, the iminium double bond has the (Z)-geometry to avoid pseudo-allylic 1,3-strain.\textsuperscript{17b-d,20} Cyclization in a 5-exo fashion via the chair-like conformation 45 will then lead to the trans-product 46 which is trapped by a nucleophile. On the other hand, 5-exo-cyclization can also proceed via the boat-like conformation 44, giving the intermediate cis-product 47. The positive charge can be stabilized by the formation of the dioxycarbenium ion 48, eventually leading to the lactone 40. Such a mechanism explains the formation of an excess of the trans-products, as cyclization is more likely to take place via a chair-like transition state.

Scheme 6.3

The trans-relationship of both substituents was secured by an X-ray crystallographic analysis of 39 as depicted in Fig 6.1. As a result of the strain in the fused system, the amide nitrogen atom is slightly deformed from planarity.

Fig 6.1. Chem3D view of the bicyclic pyrazolidinone 39.
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The \textit{trans}-relationship in the corresponding formate 41 was deduced by comparison of the coupling constants of the \(\alpha\)-methine protons of 39 and 41 (39: 4.60, d, \(^3J = 5.2\) Hz; 41: 4.61, d, \(^3J = 4.9\) Hz; whereas for 40: 5.01, d, \(^3J = 9.1\) Hz).

Both six-membered rings 38 and 42 were obtained in reasonable yields under Lewis acidic conditions (entries 1 and 5). These results form a remarkable contrast with cyclizations carried out under identical circumstances with the precursors 49-51 (Chart 6.1, yields are shown in parentheses). Treatment with TiCl\(_4\) (2 equiv, -78 °C \(\rightarrow\) rt) afforded the cyclization products 52-54 in reproducibly low yields. Several Lewis and protic acids were tried but did not give better results. The suggestion that the \textit{gem}-dimethyl function might be responsible for the low yields could be excluded as cyclization of the unsubstituted precursor 51 also proceeded in very low yield. The stereochemistry of the products 52 and 54 was concluded from the coupling constants of the (axial) protons adjacent to the chlorine atoms, showing two axial-axial and two axial-equatorial couplings (e.g. 54, 4.04 ppm, \(\delta\), \(^3J_{\alpha\alpha} = 11.6\) Hz, \(^3J_{\alpha\delta} = 4.5\) Hz). The relative configuration of 53 was not fully ascertained, but is in accordance with results detailed in Section 7.4.

\begin{center}
\textbf{Chart 6.1}
\end{center}

\begin{itemize}
\item 49 R = H, R' = Me (71%)
\item 50 R = R' = Me (86%)
\item 51 R = R' = H (60%)
\item 52 (6%)
\item 53 (8%)
\item 54 (6%)
\end{itemize}

A difference with the six-membered rings mentioned in Table 6.2 is that in the latter cases the initially formed positive charge is neither well-stabilized, nor quickly neutralized via facile formation of an olefin or an aromatic system. Possibly, the low yields are due to a highly strained transition state, caused by the presence of the pyrazolidinone moiety. This explanation is in accordance with high yields of comparable cyclization reactions, in which the pyrazolidinone part is absent from the molecule (see: Section 7.4).

The cyclizations of both silanes 36 and 37 with formic acid (entries 6 and 8) afforded the desired products 42 and 43 in relatively poor yields. When the reactions were carried out at higher temperatures, protodesilylation became a major side reaction.

A better yield of the bicyclic allene 43 was obtained by using BF\(_3\)-OEt\(_2\). Upon treatment of 43 with a strong base (DBU (1 equiv), -78 °C \(\rightarrow\) rt), isomerization led to the unstable conjugated product 55, which resembles biologically active bicyclic pyrazolidinones (eq 6.8). Reaction at low temperature afforded a mixture of starting material and product, whereas only at room temperature a complete conversion into the conjugated system 55 could be effected.
Application of other bases (LDA, KOr-Bu, NaH) did not lead to product 55 but to intractable material.

$$\text{43} \xrightarrow{\text{DBU (1 equiv)}} \text{THF, } -78 \, ^\circ\text{C} \rightarrow \pi \quad (\text{eq 6.8})$$

6.4 SYNTHESIS OF 5,7-BICYCLIC PYRAZOLIDINONES

Cyclization of a pyrazolidinone with a 4-butenyl substituent would lead to fused 5,7-bicyclic pyrazolidinones. Because cyclization of unsubstituted butenyl precursors did not give the desired products, the phenyl substituted precursor 58 was subjected to the cyclization conditions. A route that leads to this precursor is provided by work of Dorn,\(^{21}\) who studied Grignard additions to ylides such as 57.

$$\text{56} \xrightarrow{\text{PhCHO (1 equiv), } \rho\text{TSA (cat), toluene, reflux}} \text{57 (89%)}$$

$$\text{57} \xrightarrow{1) \text{MgCl}_2 (1 \text{ equiv}) \text{THF, } 0 \, ^\circ\text{C} \rightarrow \text{rt}} \xrightarrow{2) \text{6 M HCl}} \text{58 (45%)}$$

(eq 6.9)

The ylide 57 was obtained by acid-catalyzed condensation of 3-pyrazolidinone 56 with benzaldehyde (eq 6.9). Subsequent reaction with allylmagnesium chloride gave the addition product 58 after acidic work-up.

$$\text{59 (45%)} \xrightarrow{\text{SnCl}_2 \text{(2 equiv), } \text{CH}_2\text{Cl}_2, -78 \, ^\circ\text{C} \rightarrow \text{rt}} \text{60 (18%)}$$

(eq 6.10)

The glyoxylate addition occurred in moderate yield, probably as a result of the sterically crowded environment of the nitrogen atom. The best cyclization result was obtained with SnCl\(_2\), which afforded the bicyclic product 60 as a single isomer in a yield of 18% (eq 6.10). The relative configuration of 60 was not established. Cyclizations of similar precursors with a methoxy substituted phenyl group or a more highly substituted double bond did not provide any cyclization product. Surprisingly, cyclization of the phenyl group was observed in neither of
6.5 ESTIMATION OF THE INVERSION BARRIERS OF 5,6-BICYCLIC HYDRAZINES

The $^1$H and $^{13}$C NMR spectra of the 5,6-bicyclic pyrazolidinones 23 and 27 taken at room temperature showed some very broad signals as a result of slow inversion of one of the nitrogen atoms. This inversion process is visualized in eq 6.11, showing the equilibrium between 27 and its 'enantiomer' 27'. This nitrogen inversion is attended with a chair-chair interconversion of the six-membered ring. The inversion process takes place with a rate constant $k$.

![Equation 6.11](image)

The inversion process can be followed by $^1$H and $^{13}$C NMR. At low temperature, slow exchange is taking place so that all hydrogen atoms in the $^1$H NMR spectra are observed as sharp signals (Fig 6.2 and 6.3). At higher temperatures, fast exchange occurs, leading to signals of an 'average' structure. For example, the protons of the methylene groups of 27 (Fig 6.3) show separate signals at low temperature, whereas at higher temperatures they become equivalent. The temperature at which the conversion of two separate signals into one single signal is observed, is called the coalescence temperature ($T_c$). By determining the $T_c$ of a signal, a quantitative estimation of $\Delta G^\ddagger$ of the inversion process can be made, according to the following equations. The rate constant $k$ is given by the Eyring equation:22

$$k = \frac{RT}{N_A \cdot h} e^{\frac{\Delta G^\ddagger}{RT}}$$

(eq 6.12)

Approximately, the rate constant $k$ at the coalescence temperature ($k_c$) is defined as:23

$$k_c = \frac{\pi}{\sqrt{2}} \Delta \nu$$

(eq 6.13)

in which $\Delta \nu$ is the frequency difference of the signals at slow exchange. Combination of 6.12 and 6.13 will give the following equation for $\Delta G^\ddagger$:

$$\Delta G^\ddagger = RT_c \cdot \ln \frac{RT_c \cdot \sqrt{2}}{\pi \cdot N_A \cdot h \cdot \Delta \nu}$$

(eq 6.14)
Fig 6.2. $^1$H NMR (250 MHz) spectra of phthalazine 23 at various temperatures in $C_7D_8$. 

**Synthesis of bicyclic pyrazolidinones**
Fig 6.3. Selected parts of the $^1$H NMR (250 MHz) spectra of pyrazolidinone 27 at various temperatures in $C_7D_8$. 
Synthesis of bicyclic pyrazolidinones

If the appropriate values for \( R \) (8.31 J·K\(^{-1}\)·mol\(^{-1}\)), \( N_A \) (6.02·10\(^{23}\) mol\(^{-1}\)) and \( h \) (6.63·10\(^{-34}\) J·s) are used, \( \Delta G^\circ \) (kJ/mol) can be calculated according to:

\[
\Delta G^\circ = 19.1·10^3 T_c (0.97 + \log T_c - \log \Delta \nu ) \quad \text{(eq 6.15)}
\]

Of both compounds 23 and 27, \(^1\)H NMR spectra were recorded at various temperatures in C\(_7\)D\(_8\) (250 MHz) in order to determine the coalescence temperature of some signals. The data of 23 and 27 for three signals are shown in Table 6.3.

Table 6.3. Coalescence data of 23 and 27.

<table>
<thead>
<tr>
<th>( \delta ) (ppm)</th>
<th>( \Delta \nu ) (Hz)</th>
<th>( T_c ) (K)</th>
<th>( \Delta G^\circ ) (kJ/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.23</td>
<td>119</td>
<td>273</td>
<td>53.9</td>
</tr>
<tr>
<td>3.65</td>
<td>52</td>
<td>263</td>
<td>53.6</td>
</tr>
<tr>
<td>4.77</td>
<td>291</td>
<td>283</td>
<td>53.8</td>
</tr>
<tr>
<td>27</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1.16</td>
<td>88</td>
<td>273</td>
<td>54.5</td>
</tr>
<tr>
<td>2.28</td>
<td>69</td>
<td>276</td>
<td>55.7</td>
</tr>
<tr>
<td>3.06</td>
<td>127</td>
<td>278</td>
<td>54.8</td>
</tr>
</tbody>
</table>

Although estimating the height of the inversion barriers via the coalescence temperature is not a very precise method, the average value of the three signals might give a reasonable value for the \( \Delta G^\circ \). A more reliable outcome might have been obtained if the coalescence measurements were performed at different frequencies.

Assuming that the error in \( T_c \) is ± 2 K (which is a lower value), the error in \( \Delta G^\circ \) will be ± 0.4 kJ/mol. The average value for 23 is then 53.8 ± 0.4 kJ/mol and for 27 55.0 ± 0.4 kJ/mol (12.9 ± 0.1 and 13.1 ± 0.1 kcal/mol respectively). This means that 27 has a slightly higher inversion barrier than 23.

6.6 CONCLUSIONS

In this Chapter, an efficient method for the synthesis of bicyclic hydrazines and \( \alpha \)-hydrazino esters via exocyclic N-acylhydrazonium intermediates is detailed. Introduction of the appropriate nucleophilic side chains gave rise to both 5,5- and 5,6-bicyclic pyrazolidinones. The 5,6-bicyclic systems were formed in low yields if the initially formed cation was not properly stabilized by a substituent and subsequently converted into a double bond by a fast elimination process. The synthesis of one 5,7-bicyclic pyrazolidinone was achieved via this method, albeit in a rather low yield.

In accordance with cyclizations mentioned in Chapters 2 and 4, the Lewis acids TiCl\(_4\) and BF\(_3\)-OEt\(_2\) afforded the best results. Remarkably, in the case of the unsubstituted exocyclic N-acylhydrazonium ions, the use of formic acid provided better results than the Lewis acids.
Chapter 6

ACKNOWLEDGEMENT

J. H. Udding is gratefully acknowledged for his contribution to this Chapter.
J. A. J. Geenevasen is kindly acknowledged for his help in recording the high and low temperature NMR spectra of compounds 23 and 27.
K. Goubitz and J. Fraanje (Department of Crystallography, University of Amsterdam) are kindly acknowledged for the X-ray crystal structure determination.

6.7 EXPERIMENTAL SECTION

General information: for experimental details, see: Section 2.11.

General procedure A for the reactions with chloromethyl methyl ether. Sodium hydride (purchased as a 55% dispersion in oil) was washed prior to use with pentane, removing the pentane by syringe after the sodium hydride had settled. The dry solid was then mixed with DMF and the hydrazide, dissolved in DMF was added dropwise to the suspension at rt. After being stirred for 15 min at rt, the resulting clear solution was cooled to 0 °C and a solution of chloromethyl methyl ether in DMF was added. After being stirred for 15 min at 0 °C and 3 h at rt, the mixture was poured into aq satd NaCl, extracted with 1,1,1-trichloroethane (6x), dried (MgSO₄), filtered and concentrated in vacuo. The residue was subjected to flash chromatography to afford the pure hydrazides.

1-Benzyl-5,5-dimethyl-2-(methoxymethyl)-3-pyrazolidinone (19). According to the general procedure A, 1-benzyl-5,5-dimethyl-3-pyrazolidinone (500 mg, 2.45 mmol) was deprotonated with NaH (65 mg, 2.70 mmol) and alkylated with chloromethyl methyl ether (220 μL, 2.97 mmol), while all compounds were dissolved in DMF (5 mL). Work-up and flash chromatography (ethyl acetate/hexane 1:2) afforded 19 (523 mg, 2.11 mmol, 86%) as a colorless oil, Rf 0.35. IR ν 3085, 3060, 3030, 1690, 1450, 1370, 1070, 690; ¹H NMR (200 MHz) δ 1.26 (s, 6 H, (CH₃)₂C), 2.47 (s, 2 H, C(CH₃)₂), 3.29 (s, 3 H, OCH₃), 4.01 (s, 2 H, CH₂Ph), 4.35 (s, 2 H, NCH₂), 7.20-7.40 (m, 5 H, ArH).

5,5-Dimethyl-2-(methoxymethyl)-1-(3-methyl-2-butenyl)-3-pyrazolidinone (20). According to the general procedure A, 5,5-dimethyl-1-(3-methyl-2-butenyl)-3-pyrazolidinone (385 mg, 2.12 mmol) was deprotonated with NaH (56 mg, 2.33 mmol) and chloromethyl methyl ether (240 μL, 3.16 mmol), all compounds dissolved in DMF (5 mL). Work-up and flash chromatography (ethyl acetate/hexane 1:1) afforded 20 (166 mg, 0.73 mmol, 35%) as a colorless oil, Rf 0.30. IR ν 1685, 1450, 1405, 1370, 1305, 1245, 1090, 1070, 910; ¹H NMR (200 MHz) δ 1.26 (s, 6 H, (CH₃)₂C), 1.62 (s, 3 H, CH₃), 1.71 (s, 3 H, CH₃), 2.40 (s, 2 H, C(O)CH₂), 3.39 (s, 3 H, CO₂CH₃), 3.52 (d, J = 6.8 Hz, 2 H, NCH₂), 4.76 (s, 2 H, OCH₂), 5.29 (tt, J = 1.4, 6.8 Hz, 1 H, =CH).

5,5-Dimethyl-2-(methoxymethyl)-1-{2-[(trimethylsilyl)methyl]-2-propenyl}-3-pyrazolidinone (21). According to the general procedure A, 5,5-dimethyl-1-{2-[(trimethylsilyl)methyl]-2-propenyl}-3-pyrazolidinone (931 mg, 3.88 mmol) was treated with NaH (105 mg, 4.37 mmol) and chloromethyl methyl ether (480 μL, 6.25 mmol), all compounds dissolved in DMF (5 mL). Work-up and flash chromatography (ethyl acetate/hexane 1:2:1) afforded 21 (585 mg, 2.06 mmol, 53%) as a yellowish oil, Rf 0.35. IR ν 3075,
Synthesis of bicyclic pyrazolidinones

1690, 1370, 1245, 1070, 850; \( \text{JH NMR (250 MHz)} \) 6 0.02 (s, 9 H, (CH\(_3\))\(_3\)Si), 1.25 (s, 6 H, (CH\(_3\))\(_2\)C), 1.68 (s, 2 H, CH\(_2\)Si), 2.39 (s, 2 H, C(=O)CH\(_2\)), 3.28 (s, 2 H, NCH\(_2\)), 3.37 (s, 3 H, OCH\(_3\)), 4.64 (br s, 1 H, =CWH), 4.70 (s, 2 H, OCH\(_2\)).

5,5-Dimethyl-2-(methoxymethyl)-1-[4-(trimethylsilyl)-2-butynyl]-3-pyrazolidinone (22).
Following the general procedure A, 5,5-dimethyl-1-[4-(trimethylsilyl)-2-butynyl]-3-pyrazolidinone (200 mg, 0.84 mmol) was treated with NaH (22 mg, 0.92 mmol) and chloromethyl methyl ether (107 \( \mu \)L, 1.27 mmol), all compounds dissolved in DMF (2 mL). Work-up and flash chromatography (ethyl acetate/hexane 1:2) afforded 22 (127 mg, 0.45 mmol, 54%) as a colorless oil, \( R_f \) 0.30. IR \( \nu \) 2200, 1685, 1400, 1370, 1250, 1075, 850; \( \text{JH NMR (200 MHz)} \) 6 0.05 (s, 9 H, (CH\(_3\))\(_3\)Si), 1.29 (s, 6 H, (CH\(_3\))\(_2\)C), 1.43 (t, \( J = 2.4 \text{ Hz} \), 2 H, CH\(_2\)Si), 2.57 (br s, 2 H, C(=O)CH\(_2\)), 3.71 (br s, NCH\(_2\)), 4.80 (s, 2 H, OCH\(_2\)).

Methyl glyoxylate hydrate. \(^7\) To a solution of dimethyl L-tartrate (9.85 g, 55.3 mmol) in ether (100 mL) was added at 5 °C periodic acid (12.9 g, 56.4 mmol) in portions during 1 h. The white mixture was stirred until the ether layer turned colorless and a white solid precipitated. The white solid was filtered off and the ether layer was dried (CaCl\(_2\)), filtered, concentrated \( \text{in vacuo} \) and distilled to give methyl glyoxylate hydrate (7.25 g, 68.4 mmol, 62%) as a colorless oil, bp 70-80 °C (14 mm).

Methyl glyoxylate. \(^8\) A mixture of the methyl hemiacetal of methyl glyoxylate (1 equiv) and P\(_2\)O\(_5\) (1 equiv) was distilled to give anhydrous methyl glyoxylate (50-90%) as a colorless oil, bp 40-43 °C (20 mm).

General procedure B for the reactions with methyl glyoxylate or methyl glyoxylate hydrate.
To a solution of the alkylated pyrazolidinone in benzene or toluene was added at rt an excess of freshly distilled methyl glyoxylate (hydrate). After complete reaction (according to TLC), the solution was concentrated \( \text{in vacuo} \), taken up in pyridine and treated with an excess of acetic anhydride and a catalytic amount of DMAP. After being stirred at rt for 18 h, the dark brown solution was concentrated \( \text{in vacuo} \) and purified by flash chromatography to afford the pure product.

\( \alpha \)-Acetoxy-1-benzyl-5,5-dimethyl-3-pyrazolidinoneacetic acid methyl ester (34). According to the general procedure B, a solution of 1-benzyl-5,5-dimethyl-3-pyrazolidinone (374 mg, 1.83 mmol) in benzene (20 mL) was treated with methyl glyoxylate hydrate (409 mg, 3.86 mmol) and acetylated with Ac\(_2\)O (0.86 mL, 9.15 mmol) in pyridine (20 mL). Work-up and flash chromatography (ethyl acetate/hexane 1:1) afforded 34 (433 mg, 1.30 mmol, 71%) as a colorless oil, \( R_f \) 0.45. IR \( \nu \) 1750, 1705, 1370, 1230, 1040, 955, 690; \( \text{JH NMR (200 MHz)} \) 6 1.15 (s, 3 H, CH\(_3\)), 1.20 (s, 3 H, CH\(_3\)), 2.07 (s, 3 H, C(=O)CH\(_3\)), 2.21 (d, \( J = 16.4 \text{ Hz} \), 1 H, C(O)C\(_=\)H), 2.69 (d, \( J = 16.5 \text{ Hz} \), 1 H, C(O)CH\(_2\)), 3.82 (s, 3 H, CO\(_2\)CH\(_3\)), 4.14 (d, \( J = 14.4 \text{ Hz} \), 1 H, NCH\(_2\)), 4.24 (d, \( J = 14.5 \text{ Hz} \), 1 H, NCH\(_2\)), 6.45 (s, 1 H, NCH), 7.23-7.38 (m, 5 H, ArH); \( \text{13C NMR (50 MHz)} \) 6 20.5 (CH\(_3\)), 24.7 (CH\(_3\)), 27.6 (CH\(_3\)), 41.1 (C(O)CH\(_2\)), 52.7 (CO\(_2\)CH\(_3\)), 58.0 (CH\(_2\)Ph), 63.0 (NC), 76.4 (NCH), 127.2, 128.2, 128.4 (ArH), 138.2 (ArC), 164.9, 169.4, 173.5 (3 \( \times \) C(=O)).

\( \alpha \)-Acetoxy-5,5-dimethyl-1-(3-methyl-2-butenyl)-3-pyrazolidinoneacetic acid methyl ester (35). Following the general procedure B, a solution of 5,5-dimethyl-1-(3-methyl-2-butenyl)-3-pyrazolidinone (5.00 g, 28.0 mmol) in toluene (100 mL) was treated with methyl glyoxylate (5.86 g, 66 mmol) and acetylated with Ac\(_2\)O (10.5 mL, 110 mmol) in pyridine (75 mL). Work-up and flash chromatography (ethyl acetate/hexane 1:2) afforded 35 (8.47 g, 27 mmol, 97%) as a colorless oil, \( R_f \) 0.30. IR \( \nu \) 1750, 1705, 1435, 1370, 1230, 1040,
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960; $^1$H NMR (200 MHz) δ 1.15 (s, 3 H, CH$_3$), 1.35 (s, 3 H, CH$_3$), 1.69 (s, 3 H, CH$_3$), 2.11 (s, 3 H, C(=O)CH$_3$), 2.15 (d, $J$ = 16.4 Hz, 1 H, NCH), 2.60 (d, $J$ = 16.4 Hz, 1 H, C(=O)CH$_3$), 3.40-3.65 (m, 2 H, NCH$_2$), 3.76 (s, 3 H, CO$_2$CH$_3$), 5.28 (t, $J$ = 7.4 Hz, 1 H, =CH), 6.56 (s, 1 H, NCH).

α-Acetoxy-5,5-dimethyl-1-{2-[trimethylsilyl)methyl]-2-propenyl}-3-pyrazolidinoneacetic acid methyl ester (36). Following the general procedure B, a solution of 5,5-dimethyl-1-{2-[trimethylsilyl)methyl]-2-propenyl}-3-pyrazolidinone (453 mg, 1.89 mmol) in benzene (20 mL) was treated with methyl glyoxylate hydrate (717 mg, 6.76 mmol) and acetylated with Ac$_2$O (0.89 mL, 9.45 mmol) in pyridine (8 mL). Work-up and flash chromatography (ethyl acetate/hexane 1:1) afforded 36 (443 mg, 1.25 mmol, 66%) as a colorless oil, $R_f$ 0.45. IR ν 3070, 1750, 1705, 1435, 1370, 1245, 1225, 1040, 855; $^1$H NMR (250 MHz) δ 0.02 (s, 9 H, (CH$_3$)$_3$Si), 1.21 (s, 3 H, CH$_3$), 1.27 (s, 3 H, CH$_3$), 1.48 (d, $J$ = 13.5 Hz, 1 H, CH/HSi), 1.67 (d, $J$ = 13.5 Hz, 1 H, CH/HSi), 2.10 (s, 3 H, C(=O)CH$_3$), 2.17 (d, $J$ = 16.4 Hz, 1 H, C(=O)CH$_3$), 2.62 (d, $J$ = 16.4 Hz, 1 H, C(=O)CH$_3$), 3.43 (s, 2 H, NCH$_2$), 3.76 (s, 3 H, CO$_2$CH$_3$), 4.66 (br s, 1 H, =C//H), 4.89 (d, $J$ = 1.5 Hz, 1 H, =CHH), 6.44 (s, 1 H, NCH); 13C NMR (50 MHz) δ -0.4 ((CH$_3$)$_3$Si), 20.5 (CH$_3$), 23.8 (CH$_2$Si), 24.1 (CH$_3$), 27.2 (CH$_3$), 41.1 (C(=O)CH$_2$), 52.6 (CO$_2$CH$_3$), 60.2 (NCH$_2$), 62.5 (NC), 76.3 (NCH), 110.7 (=CH$_2$), 143.2 (=C), 164.7, 169.4, 173.4 (3 x C(O)).

α-Acetoxy-5,5-dimethyl-1-[4-(trimethylsilyl)-2-butynyl]-3-pyrazolidinoneacetic acid methyl ester (37). According to the general procedure B, a solution of 5,5-dimethyl-1-[4-(trimethylsilyl)-2-butynyl]-3-pyrazolidinone (400 mg, 1.68 mmol) in benzene (5 mL) was treated with methyl glyoxylate hydrate (356 mg, 3.36 mmol) and acetylated with Ac$_2$O (0.80 mL, 7.26 mmol) in pyridine (7 mL). Work-up and flash chromatography (ethyl acetate/hexane 1:2) afforded 37 (556 mg, 1.51 mmol, 90%) as a colorless oil, $R_f$ 0.30. IR ν 2200, 1755, 1710, 1370, 1250, 1040, 850; $^1$H NMR (200 MHz) δ 0.05 (s, 9 H, (CH$_3$)$_3$Si), 1.13 (s, 3 H, CH$_3$), 1.39 (s, 3 H, CH$_3$), 1.42 (t, $J$ = 2.4 Hz, 2 H, CH$_2$Si), 2.12 (s, 3 H, C(=O)CH$_3$), 2.15 (br s, 1 H, C(=O)CH//), 3.50 (dt, $J$ = 18.6, 2.3 Hz, 1 H, NCH//), 3.75 (s, 3 H, CO$_2$CH$_3$), 3.84 (d, $J$ = 18.6 Hz, 1 H, NCH//), 6.77 (s, 1 H, NCH).

General procedure C for the cyclization reactions with TiCl$_4$. To a 0.1 M solution of the hydrazide in CH$_2$Cl$_2$ was added TiCl$_4$ (2 equiv, as a solution of TiC$_2$Cl$_4$ in CH$_2$Cl$_2$) at -78 °C by a syringe. The mixture was stirred at -78 °C for 15 min and for 5-18 h at rt. The reaction mixture was poured into cold aq satd NaHCO$_3$ and the resulting suspension was filtered over Celite and extracted with CH$_2$Cl$_2$ (3 x). The combined organic layers were dried (MgSO$_4$), filtered and concentrated in vacuo. Purification of the residue by flash chromatography afforded the pure cyclization product(s).

2,3-Dihydro-3,3-dimethyl-1H-pyrazolo[1,2-b]phthalazin-1-one (23). According to the general procedure C, a solution of 19 (322 mg, 1.30 mmol) in CH$_2$Cl$_2$ (8 mL) was treated with TiCl$_4$ (2.16 mL of a 1.2 M solution, 2.60 mmol). Work-up and flash chromatography (ethyl acetate) afforded 23 (275 mg, 1.27 mmol, 98%) as white crystals, mp 78-79 °C (ether/hexane 10:1), $R_f$ 0.30. IR ν 3060, 1670, 1430, 1250, 1120, 890; $^1$H NMR (200 MHz) δ 1.39 (br s, 6 H, (CH$_3$)$_2$C), 2.47 (br s, 2 H, C(=O)CH$_3$), 3.92 (br s, 2 H, NCH$_2$), 4.75 (br s, 2 H, NCH$_2$), 7.07-7.26 (m, 4 H, ArH); $^1$H NMR (250 MHz, -40 °C, C$_7$D$_6$, see Fig 6.2) δ 0.98 (s, 3 H, CH$_3$), 1.33 (s, 3 H, CH$_3$), 2.17 (d, $J$ = 16.3 Hz, 1 H, C(=O)CH$_3$), 2.44 (d, $J$ = 16.3 Hz, 1 H, C(=O)CH$_3$), 3.41 (d, $J$ = 13.2 Hz, 1 H, NCH), 3.55 (d, $J$ = 13.2 Hz, 1 H, NCH), 4.31 (d, $J$ = 16.5 Hz, 1 H, NCH), 5.44 (d, $J$ = 16.5 Hz, 1 H, NCH), 6.80-7.22 (m, 4 H, ArH); $^1$H NMR (250 MHz, 60 °C, C$_7$D$_6$) δ 1.23 (s, 6 H, (CH$_3$)$_2$C), 2.27 (s, 2 H, C(=O)CH$_3$), 3.65 (s, 2 H, NCH$_2$), 4.77 (s, 2 H, NCH$_2$), 6.90-7.20 (m, 4 H, ArH); $^{13}$C NMR (250 MHz, 60 °C, C$_7$D$_6$) δ 1.23 (s, 6 H, (CH$_3$)$_2$C), 2.27 (s, 2 H, C(=O)CH$_3$), 3.65 (s, 2 H, NCH$_2$), 4.77 (s, 2 H, NCH$_2$), 6.90-7.20 (m, 4 H, ArH); $^{13}$C
Synthesis of bicyclic pyrazolidinones

**NMR (50 MHz)**

- C(0)CH$_2$: 41.8, 42.9 (NCH$_2$)
- 51.2 (NCH$_2$), 59.2 (NC), 125.8, 126.6, 127.2, 127.5 (ArH), 130.9, 132.2 (ArC)

**13C NMR (63 MHz, -30 °C)**

- CH$_3$: 22.2, 28.3, 40.8 (C(0)CH$_2$), 42.1 (NCH$_2$), 50.8 (NCH$_2$), 58.8 (NC), 125.3, 126.1, 126.8, 127.1 (ArH), 130.0, 131.4 (ArC), 170.3 (C(0))

**MS (EI, 70 eV)**

- m/z (relative intensity) 216 (M+, 62), 201 (100), 118 (13), 104 (45); HRMS calcd for C$_{13}$H$_{16}$N$_2$: C, 72.12; H, 7.49; N, 12.86.

**2,3-Dihydro-3,3-dimethyl-1H-pyrazolo[1,2-b]phthalazin-1-one (23)**

A solution of 19 (268 mg, 1.08 mmol) in HCOOH (10 mL) was stirred at 50 °C for 17 h. Concentration in vacuo and purification by flash chromatography (ethyl acetate) afforded 23 (122 mg, 0.56 mmol, 52%) as a white solid, R$_f$ 0.30.

**6-(1-Chloro-1-methylethyl)tetrahydro-3,3-dimethyl-1H,5H-pyrazolo[1,2-b]pyrazol-1-one (24)**

According to the general procedure C, a solution of 20 (69 mg, 0.31 mmol) in CH$_2$Cl$_2$ (3 mL) was treated with TiCl$_4$ (0.50 mL of a 1.2 M solution, 0.61 mmol). Work-up and flash chromatography (ethyl acetate) afforded 6-(1-methylethenyl)tetrahydro-3,3-dimethyl-1H,5H-pyrazolo[1,2-b]pyrazol-1-one (25) (10 mg, 0.052 mmol, 17%) as a colorless oil, R$_f$ 0.40 and 24 (49 mg, 0.21 mmol, 76%) as white crystals, mp 91-92.5 °C (ether), R$_f$ 0.30. 25: IR v 1680, 1450, 1360; 1H NMR (200 MHz) δ 1.29 (s, 3 H, CH$_3$), 1.30 (s, 3 H, CH$_3$), 1.72 (s, 3 H, CH$_3$), 2.38 (d, J = 16.7 Hz, 1 H, C(O)CH$_2$), 2.52 (d, J = 17.4 Hz, 1 H, C(O)CH$_2$), 2.61 (t, J = 8.0 Hz, 1 H, NCH$_2$), 2.75-2.90 (m, 1 H, CH), 2.97 (t, J = 7.4 Hz, 1 H, NCH$_2$), 3.25-3.55 (m, 2 H, NCH$_2$), 4.80 (br s, 2 H, =CH$_2$); 13C NMR (63 MHz) δ 20.4, 24.4, 27.3 (3 x CH$_3$), 44.4, 45.4 (C(0)CH$_2$ and NCH$_2$), 47.7 (CH), 51.5 (NCH$_2$), 57.4 (NC), 111.9 (C=O), 142.7 (C=O), 175.0 (C(0)); MS (EI, 70 eV) m/z (relative intensity) 194 (M+, 40), 179 (65), 11 (40), 83 (30), 67 (40), 56 (40); HRMS calcd for C$_{13}$H$_{16}$N$_2$: C, 57.26; H, 8.30; N, 12.14. Found: C, 57.18; H, 8.38; N, 12.03.

**6-(1-Chloro-1-methylethyl)tetrahydro-3,3-dimethyl-1H,5H-pyrazolo[1,2-b]pyrazol-1-one (26)**

A solution of 20 (82 mg, 0.36 mmol) in HCOOH (4 mL) was stirred at rt for 17 h. Concentration in vacuo and flash chromatography (ethyl acetate) afforded 26 (83 mg, 0.35 mmol, 96%) as white crystals, mp 65-67 °C (ether), R$_f$ 0.15. IR v 1680, 1450, 1360; 1H NMR (200 MHz) δ 1.32 (s, 6 H, CH$_3$), 1.54 (s, 3 H, CH$_3$), 1.55 (s, 3 H, CH$_3$), 2.38 (d, J = 16.6 Hz, 1 H, C(O)CH$_2$), 2.51 (d, J = 17.3 Hz, 1 H, C(O)CH$_2$), 2.61 (t, J = 8.0 Hz, 1 H, NCH$_2$), 2.75-2.90 (m, 1 H, CH), 2.97 (t, J = 7.4 Hz, 1 H, NCH$_2$), 3.37 (br dd, J = 9.2, 11.1 Hz, 1 H, NCH$_2$), 3.66 (dd, J = 6.3, 11.3 Hz, 1 H, NCH$_2$); 13C NMR (50 MHz) δ 24.1, 27.9, 31.1 (4 x CH$_3$), 43.5, 43.8 (NCH$_2$ and C(O)CH$_2$), 49.6 (NCH$_2$), 57.3 (NC), 69.7 (CCl), 175.0 (C(0)); MS (EI, 70 eV) m/z (relative intensity) 230 (M+, 50), 215 (100), 179 (30), 147 (30), 127 (40), 111 (45), 83 (40), 69 (60); HRMS calcd for C$_{13}$H$_{16}$N$_2$Cl: C, 57.26; H, 8.30; N, 12.14. Found: C, 57.18; H, 8.38; N, 12.03.
Hexahydro-3,3-dimethyl-6-methylene-1H-pyrazolo[1,2-a]pyridazin-1-one (27). To a solution of 21 (312 mg, 1.10 mmol) in CH₂Cl₂ (6 mL) was added at 0 °C BF₃·OEt₂ (270 µL, 2.20 mmol) and the mixture was stirred at 0 °C for 15 min and for 3 h at r.t. The solution was poured intoaq satd NaCl (100 mL) and extracted with CH₂Cl₂ (3 × 100 mL). The combined organic layers were dried (MgSO₄), filtered, concentrated in vacuo and chromatographed (ethyl acetate) to give 27 (138 mg, 0.77 mmol, 71%) as a colorless oil.

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v 1960, 1680; !H NMR (200 MHz) δ 1.28 (s, 6 H, (CH₃)₂C), 2.21 (s, J = 5.8 Hz, 2 H, NCH₂CH₂), 2.42 (s, 2 H, C(O)CH₂), 3.10-4.10 (br s, 2 H, NCH₂CH₂), 3.20 (s, 2 H, NCH₂Ce), 4.96 (s, 1 H, =CHH), 4.98 (s, 1 H, =CHH); ¹H NMR (250 MHz, -40 °C, C₇D₈, see Fig 6.3) δ 0.98 (s, 3 H, CH₃), 1.25 (s, 3 H, CH₃), 1.93 (dd, J = 3.3, 13.4 Hz, 1 H, NCH₂CH₂), 2.07 (dt, J = 5.8, 12.4 Hz, 1 H, NCH₂CH₂), 2.18 (d, J = 16.5 Hz, 1 H, C(O)CH₂), 2.45 (d, J = 16.5 Hz, 1 H, C(O)CH₂), 2.73 (d, J = 10.5 Hz, 1 H, NCH₂CH₂), 2.92 (dt, J = 3.9, 12.5 Hz, 1 H, NCH₂CH₂), 3.15 (dd, J = 10.6 Hz, 1 H, NCH₂CH₂), 4.46 (dd, J = 5.5, 12.5 Hz, 1 H, NCH₂CH₂), 4.92 (s, 1 H, =CHH), 4.98 (s, 1 H, =CHH); ¹³C NMR (50 MHz) δ 31.7 (NCH₂CH₂), 40.9 (NCH₂CH₂), 42.5 (C(O)CH₂), 55.7 (NCH₂Ce), 58.3 (NC), 112.4 (=CH₂), 140.7 (=C), 170.6 (C(=O)); ¹³C NMR (63 MHz, -30 °C) δ 22.3 (CH₂), 28.4 (CH₂), 31.7 (NCH₂CH₂), 40.8 (NCH₂CH₂), 41.9 (C(O)CH₂), 56.0 (NCH₂Ce), 58.5 (NC), 113.4 (=CH₂), 139.9 (=C), 170.8 (C(=O)); ¹³C NMR (63 MHz, 70 °C, C₇D₈) δ 25.1 ((CH₃)₂C), 32.2 (NCH₂CH₂), 41.6 (NCH₂CH₂), 43.2 (C(O)CH₂), 55.8 (NCH₂Ce), 58.2 (NC), 111.2 (=CH₂), 142.7 (=C), 170.5 (C(=O)); MS (EI, 70 eV) m/z (relative intensity) 180 (M⁺, 24), 165 (96), 137 (15), 83 (24), 67 (63), 53 (58), 41 (100); HRMS calcd for C₁₀H₁₆N₂O₂ 180.1262, found 180.1267.

Hexahydro-3,3-dimethyl-6-methylene-1H-pyrazolo[1,2-a]pyridazin-1-one (27). A solution of 21 (300 mg, 1.06 mmol) in HCOOH (8 mL) was stirred at r.t for 5 h. Concentration in vacuo and flash chromatography (ethyl acetate/hexane 1:1) afforded 27 (174 mg, 0.97 mmol, 91%) as a colorless oil, Rf 0.10.

6-Ethenylidene tetrahydro-3,3-dimethyl-5H-pyrazolo[1,2-a]pyrazol-1-one (28). To a solution of 22 (90 mg, 0.31 mmol) in CH₂Cl₂ (3 mL) was added at 0 °C BF₃·OEt₂ (79 µL, 0.63 mmol) and the mixture was stirred at 0 °C for 15 min and for 3 h at r.t. The solution was poured intoaq satd NaCl (50 mL) and extracted with CH₂Cl₂ (3 × 50 mL). The combined organic layers were dried (MgSO₄), filtered, concentrated in vacuo and chromatographed (ethyl acetate/hexane 1:1) to give 28 (49 mg, 0.28 mmol, 88%) as a colorless oil, Rf 0.25. IR ν 1960, 1680; !H NMR (200 MHz) δ 1.31 (s, 6 H, (CH₃)₂C), 2.41 (s, 2 H, C(O)CH₂), 3.38 (br s, 2 H, NCH₂), 4.07 (br s, 2 H, NCH₂), 4.89 (quintet, J = 4.0 Hz, 2 H, =CH₂); ¹³C NMR (50 MHz) δ 26.0 (br, 2 × CH₃), 42.9 (C(O)CH₂), 44.5, 51.3 (2 × NCH₂), 57.2 (NC), 80.0 (=CH₂), 98.4 (C=C=CH₂), 176.8 (C(=O)); ¹³C NMR (63 MHz, 70 °C, C₇D₈) δ 27.3 (br, 2 × CH₂), 43.8 (C(O)CH₂), 46.3, 52.7 (2 × NCH₂), 58.1 (NC), 80.1 (=CH₂), 101.1 (C=C=CH₂), 178.0 (C(=O)); 200.7 (C=C=CH₂); MS (EI, 70 eV) m/z (relative intensity) 178 (M⁺, 100), 163 (85), 135 (22), 95 (25), 83 (50), 66 (27), 39 (23); HRMS calcd for C₁₀H₁₂N₂O₃ 178.1106, found 178.1102.

6-Ethenylidene tetrahydro-3,3-dimethyl-5H-pyrazolo[1,2-a]pyrazol-1-one (28). A solution of 22 (88 mg, 0.31 mmol) in HCOOH (3 mL) was stirred at r.t for 5 h. Concentration in vacuo and flash chromatography (ethyl acetate/hexane 1:1) afforded 28 (50 mg, 0.28 mmol, 94%) as a colorless oil, Rf 0.25.

2,3,5,10-Tetrahydro-1,1-dimethyl-3-oxo-1H-pyrazolo[1,2-b]phthalazine-5-carboxylic acid methyl ester (38). Following the general procedure C, a solution of 34 (112 mg, 0.336 mmol) in CH₂Cl₂ (3
ml) was treated with TiCl₄ (1.23 mL of a 1.2 M solution, 0.67 mmol). Work-up and flash chromatography (ethyl acetate) afforded 38 (63 mg, 0.23 mmol, 68%) as white crystals, mp 123-124 °C (ether/ethanol), 

IR ν 3030, 1745, 1680, 1430, 1260, 1220, 1000; ¹H NMR (250 MHz) δ 1.42 (s, 6 H, (CH₃)₂C), 2.66 (d, J = 16.5 Hz, 1 H, CO₂CH₂), 2.31 (d, J = 16.4 Hz, 1 H, C(O)CH₂), 3.75 (s, 3 H, CO₂CH₂), 3.92 (s, 2 H, NCH₂), 5.76 (s, 1 H, NCH), 7.07-7.09 (m, 1 H, ArH), 7.21-7.26 (m, 2 H, ArH), 7.53-7.56 (m, 1 H, ArH); ¹³C NMR (50 MHz) δ 22.6 (CH₃), 28.0 (CH₃), 41.5 (C(0)CH₂), 50.9 (NCH₂), 52.6 (CO₂CH₂), 54.1 (NCH), 59.5 (NC), 127.1, 127.3, 127.6, 128.0 (ArH), 128.0, 132.7 (ArC), 169.1, 170.4 (2 x C(0)); MS (EI, 70 eV) m/z (relative intensity) 274 (M+, 25), 259 (7), 215 (35), 199 (7), 173 (47), 131 (13), 116 (9), 40 (24), 32 (86); HRMS calcd for C₁₃H₁₈N₂O₃ 274.1317, found 274.1340.

2,3,5,10-Tetrahydro-l,l-dimethyl-3-oxo-l/7-pyrazolo[1,2-a]pyrazole-5-carboxylic acid methyl ester (38). A solution of 34 (48 mg, 0.14 mmol) in HCOOH (2 mL) was stirred at 50 °C for 17 h. Concentration in vacuo and flash chromatography (ethyl acetate/hexane 1:1) afforded 38 (13 mg, 0.047 mmol, 33%) as a white solid, Rᵣ 0.25.

rel-(1S,2’S)-2-(1-Chloro-l-methylethyl)tetrahydro-5,5-dimethyl-7-oxo-l/7-pyrazolo[1,2-a]pyrazole-1-carboxylic acid methyl ester (39). According to the general procedure C, a solution of 35 (220 mg, 0.705 mmol) in CH₂Cl₂ (7 mL) was treated with TiCl₄ (1.2 mL of a 1.2 M solution, 1.57 mmol). Work-up and flash chromatography (ethyl acetate/hexane 1:1) afforded 39 (73 mg, 0.25 mmol, 36%) as an inseparable mixture with 40 (34 mg, 0.14 mmol, 20%) as a colorless oil, Rᵣ 0.35. A small amount of 39 could be obtained in pure form after another purification by flash chromatography, which solidified upon standing, mp 91-93 °C (ethyl acetate/hexane 1:5). 39: IR ν 1750, 1710; ¹H NMR (200 MHz) δ 1.32 (s, 3 H, CH₃), 1.35 (s, 3 H, CH₃), 1.52 (s, 3 H, CH₃), 1.61 (s, 3 H, CH₃), 2.31 (d, J = 17.3 Hz, 1 H, C(0)CH₂), 2.54 (d, J = 17.3 Hz, 1 H, C(O)CH₂), 2.64 (dd, J = 9.4, 8.0 Hz, 1 H, NCH₂), 3.03-3.11 (t, J = 8.0 Hz, 1 H, NCH₂ and ddd, J = 9.5, 5.3, 7.8 Hz, 1 H, CH), 3.73 (s, 3 H, CO₂CH₂), 4.60 (d, J = 5.2 Hz, 1 H, NCH); ¹³C NMR (50 MHz) δ 23.5, 29.1, 31.5, 32.0 (4 x CH₃), 41.7 (C(0)CH₂), 51.0 (NCH₂), 52.8 (CO₂CH₂), 56.9 (NC), 57.5 (CH), 57.8 (NCH), 69.9 (CCl), 171.0, 176.8 (2 x C(0)); MS (EI, 70 eV) m/z (relative intensity) 288 (M⁺, 25), 273 (40), 238 (20), 187 (20), 99 (100), 43 (40); HRMS calcd for C₁₅H₂₁N₂O₂CI 288.1240, found 288.1205. 40: ¹H NMR (200 MHz) δ 1.31 (s, 3 H, CH₃), 1.35 (s, 3 H, CH₃), 1.44 (s, 3 H, CH₃), 1.49 (s, 3 H, CH₃), 2.33 (d, J = 17.7 Hz, 1 H, CH₂), 2.49 (d, J = 17.2 Hz, 1 H, CH₂), 2.45-2.52 (m, 1 H, NCH₂), 2.91 (t, J = 8.3, 1 H, CH), 3.09 (d, J = 9.8 Hz, 1 H, NCH₂), 4.99 (d, J = 9.1 Hz, 1 H, NCH). Crystallographic data of 39.

Monoclinic, P₂₁/n, a = 16.129(2), b = 16.521(1), c = 10.270(1) Å, α = 90°, β = 119.237(8)°, γ = 90°, V = 1499.7(4) Å³, Z = 4, Dₓ = 1.28 g/cm³, λ(CuKα) = 1.5418 Å, μ(CuKα) = 23.3 cm⁻¹, F(000) = 616, r.t. Final R = 0.084 for 2402 observed reflections.

The numbering of the atoms in Tables 6.4 and 6.5 is as shown in the following structure:
Table 6.4. Bond distances of the atoms (Å), with standard deviations in parentheses.

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<th>Standard Deviation (Å)</th>
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<td>0.05(3)</td>
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<tr>
<td>C1-C2</td>
<td>1.511(6)</td>
<td>0.04(3)</td>
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<tr>
<td>C1-N1</td>
<td>1.371(6)</td>
<td>0.03(3)</td>
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Table 6.5. Bond angles of the atoms (°), with standard deviations in parentheses.

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Hexahydro-1,1-dimethyl-7-methylene-3-oxo-1H-pyrazolo[1,2-a]pyrazidinone (41). To a solution of 36 (98 mg, 0.28 mmol) in CH$_2$Cl$_2$ (3 mL) was added at 0 °C BF$_3·$Et$_2$O (68 µL, 0.55 mmol) and the mixture was stirred at 0 °C for 15 min and for 3 h at rt. The solution was poured into aq satd NaCl (50 mL) and extracted with CH$_2$Cl$_2$ (3 × 50 mL). The combined organic layers were dried (MgSO$_4$), filtered, concentrated in vacuo and chromatographed (ethyl acetate) to afford 42 (45 mg, 0.19 mmol, 69%) as a white solid, $R_f$ 0.30. IR v 3080, 1740, 1670, 1435, 1410, 1270, 1230, 1050, 910; $^{13}$C NMR (63 MHz) $\delta$ 23.5, 24.4, 25.0, 29.0 (4 x CH$_3$), 41.7 (CH$_2$), 49.4 (NCH$_2$), 52.7 (CO$_2$CH$_3$), 56.4, 56.3 (2 x CH), 56.8 (NC), 81.6 (CO), 159.7, 170.9, 177.0 (3 x C(0)); MS (El, 70 eV) m/z (relative intensity) 298 ($^{13}$C, 100), 237 (24), 197 (37), 151 (17), 83 (20), 31 (40); HRMS calcd for C$_{14}$H$_{22}$N$_2$O$_2$ 298.1529, found 298.1519; Anal. Calcd. for C$_{14}$H$_{22}$N$_2$O$_2$: C, 56.36; H, 7.43; N, 9.39. Found: C, 56.22; H, 7.31; N, 9.26.

Hexahydro-1,1-dimethyl-7-methylene-3-oxo-1H-pyrazolo[1,2-a]pyrazidinone-5-carboxylic acid methyl ester (43). To a solution of 36 (98 mg, 0.28 mmol) in CH$_2$Cl$_2$ (3 mL) was added at 0 °C BF$_3·$Et$_2$O (68 µL, 0.55 mmol) and the mixture was stirred at 0 °C for 15 min and for 3 h at rt. The solution was poured into aq satd NaCl (50 mL) and extracted with CH$_2$Cl$_2$ (3 × 50 mL). The combined organic layers were dried (MgSO$_4$), filtered, concentrated in vacuo and chromatographed (ethyl acetate) to afford 42 (45 mg, 0.19 mmol, 69%) as a white solid, $R_f$ 0.30. IR v 3080, 1740, 1670, 1435, 1410, 1270, 1230, 1050, 910; $^{13}$C NMR (63 MHz) $\delta$ 23.5, 24.4, 25.0, 29.0 (4 x CH$_3$), 41.7 (CH$_2$), 49.4 (NCH$_2$), 52.7 (CO$_2$CH$_3$), 56.4, 56.3 (2 x CH), 56.8 (NC), 81.6 (CO), 159.7, 170.9, 177.0 (3 x C(0)); MS (El, 70 eV) m/z (relative intensity) 298 ($^{13}$C, 100), 237 (24), 197 (37), 151 (17), 83 (20), 31 (40); HRMS calcd for C$_{14}$H$_{22}$N$_2$O$_2$ 298.1529, found 298.1519; Anal. Calcd. for C$_{14}$H$_{22}$N$_2$O$_2$: C, 56.36; H, 7.43; N, 9.39. Found: C, 56.22; H, 7.31; N, 9.26.

Hexahydro-1,1-dimethyl-7-methylene-3-oxo-1H-pyrazolo[1,2-a]pyrazidinone-5-carboxylic acid methyl ester (43). To a solution of 36 (98 mg, 0.28 mmol) in CH$_2$Cl$_2$ (3 mL) was added at 0 °C BF$_3·$Et$_2$O (68 µL, 0.55 mmol) and the mixture was stirred at 0 °C for 15 min and for 3 h at rt. The solution was poured into aq satd NaCl (50 mL) and extracted with CH$_2$Cl$_2$ (3 × 50 mL). The combined organic layers were dried (MgSO$_4$), filtered, concentrated in vacuo and chromatographed (ethyl acetate) to afford 42 (45 mg, 0.19 mmol, 69%) as a white solid, $R_f$ 0.30. IR v 3080, 1740, 1670, 1435, 1410, 1270, 1230, 1050, 910; $^{13}$C NMR (63 MHz) $\delta$ 23.5, 24.4, 25.0, 29.0 (4 x CH$_3$), 41.7 (CH$_2$), 49.4 (NCH$_2$), 52.7 (CO$_2$CH$_3$), 56.4, 56.3 (2 x CH), 56.8 (NC), 81.6 (CO), 159.7, 170.9, 177.0 (3 x C(0)); MS (El, 70 eV) m/z (relative intensity) 298 ($^{13}$C, 100), 237 (24), 197 (37), 151 (17), 83 (20), 31 (40); HRMS calcd for C$_{14}$H$_{22}$N$_2$O$_2$ 298.1529, found 298.1519; Anal. Calcd. for C$_{14}$H$_{22}$N$_2$O$_2$: C, 56.36; H, 7.43; N, 9.39. Found: C, 56.22; H, 7.31; N, 9.26.
171.2 (2 × C(0)), 200.8 (C=C=CH2); MS (EI, 70 eV) m/z (relative intensity) 236 (M+, 45), 221 (25), 204 (50), 186 (55), 146 (100), 135 (50), 59 (35); HRMS calcd for C12H10O2N2 236.1161, found 236.1172.

2-Ethenylidene tetrahydro-5,5-dimethyl-7-oxo-1H,5H-pyrazolo[1,2-a]pyrazole-1-carboxylic acid methyl ester (43). A solution of 37 (220 mg, 0.60 mmol) in HCOOH (6 mL) was stirred at rt for 5 h. Concentration in vacuo and flash chromatography (ethyl acetate/hexane 1:1) afforded 43 (77 mg, 0.33 mmol, 54%) as a colorless oil, Rf 0.30.

α-Acetoxy-5,5-dimethyl-1-(2-propenyl)-3-pyrazolidinoneacetic acid methyl ester (49). According to the general procedure B, a solution of 5,5-dimethyl-1-(2-propenyl)-3-pyrazolidinone (1.00 g, 6.49 mmol) in benzene (25 mL) was treated with methyl glyoxylate hydrate (1.38 g, 13.0 mmol) and acetylated with Ac2O (3.07 mL, 32.5 mmol) in pyridine (20 mL). Work-up and flash chromatography (ethyl acetate/hexane 1:2) afforded 49 (1.31 g, 4.61 mmol, 71%) as a colorless oil, Rf 0.50. IR ν 3080, 1760, 1750, 1435, 1370, 1230, 1140; 1H NMR (200 MHz) δ 1.17 (s, 3 H, CH3), 1.32 (s, 3 H, CH3), 2.13 (s, 3 H, C(0)CH3), 2.14 (d, J = 16.4 Hz, 1 H, C(0)CHH), 2.58 (d, J = 16.4 Hz, 1 H, C(0)CHH), 3.51 (dd, J = 6.6, 15.2 Hz, 1 H, NCHH), 3.65 (dd, J = 7.0, 15.2 Hz, NCHH), 3.77 (s, 3 H, C02CH3), 5.18-5.32 (m, 2 H, =CH2), 5.84-6.05 (m, 1 H, =CH), 6.60 (s, 1 H, NCH).

α-Acetoxy-5,5-dimethyl-1-(2-methyl-2-propenyl)-3-pyrazolidinoneacetic acid methyl ester (50). Following the general procedure B, a solution of 5,5-dimethyl-1-(2-methyl-2-propenyl)-3-pyrazolidinone (655 mg, 3.90 mmol) in benzene (25 mL) was treated with methyl glyoxylate hydrate (826 mg, 7.80 mmol) and acetylated with Ac2O (1.85 mL, 19.5 mmol) in pyridine (20 mL). Work-up and flash chromatography (ethyl acetate/hexane 1:2) afforded 50 (1.00 g, 3.36 mmol, 86%) as a colorless oil, Rf 0.50. IR ν 3070, 1750, 1705, 1435, 1370, 1225, 1040, 900; 1H NMR (200 MHz) δ 1.20 (s, 3 H, CH3), 1.27 (s, 3 H, CH3), 1.75 (s, 3 H, CH3), 2.13 (s, 3 H, C(O)CH3), 2.17 (d, J = 16.4 Hz, 1 H, C(O)CHH), 2.66 (d, J = 16.4 Hz, 1 H, C(O)CHH), 3.55 (s, 2 H, NCH2), 3.78 (s, 3 H, CO2CH3), 4.85 (s, 1 H, =CHH), 4.95 (s, 1 H, =CHH), 6.51 (s, 1 H, NCH).

α-Acetoxy-1-(2-propenyl)-3-pyrazolidinoneacetic acid methyl ester (51). According to the general procedure B, a solution of 1-(2-propenyl)-3-pyrazolidinone (300 mg, 2.38 mmol) was treated with methyl glyoxylate (419 mg, 4.76 mmol) in toluene (10 mL) and acetylated with Ac2O (1.12 mL, 11.9 mmol) in pyridine (10 mL). Work-up and flash chromatography (ethyl acetate/hexane 1:1) afforded 51 (363 mg, 1.42 mmol, 60%) as a colorless oil, Rf 0.35. IR ν 3080, 1760, 1710, 1365, 1225, 1050, 900; 1H NMR (200 MHz) δ 2.15 (s, 3 H, C(0)CH3), 2.20-2.40 (m, 1 H, C(0)CHH), 2.65-2.85 (m, 1 H, C(0)CHH), 3.15-3.60 (m, 4 H, 2 x NCH^), 3.79 (s, 3 H, CO2CH3), 5.20-5.31 (m, 2 H, =CH2), 5.77-5.97 (m, 1 H, =CH), 6.73 (s, 1 H, NCH).

re/(5S,7R)-Hexahydro-1,1-dimethyl-7-chloro-3-oxo-1H-pyrazolo[1,2-a]pyridazine-5-carboxylic acid methyl ester (52). Following the general procedure C, a solution of 49 (200 mg, 0.70 mmol) in CH2Cl2 (7 mL) was treated with TiCl4 (0.70 mL of a 2.0 M solution, 1.40 mmol). Work-up and flash chromatography (ethyl acetate/hexane 1:1) afforded 52 (10 mg, 0.038 mmol, 6%) as a colorless oil, Rf 0.30. IR ν 1735, 1680, 1220; 1H NMR (200 MHz) δ 1.27 (s, 6 H, (CH2)2CH), 1.74 (dt, J = 6.2, 12.4 Hz, 1 H, NCHCHCH₂CH+), 2.32 (d, J = 16.6 Hz, 1 H, C(O)CH/CH₂), 2.48 (s, J = 10.0 Hz, 1 H, NCHCH₂CH₃), 2.52 (d, J = 16.6 Hz, 1 H, C(O)CH/CH₂), 2.78 (dd, J = 4.5, 13.1 Hz, 1 H, NCHCHCH₂CH₃), 3.21 (dd, J = 4.1, 10.0 Hz, 1 H, NCHCH₂CH₃), 3.76 (s, 3 H, CO₂CH₃), 4.06 (dddd, J = 10, 12, 4.1, 4.5 Hz, 1 H, =CH), 4.98 (d, J = 5.9 Hz, 1 H, NCH); 13C NMR (63 MHz) δ 22.3, 27.7 (2 × CH₂), 34.4 (NCHCH₂), 43.0 (C(O)CH₂), 51.5, 51.9 (NCH and CHCH₂), 52.7...
Synthesis of bicyclic pyrazolidinones

(CO₂CH₃), 56.2 (NCH₂), 59.0 (NC), 169.2, 171.0 (2 x C(O)); MS (El, 70 eV) m/z (relative intensity) 260 (M⁺, 64), 245 (78), 201 (49), 159 (100), 43 (63); HRMS calcld for C₁₁H₁₇N₂O₃Cl 260.0928, found 260.0921.

re-l-(5S,7R)-Hexahydro-1,1,7-trimethyl-7-chloro-3-oxo-1H-pyrazolo[1,2-a]pyridazine-5-carboxylic acid methyl ester (53). According to the general procedure C, a solution of 50 (125 mg, 0.42 mmol) in CH₂Cl₂ (6 mL) was treated with TiCl₄ (0.70 mL of a 1.2 M solution, 0.84 mmol). Work-up and flash chromatography (ethyl acetate/hexane 1:1) afforded 53 (9 mg, 0.033 mmol, 8%) as a colorless oil, Rf 0.40. IR v 1735, 1680; ¹H NMR (200 MHz) δ 1.27 (s, 3 H, CH₃), 1.32 (s, 3 H, CH₃), 1.62 (s, 3 H, CH₃), 2.14 (dd, J = 13.7, 7.1 Hz, 1 H, NCH₂CH₂), 2.39 (d, J = 16.5 Hz, 1 H, COCH₂), 2.49 (d, J = 16.5 Hz, 1 H, COCH₂), 2.65 (dt, J = 13.5, m 1.8 Hz, NCH₂CH₂), 2.75 (d, J = 10.4 Hz, 1 H, NCH₂CH₂), 2.90 (dd, J = 10.4, 1.4 Hz, 1 H, NCH₂CH₂), 3.75 (s, 3 H, CO₂CH₃), 4.82 (dd, J = 2.4, 7.1 Hz, 1 H, NCH); ¹³C NMR (63 MHz) δ 22.5, 26.9, 27.8 (3 x CH₃), 29.7 (NCH₂CH₂), 39.9 (NCH₂), 43.6 (COCH₂), 51.8 (NCH), 52.6 (CO₂CH₃), 54.5 (NCH₂), 60.5 (NC), 65.0 (CCl).

re-l-(5S,7R)-Hexahydro-7-chloro-3-oxo-1H-pyrazolo[1,2-a]pyridazine-5-carboxylic acid methyl ester (54). Following the general procedure C, a solution of 51 (140 mg, 0.54 mmol) in CH₂Cl₂ (5 mL) was treated with TiCl₄ (0.91 mL of a 1.2 M solution, 1.09 mmol). Work-up and flash chromatography (ethyl acetate/hexane 4:1) afforded 54 (8 mg, 0.034 mmol, 6%) as a colorless oil, Rf 0.25. IR v 1735, 1690; ¹H NMR (200 MHz) δ 1.84 (dt, J = 6.0, 12.2 Hz, 1 H, NCH₂CH₂), 2.48 (t, 1 H, J = 10.4 Hz, 1 H, NCH₂CH₂), 2.53-2.65 (m, 1 H, CH₂), 2.75-2.89 (m, 2 H, COCH₂ and NCH₂CH₂), 3.35 (dd, J = 9.8, 6.3, 1 H, NCH₂CH₂), 3.58 (dt, J = 9.8, 6.3, 1 H, NCH₂CH₂), 3.77 (s, 3 H, CO₂CH₃), 3.83 (s, 3 H, CO₂CH₃), 4.04 (tt, J = 11.6, 4.5 Hz, 1 H, CH₂), 4.90 (d, J = 5.9 Hz, 1 H, NCH); ¹³C NMR (50 MHz) δ 30.3 (CH₂), 34.1 (CH₂), 50.0 (CH), 50.1 (CH), 52.6 (CO₂CH₃), 52.9 (CH), 63.2 (NCH₂), 169.0, 171.4 (2 x C(O)); MS (El, 70 eV) m/z (relative intensity) 232 (M⁺, 45), 173 (66), 130 (100); HRMS calcld for C₉H₁₄N₂O₃Cl 232.0615, found 232.0600.

2,3-Dihydro-2-ethenyl-5,5-dimethyl-7-oxo-1H,5H-pyrazolo[1,2-a]pyridazole-1-carboxylic acid methyl ester (55). To a solution of 43 (80 mg, 0.34 mmol) in THF (2 mL) was added at -78 °C DBU (50 μL, 0.34 mmol) and the mixture was allowed to warm to rt in 2 h. Concentration in vacuo and flash chromatography (ethyl acetate/hexane 4:1) afforded 55 (4 mg, 0.034 mmol, 6%) as a colorless oil, Rf 0.40. IR v 1745, 1700, 900; ¹H NMR (200 MHz) δ 1.26 (s, 6 H, 2 x CH₃), 2.63 (s, 2 H, CH₂), 3.89 (s, 3 H, CO₂CH₃), 4.04 (s, 2 H, NCH₂), 5.16 (d, J = 17.7 Hz, 1 H, =CHH), 5.38 (d, J = 10.9 Hz, 1 H, =CHH), 6.98 (dd, J = 10.9, 17.6 Hz, 1 H, =CH), 13C NMR (50 MHz) δ 22.5 (CH₂), 49.0, 49.5 (NCH₂ and CH₂), 52.4 (CO₂CH₃), 62.7 (NCH₂), 119.4 (=CH₂), 127.6 (=CH), 130.8 (=CO(O)), 159.5 (CO(O)), 165.5 (=CO(O)), 171.0 (CO(O)).

5,5-Dimethyl-1-(1-phenyl-3-butenyl)-3-pyrazolidinone (56). To a solution of 5,5-dimethyl-3-pyrazolidinone (56, 1.65 g, 14.5 mmol) in toluene (20 mL) were added benzaldehyde (1.54 g, 14.5 mmol) and a catalytic amount of pTSA. The resulting solution was refluxed under azeotropic removal of H₂O for 18 h. Concentration in vacuo and flash chromatography (ethyl acetate/hexane 1:1) afforded 56 (15 mg, 0.068 mmol, 29%) as a yellow oil, Rf 0.40. IR v 1745, 1700, 900; ¹H NMR (200 MHz) δ 1.71 (s, 6 H, (CH₃)₂C), 2.72 (s, 2 H, CH₂), 3.89 (s, 3 H, CO₂CH₃), 4.04 (s, 2 H, NCH₂), 5.16 (d, J = 17.7 Hz, 1 H, =CHH), 5.38 (d, J = 10.9 Hz, 1 H, =CHH), 6.98 (dd, J = 10.9, 17.6 Hz, 1 H, =CH), 13C NMR (50 MHz) δ 22.5 (CH₂), 49.0, 49.5 (NCH₂ and CH₂), 52.4 (CO₂CH₃), 62.7 (NCH₂), 119.4 (=CH₂), 127.6 (=CH), 130.8 (=CO(O)), 159.5 (CO(O)), 165.5 (=CO(O)), 171.0 (CO(O)).
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mL of 8 N aq HCl was added dropwise. After addition of CH₂Cl₂ (50 mL), the organic layer was dried (MgSO₄), filtered, concentrated in vacuo and chromatographed (ethyl acetate/hexane 1:1) to afford 58 (821 mg, 3.36 mmol, 45%) as a white solid, mp 108-110 °C, Rf 0.35. IR v 3410, 1680, 910, 690; ¹H NMR (250 MHz)  δ 1.18 (s, 3 H, CH₃), 1.29 (s, 3 H, CH₃), 1.78 (d, J = 16.1 Hz, 1 H, C(0)CH₂), 2.05 (d, J = 16.1 Hz, 1 H, C(0)CH₂), 2.58-3.99 (m, 2 H, CH₂), 3.96 (dd, J = 6.0, 8.6 Hz, 1 H, NCH), 4.87-5.00 (m, 2 H, =CH₂), 5.47-5.59 (m, 1 H, =CH), 7.18-7.36 (m, 5 H, ArH), 9.03 (br s, 1 H, NH); ¹³C NMR (63 MHz) δ 25.0, 27.9 (2 X CH₃), 40.0 (CH₂), 43.6 (C(0)CH₂), 63.5 (NC), 65.6 (NCH), 116.7 (=CH₂), 127.4, 128.2, 128.7 (ArH), 134.9 (=CH), 140.6 (ArC), 176.0 (C(0)); a-Acetoxy-5,5-dimethyl-1-(1-phenyl-3-butenyl)-3-pyrasolidinoneacetic acid methyl ester (59). According to the general procedure B, a solution of 58 (939 mg, 3.84 mmol) in benzene (20 mL) was treated with methyl glyoxylate hydrate (814 mg, 7.7 mmol) and acetylated with Ac₂O (1.81 mL, 19.1 mmol) in pyridine (15 mL). Work-up and flash chromatography (ethyl acetate/hexane 1:3.5) afforded 59 (650 mg, 1.74 mmol, 45%) as a colorless oil, Rf 0.30. IR v 1765, 1750, 1715, 1370, 1220, 690; ¹H NMR (200 MHz) δ (two diastereomers) 1.17, 1.23 (s, 3 H, CH₃), 1.27, 1.32 (s, 3 H, CH₃), 1.63, 1.78 (br s, 2 H, C(0)CH₂), 2.17, 2.19 (s, 3 H, C(0)CH₃), 2.74-2.79 (m, 2 H, CH₂), 3.81, 3.89 (s, 3 H, CO₂CH₃), 4.07-4.15 (m, 1 H, CH), 4.93-5.06 (m, 1 H, =CH), 6.18, 6.59 (s, 1 H, NCH), 7.24-7.54 (m, 5 H, ArH).

7-Chlorohexahydro-1,1-dimethyl-3-oxo-9-phenyl-1H,5H-pyrazolo[1,2-a][1,2]diazepine-5-carboxylic acid methyl ester (60), According to the general procedure C, a solution of 59 (100 mg, 0.27 mmol) in CH₂Cl₂ (3 mL) was treated with SnCl₄ (0.27 mL of a 2.0 M solution, 0.54 mmol). Work-up and flash chromatography (ethyl acetate/hexane 1:1.3) afforded 60 (18 mg, 0.051 mmol, 18%) as white crystals, single isomer, mp 153-154 °C (ether), Rf 0.40. IR v 1740, 1680, 1390, 690; ¹H NMR (250 MHz) δ 0.92 (s, 3 H, CH₃), 1.46 (s, 3 H, CH₃), 2.10 (d, J = 16.3 Hz, 1 H, C(0)CH₂), 2.15-2.45 (m, 3 H, CH₂ and CHH), 2.83 (d, J = 16.3 Hz, 1 H, C(0)CH₂), 2.89-3.01 (m, 1 H, CHH), 3.78 (s, 3 H, CO₂CH₃), 4.07-4.19 (m, 1 H, CHCl), 4.50 (dd, J = 2.3, 5.1 Hz, 1 H, NCHPh), 4.81 (dd, J = 10.8, 3.1 Hz, 1 H, NCH(O)), 7.25-7.38 (m, 5 H, ArH); ¹³C NMR (63 MHz) δ 24.2, 29.0 (2 X CH₃), 37.7, 42.2 (2 X CH₂), 43.6 (C(0)CH₂), 52.4 (CO₂CH₃), 53.4, 53.6 (2 X CH), 62.2 (CH), 63.4 (NC), 126.5, 127.4, 128.8 (ArH), 142.4 (ArC), 170.3, 172.0 (C(0)); Anal. Calcd. for C₁₈H₂₃N₂O₂Cl: C, 61.62; H, 6.61; N, 7.98. Found: C, 61.68; H, 6.56; N, 7.94.

6.8 REFERENCES AND NOTES


Synthesis of bicyclic pyrazolidinones


CHAPTER 7
SYNTHESIS OF CYCLIC \( \alpha \)-HYDRAZINO ACID DERIVATIVES

7.1 INTRODUCTION

About three decades ago, several monamycin antibiotics were isolated from cultures of *Streptomyces jamaicensis*.\(^1\) All of these monamycins are cyclic hexadepsipeptides, containing unusual amino acids, *i.e.* hexahydropyridazine-3-carboxylic acids, abbreviated as piperazic acids.\(^2\) Most abundant in the monamycin antibiotics are the piperazic acids 1 and 2 (Chart 7.1).

More recently, various classes of oligopeptides and cyclic hexadepsipeptides that contain similar types of piperazic acids were isolated. Examples of such oligopeptides are the antrimycins 3 and the cirratiomycins 4.\(^4\)

Examples of cyclic peptides that possess piperazic acid moieties are the azinothercin antitumor antibiotics,\(^5\) the antibiotic L-156,602\(^6\) and its derivative L-365,209\(^7\) and the tuberculostatic compound luzopeptin A.\(^8\) A summary of the piperazic acids that are present in these molecules is shown in Chart 7.1.

Chart 7.1

As a result of the diverse biological activities of these compounds, there is a strongly increasing interest in the synthesis of these piperazic acid residues. The unsaturated piperazic acid 5 was synthesized\(^9,10\) by using methodology that was developed for the synthesis of acyclic \( \alpha \)-hydrazino acids.\(^11\) The presence of the chiral auxiliary in the protected aldehyde 8 led to a highly diastereoselective conjugate addition of its enolate with di-tert-butyl azodicarboxylate (eq 7.1), affording the hydrazine 9. Removal of the auxiliary and concomitant esterification with MeOMgI, followed by treatment with trifluoroacetic acid yielded the piperazic acid 5.
Chapter 7

\[ \text{eq 7.1} \]

\[
\begin{align*}
\text{8} & \xrightarrow{a} \text{9} \xrightarrow{b, c} \text{5} \\
\end{align*}
\]

\( a \) LDA, -78 °C, then DBAD. \( b \) MeOMgl, CH\(_2\)Cl\(_2\)-MeOH. \( c \) CF\(_3\)CO\(_2\)H, CH\(_2\)Cl\(_2\).

Recently, a more refined use of this methodology was reported, in which the intermediate 1,4-adduct was converted in a one-pot procedure into the cyclic compound 11 (eq 7.2). This reaction only occurred after the addition of 26 equiv of the HMPA substitute DMPU. Subsequent cleavage of the auxiliary and the carbamates led to the desired piperazic acid 12.

\[ \text{eq 7.2} \]

\[
\begin{align*}
\text{10} & \xrightarrow{a} \text{11} \xrightarrow{b} \text{12} \\
\end{align*}
\]

\( a \) (i) LDA, -78 °C, then DBAD. (ii) DMPU. \( b \) (i) LiOH, THF-H\(_2\)O (2:1), 0 °C (ii) CF\(_3\)CO\(_2\)H, CH\(_2\)Cl\(_2\).

The hydroxy-substituted piperazic acid 7, which was found in luzopeptin A, could be obtained starting from the functionalized allylic alcohol 13 (eq 7.3). Asymmetric epoxidation, followed by oxidation and esterification afforded 14. A diastereoselective addition of hydrazine to the potassium salt of 14 led to the unstable product 15, which was immediately treated with trifluoroacetic acid to afford the desired piperazic acid 7.

\[ \text{eq 7.3} \]

\[
\begin{align*}
\text{13} & \xrightarrow{a,b,c} \text{14} \xrightarrow{d,e} \text{15} \xrightarrow{f} \text{7} \\
\end{align*}
\]

\( a \) TBHP, Ti(Oi-Pr)\(_4\), L-(+)-diethyl tartrate. \( b \) RuO\(_4\). \( c \) CH\(_2\)N\(_2\). \( d \) K\(_2\)CO\(_3\), MeOH, H\(_2\)O. \( e \) H\(_2\)NNH\(_2\). \( f \) CF\(_3\)CO\(_2\)H, H\(_2\)O.

The piperazic acid 1 occurring in monamycin was synthesized via a completely different route as shown in Scheme 7.1. A Diels-Alder reaction of the phthalazinedione 16 with the diene afforded the adduct 17 which could either be reduced to the piperazic acid 6, or oxidized to the acetate 18. Selective catalytic hydrogenation yielded the cis-hydroxy piperazic acid 14 in large excess, which, after hydrolysis, was resolved into its enantiomers with quinine. Cleavage of the phthalazine moiety with hydrazine afforded the desired piperazic acid 1.
Synthesis of cyclic α-hydrazino acid derivatives

In this Chapter a novel approach for the synthesis of cyclic hydrazino acids is detailed, which is based on the intermediacy of N-acylhydrazonium ions that are substituted with a carboxyl function. A sequence that might lead to the chlorine substituted α-hydrazino acid 2 is given in retrosynthetic form in Scheme 7.2. The free hydrazine 2 might be obtained by deprotection of the cyclization product 20, in which R and R' are appropriate protective groups.

It is known from comparable N-acyliminium ion cyclizations\textsuperscript{15} that the cationic intermediate 21 is likely to adopt a chair-like conformation, in which the N-acyliminium part has a (Z)-geometry. The preference for this geometry can be visualized by looking at the two possible conformations A and B of the hydrazonium ion.
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The \((E)\)-isomer \(B\) is less likely to be formed as a result of pseudo-allylic 1,3-strain between the two carbonyl functions, which is absent in the \((Z)\)-isomer \(A\). Attack of a nucleophile (e.g. chloride) to the intermediate \(\pi\)-complex occurs in such a way that an overall trans-addition with respect to the double bond takes place, leading to the desired trans-relationship between both substituents.

The cyclization precursor 22 could be derived from the suitably protected hydrazine 23 by subsequent alkylation with allyl bromide and methyl glyoxylate. Moreover, introduction of various nucleophilic side chains might lead to the synthesis of numerous functionalized cyclic \(\alpha\)-hydrazino acids of different ring sizes.

7.2 CHOICE OF THE PROTECTIVE GROUPS

A proper choice of the protective group \(R'\) at the amine nitrogen atom (\(N1\)) can be made by considering the results of Sections 2.6 and 6.2. In the former case, the presence of an electron-withdrawing acyl substituent at \(N1\) is considered responsible for the fact that addition of the amide type nitrogen atom (\(N2\)) to methyl glyoxylate does not take place. In the latter case, however, \(N1\) bears an alkyl substituent, thus enhancing the reactivity of \(N2\) towards methyl glyoxylate. For these reasons, the easily removable benzyl function was chosen as a protective group for \(N1\).

With respect to the protective group at \(N2\), there are several possibilities. Among them are the tert-butoxycarbonyl, the ethoxycarbonyl and allyloxy carbonyl (Alloc) function. In view with its known acid-lability, the tert-butoxycarbonyl group is not suitable. The ethoxycarbonyl group is a possible choice, but as deprotection conditions are more severe compared with those for the Alloc function (see Chapter 3), the latter one is preferred as protective group for \(N2\).

Conversion of (commercially available) ethyl carbazate (24) to the monobenzyl product 25 proved to be impossible under 'standard' alkylation conditions (eq 7.4). Independent of the amount of benzyl chloride that was used, the dibenzyl product 26 was formed in a higher yield than the monobenzyl product 25. Apparently, the nucleophilicity of \(N1\) is increased by the introduction of a benzyl substituent, so that, despite the increased steric hindrance, the initial product 25 will react faster than the starting material.

\[
\begin{array}{cccccc}
\text{EtO}_2\text{C}^- \text{N}_2^+ & | & \text{NH}_2 & & \text{BnCl (1.05 equiv),} & \text{Et}_3\text{N (1.05 equiv),} \\
& & \text{EtOH, reflux} & & \text{EtOH, reflux} \\
\text{24} & \rightarrow & \text{H}^+ \text{Bn} & + & \text{H}^+ \text{Bn} & \text{(eq 7.4)} \\
& & \text{25 (12%)} & & \text{26 (50%)} \\
\end{array}
\]

Therefore, in the case of allyl carbazate (27) an alternative route was developed for the synthesis of the monobenzyl hydrazine 29. In contrast with ethyl carbazate (24), allyl carbazate (27) is not commercially available and was synthesized by monoacylation of hydrazine hydrate.
Synthesis of cyclic α-hydrazone acid derivatives

with allyl chloroformate (eq 7.5). The highest yield was obtained with a large excess of hydrazine hydrate at -20 °C. Reaction did not take place at lower temperatures, whereas at higher temperatures the diacylated hydrazine was also obtained. The allyl carbazate (27) could be easily purified by distillation.

\[
\begin{align*}
\text{NH}_2 \text{NH}_2 \text{H}_2 \text{O} & \quad \text{a) allyl chloroformate (0.25 equiv), K}_2 \text{CO}_3 (0.6 \text{ equiv), EtOH, -20 °C → rt.} \\
\text{Alloc} & \quad \text{b) PhCHO (1.05 equiv), toluene, rt.} \\
\text{Alloc} & \quad \text{c) (i) NaBH}_3 \text{CN (1.0 equiv), pTSA (1.0 equiv), THF, rt (ii) 1 N NaOH, rt, 1 h.}
\end{align*}
\]

In order to obtain 29, allyl carbazate (27) was condensed with benzaldehyde to give the hydrazone 28, which was easily reduced with NaBH₃CN to give 29 as its hydrazine-cyanoborane complex. Hydrolysis of the complex with NaOH afforded the monobenzyl hydrazine 29, which was virtually pure according to ¹H NMR data.

7.3 SYNTHESIS OF THE PRECURSORS

The protected precursors 25 and 29 were alkylated under the ‘standard’ conditions mentioned in Chapter 4 (alkenyl halide (1.1 equiv), K₂CO₃ (1.2 equiv), LiI (cat), butanone, acetone or ethanol, reflux). The results of these alkylations are summarized in Table 7.1. In general, reasonable to good yields were obtained for the activated alkenyl halides. The less activated butenyl bromide gave rise to a lower yield (entry 9).

The precursor 39 (entry 14) was alkylated with the corresponding iodide, that was prepared from the alcohol via the mesylate. Under refluxing conditions, the propargylsilane was desilylated to give the allene 36 (entry 10) in a rather low yield. At room temperature however, the desired propargylsilane 39 was formed in a fair yield (entry 14).

The (E)-vinylsilane 40 (entry 15) was obtained upon alkylation of 29 with the bromide 76 (Chart 7.2). This bromide was prepared by a stereoselective reduction of 3-(trimethylsilyl)-
2-propynol (74) with Red-Al\textsuperscript{20} and subsequent bromination with PBr\textsubscript{3}.\textsuperscript{21} The vinylsilanes 41 (entry 17) were obtained as a 1:9:1 mixture of (Z)- and (E)-isomers after alkylation with the (E)/(Z)-mixture of the bromides 78. Partial hydrogenation of 3-(trimethylsilyl)-2-propynol (74) to 77,\textsuperscript{22} followed by bromination with PBr\textsubscript{3}\textsuperscript{21} afforded a 2.5:1 (Z)/(E)-mixture of 78, though this sequence was reported to proceed stereospecifically.\textsuperscript{22} The dioxeneone 42 (entry 18) was obtained upon treatment of 29 with chloride 79.\textsuperscript{23} Introduction of the dioxeneone residue proved to be a difficult reaction. Slight variation of the temperature and reaction time led to dramatic changes in the yield of the reaction.

Introduction of the glyoxylate moiety was performed by stirring the alkylated product in the presence of anhydrous methyl glyoxylate.\textsuperscript{24} The ease of condensation with the glyoxylate proved to be strongly dependent on the steric bulk of the alkyl group. For example, the allyl precursors 30 and 31 (Table 7.2, entries 1 and 2) reacted within 2 h to give the desired products, while for the benzyl and dioxeneone precursors 37 and 42 (entries 11 and 18) longer reaction times were required (up to 40 h). Because polymerization of unreacted methyl glyoxylate was a major side reaction, freshly distilled methyl glyoxylate had to be added after 18 h if the reaction was not completed. In some cases, large amounts (ca. 20 equiv) of methyl glyoxylate were used, so that purification by flash chromatography of the intermediate hydroxy compound was necessary. Acetylation with acetic anhydride and a catalytic amount of DMAP in pyridine led to the cyclization precursors 43-55 in good yields as summarized in Table 7.1.

7.4 CYCLIZATION REACTIONS

The cyclization reactions were carried out under ‘standard’ conditions with the Lewis acids TiCl\textsubscript{4} (2 equiv, -78 °C → rt), SnCl\textsubscript{4} (2 equiv, -78 °C → rt), Et\textsubscript{2}AlCl (2-4 equiv, -78 °C → rt), and BF\textsubscript{3}OEt\textsubscript{2} (2-6 equiv, 0 °C → rt) and the protic acid HCOOH. In contrast with the cyclizations reported in Chapters 2, 4 and 6, use of SnCl\textsubscript{4} afforded better results than TiCl\textsubscript{4}. The Lewis acid Et\textsubscript{2}AlCl was also successfully applied in some cyclization reactions. The results are shown in Table 7.2.

Cyclization of the allyl precursors 43 and 44 (entries 1 and 2) led to the unexpected formation of the five-membered rings 56 and 57 with the trans-stereoisomers as the main products. These products cannot arise from a normal 5-exo type cyclization, because the chloromethyl substituent would then be at the 4-position. A possible explanation for the formation of 43 and 44 is detailed in Scheme 7.3. Presumably, cyclization initially gives rise to the formation of the secondary carbocation 80, which is then trapped by the relatively nucleophilic amine nitrogen atom to give the aziridinium intermediate 81. Attack of chloride gives ring opening of the aziridinium moiety, thus leading to the trans-azaproline derivative 57.

In similar N-acyliminium cyclizations,\textsuperscript{15} the iminium ion is formed at -78 °C and stabilized as a dioxy carbene ion by the carbamate function (compare 82). Quenching with saturated aqueous NaHCO\textsubscript{3} at -78 °C then gives the corresponding hydroxy compound.

150
### Table 7.1. Synthesis of cyclic α-hydrazino acids.

<table>
<thead>
<tr>
<th>entry</th>
<th>alkylation product (yield)</th>
<th>glyoxylate adduct (yield)</th>
<th>acid</th>
<th>cyclization products (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>R = Et (93%)</td>
<td>Et (83%)</td>
<td>TiCl₄</td>
<td>56 R = Et (70%) c/tr 1:5</td>
</tr>
<tr>
<td>2</td>
<td>R = Allyl (89%)</td>
<td>Allyl(91%)</td>
<td>SnCl₄</td>
<td>57 R = Allyl (75%) c/tr 1:5</td>
</tr>
<tr>
<td>3</td>
<td>32 (78%)</td>
<td>Alloc</td>
<td>SnCl₄</td>
<td>58 X = Cl (32%) trans</td>
</tr>
<tr>
<td>4</td>
<td>33 (66%)</td>
<td>Alloc</td>
<td>Et₂AlCl</td>
<td>58 (27%) c/tr 1:1.8</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>Alloc</td>
<td>HCOOH</td>
<td>60 X = OCHO (68%) trans</td>
</tr>
<tr>
<td>6</td>
<td>34 (73%) E/Z 3:1</td>
<td>Alloc</td>
<td>SnCl₄</td>
<td>63 (56%) 5:1 mixture of isomers</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>Alloc</td>
<td>HCOOH</td>
<td>62 X = OCHO (66%)</td>
</tr>
<tr>
<td>8</td>
<td>35 (39%)</td>
<td>Alloc</td>
<td>SnCl₄</td>
<td>64 (65%) 1:1 mixture of isomers</td>
</tr>
<tr>
<td>9</td>
<td>36 (23%)</td>
<td>Alloc</td>
<td>TiCl₄</td>
<td>65 (45%) 1:2:1 mixture of isomers</td>
</tr>
</tbody>
</table>
Table 7.1. Continued.

<table>
<thead>
<tr>
<th>entry</th>
<th>alkylation product (yield)</th>
<th>glyoxylate adduct (yield)</th>
<th>acid</th>
<th>cyclization products (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>11</td>
<td>$\text{Bn}^+\text{Alloc}^-\text{NH}$</td>
<td>$\text{Bn}^+\text{Alloc}^-\text{NH}$</td>
<td>$\text{SnCl}_4$</td>
<td>66 (91%)</td>
</tr>
<tr>
<td>12</td>
<td>38 (58%)</td>
<td>51 (79%)</td>
<td>Et$_2$AlCl</td>
<td>67 (83%)</td>
</tr>
<tr>
<td>13</td>
<td>$\text{Bn}^+\text{Alloc}^-\text{NH}$</td>
<td>$\text{Bn}^+\text{Alloc}^-\text{NH}$</td>
<td>CF$_3$COOH</td>
<td>68 (70%)</td>
</tr>
<tr>
<td>14</td>
<td>39 (81%)</td>
<td>52 (82%)</td>
<td>BF$_3$-OEt$_2$</td>
<td>69 (30%)</td>
</tr>
<tr>
<td>15</td>
<td>40 (88%)</td>
<td>53 (74%)</td>
<td>BF$_3$-OEt$_2$</td>
<td>70 (23%) X = OAc</td>
</tr>
<tr>
<td>16</td>
<td>$\text{Bn}^+\text{Alloc}^-\text{NH}$</td>
<td>$\text{Bn}^+\text{Alloc}^-\text{NH}$</td>
<td>SnCl$_4$</td>
<td>71 (68%) X = Cl</td>
</tr>
<tr>
<td>17</td>
<td>41 (52%) E/Z 1:1.9</td>
<td>54 (79%) E/Z 1:1.2</td>
<td>SnCl$_4$</td>
<td>72 (50%)</td>
</tr>
<tr>
<td>18</td>
<td>42 (53%)</td>
<td>55 (66%)</td>
<td>CF$_3$SO$_2$SiMe$_3$</td>
<td>73 (48%)</td>
</tr>
</tbody>
</table>

a) The (E)/(Z) ratio could not be determined from the $^1$H NMR spectrum. b) Yield in one step from allyl carbazate (27).
Such a sequence might block the rearrangement and directly give the precursor 83 for the piperazic acid 1. However, when the cyclization reaction of 44 was quenched with saturated aqueous NaHCO₃ at -78 or at -30 °C, only starting material was recovered. Apparently, formation of the N-acylhydrazonium ion is more difficult than of its iminium analog. Reaction only took place at -20 °C, but quenching after stirring for 30 min at this temperature afforded a mixture of starting material and the rearranged products 57. This means that as soon as the intermediate cationic six-membered ring 80 is formed, stabilization via the aziridinium intermediate 81 takes place so that stabilization via the dioxycarbenium ion 82 does not occur.

Formation of the trans-five-membered ring was confirmed by reduction of the trans-cyclization product 57 with n-Bu₂SnH which led to 91 (Chart 7.3) clearly showing the characteristic doublet of the methyl substituent in the ¹H NMR spectrum. The structure was proven by an X-ray crystallographic analysis of the deprotected product 121 (see: Section 7.5). The formation of the cis-five-membered ring product 57 was concluded by comparison of the ¹³C NMR data of the cis- and trans-isomers of 57.

Recently, the intermediacy of an aziridinium intermediate in ring contractions has been reported in the synthesis of derivatives of azasteroids. The chloride 84 (eq 7.6) rearranges via the cationic intermediate 85 to the ring-contracted product 86.

A comparable mechanism in the case of the methallyl substituent 45 (entries 3 to 5) leads to mixtures of five- and six-membered rings. The more stable tertiary carbocation 87 (Scheme 7.4) is less prone to be stabilized by the nitrogen atom and thus gives a considerable amount of the six-membered ring 59. As attack of chloride will occur from the less hindered equatorial
side, the product will have the \textit{trans}-configuration. This stereochemistry was assigned by using NOE difference $^1$H NMR techniques on 59. Irradiation of the methyl function showed an enhancement of the signal of one of the H6 protons and of the broad signal of both H4 protons. The fact that the signal of only one of the H6 protons was enhanced leads to the conclusion that the methyl group is in the axial position. Consistent with the proposed conformation of the intermediate hydrazonium species, the ester function is also expected to be axially oriented.

The formation of the five-membered rings 58 was proven by reduction with \textit{n}-\textit{Bu}_3\text{SnH} to 92 (Chart 7.3). The relative configuration of \textit{trans}-58 was secured by NOE difference $^1$H NMR techniques. Irradiation of the methylene group adjacent to the chlorine atom showed an enhancement of the $\alpha$-methine proton, whereas irradiation of the methyl function did not. Remarkably, the reaction proceeded less stereoselectively when Et\textsubscript{2}AlCl was used as a Lewis acid so that mixtures of \textit{cis}- and \textit{trans}-products were obtained. When formic acid was used for the cyclization (entry 5), only the \textit{trans} six-membered ring 60 could be found. The tertiary carbocation 87 probably gives a faster reaction with formate as a result of the large excess of the nucleophile so that ring contraction does not take place.

Cyclization of the prenyl precursor 46 (entries 6 and 7) afforded the expected five-membered rings 61 and 62 with a \textit{trans}-relationship between both substituents. Surprisingly, the crotyl precursor 47 (entry 8) also gave the \textit{trans} five-membered ring product 63 as a single product.
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The trans-relationship between the substituents can be explained by assuming that the chair-like conformation 47-C of the precursor (eq 7.7) will lead to a more favorable transition state than the sterically hindered boat-like conformation 47-B. The preference for the formation of a five-membered ring is remarkable, because generally six-membered rings are obtained. For example, the comparable N-acyliminium ion precursors 90 led to exclusive formation of six-membered rings.15b Reduction of the cyclization product 63 with n-Bu3SnH to 93 confirmed the formation of the five-membered ring, clearly showing the signals of the ethyl substituent in the 1H NMR spectrum. These signals would be absent in the case of a six-membered ring. The trans-orientation was confirmed by NOE difference 1H NMR techniques. Irradiation of the methyl substituent of 63 showed an enhancement of the signal of the α-methylene proton.

Chart 7.3

![Chart 7.3](image)

Additional evidence for the preference for the formation of five-membered rings was obtained upon cyclization of the allene precursor 49 (entry 10). After treatment with TiCl4, the five-membered rings 65 were obtained as mixture of (E)/(Z)-isomers that could not be separated by flash chromatography.

![Chart 7.3](image)

Eq 7.8 shows a mechanism that accounts for the formation of 65. Initially, cyclization takes place to afford the vinylic cation 94. This intermediate rearranges via a 1,2-H shift to the more stable tertiary allylic cation 95, which is trapped by the nucleophile to afford 65.

The seven-membered ring 64 (entry 9) was obtained upon cyclization of the butenyl precursor 48. Although in none of the reactions mentioned in Table 7.1, cyclization of the benzyl function was observed as a side reaction, cyclization of the dibenzyl precursor 50 (entry 11) took place smoothly to give 66 in excellent yield. This is remarkable and might be partly explained by the difference in nucleophilicity with other substituents, but also by the strong preference for the formation of five-membered rings. Another reason that the side reaction did not occur might be that the molecule is likely to adopt a conformation in which the relatively large benzyl function is moved away from the glyoxylate moiety and thus will be less available for
cyclization. If cyclization takes place, ring contraction is hindered as a result of the fast formation of the aromatic system.

An additional way of blocking the ring contraction was observed upon cyclization of the allylsilane 51 (entry 12). Treatment with Et₂AlCl initially led to the silicon stabilized carbocation 96 (eq 7.9) which gave a fast elimination to the exocyclic double bond. An indication that formation of six-membered rings in such systems is a relatively slow process, is seen in entry 13. Treatment of the allylsilane precursor 51 with protic acid afforded 68 as a single product, which is explained by protodesilylation of 51 to the methallyl precursor 45 (eq 7.9) followed by cyclization to the expected six-membered ring 68 (treatment of 51 with HCOOH gave the corresponding formate 60 in 58% yield).

In an analogous way, the propargylsilane 52 (entry 14) was treated with BF₃·OEt₂ to give the allene 69 in a rather poor yield. Probably, the use of SnCl₄ or Et₂AlCl would have given a better result.

A striking difference was observed between cyclization of the (E)- and (Z)-vinylsilanes 53 and 54, respectively (entries 15 to 17). The chair-like transition state conformations of both starting materials are visualized in Scheme 7.5. The (E)-vinylsilane 53 will react via conformation 97 to the cyclic cationic intermediate 98 in which the trimethylsilyl group occupies the equatorial position.

Scheme 7.5
Because the \(\beta\)-C-Si bond is not oriented coplanar with respect to the vacant \(p\)-orbital, stabilization of the positive charge by the silicon atom and subsequent elimination is not likely to take place, thus leading to a ring contraction via the aziridinium intermediate 99. Attack of a nucleophile (which is the acetate in the BF\(_3\)-OEt\(_2\) cyclization) affords the final products 70 and 71. The stereochemistry of both products was confirmed by subjecting 71 to NOE difference \(^1\)H NMR techniques, showing an enhancement of only the \(\alpha\)-methine proton upon irradiation of the proton adjacent to the silicon atom.

Cyclization of the (Z)-precursor 54 will occur via conformation 100 and cation 101 in which the trimethylsilyl group is axially oriented. In this orientation, maximal \(\sigma-\pi\) hyperconjugative stabilization of the developing positive charge is possible, followed by fast elimination to the unsaturated six-membered ring 72, thereby excluding the formation of the aziridinium intermediate. Considering these mechanistic details, starting from the precursor 54, that was obtained as a 1:1.2 mixture of (E)- and (Z)-isomers, the corrected yields for 71 and 72 (entry 17) are 70% and 90%, respectively. Comparing the yield of the five-membered ring product 71, with the yield of 71 from the pure (E)-precursor 53 (entry 16), it is evident that the (Z)-isomer leads to exclusive formation of the six-membered ring 72. These observations are in full accord with results published by Overman and co-workers, who reported the (Z)-vinylsilane to be at least 7000 times more reactive than its (E)-analog in iminium ion cyclizations.

Cyclization of the dioxene precursor 55 (entry 18) proved to be a difficult reaction. Various Lewis acids were attempted but did not give satisfactory results. Strong Lewis acids led to decomposition of the dioxene part, whereas BF\(_3\)-OEt\(_2\) afforded only starting material. Reaction with HCOOH at higher temperatures led to opening of the dioxene residue prior to cyclization, while at room temperature only starting material was recovered. A reasonable result was obtained upon treatment of 55 with CF\(_3\)SO\(_3\)SiMe\(_3\) (4 equiv, CH\(_2\)Cl\(_2\), -78 °C \(\rightarrow\) rt, 18 h) affording the bicyclic product 73 in a satisfactory yield.

Formation of the six-membered ring is most likely the result of the mesomeric stabilization of the positive charge in the cationic intermediate 102 by the adjacent oxygen atom (103), thus precluding aziridinium stabilization by the nitrogen atom. Abstraction of the acidic proton will lead to the protected \(\beta\)-ketoester 73.
7.5 DEPROTECTION OF THE CYCLIZATION PRODUCTS

In line with deprotections of similar protected piperolic acid derivatives, \[^{15}\] \(56\) was first debenzyalted by catalytic hydrogenation (H\(_2\), Pd/C, MeOH) to the hydrazine \(104\), and then treated with 2 N HCl to hydrolyze the carbamate and methyl ester. This sequence is preferred, because the hydrazine is less prone to oxidation as long as the electron-withdrawing carbamate function is present in the molecule. Treatment with 2 N HCl unfortunately did not lead to the HCl-salt \(105\).

After stirring for two hours at 100 °C, the carbamate function was still present in the molecule according to \(^1\)H NMR data. Longer reaction times or higher temperatures (sealed tube) only led to decomposition of the starting material.

Therefore, the Alloc group was introduced, which can be converted into the easily removable tert-butoxycarbonyl group by the transprotection reaction described in Chapter 3. The intended sequence for the deprotection reaction is then as depicted in eq 7.11. First, a transprotection reaction is carried out (the nitrogen still has to be protected) to compounds \(107\), followed by a debenzylation to the hydrazines \(108\). Hydrolysis under acidic conditions should finally lead to the HCl-salts \(109\).

The results of several transprotections are summarized in Table 7.2. The desired products were not obtained in all cases. The transprotection of the five-membered rings to the desired products usually proceeded in reasonable yields (see entries 1, 2 and 5), but in some cases oxidation products were obtained in excess (entries 3 and 4). In the latter cases, deprotection of the Alloc group took place, but reprotection with Boc\(_2\)O did not occur. This was indicated by the initial isolation of the corresponding NH compounds that were readily oxidized upon standing in air to the products \(113\) and \(114\).
Table 7.2. Deprotection reactions.

<table>
<thead>
<tr>
<th>entry</th>
<th>cyclization</th>
<th>transprotection product(s) (yield)</th>
<th>debenzylation product (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>57 R = H</td>
<td>110 R = H (77%)</td>
<td>121 R = H (90%)</td>
</tr>
<tr>
<td>2</td>
<td>71 R = SiMe₃</td>
<td>111 R = SiMe₃ (64%)</td>
<td>122 R = SiMe₃ (81%)</td>
</tr>
<tr>
<td>3</td>
<td>58</td>
<td>112 (12%)</td>
<td>113 (63%)</td>
</tr>
<tr>
<td>4</td>
<td>61</td>
<td>114 (65%)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>63</td>
<td>115 (54%)</td>
<td>116 (64%)</td>
</tr>
<tr>
<td>6</td>
<td>59</td>
<td>117 (78%)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>67</td>
<td>118 (56%)</td>
<td>119 (22%)</td>
</tr>
<tr>
<td>8</td>
<td>66</td>
<td>120 (64%)</td>
<td>123 (65%)</td>
</tr>
<tr>
<td>9</td>
<td>64</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Chapter 7

Apparently, the reaction with Boc₂O is very sensitive to steric hindrance caused by the benzyl substituent and the methyl ester. This is reflected in the outcome of entries 3 and 4, in which the presence of one additional methyl group (61) hinders the reaction with Boc₂O, thus leading to the oxidation product 114.

With the six-membered rings, transprotection proved to be almost impossible. Both 59 and 67 (entries 6 and 7) were converted into the corresponding deprotected hydrazines, which were oxidized to 116 and 117. Only the benzyl derived cyclization product 66 (entry 8) afforded a reasonable amount of the transprotected product 118.

A possible explanation for this observation is detailed in eq 7.12. Pd(0)-catalyzed cleavage of the Alloc group in the presence of n-Bu₃SnH will first lead to the tin carbamate 124. If this tin carbamate is cleaved by an electrophile before reaction with Boc₂O occurs, immediate ring inversion to the thermodynamically more stable six-membered ring 126 will take place. This inversion is also observed after cleavage of the carbamate group of pipolic acid derivatives and is caused by the relief of pseudo-allylic 1,3-strain. Once the ring inversion has taken place, addition of a tert-butoxycarbonyl group is no longer possible for steric reasons. Even attempts to introduce smaller electrophiles like an acetyl function failed.

The seven-membered ring 64 (entry 9) afforded the transprotected product 120 in a reasonable yield. Probably, the methyl ester causes less steric strain in a larger, more flexible ring.

Analogous to the ethoxy derivative 56, debenzylation of 110, 111, and 120 provided a good yield of the corresponding hydrazines (entries 1, 2 and 9). The formation of the five-membered ring 121 and the trans-relationship of the substituents was secured by an X-ray crystallographic analysis of the product 121 as depicted in Fig 7.1. The amide nitrogen atom is almost completely planar, whereas the amine nitrogen atom is pyramidal.

Fig 7.1. Chem3D view of the deprotected product 121.
The replacement of the ethoxycarbonyl function by a tert-butoxycarbonyl function allows a smooth deprotection to the HCl-salt 127 by treatment of 121 with 2 M HCl at 60 °C for 2 h (eq 7.13).

\[
\begin{array}{c}
\text{HN} \quad \text{tBoc} \quad \text{Ph}_2\text{Cl} \\
\text{CO}_2\text{Me} \\
121 \\
\end{array} \quad \xrightarrow{2 \text{ M HCl}} \quad \begin{array}{c}
\text{HN} \\
\text{Cl} \quad \text{H}_3\text{N} \\
\text{CO}_2\text{Me} \\
127 \\
\end{array}
\]

(eq 7.13)

\[127 (82\%)\]

7.6 SYNTHESIS OF PROTECTED 5-HYDROXY PIPERAZIC ACID

As cyclization of the allyl precursors 43 and 44 led to five- instead of six-membered rings, a different method had to be chosen for the synthesis of the piperazic acids 1 and 2. A possibility is to use the (Z)-vinylsilane 54, which affords an unsaturated six-membered ring that might be further functionalized to the desired piperazic acid. An alternative is to start from the ketone 128 (eq 7.14) which might be obtained either from the allylsilane-derived cyclization product 67 upon ozonolysis of the double bond or from the dioxenone cyclization product 73.

Because several experiments to cleave the methylene function of 67 with ozone (without affecting the allyloxy carbonyl function) were unsuccessful, some further reactions were performed with 73.

\[
\begin{array}{c}
\text{HN} \\
\text{OH} \\
\text{CO}_2\text{H} \\
1 \\
\end{array} \quad \xrightarrow{\text{eq 7.14}} \quad \begin{array}{c}
\text{Bn} \quad \text{N} \\
\text{Alloc} \\
\text{CO}_2\text{Me} \\
128 \\
\end{array} \quad \xrightarrow{\text{eq 7.14}} \quad \begin{array}{c}
\text{Bn} \quad \text{N} \\
\text{Alloc} \\
\text{MeO}_2\text{C} \\
129 \\
\end{array}
\]

(eq 7.14)

It was already established in Chapter 5, that the dioxenone residue can be cleaved at 170 °C and that the intermediate acylketene can be trapped by a nucleophile. Thus, treatment of the product 73 with water under such circumstances led to the β-ketoacid 129 (eq 7.15), which was immediately decarboxylated to yield the γ-ketoester 128 in a fair overall yield.

\[
\begin{array}{c}
\text{Bn} \\
\text{N} \\
\text{Alloc} \\
\text{MeO}_2\text{C} \\
73 \\
\end{array} \quad \xrightarrow{\text{a}} \quad \begin{array}{c}
\text{Bn} \\
\text{N} \\
\text{Alloc} \\
\text{CO}_2\text{H} \\
129 \\
\end{array} \quad \xrightarrow{\text{b}} \quad \begin{array}{c}
\text{Bn} \\
\text{N} \\
\text{Alloc} \\
\text{CO}_2\text{Me} \\
128 \\
\end{array}
\]

(eq 7.15)

\[\text{128 (74\%)} \quad \text{129 (95\%)} \quad \text{130 (95\%)} \quad \text{c/lr 6:3:1}\]

a) \(\text{H}_2\text{O} (10 \text{ equiv}), \text{xylene, 170 °C, sealed tube, 10 min.}\) b) \(\text{NaBH}_4 (1.1 \text{ equiv}), -10 °\text{C, MeOH.}\)
This ketoester 128 could be reduced to afford the corresponding alcohols 130. Reduction with NaBH₄ (-10 °C, MeOH) led to a mixture of cis- and trans-isomers of 130 in a ratio of approximately 6:1. Attack of the hydride is more likely to take place from the less hindered equatorial side, as the axial side is shielded by the ester function.

\[
\begin{align*}
\text{trans-130} & \quad \text{cis-130} \\
\text{131 (57%)} & \quad \text{132 (33%)}
\end{align*}
\]

An attempt to convert cis-130 into the lactone 131 with sodium methoxide led to complete formation of trans-130 (eq 7.16). Apparently, under these circumstances deprotonation adjacent to the ester function gave isomerization to the thermodynamically more stable trans-product before lactonization could take place. On the other hand, under acidic conditions, isomerization could not occur so that the lactone 131 was obtained.

The formation of the lactone has three advantages: (i) the cis-relationship between the ester and the hydroxy function is fixed; (ii) the hydroxy group is adequately protected for the transprotection reaction; (iii) inversion of the six-membered ring is inhibited so that the tin carbamate should readily react with Boc₂O. In accordance with these theories, transprotection of the lactone 131 led (in moderate yield) to the fully protected hydroxypiperazic acid 132.

7.7 NMR DATA

The structures assigned to the compounds described in this Chapter, are primarily based on ¹H, ¹³C and ¹H NMR NOE difference data. In several cases, crucial information was obtained upon reduction of some cyclization products with n-B₃SnH or by an X-ray analysis of the deprotected product 121. As already described in Section 2.9, the ¹H NMR spectra of the tetrasubstituted hydrazines 43-55 show rotamers and broad signals as a result of hindered rotation around the N-N and the amide bond. The latter effect is also observed in ¹H and ¹³C NMR spectra of some of the cyclization products. Generally, the ¹H NMR spectra of five-membered rings show sharp signals, while the signals of six-membered rings are considerably broadened.

Two representative examples are shown in Fig 7.2 and 7.3. The former shows the ¹H NMR spectrum of the six-membered ring 72, obtained upon cyclization of the (Z)-vinylsilane precursor 54. The H6 protons show a broad AB-system, the α-methylene proton (H3) shows a broad singlet at 5.10 ppm and no distinction can be made between the olefinic protons.
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Fig 7.2. 
$^1$H NMR spectrum (200 MHz) of 72 at 23 °C in CDCl$_3$.

Fig 7.3. 
$^1$H NMR spectrum (200 MHz) of 71 at 23 °C in CDCl$_3$.
In some other cases, spectra were taken at a higher temperature but this did not lead to a significant improvement of the spectra.

A completely different spectrum was obtained from the (E)-vinylsilane-derived cyclization product 72 as depicted in Fig 7.3. All protons display sharp signals. The α-methylene proton (H3) at 5.01 ppm shows a doublet ($3J = 9.0$ Hz) and the H4 proton a triplet (2.00 ppm, $3J = 9.1$ Hz) as a result of identical cis-and trans-coupling constants. The methylene protons adjacent to the chlorine and the benzylic protons show sharp AB-systems. Furthermore, the protons of the Alloc group can be easily recognized.

7.8 CONCLUSIONS

It is evident that a large variety of cyclic α-hydrazino acid derivatives can be efficiently synthesized via the method described in this Chapter. Several conclusions can be drawn from the outcome of the cyclization reactions.

There is a strong preference for the formation of five-membered rings which is illustrated by the crotyl and allene precursor that both produced the corresponding five- instead of six-membered rings.

Furthermore, if a six-membered ring is formed during the cyclization, stabilization of the cationic intermediate by the amine nitrogen atom may take place, leading to a five-membered ring via an aziridinium intermediate. This ring contraction can be inhibited by stabilization of the developing positive charge by a hetero- or β-silicon atom followed by a fast elimination process.

A remarkable difference is observed in reactivity between the benzyl group and the introduced nucleophiles; Cyclization of the benzyl group takes place only if no other nucleophile is present in the molecule. In contrast with cyclizations of other types of hydrazonium ions, $\text{SnCl}_4$ and in some cases $\text{Et}_2\text{AlCl}$ afforded the best results.

The transprotection reactions did not give satisfactory results. The lack of reactivity of the activated carbonyl compounds is probably due to the steric hindrance caused by the α-methoxycarbonyl function.

Although it appeared to be difficult to obtain a suitable precursor for the naturally occurring piperazic acids, application of the dioxenone moiety eventually leads to protected 5-hydroxy-piperazic acid.

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7.6 EXPERIMENTAL SECTION

General information. For experimental details, see: Section 2.11.

1-Benzyl-2-hydrazinecarboxylic acid ethyl ester (25). A solution of ethyl carbazate (2.00 g, 19.2 mmol), benzyl chloride (2.55 g, 20.2 mmol) and Et₃N (2.80 mL, 20.2 mmol) in EtOH was refluxed for 18 h. After concentration in vacuo, the residue was taken up in water (100 mL) and extracted with CH₂Cl₂ (3 x 100 mL). The combined organic layers were dried (MgSO₄), filtered, concentrated in vacuo and chromatographed (ethyl acetate/hexane 1:1) to afford 1,1-dibenzyl-2-hydrazinecarboxylic acid ethyl ester (26) (2.73 g, 9.60 mmol, 50%) as a colorless oil, Rf 0.60 and 25 (445 mg, 0.23 mmol, 12%) as a colorless oil, Rf 0.35. 25: IR ν 3440, 3340, 1710, 690; ¹H NMR (200 MHz) δ 1.26 (t, J = 7.1 Hz, 3 H, CH₂CH₃), 4.00 (s, 2 H, NCH₂), 4.16 (q, J = 7.1 Hz, 3 H, CH₂CH₃ and NH), 6.26 (br s, 1 H, NH), 7.30-7.33 (m, 5 H, ArH). 26: IR ν 3430, 3340, 1710, 1625, 995, 935; ¹H NMR (200 MHz) δ 3.66 (br s, 2 H, OCH₂), 5.15-5.31 (m, 2 H, =CH₂), 5.77-5.97 (m, 1 H, =CH), 6.50-6.70 (m, 5 H, ArH).

Hydrazinecarboxylic acid allyl ester (27). To a solution of hydrazine hydrate (128 mL, 2.64 mmol) in EtOH (1.3 L) was added dropwise in 1.5 h allyl chloroformate (70.0 mL, 0.66 mmol) while the temperature inside the flask was kept around -20 °C. The mixture was allowed to warm to rt, stirred at ambient temperature for 1 h and after the addition of K₂CO₃ (91.2 g, 0.66 mol) it was stirred for an additional hour. After filtration and concentration in vacuo, the residue was distilled to afford 27 (59.2 g, 0.51 mol, 77%) as a colorless oil, bp 82 °C (0.3 mm), Rf 0.35 (ethyl acetate/hexane 1:1). IR ν 3460, 3350, 1710, 1625, 995, 935; ¹H NMR (200 MHz) δ 4.64 (d, J = 5.4 Hz, 2 H, OCH₂), 5.24-5.41 (m, 2 H, =CH₂), 5.90-6.06 (m, 1 H, =CH), 7.24 (s, 1 H, ArH), 7.34 (m, 2 H, ArH), 7.68 (m, 2 H, ArH), 7.86 (s, 1 H, NH), 8.01 (s, 1 H, N=CH). To a solution of pTSA (23.6 g, 124 mmol) in THF (125 mL) was added dropwise in 2.5 h a solution of the hydrazone 28 (25.3 g, 124 mmol) and NaBH₄ (9.18 g, 124 mmol) in THF (300 mL) and the mixture was stirred for one additional h at rt. The resulting mixture was diluted with ethyl acetate (600 mL) and extracted subsequently with aq said NaCl (600 mL), aq said NaHCO₃ (600 mL) and aq said NaCl (600 mL). The organic layer was dried (MgSO₄), filtered, concentrated in vacuo, taken up in 1 N NaOH (250 mL), stirred at ambient temperature for 1.5 h, neutralized with 2 M HCl and extracted with CH₂Cl₂ (3 x 100 mL). The combined organic layers were dried (MgSO₄), filtered and concentrated in vacuo to afford 29 (25.3 g, 123 mmol, 99%) as a colorless oil, Rf 0.45 (ethyl acetate/hexane 4:1). IR ν 3440, 3340, 1710, 990, 930, 690; ¹H NMR (200 MHz) δ 4.00 (s, 2 H, CH₂Ph), 4.25 (br s, 1 H, NH), 4.61 (d, J = 5.5 Hz, 2 H, OCH₂), 5.20-5.35 (m, 2 H, =CH₂), 5.82-6.01 (m, 1 H, =CH), 6.44 (br s, 1 H, NH), 7.26-7.36 (m, 5 H, ArH).

General procedure A for the alkylation reactions. To a solution of 25 or 29 in 2-butanone, EtOH or acetone were added the alkylation agent (1.1-2 equiv), K₂CO₃ (1.1-2 equiv) and a catalytic amount of LIL. After heating at reflux temperature for 18 h, the mixture was concentrated in vacuo, taken up in H₂O and extracted with...
The combined organic layers were dried (MgSO₄), filtered, concentrated in vacuo and chromatographed to afford the pure alkylated hydrazine.

1-Benzyl-1-(2-propenyl)-2-hydrazinecarboxylic acid ethyl ester (30). According to the general procedure A, 25 (1.20 g, 6.19 mmol) was alkylated by using allyl bromide (1.50 g, 12.4 mmol) and K₂CO₃ (1.71 g, 12.4 mmol) in EtOH (100 mL). Work-up and flash chromatography (ethyl acetate/hexane 1:1.8) afforded 30 (1.34 g, 5.73 mmol, 93%) as a colorless oil, \( R_f \) 0.40. IR ν 3435, 3320, 1730, 1700, 920. \(^1\)H NMR (200 MHz) δ 1.18 (t, \( J = 7.0 \) Hz, 3 H, CH₂), 3.40-3.50 (m, 2 H, NCH₂), 3.97 (br s, 2 H, CH₂Ph), 4.24 (q, \( J = 7.0 \) Hz, 2 H, CH₂CH₃), 5.17-5.26 (m, 2 H, =CH₂), 5.66 (br s, 1 H, NH), 5.83-6.00 (m, 1 H, =CH), 7.29-7.33 (m, 5 H, ArH).

1-Benzyl-1-(2-propenyl)-2-hydrazinecarboxylic acid allyl ester (31). Following the general procedure A, 29 (3.00 g, 14.6 mmol) was alkylated by using allyl bromide (3.52 g, 29.1 mmol) and K₂CO₃ (2.00 g, 14.6 mmol) in EtOH (100 mL). Work-up and flash chromatography (ethyl acetate/hexane 1:4) afforded 31 (3.20 g, 13.0 mmol, 89%) as a white solid, mp 34-36.5 °C, \( R_f \) 0.30. IR ν 3430, 3330, 1720, 690; \(^1\)H NMR (200 MHz) 5 3.45 (br s, 2 H, NCH₂), 3.99 (br s, 2 H, CH₂Ph), 4.52 (d, \( J = 5.4 \) Hz, 2 H, OCH₂), 5.15-5.28 (m, 4 H, 2 x =CH₂), 5.76-6.03 (m, 3 H, 2 x =CH and NH), 7.30-7.35 (m, 5 H, ArH).

1-Benzyl-1-(2-methyl-2-propenyl)-2-hydrazinecarboxylic acid allyl ester (32). According to the general procedure A, 29 (10.0 g, 48.5 mmol) was alkylated by using 3-chloro-2-methyl-2-propene (5.28 mL, 53.4 mmol) and K₂CO₃ (7.38 g, 53.4 mmol) in EtOH (250 mL). Work-up and flash chromatography (ethyl acetate/hexane 1:4) afforded 32 (9.81 g, 37.7 mmol, 78%) as a light yellow oil, \( R_f \) 0.30. IR ν 3440, 3340, 1720, 695; \(^1\)H NMR (200 MHz) δ 1.83 (s, 3 H, CH₃), 3.41 (br s, 2 H, NCH₂), 4.02 (br s, 2 H, CH₂Ph), 4.53 (d, \( J = 5.2 \) Hz, 2 H, OCH₂), 4.90 (d, \( J = 5.6 \) Hz, 2 H, CH₂CH₃), 5.16-5.28 (m, 2 H, =CH₂CH₃), 5.76-6.03 (m, 3 H, 2 x =CH and NH), 7.26-7.38 (m, 5 H, ArH).

1-Benzyl-1-(3-methyl-2-butenyl)-2-hydrazinecarboxylic acid allyl ester (33). According to the general procedure A, 29 (7.04 g, 34.2 mmol) was alkylated by using 4-bromo-2-methyl-2-butene (5.60 g, 37.6 mmol) and K₂CO₃ (5.20 g, 37.6 mmol) in EtOH (300 mL). Work-up and flash chromatography (ethyl acetate/hexane 1:4) afforded 33 (2.89 g, 10.5 mmol, 66% (after correction)) as a light yellow oil, \( R_f \) 0.40. IR ν 3440, 3340, 1720, 695; \(^1\)H NMR (200 MHz) δ 1.64 (d, \( J = 6.4 \) Hz, 3 H, CH₃(E)), 1.70 (d, \( J = 5.0 \) Hz, 3 H, CH₃(Z)), 3.38 (br s, 2 H, CH₂Ph), 4.52 (d, \( J = 5.3 \) Hz, 2 H, OCH₂), 5.14-5.36 (m, 3 H, CH₂ and NCH₂CH₂), 5.75-5.95 (m, 2 H, =CH and NH), 7.23-7.34 (m, 5 H, ArH).

1-Benzyl-1-(3-butyl)-2-hydrazinecarboxylic acid allyl ester (34). According to the general procedure A, 29 (10.0 g, 48.5 mmol) was alkylated by using 4-bromo-2-methyl-2-buten (5.60 g, 37.6 mmol) and K₂CO₃ (5.20 g, 37.6 mmol) in EtOH (250 mL). Work-up and flash chromatography (ethyl acetate/hexane 1:4) afforded 34 (9.18 g, 35.3 mmol, 73%) as a light yellow oil, \( R_f \) 0.40. IR ν 3440, 3340, 1725, 690; \(^1\)H NMR (200 MHz) δ 1.83 (s, 3 H, CH₃), 1.74 (s, 3 H, CH₃), 3.45 (br s, 2 H, NCH₂), 3.97 (br s, 2 H, CH₂Ph), 4.52 (d, \( J = 5.3 \) Hz, 2 H, OCH₂), 5.14-5.36 (m, 3 H, CH₂ and NCH₂CH₂), 5.75-5.95 (m, 2 H, =CH and NH), 7.23-7.34 (m, 5 H, ArH).

1-Benzyl-1-(2-butyl)-2-hydrazinecarboxylic acid allyl ester (35). According to the general procedure A, 29 (2.91 g, 14.1 mmol) was alkylated by using 4-bromo-1-butene (2.10 g, 15.5 mmol) and K₂CO₃ (2.15 g, 15.5 mmol) in EtOH (150 mL). Work-up and flash chromatography (ethyl acetate/hexane 1:4) afforded
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35 (384 mg, 1.50 mmol, 39% (after correction)) as white crystals, mp 50-51 °C, Rf 0.45. IR ν 3440, 3340, 1740, 690; 1H NMR (200 MHz) δ 2.26-2.34 (m, 2 H, NCH₂), 2.70-2.95 (br s, 2 H, NCH₂), 3.80-4.15 (m, 2 H, C≡CH₂), 4.55 (d, J = 5.4 Hz, 2 H, OCH₂), 4.98-5.21 (m, 4 H, 2 × =CH₂), 5.55-5.95 (m, 3 H, 2 × =CH and NH), 7.26-7.35 (m, 5 H, ArH).

1-Benzyl-1-(ethenylidene)methyl)-2-hydrazinecarboxylic acid allyl ester (36). According to the general procedure A, 29 (2.32 g, 11.3 mmol) was alkylated by using 4-iodo-1-(trimethylsilyl)-2-butyne (4.09 g, 12.4 mmol) and K₂CO₃ (1.71 g, 12.4 mmol) in EtOH (100 mL). Work-up and flash chromatography (ethyl acetate/hexane 1:5) afforded 36 (670 mg, 2.60 mmol, 23%) as an orange oil, Rf 0.40. IR ν 3440, 3340, 1950, 1725, 690; ¹H NMR (200 MHz) δ 3.64 (br s, 2 H, NCH₂), 4.00 (br s, 2 H, C≡CH₂), 4.54 (d, J = 5.5 Hz, 2 H, OCH₂), 4.76 (dt, J = 6.5, 2.3 Hz, 2 H, C=CH₂), 5.16-5.28 (m, 3 H, CH=C≡CH₂ and C≡C=CH₂), 5.77-5.96 (m, 2 H, =CH and NH), 7.27-7.36 (m, 5 H, ArH).

1,1-Dibenzyl-2-hydrazinecarboxylic acid allyl ester (37). According to the general procedure A, 27 (15.0 g, 130 mmol) was alkylated by using benzyl chloride (29.7 mL, 260 mmol) and K₂CO₃ (36 g, 260 mmol) in EtOH (300 mL). Work-up and flash chromatography (ethyl acetate/hexane 1:4) afforded 37 (31.9 g, 110 mmol, 83%) as a white solid, mp 52-54 °C, Rf 0.45. IR ν 3440, 3340,1725,690; ¹H NMR (200 MHz) δ 3.96 (br s, 4 H, 2 × C≡CH₂), 4.49 (d, J = 5.5 Hz, 2 H, OCH₂), 5.12-5.19 (m, 2 H, =CH₂), 5.73-5.92 (m, 2 H, =CH and NH), 7.24-7.32 (m, 10 H, ArH); Anal. Caled. for C₁₈H₂₀N₂O₂: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.90; H, 6.75; N, 9.54.

1-Benzyl-1-[(2-(trimethylsilyl)methyl)-2-propenyl]-2-hydrazinecarboxylic acid allyl ester (38). According to the general procedure A, 29 (3.42 g, 16.6 mmol) was alkylated by using 2-(chloromethyl)-3-(trimethylsilyl)-1-propene (2.97 g, 18.3 mmol) and K₂CO₃ (2.52 g, 18.3 mmol) in 2-butanone (175 mL). Work-up and flash chromatography (ethyl acetate/hexane 1:4) afforded 38 (3.20 g, 9.60 mmol, 58%) as a colorless oil, Rf 0.55. IR ν 3440, 3340, 1950, 1725, 690; ¹H NMR (200 MHz) δ -0.04 (s, 9 H, (CH₃)₃Si), 1.69 (t, J = 2.4 Hz, 2 H, CH₂Si), 3.35 (br s, 2 H, NCH₂), 3.60 (t, J = 2.3 Hz, 2 H, C≡CH₂), 3.90 (s, 2 H, CH₂Ph), 4.03 (br s, 2 H, CH₂Ph), 4.53 (d, J = 5.2 Hz, 2 H, OCH₂), 4.68 (s, 1 H, C≡C=CH₂), 4.85 (s, 1 H, C=CH₂), 5.16-5.28 (m, 2 H, CH=C≡CH₂), 5.75-5.90 (m, 2 H, =CH and NH), 7.24-7.35 (m, 5 H, ArH).

1-Benzyl-1-[(4-(trimethylsilyl)-2-butyne)-2-hydrazinecarboxylic acid allyl ester (39). According to the general procedure A, 29 (1.40 g, 6.80 mmol) was alkylated by using 4-iodo-1-(trimethylsilyl)-2-butyne (1.88 g, 7.50 mmol) and K₂CO₃ (1.03 g, 7.50 mmol) in acetone (50 mL) by stirring at rt for 18 h. Work-up and flash chromatography (ethyl acetate/hexane 1:6) afforded 39 (3.0 g, 5.50 mmol, 81%) as a colorless oil, Rf 0.55. IR ν 3440, 3340, 1720, 1240, 850, 690; ¹H NMR (200 MHz) δ -0.04 (s, 9 H, (CH₃)₂Si), 1.69 (s, 2 H, CH₂Si), 3.35 (br s, 2 H, NCH₂), 3.60 (t, J = 2.3 Hz, 2 H, NCH₂), 3.90 (s, 2 H, CH₂Ph), 4.03 (br s, 2 H, CH₂Ph), 4.53 (d, J = 5.5 Hz, 2 H, OCH₂), 4.68 (s, 1 H, C≡C=CH₂), 4.85 (s, 1 H, C=CH₂), 5.16-5.28 (m, 2 H, CH=C≡CH₂), 5.75-5.90 (m, 2 H, =CH and NH), 7.24-7.35 (m, 5 H, ArH).

1-Benzyl-1-[(E)-3-(trimethylsilyl)-2-propenyl]-2-hydrazinecarboxylic acid allyl ester (40). According to the general procedure A, 29 (6.23 g, 30.2 mmol) was alkylated by using (E)-3-bromo-1-(trimethylsilyl)-1-propene (76) (4.09 g, 21.2 mmol) and K₂CO₃ (4.18 g, 30.2 mmol) in 2-butanone (250 mL). Work-up and flash chromatography (ethyl acetate/hexane 1:4) afforded 40 (5.93 g, 18.6 mmol, 88%) as a colorless oil, Rf 0.50. IR ν 3440, 3340, 1740, 1245, 835, 690; ¹H NMR (200 MHz) δ 0.06 (s, 9 H, (CH₃)₂Si), 3.48 (br s, 2 H, NCH₂), 3.98 (br s, 2 H, CH₂Ph), 4.52 (d, J = 5.0 Hz, 2 H, OCH₂), 5.15-5.27 (m, 2 H, =CH₂), 5.70-
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5.93 (m, 2 H, CH=CH₂, NH and CHSi), 6.12 (dt, J = 18.6, 5.8 Hz, 1 H, CH₂Ctf), 7.27-7.35 (m, 5 H, ArH).

1-Benzyl-1-[(Z)-3-(trimethylsilyl)-2-propenyl]-2-hydrazinecarboxylic acid ally ester (41).
According to the general procedure A, 29 (3.71 g, 18.0 mmol) was alkylated by using 3-bromo-1-(trimethylsilyl)-1-propene 78 (2.31 g, 12.0 mmol, (£)/(Z) 1:2.5) and K₂CO₃ (2.65 g, 19.2 mmol) in 2-butaneone (130 mL). Work-up and flash chromatography (ethyl acetate/hexane 1:4) afforded 41 (1.97 g, 6.19 mmol, 52%) as a colorless oil, (£)/(Z) 1:1.9, Rf 0.50. IR v 3440, 3340, 1740, 1245, 835, 690; *H NMR (250 MHz) δ 0.07 (s, 9 H, (CH₃)₃Si), 3.55 (br s, 2 H, NCH₂), 4.00 (br s, 2 H, CH₂Ph), 4.52 (d, J = 4.8 Hz, 2 H, OCH₂), 5.18-5.28 (m, 2 H, =CH₂), 5.75-5.88 (m, 2 H, C//=CH₂, NH and CHSi), 6.41 (dt, J = 14.3, 7.2 Hz, 1 H, CH₂Ctf), 7.27-7.35 (m, 5 H, ArH).

1-Benzyl-1-[(3,3»dimethyl-5-oxo-2,4-dioxo-6-enyl)methyl]-2-hydrazinecarboxylic acid ally 1 ester (42). According to the general procedure A, 29 (4.95 g, 24.0 mmol) was alkylated by using 6-(chloromethyl)-2,2-dimethyl-1,3-dioxo-4-one (79 (4.44 g, 25.2 mmol) and K₂CO₃ (3.48 g, 25.2 mmol) in acetone (250 mL) at 45 °C for 36 h. Work-up and flash chromatography (ethyl acetate/hexane 1:2) afforded 42 (4.36 g, 12.6 mmol, 55%) as a light yellow oil, Rf 0.40. IR v 3440, 3350, 1725, 1635, 690; *H NMR (200 MHz) δ 1.66 (s, 6 H, (CH₃)₂C), 3.66 (br s, 2 H, NCH₂), 4.09 (br s, 2 H, CH₂Ph), 4.52 (d, J = 4.1 Hz, 2 H, OCH₂), 5.17-5.27 (m, 2 H, =CH₂), 5.55 (s, 1 H, C=CH), 5.75-5.95 (m, 1 H, CH₂//=CH), 6.30 (br s, 1 H, NH), 7.31 (br s, 5 H, ArH); 13C NMR (50 MHz) δ 25.0 ((CH₃)₂C), 56.6 (CH₂Ph), 63.5 (NCH₂), 94.8 (C=CH), 106.8 (COO), 118.1 (CH=CH₂), 121.9, 128.6, 129.2 (ArH), 132.2 (CH=CH), 135.0 (ArC), 160.9, 167.0 (=C and C(O)).

General procedure B for the reactions with methyl glyoxylate. To a solution of the alkylated hydrazine in toluene was added at rt an excess of freshly distilled methyl glyoxylate. After complete reaction (according to TLC), the solution was concentrated in vacuo, The residue was taken up in pyridine and treated with an excess of acetic anhydride and a catalytic amount of DMAP. After being stirred at rt for 18 h, the dark brown solution was concentrated in vacuo and purified by flash chromatography to afford the pure product.

α-Acetoxy-1-benzyl-2-(ethoxycarbonyl)-1-(2-propenyl)-2-hydrazineacetic acid methyl ester (43). Following the general procedure B, a solution of 30 (1.34 g, 5.73 mmol) in toluene (40 mL) was reacted with methyl glyoxylate (2.00 g, 11.5 mmol) for 4 h and acetylated with Ac₂O (2.71 mL, 28.7 mmol) in pyridine (30 mL). Concentration in vacuo and flash chromatography (ethyl acetate/hexane 1:4) afforded 43 (1.73 g, 4.76 mmol, 83%) as a colorless oil, Rf 0.30. IR v 1760, 1740, 1715, 1230, 690; *H NMR (200 MHz) δ (some signals appear as rotamers) 1.26 (br s, 3 H, CH₂Ctf), 1.98, 2.00 (s, 3 H, CO(CH₃)₂), 3.58 (br s, 2 H, NCH₂), 3.67, 3.73 (s, 3 H, CO₂CH₃), 4.25 (br s, 4 H, CH₂Ph and CH₂Ctf), 4.98-5.14 (m, 2 H, =CH₂), 5.24-5.99 (m, 1 H, =CH), 6.54, 6.56 (s, 1 H, NCH), 7.22-7.33 (m, 5 H, ArH).

α-Acetoxy-1-(allyloxycarbonyl)-2-benzyl-2-(2-propenyl)hydrazineacetic acid methyl ester (44). Following the general procedure B, a solution of 31 (3.20 g, 13.0 mmol) in toluene (100 mL) was reacted with methyl glyoxylate (2.29 g, 26.0 mmol) for 4 h and acetylated with Ac₂O (6.15 mL, 65.0 mmol) in pyridine (100 mL). Concentration in vacuo and flash chromatography (ethyl acetate/hexane 1:5) afforded 44 (4.45 g, 11.8 mmol, 91%) as a colorless oil, Rf 0.45. IR v 1760, 1740, 1710, 1360, 690; *H NMR (200 MHz) δ (some signals appear as rotamers) 1.97', 2.00 (s, 3 H, CO(CH₃)₂), 3.50-3.81 (m, 2 H, NCH₂), 3.66, 3.73 (s, 3 H, CO₂CH₃), 4.17-4.25 (m, 2 H, CH₂Ph), 4.68 (br s, 2 H, OCH₂), 4.98-5.34 (m, 4 H, 2 x =CH₂), 5.54-6.03 (m, 2 H, 2 x =CH), 6.55, 6.57 (s, 1 H, NCH), 7.21-7.33 (m, 5 H, ArH).

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α-Acetoxy-1-(allyloxycarbonyl)-2-benzyl-2-(methyl-2-propenyl)hydrazineacetic acid methyl ester (45). Following the general procedure B, a solution of 32 (4.00 g, 15.4 mmol) in toluene (150 mL) was reacted with methyl glyoxylate (9.5 g, 0.11 mol) for 18 h and acetylated with Ac₂O (7.3 mL, 0.08 mol) in pyridine (150 mL). Concentration in vacuo and flash chromatography (ethyl acetate/hexane 1:5) afforded 45 (5.88 g, 15.1 mmol, 98%) as a colorless oil, \( R_f 0.30 \). IR ν 1760, 1740, 1720, 690; ¹H NMR (250 MHz) δ 1.80 (s, 3 H, CH₃), 1.91 (s, 3 H, C(0)CH₃), 3.41-3.74 (m, 2 H, NCH₂), 3.64 (s, 3 H, CO₂CH₃), 3.95-4.25 (m, 2 H, CH₂Ph), 4.60-4.90 (m, 2 H, C=CH₂), 5.10-5.45 (m, 2 H, CH=CH₂), 5.75-6.05 (m, 1 H, =CH), 6.44 (br s, 1 H, NCH), 7.20-7.33 (m, 5 H, ArH).

α-Acetoxy-1-(allyloxycarbonyl)-2-benzyl-2-(3-methyl-2-butenyl)hydrazineacetic acid methyl ester (46). According to the general procedure B, a solution of 33 (800 mg, 2.90 mmol) in toluene (30 mL) was reacted with methyl glyoxylate (2.6 g, 29 mmol) for 18 h and acetylated with Ac₂O (2.76 mL, 29 mmol) in pyridine (50 mL). Concentration in vacuo and flash chromatography (ethyl acetate/hexane 1:4) afforded 46 (670 mg, 1.70 mmol, 57%) as a colorless oil, \( R_f 0.40 \). IR ν 1760, 1735, 1715, 690; ¹H NMR (250 MHz) δ 1.53-1.73 (m, 6 H, (CH₃)₂C), 1.98 (s, 3 H, C(0)CH₃), 3.40-3.75 (m, 5 H, NCH₂ and CO₂CH₃), 4.10-4.25 (m, 2 H, C=CH₂), 4.60-4.80 (m, 2 H, OCH₂), 5.15-5.45 (m, 3 H, =CH and C=CH), 5.75-6.05 (m, 1 H, CH=CH₂), 6.51 (s, 1 H, NCH), 7.19-7.34 (m, 5 H, ArH).

α-Acetoxy-1-(allyloxycarbonyl)-2-benzyl-2-(2-butenyl)hydrazineacetic acid methyl ester (47). Following the general procedure B, a solution of 34 (3.00 g, 11.5 mmol) in toluene (120 mL) was reacted with methyl glyoxylate (7.1 g, 80 mmol) for 4 h and acetylated with Ac₂O (7.5 mL, 80 mmol) in pyridine (125 mL). Concentration in vacuo and flash chromatography (ethyl acetate/hexane 1:4) afforded 47 (3.70 g, 9.5 mmol, 82%) as a colorless oil, \( R_f 0.30 \). IR ν 1760, 1710, 690; ¹H NMR (300 MHz) δ (mixture of isomers) 1.58, 1.64 (m, 3 H, CH₃), 2.01, 2.05 (s, 3 H, C(0)CH₃), 3.50-3.73 (m, 2 H, NCH₂), 3.66, 3.74 (s, 3 H, CO₂CH₃), 4.10-4.25 (m, 2 H, CH₂Ph), 4.60-4.75 (m, 2 H, OCH₂), 5.23-5.35 (m, 2 H, C=CH₂), 5.48-5.57 (m, 2 H, CH=CH₂), 5.80-6.10 (m, 1 H, CH=CH₂), 6.54 (s, 1 H, NCH), 7.19-7.34 (m, 5 H, ArH).

α-Acetoxy-1-(allyloxycarbonyl)-2-benzyl-2-(3-butenyl)hydrazineacetic acid methyl ester (48). Following the general procedure B, a solution of 35 (384 mg, 1.48 mmol) in toluene (15 mL) was reacted with methyl glyoxylate (650 mg, 7.4 mmol) for 5 h and acetylated with Ac₂O (7.76 mL, 80 mmol) in pyridine (15 mL). Concentration in vacuo and flash chromatography (ethyl acetate/hexane 1:4) afforded 48 (279 mg, 0.72 mmol, 48%) as a colorless oil, \( R_f 0.45 \). IR ν 1765, 1740, 1715, 690; ¹H NMR (200 MHz) δ (some signals appear as rotamers) 2.03, 2.06 (s, 3 H, C(0)CH₃), 2.25-2.35 (m, 2 H, NCH₂CH₂), 2.75-3.35 (m, 2 H, NCH₂), 3.70, 3.73 (s, 3 H, CO₂CH₃), 4.10-4.30 (m, 2 H, CH₂Ph), 4.68 (br s, 2 H, OCH₂), 4.88-5.03 (m, 2 H, =CH₂), 5.20-5.45 (m, 2 H, =CH₂), 5.50-6.00 (m, 2 H, 2 x =CH), 6.54 (s, 1 H, NCH), 7.22-7.40 (m, 5 H, ArH).

α-Acetoxy-1-(allyloxycarbonyl)-2-benzyl-2-(3-ethylenemethyl)hydrazineacetic acid methyl ester (49). Following the general procedure B, a solution of 36 (530 mg, 2.10 mmol) in toluene (25 mL) was reacted with methyl glyoxylate (720 mg, 8.2 mmol) for 4 h and acetylated with Ac₂O (0.70 mL, 10.3 mmol) in pyridine (25 mL). Concentration in vacuo and flash chromatography (ethyl acetate/hexane 1:6) afforded 49 (660 mg, 1.82 mmol, 85%) as a yellow oil, \( R_f 0.40 \). ¹H NMR (200 MHz) δ (some signals appear as rotamers) 2.01, 2.01 (s, 3 H, C(0)CH₃), 3.48-3.91 (m, 2 H, NCH₂), 3.68, 3.74 (s, 3 H, CO₂CH₃), 4.05-4.40 (m, 2 H, CH₂Ph), 4.55-4.95 (m, 4 H, OCH₂ and CH₂CH₂), 5.10-5.50 (m, 3 H, CH=CH₂ and C=CH), 5.75-6.10 (m, 1 H, CH=CH₂), 6.57, 6.60 (s, 1 H, NCH), 7.26-7.34 (m, 5 H, ArH).
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α-Acetoxy-1-(allyloxycarbonyl)-2,2-dibenzylhydrazineacetic acid methyl ester (50). According to the general procedure B, a solution of 37 (10.0 g, 33.8 mmol) in toluene (200 mL) was reacted with methyl glyoxylate (5.95 g, 68 mmol) for 40 h and acetylated with Ac₂O (16.0 mL, 169 mmol) in pyridine (200 mL). Concentration in vacuo and flash chromatography (ethyl acetate/hexane 1:4) afforded 50 (14.3 g, 33.6 mmol, 99%) as a colorless oil.

RT 0.30. IR ν 1760, 1735, 1715, 1220, 690; ¹H NMR (200 MHz) δ 1.77 (br s, 3 H, C(0)CH₃), 3.57 (s, 3 H, CO₂CH₃), 4.10-4.41 (m, 4 H, 2x CW₂Ph), 4.69 (br s, 2 H, OCH₂), 5.15-5.40 (m, 2 H, =0%), 5.60-6.10 (m, 1 H, =CH), 6.42 (s, 1 H, NCH), 7.21-7.37 (m, 10 H, ArH).

α-Acetoxy-1-(allyloxycarbonyl)-2-benzyl-2-(2-(trimethylsilyl)methyl)-2-propenyl)hydrazineacetic acid methyl ester (51). Following the general procedure B, a solution of 38 (1.00 g, 3.01 mmol) in toluene (30 mL) was reacted with methyl glyoxylate (2.65 g, 30.1 mmol) for 18 h (2 x) and acetylated with Ac₂O (1.42 mL, 15.1 mmol) in pyridine (30 mL). Concentration in vacuo and flash chromatography (ethyl acetate/hexane 1:4) afforded 51 (1.10 g, 2.38 mmol, 79%) as a colorless oil, RT 0.50. IR ν 1760, 1735, 1715, 1240, 850, 690; ¹H NMR (200 MHz) δ (some signals appear as rotamers) -0.10, -0.09 (s, 9 H, (CH₃)₃Si), 1.43, 1.63 (s, 2 H, CH₂Si), 1.91 (s, 3 H, C(O)CH₃), 3.25-3.70 (m, 2 H, NCH₂), 3.66 (s, 3 H, CO₂CH₃), 3.85-4.35 (m, 2 H, C₂Ph), 4.50-4.75 (m, 3 H, OCH₂ and C=CH₂), 4.88 (s, 1 H, C=CHH), 5.15-5.50 (m, 2 H, CH=CH₂), 5.75-6.10 (m, 1 H, =CH), 6.42 (s, 1 H, NCH), 7.22-7.34 (m, 5 H, ArH).

α-Acetoxy-1-(allyloxycarbonyl)-2-benzyl-2-[4-(trimethylsilyl)-2-butynyl]hydrazineacetic acid methyl ester (52). According to the general procedure B, a solution of 39 (150 mg, 0.45 mmol) in toluene (5 mL) was reacted with methyl glyoxylate (9.5 g, 0.11 mol) for 4 h at 80 °C and acetylated with Ac₂O (220 µL, 2.27 mmol) in pyridine (5 mL). Concentration in vacuo and flash chromatography (ethyl acetate/hexane 1:6) afforded 52 (170 mg, 0.37 mmol, 82%) as a light yellow oil, RT 0.35. IR ν 2210, 1765, 1735, 1715, 845, 690; ¹H NMR (200 MHz) δ (some signals appear as rotamers) 0.08, 0.09 (s, 9 H, (CH₃)₃Si), 1.40-1.55 (m, 2 H, CH₂Si), 1.75-2.00 (m, 3 H, C(0)CH₃), 3.55-3.95 (m, 5 H, NCH₂ and CO₂CH₃), 4.24 (br s, 2 H, C₂Ph), 4.66 (m, 2 H, OCH₂), 5.15-5.36 (m, 2 H, =CH₂), 5.82-5.96 (m, 1 H, =CH), 6.50 (s, 1 H, NCH), 7.26-7.37 (m, 5 H, ArH).

α-Acetoxy-1-(allyloxycarbonyl)-2-benzyl-2-[(E)-3-(trimethylsilyl)-2-propenyl)hydrazineacetic acid methyl ester (53). Following the general procedure B, a solution of 40 (5.93 g, 18.6 mmol) in toluene (200 mL) was reacted with methyl glyoxylate (13.1 g, 150 mmol) for 42 h and acetylated with Ac₂O (17.6 mL, 198 mmol) in pyridine (200 mL). Concentration in vacuo and flash chromatography (ethyl acetate/hexane 1:3) afforded 53 (6.20 g, 13.8 mmol, 74%) as a light yellow oil, RT 0.50. IR ν 1765, 1700, 1240, 835, 690; ¹H NMR (200 MHz) δ (some signals appear as rotamers) 0.06, 0.00 (s, 9 H, (CH₃)₃Si), 2.00, 2.05 (s, 3 H, C(0)CH₃), 3.68 (br s, 2 H, NCH₂), 3.75 (s, 3 H, CO₂CH₃), 4.05-4.25 (m, 2 H, CH₂Ph), 4.55-4.80 (m, 2 H, OCH₂), 5.15-5.50 (m, 2 H, =CH₂), 5.68-5.77 (m, 2 H, CH=CH₂), 5.80-6.15 (m, 1 H, =CH), 6.50, 6.60 (s, 1 H, NCH), 7.24-7.32 (m, 5 H, ArH).

α-Acetoxy-1-(allyloxycarbonyl)-2-benzyl-2-[(Z)-3-(trimethylsilyl)-2-propenyl)hydrazineacetic acid methyl ester (54). Following the general procedure B, a solution of 41 (1.95 g, 6.13 mmol) in toluene (60 mL) was reacted with methyl glyoxylate (2.70 g, 30.7 mmol) for 42 h and acetylated with Ac₂O (5.8 mL, 61 mmol) in pyridine (60 mL). Concentration in vacuo and flash chromatography (ethyl acetate/hexane 1:4) afforded 54 (2.17 g, 4.84 mmol, 79%) as a light yellow oil, (E)/(Z) 1:1.2, RT 0.50. IR ν 1760, 1740, 1720, 1240, 835, 690; ¹H NMR (250 MHz) δ 0.05 (s, 9 H, (CH₃)₃Si), 1.94 (s, 3 H, C(O)CH₃), 3.64 (br s, 2 H,
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NCH2), 3.70 (s, 3 H, CO2CH3), 4.05-4.22 (m, 2 H, CH2Ph), 4.65-4.75 (m, 2 H, OCH2), 5.15-5.35 (m, 2 H, =CH2), 5.40-6.00 (m, 2 H, CHSi and =CH), 6.42 (d, J = 14.3, 7.2 Hz, 1 H, CH2CH), 6.63 (s, 1 H, NCH), 7.22-7.32 (m, 5 H, ArH).

α-Acetoxy-1-(allyloxy carboxyl)-2-benzyl-2-{(3,3-dimethyl-5-oxo-2,4-diox-6-enyl)methyl}hydrazineacetic acid methyl ester (55). According to the general procedure B, a solution of 42 (2.22 g, 6.40 mmol) in toluene (100 mL) was reacted with methyl glyoxylate (13.1 g, 150 mmol) for 18 h and acetylated with Ac2O (3.03 mL, 32 mmol) in pyridine (80 mL). Concentration in vacuo afforded 55 (2.01 g, 4.20 mmol, 82%) as a white solid, Rf 0.25.

IR v 1760, 1700, 1635, 690; 1H NMR (200 MHz) δ (some signals appear as rotamers) 2.65 (s, 3 H, CO2CH3), 2.86-3.16 (m, 2 H, 2 x H4), 3.11 (dd, J = 12.6 Hz, 1 H, =CH2), 3.90-3.94 (m, 3 H, OCH2), 5.40-5.60 (m, 3 H, =CH2 and =CH), 5.75-6.05 (m, 1 H, =CH₂=CH), 6.38, 6.60 (s, 1 H, CH), 7.26-7.31 (m, 5 H, ArH); MS (El, 70 eV) m/z (relative intensity) 476 (M⁺, 1), 349 (57), 335 (76), 275 (1), 118 (36), 91 (100); HRMS calcd for C20H29N3O8 476.1795, found 476.1749.

General procedure C for the cyclization reactions with Lewis acids. To a 0.1 M solution of the hydrazide in CH2Cl2 (2 x) and acetylated with Ac2O (3.03 mL, 32 mmol) in pyridine (80 mL). Concentration in vacuo. Extracted with CH2Cl2 (2 x) and acetylated with Ac2O (3.03 mL, 32 mmol) in pyridine (80 mL). Concentration in vacuo. Purification of the residue by flash chromatography afforded the pure cyclization product(s).

rel-(35,55)-1-Benzyl-2-(ethoxycarbonyl)-5-(chloromethyl)-3-pyrazolidinecarboxylic acid methyl ester (trans-56). Following the general procedure C, a solution of 43 (1.23 g, 3.38 mmol) in CH2Cl2 (33 mL) was cyclized by using TiCl4, SnCl4 (2 equiv of a solution in CH2Cl2) or Et2AlCl (2 equiv of a 1.0 M solution in toluene) at -78 °C by a syringe. The mixture was stirred at -78 °C for 15 min and for 5-18 h at rt. The reaction mixture was poured into cold aq satd NaHCO3 solution in toluene (100 mL) at -78 °C by a syringe. The mixture was stirred at -78 °C for 15 min and for 5-18 h at rt. The reaction mixture was poured into cold aq satd NaHCO3 and the resulting suspension was filtered over Celite and extracted with CH2Cl2 (3 x). The combined organic layers were dried (MgSO4), filtered and concentrated in vacuo. Purification of the residue by flash chromatography afforded the pure cyclization product(s).

rel-(35,55)-1-Benzyl-2-(ethoxycarbonyl)-5-(chloromethyl)-3-pyrazolidinecarboxylic acid methyl ester (trans-57). According to the general procedure C, a solution of 44 (500 mg, 1.33 mmol) in CH2Cl2 (13 mL) was cyclized by using SnCl4 (1.33 mL of a 2.0 M solution, 2.66 mmol). Work-up and flash chromatography (ethyl acetate/hexane 1:2) afforded 57 (352 mg, 1.00 mmol, 75%) as a colorless oil, Rf 0.25. trans-57: IR v 1740, 1680, 1375, 690; 1H NMR δ 2.46-2.72 (m, 2 H, 2 x H4), 3.11 (dd, J = 8.8, 10.6 Hz, 1 H, CH3CH), 3.31-3.44 (m, 2 H, CH3CH and H5), 3.80 (d, J = 12.6 Hz, 1 H, CHCHPh), 3.61 (s, 3 H, CO2CH3), 4.24 (d, J = 12.6 Hz, 1 H, CHCHPh), 4.50-4.60 (m, 2 H, OCH2), 4.67 (t, J = 8.8 Hz, 1 H, H3), 5.17-5.35 (m, 2 H, =CH2), 5.79-5.97 (m, 1 H, =CH), 7.27-7.47 (m, 5 H, ArH); 13C NMR (50 MHz) δ 31.9 (C4), 45.0 (CH2Cl), 52.6 (CO2CH3), 59.3 (C3), 62.0 (CH2Ph), 62.1 (CH3CH2), 64.2 (C5), 127.7, 128.6, 129.5 (ArH), 137.1 (ArC), 172.8 (C(O)).

cis-57: 13C NMR (50 MHz) δ 31.9 (C4), 44.5
Cyclization of 45 with SnCl₄. Following the general procedure, a solution of 45 (1.59 g, 4.07 mmol) in CH₂Cl₂ (40 mL) was cyclized by using SnCl₄ (6.78 mL of a 1.2 M solution, 8.13 mmol). Work-up and flash chromatography (ethyl acetate/hexane 1:5) afforded \( R_f 0.40 \) and \( (3S, 5S)-2\text{-}(\text{allyloxy} \text{carbonyl})-1\text{-benzyl}-5\text{-} \) 
chloro-5-methylhexahydro-3-pyridazinecarboxylic acid methyl ester (trans-59) (479 mg, 1.32 mmol, 32%) as a colorless oil, \( R_f 0.40 \) and \( (3S, 5S)-2\text{-}(\text{allyloxy} \text{carbonyl})-1\text{-benzyl}-5\text{-} \) 
(chloromethyl)-5-methyl-3-pyrazolidinecarboxylic acid methyl ester (trans-58) (559 mg, 1.50 mmol, 38%) as a colorless oil, \( R_f 0.20 \). trans-59: IR \( v \) 1735, 1700, 690; \( ^1H \) NMR (200 MHz) \( \delta \) 1.51 (s, 3 H, CH₃), 2.19 (dd, \( J = 13.2, 10.6 \) Hz, 1 H, CH₃), 2.88 (dd, \( J = 13.2, 8.9 \) Hz, 1 H, H₄), 3.18 (d, \( J = 11.3 \) Hz, 1 H, CH₃CH₂), 3.82 (s, 3 H, CO₂CH₃), 4.00 (d, \( J = 13.2 \) Hz, 1 H, CH₂CH₃), 4.11 (d, \( J = 13.2 \) Hz, 1 H, NCH₂CH₃), 4.41-4.55 (m, 3 H, H₁ and CH₂OCH₂), 5.10-5.23 (m, 2 H, CH₂OCH₂), 5.55-5.80 (m, 1 H, =CH), 7.24-7.47 (m, 5 H, ArH); \( ^13C \) NMR (50 MHz) \( \delta \) 30.6 (CH₃), 40.0 (C₄), 52.3 (C₀), 66.3 (C₇), 68.4 (C₅), 117.4 (CH₂), 127.8, 128.2, 129.2 (ArH), 132.2 (CH₃), 137.7 (ArC), 173.1 (CO); MS (EI, 70 eV) m/z (relative intensity) 366 (M⁺, 6), 331 (31), 317 (31), 281 (28), 231 (31), 91 (100); HRMS calcld for C₂₁H₂₃N₂O₄Cl 366.1346, found 366.1381.

Cyclization of 45 with Et₂AlCl. Following the general procedure C, a solution of 45 (982 mg, 2.52 mmol) in CH₂Cl₂ (25 mL) was treated with Et₂AlCl (7.55 mL of a 1.0 M solution in toluene, 7.55 mmol). Work-up and flash chromatography (ethyl acetate/hexane 1:5) afforded \( R_f 0.40 \) and \( (3S, 5S)-2\text{-}(\text{allyloxy} \text{carbonyl})-1\text{-benzyl}-5\text{-} \) 
(chloromethyl)-5-methyl-3-pyrazolidinecarboxylic acid methyl ester (trans-58) (559 mg, 1.50 mmol, 38%) as a colorless oil, \( R_f 0.20 \). trans-59: IR \( v \) 1735, 1700, 690; \( ^1H \) NMR (200 MHz) \( \delta \) 1.51 (s, 3 H, CH₃), 2.19 (dd, \( J = 13.2, 10.6 \) Hz, 1 H, CH₃), 2.88 (dd, \( J = 13.2, 8.9 \) Hz, 1 H, H₄), 3.18 (d, \( J = 11.3 \) Hz, 1 H, CH₃CH₂), 3.82 (s, 3 H, CO₂CH₃), 4.00 (d, \( J = 13.2 \) Hz, 1 H, CH₂CH₃), 4.11 (d, \( J = 13.2 \) Hz, 1 H, NCH₂CH₃), 4.41-4.55 (m, 3 H, H₁ and CH₂OCH₂), 5.10-5.23 (m, 2 H, CH₂OCH₂), 5.55-5.80 (m, 1 H, =CH), 7.24-7.47 (m, 5 H, ArH); \( ^13C \) NMR (50 MHz) \( \delta \) 19.7 (CH₃), 23.3 (CH₃), 37.1 (C₄), 49.2 (CH₂), 52.3 (CO₂CH₃), 58.6 (CH₃), 60.2 (CH₂), 66.8 (OCH₂), 113.8 (CH₂), 127.8, 128.2, 129.2 (ArH), 132.2 (CH₃), 137.7 (ArC), 173.1 (CO); MS (EI, 70 eV) m/z (relative intensity) 366 (M⁺, 45), 331 (31), 317 (14), 281 (28), 231 (31), 91 (100); HRMS calcld for C₂₁H₂₃N₂O₄Cl 366.1346, found 366.1381.
Synthesis of cyclic α-hydrazino acid derivatives

rel-(3S,5S)-2-(Allyloxy carbonyl)-1-benzyl-5-formyloxy-5-methylhexahydro-3-pyridazinone carboxylic acid methyl ester (60). A solution of 45 (565 mg, 1.45 mmol) in HCOOH (15 mL) was stirred for 18 h at rt. Concentration in vacuo and purification by flash chromatography (ethyl acetate/hexane 1:4) afforded 60 (369 mg, 0.98 mmol, 68%) as a colorless oil, RF 0.30. IR v 1740, 1700, 690; 1H NMR (200 MHz) δ 1.51 (s, 3 H, CH3), 2.20-2.40 (m, 1 H, H4), 2.40-2.60 (m, 1 H, H4), 2.87 (d, J = 13.7 Hz, 1 H, H6), 3.38 (d, J = 13.7 Hz, 1 H, H6), 3.74 (a, 3 H, CO2CH3), 4.20 (d, J = 13.7 Hz, 1 H, CH2Ph), 4.27 (d, J = 13.7 Hz, 1 H, CH2Ph), 4.64 (d, J = 5.5 Hz, 2 H, OCH2 and br s, 1 H, H3), 5.22-5.36 (m, 2 H, =CH2), 5.80-6.05 (m, 1 H, =CH), 7.22-7.33 (m, 5 H, ArH), 7.91 (s, 1 H, CHO); 13C NMR (50 MHz) δ 24.4 (CH3), 34.9 (C4), 52.2 (CO2CH3), 54.5 (C5), 56.7 (CH2Ph), 61.0 (C6), 66.6 (OCH2), 79.4 (C5), 118.1 (=CH2), 127.3, 128.1, 128.9 (ArH), 132.2 (=CH), 137.6 (ArC), 157.0, 157.9, 172.0 (3 x CO(O)). MS (EI, 70 eV) m/z (relative intensity) 376 (M+, 43), 331 (14), 317 (7), 259 (13), 245 (26), 91 (100); HRMS calcd for C19H24N2O6Cl 376.1634, found 376.1609.

rel-(3S,4S)-2-(Allyloxy carbonyl)-1-benzyl-4-(1-chloromethylthyl)-3-pyrazolidinecarboxylic acid methyl ester (61). Following the general procedure C, a solution of 46 (140 mg, 0.35 mmol) in CH2Cl2 (4 mL) was treated with SnCl4 (0.58 mL of a 1.2 M solution, 0.70 mmol). Work-up and flash chromatography (ethyl acetate/hexane 1:4) afforded 61 (76 mg, 0.20 mmol, 58%) as a colorless oil, RF 0.25. IR v 1735, 1690, 690; 1H NMR (200 MHz) δ 1.54 (s, 3 H, CH3), 1.66 (s, 3 H, CH3), 3.13-3.28 (m, 3 H, H4 and 2 × H5), 3.81 (d, J = 12.5 Hz, 1 H, CH2Phe), 3.82 (a, 3 H, CO2CH3), 4.17 (d, J = 12.5 Hz, 1 H, CH2Phe), 4.56 (d, J = 5.3 Hz, 2 H, OCH2), 4.70 (d, J = 6.2 Hz, 1 H, H3), 5.15-5.31 (m, 2 H, =CH2), 5.70-5.95 (m, 1 H, =CH), 7.26-7.44 (m, 5 H, ArH); 13C NMR (50 MHz) δ 31.5, 31.9 (2 x CH3), 52.7 (CO2CH3), 54.9 (C5), 55.8 (C4), 61.9 (CH2Ph), 62.6 (C6), 66.5 (OCH2), 69.4 (CCl), 117.6 (=CH2), 127.5, 128.2, 129.4 (ArH), 132.3 (=CH), 137.2 (ArC), 173.4 (CO(O)). MS (EI, 70 eV) m/z (relative intensity) 380 (M+, 67), 344 (36), 295 (44), 245 (51), 91 (100); HRMS calcd for C19H24N2O6Cl 380.1503, found 380.1548.

rel-(3S,4S)-2-(Allyloxy carbonyl)-1-benzyl-4-(1-formyloxy)-1-methylthyl-3-pyrazolidinecarboxylic acid methyl ester (62). A solution of 46 (173 mg, 0.43 mmol) in HCOOH (5 mL) was stirred at rt for 18 h. Concentration in vacuo and flash chromatography (ethyl acetate/hexane 1:4) afforded 62 (110 mg, 0.28 mmol, 66%) as a colorless oil, RF 0.25. IR v 1735, 1715, 1690, 690; 1H NMR (200 MHz) δ 1.53 (s, 3 H, CH3), 1.61 (s, 3 H, CH3), 3.06 (d, J = 8.7 Hz, 2 H, × H5), 3.26-3.39 (m, 1 H, H4), 3.81 (s, 3 H, CO2CH3), 3.82 (d, J = 12.3 Hz, 1 H, CH2Phe), 4.20 (d, J = 12.3 Hz, 1 H, CH2Phe), 4.56 (d, J = 5.5 Hz, 2 H, OCH2), 4.62 (d, J = 7.4 Hz, 1 H, H3), 5.16-5.32 (m, 2 H, =CH2), 5.75-5.95 (m, 1 H, =CH), 7.27-7.43 (m, 5 H, ArH), 7.93 (s, 1 H, OH); 13C NMR (50 MHz) δ 24.2, 25.0 (2 × CH3), 52.6 (CO2CH3), 53.3 (C5), 53.7 (C4), 61.3 (C6), 61.9 (CH2Ph), 66.5 (OCH2), 81.6 (CO), 117.7 (=CH2), 127.4, 128.2, 129.4 (ArH), 132.3 (=CH), 137.1 (ArC), 159.8, 173.2 (2 × CO(O)). MS (EI, 70 eV) m/z (relative intensity) 390 (M+, 34), 345 (6), 227 (20), 91 (100); HRMS calcd for C20H26N2O6 390.1791, found 390.1749.
2-(Allyloxy carbonyl)-1-benzyl-5-chloro-1H-1,2-diazepine-3-carboxylic acid methyl ester (64). According to the general procedure C, a solution of 49 (660 mg, 1.70 mmol) in CH$_2$Cl$_2$ (17 mL) was treated with SnCl$_4$ (1.19 mL of a 1.2 M solution, 1.43 mmol). Work-up and flash chromatography (ethyl acetate/hexane 1:4) afforded 65 (280 mg, 0.77 mmol, 45%) as a yellowish oil, 1:1 mixture of isomers, 1H NMR (200 MHz) δ (one isomer) 2.61-2.75 (m, 1 H, CH$_2$), 3.31 (dd, J = 6.4, 3.1 Hz, 1 H, CH$_2$Cl), 3.55-4.00 (m, 2 H, 2 × H5), 3.71 (s, 3 H, CO$_2$CH$_3$), 4.35 (d, J = 13.4 Hz, 1 H, CH$_2$Ph), 4.47 (d, J = 13.4 Hz, 1 H, CH$_2$Ph), 4.65 (m, 2 H, OCH$_2$CH$_3$), 4.90 (dd, J = 12.2, 5.4 Hz, 1 H, =C(=O)), 5.21-5.45 (m, 2 H, =CH$_2$), 5.56-5.60 (br s, 1 H, H3), 5.83-6.10 (m, 1 H, CH$_2$Cl), 7.26-7.41 (m, 5 H, ArH); 13C NMR (50 MHz) δ (mixture of (E)/(Z) isomers) 30.4, 34.3, 35.9, 36.0 (C4 and C6), 41.9 (C7), 52.6 (CO$_2$CH$_3$), 59.6 (C3), 59.2, 61.2 (C5), 61.6 (CH$_2$Ph), 66.3 (OCH$_2$), 117.5 (C6), 127.3, 128.1, 129.5 (ArH), 152.2 (=CH), 137.0 (ArC), 172.7 (C(=O)); MS (EI, 70 eV) m/z (relative intensity) 364 (M$^+$, 52), 325 (9), 303 (6), 275 (23), 91 (100).

2-(Allyloxy carbonyl)-1-benzyl-5-chloro-1H-1,2-diazepine-3-carboxylic acid methyl ester (65). According to the general procedure C, a solution of 49 (660 mg, 1.70 mmol) in CH$_2$Cl$_2$ (17 mL) was treated with SnCl$_4$ (2.84 mL of a 1.2 M solution, 3.40 mmol). Work-up and flash chromatography (ethyl acetate/hexane 1:6) afforded 65 (280 mg, 0.77 mmol, 45%) as a yellowish oil, 1:1 mixture of (E)/(Z) isomers, 1H NMR (200 MHz) δ (one isomer) 2.61-2.75 (m, 1 H, CH$_2$Cl), 3.31 (dd, J = 6.4, 3.1 Hz, 1 H, CH$_2$Cl), 3.55-4.00 (m, 2 H, 2 × H5), 3.71 (s, 3 H, CO$_2$CH$_3$), 4.35 (d, J = 13.4 Hz, 1 H, CH$_2$Ph), 4.47 (d, J = 13.4 Hz, 1 H, CH$_2$Ph), 4.65 (m, 2 H, OCH$_2$CH$_3$), 4.90 (dd, J = 12.2, 5.4 Hz, 1 H, =C(=O)), 5.21-5.45 (m, 2 H, =CH$_2$), 5.56-5.60 (br s, 1 H, H3), 5.83-6.10 (m, 1 H, CH$_2$Cl), 7.26-7.41 (m, 5 H, ArH); 13C NMR (50 MHz) δ (mixture of (E)/(Z) isomers) 30.4, 34.3, 35.9, 36.0 (C4 and C6), 41.9 (C7), 52.6 (CO$_2$CH$_3$), 59.6 (C3), 59.2, 61.2 (C5), 61.6 (CH$_2$Ph), 66.3 (OCH$_2$), 117.5 (C6), 127.3, 128.1, 129.5 (ArH), 152.2 (=CH), 137.0 (ArC), 172.7 (C(=O)); MS (EI, 70 eV) m/z (relative intensity) 364 (M$^+$, 6), 325 (29), 305 (11), 273 (42), 193 (21), 91 (100); HRMS calcd for C$_{18}$H$_{21}$N$_2$O$_4$Cl 364.1190, found 364.1159.

2-(Allyloxy carbonyl)-3-benzyl-1,2,3,4-tetrahydro-1-phthalazinecarboxylic acid methyl ester (66). According to the general procedure C, a solution of 50 (2.00 g, 4.69 mmol) in CH$_2$Cl$_2$ (45 mL) was
treated with SnCl₄ (7.82 mL of a 1.2 M solution, 9.38 mmol). Work-up and flash chromatography (ethyl acetate/hexane 1:4) afforded 66 (1.55 mg, 4.23 mmol, 91%) as a colorless oil, R_f 0.30. IR ν 1740, 1685, 1400, 690. ¹H NMR δ 3.65-3.75 (m, 2 H, NCH₂), 3.78 (t, J = 14.1 Hz, 1 H, H8), 5.15 (d, J = 12.5 Hz, 1 H, CH=CH₂), 5.46-5.54 (d, 2 H, OCH₂), 5.80-5.96 (m, 1 H, H3), 6.08-6.17 (m, 1 H, H, CO₂CH₂), 5.83 (d, J = 12.5 Hz, 1 H, CH=CH₂), 5.45-5.54 (d, 2 H, OCH₂), 3.63 (s, 3 H, CO₂CH₂), 5.80-5.96 (m, 1 H, H3), 6.08-6.17 (m, 1 H, H, CO₂CH₂).

2-(Allyloxy carbonyl)-1-benzyl-5-methylenehexahydropyridazinecarboxylic acid methyl ester (67). According to the general procedure C, a solution of 51 (1.10 g, 2.38 mmol) in CH₂Cl₂ (25 mL) was treated with Et₂AlCl (5.95 mL of a 1.0 M solution, 5.95 mmol). Work-up and flash chromatography (ethyl acetate/hexane 1:4) afforded 67 (517 mg, 1.57 mmol, 83% (after correction)) as a colorless oil, R_f 0.35. IR ν 1750, 1685, 1400, 690; ¹H NMR δ 3.65-3.75 (m, 2 H, NCH₂), 3.78 (t, J = 14.1 Hz, 1 H, H8), 5.15 (d, J = 12.5 Hz, 1 H, CH=CH₂), 5.80-5.96 (m, 1 H, H3), 6.08-6.17 (m, 1 H, H, CO₂CH₂), 5.83 (d, J = 12.5 Hz, 1 H, CH=CH₂), 5.46-5.54 (d, 2 H, OCH₂), 5.80-5.96 (m, 1 H, H3), 6.08-6.17 (m, 1 H, H, CO₂CH₂).

rel-(3S, 5S)-2-(Allyloxy carbonyl)-1-benzyl-5-methyl-5-(trifluorooxetenoxy)hexahydropyridazinecarboxylic acid methyl ester (68). A solution of 51 (232 mg, 0.50 mmol) in CH₂Cl₂ (5 mL) was treated with CF₃CO₂H (155 µL, 2.00 mmol) at 0 °C. After being stirred at rt for 18 h, the mixture was poured into aq NaHCO₃ (25 mL) and extracted with CH₂Cl₂ (3 x 15 mL). The combined organic layers were dried (MgSO₄), filtered, concentrated in vacuo and chromatographed (ethyl acetate/hexane 1:4) to afford 68 (155 mg, 0.35 mmol, 70%) as a yellow oil, R_f 0.35. IR ν 1775, 1735, 1710, 690; ¹H NMR (200 MHz) δ 1.54 (s, 3 H, CH₃), 2.30-2.55 (m, 2 H, H₄CH₃), 3.89 (d, J = 13.7 Hz, 1 H, H8), 3.39 (d, J = 13.7 Hz, 1 H, H6), 3.76 (s, 3 H, CO₂CH₂), 4.27 (q, 2 H, CH₂Ph), 4.65 (d, J = 5.5 Hz, 2 H, OCH₂), 4.75-4.95 (m, 1 H, H3), 5.24-5.37 (m, 2 H, CH₃), 5.80-6.05 (m, 1 H, =CH), 7.26-7.34 (m, 5 H, ArH); MS (EI, 70 eV) m/z (relative intensity) 444 (M⁺, 8), 348 (13), 277 (8), 263 (7), 245 (10), 160 (42), 121 (29), 91 (100); HRMS calc for C₁₈H₂₂F₂O₄Na⁺ 444.1508, found 444.1543.

2-(Allyloxy carbonyl)-1-benzyl-4-ethenylidene-3-pyrazolidinecarboxylic acid methyl ester (69). To a solution of 52 (250 mg, 0.53 mmol) in CH₂Cl₂ (25 mL) was added at 0 °C BF₃·Et₂O (0.40 mL, 3.15 mmol) and the mixture was stirred at 0 °C for 15 min. After being stirred at rt for 4 h, the mixture was poured into aq NaCl (100 mL) and extracted with CH₂Cl₂ (3 x 50 mL). The combined organic layers were dried (MgSO₄), filtered, concentrated in vacuo and chromatographed (ethyl acetate/hexane 1:5) to afford 69 (51 mg, 0.16 mmol, 30% (after correction)) as a light yellow oil, R_f 0.20. IR ν 1950, 1745, 1685, 690; ¹H NMR
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(200 MHz) δ 3.65 (m, 2 H, 2 × H5), 3.81 (s, 3 H, CO2CH3), 3.83 (d, J = 12.4 Hz, 1 H, CH2Ph), 4.10 (d, J = 12.4 Hz, 1 H, CH2Ph), 4.59 (d, J = 5.5 Hz, 2 H, OCH2), 4.65-4.75 (m, 1 H, H3), 5.08-5.11 (m, 2 H, C=CH2), 5.18-5.34 (m, 2 H, CH2CH2), 5.77-5.97 (m, 1 H, =CH), 7.28-7.46 (m, 5 H, ArH); 13C NMR (250 MHz) δ 52.6 (CO2CH3), 55.5 (C5), 61.3 (C3), 61.8 (CH2Ph), 66.6 (OCH2), 81.1 (C=CH2), 99.0 (C4), 117.9 (C=CH2), 127.6, 128.3, 129.7 (ArH), 132.3 (=CH), 136.8 (ArC), 169.6 (CO)2, 200.3 (C=CH=CH2); MS (EI, 70 eV) m/z: (relative intensity) 328 (M+; 53), 243 (18), 193 (11), 124 (6), 91 (100); HRMS calcld for C16H20N2O4 328.1423, found 328.1401.

rel-(3R,4R,5S)-5-(Acetoxyethyl)-2-(allyloxyacetylene)-1-benzyl-4-(trimethylsilyl)-3-pyrazolidinecarboxylic acid methyl ester (70). To a solution of 53 (105 mg, 0.23 mmol) in CH2Cl2 (3 mL) was added at 0 °C BF3·OEt2 (177 µL, 1.41 mmol) and the mixture was stirred at 0 °C for 15 min. After being stirred at rt for 4 h, the mixture was poured into aq satd NaCl (25 mL) and extracted with CH2Cl2 (3 × 25 mL). The combined organic layers were dried (MgSO4), filtered, concentrated in vacuo and chromatographed (ethyl acetate/hexane 1:4) to afford 70 (24 mg, 0.06 mmol, 23%) as a light yellow oil, 1H NMR (200 MHz) δ 0.11 (s, 9 H, (CH3)2Si), 1.66 (t, J = 9.0 Hz, 1 H, H4), 1.82 (s, 3 H, C(O)CH3), 3.35-3.45 (m, 1 H, H5), 3.65-3.85 (m, 2 H, CH2CH2), 3.75 (s, 3 H, CO2CH3), 3.92 (d, J = 12.9 Hz, 1 H, CH2Ph), 4.23 (d, J = 12.9 Hz, 1 H, CH2Ph), 4.45-4.65 (m, 2 H, OCH2), 4.98 (d, J = 9.5 Hz, 1 H, H3), 5.16-5.33 (m, 2 H, CH2Ph), 5.75-5.95 (m, 1 H, =CH), 7.23-7.42 (m, 5 H, ArH); 13C NMR (50 MHz) δ 66.5 (OCH3), 70.7 (C=CH2), 81.1 (C=CH2), 99.0 (CH2Ph), 128.3 (C6), 117.4 (C=CH2), 127.3, 128.1, 129.6 (ArH), 132.6 (=CH), 137.8 (ArC), 155.8, 170.6, 173.4; MS (EI, 70 eV) m/z (relative intensity) 448 (M+; 32), 389 (6), 375 (16), 363 (9), 243 (46), 91 (100); HRMS calcld for C22H26N2O6Si 448.2030, found 448.2065.

rel-(3R,4S,5S)-2-(Allyloxyacetylene)-1-benzyl-5-(chloromethyl)-4-(trimethylsilyl)-3-pyrazolidinecarboxylic acid methyl ester (71). According to the general procedure C, a solution of 53 (925 mg, 2.06 mmol) in CH2Cl2 (25 mL) was treated with SnCl4 (3.44 mL of a 1.2 M solution, 4.13 mmol). Work-up and flash chromatography (ethyl acetate/hexane 1:4) afforded 71 (591 mg, 0.39 mmol, 68%) as a colorless oil, 1H NMR (200 MHz) δ 0.12 (s, 9 H, (CH3)2Si), 2.00 (t, J = 9.1 Hz, 1 H, H4), 3.07 (dd, J = 11.5, 4.3 Hz, 1 H, CH2CH2), 3.25 (dd, J = 11.5, 3.4 Hz, 1 H, CH2CH2), 3.47-3.56 (m, 1 H, H5), 3.78 (s, 3 H, CO2CH3), 3.99 (d, J = 12.8 Hz, 1 H, CH2Ph), 4.36 (d, J = 12.7 Hz, 1 H, CH2Ph), 4.56 (dd, J = 13.6, 5.3, 1.4 Hz, 1 H, OCH2), 4.67 (dd, J = 13.6, 5.3, 1.4 Hz, 1 H, OCH2), 5.01 (d, J = 9.0 Hz, 1 H, H3), 5.18-5.40 (m, 2 H, =CH2), 5.91-5.98 (m, 1 H, =CH), 7.26-7.31 (ArH); 13C NMR (63 MHz) δ 1.5 (CH3)2Si), 35.3 (C4), 47.7 (CH2Ph), 52.1 (CO2CH3), 62.4 (C3), 63.4 (CH2Ph), 66.5 (OCH2) and CH2Ph), 68.8 (C5), 117.4 (=CH2), 127.5, 128.4 (ArH), 132.6 (=CH), 137.8 (ArC), 155.0, 172.3 (2 × C(O)); MS (EI, 70 eV) m/z (relative intensity) 424 (M+; 47), 409 (10), 339 (13), 289 (10), 243 (20), 185 (23), 91 (100); HRMS calcld for C22H26N2O6Si 448.2030, found 448.2065.

2-(Allyloxyacetylene)-1-benzyl-1,2,3,6-tetrahydro-3-pyridazinencarboxylic acid methyl ester (72). According to the general procedure C, a solution of 54 (500 mg, 1.12 mmol) in CH2Cl2 (12 mL) was treated with SnCl4 (1.86 mL of a 1.2 M solution, 2.23 mmol). Work-up and flash chromatography (ethyl acetate/hexane 1:4) afforded 72 (152 mg, 0.36 mmol, 32%) as a colorless oil, 1H NMR (200 MHz) δ 0.45 and 72 (176 mg, 0.56 mmol, 50%) as a colorless oil, 1H NMR (200 MHz) δ 3.09 (m, 2 H, 2 × H5), 3.16 (t, J = 11.5 Hz, 1 H, H4), 3.78 (s, 3 H, CO2CH3), 3.82 (d, J = 12.5 Hz, 1 H, CH2Ph), 4.22 (d, J = 12.5 Hz, 1 H, CH2Ph), 4.60-4.80 (m, 2 H, OCH2), 5.10 (br s, 1 H, H3), 5.23-5.45
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(3 S, 5 R )-2-(Allyloxycarbonyl)-1-benzyl-5-methyl-3-pyrazolidinecarboxylic acid methyl ester (91). To a refluxing solution of \( n-\text{Bu}_3\text{SnH} \) (160 mL, 0.60 mmol) in benzene (2 mL) was added dropwise in 1 h a solution of \( 57 \) (55 mg, 0.15 mmol) and AIBN (5 mg, 0.030 mmol) in benzene (2 mL). After refluxing for 18 h, the solution was concentrated in vacuo and chromatographed (hexane, then ethyl acetate/hexane 1:4) to afford 91 (31 mg, 0.097 mmol, 65%) as a colorless oil, \( R_f 0.25 \). IR \( v \) 1740, 680, 1400, 690; \( ^1\text{H} \text{NMR} \) (200 MHz) \( \delta \) 0.98 (d, \( J = 7.1 \text{ Hz} \), 3 H, \( \text{CH}_3 \)), 2.18 (dd, \( J = 12.5, 8.7 \text{ Hz} \), 1 H, \( H_4 \)), 2.45-2.60 (m, 1 H, \( H_4 \)), 3.37 (quintet, \( J = 6.6 \text{ Hz} \), 1 H, \( H_3 \)), 3.74 (d, \( J = 12.8 \text{ Hz} \), 1 H, \( \text{CH}_2\text{Ph} \)), 3.80 (s, 3 H, \( \text{CO}_2\text{CH}_3 \)), 4.17 (d, \( J = 12.8 \text{ Hz} \), 1 H, \( \text{CH}_2\text{Ph} \)), 4.57 (d, \( J = 5.5 \text{ Hz} \), 2 H, \( \text{OCH}_2 \)), 4.59 (t, \( J = 8.9 \text{ Hz} \), 1 H, \( H_3 \)), 5.14-5.32 (m, 2 H, =CH_2), 5.76-5.95 (m, 1 H, =CH), 7.23-7.47 (m, 5 H, \( \text{ArH} \)); \( ^{13}\text{C} \text{NMR} \) (63 MHz) \( \delta \) 24.4, 25.9 (2 \( \times \) \( \text{CH}_3 \)), 47.5 (C6), 52.8 (\( \text{CO}_2\text{CH}_3 \)), 59.7 (\( \text{CH}_2\text{Ph} \)), 64.5 (C3), 67.1 (OCH2), 100.0 (C4a), 107.4 (OCO), 118.4 (=CH2), 127.8, 128.5, 128.9 (ArH), 132.0 (=CH), 135.5 (ArC), 155.0, 158.0, 162.5, 169.8 (3 \( \times \) C(O) and C(=O)); MS (El, 70 eV) \( m/z \) (relative intensity) 416 (M+, 4), 358 (18), 299 (10), 262 (5), 105 (26), 91 (35), 32 (100); HRMS calcd for \( C_{21}H_{22}N_2O_7 \) 416.1584, found 416.1573.

rel-(3 S, 5 R )-2-(Allyloxycarbonyl)-1-benzyl-5-methyl-3-pyrazolidinecarboxylic acid methyl ester (92). To a refluxing solution of \( n-\text{Bu}_3\text{SnH} \) (217 \( \mu \text{L}, 0.82 \text{ mmol}) in benzene (2 mL) was added dropwise in 1 h a solution of \( 58 \) (75 mg, 0.20 mmol) and AIBN (3.4 mg, 0.02 mmol) in benzene (2 mL). After refluxing for 18 h, the solution was concentrated in vacuo and chromatographed (hexane, then ethyl acetate/hexane 1:4) to afford 92 (35 mg, 0.11 mmol, 51%) as a colorless oil, \( R_f 0.15 \). IR \( v \) 1740, 1680, 690; \( ^1\text{H} \text{NMR} \) (200 MHz) \( \delta \) 1.25 (s, 6 H, \( \text{CH}_2\text{Ph} \)), 2.30 (d, \( J = 9.2 \text{ Hz} \), 2 H, 2 \( \times \) \( H_4 \)), 3.80 (s, 3 H, \( \text{CO}_2\text{CH}_3 \)), 3.85 (d, \( J = 12.4 \text{ Hz} \), 1 H, \( \text{CH}_2\text{Ph} \)), 3.99 (d, \( J = 12.4 \text{ Hz} \), 1 H, \( \text{CH}_2\text{Ph} \)), 4.10-4.45 (m, 2 H, \( \text{OCH}_2 \)), 4.60 (t, \( J = 9.3 \text{ Hz} \), 1 H, \( H_3 \)), 5.05-5.17 (m, 2 H, =CH_2), 5.55 (m, 1 H, =CH), 7.17-7.54 (m, 5 H, \( \text{ArH} \)).
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rel-(35,45)-2-(Allyloxy carbonyl)-1-benzyl-4-ethyl-3-pyrazolidinecarboxylic acid methyl ester (93). To a refluxing solution of n-Bu3SnH (324 µL, 1.22 mmol) in benzene (2 mL) was added dropwise in 1 h a solution of 63 (112 mg, 0.31 mmol) and AIBN (5.0 mg, 0.030 mmol) in benzene (2 mL). After refluxing for 18 h, the solution was concentrated in vacuo, taken up in THF (10 mL) and stirred with KF (93 mg, 1.22 mmol) and TBAF (122 mL of a 1.0 M solution in THF, 0.12 mmol) for 17 h. The organic layer was dried (MgSO4), filtered, concentrated in vacuo, and chromatographed (ethyl acetate/hexane 1:4) to afford 93 (39 mg, 0.12 mmol, 38%) as a colorless oil, Rf 0.25. IRv 1740, 1685, 690; 1H NMR (200 MHz) δ 0.94 (t, J = 7.5 Hz, 3 H, CH2C3), 1.40-1.55 (m, 1 H, CHHCH3), 1.70-1.90 (m, 1 H, CHHCH3), 2.65-2.73 (m, 2 H, 2 x H5), 3.15-3.18 (m, 1 H, H4), 3.82 (s, 3 H, CO2CH3), 3.75-3.85 (m, 1 H, C3HPh), 4.05-4.25 (m, 2 H, CHWPh and H3), 4.53 (d, J = 5.4 Hz, 2 H, OCH2), 5.14-5.30 (m, 2 H, =CH2), 5.76-5.90 (m, 1 H, =CH), 7.23-7.46 (m, 5 H, ArH); 13C NMR (50 MHz) δ 12.2 (CH2CH3), 24.7 (CH2CH3), 45.5 (C4), 52.5 (CO2CH3), 57.8 (C5), 61.7 (CH2Ph), 65.8 (C3), 66.5 (OCH2), 117.7 (=CH2), 127.4, 128.3, 129.6 (ArH), 132.5 (=CH), 137.4 (ArC), 173.1 (C(0)).

rel-(35,55)-2-(Ethoxycarbonyl)-5-(chloromethyl)-3-pyrazolidinecarboxylic acid methyl ester (104). A mixture of 56 (100 mg, 0.29 mmol), Pd/C (20 mg of 10% Pd on C, 0.02 mmol) and a few drops of a 1 M HCl/MeOH solution in MeOH (5 mL) was stirred under a N2-atmosphere for 2 h. After filtration over Celite, the solution was concentrated in vacuo, taken up in aq satd NaHCO3 (10 mL) and extracted with CH2Cl2 (3 x 10 mL). The combined organic layers were dried (MgSO4), filtered, concentrated in vacuo, and chromatographed (ethyl acetate/hexane 1:1) to afford 104 (57 mg, 0.23 mmol, 79%) as a colorless oil, Rf 0.39. IR v 1740, 1700, 1120, 1375, 1340; 1H NMR (300 MHz) δ 1.25 (t, J = 7.1 Hz, 3 H, CH2C3), 2.25 (ddd, J = 13.2, 7.1, 5.1 Hz, 1 H, H4), 2.54 (ddd, J = 13.2, 9.2, 4.4 Hz, 1 H, H4), 3.39 (dd, J = 11.4, 7.4 Hz, 1 H, C3HCl), 3.57 (dd, J = 11.4, 4.9 Hz, 1 H, CHHCl), 3.73 (s, 3 H, CO2CH3), 3.66-3.77 (m, 1 H, H5), 4.13-4.25 (m, 2 H, CH2CH3), 4.30-4.60 (br s, 1 H, NH), 4.66 (dd, J = 5.0, 9.2 Hz, 1 H, H3); 13C NMR (75 MHz) δ 14.6 (CH2CH3), 35.5 (C4), 44.9 (CH2C1), 52.5 (CO2CH3), 59.1 (C3 and C5), 62.2 (CH2CH3), 172.3 (C(0)); 13C NMR (50 MHz, CDCl3) δ 15.4 (CH2CH3), 36.3 (C4), 46.0 (CH2Cl), 52.5 (CO2CH3), 60.1, 60.2 (C3 and C5), 62.5 (CH2CH3), 173.1 (C(0)); MS (El, 70 eV) m/z (relative intensity) 250 (M+, 60), 201 (55), 177 (60), 119 (100), 69 (69), 25 (99); HRMS calcd for C9H15N2O4Cl250.0720, found 250.0709.

General procedure D for the transprotection reactions. To a solution of the Alloc compound and B2O-C2O2 (2 equiv) in CH2Cl2 was added Pd(PPh3)4 (0.02 equiv), immediately followed by the whole amount of n-Bu3SnH (1.1 equiv) and the mixture was stirred at rt for 2 h. Concentration in vacuo and flash chromatography (first with hexane, then with the suitable eluent) afforded the pure products.

rel-(35,55)-1-Benzyl-2-(tert-butoxycarbonyl)-5-(chloromethyl)-3-pyrazolidinecarboxylic acid methyl ester (110). Following the general procedure D, a solution of 57 (760 mg, 2.16 mmol) in CH2Cl2 (25 mL) was treated with Boc2O (990 µL, 4.31 mmol), Pd(PPh3)4 (50 mg, 0.043 mmol) and n-Bu3SnH (629 µL, 2.37 mmol). Concentration in vacuo and flash chromatography (ethyl acetate/hexane 1:4) afforded 110 (612 mg, 1.66 mmol, 77%) as a light yellow oil. IR v 30.35, 30.35, 1740, 1680, 1360, 690; 1H NMR (200 MHz) δ 1.43 (s, 9 H, (CH3)3), 2.47-2.69 (m, 2 H, 2 x H4), 3.11 (dd, J = 8.1, 10.6 Hz, 1 H, CHHCl), 3.30-3.44 (m, 2 H, CHHCl and H5), 3.77 (d, J = 12.6 Hz, 1 H, CHHPh), 3.81 (s, 3 H, CO2CH3), 4.23 (d, J = 12.6 Hz, 1 H, CHHPh), 4.59 (s, J = 8.8 Hz, 1 H, H3), 7.27-7.47 (m, 5 H, ArH).

rel-(3R,4S,5S)-1-Benzyl-2-(tert-butoxycarbonyl)-5-(chloromethyl)-4-(trimethylsilyl)-3-pyrazolidinecarboxylic acid methyl ester (111). Following the general procedure D, a solution of 71
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(434 mg, 1.02 mmol) in CH$_2$Cl$_2$ (15 mL) was treated with Boc$_2$O (0.52 mL, 2.25 mmol), Pd(PPh$_3$)$_4$ (35 mg, 0.031 mmol) and n-Bu$_3$SnH (0.30 mL, 1.13 mmol). Concentration in vacuo and flash chromatography (ethyl acetate/hexane 1:4) afforded 111 (288 mg, 0.65 mmol, 64%) as a light yellow oil, R$_f$ 0.60. IR v 1760, 1690, 1250, 840, 690; $^1$H NMR (200 MHz) $\delta$ 0.11 (s, 9 H, (CH$_3$)$_3$Si), 1.45 (s, 9 H, (CH$_3$)$_3$C), 1.97 (t, $J$ = 9.0 Hz, 1 H, H$_4$), 3.06 (dd, $J$ = 11.4, 4.3 Hz, 1 H, CH$_2$Cl), 3.24 (dd, $J$ = 11.4, 3.4 Hz, 1 H, CH$_2$Cl), 3.43-3.50 (m, 1 H, H$_5$), 3.77 (s, 3 H, CO$_2$CH$_3$), 3.96 (d, $J$ = 12.7 Hz, 1 H, CH$_2$Ph), 4.32 (d, $J$ = 12.7 Hz, 1 H, CH$_2$Ph), 4.99 (d, $J$ = 9.0 Hz, 1 H, H$_3$), 7.26-7.51 (m, 5 H, ArH); $^{13}$C NMR (50 MHz) $\delta$ 1.7 ((CH$_3$)$_3$Si), 28.3 ((CH$_3$)$_3$C), 35.1 (C$_4$), 47.9 ((CH$_3$)$_2$Cl), 52.0 (CO$_2$CH$_3$), 62.0 (C), 63.2 (CH$_2$Ph), 68.7 (C$_5$), 80.8 ((CH$_3$)$_2$C), 127.4, 128.2, 129.4 (ArH), 138.1 (ArC), 155.7, 172.8 (2 x C(0)); MS (El, 70 eV) $m/z$ (relative intensity) 440 (M$^+$, 26), 340 (90), 325 (12), 185 (13), 159 (5), 133 (8), 91 (100); HRMS calcd for C$_{21}$H$_{33}$N$_2$O$_4$ClSi 440.1898, found 440.1905.

Deprotection of 58. Following the general procedure D, a solution of trans-SS (320 mg, 0.87 mmol) in CH$_2$Cl$_2$ (10 mL) was treated with B$_2$CO (0.42 mL, 1.92 mmol), Pd(PPh$_3$)$_4$ (30 mg, 0.026 mmol) and n-Bu$_3$SnH (0.25 mL, 0.96 mmol). Concentration in vacuo and flash chromatography (ethyl acetate/hexane 1:4) afforded 112 (35, 55)-l-benzy l-2-(l-fer/-butoxy carbonyl)-5-(chloromethyl)-5-methyl-3-pyrazolidinecarboxylic acid methyl ester (112) (40 mg, 0.10 mmol, 12%) as a light yellow oil, R$_f$ 0.35 and l-benzyl-5-(chloromethyl)-3-methyl-2-pyrazoline-3-carboxylic acid methyl ester (113) (155 mg, 0.55 mmol, 63%) as a colorless oil, R$_f$ 0.25.

1-Benzyl-2-(l-fer/-butoxycarbonyl)-4-(l-chloro-1-methyIethyl)-2-pyrazoline-3-carboxylic acid methyl ester (114). According to the general procedure D, a solution of 61 (100 mg, 0.26 mmol) in CH$_2$Cl$_2$ (3 mL) was treated with Boc$_2$O (135 µL, 0.58 mmol), Pd(PPh$_3$)$_4$ (9 mg, 7.9·10$^{-3}$ mmol) and n-Bu$_3$SnH (77 µL, 0.29 mmol). Concentration in vacuo and flash chromatography (ethyl acetate/hexane 1:4) afforded 114 (50 mg, 0.17 mmol, 65%) as a colorless oil, R$_f$ 0.25. IR v 1740, 1680, 690; $^1$H NMR (200 MHz) $\delta$ 1.29 (s, 9 H, (CH$_3$)$_3$C), 1.52 (s, 3 H, CH$_3$), 2.17 (dd, $J$ = 13.0, 9.7 Hz, 1 H, H$_4$), 2.80 (dd, $J$ = 13.0, 8.7 Hz, 1 H, H$_4$), 3.16 (d, $J$ = 11.4 Hz, 1 H, CH$_2$Cl), 3.33 (d, $J$ = 11.4 Hz, 1 H, CH$_2$Cl), 3.80 (s, 3 H, CO$_2$CH$_3$), 3.97 (d, $J$ = 13.0 Hz, 1 H, CH$_2$Ph), 4.07 (d, $J$ = 13.0 Hz, 1 H, CH$_2$Ph), 4.45 (m, 1 H, H$_3$), 7.22-7.55 (m, 5 H, ArH), 113: $^1$H NMR (200 MHz) $\delta$ 1.32 (s, 3 H, CH$_3$), 3.20-3.50 (m, 1 H, H$_4$), 3.60-3.78 (m, 2 H, 2 x H$_5$). 3.82, 3.84 (s, 3 H, CO$_2$CH$_3$), 4.33, 4.42 (d, $J$ = 14.4 Hz, 1 H, C/HPh), 4.66, 4.75 (d, $J$ = 14.4 Hz, 1 H, C/HPh), 7.27-7.41 (m, 5 H, ArH).

rel-(3S,4S)-1-Benzyl-2-(l-fer/-butoxycarbonyl)-4-(1-chloro-1-methyIethyl)-3-pyrazolidinecarboxylic acid methyl ester (115). According to the general procedure D, a solution of 63 (90 mg, 0.25 mmol) in CH$_2$Cl$_2$ (3 mL) was treated with Boc$_2$O (124 µL, 0.54 mmol), Pd(PPh$_3$)$_4$ (8.5 mg, 7.4·10$^{-3}$ mmol) and n-Bu$_3$SnH (72 µL, 0.27 mmol). Concentration in vacuo and flash chromatography (ethyl acetate/hexane 1:4) afforded 115 (49 mg, 0.13 mmol, 54%) as a light yellow oil, R$_f$ 0.35. IR v 1745, 1700, 1680, 690; $^1$H NMR (200 MHz) $\delta$ 1.39 (s, 3 H, CH$_3$), 3.20-3.50 (m, 1 H, H$_4$), 3.60-3.78 (m, 2 H, 2 x H$_5$), 3.82, 3.84 (s, 3 H, CO$_2$CH$_3$), 4.33, 4.42 (d, $J$ = 14.4 Hz, 1 H, C/HPh), 4.66, 4.75 (d, $J$ = 14.4 Hz, 1 H, C/HPh), 7.27-7.41 (m, 5 H, ArH).

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1-Benzyl-5-chloro-5-methyl-1,4,5,6-tetrahydro-3-pyridazinecarboxylic acid methyl ester (116). Following the general procedure D, a solution of 59 (160 mg, 0.44 mmol) in CH_2Cl_2 (5 mL) was treated with Boc_2O (221 µL, 0.96 mmol), Pd(PPh_3)_4 (15 mg, 0.013 mmol) and t-BuSnH (127 µL, 0.48 mmol). Concentration in vacuo and flash chromatography (ethyl acetate/hexane 1:4) afforded 116 (78 mg, 0.28 mmol, 64%) as a light yellow oil, R_f 0.25. IR ν 1690, 1560, 690, 645; ^1H NMR (300 MHz) δ 1.55 (s, 3 H, CH_3), 2.59 (dd, J = 18.4, 2.8 Hz, 1 H, H_4), 2.90 (d, J = 18.2 Hz, 1 H, H_4), 2.95 (br d, J = 15 Hz, 1 H, H_6), 3.14 (dd, J = 12.8, 3.0 Hz, 1 H, H_6), 3.84 (s, 3 H, CO_2CH_3), 4.65 (d, J = 14.7 Hz, 1 H, CH_2Ph), 4.73 (d, J = 14.7 Hz, 1 H, CH_2Ph), 7.27-7.44 (m, 5 H, ArH).

1-Benzyl-3-methylene-1,4,5,6-tetrahydro-3-pyridazinecarboxylic acid methyl ester (117). According to the general procedure D, a solution of 67 (100 mg, 0.30 mmol) in CH_2Cl_2 (3 mL) was treated with Boc_2O (153 µL, 0.67 mmol), Pd(PPh_3)_4 (11 mg, 0.011 mmol) and t-Bu_3SnH (88 µL, 0.33 mmol). Concentration in vacuo and flash chromatography (ethyl acetate/hexane 1:4) afforded 117 (58 mg, 0.24 mmol, 78%) as a colorless oil, R_f 0.25. ^1H NMR (200 MHz) δ 3.14 (s, 2 H, 2 x H_4), 3.43 (s, 2 H, 2 x H_6), 3.84 (s, 3 H, CO_2CH_3), 4.61 (s, 2 H, CH_2Ph), 4.93 (s, 1 H, C=CWH), 5.03 (s, 1 H, C=CHH), 7.24-7.35 (m, 5 H, ArH).

Deprotection of 66. Following the general procedure, a solution of 66 (200 mg, 0.55 mmol) in CH_2Cl_2 (3 mL) was treated with Boc_2O (139 µL, 0.61 mmol), Pd(PPh_3)_4 (13 mg, 0.011 mmol) and t-Bu_3SnH (160 µL, 0.61 mmol). Concentration in vacuo and flash chromatography (ethyl acetate/hexane 1:4) afforded 3-benzyl-2-(tert-butoxycarbonyl)-1,2,3,4-tetrahydro-1H-phthalazinecarboxylic acid methyl ester (118) (118 mg, 0.31 mmol, 56%) as a colorless oil, R_f 0.35 and 3-benzyl-3,4-dihydro-1-phthalazinecarboxylic acid methyl ester (119) (35 mg, 0.12 mmol, 22%). ^1H NMR (200 MHz) δ 1.52,1.53 (s, 9 H, (CH_3)_3C), 3.30-4.50 (br m, 7 H, CO_2CH_3, CH_2Ph and NCH^, 5.40, 5.60 (br s, 1 H, NCH), 7.00-7.50 (m, 9 H, ArH); ^13C NMR (63 MHz) δ 28.4 ((CH_3)_3C), 52.4 (CO_2CH_3), 52.8 (NCH), 55.6 (NCH-j), 59.1 (CH_2Ph), 81.3 ((CH_3)_3O, 126.1, 127.4, 127.9, 128.3, 129.4, 131.7 (ArH), 132.0, 136.1, 138.0 (ArC), 171.5 (C(0)).

1-Benzyl-2-(tert-butoxycarbonyl)-3-chlorohexahydro-1H-diazepine-3-carboxylic acid methyl ester (120). According to the general procedure D, a solution of 64 (76 mg, 0.21 mmol) in CH_2Cl_2 (3 mL) was treated with Boc_2O (105 µL, 0.46 mmol), Pd(PPh_3)_4 (7.2 mg, 6.2×10^-3 mmol) and t-BuSnH (60 µL, 0.23 mmol). Concentration in vacuo and flash chromatography (ethyl acetate/hexane 1:4) afforded 120 (51 mg, 0.13 mmol, 64%) as a colorless oil, R_f 0.25. ^1H NMR (200 MHz) δ 3.30-5.50 (m, 7 H, ArH), 3.68 (d, J = 12.3 Hz, 1 H, C=CHPh), 3.80 (s, 3 H, CO_2CH_3), 4.13 (d, J = 13.0 Hz, 1 H, CH_2Ph), 4.50 (t, J = 8.8 Hz, 1 H, H_3), 7.27-7.44 (m, 5 H, ArH); ^13C NMR (50 MHz) δ (two diastereomers) 28.2 ((CH_3)_2C), 30.5, 34.4, 36.0, 35.9 (C4 and C6), 41.9 (C7), 52.4 (CO_2CH_3), 59.5 (C3), 60.2 (C5), 61.4 (CH_2Ph), 80.6 ((CH_3)_2C), 127.3, 128.1, 129.8 (ArH), 137.6 (ArC), 173.4 (C(0)); MS (El, 70 eV) m/z (relative intensity) 382 (M^+, 3), 327 (20), 281 (58), 163 (10), 91 (100).

rel-(3R,5S)-2-(tert-Butoxycarbonyl)-3-chloromethyl-3-pyrazolidinecarboxylic acid methyl ester (121). A mixture of 110 (120 mg, 0.33 mmol), Pd/C (30 mg of 10% Pd on C, 0.03 mmol) and a few drops of a 1 M HCl/MeOH solution in MeOH (10 mL) was stirred under a H_2-atmosphere for 1 h. After filtration
over Celite, the solution was concentrated in vacuo, taken up in aq satd NaHCO₃ (20 mL) and extracted with CH₂Cl₂ (3 x 20 mL). The combined organic layers were dried (MgSO₄), filtered, concentrated in vacuo and chromatographed (ethyl acetate/hexane 1:1) to afford 121 (81 mg, 0.29 mmol, 90%) white solid, mp 45-47 °C, Rf 0.15. IR ν 1740, 1705, 1365, 1130; ¹H NMR (200 MHz) δ 1.45 (s, 9 H, (CH₂)₃), 2.23 (ddd, J = 13.2, 7.1, 5.1 Hz, 1 H, H4), 2.54 (ddd, J = 13.2, 9.2, 4.4 Hz, 1 H, H4), 3.43 (dd, J = 11.2, 7.5 Hz, 1 H, CH2Cl), 3.60 (dd, J = 11.2, 4.8 Hz, 1 H, CH2Cl), 3.75 (s, 3 H, CO2CH3), 3.66-3.77 (m, 1 H, H5), 4.59 (dd, J = 4.9, 9.1 Hz, 1 H, H3); ¹³C NMR (50 MHz) δ 28.3 ((CH₂)₃), 35.7 (C4), 44.9 (CH2Cl), 52.4 (CO2CH3), 59.0, 59.2 (C3 and C5), 81.1 ((CH₂)₃C); MS (El, 70 eV) m/z (relative intensity) 178 (M⁺-100, 90), 119 (100), 95 (45), 91 (100), 69 (60).

Crystallographic data.
Tetragonal, P-4₂2₁c, a = 17.4709(7), b = 17.4709(7), c = 9.695 Å, α = β = γ = 90°, V = 2959.3(2) Å³, Z = 8, Dₓ = 1.25 g/cm³, λ(CuKα) = 1.5418 Å, μ(CuKα) = 23.98 cm⁻¹, F(000) = 1184, rt. Final R = 0.076 for 1164 observed reflections.
The numbering of the atoms in Tables 7.3 and 7.4 is as shown in the following structure:

![Chemical Structure of 121](image)

Table 7.3. Bond distances of the atoms (Å), with standard deviations in parentheses.

<table>
<thead>
<tr>
<th>Bond</th>
<th>Distance (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1-C4</td>
<td>1.777(8)</td>
</tr>
<tr>
<td>C1-C2</td>
<td>1.553(9)</td>
</tr>
<tr>
<td>C1-C4</td>
<td>1.51(1)</td>
</tr>
<tr>
<td>C1-N2</td>
<td>1.467(8)</td>
</tr>
<tr>
<td>C1-C2</td>
<td>1.45(1)</td>
</tr>
<tr>
<td>C1-N2</td>
<td>1.48(9)</td>
</tr>
<tr>
<td>C1-C5</td>
<td>1.49(9)</td>
</tr>
<tr>
<td>C1-N1</td>
<td>1.44(11)</td>
</tr>
<tr>
<td>C2-C3</td>
<td>1.34(10)</td>
</tr>
<tr>
<td>C2-C3</td>
<td>1.38(9)</td>
</tr>
<tr>
<td>C2-C3</td>
<td>1.39(9)</td>
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<tr>
<td>C2-C3</td>
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<tr>
<td>C2-C3</td>
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<tr>
<td>C2-C3</td>
<td>1.44(1)</td>
</tr>
<tr>
<td>C2-C3</td>
<td>1.45(1)</td>
</tr>
</tbody>
</table>

Table 7.4. Bond angles of the atoms (°), with standard deviations in parentheses.

<table>
<thead>
<tr>
<th>Bond</th>
<th>Angle (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C2-C1-C4</td>
<td>113.6(5)</td>
</tr>
<tr>
<td>C2-C1-N2</td>
<td>104.4(5)</td>
</tr>
<tr>
<td>C2-C1-C4</td>
<td>107.2(5)</td>
</tr>
<tr>
<td>C2-C1-C5</td>
<td>103.0(5)</td>
</tr>
<tr>
<td>C2-C1-C5</td>
<td>108.9(5)</td>
</tr>
<tr>
<td>C2-C1-C5</td>
<td>103.1(5)</td>
</tr>
<tr>
<td>C2-C1-C5</td>
<td>108.9(5)</td>
</tr>
<tr>
<td>C2-C1-C5</td>
<td>115.8(6)</td>
</tr>
<tr>
<td>C2-C1-C5</td>
<td>115.8(6)</td>
</tr>
<tr>
<td>C2-C1-C5</td>
<td>115.8(6)</td>
</tr>
<tr>
<td>C2-C1-C5</td>
<td>115.8(6)</td>
</tr>
<tr>
<td>C2-C1-C5</td>
<td>115.8(6)</td>
</tr>
<tr>
<td>C2-C1-C5</td>
<td>115.8(6)</td>
</tr>
</tbody>
</table>
rel-((3R,4S,5S)-2-(tert-Butoxycarbonyl)-5-chloromethyl-4-(trimethylsilyl)-3-pyrazolidinecarboxylic acid methyl ester (122). A mixture of 111 (275 mg, 0.63 mmol), Pd/C (67 mg of 10% Pd on C, 0.06 mmol) and a few drops of a 3 M HCl/MeOH solution in MeOH (7 mL) was stirred under an H2-atmosphere for 45 min. After filtration over Celite, the solution was concentrated in vacuo, taken up in aq satd NaHCO3 (10 mL) and extracted with CH2Cl2 (3 × 10 mL). The combined organic layers were dried (MgSO4, filtered, concentrated in vacuo and chromatographed (ethyl acetate/hexane 1:2) to afford 122 (178 mg, 0.51 mmol, 81%) as a colorless oil, 0.50. IR ν 1735, 1700, 1250, 840; 1H NMR (200 MHz) δ 0.10 (s, 9 H, (CH3)3Si), 1.45 (s, 9 H, (CH3)3C), 1.84 (t, J = 9.0 Hz, 1 H, H4), 3.57-3.84 (m, 6 H, C02CH3, H5 and CH2C1), 4.65 (d, J = 8.8 Hz, 1 H, H3); 13C NMR (50 MHz) δ 1.7 ((CH3)3Si), 28.2 ((CH3)3C), 36.1 (C4), 45.2 (CH2C1), 51.8 (CO2CH3), 60.6 (C3), 63.0 (C5), 81.1 ((CH3)3C), 153.2, 172.0 (2 x C(O)); MS (El, 70 eV) m/z (relative intensity) 350 (M+, 8), 279 (9), 250 (100), 191 (47), 185 (19), 133 (18); HRMS calcd for C14H27N2O4ClSi 350.1429, found 350.1468.

2-(tert-Butoxycarbonyl)-5-chlorohexahydro-1H-diazepine-3-carboxylic acid methyl ester (123). A mixture of 120 (40 mg, 0.10 mmol), Pd/C (11 mg of 10% Pd on C, 0.01 mmol) and one drop of a 3 M HCl/MeOH solution in MeOH (5 mL) was stirred under a H2-atmosphere for 1 h. After filtration over Celite, the solution was concentrated in vacuo and chromatographed (ethyl acetate/hexane 1:2) to afford 123 (182 mg, 0.50 mmol, 65%) as a colorless oil, Rf 0.50. IR ν 3450, 1720, 1685; 1H NMR (200 MHz) δ 1.45 (s, 9 H, (CH3)3C), 1.69-1.84 (m, 2 H, 2 x H6), 2.19-2.27 (m, 2 H, 2 x H4), 3.53-3.78 (m, 3 H, H5 and 2 x H7), 3.75 (s, 3 H, CO2CH3), 4.50-4.63 (m, 1 H, H3); 13C NMR (50 MHz) δ 28.0 ((CH3)2C), 30.5, 35.6, 35.8, 38.2, 38.3 (C4 and C6), 42.0 (C7), 52.1 (CO2CH2), 56.0, 56.5 (C5), 58.8 (C3), 80.9 ((CH3)2C), 172.7 (C(O)); MS (El, 70 eV) m/z (relative intensity) 292 (M+, 6), 236 (8), 192 (20), 175 (13), 167 (23), 153 (27), 131 (100).

rel-(3R,5S)-5-chloromethyl-3-pyrazolidinecarboxylic acid hydrogen chloride (127). A solution of 121 (30 mg, 0.01 mmol) in 2 M HCl was heated at 60 °C for 2 h and concentrated in vacuo to afford 127 (18
Synthesis of cyclic α-hydrazino acid derivatives

mg, 0.090 mmol, 82%) as a viscous yellow oil. H NMR (200 MHz, D2O) δ 2.46 (dt, J = 13.8, 8.4 Hz, 1 H, H4), 2.67 (ddd, J = 7.5, 12.4 Hz, 1 H, H/C(HCl)), 3.74 (dd, J = 3.8, 12.3 Hz, 1 H, H5); 13C NMR (50 MHz, D2O) δ 34.9 (C4), 44.8 (CH2Cl), 62.4, 62.6 (C3 and C5), 174.5 (C(0)).

2-(Allyloxycarbonyl)-l-benzyl-5-oxohexahydro-3-pyridazinecarboxylic acid methyl ester (128). A solution of 73 (75 mg, 0.18 mmol) and H2O (16 μL, 0.90 mmol) in xylenes (3 mL) was heated in a sealed tube for 10 min at 170 °C. Concentration in vacuo and flash chromatography (ethyl acetate/hexane 1:2) afforded 128 (44 mg, 0.13 mmol, 74%) as a colorless oil, Rf 0.35. IR ν 1730, 1710, 1690, 690; 1H NMR (200 MHz) δ 2.75-3.10 (m, 2 H, 2 × H4), 3.35-3.65 (m, 2 H, 2 × H6), 3.74 (s, 3 H, C02CH3), 4.15-4.40 (m, 2 H, Ctf2Ph), 4.69 (d, J = 5.6 Hz, 2 H, OCH2), 5.01 (t, J = 6.8 Hz, 1H, H3), 5.25-5.40 (m, 2 H, =CH2), 5.86-6.03 (m, 1 H, =CH), 7.18-7.34 (m, 5 H, ArH); 13C NMR (63 MHz) δ 38.8 (C4), 53.0 (C02CH3), 56.9 (C3), 59.9 (CH2Ph), 61.4 (C6), 76.3 (OCH2), 118.8 (=CH2), 128.1, 128.7, 129.2 (ArH), 132.3 (=CH), 136.8 (=CH), 171.3, 204.4 (2 × C(O)); MS (El, 70 eV) m/z (relative intensity) 332 (M+, 11), 302 (12), 273 (7), 169 (6), 150 (22), 105 (30), 91 (100); HRMS calcd for C17H20N2O5 332.1372, found 332.1364.

Reduction of 128. To a solution of 128 (44 mg, 0.13 mmol) in MeOH (2 mL) was added at -10 °C NaEtffy (5.5 mg, 0.151 mmol) and the mixture was stirred at -10 °C for an additional h. The mixture was poured into aq satd NaHCO3 (10 mL) and extracted with CH2Cl2 (3 × 10 mL). The combined organic layers were dried (MgSO4), filtered, concentrated in vacuo and chromatographed to yield rel-(3S,5S)-2-(allyloxycarbonyl)-l-benzyl-5-hydroxyhexahydro-3-pyridazinecarboxylic acid methyl ester (cis-130) (36 mg, 0.108 mmol, 82%) and trans-130 (6 mg, 0.018 mmol, 13%) as a colorless oil, Rf 0.35. IR ν 3450, 1730, 1680, 690; 1H NMR (200 MHz) δ 1.95-2.07 (m, 1 H, H4), 2.37-2.44 (m, 1 H, H4), 2.81-3.05 (m, 2 H, 2 x H6), 3.73 (s, 3 H, C02CH3), 3.89 (m, 1 H, H5), 4.17 (d, J = 11.9 Hz, 1 H, CHHPh), 4.55 (d, J = 12.8 Hz, 1 H, CHtfPh), 4.70 (m, 2 H, OCH2), 4.96 (s, 1 H, H3), 5.25-5.41 (m, 2 H, =CH2), 5.92-6.06 (m, 1 H, =CH), 7.21-7.39 (m, 5 H, ArH); 13C NMR (63 MHz) δ 31.5 (C4), 52.7 (C02CH3), 53.0 (C6), 59.5 (CH2Ph), 63.7 (C3), 66.5 (OCH2), 118.0 (=CH2), 127.3, 128.3, 129.2 (ArH), 132.4 (=CH), 138.0 (ArC), 156.0, 173.0 (C(O)); MS (El, 70 eV) m/z (relative intensity) 334 (M+, 92), 276 (30), 250 (72), 211 (28), 207 (21), 162 (32), 106 (93), 91 (100); HRMS calcd for C17H22N2O5 334.1529, found 334.1551.
	rans-130: IR ν 3450, 1730, 1680, 690; 1H NMR (200 MHz) δ 1.50-1.80 (m, 2 H, H4), 2.90 (m, 1 H, H6), 2.97 (dd, J = 12.8, 4.5 Hz, 1 H, H6), 3.77 (s, 3 H, C02CH3), 4.00-4.30 (m, 3 H, NCH2 and H5), 4.26 (d, J = 13.1 Hz, 1 H, CtfHPh), 4.38 (d, J = 13.1 Hz, 1 H, CHHPh), 4.64 (d, J = 5.6, 2 H, OCH2), 4.74 (m, 1 H, H5), 4.93 (t, J = 4.5 Hz, 1 H, H1), 183
5.23-5.37 (m, 2 H, =CH2), 5.83-6.00 (m, 1 H, =CH), 7.22-7.43 (m, 5 H, ArH); 13C NMR (50 MHz) δ 36.5 (C8), 46.7 (C5), 50.9 (C4), 54.2 (Cl), 61.9 (CH2Ph), 67.0 (OCH2), 118.5 (=CH2), 127.6, 128.3, 129.1 (ArH), 132.1 (=CH), 137.2 (ArC), 155.2, 172.7 (C(0)); MS (EI, 70 eV) m/z (relative intensity) 302 (M+, 30), 218 (24), 173 (4), 139 (5), 120 (7), 91 (100); HRMS calcd for C16H18N2O4 302.1267, found 302.1294.

rel-(lS,55)-3-Benzyl-6-oxa-2,3-diazabicyclo[3.2.1]octan-7-one-2-carboxylic acid tert-butil ester (132). According to the general procedure D, a solution of 131 (20 mg, 0.066 mmol) in CH2Cl2 (1 mL) was treated with B0C2O (33 μL, 0.015 mmol), Pd(PPh3)4 (2 mg, 2.10* mmol) and w-BugSnH (19 μL, 0.073 mmol). Concentration in vacuo and flash chromatography (ethyl acetate/hexane 1:1) afforded 132 (7 mg, 0.022 mmol, 33%) as a light yellow oil, R* 0.55. IR ν 1785, 1700, 690; 1H NMR (200 MHz) δ 1.49 (s, 9 H, (CH3)3C), 2.06 (d, J = 12.2 Hz, 1 H, H8), 2.30-2.45 (m, 1 H, H8), 2.90-3.05 (m, 1 H, H4), 3.15 (d, J = 13.4 Hz, 1 H, H4), 4.25 (d, J = 13.1 Hz, 1 H, O/HPh), 4.38 (d, J = 13.1 Hz, 1 H, CHHPh), 4.66-4.68 (m, 1 H, H5), 4.89 (t, J = 4.2 Hz, 1 H, HI), 7.26-7.42 (m, 5 H, ArH); 13C NMR (50 MHz) δ 28.3 ((CH3)3C), 36.6 (C8), 50.8 (C4), 61.6 (CH2Ph), 82.0 ((CH3)3C), 127.5, 128.3, 129.0 (ArH), 137.6 (ArC); MS (EI, 70 eV) m/z (relative intensity) 318 (M+, 1), 218 (87), 167 (19), 149 (12), 127 (15), 91 (100); HRMS calcd for C17H22N2O4 318.1580, found 318.1593.

7.10 REFERENCES AND NOTES

1) Hassall, C. H.; Magnus, K. E. Nature 1959, 184, 1223.
Synthesis of cyclic α-hydräzo acid derivatives


This thesis describes the reactivity and application of the different types of N-acylhydrazonium ions A-E as intermediates in the synthesis of cyclic hydrazine derivatives. An important difference from the corresponding well-known N-acyliminium ions is the presence of an electron-withdrawing nitrogen atom, leading to a more destabilized iminium ion.

In Chapter 1 a literature survey is presented on the properties and recent applications of organic hydrazine derivatives in various fields of chemistry. Furthermore, some general information is provided about the reactivity of different types of iminium ions.

In Chapter 2 cyclization reactions via the N,N'-diacylhydrazonium ions A are described, leading to protected monofunctionalized cyclic hydrazines. A typical example is shown in eq 1, in which the butynyl precursor 1 is cyclized to give the seven-membered ketone 2.

![Chemical structures](image)

Remarkably, these cyclizations provide higher yields of seven-membered rings than of six-membered rings. This is probably due to a more strained transition state in the latter case as a result of the vicinal carbamate functions. Compared with cyclization reactions of the corresponding N-acyliminium ions, more strongly acidic conditions (TiCl₄) are required to form the reactive intermediates. This is in accord with the expected more difficult formation of the hydrazonium ions as a result of the destabilizing effect of the nitrogen substituent.

Chapter 3 reports a search for a convenient method to deprotect cyclic hydrazines which are protected with an allyloxycarbonyl (Alloc) function. Palladium(0)-catalyzed cleavage of the Alloc group in the presence of the hydride donor n-Bu₃SnH initially furnishes a ditin carbamate, which can either be cleaved with an acid to give the (protonated) free hydrazine or be reacted with an activated carbonyl compound to form a new amide bond. An example of the latter
Summary

possibility is shown in eq 1, in which the cyclic ketone 2 is 'transprotected' to give the monoprotected product 3.

Chapter 4 deals with the synthesis of various bridged bicyclic hydrazines such as 5 and 7 (eqs 2 and 3). These compounds are obtained upon cyclization of the corresponding precursors 4 and 6 via the endocyclic N-acylhydrazonium ions B. The strong Lewis acid TiCl₄ also provides the best results in these types of cyclization reactions, except in the case of silicon nucleophiles. This methodology provides an effective route for the synthesis of different [3.2.1] and [2.2.1] bicyclic hydrazines.

\[
\begin{align*}
4 & \xrightarrow{\text{TiCl}_4} 5 & \text{(eq 2)} \\
6 & \xrightarrow{\text{BF}_3\cdot\text{OEt}_2} 7 & \text{(eq 3)}
\end{align*}
\]

A comparable strategy is utilized for the synthesis of some azatropane derivatives as described in Chapter 5. In order to introduce the desired functionalities, a protected β-ketoester is used as a nucleophile in the cyclization reaction. Cyclization of 8 leads to a high yield of the desired cyclization product 9 (eq 4), which is converted into different azatropane derivatives such as 10. Attempts to cyclize precursors which lack the geminal methyl substituents were unsuccessful.

\[
\begin{align*}
8 & \xrightarrow{\text{BF}_3\cdot\text{OEt}_2} 9 & \text{(eq 4)} \\
 & \xrightarrow{\text{MeO}_2\text{C}} 10
\end{align*}
\]

In Chapter 6 the synthesis of bicyclic hydrazines via the exocyclic N-acylhydrazonium ions C and D are described. Examples of both cases are shown in eq 5, in which the bicyclic hydrazine 13 and the bicyclic α-hydrazino ester 14 are formed. Cyclization reactions to form 5,5- and 5,6-bicyclic pyrazolinones occur in good yields, if the initially formed cationic intermediates are properly stabilized by substituents.
Cyclization reactions via the N-acylhydrazonium intermediates E are described in Chapter 7. A remarkable example is shown in eq 6, in which cyclization of the allyl precursor 15 only affords the five-membered rings 18, whereas a six-membered ring is expected. The formation of the five-membered rings is explained by assuming the intermediacy of the aziridinium ion 17, which is formed by stabilization of the carbocation 16 via the amine nitrogen atom. Nucleophilic ring opening then gives the pyrazolidines 18.

In general, it is found that such a ring contraction takes place if the initially formed cationic intermediate is not properly stabilized by a substituent. A preference for the formation of five-membered rings is also observed in some other cyclization reactions, giving only the 5-exo product, while the 6-endo product is expected.

In contrast with the cyclization reactions discussed in the previous Chapters, in these cases higher yields are obtained if the milder Lewis acids SnCl₄ and Et₂AlCl are used. Various protected five- and six-membered α-hydrazino esters can be synthesized via this method. The formation of six-membered rings opens a route to precursors of naturally occurring piperazic acids (hexahydro-3-pyridazinecarboxylic acids). The cyclization product 19 (eq 7) can be converted into the ketoester 20, which upon reduction and transprotection affords the fully protected 5-hydroxypiperazic acid 21.
SAMENVATTING
SYNTHÉSE VAN CYCLISCH HYDRAZINEN EN α-HYDRAZINOZUUR-DERIVATEN VIA N-ACYLHYDRAZONIUMIONEN

In dit proefschrift worden de reaktiviteit en toepassingen van de verschillende N-acyl-hydrazoniumionen A-E beschreven als intermediairen in de synthese van cyclische hydrazinederivaten. Een belangrijk verschil met de overeenkomstige N-acyliminiumionen is de aanwezigheid van een elektronenzuigend stikstofatoom dat het iminiumion extra destabiliseert.

![Chemische structuren](image)

Hoofdstuk 1 omvat een literatuuronderzoek naar eigenschappen en recente toepassingen van organische hydrazinederivaten in uiteenlopende richtingen. Tevens wordt ingegaan op een aantal eigenschappen van verschillende soorten iminiumionen.

In Hoofdstuk 2 worden cyclisatiereakties via de N,N'-diacylhydrazonium intermediairen A beschreven, die leiden tot beschermde, monogesubstitueerde, cyclische hydrazinen. Een illustratief voorbeeld is weergegeven in vgl. 1, waar cyclisatie van de butynylprecursor 1 leidt tot het cyclische keton 2.

![Cyclisatie reactie](image)

Opvallend aan deze cyclisatiereakties is de relatief gemakkelijke vorming van zevenringen vergeleken met zesringen. Dit wordt waarschijnlijk veroorzaakt door een meer gespannen overgangstoestand in het geval van de zesringen als gevolg van spanning tussen de twee carbachlormaatgroepen. Verder blijkt dat, vergeleken met cyclisaties van overeenkomstige N-acyliminiumionen, sterkere Lewiszuren (zoals TiCl₄) een beter resultaat geven. Dit komt overeen met de te verwachten moeilijkere vorming van de reaktieve intermediairen door de aanwezigheid van de destabiliserende stikstofsustituut.

Hoofdstuk 3 omvat onderzoek naar het ontwikkelen van een geschikte methode om hydrazinen, die met een allyloxy carbonyl (Alloc) groep zijn beschermde te ontschermen. Een Pd(0)-gekatalyseerde splitsing van de allylcarbamaten in aanwezigheid van de hydridedonor n-
Samenvatting

Bu₃SnH geeft een ditincarbamaat, dat vervolgens of onder invloed van zuur het (geprotoneerde) vrije hydrazine geeft, of met een geactiveerde carbonylverbinding kan reageren onder vorming van een amidebinding. Een voorbeeld van de laatste reaktie is weergegeven in vgl. 1, waarbij 'transprotectie' van het keton 2 leidt tot het monobeschermde produkt 3.

In Hoofdstuk 4 wordt de synthese behandeld van verschillende gebruinde hydrazinen zoals 5 en 7 (vgl. 2 en 3). De synthese van deze verbindingen verloopt door cyclisatie van de overeenkomstige precursors 4 en 6 via de endocyclische N-acylhydrazoniumionen B. Ook in dit type cyclisatierreakties blijkt het sterke Lewiszuur TiCl₄ de beste resultaten te geven, behalve in het geval van siliciumnucleofielen. Het gebruik van mierenzuur leidt niet in alle gevallen tot ringsluiting. Deze methode biedt een geschikte route voor de synthese van diverse [3.2.1] en [2.2.1] bicyclische hydrazinen.

\[ \text{(vgl. 2)} \]

\[ \text{(vgl. 3)} \]

Dezelfde methode wordt tevens in Hoofdstuk 5 toegepast in de synthese van een aantal azatropaanderivaten. Voor het invoeren van verschillende functionaliteiten wordt gebruik gemaakt van een beschermde β-ketoester als nucleofixe zijketen. Cyclisatie van de precursor 8 leidt in hoge opbrengst tot het gewenste cyclisatieprodukt 9, dat uiteindelijk onder meer kan worden omgezet in het azatropaanderivaat 10. Pogingen om precursors te cycliseren waar de geminale methylsubstituenten ontbreken, verliepen zonder succes.

\[ \text{(vgl. 4)} \]

In Hoofdstuk 6 wordt de synthese beschreven van bicyclische hydrazinen via de exocyclische N-acylhydrazoniumionen C en D. Voorbeelden van beide zijn de cyclisaties tot 13 en 14 (vgl. 5), waarbij in het laatste geval een bicyclisch α-hydradinozuur wordt gevormd.

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Cyclisaties tot 5,5- en 5,6-bicyclische pyrazolidines verlopen in goede opbrengsten, indien het initieel gevormde carbokation in voldoende mate door substituaten wordt gestabiliseerd.


In het algemeen wordt gevonden dat, indien het primair gevormde kation niet door een substituent wordt gestabiliseerd, een dergelijke ringcontractie optreedt. Verder blijkt ook in een aantal andere cyclisatieroakties een opmerkelijke voorkeur voor 5-exo- boven 6-endo-cyclisatie op te treden.

In tegenstelling tot de in eerdere hoofdstukken besproken cyclisatieroakties, blijken in deze gevallen mindere Lewiszuren zoals SnCl₄ en Et₂AlCl de hoogste opbrengsten te geven. Diverse beschermde vijf- en zesring α-hydrazinozuren kunnen via deze methode worden gesynthetiseerd. De vorming van zesringen opent een route naar precursors van natuurlijke piperazinezuren (hexahydro-3-pyridazinecarbonzuren). Het cyclisatieprodukt 19 (vgl. 7) kan worden omgezet in de ketoester 20, die vervolgens na reduktie en transprotectie het volledig beschermde 5-hydroxypiperazinezuur 21 geeft.