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Studies on the synthesis and reactivity of *N*-3-epoxyhydantoins

Epoxidation with different oxidants and attempts at nucleophilic ring-opening.

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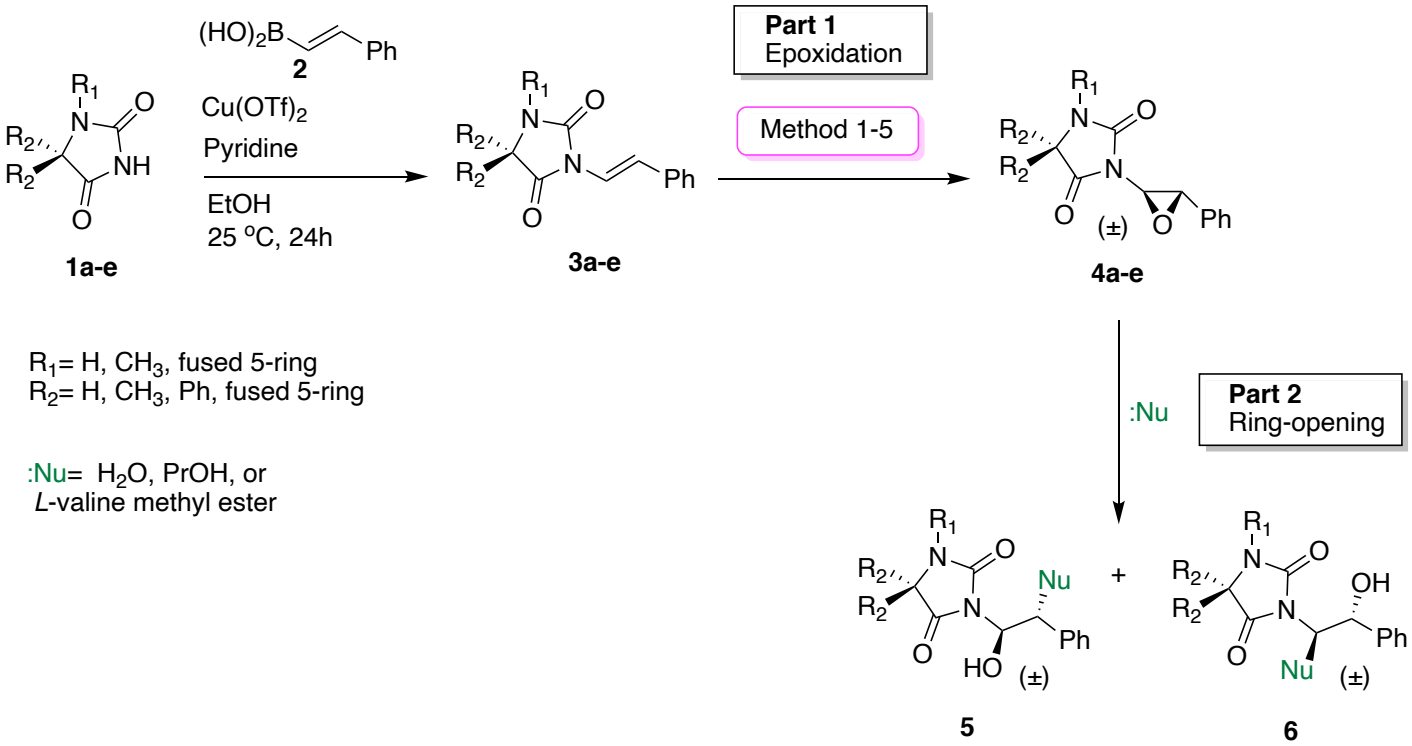
In the end I did it, and I am proud of myself for finishing, keeping my joy of chemistry!

Abstract

N-3-Epoxyhydantoins are a new structural class of hydantoins where the substituent on the *N*-3 position contains an epoxide. The Sandtorv group recently accessed the structural class by epoxidating the corresponding *N*-3-alkenylhydantoins using *m*-CPBA. Both hydantoin structures and compounds containing epoxides are known to present a wide range of biological activities, for example against epilepsy, cancer, bacteria, and fungi. This makes *N*-3-epoxyhydantoins interesting to study, as they might be biologically active structures.

This project has three parts. The first part examines greener alternatives to *m*-CPBA for the epoxidation of some *N*-3-alkenylhydantoins. A greener epoxidation method using oxone as oxidant is presented, epoxidizing two of the tested *N*-3-alkenylhydantoins in excellent yields. The second part investigates the reactivity of the synthesized epoxides to some nucleophiles. The ring-opened *N*-3-epoxyhydantoins were discovered to be unstable and quickly decomposed. In the third part, a teaching activity in green chemistry aimed for chemistry education is presented and discussed.



Abbreviations

AE	Atom economy
ATR	Attenuated total reflectance
COSY	Correlation spectroscopy
d	Doublet
δ	Chemical shift
DCM	Dichloromethane
DEPT	Distortionless Enhancement by Polarization Transfer
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
E-factor	Environmental impact factor
ESI	Electrospray ionization
HMBC	Heteronuclear multiple bond correlation spectroscopy
HRMS	High-resolution mass spectrometry
HSQC	Heteronuclear single quantum correlation
IR	Infrared spectroscopy
IS	Internal standard
J	Coupling constant
LK20	Kunnskapsløftet 2020
m	Multiplet
***m*-CBA**	*meta*-Chlorobenzoic acid
***m*-CPBA**	*meta*-Chloroperoxy-benzoic acid
mp	Melting point
m/z	Mass-to-charge ratio
NMR	Nuclear magnetic resonance
q	Quartet
R_f	Retardation factor
RT	Room temperature
SM	Starting material
t	Triplet
TEA	Triethylamine
TFE	2,2,2-Trifluoroethanol
TLC	Thin layer chromatography
TMP	2,2,6,6-Tetramethyl-piperidine

Contents

1 Introduction

1.1 Hydantoin: Structure and Synthesis

Hydantoin (**1a**) is a five-membered heterocycle containing two nitrogen atoms in positions 1 and 3 and two carbonyl groups in positions 2 and 4 of the ring-system (Figure 1).[1] The compound was first discovered and isolated in 1861 by Adolf von Baeyer in his study on uric acid.[2] The structure has four derivatization sites on *C*-5, *N*-1, and *N*-3. The *C*-5 carbon contains two protons in the α-position to a carbonyl, and the nitrogen atoms each have an acidic proton.[2,3] This gives the heterocycle a lot of possibilities for functionalization and makes it a versatile building block in organic synthesis.[1] The *C*-5 carbon can for instance participate in aldol condensations or carbonyl α-substitutions like alkylation and halogenation.[4] The carbonyl groups can react in nucleophilic additions,[4] and the nitrogen positions can undergo cross-coupling reactions.[5-7]

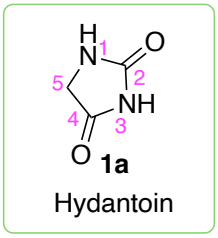


Figure 1. The hydantoin framework with positions numbered.

In coupling reactions, the competition between the two nitrogen positions is determined by their different acidic properties.[5] The literature reports the imide *N*-3 nitrogen to have a pK_a of 14.7,[8] while the cyclic amide *N*-1 nitrogen is expected to have p*Ka* of around 24.[9] This shows that *N*-3 has a considerably more acidic proton than *N*-1. The acidic properties of the nitrogen atoms can be explained by resonance and inductive effects from the carbonyl groups in positions 2 and 4.[4] The carbonyl groups can stabilize deprotonated nitrogen anions by delocalizing the negative charge, resulting in weaker N-H bonds.[7] The deprotonated *N*-3 anion next to two carbonyl groups can be stabilized by one more resonance structure compared to the deprotonated *N*-1 anion next to one carbonyl group.[4] This gives *N*-3 the weakest N-H bond, making it the most available, favored reaction site in coupling reactions.[5]

Another aspect to consider regarding the reactivity of hydantoin is steric hindrance. In unsubstituted hydantoin the carbonyl groups are most bulky, as hydrogen atoms are smaller in size. Even though the *N*-3 position in general is favored in coupling reactions, research from Thilmany *et al*. shows that coupling of unsubstituted hydantoin can cause competition between the two nitrogen atoms.[5] This results in less regioselective reactions.[5] Their research shows that the substitution pattern of hydantoin

significantly affects this competition. They report that 5,5-Disubstituted hydantoins give *N*-3-substituted products in higher yields than 5-monosubstituted and unsubstituted hydantoins. From this, the competition seems to go more in favor of *N*-3 substitution by substitution at *C*-5, due to more steric hindrance of *N*-1.[5] This further makes the reaction regioselectively take place in the *N*-3 position.[5]

Hydantoin-containing compounds are found in many applications. As seen in Figure 2, hydantoins are used in agriculture (**7**),[10] cosmetics (**8**),[11] and marketed drugs (**1c**, **9-10**)[12]. Phenytoin (**1c**)[12] works by slowing down brain impulses that cause epileptic seizures, nitrofurantoin (**10**)[13] is used to treat urinary tract infections, and nilutamide (**11**)[14] is used in treatment of prostate cancer. The global society faces big challenges when it comes to treating lethal diseases like cancers and defeating antimicrobial resistance, and there is a great for the development of new medicines.[15-16] Parts of the hydantoin field is still unexplored, making it an interesting scaffold considering its large number of existing applications in pharmacologically and biologically active compounds.

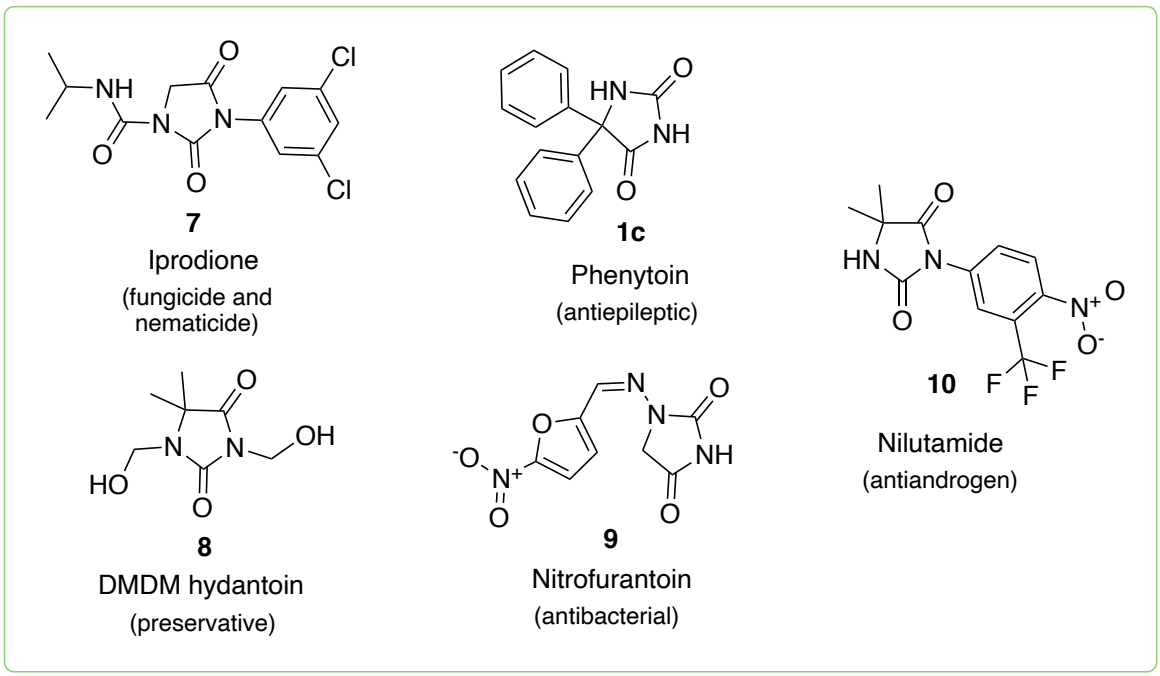
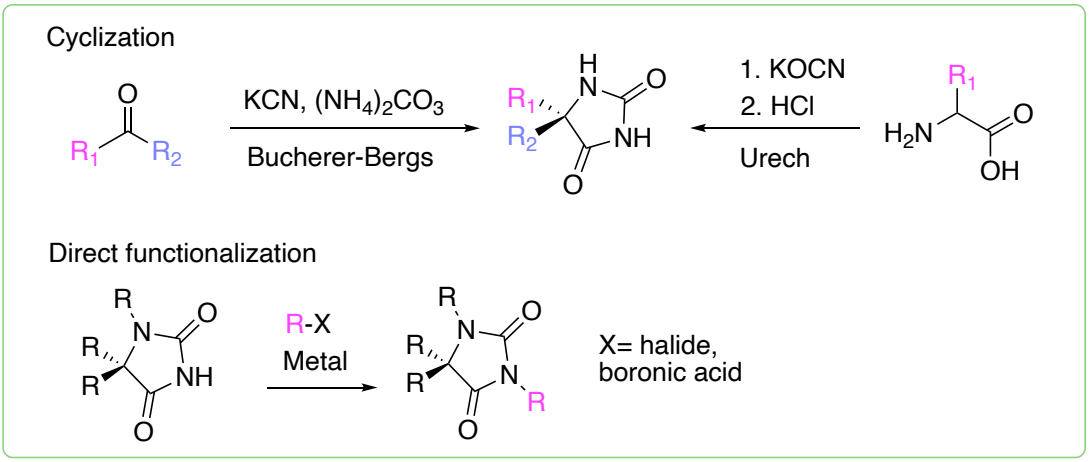


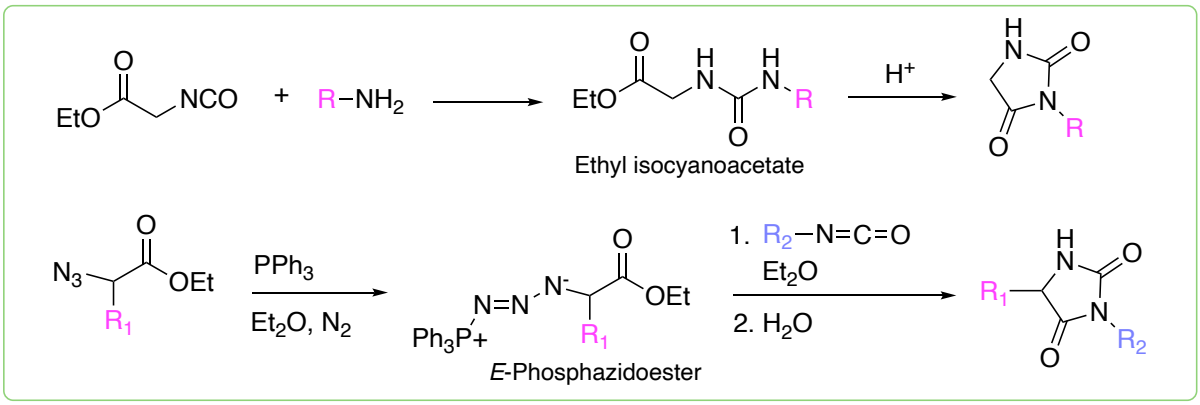
Figure 2. Applications of some hydantoin-containing compounds.

To synthesize hydantoins, there are two general methods: cyclization and direct functionalization (Scheme 1). Most reported syntheses are cyclization reactions, where the hydantoin ring itself is ring-closed from linear precursors that already contain the desired substituent(s). There exist many possible precursors and synthesis methods that are well established.[1] Direct functionalization is a newer approach, where the desired substituent(s) are chemo- and regioselectively introduced to relevant sites of the ring-system.[1] This makes use of a hydantoin substrate, unlike the cyclization methods.



Scheme 1. Hydantoin synthesis by cyclization and direct functionalization.

Among cyclizations, the Bucherer-Bergs[2,3] and the Urech syntheses[17] as seen in Scheme 2 are classical methods. These are used to synthesize *C*-5-substituted hydantoins, for example the biologically active phenytoin. Other methods are used to synthesize *N*-3-substituted hydantoins. One reacts ethyl isocyanatoacetate with benzylamine or aniline derivates and forms a urea intermediate which is further cyclized to the desired hydantoin under acidic conditions.[3] Another method reacts *E*-phosphazidoester derivates with isocyanates and the cyclization occurs when adding water to the reaction (Scheme 2).[3] Cyclization do not come without limitations, as they often require harsh conditions. This is seen in the Urech synthesis and the ethyl isocyanoacetate method, both of which use a strong acid as hydrochloric acid. Other undesirable aspects are their use of toxic chemicals like cyanide compounds,[18] aniline derivates[19] and isocyanates.[20] In addition, cyclizations often requires multiple steps as the desired precursor must be synthesized before the cyclization. This can result in the synthesis being inefficient and requiring many chemicals.[3]

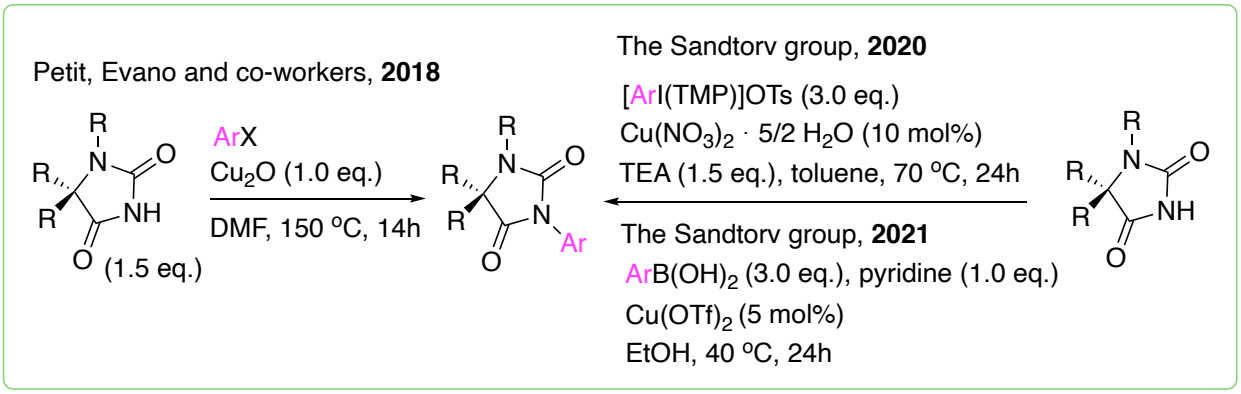


Scheme 2. Synthesis of *N*-3-substituted hydantoins by cyclization reactions.

As seen in Scheme 1, most direct functionalizations are done by coupling reactions binding two atoms together in one step, with the aid of a metal catalyst. This gives potentially quicker and cheaper access to modified hydantoins than with cyclization methods.[6] Coupling reactions have been used to introduce

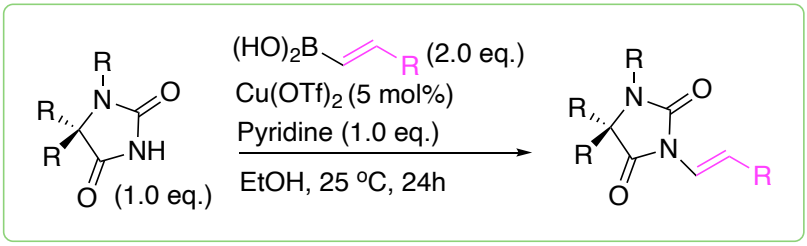
alkyl, aryl, and alkenyl groups to the ring-system.[6-7, 21] However, the field has been unexplored with only a few reported procedures, but has recently seen several breakthroughs.

In 2019, Petit, Evano and co-workers reported a Cu(I)-mediated coupling reaction using an aryl halide to selectively arylate the *N*-3 position of hydantoin under ligand- and base-free conditions (Scheme 3).[5] They report good to excellent yields, especially on C-5-disubstituted structures. However, the method is performed in a pressure tube at 150°C, requiring inert atmosphere, toxic *N*,*N*-Dimethylformamide (DMF),[22] and has a scope to only *N*-1 and/or *C*-5-substituted hydantoins.[5] Inspired by their work, the Sandtorv group have reported two other methods using milder conditions. First a synthesis using asymmetric diaryliodonium salt as arylation agent, a Cu(II) catalyst, and triethylamine (TEA) as a base and ligand, enabling the reaction to proceed on *N*-1- and *C*-5-unsubstituted hydantoins where aryl halides fail.[6] Secondly a Chan-Lam-inspired method using an arylboronic acid and Cu(II) catalyst (Scheme 3).[7]



Scheme 3. *N*-3-Arylation of hydantoins by direct functionalization with three methods using different arylation agents.

In the same work, the Sandtorv group reported a procedure using alkenylboronic acids, Cu(II) catalyst and pyridine to form a C(sp^2)-N bond coupling between the alkene and hydantoin (Scheme 4).[7] This method uses even milder conditions, since it is performed at 25 °C. The method has been tested on a wide scope of cyclic imides and hydantoins with varying substituents. The group has performed many reactions using (*E*)-styrylboronic acid which has phenyl as its R-group, and this has provided thirteen C(sp^2)-N-coupled hydantoin structures in good to excellent yields of 77-100%.[7]



Scheme 4. C(sp^2)-N Coupling of hydantoins and a boronic acids.

1.2 Epoxides: Structure, Synthesis and Reactivity

Epoxides are cyclic ethers with a three-membered ring of one oxygen atom bound to two carbon atoms (Figure 3). The three-ring provides an angle strain that makes epoxides highly reactive.[4] Since much strain is released by ring-opening, the epoxide carbons are prone to nucleophilic attacks. This makes them versatile intermediates in synthesis since they can be transformed into many compounds like diols,[23] alkoxy- and amino alcohols[24-25] through ring-opening reactions with different nucleophiles.[4]

Epoxide-carrying compounds present a wide range of biological activities (Figure 3).[26] For example nannocystin A (**11**) has antifungal effect against the yeast *C.albincans,* and antiproliferative properties against 472 cancer cell lines.[27] (±) Flavipucine (**12**) exhibits activity against several bacteria and fungi,[28] and L-755,807 (**13**) has inhibitory activity against amyloid-β-aggregation causing Alzheimer's disease.[26] These compounds have similarities to hydantoins in that they are all amides. This makes epoxy substituted hydantoins interesting to study, as they might also be biologically active structures.

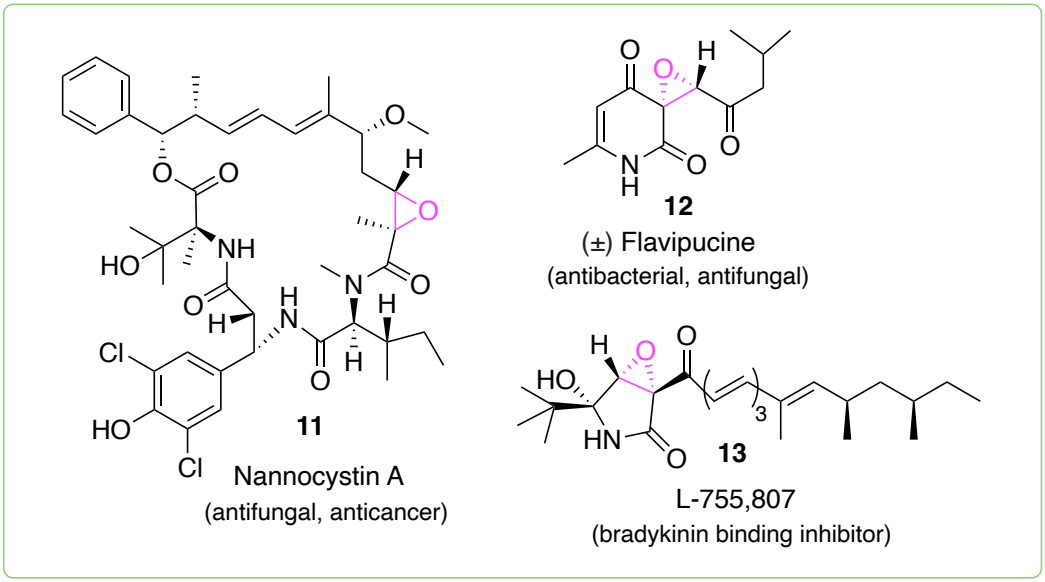
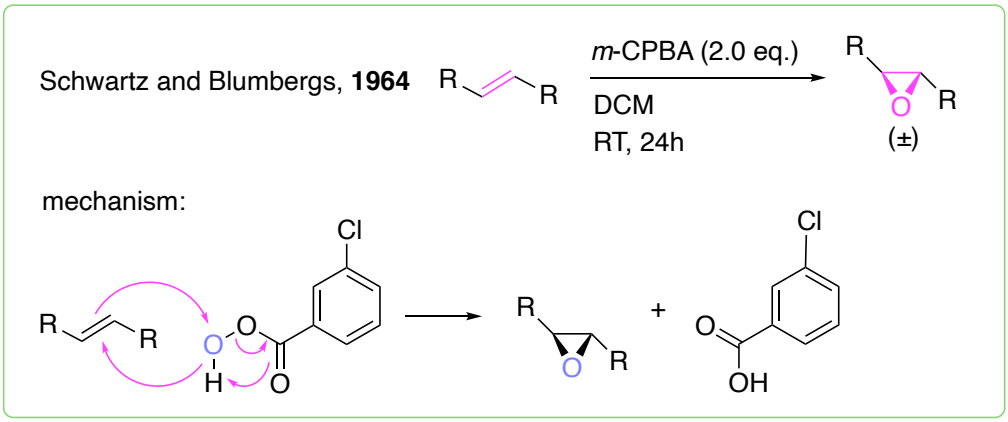


Figure 3. Examples of some biologically active epoxides. The epoxy group is marked in pink.

Epoxides can be synthesized by epoxidation of alkenes. Epoxidation is a special case of oxidation, where the reaction forms two new bonds from the alkene carbon atoms to one oxygen atom supplied by an oxidant.[4] It is one of the most studied reactions in organic synthesis. The spark for its exploration was given by Tsutomu Katsuki and Karl B. Sharpless, reporting an enantioselective epoxidation method of allylic alcohols using a titanium complex.[29] After their contributions, a variety of metal complexes have been used for the racemic and enantioselective epoxidation of alkenes.[30] With the advent of organocatalysis, much effort has been devoted to develop metal-free methods to perform the

epoxidation,[31] as metal complexes often contain toxic heavy-metals and must be manufactured in multistep syntheses.[32] Below, some of the developed methods for racemic epoxidation are presented.

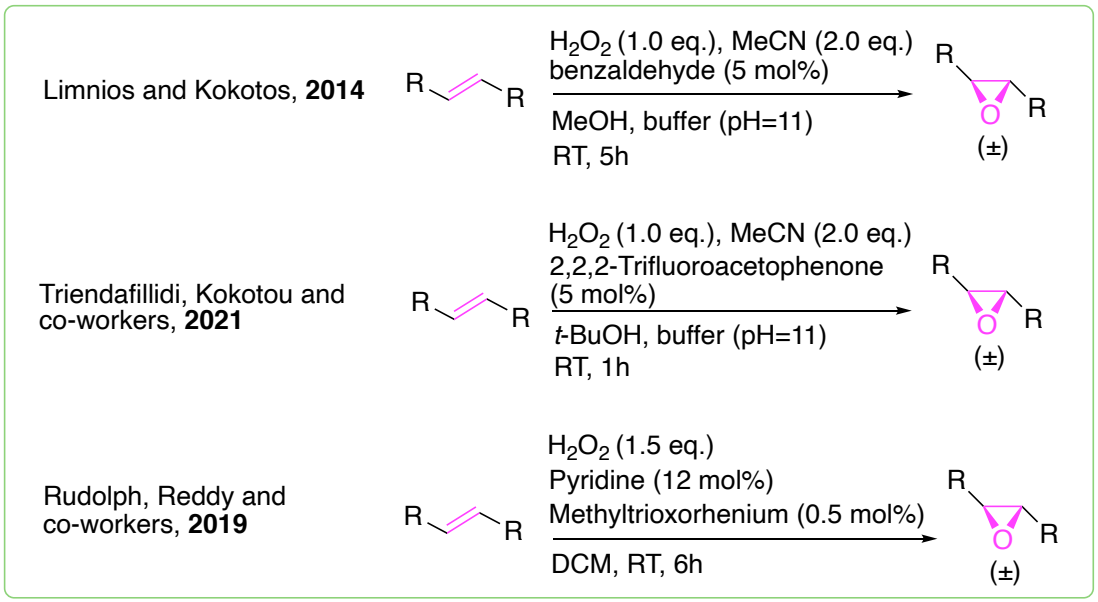
The first organic molecule used in epoxidation was the peracid *meta*-chloroperoxybenzoic acid (*m*-CPBA).[33] Peracids are strongly oxidating agents that can react directly with alkenes and form their corresponding epoxides without a catalyst.[4] Epoxidation with *m*-CPBA can proceed with simple reaction conditions, only requiring the peracid and an organic solvent such as dichloromethane (DCM) (Scheme 5).[34] The method has been used to epoxidize a wide scope of alkenes with heteroatoms, strained rings, and sterically hindering groups in excellent yields.[34] A limitation is that the reaction only transfers one oxygen atom from *m*-CPBA to the alkene, resulting in a big carboxylic acid byproduct, generating much chemical waste as seen in the mechanism shown in Scheme 5.[35] *m*-CPBA is also undesired since it is strongly irritating and flammable.[36]



Scheme 5. Alkene epoxidation with Method 1 using *m*-CPBA as oxidant, and the mechanism for the epoxidation.[35]

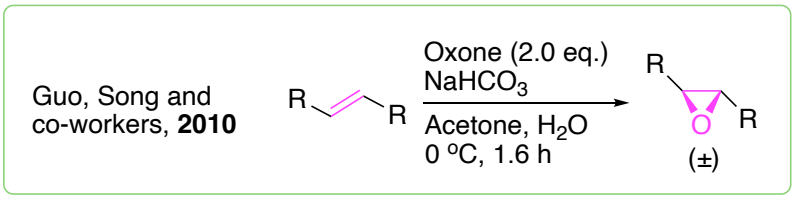
Another oxidant widely used in alkene epoxidation is hydrogen peroxide. Epoxidation with hydrogen peroxide has several advantages compared to using *m*-CPBA, as hydrogen peroxide is associated with less hazards and gives water as its only byproduct.[31,37] However, for the epoxidation to proceed, hydrogen peroxide needs to be coupled with a catalyst to form a reactive intermediate that executes the epoxidation. The catalyst can be heterogenous or homogenous, leading to different reactions (Scheme 6). In 2014, Limnios and Kokotos developed an aldehyde-catalyzed method using acetonitrile as oxidation mediator, an organic solvent, and a basic buffer solution.[31] In 2021, Triendafillidi, Kokotou and co-workers developed a method performed in similar conditions, using the ketone 2,2,2-trifluoroacetophenone as catalyst.[38] Another method using methyltrioxorhenium as catalyst, pyridine as a ligand and an organic solvent was developed in 2019 by Rudolph, Reddy and co-workers.[39] Of the thee methods, only this method has been used on C(sp^2)-N-coupled alkenes. It is

reported used on adenine and uracil derivates, producing their corresponding epoxides in yields of 75-89%.[40]



Scheme 6. Alkene epoxidation using hydrogen peroxide as oxidant with different catalysts and reaction conditions.

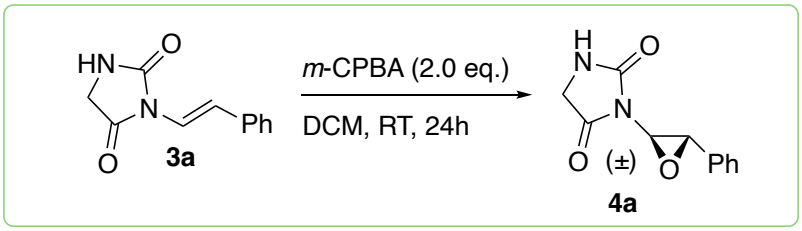
In addition to using metal complexes, peracids and peroxides, epoxidation can be carried out using potassium peroxymonosulfate ($2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$), as part of a mixture with sulfate salts called oxone. Oxone is a much-used oxidant which generates dimethyldioxirane *in situ* from the solvent acetone, which in turn executes the epoxidation.[41] The reaction can be performed in an ice bath, using water, acetone, oxone, and sodium bicarbonate (Scheme 7).[42] The method uses mild reagents except from oxone, which is associated with hazards like being corrosive and irritating.[43] Oxone is however widely used, as it is a green, cheap and safe oxidant that generates non-toxic $KHSO_4$ and oxygen gas as its only byproducts.[44] Guo, Song and co-workers report an excellent yield of 92% when performing the reaction on a C(sp^2)-N-coupled cyclic alkene.[42]



Scheme 7. Alkene epoxidation with oxone as oxidant.

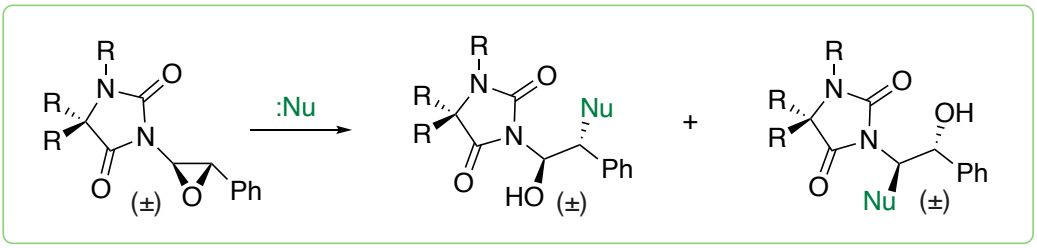
When it comes to hydantoins, some structures with epoxy groups have been synthesized. One 5-epoxy-5-phenyl-substituted structure is reported in the literature. A 5-dimethyl-substituted structure with one epoxy group substituted to each of the two nitrogen atoms *N*-1 and *N*-3 is also reported, but there are no examples of hydantoins that only has an epoxy group substituted to *N*-3.[45,46] Thus, *N*-3-substituted epoxyhydantoins are unexplored structures. Recently, Thomas N. Solvi of the Sandtorv group attempted to epoxidize (*E*)-3-styrylhydantoin (**3a**) with *m*-CPBA. This formed the corresponding

N-3-epoxyhydantoin (**4a**) in an excellent yield of 93% (Scheme 8).[47] Later, Kristian Sørnes accessed a *N*-1-arylated *N*-3-epoxyhydantoin using the same conditions.[48] *N*-3-epoxyhydantoins have not been synthesized by other means than using the *m*-CPBA method, and the scope of *N*-3-alkenylhydantoins possible to epoxidize has not been investigated. The reactivity of the *N*-3-epoxyhydantoins is also undiscovered. This makes *N*-3-epoxyhydantoins interesting structures for further studies.



Scheme 8. Epoxidation of a 3-substituted C(sp^2)-N-coupled hydantoin synthesized by Solvi of the Sandtorv group.

As mentioned initially, epoxides are reactive towards nucleophiles and can participate in ring-opening reactions (Scheme 9). The ring-opening can occur by S_N1 or S_N2 reactions *via* a backside attack of one of the epoxide carbons by the nucleophile. Many different nucleophiles can be used; strong ones like Grignard reagents, hydrides, amines and alkoxides, or weaker ones like water or alcohols in the presence of an acid catalyst.[4] When the epoxide carbons are primary and secondary and a strong, non-basic nucleophile is used at elevated temperatures, the least hindered carbon is mostly attacked through an S_N2 reaction.[4,35] If one of the carbons is tertiary and a moderately good nucleophile is used at low temperatures, the most hindered carbon is mostly attacked through an S_N1 reaction. As the nucleophile can attack both the epoxide carbons, epoxide ring-opening mostly gives a mixture of regioisomers. The product from the most favored site of attack likely dominates.[4]



Scheme 9. General reaction sequence for nucleophilic ring-opening of an epoxide.

Several methods to elicit nucleophilic ring-opening of epoxides are reported in the literature. One method uses hot water and 1,4-dioxane as solvent in a ratio of 1:1 to perform ring-opening. This method reports the corresponding diol of styrene oxide in a yield of 95 %.[23] In the same ratio, several epoxides are reported ring-opened by amines and thiols.[23] Another method uses amino acid esters like *L*-valine methyl ester to ring-open epoxides, by using 2,2,2-trifluoroethanol as solvent under reflux.[25] The reaction times and the products from the ring-opening reactions depend on the alkene substrate and the chosen nucleophile.[23,25]

1.3 Green chemistry

Green chemistry is a field striving to achieve sustainability on a molecular level. Paul Anastas and John Warners defines it as the "design of chemical products and processes to reduce or eliminate the use and generation of hazardous substances".[49] In the past decade, the field has received wide interest due to its ability to harness chemical innovation to meet both environmental and economic goals. The most important aspect in green chemistry is the concept of design, as design requires intention and planning. Twelve principles are constructed as "design rules". These are used in many areas of society, like in industry, research, and education.[49] In the Norwegian curriculum from 2020, the principles are incorporated into the competence goals in chemistry.[50] Each principle will now be presented.

Principle 1. Waste prevention. Waste management can be expensive and hazardous for humans and the environment, making it desirable to avoid generating waste whenever possible. The environmental impact of the waste depends on the toxicity of the substance. A quantification of the amount of waste produced per kilo product can be mad by calculating the environmental impact factor (E-factor, equation 1). The E-factor is based on the reaction yield, the starting materials used and solvents (water is not included). When byproducts cannot be avoided, isolation and further use should be included.[49]

$$\mathrm{E-factor} = \frac{\mathrm{m_{starting\ materials} - m_{products}}}{\mathrm{m_{products}}} \qquad (1)$$

Principle 2. Atom economy. Atom economy (AE) measures the amount of atoms from the reagents that are incorporated into the final product (equation 2).[49] By this, it evaluates how efficient or inefficient a chemical reaction is. All solvents except water are included in the calculation.

$$\mathrm{AE} = \frac{M_{m,\ \mathrm{products}}}{\sum M_{m,\ \mathrm{reactants}}} \qquad (2)$$

Principle 3. Less hazardous synthesis. In the last decade, greener synthesis methods have been developed, which is a development that should continue. To get an overview of how hazardous a synthesis is, all the chemicals and equipment used should be risk assessed. By replacing hazardous chemicals and equipment with less hazardous alternatives, syntheses can be improved.[49]

Principle 4. Design safer chemicals. Several chemical processes use reagents that are toxic and hazardous for both human health the environment. There is need for designing new chemical reagents that maintain similar function, while reducing toxicity.[49]

Principle 5. Safer solvents and auxiliaries. Solvents pose a big challenge in green chemistry, as many common solvents are toxic, flammable and/or corrosive. They also generate the most chemical waste in a synthesis, and reuse is often associated with energy-intensive distillation. Solvent volatility has led to serious accidents and pollution in the past. The ideal process is solvent free. If that is impossible, greener alternatives should be considered, like water, supercritical fluids, and ionic liquids.[49]

Principle 6. Energy efficiency. Chemical reactions and processes can sometimes require an intensive input of energy. This can be minimized by reducing the energy barrier, either through more reactive reactants or through the use of catalysts, to perform the reaction at room temperature. This must be considered carefully, since reactants with a lower activation energy often are more reactive, and catalysts are often metal-based and might be toxic, expensive, and non-sustainable.[4] Another important act is to use renewable energy sources: solar power, wind power, hydro power etc.[49]

Principle 7. Use renewable feedstocks. Raw materials and feedstocks from renewable sourses should be used, if possible. Plant-based sources are better than petrochemical sources.[49]

Principle 8. Reduce derivates. Unnecessary derivatization like protection, deprotection, and temporary modifications should be minimized or avoided as such processes generate extra waste.[50]

Principle 9. Catalysis. Catalysis increases reaction efficiency by lowering the activation barrier and gives greater product selectivity. This reduces the amount of stochiometric reagents, causing less waste to be generated. Catalysis also reduces energy demand and reaction time, and the catalysts themselves can be reused in other syntheses.[49]

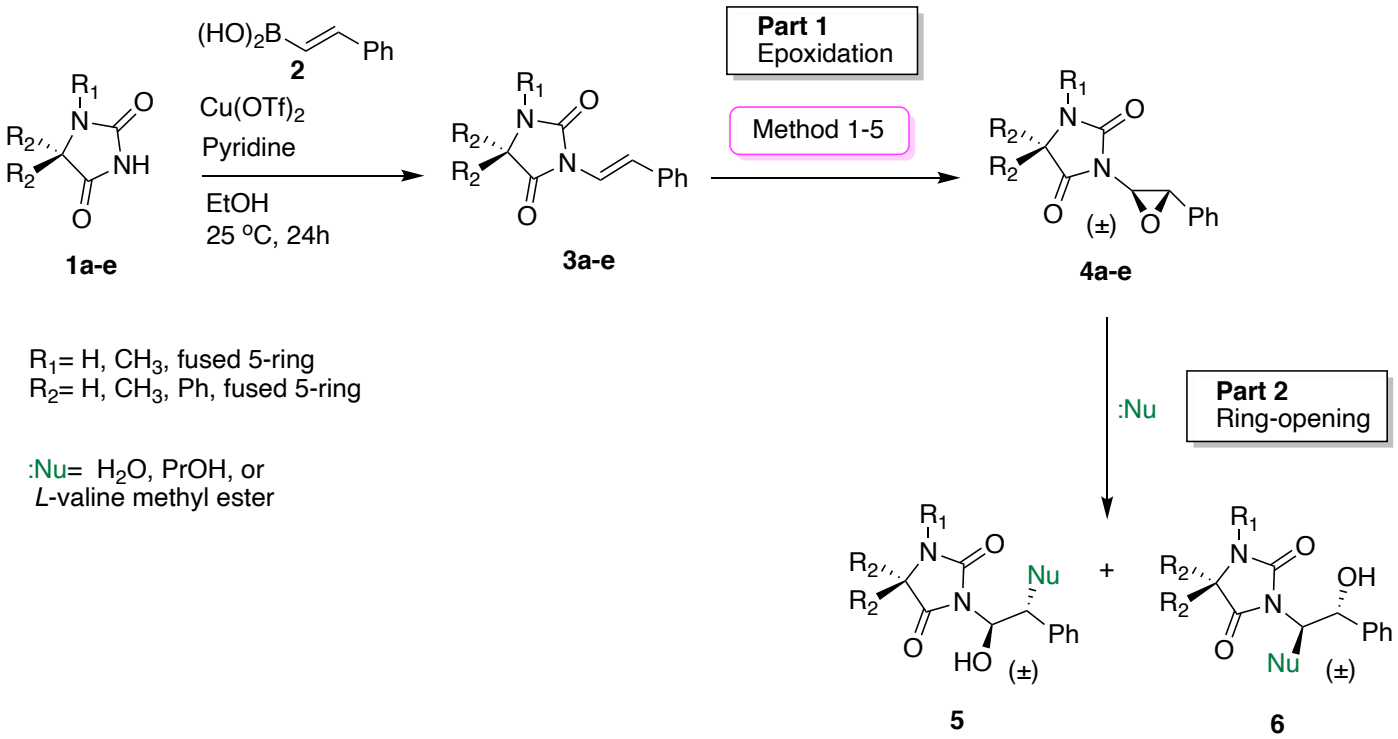
Principle 10. Design for degradation. It is desirable to create chemical products that at the end of their function decompose into products that do not persist in the environment.[49]

Principle 11. Real-time analysis for pollution prevention. Analytical methods should be developed to monitor and control syntheses *in situ*, prior to formation of hazardous substances.[49]

Principle 12. Safer chemistry for accident prevention. In the working environment, dangerous substances and processes have multiplied. To prevent accidents like releases, explosions, and fires, it is essential that hazards are identified and assessed. The aim is to replace hazardous chemicals and processes with safer alternatives to minimize the potential for chemical accidents whenever possible.[49]

1.4 Description and aim of the project

The focus of this project is to prepare and study the reactivity of some *N*-3-epoxyhydantoins. As seen in chapter 1.3, sustainability and green chemistry have received increased focus in the world and within the scientific community. As epoxidation with *m*-CPBA is associated with several hazards and generates a big carboxylic acid molecule as chemical waste, it is interesting to study if *N*-3-epoxyhydantoins can be produced by more sustainable methods. The project contains three parts (Scheme 10). In the first part, the *m*-CPBA method and four potentially greener epoxidation methods are investigated for the epoxidation of *N*-3-alkenylhydantoins. In the second part, some of the synthesized *N*-3-epoxyhydantoins are reacted with a selection of nucleophiles to investigate their reactivity. In the third part, it will be proposed a teaching activity designed for chemistry education.



Scheme 10. Part 1: epoxidizing *N*-3-alkenylhydantoins with Method 1-5, and Part 2: attempts at ring-open the epoxides with different nucleophiles.

Research Questions

In this master's project, three research questions are considered:

Q1: Can *N*-3-epoxyhydantoins be synthesized with a greener method than the *m*-CPBA method?

- If yes, are there any limitations with this or these methods compared to the *m*-CPBA method, both synthetically and according to the principles of green chemistry?
- If no, what can be possible reasons why the alternative methods are not able to epoxidize the *N*-3-alkenylhydantoins?

Q2: How do *N*-3-epoxyhydantoins react after being treated with water, 1-propanol, and *L*-valine methyl ester? Are the epoxides ring-opened by any of the nucleophiles?

- If yes, what can we say about the products that are formed and what knowledge does it contribute to *N*-3-epoxyhydantoins and their reactivity?
- If no, what can be possible reasons for the stability of the epoxides towards attack by the nucleophile(s)?

Q3: How can this project be applied in a teaching activity that can be used in chemistry education?

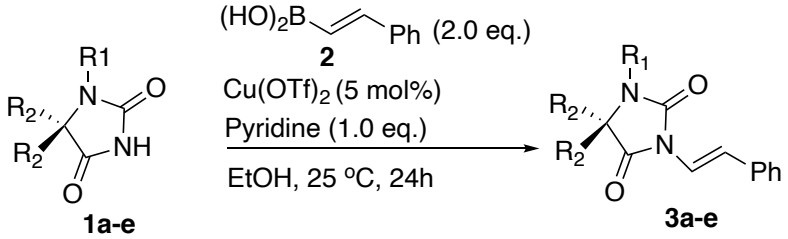
2 Results and Discussion

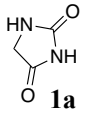
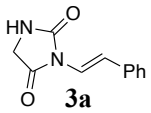
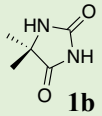
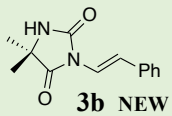
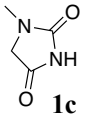
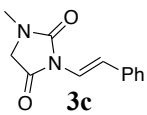
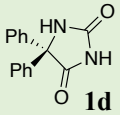
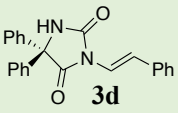
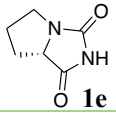
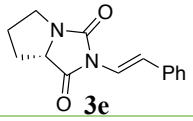
In this section, the results from the synthesis of *N*-3-epoxyhydantoins and attempts at ring-opening the epoxides are presented and discussed. One example of assigning the NMR signals for a structure using advanced NMR techniques is given and a possible teaching activity is presented and discussed.

2.1 Synthesis of *N*-3-alkenylhydantoins

To synthesize *N*-3-epoxyhydantoins in the project the corresponding alkenes, *N*-3-alkenylhydantoins first had to be produced. *N*-3-alkenylhydantoins were synthesized by Cu-catalyzed C(sp^2)-N-coupling reactions using the method that was reported in the Sandtorv group in 2021.[7] Five hydantoins (**1a-e**) with varying substituent patterns on *C*-5 and *N*-1 and different substituent natures were selected to be coupled, to investigate the substituent effects on the hydantoins' reactivity. (*E*)-Styrylboronic acid (**2**) was selected as the coupling partner, since it is an easily accessible alkenylboronic acid that has been reported to produce *N*-3-alkenylhydantoins in good to excellent yields from previous syntheses in the group.[7] The reaction conditions and results from the coupling reactions are presented in Table 1.

Table 1. Results and reaction conditions from the coupling reactions of the hydantoins **1a-e** with (*E*)-styrylboronic acid (**2**).



Entry	Hydantoin	Scale (mmol)	Product	Yield (%)
1	 **1a**	1.5	 **3a**	76
2				
3	 **1b**	1.5	 **3b NEW**	87
4		2.5		77
5	 **1c**	1.5	 **3c**	88
6		2.5		92
7	 **1d**	1.5	 **3d**	85
8	 **1e**	1.5	 **3e**	93

The five *N*-3-aleknylhydantoins **3a-e** were synthesized multiple times to provide enough alkene starting material for further epoxidation by five different methods. The coupling reactions proceeded as expected and produced compound **3a-e** in high purity at yields of 76-93 %. All the compounds were purified by column chromatography using both new and reported eluent systems from Berntsen *et al*.[7] The purifications were efficient and made it possible to isolate all the coupling products (**3a-e**) in a satisfying purity at good to excellent yields without complications.

The ^{1}H NMR spectra of the synthesized compounds **3a-e** show signals that are easily identified. The spectra show two distinct doublets in the sp^2-area with chemical shifts between 6.00-8.00 ppm and coupling constants of 15.1 Hz, characteristic for *trans*-alkenes.[51] They also show some signals with chemical shifts between 7.00-8.00 ppm with varying multiplicity, from the aromatic protons in the phenyl ring.[51] In addition, signals from aliphatic hydrogen atoms at *C*-5 and/or *N*-1 are seen in the sp^3-area, dependent of the substitution of the hydantoin substrate.[51] All the *N*-3-alkenylhydantoins **(3a-e)** except compound **3b** have been recently synthesized and reported in the Sandtorv group. The ^{1}H NMR spectra of the synthesized products are in good accordance with the reported data.[7]

The results from the coupling reactions performed on the different reaction scales of 1.5 and 2.5 mmol are diverging. The coupling of compound **1b** provided compound **3b** in yields of 87 and 77 % in the reaction scales, indicating that synthesis at a larger reaction scale lowered the yield of the reaction. This result is opposite of the result from coupling compound **1c**, which produced compound **3c** in yields of 88 and 92 % at equivalent reaction scales, indicating that synthesis on a larger reaction scale increases the yield of the reaction. A possible explanation for this result could be that reactions on smaller scales might get more affected by product loss in the course of the reaction. However, the difference in the yields of compound **3c** synthesized on 1.5 and 2.5 mmol scales is 4 percentage points, and are likely within what is considered experimental errors. This makes it uncertain whether the small increase in yield is random or due to the increase in reaction scale. Since reported results from Berntsen *et al.* points in the same direction, where compound **1a** coupled with (*E*)-styrylboronic acid on a 0.4 and 1.5 mmol scale produced compound **3a** in yields of 77 and 88%, it may appear that higher reaction scales increases the yield from the coupling reaction.[7]

The reproduced *N*-3-alkenylhydantoins (**4a**, **4c-e**) were isolated in lower yields than reported yields from Berntsen *et al*. Compound **3a** was isolated in a yield of 76 % on a 1.5 mmol scale, which is considerably lower than the reported yield of 88 % on the same reaction scale.[7] Compound **1c-e** synthesized on a 1.5 mmol scale were isolated in yields of 1-12 percentage points lower than the yields

reported on a 0.4 mmol scale.[7] A possible reason for this could be that some product may have been lost in the purifications by column chromatography. Another factor that probably affected the yields is the quality of the (*E*)-styrylboronic acid (**2**) that was used in the reactions. A recorded ^{1}H NMR spectrum (Appendix A) of the boronic acid ordered from Sigma-Aldrich shows that it contained a significant amount of impurities. Among the impurities a "bump" is seen in the sp^{2}-region, which can indicate that a polymer of the boronic acid may have been present in a mixture with the alkenylboronic acid, as polymers are large, disordered molecules that don't give sharp signals in ^{1}H NMR.[51] Some styrene peaks are also seen, confirming this assumption as styrene loves to polymerize.[51] The ^{1}H NMR spectrum of the (*E*)-styrylboronic acid (**2**) used by Berntsen *et al*., that was made and not purchased, shows that it contained less impurities (Appendix A).[52] Using a less pure (*E*)-styrylboronic acid makes less coupling agent available for reaction with the hydantoins, reducing the yield from the reaction.

When it comes to the hydantoins reactivity in the coupling reactions, the results show that the coupling of 5,5-disubstituted and/or *N*-1-substituted substrates provided coupling products in the highest yields. The results from the reactions at a 1.5 mmol scale show that the *N*-1-substituted structures **1e** and **1c** provided coupling products in the highest yields of 93 and 88 %, the 5,5-disubstituted structures **1b** and **1d** gave products in yields of 87 and 93 %, and the unsubstituted **1a** gave coupling product in the lowest yield of 76 %. The results from Thilmany *et al.* and Berntsen *et al.* point in the same direction and confirm that coupling reactions of hydantoins are most selective on 5.5-disubstituted substrates.[5,7] The increased selectivity of 5,5-disubstituted substrates can be explained by steric hindrance, as *C*-5 substitution makes the *N*-1 nitrogen more hindered than *N*-3. This decreases the competition between the two nitrogen atoms in the coupling reaction, which increases the yield of the *N*-3-coupled product.[5] The increased selectivity on *N*-1-substituted substrates can be explained by the *N*-1 position being unavailable, which only makes the reaction possible to take place at the *N*-3 position.

In this coupling reaction, pyridine is one of the reagents. The results from an optimalization study show that the reaction is inefficient in the absence of pyridine, but the function of pyridine is not fully understood.[7] With weak basic properties, pyridine can be used as a base and deprotonate the nitrogen atom to be coupled in the reaction, activating the hydantoin.[53] Another function of pyridine can be to act as ligand for the copper catalyst.[53] In addition, the coupling reaction uses a boronic acid. Boronic acids can be dehydrated and form boroxines in an equilibrium reaction.[54] It is unclear whether boronic acid or boroxine is the active coupling partner in the reaction. As boroxines are stabilized by nitrogen bases, a third role of pyridine can be to stabilize boroxine and make the coupling reaction possible.[55]

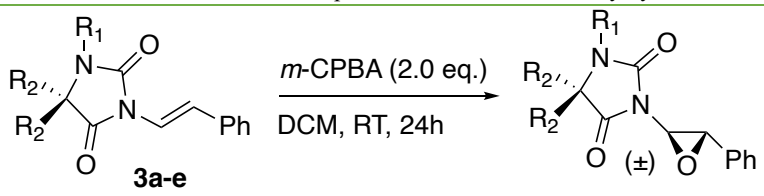
2.2 Synthesis of *N*-3-epoxyhydantoins

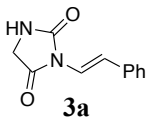
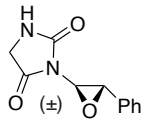
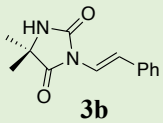
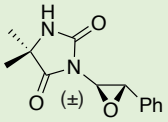
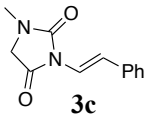
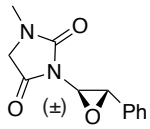
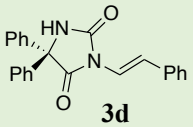
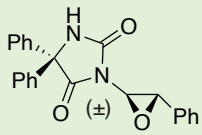
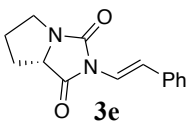
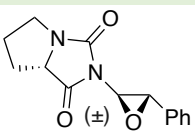
After the synthesis of *N*-3-alkenylhydantoins, the five epoxidation methods presented in the introduction were tested to investigate whether they could give produce the compounds corresponding *N*-3-epoxyhydantoins. The results from the epoxidations are now presented and discussed, and at last the methods are compared and evaluated against relevant principles of green chemistry.

2.2.1 Epoxidation with *m*-CPBA

The *m*-CPBA method, hereby called method 1, was the first epoxidation method tested on the *N*-3-alkenylhydantoins.[34] It was first investigated whether Solvi's result of epoxidizing compound **3a** to **4a** in a yield of 93 % was reproducible.[47] The method was then used on several *N*-3-alkenylhydantoins **(3b-e)**, to see if it was compatible with structural variations and different substituent natures. The reaction conditions and the results from the epoxidations are presented in Table 2.

Table 2. Results and reaction conditions from the epoxidations of the *N*-3-alkenylhydantoins **3a-e** with method 1.



Entry	Alkene	Scale (mmol)	Product	Yield (%)
1	 **3a**	0.2	 **4a**	92
2	 **3b**	0.2	 **4b NEW**	81
3		0.6		85
4	 **3c**	0.2	 **4c NEW**	60
5		1.5		62
6	 **3d**	0.2	 **4d NEW**	85
7	 **3e**	0.2	 **4e NEW**	61

The result from epoxidizing compound **3a** to **4a** shows that Solvi's result was reproducible. Compound **4a** was isolated in an excellent yield of 92 % with spectroscopic data that are consistent with the data reported by Solvi.[48] Extraction with the base K_2CO_3 removed aromatic impurities of excess *m*-CPBA and the corresponding acid byproduct *meta*-Chlorobenzoic acid (*m*-CBA) and made it possible to isolate compound **4a**. The ^{1}H NMR spectrum of compound **4a** shows that there remained is small amount of solvent molecules in the isolated product, from acetone and grease or hexane. Neither high vacuum drying (24 h) or oven drying (80ºC, overnight) proved effective at removing the impurities. This could indicate that the crystals of compound **4a** and the solvent molecules were tightly bonded.

The epoxidation of compound **3b** also proceeded successfully and produced compound **4b** which is new. Compound **4b** was purified in the same way as compound **4a** and was also isolated with a small amount of acetone where the solvent molecules seemed to be tightly bonded to the product. Compound **4b** was isolated in two different reaction scales of 0.2 and 0.6 mmol in yields of 81 and 85 %. These yields are close to the yield of compound **4a** of 92 %. This shows that the method was able to successfully epoxidize a 5,5-dimethyl-substituted substrate. Since the synthesis and purification of compound **4b** was performed using the same conditions as in the synthesis of compound **4a**, it is unclear whether the drop in yield is coincidental or related to using a 5,5-disubstituted more steric hindered substrate. Steric hindered structures are less available in chemical reactions, and might give a transition state with higher energy, which can make reactions with them less favorable.[4]

The new 5,5-diphenyl-substituted compound **4d** was also synthesized with the *m*-CPBA method. This compound was first purified with extraction with K_2CO_3 like compound **4a**-**b**, but the vacuum dried organic phase contained a considerable amount of aromatic impurities. Further purification was performed by column chromatography, which enabled isolation of compound **4d**. This compound was as the other *N*-3-epoxyhydantoins also seen to co-crystallize with solvent molecules like water and hexane from the purifications, which were difficult to remove. Although both extraction and column chromatography were performed to isolate compound **4d**, it was isolated in a good yield of 85 % on a 0.2 mmol scale. The yield of the compound **4d** synthesized on a 0.2 mmol scale is very close to the yield of compound **4b** of 81 % on the same scale, which is also 5,5-disubstituted.

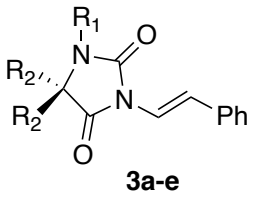
The new compounds **4c** and **4e** were also possible to synthesize using *m*-CPBA. A common feature of the syntheses of these compounds, were that the product isolations required several purification steps than the other *N*-3-epoxyhydantoins. The purification was like on the other structures first attempted by extraction with K_2CO_3, which removed a considerable amount of the aromatic impurities, but did

not remove them completely. A second extraction with K_2CO_3 was performed, without any visible effect on the impurities. Further purification was then performed using column chromatography, and this provided compound **4c** and **4e** as pure compounds, with some weak solvent impurities like seen previously. The purifications with two extra steps compared to the other compounds probably caused loss of some reaction product. This can be one possible explanation why the compounds synthesized on a 0.2 mmol scale were isolated in considerably lower yields of 60 % and 61 %, compared to the other *N*-3-epoxyhydantoins synthesized at the same reaction scale. Another factor that might have affected the yields can be the substitution patterns of substrates. Both substrate **3c** and **3e** have alkyl groups substituents to *N*-1, unlike substrate **3b** and **3d** which have substituents on *C*-5. It may appear that *N*-1-substituted substrates do not go well with the epoxidation reaction, for example if they can react in a side reaction. However, no signs of side reactions were seen in their crude ^{1}H NMR spectra.

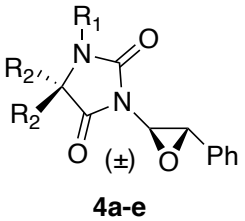
2.2.2 Epoxidation with hydrogen peroxide

After synthesizing the *N*-3-epoxyhydantoins **4a-e** with the *m*-CPBA method, it was desirable to investigate if the structures could be produced with a greener, more atom-effective method. For this investigation, three reported methods using hydrogen peroxide as oxidant under varied conditions were tested on the *N*-3-alkenylhydantoins, hereby called method 2-4. The reaction conditions and the results from the epoxidations are presented in Table 3.

Table 3. Results and reaction conditions from epoxidation of the *N*-3-alkenylhydantoins **3a-b** with method 2-4.



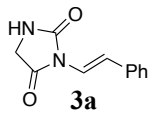
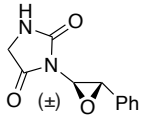
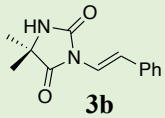
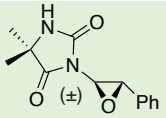
Method 2-4
RT



Method 2
H_2O_2 (1.0 eq.), MeCN (2.0 eq.)
benzaldehyde (5 mol%)
MeOH, buffer 1,[i] pH=11, 5h

Method 3
H_2O_2 (1.0 eq.), MeCN (2.0 eq.)
2,2,2-trifluoroacetophenone (5 mol%)
t-BuOH, buffer 2,[ii] pH=11, 1h

Method 4
H_2O_2 (1.5 eq.), pyridine (12 mol%)
Methyltrioxorhenium (0.5 mol%)
DCM, 6h

Entry	Alkene	Method	Product	Yield (%)	SM (%)
1	 **3a**	2	 **4a**	0	-
2		3		0	-
3		4		0	-
4	 **3b**	2	 **4b NEW**	0	-
5		3		12[iii]	50[iii]
6		4		14[iii]	53[iii]

[i] Buffer 1: 0.6 M K_2CO_3, 4 x 10^{-4} M EDTA disodium salt. [ii] Buffer 2: 0.6 M M K_2CO_3, 4 x 10^{-5} M EDTA tetrasodium salt.

[iii] The yields of the products and starting materials (SM) in entry 5-6 were determined by ^{1}H NMR using mesitylene as IS.

The results show that compound **3a-b** were not epoxidized by method 2 using hydrogen peroxide with benzaldehyde as the catalyst.[38] At the end of the reaction time, the recorded crude ^{1}H NMR spectra of the reaction mixtures showed no epoxide signals, only signals from unreacted starting material, solvents, and unknown impurities. Since the hydantoin structure has two nucleophilic nitrogen atoms, it is a possibility that they can have reacted with benzaldehyde in unwanted side reactions and destroyed the catalyst.[4] In the literature, hydantoins and aldehydes are reported be condensed under basic conditions, forming 5-alkylidene hydantoins.[1] Since the buffer used in the method is basic with pH=11, the conditions can have been basic enough to perform the condensation.[1] Another possible reason why the method is not able to epoxidize compound **3a-b**, may be because the C(sp^2)-N bond can have been electron-poor, and less reactive. The inductive effect from *N*-3 directly bound to one of the sp^2-hybridized carbon atoms, results in the *N*-3-alkenylhydantoins being electron-poor. Electron-poor alkenes are known to be less reactive than electron-rich structures, with a less reactive π-bond.[4] As Method 2 failed to epoxidize compound **3a-b,** it was rejected and was not tested on more structures.

The epoxidation of compound **3a-b** with method 3-4 using hydrogen peroxide with 2,2,2-trifluoroacetophenone or methyltrioxorhenium as catalysts provided similar results. Both methods were unable to epoxidize compound **3a** to the corresponding epoxide **but** were capable of epoxidizing compound **3b** to **4b** to a certain extent (Figure 4). The epoxidation however did not occur completely, and the ^{1}H NMR spectra of the crude mixtures formed at the end of the reaction times only show weak

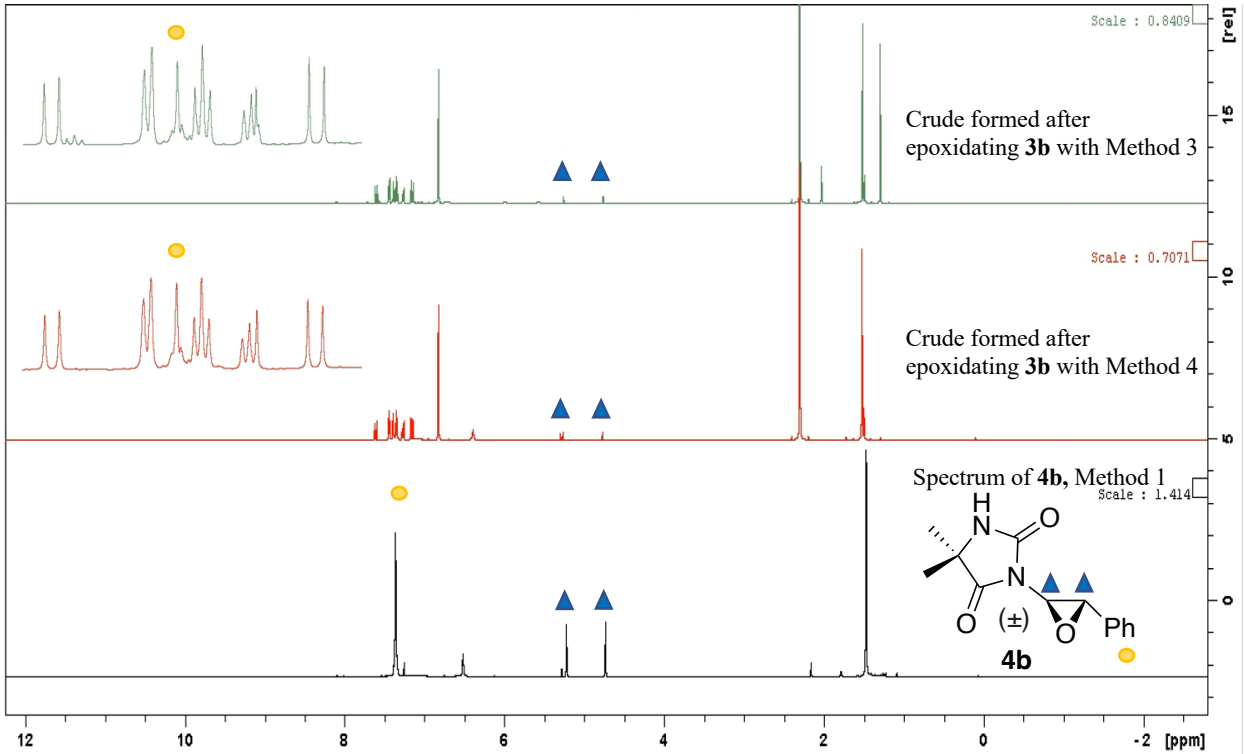


Figure 4. ^{1}H NMR (600 MHz, $CDCl_3$) crude spectra from epoxidizing compound **3b** with method 3-4, using mesitylene as IS. The results from the methods are compared to a pure ^{1}H NMR (600 MHz, $CDCl_3$) spectrum of the desired product **4b**.

product signals and intense signals from the starting materials. The starting material **3b** and its corresponding epoxide **4b** gave TLC spots with almost identical R_f-values. The same was seen for the other *N*-3-alkenylhydantoins and their corresponding epoxides. This, combined with the structures giving weak product signals made separation difficult made product isolation difficult, and it was not attempted. The yields of the product **4b** and the starting material (SM) **3b** were determined by NMR, using an internal standard (IS). The yield determination was possible since the starting material and the product both had been isolated in the previous syntheses with *m*-CPBA.

The NMR yields of compound **4b** synthesized with method 3 and 4 were calculated to be 12 and 14 %. Although compound **4b** was formed in poor yields by both methods, the results show that the 5,5-dimethyl-substituted substrate **3b** was considerably more reactive towards epoxidation than the *C*-5 unsubstituted substrate **3a**. From these results it can seem like *C*-5-substitution of the hydantoin-ring significantly affect the *N*-3-alkenylhydantoins possibility to be epoxidized. It is for example a possibility that the lack of acidic *C*-5 protons in the α-position to a carbonyl that causes this hydantoin to react a bit more like it is desired and makes it form some amount of the epoxide product.[39-40] The NMR yields of the starting materials were 50 and 53 %, showing that much unreacted starting material remained in the reaction mixtures at the end of the reaction times. This shows that method 3 and 4 however were inefficient at epoxidizing *N*-3-alkenylhydantoins, and for this reason method 2 and 3 were not tested on more structures.

The NMR yield determination was done using mesitylene as an internal standard. Mesitylene was selected as it was not in the reaction mixtures and gives ^{1}H NMR signals that are easily identified, that don't overlap with other reactant or product signals.[51] To ensure that the NMR yields that were calculated with mesitylene as IS were credible and consistent with isolated yields, both the isolated yield and NMR yield of compound **4a** synthesized with method 1 were calculated and compared in a separate synthesis of the structure. This produced compound **4a** in an isolated yield of 89 % and a NMR yield of 88 %. This shows that the results are in good accordance with one another (calculation in Appendix D). This makes it is reasonable to believe that the NMR yields of other *N*-3-epoxyhydantoins also correspond well to the reality. However, NMR yields are more uncertain than isolated yields, making isolated yields desired whenever product isolation is possible.[51]

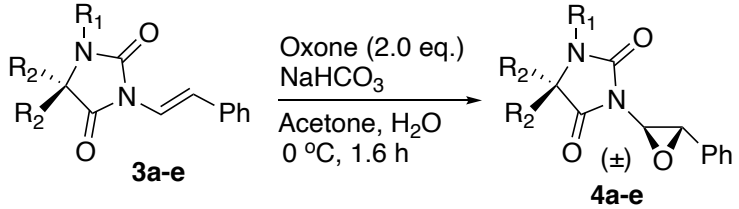
The results from the epoxidations with method 2-4 show that the methods gave either no yields or poor yields of the compounds **4a-b** that were attempted synthesized. None of the methods enabled the epoxidation of the *C*-5-unsubstituted hydantoin substrate **3a** to **4a**. Although compound **3b** was seen

possible to epoxidize by both method 3 and 4, the epoxide **4b** was present in the crude mixtures in poor yields and was not isolated. For these reasons, none of the hydrogen peroxide methods were seen to be efficient or well-suited for epoxidation of *N*-3-alkenylhydantoins. A possible reason for the failure of the methods can be that hydrogen peroxide is not a strong or energy-rich enough oxidant to epoxidize the electron-poor C(sp^2)-N double bond of the *N*-3-alkenylhydantoins completely.[4] As the NMR yields of compound **4b** synthesized by Method 3 and 4 are similar, homogenous, and heterogenous catalysts were seen equally able to activate hydrogen peroxide and epoxidize compound **3b** to **4b** at a low efficiency.

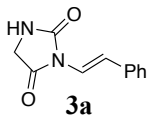
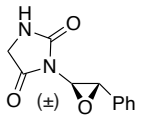
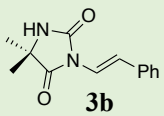
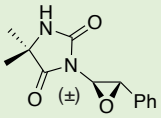
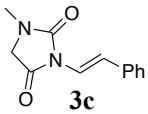
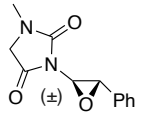
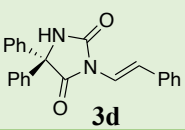
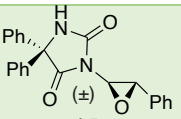
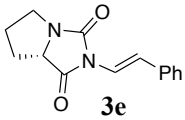
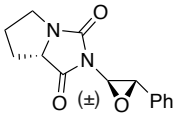
2.2.3 Epoxidation with oxone

After the three hydrogen peroxide methods were seen ineffective to epoxidize the synthesized *N*-3-alkenylhydantoins, an epoxidation method using oxone, hereby called method 5 was further tested. The reaction conditions and the obtained results from the method are presented in Table 4.

Table 4. Results and reaction conditions from epoxidizing the *N*-3-alkenylhydantoins **4a-e** with method 5.



3a-e → **4a-e**

Entry	Alkene	Product	Yield (%)	SM (%)
1	 **3a**	 **4a**	87	-
2	 **3b**	 **4b NEW**	95	-
3	 **3c**	 **4c NEW**	48**	28**
4	 **3d**	 **4d NEW**	2**	55**
5	 **3e**	 **4e NEW**	31**	55**

**The yields of the products and starting materials in entry 3-5 were determined by ^{1}H NMR using mesitylene as IS.

Method 5 was as the other epoxidation methods first tested on compound **3a**-**b**.[42] The results from the epoxidations show that both the structures corresponding epoxides **4a** and **4b** were isolated in excellent yields of 87 % and 95 %. This is in accordance with the yield of a cyclic C(sp^2)-N-bonded structure that is reported epoxidized in a yield of 92 % by the method.[42] Compound **4a**-**b** were both isolated after a simple extraction with ethyl acetate. Like seen in the reaction products synthesized by method 1, compound **4a**-**b** synthesized by the oxone method were also isolated with weak solvent impurities, probably for the same reason as previously discussed.

Compound **3c** was not completely epoxidized by method 5. The ^{1}H NMR spectrum of the vacuum dried extracted organic phase from the reaction showed that the epoxidation resulted in a mixture of alkene starting material and the desired epoxide product **4c**. Since the *N*-3-alkenylhydantoins and *N*-3-epoxyhydantoins were difficult to separate, compound **4c** was not isolated and its yield was determined by ^{1}H NMR, using mesitylene as internal standard. This showed that the product was present in an NMR yield of 48 %, and the unreacted alkene starting material **3c** in a yield of 28 %. Although the yield of 48 % can be considered alright for a greener epoxidation method, the method is unusable it is not possible to isolate the reaction product. In two separate syntheses, the reaction time was tried increased to 24h and the equivalents of oxone was tried increased to 3.0 eq. The ^{1}H NMR spectra of the crude mixtures at end of the reaction times showed that the parameter changes did not make the epoxidation of compound **3c** occur more completely.

Compound **3d** and **3e** were neither epoxidized completely, and their corresponding epoxides were not isolated. Compound **4d** was formed in a poor NMR yield of 2 %, and the unreacted starting material **3d** was present in a yield of 55 %. This result stood out from the others, by the markedly small amount of starting material that had reacted. One thing that distinguishes the substrate **3d** from the other *N*-3-epoxyhydantoins is that it is quite steric hindered, with two phenyl groups substituted to *C*-5. This can have made the structure unavailable for a reaction with oxone, or it can have caused the transition state of the reaction to require more energy, making the epoxidation less favorable. However, this did not seem to affect the isolated yield of compound **4d** synthesized with method 1 in a yield of 85 %.

The epoxidation of compound **3e** provided compound **4e** in a yield of 31 %, and the unreacted starting material **3e** was present in a yield of 55 %. This shows that less than half of the weighed starting material had reacted with oxone. This poor yield can also be due to steric hinderance of the hydantoin substrate, making it less available and reactive with oxone. Epoxidation of compound **3d** and **3e** produced the epoxides in lowest NMR yields. Compound **3d** and **3e** substrates are the most bulky

N-3-alkenylhydantoins that were tested. This supports the assumption that steric hindrance might be a reason for the lower yields that were obtained from the epoxidation of compound **4d** and **4e**.

As seen in Figure 5, the epoxidation of compound **3c-e** with Method 5 led to divergent results. All the structures were to some extent epoxidized, but in very varying yields. This indicates that the substitution pattern of hydantoin is crucial for the *N*-3-alkenylhydantoins reactivity towards epoxidation. The variation in the yields obtained seem random, without showing any clear trends of unsubstituted, *C*-5- or *N*-1-substituted substrates. To explain the divergent results, several structures had to be tested. This could have shown a trend for the obtained results.

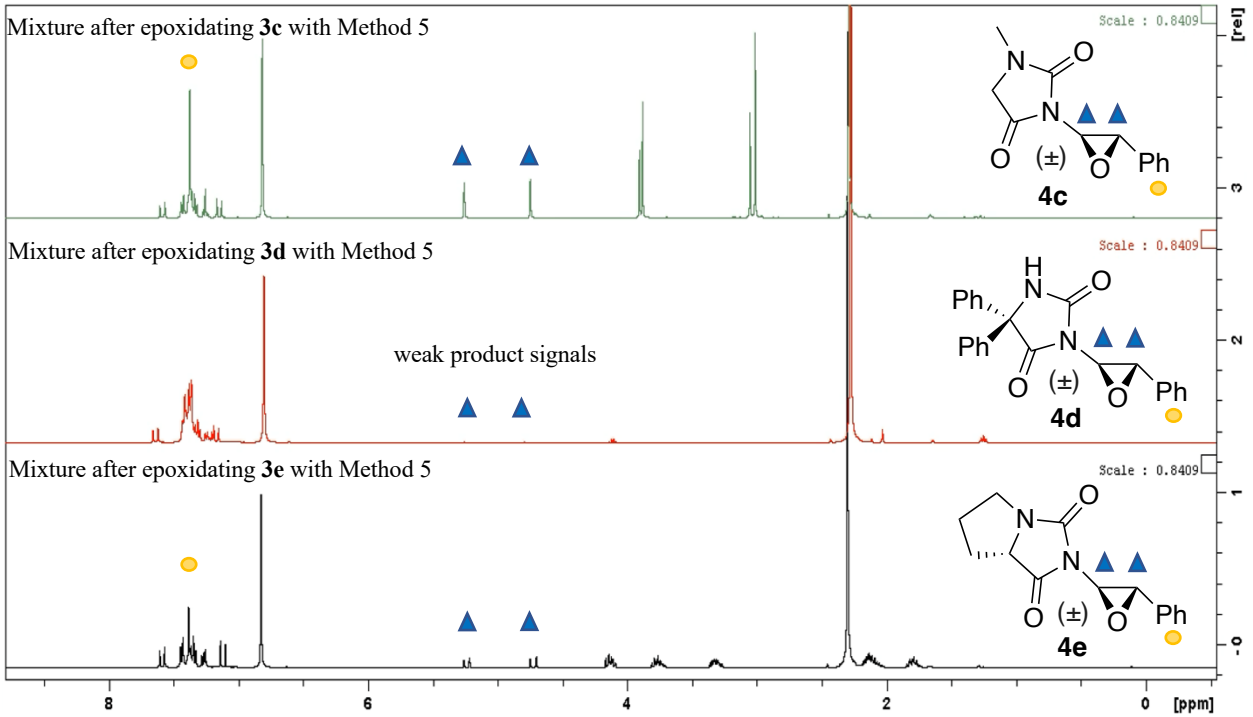


Figure 5. ^{1}H NMR spectra (400 MHz, $CDCl_3$) of compound **3c-e** epoxidized with Method 5 with mesitylene as IS.

2.2.4 Comparison of the epoxidation methods and evaluation by principles of green chemistry

The results from the epoxidations show that only method 1 and 5 were suitable for further use, as they were the only ones that epoxidizing the *N*-3-alkenylhydantoins completely and producing their corresponding epoxides in high yields. Even though method 2-4 use the most environmentally benign, atom effective hydrogen peroxide as oxidant,[31] these methods were inefficient and useless for epoxidating *N*-3-alkenylhydantoins, giving poor yields and product mixtures where the product was difficult to isolate.

Method 1 was efficient on all the tested *N*-3-alkenylhydantoins **3a-e**, while method 5 only efficiently epoxidized compound **3a-b** to their corresponding epoxides. Method 1 was from this seen to be the most diverse method for the epoxidation of *N*-3-alkenylhydantoins, able to epoxidize five structurally different *N*-3-alkenylhydantoins without showing any significant synthetic weaknesses.

The ^{1}H NMR spectra of compound **4a-b** epoxidized with method 1 and 5 show that both methods gave products in a high purity, with weak impurities from grease and solvents. This makes none of the methods favorable over the other according to the epoxide's purity (Figure 6-7). Like previously discussed, both methods enabled isolation of compound **4a-b** in good to excellent yields. To determine which of these methods that is preferred in further syntheses of *N*-3-epoxyhydantoins, the methods will now be evaluated against the most relevant principles of green chemistry.

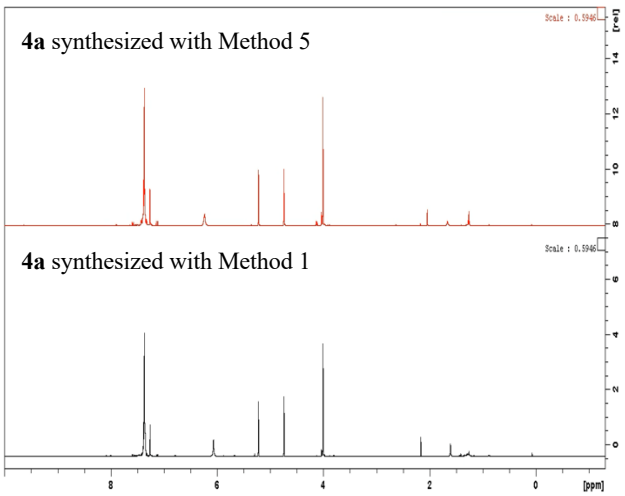


Figure 6. The ^{1}H NMR spectra (600 MHz, $CDCl_3$) of compound **4a** synthesized with method 1 and 5.

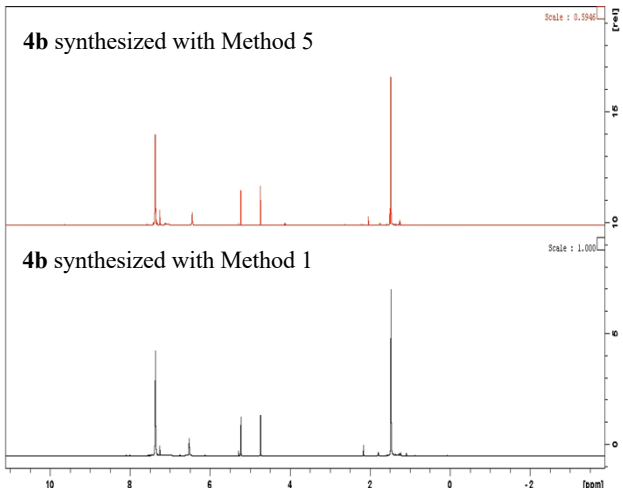
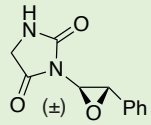
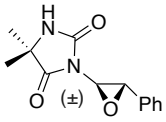


Figure 7. The ^{1}H NMR spectra (600 MHz, $CDCl_3$) of compound **4b** synthesized with method 1 and 5.

First, the hazards and environmental effects of the reagents and solvents used in the methods are evaluated, related to principle 3-5 and 12 of green chemistry about making chemical syntheses safer. As mentioned in the introduction, both *m*-CPBA and oxone are associated with several hazards as being irritating and corrosive, resulting in risks when handling both.[36,43] The other reagents and solvents that are used in method 5 are $NaHCO_3$, water and acetone, all being mild and non-toxic. Water and acetone are environmentally safe and are on the top of the list of green chemicals.[49] Method 1 as performed in the project uses dichloromethane as solvent, which is toxic and suspected of causing cancer and is undesired to use regarding health and safety.[56] This makes method 5 favorable over method 1, as it uses acetone as the reaction solvent and avoids the use of DCM.

Further the methods are evaluated according to principle 1 and 2, waste prevention and atom economy. From the epoxidations of compound **3a-b** with method 1 and 5, the calculated E-factor and AE are presented in Table 5. The calculations show that method 5 clearly gives the highest E-factor, producing five and seven times more chemical waste from the same epoxidations done with method 1. The atom economies are more alike but show that method 5 has a slightly lower atom economy than method 1. This makes method 1 the greenest method according to principle 1-2, producing least chemical waste and incorporating the largest proportion of the reagents into the final product.[49]

Table 5. Yields from epoxidating the *N*-3-alkenylhydantoins **3a-b** with method 1 and 5, E-factor and AE.

Method	Product	Yield (%)	E-factor	AE (%)
1	 **4a**	92	67.6	58
5		81	472	43
1	 **4b NEW**	87	68.0	61
5		95	381	46

The type of waste produced by the epoxidation methods is worth noticing when evaluating the methods according to principle 10 of green chemistry, design for degradation. Oxone produces the inorganic salt $KHSO_4$ and oxygen gas as its byproducts, while *m*-CPBA generates its corresponding carboxylic acid *meta*-chlorobenzoic acid (*m*-CBA). Of these byproducts, $KHSO_4$ and oxygen are non-toxic,[44] while *m*-CBA is irritating, and an organic chemical that can be hazardous for the environment and needs to be collected in a container for organic waste.[57] This makes method 5 favorable based on this principle. When it comes to energy efficiency related to principle 6 both method 1 and 5 are favorable. They don't require intensive energy use, as they are performed in room temperature and on an ice bath.

As now have been discussed, method 1 and 5 both have strengths and weaknesses according to the principles of green chemistry. Though method 1 produces less chemical waste and is more atom effective, method 5 is less hazardous and more environmentally friendly in terms of the reagents and solvents used and the biproducts generated. As the goal in green chemistry is to reduce or eliminate the use and generation of hazardous substances, method 5 can be considered the greenest method.[49]

2.2.5 Stereoisomers of the *N*-3-epoxyhydantoins

All the synthesized *N*-3-epoxyhydantoins were isolated as mixtures of stereoisomers, as all the five methods performed racemic epoxidations. Of the *N*-3-epoxyhydantoins, compound **4a-d** have two chiral centers each, and can form four possible stereoisomers (Figure 8).[4] The ^{1}H NMR analysis of the compounds did not detect any stereoisomers, as the signals from the protons on the chiral centers at the two epoxide carbons only gave one doublet signal each (Figure 9).[4,51] This gives information of it only being one enantiomeric pair present in the product mixtures, since diastereomers have different signals in ^{1}H NMR. As the *N*-3-alkenylhydantoin substrates were *trans*-alkenes, the formed products will be *trans*-epoxides since the epoxidation is expected to occur in a concerted mechanism.[35] The enantiomeric pair that has the absolute configuration *R*, *S* and *S*, *R* is with reasonable certainty the enantiomeric pair in present in the product mixture since the other pair has a *cis*-stereochemistry.[4,51]

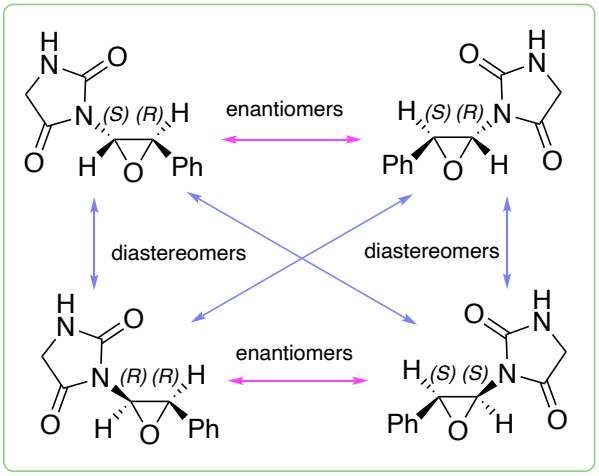


Figure 8. The four possible stereoisomers of compound **4a** containing two chiral carbon atoms.

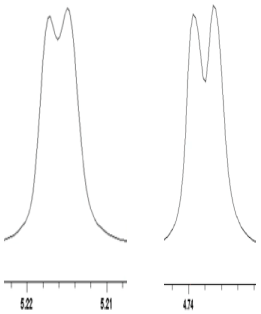


Figure 9. ^{1}H NMR (600 MHz, $CDCl_3$) of **4a** synthesized by method 5, showing the doublet assigned to the protons on the two chiral carbon atoms.

Compound **4e** differs from compound **4a-d** by containing three chiral centers, leading to a possibility of eight stereoisomers.[4] The ^{1}H NMR spectrum of the compound shows two stereoisomers, observed as two double doublets (Figure 10). This multiplicity differ from the ^{1}H NMR signals from the epoxide protons from the other synthesized *N*-3-epoxyhydantoins (**4a-d**), seen as two regular doublets. The double doublets must come from two diastereomers of **4e**, as enantiomers give identical signals in ^{1}H NMR.[4] The ^{1}H NMR analysis shows that the two diastereomers are present in a 50:50 ratio. The diastereomers enantiomers are also expected to be present in the product mixture. The structures of the diastereomers with enantiomeric pairs present in the product mixture of **4e** was not determined.

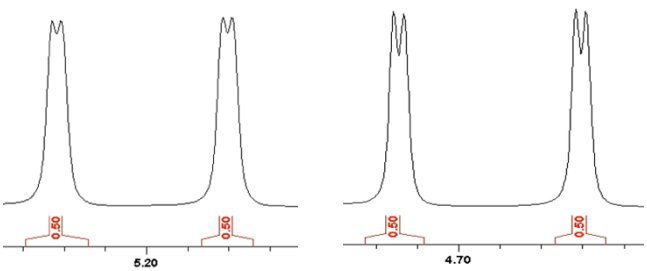
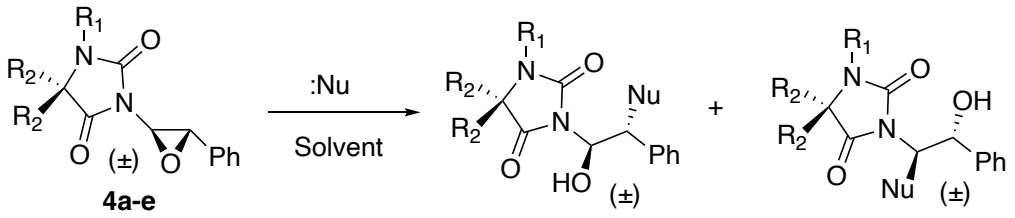


Figure 10. ^{1}H NMR (600 MHz, CDCl3) of **4e** synthesized by method 1 showing the signals of the two diastereomers in a 50:50 ratio.

2.3 Ring-opening of the *N*-3-epoxyhydantoins

Some of the synthesized *N*-3-epoxyhydantoins were reacted with a selection of nucleophiles to investigate their reactivity and ability to undergo ring-opening. Compound **4a-c** were chosen as substrates as they have varied substitution patterns on *C*-5 and *N*-1 and were expected to have different reactivities with nucleophiles. As nucleophiles, water, 1-propanol, and the amino acid ester *L*-valine methyl ester were selected, as they have varied nucleophilicity and are expected to give different ring-opening products in reaction with epoxides. Their expected ring-opening products are diols,[23] β-alkoxy alcohols[4] and β-amino alcohols.[25] These functional groups can be used in further reactions, making the nucleophiles interesting for the investigation of the *N*-3-epoxyhydantoins reactivity. The reaction conditions and results from the nucleophilic ring-opening reactions are presented in Table 6.

Table 6. Results and reaction conditions for the attempts at ring-opening the *N*-3-epoxyhydantoins **4a-c.**



Entry	Epoxide	Nucleophile	Time (h)	T (°C)	Outcome
1	**4a**	H_2O	48	100	ring-opening
2	**4b**	H_2O	24	100	ring-opening
3	**4c**	H_2O	48	100	ring-opening
4	**4a**	1-propanol	72	90	no reaction
5	**4b**	1-propanol	48	90	ring-opening
6	**4c**	1-propanol	72	90	no reaction
7	**4b**	*L*-valine methyl ester	20 min	70	ring-opening

The first nucleophile tested to ring-open the *N*-3-epoxyhydantoins was water. The ring-opening reaction of compound **4a-c** was performed under the same conditions as reported of Wang *et. al* using water and 1,4-dioxane as solvent refluxed at 100°C.[23] The reactions were monitored by TLC and were ended after 24-48h when the epoxide spot on the TLC-plate had disappeared. All the three ring-opening reactions with water proceeded with a color change of the mixtures from colorless to yellow or orange, indicating that a reaction had occurred. This was also confirmed of the ^{1}H NMR spectra of the crude materials, showing that the two characteristic epoxide doublets and aromatic multiplett that integrates to 5H no longer was present. However, neither of the ^{1}H NMR spectra showed signs of 1,2-diols, which was the expected reaction product from the hydrolysis reactions.[4,23]

The recorded crude ^{1}H NMR spectra from ring-opening compound **4a** with water show many signals.

From the NMR-analysis it looks like the *N*-3-epoxyhydantoins corresponding hydantoins were formed instead of their corresponding 1,2-diols. The ^{1}H NMR spectra of the ring-opened compound **4a** (Figure 11) shows a singlet on 1.55 ppm with the same chemical shift as the two protons of the *C*-5 position of hydantoin (**1a**). This is seen most clearly in the ^{1}H NMR spectrum of the water phase formed after an attempt at purifying the ring-opened product by extracting the crude with saturated $NaHCO_3$. The reason for this formation, can be that the ring-opened 1,2-diols can have been so unstable that they only exist a short time before quickly being decomposed to the hydantoin skeleton.

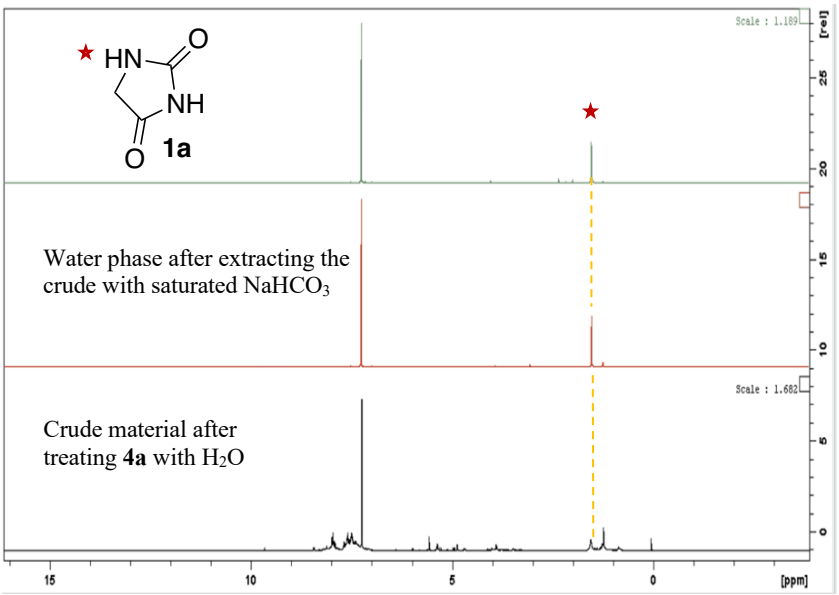


Figure 11. ^{1}H NMR ($CDCl_3$, 400 MHz) of the reaction outcome after treating **4a** with H_2O. The CH_2 signal from hydantoin is marked with a yellow dotted line.

The ^{1}H NMR spectra of compound **4b** and **4c** after treating them with water under the same conditions also show signals with the same chemical shifts as their original hydantoin nuclei (Figure 12-13). The ^{1}H NMR spectrum of the crude material formed after the ring-opening reaction of compound **4b** shows one weak singlet with the same chemical shift on 1.47 ppm as the CH_3 peak in 5,5-dimethylhydantoin (**1b**). The signal is weak in the spectrum of the crude material, which indicates that 5,5-dimethylhydantoin is present in small quantities. The ^{1}H NMR spectrum of compound **4c** treated with water shows two peaks with the same chemical shifts as the hydantoin signals from the CH_2 and CH_3 protons from 1-methylhydantoin (**1c**) on 3.92 and 2.97 ppm.

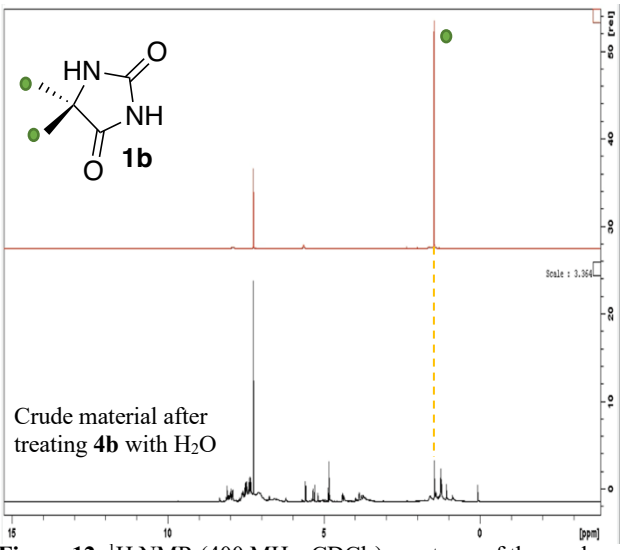


Figure 12. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the crude material formed after treating **4b** with H_2O compared to the ^{1}H NMR spectrum of **1b**.

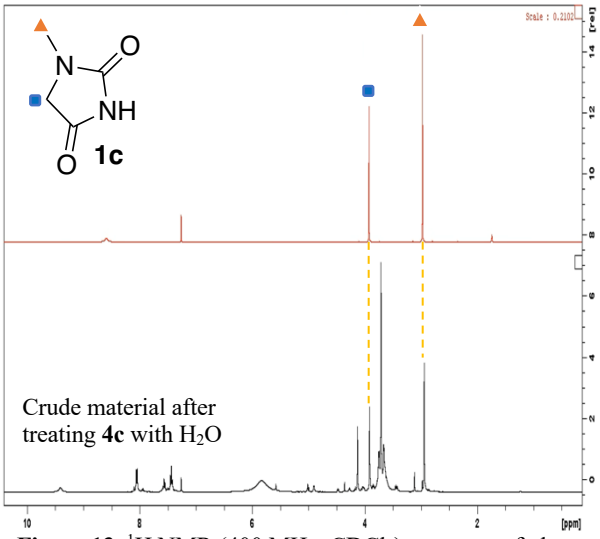


Figure 13. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the crude material formed after treating **4c** with H_2O compared to the ^{1}H NMR spectrum of **1c**.

While water ring-opened all the three *N*-3-epoxyhydantoins (**4a-c**), the reactions with 1-propanol as nucleophile and 1,4-dioxane as solvent only ring-opened compound **4b**. This shows that compound **4b** was the most reactive substrate towards a nucleophilic attack. The ^{1}H NMR spectrum of the crude material formed after treating **4b** with 1-propanol (Figure 14) shows the similar results as the ring-opening reactions with water where only one peak from the CH_3 groups in 5,5-dimethylhydantoin was identified. This indicates that the expected β-alkoxy alcohol also may have been too unstable to be isolated. That only compound **4b** was ring-opened with 1-propanol was unexpected, as alcohols are stronger nucleophiles than water that more easily donate a free electron pair.[4] Since alcohols are weak nucleophiles, an acid catalyst might had been necessary to facilitate the hydrolysis of the epoxides **4a** and **4c** with 1-propanol.[4] This not being needed in the ring-openings with water can be since water can act as both a modest acid catalyst and a nucleophile in the reaction.[4,23]

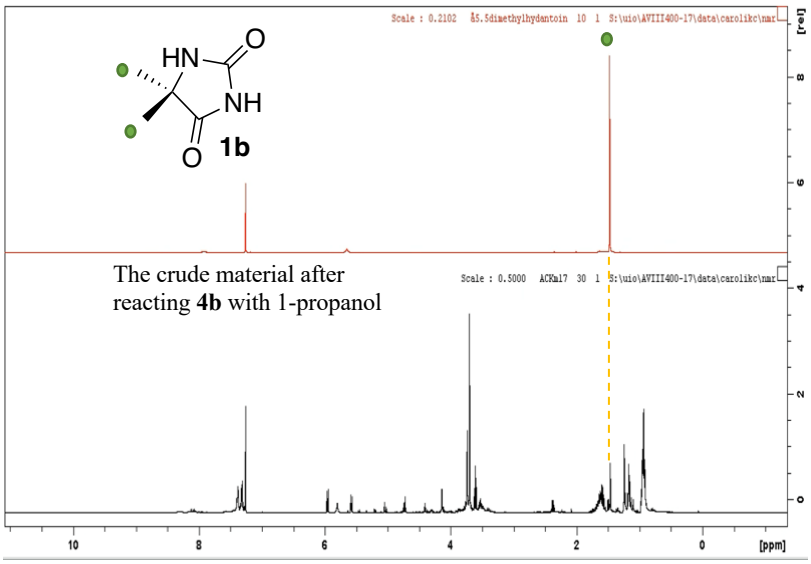


Figure 14. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the crude material formed after treating **4b** with 1-propanol compared to the ^{1}H NMR spectrum of compound **1b**.

Lastly one attempt at ring-opening compound **4b** using the amine, *L*-valine methyl ester in identical conditions as described in the procedure from Philippe *et al.*, using the amino acid ester and 2,2,2-trifluoroethanol as solvent under reflux at 70 °C.[25] Compound **4b** was the only *N*-3-epoxyhydantoin that was attempted ring-opened with the method, and it was ring-opened after 20 minutes. This was observed in the TLC-analysis of the crude material that were taken every 10 minutes from the reaction was started. As an amine, *L*-valine methyl ester is a stronger nucleophile than water and alcohols. This can be a possible reason for the big increase in reaction efficiency in this ring-opening reaction.[4] The ^{1}H NMR spectrum of the reaction mixture (Figure 15) did not show signals from the expected β-amino alcohol,[25] only a singlet from the CH_3 protons in compound **1b**, likely for the same reasons as previously discussed.

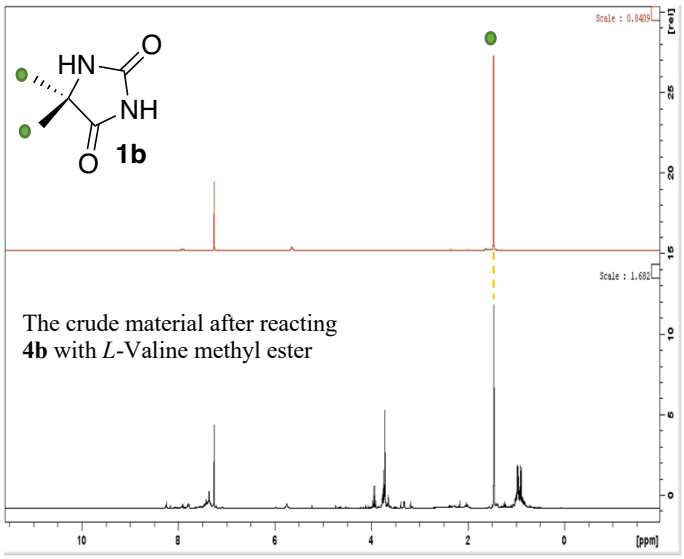
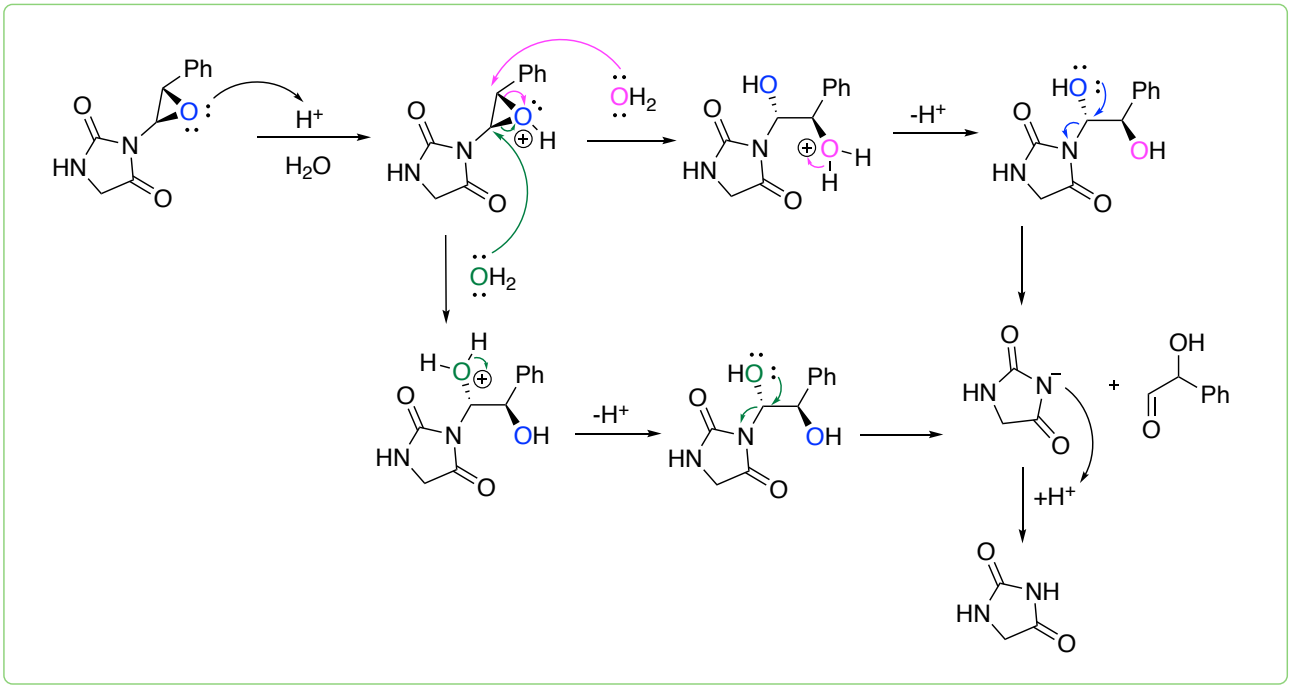


Figure 15. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the crude material formed after treating **4b** with *L*-Valine methyl ester compared to the ^{1}H NMR spectrum of **1b**.

As the ring-opening reactions of the *N*-3-epoxyhydantoins did not show any signs of the expected ring-opening products, none of the crude materials were attempted purified. In addition, the TLC-plates of the crude materials showed over five spots for each reaction, indicating that it would have been time consuming with a complete product isolation, without knowing which spot that was from the reaction product. As the hydantoin chores that are assumed to be present at the end of the ring-opening reactions not were enabled isolated, there is an uncertainty whether they were the final products that were formed as a result of the ring-opening reactions.

Scheme 11 shows a proposed mechanism of how the ring-opening reactions with water might have occurred, and how the reactions can have led to a formation the hydantoin substrates that were used in the coupling reactions. The reaction mechanism is proposed for the ring-opening of compound **4a** with

water. The mechanism is first expected to occur like a regular acid-catalyzed epoxide ring-opening reaction, involving the epoxide oxygen to be protonated followed by an S_N2-like backside attack from water on the protonated epoxide.[4] This leads to a *trans*-1,2-diol epoxide. If the reaction occurred as expected, the 1,2-diol would have been a stable product enabled isolated.[4] As this is not observed it is a possibility that an electron pair from the alcohol oxygen closest to the hydantoin-ring can have attacked the carbon atom bound to *N*-3 nitrogen, causing bond breakage of the C-N bond. This form an unstable nitrogen anion that is easily protonated and can result in the original hydantoin substrate being re-formed.



Scheme 11. Proposed mechanism for the ring-opening of compound **4a** using water as nucleophile.

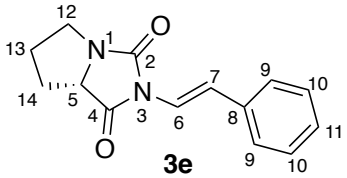
2.4 NMR structure solution

In this section, the ^{1}H- and ^{13}C NMR signals of compound **3e** are assigned as an example of how the structures were assigned using the advanced NMR techniques presented in Table 7.

Table 7. The advanced NMR techniques used in the structure solution with associated usage areas.[52]

DEPT	Shows the multiplicity of the carbon atoms giving the ^{13}C NMR signals. The proton pulse can be set on different angles on 45, 90 or 135° and show varied multiplicities; C, CH, CH_2, CH_3.
COSY	Shows correlations between protons that are coupled with each other over 1-3 bonds.
HSQC	Shows which protons that are directly attached to which carbon atoms.
HMBC	Shows correlations between protons and carbon atoms that are separated by multiple bonds (2-4).

The first step in the structure solution is to extract significant data from the compound's ^{1}H NMR and ^{13}C NMR spectrums, as presented in Table 8 and 9 for compound **3e** (Figure 16). The ^{1}H NMR spectrum of **3e** shows fourteen protons in eleven varied chemical environments. This fits with the structure, as it has two pairs of protons in position 9 and in position 10 that are in magnetically equivalent environments. Signals from seven protons are detected in the sp^3-area with chemical shifts over 4.5 ppm. These can be assigned to the protons in the fused ring of **3e**.[51] The five remaining signals are in the sp^2-area with higher chemical shifts and must come aromatic and vinylic protons in **3e.**[51]



3e

Figure 16. Compound **3e** with numbered positions.

Table 8. Shows the spectroscopic data from the ^{1}H NMR spectrum of **3e.**

δ(ppm)	Integral	*J* (Hz)	Multiplicity
7.56	1	15.1	d
7.41	2	7.4	d
7.32	2	7.7	t
7.24	1	7.4	t
7.09	1	15.1	d
4.14	1	9.1, 7.7	dd
3.77	1	11.3, 7.7	dt
3.32	1	11.3, 7.5, 4.5	ddd
2.31	1	12.7, 7.3, 3.8	dtd
2.19-2.05	2	-	m
1.79	1	12.7, 9.2	dq

Table 9. Shows the spectroscopic data from the ^{13}C NMR and DEPT135 spectrum of **3e.**

δ(ppm)	DEPT135	Multiplicity
171.7	no signal	s
158.4	no signal	s
135.7	no signal	s
128.7	+	d
127.7	+	d
126.2	+	d
120.3	+	d
118.1	+	d
62.6	+	d
45.7	-	t
27.6	-	t
26.9	-	t

The ^{13}C NMR spectrum of **3e** shows twelve carbon signals, which is in accordance with the structure containing twelve different carbon environments as the two carbon atoms in position 9 and the two carbon atoms in position 10 are magnetically equivalent. With chemical shifts under 100 ppm, four signals from sp^3-hydridized carbons are shown, which fits with the fused-ring carbons. The remaining signals are in the sp^2-area over 100 ppm and corresponds to the five aromatic carbons and the two carbonyl carbons as they are expected the highest chemical shifts in ^{13}C NMR.[51]

After now have given an overview of the spectroscopic data, the next step is to assign the signals. The three ^{13}C NMR signals with highest chemical shifts can be assigned to the quaternary carbons of **3e**, as they are not present in the DEPT135 spectrum. As carbonyl carbons have highest chemical shifts among carbon atoms, the carbons in position 4 and 2 can be assigned to the signals on 171.7 and 158.4 ppm, and the aromatic carbon in position 8 to the signal on 135.7 ppm.[51] Of the remaining signals over 100 ppm, the HSQC spectrum (Figure 17) shows a correlation between the signal on 120.3 ppm and the doublet from the *trans*-alkene on 7.56 ppm, seen on its coupling constant on 15.1 Hz. The doublet can be assigned to the *trans*-proton in position 6, that is neighbor with the electron withdrawing *N*-3 expected the highest chemical shift.[7] The signal on 118.1 ppm has a correlation to the doublet at 7.09 ppm with J= 15.1 Hz and can be assigned to the other *trans*-alkene proton in position 7.

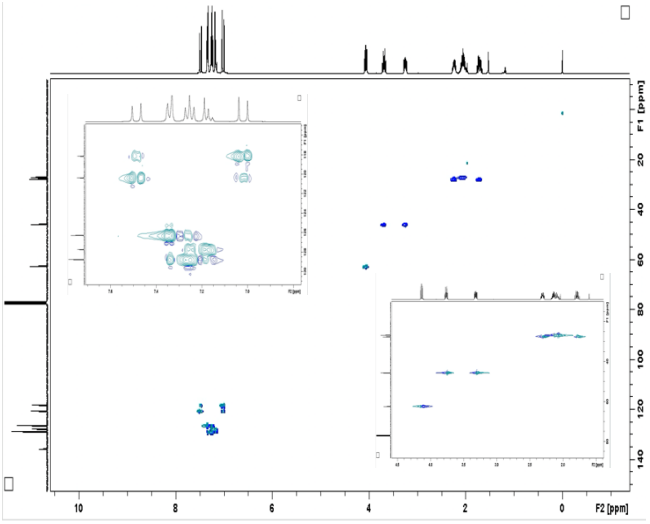


Figure 17. Shows the HSQC (600 MHz, $CDCl_3$) spectrum of **3e** with proton-carbon correlations.

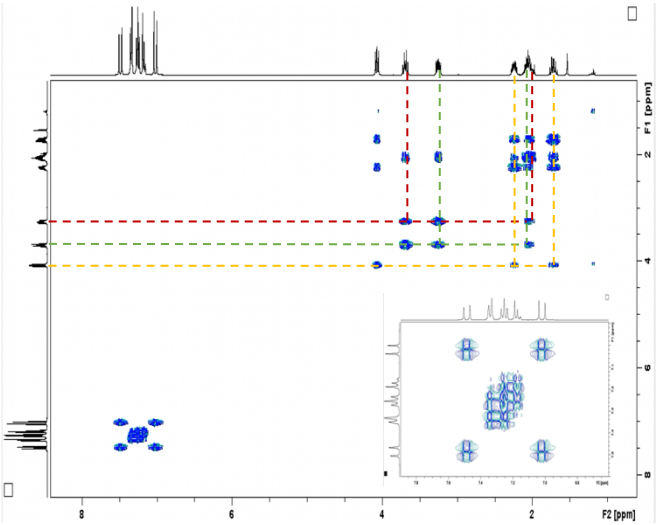


Figure 18. Shows the COSY (600 MHz, $CDCl_3$) spectrum of **3e** with proton-proton correlations.

The three remaining sp^2-signals in the ^1H NMR spectrum must come from the carbon and hydrogen atoms in the aromatic ring in position 9-11. The triplet at 7.24 ppm correlating to the signal on 127.7 ppm must be from the proton in position 11, as it is the only aromatic signal expected to integrate to 1H. The doublet at 7.41 ppm integrating to 2H correlates to the signal on 126.2 ppm and can be assigned to the protons in position 9, as the multiplicity as a doublet and the COSY spectrum (Figure

18) shows that the protons only have one coupling partner. The triplet at 7.32 ppm integrating to 2H correlates to the signal on 128.7 ppm. This fits with the aromatic protons and carbon atoms in position 10 with two magnetically non-equivalent neighboring protons as coupling partners.

The ^{1}H NMR spectrum shows complex coupling patterns of the six signals in the sp^3-area, from the protons in the fused ring. The hindered bond rotation in the ring results in diastereotopic protons on two of the carbons, that each produce distinct chemical shifts. The HSQC shows that the doublet of doublets (dd) at 4.14 ppm correlates to the signal on 62.6 ppm. The DEPT135 shows that the ^{13}C signal is from a positive and must be from a CH carbon as **3e** does not have any CH_3 carbons. Consequently, the doublet of doublets and the signal on 62.6 ppm must come from the proton and carbon in position 5. The multiplicity as a dd indicates that its neighbor carbon, C-14 has two diastereotopic protons, resulting in two doublets with different coupling constants.

The COSY of **3e** shows that the diastereotopic protons on C-14 give a doublet of quartets (dq) at 1.79 ppm and a doublet of triplet of doublets (dtd) at 2.31, as the dd from C-5 has these signals as coupling partners (Figure 18, yellow dashed lines). The HSQC shows that the carbon signal on 27.6 ppm correlates to both the dq and dtd, confirming that the protons are diastereotopic. Now, it is only three remaining signals in ^{1}H NMR, and two in ^{13}C NMR, and assigning the protons and carbons in position 12-13. Of the carbons, C-12 is expected to have highest chemical shift as it is bonded to the electron withdrawing *N*-1 nitrogen. The CH_2 signal on 45.7 ppm can therefore be assigned to C-12. The HSQC shows that this carbon signal correlates to both the doublet of triplets (dt) at 3.77 ppm and the doublet of doublet of doublets (ddd) at 3.32 ppm. This shows that the protons on C-12 also are diastereotopic.

The coupling pattern of the protons at C-12 can be explained by looking at proton correlations and coupling constants. The COSY shows that both the diastereotopic protons have the two protons on C-13 as coupling partners (Figure 18, red and green dashed lines). However, one of the diastereotopic protons couples to the protons with the same coupling constants, leading to a triplet, while the other couples to the protons with different coupling constants, leading to two doublets. In addition, a geminal coupling between the diastereotopic protons leads to a doublet in both signals.

Lastly, the multiplett on 2.19-2.05 ppm integrating 2H can be assigned the protons on C-13, expected the highest multiplicity as they are in the middle of a fused-ring.[51] The HSQC shows that the multiplett correlates to the ^{13}C signal on 26.8 ppm. After assigning the signals, HMBC (Appendix A) was used to confirm that the correlations over several bindings were in accordance with the structure solution.

2.5 Application in education

2.5.1 Establishing relevancy

This master project was made possible through "Lektorprogrammet" at the University of Oslo, a program aiming to give solid pedagogical competence and deeper subject specialization than other teacher programs.[58] From this context, it is now relevant to briefly discuss how the research performed can be used in chemistry education.

Chemistry is a school subject that has its identity strongly tied to experimentation and exploration, with the aim to learn the students the scientific way of working.[59] This way of working involves formulating their own research questions, experiment, register and interpret of data, think critically, discuss, and communicate obtained results. It can be considered a type of active, exploratory learning that has been shown to improve students' learning in subjects.[59-61]

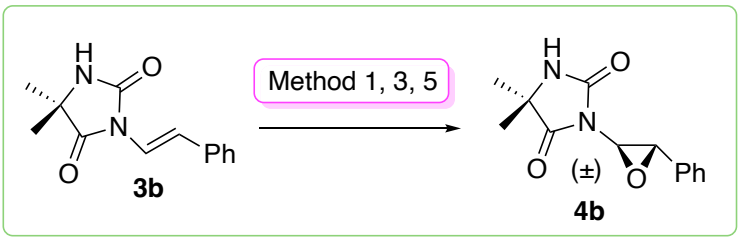
One way to make the students practice the scientific way of working can be to implement a case study where they get a case to solve based on a real-life issue that researchers encounter.[62] Case studies are used for many purposes, as developing concepts, solve problems or to demonstrate the application of theory to a real-life situation.[62-63] Related to the scientific way of working a case study can particularly train students in interpretation of data, critical thinking, discussion, and communication of results or findings. For a case study to be effective it should tell an interesting story, be relevant for the students and have problems to solve.[62-63] A case study can be implemented in the whole class or in smaller groups. Regardless of how the case is used, case studies are seen to promote deeper learning and increase student motivation and participation in the chemistry subject.[62]

In the Norwegian school system, the new curriculum "Kunnskapsløftet 2020" (LK20) was introduced, with the vision to increase students' learning in subjects.[64] This is to be achieved by an increased focus on students' exploration, more in-depth learning, and focus on overall themes and the interdisciplinary.[63] Green chemistry is a topic that gets a greater place in the new curriculum, as it is linked to specific competence goals in chemistry and sustainable development is made an interdisciplinary theme in all subjects.[64] Based on this, a case study in green chemistry fits well into the new curriculum vision if planned and implemented properly.

2.5.2 A proposed teaching activity and didactical analysis

In this section, a teaching activity based on the research in the project that is anchored in competence goals from LK20 will be presented. Considering chapter 2.4.1, the teaching activity was decided to be established as a case study. For this case study, green chemistry was chosen as the theme, as it is central in the project and can be linked to several of the new competence goals in the chemistry subject.

The research aiming to find a new, greener method for the epoxidation of *N*-3-alkenylhydantoins can be used in a teaching activity that encompass much of the school chemistry. Three of the tested methods (Method 1, 3 and 5) which use *m*-CPBA, H_2O_2 and oxone as oxidants can be used to make a case study where the students shall evaluate the synthesis routes according to principles of green chemistry and argument for which route that is preferred for with respect to green chemistry. Epoxidation of compound **3b** is a suitable reaction to explore in a case study, as **3b** to some extent provided its corresponding epoxide **4b** by means of all the three tested oxidants (Scheme 12).



Scheme 12. The epoxidation reaction to be studied in the case study.

The case study can be implemented as an explorative learning activity, where the students get to formulate their own research questions to investigate in the case work. Practically the case study can be organized in three parts, first a preparation work, thereby a casework where the students work with the case in smaller groups, and a whole class discussion where the groups share their thoughts and a proposed answer to the case. Each part will be explained more in detail, but first the teaching activity will be linked to concrete competence goals in chemistry.

A case study evaluating synthesis routes according to principles of green chemistry can primarily be linked to three competence goals in chemistry 1 in LK20:[64]

- "Use information from safety data sheets to make assessments related to health, environment, and safety in practical work"
- "Use data, simulations and calculations in interpretations and to draw conclusions"
- "Explain principles for green chemistry and discuss how the application of the principles can contribute to sustainable development"

The competence goals can be further broken down into three learning objectives for the case work:

1) Perform a risk assessment for an organic synthesis
2) Evaluate synthesis routes according to principles of green chemistry
3) Explain how application of the principles of green chemistry can contribute to sustainable development

The case study can be implemented in a normal classroom setting. Prior to the case day, the students are given preparation tasks to give them necessary background knowledge to solve the case. On the case day, the students can first be organized in expert groups where each group are assigned one epoxidation route to risk assess and evaluate against principles of green chemistry. Then, they can be re-organized in new groups with students' experts on different synthesis routes. In these all the students must share their knowledge for the group to be able to compare the synthesis routes and come up with arguments of which route is preferred due to green chemistry. Lastly, the teacher can lead a whole class discussion to summarize the case work. The case study is designed to use two chemistry sessions.

The learning conditions are students that have a beginner background in organic chemistry. The two main themes of the lesson; risk assessment of syntheses and the principles of green chemistry are new to the students. To avoid too high cognitive load, the case study is recommended after these concepts have been reviewed in separate lessons. This because the case already presents a lot of new material to the students, as complex organic molecules, new reagents, and epoxidation. The preparation tasks attempts to give the students an introduction and an academic background in this prior to the case day.

The content of the case study is presented in a booklet that the students receives. This booklet includes background information, case-description, preparation work and tasks for the case day. The case study is based on principles of active, explorative learning,[65] with one degree of freedom.[66] The students are presented the main problem and method, but the results/findings are up to the students to discover. An organization of the case study in expert groups and mixed groups on three persons will ensure that all the students are active and have something to contribute with to the discussions.

The evaluation of the students learning can be done in two ways. An evaluation of their learning can be based on the observation of their oral skills and participation in the group- and whole class discussions during the case study. In addition, the student's theoretical knowledge can be evaluated by the answers they give regarding the questions in the booklet.

2.5.3 The teaching activity

Solving a real-life issue in green chemistry

Purpose

In this case study, a real-life issue in green chemistry is to be solved. This is to be done by risk assessing and evaluating three different organic synthesis routes against principles of green chemistry.

Background

In organic chemistry, new molecules are synthesized and characterized. Some of these are researched for biological activities and use as candidates for future medicines. Two organic structure classes that perform a wide range of biological activities are hydantoins and epoxides. They are ring-structures that contain one or more atoms that are not carbon or hydrogen and have the core structures shown in Figure 1. Several structures containing the hydantoin or the epoxide core are seen to be biologically active. For example, phenytoin and nilutamide are hydantoins that are used in epilepsy and cancer medicines, and ± flavipucine is an epoxide used to treat microbial infections (Figure 1).

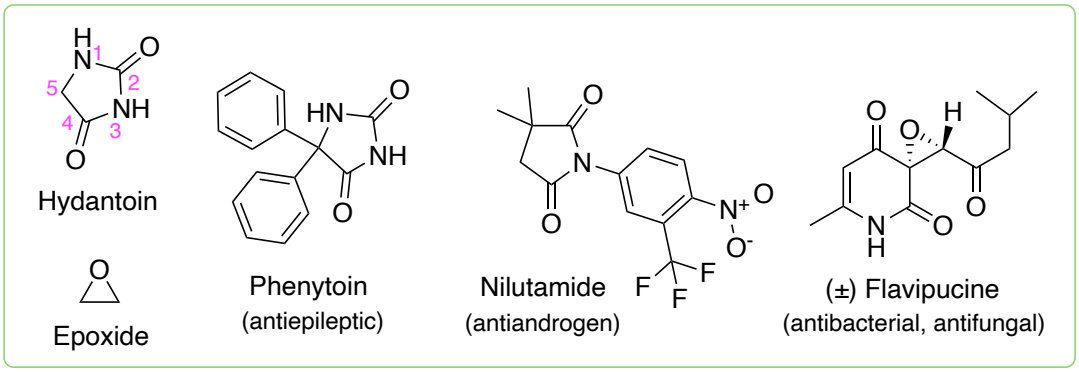
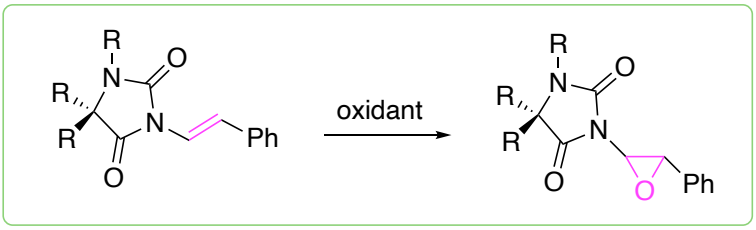


Figure 1. The hydantoin structure with positions numbered, the epoxy group, and some biologically active examples.

As many hydantoins and epoxides have been seen to be biologically active, structures with both the hydantoin ring and an epoxide ring are interesting as they might be biologically active. Synthesis of such structures can be done using a hydantoin with an alkene group as starting material. The alkene can then be converted into an epoxide if it is treated with a suitable oxidant under appropriate conditions. This reaction is a special case of oxidation called epoxidation, where both alkene carbon atoms become bonded to the same oxygen atom as illustrated in Scheme 1.

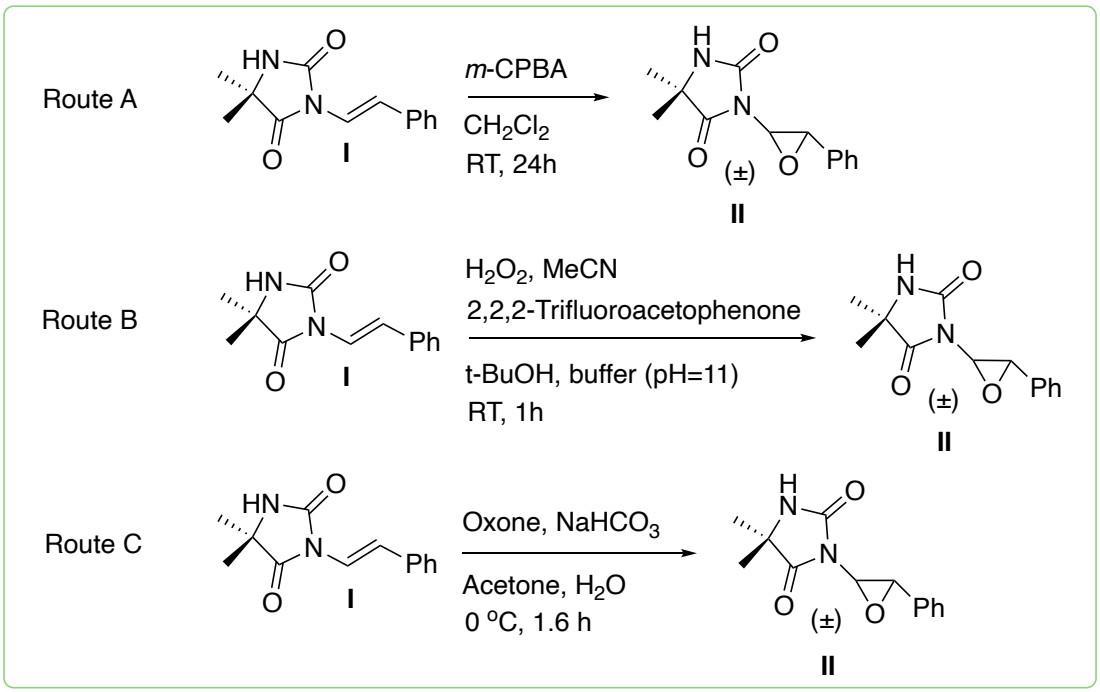


Scheme 1. Reaction sequence for epoxidation of a hydantoin with an alkene group.

Case

You are employed by the company Greener Syntheses AS, which works to develop safer and more environmentally friendly syntheses. In their research, organic chemists at the University of Oslo (UiO) recently synthesized the new epoxide **II**. The synthesis was done by epoxidation the epoxides corresponding alkene **I**. The organic chemists found three synthesis routes that were able to carry out the epoxidation. These differ using the varied oxidants: *meta*-Chloroperoxybenzoic acid (*m*-CPBA), hydrogen peroxide (H_2O_2) and the triple salt oxone ($KHSO_5 \cdot \frac{1}{2}KHSO_4 \cdot \frac{1}{2}K_2SO_4$), under varied reaction conditions (Scheme 2).

You and your employees in Greener Syntheses AS are given the task of examining the synthesis routes and give chemists at UiO an evaluation of which synthesis route to choose for further production of epoxide **II**. The chemists wants your evaluation of the synthesis routes according to three factors: efficiency, environmental impact, and safety. You receive reaction conditions, experimental procedures, and experimental data from the performance of all the epoxidation routes on compound **I**. With your colleagues, you shall agree on which synthetic route you would advise the organic chemists to continue with. As an expert in green chemistry, the chemists expect your arguments to be supported by the principles of green chemistry.



Scheme 2. The three epoxidation routes A-C to be evaluated in the case study.

Experimental procedures

Route A: Compound **I** (46.1 mg, 0.2 mmol, 1.0 eq.) was added to a round-bottomed flask and solved in CH_2Cl_2 (2 mL). *m*-CPBA (69.0 mg, 0.4 mmol, 2.0 eq.) was added, and the mixture was stirred in room temperature for 24h. The mixture was solved in CH_2Cl_2 (10 mL) and extracted it with 1M K_2CO_3 (2x 5 mL), water (3 x 5 mL) and saturated NaCl (5 mL). The organic phase was dried with Na_2SO_4, filtered, and dried in *vacuo*, and compound **II** was isolated.

Route B: Compound **I** (46.1 mg, 0.2 mmol, 1.0 eq.) and 2,2,2-trifluoroacetophenone (1.74 mg, 0.010 mmol, 5 mol%) were placed in a round bottom flask. *t*-BuOH (0.3 mL), buffer 2 (0.3 mL), MeCN (20.0 µL, 0.4 mmol, 2.0 eq.) and 30% aqueous H_2O_2 (40.0 µL, 0.4 mmol, 2.0 eq.) were added. The mixture was stirred in room temperature for 1 h. A catalytic amount of MnO_2 was then added, and the crude was filtered and dried in *vacuo*. Compound **II** was not enabled isolated, but the mass present in the reaction mixture was calculated from NMR using an internal standard.

Route C: Saturated $NaHCO_3$ (4 mL) was added to a solution of compound **I** (35.0 mg, 0.152 mmol, 1.0 eq.) in acetone (6 mL) at 0 ºC in a round bottom flask. The mixture was stirred for 0.5 h, and Oxone (0.0934 g, 0.304 mmol, 2.0 eq.) solved in water (2 mL) was added dropwise over 15 min. The mixture was stirred at 0 ºC for additional 50 min, then diluted with water (15 mL) and extracted with EtOAc (3 x 10 mL). The combined organic phase was dried over Na_2SO_4, filtered, and dried in *vacuo*, and compound **II** was isolated.

Preparation work

1. Read through the background information and the case description for the case study. Mark words or formulations in the text you don't understand or find difficult.

2. Based on the case, formulate two concrete research questions you want to explore and get answered on the case day. Explain briefly how you want to investigate them on the case-day.

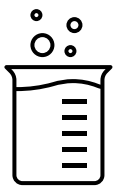
   1)

   2)

3. Write down the general equation for calculating % yield in an organic synthesis.

4. Explain principle 1, 2, 3, 5, 6, 9, and 12 of green chemistry. Include equations for calculating E-factor and atom economy (AE).

   1) waste prevention
   2) atom economy
   3) less hazardous synthesis
   5) safer solvents and auxiliaries
   6) design for energy efficiency,
   9) catalysis and
   12) safer chemistry for accident prevention.



Tasks for the case day

1. Calculate the % yield of **II** from the epoxidation route that are studied in your expert group by using the experimental data in Table 1. Molar masses: **I**: 230.27 g/mol, **II**: 246.27 g/mol

Table 1. Results from the syntheses of compound **II** (g) with Method A-C. Compound **II** was only isolated with Method A-B. The amount of **II** (g) produced in the synthesis with Method C was calculated by NMR.

Route	Synthesized compound II (mg)	Appearance
A	40.2	White solid
B	4.33	Light green crude
C	35.7	White solid

* The yield calculated for **II** synthesized with method B is a NMR yield, not isolated yield.
All the yields can be calculated using the regular formula for % yield.

2. Perform a risk assessment of the chemicals and equipment used in the synthesis route your group is studying, by filling out Table 2.

Table 2. General risk assessment.

Chemical /Equipment	What are the hazards?	What can we do to prevent them?	What can we do to reduce the consequences if an accident occurs?

3. Based on your risk assessment, discuss what you consider as the biggest risks in the synthesis. Do you see any possible measures that can make the synthesis safer?

4. Evaluate the synthesis from principle 1, 2, 3, 5, 6, 9, and 12 of Green Chemistry.

3 Conclusion

In this project it was performed a synthesis study of *N*-3-epoxyhydantoins, and it was attempted to ring-open some of the epoxides with some nucleophiles containing different chemical properties.

Five *N*-3-alkenylhydantoins (**3a-e**) were first synthesized by Cu-catalyzed coupling reactions of (*E*)-Styrylboronic acid (**2**) and varied hydantoins (**1a-e**). Five *N*-3-alkenylhydantoins were provided in high purity in yields of 76-93%, one being a new structure. The coupling reaction was seen to be most efficient on 5,5-disubsituted and/or *N*-1 substituted hydantoin substrates.

The *N*-3-alkenylhydantoins were epoxidated with five different methods, giving varied results. method 1 using *m*-CPBA successfully epoxidized all the tested compounds **3a-e** to their corresponding epoxides **4a-e** in yields of 60-92 % and provided four new structures. Of the methods using H_2O_2, method 2 was unable to epoxidize compound **3a-b** and was rejected. Method 3 and 4 were also unable to epoxidize compound **3a**, but epoxidized compound **3b** in NMR yields of 12 and 14 %. As compound **4b** was synthesized in low yields and was seen difficult to isolate, also these methods were deficient. Method 5 using oxone successfully epoxidized compound **3a-b** in yields of 87 and 95 %, but epoxidized compound **3c-e** in a NMR yields of 2-48 %. This makes method 1 the most diverse method tested. method 5 was seen greener than method 1 and can be used to epoxidize compound **3a-b**.

The attempts at ring-opening the *N*-3-epoxyhydantoins (**4a-c**) with water, 1-propanol and *L*-valine methyl ester gave varied reaction outcomes. All the three *N*-3-epoxyhydantoins (**4a-c**) were ring-opened with water, compound **4b** was ring opened by 1-propanol, and **4a** was ring opened by *L*-valine methyl ester. However, none of the expected ring-opening products were observed in the ^{1}H NMR spectra and were not enabled isolated. This indicates that ring-opened *N*-3-epoxyhydantoins are unstable structures, easily decomposed. A possible mechanism for their decomposition was proposed.

At last, a possible teaching activity in green chemistry was presented. It is related to three of the epoxidation methods used in the project and is pedagogically anchored in the new Norwegian curriculum for the chemistry subject (LK20).

4 Further work

As it was not found a greener method to replace the *m*-CPBA method for more than two hydantoin substrates, further studies would be interesting. It could be interesting to do an optimalization study of the oxone method (method 5), to investigate if it can epoxidize compound **3c-e** completely in other reaction conditions, for example by using different reaction times or other equivalents of oxone. It would also be interesting to test method 5 on several *N*-3-alkenylhydantoins to get a deeper insight in the methods scope of structures it can be used on, and structures it has limitations for. In addition, attempts at ring-open the *N*-3-epoxyhydantons with several nucleophiles could have been interesting to see if it could enable product isolation, or if the ring-opened *N*-3-epoxyhydantoins in most conditions are unstable structures decomposing to their original hydantoin substrates after having been attacked by a nucleophile.

5 Experimental section

5.1 General

All chemicals were used as delivered from Sigma Aldrich, Cambridge Chemicals, VWR and Flurochem. NMR-solvents were used as delivered from Sigma Aldrich and Cambridge Isotope Laboratories. Hexane, dichloromethane, and ethyl acetate were distilled prior to use. Other solvents were used as delivered. All water used was of Type II.

Thin layer chromatography (TLC) was performed on 60 F_{254} silica coated aluminum plates from Merck. TLC spots were visualized using UV-light and $KMnO_4$-stain (1.5 g $KMnO_4$, 10 g K_2CO_3 and 1.25 mL 10% NaOH in 200 mL water). Column chromatography was performed manually on silica gel from Merck (Silica gel 60, 0.040-0.063 mm) using glass columns.

NMR spectra were recorded with Bruker AVIIIHD400 and AVII600 spectrometers at 25 °C. All spectra were calibrated using the NMR-solvent peaks for $CDCl_3$ (^{1}H: 7.26 ppm, ^{13}C: 77.0 ppm) or DMSO-d_6 (^{1}H: 2.05 ppm, ^{13}C: 39.5 ppm).[1] Chemical shifts are reported in parts per million and coupling constants are reported in Hz. ^{1}H NMR multiplicities are reported as singlet (s), broad singlet (br. s.), doublet (d), triplet (t), quartet (q), multiplet (m), with combinations used when applicable (ex. dd being a doublet of doublets). All ^{13}C NMR spectra were recorded ^{1}H decoupled. The ^{1}H and ^{13}C signals in all new compounds were assigned using the 2D NMR-techniques COSY, HSQC, HMBC and DEPT135, the spectrums are included in the appendix.

Two aqueous buffer solutions with pH=11 were prepared, 1) 0.6 M K_2CO_3, 4 x 10^{-4} M EDTA disodium salt and 2) 0.6 M K_2CO_3, 4 x 10^{-5} M EDTA tetrasodium salt. In reactions using <10 mg catalyst, standard solutions from the reaction solvents were used to transfer the catalyst.

All melting points (mp) were measured by a Büchi B-545 melting point apparatus. High resolution mass spectra (HRMS) were obtained by electron spray ionization (ESI) on a Bruker maXis II ETD QTOF spectrometer by Lina Aarsborg, Sverre Løyland and Erlend Steinvik.

Fourier transformed IR spectra were recorded in ATR (Bruker ATR A225/Q) on a Vertex 80 Bruker infrared spectrometer with a DTGS detector. Vibration frequencies are reported using wavenumbers measured in reciprocal centimeters (cm^{-1}), assigned using standard IR absorption tables.[52,67]

5.2 Synthesis of *N*-3-alkenylhydantoins

General procedures

N-alkenylhydantoins were prepared according to the reported procedure from Berntsen et al. on two different reaction scales.[7] The *N*-3-alkenylhydantoins obtained were further used as substrates to be epoxidized.

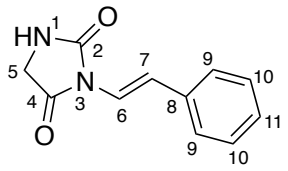
1.5 mmol scale

Hydantoin (1.5 mmol, 1.0 eq.), (*E*)-Styrylboronic acid (443.9 mg, 3.0 mmol, 2.0 eq.), $Cu(OTf)_2$ (27.1 mg, 0.075 mmol, 5 mol %) and ethanol (6 mL) were added to a 25 mL round-bottom flask. Pyridine (148 µL, 1.5 mmol, 1.0 eq.) was added to the mixture via a syringe. The flask was equipped with a cooler to give access to air and stirred in 25 °C for 24 h. The crude mixture was purified with column chromatography using the specified eluent systems, and dried in *vacuo*.

2.5 mmol scale

Hydantoin (2.5 mmol, 1.0 eq.), (*E*)-Styrylboronic acid (739.9 mg, 5.0 mmol, 2.0 eq.), $Cu(OTf)_2$ (45.2 mg, 0.125 mmol, 5 mol %) and ethanol (10 mL) were added to a 25 mL round-bottom flask. Pyridine (247 µL, 2.5 mmol, 1.0 eq.) was added to the mixture via a syringe. The reaction was performed under the same conditions as on a 1.5 mmol scale.

(*E*)-3-styrylhydantoin (3a)



Following the general procedure in chapter 5.2. on a 1.5 mmol scale, **3a** was obtained after purification with column chromatography (silica gel, 9:2 $CHCl_3$/MeCN) as a colorless solid (230.5 mg, 1.14 mmol, 76 %).

^{1}H NMR (400 MHz, DMSO-d_6): δ 8.45 (br. s., 1H, H-1), 7.45-7.41 (m, 3H (aromatic protons overlapping with a vinylic proton), H-9, H-7), 7.34 (t, *J*= 7.4 Hz, 2H, H-10), 7.26-7.23 (m, 1H, H-11), 7,09 (d, *J*= 15.1 Hz, 1H, H-7), 4.00 (s, 2H, H-5).

^{13}C NMR (101 MHz, DMSO-d_6): δ 170.9 (C-4), 155.9 (C-2), 136.1 (C-8), 129.3 (C-10), 127.9 (C-11), 126.3 (C-9), 119.0 (C-6), 118.6 (C-7), 45.8 (C-5).

IR (ATR)**:** (cm^{-1}(appearance)): 3236, 3074, 2970, 1703, 1647, 962.

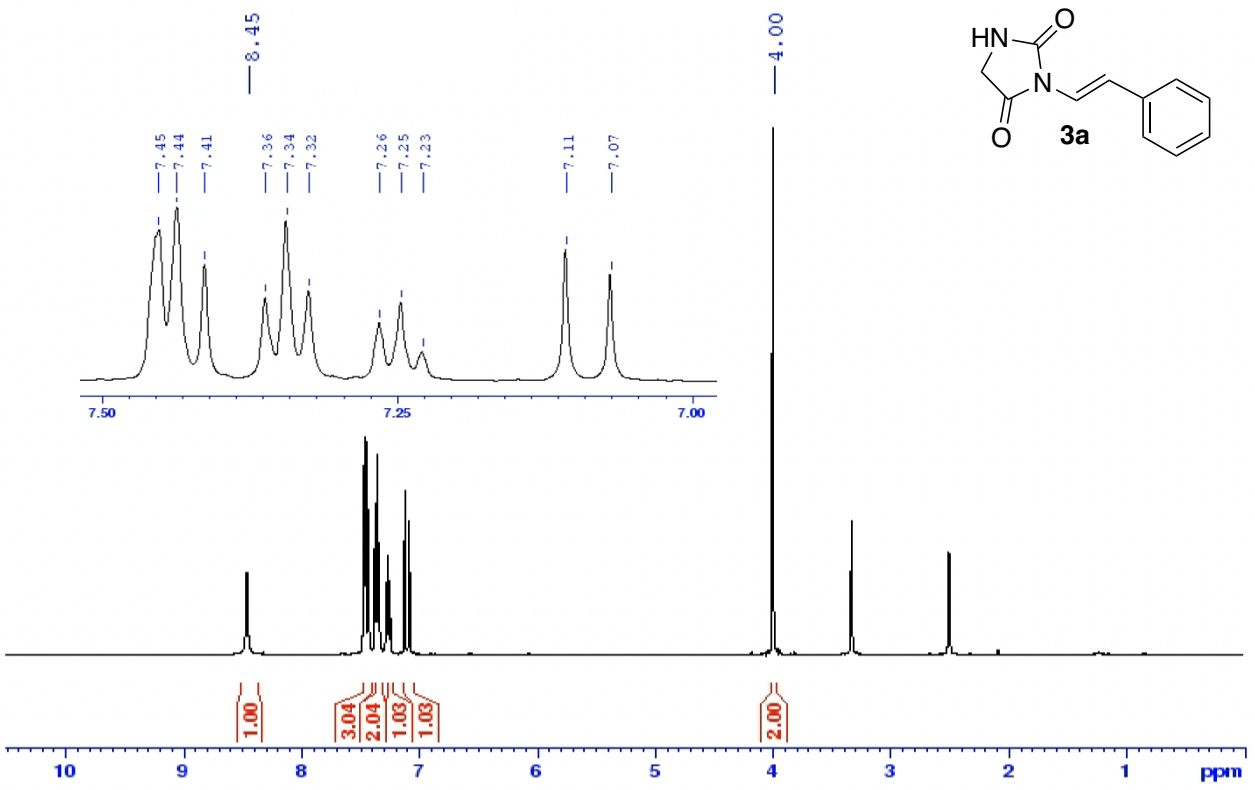
HRMS (ESI, CH_3CN): *m/z* $[C_{11}H_{10}N_2O_2 + Na]^+$: calculated: 225.0634, found: 225.0635.

mp: 224-226 °C.

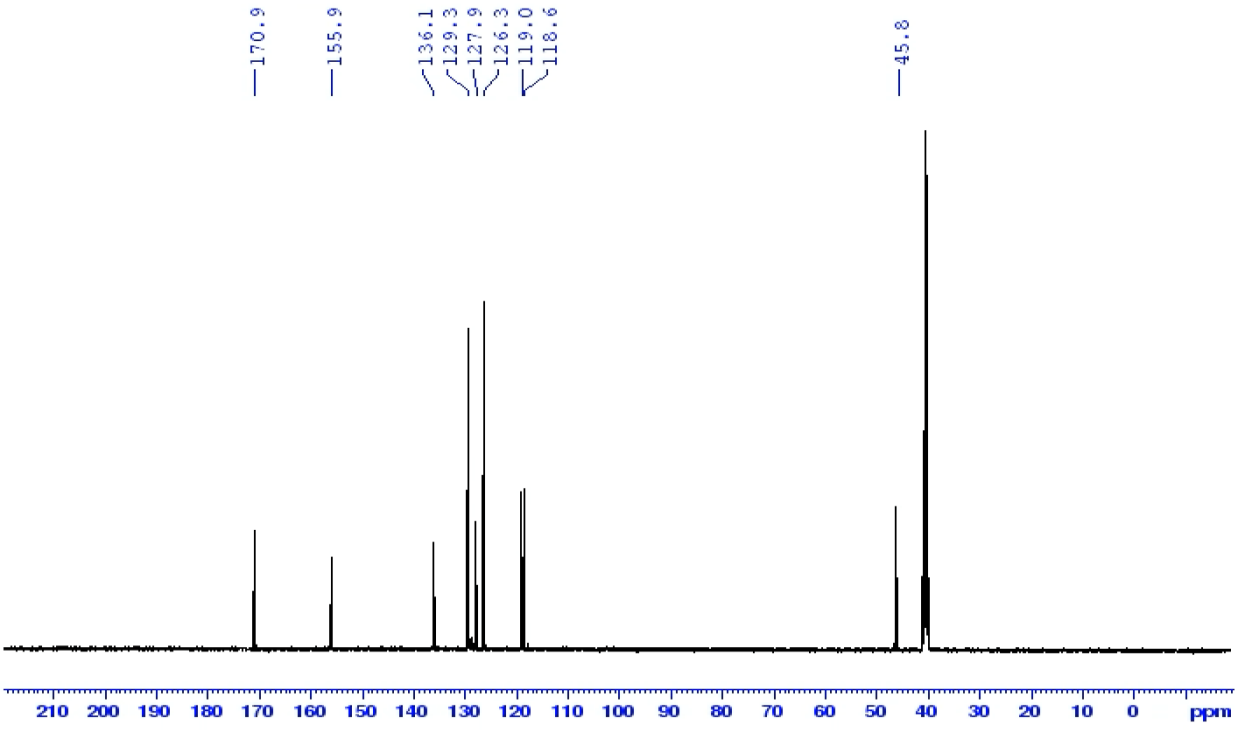
R_f(9:2 $CHCl_3$ /MeCN): 0.27.

The spectroscopic data is in accordance with the literature.[7]

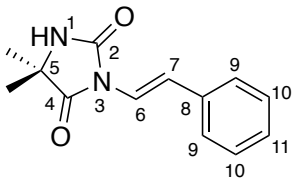
^{1}H NMR (400 MHz, DMSO-d_6) spectrum of 3a



^{13}C NMR (101 MHz, DMSO-d_6) spectrum of 3a



(*E*)-5,5-dimethyl-3-styrylhydantoin (3b)



1.5 mmol scale:

Following the general procedure in chapter 5.2. on a 1.5 mmol scale, **3b** was obtained after purification with column chromatography (silica gel, 7:4, hexane/acetone) as a light green solid (299.7 mg, 1.30 mmol, 87 %).

2.5 mmol scale:

Following the general procedure in chapter 5.2. on a 2.5 mmol scale, **3b** was obtained after purification with column chromatography (silica gel, 7:4, hexane/acetone) as a light green solid (442.3 mg, 1.92 mmol, 77 %).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.59 (d, *J*= 15.1 Hz, 1H, H-6), 7.43 (d, *J*= 7.6 Hz, 2H, H-9), 7.33 (t, *J*= 7.6 Hz, 2H, H-10), 7.26-7-23 (m, 1H, H-11, overlap with chloroform signal), 7.13 (d, *J*= 15.1 Hz, 1H, H-7), 6.89 (br. s, 1H, H-1), 1.52 (s, 6H, $(CH_3)_2$).

^{13}C NMR (151 MHz, $CDCl_3$): δ 175.4 (C-4), 154.9 (C-2), 135.7 (C-8), 128.7 (C-10), 127.8 (C-10), 127.7 (C-11), 126.3 (C-9), 126.2 (C-9), 120.4 (C-6), 117.9 (C-7), 58.0 (C-5), 25.2 $(CH_3)_2$.

IR (ATR)**:** (cm^{-1}(appearance)): 3121, 3113, 2986, 1774, 1715, 962.

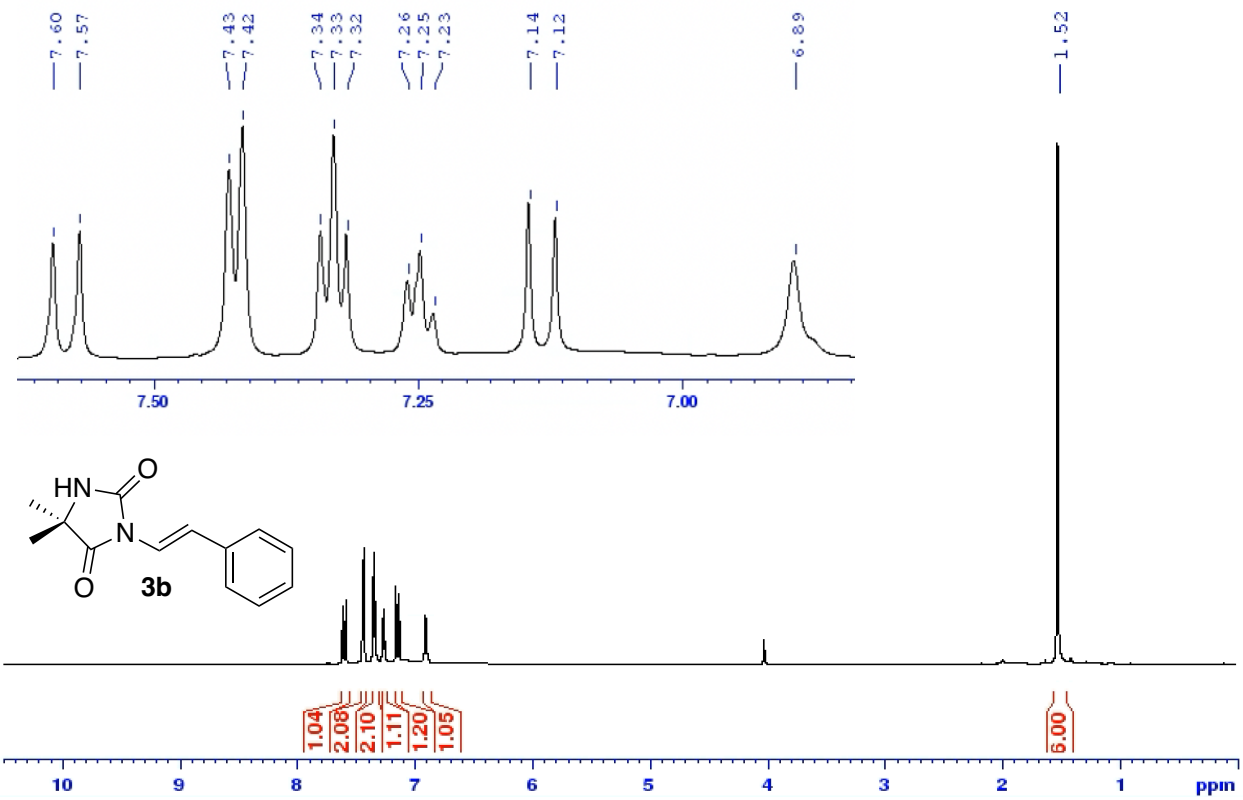
HRMS (ESI, CH_3CN): *m/z* $[C_{13}H_{14}N_2O_2 + Na]^+$: calculated: 253.0947, found: 253.0947.

mp: 148-149 °C.

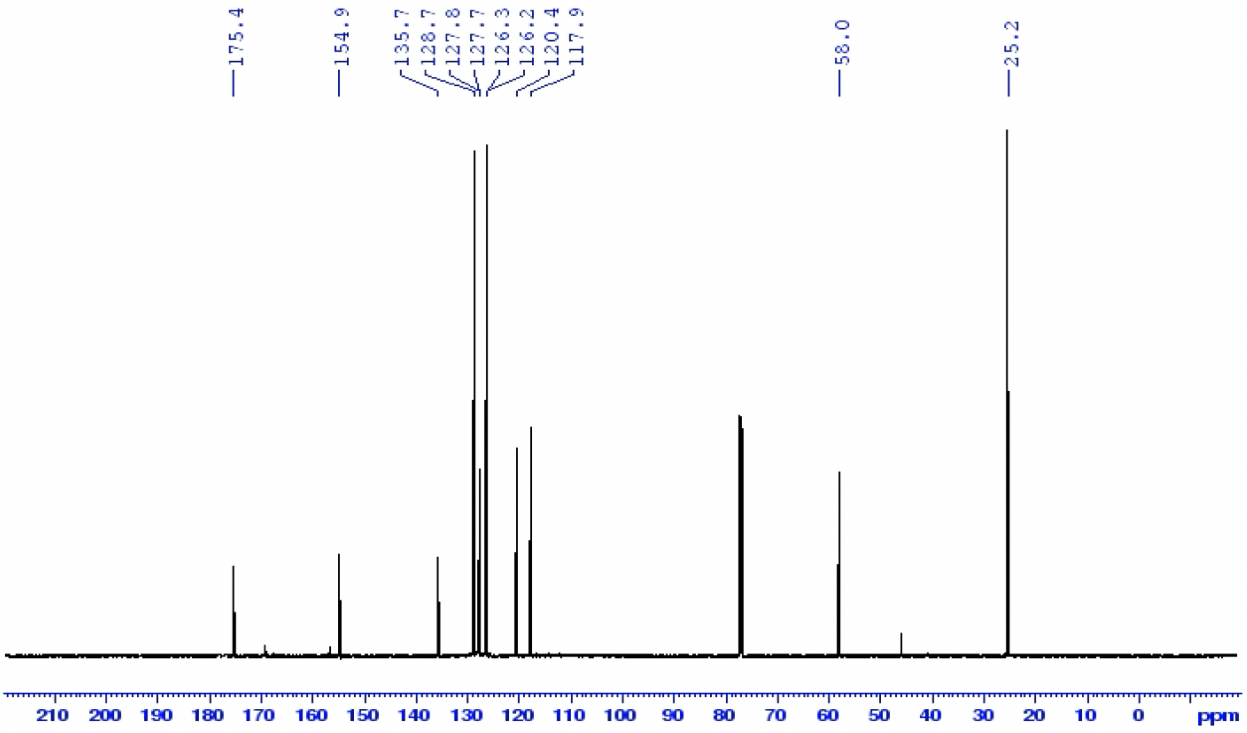
R_f (7:4 hexane/ acetone): 0.31.

This compound has not been reported in the literature.

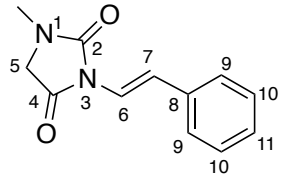
^{1}H NMR (600 MHz, $CDCl_3$) spectrum of 3b



^{13}C NMR (151 MHz, $CDCl_3$) spectrum of 3b



(*E*)-1-methyl-3-styrylhydantoin (3c)



1.5 mmol scale:

Following the general procedure in chapter 5.2. on a 1.5 mmol scale, **3c** was obtained after purification with column chromatography (silica gel, 7:2:1, chloroform/hexane/acetone) as a colorless solid (285.4 mg, 1.32 mmol, 88 %).

2.5 mmol scale:

Following the general procedure in chapter 5.2. on a 2.5 mmol scale, **3c** was obtained after purification with column chromatography (silica gel, 7:2:1, chloroform/hexane/acetone) as a colorless solid (497.4. mg, 2.30 mmol, 92 %).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.57 (d, *J*= 15.2 Hz, 1H, H-6), 7.42 (d, *J*= 7.7 Hz, 2H, H-9), 7.32 (t, *J*= 7.8 Hz, 2H, H-10), 7.24 (t, 1H, *J*= 7.7 Hz, H-11, overlap with chloroform signal), 7.13 (d, *J*= 15.0 Hz, 1H, H-7), 3.91 (s, 1H, H-5), 3.05 (s, 3H, CH_3).

^{13}C NMR (151 MHz, $CDCl_3$): δ 167.5 (C-4), 154.9 (C-2), 135.8 (C-8), 128.7 (C-10), 127.6 (C-9), 126.2 (C-11), 120.0 (C-6), 118.1 (C-7), 51.0 (C-5), 29.8 (CH_3).

IR (ATR)**:** (cm^{-1}(appearance)): 3080, 3033, 2864, 1774, 1711, 948.

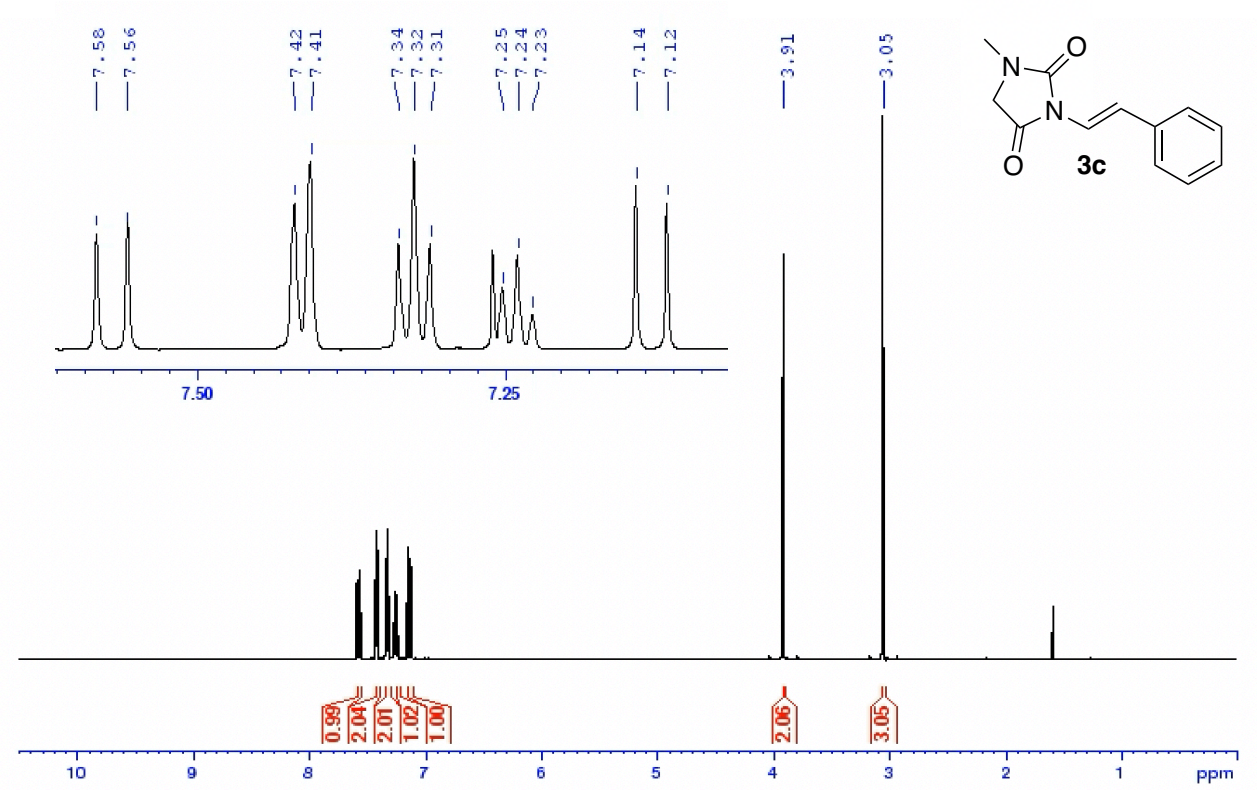
HRMS (ESI, CH_3CN): *m/z* $[C_{12}H_{12}N_2O_2 + Na]^+$: calculated: 239.0790, found: 239.0791.

mp: 134-135 °C.

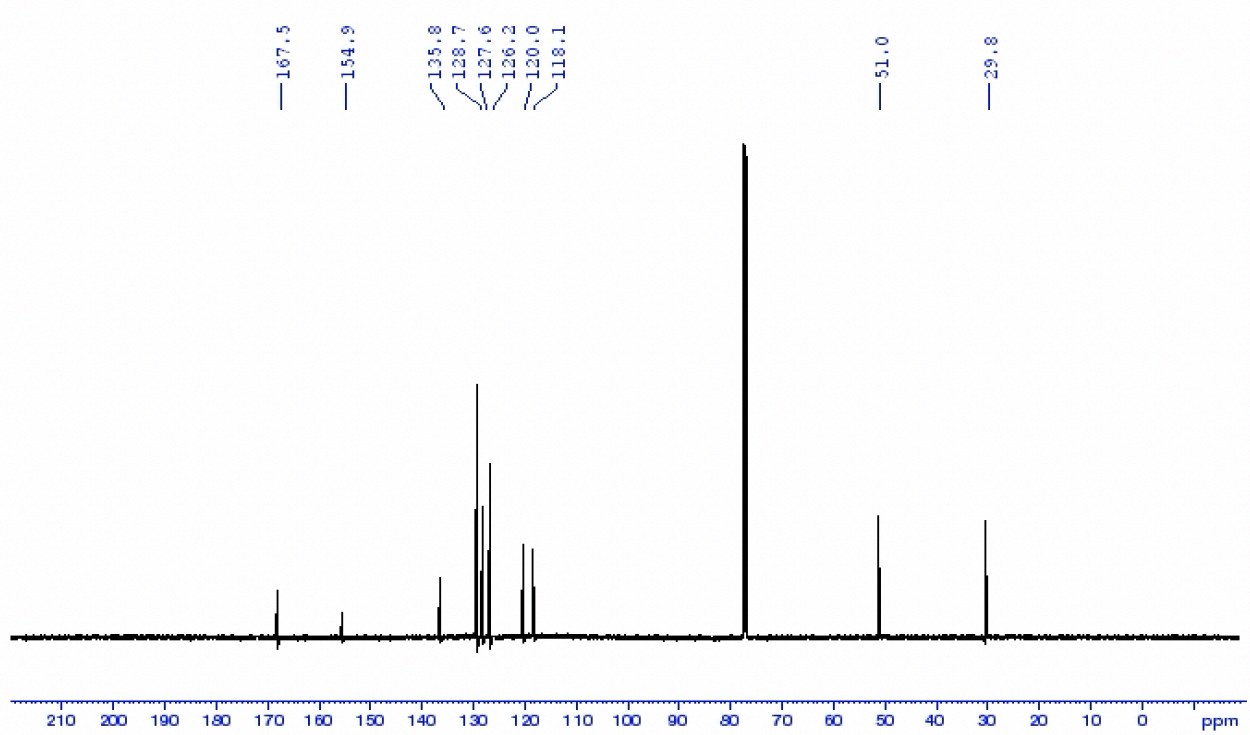
R_f (7:2:1 chloroform/hexane/ acetone): 0.43.

The spectroscopic data is in accordance with the literature.[7]

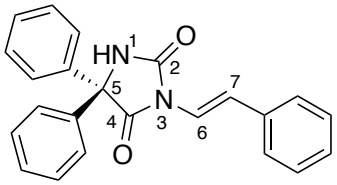
^{1}H NMR (600 MHz, $CDCl_3$) spectrum of 3c



^{13}CNMR (151 MHz, $CDCl_3$) spectrum of 3c



(*E*)-5,5-diphenyl-3-styrylhydantoin (3d)



Following the general procedure in chapter 5.2. on a 1.5 mmol scale, **3d** was obtained after purification with column chromatography with a gradient (silica gel, 9:3 → 7:3, hexane/EtOAc) as a colorless solid (451.9 mg, 1.28 mmol, 85 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (d, *J*= 15.1 Hz, 1H, H-6), 7.44-7.36 (m, 12H, aromatic protons), 7.33 (t, *J*= 7.7 Hz, 2H, aromatic protons), 7.25 (t, *J*= 7.3 Hz, 1H, aromatic proton overlapping with chloroform signal), 7.18 (d, *J*= 15.1 Hz, 1H, H-7), 7.04 (br. s., 1H, H-1).

^{13}C NMR (101 MHz, $CDCl_3$): δ 171.3 (C-2), 154,6 (C-4), 138.9, 135.5, 129.0, 128.8, 128.7, 127.8, 126.9, 126.3, 120.9, 117.7 (aromatic carbons), 69.3 (C-5).

IR (ATR)**:** (cm^{-1}(appearance)): 3182, 3024, 2918, 1745, 1717, 953.

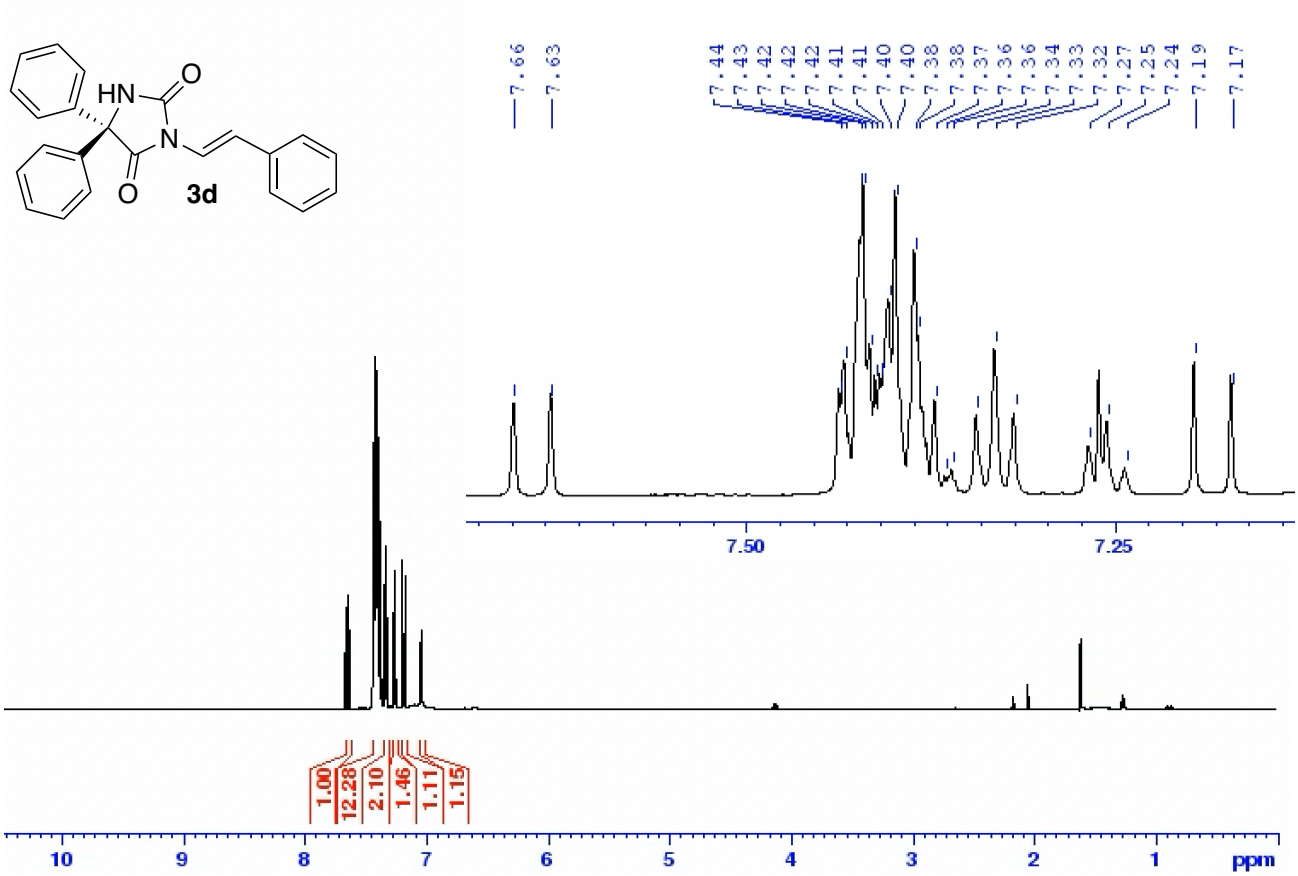
HRMS (ESI, CH_3CN): *m/z* $[C_{23}H_{18}N_2O_2 + Na]^+$: calculated: 377.1260, found: 377,1259.

mp: 215-218 °C.

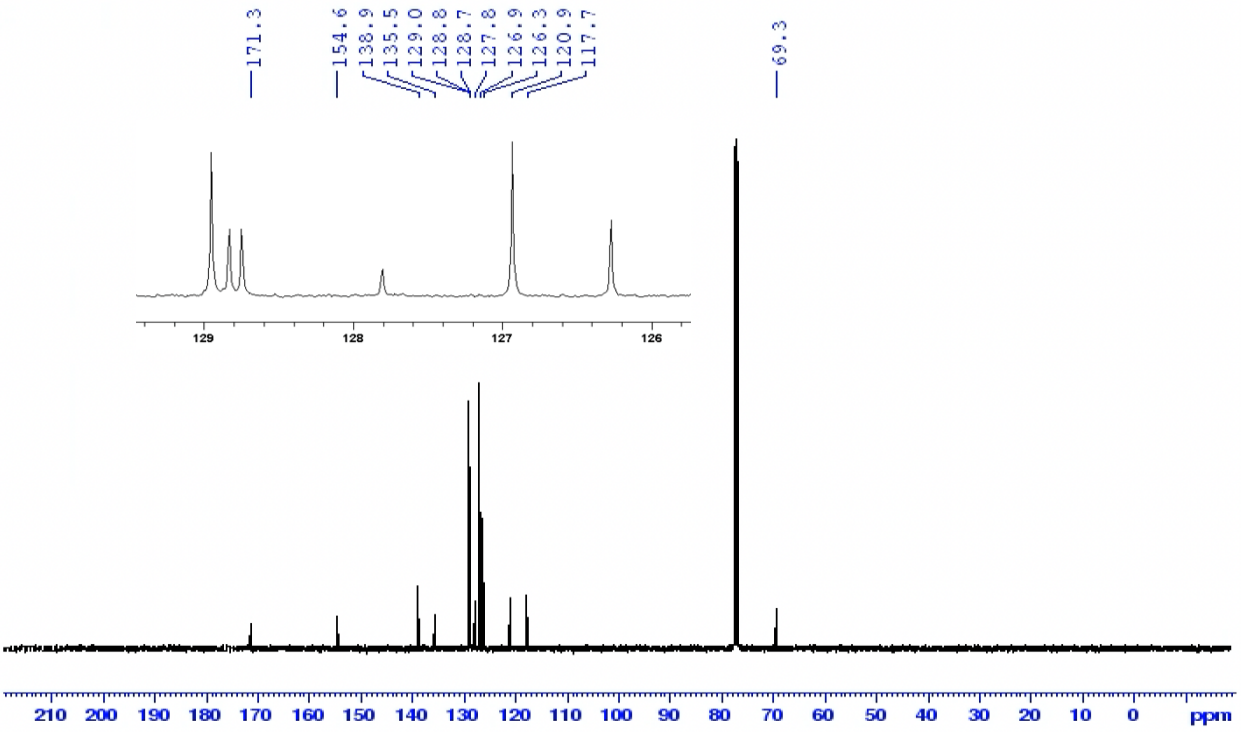
R_f (9:3 hexane:EtOAc): 0.45.

The spectroscopic data is in accordance with the literature.[7]

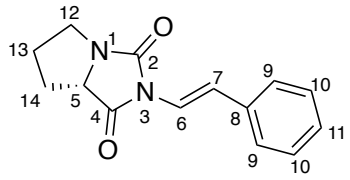
^{1}H NMR (600 MHz, $CDCl_3$) spectrum of 3d



^{13}C NMR (151 MHz, $CDCl_3$) spectrum of 3d



(*S*,*E*)-2-styryltetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1,3(2*H*)-dione (3e)



Following the general procedure in chapter 6.2. on a 1.5 mmol scale, **3e** was obtained after purification with column chromatography (silica gel, 2:1 hexane/ EtOAc) as an off-white colorless solid (338.0 mg, 1.40 mmol, 93 %).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.56 (d, *J*= 15.1 Hz, 1H, H-6), 7.41 (d, *J*= 7.4 Hz, 2H, H-9), 7.32 (t, *J*= 7.7 Hz, 2H, H-10), 7.24 (t, *J*= 7.4 Hz ,1H, H-11 (overlap with chloroform signal)), 7.09 (d, *J*= 15.1 Hz, 1H, H-7), 4.14 (dd, *J*= 9.1, 7.7 Hz, 1H, H-5), 3.77 (dt, *J*= 11.3, 7.7 Hz, 1H, H-12), 3.32 (ddd, *J*= 11.3, 7.5 ,4.5 Hz, 1H, H-12), 2.31 (dtd, *J*= 12.7, 7.3, 3.8 Hz, 1H, H-14), 2.19-2.05 (m, 2H, H-13), 1.79 (dq, *J*= 12.7, 9.2 Hz, 1H, H-14).

^{13}C NMR (151 MHz, $CDCl_3$): δ 171.7 (C-4), 158.4 (C-2), 135.7 (C-8), 128.7 (C-10), 127.7 (C-11), 126.2 (C-9), 120.3 (C-6), 118.1 (C-7), 62.6 (C-5), 45.7 (C-12), 27.6 (C-14), 26.8 (C-13).

IR (ATR): (cm^{-1}(appearance)): 3024, 2980, 2891, 1718, 1700, 953.

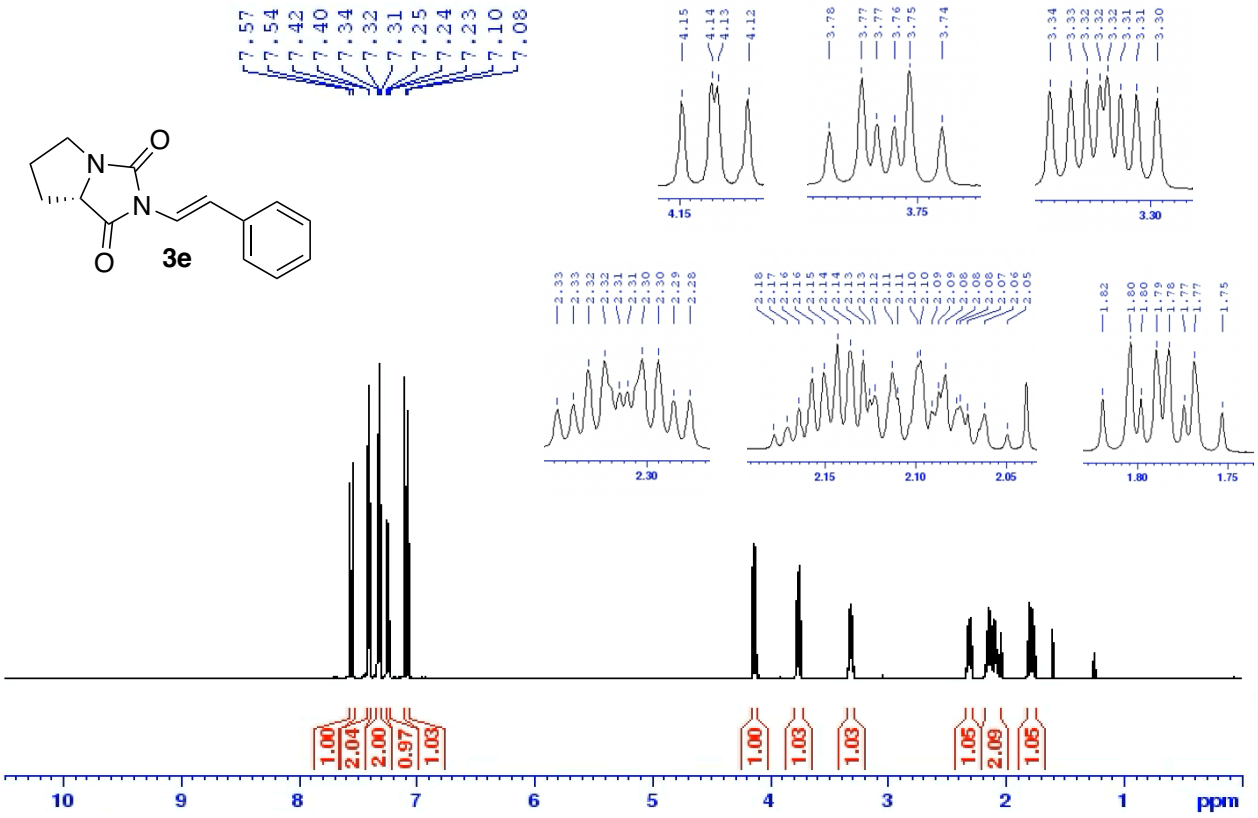
HRMS (ESI, CH_3CN): *m/z* $[C_{14}H_{14}N_2O_2 + Na]^+$: calculated: 265,0947, found: 265,0947.

mp.: 149-150 °C.

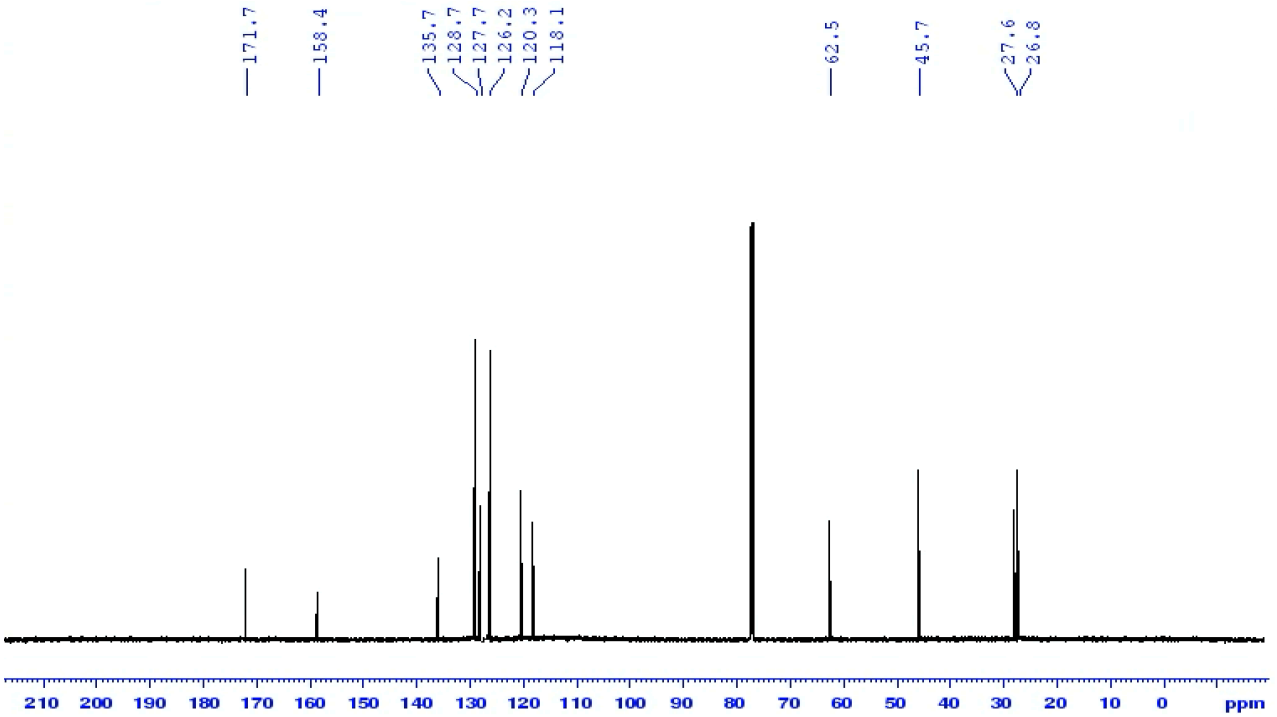
R_f (2:1 hexane/ EtOAc): 0.40.

The spectroscopic data is in accordance with the literature.[7] The compounds mp. is not reported.

^{1}H NMR (600 MHz, $CDCl_3$) spectrum of 3e



^{13}C NMR (151 MHz, $CDCl_3$) spectrum of 3e



5.3. Synthesis of *N*-3-epoxyhydantoins

Method 1: *N*-3-alkenylhydantoin (0.2 mmol, 1.0 eq.) was added to a 10 mL round-bottomed flask, solved in CH_2Cl_2 (2 mL). *m*-CPBA (69.0 mg, 0.4 mmol, 2.0 eq.) was added, and the mixture was stirred in room temperature for 24h. The mixture was solved in CH_2Cl_2 (10 mL) and extracted with 1M K_2CO_3 (2x 5 mL), washed with water (3 x 5 mL) and saturated NaCl (1x 5 mL). The organic phase was dried with Na_2SO_4, filtered, and dried in *vacuo*.[34]

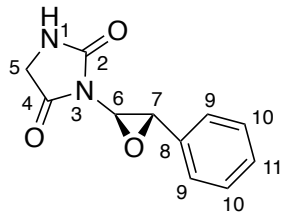
Method 2: *N*-3-alkenylhydantoin (0.2 mmol, 1.0 eq.) and benzaldehyde (10.4 mg, 0.010 mmol, 5 mol%) were placed in a 5 mL round bottom flask. MeOH (0.2 mL), buffer 1 (0.2 mL), MeCN (20.0 µL, 0.4 mmol, 2.0 eq.) and 30% aqueous H_2O_2 (40.0 µL, 0.4 mmol, 2.0 eq.) were added, and the mixture was stirred in room temperature for 18h. The crude was added a catalytic amount of MnO_2, filtered and dried in *vacuo*.[31]

Method 3: *N*-3-alkenylhydantoin (0.2 mmol, 1.0 eq.) and 2,2,2-trifluoroacetophenone (1.74 mg, 0.010 mmol, 5 mol%) were placed in a 5 mL round bottom flask. *t*-BuOH (0.3 mL), buffer 2 (0.3 mL), MeCN (20.0 µL, 0.4 mmol, 2.0 eq.) and 30% aqueous H_2O_2 (40.0 µL, 0.4 mmol, 2.0 eq.) were added. The mixture was stirred in room temperature for 1 h. The crude was added a catalytic amount of MnO_2, filtered and dried in *vacuo*.[39]

Method 4: *N*-3-alkenylhydantoin (0.2 mmol, 1.0 eq.) and methyltrioxorhenium (0.249 mg, 0.0010 mmol, 0.5 mol %) were dissolved in CH_2Cl_2 (1 mL). Pyridine (1.90 µL, 0.0240 mmol, 12 mol %) and 30 % aqueous H_2O_2 (30.0 µL, 0.3 mmol, 1.5 eq.) were added dropwise with a syringe. The mixture was stirred in room temperature for 6h. The crude was added a catalytic amount of MnO_2, filtered and dried in *vacuo*.[40]

Method 5: Saturated $NaHCO_3$ solution (4 mL) was added to a solution of *N*-3-alkenylhydantoin (0.152 mmol, 1.0 eq.) in acetone (6 mL) at 0 ºC in a 50 mL round bottom flask. The mixture was stirred for 0.5 h, and a solution of Oxone (0.0934 g, 0.304 mmol, 2.0 eq.) in water (2 mL) was added dropwise with a syringe over 15 min. The mixture was stirred at 0 ºC for additional 50 min, diluted with water (15 mL) and extracted with ethyl acetate (3 x 10 mL). The combined organic phase was dried with Na_2SO_4, filtered, and dried in *vacuo*.[43]

3-(3-phenylenyloxiran-2-yl)hydantoin (4a)



The compound was prepared and purified like described in method 1, yielding **4a** as a colorless crystalline solid (40.4 mg, 0.185 mmol, 92 %).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38-7.35 (m, 5H, H-9-11), 6.07 (br. s., 1H, H-1), 5.22 (s, 1H, H-6), 4.74 (s, 1H, H-7), 4.00 (s, 2H, H-5).

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.3 (C-4), 156.7 (C-2), 134.7 (C-8), 129.0 (C-10), 128.7 (C-11), 126.0 (C-9), 61.9 (C-6), 54.8 (C-7), 46.1 (C-5).

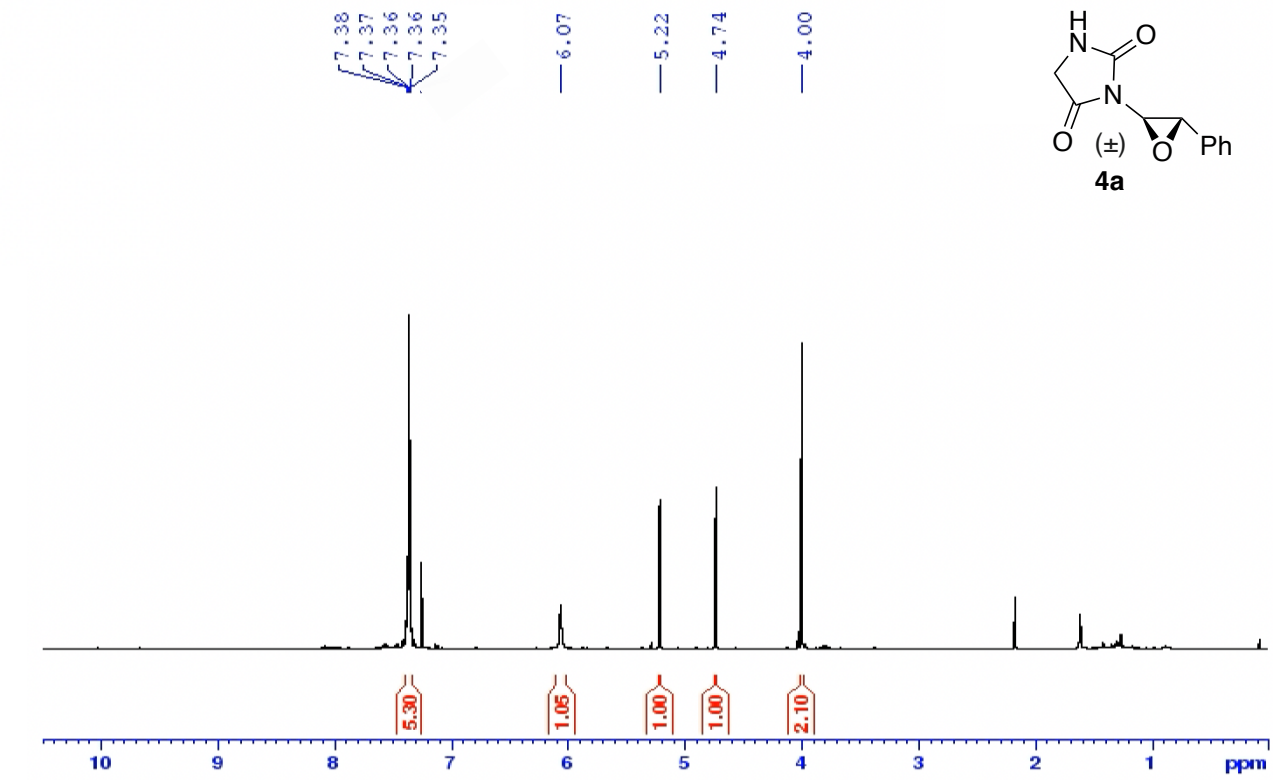
IR (ATR): (cm^{-1} (appearance)): 3260, 3107, 2937, 1738, 1713, 1231, 905.

HRMS (ESI, CH_3CN): *m/z* $[C_{11}H_{10}N_2O_3 + Na]^+$: calculated: 241,0584, found: 241,0584.

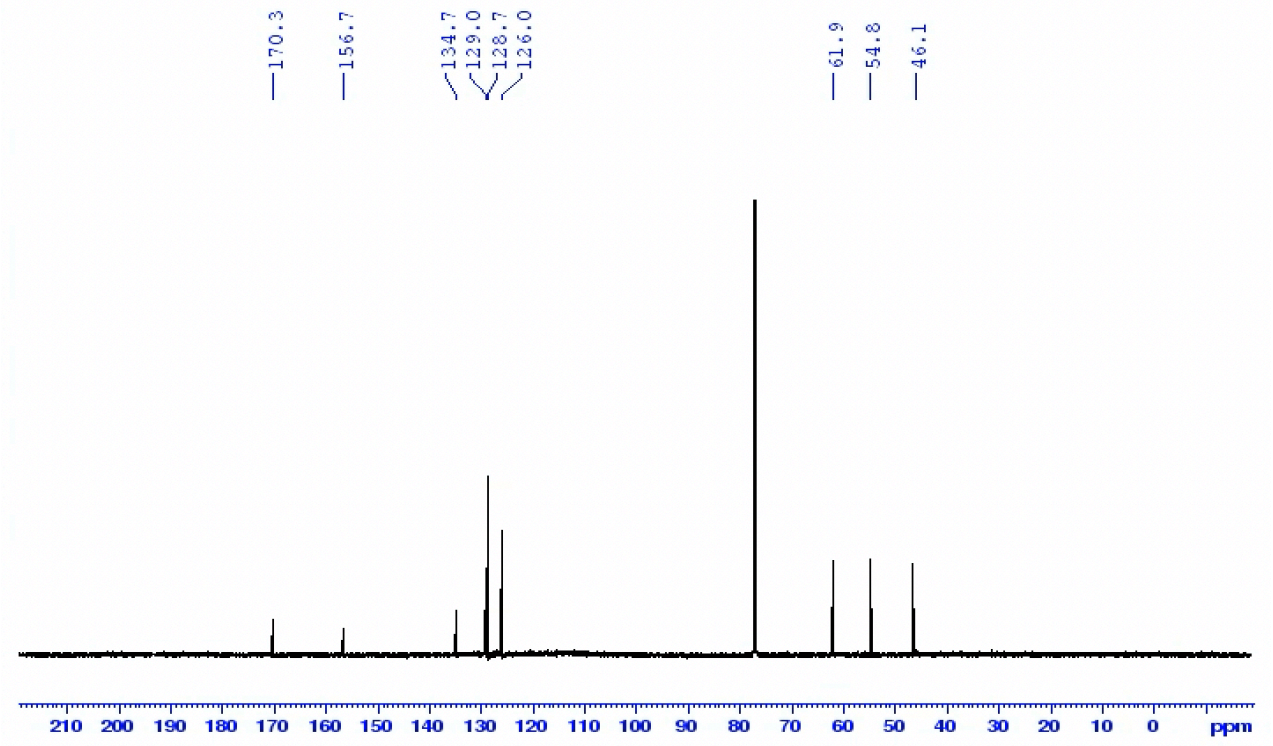
mp: 128-130 °C.

This compound has not been reported in the literature.

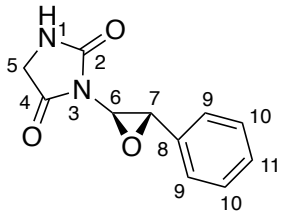
^{1}H NMR (600 MHz, $CDCl_3$) spectrum of 4a (Method 1)



^{13}C NMR (151 MHz, $CDCl_3$) spectrum of 4a (Method 1)



3-(3-phenylenyloxiran-2-yl)hydantoin (4a)



The compound was prepared and purified like described in Method 5, yielding **4a** as a colorless crystalline solid (28,8 mg, 0,132 mmol, 87 %).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37 (s, 5H, H-9-11), 6.32 (br. s., 1H, H-1), 5.22 (s, 1H, H-6), 4.74 (s, 1H, H-)7, 4.01 (s, 2H, H-5).

^{13}C NMR (151 MHz, $CDCl_3$): δ 170.4 (C-4), 156.8 (C-2), 134.7 (C-8), 129.0 (C-10) 128.7 (C-11), 126.0 (C-9), 61.9 (C-6), 54.8 (C-7), 46.1 (C-5).

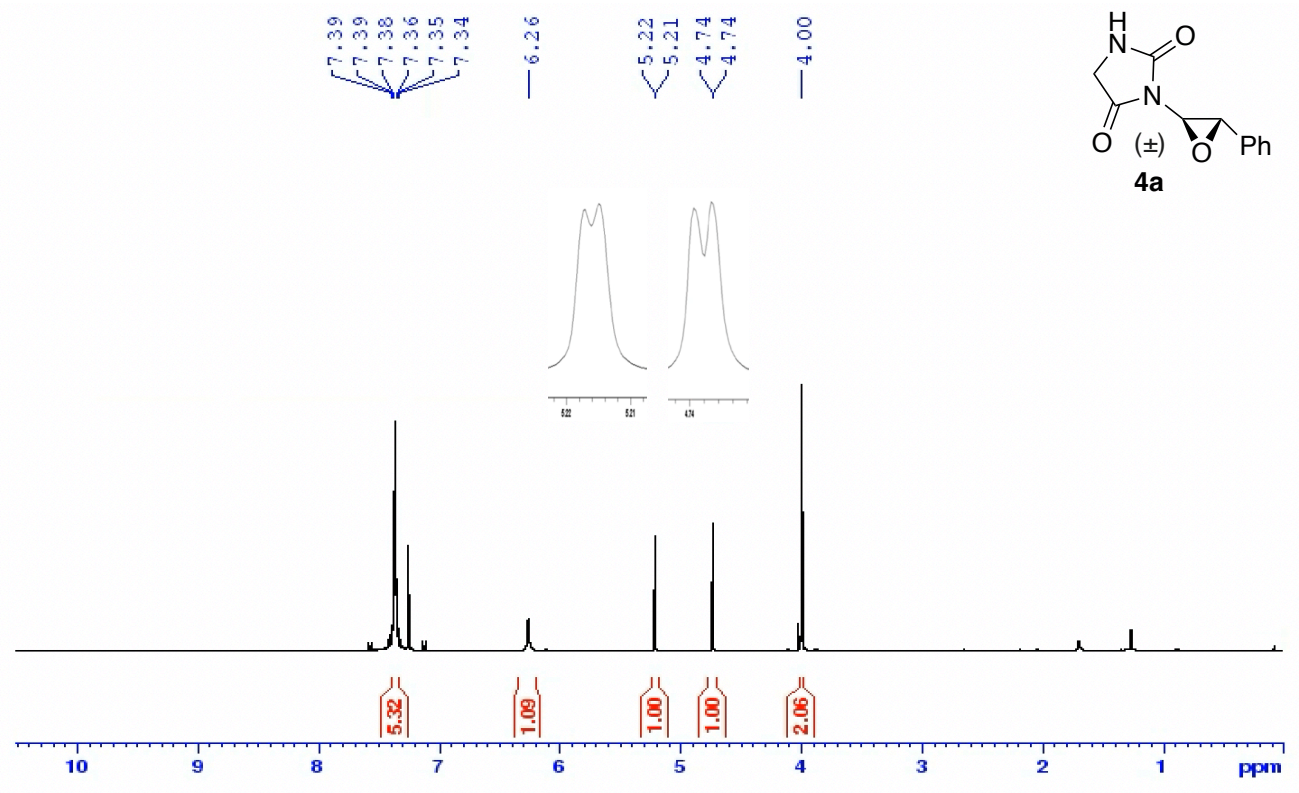
IR (ATR): (cm^{-1} (appearance)): 3269, 3032, 2932, 1744, 1715, 1229, 884.

HRMS (ESI, CH_3CN): *m/z* $[C_{11}H_{10}N_2O_3 + Na]^+$: calculated: 241,0583, found: 241,0584.

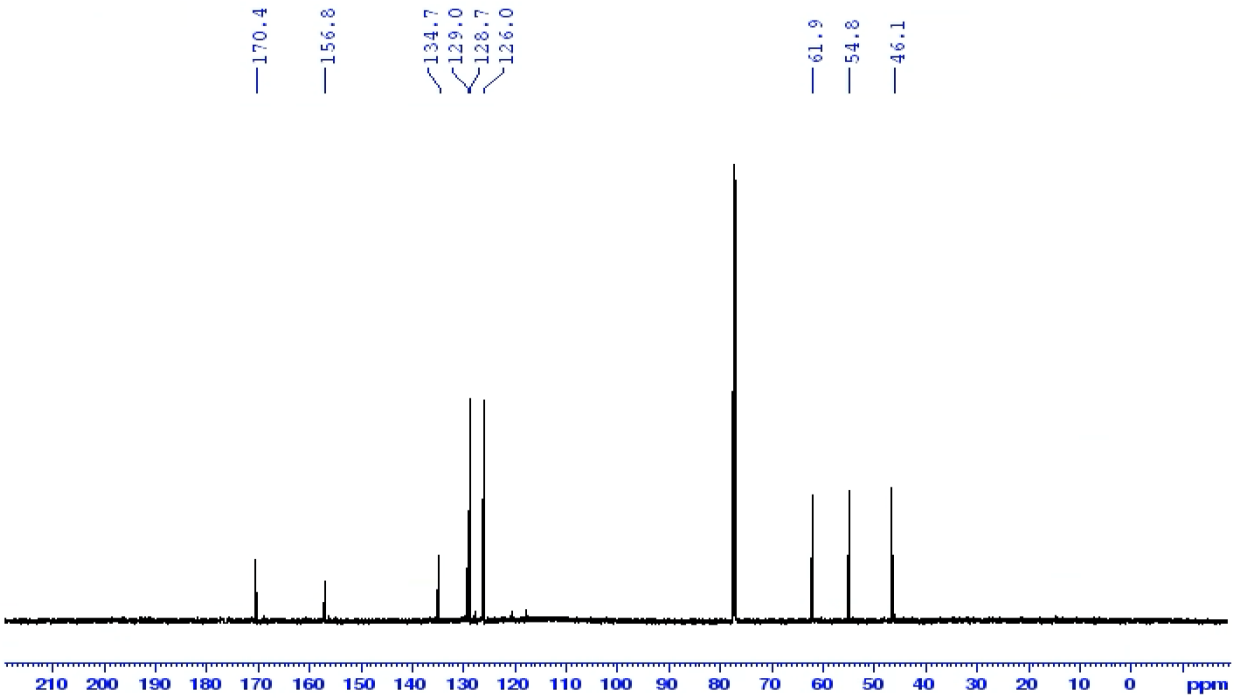
mp: 128-130 ºC.

This compound has not been reported in the literature.

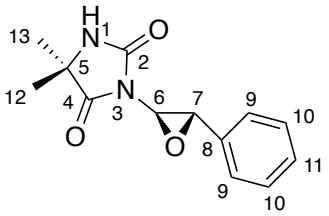
^{1}H NMR (600 MHz, $CDCl_3$) spectrum of 4a (Method 5)



^{13}C NMR (151 MHz, $CDCl_3$) spectrum of 4a (Method 5)



5,5-dimethyl-3-(3-phenyloxiran-2-yl) hydantoin(4b)



0.2 mmol scale:

The compound was prepared and purified like described in method 1, yielding **4b** as a white crystalline solid (40.2 mg, 0.163 mmol, 81%).

0.6 mmol scale:

The compound was prepared and purified like described in method 1, but on a 0.6 mmol scale. In a 25 mL round bottom flask **3b** (142 mg ,0.6 mmol, 1.0 eq.), *m*-CPBA (213 mg, 1.2 mmol, 2 eq.) and DCM (6 mL) was added, and the mixture was and stirred in room temperature for 24h. The reaction mixture was solved in DCM (24 mL) and extracted with 1 M K_2CO_3 (2 x 20 mL), H_2O (3 x 20 mL), and saturated NaCl (1x 20 mL). The collected organic phase was dried with Na_2SO_4, filtered and dried *in vacuo*. This yielded **4c** as a white crystalline solid (129 mg, 0.523 mmol, 85 %).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39-7.37 (m, 5H, H-9-11), 6.52 (br.s., 1H, H-1), 5.23 (d, *J*= 1.5 Hz, 1H, H-6), 4.74 (d, *J*= 1.5 Hz, 1H, H-7), 1.48, 1.47 (s, 6H, signal overlap from the diastereotopic CH_3 groups, H-12-13).

^{13}C NMR (151 MHz, $CDCl_3$): δ 176.6 (C-4), 155.2 (C-2), 134.9 (C-8), 129.0 (C-10), 128.6 (C-11), 126.0 (C-9), 62.1 (C-5), 58.5 (C-6), 54.8 (C-7), 25.0 (C-12), 25.0 (C-13).

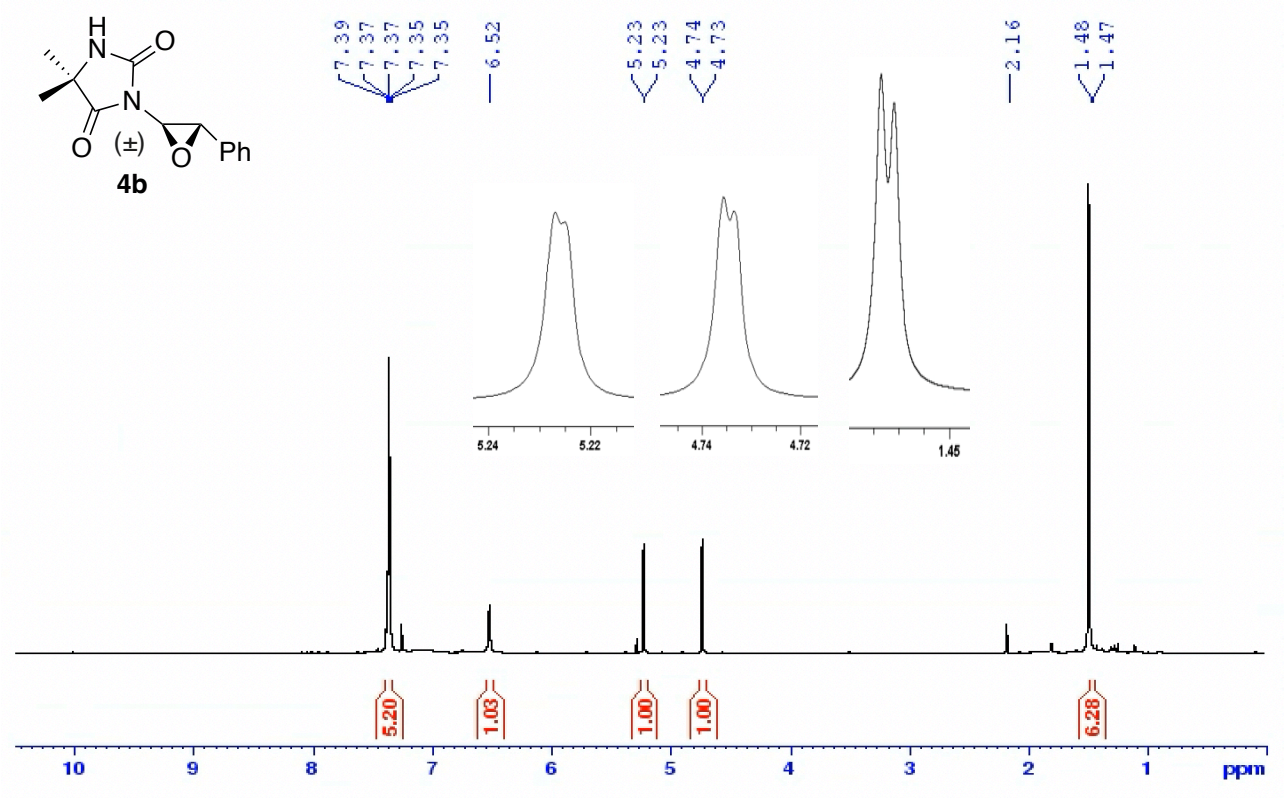
IR (ATR): (cm^{-1} (appearance)): 3271, 3034, 2982, 1744, 1715, 1229, 885.

HRMS (ESI, CH_3CN): *m/z* $[C_{13}H_{14}N_2O_3 + Na]^+$: calculated: 269.0896, found: 269.0897.

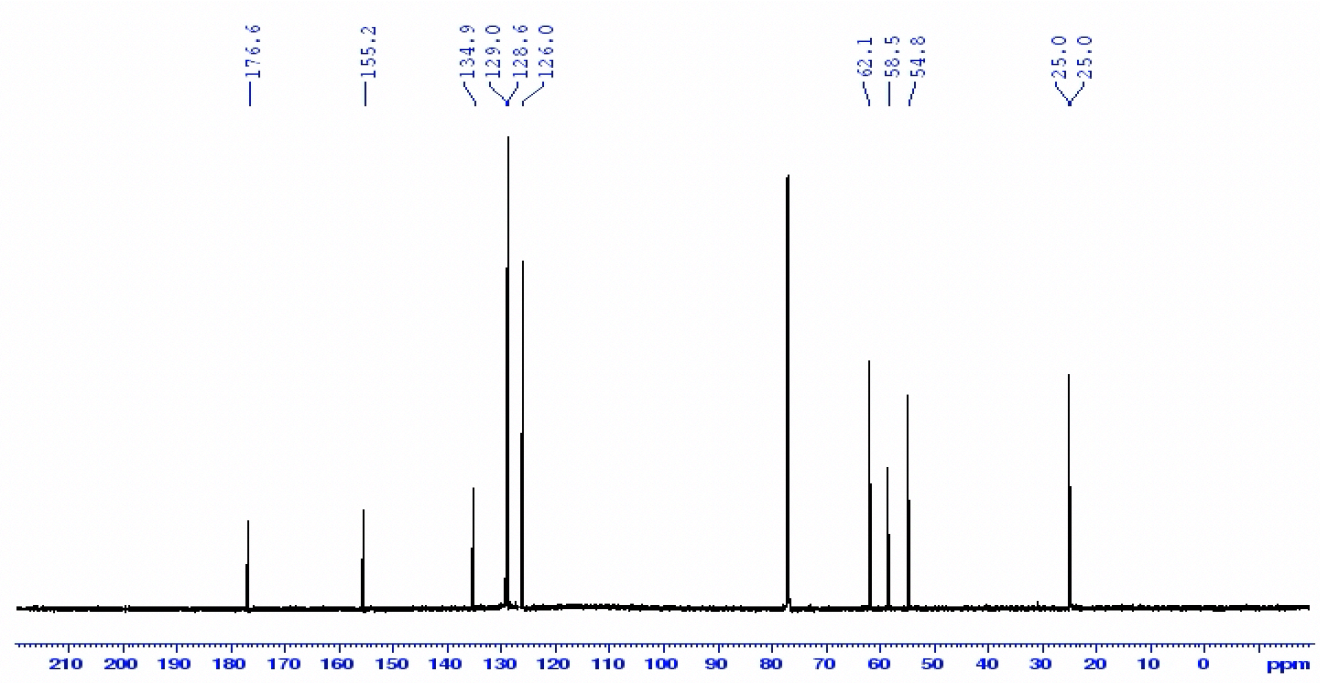
mp.: 93-94 °C.

This compound has not been reported in the literature.

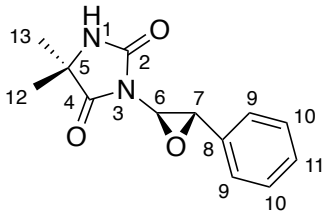
^{1}H NMR (600 MHz, $CDCl_3$) spectrum of 4b (Method 1)



^{13}C NMR (151 MHz, $CDCl_3$) spectrum of 4b (Method 1)



5,5-dimethyl-3-(3-phenyloxiran-2-yl) imidazolidine-2,4-dione (4b)



This compound was prepared and purified like described in method 5, yielding **4b** as a white crystalline solid (35.7 mg, 0.145 mmol, 95 %).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38-7.35 (m, 5H, H-9-11), 6.45 (br.s., 1H, H-1), 5.23 (d, *J*= 1.6 Hz, 1H, H-6), 4.74 (d, *J*= 1.7 Hz, 1H, H-7), 1.48, 1.47 (2s, 6H, H-12-13).

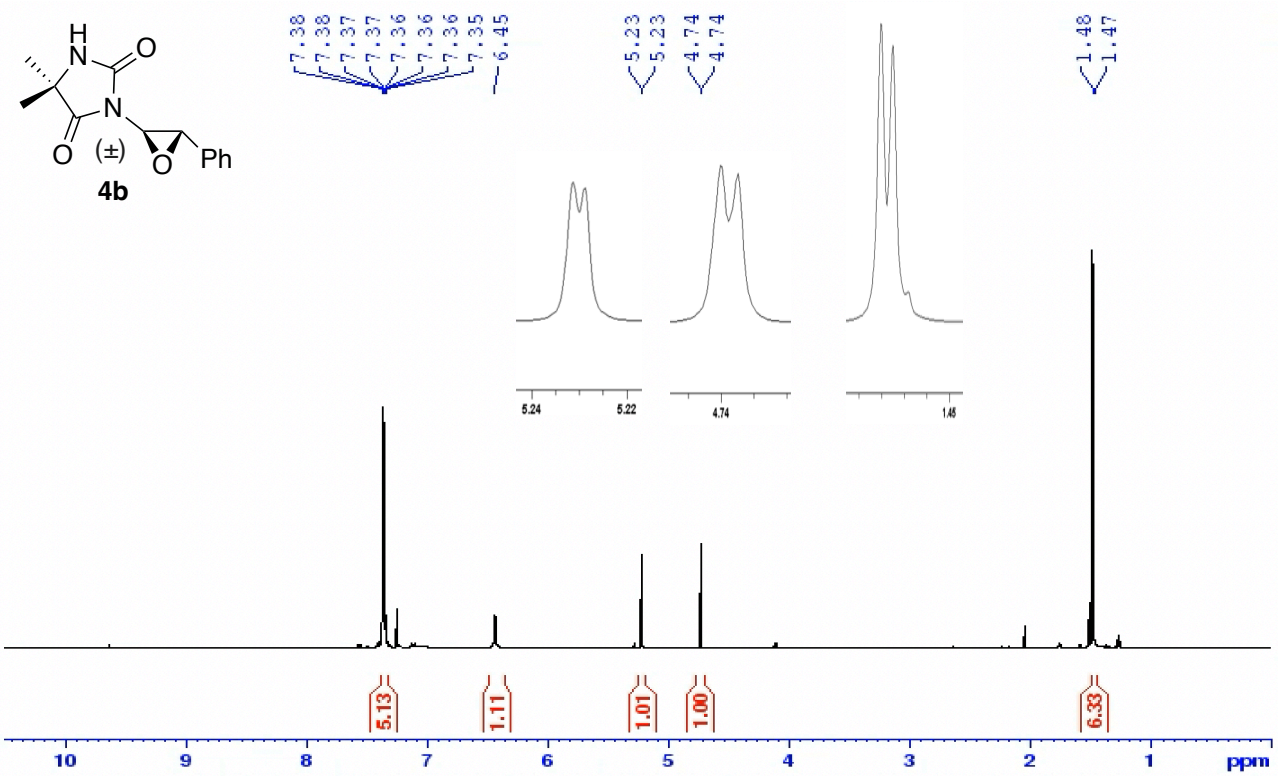
^{13}C NMR (151 MHz, $CDCl_3$): δ 176.6 (C-4), 155.1 (C-2), 134.9 (C-8), 129.0 (C-10), 128.6 (C-11), 126.0 (C-9), 62.1 (C-5), 58.5 (C-6), 54.8 (C-7), 25.1 (C-12), 25.0 (C-13).

HRMS (ESI, CH_3CN): *m/z* $[C_{13}H_{14}N_2O_3 + Na]^+$: calculated: 269.0896, found: 269.0897.

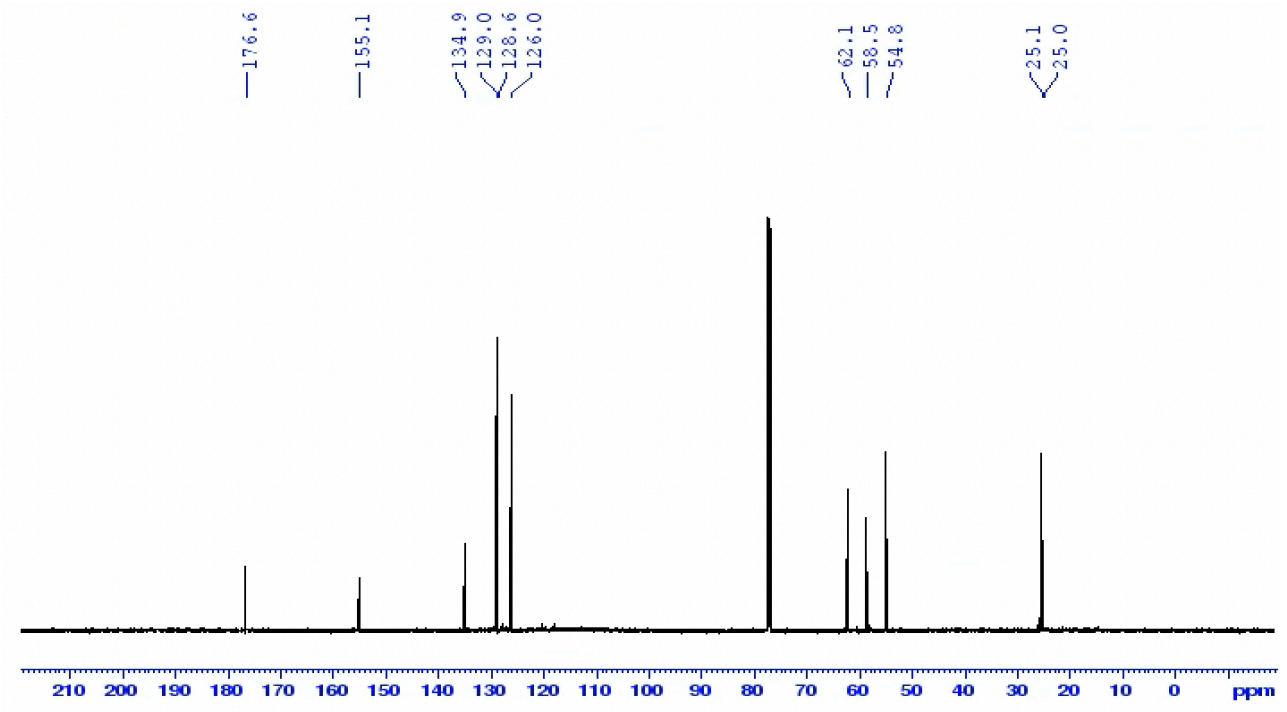
mp.: 93-94 ^{o}C.

This compound has not been reported in the literature.

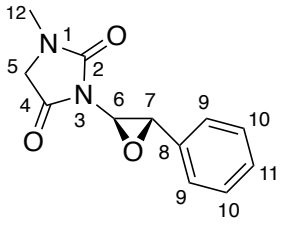
^{1}H NMR (600 MHz, $CDCl_3$) spectrum of 4b (Method 5)



^{13}C NMR (151 MHz, $CDCl_3$) spectrum of 4b (Method 5)



1-methyl-3-(3-phenyloxiran-2-yl)imidazolidine-2,4-dione (4c)



0.2 mmol scale:

This compound was prepared and purified like described in method 1, but the described extraction was done two times. The compound was further purified with column chromatography (silica gel, 7:3, hexane/acetone) as a colorless solid (27.9 mg, 0.120 mmol, 60 %).

1.5 mmol scale:

The compound was prepared and purified like described in method 1, but on a 1.5 mmol scale using a 25 mL round-bottom flask with **3c** (330 mg,1.5 mmol, 1.0 eq.), *m*-CPBA (527 mg, 3.0 mmol, 2.0 eq.) and 16 mL DCM. For the extraction, the reaction mixture was solved in 40 mL DCM and extracted with 1 M K_2CO_3 (2 x 20 mL), H_2O (3 x 20 mL), and saturated NaCl (1x 20 mL). The collected organic phase was dried with Na_2SO_4, filtered and dried *in vacuo*. The compound was further purified with column chromatography (silica gel, 7:3, chloroform/hexane/acetone), yielding **4c** as a colorless solid (219 mg, 0.942 mmol, 62 %).

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37-7.34 (m, 5H, H-9-11), 5.24 (d, *J*= 1.5 Hz, 1H, H-6), 4.73 (d, *J*= 1.5 Hz, 1H, H-7), 3.89, (s, 2H, H-5), 3.01 (s, 3H, H-12).

^{13}C NMR (151 MHz, $CDCl_3$): δ 169.0 (C-4), 155.2 (C-2), 134.9 (C-8), 128.9 (C-10), 128.6 (C-11), 126.0 (C-9), 62.2 (C-5), 54.8 (C-6), 51.3 (C-7), 29.7 (C-12).

IR (ATR): (cm^{-1} (appearance)): 3477, 3032, 2937, 1744, 1713, 1244, 881.

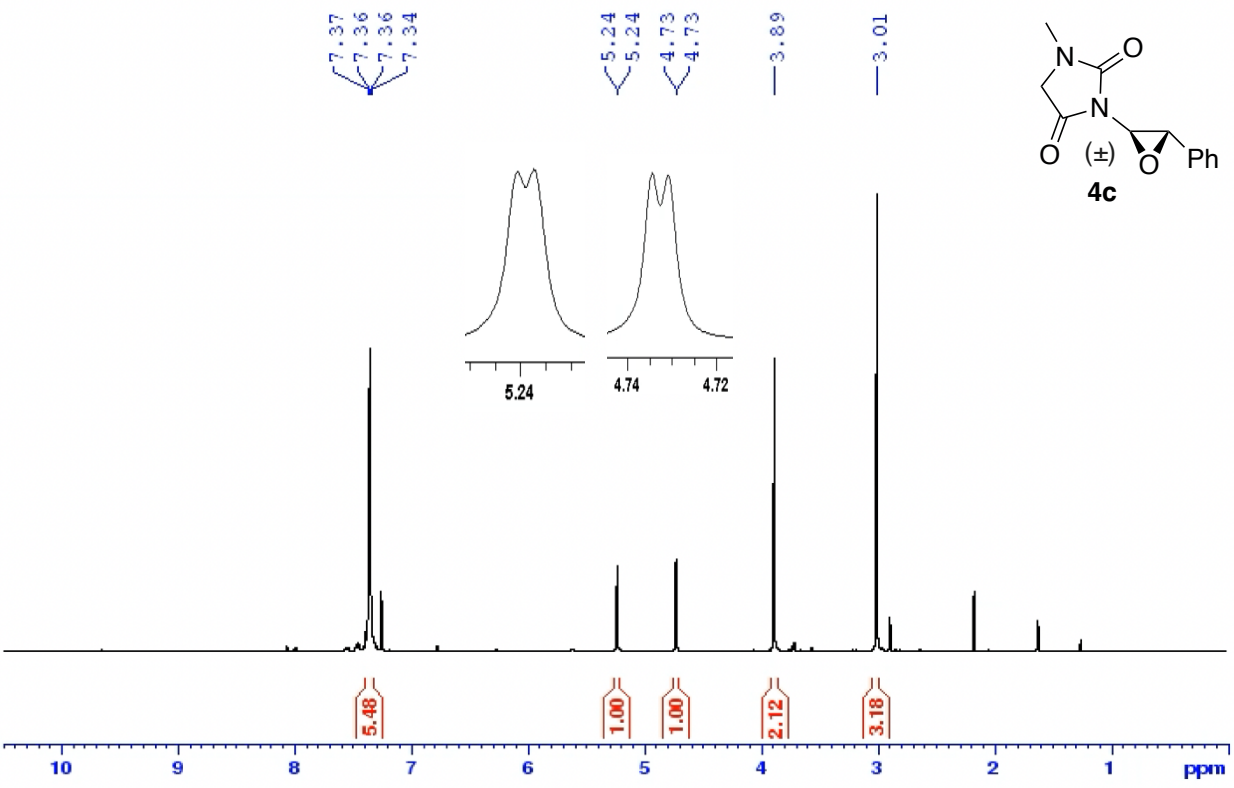
HRMS (ESI, CH_3CN): *m/z* $[C_{13}H_{14}N_2O_3 + Na]^+$: calculated: 411.0719, found: 411.0718.

mp.: 62-64 °C.

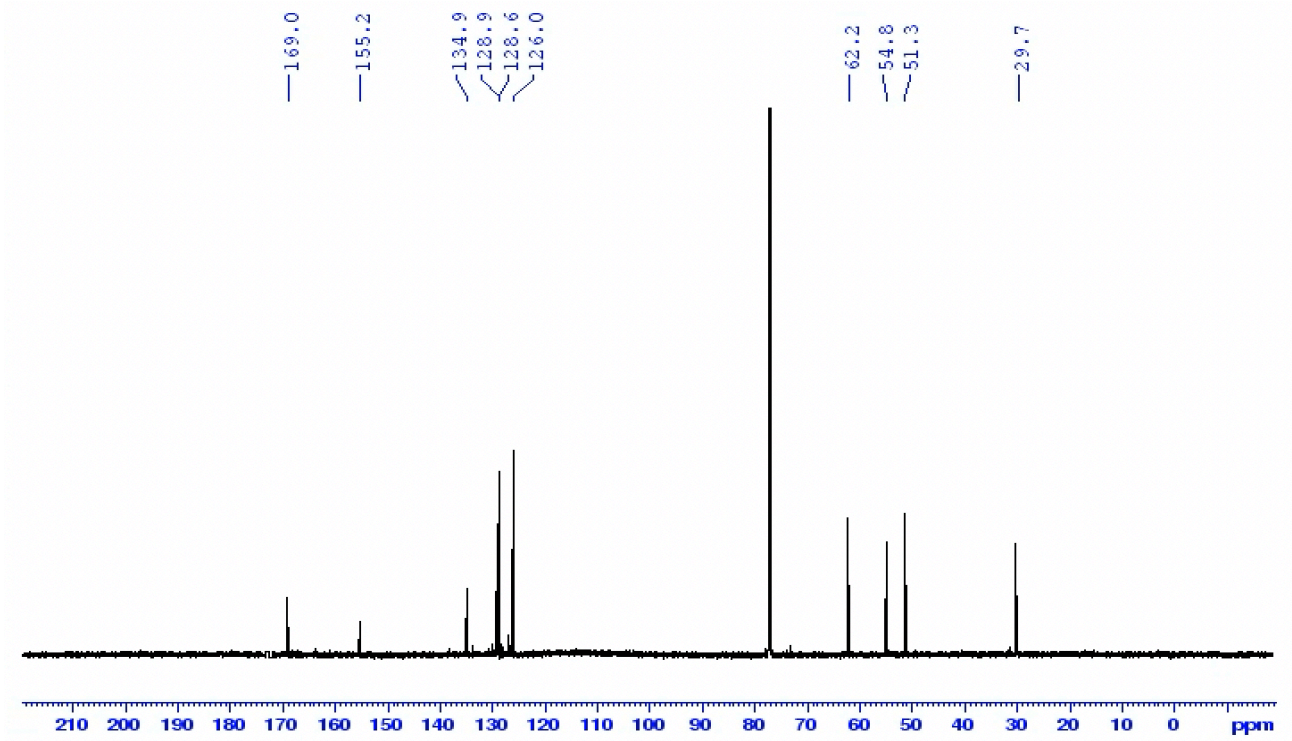
R_f (7:3, hexane/acetone): 0.30.

This compound has not been reported in the literature

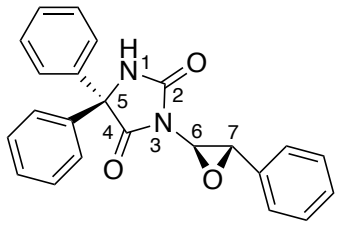
^{1}H NMR (600 MHz, $CDCl_3$) spectrum of 4c (Method 1)



^{13}C NMR (151 MHz, $CDCl_3$) spectrum of 4c (Method 1)



5,5-diphenyl-3-(3-phenyloxiran-2-yl) imidazolidine-2,4-dione (4d)



This compound was prepared and extracted like described in Method 1. The compound was further purified with column chromatography (silica gel, 7:3 hexane/ EtOAc), yielding **4d** as a white crystalline solid (63.0 mg, 0.170 mmol, 85 %). The synthesis was done in my graduate research project spring 2021.

^{1}H NMR (600 MHz, $CDCl_3$): δ 7.39-7.36 (m, 15H, aromatic protons), 6.63 (br. s., 1H, H-1), 5.26 (d, *J*= 1,3 Hz, 1H, H-6), 4.81 (d, *J*= 1,4 Hz, 1H, H-7).

^{13}C NMR (151 MHz, $CDCl_3$): δ 172.7 (C-4), 154.9 (C-2), 138.6, 138.5, 134.7, 129.0, 128.9, 128.9, 128.6, 126.9, 126.8, 126.0 (aromatic carbons), 69.8 (C-5), 62.3 (C-6), 54.8 (C-7).

IR (ATR): (cm^{-1} (appearance)): 3275, 3061, 2922, 1740, 1718, 1246, 902.

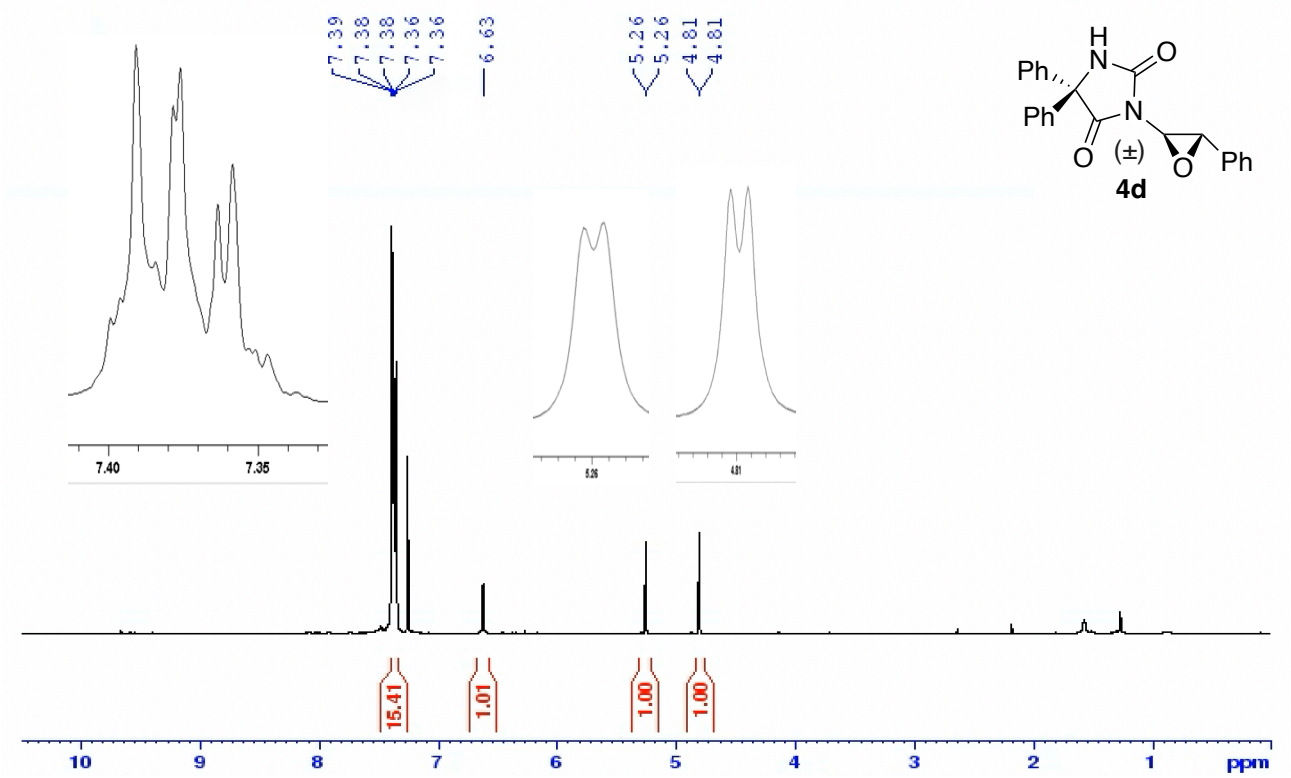
HRMS (ESI, CH_3CN): *m/z* $[C_{23}H_{18}N_2O_3 + Na]^+$: calculated: 393,1210, found: 393,1209.

mp.: 75-80 °C.

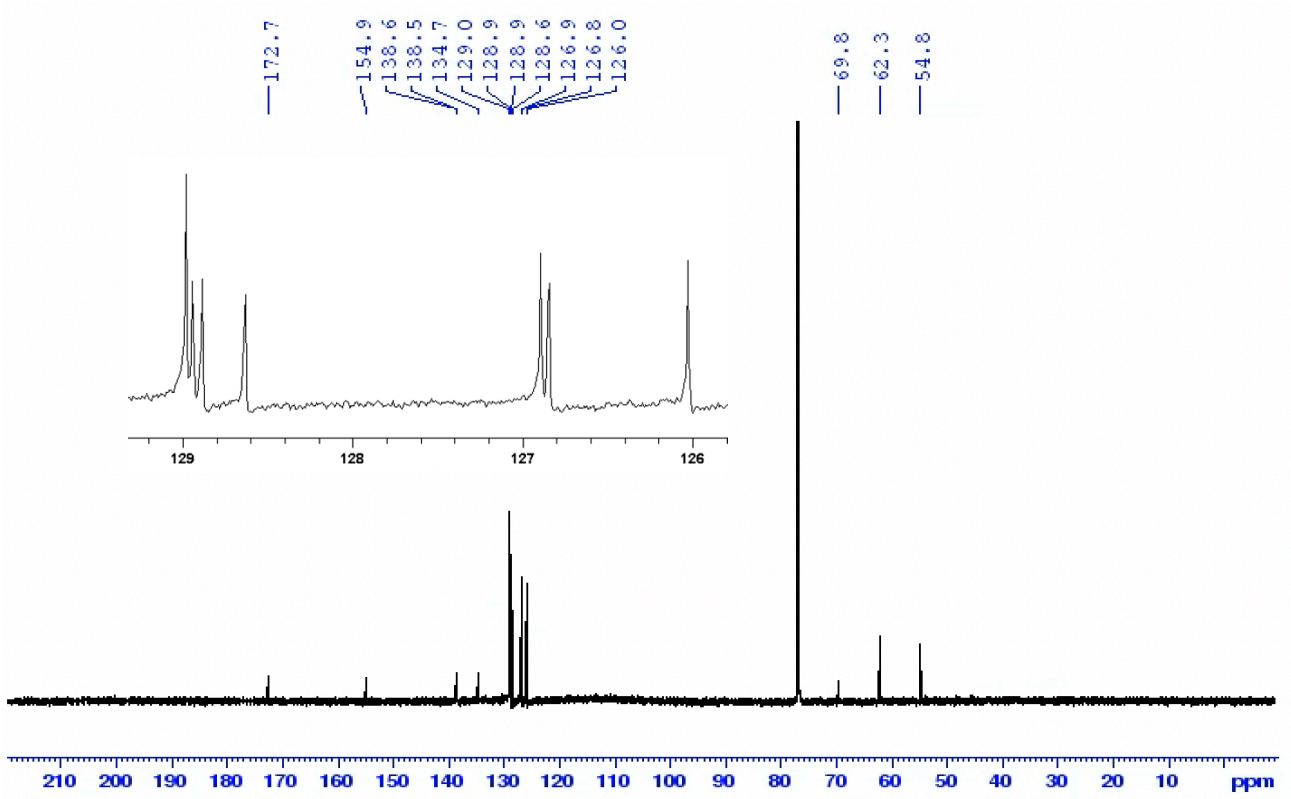
R_f (7:3 hexane/ EtOAc): 0.29

The compound has not been reported in the literature

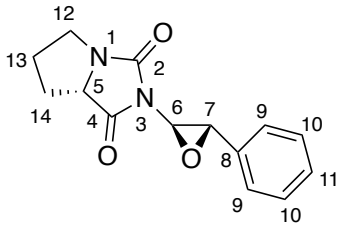
^{1}H NMR (600 MHz, $CDCl_3$) spectrum of 4d (Method 1)



^{13}C NMR (151 MHz, $CDCl_3$) spectrum of 4d (Method 1)



(7a*S*)-2-(3-phenyloxiran-2-yl)tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1,3(2*H*)-dione (4e)



This compound was prepared and purified like described in Method 1, but the described extraction was performed two times. Further purification was done with column chromatography (silica gel, 2:1 hexane/ EtOAc), yielding **4e** as a colorless oil (31.3 mg, 0.121 mmol, 61 %).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38-7.33 (m, 5H, H-9-11), 5.22, 5.18 (2d, *J*= 1.5, 1.5 Hz, 1H, H-6), 4.72, 4.67 (2d, *J*= 1.5, 1.5 Hz, 1H, H-7), 4.12-4.08 (m, 1H, H-5), 3.75-3.70 (m, 1H, H-12), 3.28 (ddd, (ddd, *J*= 11.3, 7.5 ,4.5 Hz, 1H, H-12), 2.30-2.25 (m, 1H, H-14), 2.17-2.03 (m, 2H, H-13), 1.81-1.74 (m, 1H, H-14).

^{13}C NMR (101 MHz, $CDCl_3$): δ 173.2, 173,0 (C-4), 158.7 (C-2), 134.8 (C-8), 128.9, 128.6 (C-10), 127.3 (C-11), 126.0, 126.0 (C-9), 63.0, 62.9 (C-5), 62.3, 62.2 (C-6), 54.8, 54.6 (C-7), 45.5 (C-12), 27.5, 27.4 (C-14), 26.8 (C-13).

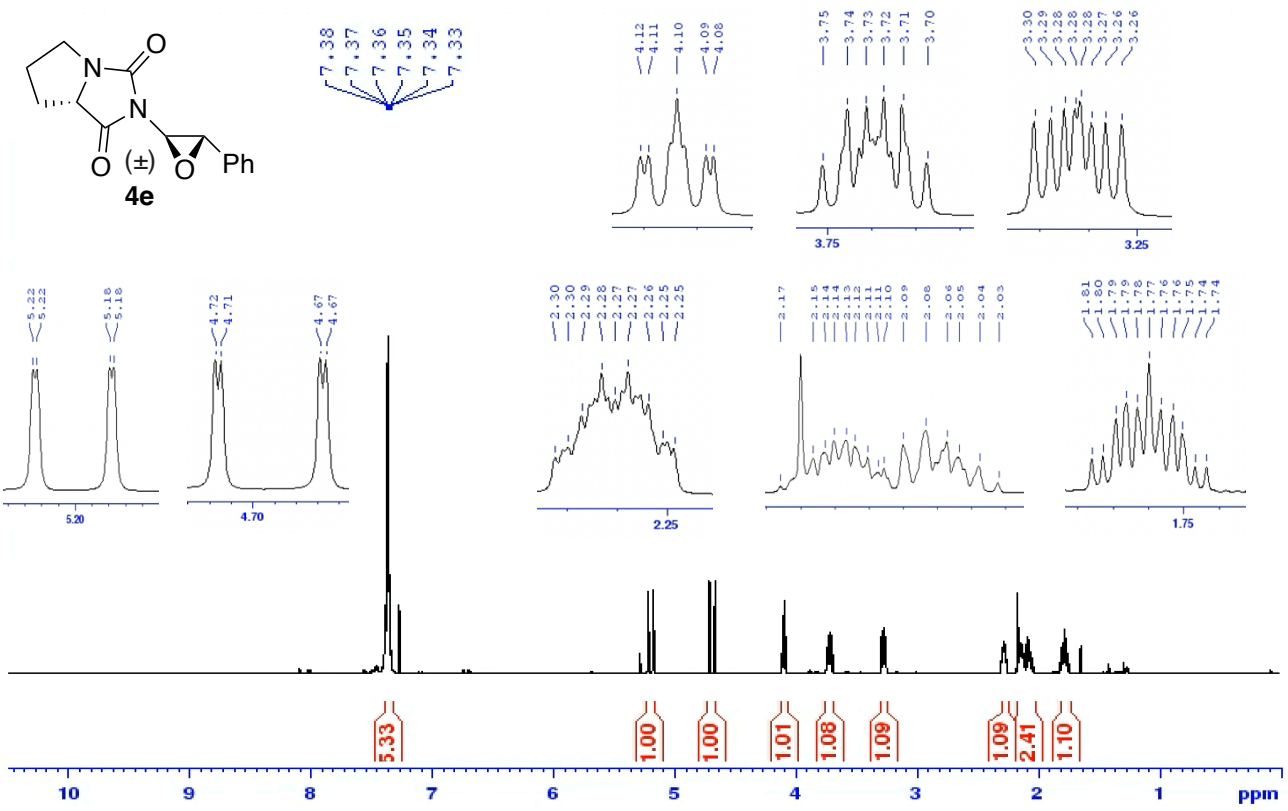
IR (ATR): (cm^{-1} (appearance)): 3477, 2991, 2899, 1740, 1713, 1234, 895.

HRMS (ESI, CH_3CN): *m/z* $[C_{14}H_{14}N_2O_3 + Na]^+$: calculated: 281.0897, found: 281.0897.

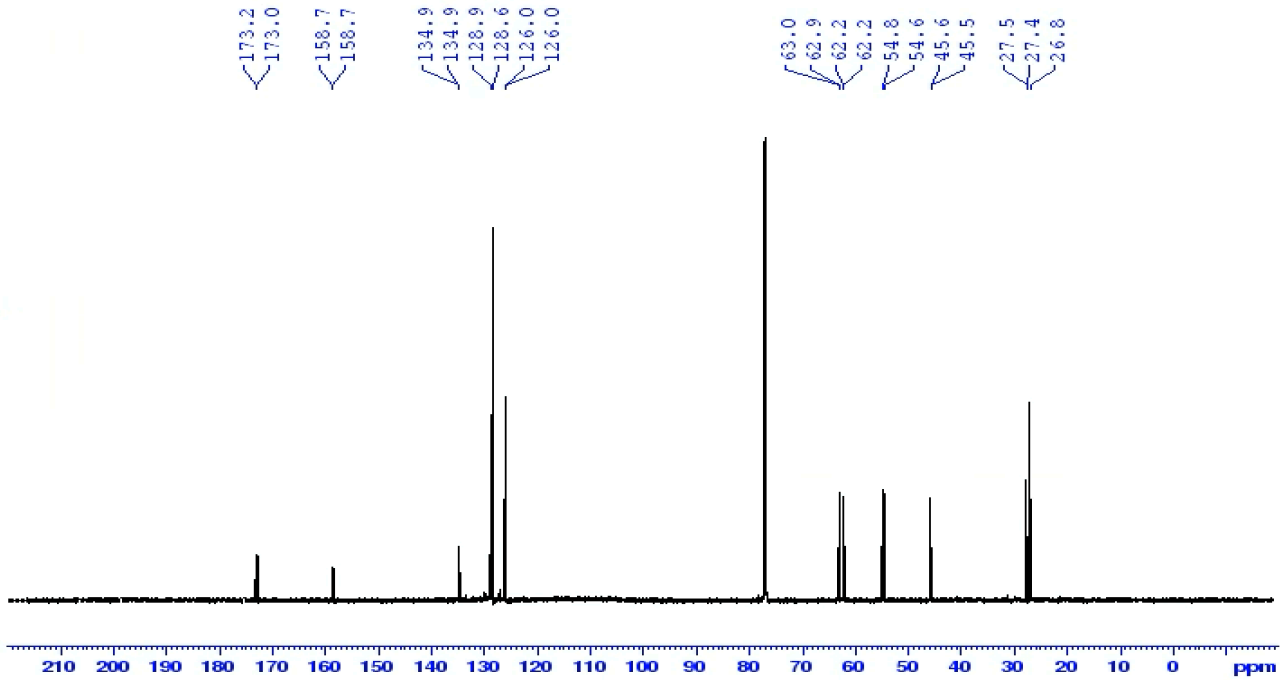
R_f (2:1 hexane/ EtOAc): 0.31.

The compound has not been reported in the literature.

^{1}H NMR (600 MHz, $CDCl_3$) spectrum of 4e (Method 1)



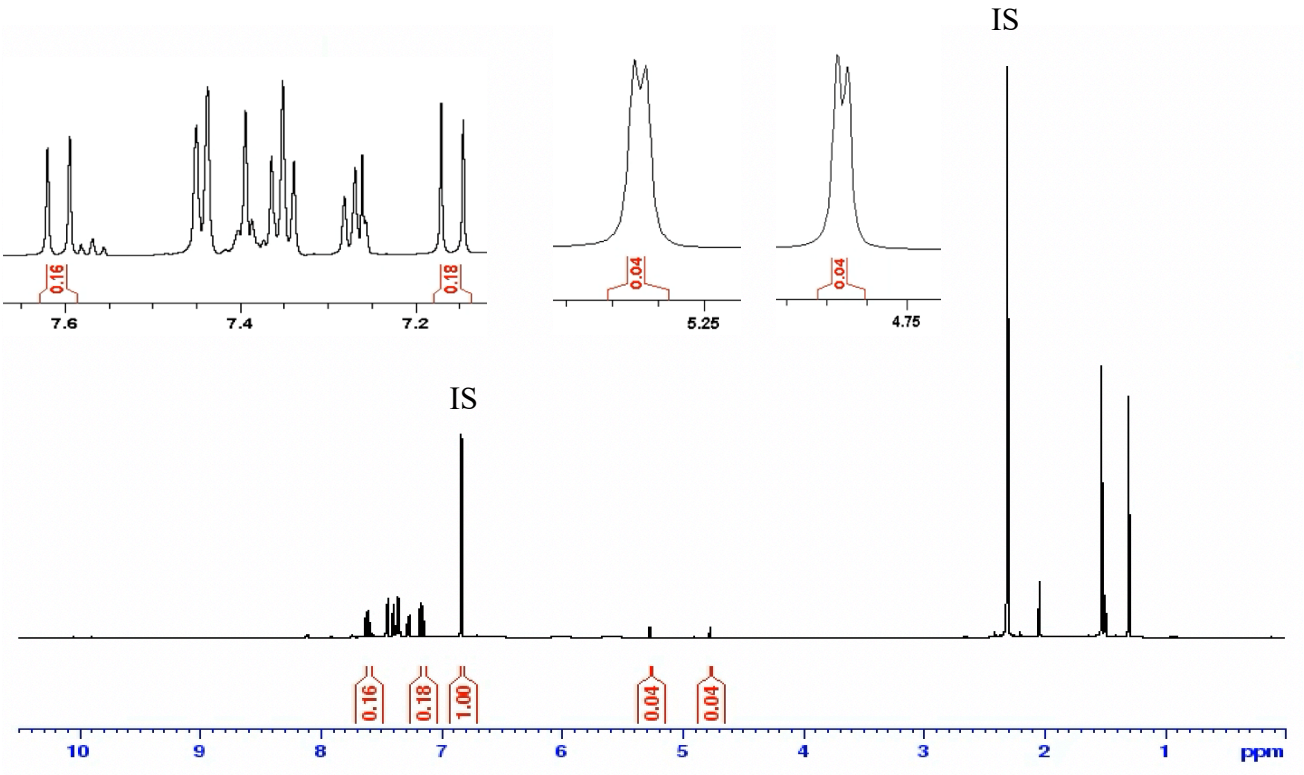
^{13}C NMR (600 MHz, $CDCl_3$) spectrum of 4e (Method 1)



Attempted synthesis of 4b with Method 3

Compound **4b** was attempted synthesized with Method 3 but was not enabled isolated. At the end of the reaction time the crude mixture was dried *in vacuo*. Then 23.8 mg mesitylene was added as IS using a syringe, and $CDCl_3$ was added until the crude material was completely solved. The mixture was stirred until observed homogenous. A ^1H NMR spectrum of the mixture was recorded, and from the spectrum the NMR yield of **4b** was calculated (4.33 mg, 0.0176 mmol, 12 %) and the NMR yield of the starting material **3b** (24.6 mg, 0.100 mmol 50 %).

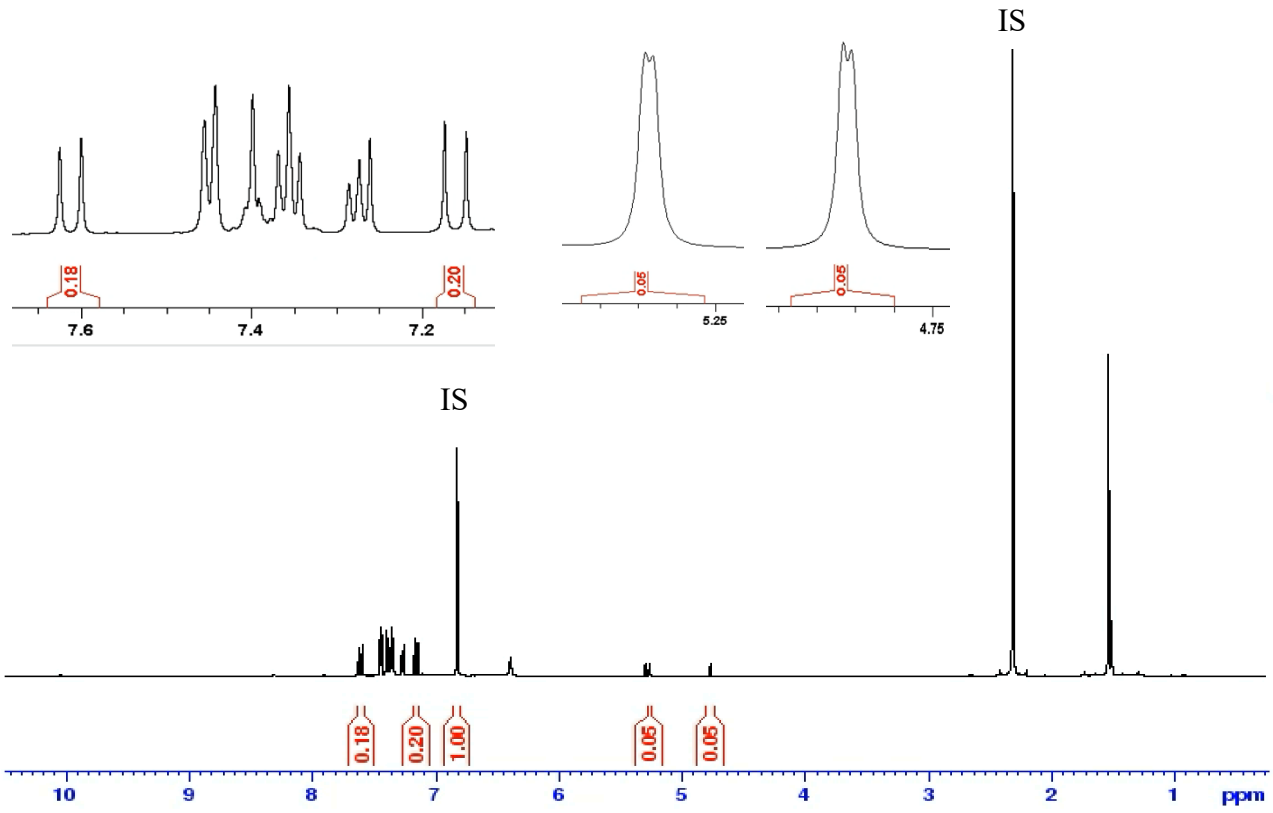
^1H NMR (600 MHz, $CDCl_3$) spectrum of the crude formed after epoxidating 3b with method 3



Attempted synthesis of 4b with Method 4

Compound **4b** was synthesized with Method 4 but was not enabled isolated. At the end of the reaction time the crude mixture was dried *in vacuo*. Then 12.8 mg mesitylene was added as IS using a syringe, and $CDCl_3$ was added until the crude material was completely solved. The mixture was stirred until observed homogenous. A ^1H NMR spectrum of the mixture was recorded, and from the spectrum the NMR yield of the **4b** was calculated (6.90 mg, 0.0280 mmol, 14 %), and the NMR yield of the starting material **3b** (26.4 mg, 0.107 mmol, 53 %).

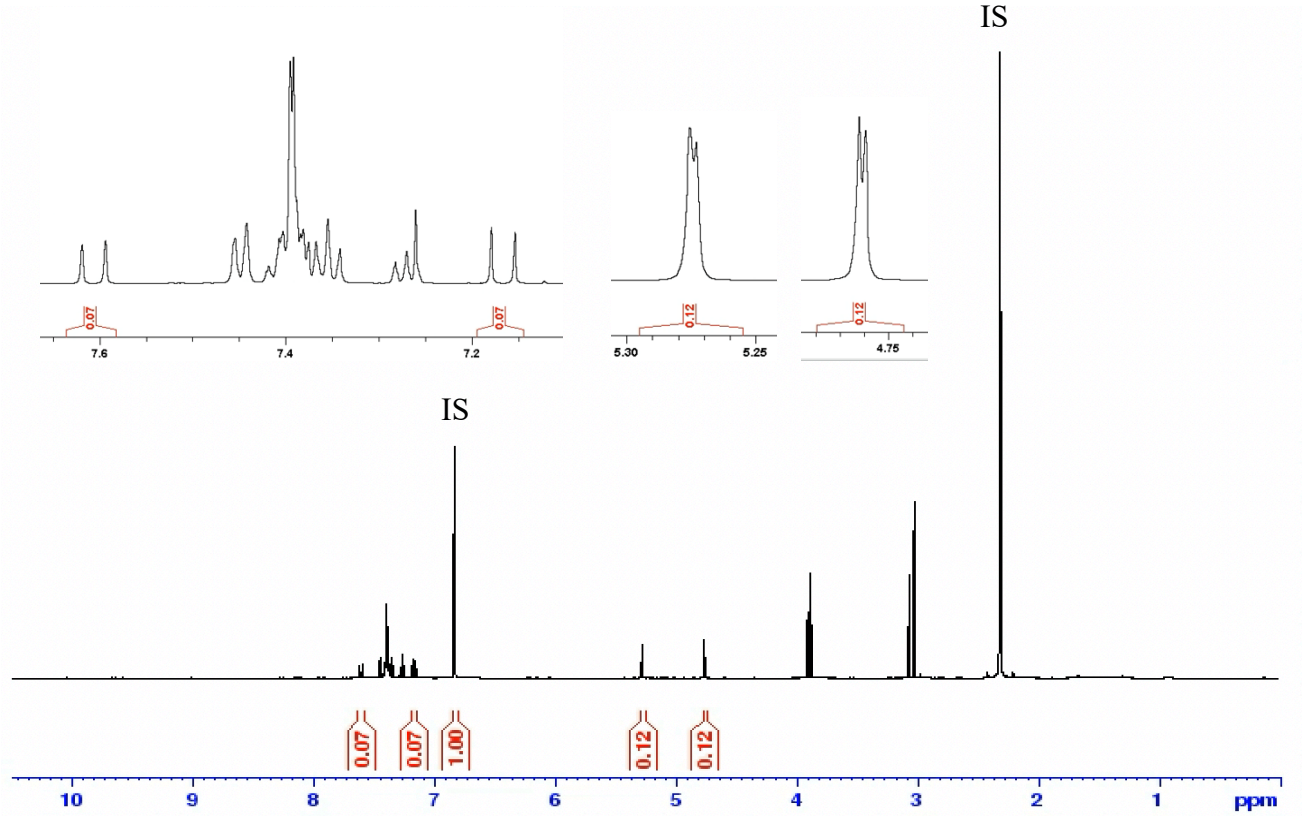
^1H NMR (600 MHz, $CDCl_3$) spectrum of the crude formed after epoxidating 3b with method 4



Attempted synthesis of 4c with Method 5

Compound **4c** was synthesized with Method 5 but was not enabled isolated. At the end of the reaction time the reaction mixture was extracted as described in Method 5. The collected organic phase was dried *in vacuo* and was added 24.7 mg mesitylene as IS using a syringe. $CDCl_3$ was added until the crude material was completely solved. The mixture was stirred until observed homogenous. A ^1H NMR spectrum of the mixture was recorded, and from the spectrum the NMR yield **4c** was calculated (17.1 mg, 0.0735 mmol, 48 %) and the NMR yield of the starting material **3c** (9.28 mg, 0.0429 mmol, 28 %).

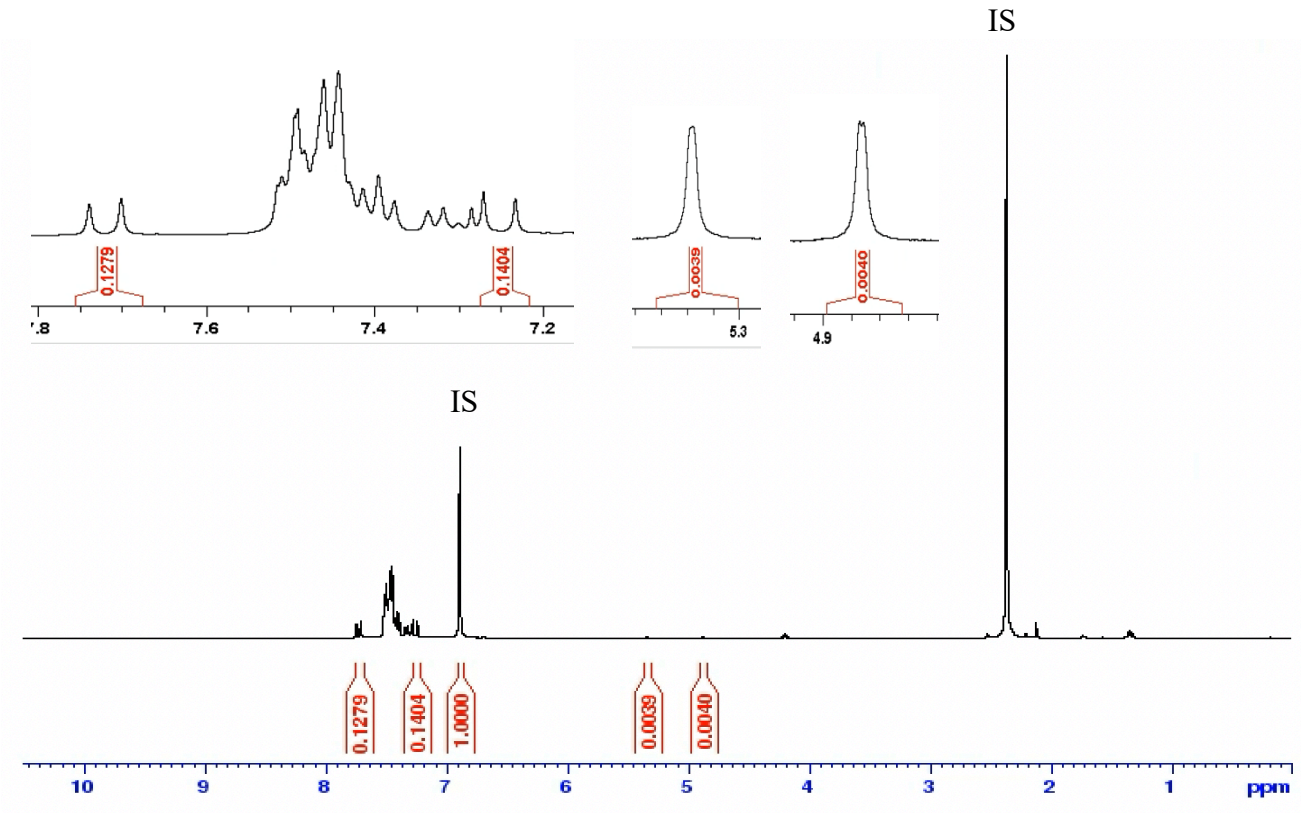
^1H NMR (600 MHz, $CDCl_3$) spectrum of the crude from epoxidating 3c with method 5



Attempted synthesis of 4d with Method 5

Compound **4d** was synthesized with Method 5 but was not enabled isolated. At the end of the reaction time, the reaction mixture was extracted as described in Method 5. The collected organic phase was dried *in vacuo* and added 25.3 mg mesitylene as IS using a syringe. $CDCl_3$ was added until the crude material was completely solved. The mixture was stirred until observed homogenous. A 1H NMR spectrum of the mixture was recorded, and from the spectrum the NMR yield of **4d** was calculated (0.908 mg, 0.0025 mmol, 2 %), and the NMR yield of the starting material **3d** was (29.8 mg, 0.084 mmol, 55 %)

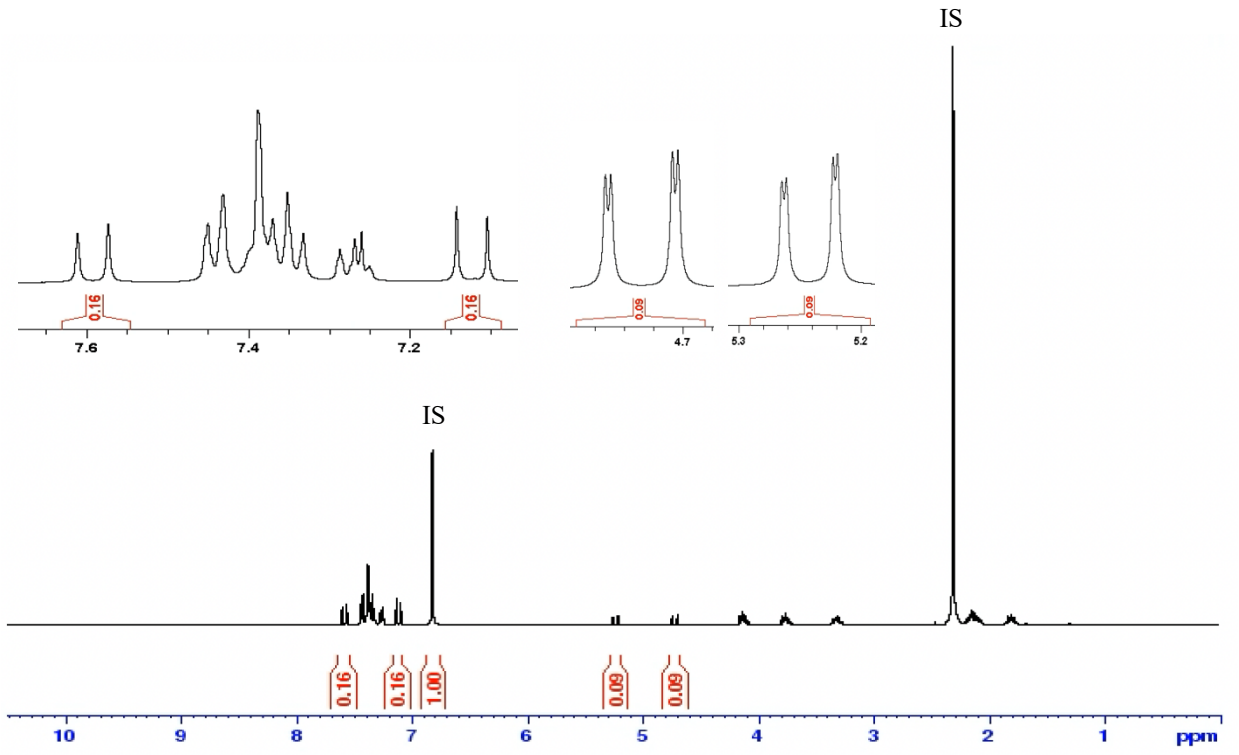
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the crude from epoxidating 3d with method 5



Attempted synthesis of 4e with Method 5

Compound **4e** was synthesized with Method 5 but was not enabled isolated. At the end of the reaction time the reaction mixture was extracted as described in Method 5. The collected organic phase was dried *in vacuo* and added 21.0 mg mesitylene as IS using a syringe. $CDCl_3$ was added until the crude material was completely solved. The mixture was stirred until observed homogenous. A ^1H NMR spectrum was recorded, and from the spectrum the NMR yield of **4e** was calculated (12.1 mg, 0.0469 mmol, 31 %), and the NMR yield of the starting material **3e** (20.2 mg, 0.0834 mmol, 55 %)

^1H NMR (400 MHz, $CDCl_3$) spectrum of the crude from epoxidating 3e with method 5



5.4 Ring-opening of the *N*-3-epoxyhydantoins

Here, the three reaction conditions for nucleophilic ring-opening of the *N*-3-epoxyhydantoins are given. Crude ^{1}H NMR spectrums from the nucleophilic ring-openings are found in appendix C.

Ring-opening with water

N-3-epoxyhydantoin (0.2 mmol) solved in 1.4-dioxane (2 mL), with 1:1 ratio substrate and solvent. The mixture was stirred under reflux in 100 ^{o}C for 24-48 hours. The reaction was ended when the epoxide was no longer observed on ^{1}H NMR.[23]

Ring-opening with 1-propanol

N-3-epoxyhydantoin (0.2 mmol) solved in 1.4-dioxane (2 mL) were stirred under reflux in 90 ^{o}C. The reaction was ended when the epoxide was no longer observed on the crude ^{1}H NMR or after 3 days.

Ring-opening with *L*-valine methyl ester

L-Valine methyl ester (99.4 mg, 0.593 mmol) and potassium carbonate (136.6 mg, 0.988 mmol) were suspended in water (2 mL). The free amino acid was extracted with diethyl ether (3 x 6 mL). The organic phase was dried with $MgSO_4$, filtrated and dried *in vacuo*. Immediately the free amino acid was diluted in trifluoroethanol (1 mL). Then the epoxide **4b** (36.9 mg, 0.150 mmol) was added. The reaction was monitored by TLC every 10 minutes and was ended when the epoxide spot disappeared.[25]

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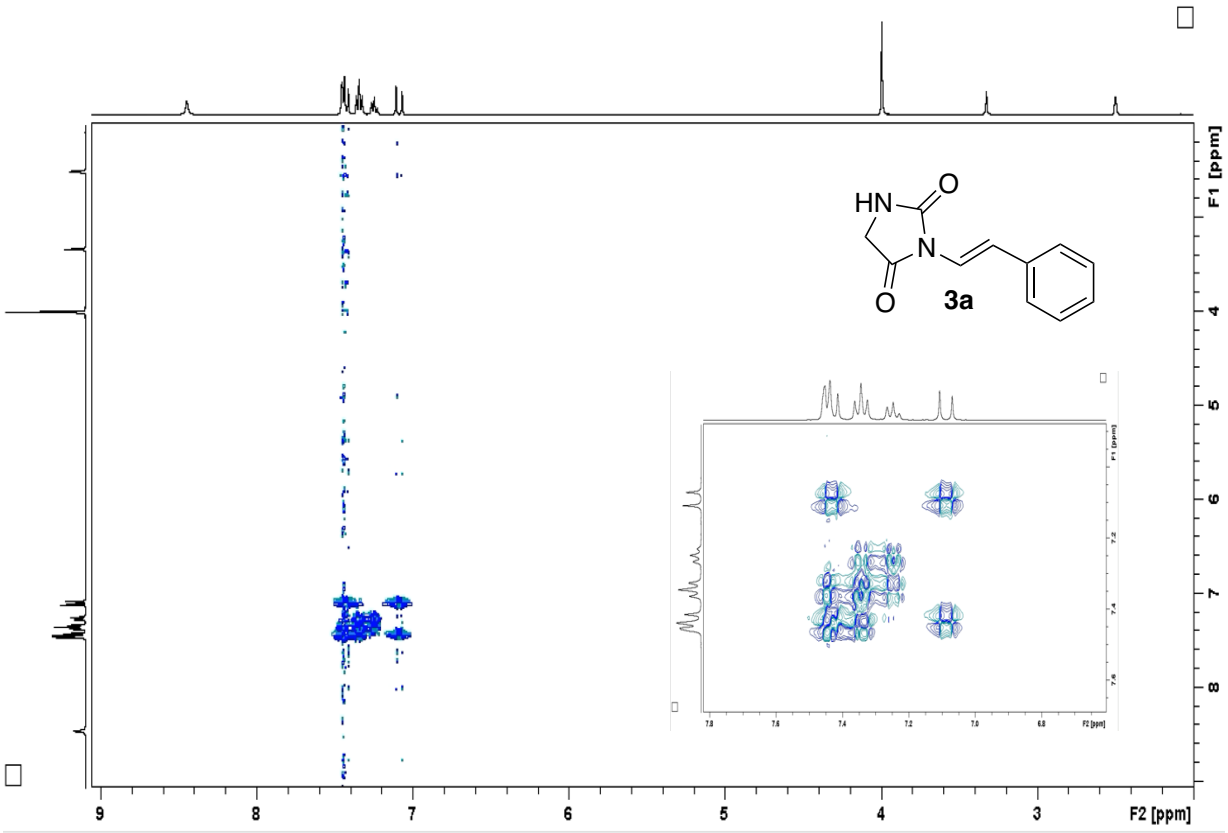
Appendix

The appendix contains supplementary spectroscopic data acquired for this thesis. It is divided into three sections. Spectra of *N*-3-alkenylhydantoins are located in section A, spectra of *N*-3-epoxyhydantoins in section B, and crude spectra from the epoxide ring-openings in section C. In section D it is given examples of calculations of E-factor, AE, experimental yield and NMR yield.

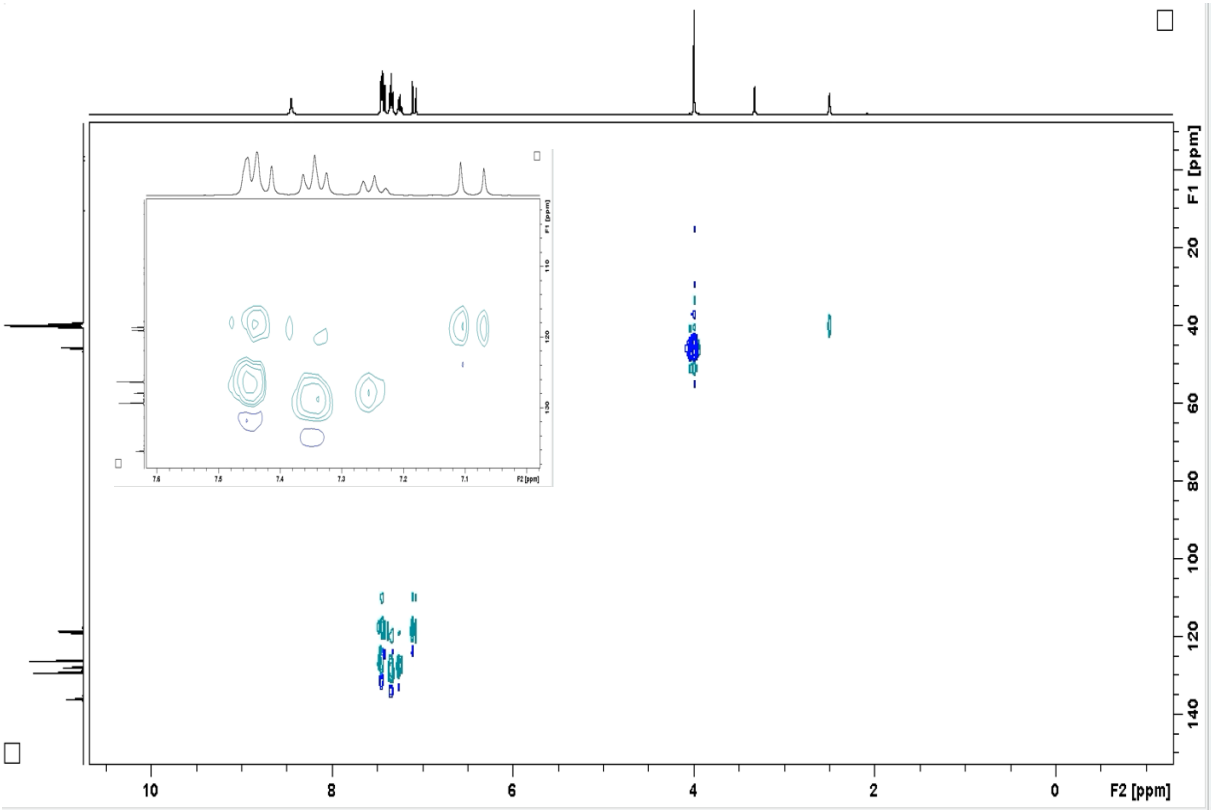
A. Spectroscopic data of the *N*-3-alkenylhydantoins

(*E*)-3-styrylhydantoin (3a)

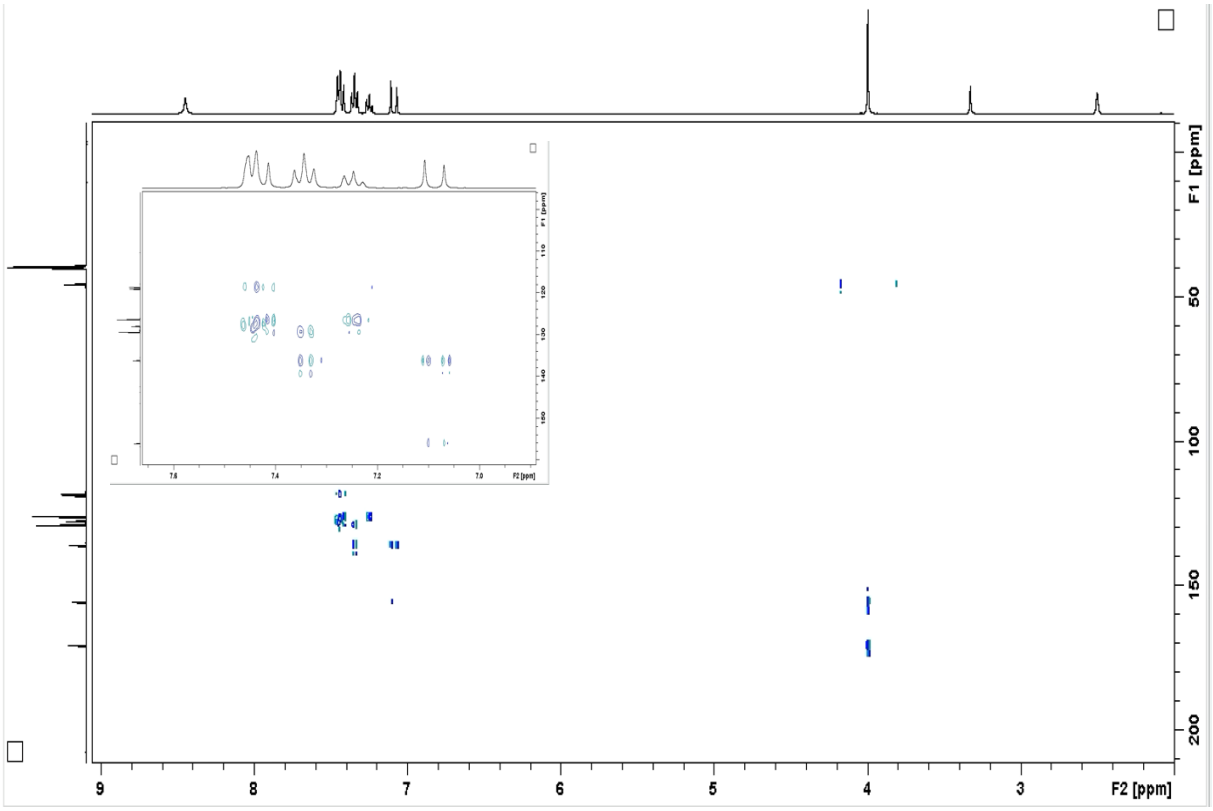
COSY(400 MHz, DMSO-d_6) spectrum of **3a**



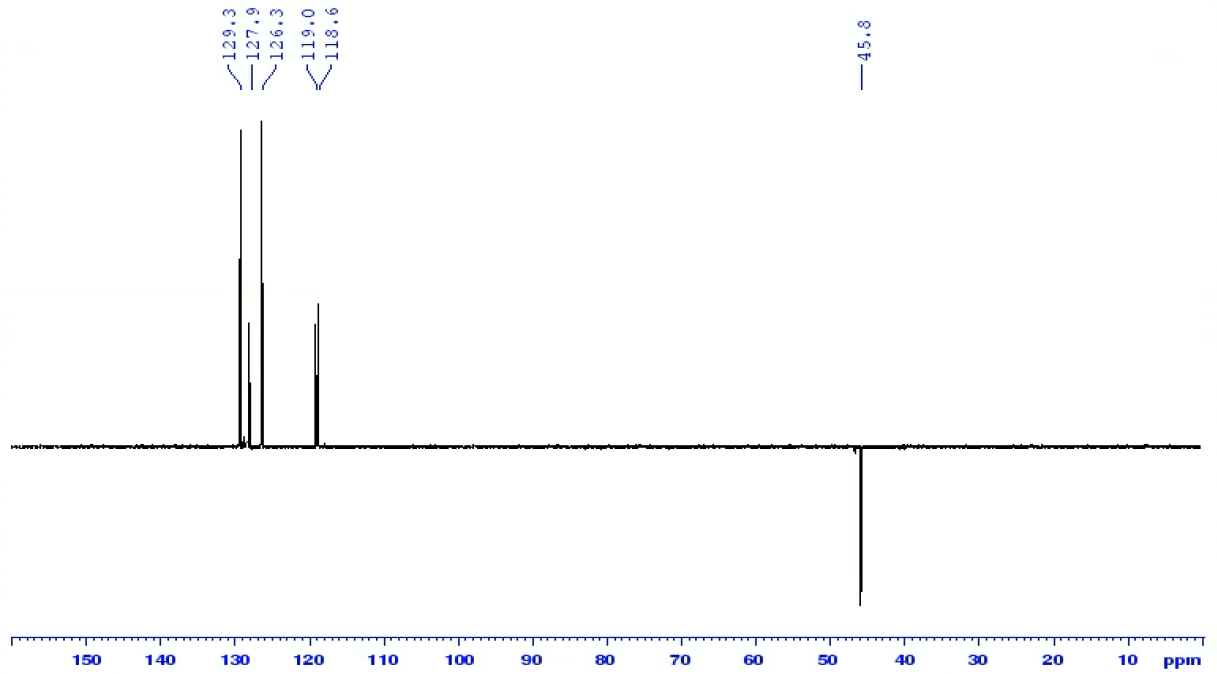
HSQC (400 MHz, DMSO-d_6) spectrum of **3a**



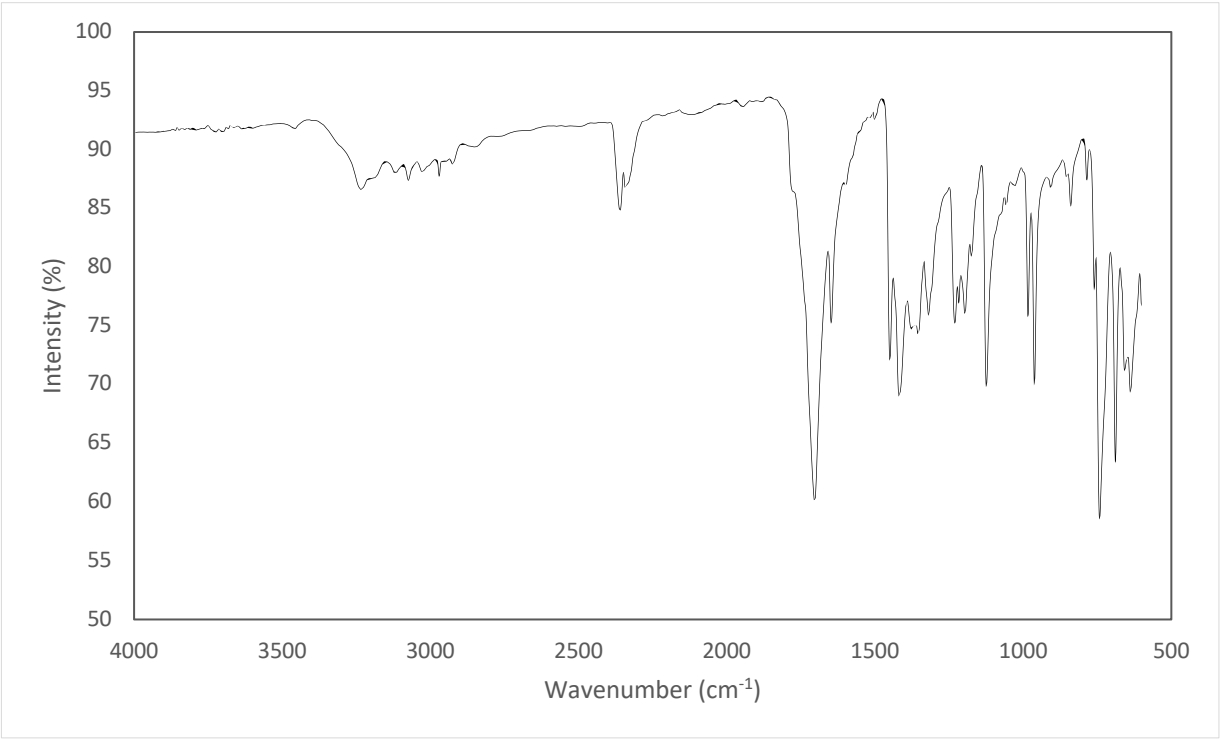
HMBC (400 MHz, DMSO-d_6) spectrum of **3a**



DEPT135 (101 MHz, DMSO-d_6) spectrum of **3a**

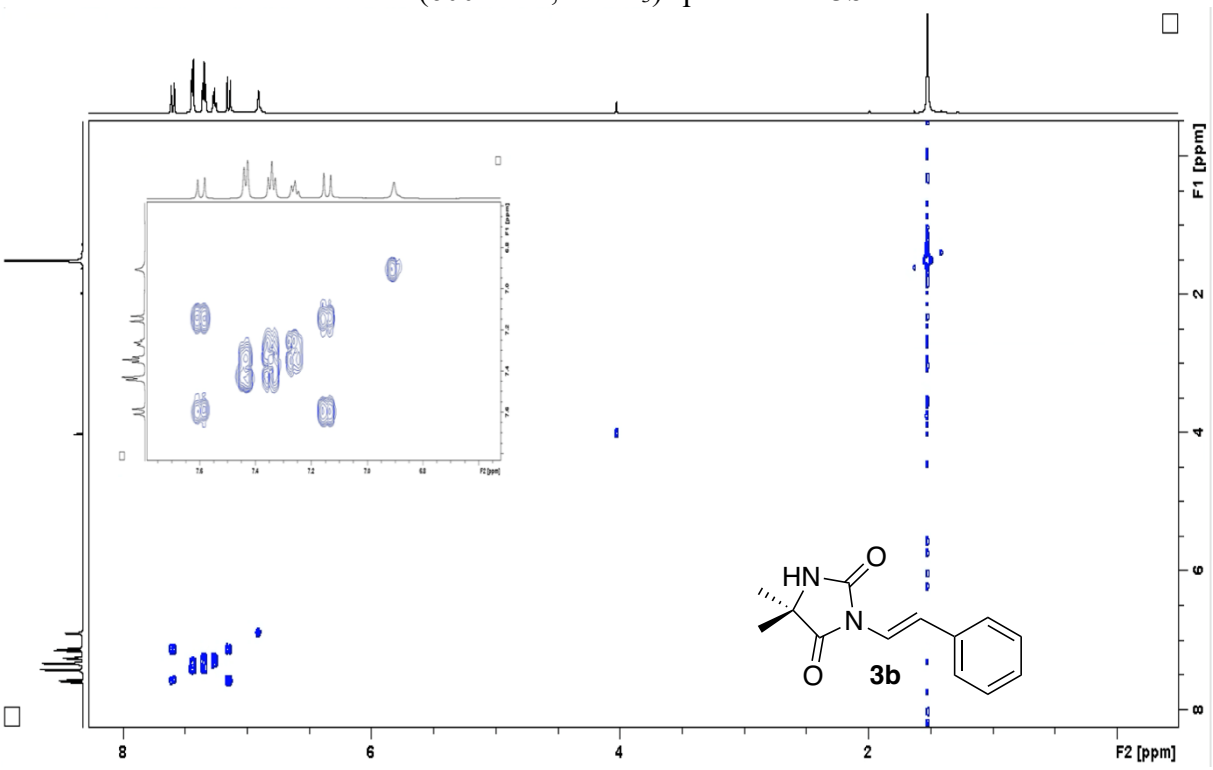


IR-spectrum of **3a**

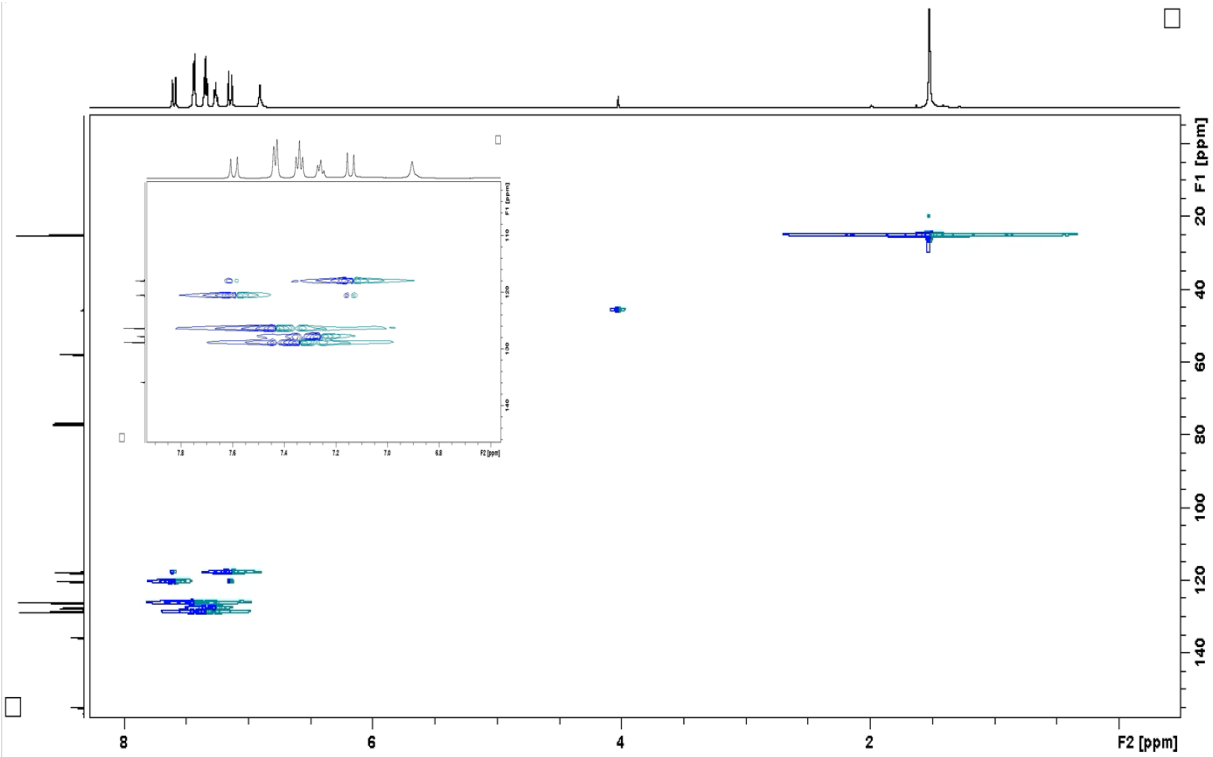


(*E*)-5,5-dimethyl-3-styrylhydantoin (3b)

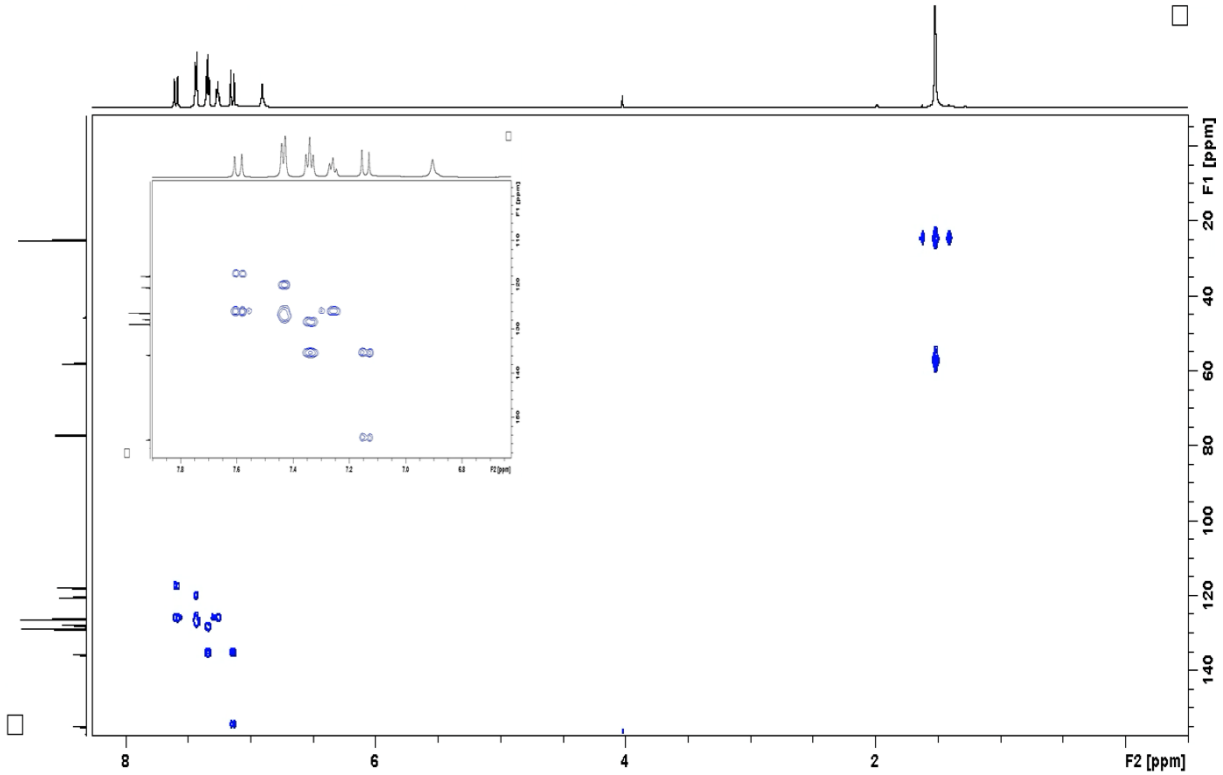
COSY (600 MHz, $CDCl_3$) spectrum of **3b**



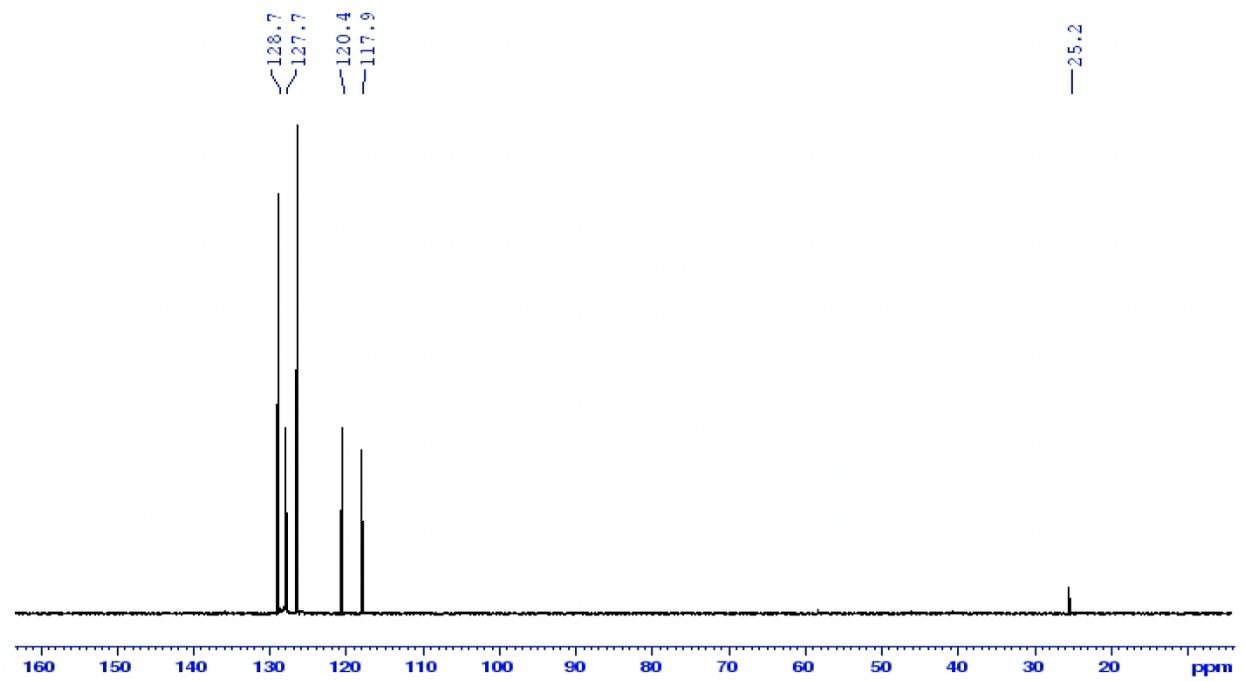
HSQC (600 MHz, $CDCl_3$) spectrum of **3b**



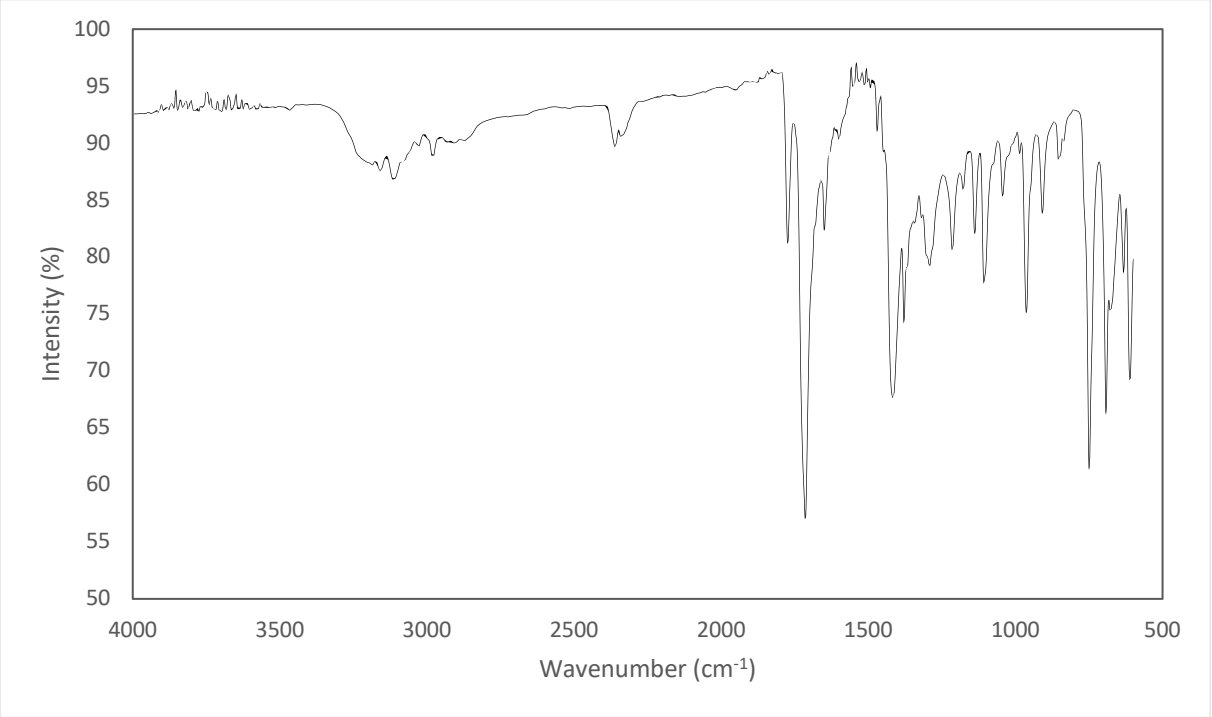
HMBC (600 MHz, $CDCl_3$) spectrum of **3b**



DEPT90 (151 MHz, $CDCl_3$) spectrum of **3b**

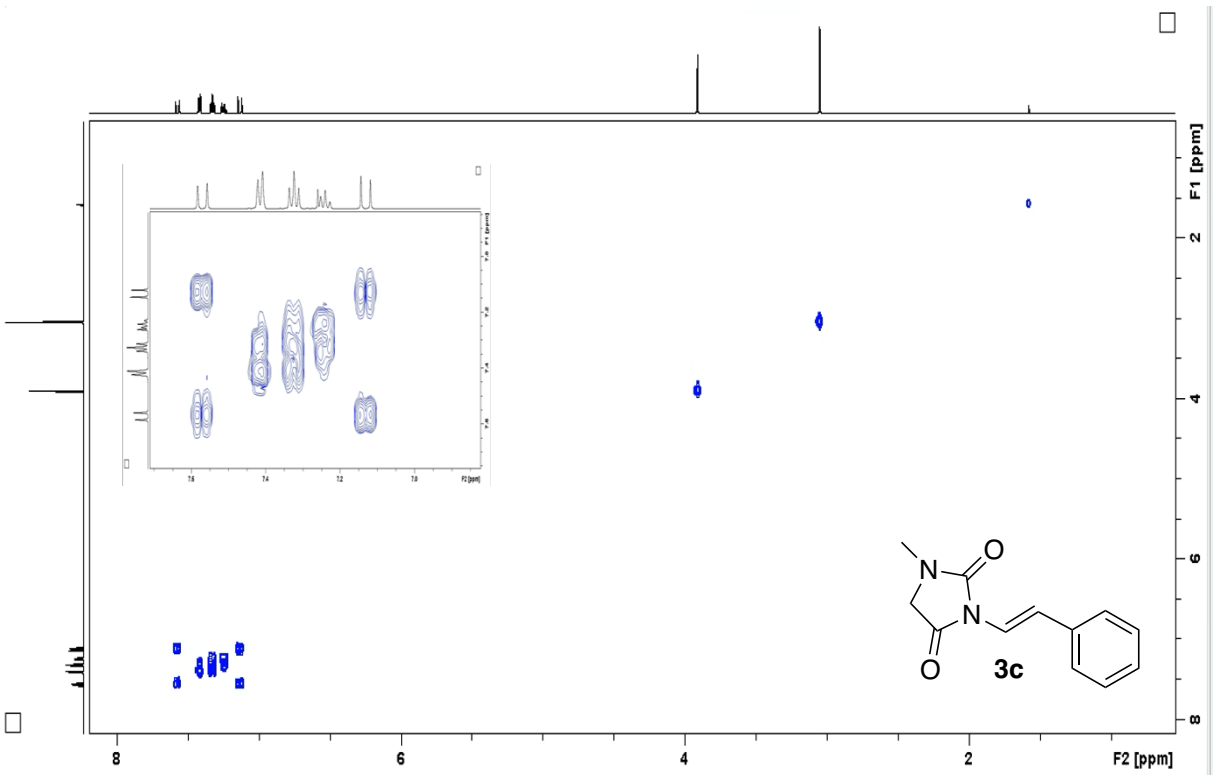


IR-spectrum of **3b**

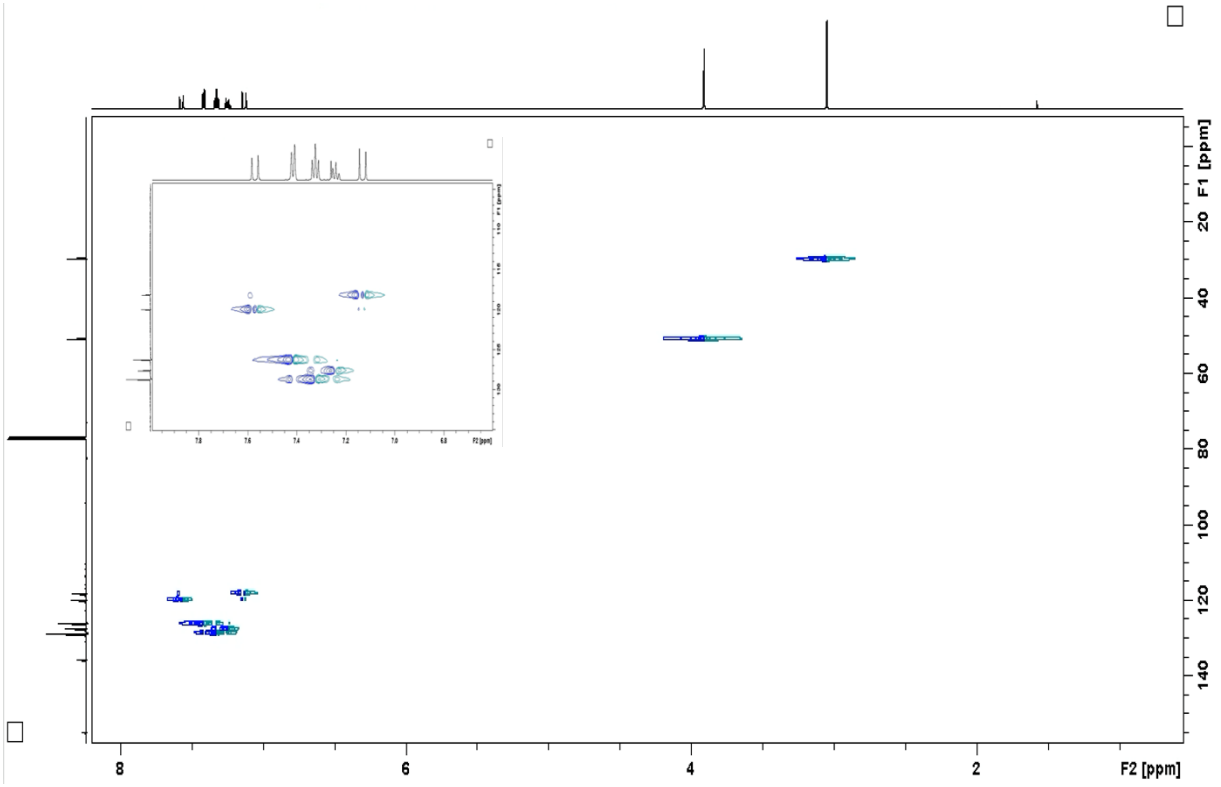


(*E*)-1-methyl-3-styrylhydantoin (3c)

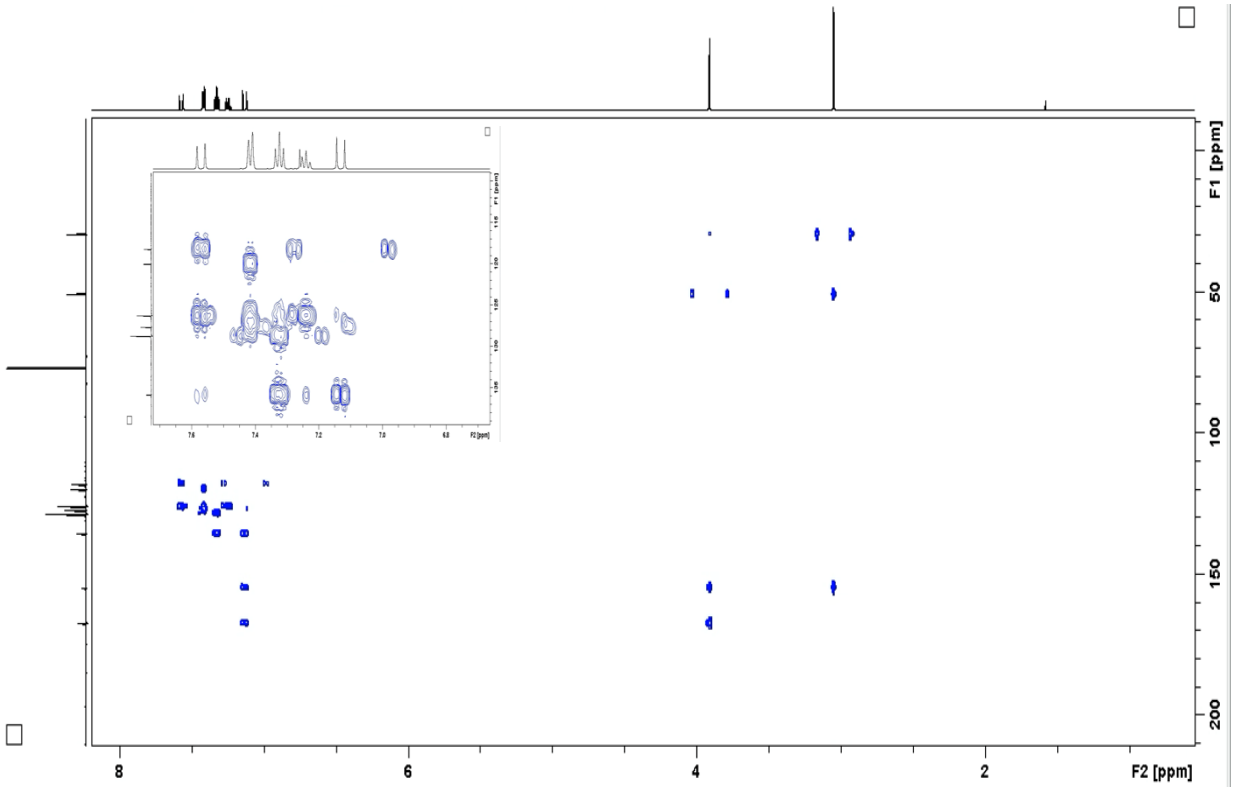
COSY (600 MHz, $CDCl_3$) spectrum of **3c**



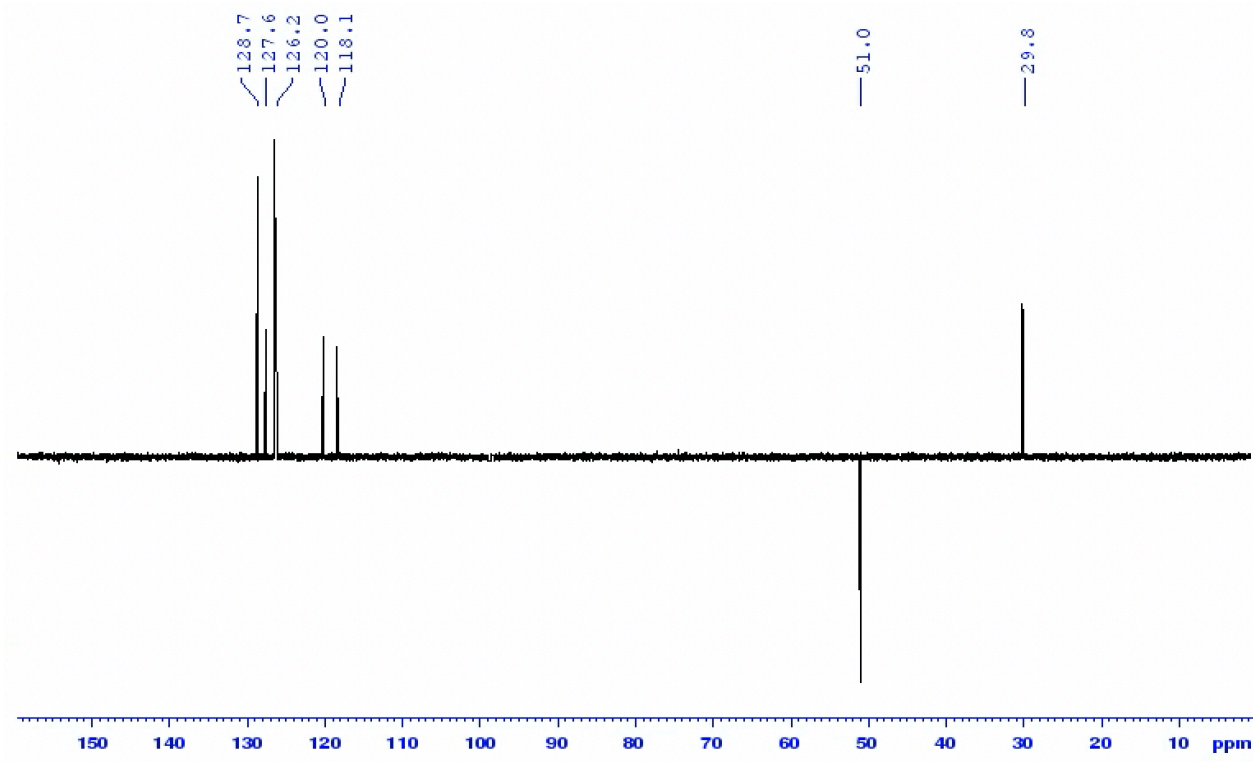
HSQC (600 MHz, $CDCl_3$) spectrum of **3c**



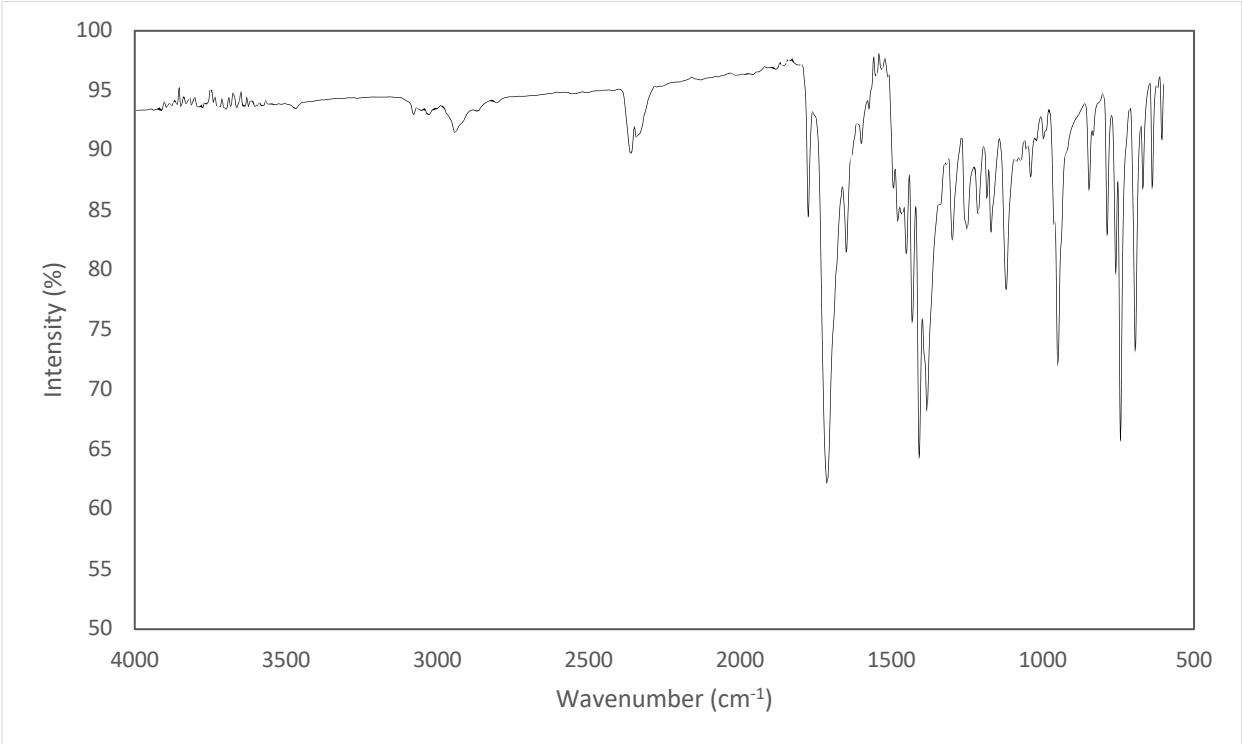
HMBC (600 MHz, $CDCl_3$) spectrum of **3c**



DEPT135 (151 MHz, $CDCl_3$) spectrum of **3c**

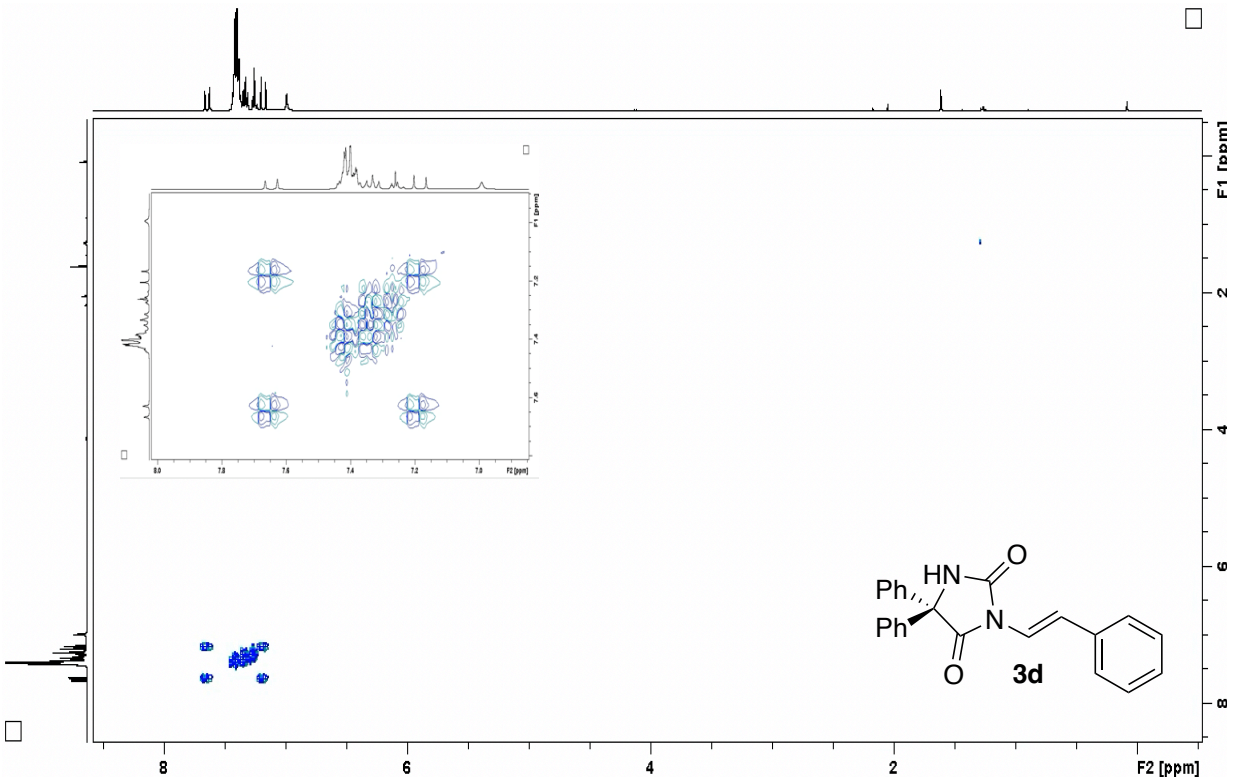


IR-spectrum of **3c**

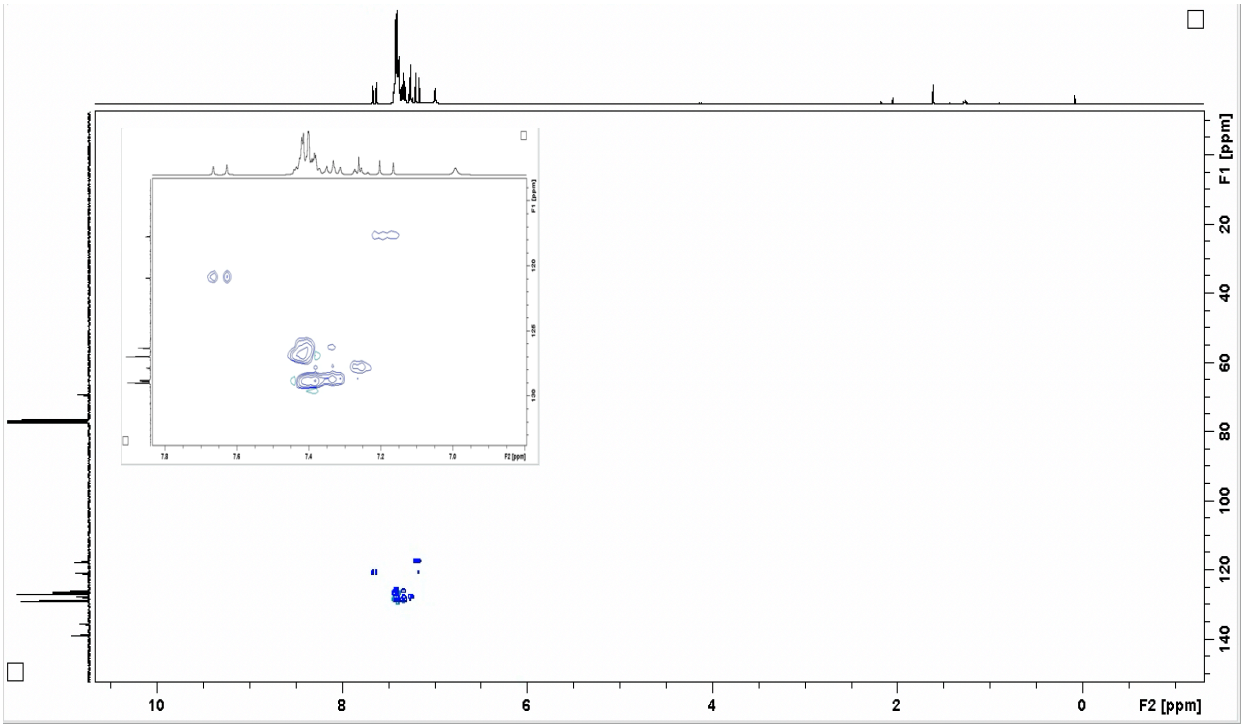


(*E*)-5,5-diphenyl-3-styrylhydantoin (3d)

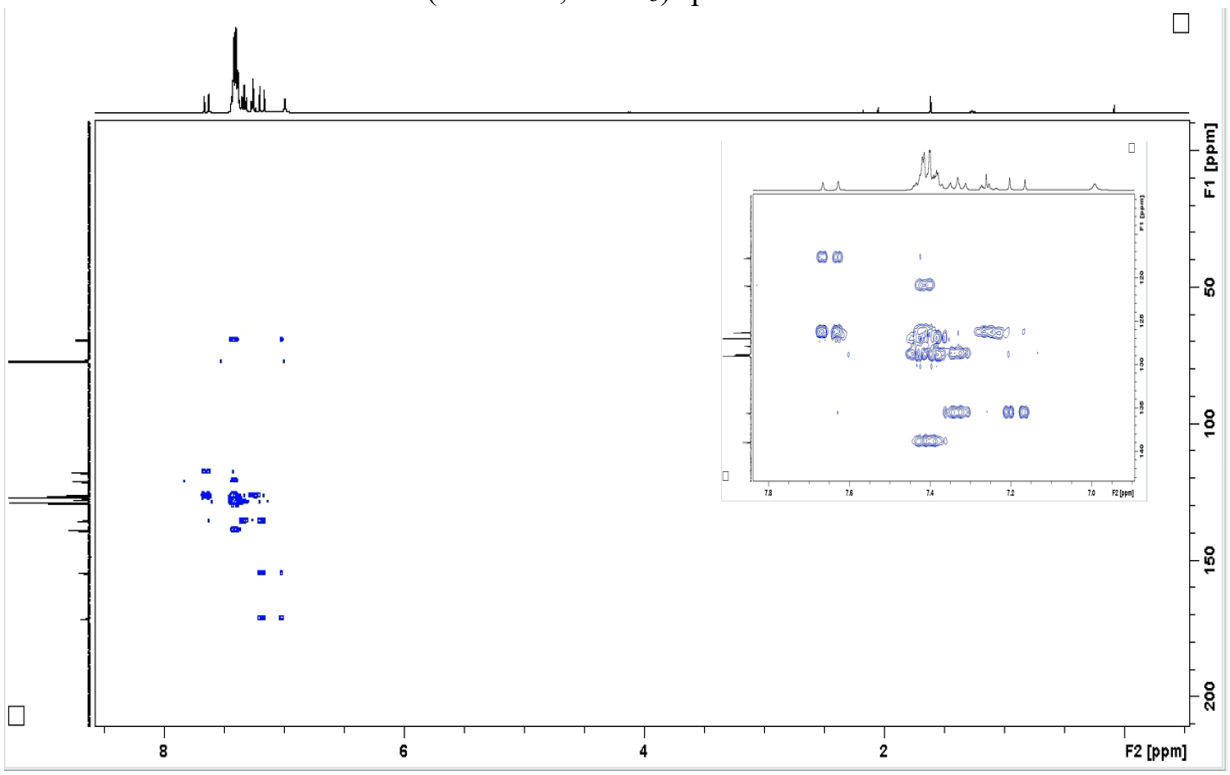
COSY (600 MHz, $CDCl_3$) spectrum of **3d**



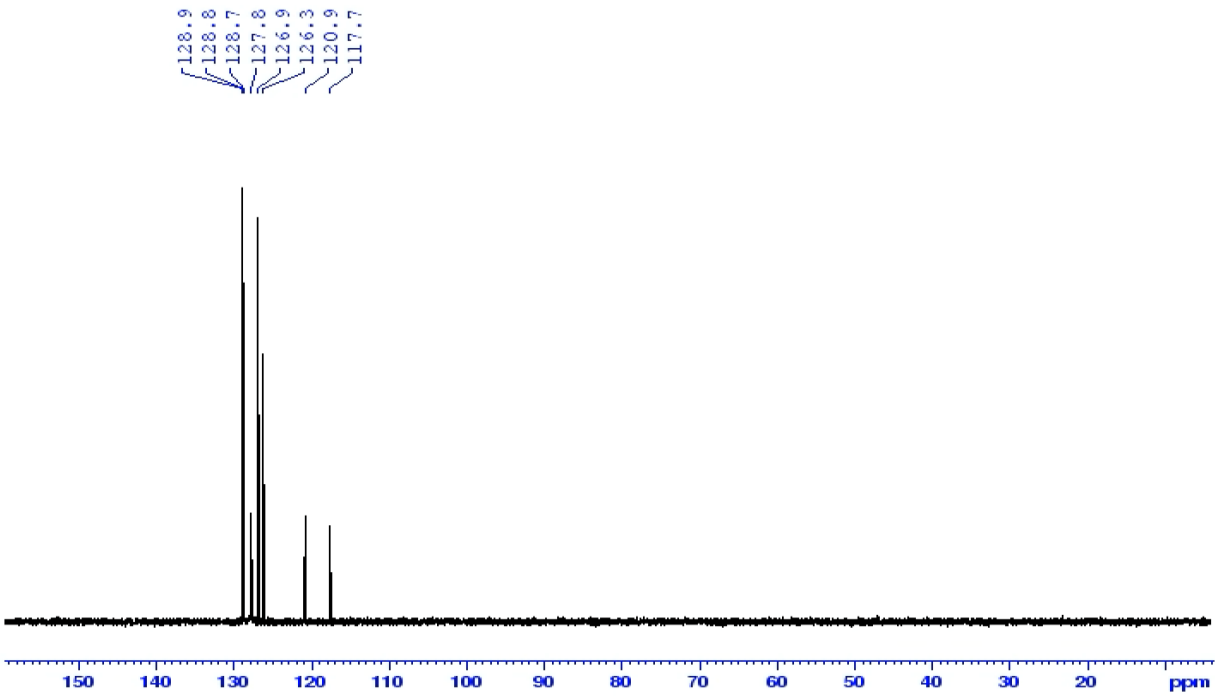
HSQC (600 MHz, $CDCl_3$) spectrum of **3d**



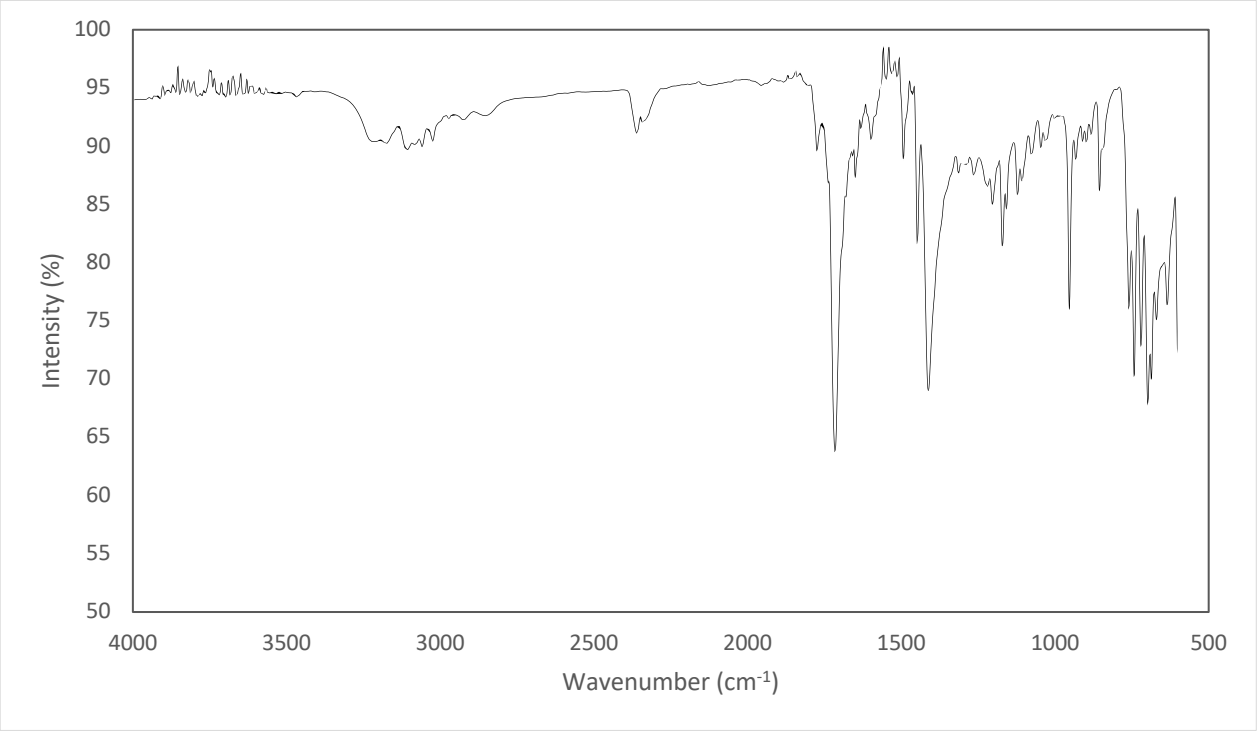
HMBC (600 MHz, $CDCl_3$) spectrum of **3d**



DEPT135 (151 MHz, $CDCl_3$) spectrum of **3d**

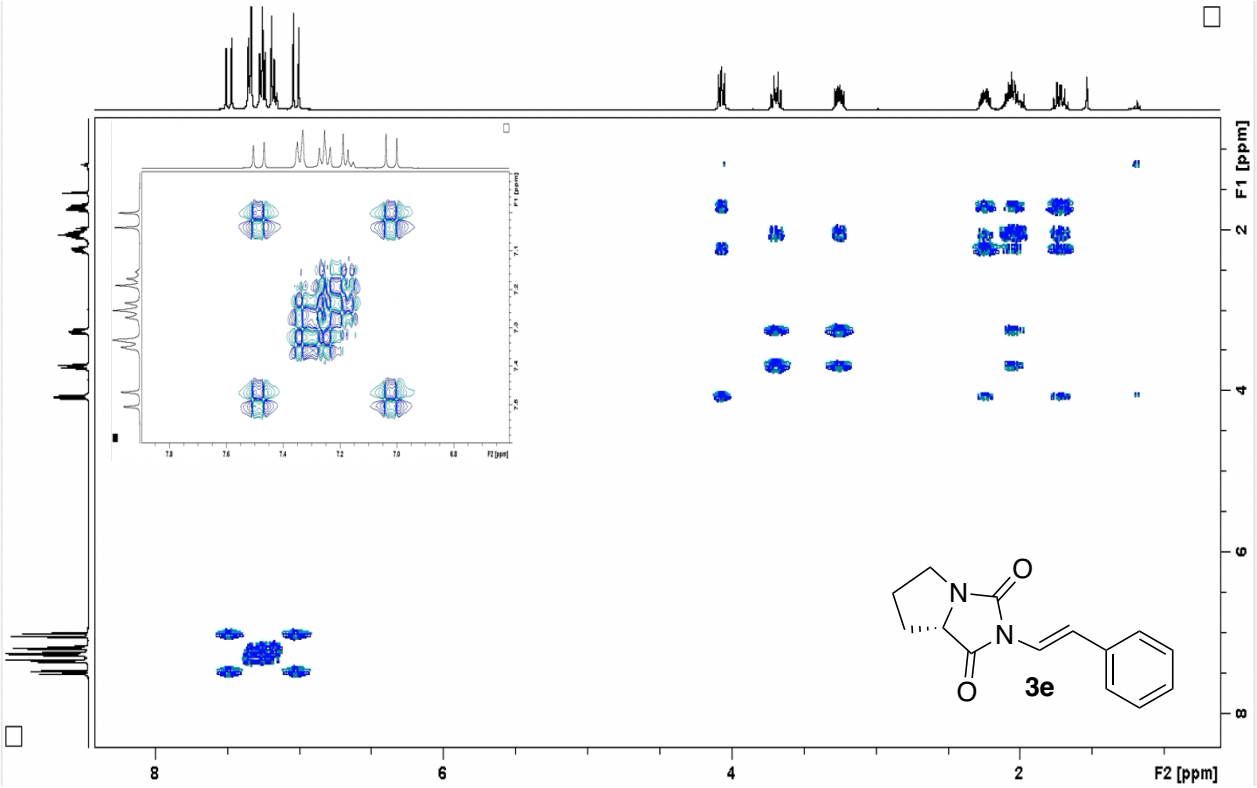


IR-spectrum of **3d**

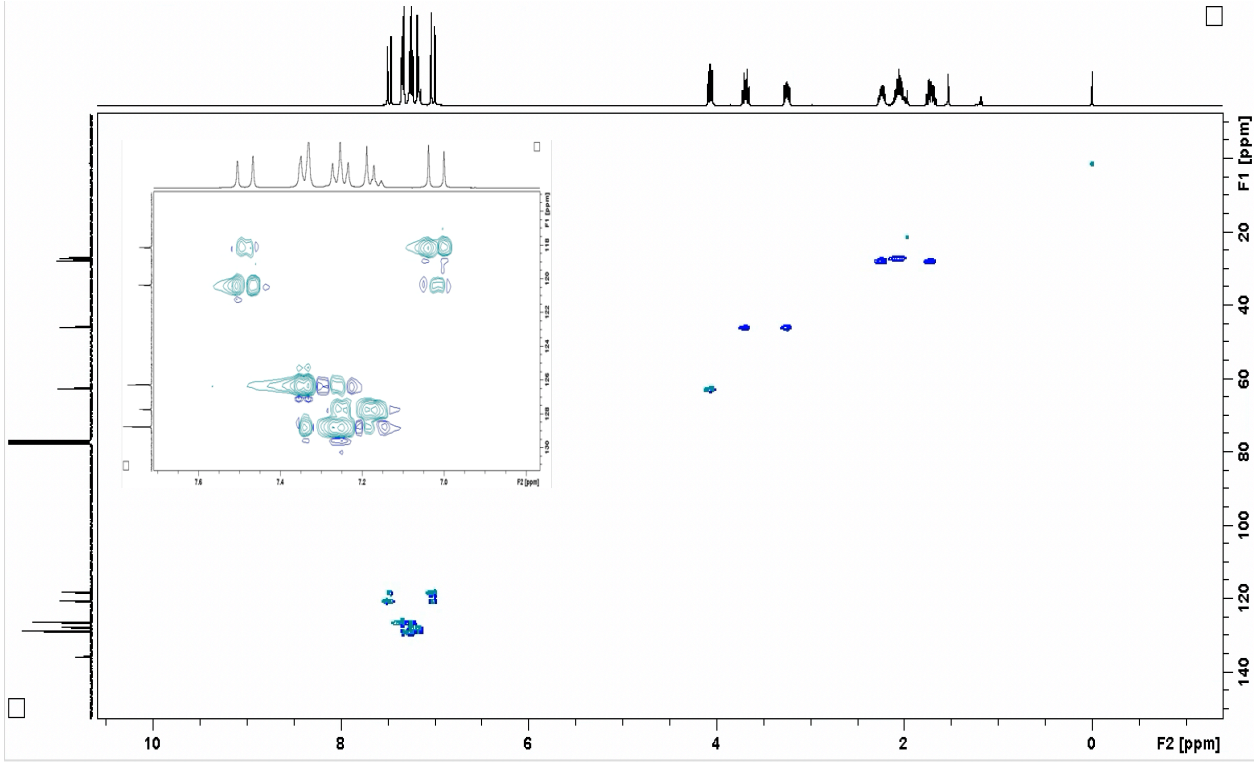


(*S*,*E*)-2-styryltetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1,3(2*H*)-dione (3e)

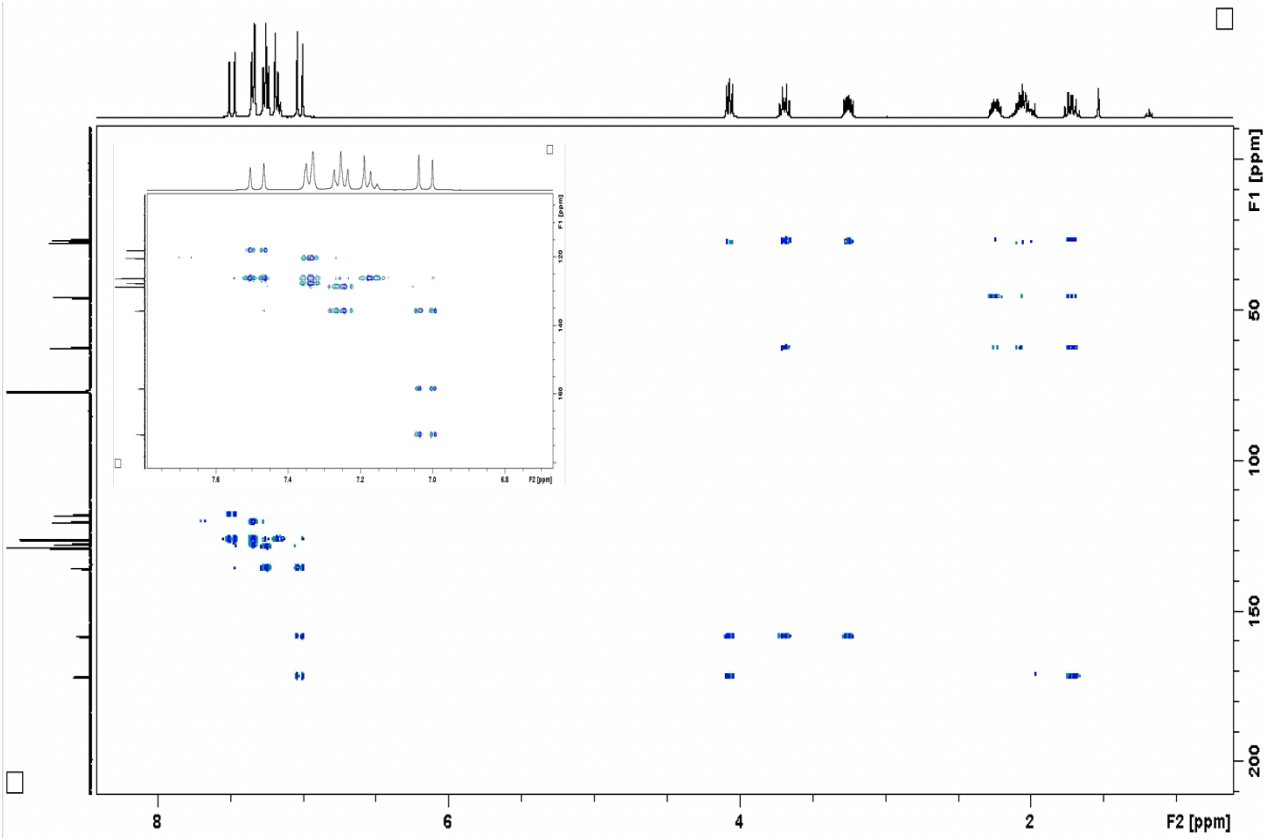
COSY (600 MHz, $CDCl_3$) spectrum of **3e**



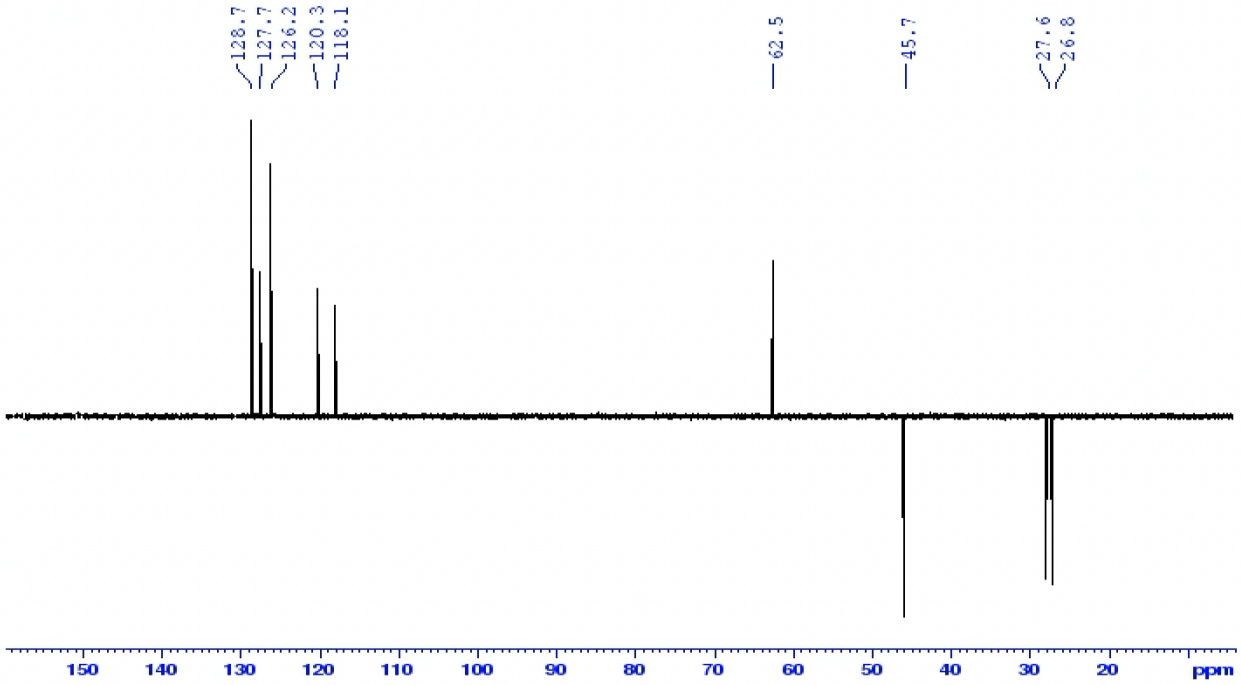
HSQC (600 MHz, $CDCl_3$) spectrum of **3e**



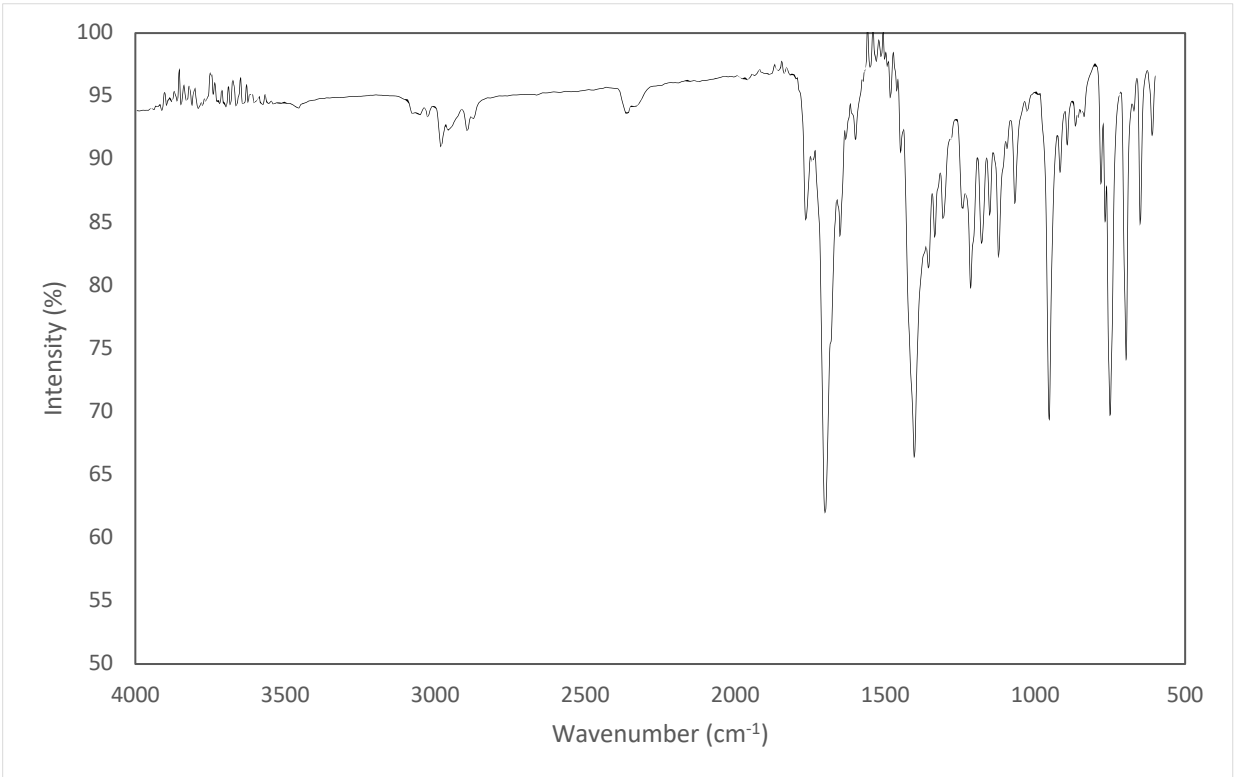
HMBC (600 MHz, $CDCl_3$) spectrum of **3e**



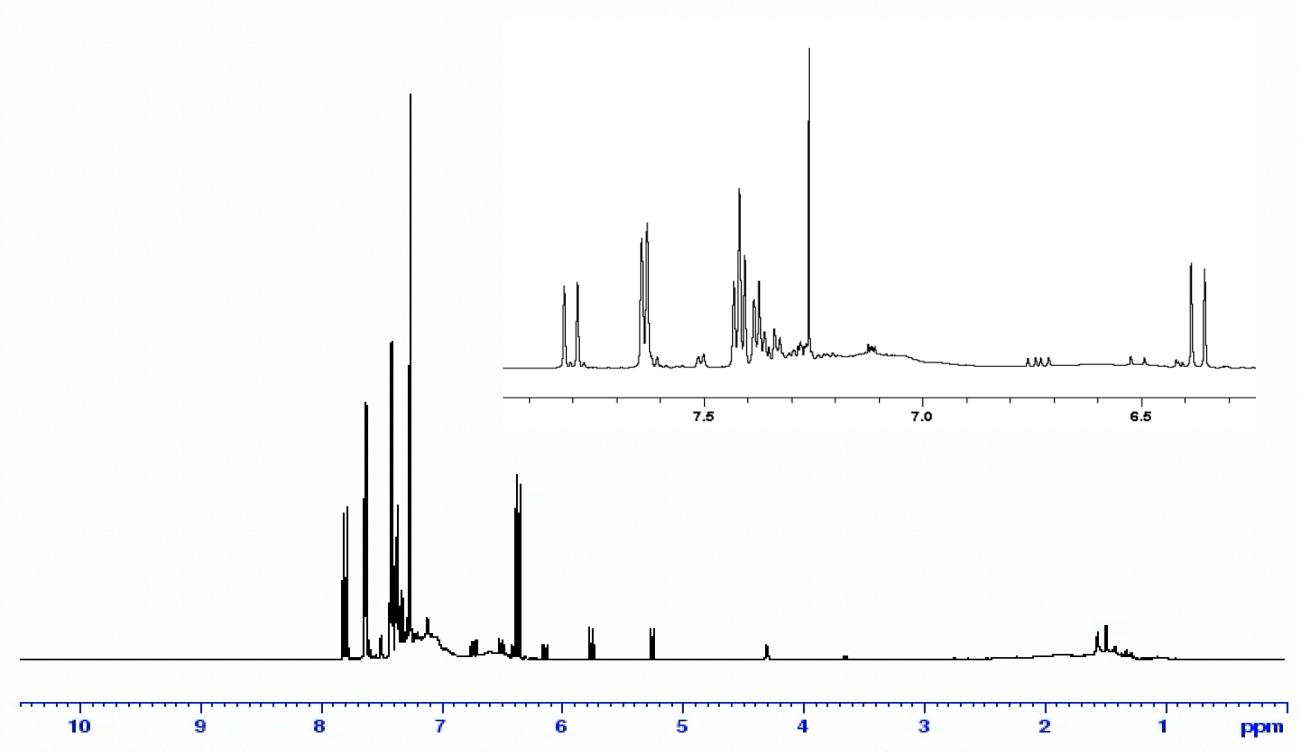
DEPT135 (151 MHz, $CDCl_3$) spectrum of **3e**



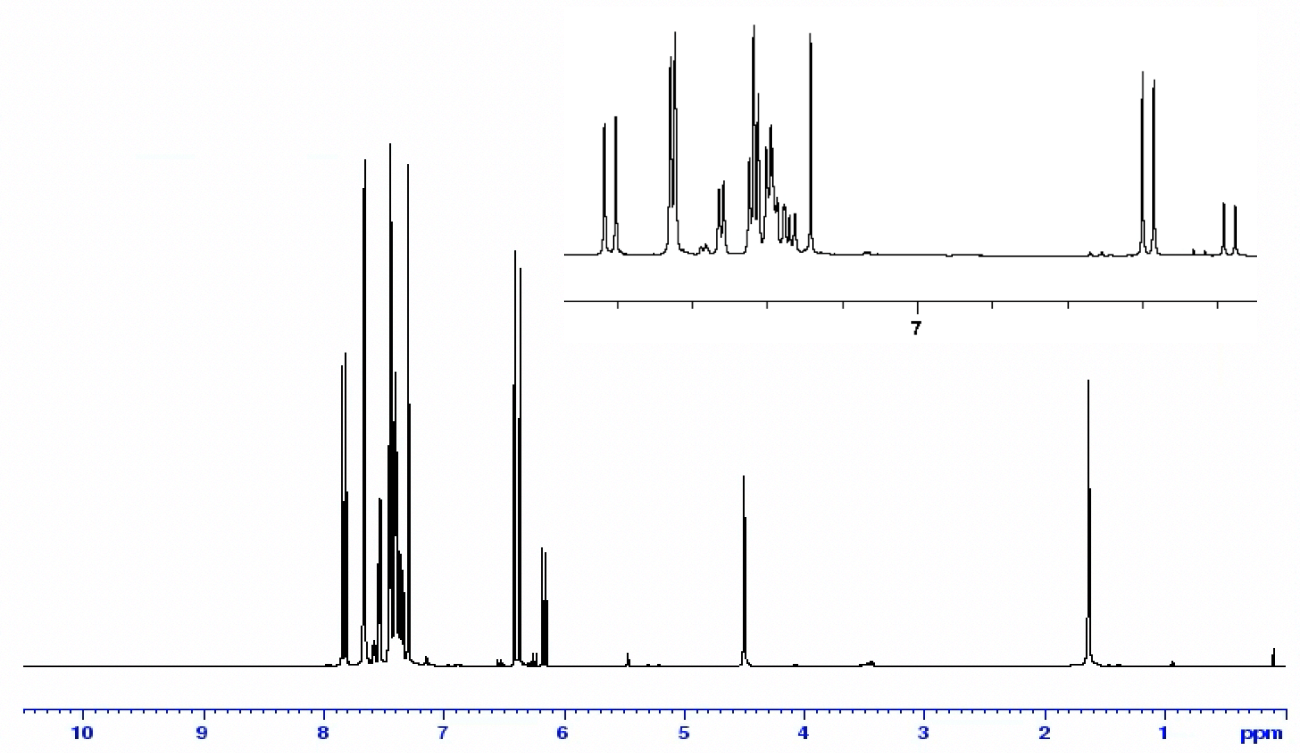
IR-spectrum of **3e**



^{1}H NMR ($CDCl_3$, 600 MHz) spectrum of the (*E*)-Styrylboronic acid (**2**) used in the project



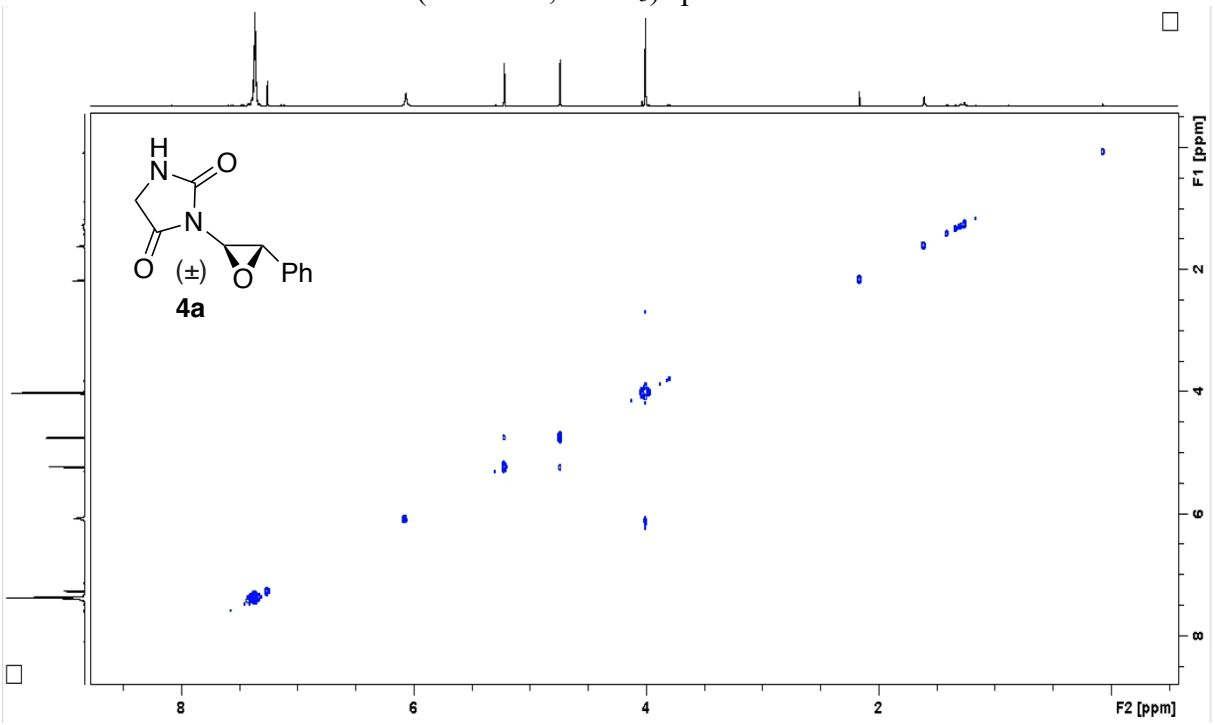
^{1}H NMR ($CDCl_3$, 600 MHz) spectrum of the (*E*)-Styrylboronic acid (**2**) Berntsen et al. used



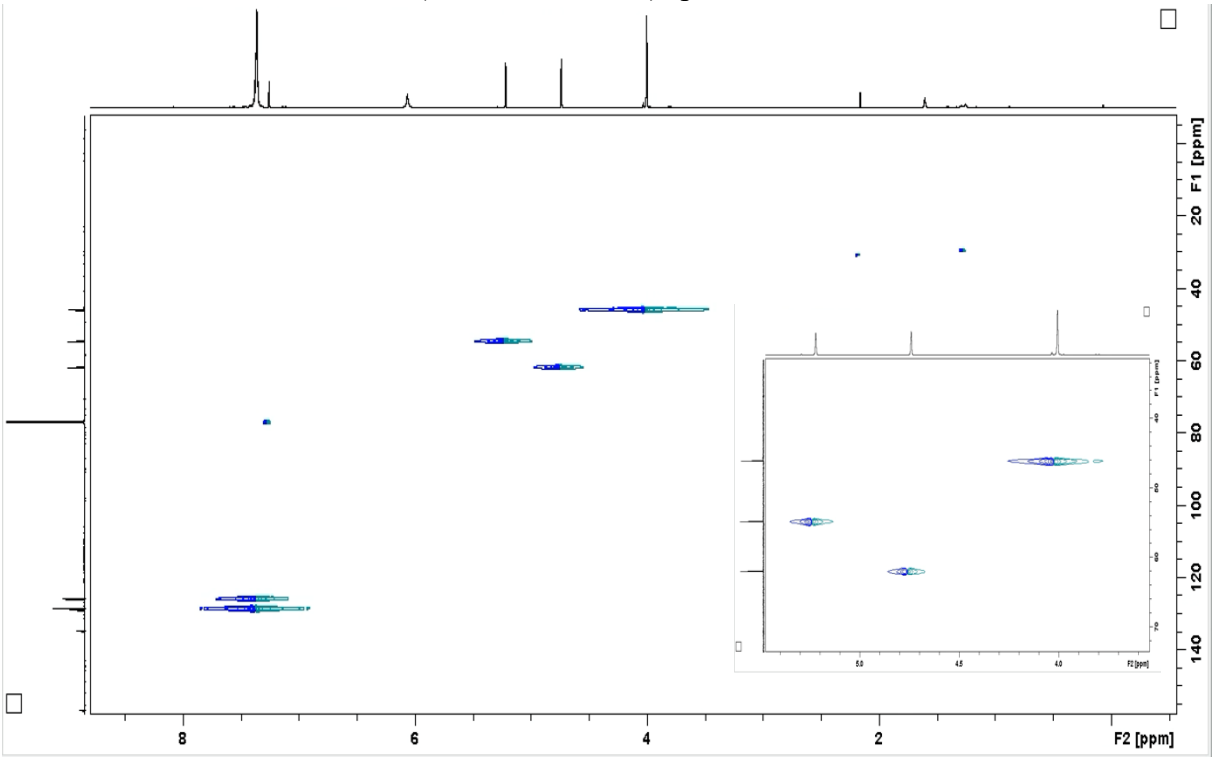
B. Spectroscopic data of the *N*-3-epoxyhydantoins (Method 1)

3-(3-phenylenyloxiran-2-yl)hydantoin (4a)

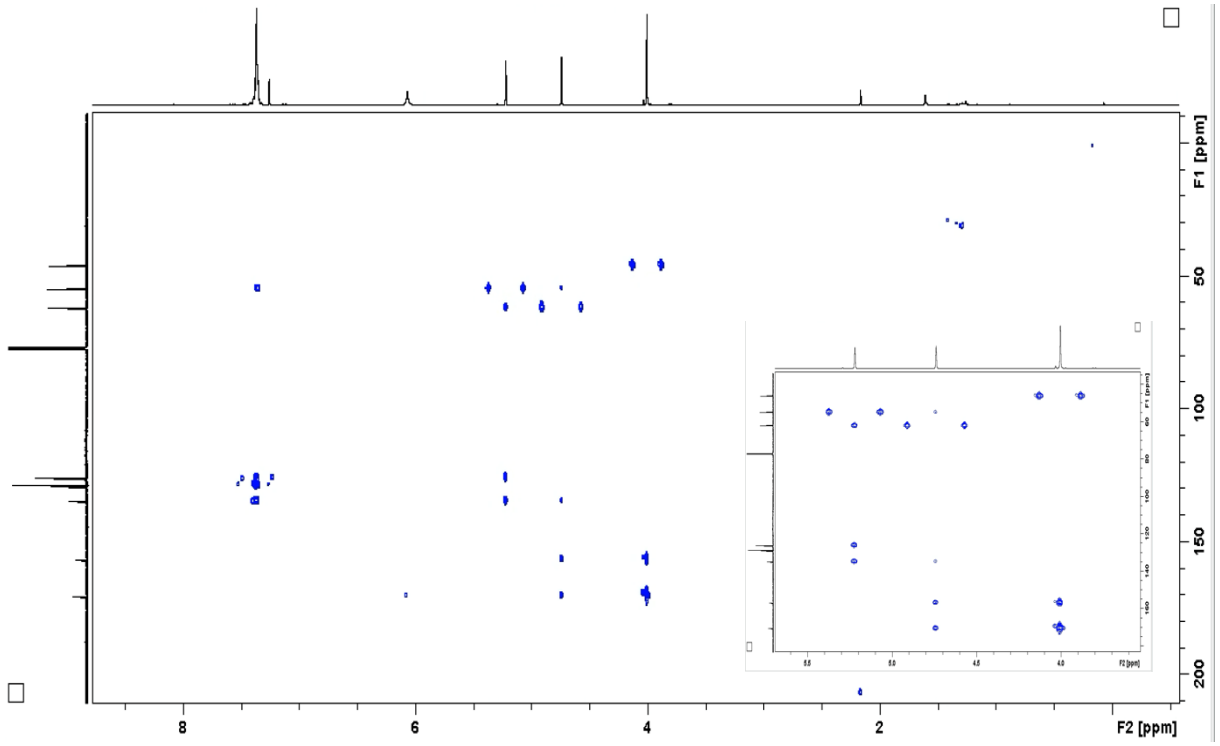
COSY (600 MHz, $CDCl_3$) spectrum of **4a**



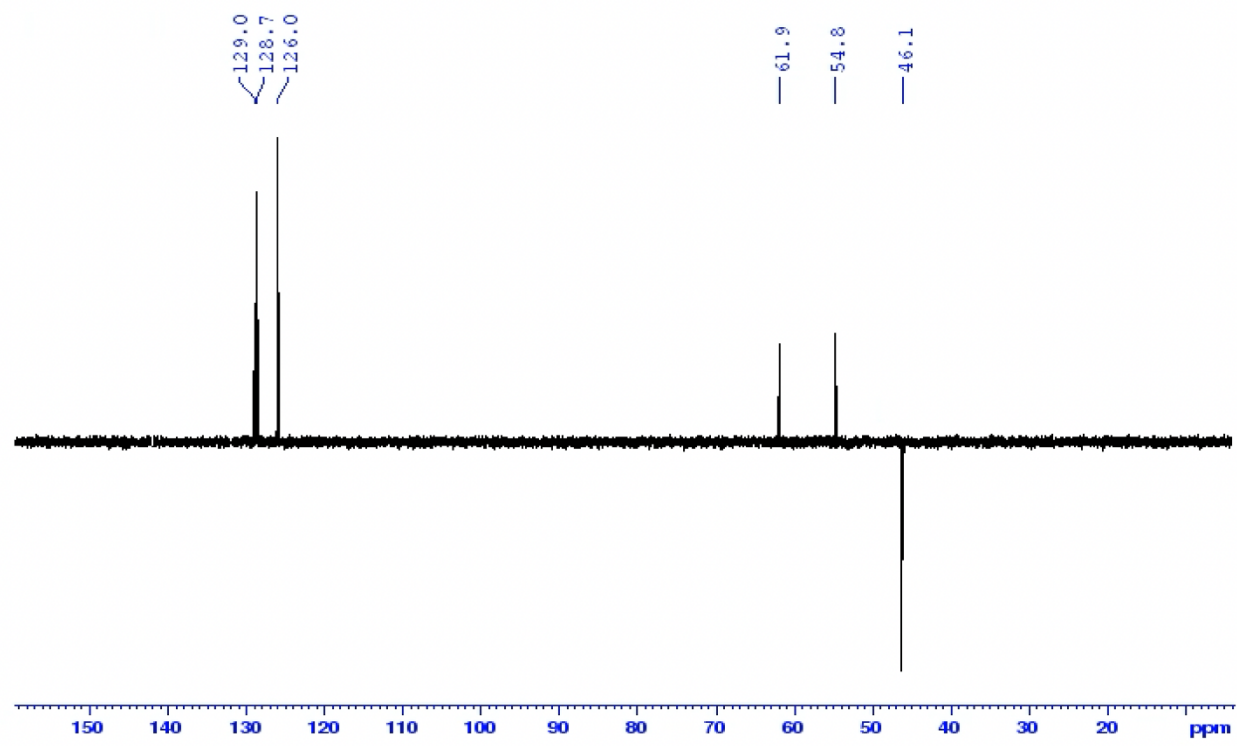
HSQC (600 MHz, $CDCl_3$) spectrum of **4a**



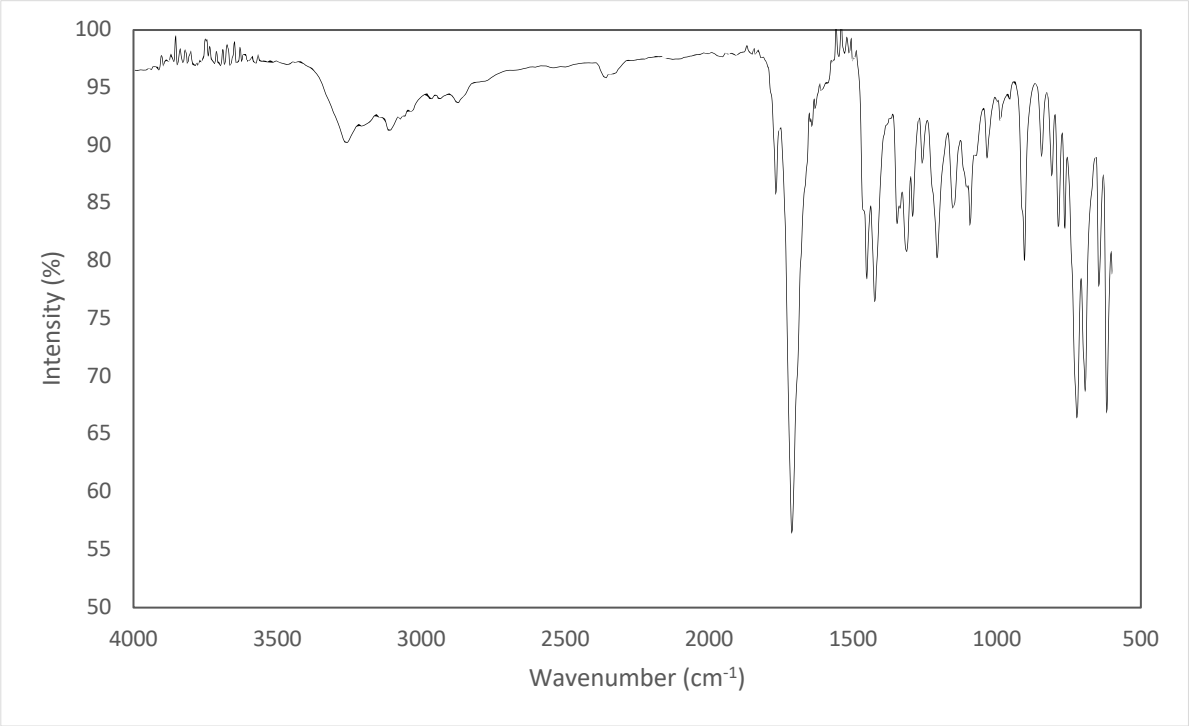
HMBC (600 MHz, $CDCl_3$) spectrum of **4a**



DEPT135 (151 MHz, $CDCl_3$) spectrum of **4a**

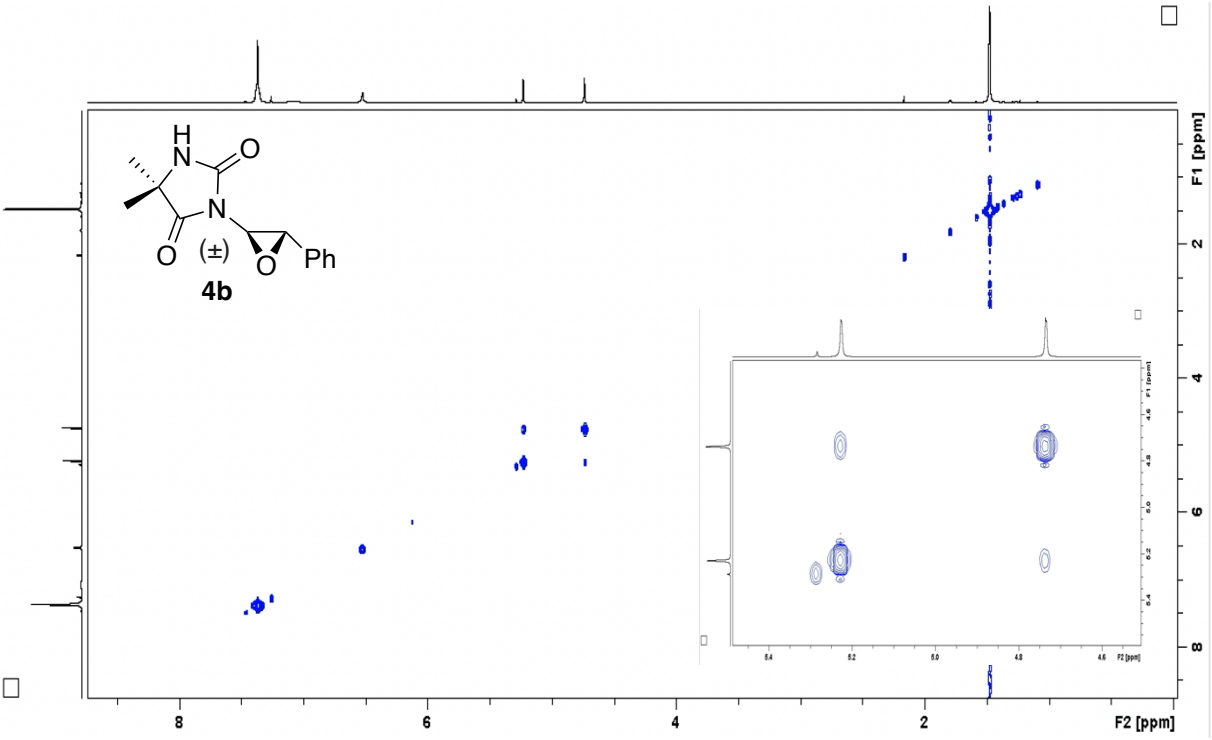


IR-spectrum of **4a**

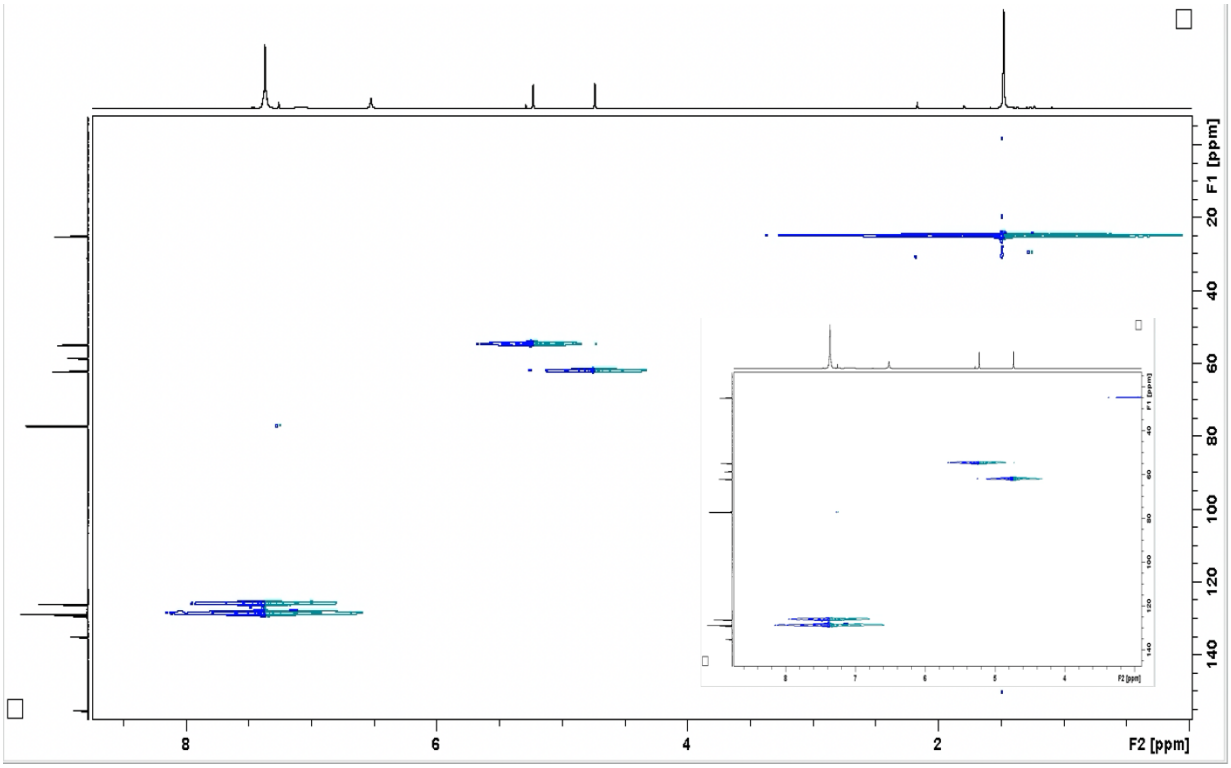


5.5-dimethyl-3-(3-phenyloxiran-2-yl) hydantoin(4b)

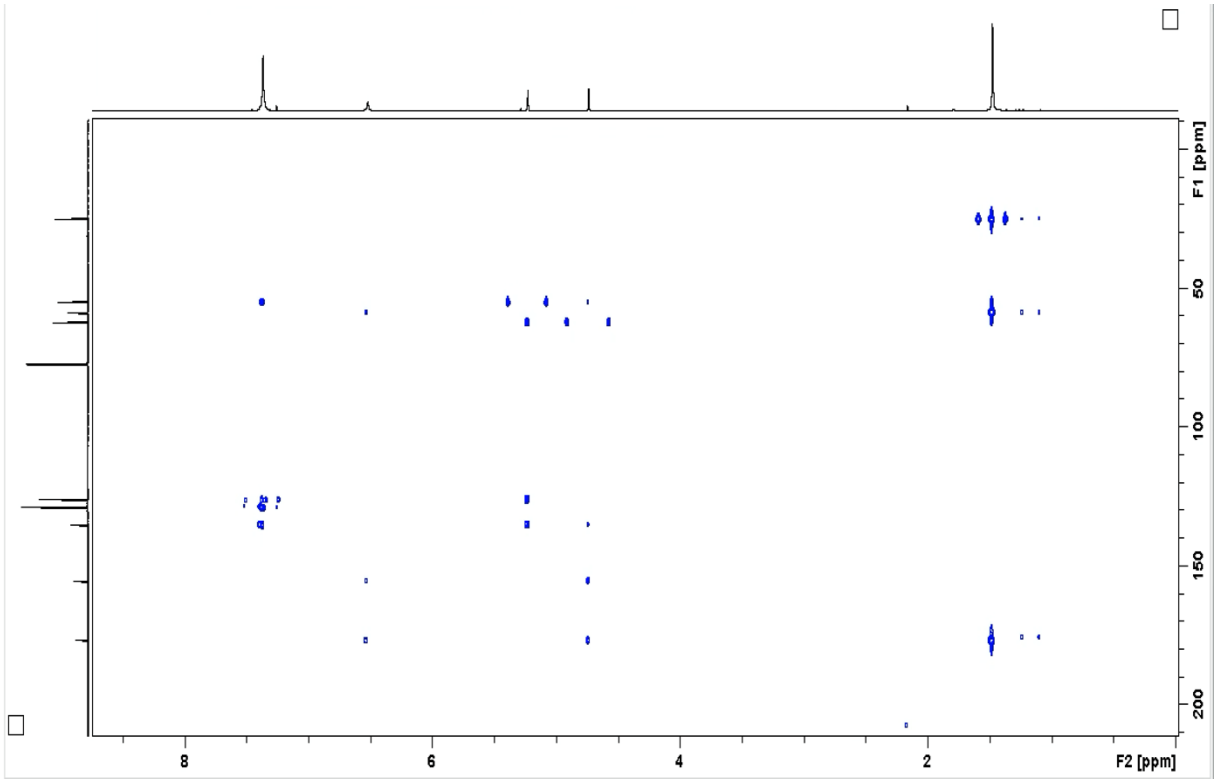
COSY (600 MHz, $CDCl_3$) spectrum of **4b**



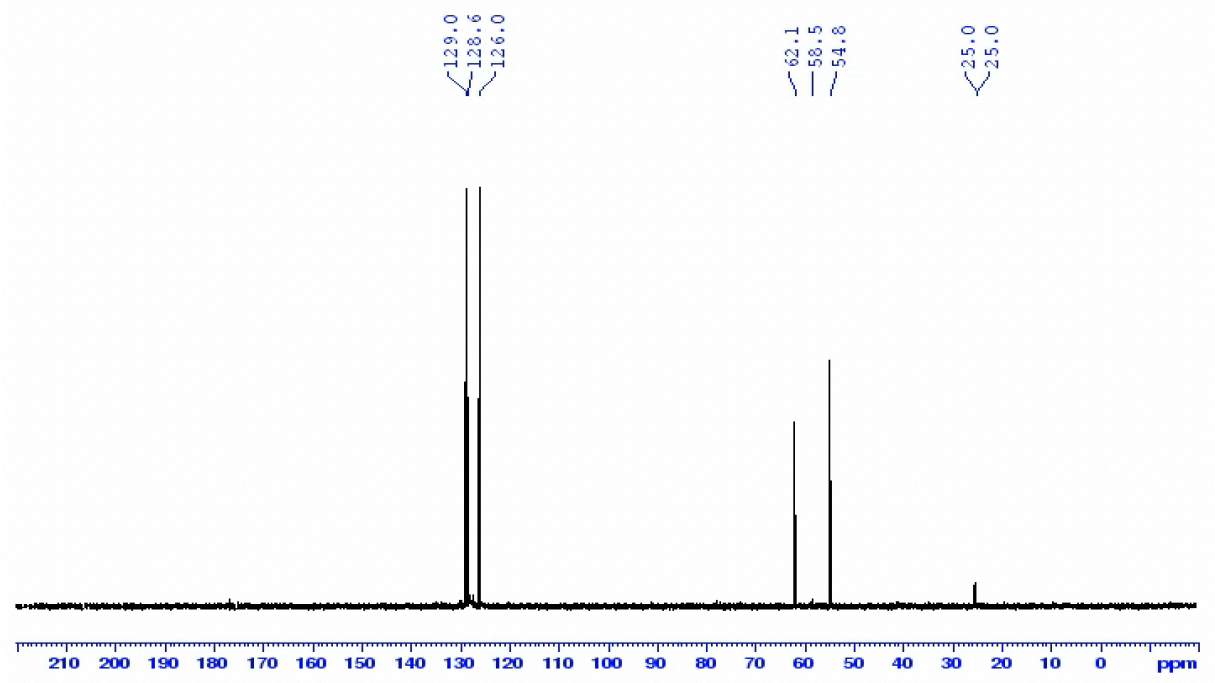
HSQC (600 MHz, $CDCl_3$) spectrum of **4b**



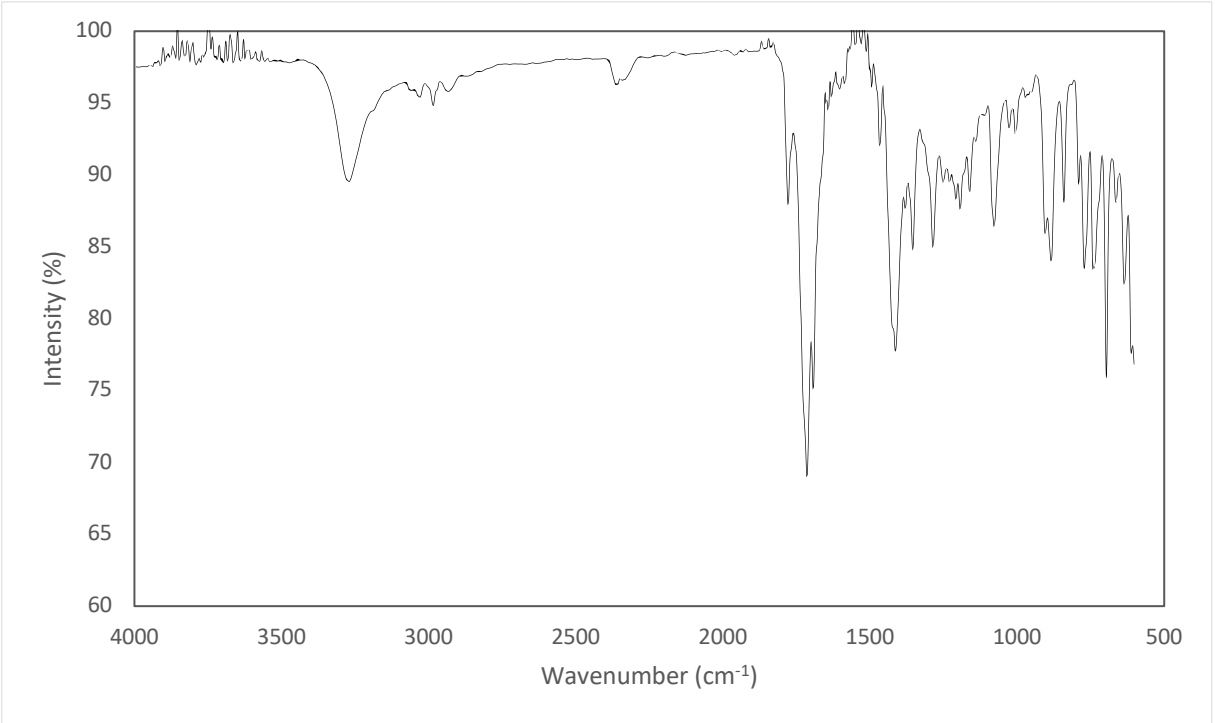
HMBC (600 MHz, $CDCl_3$) spectrum of **4b**



DEPT90 (151 MHz, $CDCl_3$) spectrum of **4b**

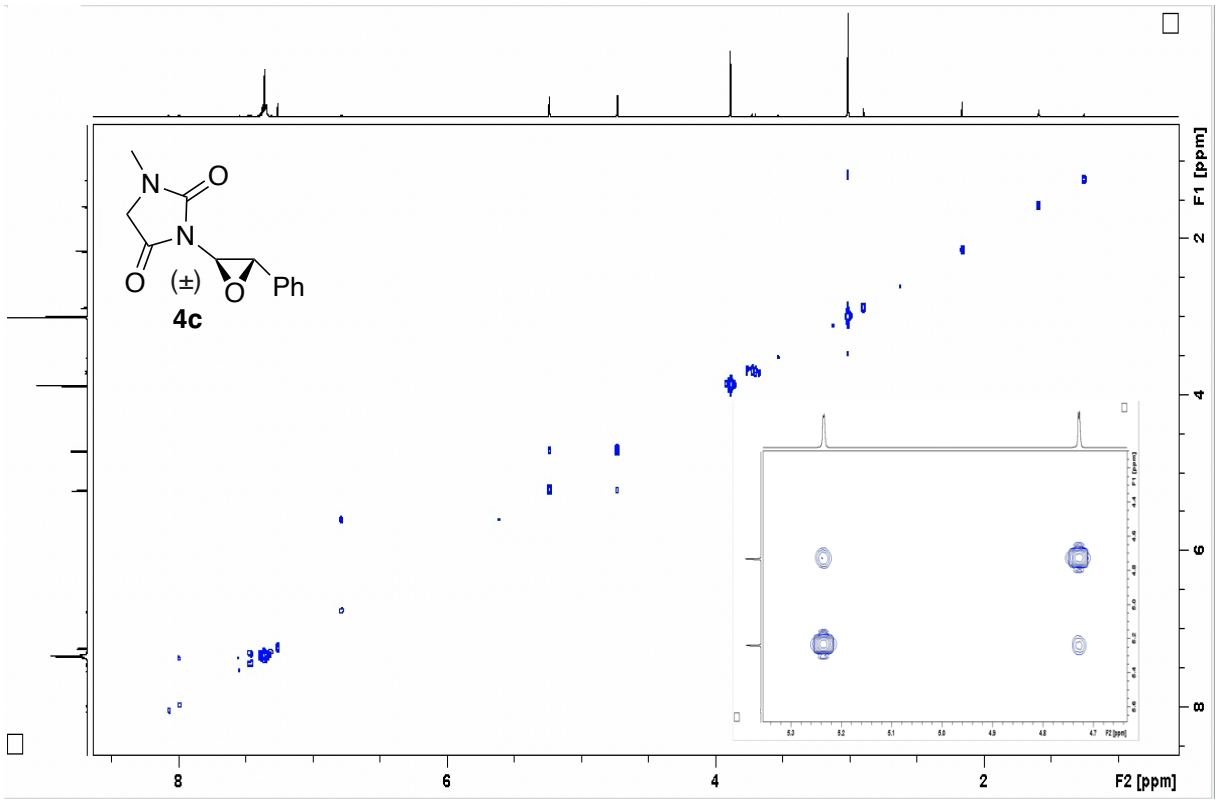


IR-spectrum of **4b**

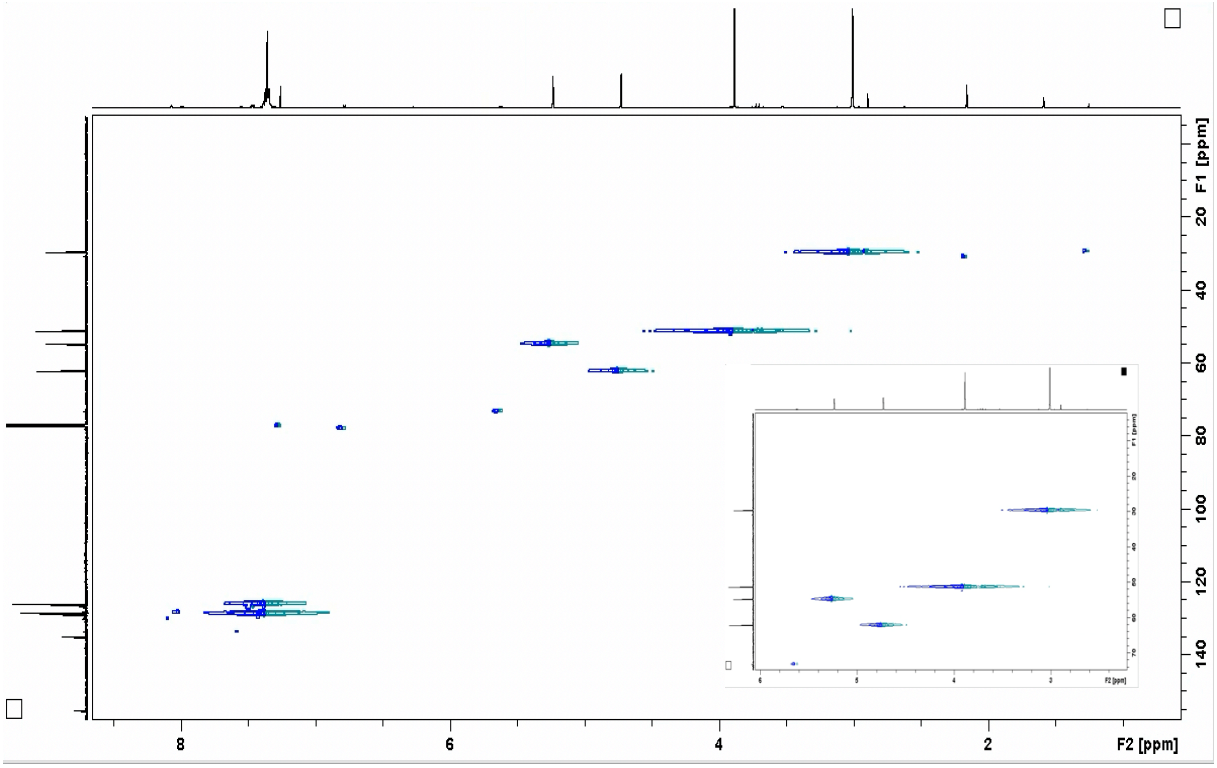


1-methyl-3-(3-phenyloxiran-2-yl)hydantoin (4c)

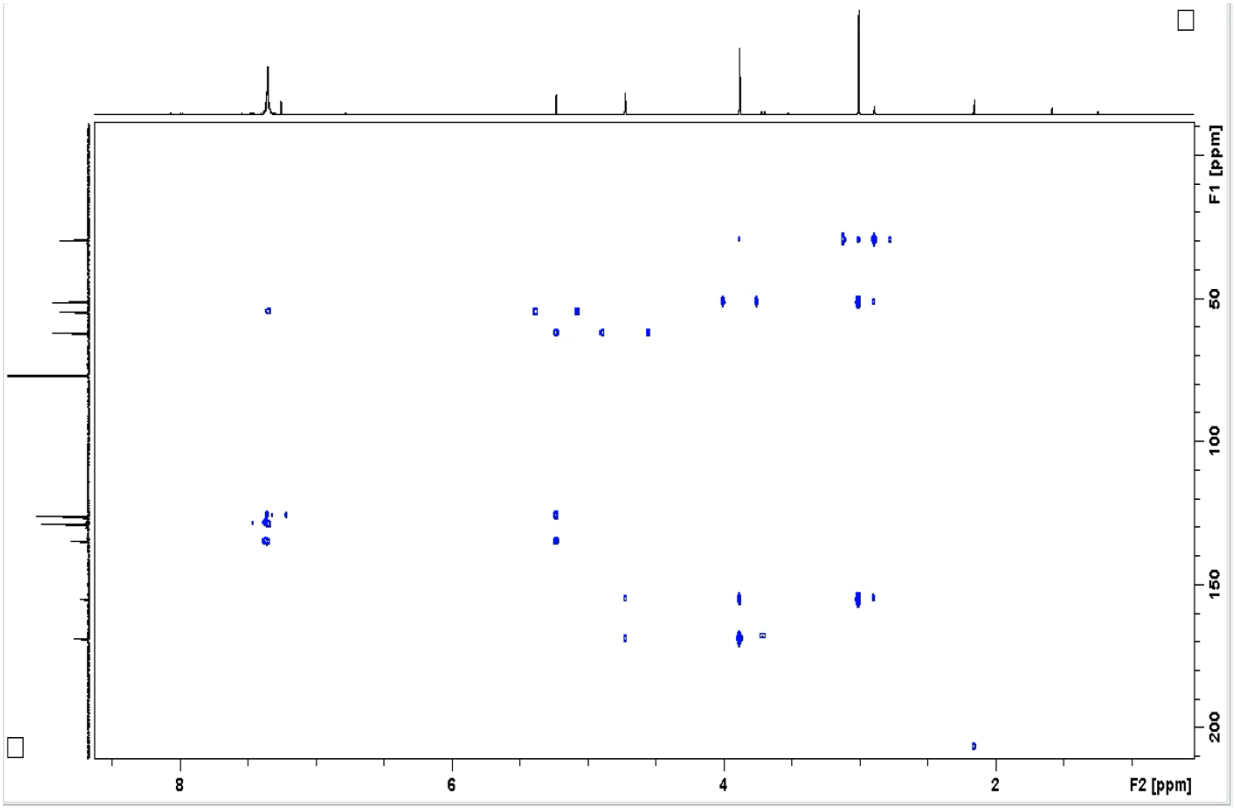
COSY (600 MHz, $CDCl_3$) spectrum of **4c**



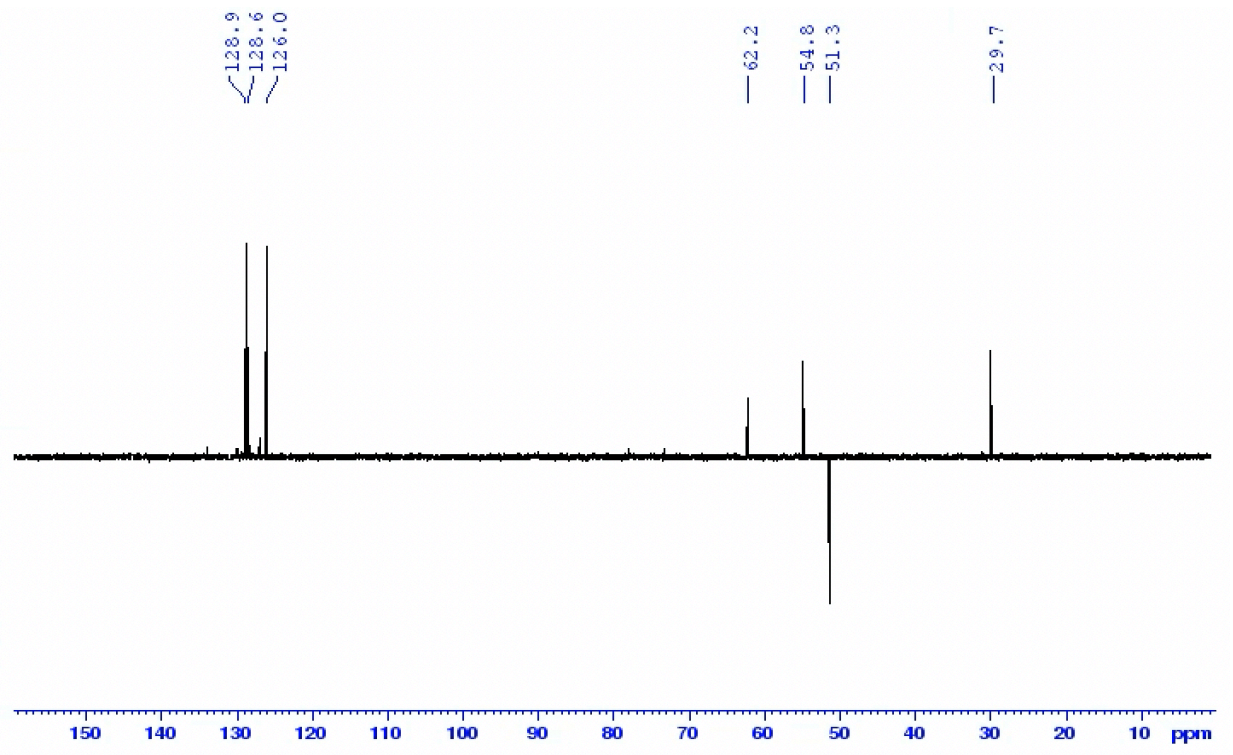
HSQC (600 MHz, $CDCl_3$) spectrum of **4c**



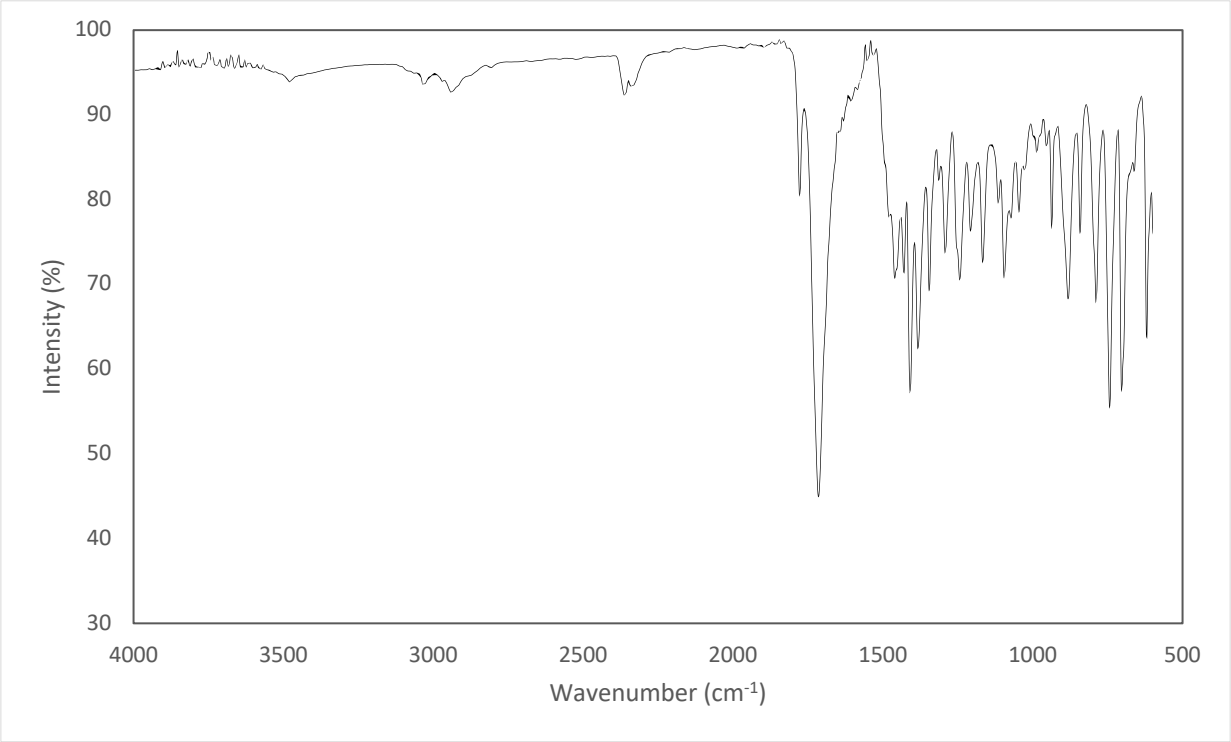
HMBC (600 MHz, $CDCl_3$) spectrum of **4c**



DEPT135 (151 MHz, $CDCl_3$) spectrum of **4c**

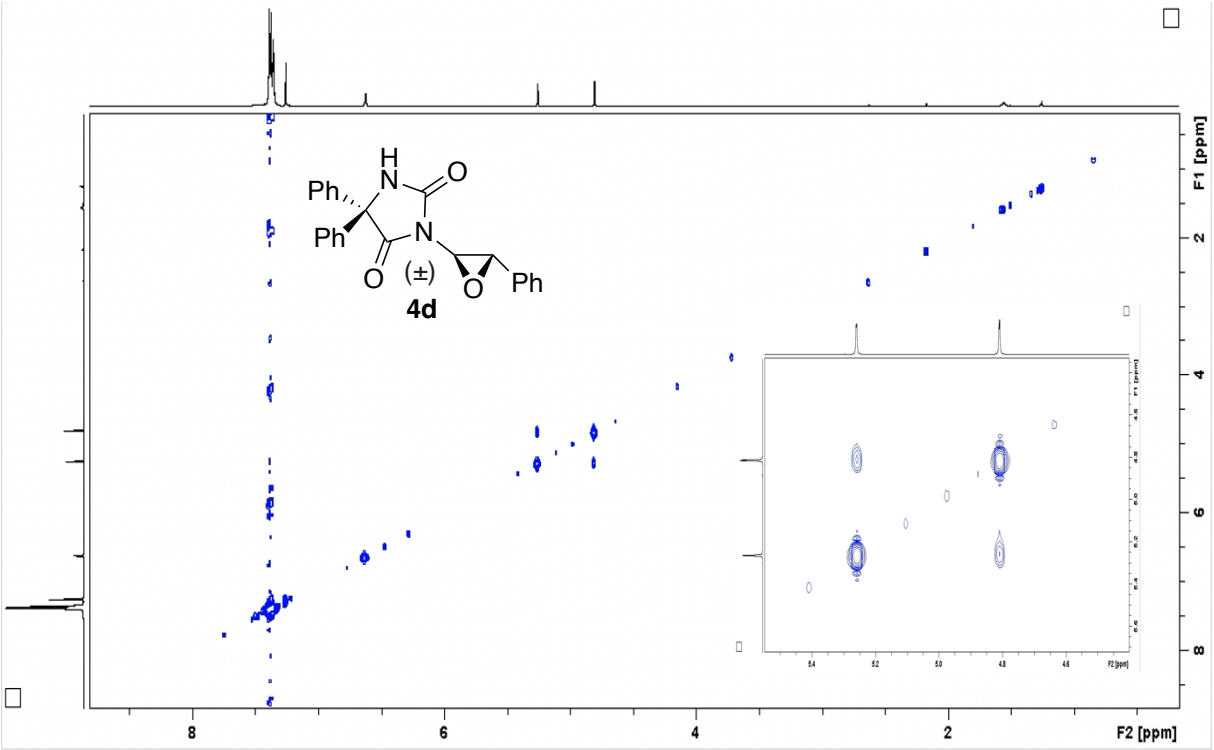


IR spectrum of **4c**

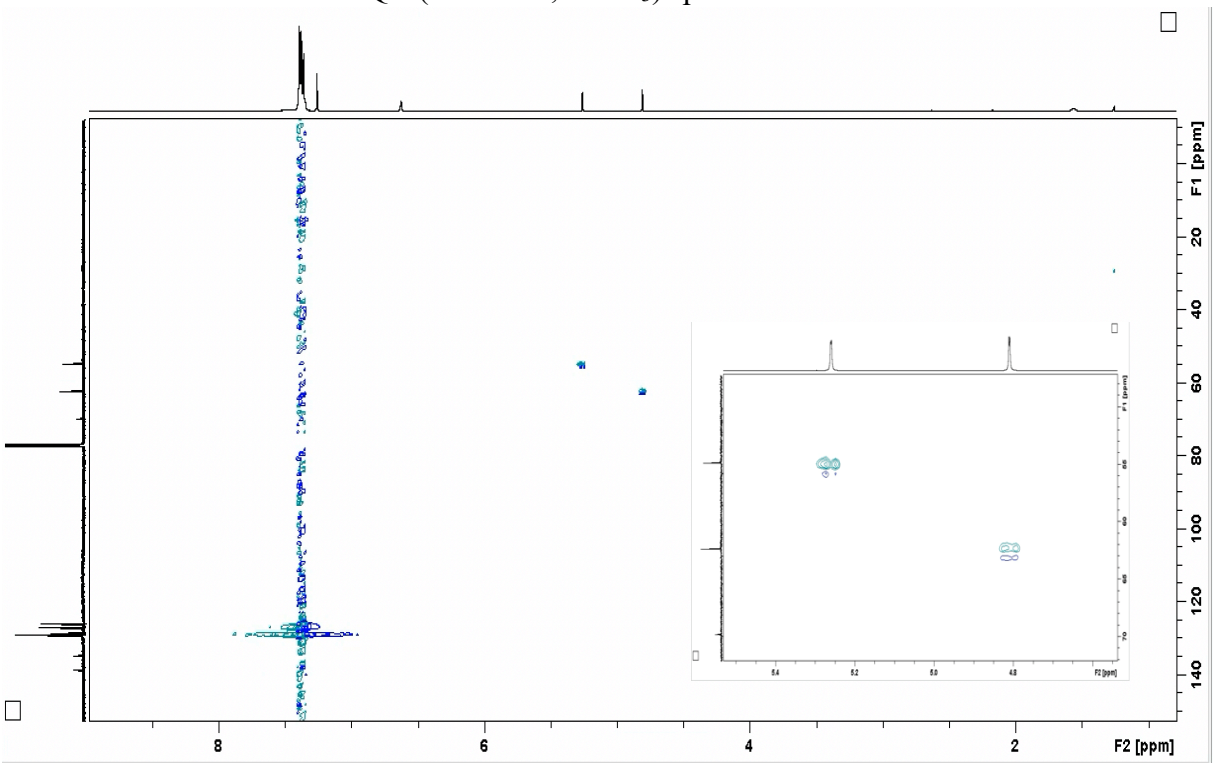


5.5-diphenyl-3-(3-phenyloxiran-2-yl)hydantoin (4d)

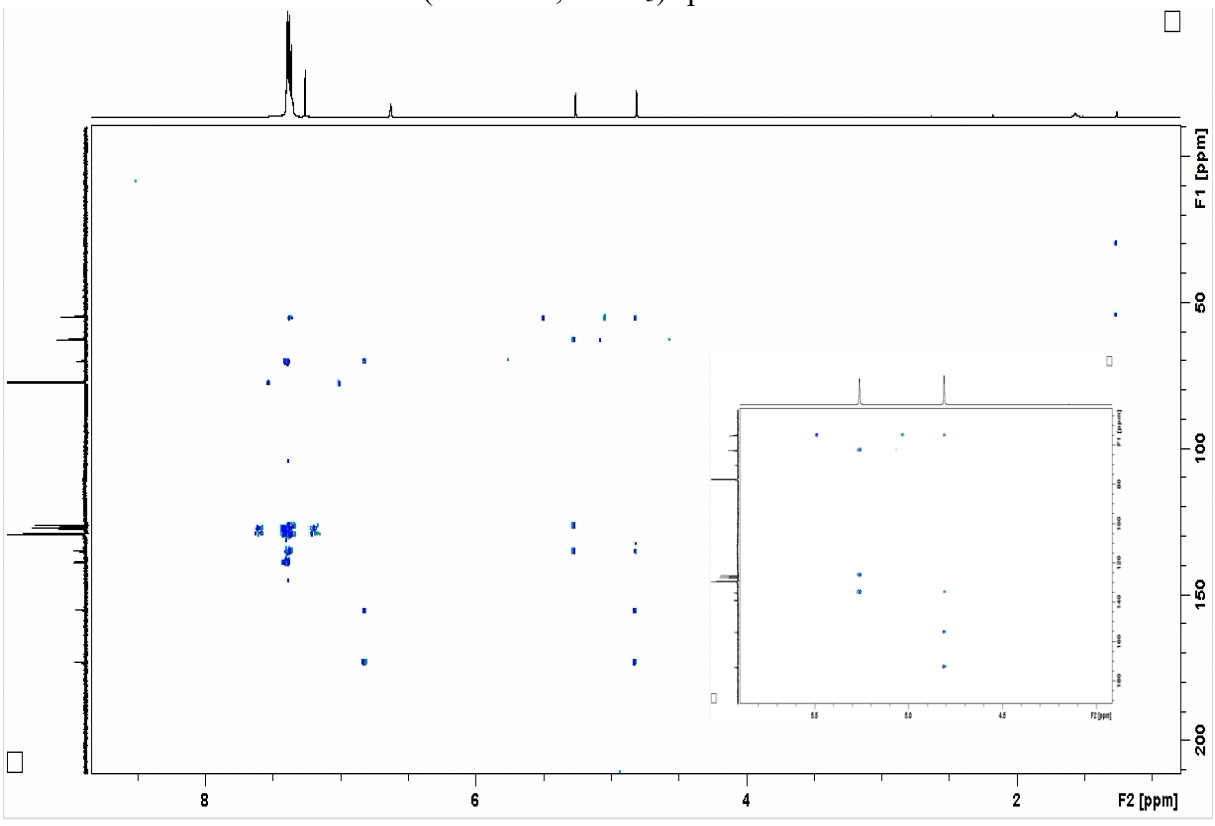
COSY (600 MHz, $CDCl_3$) spectrum of **4d**



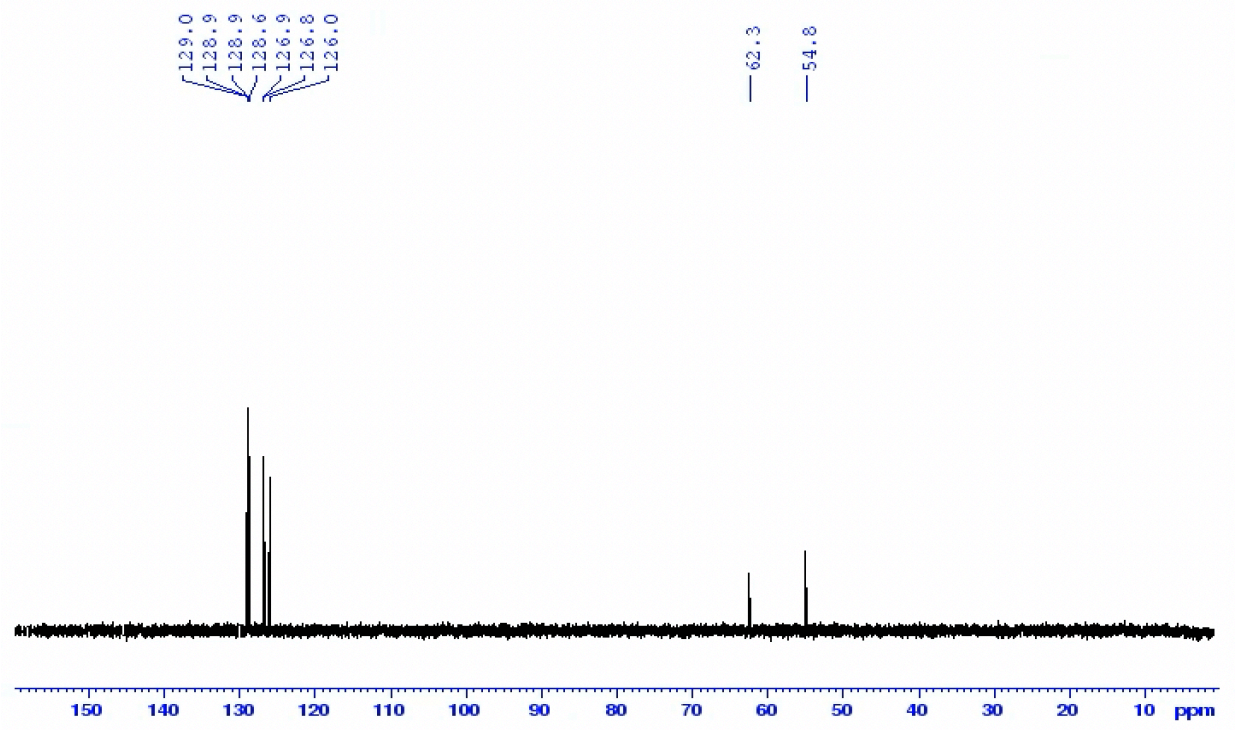
HSQC (600 MHz, $CDCl_3$) spectrum of **4d**



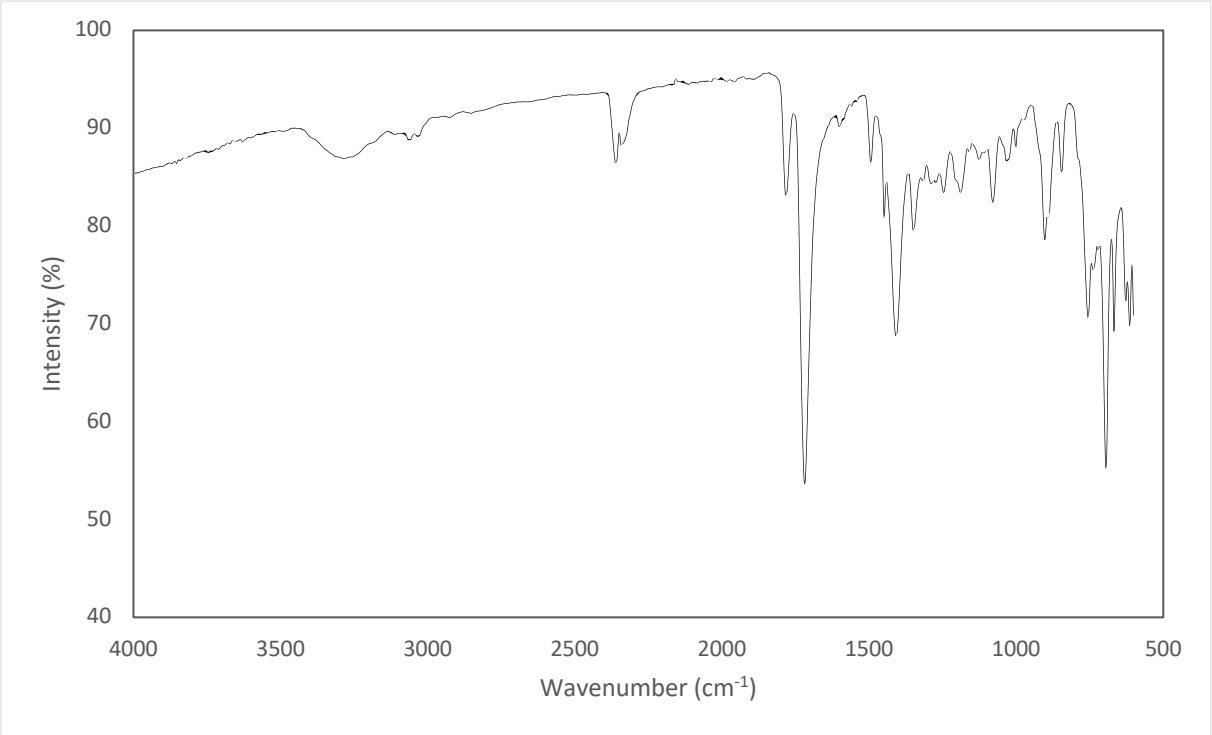
HMBC (600 MHz, $CDCl_3$) spectrum of **4d**



DEPT135 (151 MHz, $CDCl_3$) spectrum of **4d**

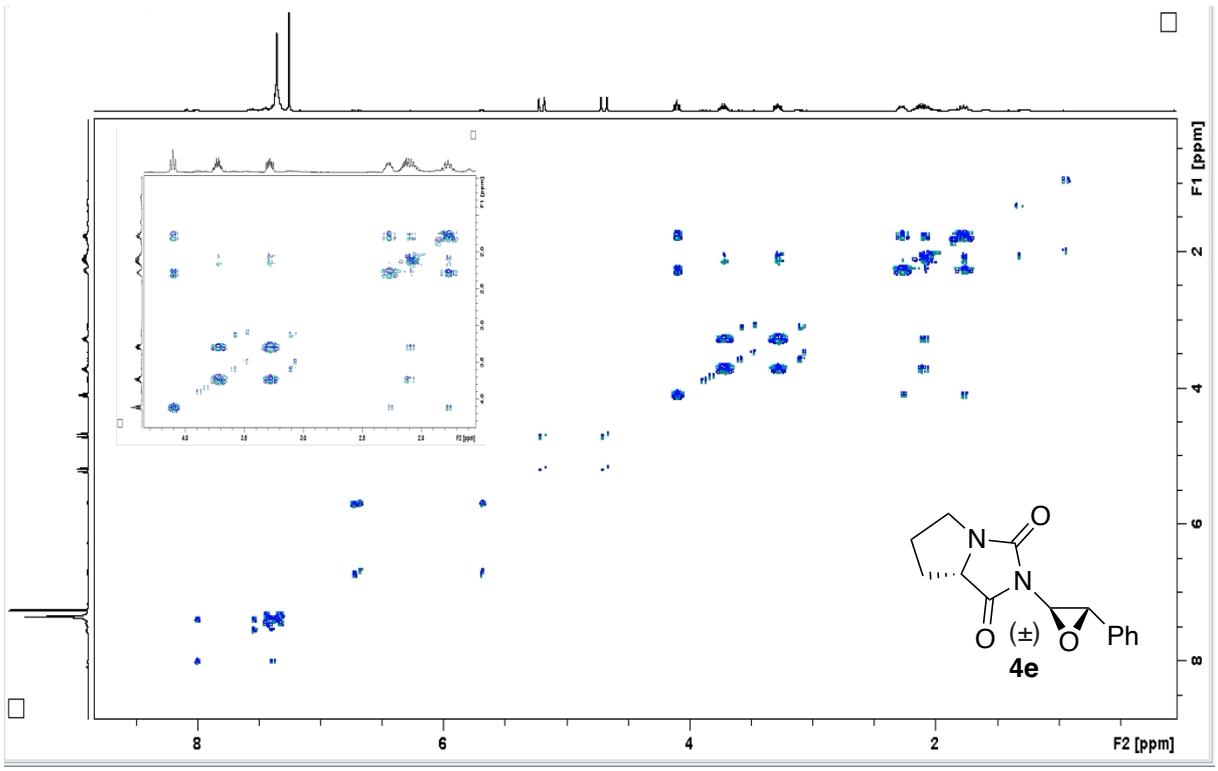


IR-spectrum of **4d**

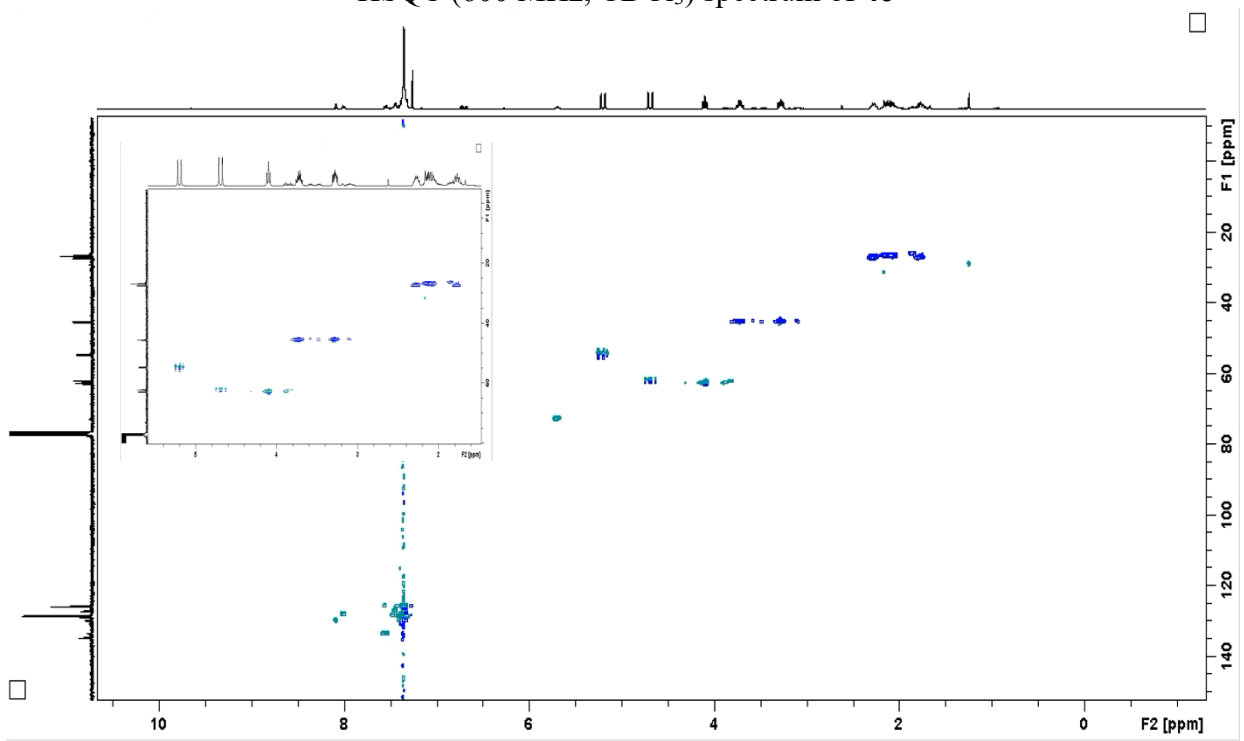


(7a*S*)-2-(3-phenyloxiran-2-yl)tetrahydro-1*H*-pyrrolo[1,2-*c*]imidazole-1,3(2*H*)-dione (4e)

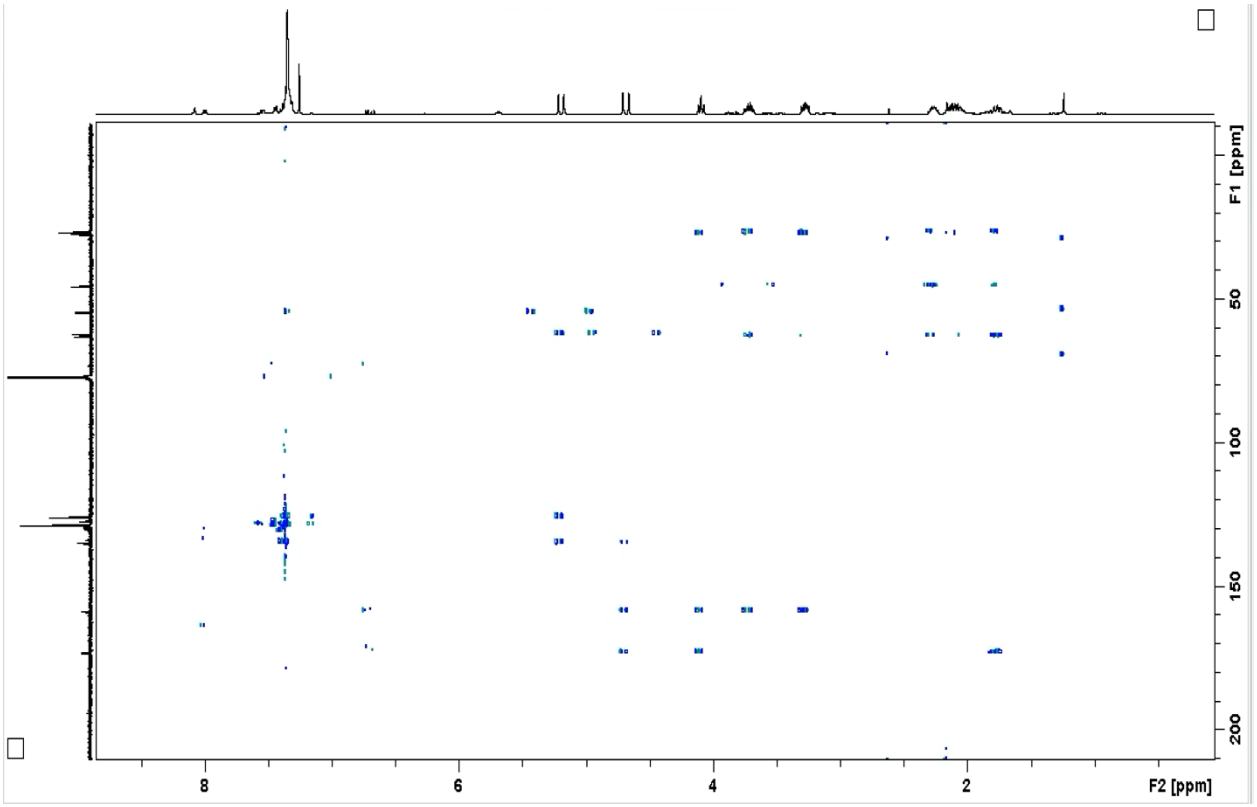
COSY (600 MHz, $CDCl_3$) spectrum of **4e**



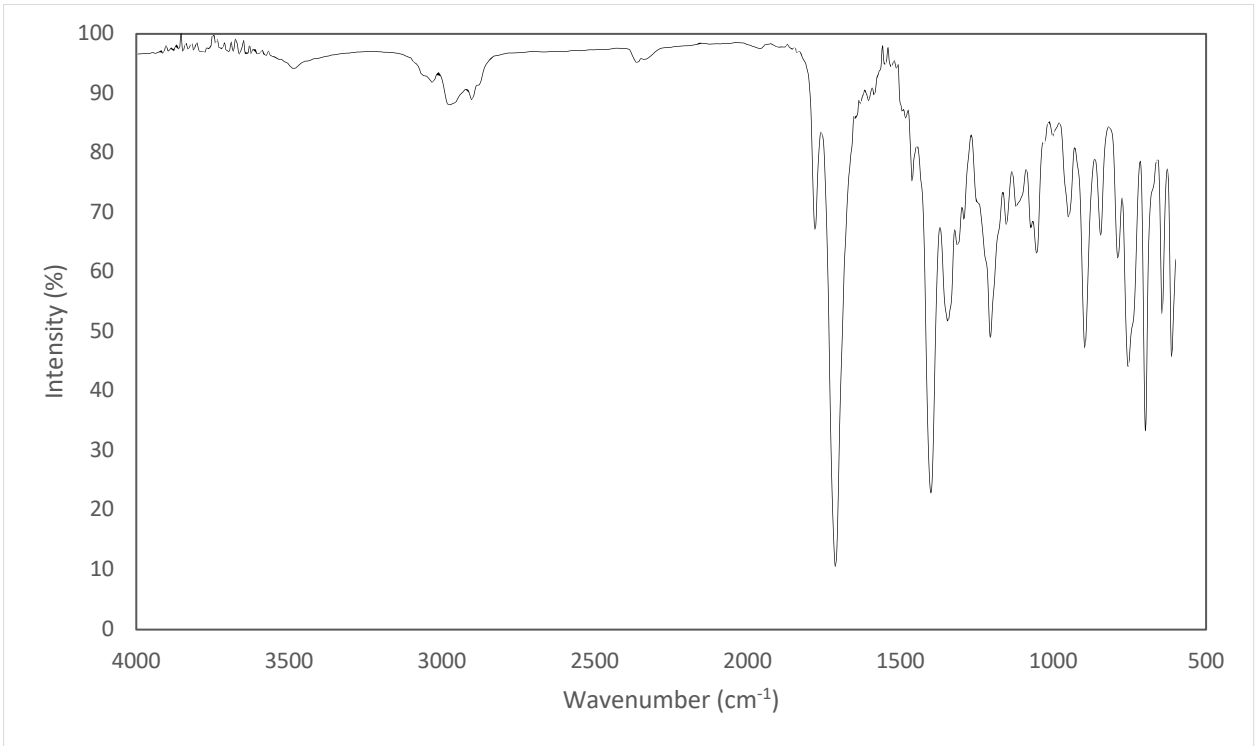
HSQC (600 MHz, $CDCl_3$) spectrum of **4e**



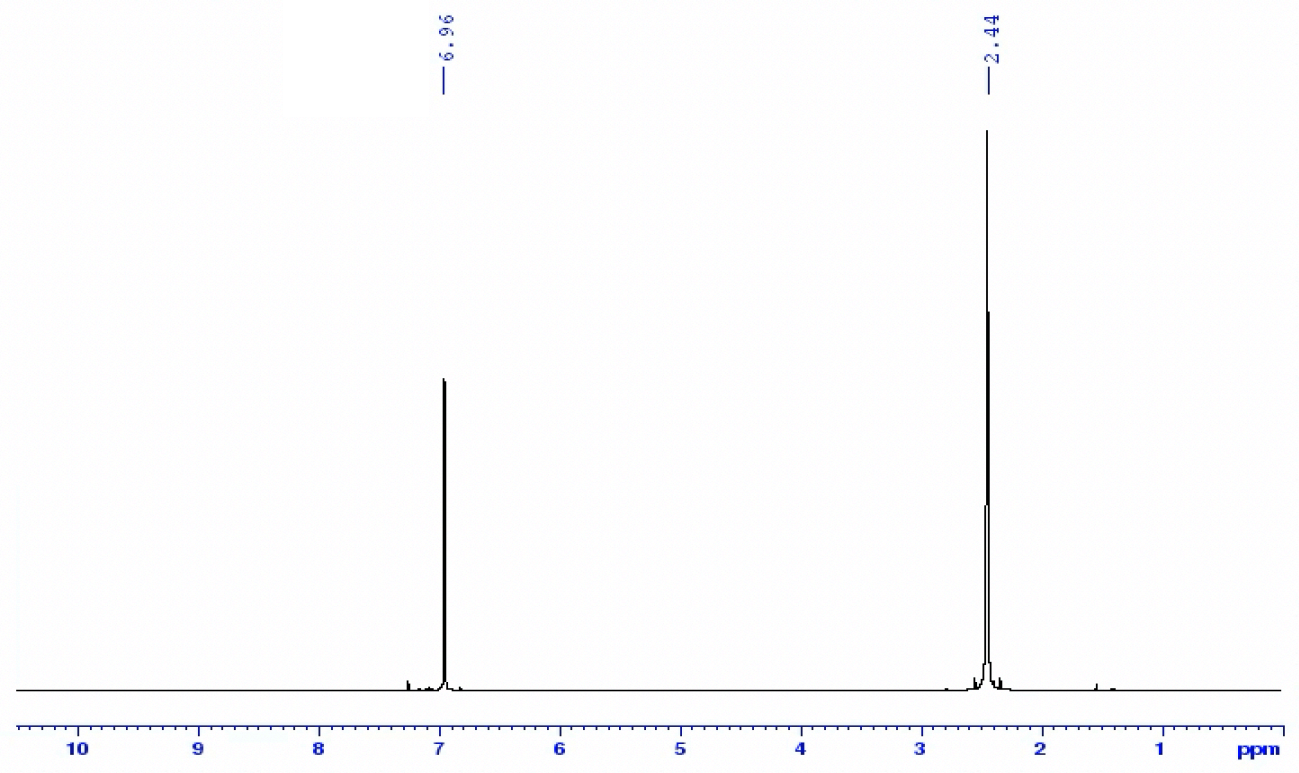
HMBC (600 MHz, $CDCl_3$) spectrum of **4e**



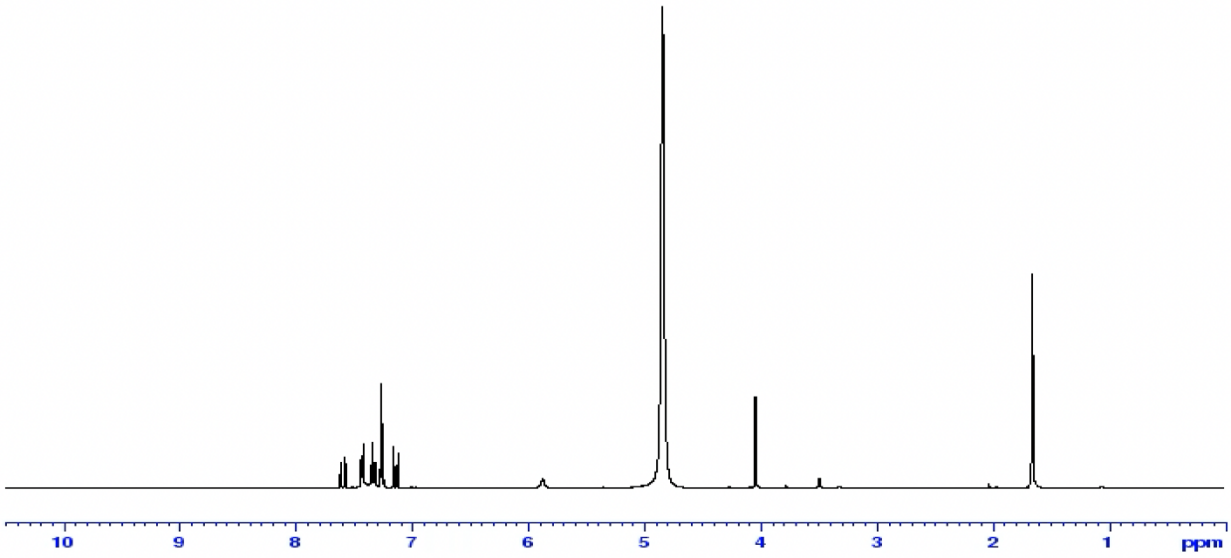
IR spectrum of **4e**



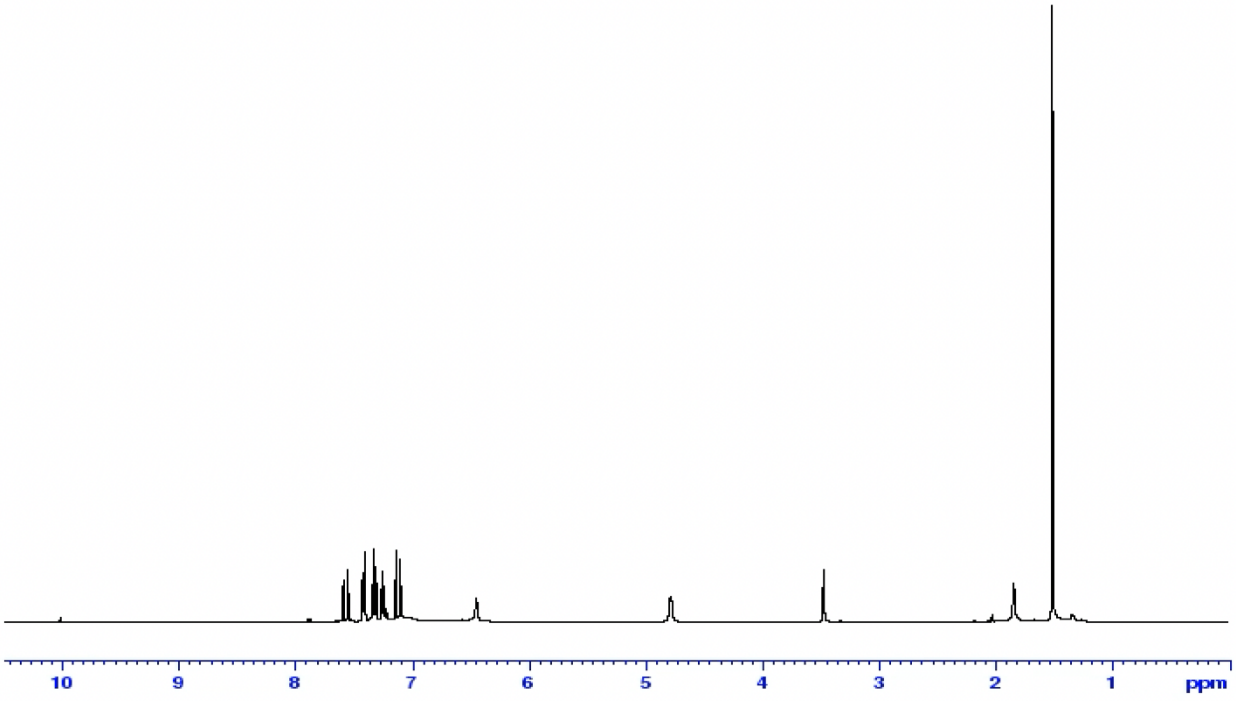
^{1}H NMR ($CDCl_3$, 600 MHz) spectrum of Mesitylene



^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of the crude after epoxidizing compound **3a** with Method 2

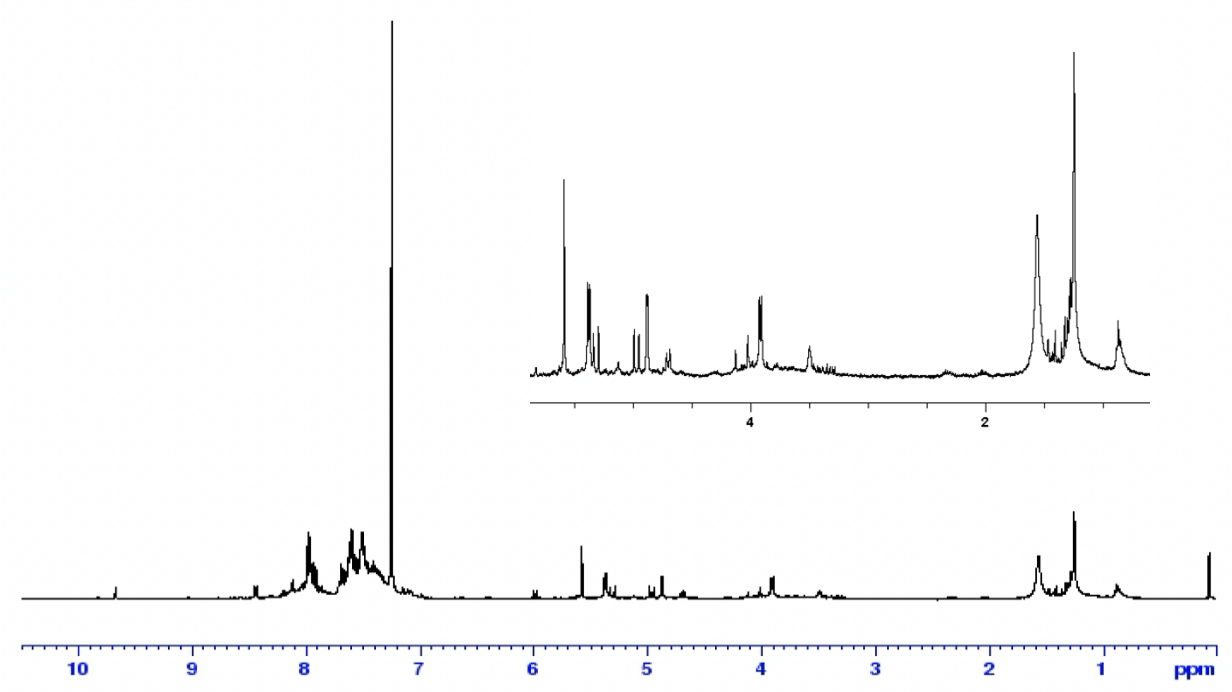


^{1}H NMR ($CDCl_3$, 400 MHz) spectrum of the crude after epoxidizing compound **3b** with Method 2

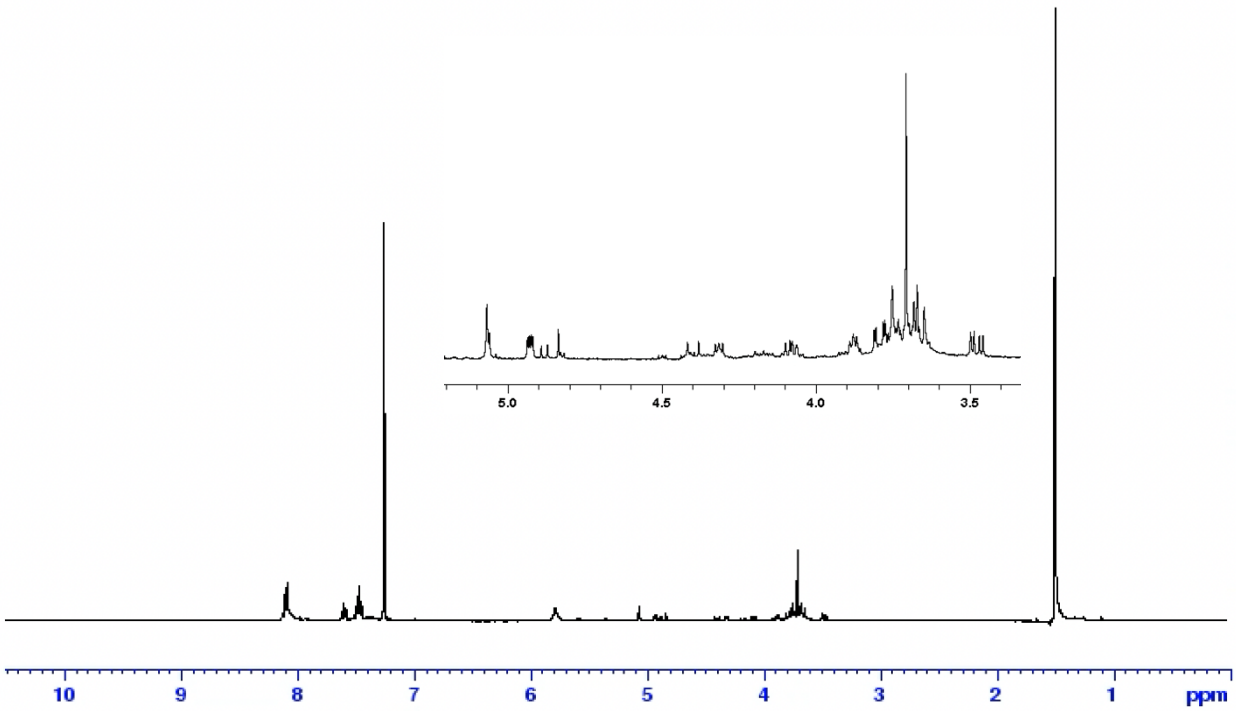


C. Crude spectrums from epoxide-ring opening reactions

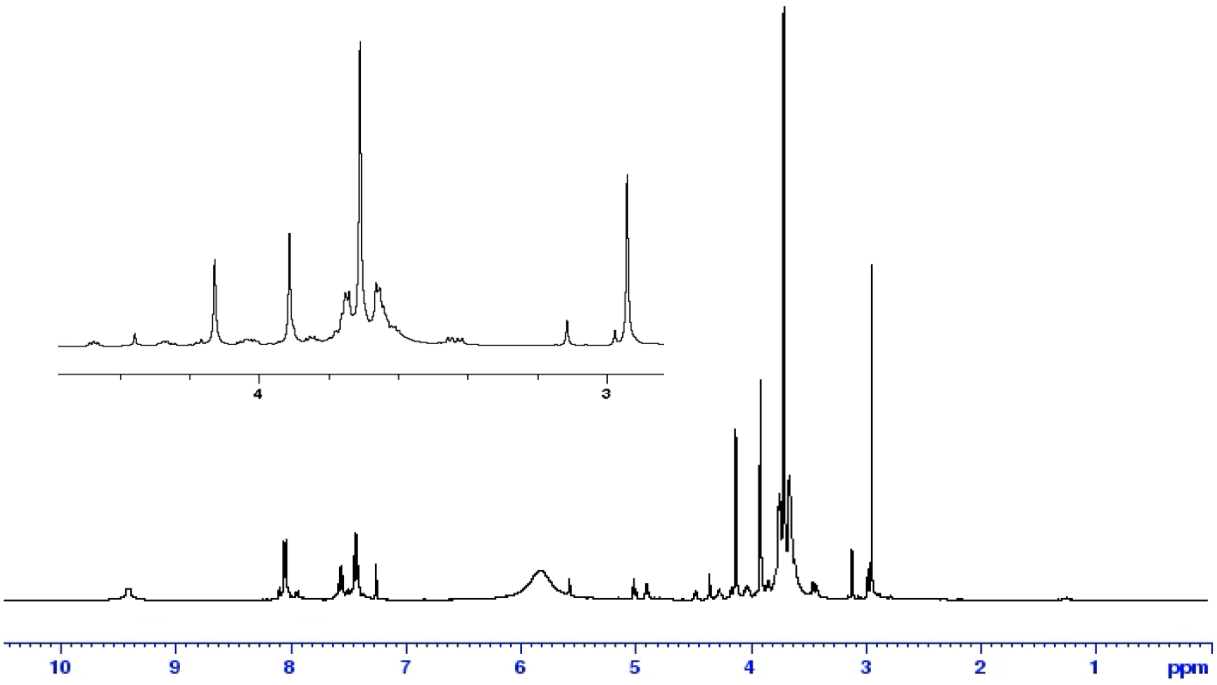
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the crude material after treating **4a** with water



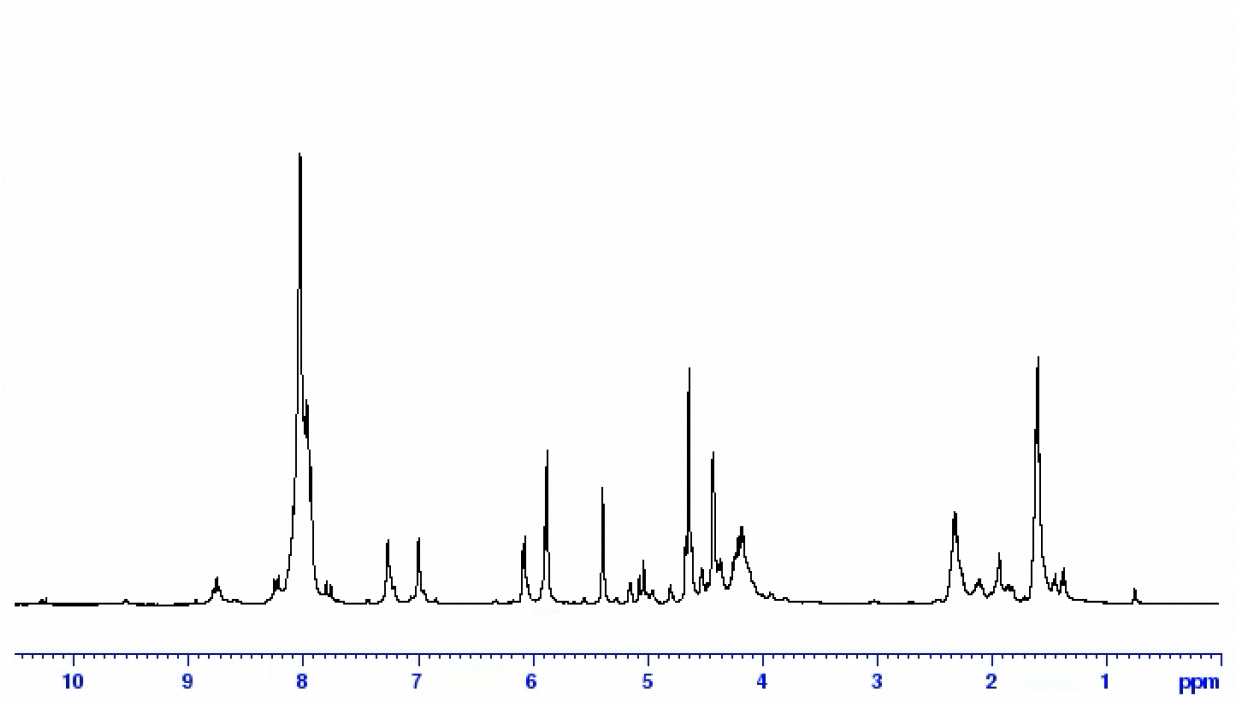
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the crude material after treating **4b** with water



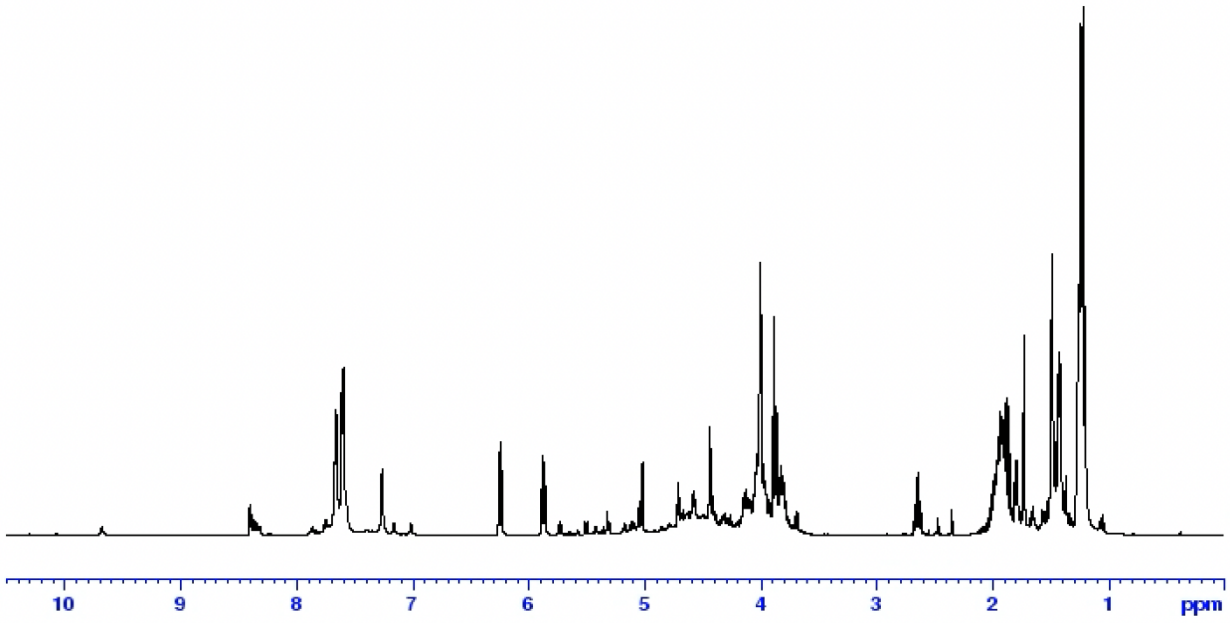
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the crude material after treating **4c** with water



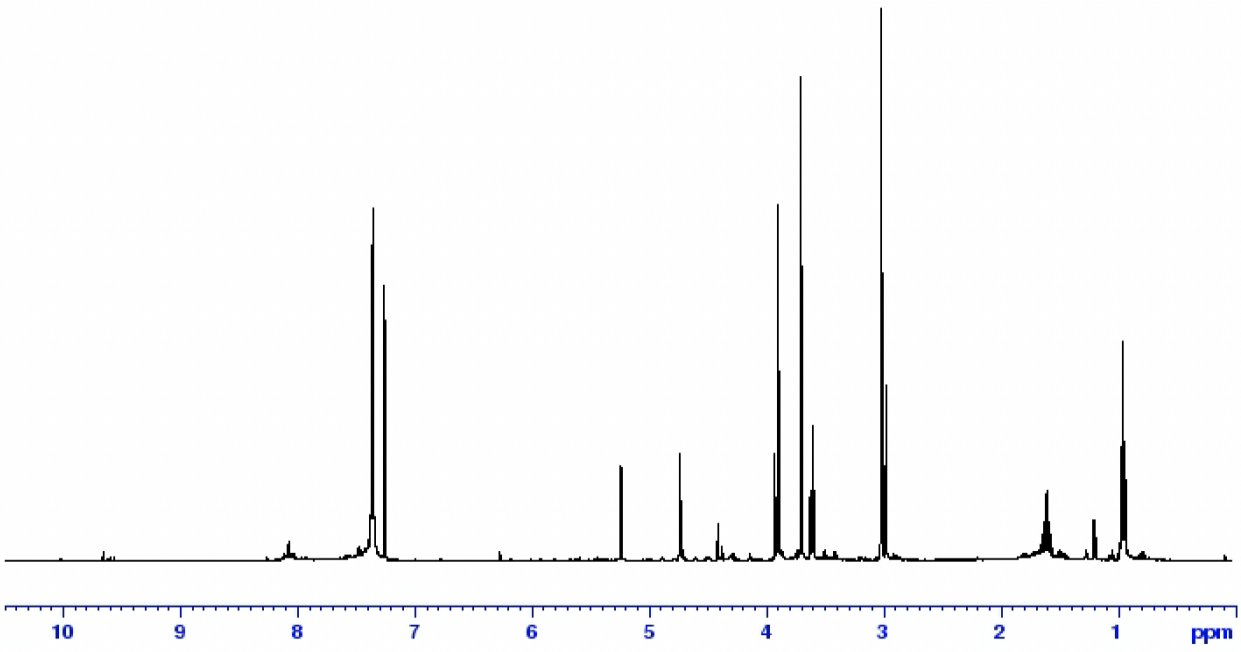
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the crude material after treating **4a** with 1-propanol



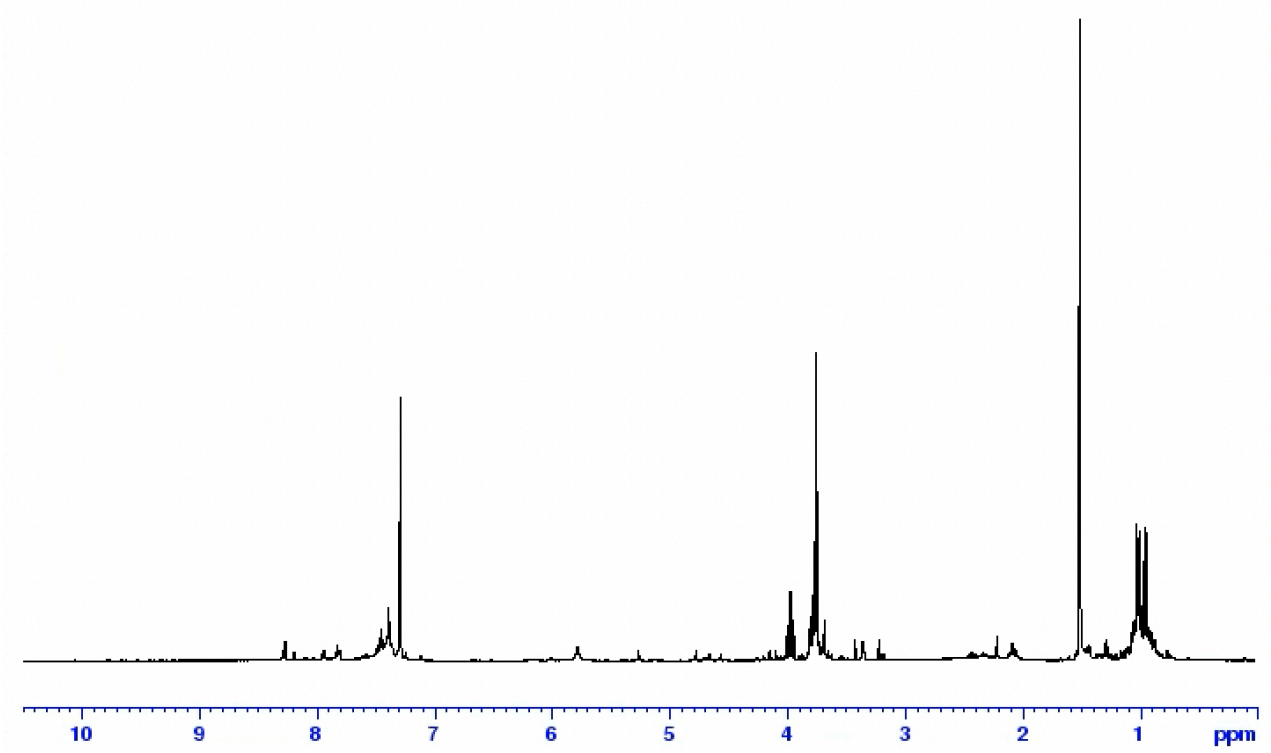
^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the crude material after treating **4b** with 1-propanol



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the crude material after treating **4c** with 1-propanol



^{1}H NMR (400 MHz, $CDCl_3$) spectrum of the crude material after treating **4b** with *L*-valine methyl ester



D. Calculation examples

E-factor

The E-factor of the reactions were calculated using equation 1. An example is shown for compound **4c** synthesized by method 1. In method 1 the masses of reactants and solvents used in the reaction were 0.040442 g of the starting material **3c**, 0.069028 g *m*-CPBA, and 2 mL DCM equivalent to 2.66 g. Compound **4c** was isolated in a yield of 0.040442 g.

$$\mathrm{E-factor} = \frac{\mathrm{m_{starting\ materials} - m_{products}}}{\mathrm{m_{products}}} \qquad (1)$$

$$\mathrm{E-factor} = \frac{(\mathrm{m_{3c} + m_{m-CPBA} + m_{DCM} - m_{4c}})}{\mathrm{m_{4c}}} = \frac{(0.040442\ \mathrm{g} + 0.069028\ \mathrm{g} + 2.66\ \mathrm{g} - 0.0404\ \mathrm{g})}{0.0404\ \mathrm{g}} = 67.6\ \frac{\mathrm{kg\ waste}}{\mathrm{kg\ product}}$$

AE (%)

The atom economy of the reactions were calculated using equation 2. An example is shown for compound **4c** synthesized by method 1. The reactants used were the *N*-3-alkenylhydantoin **3c** with M_m= 202.21 g/mol, *m*-CPBA with M_m= 172.57 g/mol and of the product **4c** with M_m=218.21 g/mol.

$$\mathrm{AE} = \frac{M_{m,\ \mathrm{products}}}{\sum M_{m,\ \mathrm{reactants}}} \qquad (2)$$

$$\mathrm{AE} = \frac{218.21\ \mathrm{g/mol}}{202.21\ \mathrm{g/mol} + 172.57\mathrm{g/mol}} \cdot 100 = 58\ \%$$

Yield determination

Here an example calculating the experimental yield and NMR yield of compound **4a.**

Compound **4a** were synthesized several times, and the spectrum shown in the experimental part is from another experiment synthesizing the compound. Here the synthesis of **4a** was done to check the correspondence between experimental yield and NMR yield.

1)Experimental yield of **4a**

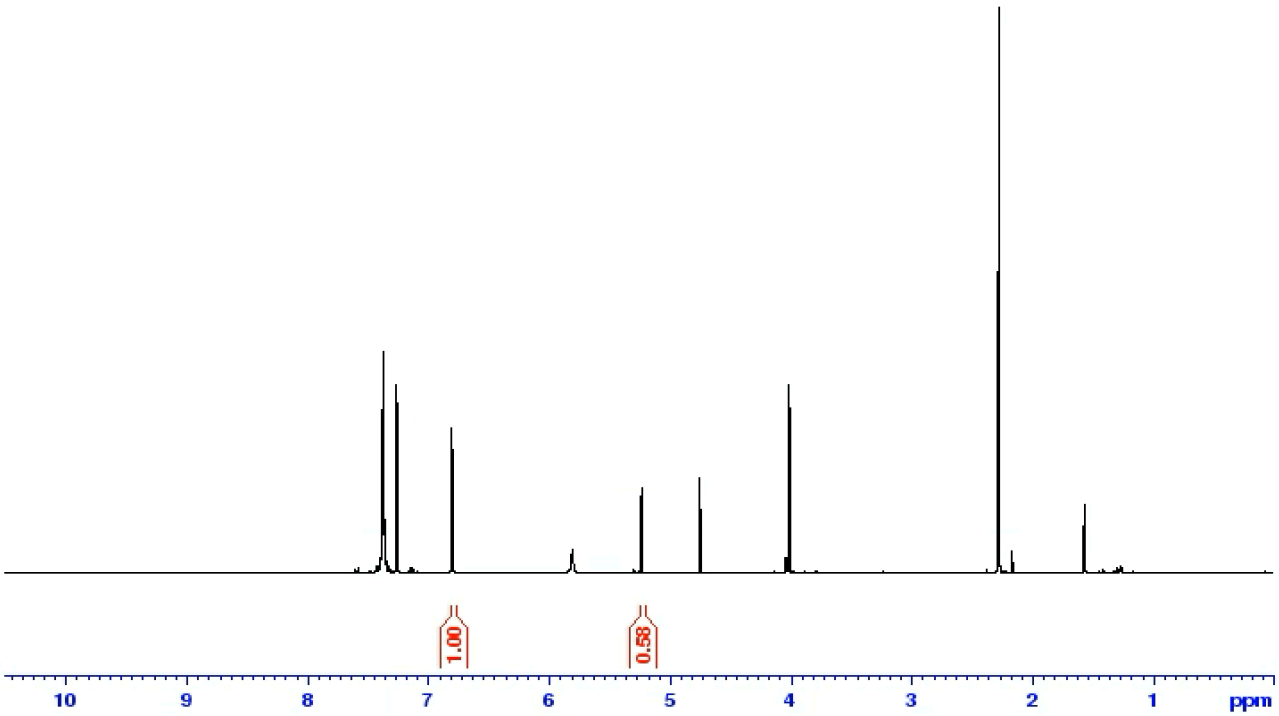
After epoxidation and extraction described in method 1 chapter 6.3, **4a** was isolated in 39.0 mg. Theoretical yield was 0.0002 mol, and the molar mass of **4a** is 218.21 g/mol.

$$\%\ \text{Yield} = \frac{0.0390\text{g}/218.21\text{g}\ /\text{mol}}{0.0002\ \text{mol}} \cdot 100 = 89\ \%$$

2)NMR yield of **4a**

After epoxidation and extraction described in method 1 chapter 6.3, 0.0122 g mesitylene as internal standard was weighed into the reaction flask with **4a**. The mixture was diluted with $CDCl_3$ until all the reaction product was solved and stirred until a homogenous mixture was formed. ^{1}H NMR was taken, with D1= 10. Below the ^{1}H NMR spectrum of compound **4a** with mesitylene as IS is shown.

^{1}H NMR spectrum ($CDCl_3$, 600 MHz) of **4a** with mesitylene as IS



One signal from mesitylene is representing 3H= N_B is integrated to 1.00, and one of the epoxide hydrogen signals from **4a** is integrated to 0.58 representing 1H= N_A each. Equation 3 and 4 are used in the calculations.

$$r_{A/B} = \frac{n_A}{n_B} = \frac{\text{integral}_A/N_A}{\text{integral}_B/N_B} \qquad (3)$$

$$n_{IS,mesitylene} = \frac{0.0122\text{g}}{120.19\frac{\text{g}}{\text{mol}}} = 0.0001015\ \text{mol}$$

$$r_{A/B} = \frac{\frac{0.58}{1}}{\frac{1.00}{3}} = 1.74$$

$$n_A = n_{IS} \cdot r_{A/IS} \qquad (4)$$

$$n_A = 0.0001015\ \text{mol} \cdot 1.74 = 0.0001766\ \text{mol}$$

$$\text{NMR yield} = \frac{0.0001766\text{mol}}{0.0002\ \text{mol}} \cdot 100 = 88\ \%$$