Thesis for the Master's degree in chemistry

Håkon Sætren Gulbrandsen

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

60 study points

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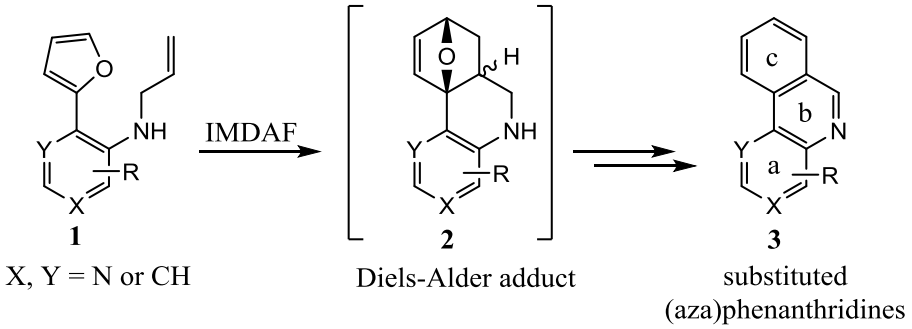
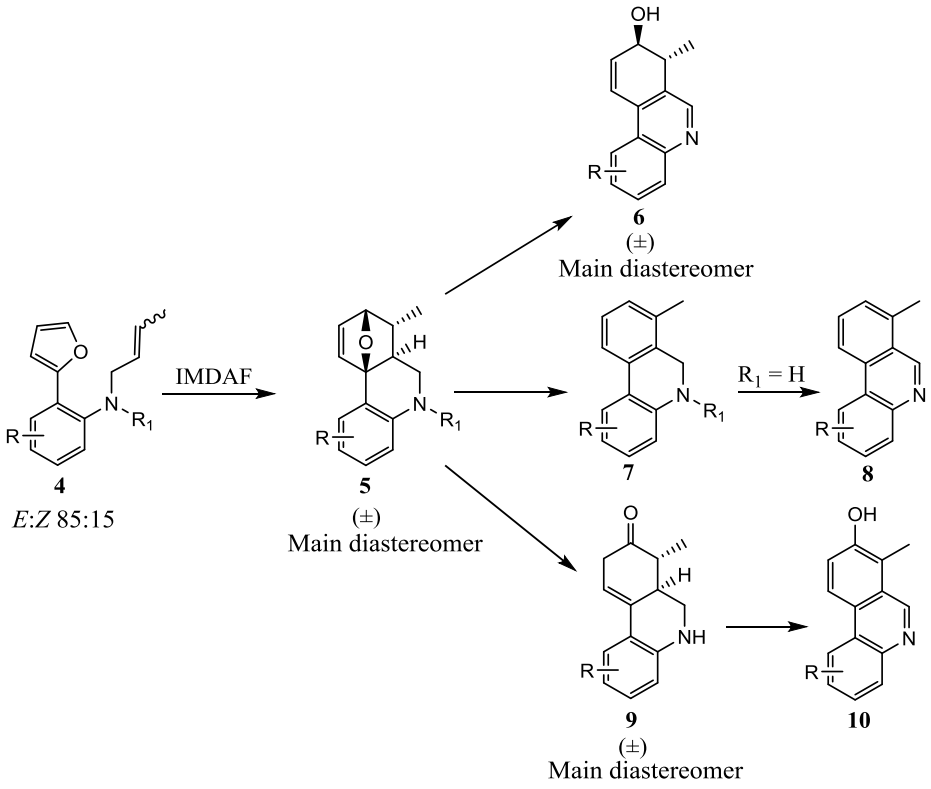
Abstract

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).[1-3]



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

HMBC	heteronuclear multiple bond correlation experiment
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectra
HSQC	heteronuclear single quantum coherence spectroscopy (NMR)
hν	irradiation (UV)
Hz	hertz
IMDAF	intramolecular Diels-Alder reaction of furan
J	coupling constant (NMR)
L	ligand
LA	Lewis acid
LUMO	lowest unoccupied molecular orbital
M	molar
m	multiplet (NMR)
M^+	molecular ion peak (MS)
Me	methyl
MeCN	acetonitrile
MeI	iodomethane
MHz	megahertz
MIC	minimum inhibitory concentration
Min	minutes
Mol. Sieves	molecular sieves
mp	melting point
MRSA	methicillin-resistant *Staphylococcus aureus*
MS	mass spectroscopy
MW	microwave
m/z	mass per charge (MS)
n	normal
NBS	*N*-bromosuccinimide
n.d.	not determined
NMP	*N*-methyl pyrrolidone
NMR	nuclear magnetic resonance spectroscopy
NOE	nuclear overhauser effect
NOESY	nuclear overhauser effect spectroscopy (NMR)
o	*ortho*
OAc	acetate
OTf	triflate
Ox	oxidation
p	*para*
PhH	benzene
PhMe	toluene
PMB	*p*-methoxybenzyl
Pr	propyl
q	quartet (NMR)

QBA	quaternary benzo[*c*]phenanthridinium alkaloids
R	substituent
Red	reduction
r.t.	room temperature
σ	sigma
s	singlet (NMR)
SAR	structure activity relationship
sat.	saturated
t	triplet (NMR)
TBAB	tetrabutylammonium bromide
TBDMS	*tert*-butyldimethylsilane
TBTH	tri-*n*-butyltin hydride
t-Bu	*tert*-butyl
tert	tertiary
THF	tetrahydrofuran
UV	ultraviolet
WHO	world health organization

1. INTRODUCTION

Our group has previously studied the intramolecular Diels-Alder reaction of furans (IMDAF) of *ortho*-furyl(allylamino)(aza)arenes.[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 *o*-furyl(allylamino)arenes, we have decided to introduce substituted *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 *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).

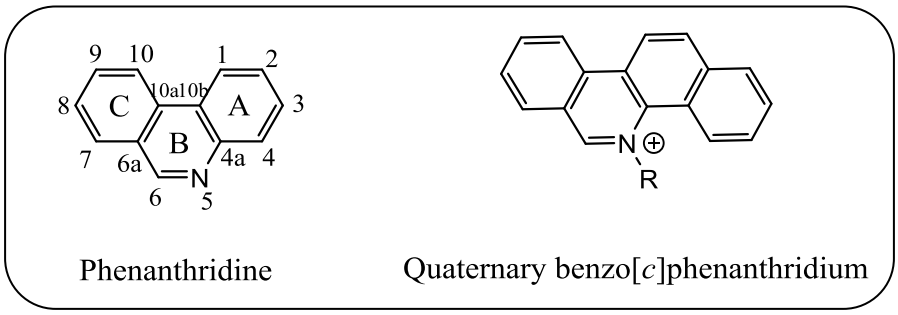


Figure 1.1. Phenanthridine and a general quaternary benzo[*c*]phenanthridium compound. Numbering of the phenanthridine ring-system is shown.

Several plant families are known to produce phenanthridine alkaloids. Amongst these are the families *Amaryllidaceae, Fumariacea*, *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]

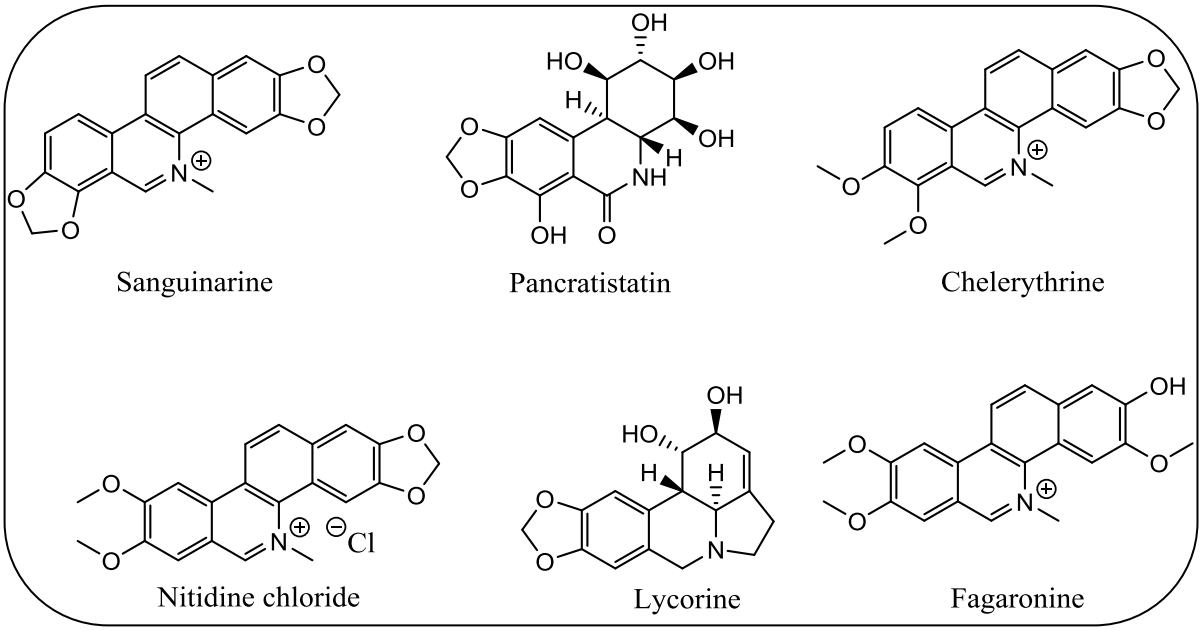


Figure 1.2. Phenanthridine alkaloids studied for their biological activity.[9-14]

1.1.2 Current use of phenanthridine-containing compounds in medicine

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.[15] Sanguinarine and chelerythrine are employed in dental care applications due to their anti-plaque properties.[16] A mixture of chelerythrine and sanguinarine ("sanguiritrin") is marketed as an antifungal and anti-inflammatory drug in Russia.[17,18] Ethidium bromide, propidium iodide and macarpine (Figure 1.3), are used as DNA-binding fluorescent tags in biochemistry laboratories.[4]

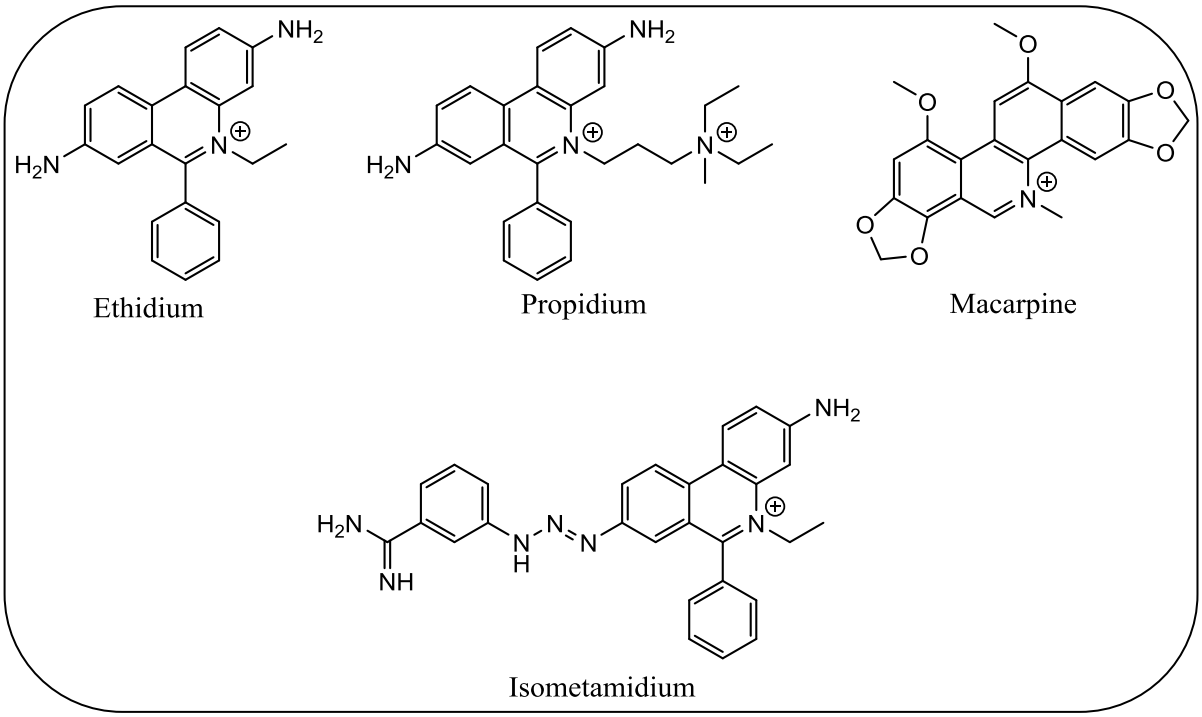


Figure 1.3. Synthetic and naturally occurring phenanthridines that has been employed for their biological activity in medicine or in laboratories.

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,[19] 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.[20,21] Pneumonia caused by multi-drug resistant *Streptococcus pneumoniae* is also a topic of great concern.[20]

There is a broad scientific consensus that there is a need for new and effective antibacterial agents.[21,22] 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.[20] The problem of drug resistance has so far been restricted to

Gram-positive bacteria (GPB), including the mentioned *S. aureus* and *S. pneumoniae*.[23] 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*.[23] Both bacteria are known to cause potentially fatal infections, including pneumonia.[24]

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.[25] A series of naphthyridines (**1**-**4**, figure 1.4) were synthesized by Chrzastek *et al.*, [26] 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.[27] The naphthyridines also showed activity towards GNB, with measured MIC values ranging from 0.2-1.2 µg/mL.

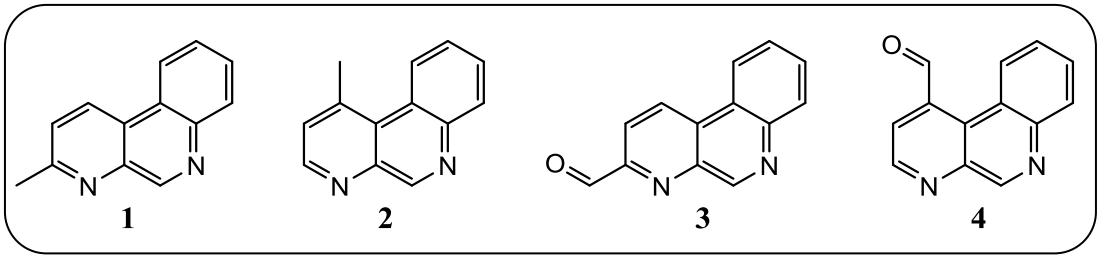
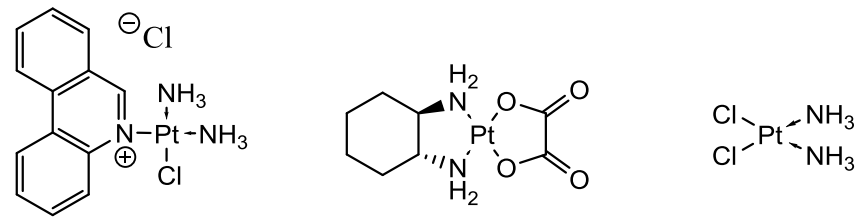


Figure 1.4. Naphthyridines synthesized by Chrzastek *et al*., showing significant antibacterial activity.[26]

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.[28] 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;[29] 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.[29] Several compounds have been recently found to inhibit FtsZ,[30,31] but no antibacterial agent employing this mechanism is available on the market.[32] Sanguinarine (Figure 1.2) displays activity against both GPB and GNB,[29] but a MIC value of 25 µg/mL is not comparable to antibacterial agents on the market.[9] It is also found that sanguinarine may have harmful adverse effects for mammals.[29]

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,[33] while chelerythrine chloride (Figure 1.2) is an antiplatelet agent with possible use in the treatment of thrombosis.[34] Several phenanthridines have shown promising anti-tumor activity and non-toxicity towards mammalian cells.[12,35,36] Platinum-bound phenanthridine, "phenanthriplatin" (Figure 1.4), has been screened for anti-tumor activity,[37] and is reported to "exhibit significantly greater activity than the Food and Drug Administration-approved drugs cisplatin and oxaliplatin".



Phenanthriplatin Oxaliplatin Cisplatin

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.*[38] 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.[38] The authors emphasized the importance of further exploration of substitution patterns, and synthesis of similar compounds.

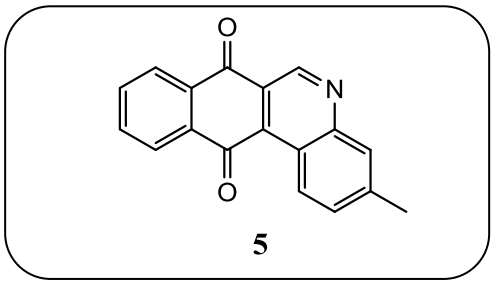


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Figure 1.6. A phenanthridine derivative synthesized by De Kimpe *et al.* found to be very potent towards mycobacteria.[38]

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

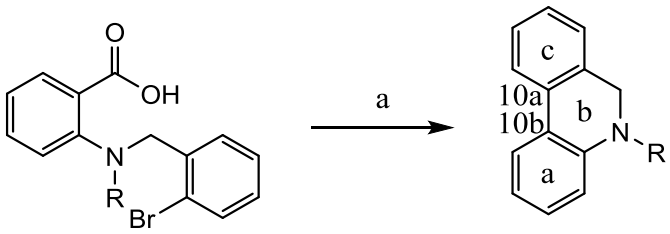
toxicity, often abbreviated “ADME-Tox”, of the compounds to make them suitable as drugs. Furthermore, the opportunity to introduce of a wide array of functional groups in a variety of positions is essential to obtain a comprehensive structure-activity-relationship (SAR).[39] The very first step of this 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 phenanthridine 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.[38,40] Shen *et al.* employed this approach to synthesize the phenanthridine ring system from substituted *N*-(*o*-bromobenzyl)anilines **6** (Scheme 1.1).[40] The synthesis route was found to be successful only for a few *N*-substituted substrates, even at elevated temperatures.



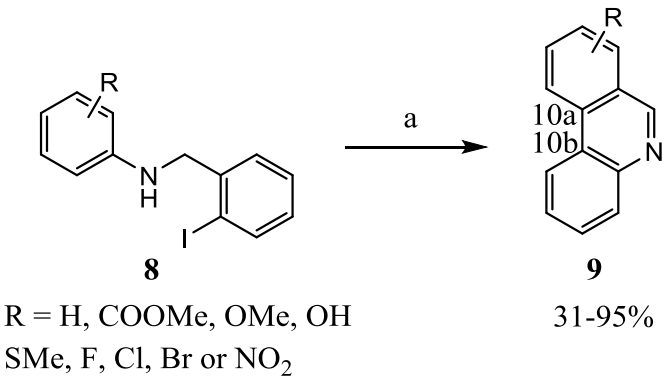
6a, R = H
6b, R = Me
6c, R = Ac

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

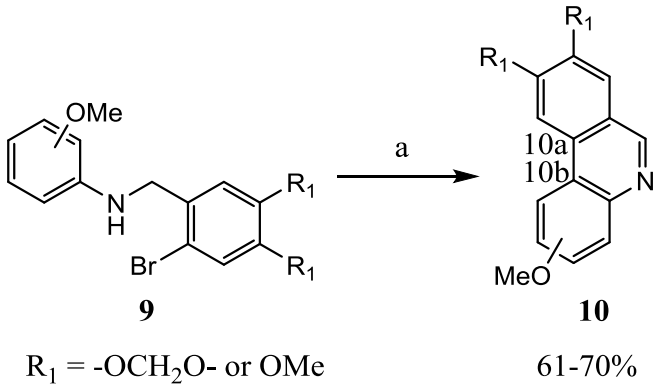
Scheme 1.1. Literature synthesis of phenanthridines by palladium-catalyzed formation of the C10a-C10b bond.[40] Reagents and conditions: **a** – $Pd(OAc)_2$, PPh_3, K_2CO_3, NMP, 120 °C.

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),[41] while Rosa *et al*. employed azobisisobutyronitrile (AIBN) and tri-*n*-butyltin hydride (TBTH) to initiate the reaction (Scheme 1.3).[42]



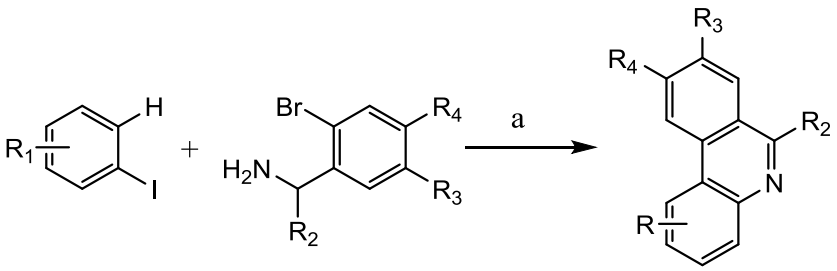
Scheme 1.2. Literature synthesis of phenanthridines by a photochemically initiated radical reaction in the presence of I_2, to form the C10a-C10b bond.[41] Reagents and conditions: **a** – MeCN, hν.



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

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).[43-45]

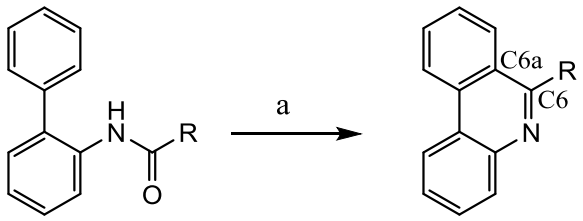


11 **12** **13**

R_1 = H, Me, Et, OMe, Cl, CF_3 R_2 = H, Me, Ph; R_3 = H, F, -OCH_2O-; R_4 = H, -OCH_2O- 22-95%

Scheme 1.4. Literature synthesis of phenanthridines by multiple bond formations in a palladium tandem reaction.[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,[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 **14** (Scheme 1.5).

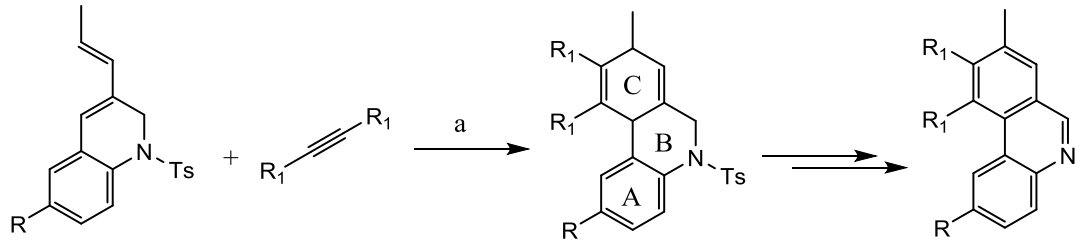


14 **15**

R = Et, Ph, CH_2Cl, *o*-nitrophenyl, *m*-nitrophenyl or *p*-nitrophenyl 61-80%

Scheme 1.5. The original Morgan-Walls reaction to yield phenanthridines.[46] Reagents and conditions: **a** – $POCl_2$.

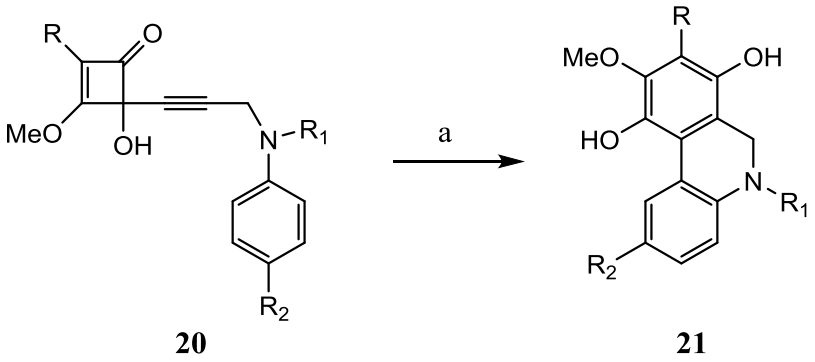
Mondal *et al*. synthesized the phenanthridine ring system by constructing the C-ring through a Diels-Alder reaction (Scheme 1.6).[47]



R = H, Me, OMe, Cl, Br, F or NO_2 | R_1 = COOMe or COOEt | 66-81%

Scheme 1.6. Literature synthesis of the phenanthridine ring system through a Diels-Alder reaction.[47] Reagents and conditions: **a** – PhMe, reflux.

Finally, ring expansion reactions has been employed to synthesize phenanthridines, reportedly through radical or transition-metal catalyzed mechanisms.[48,49] 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).



R = OCH_3 or Ph
R_1 = *n*-Bu, allyl, Boc or 4-pentenyl
R_2 = H or OCH_3

42-70%

Scheme 1.7. Literature synthesis of dihydrophenanthridines by ring expansion.[49] Reagents and conditions: **a** – PhMe, reflux.

1.3 Chemistry of named reactions

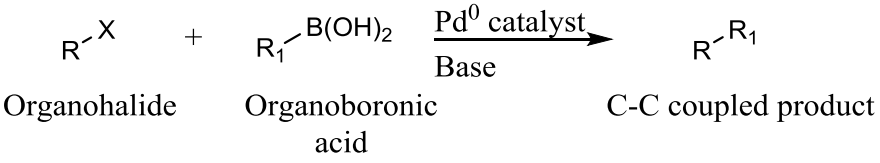
This section describes the common chemistry involved in the synthesis of phenanthridines. A Suzuki coupling reaction was employed for the introduction of the furyl group (Section 1.3.1). Cyclization to give the fused phenanthridine ring system was achieved by an intramolecular Diels-Alder reaction (Section 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,[50] 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.[51] The far-reaching scope of the reaction,[52] mild reaction conditions, and the tolerance of most functional groups has made the Suzuki coupling a common choice when synthesizing natural products and drugs.[53] A large amount of organoboronic acids are commercially available. Additionally, organoboranes have been shown to be non-toxic,[54] not environmentally polluting,[55] 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.[3,56] Catalyst loading has been reported as low as 0.001 mol%,[57] making the Suzuki-Miyaura reaction attractive towards industrial synthesis.[58]

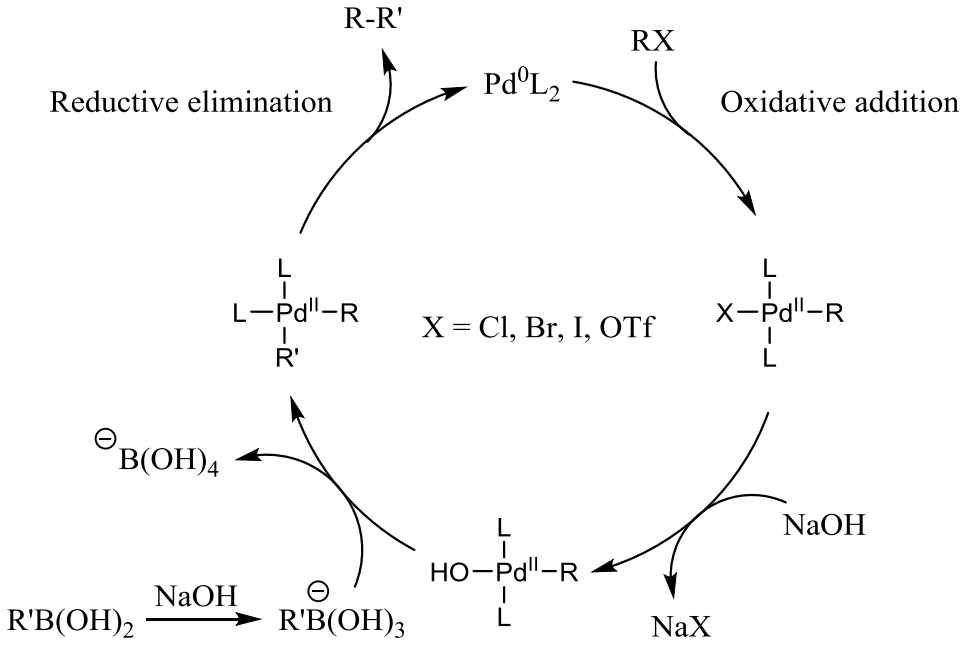
The Suzuki-Miyaura reaction is generally accepted to follow a mechanism depicted in Scheme 1.9,[52,59] where NaOH is used as an example base. The mechanism is similar to other palladium-catalyzed cross-coupling reactions, with the nature of the organometal coupling partner being the major difference.[60] The activation of the catalyst is not included in the

illustration, but this is commonly achieved by *in situ* generation of the active Pd^0-complex from a more stable palladium source such as $Pd(OAc)_2$.



R, R_1 = aryl, vinyl, alkyl
X = 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.



Scheme 1.9. Generally accepted mechanism of the Suzuki-Miyaura reaction.[59,60]

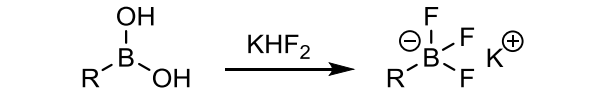
The mechanism of the reaction can be divided into five individual steps.

1. Initially, oxidative addition of the organohalide to a low-coordinate Pd^0 complex occurs, yielding a Pd^{II}-complex.
2. Hydrolysis of the Pd^{II}-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 Pd^{II}-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 betweem 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.



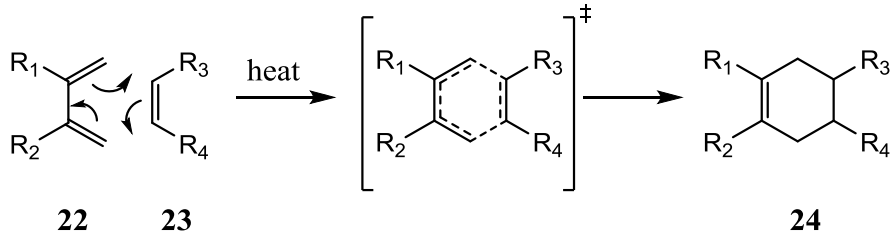
Organoboronic acid Organotrifluoroborate

R = aryl, vinyl or alkyl

Scheme 1.10. Literature conversion of an organoboroinic acid to the corresponding potassium organotrifluoroborate.[63]

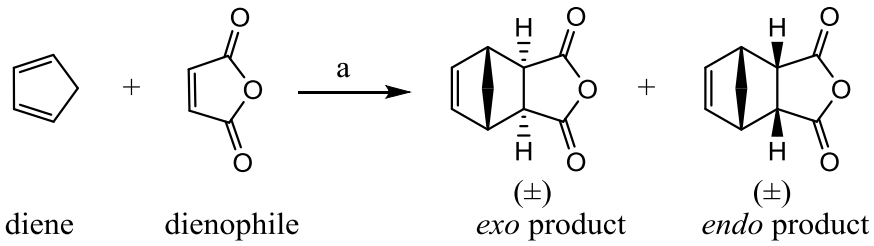
1.3.2 The intermolecular Diels-Alder reaction

The Diels-Alder reaction was first reported in 1928 by Diels and Alder, and is a [4 + 2] cycloaddition reaction (Scheme 1.11).[64] The reaction mechanism is concerted,[65] 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.[65,66] Reactions involving furan as a diene was among the earliest reported,[67] despite furan being an aromatic system.[68] The use of furan as a diene has later been explored in detail,[69] 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.[70]



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).[71]



Scheme 1.12. Formation of *exo* and *endo* products after an intermolecular Diels-Alder reaction.

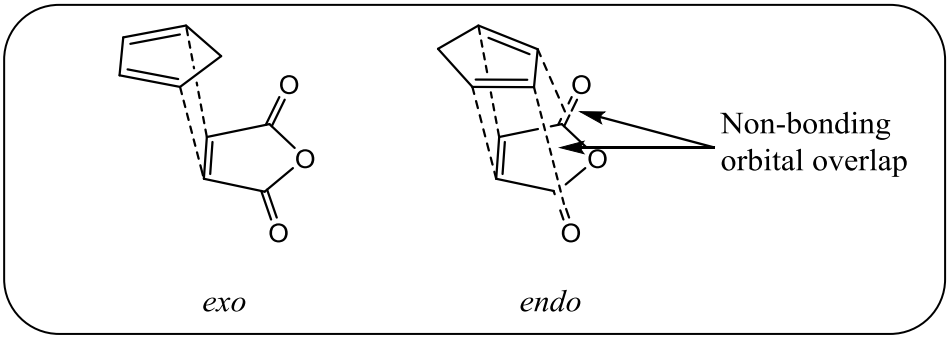


Figure 1.7. Illustration of orbital overlap during formation of the *exo* and *endo* products from Scheme 1.12.

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.[70] 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).

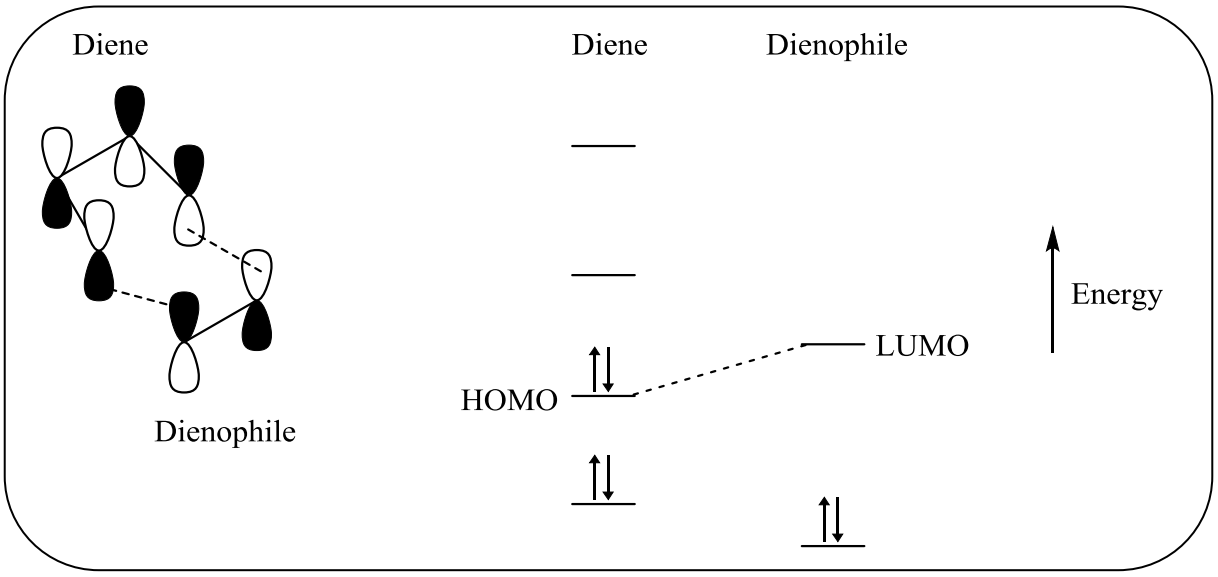


Figure 1.8. Illustration of FMO overlap between an electron rich diene and an electron poor dienophile. A general energetic comparison is also shown.

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).

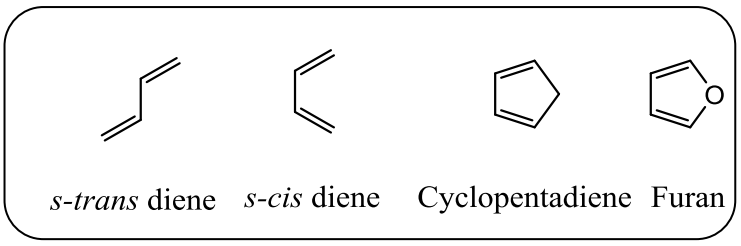
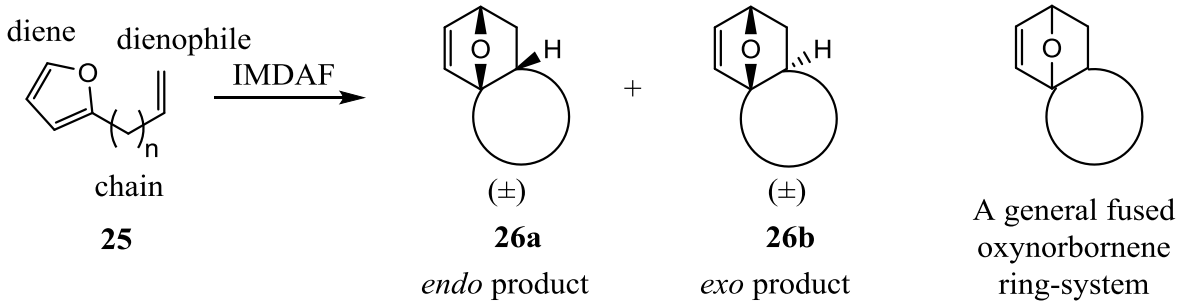


Figure 1.9. Different confirmations of dienes, and the cyclic dienes cyclopentatiene and furan.

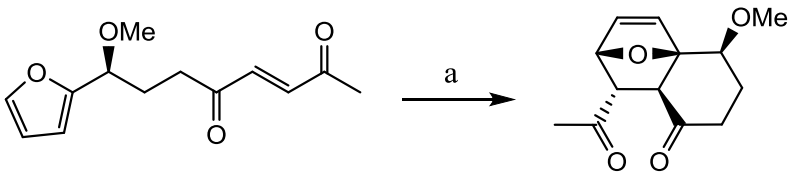
1.3.3 The intramolecular Diels-Alder reaction of furan (IMDAF)

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).



Scheme 1.13. Example of an IMDAF of a simple substrate, and the oxynorbornene ring-system.

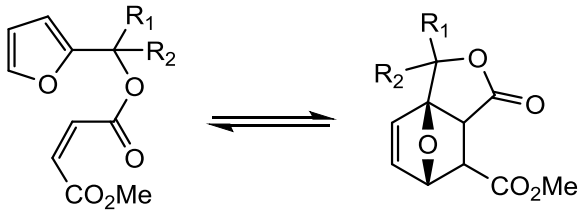
Analysis of intramolecular Diels-Alder reactions is generally more complex than intermolecular reactions, since the connecting chain's ability to fold into the required conformations has to be considered in addition to the stabilities of the *exo*/*endo* products and the stabilizing effects of orbital overlap in the transition states.[71] For IMDAF cyclizations of 2-furanyl substrates, *exo* stereoselectivity is commonly observed.[1,69,72,73] 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).[73]



27 **28**, 67%
single diastereomer

Scheme 1.14. Literature example of an IMDAF cyclization where stereochemistry is directed by a methoxy-substituent. Reagents and conditions: **a** – ZnI_2, CH_2Cl_2.

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.[74-76] The effect was for a long time contributed to a "reactive rotamer effect",[76] arguing that a larger percentage of the rotamers were in the active conformation. Dolata *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.[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.



29 **30**

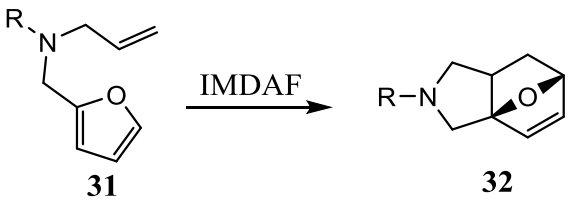
R_1, R_2 = see table 1.1

Scheme 1.15. Study on substituent effect on IMDAF reaction rate by Dolata *et al.*[75]

Tabel 1.1. Study on substituent effect on IMDAF reaction rate by Dolata *et al.,*[75] Scheme 1.15.

Entry	R_1	R_2	Relative rate
1	H	H	1
2	H	Me	8.35
3	Me	Me	2123
4	H	*t*-Bu	8.32

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).[77]



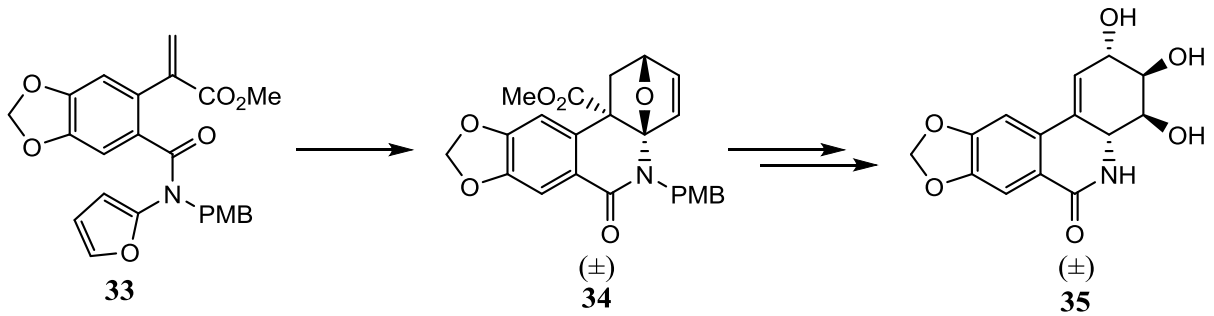
31 **32**

R = H, Mesityl, Bn, CPh_3 R = H, Mesityl, Bn, 0%
R = CPh_3, 85%

Scheme 1.16. IMDAF cyclization of *N*-(furylmethyl)allylamino substrates by Sammes *et al.*[77]

Substitution on the furan moiety is also observed to positively influence the reaction rate of IMDAF cyclizations.[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.[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.[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).[72]



33 (±) **34** (±) **35**

Lycoricidine

Scheme 1.17. Literature synthesis of (±)-lycoricidine by Padwa *et al.*[72]

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.[83] 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.

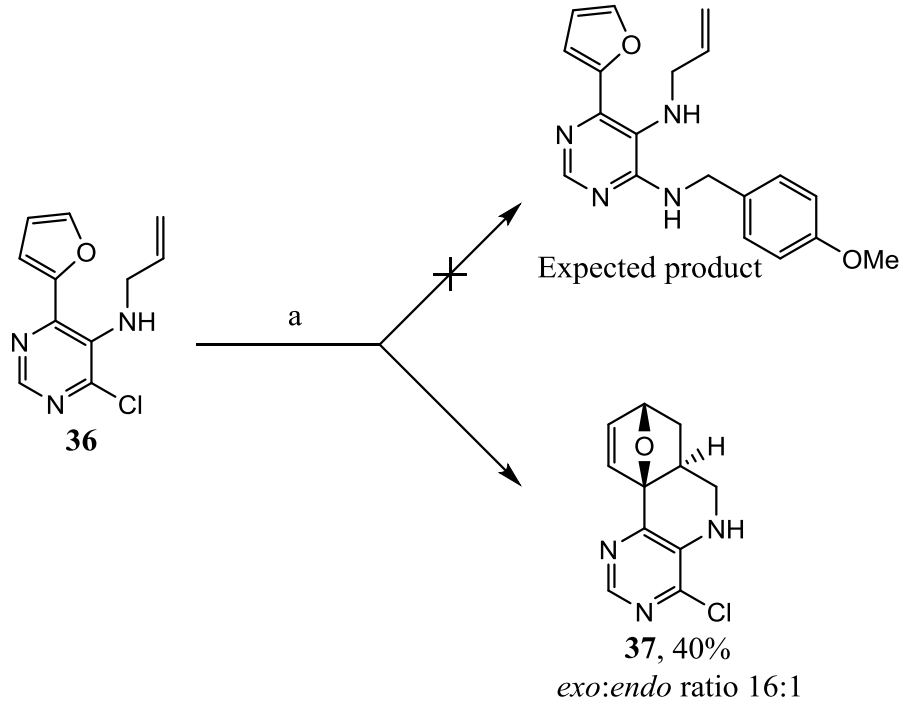
Intramolecular Diels-Alder reactions have been shown to be improved by utilizing microwave reators; yields have been increased, reaction times reduced, and stereoselectivity increased.[2,84-86] Although a "microwave effect" is often referred to, there is still much dispute about whether or not it exists.[83,87] The subject is complicated further through the use of domestic microwave ovens, where precise temperature measuring is impossible.[88] 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.[89] 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,[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).

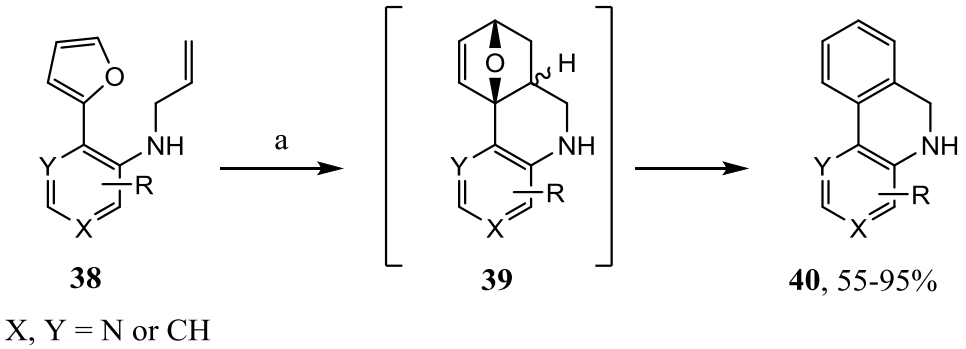


Scheme 1.18. Initially observed IMDAF of *o*-furyl(allylamino)azaarene **36**.[3] The *exo* cyclization product **37** is shown. Reagents and conditions: **a** – NEt_3, (4-methoxyphenyl)methanamine, *n*-BuOH, 100 °C.

The discovery lead to the exploration of the IMDAF of (hetero)arenes with allylamino or allyloxy substituents.[1,3] The study revealed that substrates with a chloride substituent located in an *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 *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.[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.[2,3] 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).

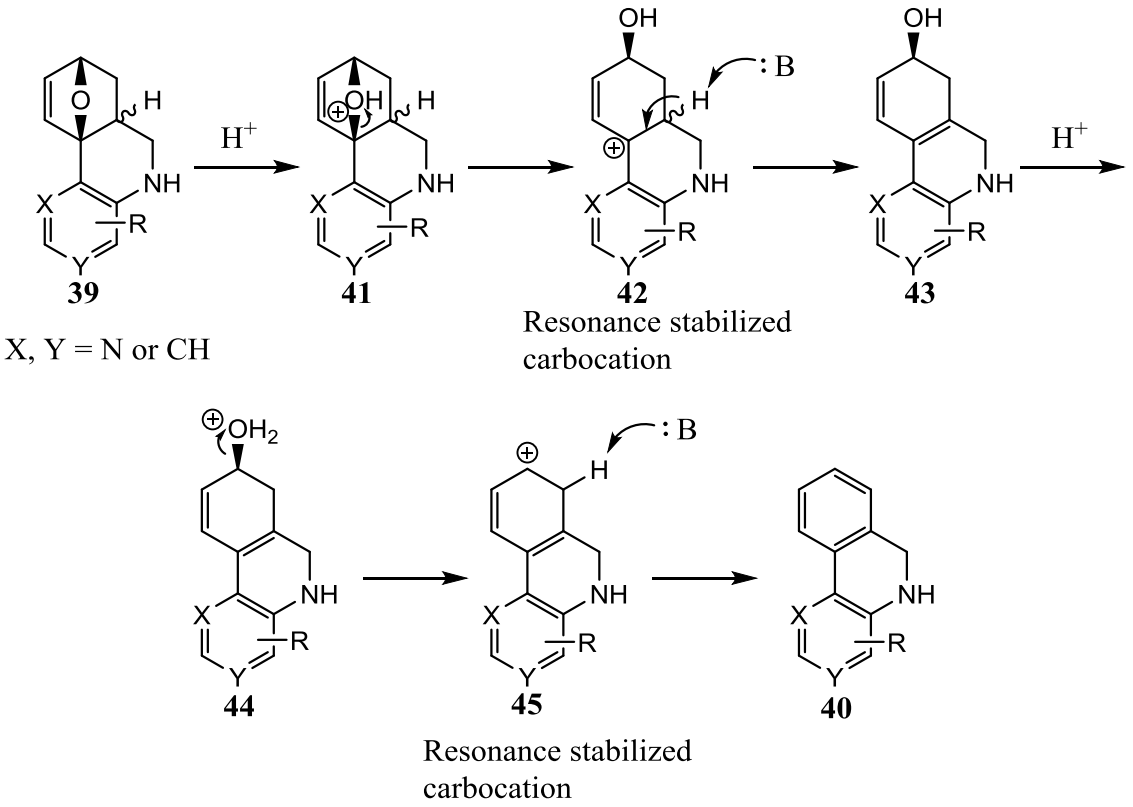


38 **39** **40**, 55-95%

X, Y = N or CH

Scheme 1.19. Microwave-mediated one-pot synthesis of dihydrophenanthridines from *o*-furyl(allylamino)(aza)arenes.[2,3] 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]



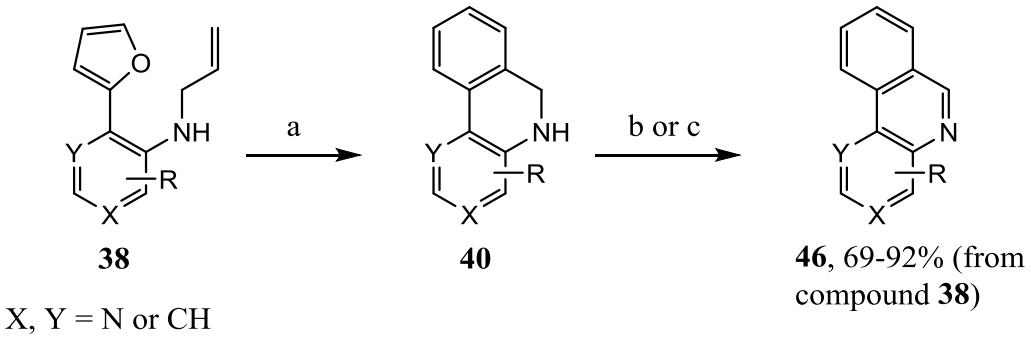
Scheme 1.20. Proposed mechanism for the ring-opening and water elimination of the oxynorbornene ring system of compound **39** to yield dihydrophenanthridines **40**.[3]

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 E_1-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.[3] 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.



38

X, Y = N or CH

40

46, 69-92% (from compound **38**)

Scheme 1.21. Microwave-mediated one-pot synthesis of phenanthridines (**46**) from *o*-furyl(allylamino)(aza)arenes (**38**).[2] Reagents and conditions: **a** – cat. HCl, MeCN, MW, 100-180 °C. **b** – hv, air, MeCN. **c** – DDQ, CH_2Cl_2.

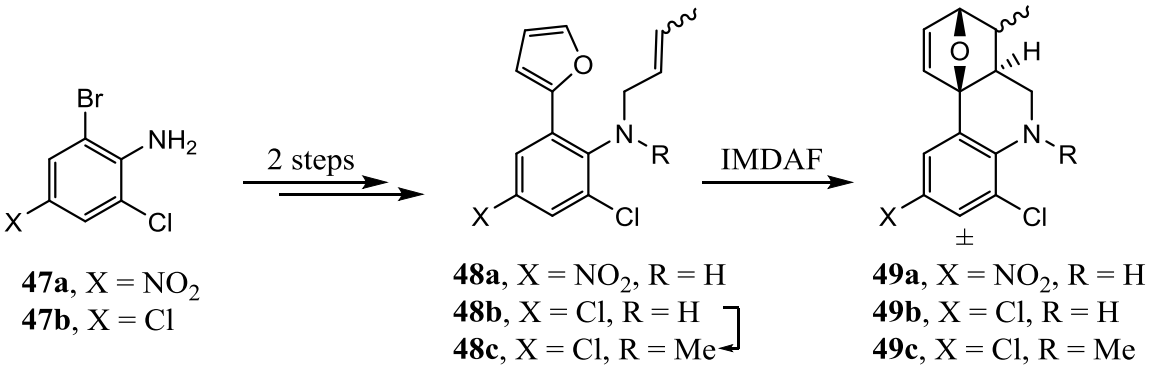
The mechanism of the oxidation with UV-irradiation and air is currently not known. There are several reports of oxidation through irradiation of UV-light of similar compounds,[91,92] but sadly, no mechanism for this oxidation has so far been postulated. Similar oxidations has also been reported using $CHCl_3$ 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).



47a, X = NO_2
47b, X = Cl

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

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.[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.[1,2] Although not being explored further, this is presumed to be caused by the electron-withdrawing nature of the substituents.

Substituents *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.[1] This information is summarized in Figure 2.1.

Finally, *N*,*N*-dialkylated substrates have been briefly screened.[1] The substrates displayed higher reactivity, but with a loss in stereoselectivity. *N*-Boc derivatives did not show any reactivity.

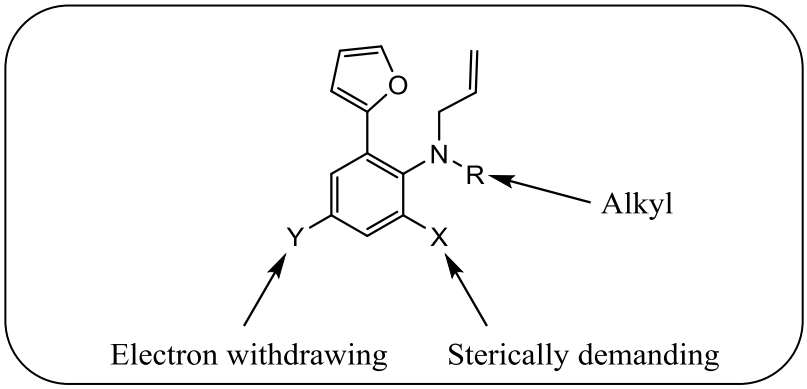


Figure 2.1. Substitution patterns found to facilitate the IMDAF reaction of *o*-furyl(allylamino)arenes.

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 **57**.
- To determine of the the diastereoselectivity of the IMDAF adducts **49** of substrates **48**, compared to the *o*-furyl(allylamino)arene analogs **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 *o*-furyl(crotylamino)arenes **48** (Scheme 2.1) were chosen as starting materials for the IMDAF-cyclizations to give phenanthridines. The *N*-methylated substrate **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

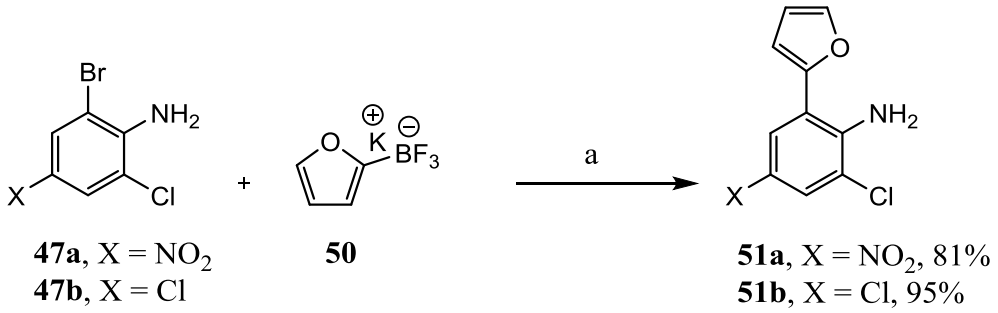
As described in Section 1.3.1, an electron rich organoboronic species and an electron deficient aryl halide is wanted to obtain high reactivity in Suzuki-Miyaura reactions. Furan, being an aromatic heterocyclic five-membered ring, is an electron rich system[68] and therefore an excellent candidate for 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_2Cl_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.



47a, X = NO_2 **50** **51a**, X = NO_2, 81%
47b, X = Cl **51b**, X = Cl, 95%

Scheme 2.2. Reagents and conditions: **a** – K_2CO_3, $Pd(OAc)_2$, PPh_3, EtOH/H_2O (95:5), reflux.

The Suzuki reaction with 2-furanylboronic 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.[62] The more stable 2-furanyltrifluoroborate have therefore been synthesized in bulk in our group, following a literature procedure.[63]

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.

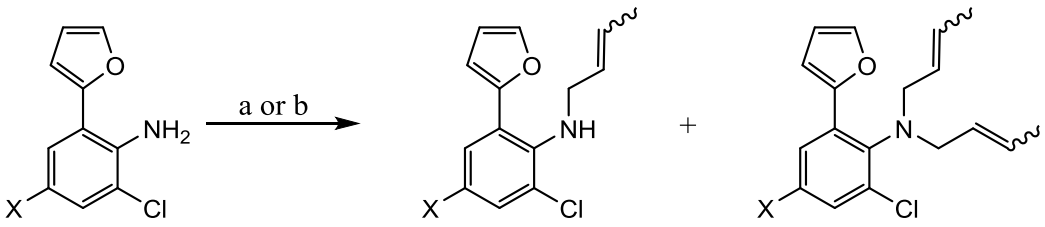
In previous related studies, a broad array of anilines and aminoazaarenes have been *N*-allylated with a variety of different conditions.[1,3] Furthermore, *N*,*N*-diallylation has been found to readily occur, even when the amount of base and allyl bromide are kept close to one equivalent. For this reason, 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.[1] 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.[97] 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.[3] 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.



51a, X = NO_2
51b, X = Cl

48a, X = NO_2, 76%, *E*:*Z* 85:15
48b, X = Cl, 91%, *E*:*Z* 85:15

52a, X = NO_2, 7%, mixture of isomers (72:26:2)
52b, X = Cl, 0%

Scheme 2.3. Reagents and conditions: **a** – Table 2.1, entry 4. **b** – Table 2.1, entry 3.

Interestingly, the *N*,*N*-dicrotylated dichloro compound **52b** was not observed by ^{1}H 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.

Entry	Substrate	Eq. crotyl-Br	Base	Eq. base	Solvent	Temp. (°C)	Time (h)	Additive	Unreacted S.M.[a] (%)	Yield[b] (%)		*E*:*Z* ratio of isolated 48
										48	52	
1	**51b**	1.3	NaH	1.3	PhMe	35[c]	21	15-crown-5-ether	24	54	0	85:15
2	**51b**	1.3	NaH	1.2	THF	r.t.[d]	6.5	TBAB	4	73	0	85:15
3	**51b**	1.2	NaH	1.2	THF	r.t.[d]	2	TBAB[e]	<1	91	0	85:15
4	**51a**	1.2	NaH	1.2	THF	r.t.[d]	4	TBAB[e]	<1	76	7	85:15

[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 pK_a values of *p*-nitro- and *p*-chloroaniline are 1.00 and 3.98, respectively.[98] 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.

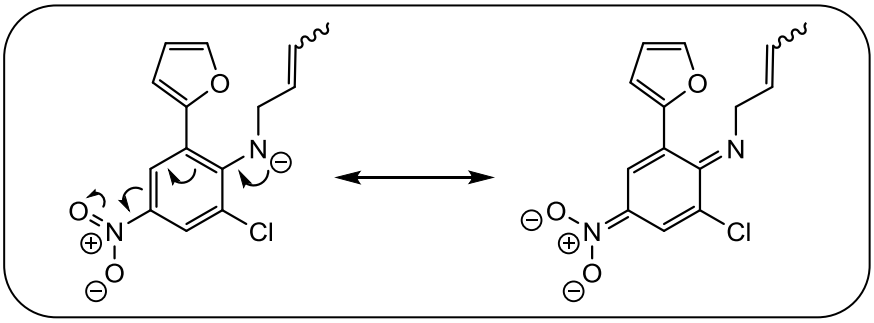
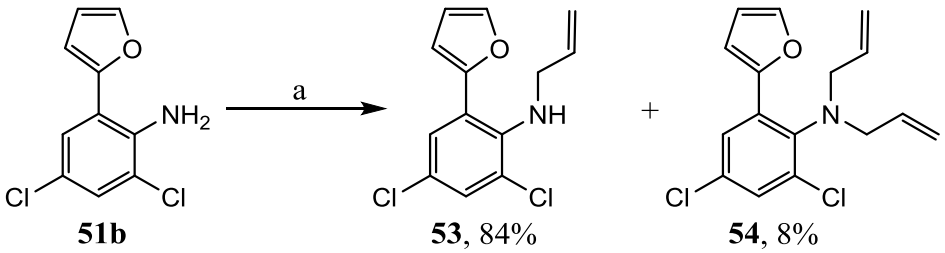


Figure 2.2. Resonance stabilization of deprotonated compound **48a**. Not all resonance structures shown.

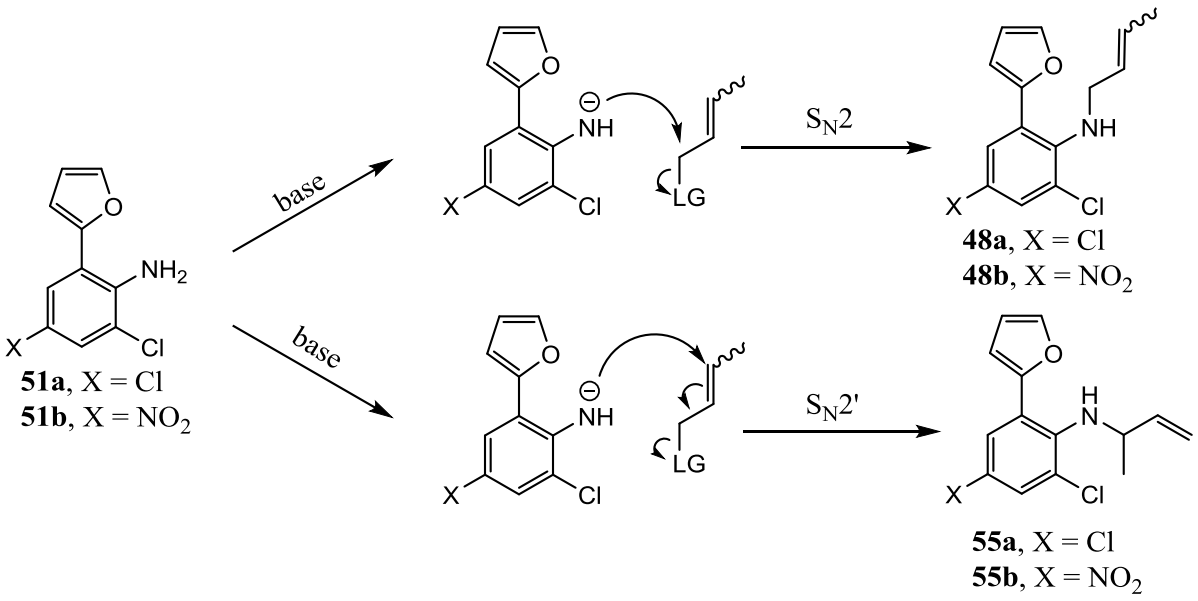
In work done in our research group by Read,[3] allylation of dichloro aniline **51b** yielded the diallylated product **54** as a byproduct with conditions given in Scheme 2.4.



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

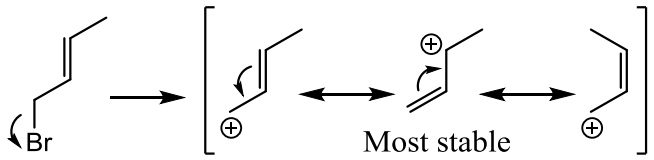
There are important differences when comparing the conditions from Read (Scheme 2.4) and the conditions employed herein (Scheme 2.3). Exchanging the solvent from THF to the more polar DMF not only increases the solubility of the base, but also helps to stabilize ionic species, i.e. the deprotonated anilines. 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_N2-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_N2'-type nucleophilic attack ("S_N2 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_N2-type mechanism should be both kinetically and thermodynamically[95] favored versus S_N2'.



Scheme 2.5. Deprotonation of compound **51** followed by nucleophilic attacks to form compounds **48** or **55**.

An S_N1-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_N1 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_N2 mechanism.[100]



Scheme 2.6. The first step of a theorized S_N1 reaction of (*Z*)-crotyl bromide.

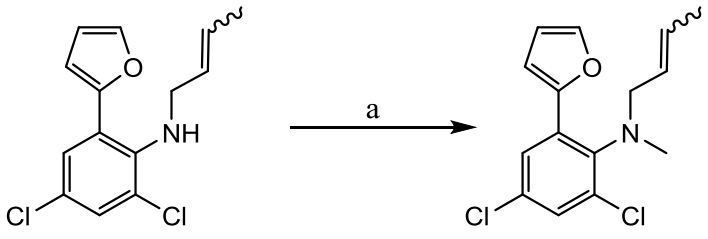
2.1.5 Synthesis of N-(but-2-en-1-yl)-2,4-dichloro-6-(furan-2-yl)-N-methylaniline (48c)

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).[1] 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.



E:*Z* 85:15
48b

E:*Z* 85:15
48c, 92 %

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.

Entry	Eq. MeI	Base	Eq. base	Solvent	Temp. (°C)	Time (h)	Additive	Unreacted S.M.[a] (%)	Yield 48c[b] (%)	*E*:*Z* ratio of isolated compound
1	1.2	NaH	1.3	THF	r.t.[c]	3	TBAB	>99	0	-
2	2	KH	2	PhMe	40[d]	24	18-crown-6-ether	19	59	85:15
3	2.3	KH	2.3	PhMe	40[d]	0.75	18-crown-6-ether	<1	92	85:15

[a]by ^{1}H NMR of crude product.
[b]of isolated products.
[c]addition of base and MeI at 0 °C, then stirred at r.t.
[d]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 desbribes 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.

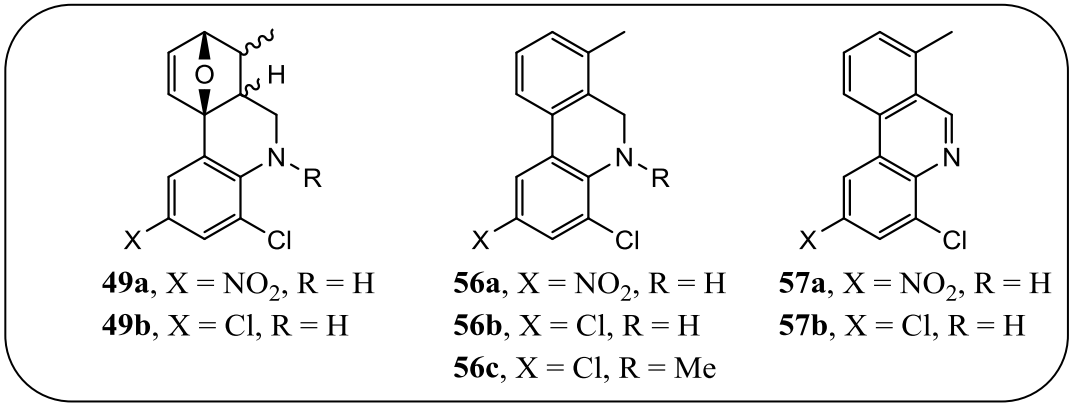
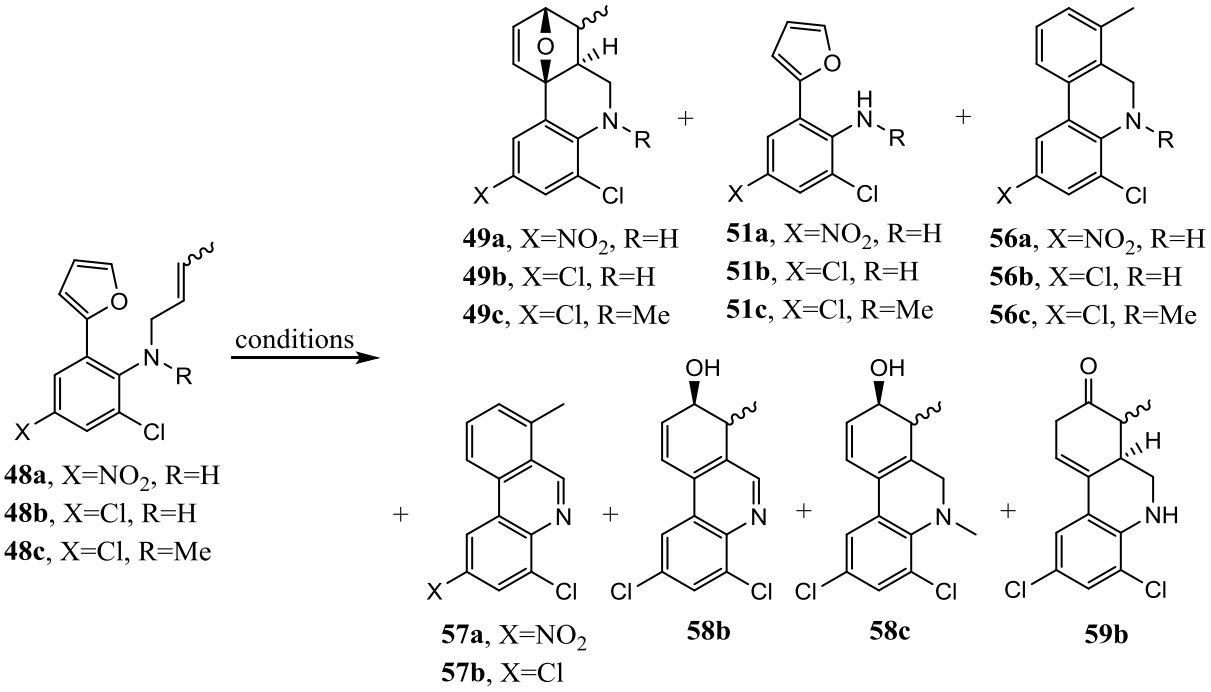


Figure 2.3. Compounds described in this section.

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 distrubution 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.[80] Therefore, the initial MW conditions are chosen to be slightly harsher than the reported conditions for *N*-allylamino analogs.[2,3]

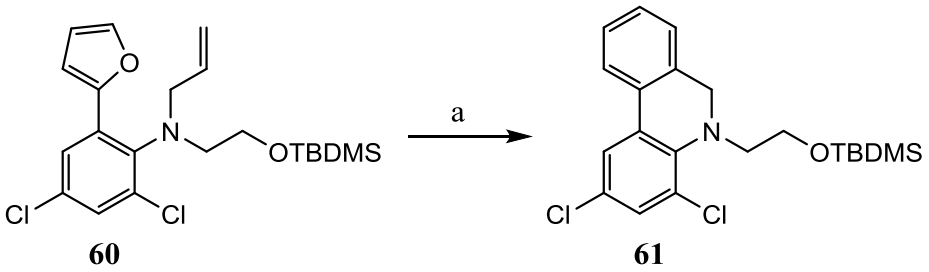
Table 2.3. Screening of conditions for microwave-mediated IMDAF of compounds **48.**

Entry	Compound	X	R	Additive	Solvent	Temp (°C)	Time (h)	Product distribution[a]						
								48	**49**	**56**	**57**	**58**	**59**	**51**
1	**48a**	NO_2	H	HCl	MeCN	150	1	<1	–	81	10	–	–	9
2				HCl	MeCN	100	2	46	–	54	–	–	–	<1
3				HCl	MeCN	100	4	22	–	78	–	–	–	<1
4				HCl	MeCN	100	6	10	–	90	–	–	–	<1
5				HCl	MeCN	100	8	<1	–	93	3	–	–	4
6				H_2O	MeCN/PhMe	150	1	<1	>99	–	–	–	–	–
7				H_2O	MeCN	150	1	<1	>99	–	–	–	–	–
8				–	MeCN	150	1	<1	>99	–	–	–	–	–
9	**48b**	Cl	H	HCl	MeCN	150	1	6	–	64	15	–	–	13
10				HCl	MeCN	150	2	1	–	64	21	–	–	14
11				HCl	MeCN	100	4	64	–	14	11	–	–	14
12				HCl	MeCN	100	8	50	–	25	10	–	–	15
13				H_2O	MeCN/PhMe	150	2	2	–	84	2	6	7	–
14				H_2O	MeCN	150	2	<1	–	81	8	10	1	–
15				H_2O	MeCN	150	2.5	<1	–	93	2	3	2	–
16				–	MeCN[b]	150	2	<1	–	85	2	7	6	–
17				Mol. Sieves	MeCN[b]	150	2	–	–[c]	–[c]	–	–[c]	–[c]	–
18				NaOH	MeCN	150	3	<1	>99	–	–	–	–	–
19	**48c**	Cl	Me	H_2O	MeCN	150	3	61	33	1	–	6[d]	–	–
20				H_2O	MeCN	150	4	51	35	4	–	9[d]	–	–
21				H_2O	MeCN	150	5	45	27	10	–	18[d]	–	–
22				HCl	MeCN	180	2	8	–	83	–	–	–	7[e]
23				HCl	MeCN	180	3	4	–	91	–	–	–	5[e]

[a]by ^{1}H NMR of the crude product.
[b]Dry MeCN from solvent-drying system.
[c]present in the reaction mixture, but no ratio could be identified.
[d]Based on NMR signals presumed to belong to compound **58c**.
[d]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 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).



60 **61**

Scheme 2.9. Reported microwave-mediated IMDAF of *o*-furyl(allylamino)arene **60** to yield dihydrophenanthridine **61**.[3] Reagents and conditions: **b** – cat. H_2O, 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 ^{1}H 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.

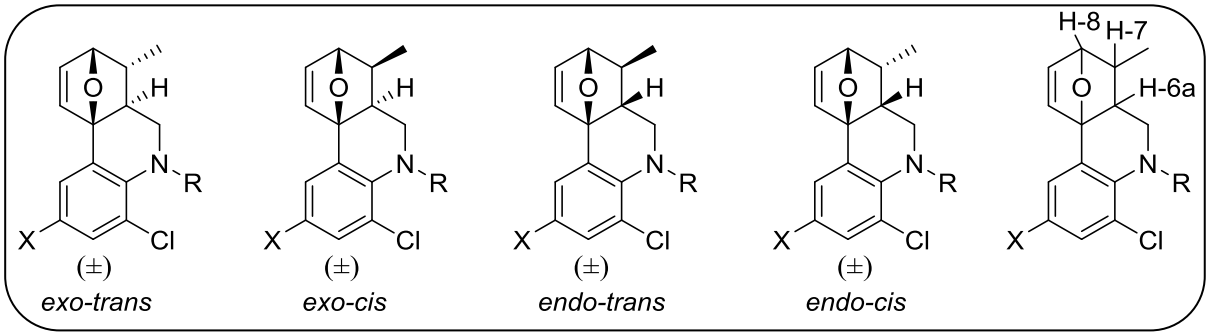
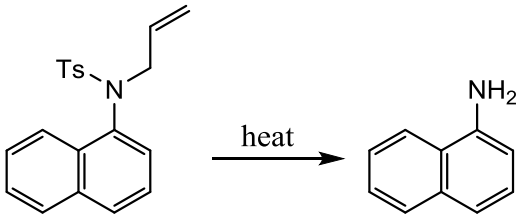


Figure 2.4. The four diastereomers of tetrahydro-8,10a-epoxyphenanthridines **49** and their relative stereochemistry. Numbering of relevant hydrogens is also shown.

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]

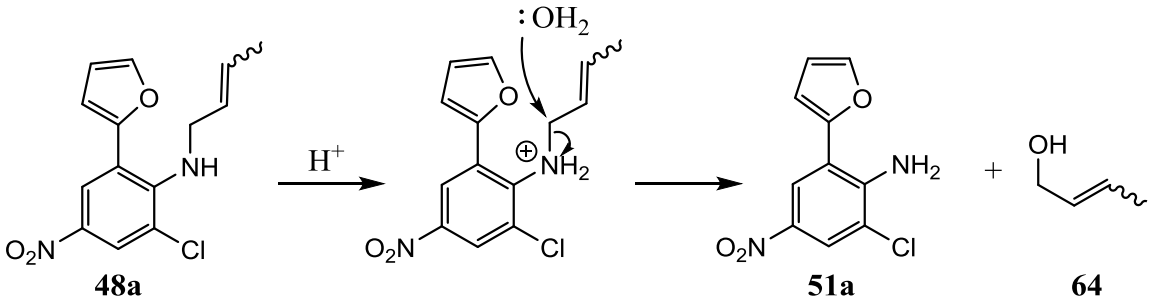
Loss of allylic moieties from *N*-allylanilines has previously been reported for *N*-allylanilines at highly elevated temperatures to undergo aza-Claisen rearrangements (Scheme 2.10).[106,107]



62 **63**

Scheme 2.10. Deallylation of *N*-allyl-1-naphthylamine when heated to 260 °C, as reported by Inada *et al.*[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 S_N2-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.



48a **51a** **64**

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.*[3] was employed, it was found that water was acidic enough to catalyze the 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,[2,3] 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 ^{1}H 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 ^{1}H 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.[1,3]

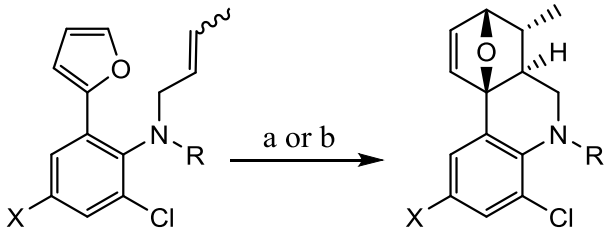
The *N*-methylated substrate **48c** required tougher reaction conditions than the analog **48b**. This was unexpected, as *N*-substituted compounds generally are cyclized under milder conditions than their unsubstituted analogs (see Section 2.1.1).[1] The Diels-Alder adduct **49c** also proved to be 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 ^{1}H 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.



E:Z 85:15
48a, X = NO_2, R = H
48b, X = Cl, R = H

Main diastereomer
49a, X = NO_2, R = H, 68%
49b, X = Cl, R = H, 11%

Scheme 2.12. Reagents and conditions: **a** – MeCN, MW, 100 °C. **b** – cat. NaOH, MeCN, MW, 150 °C.

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 *exo-trans* and *exo-cis* being the two major diastereomers (Figure 2.4, page 45).

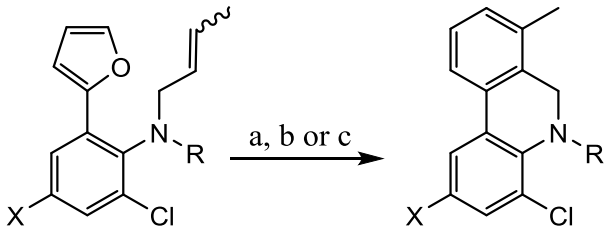
The dichloro Diels-Alder adduct **49b** was also formed quantitatively, but was only stable under basic conditions. All attempts of neutralization lead to instantaneous decomposition into a wide array of compounds, including alcohol **58b**. For synthesis purposes, synthesizing compound **49b** and immediately 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 ^{1}H NMR spectra.

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

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 *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**.



E:Z 85:15

48a, X = NO_2, R = H
48b, X = Cl, R = H
48c, X = Cl, R = Me

56a, X = NO_2, R = H, 85%
56b, X = Cl, R = H, 77%
56c, X = Cl, R = Me, 66%

Scheme 2.13. Reagents and conditions: **a** – cat. HCl, MeCN, MW, 150 °C. **b** – cat. H_2O, MeCN, MW, 150 °C. **c** – cat. HCl, MeCN, MW, 180 °C.

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-CH_2Cl_2-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.[2] 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,[2] which affected the yield of the unoxidized product **56b**. To illustrate the rate of oxidation, Figure 2.5 shows a comparison of ^{1}H 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).

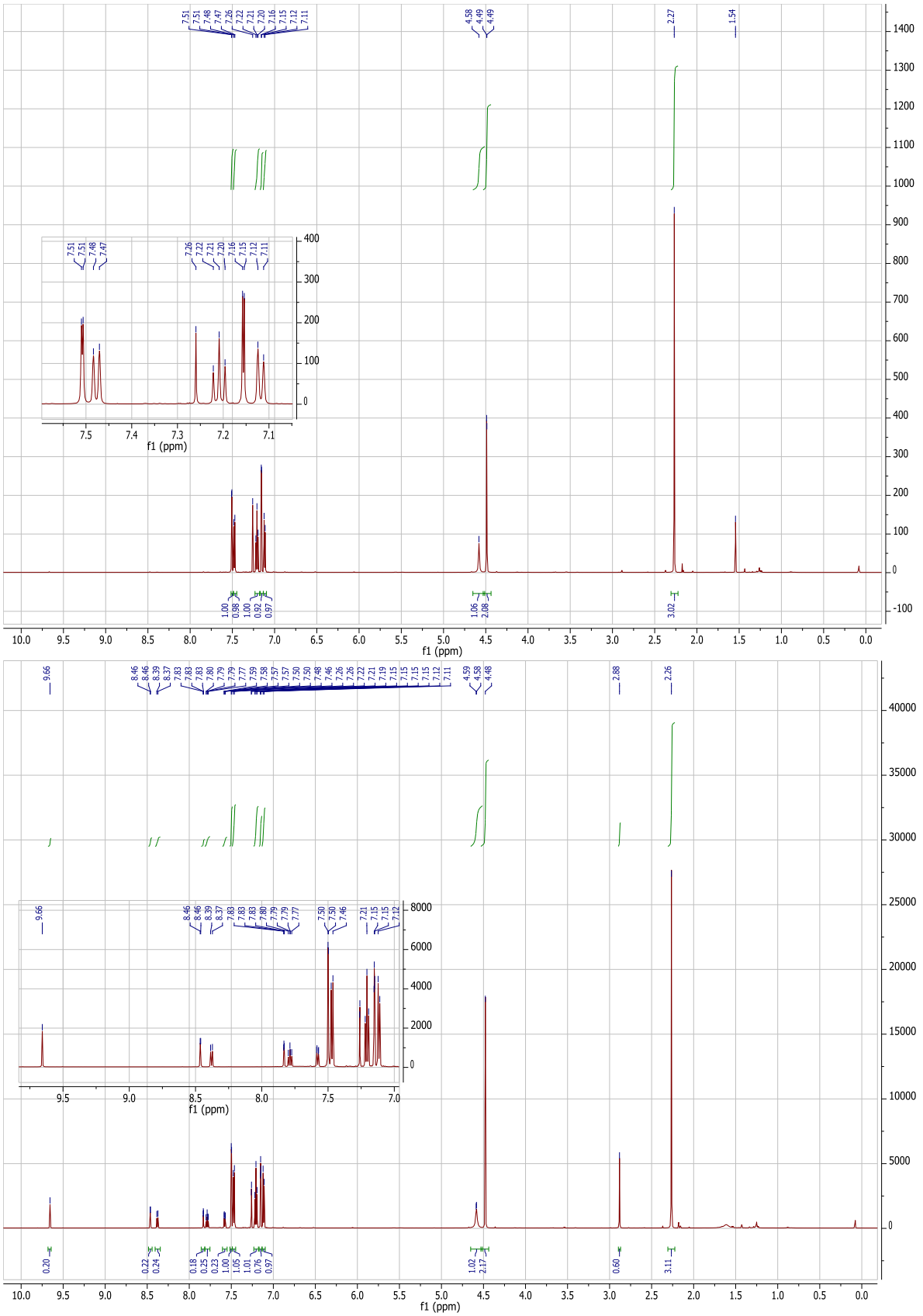


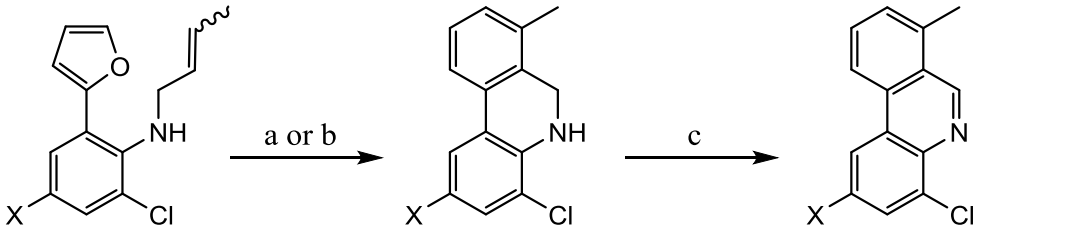
Figure 2.5. ^{1}H NMR spectra of 2,4-dichloro-7-methyl-5,6-dihydrophenanthridine (**56b**) before (top) and after (bottom) approximately 8 hours of NMR experiments. The bottom spectrum shows circa 17% oxidized compound **57b**.

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.



E:Z 85:15
48a, X = NO_2
48b, X = Cl

56a, X = NO_2
56b, X = Cl

57a, X = NO_2, 77%
57b, X = Cl, 91%

Scheme 2.14. Reagents and conditions: **a** – cat. HCl, MeCN, MW, 150 °C. **b** – cat. H_2O, MeCN, MW, 150 °C. **c** – air, hν, MeCN.

The oxidation with UV/air was found to be exceptionally clean, as promised by literature reports.[2,3] 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_2Cl_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,[2] 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).

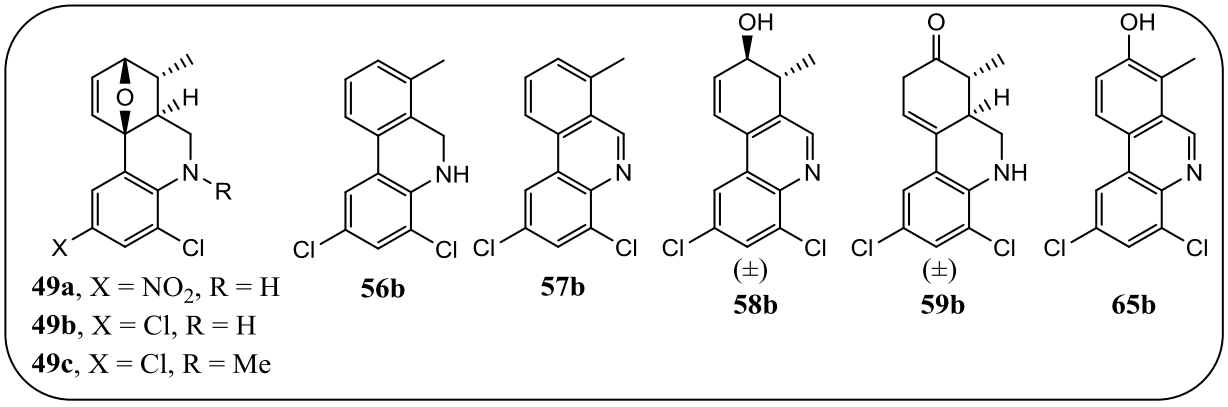
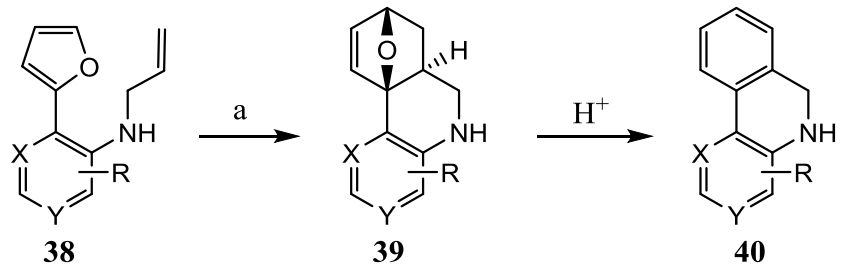


Figure 2.6. Compounds described in this section.

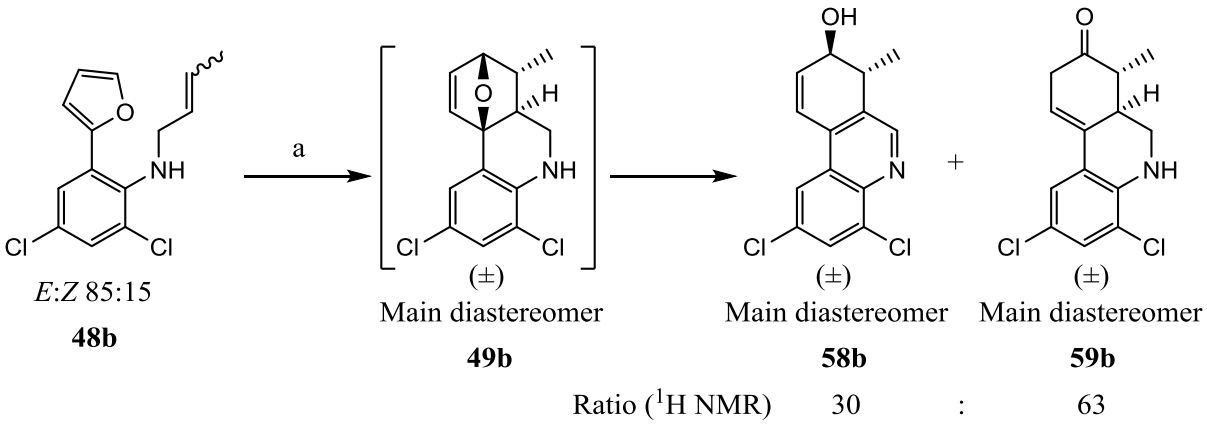
2.3.1 Motivation and initial results

In previous projects in our group, *o*-furyl(allylamino)arenes have been cyclized by heating in PhMe[1] when selectivity towards dihydrophenanthridines **56** were unacceptable in acid-catalyzed microwave-mediated conditions. Subsequent stirring with acid yields the dihydrophenanthridine as a two-step procedure (Scheme 2.15).[108]



Scheme 2.15. IMDAF of a general *o*-furyl(allylamino)arene followed by addition of acid to form a dihydrophenanthridine. Reagents and conditions: **a** – PhMe, 100 °C or xylenes, 150 °C.

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).

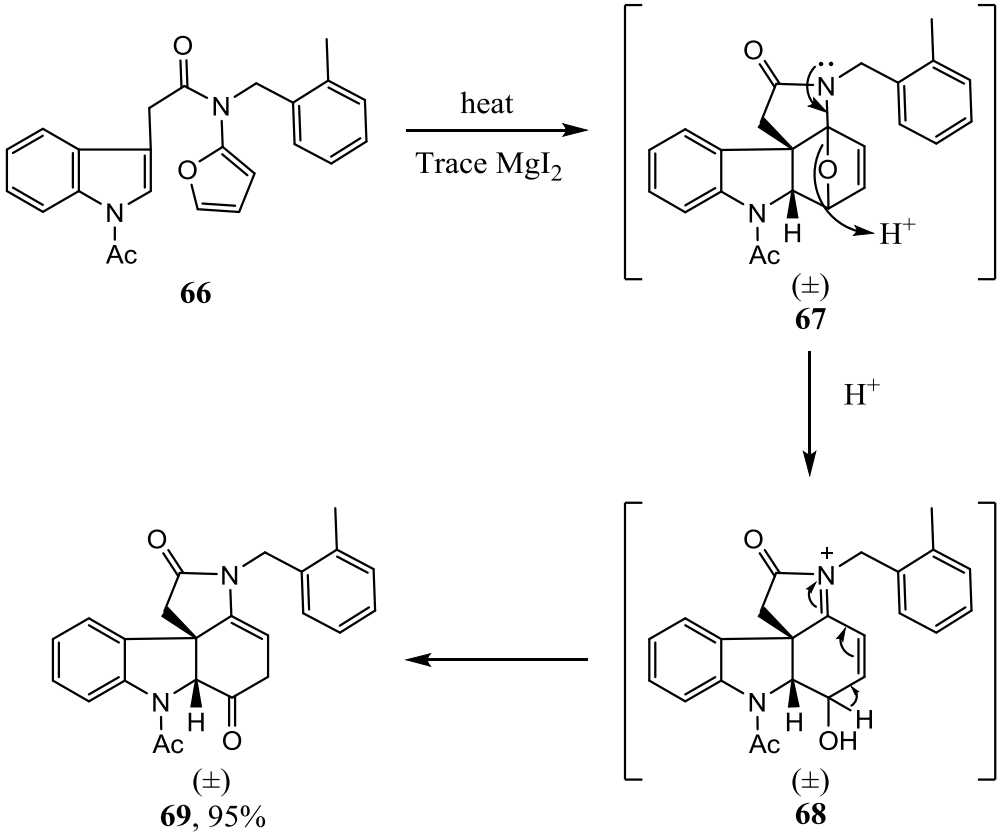
The relative stereochemistry of ketone **59b** was determined by NOESY NMR (Spectrum 78) to be as shown in Scheme 2.16. NOE interactions were observed between the methyl and H-6a, but not between H-6a and H-7, suggesting a *trans* relationship between the hydrogens.

The presence of the oxygen functionality in the C-ring makes both the alcohol **58b** and the ketone **58b** 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).

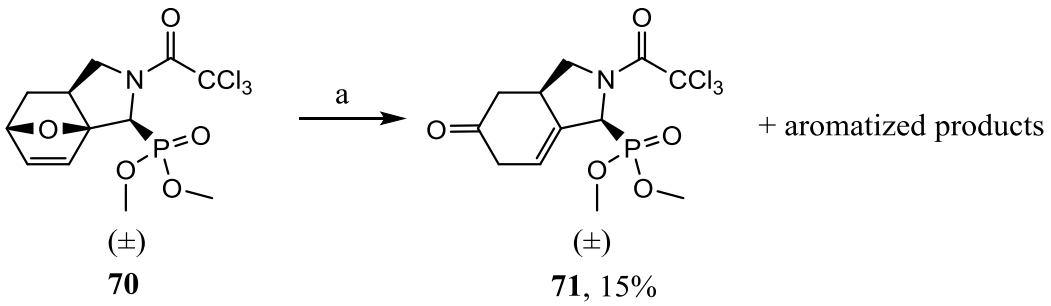
Ring-opened oxanorbornene ring systems that are unable to aromatize, i.e. that are substituted in the bridgehead position, are well known in the literature to isomerize to β,γ-unsaturated

ketones when heated at high temperatures.[72,82,109] Padwa *et al.* employed this rearrangement as a key step in a total synthesis of racemic strychnine (Scheme 2.17).[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 β,γ-unsaturated ketone **69**.



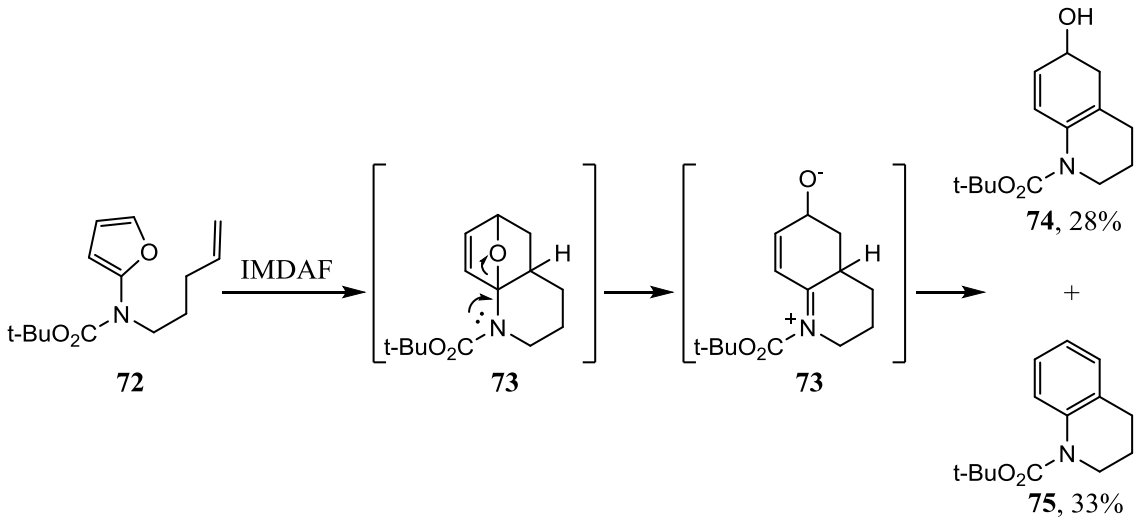
Scheme 2.17. IMDAF and a following rearrangement cascade as a key step in a total synthesis of strychnine by Padwa *et al.*[82]

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.[65] There has also been reports of Lewis acids catalyzing the ring-opening and rearrangement of oxanorbornenes to form β,γ-unsaturated ketones (Scheme 2.18),[110] meaning the function of the Lewis acid in Scheme 2.17 might be twofold.



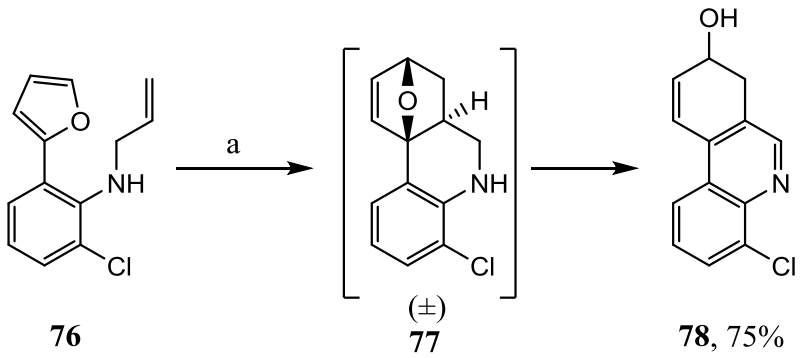
Scheme 2.18. Literature report of a Lewis acid-catalyzed ring-opening and rearrangement of an oxanorbornene ring system **70** to give a β,γ-unsaturated ketone **71**.[110] Reagents and conditions: **a** – $FeCl_3$, CH_2Cl_2, reflux.

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]

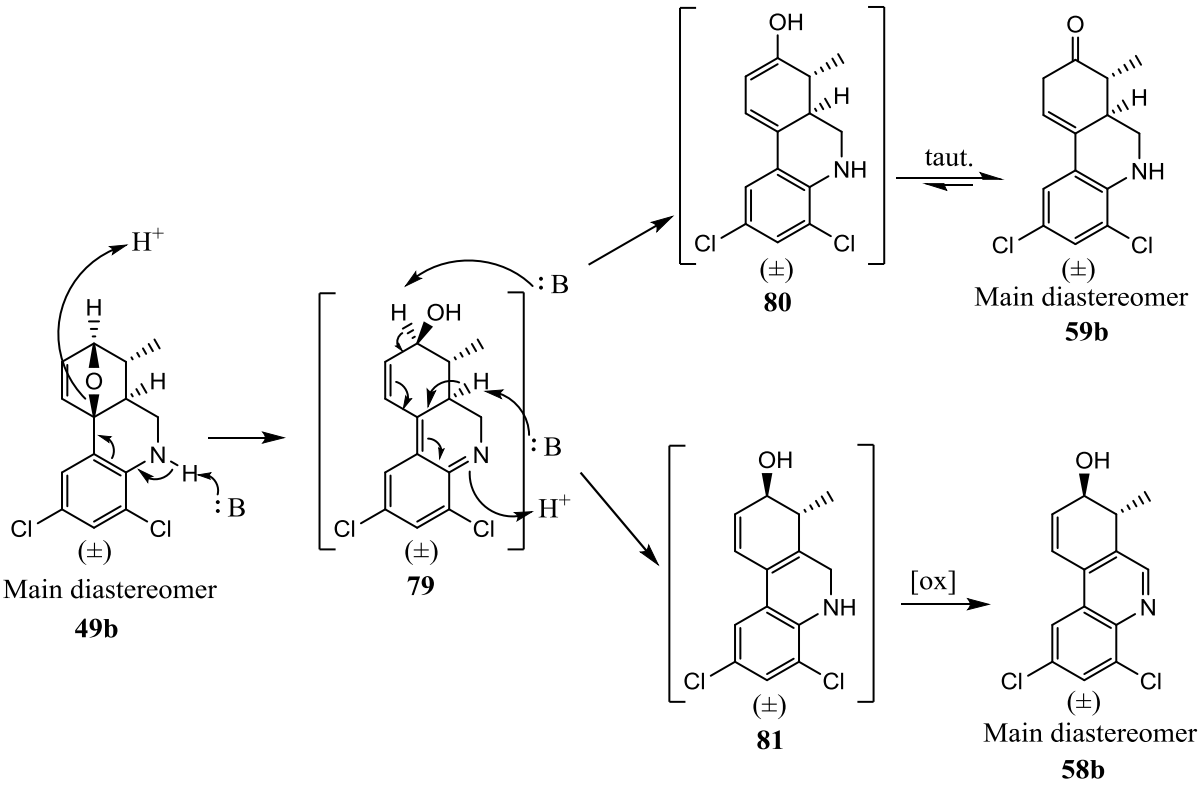
In our group, ring-opening and oxidation to form alcohol **78** has previously been encountered for a single substrate.[3] Compound **76** was heated at 100 °C in PhMe to yield a mixture of Diels-Alder adduct **77** and alcohol **78**. When the substrate was heated in the presence of catalytic amounts of water (Scheme 2.20), the adduct was fully converted to alcohol **78**. The reaction was not looked further into at the time.



76 **77** **78**, 75%

Scheme 2.20. Previously observed ring-opening and oxidation to yield the allylic alcohol **78**. Reagents and conditions: **a** – cat. H_2O, 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),[82] 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.



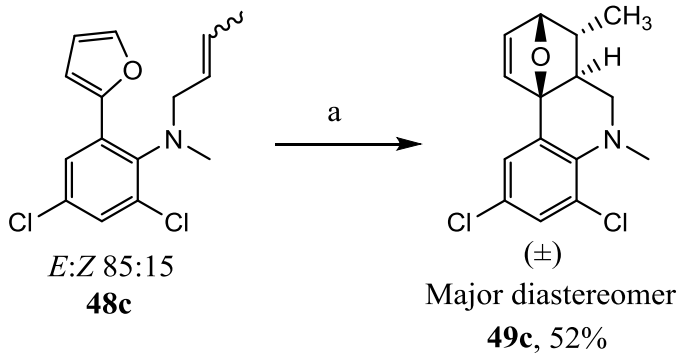
Scheme 2.21. Proposed mechanism to rationalize the formation of ketone **59b** and alcohol **58b** with correct observed stereochemistries from Diels-Alder adduct **49b**.

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 E_2-type elimination. The fact that water elimination occurs readily under microwave conditions could be attributed to the more polar solvent (MeCN) allowing for an E_1-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.

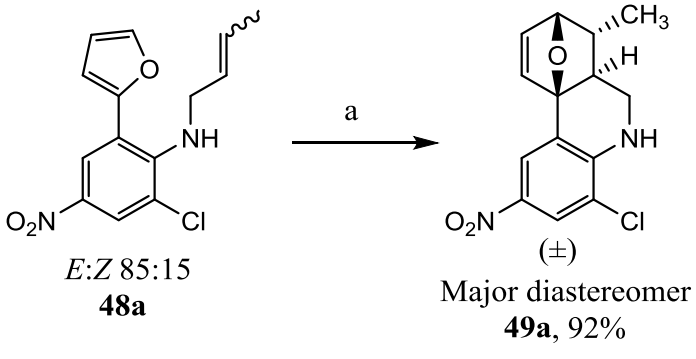


E:*Z* 85:15
48c

(±)
Major diastereomer
49c, 52%

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.



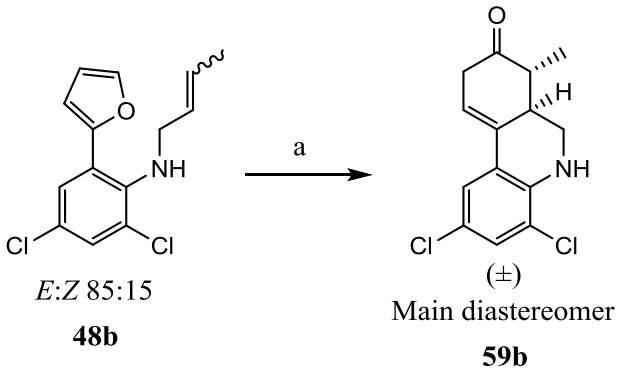
E:*Z* 85:15
48a

(±)
Major diastereomer
49a, 92%

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.



E:*Z* 85:15

48b

(±)

Main diastereomer

59b

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).

Entry	Additive	PhMe dried over	Freshly purified substrate x	Notes	Product distribution[a]			Color of reaction mixture
					58b	59b	56b	
1	–	Mol. Sieves[b]	No	–	30	63	7	Brown
2	H_2O	Mol. Sieves[b]	No	Vigorous stirring.	64	17	18	Brown
3	–	Mol. Sieves[b]	No	Filtered to remove potential silica residue from starting material.	45	46	9	Brown
4	–	Mol. Sieves[b]	Yes	–	72	17	11	Brown
5	–	Na	Yes	Reaction mixture degassed with needle **in contact with** solution.	86	14	0	Brown
6	–	Na	Yes	Reaction mixture degassed with needle **not in contact with** solution.	>99	0	0	Clear yellow
7	–	Na	No	Reaction mixture degassed with needle **not in contact with** solution.	>99	0	0	Clear yellow

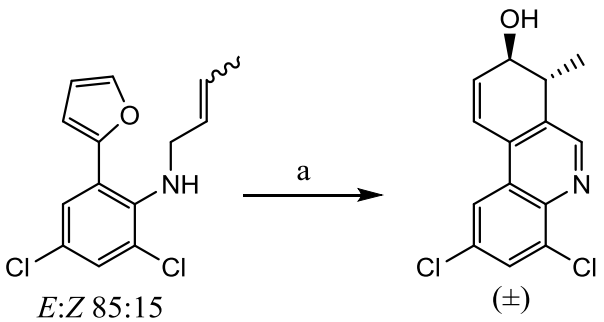
[a]by ^{1}H NMR of the crude product.
[b]Molecular sieves with 3 Å pore size.

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 dihydrophenanthridine **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,[110] 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).

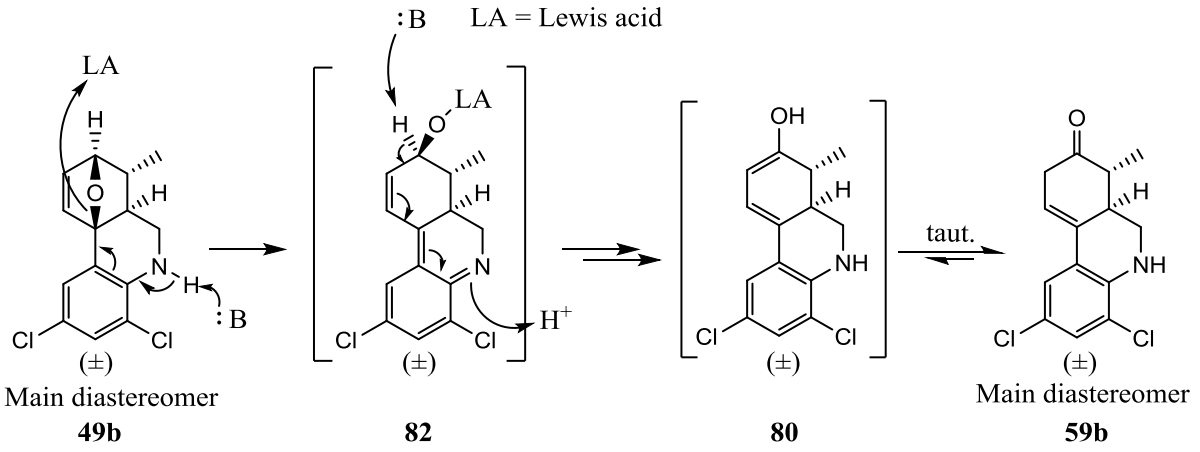
Alcohol **58b** was synthesized following the precautions described in entry 7, and isolated in decent yields. The compound was found to slightly decompose on silica, as judged by 2D-TLC analysis. The crude product was therefore purified using a very short column, which seemed to still result in decomposition,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



E:*Z* 85:15 **48b** (±) **58b**, 53%

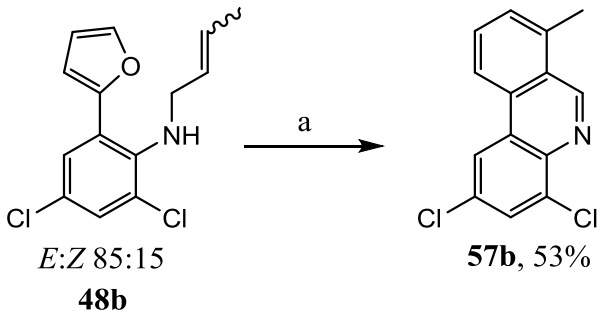
Scheme 2.25. Reagents and conditions: **a** – PhMe, 100 °C.

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,[73] 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**.

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.



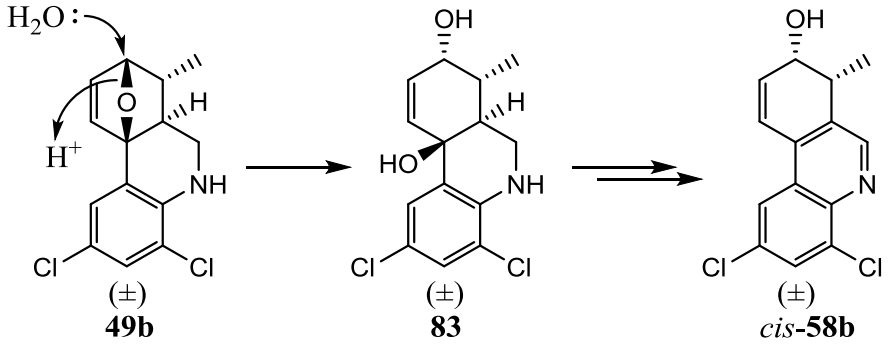
E:*Z* 85:15
48b

57b, 53%

Scheme 2.27. Reagents and conditions: **a** – $MgBr_2$, PhMe, 100 °C.

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 invertion 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**.

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.[113] None of the calculated coupling constants matched the observed value of 3.3 Hz (600 MHz, $CDCl_3$).

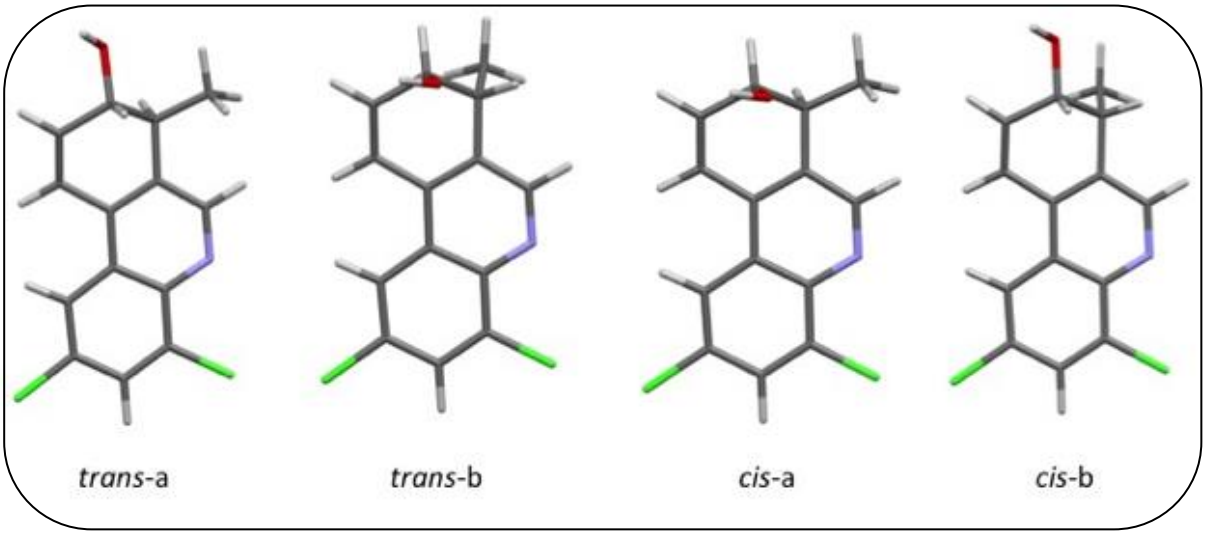


Figure 2.8. Optimized geometries (B3LYP/cc-pTVP) for the alcohol **58b**.

Table 2.5. Calculated dihedral angles between H-7 and H-8, and the corresponding calculated coupling constant.

	Position Me	**Position OH**	**Relative energies (kJ/mol)[a]**	**H7-H8 dihedral angle (°)[a]**	**calculated ^3J (Hz)[b]**
trans-a[c]	equatorial	equatorial	3.29	171.8	8.04
trans-b[c]	axial	axial	0.00	79.8	1.33
cis-a[c]	axial	equatorial	5.76	51.8	2.54
cis-b[c]	equatorial	axial	2.36	49.1	4.67

[a]Calculated using B3LYP/cc-pTVP.
[b]Calculated using http://www.stenutz.eu/conf/haasnoot.php.[113]
[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 $CDCl_3$.[114] Computational 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]

Position[a]	^{1}H NMR ($CDCl_3$)[b]				^{13}C NMR ($CDCl_3$)[b]			
	Calc. δ *cis* (*J*)	Calc. δ *trans* (*J*)	Exp. δ (*J*), minor isomer[c]	Exp. δ (*J*), major isomer	Calc. δ *cis*	Calc. δ *trans*	Exp. δ, minor isomer[c]	Exp. δ, major isomer
1	7.93 (1.8)	8.00 (1.8)	7.84 (2.1)	7.89 (2.1)	120.7	120.5	121.0	120.7
2	–	–	–	–	136.0	136.1	–[d]	132.2
3	7.69 (1.8)	7.69 (1.8)	7.70 (2.1)	7.73 (2.1)	128.1	128.0	129.6	129.5
4	–	–	–	–	140.4	140.4	–[d]	135.1
4a	–	–	–	–	141.3	141.1	142.8	142.4
6	8.66	8.69 (0.98)	8.77	8.78	149.3	150.4	150.5	151.6
6a	–	–	–	–	132.3	132.5	–[d]	132.0
7	3.26 (8.2, 7.5)	3.34 (7.9, 3.2, 0.98)	3.14 (-[d,e])	3.35 (7.4, 3.3)	37.8	38.9	36.4	38.6
8	4.79 (8.2, 3.5)	4.27 (3.2, 5.9)	4.62 (-[d])	4.27 (5.2, 3.3)	69.0	67.7	68.6	68.5
9	6.42 (11.4, 3.5)	6.50 (11.2, 3.2)	6.51 (9.9, 3.9)	6.60 (9.8, 5.2)	141.6	135.4	137.7	134.2
10	7.06 (11.4)	7.30 (11.2)	7.05 (9.9)	7.18 (9.8)	121.1	123.6	121.3	121.7
10a	–	–	–	–	134.4	132.8	–[d]	133.5
10b	–	–	–	–	123.7	124.0	125.6	125.7
CH_3	1.34 (7.5)	1.21 (7.9)	1.47 (7.2)	1.23 (7.4)	11.4	17.0	12.2	18.5

[a]For numbering, see Figure 2.9.

[b]Calculated and experimental δ 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.

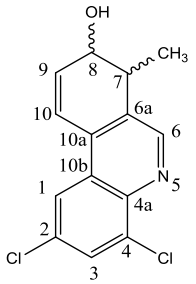


Figure 2.9. Numbering of compound **58b**.

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.

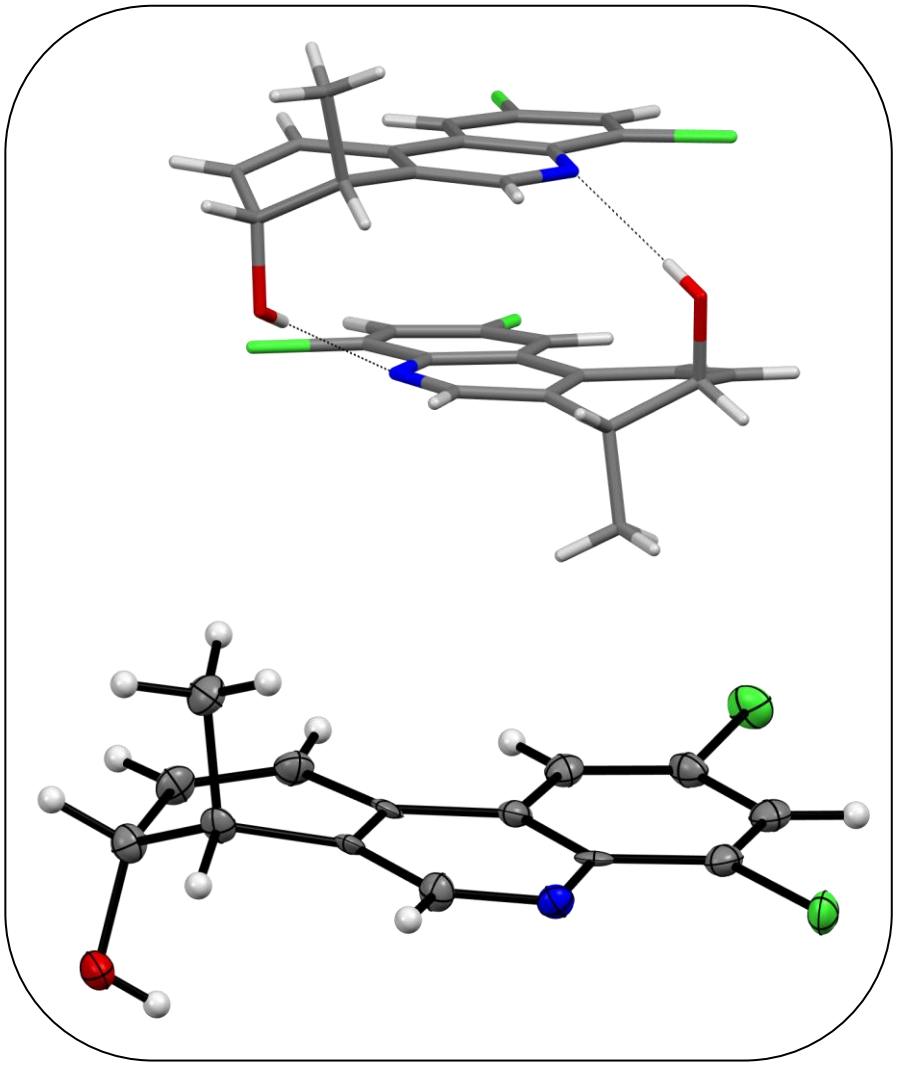
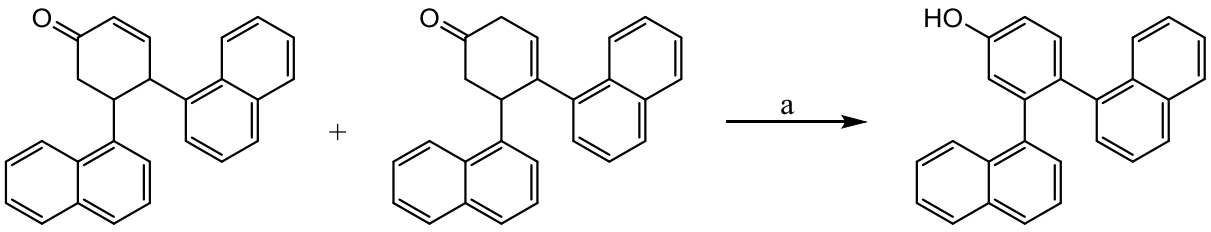


Figure 2.10. Results from X-ray crystallography of *trans* compound **58b**, showing the compound as a single molecule (bottom), and as hydrogen-bound dimers (top).

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

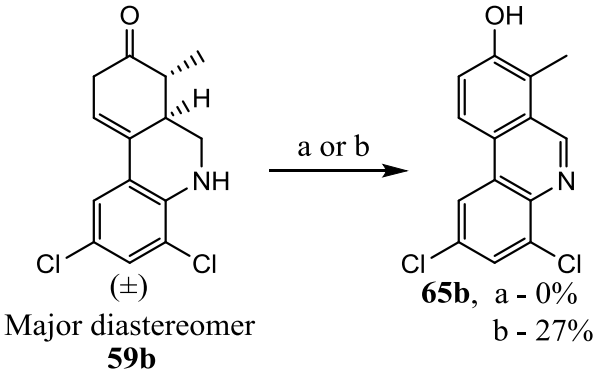
There are numerous examples of oxidations of β,γ-unsaturated ketones to yield phenols in the

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

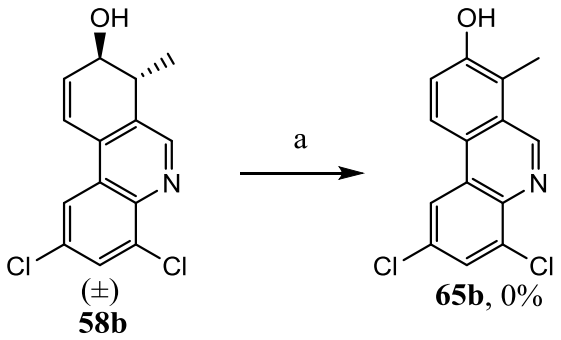
It was initially attempted to oxidize ketone **59b** to yield the phenol **65b** with a gentle oxidating method, namely irradiation of UV-light while bubbling air through, similarly to the oxidation of dihydrophenanthridines **56** in Section 2.2.4. This resulted in no conversion of the starting material.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



Scheme 2.30. Reagents and conditions: **a** – hv, air, MeCN. **b** – DDQ, CH_2Cl_2.

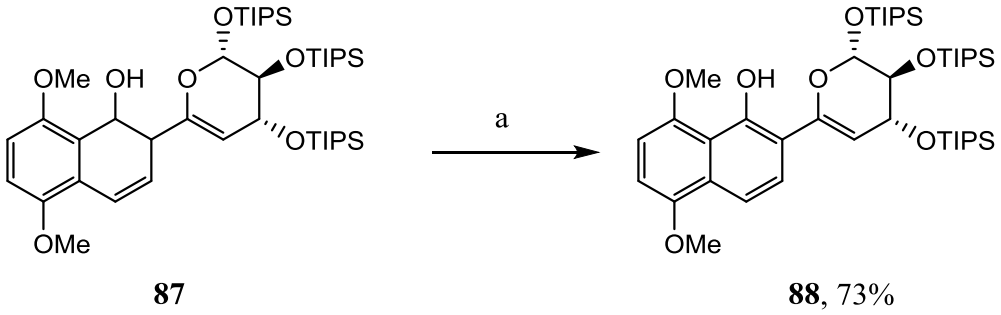
The oxidation (Scheme 2.30) was only tried once due to shortage of ketone starting material. Full conversion of starting material was achieved, and no other compounds were identified by TLC or ^{1}H NMR of the crude product, or during chromatography. The reason for the low isolated yield is therefore 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 decompositioned when treated with DDQ.



Scheme 2.31. Reagents and conditions: **a** – DDQ, CH_2Cl_2.

In the literature, compounds similar to alcohol **58b** have been oxidized to the respective phenols by DDQ (Scheme 2.32).[119]



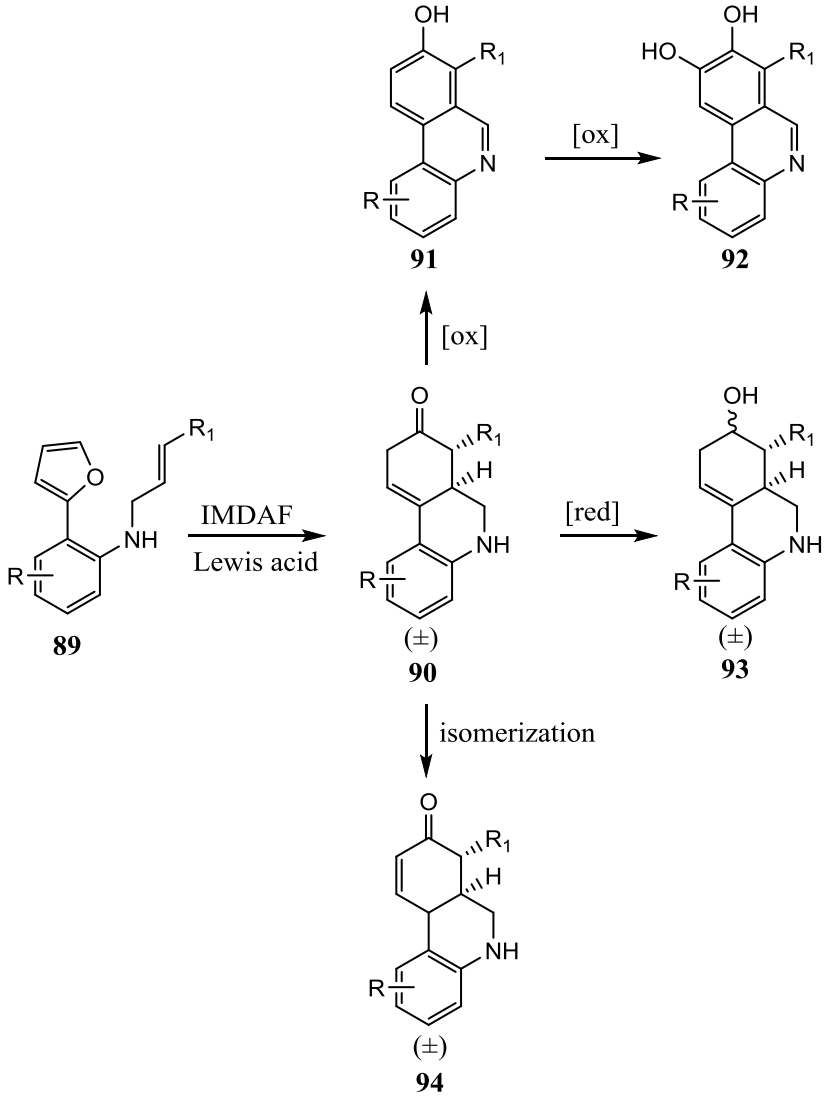
Scheme 2.32. Literature oxidation of a cyclohexadienol with DDQ.[119] Reagents and conditions: **a** – DDQ, dioxane.

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.

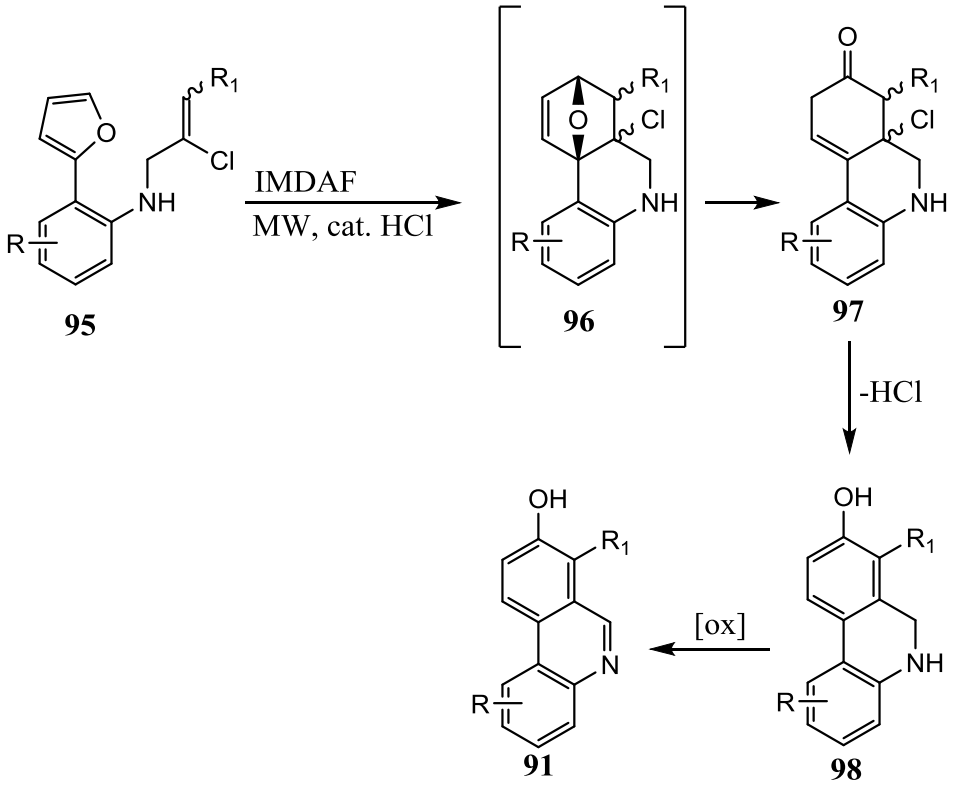
3. Future research

The work performed during this project have brought up multiple interesting reactions that deserves further investigation. The β,γ-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 α,β-unsatured 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.



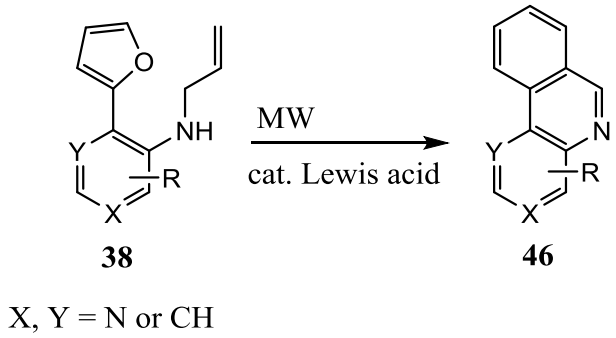
Scheme 3.1. Potential synthesis of ketone **90** from a general substrate **89**, and opportunities for further synthesis.

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,[82] since the bridgehead position is substituted.



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

IMDAF of substrate **48b** in the presence of $MgBr_2$ 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,[111] potentially allowing for more complex and delicate substrates, as often employed in synthesis of natural products.

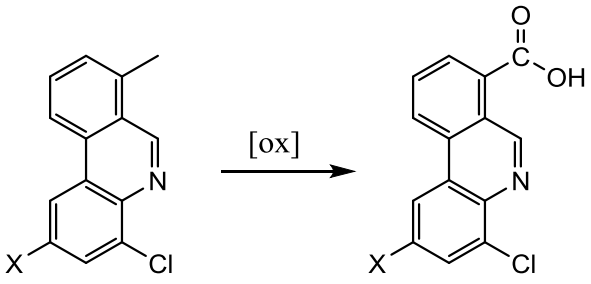


38 **46**

X, Y = N or CH

Scheme 3.3. Potential microwave-mediated one-pot synthesis of phenanthridines **46** from substrates **38**.

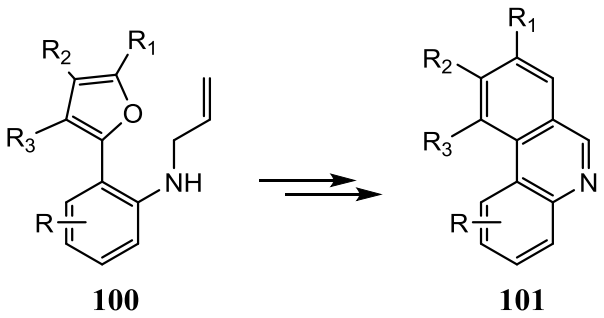
Oxidation of 7-methylphenenathridines **57** synthesised herein to the carboxylic acids **99** (Scheme 3.4) is a subject that may further expand the scope of substituents possible to introduce in the C-ring of the phenanthridine. This oxidation could be catalyzed by for instance vanadyl salts,[123,124]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



57a, X = NO_2 **99a**, X = NO_2
57b, X = Cl **99b**, X = Cl

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,[125] meaning milder cyclization conditions can be employed.



100 **101**

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 $MgBr_2$ 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.

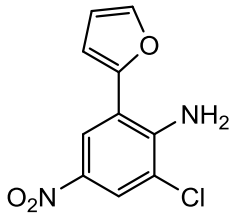
5. EXPERIMENTAL

^{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 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_2Cl_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 ^{o}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 by 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}C).[114] 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 of their two conformers.

Synthesis of 2-chloro-6-(furan-2-yl)-4-nitroaniline (51a)[1]



51a

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_2O 95:5 (v/v) (200 mL). The resulting mixture was degassed with N_2 and refluxed for 5 h. The reaction mixture was filtered through silica gel eluting with CH_2Cl_2 (200 mL), and concentrated under reduced pressure. The product was isolated by flash chromatography on silica gel eluting with EtOAc:CH_2Cl_2.hexanes (1:4:45). Yield 1.90 g (81%) as a yellow solid.

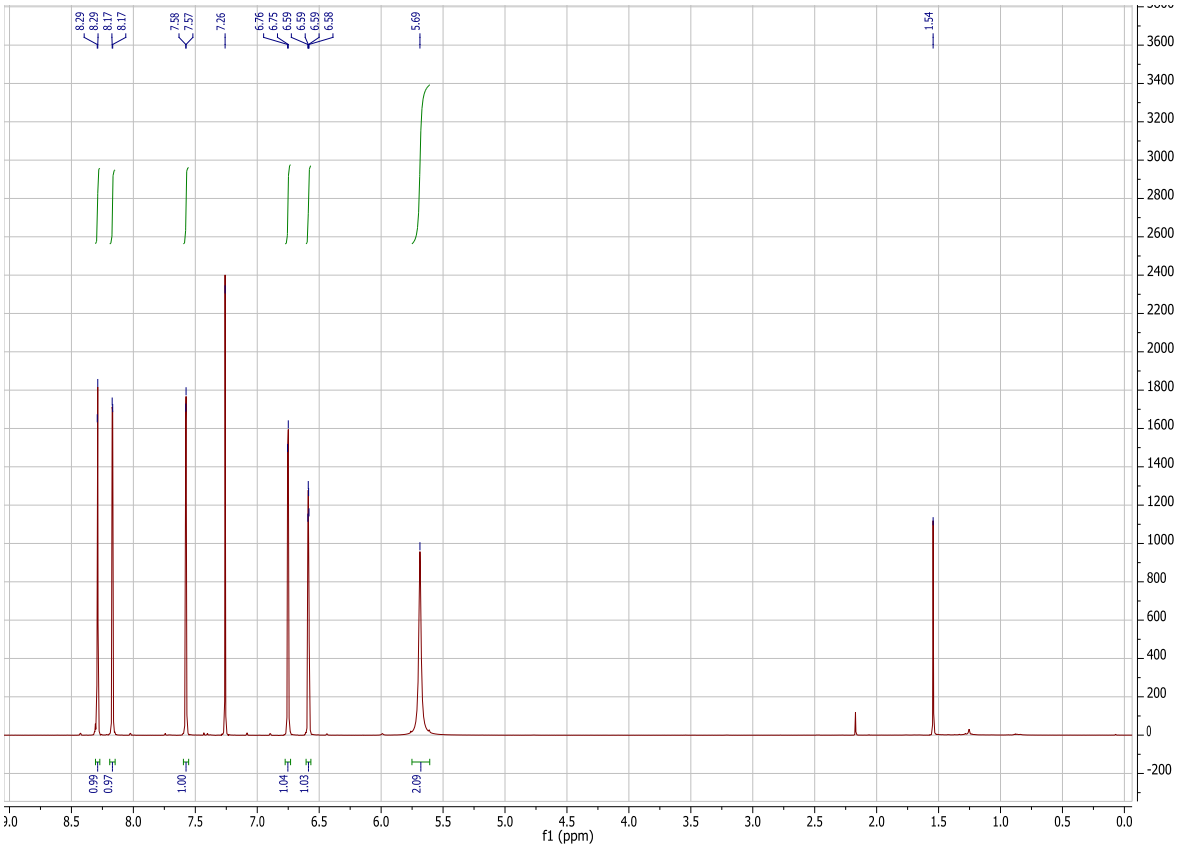
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.29 (d, *J* = 2.5 Hz, 1H, H-5), 8.17 (d, J = 2.5 Hz, 1H, H-3), 7.58-7.57 (m, 1H, H-5 in furyl), 6.75 (d, *J* = 3.4 Hz, 1H, H-3 in furyl), 6.59 (dd, *J* = 3.4, 1.8 Hz, 1H, H-4 in furyl), 5.69 (s, 2H, NH_2).

^{13}C NMR (150 MHz, $CDCl_3$) δ 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).

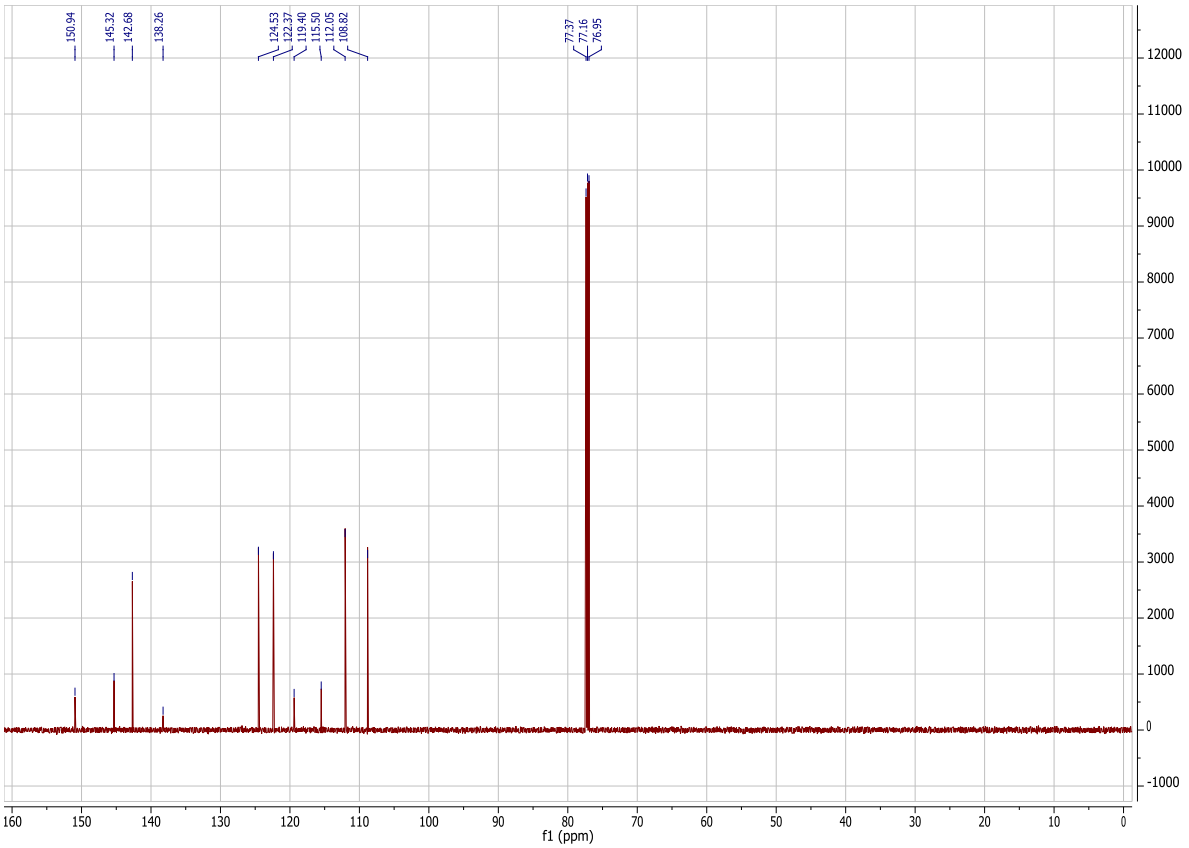
MS EI m/z (rel. %) 240/238 (34/100), 209 (11), 208 (9), 192 (13), 166 (7), 164 (21), 163 (10), 129 (8), 128 (17), 102 (11).

M.p. 180-181 °C (lit.[1] 180-182 °C)

Compound is known in the literature.[1]

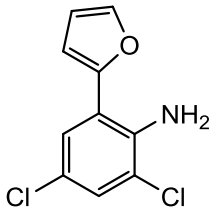


Spectrum 1. 600 MHz, $CDCl_3$, ^{1}H NMR spectrum of 2-chloro-6-(furan-2-yl)-4-nitroaniline (**51a**).



Spectrum 2. 150 MHz, $CDCl_3$, ^{13}C NMR of 2-chloro-6-(furan-2-yl)-4-nitroaniline (**51a**).

Synthesis of 2,4-dichloro-6-(furan-2-yl)aniline (51b)[2]



51b

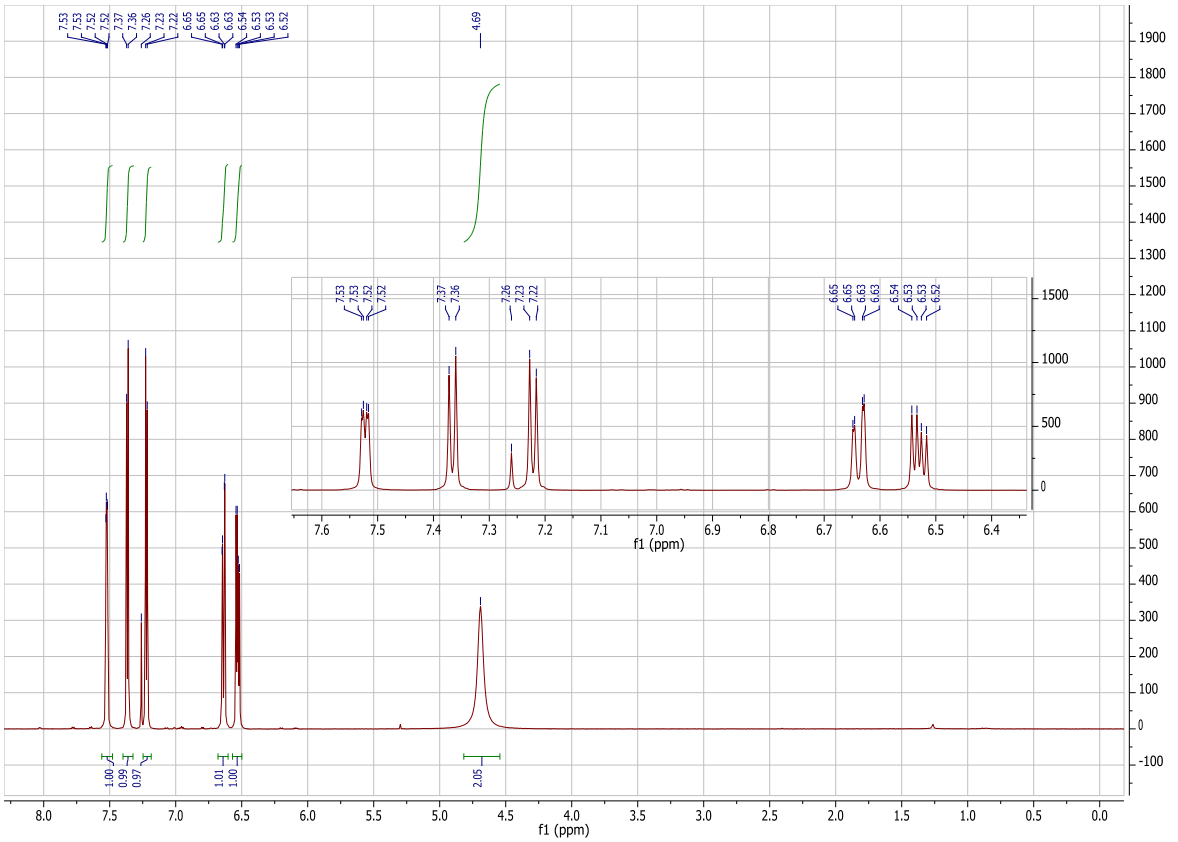
Potassium carbonate (2.50 g, 18.1 mmol), potassium (furan-2-yl)trifluoroborate (3.29 g, 18.9 mmol), triphenylphosphine (798 mg, 3.04 mmol) and palladium acetate (129 mg, 0.575 mmol) were subsequently added to a stirring solution of 2-bromo-4,6-dichloroaniline (**47b**) (3.29 g, 13.7 mmol) in EtOH/H_2O 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).

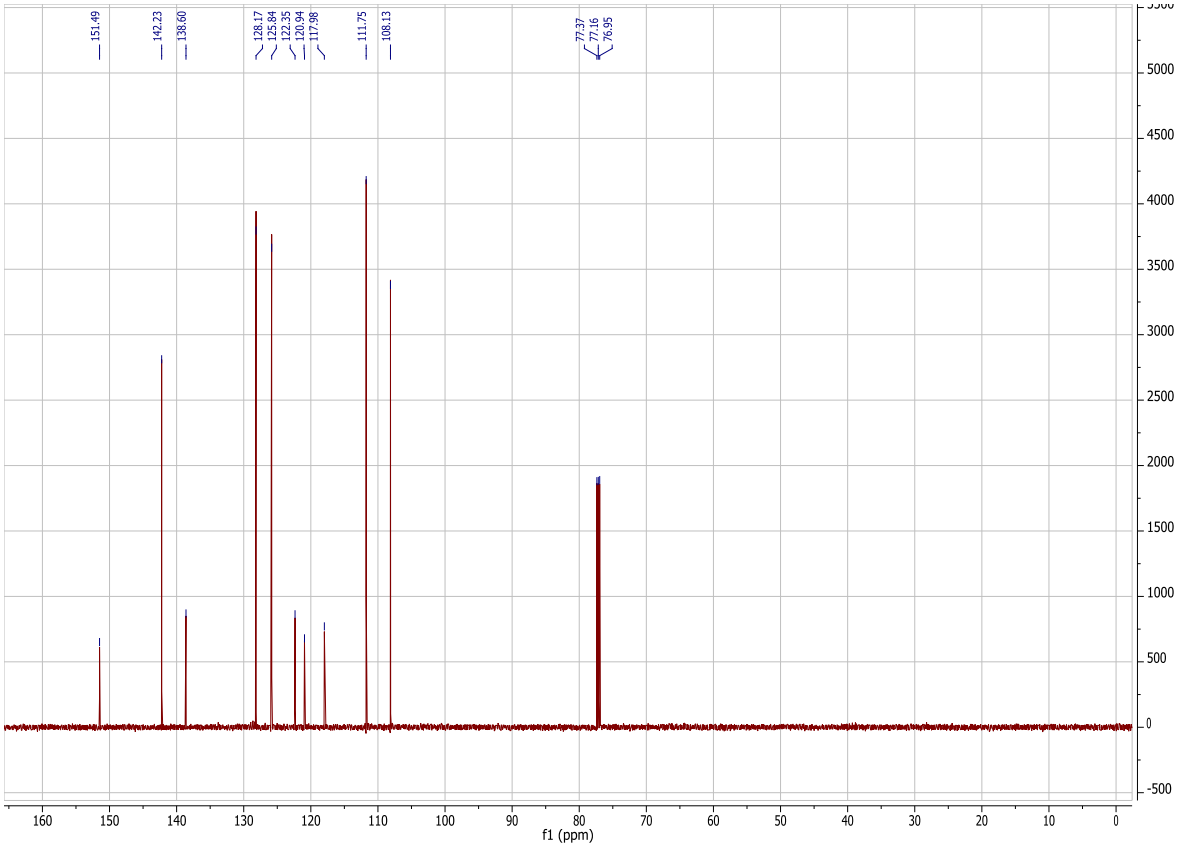
^{13}C NMR (150 MHz, $CDCl_3$) δ 151.49, 142.23, 138.60, 128.17, 125.84, 122.35, 120.94, 117.98, 111.75, 108.13, 77.37, 77.16, 76.95. ^{13}C NMR data in agreement with literature.[2]

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).

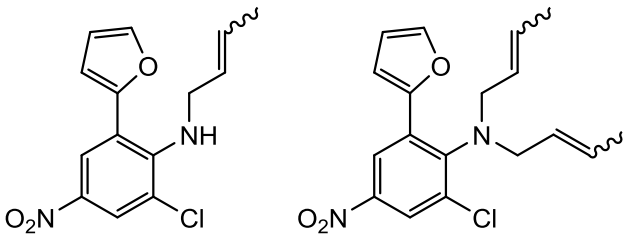


Spectrum 3. 200 MHz, $CDCl_3$, ^{1}H NMR of 2,4-dichloro-6-(furan-2-yl)aniline (**51b**).



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)



48a **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_2Cl_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}H NMR (600 MHz, $CDCl_3$) δ 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, =C*H*CH_3), 5.45-5.40 (m, 1H, CH_2C*H*=), 4.96 (br s, 1H, NH), 3.53-3.44 (m, 2H, CH_2), 1.66 (dq, *J* = 6.6, 1.4 Hz, 3H, CH_3).

^{13}C NMR (150 MHz, $CDCl_3$) δ 150.19 (C-2 in furyl) 148.25 (C-1), 142.52 (C-5 in furyl), 138.55 (C-4), 129.64 (=<u>C</u>HCH$_3$), 127.21 (CH_2<u>C</u>H=), 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).

MS EI m/z (rel. %) 294/292 (23/70, M^+), 277 (12), 251 (19), 236 (53), 55 (100).

HRMS calcd. for $C_{14}H_{13}ClN_2O_3$ 292.0615, found 292.0612.

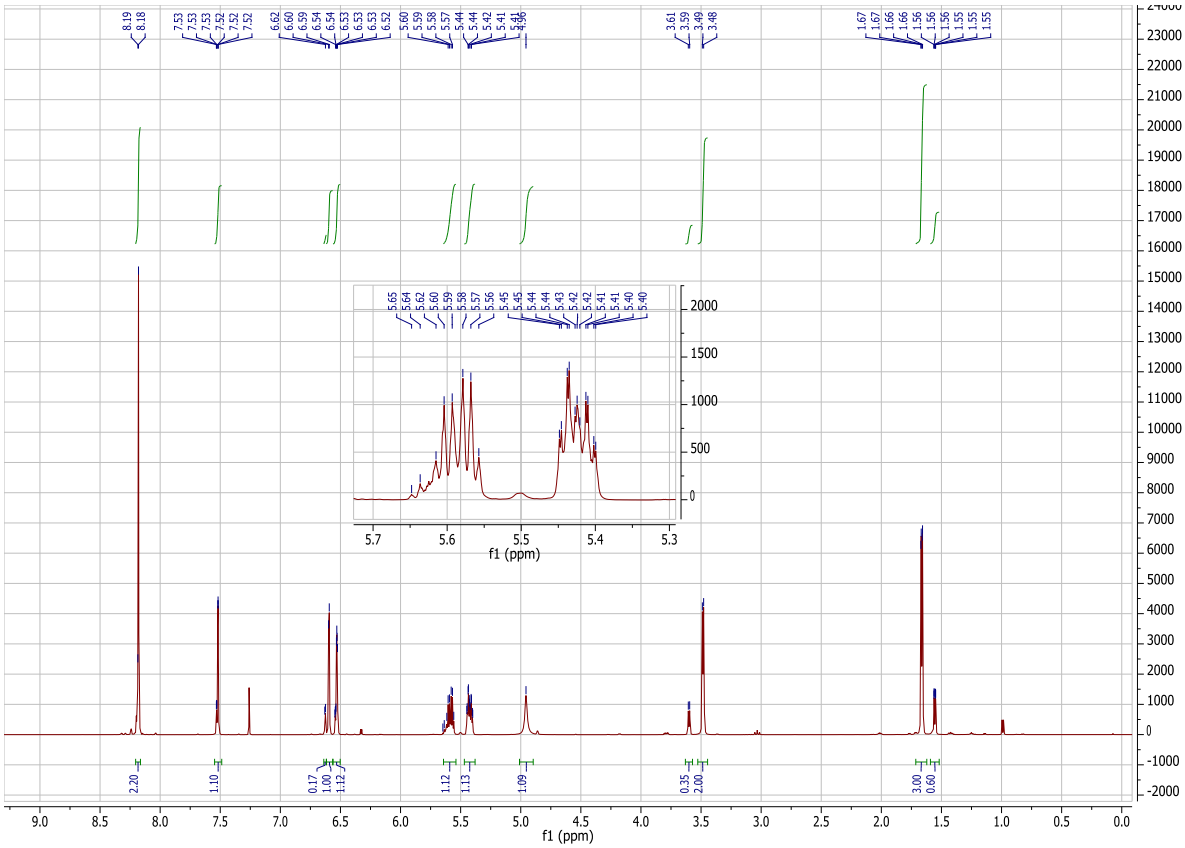
N,*N*-di(But-2-en-1-yl)-2-chloro-6-(furan-2-yl)-4-nitroaniline (**52a**)

^{1}H NMR (600 MHz, $CDCl_3$) δ 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 $CH_2C\underline{H}$= and 2x =$C\underline{H}CH_3$), 3.63 (d, *J* = 6.7 Hz, 4H, 2x NCH_2), 1.62 (dd, *J* = 6.3, 1.1 Hz, 6H, 2x CH_3).

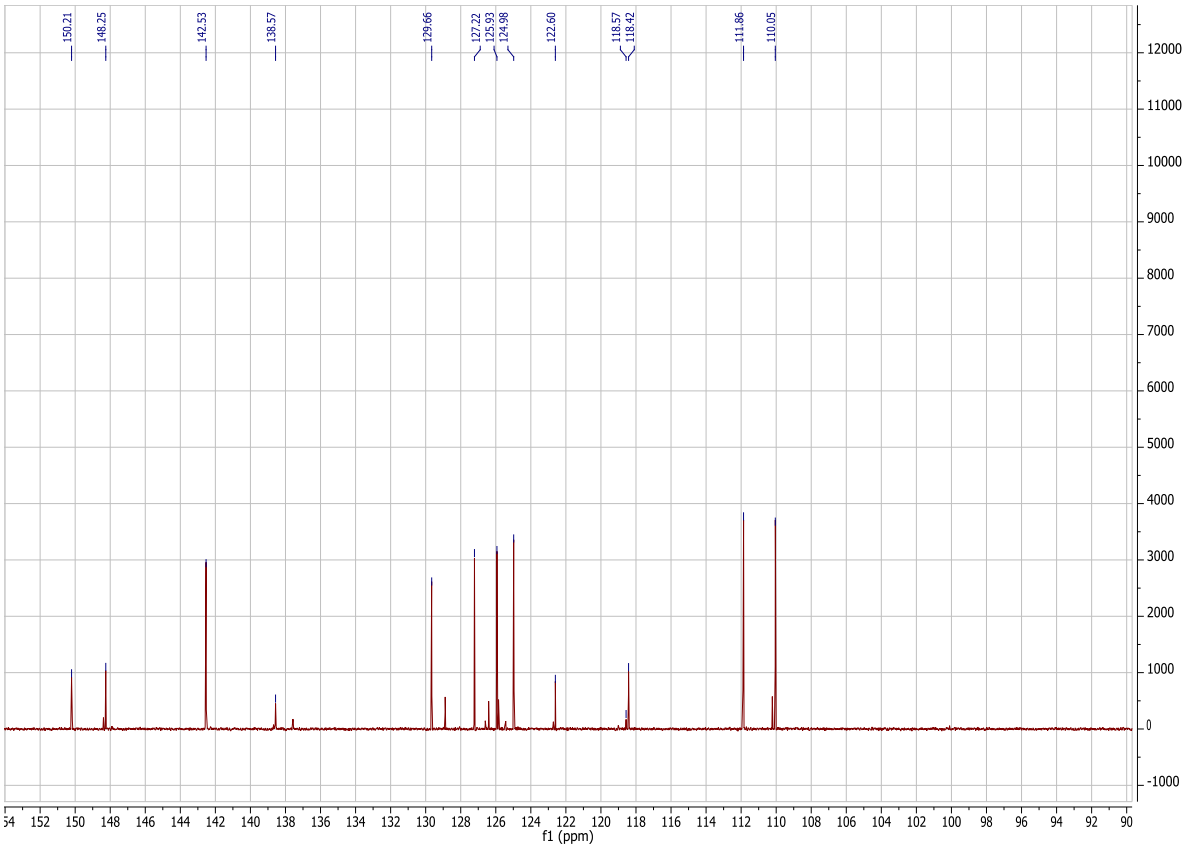
^{13}C NMR (150 MHz, $CDCl_3$) δ 150.06 (C-1 or C-2 in furyl), 149.92 (C-1 or C-2 in furyl), 144.06 (C-4), 142.76 (C-5 in furyl), 135.50 (C-2), 132.00 (C-6), 129.33 (=$\underline{C}HCH_3$), 127.59 ($CH_2\underline{C}H$=), 124.44 (C-3), 121.72 (C-5), 112.15 (C-4 in furyl), 111.04 (C-3 in furyl), 54.19 (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).

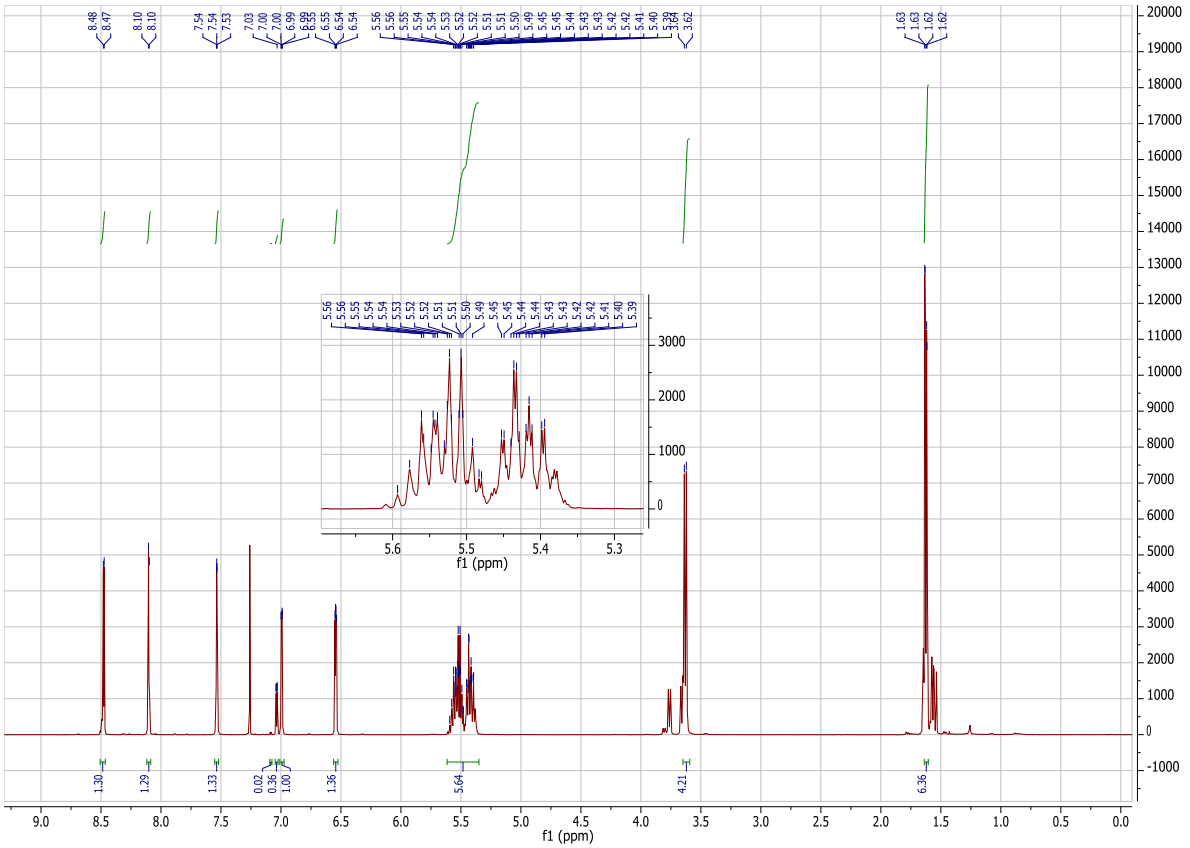
HRMS calcd. for $C_{18}H_{17}ClN_2O_3$ 346.1084, found 346.1079.



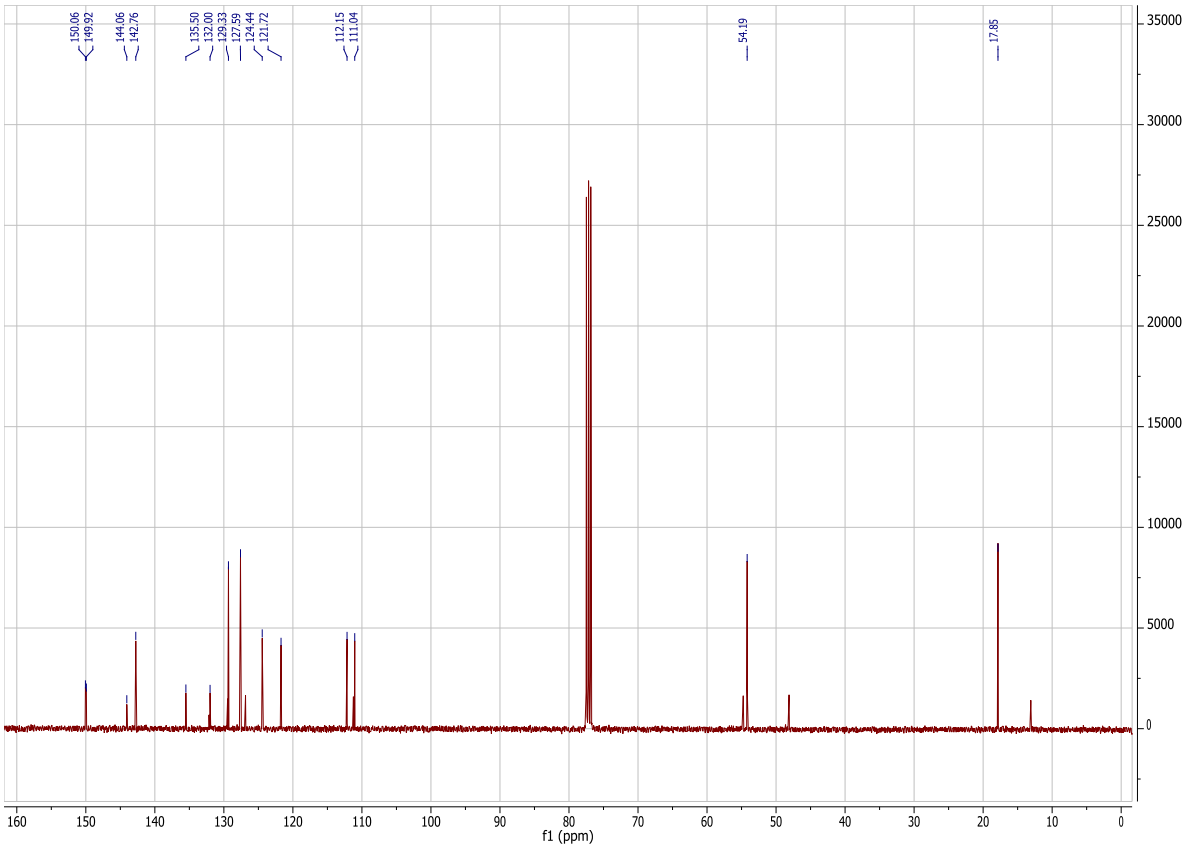
Spectrum 5. 600 MHz, $CDCl_3$, ^1H NMR of *N*-(but-2-en-1-yl)-2-chloro-6-(furan-2-yl)-4-nitroaniline (**48a**).



Spectrum 6. 150 MHz, $CDCl_3$, ^1H NMR of *N*-(but-2-en-1-yl)-2-chloro-6-(furan-2-yl)-4-nitroaniline (**48a**).

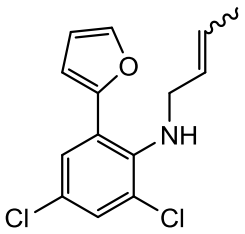


Spectrum 7. 600 MHz, $CDCl_3$, ^1H NMR of *N*,*N*-di(but-2-en-1-yl)-2-chloro-6-(furan-2-yl)-4-nitroaniline (**52a**).



Spectrum 8. 150 MHz, $CDCl_3$, ^{13}C 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)



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 (3×75 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_2Cl_2 in hexanes. Yield 1.22 g (91%) as a colorless oil, mixture of *E/Z* isomers (ratio 85:15).

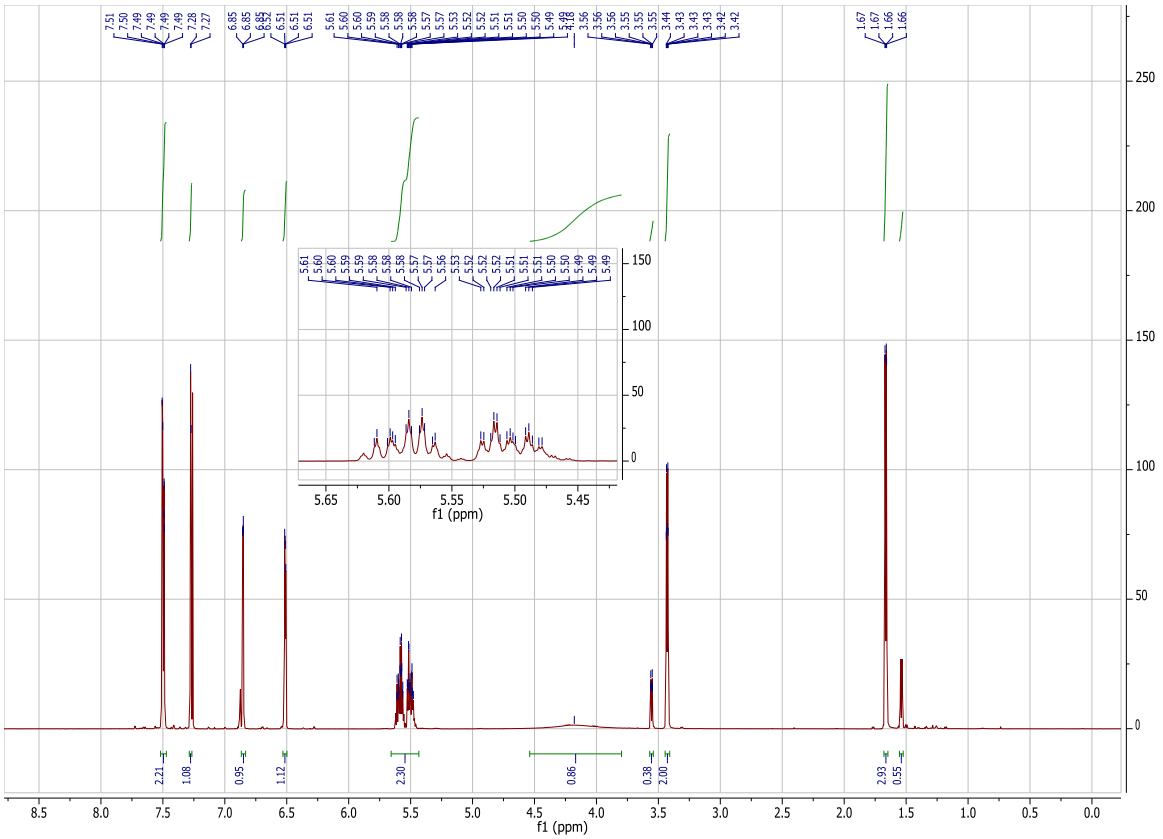
NMR data is reported for the major isomer.

^{1}H NMR (400 MHz, $CDCl_3$) δ 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).

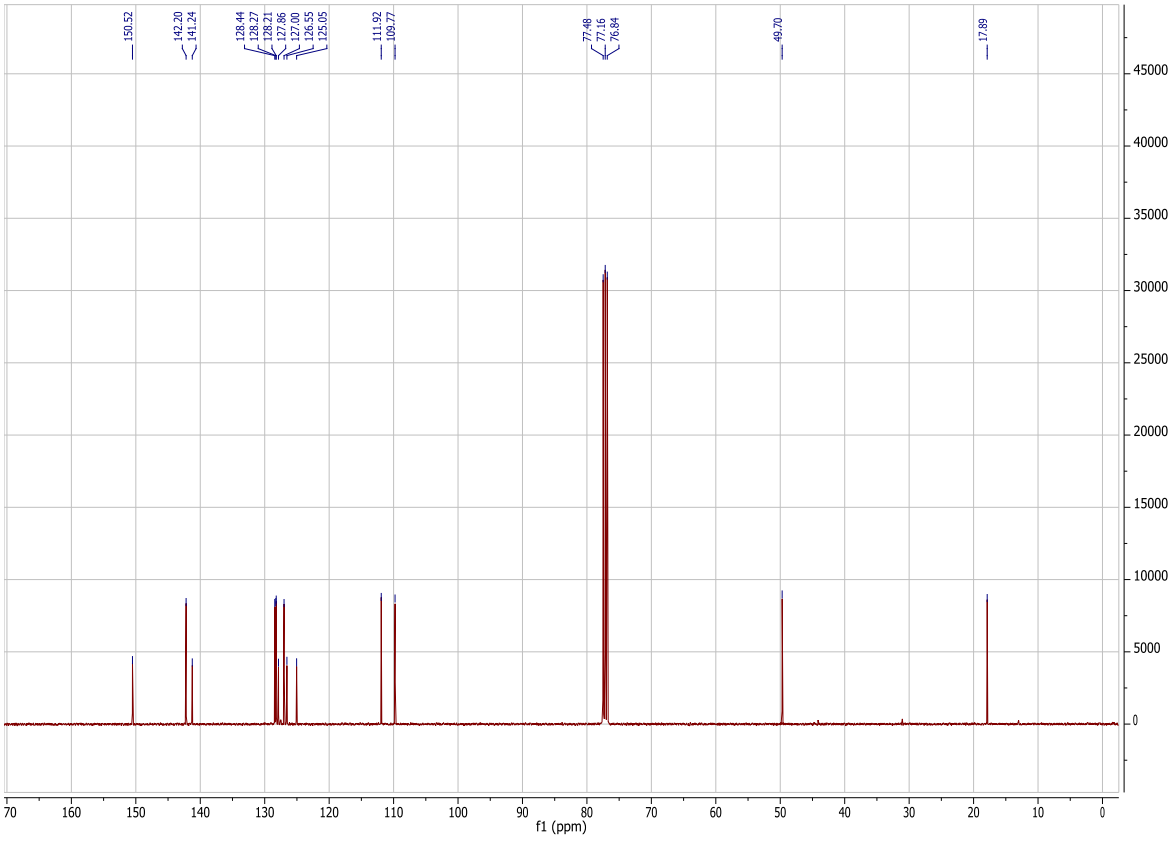
^{13}C NMR (100 MHz, $CDCl_3$) δ 150.52 (C-2 in furyl), 142.20 (C-5 in furyl), 141.24 (C-1), 128.44 (CH=), 128.27 (CH=), 128.21 (C-3), 127.86 (C-2 or C-4), 127.00 (C-5), 126.55 (C-2 or C-4), 125.05 (C-6), 111.92 (C-4 in furyl), 109.77 (C-3 in furyl), 49.70 (CH_2), 17.89 (CH_3).

MS EI m/z (rel. %) MS 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 $C_{14}H_{13}Cl_2NO$ 281.0374, found 281.0381.

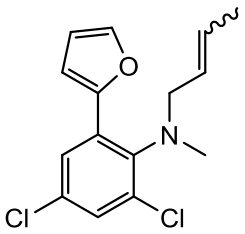


Spectrum 9. 600 MHz, $CDCl_3$, ^{1}H NMR of *N*-(but-2-en-1-yl)-2,4-dichloro-6-(furan-2-yl)aniline (**48b**).



Spectrum 10. 150 MHz, $CDCl_3$, ^{13}C 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)



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 CH_2Cl_2 (2×25 mL). The combined organic phases were dried ($MgSO_4$) 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).

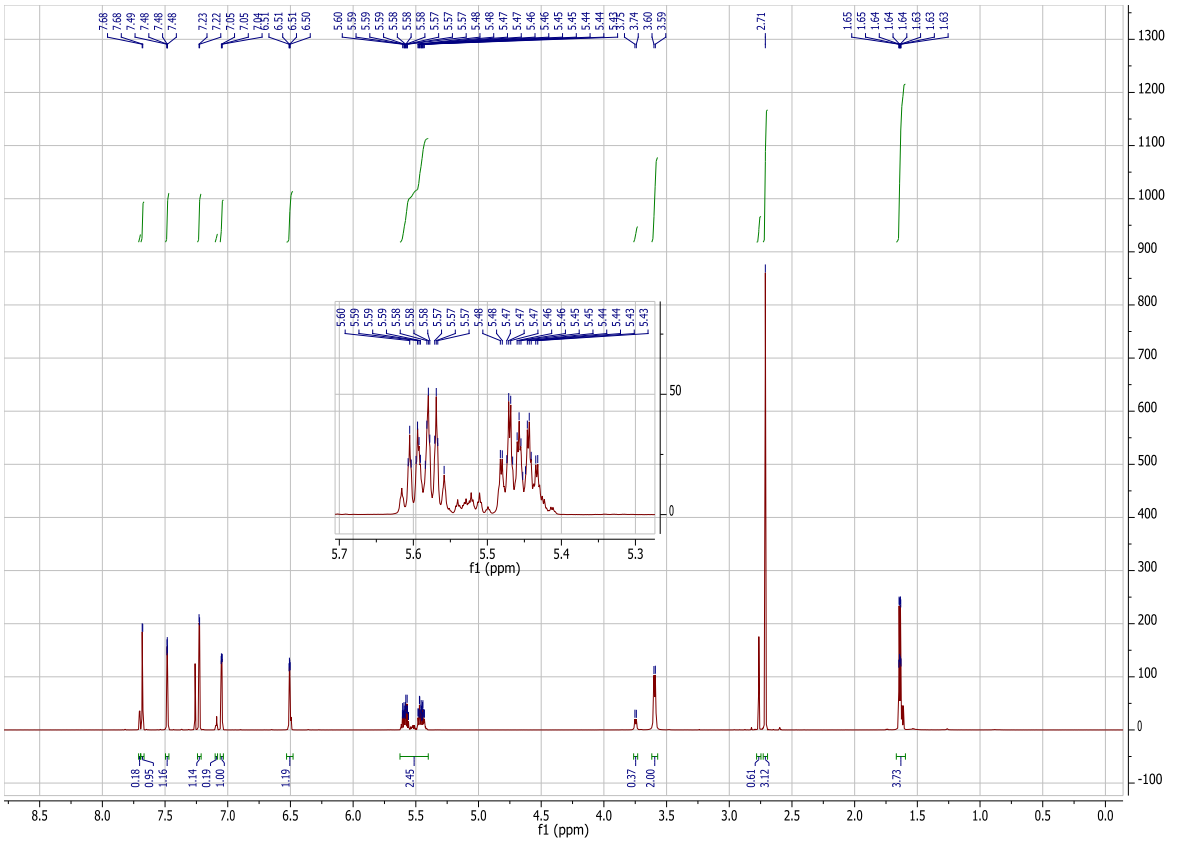
NMR data is reported for the major isomer.

^{1}H NMR (600 MHz, $CDCl_3$) 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, NCH_2), 2.71 (s, 3H, NCH_3), 1.64 (dq, *J* = 6.4, 1.2 Hz, 3H, CH_3).

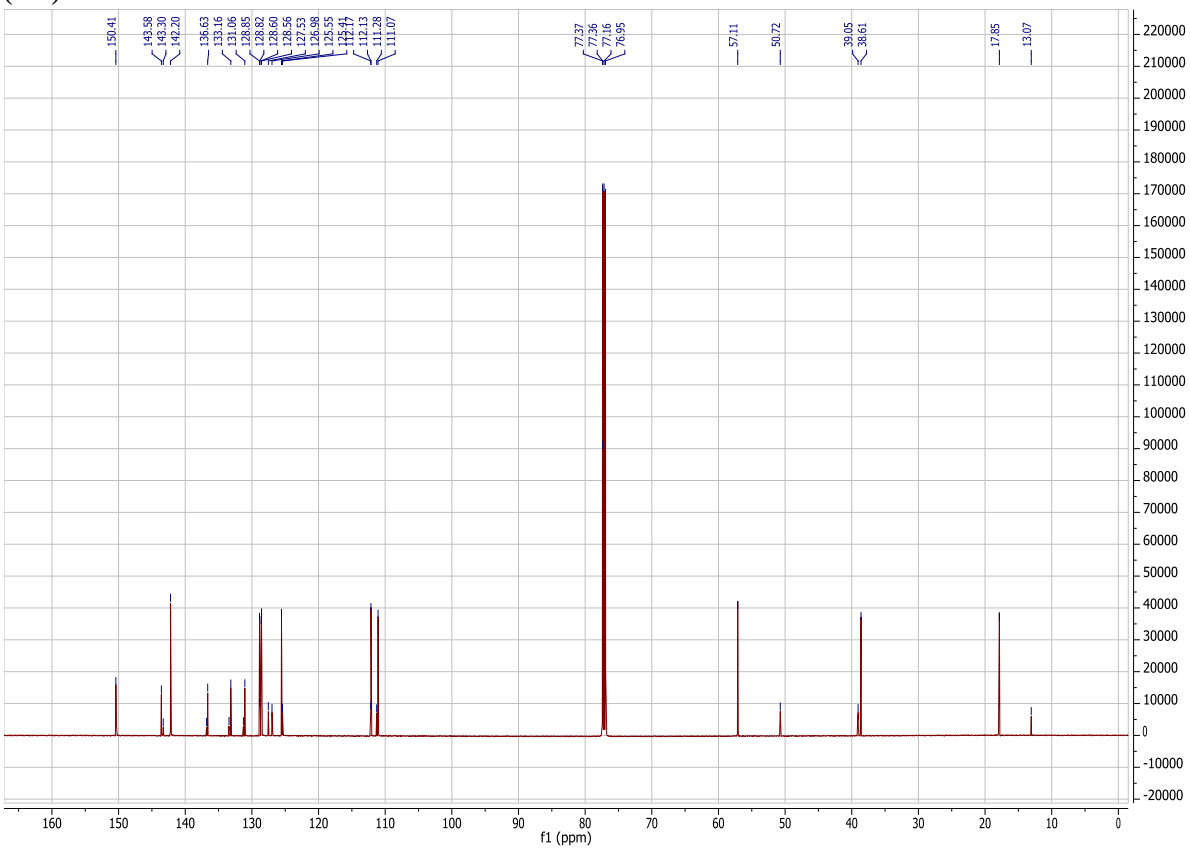
^{13}C NMR (150 MHz, $CDCl_3$) δ 150.41 (C-2 in furyl), 143.58 (C-1), 142.20 (C-5 in furyl), 136.63 (C-2), 133.16 (C-4), 131.06 (C-6), 128.85 (C-3), 128.60 (CH=), 128.56 (CH=), 125.55 (C-5), 112.13 (C-4 in furyl), 111.07 (C-3 in furyl), 57.11 (NCH_2), 38.61 (NCH_3), 17.85 (CH_3).

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 $C_{15}H_{15}Cl_2NO$ 295.0531, found 295.0527.

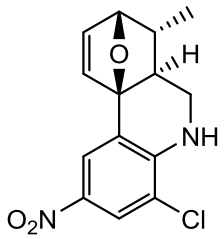


Spectrum 11. 600 MHz, $CDCl_3$,^{1}H NMR of *N*-(but-2-en-1-yl)-2,4-dichloro-6-(furan-2-yl)-N-methylaniline (**48c**).



Spectrum 12. 150 MHz, $CDCl_3$, ^{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)



(±)

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.

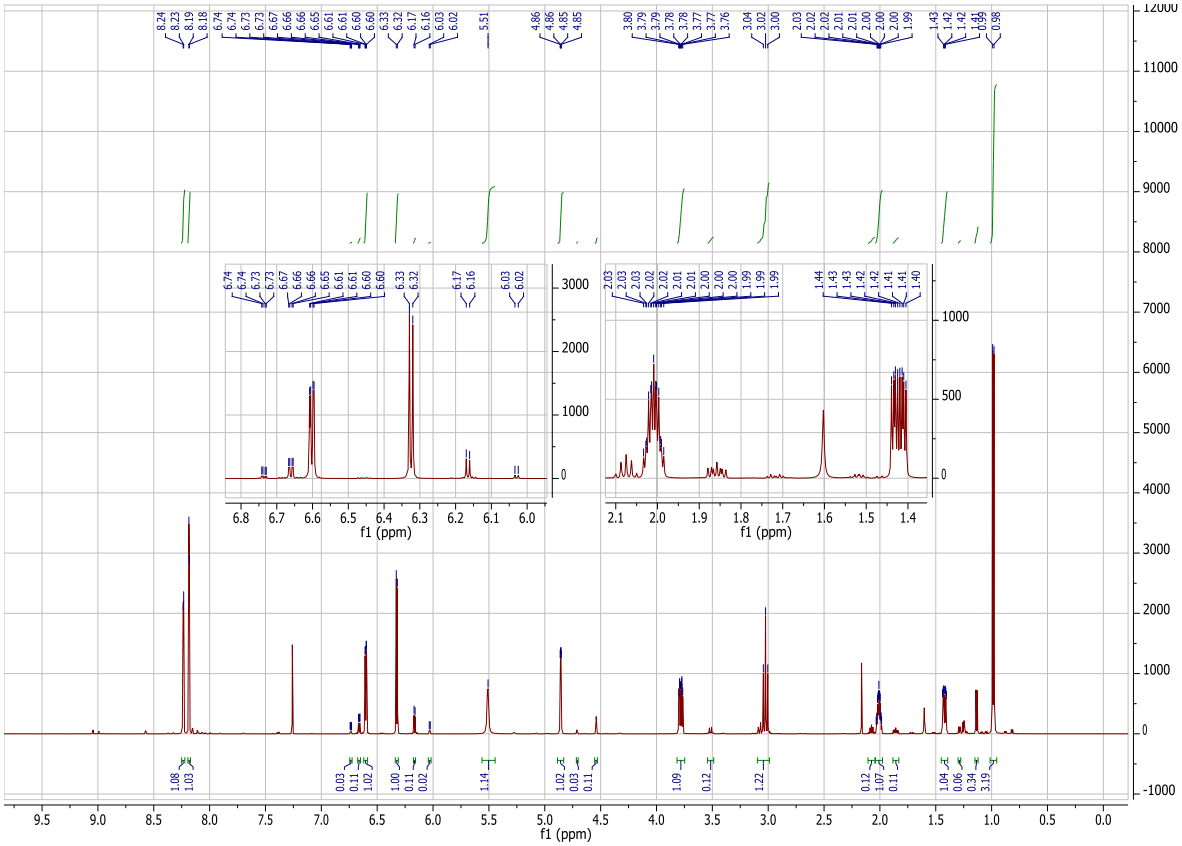
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.23 (d, *J* = 2.5 Hz, 1H, H-1), 8.18 (d, *J* = 2.5 Hz, 1H, H-3), 6.60 (dd, *J* = 5.7, 1.7 Hz, 1H, H-9), 6.32 (d, *J* = 5.7 Hz, 1H, H-10), 5.51 (s, 1H, NH), 4.86 (dd, *J* = 4.5, 1.7 Hz, 1H, H-8), 3.78 (ddd, *J* = 11.9, 5.5, 4.5 Hz, 1H, H_a in H-6), 3.06-3.01 (m, H_b in 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, $CDCl_3$) δ 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).

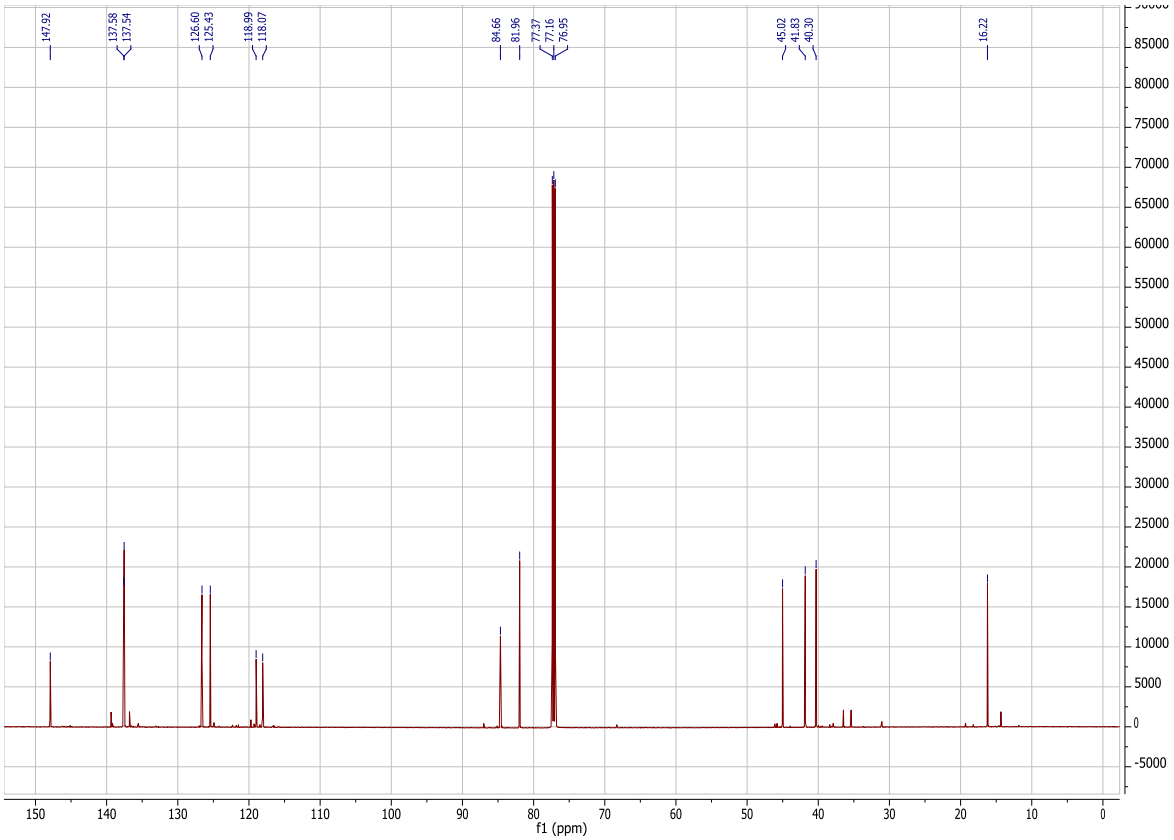
MS EI m/z (rel. %) 294/292 (32/100), 291 (16), 276 (15), 175 (38), 174 (36), 173 (53), 263 (23), 251 (15), 249 (29), 236 (56), 235 (32), 227 (25), 217 (16), 209 (23).

HRMS HRMS (EI) calcd for $C_{14}H_{13}ClN_2O_3$ 292.0615, found 292.0616.

M.p. 141-145 °C.

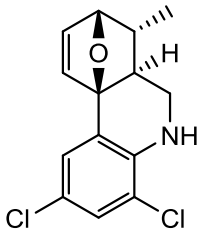


Spectrum 13. 600 MHz, $CDCl_3$, ^1H NMR of (±)-(*6aS,7R,8R,10aS*)-4-chloro-7-methyl-2-nitro-6,6a,7,8-tetrahydro-*5H*-8,10a-epoxyphenanthridine (**49a**).



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)



(±)

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:CH_2Cl_2:hexanes 1:1:18. Yield 13 mg (11%) as a white solid.

All NMR experiments except ^{1}H 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.

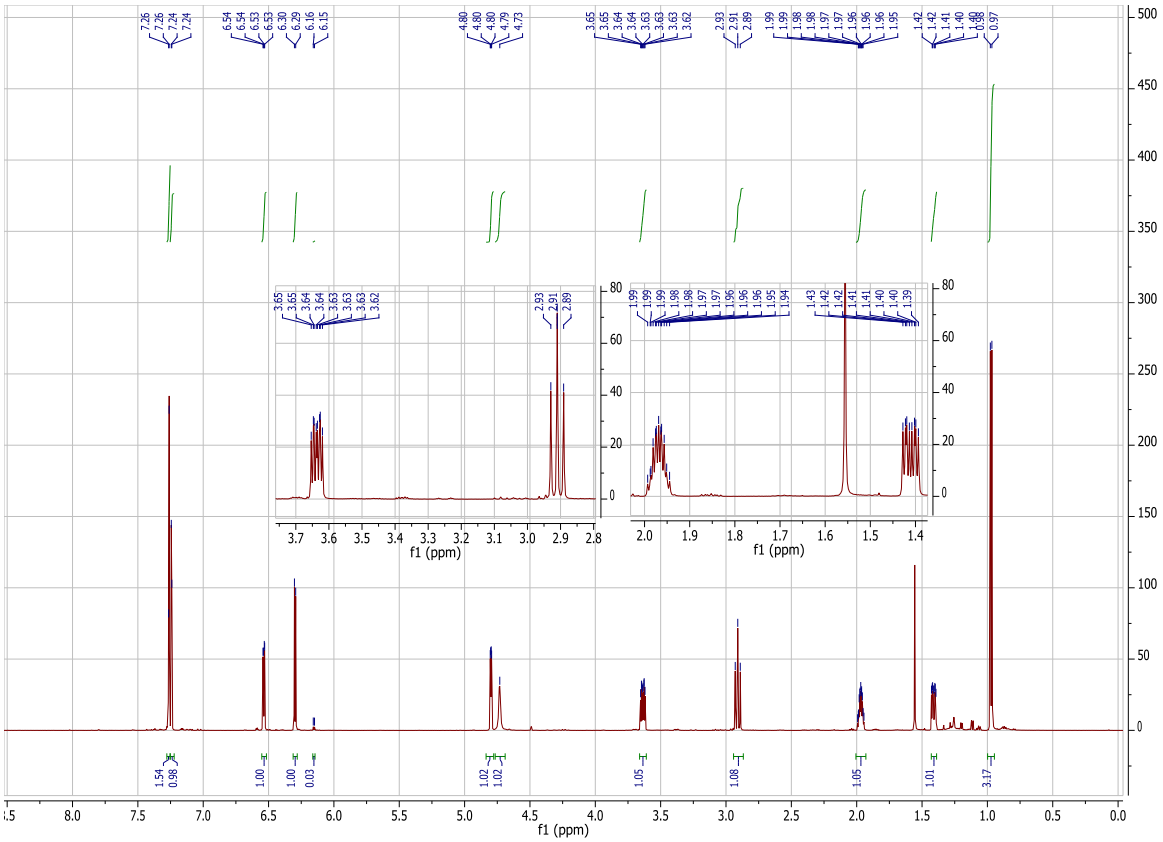
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27-7.25 (m, 1H, H-1 or H-3), 7.24 (d, *J* = 2.3 Hz, 1H, H-1 or H-3), 6.53 (dd, *J* = 5.7, 1.2 Hz, 1H, H-9), 6.30 (d, *J* = 5.7 Hz, 1H, H-10), 4.80 (dd, *J* = 4.4, 1.2 Hz, 1H, H-8), 4.74 (s, 1H, NH), 3.66-3.61 (m, 1H, H-α in H-6), 2.91 (app t, *J* = 11.6 Hz, 1H, H-β in 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, CH_3).

^{13}C NMR (150 MHz, $CDCl_3$) 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 (CH_3).

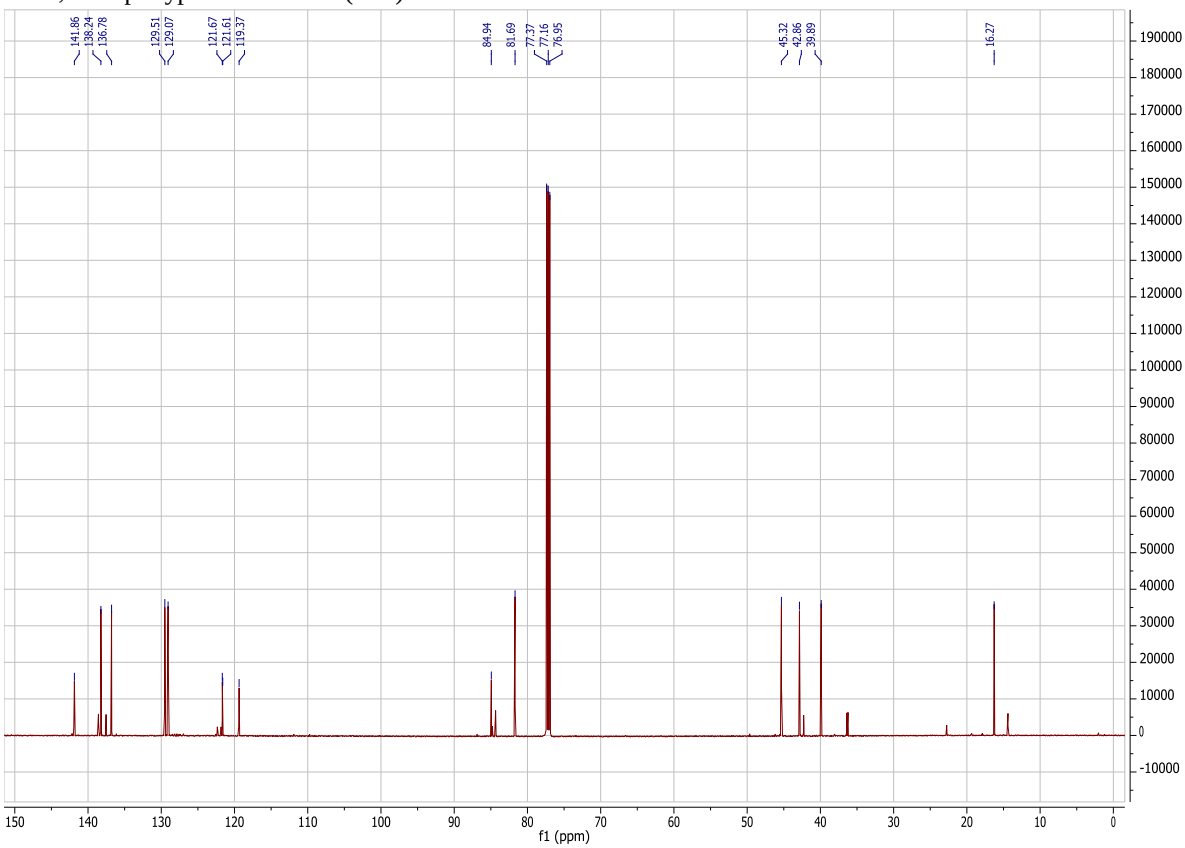
MS EI m/z (rel. %) n.d.

HRMS n.d.

M.p. n.d.

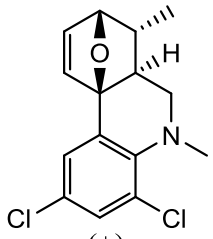


Spectrum 15. 600 MHz, $CDCl_3$, ^1H NMR of (±)-(*6aS,7R,8R,10aS*)-2,4-dichloro-7-methyl-6,6a,7,8-tetrahydro-*5H*-8,10a-epoxyphenanthridine (**49b**).



Spectrum 16. 150 MHz, $CDCl_3$, ^{13}C 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-epoxyphenanthridine (49c)



(±)

49c

A solution of compound **48c** (157 mg, 0.530 mmol) in dry xylenes (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.

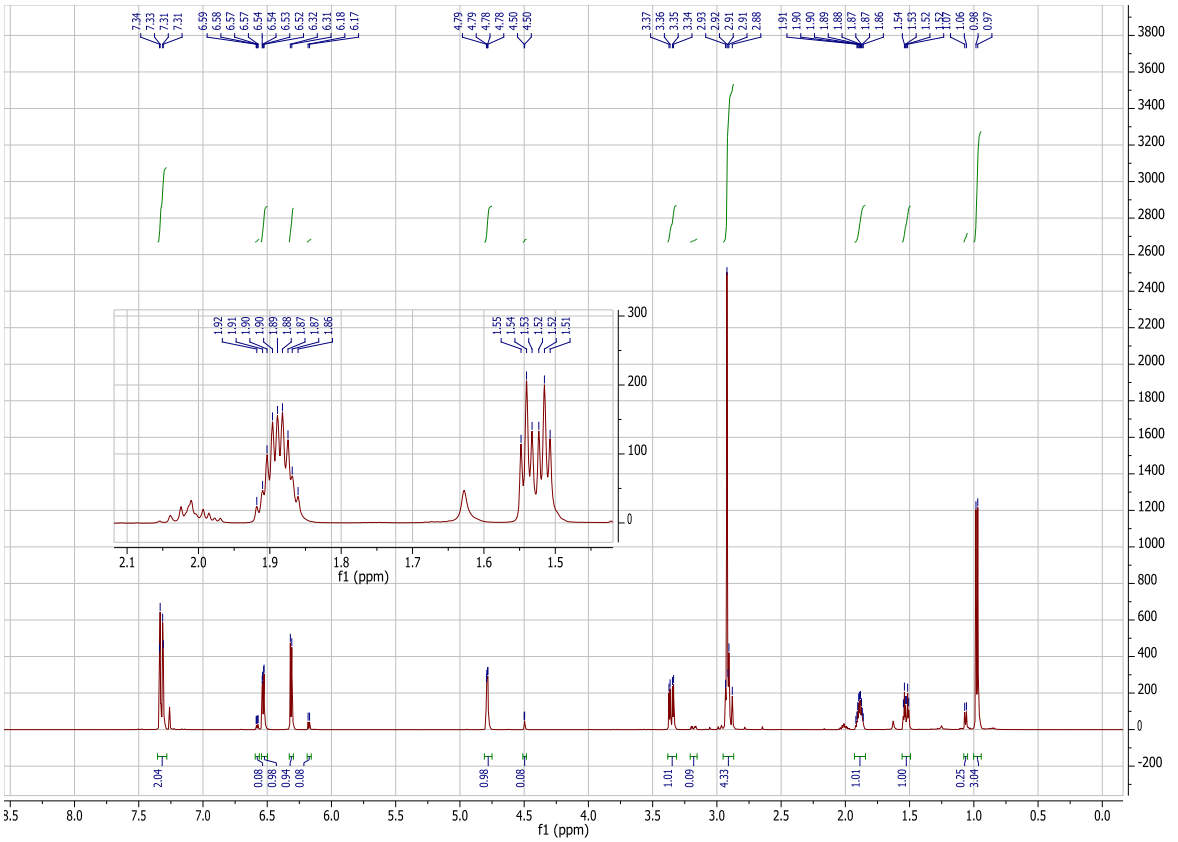
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, *J* = 2.5 Hz, 1H, H-1), 7.31 (d, *J* = 2.5 Hz, 1H, H-3), 6.53 (dd, *J* = 5.7, 1.4 Hz, 1H, H-9), 6.31 (d, *J* = 5.7 Hz, 1H, H-10), 4.79 (dd, *J* = 4.4, 1.4 Hz, 1H, H-8), 3.35 (dd, *J* = 13.6, 4.3 Hz, 1H, H_a in H-6), 2.95-2.87 (m, 4H, NCH_3 and H_b in H-6), 2.92-1.86 (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).

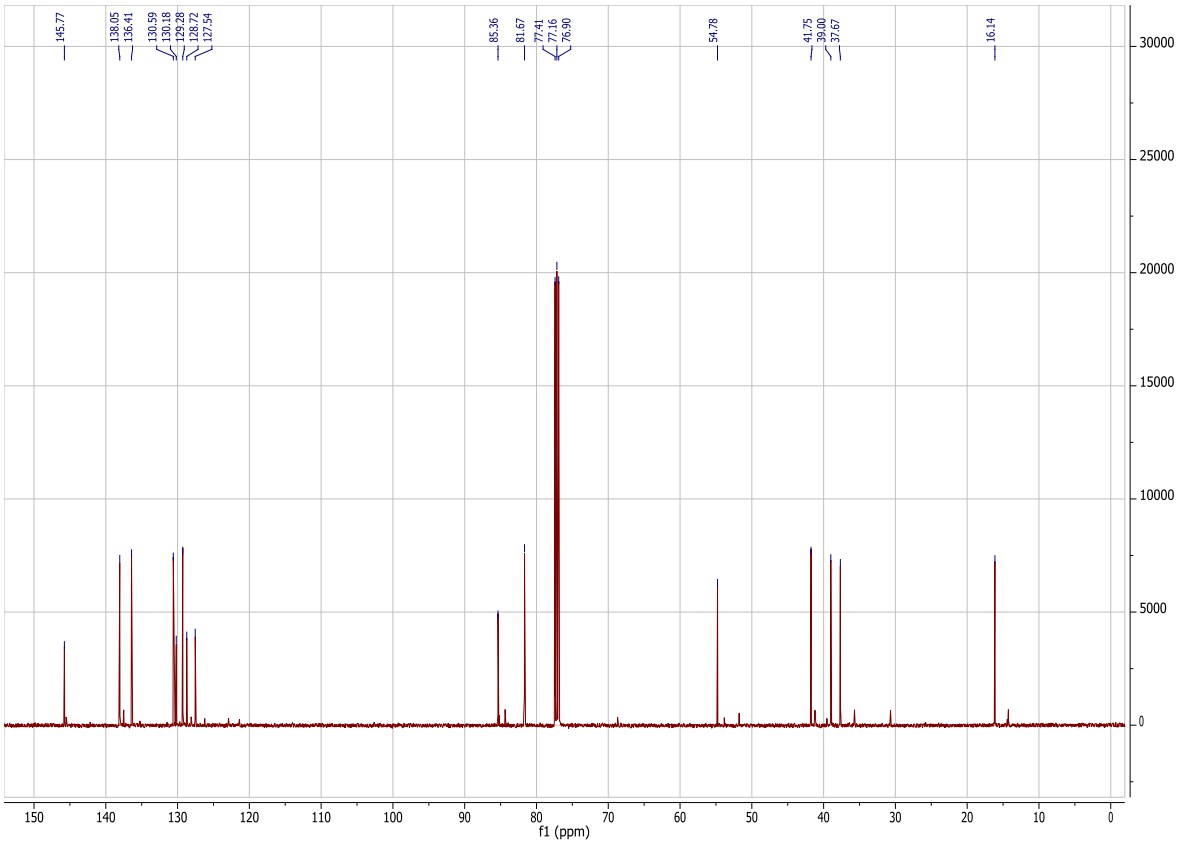
MS EI m/z (rel. %) 299/297/295 (11/63/100, M^+), 280 (23), 278 (44), 276 (47), 262 (27), 252 (43), 240 (30), 239 (33), 238 (37), 225 (22), 212 (24), 202 (12).

HRMS calcd for $C_{15}H_{15}Cl_2NO$ 295.0531, found 295.0535.

M.p. 114-116 ^{o}C.

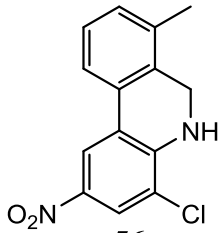


Spectrum 17. 500 MHz, $CDCl_3$, ^1H NMR of (±)-(*6aS,7R,8R,10aS*)-2,4-dichloro-5,7-dimethyl-6,6a,7,8-tetrahydro-8,10a-epoxyphenanthridine (**49c**).



Spectrum 18. 125 MHz, $CDCl_3$, ^{13}C NMR of (±)-(*6aS,7R,8R,10aS*)-2,4-dichloro-5,7-dimethyl-6,6a,7,8-tetrahydro-8,10a-epoxyphenanthridine (**49c**).

Synthesis of 4-chloro-7-methyl-2-nitro-5,6-dihydrophenanthridine (56a)



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 $NaHCO_3$ (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 CH_2Cl_2-EtOAc-hexanes (1:1:8 to 1:1:3). Calc. yield 63 mg (85%) as an orange solid.

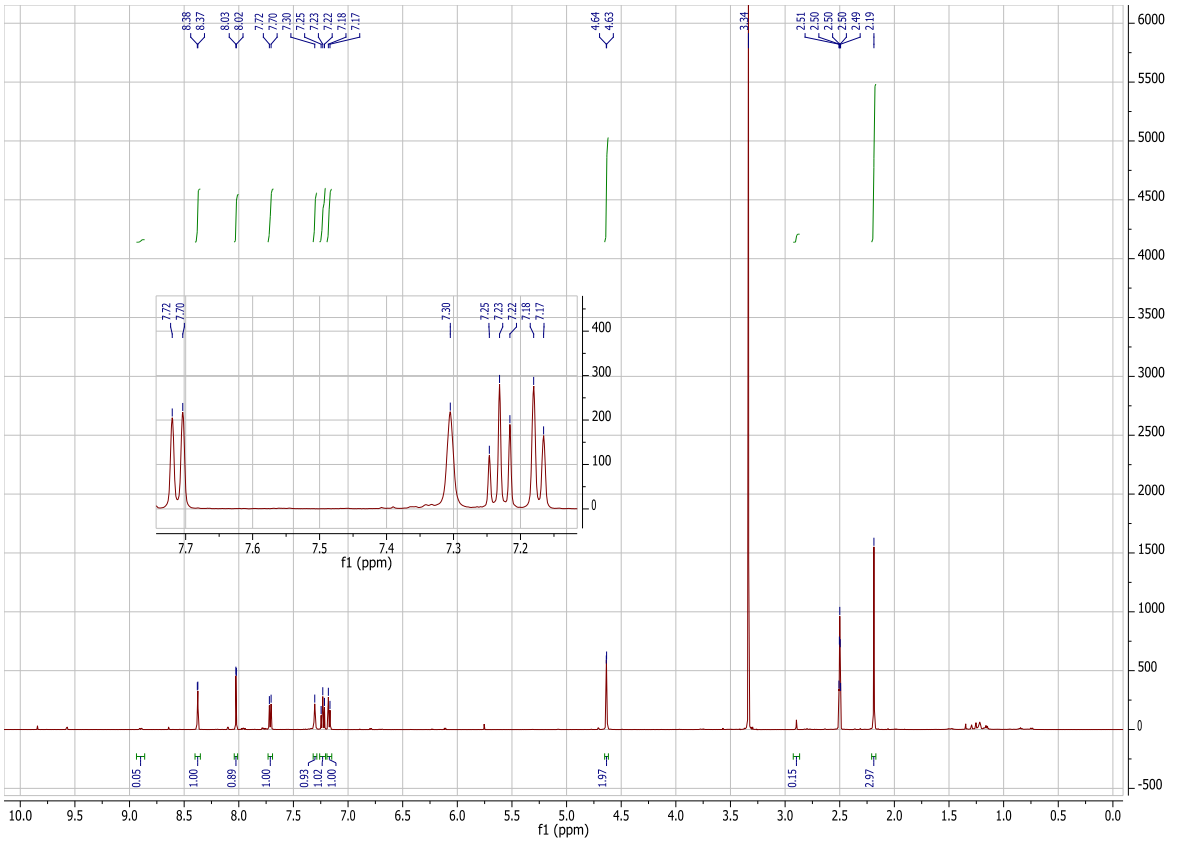
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.38 (d, J = 2.4 Hz, 1H, H-1), 8.02 (d, J = 2.4 Hz, 1H, H-3), 7.71 (d, J = 7.8 Hz, 1H, H-10), 7.30 (s, 1H, NH), 7.25-7.21 (m, 1H, H-9), 7.17 (d, J = 7.4 Hz, 1H, H-8), 4.63 (s, 2H, H-6), 2.19 (s, 3H, CH_3).

^{13}C NMR (125 MHz, DMSO-d_6) 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 (CH_3).

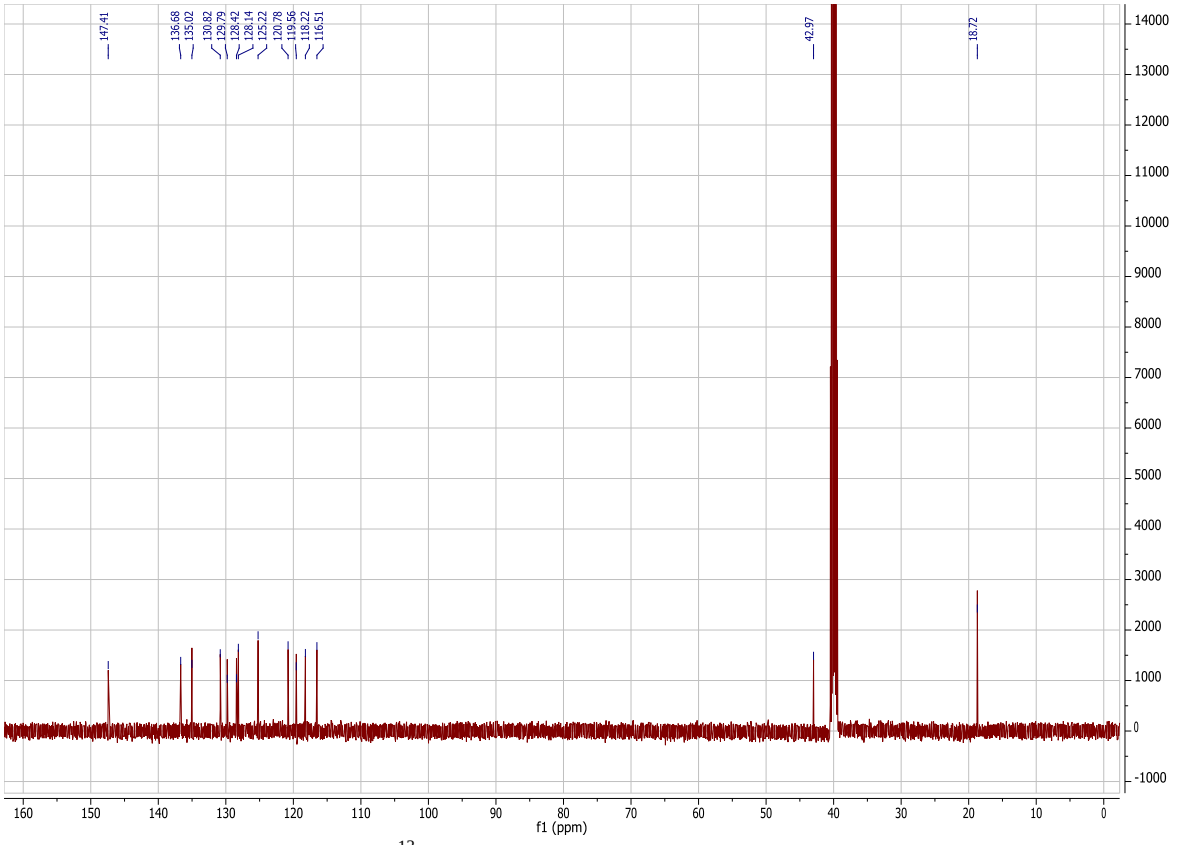
MS EI m/z (rel. %) 276/274 (16/64, M^+), 275 (38), 273 (100), 272 (15), 242 (4), 229 (14), 228 (9), 227 (48), 192 (16), 191 (9), 190 (11).

HRMS calcd. for $C_{14}H_{11}ClN_2O_2$ 274.0509, found 274.0504.

M.p. 185-187 ^{o}C.

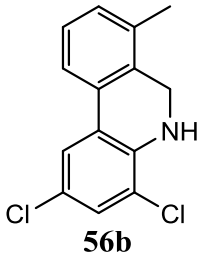


Spectrum 19. 500 MHz, DMSO-d_6, ^{1}H NMR of 4-chloro-7-methyl-2-nitro-5,6-dihydrophenanthridine (**56a**).



Spectrum 20. 125 MHz, DMSO-d_6, ^{13}C NMR of 4-chloro-7-methyl-2-nitro-5,6-dihydrophenanthridine (**56a**).

Synthesis of 2,4-dichloro-7-methyl-5,6-dihydrophenanthridine (56b)



56b

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 CH_2Cl_2-EtOAc-hexanes (1:4:45). Yield 72 mg (77%) as a colorless solid.

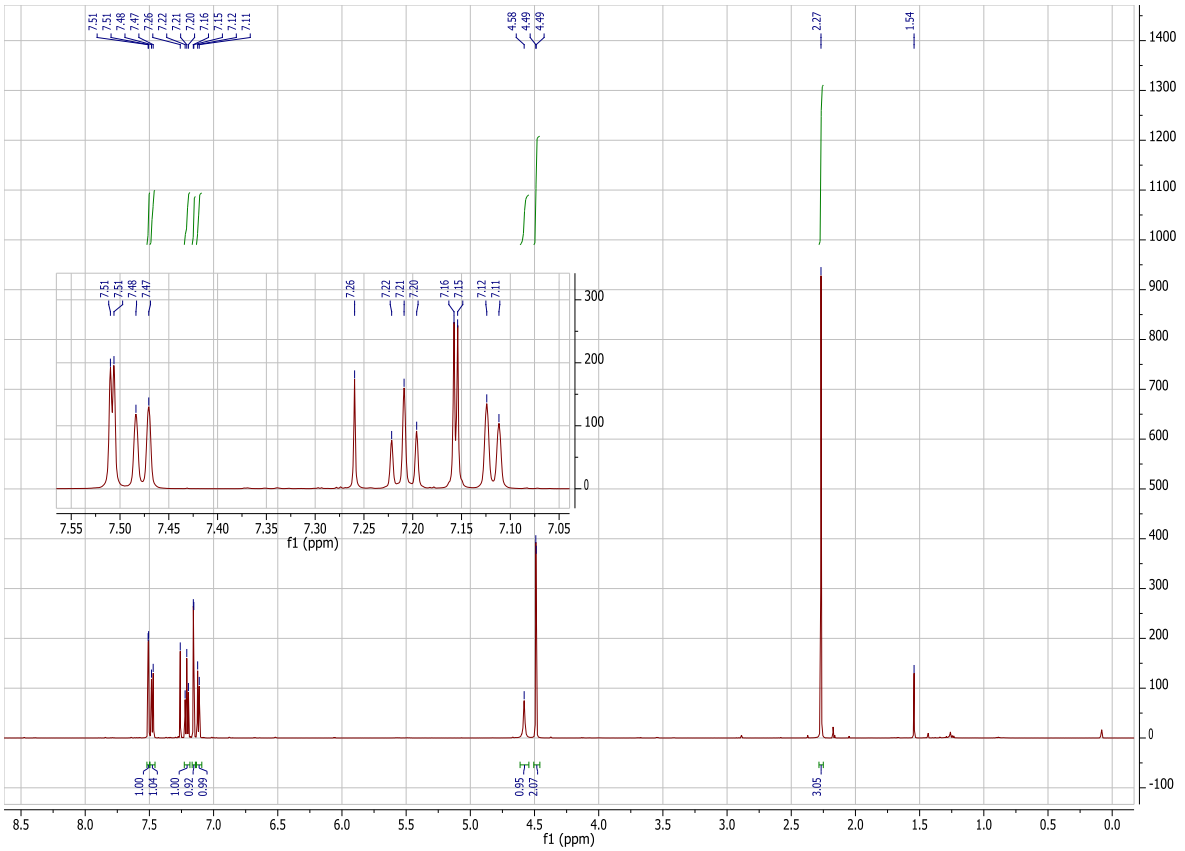
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.51 (d, *J* = 2.2 Hz, 1H, H-1), 7.48 (d, *J* = 7.9 Hz, 1H, H-10), 7.23-7.19 (m, 1H, H-9), 7.16 (d, *J* = 2.2 Hz, 1H, H-3), 7.12 (d, *J* = 7.5 Hz, 1H, H-8), 4.58 (s, 1H, NH), 4.49 (s, 2H NCH_2), 2.27 (s, 3H, CH_3).

^{13}C NMR (150 MHz, $CDCl_3$) 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 (NCH_2), 19.06 (CH_3).

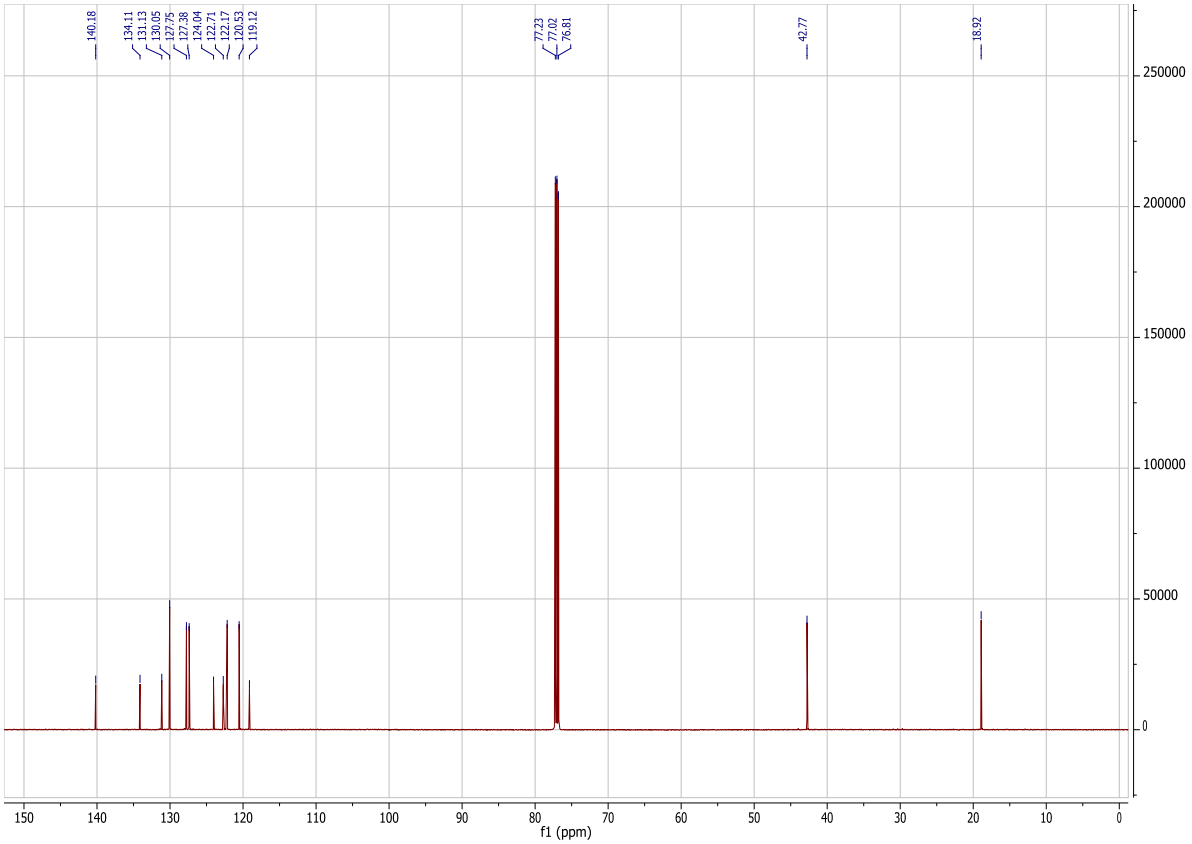
MS EI m/z (rel. %) 267/265/263 (5/30/50, M^+), 266/264/262 (14/69/100), 227 (5), 191 (7), 190 (8), 96 (10).

HRMS calcd. for $C_{14}H_{11}Cl_2N$ 263.0269, found 263.0259.

M.p. 108-111 ^oC.

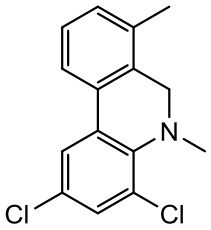


Spectrum 21. 600 MHz, $CDCl_3$, ^{1}H NMR of 2,4-dichloro-7-methyl-5,6-dihydrophenanthridine (**56b**).



Spectrum 22. 150 MHz, $CDCl_3$, ^{13}C NMR of 2,4-dichloro-7-methyl-5,6-dihydrophenanthridine (**56b**).

Synthesis of 2,4-dichloro-5,7-dimethyl-5,6-dihydrophenanthridine (56c)



56c

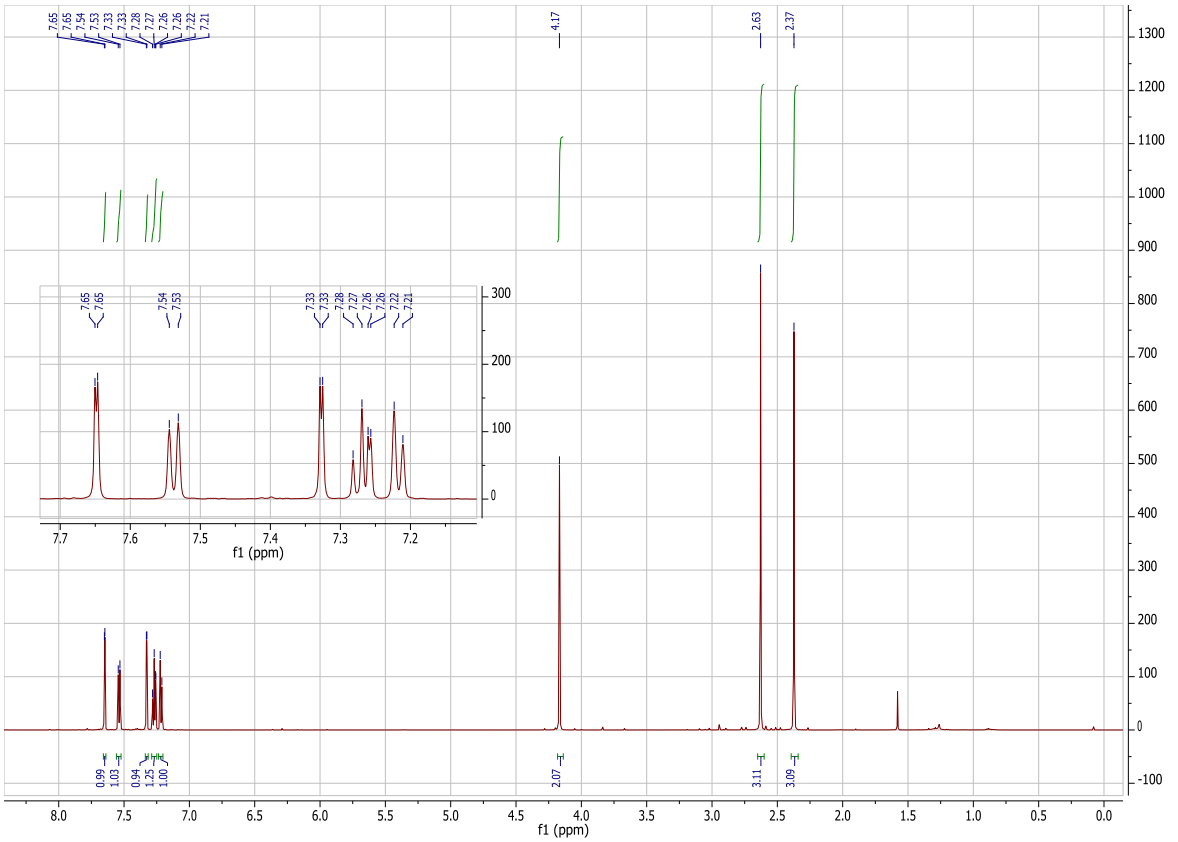
Degassed MeCN (15mL) was transferred to a microwave vessel, and compound **48c** (80 mg, 0.270 mmol) and 0.5M aq. HCl (0.1 mL, 0.2 equivs.) were added. The reaction mixture was degassed with Ar and heated at 180 °C in a microwave oven for 5 h. The reaction mixture was neutralized with $NaHCO_3$ (6.7 mg, 0.080 mmol) and concentrated under reduced pressure. The product was isolated by flash chromatography on silica gel eluting with CH_2Cl_2-hexanes (1:9). Yield 50 mg (66%) as a colorless oil.

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.65 (d, *J* = 2.3 Hz, 1H, H-1), 7.54 (d, *J* = 7.7 Hz, 1H, H-10), 7.33 (d, *J* = 2.3 Hz, 1H, H-3), 7.29-7.25 (m, 1H, H-9), 7.22 (d, *J* = 7.5 Hz, 1H, H-8), 4.17 (s, 2H, H-6), 2.63 (s, 3H, NCH_3), 2.37 (s, 3H, CH_3).

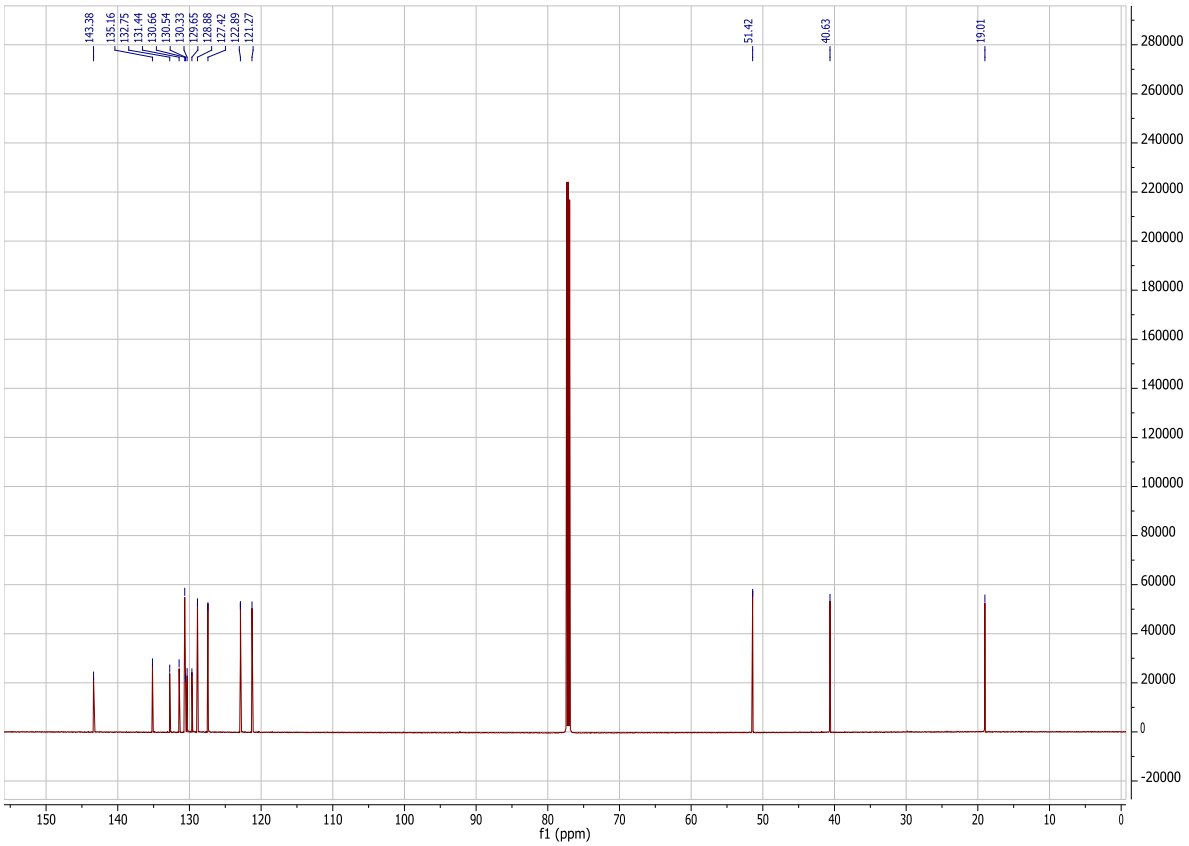
^{13}C NMR (150 MHz, $CDCl_3$) δ 143.38 (C-4a), 135.16 (C-7), 132.75 (C-10b), 131.44 (C-6a), 130.66 (C-8), 130.54 (C-4), 130.33 (C-10a), 129.65 (C-2), 128.88 (C-3), 127.42 (C-9), 122.89 (C-1), 121.27 (C-10), 51.42 (NCH_2), 40.63 (NCH_3), 19.01 (CH_3).

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

HRMS calcd. for $C_{15}H_{13}Cl_2N$ 277.0425, found 277.0415.

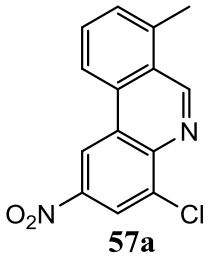


Spectrum 23. 600 MHz, $CDCl_3$, ^{1}H NMR of 2,4-dichloro-5,7-dimethyl-5,6-dihydrophenanthridine (**56c**).



Spectrum 24. 150 MHz, $CDCl_3$, ^{13}C NMR of 2,4-dichloro-5,7-dimethyl-5,6-dihydrophenanthridine (**56c**).

Synthesis of 4-chloro-7-methyl-2-nitrophenanthridine (57a)



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 $NaHCO_3$ (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 CH_2Cl_2; yield 50 mg (77%) as a pale yellow solid.

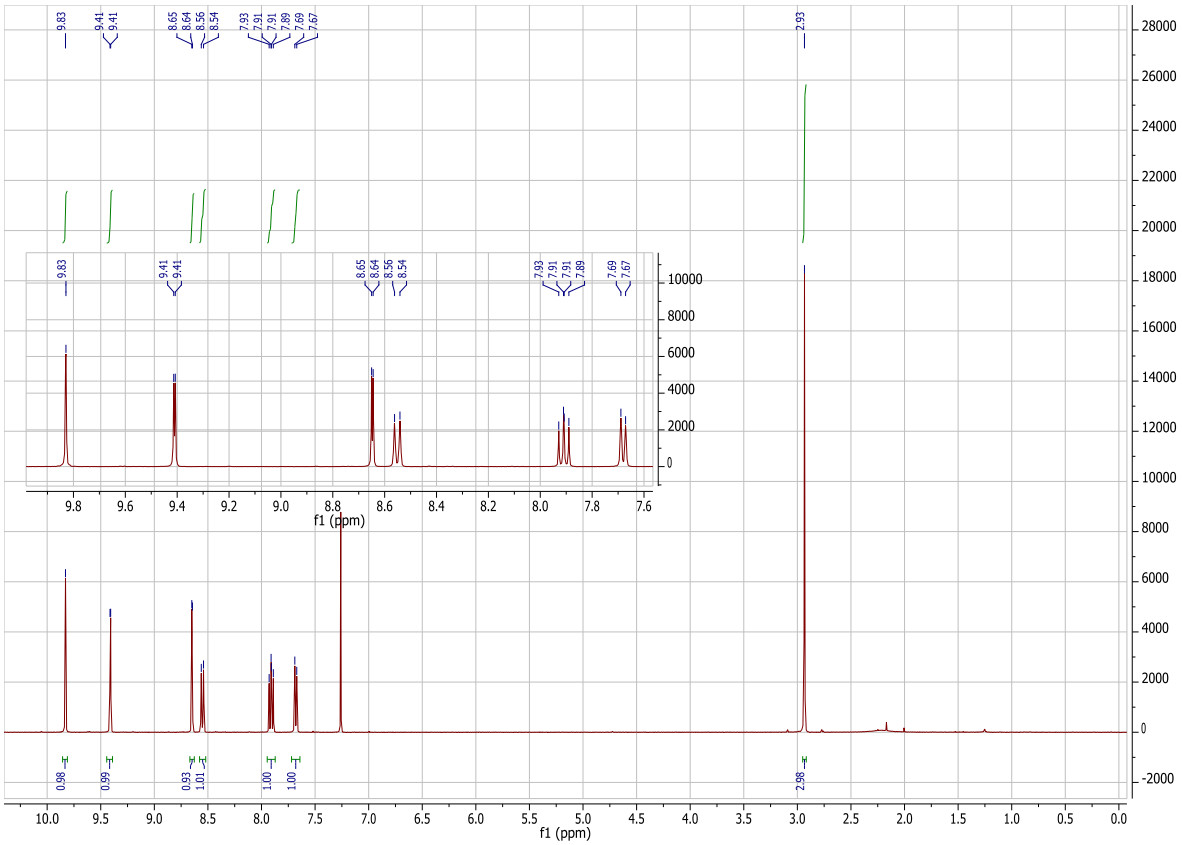
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.84 (s, 1H, H-6), 9.44 (d, *J* = 2.0 Hz, 1H, H-2 or H-4), 8.66 (d, *J* = 2.0 Hz, 1H, H-2 or H-4), 8.57 (d, *J* = 8.4 Hz, 1H, H-10), 7.94-7.88 (m, 1H, H-9), 7.68 (d, *J* = 7.3 Hz, 1H, H-8), 2.94 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) 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 (CH_3).

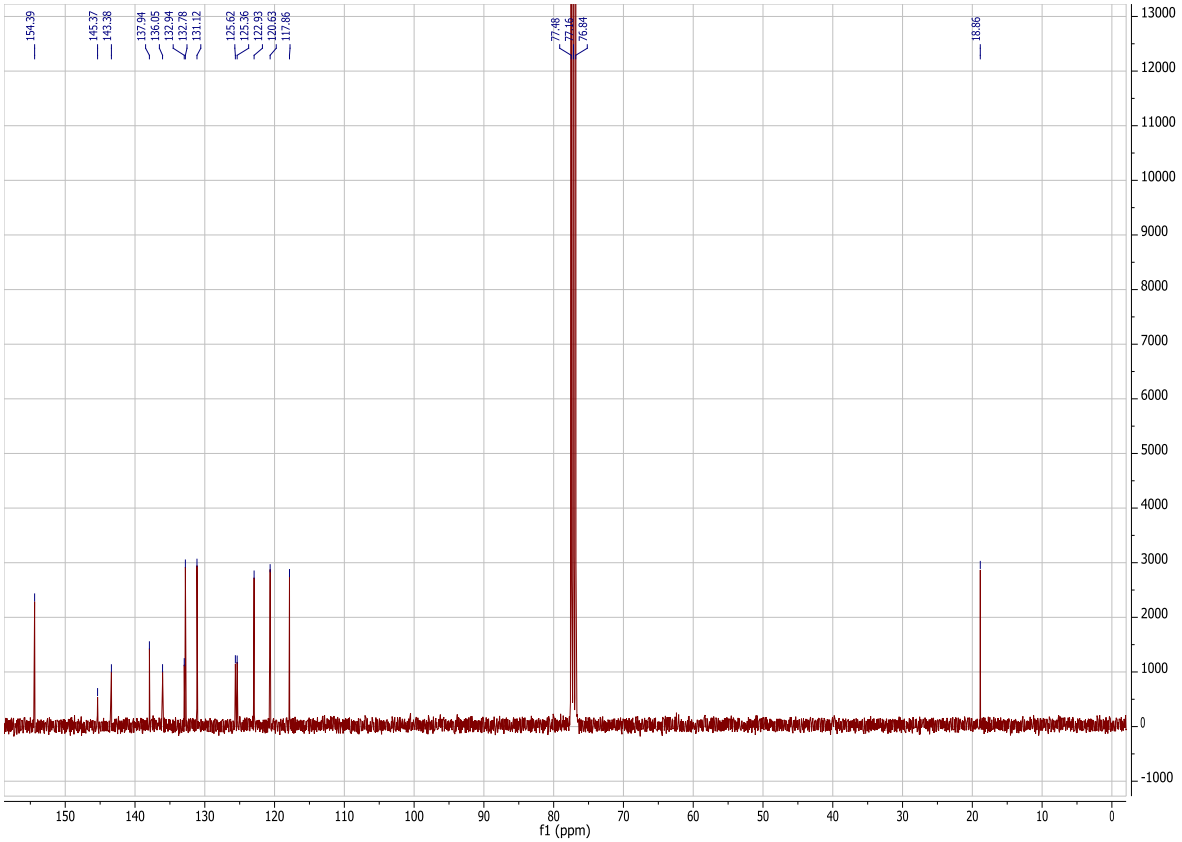
MS EI m/z (rel. %) 274/272 (31/100, M^+) 226 (21), 216 (5), 214 (22), 199 (6), 191 (20), 190 (30), 164 (8), 163 (10).

HRMS calcd. for $C_{14}H_{11}Cl_2NO$ 272.0353, found 272.0355.

M.p. 245-248 ^oC.

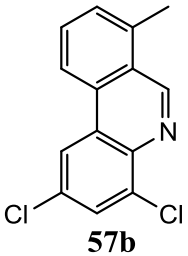


Spectrum 25. 400 MHz, $CDCl_3$, ^{1}H NMR of 4-chloro-7-methyl-2-nitrophenanthridine (**57a**).



Spectrum 26. 100 MHz, $CDCl_3$, ^{13}C NMR of 4-chloro-7-methyl-2-nitrophenanthridine (**57a**).

Synthesis of 2,4-dichloro-7-methylphenanthridine (57b)



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_2Cl_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_2Cl_2-EtOAc-hexanes (1:4:20); yield 56 mg (53%) colorless solid.

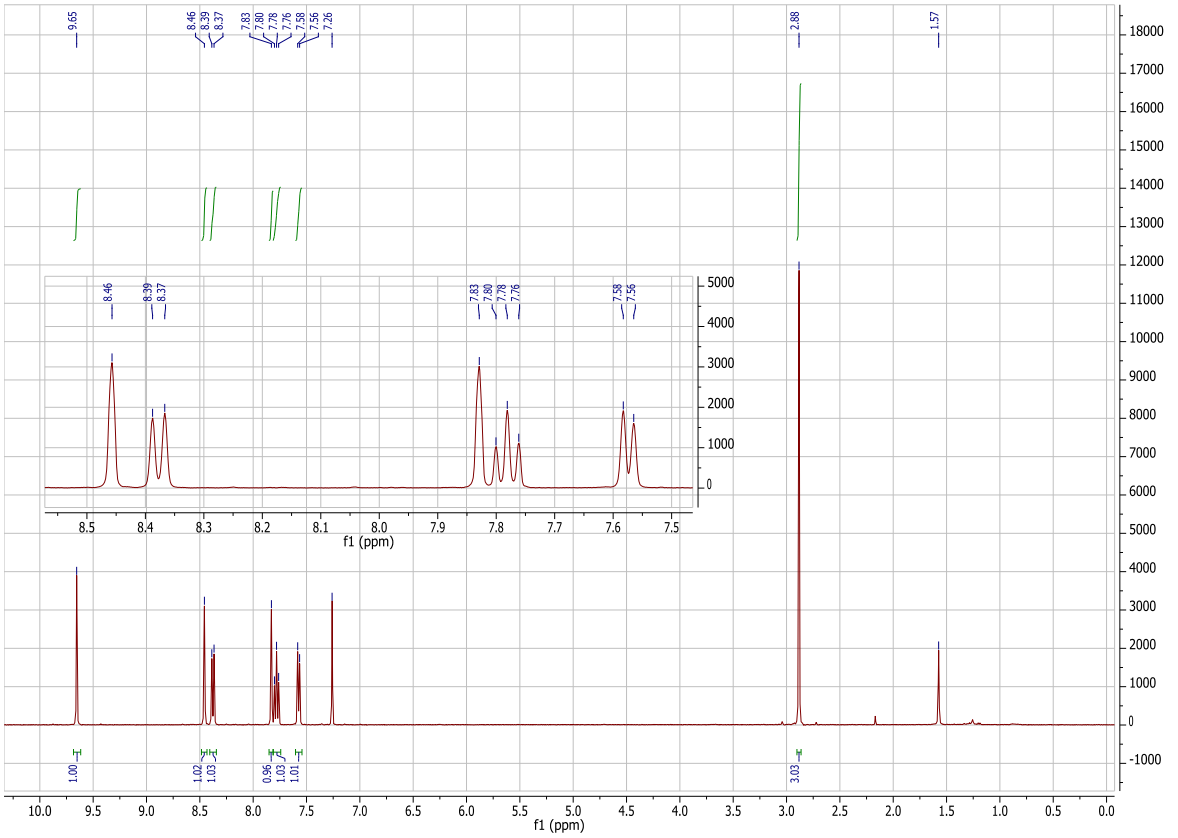
^{1}H NMR (400 MHz, $CDCl_3$) δ 9.66 (s, 1H, H-6), 8.47 (d, *J* = 2.1 Hz, 1H, H-1), 8.39 (d, *J* = 8.4 Hz, 1H, H-10), 7.84 (d, *J* = 2.1 Hz, 1H, H-3), 7.81-7.75 (m, 1H, H-9), 7.58 (d, *J* = 7.2 Hz, 1H, H-8), 2.89 (s, 3H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) δ 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).

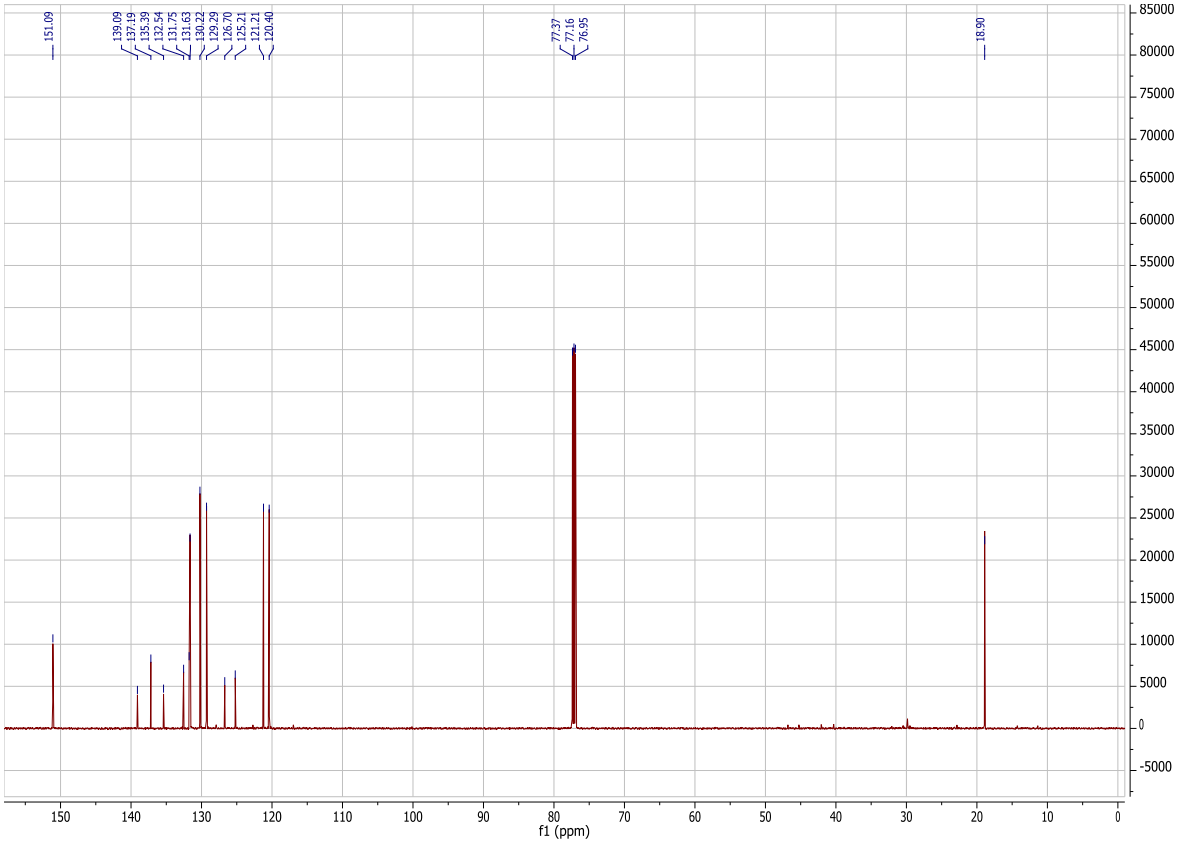
MS EI m/z (rel. %) 265/263/261 (9/64/100), 226 (13), 225 (7) 191 (10), 190 (16).

HRMS calcd. for $C_{14}H_9Cl_2N$ 261.0112, found 261.0113.

M.p. 180-182 ^oC.

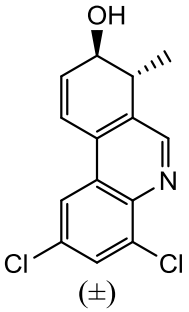


Spectrum 27. 400 MHz, $CDCl_3$, ^{1}H NMR of 2,4-dichloro-7-methylphenanthridine (**57b**).



Spectrum 28. 100 MHz, $CDCl_3$, ^{13}C NMR of 2,4-dichloro-7-methylphenanthridine (**57b**).

Synthesis of (±)-(7R,8R)-2,4-dichloro-7-methyl-7,8-dihydrophenanthridin-8-ol (58b)



(±)

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.

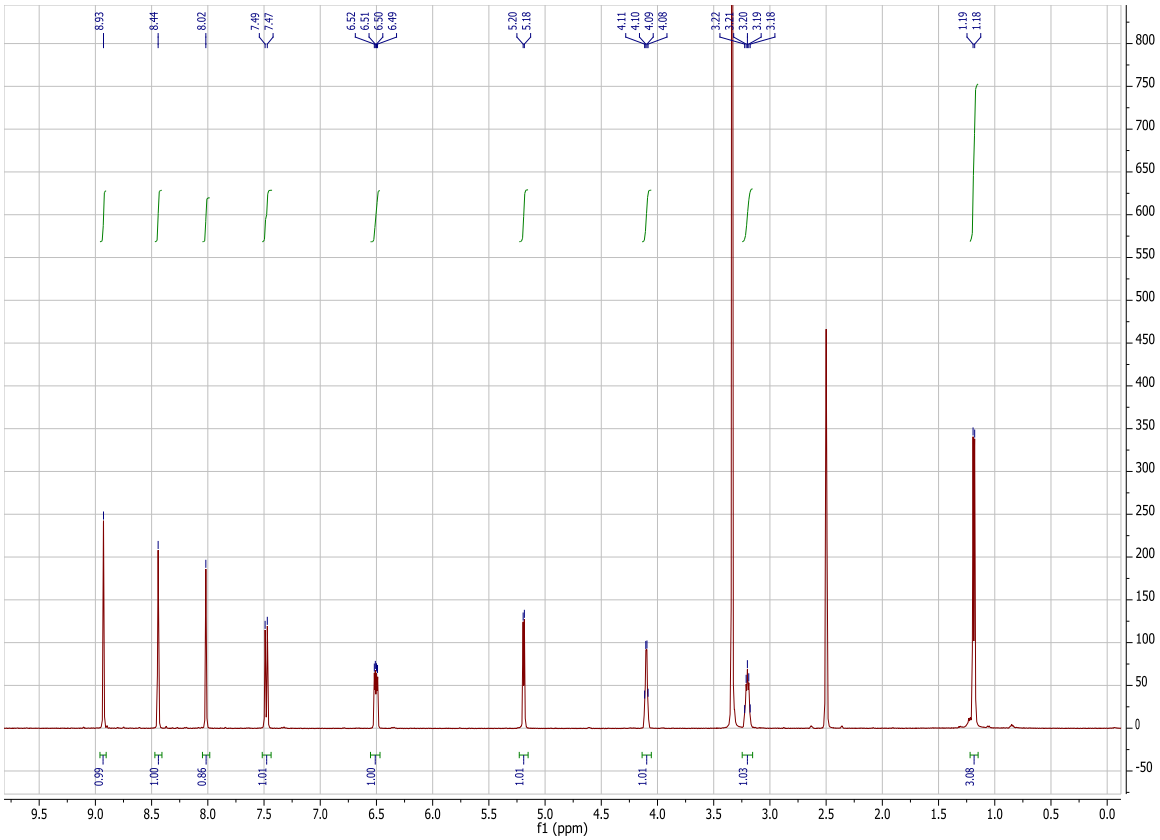
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.70 (s, 1H, H-6), 8.44 (s, 1H, H-1), 8.02 (s, 1H, H-3), 7.48 (d, J = 9.8 Hz, 1H, H-10), 6.51 (dd, J = 9.8, 4.8 Hz, 1H, H-9), 5.18 (d, J = 5.7 Hz, 1H, OH), 4.11-4.08 (m, 1H, H-8), 3.21 (qd, J = 7.3, 4.5 Hz, 1H, H-7), 1.20 (d, J = 7.3 Hz, 3H, CH_3).

^{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).

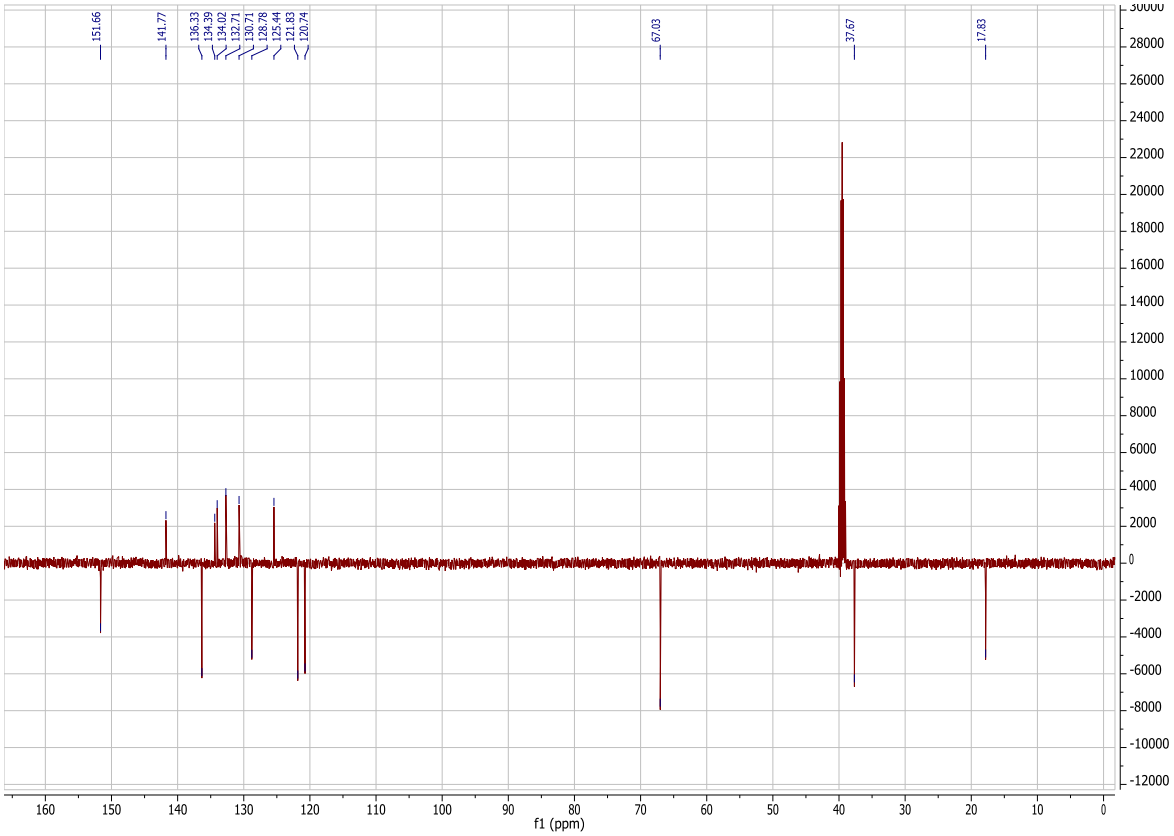
MS EI m/z (rel. %) 283/281/279 (2/14/22), 265 (15), 264 (36), 263 (65), 261 (100), 250 (14), 248 (7), 226 (9), 225 (7), 191 (9), 190 (15), 164 (6), 163 (6).

HRMS calcd. for $C_{14}H_{11}Cl_2NO$ 279.0218, found 279.0215.

M.p. 175-177 ^{o}C.

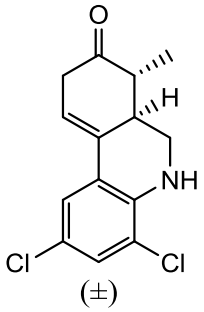


Spectrum 29. 500 MHz, DMSO-d_6, ^{1}H NMR of (±)-(*7R,8R*)-2,4-dichloro-7-methyl-7,8-dihydrophenanthridin-8-ol (**58b**).



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)



(±)

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.

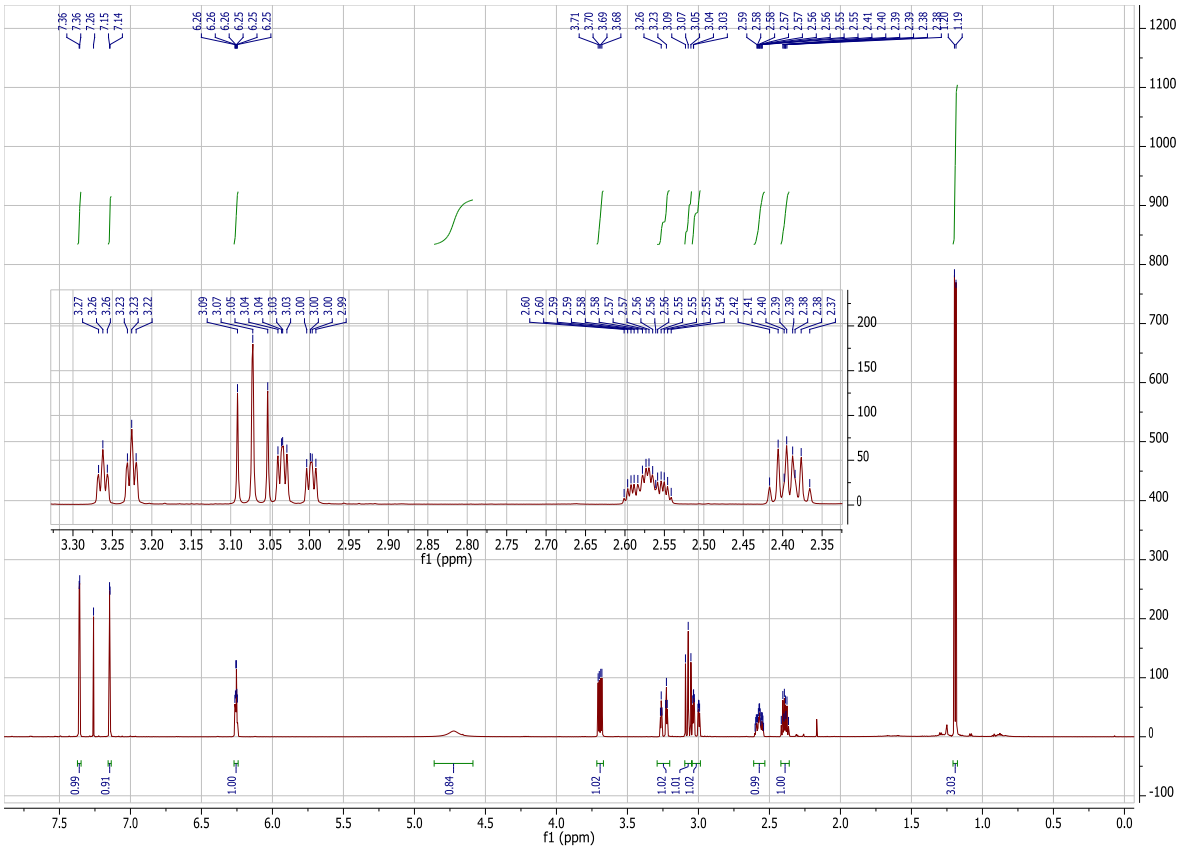
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36 (d, *J* = 2.2 Hz, 1H, H-1), 7.15 (d, *J* = 2.2 Hz, 1H, H-3), 6.26 (td, *J* = 4.0, 2.5 Hz, 1H, H-10), 4.72 (s, 1H, NH), 3.69 (dd, *J* = 11.1, 4.8 Hz, 1H, H_a in H-6), 3.27-3.21 (m, 1H, H_a in H-9), 3.10-2.97 (m, 2H, H_b in H-6 and H_b in H-9), 2.61-2.54 (m, 1H, H-6a), 2.39 (dq, *J* = 11.1, 6.5 Hz, 1H, H-7), 1.19 (d, *J* = 6.5 Hz, 3H, CH_3).

^{13}C 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).

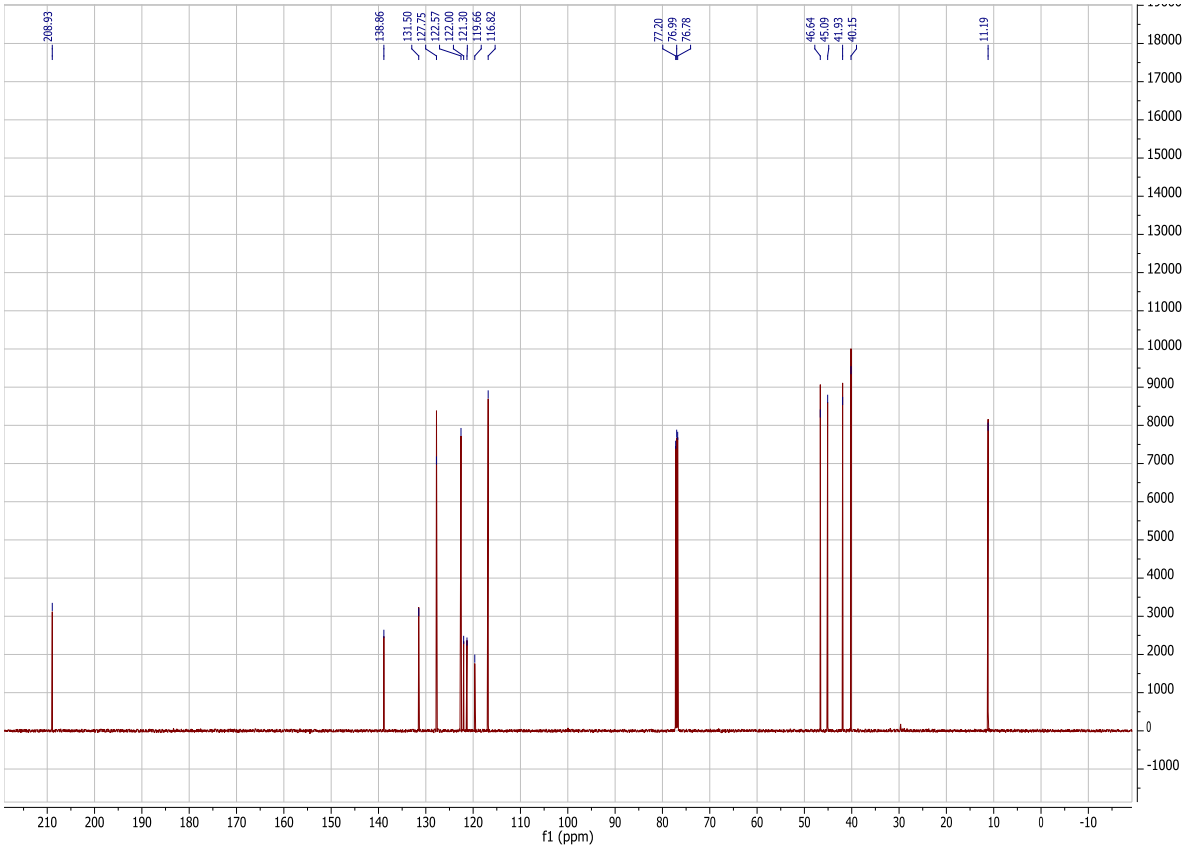
MS EI m/z (rel. %) 285/283/281 (9/63/100, M^+), 252 (8), 240 (31), 238 (49), 228 (10), 226 (58), 224 (83), 200 (18), 198 (29), 188 (15).

HRMS calcd. for $C_{14}H_{13}Cl_2NO$ 281.0374, found 281.0368.

M.p. 194-195 °C.

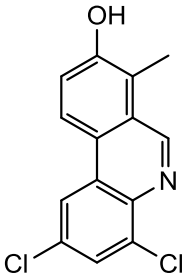


Spectrum 31. 600 MHz, $CDCl_3$, ^1H NMR of (±)-(*6aR,7R*)-2,4-dichloro-7-methyl-5,6a,7,9-tetrahydrophenanthridin-8(6H)-one (**59b**).



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



65b

A solution of compound **59b** (99 mg, 0.35 mmol) and DDQ (97 mg, 0.43 mmol) in dry CH_2Cl_2 (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.

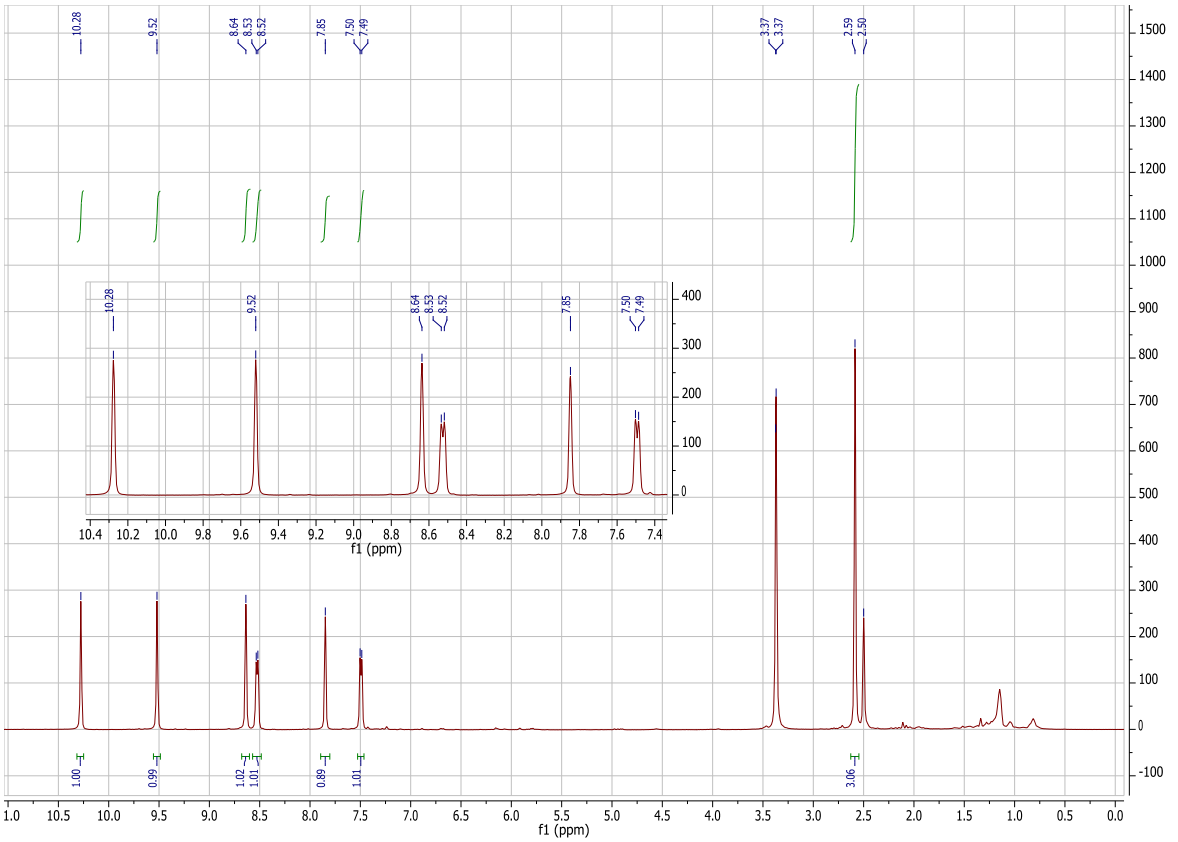
^{1}H NMR (500 MHz, DMSO-d_6) δ 10.28 (s, 1H, OH), 9.52 (s, 1H, H-6), 8.64 (s, 1H, H-1), 8.53 (d, J = 8.1 Hz, 1H, H-10), 7.85 (s, 1H, H-3), 7.49 (d, J = 8.1 Hz, 1H, H-9), 2.59 (s, 3H, CH_3).

^{13}C NMR (125 MHz, DMSO-d_6) 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 (CH_3).

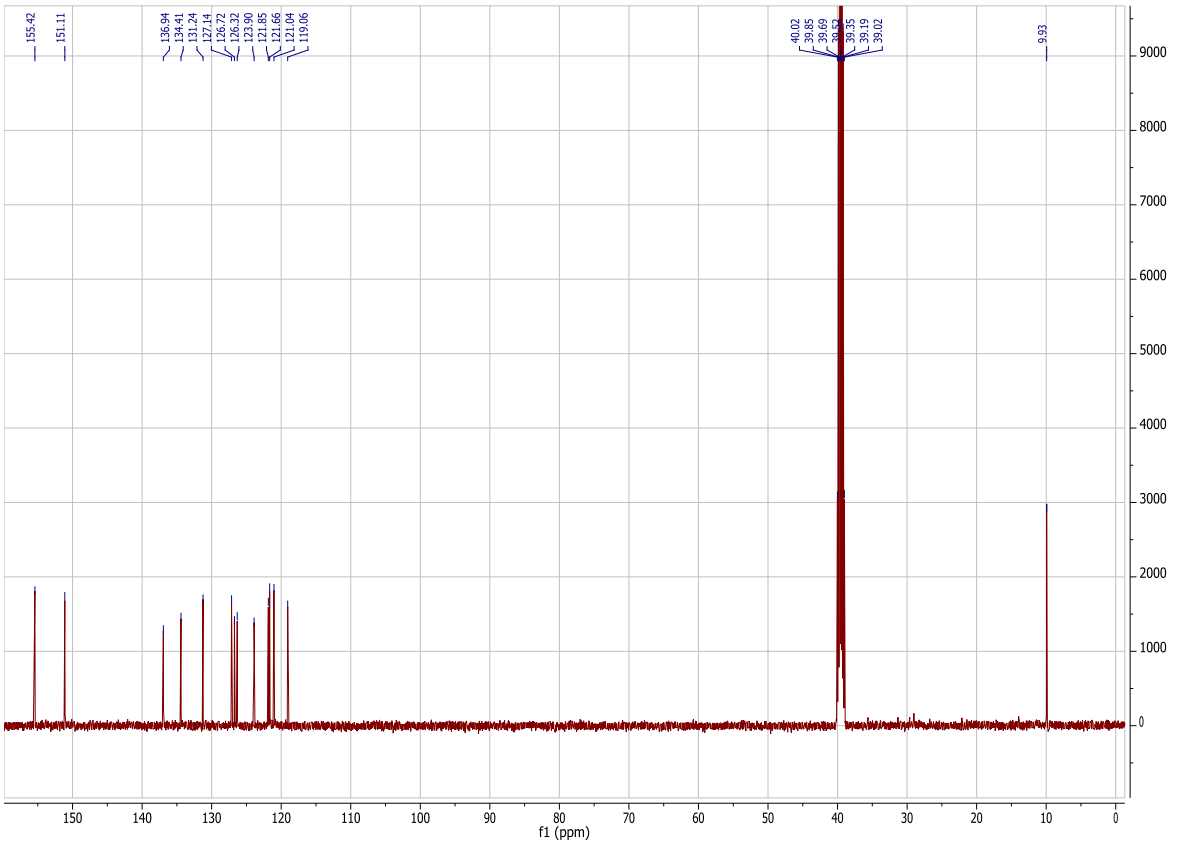
MS EI m/z (rel. %) 281/279/277 (8/65/100, M^+), 250 (10), 248 (16), 242 (3), 214 (4), 213 (3), 178 (3), 177 (7).

HRMS calcd. for $C_{14}H_9Cl_2NO$ 277.0061, found 277.0066.

M.p. 215-220 ^oC (dec.).

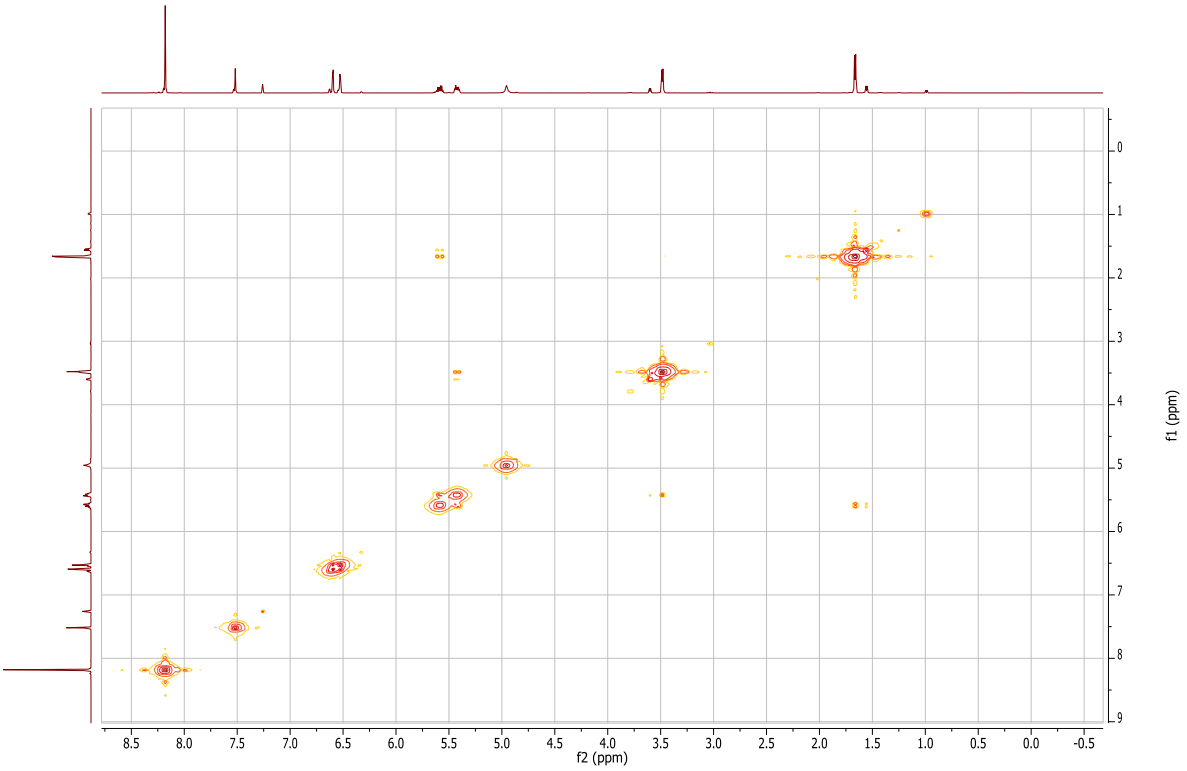


Spectrum 33. 500 MHz, DMSO-d_6, ^{1}H NMR of 2,4-dichlorophenanthridin-8-ol (**65b**).

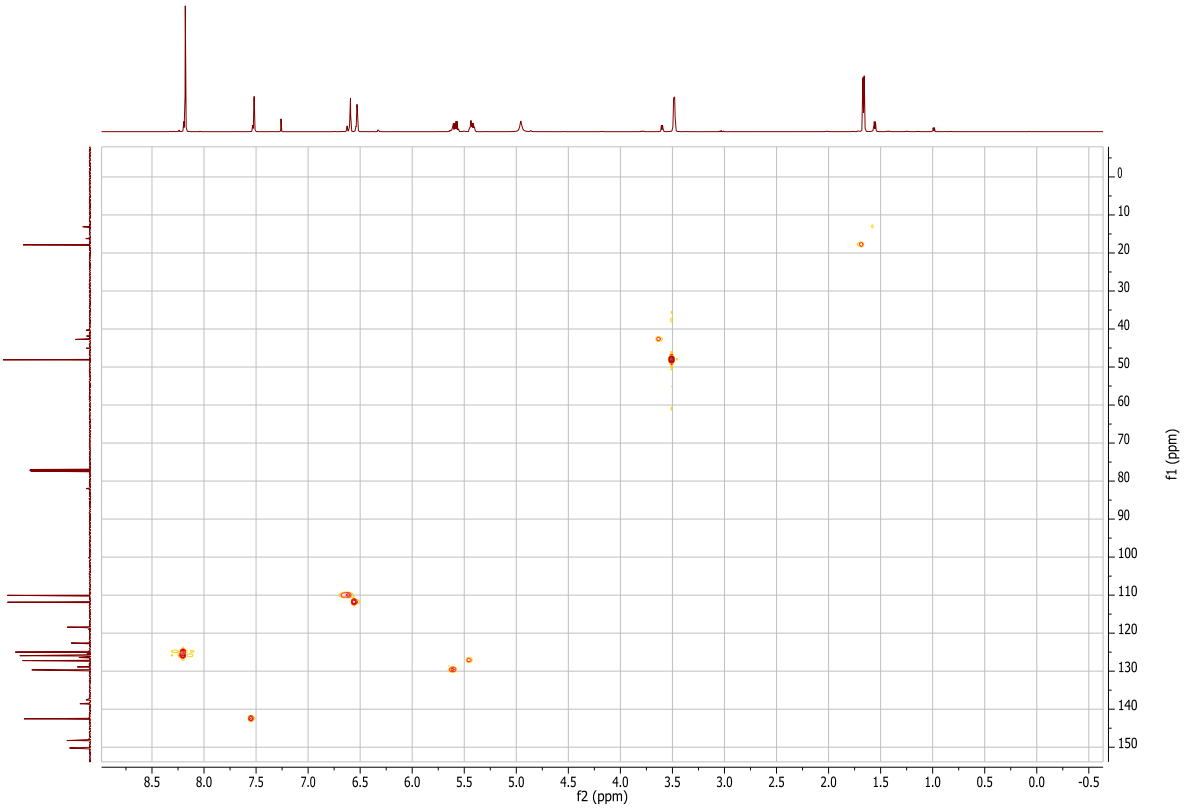


Spectrum 34. 125 MHz, DMSO-d_6, ^{13}C NMR of 2,4-dichlorophenanthridin-8-ol (**65b**).

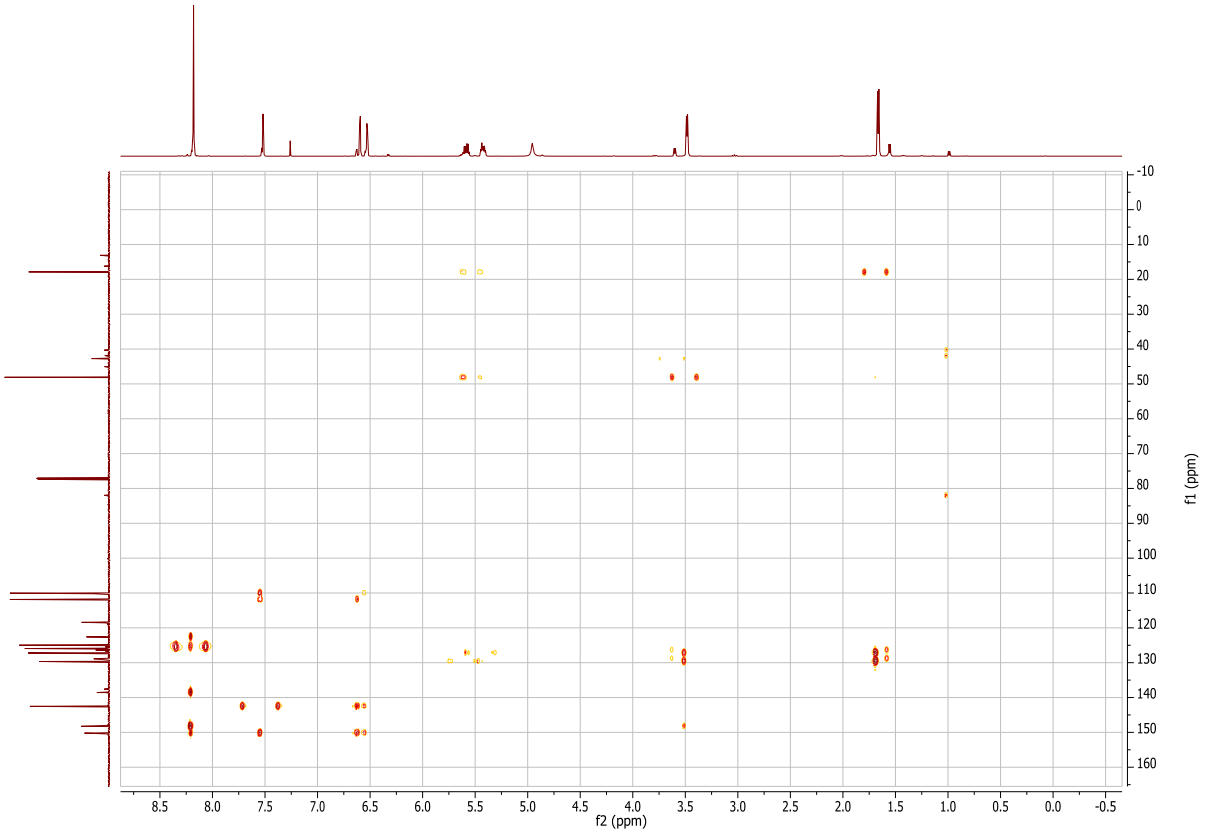
6. APPENDIX



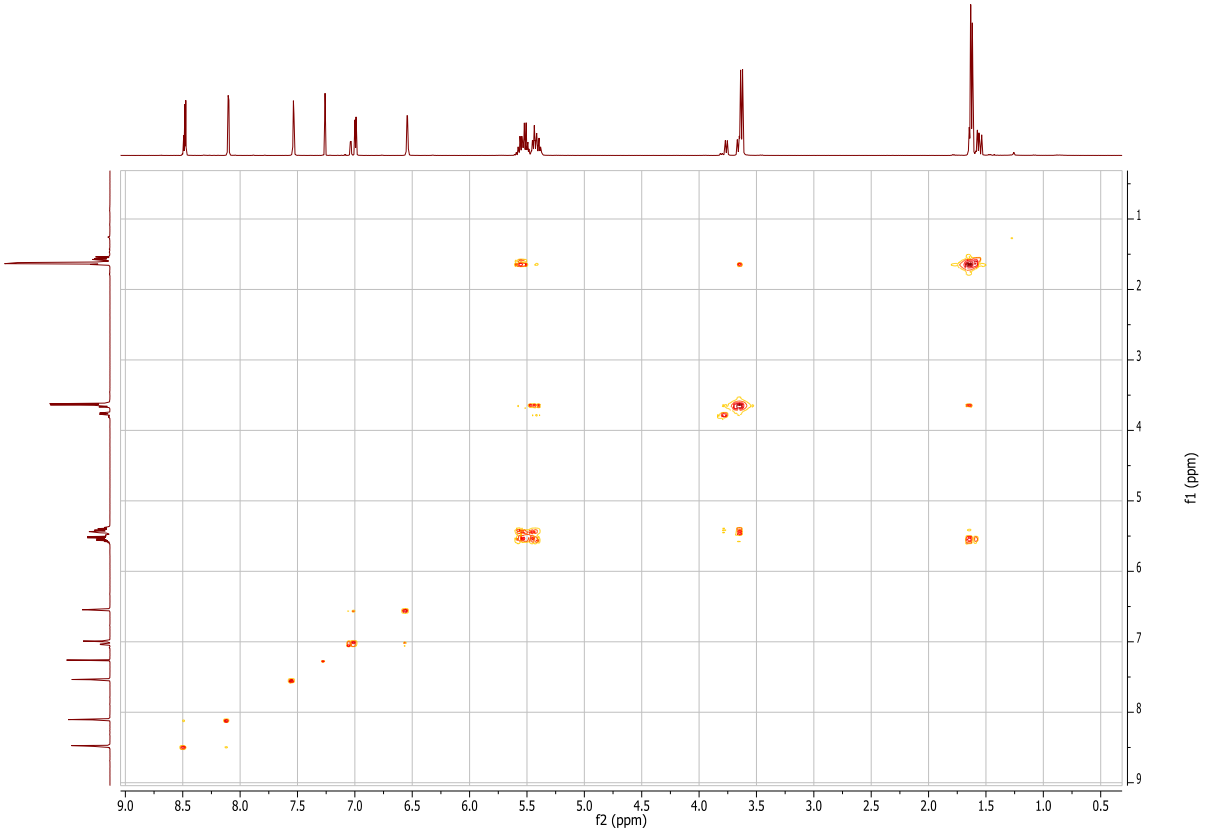
Spectrum 35. 600 MHz, $CDCl_3$, COSY of *N*-(but-2-en-1-yl)-2-chloro-6-(furan-2-yl)-4-nitroaniline (**48a**).



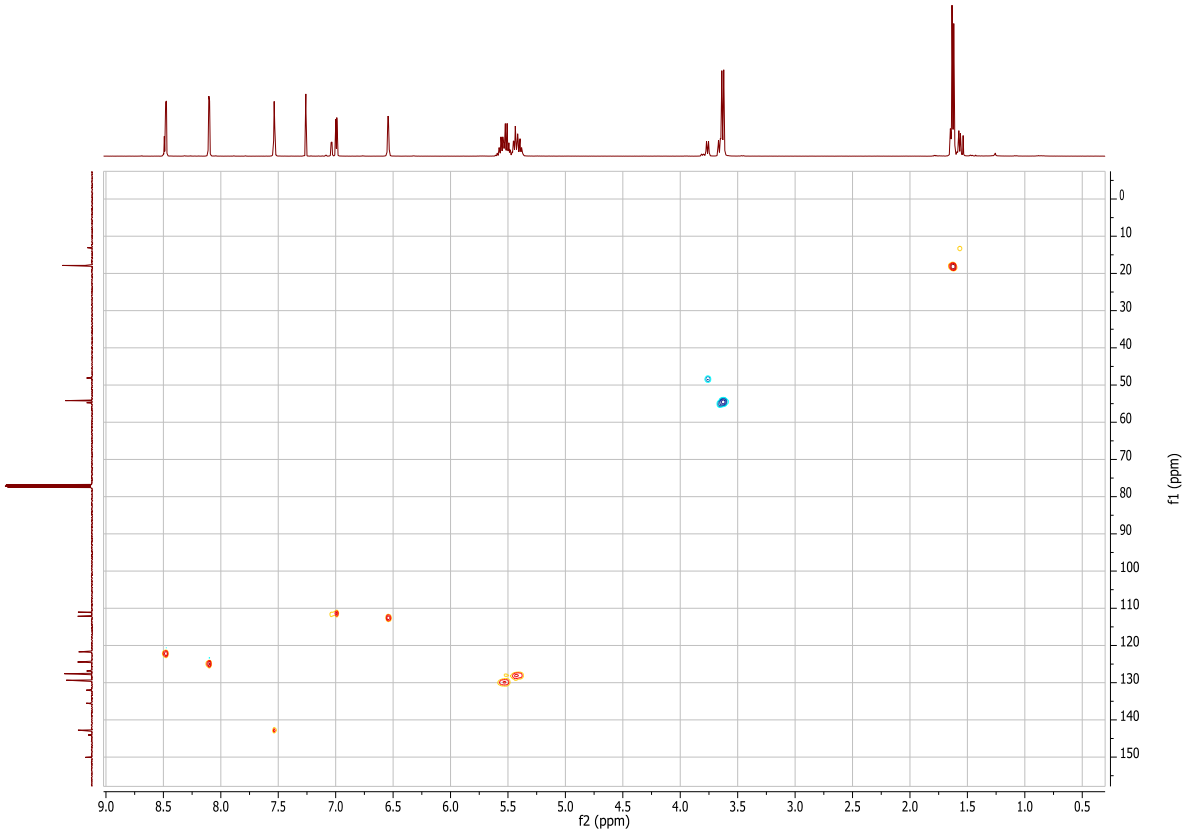
Spectrum 36. 600 MHz, $CDCl_3$, HSQC of *N*-(but-2-en-1-yl)-2-chloro-6-(furan-2-yl)-4-nitroaniline (**48a**).



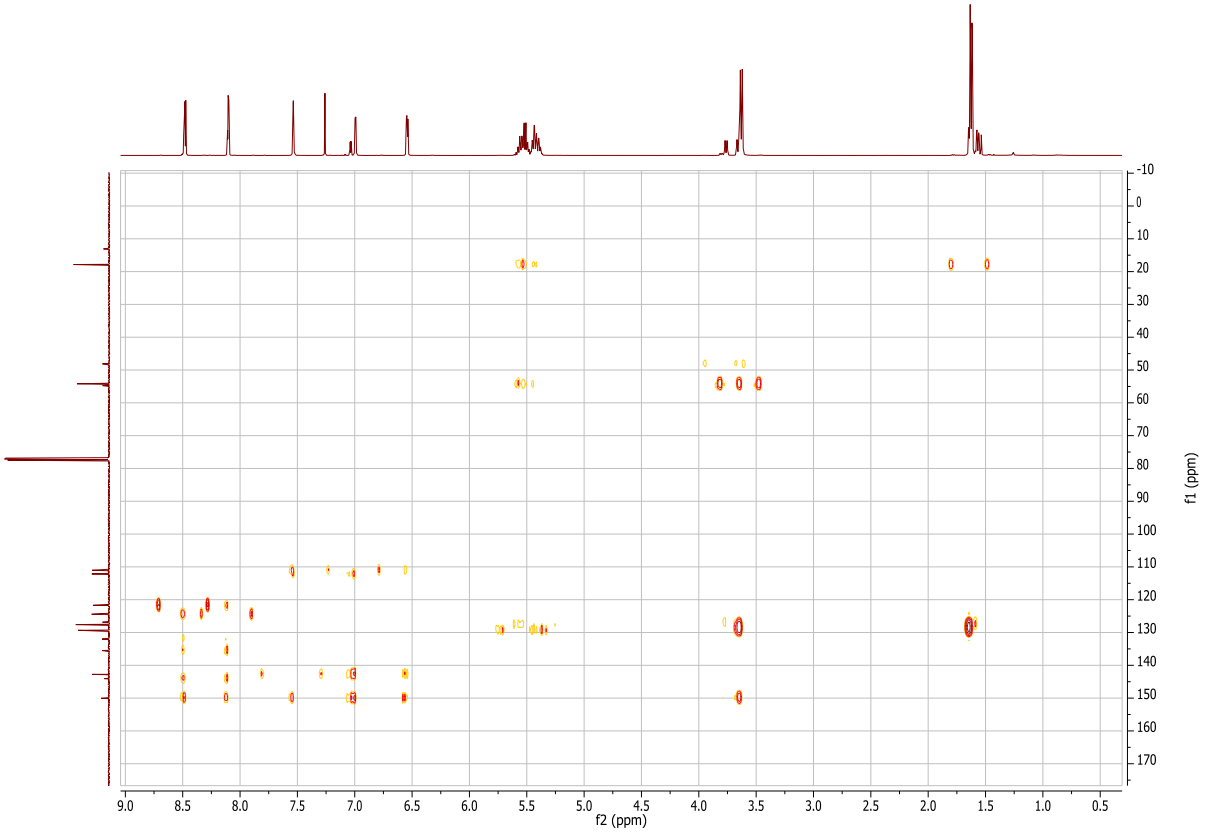
Spectrum 37. 600 MHz, $CDCl_3$, HMBC of *N*-(but-2-en-1-yl)-2-chloro-6-(furan-2-yl)-4-nitroaniline (**48a**).



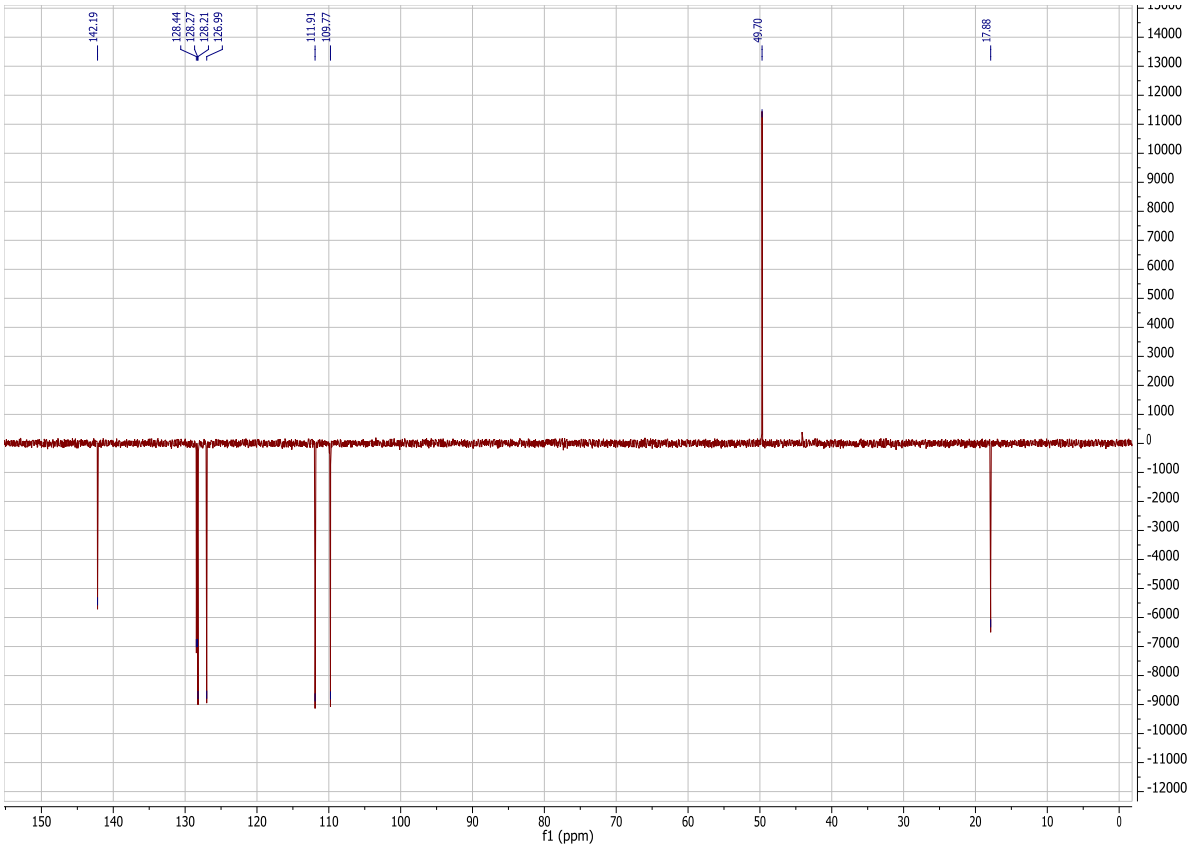
Spectrum 38. 400 MHz, $CDCl_3$, COSY of *N*,*N*-di(but-2-en-1-yl)-2-chloro-6-(furan-2-yl)-4-nitroaniline (**52a**).



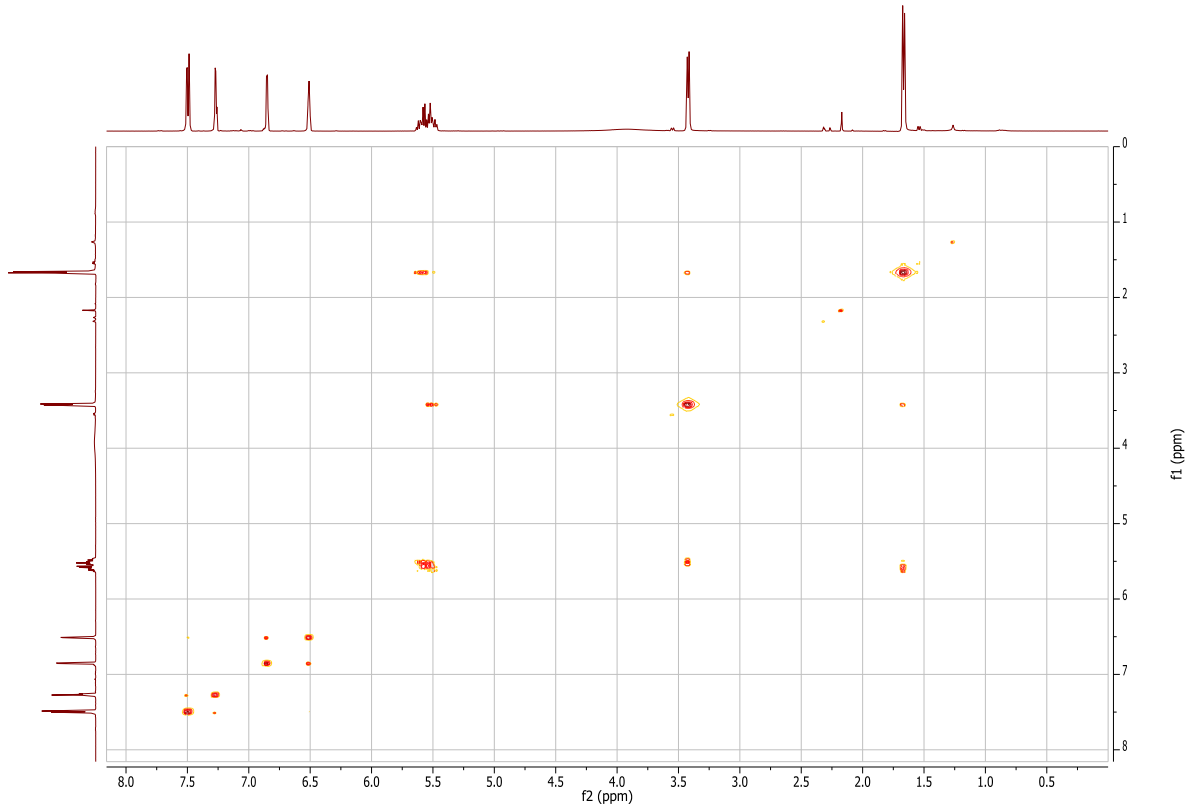
Spectrum 39. 400 MHz, $CDCl_3$, HSQC of *N*,*N*-di(but-2-en-1-yl)-2-chloro-6-(furan-2-yl)-4-nitroaniline (**52a**).



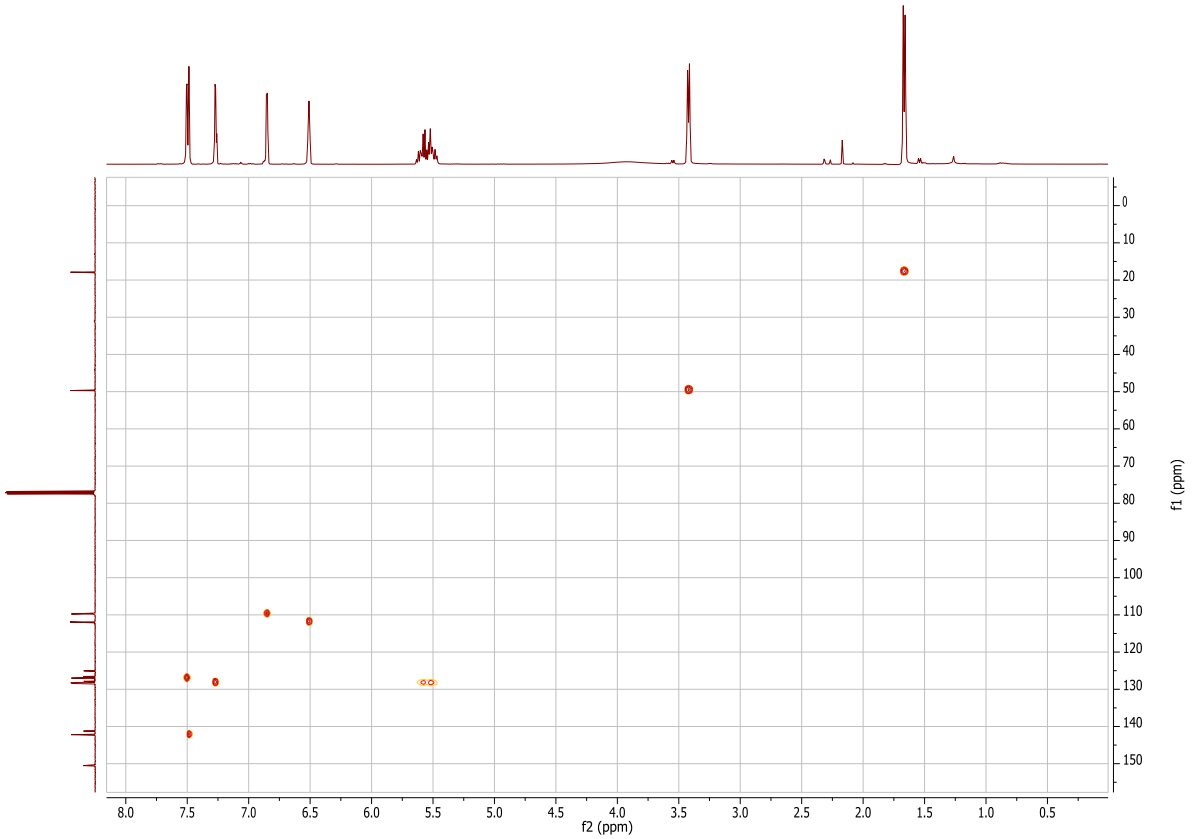
Spectrum 40. 400 MHz, $CDCl_3$, HMBC of *N*,*N*-di(but-2-en-1-yl)-2-chloro-6-(furan-2-yl)-4-nitroaniline (**52a**).



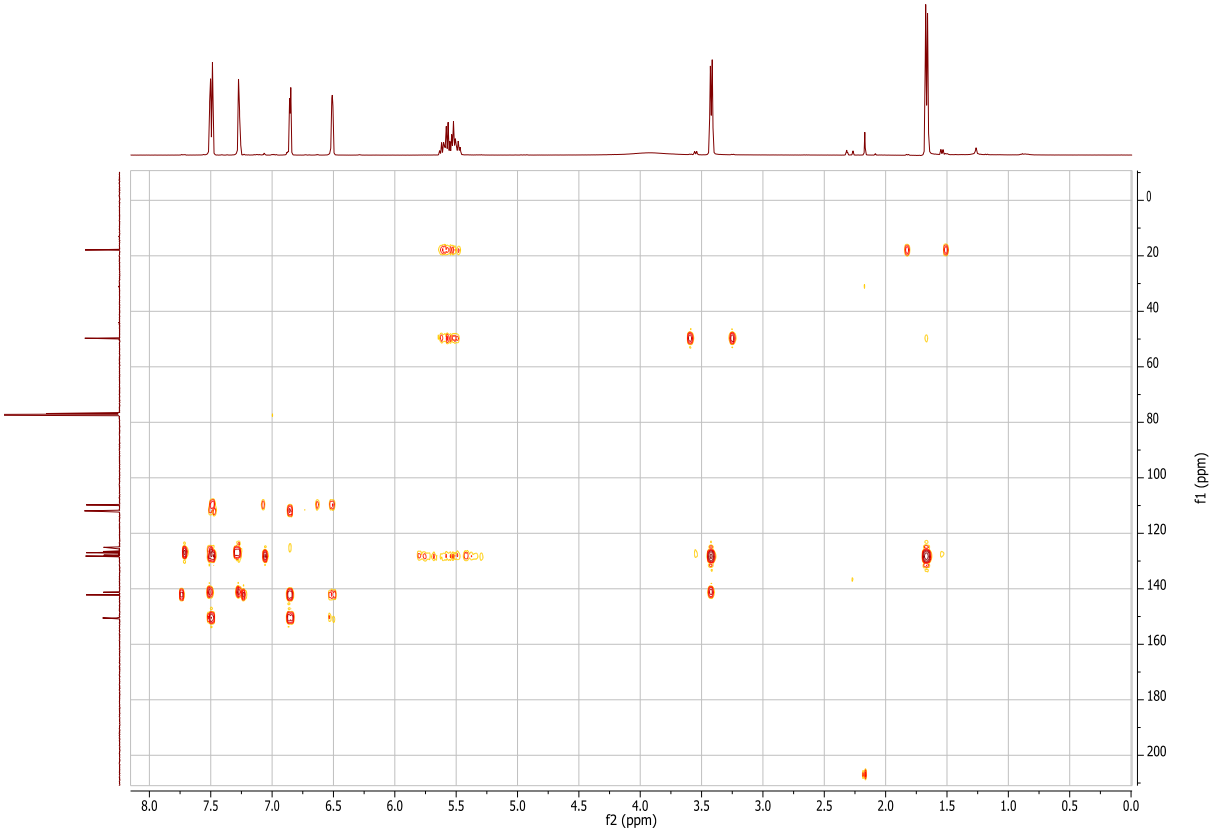
Spectrum 41. 400 MHz, $CDCl_3$, ^{13}C DEPT of *N*-(but-2-en-1-yl)-2,4-dichloro-6-(furan-2-yl)aniline (**48b**).



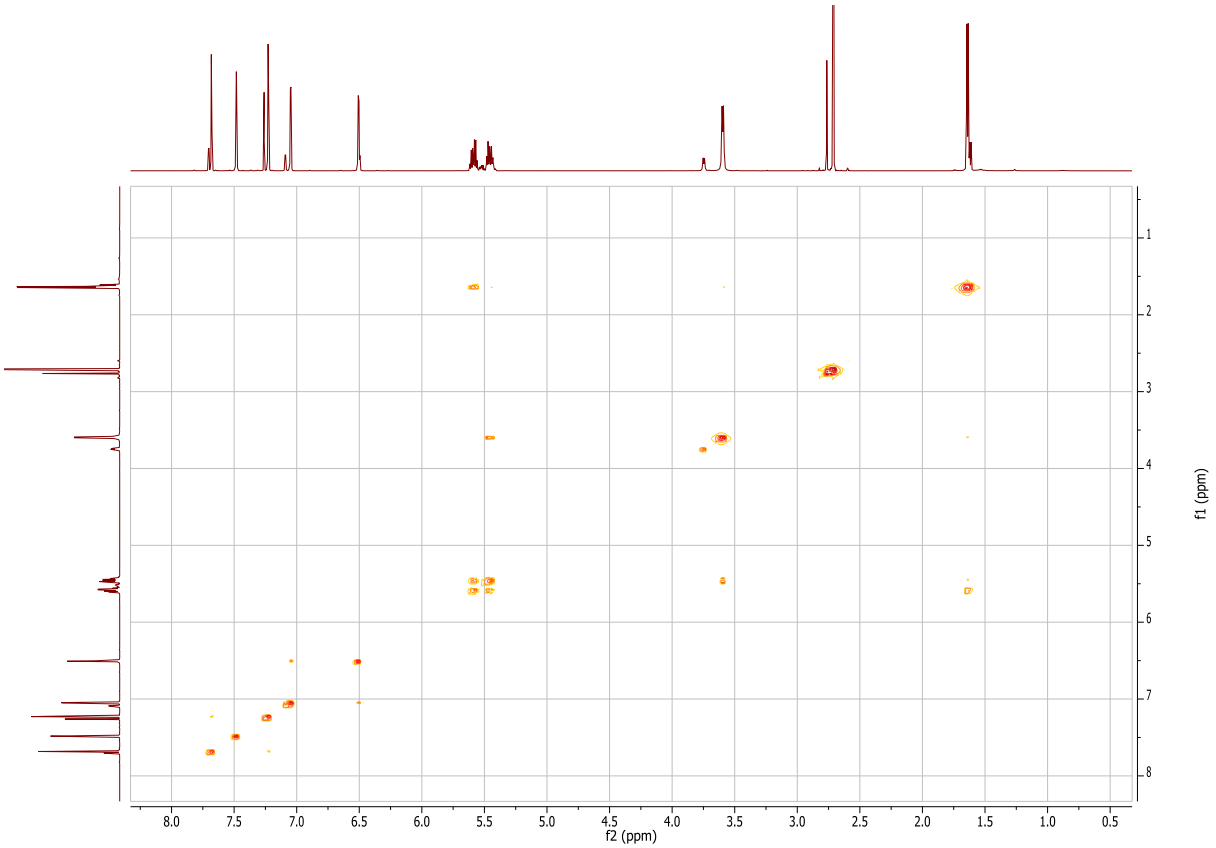
Spectrum 42. 400 MHz, $CDCl_3$, COSY of *N*-(but-2-en-1-yl)-2,4-dichloro-6-(furan-2-yl)aniline (**48b**).



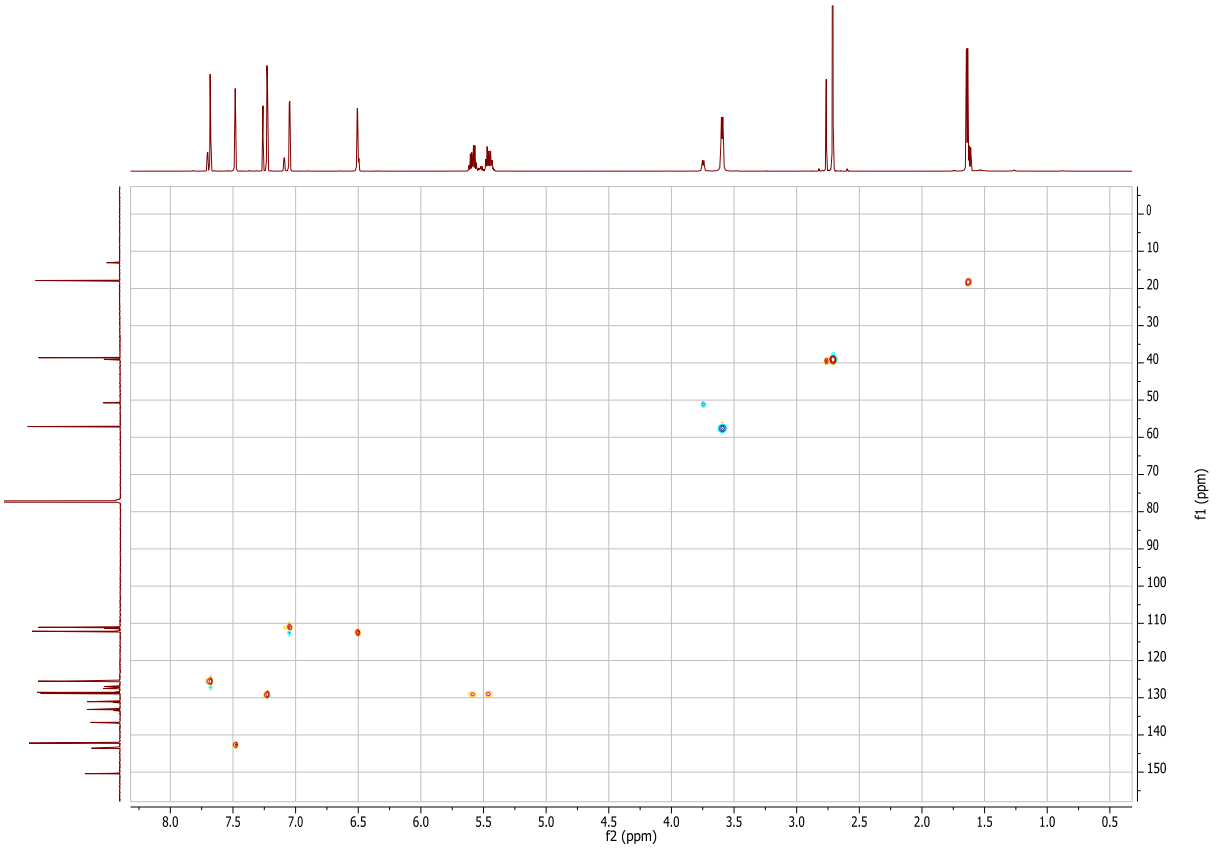
Spectrum 43. 400 MHz, $CDCl_3$, HSQC of *N*-(but-2-en-1-yl)-2,4-dichloro-6-(furan-2-yl)aniline (**48b**).



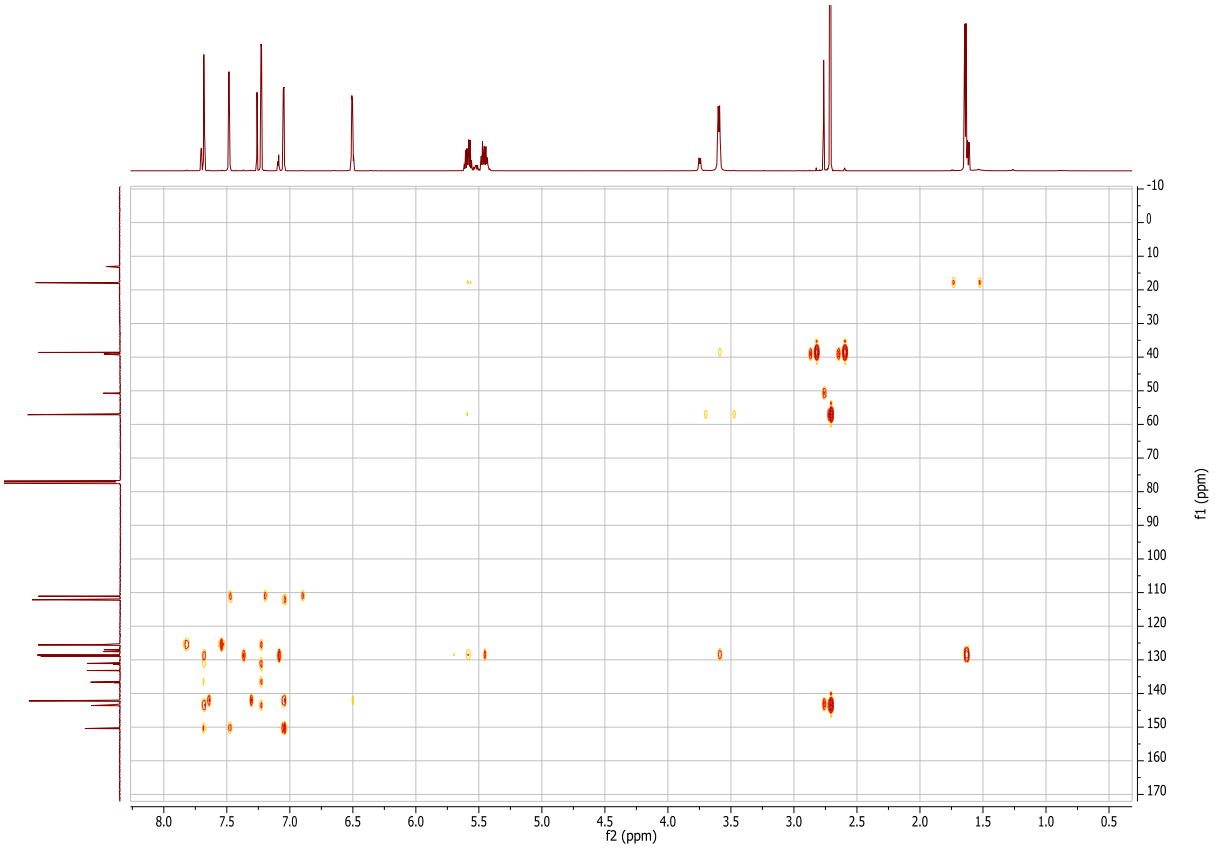
Spectrum 44. 400 MHz, $CDCl_3$, HMBC of *N*-(but-2-en-1-yl)-2,4-dichloro-6-(furan-2-yl)aniline (**48b**).



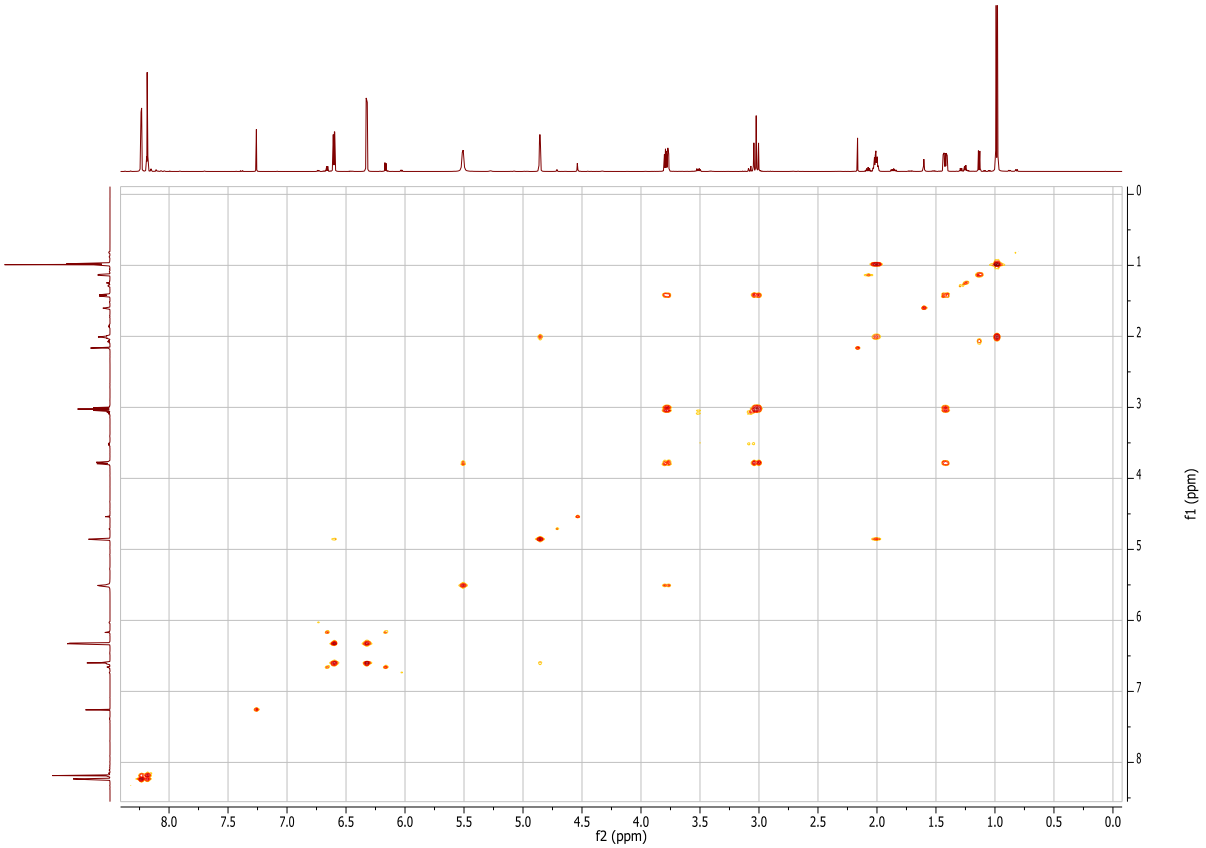
Spectrum 45. 600 MHz, $CDCl_3$, COSY of *N*-(but-2-en-1-yl)-2,4-dichloro-6-(furan-2-yl)-*N*-methylaniline (**48c**).



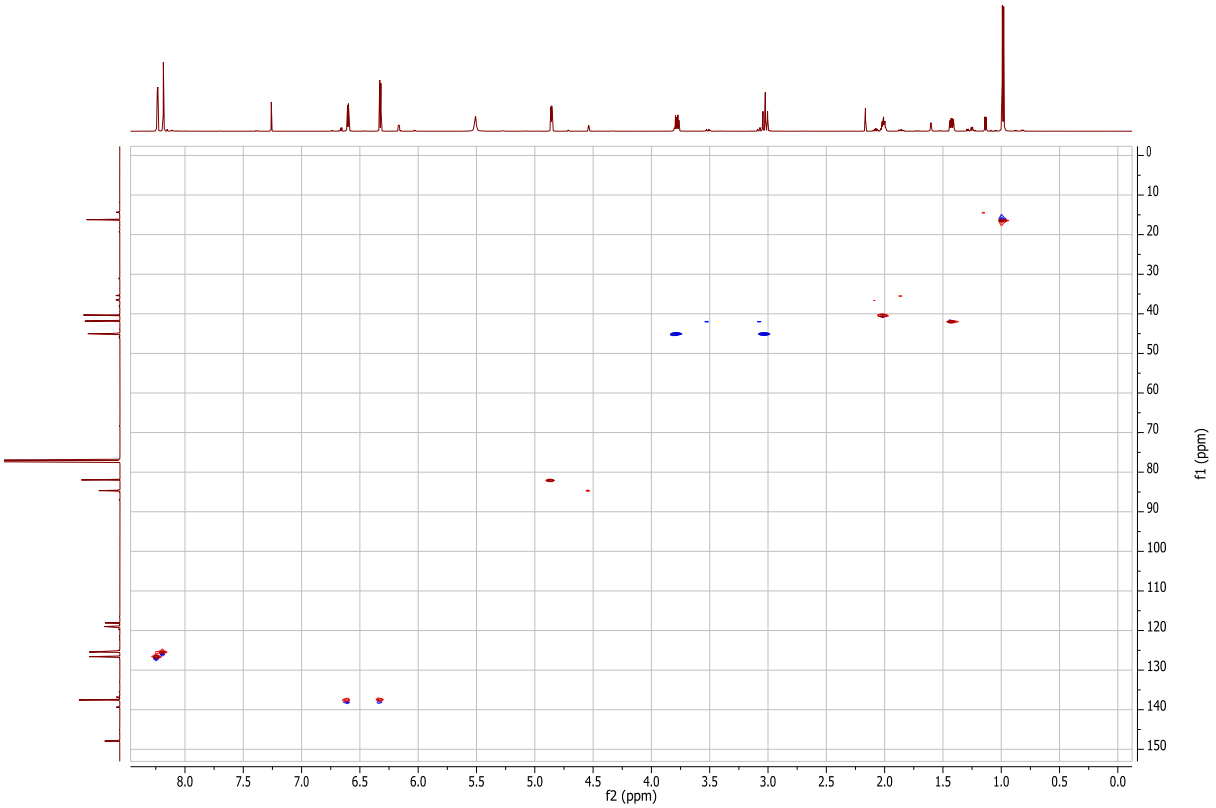
Spectrum 46. 600 MHz, $CDCl_3$, HSQC of *N*-(but-2-en-1-yl)-2,4-dichloro-6-(furan-2-yl)-*N*-methylaniline (**48c**).



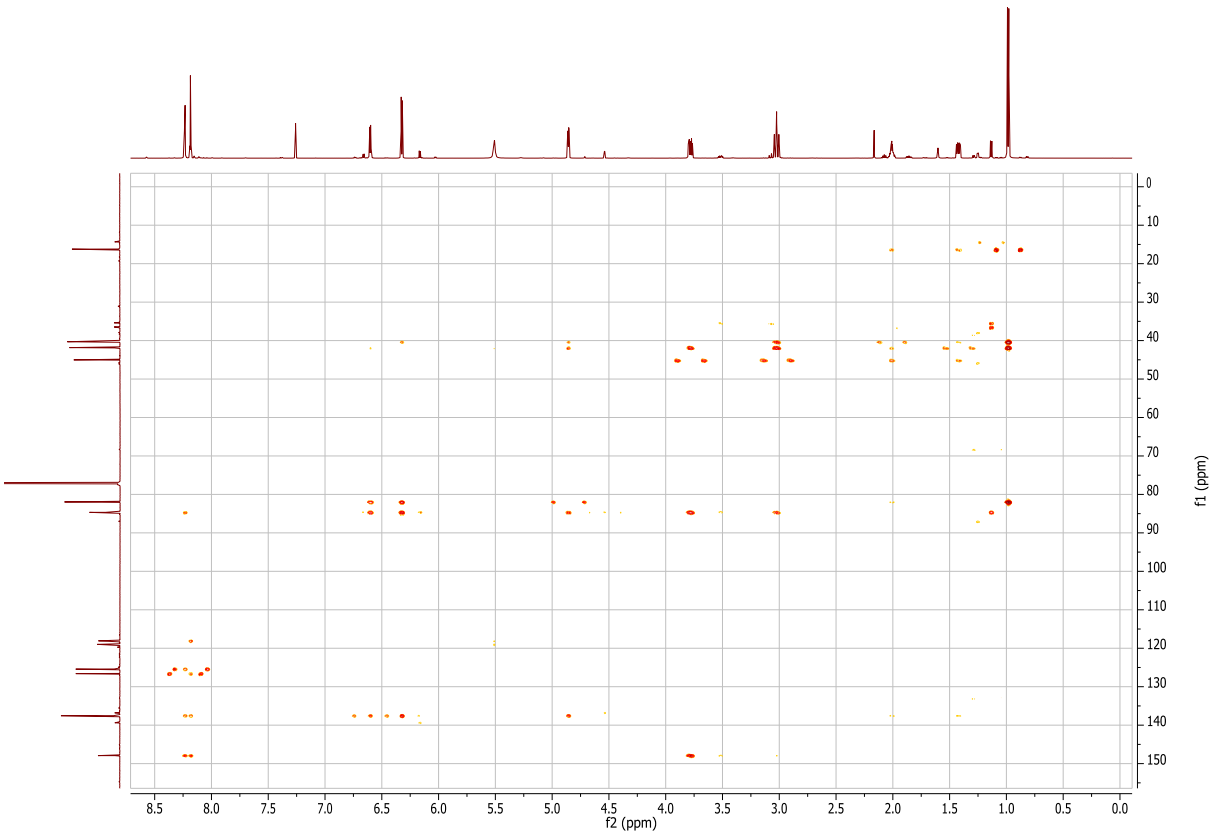
Spectrum 47. 600 MHz, $CDCl_3$, HMBC of *N*-(but-2-en-1-yl)-2,4-dichloro-6-(furan-2-yl)-*N*-methylaniline (**48c**).



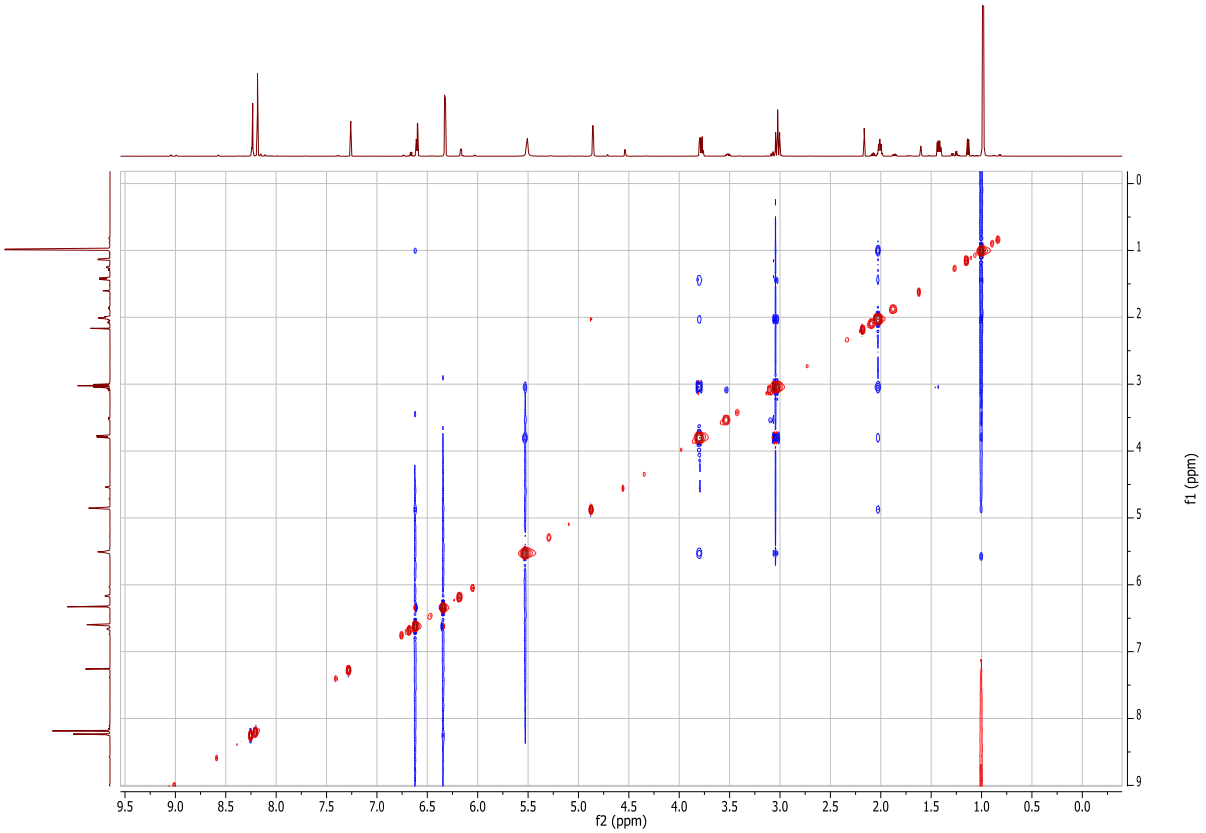
Spectrum 48. 600 MHz, $CDCl_3$, COSY of (±)-(*6aS,7R,8R,10aS*)-4-chloro-7-methyl-2-nitro-6,6a,7,8-tetrahydro-*5H*-8,10a-epoxyphenanthridine (**49a**).



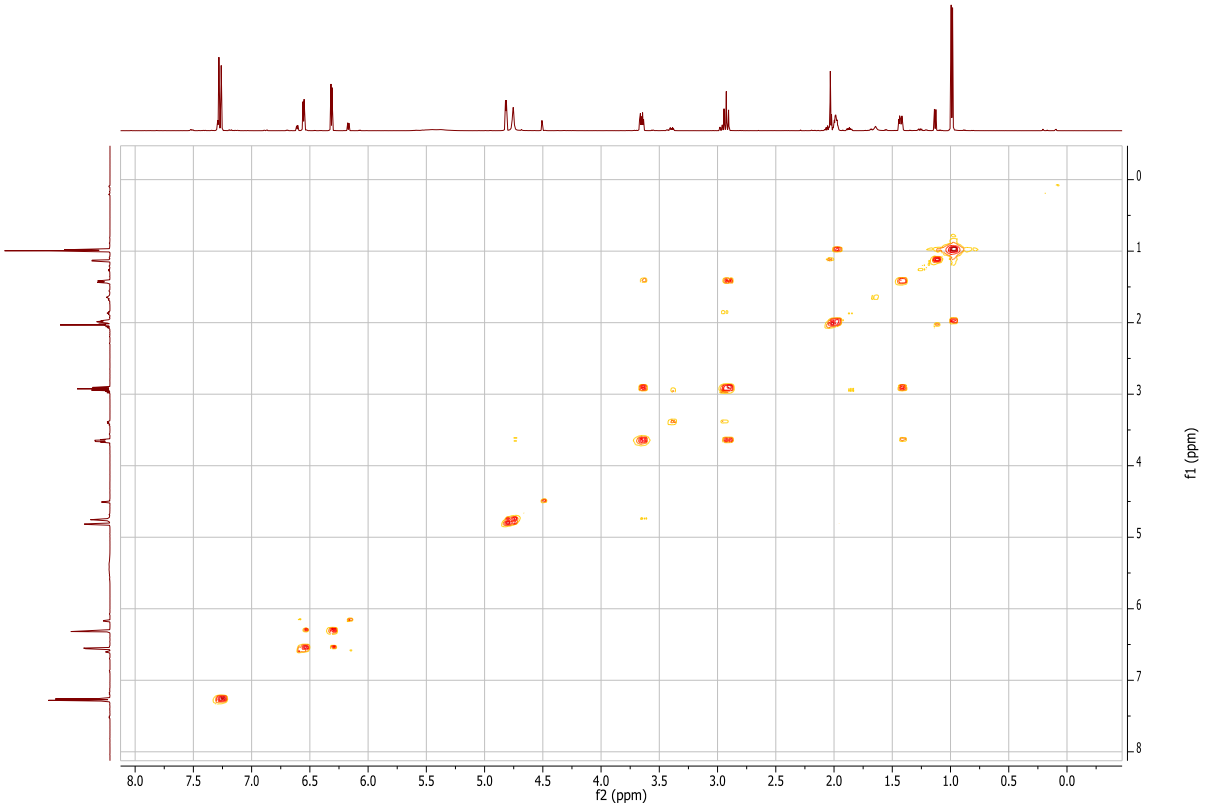
Spectrum 49. 600 MHz, $CDCl_3$, HSQC of (±)-(*6aS,7R,8R,10aS*)-4-chloro-7-methyl-2-nitro-6,6a,7,8-tetrahydro-*5H*-8,10a-epoxyphenanthridine (**49a**).



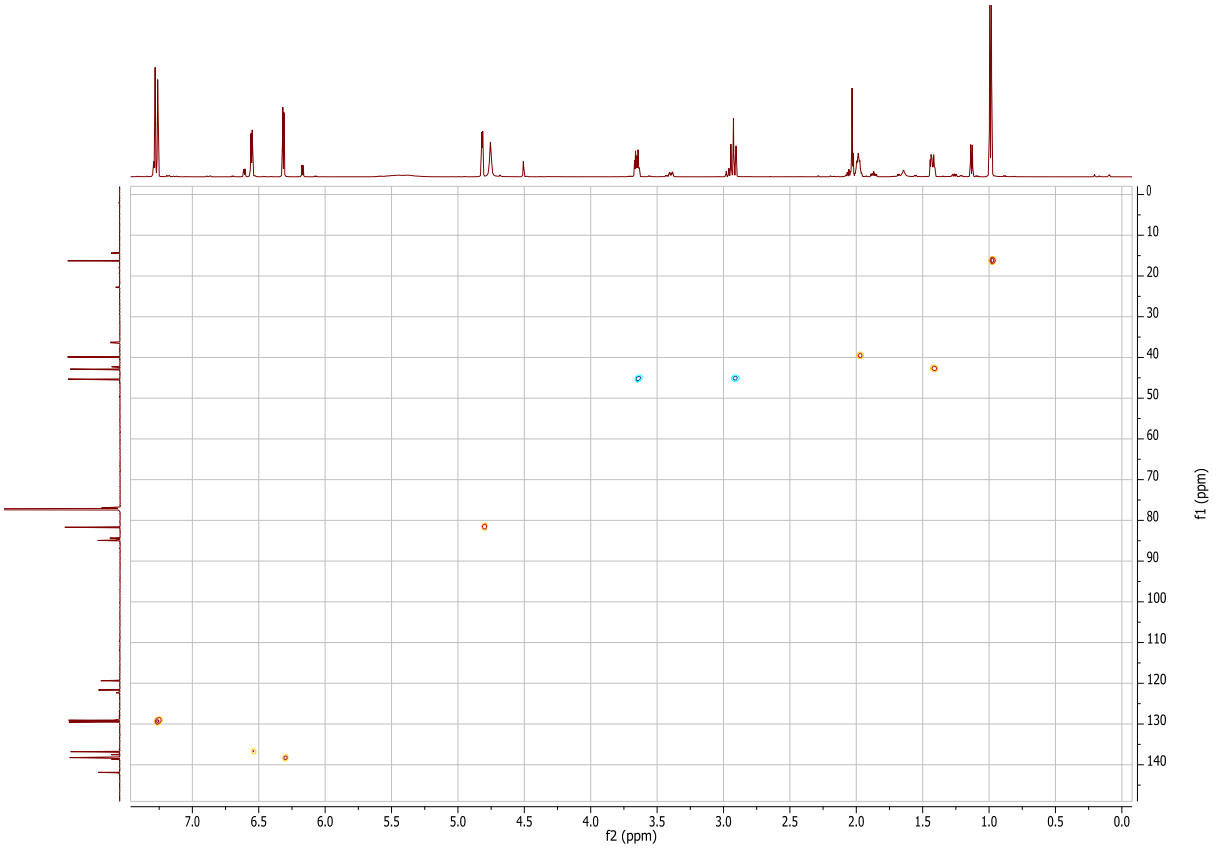
Spectrum 50. 600 MHz, $CDCl_3$, HMBC of (±)-(*6aS,7R,8R,10aS*)-4-chloro-7-methyl-2-nitro-6,6a,7,8-tetrahydro-*5H*-8,10a-epoxyphenanthridine (**49a**).



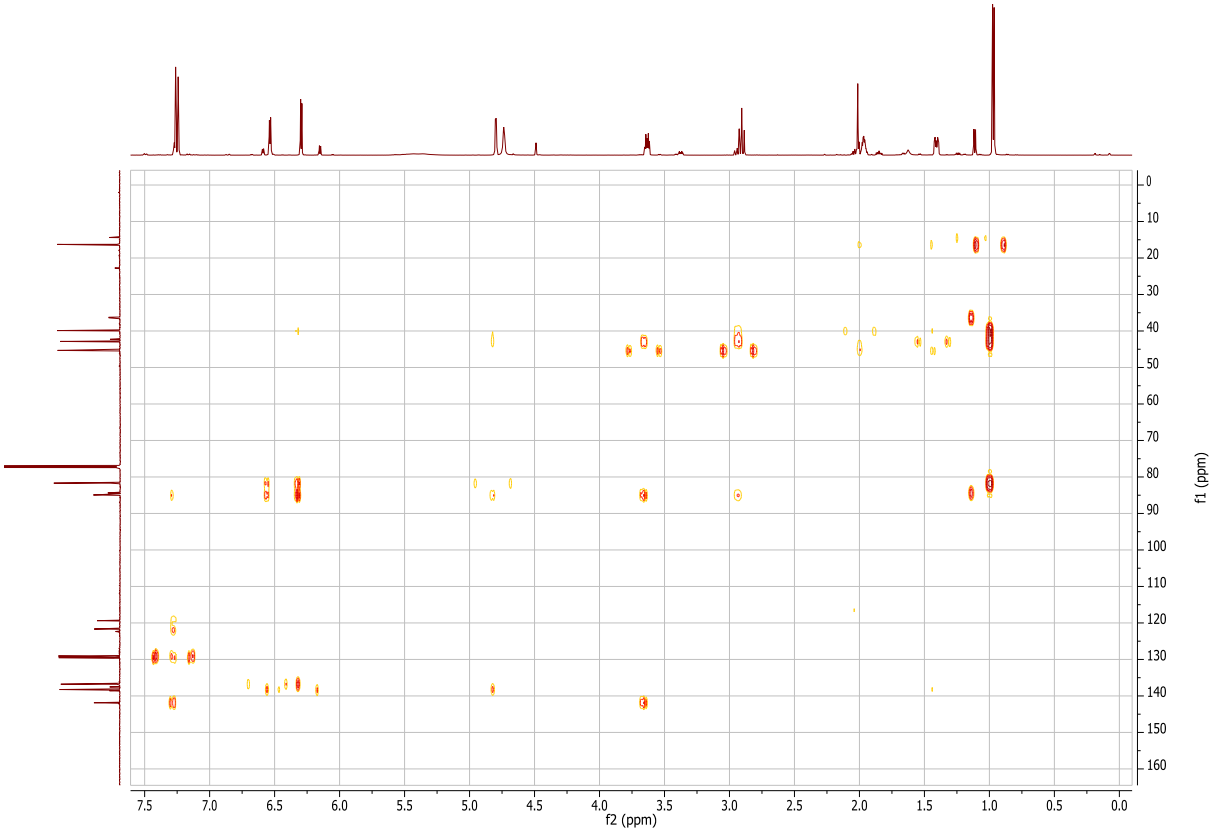
Spectrum 51. 600 MHz, $CDCl_3$, NOESY of (±)-(*6aS,7R,8R,10aS*)-4-chloro-7-methyl-2-nitro-6,6a,7,8-tetrahydro-*5H*-8,10a-epoxyphenanthridine (**49a**).



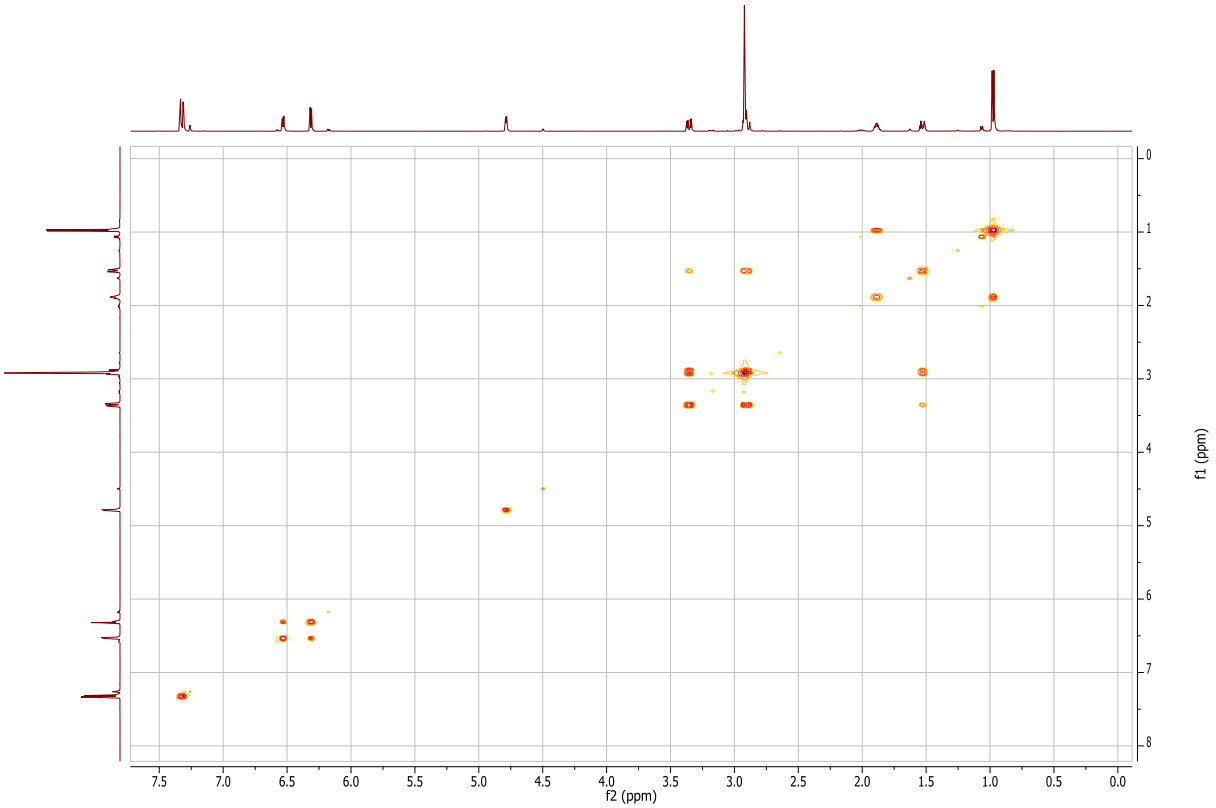
Spectrum 52. 600 MHz, $CDCl_3$, COSY of (±)-(*6aS,7R,8R,10aS*)-2,4-dichloro-7-methyl-6,6a,7,8-tetrahydro-*5H*-8,10a-epoxyphenanthridine (**49b**).



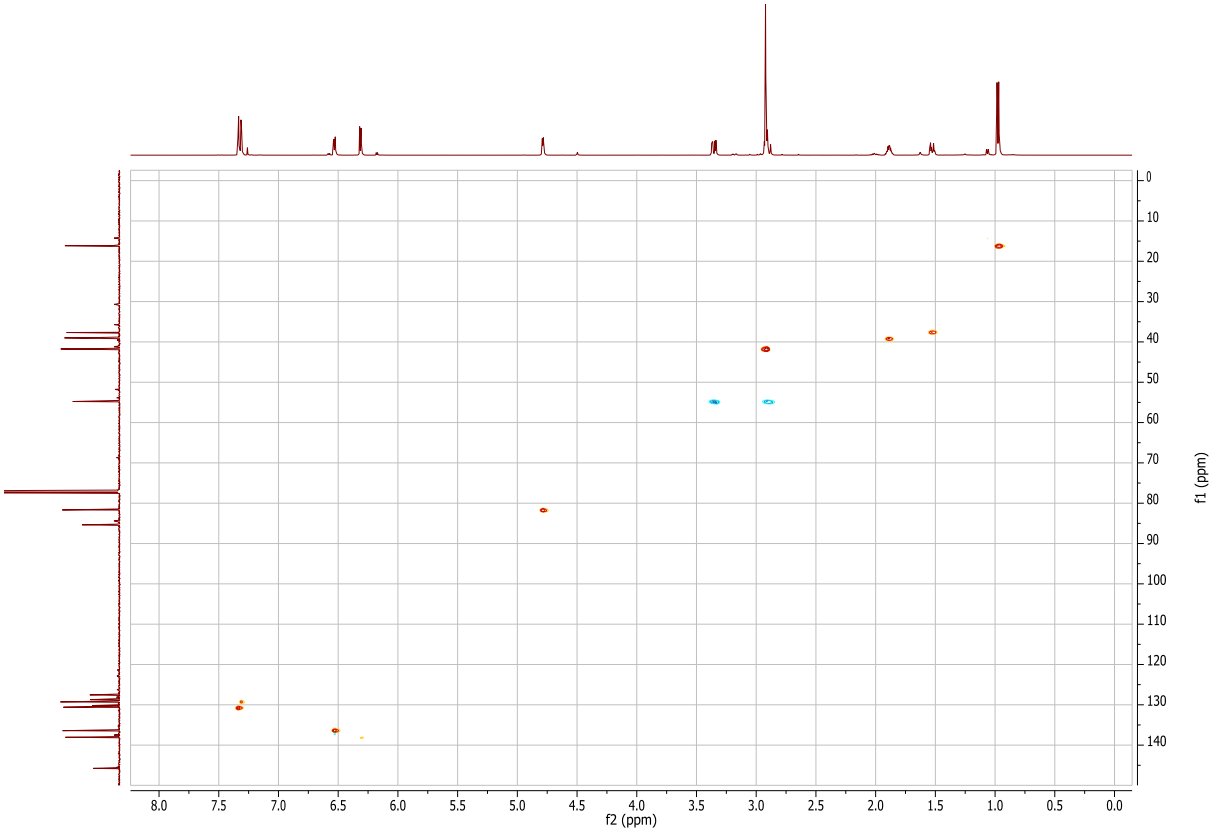
Spectrum 53. 600 MHz, $CDCl_3$, HSQC of (±)-(*6aS,7R,8R,10aS*)-2,4-dichloro-7-methyl-6,6a,7,8-tetrahydro-*5H*-8,10a-epoxyphenanthridine (**49b**).



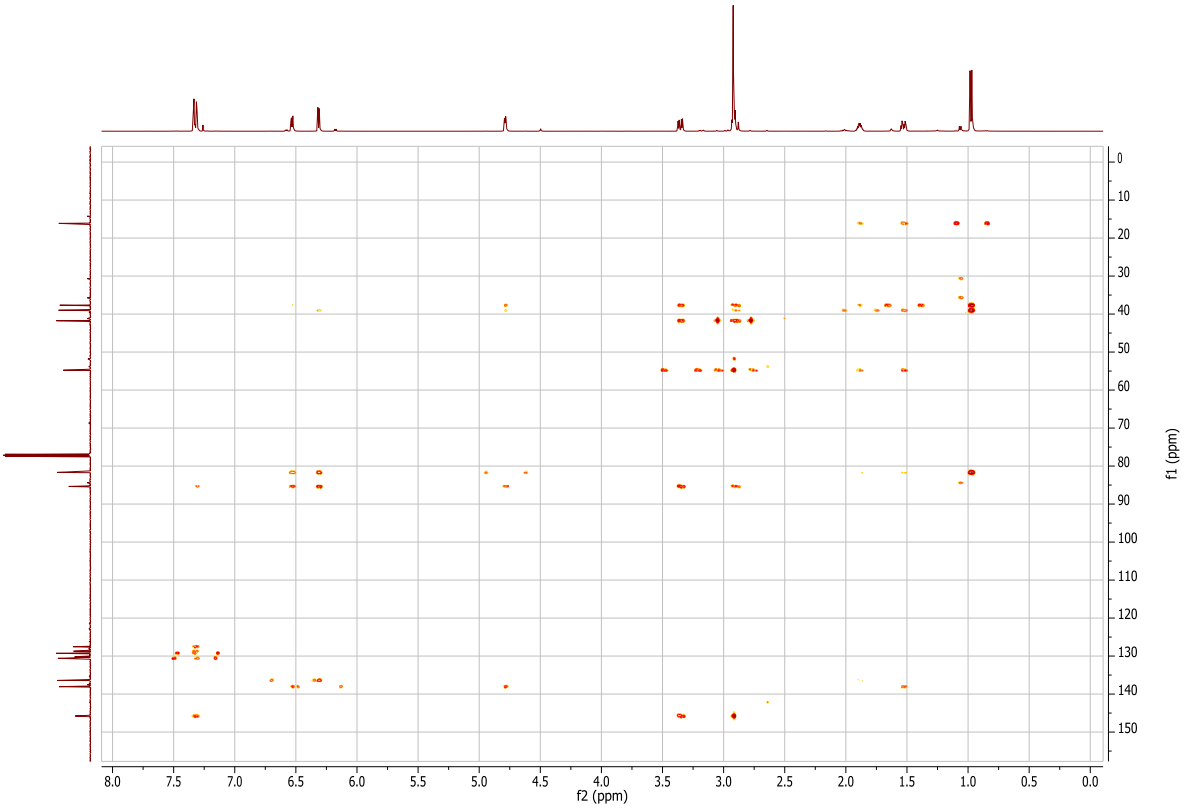
Spectrum 53. 600 MHz, $CDCl_3$, HMBC of (±)-(*6aS,7R,8R,10aS*)-2,4-dichloro-7-methyl-6,6a,7,8-tetrahydro-*5H*-8,10a-epoxyphenanthridine (**49b**).



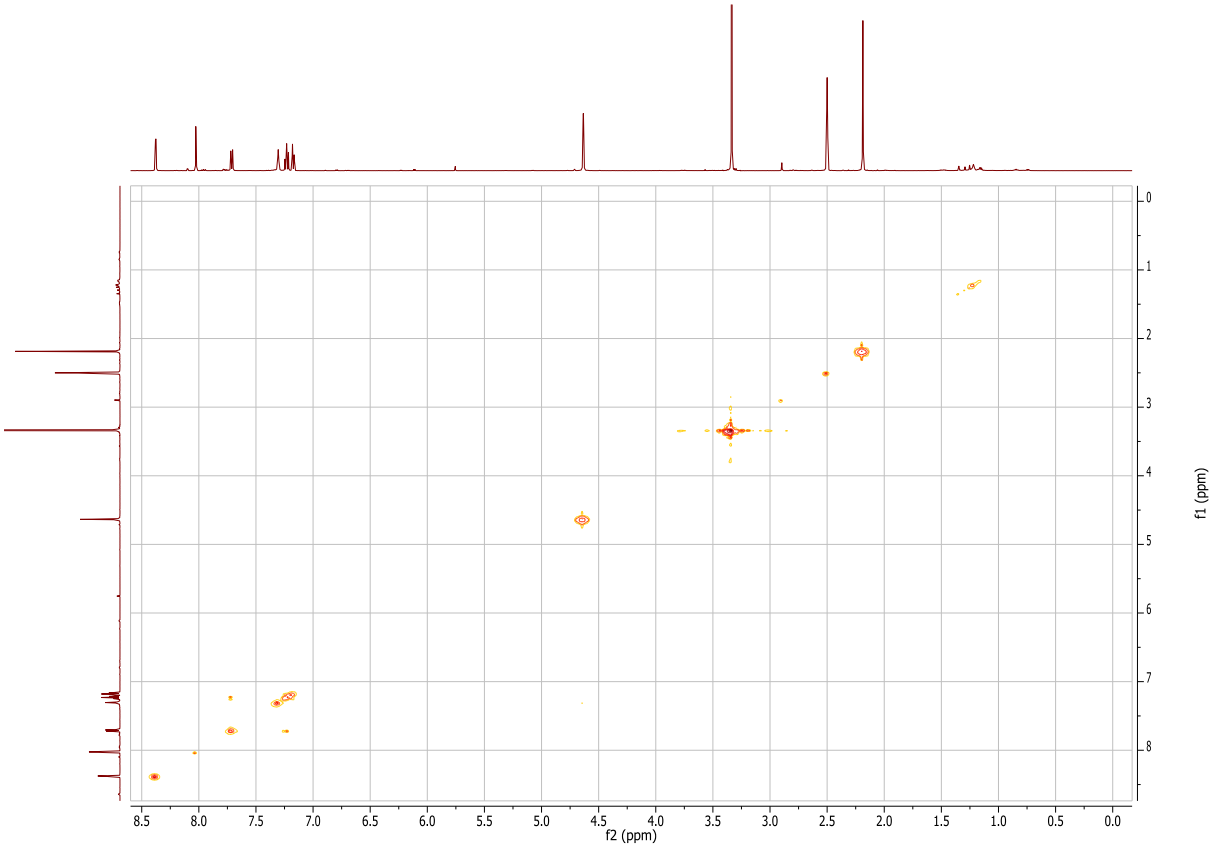
Spectrum 54. 500 MHz, $CDCl_3$, COSY of (±)-(*6aS,7R,8R,10aS*)-2,4-dichloro-5,7-dimethyl-6,6a,7,8-tetrahydro-8,10a-epoxyphenanthridine (**49c**).



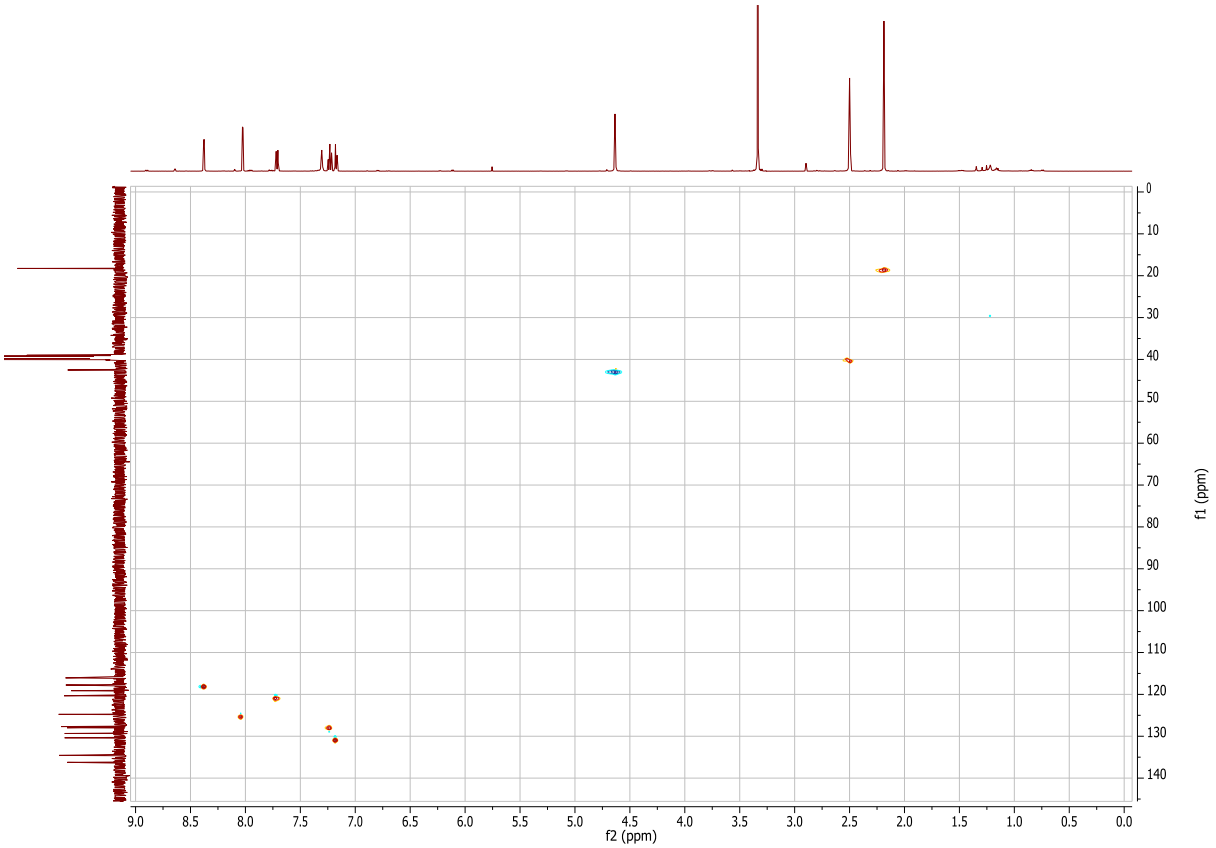
Spectrum 55. 500 MHz, $CDCl_3$, HSQC of (±)-(*6aS,7R,8R,10aS*)-2,4-dichloro-5,7-dimethyl-6,6a,7,8-tetrahydro-8,10a-epoxyphenanthridine (**49c**).



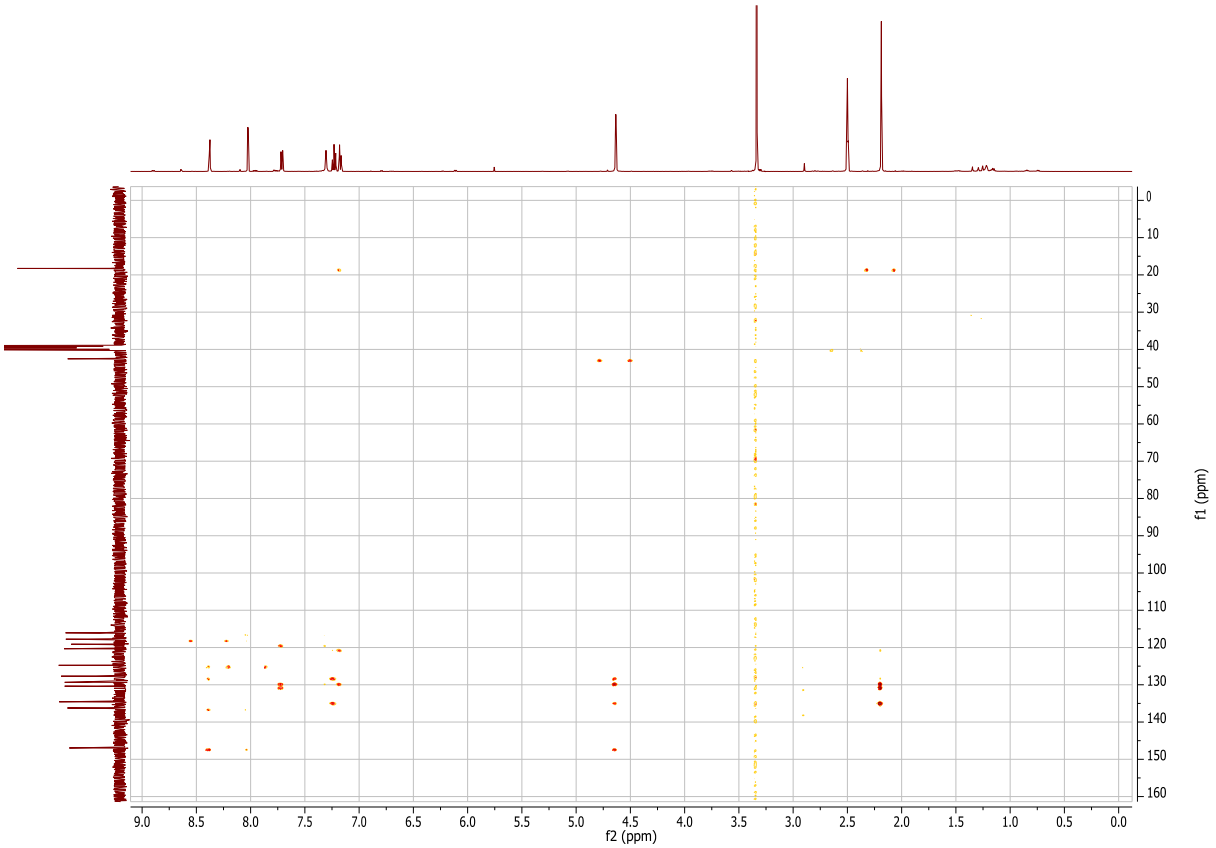
Spectrum 56. 500 MHz, $CDCl_3$, HMBC of (±)-(*6aS,7R,8R,10aS*)-2,4-dichloro-5,7-dimethyl-6,6a,7,8-tetrahydro-8,10a-epoxyphenanthridine (**49c**).



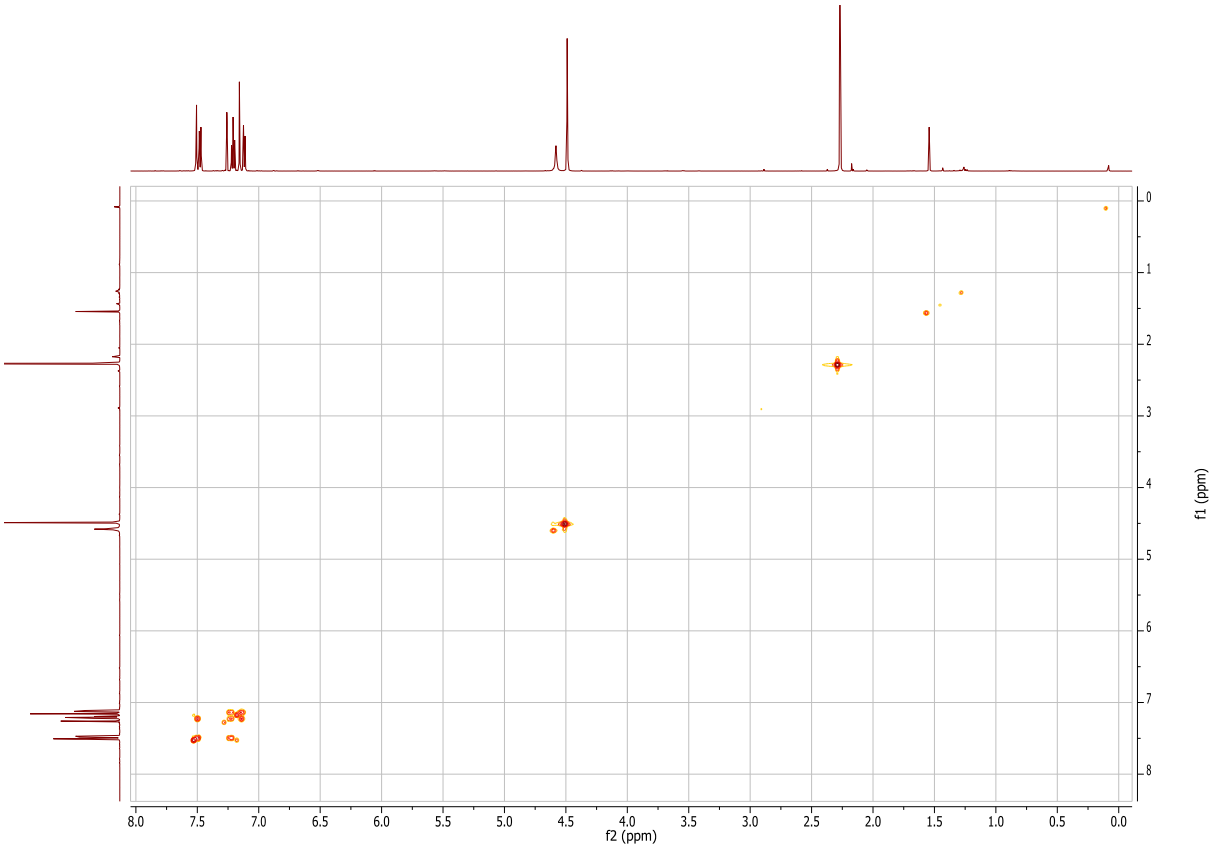
Spectrum 57. 500 MHz, DMSO, COSY of 4-chloro-7-methyl-2-nitro-5,6-dihydrophenanthridine (**56a**).



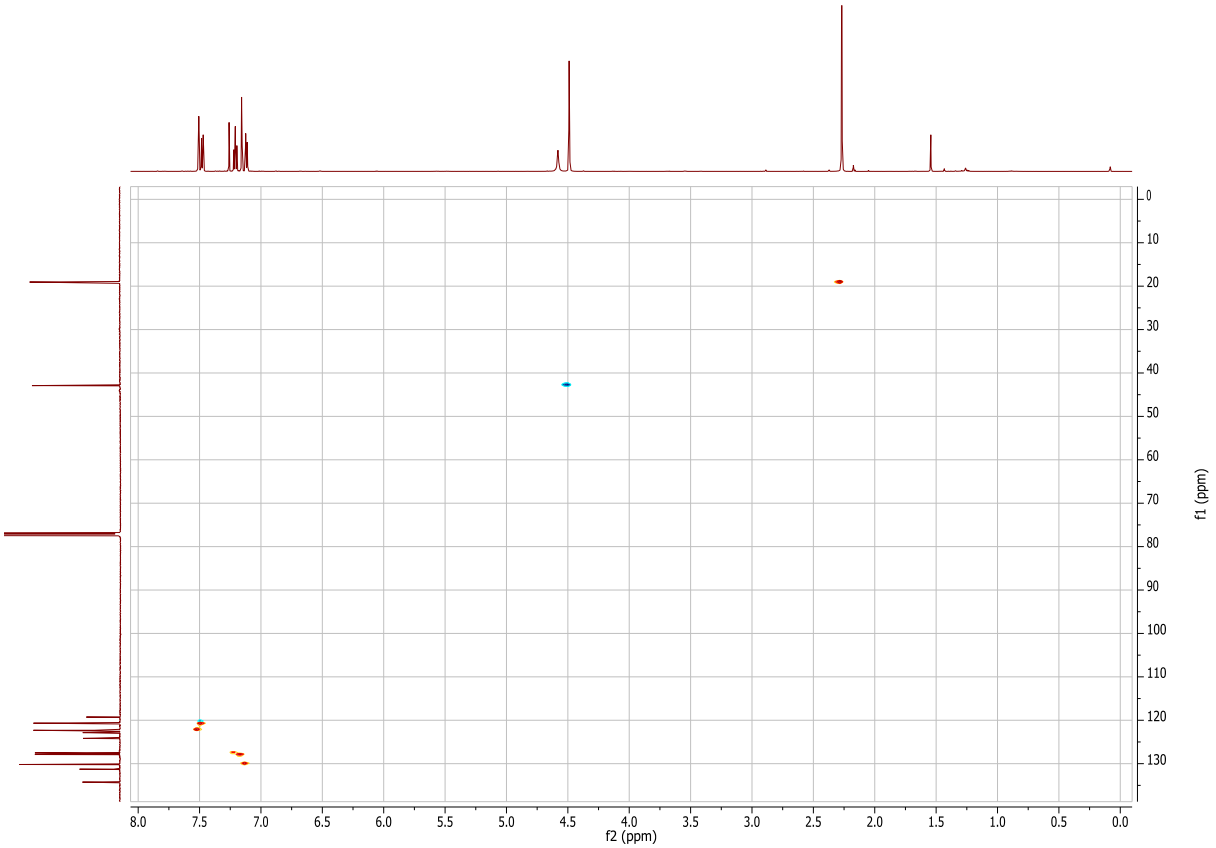
Spectrum 58. 500 MHz, DMSO, HSQC of 4-chloro-7-methyl-2-nitro-5,6-dihydrophenanthridine (**56a**).



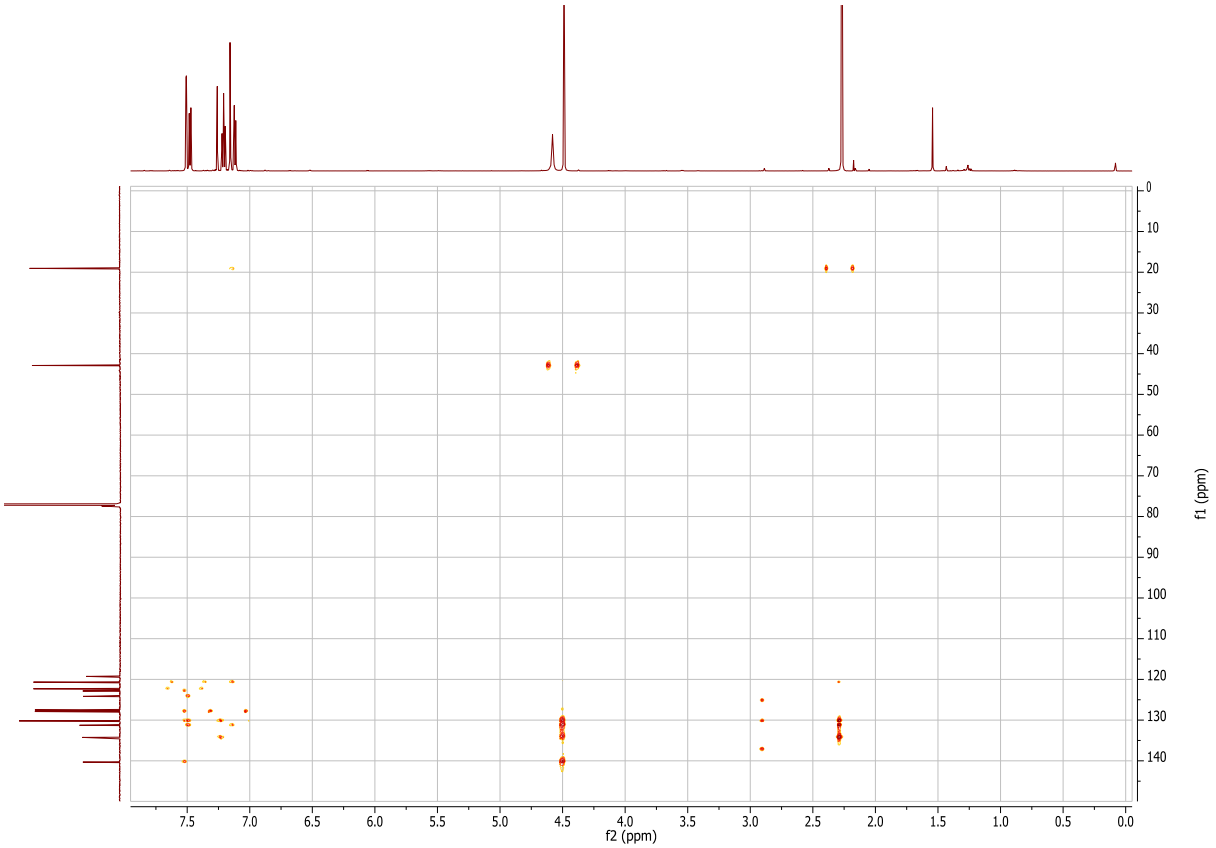
Spectrum 59. 500 MHz, DMSO, HMBC of 4-chloro-7-methyl-2-nitro-5,6-dihydrophenanthridine (**56a**).



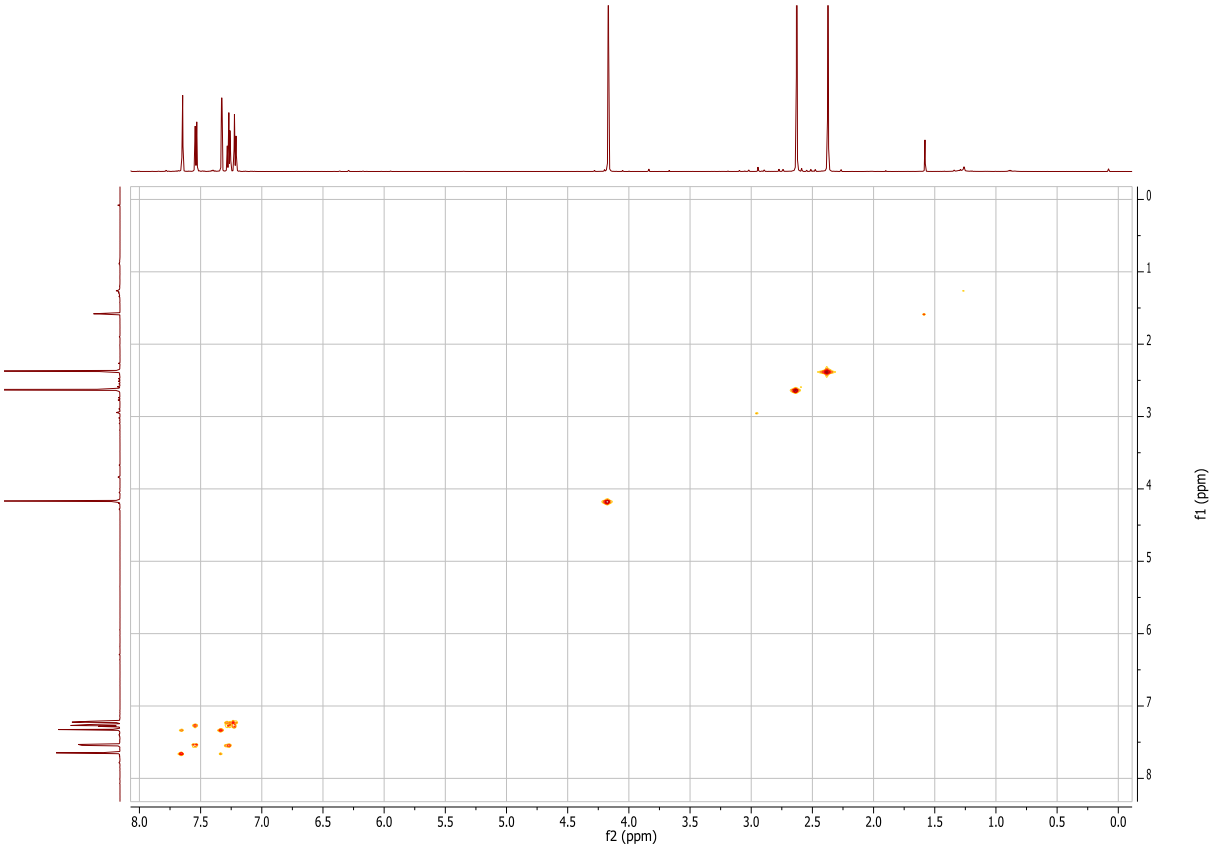
Spectrum 60. 600 MHz, $CDCl_3$, COSY of 2,4-dichloro-7-methyl-5,6-dihydrophenanthridine (**56b**).



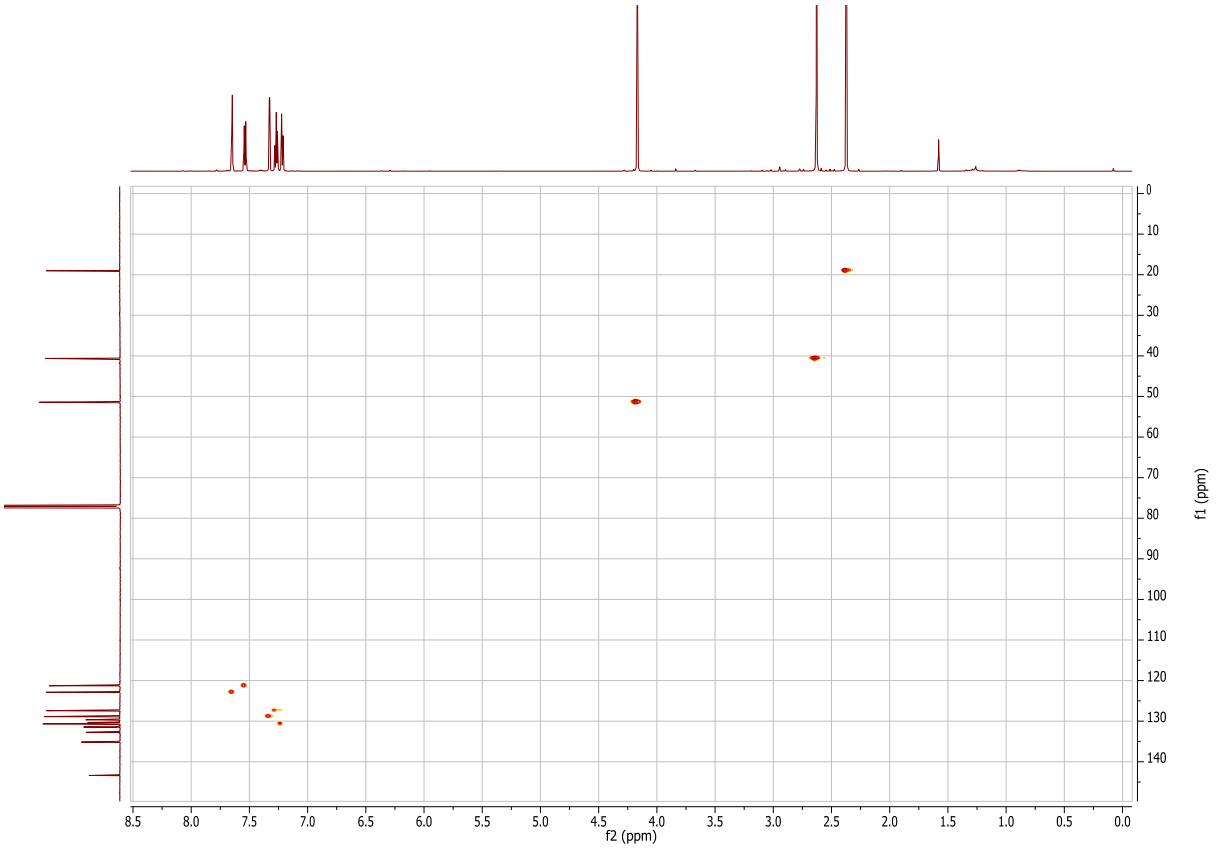
Spectrum 61. 600 MHz, $CDCl_3$, HSQC of 2,4-dichloro-7-methyl-5,6-dihydrophenanthridine (**56b**).



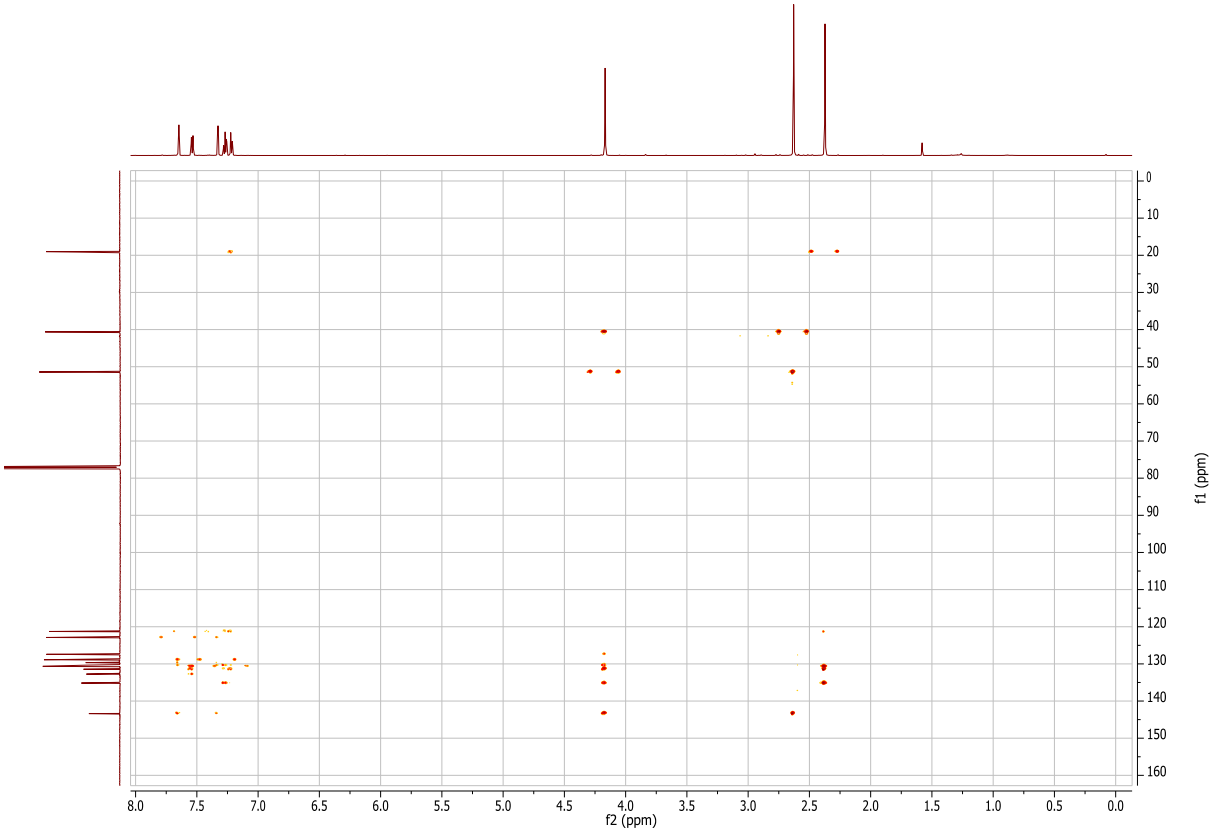
Spectrum 62. 600 MHz, $CDCl_3$, HMBC of 2,4-dichloro-7-methyl-5,6-dihydrophenanthridine (**56b**).



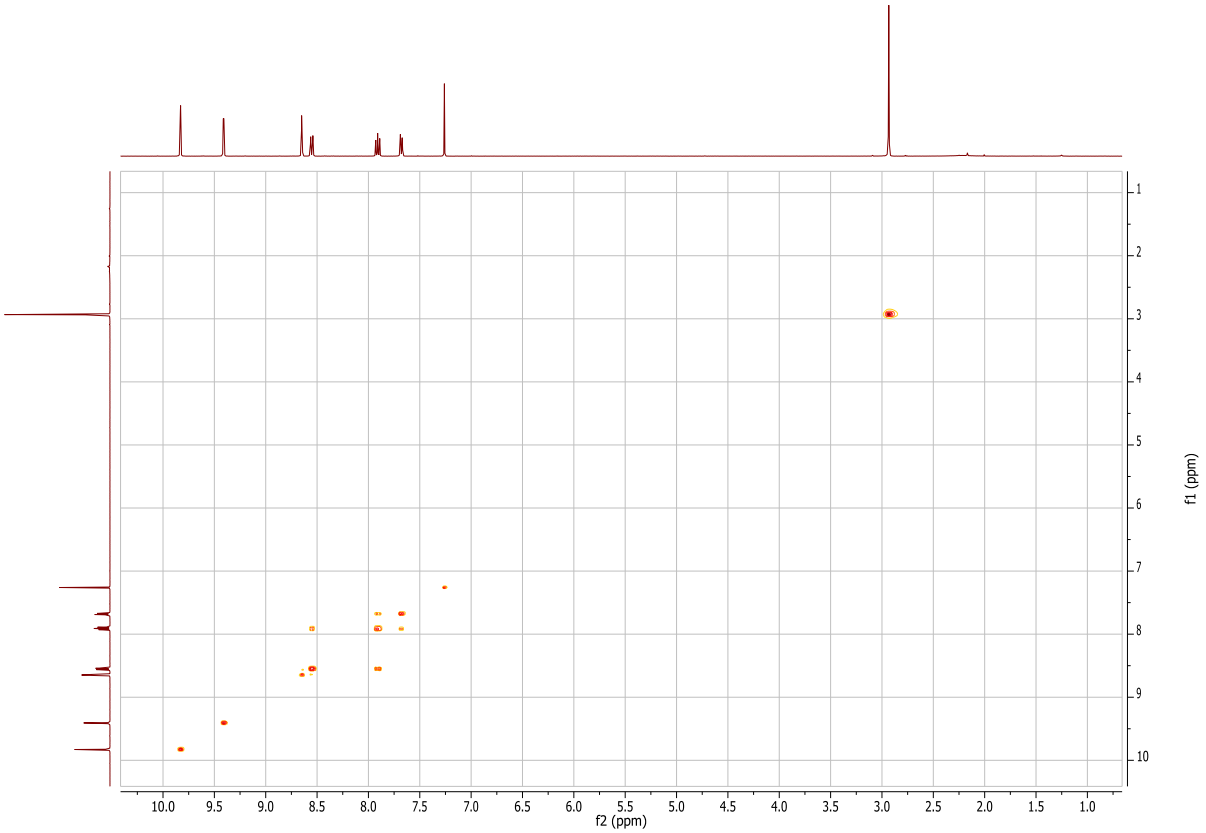
Spectrum 63. 600 MHz, $CDCl_3$, COSY of 2,4-dichloro-5,7-dimethyl-5,6-dihydrophenanthridine (**56c**).



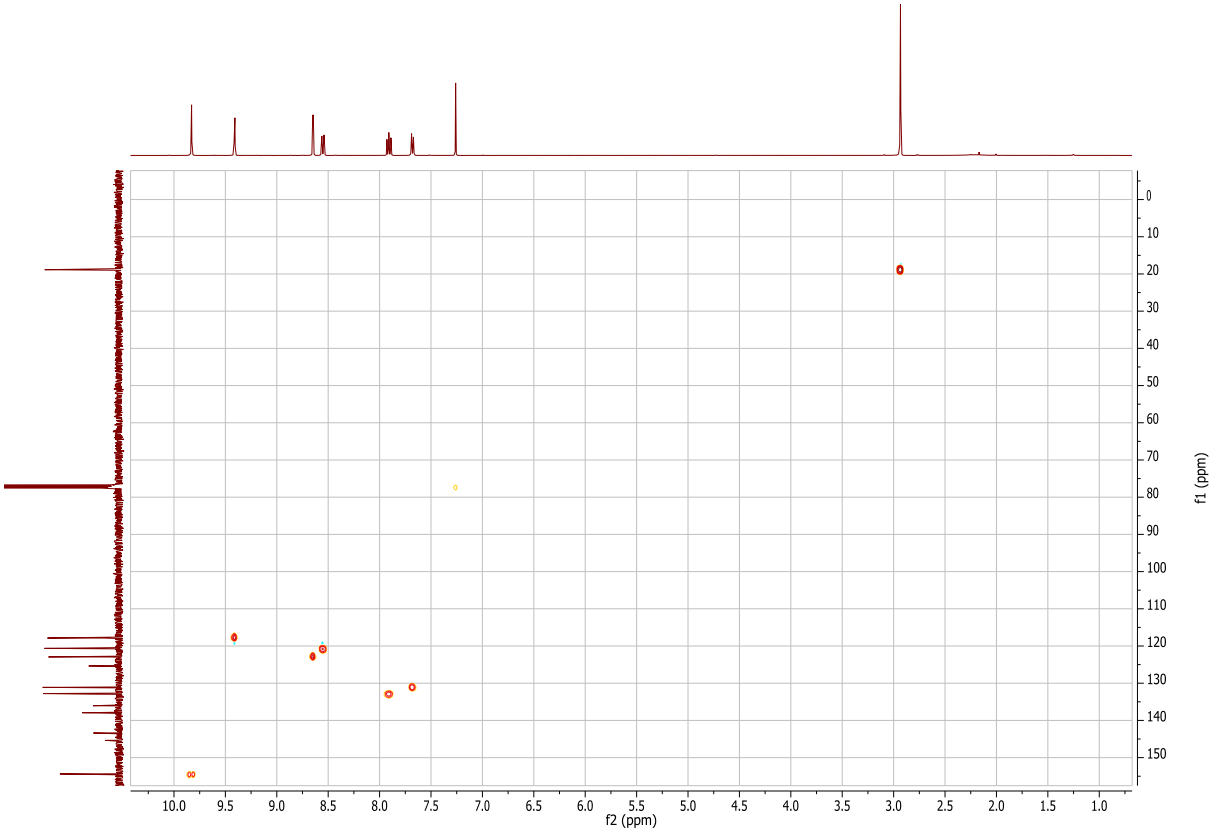
Spectrum 64. 600 MHz, $CDCl_3$, HSQC of 2,4-dichloro-5,7-dimethyl-5,6-dihydrophenanthridine (**56c**).



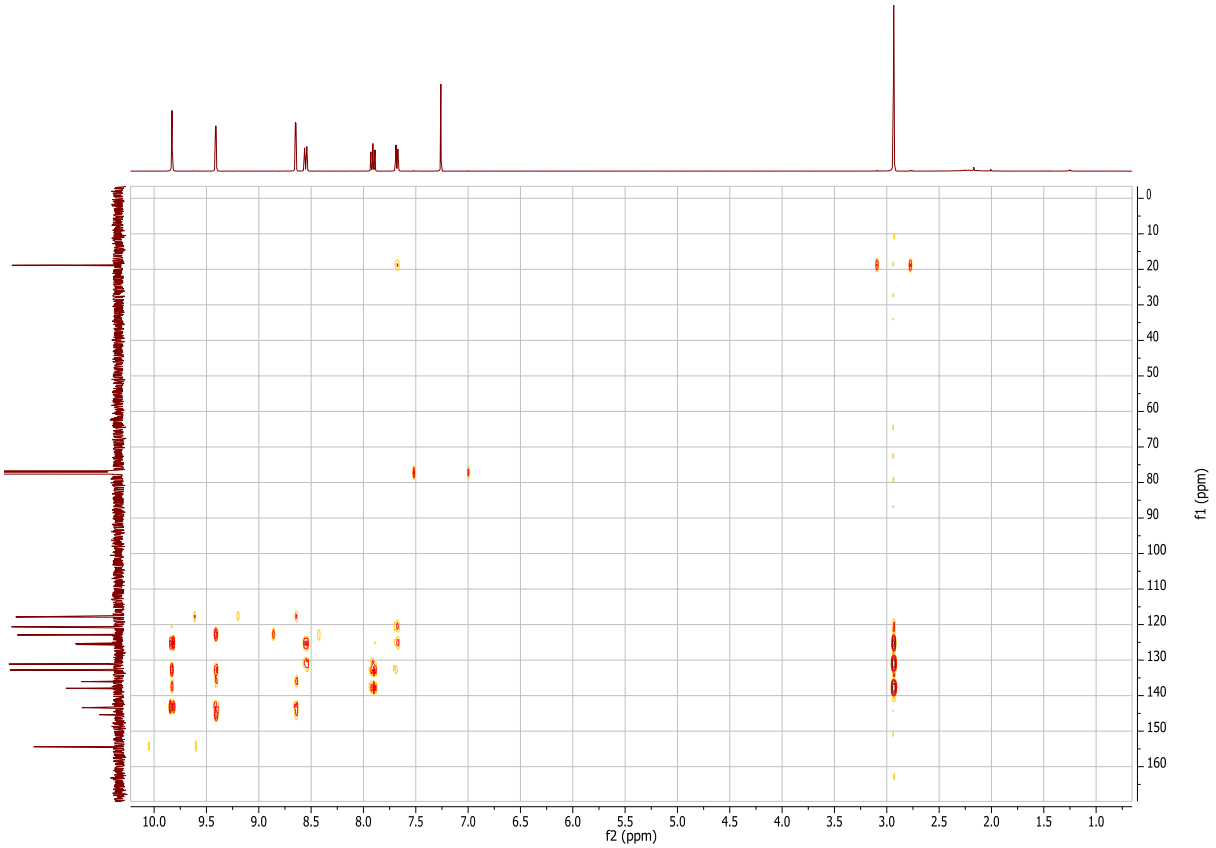
Spectrum 65. 600 MHz, $CDCl_3$, HMBC of 2,4-dichloro-5,7-dimethyl-5,6-dihydrophenanthridine (**56c**).



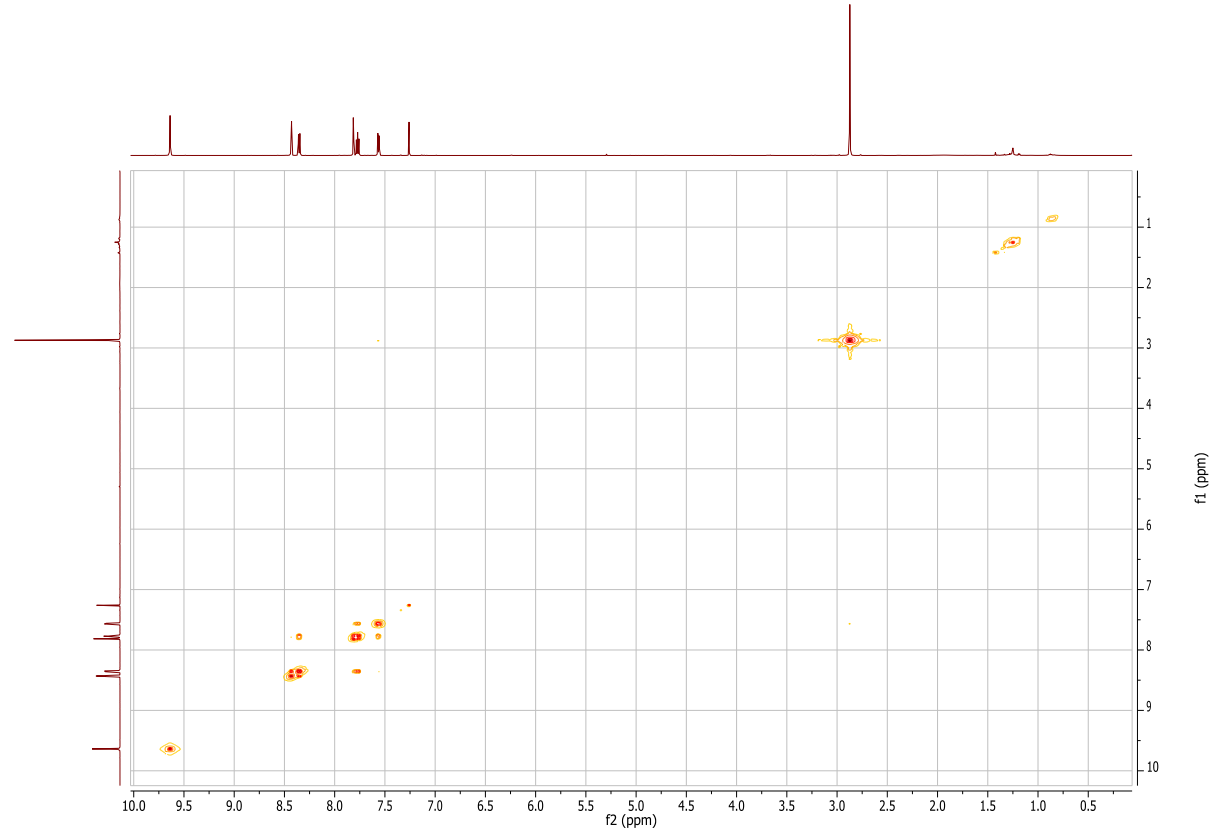
Spectrum 66. 400 MHz, $CDCl_3$, COSY of 4-chloro-7-methyl-2-nitrophenanthridine (**57a**).



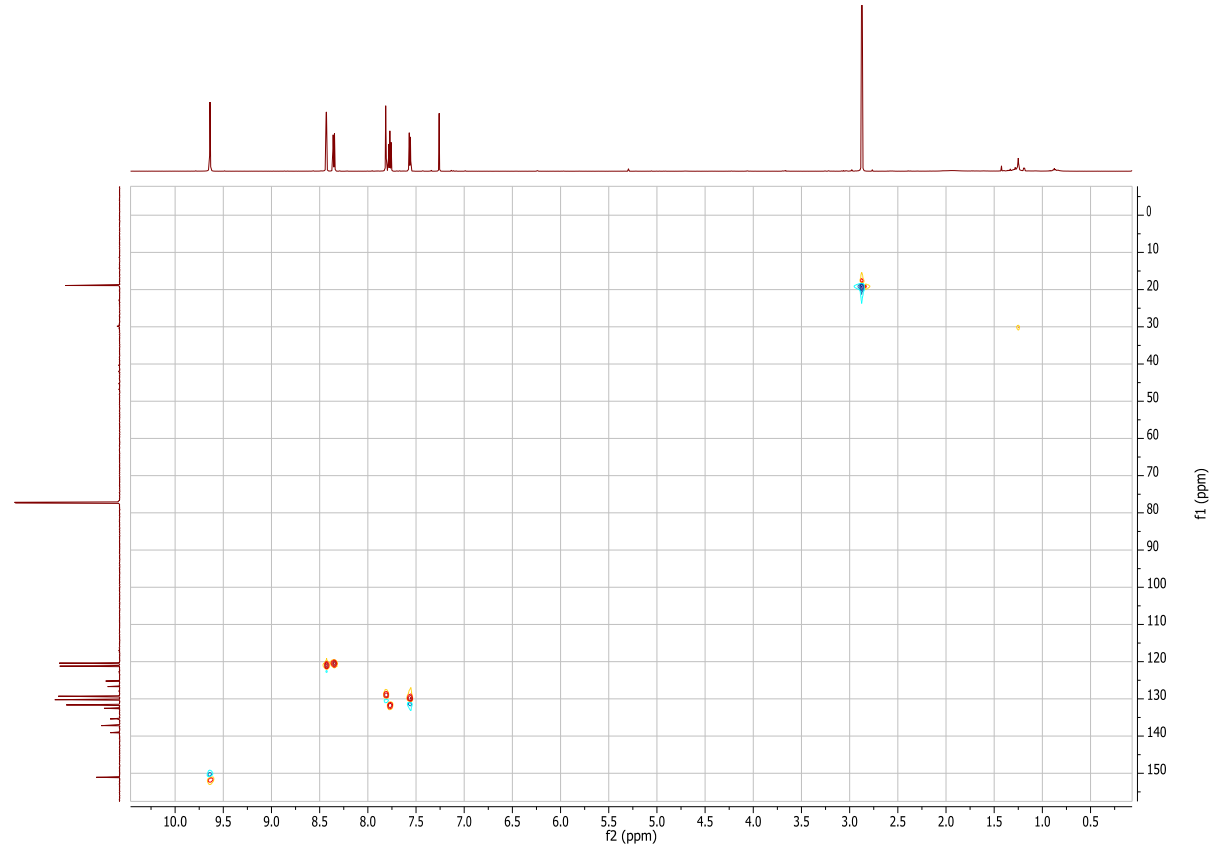
Spectrum 67. 400 MHz, $CDCl_3$, HSQC of 4-chloro-7-methyl-2-nitrophenanthridine (**57a**).



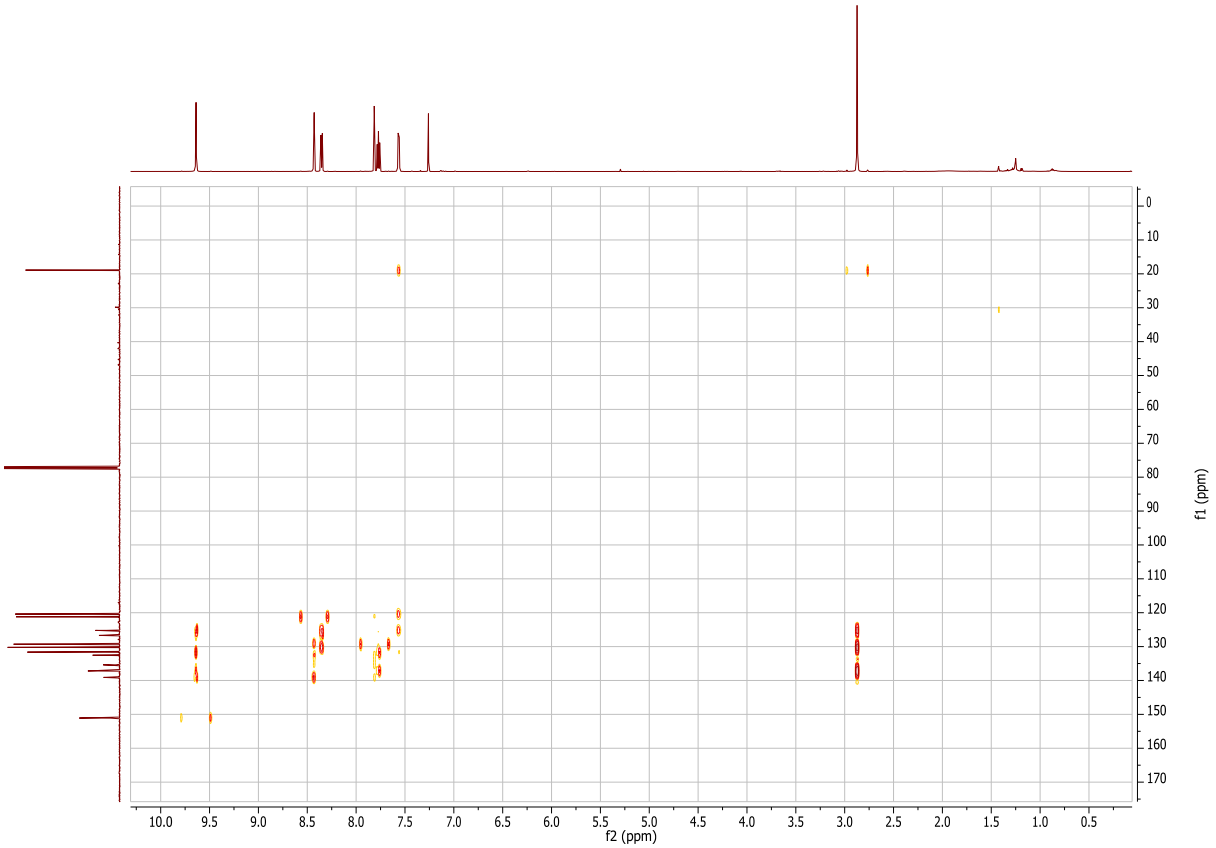
Spectrum 68. 400 MHz, $CDCl_3$, HMBC of 4-chloro-7-methyl-2-nitrophenanthridine (**57a**).



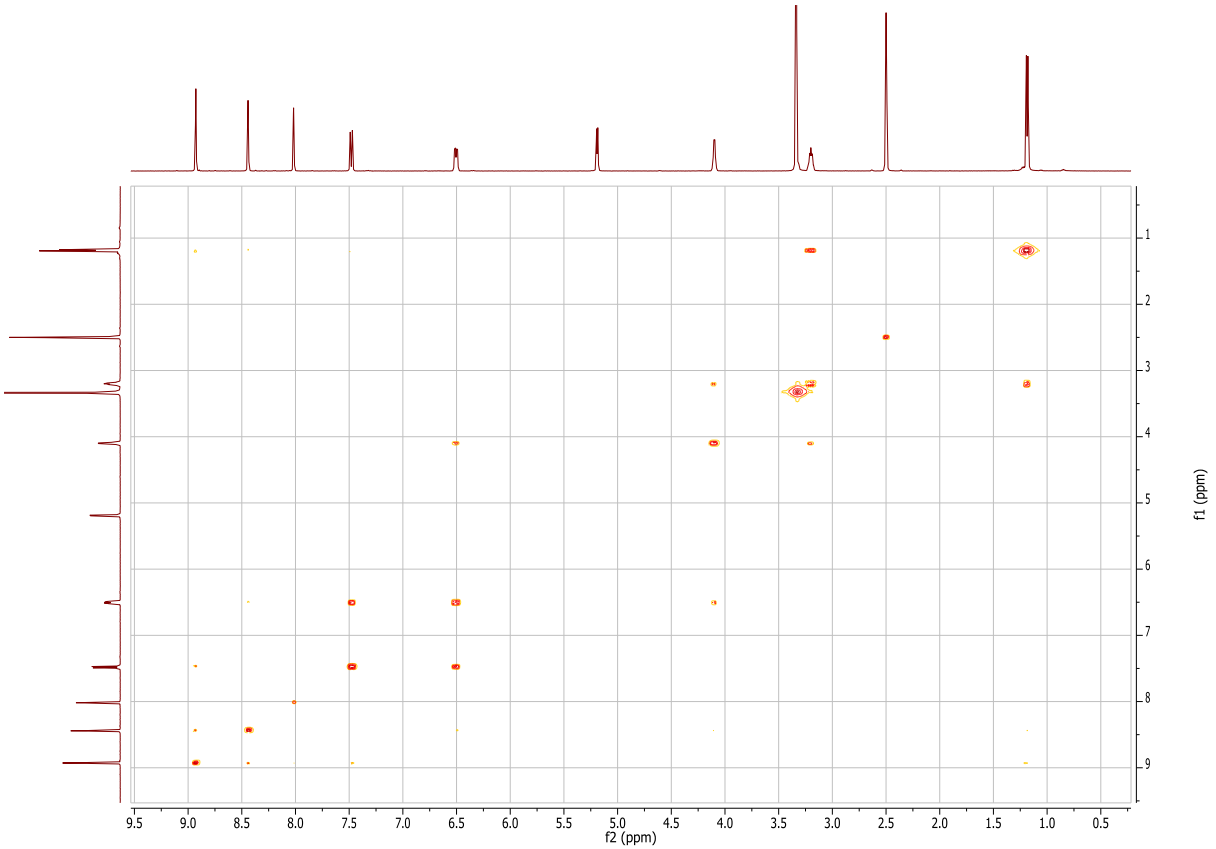
Spectrum 69. 600 MHz, $CDCl_3$, COSY of 2,4-dichloro-7-methylphenanthridine (**57b**).



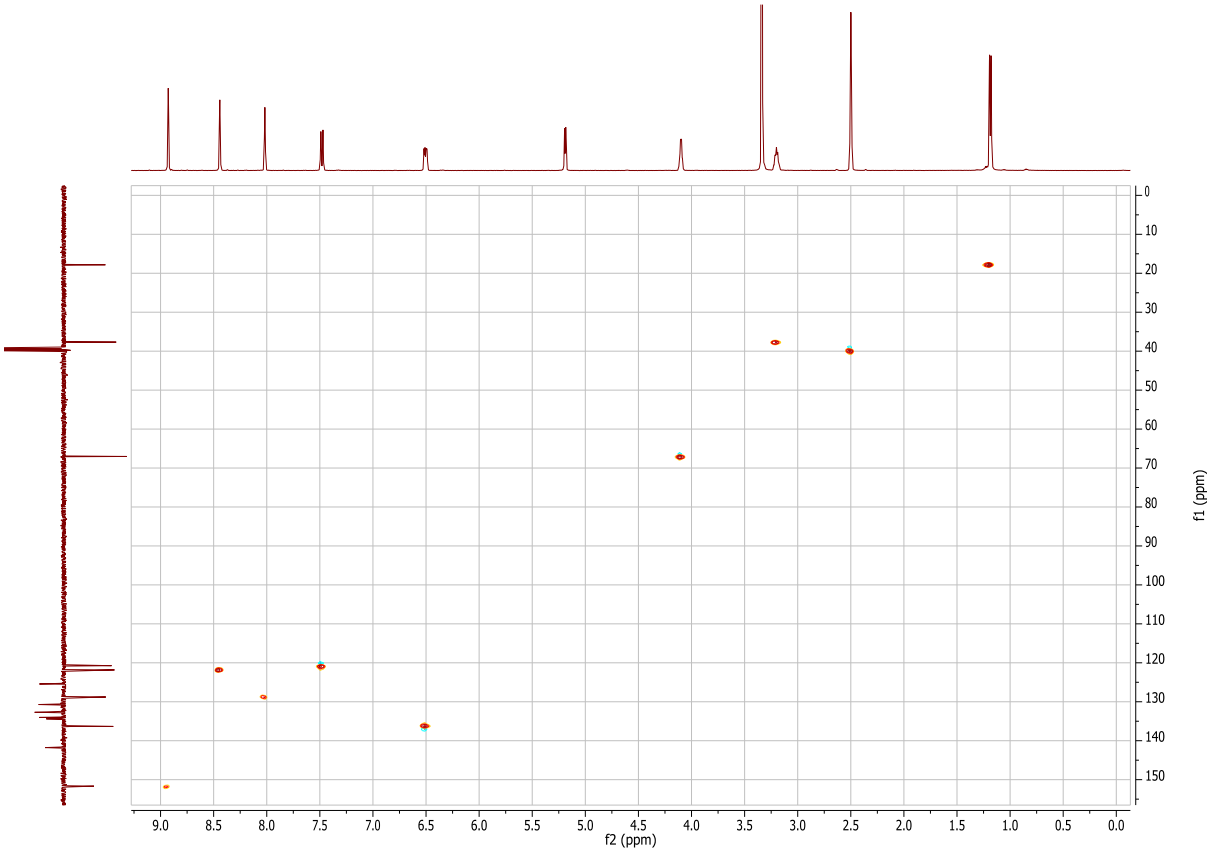
Spectrum 70. 600 MHz, $CDCl_3$, HSQC of 2,4-dichloro-7-methylphenanthridine (**57b**).



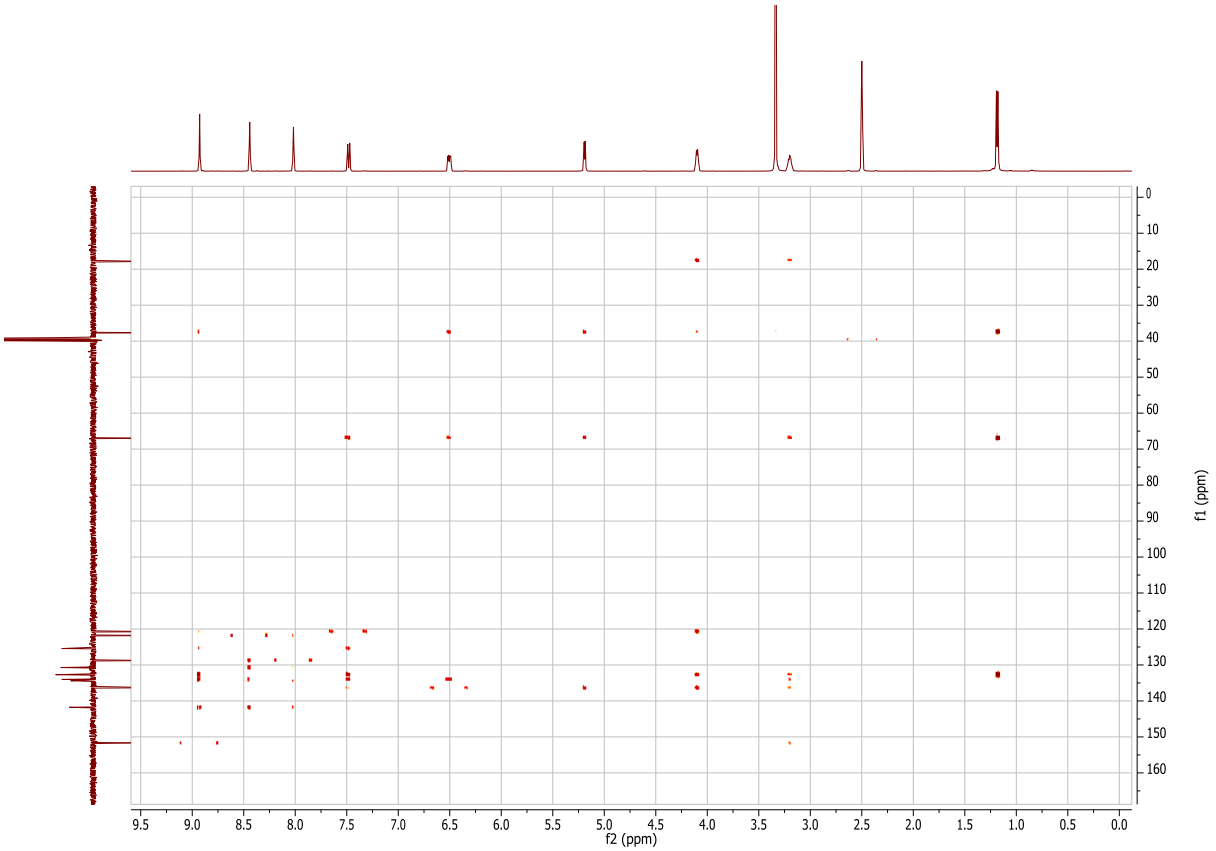
Spectrum 71. 600 MHz, $CDCl_3$, HMBC of 2,4-dichloro-7-methylphenanthridine (**57b**).



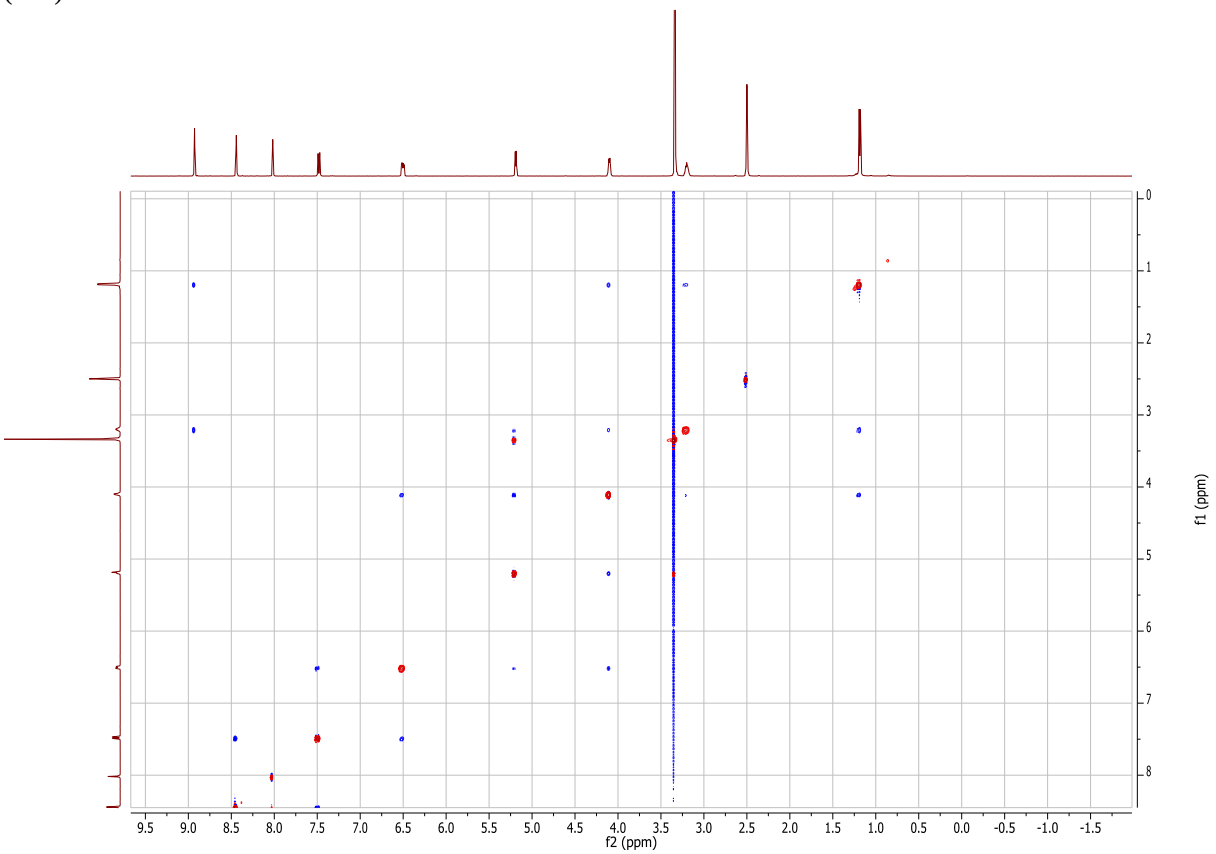
Spectrum 72. 500 MHz, DMSO, COSY of (±)-(*7R,8R*)-2,4-dichloro-7-methyl-7,8-dihydrophenanthridin-8-ol (**58b**).



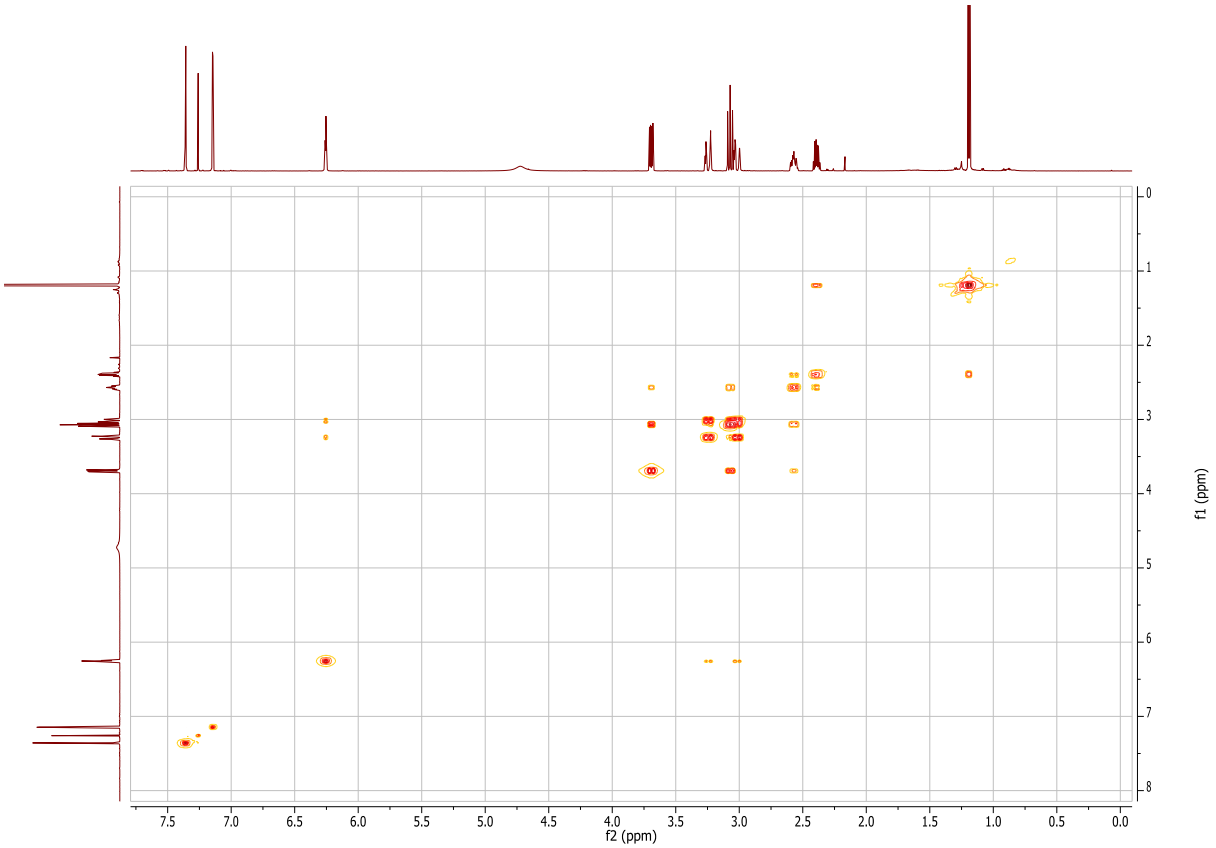
Spectrum 73. 500 MHz, DMSO, HSQC of (±)-(*7R,8R*)-2,4-dichloro-7-methyl-7,8-dihydrophenanthridin-8-ol (**58b**).



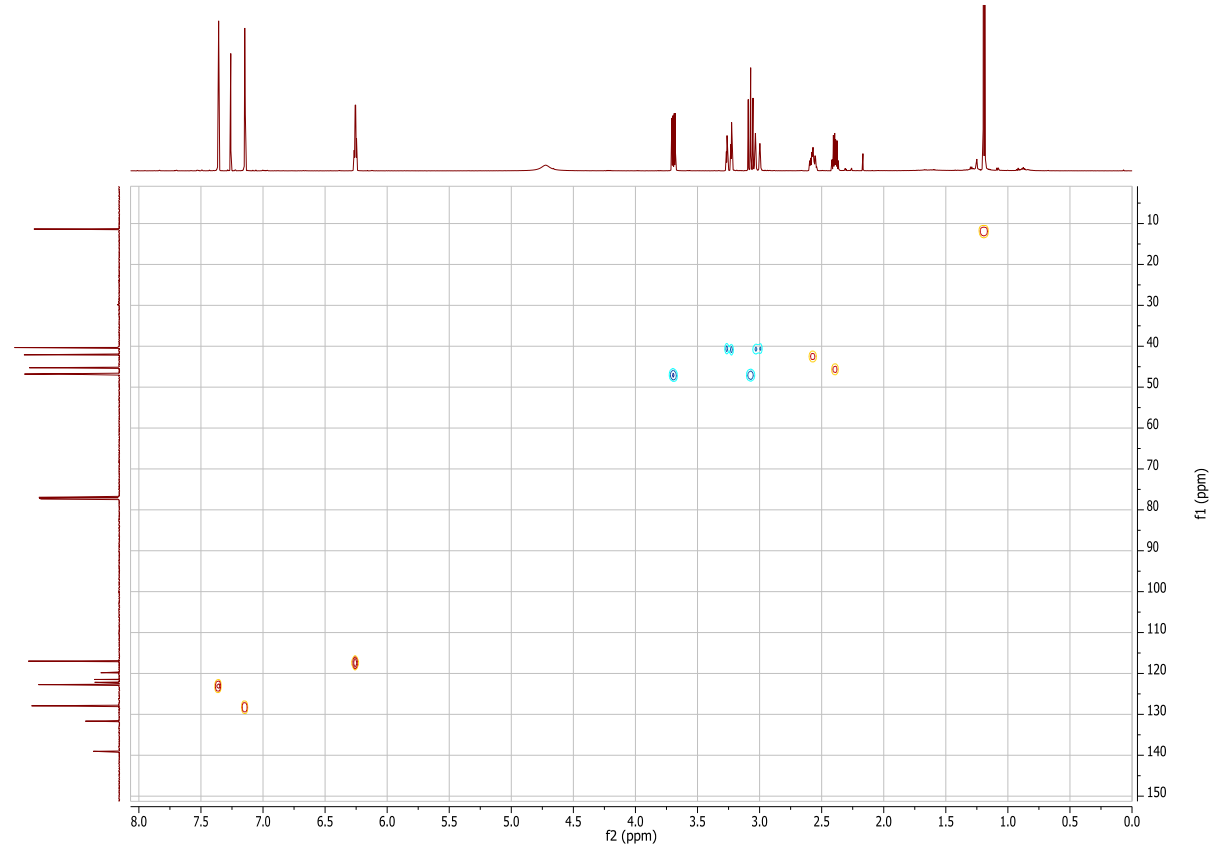
Spectrum 74. 500 MHz, DMSO, HMBC of (±)-(*7R,8R*)-2,4-dichloro-7-methyl-7,8-dihydrophenanthridin-8-ol (**58b**).



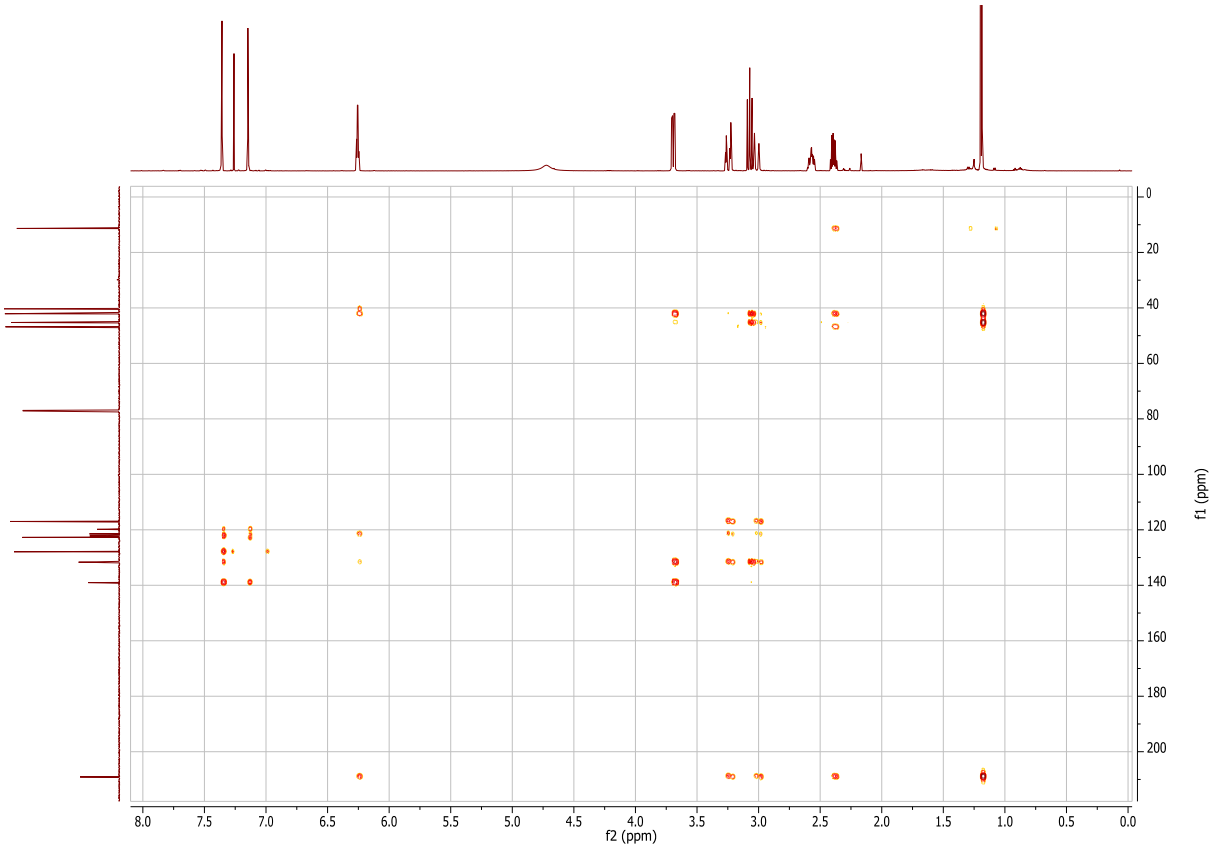
Spectrum 75. 500 MHz, DMSO, NOESY of (±)-(*7R,8R*)-2,4-dichloro-7-methyl-7,8-dihydrophenanthridin-8-ol (**58b**).



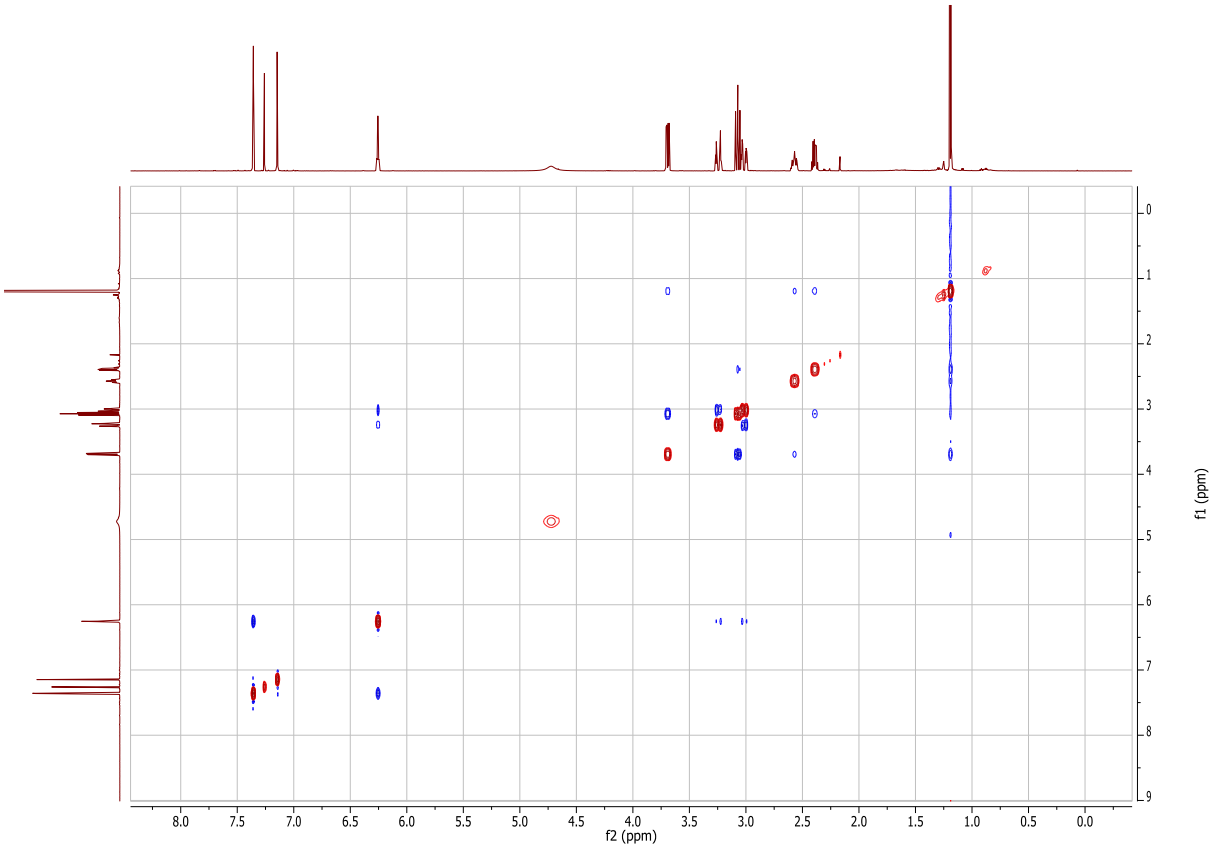
Spectrum 76. 600 MHz, $CDCl_3$, COSY of (±)-(*6aR,7R*)-2,4-dichloro-7-methyl-5,6,6a,7-tetrahydrophenanthridin-8(*9H*)-one (**59b**).



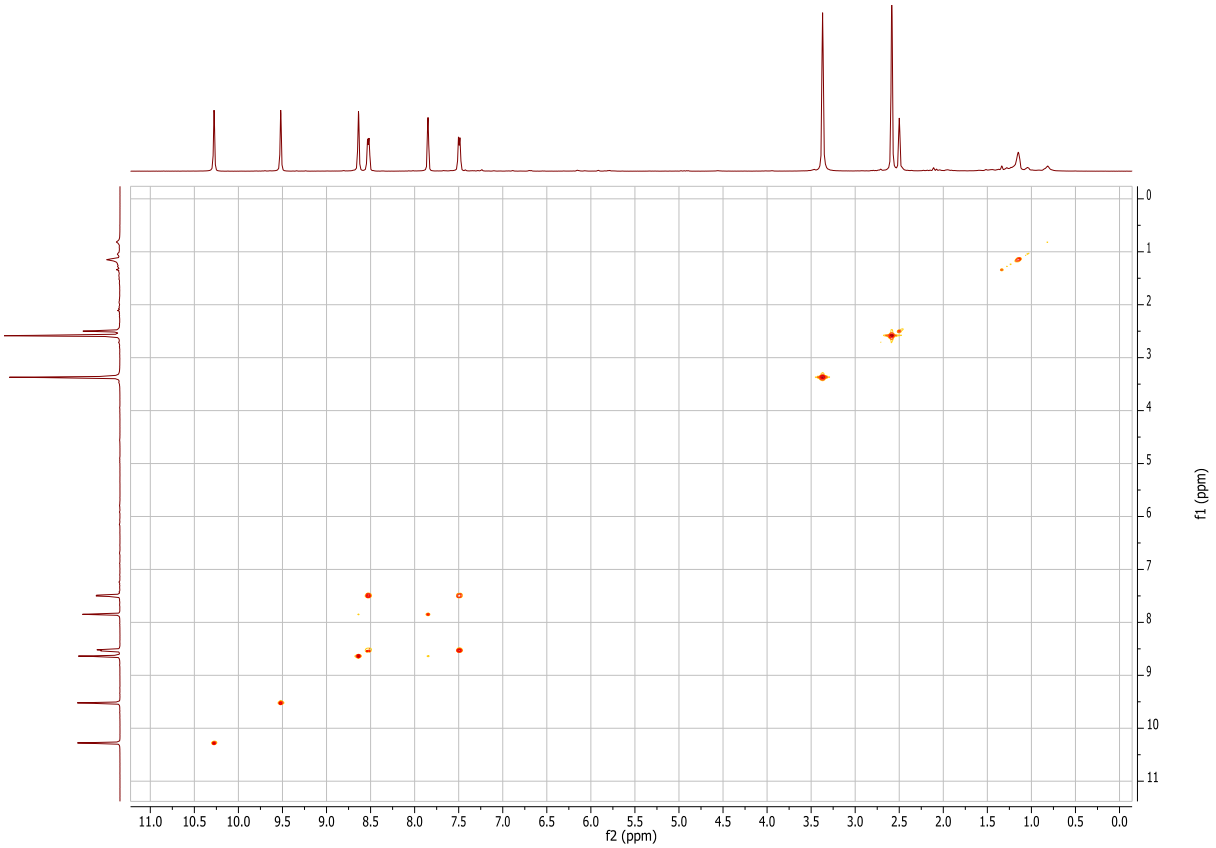
Spectrum 76. 600 MHz, $CDCl_3$, HSQC of (±)-(*6aR,7R*)-2,4-dichloro-7-methyl-5,6,6a,7-tetrahydrophenanthridin-8(*9H*)-one (**59b**)



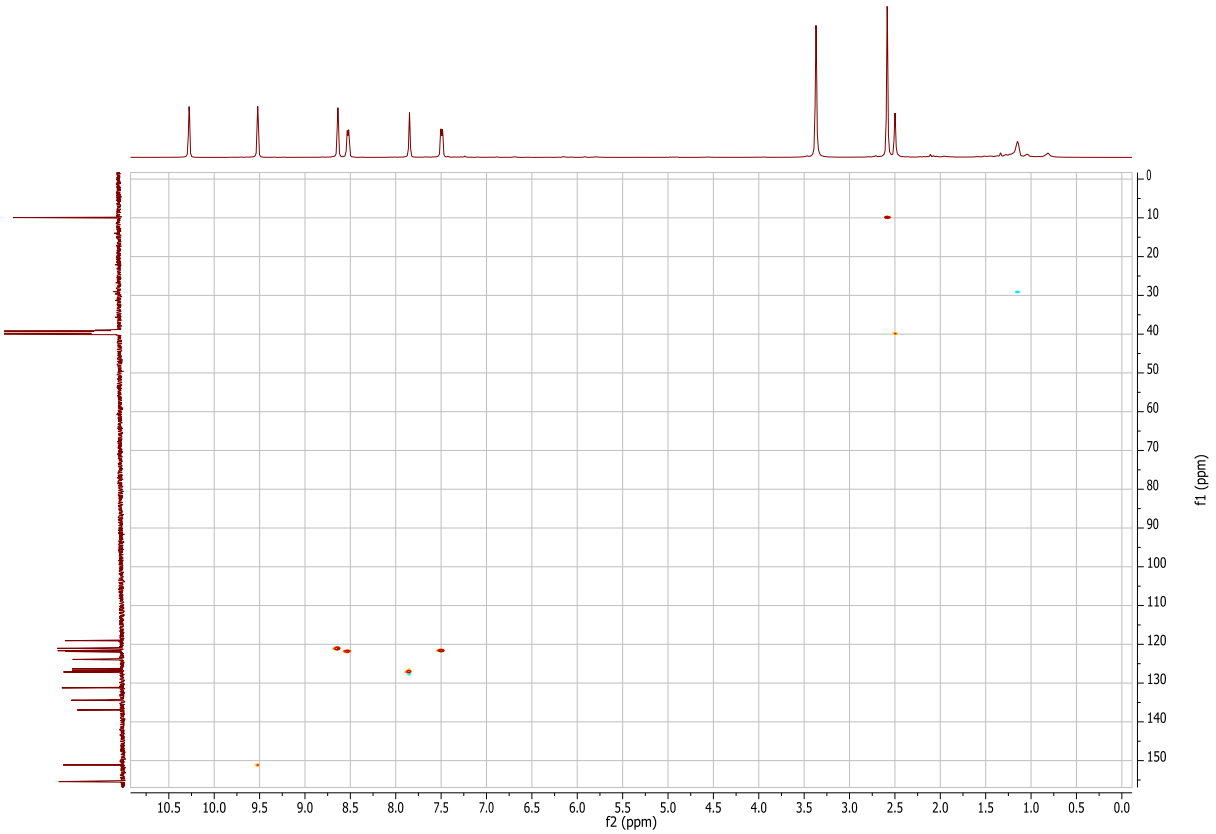
Spectrum 77. 600 MHz, $CDCl_3$, HMBC of (±)-(*6aR,7R*)-2,4-dichloro-7-methyl-5,6,6a,7-tetrahydrophenanthridin-8(*9H*)-one (**59b**)



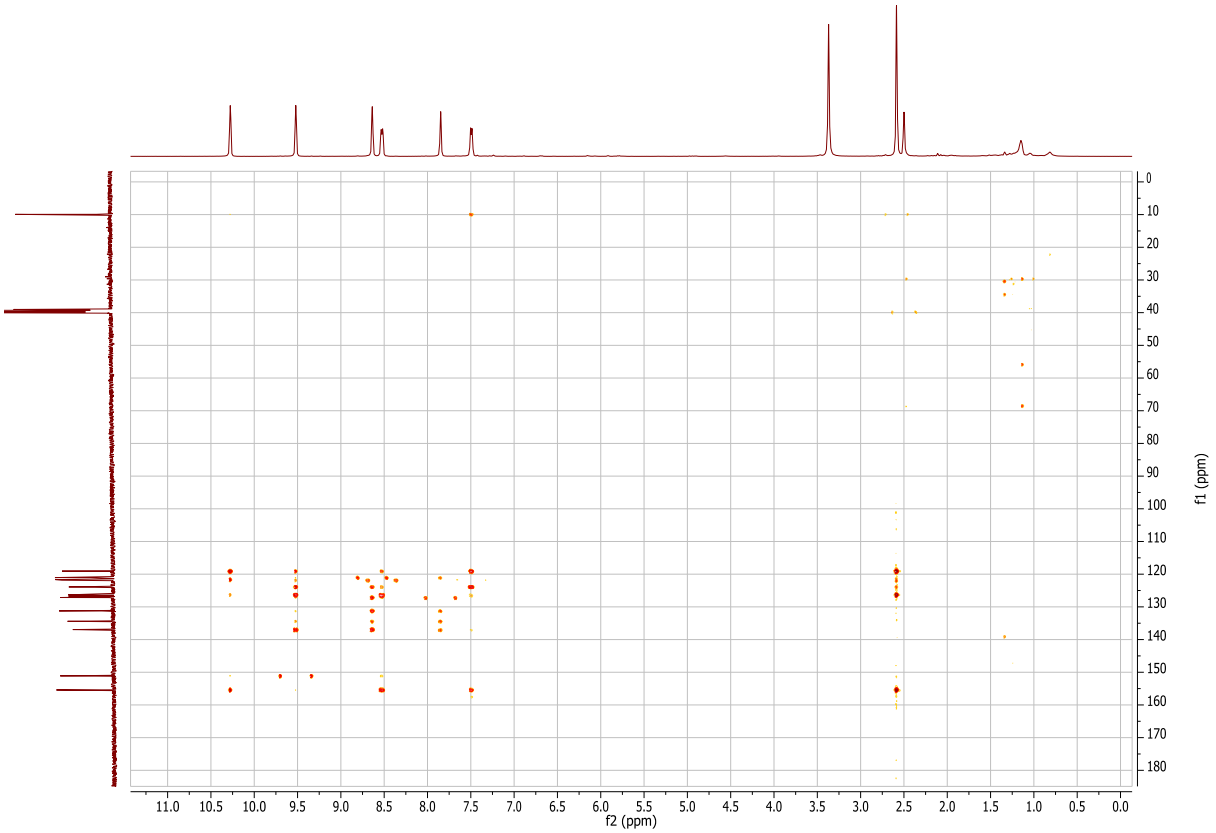
Spectrum 78. 600 MHz, $CDCl_3$, NOESY of (±)-(*6aR,7R*)-2,4-dichloro-7-methyl-5,6,6a,7-tetrahydrophenanthridin-8(*9H*)-one (**59b**).



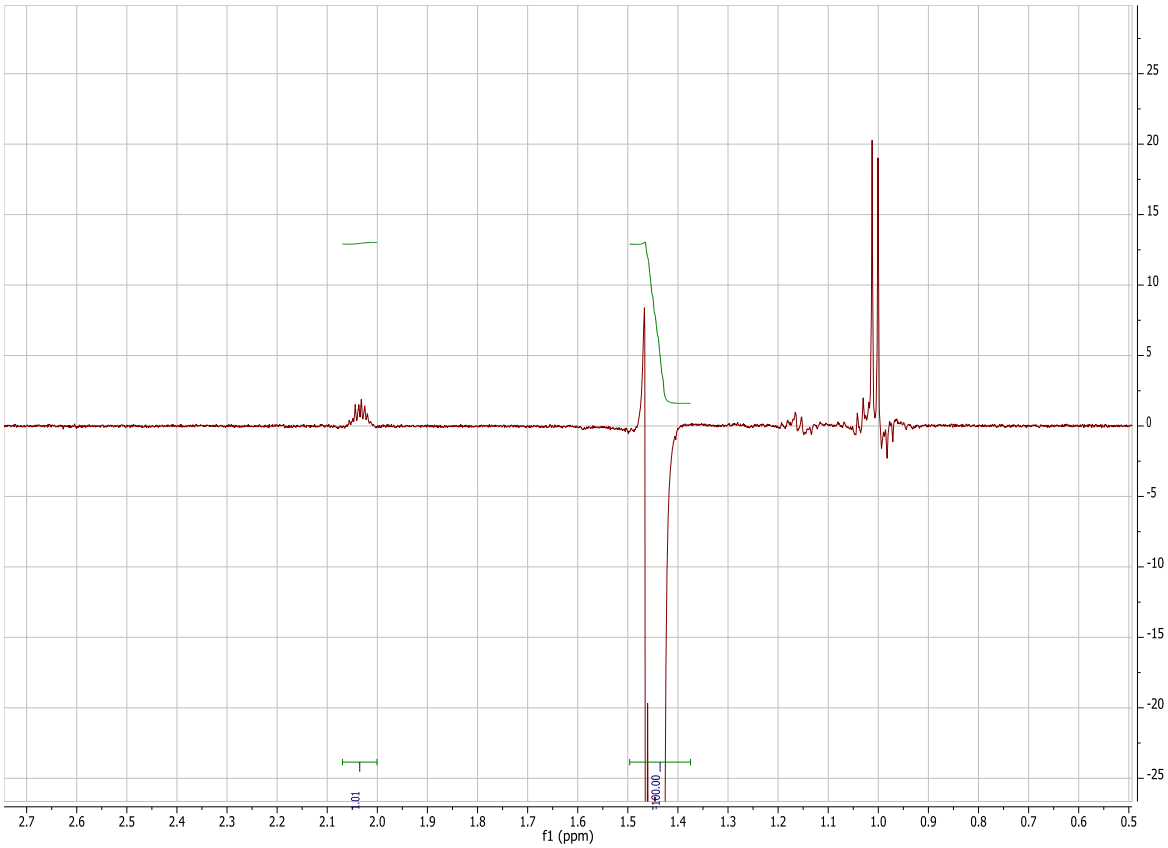
Spectrum 79. 500 MHz, DMSO, COSY of 2,4-dichlorophenanthridin-8-ol (**65b**).



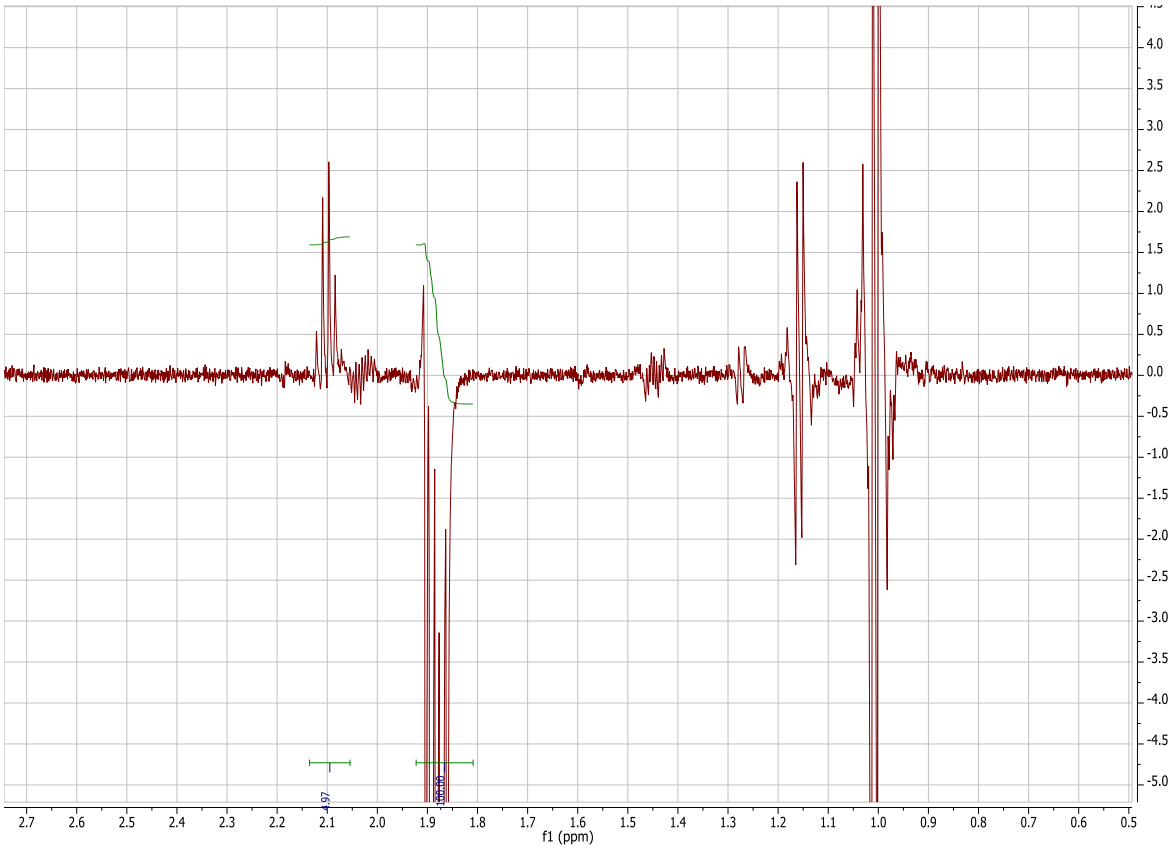
Spectrum 80. 500 MHz, DMSO, HSQC of 2,4-dichlorophenanthridin-8-ol (**65b**).



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



Spectrum 82. 600 MHz, $CDCl_3$, 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, $CDCl_3$, 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).

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