Thesis for the Master’s degree in chemistry

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Synthesis of C-Ring Functionalized Phenanthridines employing Intramolecular Diels-Alder of Furan (IMDAF) as the Key Step

60 study points

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Håkon Sætren Gulbrandsen

Oslo, May 2014
Abstract

A synthetic strategy towards the (aza)phenanthridine ring-system (3) employing an intramolecular Diels-Alder of furan (IMDAF) as the key step, has previously been developed in our research group (Scheme 1).

Scheme 1. Synthesis route towards (aza)phenanthridines.

The exploration of this synthetic pathway has until now been focused on substitution in the phenanthridine A-ring. Herein is described the synthesis of (partly reduced) phenanthridines functionalized in the C-ring by employing a substituted allylic moiety, and by selective ring-opening of the intramolecular Diels-Alder adduct 7 (Scheme 2).

Scheme 2. Synthesis of phenanthridines substituted in the C-ring presented herein.

(Note: Numbering used in this abstract is not the same as the numbering in the report.)
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Abbreviations and symbols

Ac  acetyl
AIBN azobisisobutyronitrile
aq. aqueous
Ar aryl
Bn benzyl
Boc tert-butoxycarbonyl
Bu butyl
BuOH butanol
C carbon
$^{13}$C carbon spectrum (NMR)
°C degree Celsius
Calcd. calculated
COSY correlation spectroscopy (NMR)
d doublet (NMR)
d deuterated
δ chemical shift (NMR)
dd doublet of doublets (NMR)
ddd doublet of doublet of doublets (NMR)
DDQ 2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DMF dimethylformamide
DMSO dimethyl sulfoxide
DNA deoxyribonucleic acid
dq doublet of quartets
EDG electron donating group
EI electron impact (MS)
eq. equivalent(s)
Et ethyl
et al. et alii
EtOAc ethyl acetate
EtOH ethanol
EWG electron withdrawing group
Exp. experimental
FMO frontier molecular orbital
FtsZ filamenting temperature-sensitive mutant Z
GHz gigahertz
GNB Gram-negative bacteria
GPB Gram-positive bacteria
h hour(s)
$^1$H proton spectrum (NMR)
HIV human immunodeficiency virus
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>HMBC</td>
<td>heteronuclear multiple bond correlation experiment</td>
</tr>
<tr>
<td>HOMO</td>
<td>highest occupied molecular orbital</td>
</tr>
<tr>
<td>HRMS</td>
<td>high resolution mass spectra</td>
</tr>
<tr>
<td>HSQC</td>
<td>heteronuclear single quantum coherence spectroscopy (NMR)</td>
</tr>
<tr>
<td>hv</td>
<td>irradiation (UV)</td>
</tr>
<tr>
<td>Hz</td>
<td>hertz</td>
</tr>
<tr>
<td>IMDAF</td>
<td>intramolecular Diels-Alder reaction of furan</td>
</tr>
<tr>
<td>J</td>
<td>coupling constant (NMR)</td>
</tr>
<tr>
<td>L</td>
<td>ligand</td>
</tr>
<tr>
<td>LA</td>
<td>Lewis acid</td>
</tr>
<tr>
<td>LUMO</td>
<td>lowest unoccupied molecular orbital</td>
</tr>
<tr>
<td>M</td>
<td>molar</td>
</tr>
<tr>
<td>m</td>
<td>multiplet (NMR)</td>
</tr>
<tr>
<td>$M^+$</td>
<td>molecular ion peak (MS)</td>
</tr>
<tr>
<td>Me</td>
<td>methyl</td>
</tr>
<tr>
<td>MeCN</td>
<td>acetonitrile</td>
</tr>
<tr>
<td>MeI</td>
<td>iodomethane</td>
</tr>
<tr>
<td>MHz</td>
<td>megahertz</td>
</tr>
<tr>
<td>MIC</td>
<td>minimum inhibitory concentration</td>
</tr>
<tr>
<td>Min</td>
<td>minutes</td>
</tr>
<tr>
<td>Mol. Sieves</td>
<td>molecular sieves</td>
</tr>
<tr>
<td>mp</td>
<td>melting point</td>
</tr>
<tr>
<td>MRSA</td>
<td>methicillin-resistant Staphylococcus aureus</td>
</tr>
<tr>
<td>MS</td>
<td>mass spectroscopy</td>
</tr>
<tr>
<td>MW</td>
<td>microwave</td>
</tr>
<tr>
<td>$m/z$</td>
<td>mass per charge (MS)</td>
</tr>
<tr>
<td>n</td>
<td>normal</td>
</tr>
<tr>
<td>NBS</td>
<td>N-bromosuccinimide</td>
</tr>
<tr>
<td>n.d.</td>
<td>not determined</td>
</tr>
<tr>
<td>NMP</td>
<td>N-methyl pyrrolidone</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance spectroscopy</td>
</tr>
<tr>
<td>NOE</td>
<td>nuclear overhauser effect</td>
</tr>
<tr>
<td>NOESY</td>
<td>nuclear overhauser effect spectroscopy (NMR)</td>
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<tr>
<td>o</td>
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</tr>
<tr>
<td>OAc</td>
<td>acetate</td>
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<td>triflate</td>
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<td>oxidation</td>
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<td>para</td>
</tr>
<tr>
<td>PhH</td>
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</tr>
<tr>
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<tr>
<td>PMB</td>
<td>p-methoxybenzyl</td>
</tr>
<tr>
<td>Pr</td>
<td>propyl</td>
</tr>
<tr>
<td>q</td>
<td>quartet (NMR)</td>
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1. INTRODUCTION

Our group has previously studied the intramolecular Diels-Alder reaction of furans (IMDAF) of ortho-furyl(allylamino)(aza)arenes.\textsuperscript{1-3} The initially formed ring-system has been found to easily ring-open, eliminate water and oxidize, providing a few-step high-yielding synthesis route to (aza)phenanthridines. Phenanthridines are an interesting class of compounds due to their broad spectrum of biological activities, and thereby their potential use in medicine. After exploring the substitution patterns of \textit{o}-furyl(allylamino)arenes, we have decided to introduce substituted \textit{N}-allyl moieties to allow further functionalization of the phenanthridine, and to expand the scope of this synthesis strategy. Herein, we discuss the synthesis of functionalized phenanthridines through IMDAF of \textit{o}-furyl(crotylamino)arenes and the chemistry of the intermediates.

To understand the motivation for exploring and expanding this synthesis strategy towards phenanthridines, the report includes a general introduction of the biological properties of alkaloids containing the phenanthridine ring-system, and the urgent need for novel antibacterial agents. This is followed by a brief overview of synthetic strategies of phenanthridines. After a section explaining the common chemistry employed herein, the basic principles of microwave-based heating are briefly explained. Then there is a section including the discovery and development of the IMDAF-based strategy in our group. Chapter 2 contains in-depth details regarding synthesis, and discussion of the results and observations encountered during this project. The report is finished off with possible future research which has resulted from work performed herein, a conclusion of what has been achieved, and finally experimental details, appendix and the reference list.
1.1 Naturally occurring phenanthridine alkaloids and their biological activities

This section gives an overview of naturally occurring phenanthridine-containing alkaloids, their biological activities, and their potential use in medicine in the future.

1.1.1 Phenanthridine alkaloids

Alkaloids are nitrogen containing secondary plant metabolites that often contains heterocyclic structures. Alkaloids with the backbone structure of phenanthridine (Figure 1.1) are well known, and plant extracts being employed in traditional medicine around the world, have later been found to contain phenanthridine alkaloids.\(^4,5\) A phenanthridine subgroup of great medicinal interest is the quaternary benzo[c]phenanthridinium alkaloids (QBAs) (Figure 1.1).

![Figure 1.1. Phenanthridine and a general quaternary benzo[c]phenanthridium compound. Numbering of the phenanthridine ring-system is shown.](image)

Several plant families are known to produce phenanthridine alkaloids. Amongst these are the families *Amaryllidaceae*, *Fumariaceae*, *Papaveraceae* and *Rutaceae*.\(^6,8\) Figure 1.2. shows several phenanthridine alkaloids with interesting biological activities. This includes activity towards bacteria,\(^9\) mycobacteria,\(^10\) malaria,\(^11\) an array of cancer cell lines,\(^12\) in addition to anti-inflammatory activity\(^13\) and acetylcholinesterase inhibition.\(^14\)
Several synthetic or naturally occurring phenanthridine compounds are, or has been on the market as drugs for various diseases: Dimidium bromide, ethidium bromide and isometamidium chloride (Figure 1.3) have been employed as trypanocides for cattle. Sanguinarine and chelerythrine are employed in dental care applications due to their anti-plaque properties. A mixture of chelerythrine and sanguinarine (“sanguiritrin”) is marketed as an antifungal and anti-inflammatory drug in Russia. Ethidium bromide, propidium iodide and macarpine (Figure 1.3), are used as DNA-binding fluorescent tags in biochemistry laboratories.
1.1.3 Drug resistance and the future prospects for phenanthridine-based drugs

Drug resistance is a global problem that has been receiving much attention the last 20 years, and rightfully so. World Health Organization (WHO) recently published their first ever report on the growing concern of drug resistance,\(^1\) which is observed related to bacterial infections, tuberculosis, HIV and malaria. The report is based on data from 114 countries, and describes the possibility of a “post-antibiotic era” where “common infections and minor injuries can kill”, due to extensive drug resistance towards practically all antibacterial agents on the market. During the recent years, methicillin-resistant *Staphylococcus aureus* (MRSA) has received much attention, due to a worldwide increase in mortality.\(^2\) Pneumonia caused by multi-drug resistant *Streptococcus pneumoniae* is also a topic of great concern.\(^2\)

There is a broad scientific consensus that there is a need for new and effective antibacterial agents.\(^2\) Drug resistance has been observed for all classes of antibacterial agents currently on the market, most of which were discovered between 1940-1970 through extensive screening of natural products.\(^2\) The problem of drug resistance has so far been restricted to
Gram-positive bacteria (GPB), including the mentioned *S. aureus* and *S. pneumoniae*. There is however an increasing concern regarding the emergence of pan-resistant, i.e. resistant to all classes of antibacterial agents, Gram-negative bacteria (GNB), such as *Acinetobacter baumannii* and *Pseudomonas aeruginosa*. Both bacteria are known to cause potentially fatal infections, including pneumonia.

Antibacterial activity of a compound is measured through its minimum inhibitory concentration (MIC), which is defined as the lowest concentration of an antimicrobial that will inhibit the visible growth of a microorganism after overnight incubation. A series of naphthyridines (1-4, figure 1.4) were synthesized by Chrzastek et al., with respective MIC values measured to between 0.1-1.2 µg/mL for *S. aureus*. Similar results were observed against other GPB. These results are comparable to vancomycin, a traditional antibiotic. The naphthyridines also showed activity towards GNB, with measured MIC values ranging from 0.2-1.2 µg/mL.

**Figure 1.4.** Naphthyridines synthesized by Chrzastek et al., showing significant antibacterial activity.

Parhi et al. recently synthesized a variety of substituted QBAs with single-digit µg/mL MIC values towards drug-sensitive and drug-resistant GPB, including MRSA. The synthesized QBAs were generally more potent than available antibiotics towards the drug-resistant bacteria, but not towards the drug-sensitive bacteria.

Sanguinarine has been found to have a unique mechanism of action compared to currently available antibacterial agents, namely the inhibition of FtsZ, a protein which is important for constructing new cell walls during prokaryote cell division. Furthermore, it has been theorized that bacteria may not be able to develop resistance towards FtsZ-targeting drugs by altering FtsZ itself. Several compounds have been recently found to inhibit FtsZ, but no antibacterial agent employing this mechanism is available on the market. Sanguinarine (Figure 1.2) displays activity against both GPB and GNB, but a MIC value of 25 µg/mL is not comparable to antibacterial agents on the market. It is also found that sanguinarine may have harmful adverse effects for mammals.
In addition to the antibacterial activity described, phenanthridines have shown interesting properties in other fields of medicine. Nitidine chloride (Figure 1.2) is employed in traditional malaria treatment, and is considered to be a lead molecule for anti-malaria drug development, while chelerythrine chloride (Figure 1.2) is an antiplatelet agent with possible use in the treatment of thrombosis. Several phenanthridines have shown promising anti-tumor activity and non-toxicity towards mammalian cells. Platinum-bound phenanthridine, “phenanthriplatin” (Figure 1.4), has been screened for anti-tumor activity, and is reported to “exhibit significantly greater activity than the Food and Drug Administration-approved drugs cisplatin and oxaliplatin”.

![Figure 1.4](image)

Figure 1.4. Phenanthriplatin and similar platinum-based anti-tumor drugs currently in use.

A series of benzo[j]phenanthridines were synthesized and tested for antimycobacterial activity by De Kimpe et al. MIC values measured for one of the tested compounds (5, Figure 1.6) was lower than the MIC value for isoniazid, a first-line drug employed against tuberculosis. However, high toxicity and unacceptable selectivity currently makes this class of compounds unsuitable for medical use. The authors emphasized the importance of further exploration of substitution patterns, and synthesis of similar compounds.

![Figure 1.6](image)

Figure 1.6. A phenanthridine derivative synthesized by De Kimpe et al. found to be very potent towards mycobacteria.

Based on the arguments above, it seems evident that there is a potential for developing phenanthridine-based drugs. However, a great amount of work is required to further enhance effectivity and properties related to absorption, distribution, metabolism, excretion and
toxicity, often abbreviated “ADME-Tox”, of the compounds to make them suitable as drugs. Furthermore, the opportunity to introduce of a wide array of functional groups in a variety of positions is essential to obtain a comprehensive structure-activity-relationship (SAR). The very first step of this work is therefore to obtain a flexible and preferably simple synthesis route towards phenanthridines.

1.2 Current synthesis strategies of the phenanthridine ring-system

This section describes the main strategies of current literature syntheses of phenanthidine ring systems. In these strategies, the key step is often to combine two fragments representing the A- and C-ring, forming the B-ring and thus the fused tricyclic system in the process.

1.2.1 Bond formation between C10a-C10b as the key step

The titled approach is the most common synthesis strategy of phenanthridines in the literature, and is often achieved through palladium-catalyzed carbon-carbon bond formation. Shen et al. employed this approach to synthesize the phenanthidine ring system from substituted N-(o-bromobenzyl)anilines 6 (Scheme 1.1). The synthesis route was found to be successful only for a few N-substituted substrates, even at elevated temperatures.

**Scheme 1.1.** Literature synthesis of phenanthridines by palladium-catalyzed formation of the C10a-C10b bond.

| 6a, R = H | 7a, R = H, 0% |
| 6b, R = Me | 7b, R = Ac, 58% |
| 6c, R = Ac | 7c, R = Me, 72% |

Reagents and conditions: a – Pd(OAc)$_2$, PPh$_3$, K$_2$CO$_3$, NMP, 120 °C.

Carbon-carbon bond formation is also achieved by radical reactions. Linsenmeier et al. synthesized phenanthridines through a radical mechanism initiated by UV-irradiation of the
reaction mixture (Scheme 1.2),\textsuperscript{41} while Rosa \textit{et al.} employed azobisisobutyronitrile (AIBN) and tri-\textit{n}-butyltin hydride (TBTH) to initiate the reaction (Scheme 1.3).\textsuperscript{42}

\begin{align*}
\text{R = H, COOMe, OMe, OH} \\
\text{SMe, F, Cl, Br or NO}_2 \quad 31-95\%
\end{align*}

\textbf{Scheme 1.2.} Literature synthesis of phenanthridines by a photochemically initiated radical reaction in the presence of I$_2$, to form the C10a-C10b bond.\textsuperscript{41} Reagents and conditions: a – MeCN, hv.

\begin{align*}
\text{R}_1 &= -\text{OCH}_2\text{O}- \text{ or OMe} \\
61-70\%
\end{align*}

\textbf{Scheme 1.3.} Literature synthesis of phenanthridines by an AIBN/TBTH-initiated radical reaction to form the C10a-C10b bond.\textsuperscript{42} Reagents and conditions: a – AIBN, TBTH, PhH, reflux.

\textit{1.2.2 Other approaches}

Recently published papers on synthesis of the phenanthridine ring-system often includes palladium-catalyzed cascade or tandem reactions, where multiple bonds in the B-ring are formed sequentially (Scheme 1.4).\textsuperscript{43-45}
Scheme 1.4. Literature synthesis of phenanthridines by multiple bond formations in a palladium tandem reaction.\textsuperscript{44} Reagents and conditions: \(a\) – norbornene, Pd(OAc)$_2$, PPh$_3$, CsCO$_3$, DMF, 130 °C, then O$_2$ after full conversion.

Morgan and Walls published their phenanthridine synthesis in 1931,\textsuperscript{46} a reaction which now is known as the Morgan-Walls cyclization. In this strategy, the C6-C6a bond is formed by dehydrative ring closure of acyl-\(o\)-aminobiphenyls \textbf{14} (Scheme 1.5).

\[
\begin{align*}
R & = \text{Et, Ph, CH}_2\text{Cl, } o\text{-nitrophenyl, } m\text{-nitrophenyl or } p\text{-nitrophenyl} \\
R & = 61\text{-}80\%
\end{align*}
\]

Scheme 1.5. The original Morgan-Walls reaction to yield phenanthridines.\textsuperscript{46} Reagents and conditions: \(a\) – POCl$_2$.

Mondal \textit{et al.} synthesized the phenanthridine ring system by constructing the C-ring through a Diels-Alder reaction (Scheme 1.6).\textsuperscript{47}
Scheme 1.6. Literature synthesis of the phenanthridine ring system through a Diels-Alder reaction. Reagents and conditions: a – PhMe, reflux.

Finally, ring expansion reactions has been employed to synthesize phenanthridines, reportedly through radical or transition-metal catalyzed mechanisms. This approach is generally not well explored, and often employs complex starting materials. Moore et al. synthesized a series of highly substituted dihydrophenanthridines 21 using this approach (Scheme 1.7).

Scheme 1.7. Literature synthesis of dihydrophenanthridines by ring expansion. Reagents and conditions: a – PhMe, reflux.
1.3 Chemistry of named reactions

This section describes the common chemistry involved in the synthesis of phenanthridines. A Suzuki coupling reaction was employed for the introduction of the furyl group (Section 1.3.1). Cyclization to give the fused phenanthidine ring system was achieved by an intramolecular Diels-Alder reaction (Section 1.3.3). Dihydrophenanthridines were oxidized with irradiation of UV light in the presence of air. This mechanism is currently not well understood, and is discussed briefly in Section 1.5.3.

1.3.1 The Suzuki-Miyaura reaction

The Suzuki-Miyaura reaction, commonly referred to as the Suzuki reaction, is a coupling reaction employing organohalides and organoboranes in the presence of a palladium catalyst to form new carbon-carbon bonds (Scheme 1.8). The reaction was first reported by Suzuki and Miyaura in 1979, and their continuous expansion of the scope of the synthetic method ultimately lead to Akira Suzuki received the Nobel Prize in chemistry in 2010. The Suzuki-Miyaura reaction has become one of the most flexible and important cross-coupling reactions for carbon-carbon bond formation. The far-reaching scope of the reaction, mild reaction conditions, and the tolerance of most functional groups has made the Suzuki coupling a common choice when synthesizing natural products and drugs. A large amount of organoboronic acids are commercially available. Additionally, organoboranes have been shown to be non-toxic, not environmentally polluting, and are easily removed from the wanted reaction products. These are problems often encountered with older approaches like the Stille coupling reaction, where organotin coupling partners are employed. Catalyst loading has been reported as low as 0.001 mol%, making the Suzuki-Miyaura reaction attractive towards industrial synthesis.

The Suzuki-Miyaura reaction is generally accepted to follow a mechanism depicted in Scheme 1.9, where NaOH is used as an example base. The mechanism is similar to other palladium-catalyzed cross-coupling reactions, with the nature of the organometal coupling partner being the major difference. The activation of the catalyst is not included in the
illustration, but this is commonly achieved by *in situ* generation of the active Pd⁰-complex from a more stable palladium source such as Pd(OAc)₂.

\[
R^-X + \text{R}_1\text{B(OH)}_2 \xrightarrow{\text{Pd⁰ catalyst \ Base}} \text{R}^-\text{R}_1
\]

Organohalide  Organoboronic acid  C-C coupled product

\[R, R_1 = \text{aryl, vinyl, alkyl} \]

\[X = \text{halide, OTf} \]

**Scheme 1.8.** A general example of a Suzuki-Miyaura reaction to form a carbon-carbon bond from an organohalide and an organoboronic acid.

The mechanism of the reaction can be divided into five individual steps.

1. Initially, oxidative addition of the organohalide to a low-coordinate Pd⁰ complex occurs, yielding a PdⅡ-complex.

2. Hydrolysis of the PdⅡ-complex in the presence of a base, forming the respective halide salt in the process. This step is unique for the Suzuki-Miyaura reaction.

3. Transmetallation, i.e. the transfer of an organic group from a boron reagent to the PdⅡ-complex.

4. Isomerization from the *trans*-complex to the *cis*-complex (not shown in Scheme 1.9).
5. Reductive elimination to recover the initial Pd\(^0\)-complex and to form a carbon-carbon
bond between the two organic moieties.

Oxidative addition is often the rate-determining step for catalytic cycles, including the cycle
depicted.\(^{52,60}\) Furthermore, the rate of oxidative addition is known to increase with decreasing
electron density of the organohalide,\(^{60}\) meaning electron poor organohalides are optimal for
the Suzuki reaction. The addition is also affected by the halide, with the reactivity order being
I > Br, OTf >> Cl. Contrary to the oxidative addition, transmetallation is favored by the
organoboronic reagent being electron rich.\(^{60}\) Opposite electronic properties between the two
organic moieties, i. e. one electron rich and one electron poor, are optimal to facilitate
reductive elimination. The ligands bound to the palladium complex are optimally σ-donating
to aid the oxidative addition, and sterically demanding to aid the elimination of the product.\(^{60}\)
Bulky phosphines are therefore often employed as ligands for cross-coupling reactions.

There are a few disadvantages of the Suzuki-Miyaura reaction compared to other palladium-
catalyzed coupling reactions. Firstly, compounds sensitive to bases may be unsuited for the
Suzuki-Miyaura reaction, due to the necessity of a base to fulfill the catalytic circle (Scheme
1.9). Secondly, organoboranes are generally not stable under atmospheric conditions, as they
can react with atmospheric dioxygen resulting in the decomposition of the reagent.\(^{61}\) This
degradation is often circumvented by transforming the boronic acids into their respective
potassium trifluoroborate salts (Scheme 1.10).\(^{62}\) In addition to protecting the reagent from
decomposition, trifluoroborates can be subject to further functionalization, or employed
directly in Suzuki reactions.

\[
\begin{align*}
\text{OH} & \quad \text{KHF}_2 \\
R\text{B(OH)}_2 & \quad \text{OF} \\
\text{Organoboronic acid} & \quad \text{Organotrifluoroborate}
\end{align*}
\]

**Scheme 1.10.** Literature conversion of an organoboronic acid to the corresponding potassium
organotrifluoroborate.\(^{63}\)
1.3.2 The intermolecular Diels-Alder reaction

The Diels-Alder reaction was first reported in 1928 by Diels and Alder, and is a [4 + 2] cycloaddition reaction (Scheme 1.11). The reaction mechanism is concerted, meaning all bonds are formed and broken in a single step. The Diels-Alder reaction generally proceeds by simply heating the reaction mixture, but both Lewis acids and organic catalysts have been found to increase the reaction rate and stereoselectivity of the reaction. Reactions involving furan as a diene was among the earliest reported, despite furan being an aromatic system. The use of furan as a diene has later been explored in detail, and is commonly employed in synthesis of natural products. Diels-Alder reactions with “normal demand”, i.e. electron rich dienes and electron poor dienophiles, are the most common, although “inverse demand” reactions are widely known.

![Scheme 1.11](image)

Scheme 1.11. A general Diels-Alder reaction between a diene and dienophile.

Diels-Alder reactions can occur with either endo or exo stereochemistry (Scheme 1.12), depending on the orientation of the substrates when the reaction occurs. For intermolecular Diels-Alder reactions, favorization towards the endo stereochemistry is often observed because of favorable non-bonding orbital overlap between the two substrates (Figure 1.7).

![Scheme 1.12](image)

Scheme 1.12. Formation of exo and endo products after an intermolecular Diels-Alder reaction.
Frontier molecular orbital (FMO) analysis is a common method to predict the likelihood of cycloadditions; the closer in energy the frontal orbitals are, the more readily the cycloaddition occurs. For normal demand Diels-Alder reactions, electrons are transferred from the bonding Highest Occupied Molecular Orbital (HOMO) of the diene to the antibonding Lowest Unoccupied Molecular Orbital (LUMO) of the dienophile to form new bonds between the substrates (Figure 1.8).

Dienophiles permanently locked in an s-cis confirmation are generally very good candidates for Diels-Alder reactions, whereas the most common examples are cyclic dienes such as cyclopentadiene and furan (Figure 1.9).
1.3.3 The intramolecular Diels-Alder reaction of furan (IMDAF)

The IMDAF reaction leads to the formation of a complex fused ring-system (26a and 26b) containing an oxynorbornene structure. The substrate (25) are often divided into three parts; the diene, the dienophile and the chain connecting the two (Scheme 1.13).

Analysis of intramolecular Diels-Alder reactions is generally more complex than intermolecular reactions, since the connecting chain’s ability to fold into the required conformations has to be considered in addition to the stabilities of the exo/endo products and the stabilizing effects of orbital overlap in the transition states. For IMDAF cyclizations of 2-furanyl substrates, exo stereoselectivity is commonly observed. The rate and diastereoselectivity of IMDAF cycloadditions are greatly affected by substituents. For substrates with a single sterically demanding substituent on the chain, the diastereoselectivity is often governed by the steric repulsions, with the sterically demanding substituent typically being positioned in a pseudoequatorial position in the transition state and product (Scheme 1.14).
Scheme 1.14. Literature example of an IMDAF cyclization where stereochemistry is directed by a methoxy-substituent. Reagents and conditions: a – ZnI₂, CH₂Cl₂.

Substituents on the chain have previously been shown to increase the reaction rate of [4 + 2] cycloadditions, but the reason for this has been subject to debate.\textsuperscript{74-76} The effect was for a long time contributed to a “reactive rotamer effect”,\textsuperscript{76} arguing that a larger percentage of the rotamers were in the active conformation. Dolata \textit{et al.} synthesized a series of substituted substrates 29 to undergo IMDAF cycloadditions (Scheme 1.15), measured the relative reaction rates (Table 1.1), and developed an accepted model of the reaction.\textsuperscript{75} Their calculations suggested that the rate increasing effect was a result of a reduction of $\Delta G^\ddagger$ of the reaction, as opposed to a rotamer effect.

Scheme 1.15. Study on substituent effect on IMDAF reaction rate by Dolata \textit{et al.}\textsuperscript{75}

<table>
<thead>
<tr>
<th>Entry</th>
<th>$R_1$</th>
<th>$R_2$</th>
<th>Relative rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>H</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>H</td>
<td>Me</td>
<td>8.35</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>Me</td>
<td>2123</td>
</tr>
<tr>
<td>4</td>
<td>H</td>
<td>$t$-Bu</td>
<td>8.32</td>
</tr>
</tbody>
</table>
To illustrate the effects of sterically demanding substituents, Sammes et al. employed a $N$-bound trityl group to force the IMDAF cyclization of a substrate (31) that did not cyclize otherwise (Scheme 1.16).\(^\text{77}\)

![Scheme 1.16. IMDAF cyclization of $N$-(furylmethyl)allylamino substrates by Sammes et al.\(^\text{77}\)](image.png)

Substitution on the furan moiety is also observed to positively influence the reaction rate of IMDAF cyclizations.\(^\text{69,78}\) The increased reaction rates of halogenated furans is largely credited to the increase of reactant energy, and the stabilization of the product, with the halide being attached to a more alkylated and thereby more electropositive framework.\(^\text{78}\)

Due to the complexity of the cyclization adducts and the often good diastereoselectivity, IMDAF is commonly used in the synthesis of natural products with fused ringstructures.\(^\text{72,79-82}\) For instance, Padwa et al. published a total synthesis of the phenanthridine alkaloid lycoridicine (35) as a racemic mixture, employing IMDAF as the key step (Scheme 1.17).\(^\text{72}\)

![Scheme 1.17. Literature synthesis of (±)-lycoridicine by Padwa et al.\(^\text{72}\)](image.png)
1.4 Microwave synthesis

Microwave reactors employ microwave irradiation to heat the reaction mixtures, as opposed to conventionally heating in an oil bath or with a heating mantle. The heating effect, commonly referred to as dielectric heating, occurs when polar molecules are polarized as a consequence of dipole-dipole interactions with the electromagnetic field. The absorbed energy dissipates as heat due to agitation and intermolecular friction between molecules when their orientation is changed at a high frequency, commonly 2.45 GHz. Non-polar solvents, such as alkanes and PhMe do not absorb microwave radiation, and are therefore not heated when irradiated. Non-polar solvents are therefore generally not suited for microwave-mediated synthesis.

Intramolecular Diels-Alder reactions have been shown to be improved by utilizing microwave reactors; yields have been increased, reaction times reduced, and stereoselectivity increased. Although a “microwave effect” is often referred to, there is still much dispute about whether or not it exists. The subject is complicated further through the use of domestic microwave ovens, where precise temperature measuring is impossible. To contest the theory of a microwave effect, Lentz et al. reproduced an experiment where microwave-mediation was reported to increase reaction rate, compared to when the reaction mixture was heated conventionally. When the experiment was reproduced with precise temperature and pressure control, no difference in reactive rates was observed. Thus, the main advantage of microwave heating versus conventional heating appears to be rapid heating and even heat distribution in the reaction mixture.

1.5 Previous development of the intramolecular Diels-Alder of furan (IMDAF)-based phenanthridine synthesis strategy in our group

This section describes the discovery and the initial exploration of the IMDAF-based synthesis route towards (aza)phenanthridines within our group.
1.5.1 Initial discovery of the IMDAF of o-furyl(allylamino)(aza)arenes

While synthesizing pyridines to be tested for antimycobacterial activity,\textsuperscript{3,90} it was found that one of the synthetic intermediates (36) underwent IMDAF to form a complex ring system when heated (Scheme 1.18).

\textbf{Scheme 1.18.} Initially observed IMDAF of o-furyl(allylamino)azaarene 36.\textsuperscript{3} The \textit{exo} cyclization product 37 is shown. Reagents and conditions: a – NEt\textsubscript{3}, (4-methoxyphenyl)methanamine, n-BuOH, 100 °C.

The discovery lead to the exploration of the IMDAF of (hetero)arenes with allylamino or allyloxy substituents.\textsuperscript{1,3} The study revealed that substrates with a chloride substituent located in an \textit{ortho}-position to the allylamino group underwent IMDAF more readily. This was supported by computational studies, showing that the chloride substituent increased the energy of the minimum conformation of the substrate, resulting in a reduction the activation energy to undergo IMDAF. An \textit{exo} stereoselectivity was observed for all substrates that cyclized to give ring-systems similar to compound 37, which is consistent with IMDAF of related substrates in the literature.\textsuperscript{77,81}
### 1.5.2 Expanding the scope: Synthesis of the phenanthridine ring-system

Employing microwave irradiation to heat the reaction mixtures was found to greatly enhance the scope of the synthesis strategy.\(^2\text{-}^3\) Several substrates that did not undergo IMDAF when heated in PhMe or xylenes cyclized readily when heated in MeCN with microwave irradiation. Furthermore, addition of catalytic amounts of 2 M HCl was found to ring-open and eliminate water from the IMDAF adducts. This leads to a convenient microwave-mediated one-pot synthesis of dihydrophenanthridines (40) from o-furyl(allylamino)(aza)arenes (38) (Scheme 1.19).

![Scheme 1.19](image)

**Scheme 1.19.** Microwave-mediated one-pot synthesis of dihydrophenanthridines from \(o\)-furyl(allylamino)(aza)arenes.\(^2\text{-}^3\) Reagents and conditions: a – HCl, MeCN, MW, 100-180 °C.

The ring-opening and water elimination from the IMDAF adduct is presumed to follow a mechanism depicted in Scheme 1.20.\(^3\)
Scheme 1.20. Proposed mechanism for the ring-opening and water elimination of the oxynorbornene ring system of compound 39 to yield dihydrophenanthridines 40. In the proposed mechanism, the oxygen in the fused oxynorbornene ring system 39 is initially protonated, followed by ring-opening to yield the resonance stabilized carbocation 41. Deprotonation leads to the formation of allylic alcohol 42, and regenerates the acid employed for ring-opening. The alcohol is then thought to eliminate through an E1-style elimination through a second resonance stabilized carbocation 45, to give the water eliminated compound 40.

The positive effect observed when the substrates are heated by microwave-irradiation is mostly credited to factors discussed in Section 1.4. There are, however, another factor to be taken into account, namely the Retro-Diels-Alder reaction which is often in an equilibrium with the Diels-Alder reaction at high temperatures. Ring-opening and aromatization of the Diels-Alder adduct in situ allows for full conversion of the starting material, with practically no Retro-Diels-Alder reactions occurring.
1.5.3 Oxidation of dihydrophenanthridines to phenanthridines

It was found that most dihydrophenanthridines synthesized by the route described in Section 1.5.2 oxidized rapidly by irradiation of UV-light, and in the presence of air.\(^2,3\) This allowed for a clean and simple two-step synthesis of fully oxidized (aza)phenanthridines (46) from o-furyl(allylamino)(aza)arenes (38) (Scheme 1.21). Oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) was found to give the product in yields similar to the oxidation employing irradiation of UV light. The few dihydrophenanthridines that were found to be oxidizing slowly when irradiated with UV-light were readily oxidized in the presence of DDQ.

![Scheme 1.21. Microwave-mediated one-pot synthesis of phenanthridines (46) from o-furyl(allylamino)(aza)arenes (38). Reagents and conditions: a – cat. HCl, MeCN, MW, 100-180 °C. b – hν, air, MeCN. c – DDQ, CH\(_2\)Cl\(_2\).](image)

The mechanism of the oxidation with UV-irradiation and air is currently not known. There are several reports of oxidation through irradiation of UV-light of similar compounds,\(^91,92\) but sadly, no mechanism for this oxidation has so far been postulated. Similar oxidations has also been reported using CHCl\(_3\) or CCl\(_4\) as solvents, in which the solvent has been believed to be involved in the oxidation via a radical mechanism.\(^93,94\)
2. SYNTHESIS AND DISCUSSION

This section describes the synthesis of and IMDAF cyclizations of o-furyl(crotylamino)arenes 48. The compounds and observations encountered are discussed in context with current synthesis strategies towards phenanthridines in the literature.

2.1 Generation of starting materials

This section describes the synthesis of o-crotylamino-furyl-arenes 48 that are used as starting materials for the intramolecular Diels-Alder on furan (IMDAF) reactions (Scheme 2.1).

Scheme 2.1. Commercially available anilines 47, and o-crotylamino-furyl-arenes 48 employed for IMDAF cyclizations to yield 8,10a-epoxyphenanthridines 49.

2.1.1 Choice of starting materials

Our group has previously found that a sterically demanding substituent ortho to the allylamino group influences the IMDAF of o-allylamino-furyl-arenes in a positive manner.\textsuperscript{1} Introduction of a chlorine substituent in this position has previously given satisfactory results (Section 1.5.1).

Compounds with a nitro or chloro substituent in the para position to the allylamino group have previously been found to undergo Diels-Alder under milder conditions than the non-
substituted analogs.\textsuperscript{1,2} Although not being explored further, this is presumed to be caused by the electron-withdrawing nature of the substituents.

Substituents \textit{meta} to the allylic nitrogen has not been thoroughly explored, but has so far not been found to influence the reaction in a clear way.\textsuperscript{1} This information is summarized in Figure 2.1.

Finally, \textit{N,N}-dialkylated substrates have been briefly screened.\textsuperscript{1} The substrates displayed higher reactivity, but with a loss in stereoselectivity. \textit{N}-Boc derivatives did not show any reactivity.

![Substitution patterns found to facilitate the IMDAF reaction of \textit{o}-furyl(allylamino)arenes.](image)

**Figure 2.1.** Substitution patterns found to facilitate the IMDAF reaction of \textit{o}-furyl(allylamino)arenes.

Introduction of the but-2-en-1-yl (crotyl) moiety versus the previously explored allyl moiety, accomplishes several purposes:

- Introduction of functionality in the final products, most notably the water eliminated and fully oxidized 7-methylphenanthridines \textsuperscript{57}.
- To determine of the the diastereoselectivity of the IMDAF adducts \textsuperscript{49} of substrates \textsuperscript{48}, compared to the \textit{o}-furyl(allylamino)arene analogs \textsuperscript{36}.
- Introduction of a fourth stereocenter in the Diels-Alder adduct. This increases the complexity of the product, and thereby the scope of the synthetic strategy.

With this experience and thoughts in mind, the \textit{o}-furyl(crotylamino)arenes \textsuperscript{48} (Scheme 2.1) were chosen as starting materials for the IMDAF-cyclizations to give phenanthridines. The \textit{N}-methylated substrate \textsuperscript{48c} was included to explore how a tertiary nitrogen would affect the synthesis strategy, and the chemistry of the synthetic intermediates.
2.1.2 The eligibility of o-bromoanilines in the Suzuki-Miyaura reaction

As described in Section 1.3.1, an electron rich organoboronic species and an electron deficient aryl halide is wanted to obtain high reactivity in Suzuki-Miyaura reactions. Furan, being an aromatic heterocyclic five-membered ring, is an electron rich system\(^{68}\) and therefore an excellent candidate for the organoboronic species. Unsubstituted aniline is an electron rich aromatic system, due to the electron donating resonance structures of the amine.\(^{95}\) 2-Bromoaniline itself is therefore expected to be a poor substrate in the Suzuki coupling reaction. In the literature, 2-bromoaniline has been employed as an aryl halide in the Suzuki coupling reaction, obtaining poor yields.\(^{96}\) It should be mentioned that the referenced authors employed an electron poor coupling partner, which could contribute to the low yield.

The o-bromoanilines 47 (Scheme 2.1) used for generation of starting materials are substituted with two EWGs, reducing the electron density in the aromatic system, and thereby making the anilines decent substrates for the Suzuki-Miyaura reaction. To demonstrate this, our group has previously coupled a variety of similar o-bromoanilines, including compounds 47, to furan-2-yl with moderate to excellent yields.\(^{3}\)

2.1.3 Synthesis of 2-chloro-6-(furan-2-yl)-4-nitroaniline (51a) and 2,4-dichloro-6-(furan-2-yl)aniline (51b)

o-(Furyl)anilines 51 were synthesized following literature procedures,\(^{1,2}\) with altered procedures regarding work-up and purification. Before evaporating the solvents, the reaction mixture was filtered through a short silica plug to remove inorganic salts and excess base. The eluent system used during flash chromatography to isolate compound 51a is also changed to an EtOAc:CH\(_2\)Cl\(_2\):hexanes system, similar to the literature procedure for compound 51b.\(^{2}\) This eluent system was found to give less tailing during chromatography.

Suzuki-Miyaura cross-coupling reactions between the o-bromoanilines 47 with potassium 2-furyltrifluoroborate\(^{63}\) (50) gives the desired o-(furan-2-yl)anilines 51 (Scheme 2.2). The yields obtained herein are slightly higher than the reported yields of 70\% and 94\% for compound 51a and 51b, respectively.
Scheme 2.2. Reagents and conditions: a – K$_2$CO$_3$, Pd(OAc)$_2$, PPh$_3$, EtOH/H$_2$O (95:5), reflux.

The Suzuki reaction with 2-furanylbromonic acid would also yield anilines 51 as the reaction product. However, heteroarylboronic acids such as tiophenyl- and furylboronic acids are readily degraded under the conditions employed during Suzuki reactions. The more stable 2-furanyltrifluoroborate have therefore been synthesized in bulk in our group, following a literature procedure.

### 2.1.4 Synthesis of N-(but-2-en-1-yl)-2-chloro-6-(furan-2-yl)-4-nitroaniline (48a) and N-(but-2-en-1-yl)-2,4-dichloro-6-(furan-2-yl)aniline (48b)

Due to availability issues, a 85:15 E:Z mixture of 1-bromobut-2-ene (crotyl bromide) was employed in all crotylation experiments. The E- and Z-isomers of crotylated compounds 48 and 52 were only partially separable by flash chromatography, and the compounds were therefore isolated as mixtures.

In previous related studies, a broad array of anilines and aminoazaarenes have been N-allylated with a variety of different conditions. Furthermore, N,N-diallylation has been found to readily occur, even when the amount of base and allyl bromide are kept close to one equivalent. For this reason, a brief screening of conditions for crotylation of compounds 51 were initiated (Scheme 2.3, Table 2.1).

Deprotonation with NaH had given satisfactory results in the past, so these conditions were tested first (Table 2.1, entry 1). Crown ethers has previously been employed with great success in N-allylations of similar substrates. By stabilizing the alkali metal ions, often Na or K, crown ethers increase the anion solubility and thereby reactivity of alkali salts in organic
solvents. The conversion for these conditions were not satisfying, even when the reaction was left overnight.

Deprotonation with NaH in the presence of tetrabutylammonium bromide (TBAB) (entry 2) provided satisfying results for the time being, and further screening of conditions was not necessary. Minor alterations of these conditions, most notably drying the TBAB under vacuum at 40 °C for 1 hour before addition, improved the yield from good to excellent (entry 3). This is most likely due to the hygroscopic nature of TBAB. Storage for an extended period of time without precautions against moisture accumulates water in the TBAB, which obviously degrades the NaH. The reasoning for introducing TBAB to the reaction mixture is not well known, but it has obtained positive results in previous work in our group. Applying these conditions for the N-crotylation of compound 51a was successful, although longer reaction time was necessary to obtain full conversion (entry 4). In all experiments (Table 2.1, entries 1-4), the E:Z ratio of 85:15 was retained from the isomeric mixture of crotyl bromide.

In the synthesis of compounds 48, o-(furan-2-yl)anilines 51 were crotylated with NaH and crotyl bromide in the presence of TBAB in THF (Scheme 2.3), obtaining the N-crotylamino-furyl-arenes 52 in good to excellent yields.

Interestingly, the N,N-dicrotylated dichloro compound 52b was not observed by 1H NMR or TLC when synthesizing compound 48b. For the nitro-analog, N,N-dicrotylated compound 52b was isolated as a byproduct, partially explaining the lower yield of the wanted product. Compound 52b is isolated as a mixture of three isomers (cis-cis, cis-trans, trans-trans), in a ratio of 72:26:2. This is identical to the expected ratio distribution calculated from a crotyl source with an E:Z ratio of 85:15.
Table 2.1. Crotylation of compound 51 – Step a, Scheme 2.3.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Eq. crotyl-Br</th>
<th>Base</th>
<th>Eq. base</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Additive</th>
<th>Unreacted S.M.(^a) (%)</th>
<th>Yield(^b) (%)</th>
<th>$E:Z$ ratio of isolated 48</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>51b</td>
<td>1.3</td>
<td>NaH</td>
<td>1.3</td>
<td>PhMe</td>
<td>35(^c)</td>
<td>21</td>
<td>15-crown-5-ether</td>
<td>24</td>
<td>54</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>51b</td>
<td>1.3</td>
<td>NaH</td>
<td>1.2</td>
<td>THF</td>
<td>r.t.(^d)</td>
<td>6.5</td>
<td>TBAB</td>
<td>4</td>
<td>73</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>51b</td>
<td>1.2</td>
<td>NaH</td>
<td>1.2</td>
<td>THF</td>
<td>r.t.(^d)</td>
<td>2</td>
<td>TBAB(^e)</td>
<td>&lt;1</td>
<td>91</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>51a</td>
<td>1.2</td>
<td>NaH</td>
<td>1.2</td>
<td>THF</td>
<td>r.t.(^d)</td>
<td>4</td>
<td>TBAB(^e)</td>
<td>&lt;1</td>
<td>76</td>
<td>7</td>
</tr>
</tbody>
</table>

\(^a\)by \(^1\)H NMR of the crude product.
\(^b\)of isolated products.
\(^c\)addition of base at r.t., then stirred at 35 °C.
\(^d\)addition of base at 0 °C, then stirred at r.t.
\(^e\)dried under vacuum at 40 °C for 1 hour before addition.
The difference in reactivity may be explained by the acidity of the aniline. The nitro group in the 4-position of compound 48a stabilizes the negative charge on the deprotonated species (Figure 2.2), making the 4-nitro aniline considerably more acidic than the 4-chloro analog. For comparison, the pKₐ values of p-nitro- and p-chloroaniline are 1.00 and 3.98, respectively. An important consequence of this is that compound 48b, if deprotonated, would be more reactive than compound 48a due to the lesser stabilized anion. For compound 48a, the electron donating N-crotyl moiety may be sufficient to stop further deprotonation and subsequent crotylation under the given conditions.

![Figure 2.2. Resonance stabilization of deprotonated compound 48a. Not all resonance structures shown.](image)

In work done in our research group by Read,³ allylation of dichloro aniline 51b yielded the diallylated product 54 as a byproduct with conditions given in Scheme 2.4.

![Scheme 2.4. Previous work by Read.³ Reagents and conditions: a – Allyl iodide, KH, 18-crown-6-ether, DMF, 40 °C.](image)

There are important differences when comparing the conditions from Read (Scheme 2.4) and the conditions employed herein (Scheme 2.3). Exchanging the solvent from THF to the more polar DMF not only increases the solubility of the base, but also helps to stabilize ionic species, i.e. the deprotonated anilines. Employing the stronger base potassium hydride instead of sodium hydride is also likely to increase the deprotonation of 48b. Lastly, the introduction of a better leaving group in allyl iodide (compared to crotyl bromide) and the increased temperature also increases the probability of a double addition to form compound 54.
The mechanism for crotylation was presumed to be an S\textsubscript{N}2-type mechanism, as opposed to other types of nucleophilic substitution mechanisms, which would yield 4-substituted N-(but-3-en-2-yl)-2-chloro-6-(furan-2-yl)-anilines 55 (Scheme 2.5) instead of, or in addition to compounds 48. The S\textsubscript{N}2'-type nucleophilic attack ("S\textsubscript{N}2 prime") is happening on a more sterically hindered carbon, in addition to the fact that the products 55 have a terminal double bond. Thus, the S\textsubscript{N}2-type mechanism should be both kinetically and thermodynamically\(^ {95}\) favored versus S\textsubscript{N}2'.

An S\textsubscript{N}1-type mechanism would in theory give a mixture of compounds 48 and 55, as the cationic charge would be stabilized by resonance (Scheme 2.6). The rearranged compound 55 would be expected to be the main product, due to its respective carbocation being the more stable. As shown in Scheme 2.6, a partial racemization of the double bond could also be expected if the reaction followed the S\textsubscript{N}1 pathway. The theoretical products 55 were not observed by \(^1\)H NMR or by TLC analysis during crotylation of anilines 51, which is consistent with similar experiments in the literature.\(^ {99}\) Kania et al. synthesized N-allylic purines employing a series of substituted allyl bromides, never observing products originating from other mechanisms than the S\textsubscript{N}2 mechanism.\(^ {100}\)

Scheme 2.5. Deprotonation of compound 51 followed by nucleophilic attacks to form compounds 48 or 55.
Scheme 2.6. The first step of a theorized $S_N1$ reaction of (Z)-crotyl bromide.

2.1.5 Synthesis of $N$-(but-2-en-1-yl)-2,4-dichloro-6-(furan-2-yl)-$N$-methylaniline (48c)

$N$-methylated compound 48c was included as a starting material to eliminate the hydrogen situated at the crotylated nitrogen in substrates 48, and to explore how the absence of this hydrogen influenced the reactivity of the intermediates throughout the synthetic pathway.

Several conditions and bases were tested for the $N$-methylation of compound 48b (Scheme 2.7). The initial conditions were similar to the crotylation conditions in Section 2.1.4 (Table 2.2, entry 1), but no conversion was observed after three hours. This is very interesting considering no $N,N$-dicrotylation was observed with similar conditions (Scheme 2.3), indicating that the mono-crotylated compound 48b is, in fact, not deprotonated under these conditions.

Similar compounds have been $N$-methylated by KH in the presence of 18-crown-6-ether in PhMe and two equivalents of base at slightly elevated temperatures (entry 2). This approach was found to give decent conversion after 24 hours, but also large amounts of breakdown illustrated by the rather low yield.

An increase of the amount of base and electrophile was found to give full conversion of the starting material in less than an hour. Compound 48c was isolated in excellent yields.

Scheme 2.7. Reagents and conditions: a – Table 2.2, entry 3.
Table 2.2. N-methylation of compound 48b – Step a, Scheme 2.7.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Eq. MeI</th>
<th>Base</th>
<th>Eq. base</th>
<th>Solvent</th>
<th>Temp. (°C)</th>
<th>Time (h)</th>
<th>Additive</th>
<th>Unreacted S.M. (%)</th>
<th>Yield 48c (%)</th>
<th>E:Z ratio of isolated compound</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>KH</td>
<td>2</td>
<td>PhMe</td>
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<td>18-crown-6-ether</td>
<td>19</td>
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<td>18-crown-6-ether</td>
<td>&lt;1</td>
<td>92</td>
<td>85:15</td>
</tr>
</tbody>
</table>

*by 1H NMR of crude product.
*of isolated products.
*addition of base and MeI at 0 °C, then stirred at r.t.
*addition of base and MeI at r.t., then stirred at 40 °C.

Compound 48c was surprisingly lipophilic (R_f = 0.80 in hexanes on silica), and was purified twice by chromatography in order to remove parafin oil originating from the KH slurry. The E:Z ratio of 85:15 was retained for all experiments, and no quaternary ammonium salts were observed during the synthesis of compound 48c.

### 2.2 Microwave-mediated IMDAF of o-furyl(crotylamino)arenes 48

This section describes the screening of microwave (MW) conditions for the IMDAF reaction of compounds synthesized as described in Section 2.1. Microwave-mediated synthesis of 8,10a-epoxyphenanthridines 49 and dihydrophenanthridines 56, and a microwave-mediated two-step synthesis of phenanthridines 57 (Figure 2.3) is also described.

Figure 2.3. Compounds described in this section.
2.2.1 Screening of conditions for the microwave-mediated IMDAF of o-furyl(crotylamino)arenes 48

Conditions were screened for the microwave-mediated IMDAF reactions of compounds 48 with addition of 0.2 equivalents of 0.5 M aqueous HCl or NaOH (Scheme 2.8, Table 2.3). The product distribution in Table 2.3 is based on comparison of integrals in the $^1$H NMR spectra of the crude products after evaporation of solvents. In experiments where acid was added to the reaction mixture, the solution was neutralized with NaHCO$_3$ before evaporation of solvents.

Scheme 2.8. Products formed when substrates 48 undergoes microwave-mediated IMDAF with varying conditions (Table 2.3).

The crotylamino substrates 48 were expected to react slower than the allylamino analogs, due to the introduction of steric bulk in the dienophile region of the Diels-Alder substrate. Therefore, the initial MW conditions are chosen to be slightly harsher than the reported conditions for N-allylamino analogs.

48a, X=NO$_2$, R=H  
48b, X=Cl, R=H  
48c, X=Cl, R=Me

49a, X=NO$_2$, R=H  
49b, X=Cl, R=H  
49c, X=Cl, R=Me

50a, X=NO$_2$, R=H  
50b, X=Cl, R=H  
50c, X=Cl, R=Me

51a, X=NO$_2$, R=H  
51b, X=Cl, R=H  
51c, X=Cl, R=Me

52a, X=NO$_2$, R=H  
52b, X=Cl, R=H  
52c, X=Cl, R=Me

53a, X=NO$_2$, R=H  
53b, X=Cl, R=H  
53c, X=Cl, R=Me

54a, X=NO$_2$, R=H  
54b, X=Cl, R=H  
54c, X=Cl, R=Me

55a, X=NO$_2$, R=H  
55b, X=Cl, R=H  
55c, X=Cl, R=Me

56a, X=NO$_2$, R=H  
56b, X=Cl, R=H  
56c, X=Cl, R=Me

57a, X=NO$_2$, R=H  
57b, X=Cl, R=H

58a, X=Cl, R=H  
58b, X=Cl, R=H  
58c, X=Cl, R=H

59a, X=Cl, R=H
Table 2.3. Screening of conditions for microwave-mediated IMDAF of compounds 48.

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<tr>
<th>Entry</th>
<th>Compound</th>
<th>X</th>
<th>R</th>
<th>Additive</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Time (h)</th>
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<th>49</th>
<th>56</th>
<th>57</th>
<th>58</th>
<th>59</th>
<th>51</th>
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<td>–</td>
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<td>–</td>
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<td>–</td>
<td>–</td>
<td>5&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
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</table>

<sup>a</sup>by <sup>1</sup>H NMR of the crude product.<br /><sup>b</sup>Dry MeCN from solvent-drying system.<br /><sup>c</sup>present in the reaction mixture, but no ratio could be identified.<br /><sup>d</sup>Based on NMR signals presumed to belong to compound 58c.<br /><sup>e</sup>Based on NMR signals presumed to belong to compound 51c.
The 4-nitro substituted compound 48a was initially heated at 150 °C for one hour, resulting in good conversion and acceptable selectivity towards the dihydrophenanthridine 56a (Table 3.3, entry 1). It was found that lowering the temperature resulted in better selectivity towards this product, reducing the extent of both the oxidization and deallylation reactions (entries 2-5). After heating at 100 °C for eight hours, satisfying conversion of the starting material was met (entry 5).

It was found in a related project that water was acidic enough transform a similar Diels-Alder adduct to a dihydrophenanthridine (Scheme 2.9).³ Utilizing the conditions described in the literature (entry 6), it was found that water was not acidic enough to catalyze the transformations towards the water-eliminated compound 56a, and the Diels-Alder adduct 49a was formed quantitatively. The use of PhMe as a co-solvent is due to the lipophilicity of the substrates in the literature procedure.³ Simplifications of these conditions by employing pure MeCN as solvent and not employing any additive were found to give similar results (entries 7-8).

![Scheme 2.9](image)

**Scheme 2.9.** Reported microwave-mediated IMDAF of o-furyl(allylamino)arene 60 to yield dihydrophenanthridine 61.³ Reagents and conditions: b – cat. H₂O, MeCN/PhMe 1:1, MW, 150 °C.

The Diels-Alder adduct 49a was formed as a mixture of four diastereomers in the ratio 227:42:6:1, as determined by ¹H NMR of the crude product. The four diastereomers originate from the exo/endo reaction mechanisms of the Diels-Alder, and the cis/trans mixture of the starting material (48a). From the exo-selectivity of IMDAF reactions in the literature,¹,³,₈¹ and the 85:15 trans/cis ratio of the starting material, we are expecting to see the same 85:15 ratio between the two exo diastereomers and between the two endo diastereomers. We also expected the exo diastereomers to be the most abundant.

The two major diastereomers of compound 49a were identified as the exo-trans and the exo-cis diastereomers (Figure 2.4), respectively, by NOESY NMR. For the two major isomers, the cis stereochemistry of H-8 and the methyl group was determined by a standard NOESY
experiment (Spectrum 51), but the relationship between H-6a and H-7 was inconclusive due to COSY-signals in the spectrum. The stereochemistry between H-6a and H-7 was therefore determined by selective NOESY NMR with irradiation on the signal of the H-6a of the two major diastereomers (Spectra 82 and 83). Comparison of the relative integrals of the H-7 signals revealed that the most abundant diastereomer had the H-6a and H-7 protons situated in a trans relationship, while there was a cis relationship in the second most abundant diastereomer, where the intensity of the NOE effect was found to be almost five times larger.

The observed ratio between the exo-trans and the exo-cis diastereomers is circa 86:14, which fits the expected diastereomeric distribution. The observed ratio between the two minor diastereomers is also circa 86:14. It is therefore presumed that the minor diastereomers, in descending order, are the endo-trans and endo-cis diastereomers. Based on the observed ratios, the exo selectivity of the IMDAF forming compound 49a is calculated to 97-98%. This is significantly better than the selectivities reported for IMDAF reactions of similar N-allyl substrates,\(^1\) perhaps due to steric repulsions between the methyl group and the oxygen in the transition state leading to the endo product.

![Figure 2.4](image)

**Figure 2.4.** The four diastereomers of tetrahydro-8,10a-epoxyphenanthridines 49 and their relative stereochemistry. Numbering of relevant hydrogens is also shown.

It was observed that the decrotylated product 51a was not formed when acid was avoided in the reaction mixture. This is very interesting, due to the fact that there are no reports of acid-catalyzed cleavage of N-allylanilines in the literature. Furthermore, N-allylanilines are commonly treated with acidic conditions, for instance during reduction of nitro groups,\(^{101}\) cleavage of N-boc groups,\(^{47}\) hydrolysis of amides,\(^{102}\) and deformylations.\(^{103}\) In the literature, allylaminoarenes are deallylated in the presence of transition-metal catalysts.\(^{104,105}\)

Loss of allylic moieties from N-allylanilines has previously been reported for N-allylanilines at highly elevated temperatures to undergo aza-Claisen rearrangements (Scheme 2.10).\(^{106,107}\)
Scheme 2.10. Deallylation of N-allyl-1-naphthylamine when heated to 260 °C, as reported by Inada et al.\textsuperscript{106}

A combination of the acidic conditions and the elevated temperatures in the microwave reactor might explain the observed degradation of the o-furyl(crotylamino)arenes (48). A proposed acid-catalyzed mechanism to account for the decrotylation of substrate 48a to form aniline 51a is shown in Scheme 2.11. The substrate is protonated by the acid, followed by a nucleophilic attack on the carbon alpha to nitrogen, expelling the positively charged anilinium ion as a leaving group. The byproduct would in this case be crotyl alcohol (64) which has a boiling point of 121 °C, meaning it could have been removed when the crude product is concentrated under vacuum. Other types of nucleophilic substitution reactions could also be considered, but for the reasons given earlier (see Section 2.1.4), the SN2-type is presumed to be the most likely. It was not attempted to identify crotyl alcohol in the reaction mixtures, but this could for instance be done by gas chromatography (GC) analysis of the reaction mixture.

Scheme 2.11. Proposed acid-catalyzed mechanism of decrotylation of substrate 48a to give aniline 51a.

Heating the dichloro substrate 48b at 150 °C resulted in acceptable combined ratios for compounds 56b and 57b, although neither product was formed selectively (entry 9-10). Extensive decrotylation to yield the aniline 51b was also observed, which is often difficult to separate from the wanted product. The reaction temperature was therefore lowered, unfortunately resulting in the same amount of decrotylation as well as unsatisfying conversion of starting material (entries 11-12).
When conditions reported by Read et al. was employed, it was found that water was acidic enough to catalyze the transformations to give dihydrophenanthridine 56b. Similarly to substrate 48a, decrotylation did not occur when the use of acid was avoided in the reaction mixture. However, new byproducts were observed. These were identified as the allylic alcohol 58b and the β,γ-unsaturated ketone 59b, which are discussed in great detail in Section 2.3. Employing pure MeCN as solvent was shown to give similar results as the PhMe/MeCN solvent system (entry 14), and increasing the reaction time was found to decrease the amount of the alcohol 58b, presumably due to water elimination to give the aromatic compound 56b (entry 15).

Employing dry MeCN as solvent (entry 16) gave similar results as adding water, presumably because of the hygroscopicity of MeCN. Since the solvent had to be degassed to avoid decomposition of reagents, the solvent may have been exposed to atmospheric moisture for a very brief period of time, meaning there could have been trace amounts of water in the solvent. Adding molecular sieves to the reaction mixture as a water scavenger resulted in a complex mixture containing compounds 49b, 56b, 58b and 59b, as well as several unknown compounds (entry 17). No ratio was identifiable by 1H NMR, due to overlapping signals.

When water seemingly could not be avoided in the reaction mixture, catalytic amounts of 0.5M aqueous NaOH was added to prevent protonation of the adduct 49b and the subsequent ring-opening and water elimination (see Scheme 1.20, page 30) (entry 18). This approach was successful, and the only observed products were a mixture of three diastereomers of the Diels-Alder adduct 49b in the ratio 74:13:1 (by 1H NMR of the crude product). The order of diastereomers are presumed to be similar to Diels-Alder adduct 49a, with exo-trans being the major diastereomer. Given this assumption, the observed exo selectivity is 98-99%, and the ratio between products from cis and trans circa 15:85. Once again, the exo selectivity is significantly better than the reported ratios when similar N-allyl substrates undergoes IMDAF.

The N-methylated substrate 48c required tougher reaction conditions than the analog 48b. This was unexpected, as N-substituted compounds generally are cyclized under milder conditions than their unsubstituted analogs (see Section 2.1.1). The Diels-Alder adduct 49c also proved to be more tolerant to acid, as heating at 150 °C with the addition of water resulted in a mixture of the starting material 48c, the adduct 49c and a compound presumed to be the alcohol 58c (entries 19-21). The temperature was therefore raised to 180 °C, and...
diluted aqueous HCl was added to facilitate the ring-opening and elimination of water from the Diels-Alder adduct 49c, successfully giving the dihydrophenanthridine 56c, with only a small amount of decrotylation observed (entry 22-23). With a similar approach as for substrate 48b, one can suspect that heating at 180 °C with the addition of NaOH would result in full conversion of starting material, and no ring-opening of the Diels-Alder adduct. However, these conditions were not tested due to time constraints.

The byproducts 51c and 58c were never isolated and structurally elucidated, but the 1H NMR spectra obtained from impure fractions after chromatography matched their expected spectra.

2.2.2 Microwave-mediated synthesis of (±)-(6aS,7R,8R,10aS)-4-chloro-7-methyl-2-nitro-6,6a,7,8-tetrahydro-5H-8,10a-epoxyphenanthridine (49a) and (±)-(6aS,7R,8R,10aS)-2,4-dichloro-7-methyl-6,6a,7,8-tetrahydro-5H-8,10a-epoxyphenanthridine (49b)

Substituted 8,10a-epoxyphenanthridines 49 were synthesized by microwave-mediated IMDAF of the corresponding o-furyl(crotylamino)arene 48 in MeCN (Scheme 2.12). In the case of substrate 48b, addition of catalytic amounts of 0.5M NaOH was necessary to prevent ring-opening of the target molecule.

![Scheme 2.12](image)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Reaction Conditions</th>
<th>Isolated Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>48a, X = NO₂, R = H</td>
<td>a – MeCN, MW, 100 °C</td>
<td>68%</td>
</tr>
<tr>
<td>48b, X = Cl, R = H</td>
<td>b – cat. NaOH, MeCN, MW, 150 °C</td>
<td>11%</td>
</tr>
</tbody>
</table>

Nitro compound 49a was formed quantitatively with the given reaction conditions. However, similar to other nitro substituted compounds synthesized herein, flash chromatography proved to be challenging due to the compound tailing on the column. This, in addition to potential breakdown due to prolonged time in contact with silica reduced the isolated yield to 68%. A
gradient eluent system, in contrast to the isocratic eluent system employed, was later found to solve problems related to purification of this compound (see Section 2.3.2). There was unfortunately not enough time to repeat this experiment with the improved eluent system. The product was isolated as a diastereomeric mixture with ratio 39:7:1, with 
\textit{exo-trans} and \textit{exo-cis} being the two major diastereomers (Figure 2.4, page 45).

The dichloro Diels-Alder adduct 49b was also formed quantitatively, but was only stable under basic conditions. All attempts of neutralization lead to instantaneous decomposition into a wide array of compounds, including alcohol 58b. For synthesis purposes, synthesizing compound 49b and immediately reacting it further appears to be uncomplicated, as the reaction mixture is very clean.

Purification of compound 49b by flash chromatography on silica gel yielded 11\%, as well as significant amounts of alcohol 58b, although the fractions containing the alcohol were not clean. The fact that the Diels-Alder adduct 49b was unstable on silica gel was expected, because of the acidic nature of the silica gel. However, due to the lack of other stationary phases, purification on silica gel was attempted nevertheless, in fear that the product would decompose upon storage. Flash chromatography on basic or neutral alumina is expected to give adduct 49b in better yields. Only one diastereomer of adduct 49b was isolated, which identified as the main diastereomer in the crude product by comparison of the \textit{^1}H NMR spectra.

The \textit{N}-methylated substrate compound 49c was not synthesized through microwave-mediated IMDAF of substrate 48c, due to the lack of selectivity towards this product.

\textbf{2.2.3 Microwave-mediated synthesis of 4-chloro-7-methyl-2-nitro-5,6-dihydrophenanthridine (56a), 2,4-dichloro-7-methyl-5,6-dihydrophenanthridine (56b) and 2,4-dichloro-5,7-dimethyl-5,6-dihydrophenanthridine (56c)}

Substituted 5,6-dihydrophenanthridines 56 were synthesized by microwave-mediated IMDAF of the corresponding \textit{o}-furyl(crotylamino)arene 48 in MeCN with addition of an acidic additive (Scheme 2.13). The acidity of the additive varies with the substrate, or more specifically the stability of the oxanorbornene ring system of the Diels-Alder adduct 49.

Dihydrophenanthridine 56a was found to rapidly crystallize when the microwave vessel was cooled to room temperature. The orange crystals were filtered and washed with small amounts of cold MeCN, yielding compound 56a in 58%. The crystallized compound was hard to dissolve in conventional NMR solvents, but it was found that sonication with ultra-sound solved this problem. Since crystallization is not a preferable purification method for small scale synthesis, purification by flash chromatography was attempted. Similarly to compound 49a, the overall poor solubility of the product proved to be a challenge, as the compound tailed extensively on the column during chromatography. A gradient tri-solvent eluent system of EtOAC-CH₂Cl₂-hexanes partially solved the purification issues, but the most important factor was the very clean reaction mixture resulting from the reduced reaction temperature (see Table 2.3, entry 5, page 43).

Similar 2-nitrodihydrophenanthridines have been found to oxidize rather slowly compared to related species in the presence of air/UV light. This was not true for compound 56a, which was observed to oxidize only slightly slower than compound 56b.

Dichlorodihydrophenanthridine 56b was isolated in good yields, although being formed with excellent selectivity in the crude product. This compound was also found to oxidize to phenanthridine 57b very quickly in the presence of air or UV light, which affected the yield of the unoxidized product 56b. To illustrate the rate of oxidation, Figure 2.5 shows a comparison of ¹H NMR spectra from the same sample before and after a series of NMR experiments. The latter spectrum shows circa 17% oxidation after approximately 8 hours under argon atmosphere and while stored in the dark (injected in the NMR instrument).
Figure 2.5. $^1$H NMR spectra of 2,4-dichloro-7-methyl-5,6-dihydrophenanthridine (56b) before (top) and after (bottom) approximately 8 hours of NMR experiments. The bottom spectrum shows circa 17% oxidized compound 57b.
To limit the oxidation of both compound 56a and 56b, the reaction mixtures and crude products were stored under argon and protected from light, and the products were isolated as quickly as possible.

As predicted, the N-methylated dihydrophenanthridine 56c did not show any signs of spontaneous oxidation, as this would form a quaternary phenanthridinium salt. From the ratio of the $^1$H NMR of the reaction mixture, compound 56c was expected to be isolated in a higher yield. Only three compounds were observed after flash chromatography, namely substrate 48c, target molecule 56c and decrotylated compound 56c. These observations point toward partial decomposition, either during heating or during purification.

2.2.4 Microwave-mediated two-step synthesis of 4-chloro-7-methyl-2-nitrophenanthridine (57a) and 2,4-dichloro-7-methylphenanthridine (57b)

Substituted phenanthridines 57 were synthesized in a two-step procedure where the corresponding o-furyl(crotylamino)arene 48 underwent microwave-mediated IMDAF under acidic conditions to form dihydrophenanthridines 56. The crude product was then dissolved in MeCN and irradiated with “black” UV-light while air was bubbled through the solution (Scheme 2.14). Purification was only performed after the final step.

![Scheme 2.14](image)


The oxidation with UV/air was found to be exceptionally clean, as promised by literature reports. When oxidation conditions were tested with a 5:1 mixture of compounds 56a and 57a, respectively, phenanthridine 57a was formed quantitatively and no purification of the product was needed. In the two-step reaction, filtration through a short silica plug eluting with
CH$_2$Cl$_2$ proved to be sufficient purification to yield the target phenanthridine 56a in good yield. It should be mentioned that compound 57a was significantly easier to solubilize than the dihydrophenanthridine 56a, eliminating all purification challenges related to solubility issues.

Full conversion of dihydrophenanthridine 56b to the oxidized compound 57b was reached in four hours, as opposed to almost six hours for the 2-nitro compounds. Also in this case, the crude product after oxidation was very clean. Flash chromatography through a short column yielded compound 57b in an excellent yield over two steps.

### 2.2.5 Conclusion

A total of seven novel 8,10a-epoxyphenanthridines 49, dihydrophenanthridines 56 and phenanthridines 57 with substituents in the C-ring has been synthesized by microwave-mediated methods. The yields herein are generally in the same range as for similar compounds in the literature, with the exception of the Diels-Alder adducts 49. Especially dichloro adduct 49b was found to be highly unstable, and thus isolated in poor yields although being formed quantitatively. For synthesis purposes, multi-step approaches employing the crude mixtures of adducts 49a or 49b appears to be unproblematic for non-acidic conditions.

### 2.3 Conventional heating of o-furyl(crotylamino)arenes 48 to undergo IMDAF

This section describes the reactivity of o-furyl(crotylamino)arenes 48 when heated conventionally in PhMe or xylenes to undergo IMDAF, as well as the products formed when Diels-Alder adduct 49b was ring-opened. Synthesis of 8,10a-epoxyphenanthridines 48, alcohol 58b, ketone 59b, phenanthridine 57b and phenol 65b is also described in this section (Figure 2.6).
2.3.1 Motivation and initial results

In previous projects in our group, o-furyl(allylamino)arenes have been cyclized by heating in PhMe when selectivity towards dihydrophenanthridines were unacceptable in acid-catalyzed microwave-mediated conditions. Subsequent stirring with acid yields the dihydrophenanthridine as a two-step procedure (Scheme 2.15).

Due to the instability of the oxanorbornene ring system in compound 49b, and that attempts at obtaining dry microwave conditions with MeCN were seemingly unsuccessful, compound 48b was conventionally heated in PhMe to undergo IMDAF. To our surprise, the Diels-Alder adduct 49b ring-opened even in dry PhMe, yielding a mixture of an allylic alcohol 58b and a β,γ-unsaturated ketone 59b in a ratio of roughly 1:2, respectively (Scheme 2.16), as well as a small amount of the water eliminated dihydrophenanthridine 56b.
Scheme 2.16. Initial results when heating substrate 48b in dry PhMe. Reagents and conditions: a – PhMe, 100 °C.

NOESY NMR (Spectrum 75) was not conclusive to identify a cis or trans relationship between the methyl and hydroxyl group of the alcohol 58b, as NOE interactions were observed between all protons in the relevant area (except between the methyl and hydroxyl group). The relative stereochemistry was eventually determined to be the trans compound as depicted, with help from computational experiments performed by Martin Hennum (Table 2.6, Section 2.3.3), and eventually by X-ray crystallography (Figure 2.10, Section 2.3.3).

The relative stereochemistry of ketone 59b was determined by NOESY NMR (Spectrum 78) to be as shown in Scheme 2.16. NOE interactions were observed between the methyl and H-6a, but not between H-6a and H-7, suggesting a trans relationship between the hydrogens.

The presence of the oxygen functionality in the C-ring makes both the alcohol 58b and the ketone 59b very interesting synthetic intermediates towards synthesis of natural products, where o-diols and o-diethers are common functionality patterns (Section 1.1). It was therefore decided to further investigate the factors contributing to the formation of the alcohol 58b and the ketone 59b.

2.3.2 The formation of 2,4-dichloro-7-methyl-7,8-dihydrophenanthridin-8-ol (58b) and 2,4-dichloro-7-methyl-5,6a,7,9-tetrahydrophenanthridin-8(6H)-one (59b).

Ring-opened oxanorbornene ring systems that are unable to aromatize, i.e. that are substituted in the bridgehead position, are well known in the literature to isomerize to β,γ-unsaturated
ketones when heated at high temperatures.\textsuperscript{72,82,109} Padwa \textit{et al.} employed this rearrangement as a key step in a total synthesis of racemic strychnine (Scheme 2.17).\textsuperscript{82} In their synthetic pathway, substrate 66 undergoes IMDAF in the presence of a catalytic amount of Lewis acid to form adduct 67. Nitrogen-assisted ring-opening takes place to form alcohol 68. The alcohol is deprotonated and tautomerizes to yield $\beta,\gamma$-unsaturated ketone 69.

\begin{center}
\textbf{Scheme 2.17.} IMDAF and a following rearrangement cascade as a key step in a total synthesis of strychnine by Padwa \textit{et al.}\textsuperscript{82}
\end{center}

The reasoning for the presence of Lewis acid in the reaction mixture is not mentioned in the article, but it is well known in the literature that Lewis acids catalyze Diels-Alder reactions.\textsuperscript{65} There has also been reports of Lewis acids catalyzing the ring-opening and rearrangement of oxanorbornenes to form $\beta,\gamma$-unsaturated ketones (Scheme 2.18),\textsuperscript{110} meaning the function of the Lewis acid in Scheme 2.17 might be twofold.
Scheme 2.18. Literature report of a Lewis acid-catalyzed ring-opening and rearrangement of an oxanorbornene ring system 70 to give a β,γ-unsaturated ketone 71.\(^{110}\) Reagents and conditions: \(\text{a} = \text{FeCl}_3, \text{CH}_2\text{Cl}_2, \text{reflux.}\)

Ring-opening and deprotonation of oxanorbornene systems to yield allylic alcohols similar to compound 58b is also known in the literature, either as the main product,\(^{111}\) or as a minor product along with an aromatized compound (Scheme 2.19).\(^{112}\) In the latter case, extended reaction times were found to convert the alcohol 75 to the aromatized product 76.

Scheme 2.19. A reported IMDAF of substrate 72, followed by nitrogen-assisted ring-opening to yield a mixture of allylic alcohol 74 and aromatized compound 75.\(^{112}\)

In our group, ring-opening and oxidation to form alcohol 78 has previously been encountered for a single substrate.\(^3\) Compound 76 was heated at 100 °C in PhMe to yield a mixture of Diels-Alder adduct 77 and alcohol 78. When the substrate was heated in the presence of catalytic amounts of water (Scheme 2.20), the adduct was fully converted to alcohol 78. The reaction was not looked further into at the time.
Scheme 2.20. Previously observed ring-opening and oxidation to yield the allylic alcohol 78. Reagents and conditions: a – cat. H$_2$O, PhMe, 100 °C.

Scheme 2.21 shows a proposed mechanism to explain the formation of the ketone 59b and the alcohol 58b. The mechanism is based on the mechanism published by Padwa et al. (Scheme 2.17), and accounts for the observed major relative stereochemistries of both products. First, the Diels-Alder adduct 49b undergoes a nitrogen-assisted ring-opening of the oxygen-bridge through resonance. This can be done without the addition of an external acid. From the ring-opened compound 79, deprotonation of two different hydrogens may occur. If H-8 (geminal to OH) is deprotonated, the resulting compound is an enol (80), which can tautomerize to the more stable ketone 59b. If H-6a (the bridgehead hydrogen) is deprotonated, compound 81 is formed, which can be oxidized to give the observed alcohol 58b. Both the resulting anions can be stabilized through resonance, but the bridgehead hydrogen is predicted to be more acidic than the hydrogen in the H-8 position due to the electron-donating nature of the hydroxyl group.
Scheme 2.21. Proposed mechanism to rationalize the formation of ketone 59b and alcohol 58b with correct observed stereochemistries from Diels-Alder adduct 49b.

The oxidation of the theorized compound 81 to give the isolated alcohol 58b has not been studied in detail. Whether oxidation is occurring during the reaction or when the reaction mixture is exposed to air is currently unknown.

Another important question to be asked is why water is not eliminated from alcohol 81 or 58b during the reaction, to yield (dihydro)phenanthridine 56b or 57b. The alcohol was found to be stable even when stirred in a two-phase system of PhMe and 2 M aqueous HCl for several hours. This stability could be explained by the trans stereochemistry of alcohol 58b, eliminating the possibility of a hydrogen anti to the hydroxyl group, and thereby the option of an E₂-type elimination. The fact that water elimination occurs readily under microwave conditions could be attributed to the more polar solvent (MeCN) allowing for an E₁-type elimination to occur, by stabilizing the intermediate carbocation formed (see Scheme 1.20, page 30).

To test the mechanism depicted in Scheme 2.21, N-methylated substrate 48c was reacted under similar conditions (Scheme 2.22). Since the substrate did not undergo IMDAF when heated at 100 °C in PhMe, xylenes was employed to heat the reaction mixture at 140 °C for
four days. This resulted in 60% conversion of the starting material, and with good isolated yields of the Diels-Alder adduct 49c with respect to the conversion. No ring-opened compounds were observed by TLC or $^1$H NMR of the crude product. These observations support the mechanism depicted in Scheme 2.21, since the nitrogen cannot be deprotonated to support the ring-opening of the oxygen-bridge. Unfortunately, there was not enough time or starting material to repeat the synthesis of compound 49c under these conditions to improve the conversion and yield.

Scheme 2.22. Reagents and conditions: a – xylenes, 140 °C.

The nitro-substituted adduct 49a was again found to be more stable than the dichloro analog 49b (see Section 2.2.1). The Diels-Alder adduct was formed quantitatively when substrate 48a was heated in PhMe (Scheme 2.23), and was isolated in excellent yield. Similarly to microwave procedures (Table 2.3, page 43), no ring-opening of compound 49a was observed even if water was added to the reaction mixture. The reason why yields of compound 49a are superior to the yield reported in Section 2.2.2 is because a gradient eluent system was used during chromatography, which was found to significantly reduce tailing on the column.

Scheme 2.23. Reagents and conditions: a – PhMe, 100 °C.
The proposed mechanism in Scheme 2.21 is also supported by the higher stability of nitro-substituted adduct 49a compared with the analog 49b. The strongly electron withdrawing substituent must reduce the nucleophilicity of the amine, decreasing the probability of a nitrogen-assisted ring opening.

On one occasion, ketone 59b was formed as the sole product in a 85:15 diastereomeric ratio, when substrate 48b was heated under dry conditions (Scheme 2.24). These results were not reproducible, even though great effort was put into working dry and inert.

![Scheme 2.24](image)

Scheme 2.24. Non-reproducible synthesis of compound 59b. Reagents and conditions: a – PhMe, 100 °C.

In most cases, the reaction mixture after heating had a dirty brown color (initially colorless), and contained a mixture of the alcohol 58b, the ketone 59b and a small amount of dihydrophenanthridine 56b. The product distribution was generally not reproducible. The fact that the water-eliminated product was observed in the reaction mixture was interesting. As the alcohol 58b was found to not readily eliminate water, the theorized alcohol 81 is not presumed to eliminate easily either. These observations combined indicated that the presence of water was not the only factor that influenced the product distribution. To identify a potential unknown variable in the reaction conditions, a series of systematic alterations of the reaction procedure was initiated (Table 2.4). Entry 1 shows the product distribution from the initial reaction (Scheme 2.16).

Based on the knowledge from Scheme 2.20, substrate 48b was heated in PhMe with addition of water (Table 2.4, entry 2). Again, both the alcohol 58b and the ketone 59b was formed, but this time the alcohol was the major product. It seemed like dry conditions favored the formation of ketone 59b, while wet conditions favored the formation of the alcohol 58b. However, full selectivity towards the alcohol was not achieved, even with vigorous stirring.
**Table 2.4.** Product distributions when substrate 48b is heated in PhMe to undergo IMDAF (Scheme 2.16).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>PhMe dried over</th>
<th>Freshly purified substrate x</th>
<th>Notes</th>
<th>Product distribution</th>
<th>Color of reaction mixture</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>58b  59b  56b</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>–</td>
<td>Mol. Sieves³</td>
<td>No</td>
<td>–</td>
<td>30 63 7</td>
<td>Brown</td>
</tr>
<tr>
<td>2</td>
<td>H₂O</td>
<td>Mol. Sieves³</td>
<td>No</td>
<td>Vigorous stirring.</td>
<td>64 17 18</td>
<td>Brown</td>
</tr>
<tr>
<td>3</td>
<td>–</td>
<td>Mol. Sieves³</td>
<td>No</td>
<td>Filtered to remove potential silica residue from starting material.</td>
<td>45 46 9</td>
<td>Brown</td>
</tr>
<tr>
<td>4</td>
<td>–</td>
<td>Mol. Sieves³</td>
<td>Yes</td>
<td>–</td>
<td>72 17 11</td>
<td>Brown</td>
</tr>
<tr>
<td>5</td>
<td>–</td>
<td>Na</td>
<td>Yes</td>
<td>Reaction mixture degassed with needle in contact with solution.</td>
<td>86 14 0</td>
<td>Brown</td>
</tr>
<tr>
<td>6</td>
<td>–</td>
<td>Na</td>
<td>Yes</td>
<td>Reaction mixture degassed with needle not in contact with solution.</td>
<td>&gt;99 0 0</td>
<td>Clear yellow</td>
</tr>
<tr>
<td>7</td>
<td>–</td>
<td>Na</td>
<td>No</td>
<td>Reaction mixture degassed with needle not in contact with solution.</td>
<td>&gt;99 0 0</td>
<td>Clear yellow</td>
</tr>
</tbody>
</table>

*by ¹H NMR of the crude product.

³Molecular sieves with 3 Å pore size.

---

**Figure 2.7.** Reaction mixtures after 6 days of heating in PhMe. The reaction mixtures were degassed with needles in contact with (left) or above (right) the solution.
It was theorized that trace amounts of silica in the starting material could catalyze water elimination, and thereby be responsible for the observed dihydrophenanthidine 56b in the reaction mixture. An experiment was therefore conducted where the reaction mixture was filtered (entry 3), obtaining similar results as previous entries. Purifying the starting material immediately before heating in PhMe (entry 4) resulted in seemingly increased selectivity towards the alcohol product 58b.

Changing the drying agent of the PhMe from molecular sieves to Na resulted in drastically cleaner crude products (entry 5). Surprisingly, the main product of the reaction was the alcohol 58b, which had earlier been found to be the main product in the presence of catalytic amounts of water (entry 2). Based on the literature reports of Lewis acids catalyzing the transformations to give β,γ-unsaturated ketones, it was examined if the needles used during degassing could be the source of trace amounts of Lewis acids in the reaction mixture. Two experiments were conducted side by side, employing the same batch of freshly purified starting material, PhMe from the same flask, same concentration and with identical reaction times. The only difference was whether or not the needle was in contact with the reaction mixture while degassing. Astonishingly, the ketone was not observed for the experiment where the reaction mixture was degassed with the needle above the solution (entry 6). Furthermore, the reaction mixture looked drastically cleaner visually (Figure 2.7). This result was found to be reproducible, also when the starting material was not freshly purified (entry 7).

Alcohol 58b was synthesized following the precautions described in entry 7, and isolated in decent yields. The compound was found to slightly decompose on silica, as judged by 2D-TLC analysis. The crude product was therefore purified using a very short column, which seemed to still result in decomposition, lowering the yield of the isolated product.

Scheme 2.25. Reagents and conditions: a – PhMe, 100 °C.
3 Å molecular sieves are mesoporous materials that are made from silica and aluminum oxides, among else. They do in other words possess a certain degree of Lewis acidity, which could explain why changing the drying agent to Na resulted in such a difference in product distributions. The role of the Lewis acid may for instance be to facilitate the ring-opening of compound 49b by complexing to the oxygen, making the hydrogen in the position geminal to the hydroxyl more acidic than the hydrogen in the bridgehead position (Scheme 2.26) in the ring-opened intermediate 82.

![Scheme 2.26. Proposed Lewis-acid catalyzed formation of ketone 59b from Diels-Alder adduct 49b.](image)

In an attempt to synthesize ketone 59b exclusively, substrate 48b was heated in PhMe with addition of 0.2 equivalents of anhydrous MgBr\(_2\) (Scheme 2.27). Surprisingly, the fully oxidized phenanthridine 57b was formed as the major product, and was isolated in decent yield.

![Scheme 2.27. Reagents and conditions: a – MgBr\(_2\), PhMe, 100 °C.](image)
2.3.3 The relative stereochemistry of 2,4-dichloro-7-methyl-7,8-dihydrophenanthridin-8-ol (58b)

The relative stereochemistry of alcohol 58b remained unknown after NOESY NMR analysis. The alcohol was formed in an 85:15 ratio of diastereomers. The major isomer presumed to be the trans compound formed as depicted in Scheme 2.21, but due to the theoretical chance of inversion of stereochemistry through an $S_N2$-type nucleophilic attack from water (Scheme 2.28), the relative stereochemistry was not necessarily obvious.

![Scheme 2.28. Theoretical transformation of the Diels-Alder adduct 49b to give the cis diastereomer of alcohol 58b.](image)

Several attempts were made at growing crystals suitable for X-ray crystallography, but for a long time, all attempts lead to either crystalline needles that were too narrow for analysis, or no crystals at all. As an attempt to identify a relative stereochemistry, PhD student Martin Hennum optimized the geometries for both the trans and cis diastereomers (using B3LYP/cc-pTVP) to identify the dihedral angle between H-7 and H-8 (Figure 2.8, Table 2.5). The angle was then used to calculate the coupling constants, employing the Karplus equation. None of the calculated coupling constants matched the observed value of 3.3 Hz (600 MHz, CDCl$_3$).
Table 2.5. Calculated dihedral angles between H-7 and H-8, and the corresponding calculated coupling constant.

<table>
<thead>
<tr>
<th>Position Me</th>
<th>Position OH</th>
<th>Relative energies (kJ/mol)</th>
<th>H7-H8 dihedral angle (°)</th>
<th>Calculated $^3J$ (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>trans-$a'$</td>
<td>equatorial</td>
<td>3.29</td>
<td>171.8</td>
<td>8.04</td>
</tr>
<tr>
<td>trans-$b'$</td>
<td>axial</td>
<td>0.00</td>
<td>79.8</td>
<td>1.33</td>
</tr>
<tr>
<td>cis-$a'$</td>
<td>axial</td>
<td>5.76</td>
<td>51.8</td>
<td>2.54</td>
</tr>
<tr>
<td>cis-$b'$</td>
<td>equatorial</td>
<td>2.36</td>
<td>49.1</td>
<td>4.67</td>
</tr>
</tbody>
</table>

$^a$Calculated using B3LYP/cc-pTVP.  
$^c$See Figure 2.8.

As a last resort, Hennum calculated $^1$H and $^{13}$C NMR data for both the cis and trans diastereomers in CDCl$_3$. Computation details is reported in the experimental section. Experimental NMR data was compared with the calculated $^1$H and $^{13}$C NMR data (Table 2.6), and the major and minor diastereomers fitted the calculated data for the trans and cis compounds, respectively.

The most notable differences between the two isomers are the $^1$H data for H-7, H-8, H-9 and H-10, as well as $^1$H and $^{13}$C data for the methyl group. All of these point towards trans being the major diastereomer. Also the coupling constants between H-7 and H-8 matches the experimental values; for the major isomer, a coupling constant of 3.3 Hz was observed, versus a value of 3.2 Hz calculated for the trans compound. For the minor isomer, an apparent pentet with a “coupling constant” of circa 7 Hz was observed, versus a calculated value of 8.2 Hz for the cis diastereomer. Thus, the major isomer was assigned as the trans diastereomer.
Table 2.6. Experimental and calculated $^1$H and $^{13}$C NMR data for compound 58b.$^{114}$

<table>
<thead>
<tr>
<th>Position</th>
<th>$^1$H NMR (CDCl$_3$)$^b$</th>
<th>$^{13}$C NMR (CDCl$_3$)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Calc. $\delta$ cis ($J$)</td>
<td>Calc. $\delta$ trans ($J$)</td>
</tr>
<tr>
<td>1</td>
<td>7.93 (1.8)</td>
<td>8.00 (1.8)</td>
</tr>
<tr>
<td>2</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>3</td>
<td>7.69 (1.8)</td>
<td>7.69 (1.8)</td>
</tr>
<tr>
<td>4</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>4a</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>6</td>
<td>8.66</td>
<td>8.69 (0.98)</td>
</tr>
<tr>
<td>6a</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>7</td>
<td>3.26 (8.2, 7.5)</td>
<td>3.34 (7.9, 3.2, 0.98)</td>
</tr>
<tr>
<td>8</td>
<td>4.79 (8.2, 3.5)</td>
<td>4.27 (3.2, 5.9)</td>
</tr>
<tr>
<td>9</td>
<td>6.42 (11.4, 3.5)</td>
<td>6.50 (11.2, 3.2)</td>
</tr>
<tr>
<td>10</td>
<td>7.06 (11.4)</td>
<td>7.30 (11.2)</td>
</tr>
<tr>
<td>10a</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>10b</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CH$_3$</td>
<td>1.34 (7.5)</td>
<td>1.21 (7.9)</td>
</tr>
</tbody>
</table>

$^a$For numbering, see Figure 2.9.

$^b$Calculated and experimental $\delta$ values in ppm, and $J$ values in Hz.

$^c$Data from a spectrum of a mixture of diastereomers.

$^d$Not possible to determine.

$^e$apparent pentet, "$J$" circa 7 Hz.

![Figure 2.9. Numbering of compound 58b.](image-url)
Some time after the calculations presented in Table 2.7 were performed, a crystal of crystallography quality was discovered in an NMR tube containing only the major isomer of alcohol 58b, where all the solvent had evaporated. X-ray crystallography revealed that the major isomer was the trans compound (Figure 2.10), as concluded from the computational studies.

**Figure 2.10.** Results from X-ray crystallography of trans compound 58b, showing the compound as a single molecule (bottom), and as hydrogen-bound dimers (top).

### 2.3.4 Synthesis of 2,4-dichloro-7-methylphenanthridin-8-ol (65b)

There are numerous examples of oxidations of β,γ-unsaturated ketones to yield phenols in the
literature, utilizing a variety of conditions such as \( N \)-bromosuccinimide (NBS),\(^{115} \) transition-metal catalysts,\(^{116} \) cerium(IV) salts,\(^{117} \) and DDQ (Scheme 2.29).\(^{118} \)

![Scheme 2.29](image)

**Scheme 2.29.** Literature oxidation of a mixture of ketones 84 and 85 with DDQ. Reagents and conditions: a – DDQ, dioxane.

It was initially attempted to oxidize ketone 59b to yield the phenol 65b with a gentle oxidating method, namely irradiation of UV-light while bubbling air through, similarly to the oxidation of dihydrophenanthridines 56 in Section 2.2.4. This resulted in no conversion of the starting material. Oxidation was then performed with DDQ, giving the fully aromatized phenanthridin-8-ol 65b in poor yields (Scheme 2.30).

![Scheme 2.30](image)

**Scheme 2.30.** Reagents and conditions: a – hv, air, MeCN. b – DDQ, CH₂Cl₂.

The oxidation (Scheme 2.30) was only tried once due to shortage of ketone starting material. Full conversion of starting material was achieved, and no other compounds were identified by TLC or \(^1\)H NMR of the crude product, or during chromatography. The reason for the low isolated yield is therefore not clear.

Oxidation of the alcohol 58b was also attempted (Scheme 2.31), which resulted in rapid conversion of the starting material to yield innumerable products, where none matched the \(^1\)H NMR data of the target product 65b. The conclusion was therefore that no desired oxidation did occur, and that the starting material decomposed when treated with DDQ.
In the literature, compounds similar to alcohol 58b have been oxidized to the respective phenols by DDQ (Scheme 2.32). \(^{119}\)

**Scheme 2.31.** Reagents and conditions: a – DDQ, CH\(_2\)Cl\(_2\).

**Scheme 2.32.** Literature oxidation of a cyclohexadienol with DDQ. \(^{119}\) Reagents and conditions: a – DDQ, dioxane.

2.3.5 Conclusion

Conventional heating of substrates 48 to undergo IMDAF was performed. Adducts 49a and 49c did not show signs of ring-opening when heated in dry PhMe, while compound 49b readily ring-opened to give alcohol 58b. Presence of trace amounts of Lewis acid in the reaction mixture was found to catalyze the rearrangement of adduct 49b to ketone 59b, which could be oxidized to the phenol 65b. Heating substrate 48b in the presence of 0.2 equivalents of MgBr\(_2\) was found to give phenanthridine 57b directly.
3. Future research

The work performed during this project have brought up multiple interesting reactions that deserves further investigation. The \( \beta,\gamma \)-unsaturated ketone 59b would be an important intermediate towards natural products, as exemplified by Padwa et al.\(^{82}\) Identification of the Lewis acid catalyzing the formation of ketone 59b could lead to a straightforward synthesis of this product, as well as the rearrangement of more stable IMDAF adducts like 49a and 49c. Ketones 90 be (stereoselectively) reduced,\(^{120}\) oxidized,\(^{121}\) or isomerized to \( \alpha,\beta \)-unsaturated ketones 94,\(^{122}\) to mention some possibilities (Scheme 3.1). An oxidation of phenols 91 to the catechols 92 is particularly interesting, because of the \( o \)-diether or \( o \)-diol functionality often present in phenanthridine natural products.

![Scheme 3.1. Potential synthesis of ketone 90 from a general substrate 89, and opportunities for further synthesis.](image-url)
If selective ring-opening to form ketones 59 is not possible, Scheme 3.2 illustrates a theorized synthesis of a ketone analog 97 and phenol 65, starting from differently substituted allyl moiety 92. The IMDAF adduct 96 is expected to rearrange when heated, since the bridgehead position is substituted.

**Scheme 3.2.** Alternative synthesis of phenol 91.

IMDAF of substrate 48b in the presence of MgBr₂ unexpectedly produced the fully oxidized phenanthridine 57b directly. Based on these results, it would be very interesting to test the addition of Lewis acids in microwave-mediated reactions (Scheme 3.3). If phenanthridines could be synthesized successfully in a one-pot procedure, the overall viability of the synthetic strategy would increase, as a separate oxidation step is unnecessary. The Diels-Alder catalyzing properties of Lewis acids could also result in milder cyclization conditions, potentially allowing for more complex and delicate substrates, as often employed in synthesis of natural products.
Scheme 3.3. Potential microwave-mediated one-pot synthesis of phenanthridines 46 from substrates 38.

Oxidation of 7-methylphenanthridines 57 synthesised herein to the carboxylic acids 99 (Scheme 3.4) is a subject that may further expand the scope of substituents possible to introduce in the C-ring of the phenanthridine. This oxidation could be catalyzed by for instance vanadyl salts,\textsuperscript{123,124} which have previously given high yields for electron deficient aromatic systems.\textsuperscript{124}

Scheme 3.4. Oxidation of 7-methylphenanthridines 57 to produce benzoic acids 99.

Finally, further substitution of the C-ring could be achieved by employing substituted 2-furanyl moieties (Scheme 3.5). In addition to the implementation of functionality in the product, halo-substituted furans have shown much higher reactivity towards IMDAF cyclizations than unsubstituted analogs,\textsuperscript{125} meaning milder cyclization conditions can be employed.
Scheme 3.5. Synthesis of C-ring functionalized phenanthridines by IMDAF of substituted furans.
4. CONCLUSION

During this project, phenanthridines with substituents in the C-ring has successfully been synthesized by microwave-mediated or conventional heating of o-furyl(crotylamino)arenes to undergo IMDAF cyclization.

Following microwave-mediated synthesis route published by our research group, 7-methyldihydrophenanthridines 56 and 7-methylphenanthridines 57 were synthesized generally good yields. It was also found that Diels-Alder adducts 49a and 49b were formed quantitatively by minor alterations of the reaction conditions. It was found that the exo selectivities for the substrates described herein were significantly higher than for N-allyl analogs previously employed.

The oxanorbornene ring system of Diels-Alder adduct 49b was found to be exceptionally labile, and the compound was only stable under basic conditions. When compound 49b was formed under dry conditions, trace amounts of Lewis acid originating from laboratory equipment and molecular sieves was found to catalyze the rearrangement to ketone 59b. If no Lewis acid was present, adduct 49b ring-opened and oxidized, yielding alcohol 58b. Mechanisms to account for the formation of both compounds have been proposed. Ketone 59b was oxidized to phenol 65, although the reaction currently needs to be optimized to improve the yield. Compounds 58b, 59b and 65b are all very interesting intermediates toward synthesis of natural products, due to the oxygen functionality in the C-ring.

Finally, IMDAF of substrate 58b in the presence of MgBr₂ interestingly produced the fully oxidized phenanthridine 57b. Further exploration of this approach may potentially allow for one-pot procedures of phenanthridines, without requiring successive oxidation.
5. EXPERIMENTAL

$^1$H NMR spectra were recorded at 600 MHz with a Bruker AV 600 instrument or a Bruker AVII 600 instrument, at 500 MHz with a Bruker DRX 500 instrument, at 400 MHz with a Bruker AVII 400 instrument, at 300 MHz with a Bruker DPX 300 or at 200 MHz with a Bruker DPX 200 instrument. The decoupled $^{13}$C NMR spectra were recorded at 150, 125, 75 or 50 MHz using instruments mentioned above. All $J$ values are reported in Hertz. Mass spectra under electron impact conditions were recorded with a VG Prospec instrument at 70 eV ionizing voltage, and are presented as $m/z$ (% rel. int.). HRMS-EI was performed with a double-focusing magnetic sector instrument mentioned above. Single-crystal X-ray crystallography was performed with a Bruker Vantage D8 single crystal diffractometer with MoKα irradiation at a temperature of 105 K. Cell and structure refinement was done with APEX2 and SHELXL-2013 software, respectively. Microwave experiments were carried out in sealed vessels in a synthesis reactor Monowave 300, Anton Paar GmbH, equipped with a Ruby thermometer and internal IR probe. Melting points were determined with a Büchi Melting Point B-545 apparatus and are uncorrected. Flash chromatography was performed on silica gel (Merck no. 09385). The UV lamp used in oxidation reactions was emitting at 315–400 nm with peaks at 352 and 368 nm. HPLC grade MeCN was degassed by freeze–pump–thaw cycling using N$_2$(l) and flushed with Ar. Dry CH$_2$Cl$_2$, THF and MeCN were obtained from solvent purification system, MB SPS-800 from MBraun, Garching, Germany. Hexanes were distilled before use. PhMe was distilled from CaH$_2$ and stored over 3 Å molecular sieves or Na. Tetrabutylammonium bromide (TBAB) was dried under vacuum at 40 °C. Potassium (furan-2-yl)trifluoroborate was synthesized in bulk by another member of our group, following a literature procedure.$^{63}$ All other reagents were commercially available and used as received.

All calculations were performed by PhD student Martin Hennum. DFT calculations were performed with Gaussian 09 d01. Conformational search and subsequent optimization of the cis and trans isomer of the alcohol 58b gave two minima for each isomer at the B3LYP/6-31+G(d,p) level of theory using an ultrafine grid. NMR shifts were calculated using the mPW1PW91 functional with 6-311+G(2d,p) as basis set and an ultrafine grid. Solvation effects (chloroform) were included as single point corrections with the SMD method. The acquired NMR shifts were scaled as by Lodewyk et. al. (slope: -1.0823, intercept: 31.8486 for
$^1$H and slope: -1.0448, intercept: 186.0596 for $^{13}\text{C}$). Coupling constants and energies were calculated B3LYP/6-31+g(d,p) level of theory with an ultrafine grid. The presented calculated NMR shifts and coupling constants of cis and trans of compound 58b is the Boltzmann weighted sum of their two conformers.
Synthesis of 2-chloro-6-(furan-2-yl)-4-nitroaniline (51a)\textsuperscript{1}

\[
\begin{array}{c}
\text{O}_2\text{N} \\
\text{NH}_2 \\
\text{Cl} \\
\text{51a}
\end{array}
\]

Potassium carbonate (2.76 g, 19.9 mmol), potassium (furan-2-yl)trifluoroborate (2.61 g, 15.0 mmol), triphenylphosphine (691 mg, 2.63 mmol) and palladium acetate (170 mg, 0.757 mmol) were subsequently added to a stirring solution of 2-chloro-4-nitro-6-(furan-2-yl)aniline (47a) (2.53 g, 10.1 mmol) in EtOH/H\textsubscript{2}O 95:5 (v/v) (200 mL). The resulting mixture was degassed with N\textsubscript{2} and refluxed for 5 h. The reaction mixture was filtered through silica gel eluting with CH\textsubscript{2}Cl\textsubscript{2} (200 mL), and concentrated under reduced pressure. The product was isolated by flash chromatography on silica gel eluting with EtOAc:CH\textsubscript{2}Cl\textsubscript{2}:hexanes (1:4:45). Yield 1.90 g (81\%) as a yellow solid.

\textsuperscript{1}\textbf{H NMR} (600 MHz, CDCl\textsubscript{3}) $\delta$ 8.29 (d, $J = 2.5$ Hz, 1H, H-5), 8.17 (d, $J = 2.5$ Hz, 1H, H-3), 7.58-7.57 (m, 1H, H-5 in furyl), 6.75 (d, $J = 3.4$ Hz, 1H, H-3 in furyl), 6.59 (dd, $J = 3.4$, 1.8 Hz, 1H, H-4 in furyl), 5.69 (s, 2H, NH\textsubscript{2}).

\textsuperscript{13}\textbf{C NMR} (150 MHz, CDCl\textsubscript{3}) $\delta$ 150.94 (C-2 in furyl), 145.32 (C-1), 142.68 (C-5 in furyl), 138.26 (C-4), 124.53 (C-3), 122.37 (C-5), 119.40 (C-2), 115.50 (C-6), 112.05 (C-4 in furyl), 108.82 (C-3 in furyl).

\textbf{MS EI} m/z (rel. %) 240/238 (34/100), 209 (11), 208 (9), 192 (13), 166 (7), 164 (21), 163 (10), 129 (8), 128 (17), 102 (11).

\textbf{M.p.} 180-181 °C (lit.\textsuperscript{1} 180-182 °C)

Compound is known in the literature.\textsuperscript{1}
Spectrum 1. 600 MHz, CDCl₃, $^1$H NMR spectrum of 2-chloro-6-(furan-2-yl)-4-nitroaniline (51a).

Spectrum 2. 150 MHz, CDCl₃, $^{13}$C NMR of 2-chloro-6-(furan-2-yl)-4-nitroaniline (51a).
Potassium carbonate (2.50 g, 18.1 mmol), potassium (furan-2-yl)trifluoroborate (3.29 g, 18.9 mmol), triphenylphosphine (798 mg, 3.04 mmol) and palladium acetate (129 mg, 0.575 mmol) were subsequently added to a stirring solution of 2-bromo-4,6-dichloroaniline (47b) (3.29 g, 13.7 mmol) in EtOH/H_2O 95:5 (v/v) (160 mL). The resulting mixture was degassed with N_2 and refluxed for 4 h. The reaction mixture was filtered through silica gel eluting with CH_2Cl_2 (150 mL), and concentrated under reduced pressure. The product was isolated by flash chromatography on silica gel using EtOAc/CH_2Cl_2/hexane (1:4:45). Yield 2.71 g (95%) as a pale pink solid.

^{1}H NMR (200 MHz, CDCl_3) δ 7.52 (dd, J = 1.8, 0.6 Hz, 1H, H-5 in furyl), 7.37 (d, J = 2.4 Hz, 1H, H-5), 7.22 (d, J = 2.4 Hz, 1H, H-3), 6.64 (dd, J = 3.4, 0.6 Hz, 1H, H-3 in furyl), 6.53 (dd, J = 3.4, 1.8 Hz, 1H, H-4 in furyl), 4.69 (s, 2H, NH_2).

^{13}C NMR (150 MHz, CDCl_3) δ 151.49, 142.23, 138.60, 128.17, 125.84, 122.35, 120.94, 117.98, 111.75, 108.13, 77.37, 77.16, 76.95. ^{13}C NMR data in agreement with literature.^{2}

MS EI m/z (rel. %) 231/229/227 (9/61/94), 202/200/198 (10/65/100), 164 (23), 162 (8), 128 (10), 127 (12).

M.p. 66-67 °C (lit.^{2} 66-68 °C).
**Spectrum 3.** 200 MHz, CDCl$_3$, $^1$H NMR of 2,4-dichloro-6-(furan-2-yl)aniline (51b).

**Spectrum 4.** 150 MHz, CDCl$_3$, $^{13}$C NMR of 2,4-dichloro-6-(furan-2-yl)aniline (51b).
Synthesis of \(N\)-(but-2-en-1-yl)-2-chloro-6-(furan-2-yl)-4-nitroaniline (48a) and \(N,N\)-di(but-2-en-1-yl)-2-chloro-6-(furan-2-yl)-4-nitroaniline (52a)

Dried tetrabutylammonium bromide (2.34 g, 7.36 mmol) was added to a stirring solution of compound 51a (881 mg, 3.69 mmol) in dry THF (30 mL) and the mixture was degassed with Ar. Sodium hydride (ca. 60% in mineral oil, 176 mg, 4.41 mmol) was added at 0 °C. The resulting mixture was allowed to reach ambient temperature and stirred for 10 min before 1-bromobut-2-ene (\(E/Z\) ratio 85:15, 548 mg, 4.06 mmol) was added. The resulting mixture was allowed to reach ambient temperature and stirred for 4 h before quenching with water (20 mL) and EtOAc (30 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3×50 mL). The combined organic phases were dried (MgSO\(_4\)) and concentrated under reduced pressure. The product was purified by flash chromatography on silica gel eluting with 10-30% CH\(_2\)Cl\(_2\) in hexanes. Yield 816 mg (76%) of compound 48a as a yellow oil, mixture of \(E/Z\) isomers (ratio 85:15) and 68 mg (5%) of compound 52a as a yellow oil, mixture of 3 isomers (ratio ca 72:26:2).

NMR data for the major isomers are given.

\(N\)-(But-2-en-1-yl)-2-chloro-6-(furan-2-yl)-4-nitroaniline (48a)

\(^1\text{H NMR}\) (600 MHz, CDCl\(_3\)) \(\delta\) 8.18 (s, 2H, H-5 and H-3), 7.52 (dd, \(J = 1.8, 0.8\) Hz, 1H, H-5 in furyl), 6.59 (dd, \(J = 3.3, 0.8\) Hz, 1H, H-3 in furyl), 6.53 (dd, \(J = 3.3, 1.8\) Hz, 1H, H-4 in furyl), 5.66-5.54 (m, 1H, \(=\text{CCH}_3\)), 5.45-5.40 (m, 1H, \(\text{CH}_2\text{C}=\)), 4.96 (br s, 1H, NH), 3.53-3.44 (m, 2H, \(\text{CH}_2\)), 1.66 (dq, \(J = 6.6, 1.4\) Hz, 3H, \(\text{CH}_3\)).

\(^{13}\text{C NMR}\) (150 MHz, CDCl\(_3\)) \(\delta\) 150.19 (C-2 in furyl) 148.25 (C-1), 142.52 (C-5 in furyl), 138.55 (C-4), 129.64 (\(=\text{CCH}_3\)), 127.21 (\(\text{CH}_2\text{C}=\)), 125.92 (C-3 or C-5), 124.96 (C-3 or C-5), 122.59 (C-2), 118.42 (C-6), 111.86 (C-4 in furyl), 110.04 (C-3 in furyl), 48.09 (CH\(_2\)), 17.85 (CH\(_3\)).

\(\text{MS EI}\) \(m/z\) (rel. %) 294/292 (23/70, \(M^+\)), 277 (12), 251 (19), 236 (53), 55 (100).
HRMS calcd. for C_{14}H_{13}ClN_{2}O_{3} 292.0615, found 292.0612.

\( N,N\text{-di(But-2-en-1-yl)-2-chloro-6-(furan-2-yl)-4-nitroaniline (52a)} \)

\(^1\text{H NMR}\) (600 MHz, CDCl\(_3\)) \( \delta \) 8.48 (d, \( J = 2.8\) Hz, 1H, H-5), 8.10 (d, \( J = 2.7\) Hz, 1H, H-3), 7.54 – 7.53 (m, 1H, H-5 in furyl), 7.00 – 6.98 (m, 1H, H-3 in furyl), 6.54 (dd, \( J = 3.4, 1.8\) Hz, 1H, H-4 in furyl), 5.64 – 5.35 (m, 4H, 2x CH\(_2\)CH\(=\) and 2x \(=\text{CHCH}_3\)), 3.63 (d, \( J = 6.7\) Hz, 4H, 2x NCH\(_2\)), 1.62 (dd, \( J = 6.3, 1.1\) Hz, 6H, 2x CH\(_3\)).

\(^{13}\text{C NMR}\) (150 MHz, CDCl\(_3\)) \( \delta \) 150.06 (C-1 or C-2 in furyl), 149.92 (C-1 or C-2 in furyl), 144.06 (C-4), 142.76 (C-5 in furyl), 135.50 (C-2), 132.00 (C-6), 129.33 (\(=\text{CHCH}_3\)), 127.59 (CH\(_2\)CH\(=\)), 124.44 (C-3), 121.72 (C-5), 112.15 (C-4 in furyl), 111.04 (C-3 in furyl), 54.19 (NCH\(_2\)), 17.85 (CH\(_3\)).

MS EI m/z (rel. %) 348/346 (14/41), 331 (7), 311 (9), 292 (7), 291 (21), 290 (12), 275 (7), 263 (30), 257 (16), 245 (11), 236 (9), 217 (13), 203 (16), 55 (100).

HRMS calcd. for C\(_{18}\)H\(_{17}\)ClN\(_2\)O\(_3\) 346.1084, found 346.1079.
Spectrum 5. 600 MHz, CDCl₃, ¹H NMR of N-(but-2-en-1-yl)-2-chloro-6-(furan-2-yl)-4-nitroaniline (48a).

Spectrum 6. 150 MHz, CDCl₃, ¹H NMR of N-(but-2-en-1-yl)-2-chloro-6-(furan-2-yl)-4-nitroaniline (48a).
Spectrum 7. 600 MHz, CDCl₃, ¹H NMR of N,N-di(but-2-en-1-yl)-2-chloro-6-(furan-2-yl)-4-nitroaniline (52a).

Spectrum 8. 150 MHz, CDCl₃, ¹³C NMR of N,N-di(but-2-en-1-yl)-2-chloro-6-(furan-2-yl)-4-nitroaniline (52a).
Synthesis of \(N\)-(but-2-en-1-yl)-2,4-dichloro-6-(furan-2-yl)aniline (48b)

Dried tetrabutylammonium bromide (1.62 g, 5.03 mmol) was added to a stirring solution of compound 51b (1.08 g, 4.74 mmol) in dry THF (75 mL) and the mixture was degassed with Ar. Sodium hydride (ca. 60% in mineral oil, 253 mg, 6.33 mmol) was added at 0 °C. The resulting mixture was allowed to reach ambient temperature and stirred for 10 min before 1-bromobut-2-ene (\(E/Z\) ratio 85:15, 0.83 g, 6.14 mmol) was added. The resulting mixture was stirred for 120 min before quenching with water (40 mL) and EtOAc (75 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3\times75 mL). The combined organic phases were dried (MgSO\(_4\)) and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel eluting with 3-10% CH\(_2\)Cl\(_2\) in hexanes. Yield 1.22 g (91%) as a colorless oil, mixture of \(E/Z\) isomers (ratio 85:15).

NMR data is reported for the major isomer.

\(^1\text{H NMR}\) (400 MHz, CDCl\(_3\)) \(\delta\) 7.51 (d, \(J = 2.5\) Hz, 1H, H-5), 7.49 (d, \(J = 1.8\) Hz, 1H, H-5 in furyl), 7.27 (d, \(J = 2.5\) Hz, 1H, H-3), 6.85 (d, \(J = 3.3\) Hz, 1H, H-3 in furyl), 6.51 (dd, \(J = 3.3\), 1.8 Hz, 1H, H-4 in furyl), 5.66-5.46 (m, 2H, CH=CH), 3.99 (s, 1H, NH), 3.42 (d, \(J = 6.0\) Hz, 2H, CH\(_2\)), 1.67 (d, \(J = 6.0\) Hz, 3H, CH\(_3\)).

\(^{13}\text{C NMR}\) (100 MHz, CDCl\(_3\)) \(\delta\) 150.52 (C-2 in furyl), 142.20 (C-5 in furyl), 141.24 (C-1), 128.44 (CH=), 128.27 (CH=), 128.21 (C-3), 127.86 (C-2 or C-4), 127.00 (C-5), 126.55 (C-2 or C-4), 125.05 (C-6), 111.92 (C-4 in furyl), 109.77 (C-3 in furyl), 49.70 (CH\(_2\)), 17.89 (CH\(_3\)).

MS \(\text{EI}\) \(m/z\) (rel. %) MS \(\text{EI}\) \(m/z\) (rel %) 285/283/281 (8/50/76, \(M^+\)), 266 (11), 254 (14), 252 (22), 240 (29), 238 (30), 227 (40), 226 (23), 225 (41), 202 (17), 200 (68), 198 (100).

HRMS calcd. for C\(_{14}\)H\(_{13}\)Cl\(_2\)NO 281.0374, found 281.0381.
Spectrum 9. 600 MHz, CDCl₃, ¹H NMR of N-(but-2-en-1-yl)-2,4-dichloro-6-(furan-2-yl)aniline (48b).

Spectrum 10. 150 MHz, CDCl₃, ¹³C NMR of N-(but-2-en-1-yl)-2,4-dichloro-6-(furan-2-yl)aniline (48b).
Synthesis of N-(but-2-en-1-yl)-2,4-dichloro-6-(furan-2-yl)-N-methylaniline (48c)

18-Crown-6-ether was added to a stirring solution of compound 48b (222 mg, 0.787 mmol) in dry PhMe (20 mL). The resulting mixture was degassed with Ar, added potassium hydride (ca. 30% in parafin oil, 280 mg, 2.10 mmol), stirred for 5 min, then added MeI (0.13 mL, 2.1 mmol). The reaction mixture was heated at 40 °C for 50 min before quenching with water (20 mL). The phases were separated, and the aqueous phase was extracted with CH₂Cl₂ (2×25 mL). The combined organic phases were dried (MgSO₄) and concentrated under reduced pressure. The crude product was purified twice by flash chromatography on silica gel eluting with hexanes. Yield 214 mg (92%) as a colorless oil, mixture of E:Z isomers (ratio 84:16).

NMR data is reported for the major isomer.

¹H NMR (600 MHz, CDCl₃) δ 7.68 (d, J = 2.5 Hz, 1H, H-5), 7.48 (dd, J = 1.8, 0.6 Hz, 1H, H-5 in furyl), 7.23 (d, J = 2.5 Hz, 1H, H-3), 7.05 (dd, J = 3.4, 0.6 Hz, 1H, H-3 in furyl), 6.51 (dd, J = 3.4, 1.8 Hz, 1H, H-4 in furyl), 5.64-5.41 (m, 2H, CH=CH), 3.60 (d, J = 6.8 Hz, 2H, NCH₂), 2.71 (s, 3H, NCH₃), 1.64 (dq, J = 6.4, 1.2 Hz, 3H, CH₃).

¹³C NMR (150 MHz, CDCl₃) δ 150.41 (C-2 in furyl), 143.58 (C-1), 142.20 (C-5 in furyl), 136.63 (C-2), 133.16 (C-4), 131.06 (C-6), 128.85 (C-3), 128.60 (CH=), 128.56 (CH=), 125.55 (C-5), 112.13 (C-4 in furyl), 111.07 (C-3 in furyl), 57.11 (NCH₂), 38.61 (NCH₃), 17.85 (CH₃).

MS EI m/z (rel. %) 299/297/295 (9/65/100, M⁺), 280 (12), 268 (12), 266 (24), 260 (36), 254 (29), 226 (12), 212 (71), 205 (15), 185 (11), 177 (22), 149 (17).

HRMS calcd. for C₁₅H₁₅Cl₂NO 295.0531, found 295.0527.
Spectrum 11. 600 MHz, CDCl₃, $^1$H NMR of $N$-(but-2-en-1-yl)-2,4-dichloro-6-(furan-2-yl)-N-methylaniline (48c).

Spectrum 12. 150 MHz, CDCl₃, $^{13}$C NMR of $N$-(but-2-en-1-yl)-2,4-dichloro-6-(furan-2-yl)-N-methylaniline (48c).
Synthesis of (±)-(6aS,7R,8R,10aS)-4-chloro-7-methyl-2-nitro-6,6a,7,8-tetrahydro-5H-8,10a-epoxyphenanthridine (49a)

Method A. A solution of compound 48a (180 mg, 0.615 mmol) in dry PhMe (20 mL) was degassed with Ar and stirred at 100 °C for 27 h. The reaction mixture was concentrated under reduced. The product was isolated by flash chromatography on silica gel eluting with gradient EtOAc-hexanes (1:4 to 2:3). Yield 167 mg (93%) as a yellow solid, mixture of 3 diastereomers (ratio 40:6:1).

Method B. Degassed MeCN (15 mL) was transferred to a microwave vessel, and compound 48a (204 mg, 0.700 mmol) and water (ca. 0.10 mL) were added. The reaction mixture was degassed with Ar and heated at 150 °C in a microwave oven for 1 h. The reaction mixture was concentrated under reduced pressure. The product was isolated by flash chromatography on silica gel eluting with EtOAc-hexanes (1:3). Yield 135 mg (66%) as a yellow solid, mixture of 3 diastereomers (ratio 37:6:1).

NMR data is reported for the major isomer.

$^1$H NMR (600 MHz, CDCl$_3$) $\delta$ 8.23 (d, $J = 2.5$ Hz, 1H, H-1), 8.18 (d, $J = 2.5$ Hz, 1H, H-3), 6.60 (dd, $J = 5.7$, 1.7 Hz, 1H, H-9), 6.32 (d, $J = 5.7$ Hz, 1H, H-10), 5.51 (s, 1H, NH), 4.86 (dd, $J = 4.5$, 1.7 Hz, 1H, H-8), 3.78 (ddd, $J = 11.9$, 5.5, 4.5 Hz, 1H, H$_a$ in H-6), 3.06-3.01 (m, H$_b$ in H-6), 2.05-1.99 (m, 1H, H-7), 1.42 (ddd, $J = 11.9$, 5.5, 3.3 Hz, 1H, H-6a), 0.98 (d, $J = 7.1$ Hz, 3H, CH$_3$).

$^{13}$C NMR (150 MHz, CDCl$_3$) $\delta$ 147.92 (C-4a), 137.59 (C-10 and C-2), 137.54 (C-9), 126.60 (C-1), 125.43 (C-3), 118.99 (C-10b), 118.07 (C-4), 84.66 (C-10a), 81.96 (C-8), 45.02 (C-6), 41.83 (C-6a), 40.30 (C-7), 16.22 (CH$_3$).

MS EI m/z (rel. %) 294/292 (32/100), 291 (16), 276 (15), 175 (38), 174 (36), 173 (53), 263 (23), 251 (15), 249 (29), 236 (56), 235 (32), 227 (25), 217 (16), 209 (23).
HRMS HRMS (EI) calcd for C_{14}H_{13}ClN_{2}O_{3} 292.0615, found 292.0616.

M.p. 141-145 °C.

Spectrum 13. 600 MHz, CDCl₃, $^1$H NMR of (±)-(6aS,7R,8R,10aS)-4-chloro-7-methyl-2-nitro-6,6a,7,8-tetrahydro-5$H$-8,10a-epoxyphenanthridine (49a).
Spectrum 14. 150 MHz, CDCl$_3$, $^{13}$C NMR of (±)-(6aS,7R,8R,10aS)-4-chloro-7-methyl-2-nitro-6,6a,7,8-tetrahydro-5H-8,10a-epoxyphenanthridine (49a).
Synthesis of (±)-(6aS,7R,8R,10aS)-2,4-dichloro-7-methyl-6,6a,7,8-tetrahydro-5H-8,10a-epoxyphenanthridine (49b)

Degassed MeCN (15 mL) was transferred to a microwave vessel, and compound 48b (119 mg, 0.422 mmol) and 0.5 M aq. NaOH (0.10 mL, 0.2 eqv.) were added. The reaction mixture was degassed with Ar and heated at 150 °C in a microwave oven for 3 h. The reaction mixture was concentrated under reduced pressure. The product was isolated by flash chromatography on silica gel eluting with EtOAc:CH₂Cl₂:hexanes 1:1:18. Yield 13 mg (11%) as a white solid.

All NMR experiments except ¹H NMR (spectrum 15) are recorded of the crude reaction product (containing cat. amounts of NaOH and some amount of MeCN), due to rapid decomposition of the pure product. NMR data is reported for the major isomer.

¹H NMR (600 MHz, CDCl₃) δ 7.27-7.25 (m, 1H, H-1 or H-3), 7.24 (d, J = 2.3 Hz, 1H, H-1 or H-3), 6.53 (dd, J = 5.7, 1.2 Hz, 1H, H-9), 6.30 (d, J = 5.7 Hz, 1H, H-10), 4.80 (dd, J = 4.4, 1.2 Hz, 1H, H-8), 4.74 (s, 1H, NH), 3.66-3.61 (m, 1H, H-α in H-6), 2.91 (app t, J = 11.6 Hz, 1H, H-β in H-6), 1.99-1.94 (m, 1H, H-7), 1.41 (ddd, J = 12.0, 5.3, 3.7 Hz, 1H, H-6a), 0.97 (d, J = 7.1 Hz, 3H, CH₃).

¹³C NMR (150 MHz, CDCl₃) δ 141.86 (C-4a), 138.24 (C-9), 136.78 (C-10), 129.51 (C-1 or C-3), 129.07 (C-1 or C-3), 121.67 (C-2 or C-10b), 121.61 (C-2 or C-10b), 119.37 (C-4), 84.94 (C-10a), 81.69 (C-8), 45.32 (C-6), 42.86 (C-6a), 39.89 (C-7), 16.27 (CH₃).

MS EI m/z (rel. %) n.d.

HRMS n.d.

M.p. n.d.
Spectrum 15. 600 MHz, CDCl₃, ¹H NMR of (±)-(6aS,7R,8R,10aS)-2,4-dichloro-7-methyl-6,6a,7,8-tetrahydro-5H-8,10a-epoxyphenanthridine (49b).

Spectrum 16. 150 MHz, CDCl₃, ¹³C NMR of (±)-(6aS,7R,8R,10aS)-2,4-dichloro-7-methyl-6,6a,7,8-tetrahydro-5H-8,10a-epoxyphenanthridine (49b).
Synthesis of (±)-(6aS,7R,8R,10aS)-2,4-dichloro-5,7-dimethyl-6,6a,7,8-tetrahydro-8,10a-epoxyphenantridine (49c)

A solution of compound 48c (157 mg, 0.530 mmol) in dry xylene (20 mL) was degassed with argon and stirred at 140 °C for 50 h. The reaction mixture was concentrated under reduced pressure, and the product isolated by flash chromatography on silica gel eluting with EtOAc-hexanes (1:19); yield 82 mg (52%) as a colorless solid, mixture of 2 diastereomers (92:8).

NMR data are given for the major isomer.

$^1$H NMR (500 MHz, CDCl$_3$) δ 7.34 (d, $J = 2.5$ Hz, 1H, H-1), 7.31 (d, $J = 2.5$ Hz, 1H, H-3), 6.53 (dd, $J = 5.7, 1.4$ Hz, 1H, H-9), 6.31 (d, $J = 5.7$ Hz, 1H, H-10), 4.79 (dd, $J = 4.4, 1.4$ Hz, 1H, H-8), 3.35 (dd, $J = 13.6, 4.3$ Hz, 1H, H$_a$ in H-6), 2.95-2.87 (m, 4H, NCH$_3$ and H$_b$ in H-6), 2.92-1.86 (m, H-7), 1.55-1.50 (m, 1H, H-6a), 0.98 (d, $J = 7.0$ Hz, 3H, CH$_3$).

$^{13}$C NMR (125 MHz, CDCl$_3$) δ 145.77 (C-4a), 138.05 (C-10), 136.41 (C-9), 130.59 (C-1), 130.18 (C-10b), 129.28 (C-3), 128.72 (C-2), 127.54 (C-4), 85.36 (C-10a), 81.67 (C-8), 54.78 (C-6), 41.75 (NCH$_3$), 39.00 (C-7), 37.67 (C-6a), 16.14 (CH$_3$).

MS EI m/z (rel. %) 299/297/295 (11/63/100, $M^+$), 280 (23), 278 (44), 276 (47), 262 (27), 252 (43), 240 (30), 239 (33), 238 (37), 225 (22), 212 (24), 202 (12).

HRMS calcd for C$_{15}$H$_{15}$Cl$_2$NO 295.0531, found 295.0535.

M.p. 114-116 °C.
Spectrum 17. 500 MHz, CDCl₃, ¹H NMR of (±)-(6aS,7R,8R,10aS)-2,4-dichloro-5,7-dimethyl-6a,7,8-tetrahydro-8,10a-epoxyphenanthridine (49c).

Spectrum 18. 125 MHz, CDCl₃, ¹³C NMR of (±)-(6aS,7R,8R,10aS)-2,4-dichloro-5,7-dimethyl-6a,7,8-tetrahydro-8,10a-epoxyphenanthridine (49c).
Synthesis of 4-chloro-7-methyl-2-nitro-5,6-dihydrophenanthridine (56a)

Method A. Degassed MeCN (15 mL) was transferred to a microwave vessel, and compound 48a (79 mg, 0.27 mmol) and 0.5 M aq. HCl (0.1 mL, 0.2 equivs.) were added. The reaction mixture was degassed with Ar and heated at 100 °C in a microwave oven for 8 h. The reaction mixture was neutralized with NaHCO₃ (6.5 mg, 0.077 mmol) and concentrated under reduced pressure. A 20:1 mixture of compounds 56a and 57a was isolated by flash chromatography on silica gel eluting with gradient CH₂Cl₂-EtOAc-hexanes (1:1:8 to 1:1:3). Calc. yield 63 mg (85%) as an orange solid.

¹H NMR (500 MHz, DMSO-d₆) δ 8.38 (d, J = 2.4 Hz, 1H, H-1), 8.02 (d, J = 2.4 Hz, 1H, H-3), 7.71 (d, J = 7.8 Hz, 1H, H-10), 7.30 (s, 1H, NH), 7.25-7.21 (m, 1H, H-9), 7.17 (d, J = 7.4 Hz, 1H, H-8), 4.63 (s, 2H, H-6), 2.19 (s, 3H, CH₃).

¹³C NMR (125 MHz, DMSO-d₆) δ 146.96 (C-4a), 136.23 (C-2), 134.57 (C-7), 130.37 (C-8), 129.34 (C-6a), 127.97 (C-10a), 127.69 (C-9), 124.77 (C-3), 120.33 (C-10), 119.11 (C-10b), 117.76 (C-1), 116.06 (C-4), 42.52 (C-6), 18.27 (CH₃).

MS EI m/z (rel. %) 276/274 (16/64, M⁺), 275 (38), 273 (100), 272 (15), 242 (4), 229 (14), 228 (9), 227 (48), 192 (16), 191 (9), 190 (11).

HRMS calcd. for C₁₄H₁₁ClN₂O₂ 274.0509, found 274.0504.

M.p. 185-187 °C.
Spectrum 19. 500 MHz, DMSO-$d_6$, $^1$H NMR of 4-chloro-7-methyl-2-nitro-5,6-dihydrophenanthridine (56a).

Spectrum 20. 125 MHz, DMSO-$d_6$, $^{13}$C NMR of 4-chloro-7-methyl-2-nitro-5,6-dihydrophenanthridine (56a).
Degassed MeCN (15mL) was transferred to a microwave vessel, and compound 48b (105 mg, 0.372 mmol) and water (ca. 0.10 mL) were added. The reaction mixture was degassed with Ar and heated at 150 °C in a microwave oven for 2.5 h. The reaction mixture was concentrated under reduced pressure and the product was isolated by flash chromatography on silica gel eluting with CH₂Cl₂-EtOAc-hexanes (1:4:45). Yield 72 mg (77%) as a colorless solid.

**¹H NMR (600 MHz, CDCl₃) δ**

7.51 (d, \( J = 2.2 \) Hz, 1H, H-1), 7.48 (d, \( J = 7.9 \) Hz, 1H, H-10), 7.23-7.19 (m, 1H, H-9), 7.16 (d, \( J = 2.2 \) Hz, 1H, H-3), 7.12 (d, \( J = 7.5 \) Hz, 1H, H-8), 4.58 (s, 1H, NH), 4.49 (s, 2H NCH₂), 2.27 (s, 3H, CH₃).

**¹³C NMR (150 MHz, CDCl₃) δ**

140.32 (C-4a), 134.25 (C-7), 131.27 (C-6a), 130.19 (C-8 and C-10a), 127.89 (C-3), 127.52 (C-9), 124.18 (C-10b), 122.85 (C-2), 122.31 (C-1), 120.67 (C-10), 119.27 (C-4), 42.91 (NCH₂), 19.06 (CH₃).

**MS EI m/z (rel. %)**

267/265/263 (5/30/50, \( M^+ \)), 266/264/262 (14/69/100), 227 (5), 191 (7), 190 (8), 96 (10).

**HRMS** calcd. for C₁₄H₁₁Cl₂N 263.0269, found 263.0259.

**M.p.** 108-111 °C.
Spectrum 21. 600 MHz, CDCl₃, ¹H NMR of 2,4-dichloro-7-methyl-5,6-dihydrophenanthridine (56b).

Spectrum 22. 150 MHz, CDCl₃, ¹³C NMR of 2,4-dichloro-7-methyl-5,6-dihydrophenanthridine (56b).
Degassed MeCN (15mL) was transferred to a microwave vessel, and compound 48c (80 mg, 0.270 mmol) and 0.5M aq. HCl (0.1 mL, 0.2 equivs.) were added. The reaction mixture was degassed with Ar and heated at 180 °C in a microwave oven for 5 h. The reaction mixture was neutralized with NaHCO₃ (6.7 mg, 0.080 mmol) and concentrated under reduced pressure. The product was isolated by flash chromatography on silica gel eluting with CH₂Cl₂-hexanes (1:9). Yield 50 mg (66%) as a colorless oil.

\[\text{\textsuperscript{1}H NMR (600 MHz, CDCl}_3\text{) } \delta \text{ 7.65 (d, } J = 2.3 \text{ Hz, 1H, H-1), 7.54 (d, } J = 7.7 \text{ Hz, 1H, H-10), 7.33 (d, } J = 2.3 \text{ Hz, 1H, H-3), 7.29-7.25 (m, 1H, H-9), 7.22 (d, } J = 7.5 \text{ Hz, 1H, H-8), 4.17 (s, 2H, H-6), 2.63 (s, 3H, NCH}_3\text{), 2.37 (s, 3H, CH}_3\text{).}\]

\[\text{\textsuperscript{13}C NMR (150 MHz, CDCl}_3\text{) } \delta \text{ 143.38 (C-4a), 135.16 (C-7), 132.75 (C-10b), 131.44 (C-6a), 130.66 (C-8), 130.54 (C-4), 130.33 (C-10a), 129.65 (C-2), 128.88 (C-3), 127.42 (C-9), 122.89 (C-1), 121.27 (C-10), 51.42 (NCH}_2\text{), 40.63 (NCH}_3\text{), 19.01 (CH}_3\text{).}\]

\[\text{MS EI m/z (rel. %) 281/279/277 (4/32/50, } M^+\text{), 280/278/276 (13/70/100), 263 (3), 262 (4), 261 (5), 241 (2), 225 (2), 191 (4), 190 (6).}\]

\[\text{HRMS calcd. for C}_{15}\text{H}_{13}\text{Cl}_2\text{N 277.0425, found 277.0415.}\]
Spectrum 23. 600 MHz, CDCl₃, ¹H NMR of 2,4-dichloro-5,7-dimethyl-5,6-dihydrophenanthridine (56c).

Spectrum 24. 150 MHz, CDCl₃, ¹³C NMR of 2,4-dichloro-5,7-dimethyl-5,6-dihydrophenanthridine (56c).
Synthesis of 4-chloro-7-methyl-2-nitrophenanthridine (57a)

Degassed MeCN (15 mL) was transferred to a microwave vessel, and compound 48a (70 mg, 0.24 mmol) and 0.5M aq. HCl (0.10 mL, 0.2 equivs.) were added. The reaction mixture was degassed with Ar and heated at 100 °C in a microwave oven for 8 h. The reaction mixture was neutralized with NaHCO₃ (6.2 mg, 0.074 mmol), transferred to a quartz tube, and irradiated with ‘black’ UV light for 5.75 h while bubbling air through. The reaction mixture was concentrated under reduced pressure and the product was isolated by dry flash chromatography on silica gel eluting with CH₂Cl₂; yield 50 mg (77%) as a pale yellow solid.

¹H NMR (400 MHz, CDCl₃) δ 9.84 (s, 1H, H-6), 9.44 (d, J = 2.0 Hz, 1H, H-2 or H-4), 8.66 (d, J = 2.0 Hz, 1H, H-2 or H-4), 8.57 (d, J = 8.4 Hz, 1H, H-10), 7.94-7.88 (m, 1H, H-9), 7.68 (d, J = 7.3 Hz, 1H, H-8), 2.94 (s, 3H, CH₃).

¹³C NMR (100 MHz, CDCl₃) δ 154.39 (C-6), 145.37 (C-2), 143.38 (C-4a), 137.94 (C-10a), 136.05 (C-4), 132.94 (C-7), 132.78 (C-9), 131.12 (C-8), 125.62 (C-10b), 125.36 (C-6a), 122.93 (C-1), 120.63 (C-10), 117.86 (C-3), 18.86 (CH₃).

MS EI m/z (rel. %) 274/272 (31/100, M⁺) 226 (21), 216 (5), 214 (22), 199 (6), 191 (20), 190 (30), 164 (8), 163 (10).

HRMS calcd for C₁₄H₁₁Cl₂NO 272.0353, found 272.0355.

M.p. 245-248 °C.
Spectrum 25. 400 MHz, CDCl₃, ¹H NMR of 4-chloro-7-methyl-2-nitrophenanthridine (57a).

Spectrum 26. 100 MHz, CDCl₃, ¹³C NMR of 4-chloro-7-methyl-2-nitrophenanthridine (57a).
Synthesis of 2,4-dichloro-7-methylphenanthridine (57b)

Method A. Degassed MeCN (15 mL) was transferred to a microwave vessel, and compound 48b (89 mg, 0.31 mmol) and water (ca. 0.10 mL) were added. The mixture was degassed with Ar and heated at 150 °C in a microwave oven for 2.5 h. The reaction mixture was transferred to a quartz tube, and irradiated with ‘black’ UV light for 4 h while bubbling air through. The reaction mixture was concentrated under reduced pressure and the product was isolated by flash chromatography on silica gel eluting with CH$_2$Cl$_2$-EtOAc-hexanes (1:4:20). Yield 75 mg (91%) as a colorless solid.

Method B. MgBr$_2$ (20 mg, 0.11 mmol) was added to a stirring solution of compound 48b (119 mg, 0.422 mmol) in dry PhMe (20 mL). The reaction mixture was degassed with argon and heated at 100 °C for 140 h. The reaction mixture was concentrated under reduced pressure and the product was isolated by flash chromatography on silica gel eluting with CH$_2$Cl$_2$-EtOAc-hexanes (1:4:20); yield 56 mg (53%) colorless solid.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.66 (s, 1H, H-6), 8.47 (d, $J = 2.1$ Hz, 1H, H-1), 8.39 (d, $J = 8.4$ Hz, 1H, H-10), 7.84 (d, $J = 2.1$ Hz, 1H, H-3), 7.81-7.75 (m, 1H, H-9), 7.58 (d, $J = 7.2$ Hz, 1H, H-8), 2.89 (s, 3H, CH$_3$).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 151.15 (C-6), 139.23 (C-4a), 137.19 (C-7), 135.49 (C-2 or C-4), 132.57 (C-2 or C-4), 131.82 (C-10a), 131.62 (C-9), 130.24 (C-8), 129.32 (C-3), 126.77 (C-10b), 125.30 (C-6a), 121.25 (C-1), 120.44 (C-10), 18.90 (CH$_3$).

MS EI m/z (rel. %) 265/263/261 (9/64/100), 226 (13), 225 (7) 191 (10), 190 (16).

HRMS calcd. for C$_{14}$H$_9$Cl$_2$N 261.0112, found 261.0113.

M.p. 180-182 °C.
Spectrum 27. 400 MHz, CDCl₃, ¹H NMR of 2,4-dichloro-7-methylphenanthridine (57b).

Spectrum 28. 100 MHz, CDCl₃, ¹³C NMR of 2,4-dichloro-7-methylphenanthridine (57b).
Synthesis of (±)-(7R,8R)-2,4-dichloro-7-methyl-7,8-dihydrophenanthridin-8-ol (58b)

A solution of compound 48b (190 mg, 0.678 mmol) in dry PhMe (20 mL) was degassed with argon and stirred at 100 °C for 6 d. The reaction mixture was concentrated under reduced pressure, and the product isolated by flash chromatography on silica gel eluting with EtOAc-hexanes (2:3). Yield 100 mg (53%) as a colorless solid, mixture of diastereomers (ratio 20:1).

NMR data for the major diastereomer is reported.

$^1$H NMR (500 MHz, DMSO-$d_6$) δ 8.70 (s, 1H, H-6), 8.44 (s, 1H, H-1), 8.02 (s, 1H, H-3), 7.48 (d, $J = 9.8$ Hz, 1H, H-10), 6.51 (dd, $J = 9.8$, 4.8 Hz, 1H, H-9), 5.18 (d, $J = 5.7$ Hz, 1H, OH), 4.11-4.08 (m, 1H, H-8), 3.21 (qd, $J = 7.3$, 4.5 Hz, 1H, H-7), 1.20 (d, $J = 7.3$ Hz, 3H, CH$_3$).

$^{13}$C NMR (125 MHz, DMSO-$d_6$) δ 151.66 (C-6), 141.77 (C-4a), 136.33 (C-9), 134.39 (C-4), 134.02 (C-10a), 132.71 (C-6a), 130.71 (C-2), 128.78 (C-3), 125.44 (C-10b), 121.83 (C-1), 120.74 (C-10), 67.03 (C-8), 37.67 (C-7), 17.83 (CH$_3$).

MS EI m/z (rel. %) 283/281/279 (2/14/22), 265 (15), 264 (36), 263 (65), 261 (100), 250 (14), 248 (7), 226 (9), 225 (7), 191 (9), 190 (15), 164 (6), 163 (6).

HRMS calcd. for C$_{14}$H$_{11}$Cl$_2$NO 279.0218, found 279.0215.

M.p. 175-177 °C.
Spectrum 29. 500 MHz, DMSO-$d_6$ $^1$H NMR of (±)-(7R,8R)-2,4-dichloro-7-methyl-7,8-dihydrophenanthridin-8-ol (58b).

Spectrum 30. 125 MHz, DMSO-$d_6$ $^{13}$C APT NMR of (±)-(7R,8R)-2,4-dichloro-7-methyl-7,8-dihydrophenanthridin-8-ol (58b).
Synthesis of (±)-(6aR,7R)-2,4-dichloro-7-methyl-5,6,6a,7-tetrahydrophenanthridin-8(9H)-one (59b)

A solution of compound 48b (408 mg, 1.44 mmol) in dry PhMe (25 mL), degassed with argon, was stirred at 100 °C for 96 h. The reaction mixture was concentrated under reduced pressure and the product was isolated by flash chromatography on silica gel eluting with EtOAc-hexanes (3:22); yield 236 mg (58%) colorless solid.

1H NMR (600 MHz, CDCl$_3$) δ 7.36 (d, $J = 2.2$ Hz, 1H, H-1), 7.15 (d, $J = 2.2$ Hz, 1H, H-3), 6.26 (td, $J = 4.0$, 2.5 Hz, 1H, H-10), 4.72 (s, 1H, NH), 3.69 (dd, $J = 11.1$, 4.8 Hz, 1H, H$_a$ in H-6), 3.27-3.21 (m, 1H, H$_a$ in H-9), 3.10-2.97 (m, 2H, H$_b$ in H-6 and H$_b$ in H-9), 2.61-2.54 (m, 1H, H-6a), 2.39 (dq, $J = 11.1$, 6.5 Hz, 1H, H-7), 1.19 (d, $J = 6.5$ Hz, 3H, CH$_3$).

13C NMR (150 MHz, CDCl$_3$) δ 209.10 (C-8), 139.03 (C-4a), 131.67 (C-10a), 127.92 (C-3), 122.73 (C-1), 122.17 (C-2 or C-4), 121.47 (C-10b), 119.82 (C-2 or C-4), 116.99 (C-10), 46.81 (C-6), 45.26 (C-7), 42.09 (C-6a), 40.32 (C-9), 11.35 (CH$_3$).

MS EI m/z (rel. %) 285/283/281 (9/63/100, $M^+$), 252 (8), 240 (31), 238 (49), 228 (10), 226 (58), 224 (83), 200 (18), 198 (29), 188 (15).

HRMS calcd. for C$_{14}$H$_{13}$Cl$_2$NO 281.0374, found 281.0368.

M.p. 194-195°C.
Spectrum 31. 600 MHz, CDCl$_3$, $^1$H NMR of (±)-(6aR,7R)-2,4-dichloro-7-methyl-5,6a,7,9-tetrahydrophenanthridin-8(6H)-one (59b).

Spectrum 32. 150 MHz, CDCl$_3$, $^{13}$C NMR of (±)-(6aR,7R)-2,4-dichloro-7-methyl-5,6a,7,9-tetrahydrophenanthridin-8(6H)-one (59b).
Synthesis of 2,4-dichloro-7-methylphenanthridin-8-ol

A solution of compound 59b (99 mg, 0.35 mmol) and DDQ (97 mg, 0.43 mmol) in dry CH₂Cl₂ (20 mL) was stirred at ambient temperature under Ar atmosphere for 50 min. The reaction mixture was concentrated under reduced pressure and the product was isolated by flash chromatography on silica gel eluting with EtOAc-hexanes (3:7); yield 26 mg (27%) colorless solid.

¹H NMR (500 MHz, DMSO-d₆) δ 10.28 (s, 1H, OH), 9.52 (s, 1H, H-6), 8.64 (s, 1H, H-1), 8.53 (d, J = 8.1 Hz, 1H, H-10), 7.85 (s, 1H, H-3), 7.49 (d, J = 8.1 Hz, 1H, H-9), 2.59 (s, 3H, CH₃).

¹³C NMR (125 MHz, DMSO-d₆) δ 155.42 (C-8), 151.11 (C-6), 136.94 (C-4a), 134.41 (C-4), 131.24 (C-2), 127.14 (C-3), 126.72 (C-10b), 126.32 (C-6a), 123.90 (C-10a), 121.85 (C-10), 121.66 (C-9), 121.04 (C-1), 119.06 (C-7), 9.93 (CH₃).

MS EI m/z (rel. %) 281/279/277 (8/65/100, M⁺), 250 (10), 248 (16), 242 (3), 214 (4), 213 (3), 178 (3), 177 (7).

HRMS calcd. for C₁₄H₉Cl₂NO 277.0061, found 277.0066.

M.p. 215-220 °C (dec.).
Spectrum 33. 500 MHz, DMSO-d$_6$, $^1$H NMR of 2,4-dichlorophenanthridin-8-ol (65b).

Spectrum 34. 125 MHz, DMSO-d$_6$, $^{13}$C NMR of 2,4-dichlorophenanthridin-8-ol (65b).
6. APPENDIX

Spectrum 35. 600 MHz, CDCl$_3$, COSY of N-(but-2-en-1-yl)-2-chloro-6-(furan-2-yl)-4-nitroaniline (48a).

Spectrum 36. 600 MHz, CDCl$_3$, HSQC of N-(but-2-en-1-yl)-2-chloro-6-(furan-2-yl)-4-nitroaniline (48a).
Spectrum 37. 600 MHz, CDCl₃, HMBC of N-(but-2-en-1-yl)-2-chloro-6-(furan-2-yl)-4-nitroaniline (48a).

Spectrum 38. 400 MHz, CDCl₃, COSY of N,N-di(but-2-en-1-yl)-2-chloro-6-(furan-2-yl)-4-nitroaniline (52a).
Spectrum 39. 400 MHz, CDCl₃, HSQC of \(N,N\)-di(2-en-1-yl)-2-chloro-6-(furan-2-yl)-4-nitroaniline (52a).

Spectrum 40. 400 MHz, CDCl₃, HMBC of \(N,N\)-di(2-en-1-yl)-2-chloro-6-(furan-2-yl)-4-nitroaniline (52a).
Spectrum 41. 400 MHz, CDCl$_3$, $^1$C DEPT of $N$-(but-2-en-1-yl)-2,4-dichloro-6-(furan-2-yl)aniline (48b).

Spectrum 42. 400 MHz, CDCl$_3$, COSY of $N$-(but-2-en-1-yl)-2,4-dichloro-6-(furan-2-yl)aniline (48b).
Spectrum 43. 400 MHz, CDCl₃, HSQC of N-(but-2-en-1-yl)-2,4-dichloro-6-(furan-2-yl)aniline (48b).

Spectrum 44. 400 MHz, CDCl₃, HMBC of N-(but-2-en-1-yl)-2,4-dichloro-6-(furan-2-yl)aniline (48b).
Spectrum 45. 600 MHz, CDCl$_3$, COSY of N-(but-2-en-1-yl)-2,4-dichloro-6-(furan-2-yl)-N-methylaniline (48c).

Spectrum 46. 600 MHz, CDCl$_3$, HSQC of N-(but-2-en-1-yl)-2,4-dichloro-6-(furan-2-yl)-N-methylaniline (48c).
Spectrum 47. 600 MHz, CDCl₃, HMBC of N-(but-2-en-1-yl)-2,4-dichloro-6-(furan-2-yl)-N-methylaniline (48c).

Spectrum 48. 600 MHz, CDCl₃, COSY of (±)-(6aS,7R,8R,10aS)-4-chloro-7-methyl-2-nitro-6,6a,7,8-tetrahydro-5H-8,10a-epoxyphenanthridine (49a).
Spectrum 49. 600 MHz, CDCl$_3$, HSQC of (±)-(6aS,7R,8R,10aS)-4-chloro-7-methyl-2-nitro-6,6a,7,8-tetrahydro-5H-8,10a-epoxyphenanthridine (49a).

Spectrum 50. 600 MHz, CDCl$_3$, HMBC of (±)-(6aS,7R,8R,10aS)-4-chloro-7-methyl-2-nitro-6,6a,7,8-tetrahydro-5H-8,10a-epoxyphenanthridine (49a).
Spectrum 51. 600 MHz, CDCl₃, NOESY of (±)-(6aS,7R,8R,10aS)-4-chloro-7-methyl-2-nitro-6,6a,7,8-tetrahydro-5H-8,10a-epoxyphenanthridine (49a).

Spectrum 52. 600 MHz, CDCl₃, COSY of (±)-(6aS,7R,8R,10aS)-2,4-dichloro-7-methyl-6,6a,7,8-tetrahydro-5H-8,10a-epoxyphenanthridine (49b).
Spectrum 53. 600 MHz, CDCl₃, HSQC of (±)-(6aS,7R,8R,10aS)-2,4-dichloro-7-methyl-6,6a,7,8-tetrahydro-5H-8,10a-epoxyphenanthridine (49b).

Spectrum 53. 600 MHz, CDCl₃, HMBC of (±)-(6aS,7R,8R,10aS)-2,4-dichloro-7-methyl-6,6a,7,8-tetrahydro-5H-8,10a-epoxyphenanthridine (49b).
Spectrum 54. 500 MHz, CDCl₃, COSY of (±)-(6aS,7R,8R,10aS)-2,4-dichloro-5,7-dimethyl-6,6a,7,8-tetrahydro-8,10a-epoxyphenanthridine (49c).

Spectrum 55. 500 MHz, CDCl₃, HSQC of (±)-(6aS,7R,8R,10aS)-2,4-dichloro-5,7-dimethyl-6,6a,7,8-tetrahydro-8,10a-epoxyphenanthridine (49c).
Spectrum 56. 500 MHz, CDCl₃, HMBC of (±)-(6aS,7R,8R,10aS)-2,4-dichloro-5,7-dimethyl-6,6a,7,8-tetrahydro-8,10a-epoxyphenanthridine (49c).

Spectrum 57. 500 MHz, DMSO, COSY of 4-chloro-7-methyl-2-nitro-5,6-dihydrophenanthridine (56a).
Spectrum 58. 500 MHz, DMSO, HSQC of 4-chloro-7-methyl-2-nitro-5,6-dihydrophenanthridine (56a).

Spectrum 59. 500 MHz, DMSO, HMBC of 4-chloro-7-methyl-2-nitro-5,6-dihydrophenanthridine (56a).
Spectrum 60. 600 MHz, CDCl$_3$, COSY of 2,4-dichloro-7-methyl-5,6-dihydrophenanthridine (56b).

Spectrum 61. 600 MHz, CDCl$_3$, HSQC of 2,4-dichloro-7-methyl-5,6-dihydrophenanthridine (56b).
Spectrum 62. 600 MHz, CDCl₃, HMBC of 2,4-dichloro-7-methyl-5,6-dihydrophenanthridine (56b).

Spectrum 63. 600 MHz, CDCl₃, COSY of 2,4-dichloro-5,7-dimethyl-5,6-dihydrophenanthridine (56c).
Spectrum 64. 600 MHz, CDCl₃, HSQC of 2,4-dichloro-5,7-dimethyl-5,6-dihydrophenanthridine (56c).

Spectrum 65. 600 MHz, CDCl₃, HMBC of 2,4-dichloro-5,7-dimethyl-5,6-dihydrophenanthridine (56c).
Spectrum 66. 400 MHz, CDCl₃, COSY of 4-chloro-7-methyl-2-nitrophenanthridine (57a).

Spectrum 67. 400 MHz, CDCl₃, HSQC of 4-chloro-7-methyl-2-nitrophenanthridine (57a).
Spectrum 68. 400 MHz, CDCl₃, HMBC of 4-chloro-7-methyl-2-nitrophenanthridine (57a).

Spectrum 69. 600 MHz, CDCl₃, COSY of 2,4-dichloro-7-methylphenanthridine (57b).
Spectrum 70. 600 MHz, CDCl₃, HSQC of 2,4-dichloro-7-methylphenanthridine (57b).

Spectrum 71. 600 MHz, CDCl₃, HMBC of 2,4-dichloro-7-methylphenanthridine (57b).
Spectrum 72. 500 MHz, DMSO, COSY of (±)-(7R,8R)-2,4-dichloro-7-methyl-7,8-dihydrophenanthridin-8-ol (58b).

Spectrum 73. 500 MHz, DMSO, HSQC of (±)-(7R,8R)-2,4-dichloro-7-methyl-7,8-dihydrophenanthridin-8-ol (58b).
Spectrum 74. 500 MHz, DMSO, HMBC of (±)-(7R,8R)-2,4-dichloro-7-methyl-7,8-dihydrophenanthridin-8-ol (58b).

Spectrum 75. 500 MHz, DMSO, NOESY of (±)-(7R,8R)-2,4-dichloro-7-methyl-7,8-dihydrophenanthridin-8-ol (58b).
Spectrum 76. 600 MHz, CDCl₃, COSY of (±)-(6aR,7R)-2,4-dichloro-7-methyl-5,6,6a,7-tetrahydrophenanthridin-8(9H)-one (59b).

Spectrum 76. 600 MHz, CDCl₃, HSQC of (±)-(6aR,7R)-2,4-dichloro-7-methyl-5,6,6a,7-tetrahydrophenanthridin-8(9H)-one (59b)
Spectrum 77. 600 MHz, CDCl₃, HMBC of (±)-(6aR,7R)-2,4-dichloro-7-methyl-5,6,6a,7-tetrahydrophenanthridin-8(9H)-one (59b).

Spectrum 78. 600 MHz, CDCl₃, NOESY of (±)-(6aR,7R)-2,4-dichloro-7-methyl-5,6,6a,7-tetrahydrophenanthridin-8(9H)-one (59b).
Spectrum 79. 500 MHz, DMSO, COSY of 2,4-dichlorophenanthridin-8-ol (65b).

Spectrum 80. 500 MHz, DMSO, HSQC of 2,4-dichlorophenanthridin-8-ol (65b).
**Spectrum 81.** 500 MHz, DMSO, HMBC of 2,4-dichlorophenanthridin-8-ol (65b).

**Spectrum 82.** 600 MHz, CDCl₃, Selective NOESY of (±)-(6aS,7R,8R,10aS)-4-chloro-7-methyl-2-nitro-6,6a,7,8-tetrahydro-5H-8,10a-epoxyphenanthridine (49a). Irradiation of H-6a of major diastereomer. (Integral reads 1.01).
Spectrum 83. 600 MHz, CDCl₃, Selective NOESY of (±)-(6aS,7R,8R,10aS)-4-chloro-7-methyl-2-nitro-6,6a,7,8-tetrahydro-5H-8,10a-epoxyphenanthridine (49a). Irradiation of H-6a of second-to-major diastereomer. (Integral reads 4.97).
7. References


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