RADICAL ENDEAVOURS

THE PURSUIT OF NOVEL RADICAL CYCLISATION TECHNOLOGIES

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Abstract

This thesis describes attempts to develop new technically clean radical cyclisation technologies. The work focuses on novel radical oxidation processes, whereby selective hydrogen-atom abstraction forms carbon-centred radicals able to undergo intermolecular radical additions, or cyclisation to form 5- 6-membered rings.

A new and unreported cyclisation pathway has been identified, albeit a low yielding pathway. This novel N-halosuccinimide cyclisation technology constructs cyclic architectures of med-chem importance and crucially without the requirement for tin or other toxic metals.

Particularly noteworthy was the use of *N*-iodosuccinimide to promote cyclisation of dihydro-isoindol-1-one derivatives (Figure 1a).

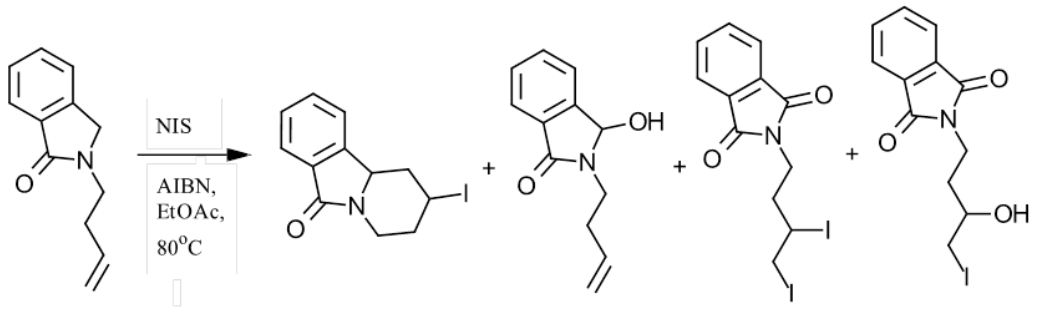

Figure 1a Resulting products of NIS reaction, successful cyclisation

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Preface

“So what do you do?” is a question everyone is invariably asked at one point in their life, possibly by an estranged relative or an acquaintance of an acquaintance at some party. Using a party for an illustrative example, when I’m asked this exact question, first I convince them “I’m a chemist” does not mean I work at a local pharmacy and is in fact referring to being a student of the science that is Chemistry. The conversation swiftly moves on to “What sort of Chemist?” (Or at least after the “I didn’t like chemistry at school” diatribe). My response “an Organic Chemist” has usually mixed responses, either empathic nods or “do you work with plants and stuff?” it really depends on the party. The challenge at this point is now to communicate exactly what it is that you are interested in.

I’m primarily interested in the use of free radicals in organic synthesis. Free radicals the term is well known to most people, most of the PR has already been done by companies wishing to sell the odd fruit juice or skin care product. But the actual understanding of what exactly free radicals are and their uses in synthetic chemistry are by and large not known by most party revellers.

So “what are free radicals?” a person might ask during such a party out of politeness or a pathological fear of silences. “A radical is an atomic or molecular species having an unpaired, or odd, electron; this makes radicals highly chemically reactive towards other substances and themselves”.

“So what are you using the radicals for?” the fictional and now slightly peakish party goer asks. “Well I’m interested in using radicals for developing new synthetically useful addition and cyclisation reactions”.

The reveller after an unfortunate episode beside an imitation tropical plant regained composure and retorted with a hint of contempt “what is the point?” before returning to heave over the plastic plant once more.

It is an adept question, the best way to answer such a question is to first explain that radical reactions can offer a number of advantages over ionic transformations; the first being that although carbon centred radicals are extremely reactive, radical addition reactions can proceed under mild, neutral conditions, and the reactivity of radicals does not compromise a high level of chemio-, regio-, and stereoselectivity. Even conformational restrictions often increase the rates and increase the stereoselectivity of radical cyclisations. Another advantage of using radicals is that they are not cluttered with counterions or aggregation spheres, because they are neutral and because their reactions have early transition states, Radical intermediates are ideally suited for the synthesis of crowded bonds. Radical reactions do not need to be dry, and the protection of alcohols, amines, and related functional groups is often unnecessary. The same is rarely true for reactions involving carbanions or carbocations due to their respective basicity, nucleophilicity and electrophilicity.

With these advantages it is perhaps surprising that radicals have made limited inroads in being used in industry, which is mainly due to the dependency of

radical chemistry on trialkyl-tin hydrides (e.g. Bu_3SnH). But there lies the scope a lot of untapped potential for organic chemists. With every year comes a new radical methodology for constructing and functionalising molecules. The remit of this thesis is within this race for new, cleaner and more efficient technologies.

David S. J. Creighton

Acknowledgements

I would like to take this opportunity to unreservedly thank both of my advisors Dr Victor Chechik and Dr Andrew Parsons for their support, generosity and patience throughout my time at the University of York. And from whom I have learnt a great deal and imparted what will be a sustained future interest in free-radical chemistry.

To the Chechik group I extend my thanks and best wishes in their future endeavours, in particular I would like to thank Dr Robert Thatcher our talented post-doc for giving up his time to show me the ropes and nuances of 2D NMR spectroscopy. I would also like to thank Joe Atkin for all his help and wish him the best of luck in the future with his PhD.

I would like to thank Professor Peter O'Brien and his group for accommodating me after the B-Block fire in February 2012. I greatly enjoyed my time in D-block and wish them well for the future.

I would like to extend my gratitude to the Chemistry Graduate School for their faultless service, and the University Senate for its magnanimity.

I would also like to take this opportunity to apologize to all affected individuals for my NMR queue etiquette, penchant for Hawaiian shirts and general misanthropy.

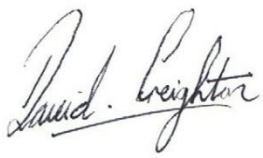
There countless individuals throughout my time at York I owe a great debt too, for their insight, financial support and the occasional donation of a scotch or two. I can't thank you enough.

Goodbye and Good luck

Author's declaration

I declare that the work in this Thesis was carried out in accordance with the regulations of the University of York. The work is original except where indicated by special reference in the text, and no part of the Thesis has been submitted for any other degree.

Signature,



Chapter One: Introduction

1.1 The "Roots" of Radicals

The word radical comes from the later Latin *Radicalis* "of roots" and Latin Radix meaning "root". I intend to use this chapter to get to the roots of where radical chemistry began and show how it has anchored itself in organic synthesis and its future.

I have chosen to begin the story of radicals unconventionally with the assassination of an Emperor.[1] In 1881 the self-proclaimed "Narodnaya Volya" (or People's Will) were a radical revolutionary group, who felt the drastic need to end Tsar Alexander II's life, who died of his injuries after they detonated a bomb underneath his carriage. This audacious regicide had a swift and formulaic response, triggering retrograde political reforms throughout the Russian Empire by Alexander II's less enlightened successors.[2]

The relevance of this geo-political turbulence to the genesis of radical chemistry was the emigration of a young Moses Gomberg along with his family to the United States of America in 1884 to avoid the presumably unjust imprisonment. Gomberg's story from a refugee to great of organic chemistry is an inspiring one,[3] where he overcame many obstacles to become a successful scientist, but I shall refrain from telling this story as it is the story of radicals and Gomberg's part to play is what I want to impart to the reader.

The event leading to Gomberg's discovery of stable and persistent organic free radicals begins with Moses paying a visit to Victor Meyer's laboratory with the sole intention of synthesising a compound which other chemists had failed to make. That compound was tetraphenylmethane (Ph_4C), which had already claimed many a scalp including Gomberg's host Meyer. Armed with some youthful bravado, Gomberg demonstrated his technical skill and chemical intuition in the lab and designed a completely new synthesis and after a few days of intensive lab work he isolated a small amount of the desired compound. His success spurred him on to attempt to isolate the next fully phenylated hydrocarbon hexaphenylethane ($Ph_3C\text{-}CPh_3$), not a man to take it easy.[4]

The synthesis of this compound involved the treatment of triphenylmethyl chloride (or trityl chloride, Ph_3CCl) with metallic sodium. The reaction however did not proceed. Gomberg moved to rectify this by deploying silver instead of sodium. This time the reaction did proceed, and he isolated a white crystalline substance. On analyzing the compound using elemental analysis and to his surprise he concluded the compound contained oxygen.

Using the process of elimination Gomberg determined that the source of the oxygen was atmospheric, and he repeated the experiment in the absence of air. This time the crystals did not form and instead he isolated a different compound that did not contain oxygen but was not hexaphenylethane. Gomberg had rationalised that the oxygenated compound was in fact triphenylmethyl peroxide ($Ph_3C\text{-}O\text{-}OPh_3$). The second compound however demonstrated interesting reactivity comparable to highly unsaturated hydrocarbons. Gomberg concluded

although reluctantly that to explain this reactivity he had synthesised a free radical, triphenylmethyl $Ph_3C\bullet$ (Figure 1b).

Gomberg's work was not immediately heralded by his peers and caused great debate as to whether a radical even need be invoked.[5]

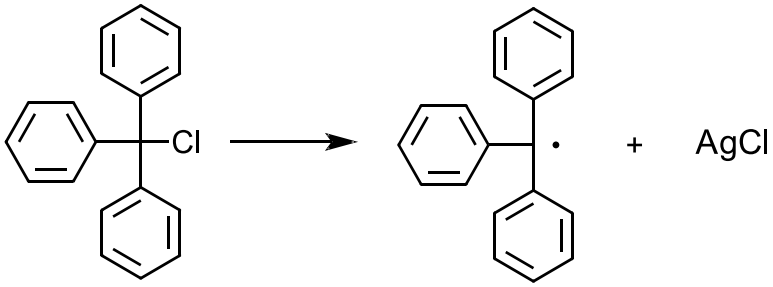


Figure 1b Trityl chloride reacting with silver forming the triphenyl methyl radical

Radicals unfortunately continued to be regarded as esoteric constructs with no relation to organic chemistry. However finally in 1937, three papers appeared that did much to cement the role of radicals in organic chemistry. The first paper was a review by Hey and Waters.[6] The second was the work by Kharasch, Engelmann and Mayo[7] on the unusual mode of addition of hydrogen bromide to alkenes, which was demonstrated to involve a radical chain reaction. The third was the kinetic analysis of vinyl polymerisation which was also shown to be a radical chain process by Flory,[8] who proposed the concept of chain transfer. These three publications made radicals acceptable to the mainstream scientific community and marked a watershed in the development of radical chemistry.

Radical chemistry accelerated from 1939 onwards, though unfortunately this progress was catalysed by the all too familiar feature of 20th century, mechanised

warfare. Chemists were called upon by the Allied and Axis war efforts in WWII to develop and supply synthetic rubbers. This became a greater priority for Allied nations due to the expansion of the Japanese Empire into Southeast Asia in 1942 which consolidated Axis control over global natural rubber supplies. Natural rubber was a strategically vital resource for the United States which lagged behind in synthetic rubber production. Rubber was needed for an array of different components in war machines. As a result polymer chemistry became vitally important; as vinyl polymerisations were radical processes this meant radical chemistry became a priority area of funding and research.

Academic interest in radical chemistry continued after the war and began to concentrate developing new classes of radical additions for synthetic purposes.[9]

Simple examples of radical cyclisations emerged in the 1960's, [10] and they are now established as an important method of forming rings, particularly 5- and 6-membered rings. A number of reviews in the area have been reported, discussing radical cyclisation methodologies based on reagents including tributyltin hydride and samarium diiodide[11]. This forms a large percentage of radical cyclisations used in organic synthesis, with elaborate radical cascade sequences forming polycyclic natural products.[12]

1.2 Radical Cyclisations in Literature

There are numerous beautiful examples of these cyclisations in literature; a personal favourite of mine is Curran's classic total synthesis of hirsutene[13] in

1985, a masterful showcase of the tributyltin hydride radical methodology (Figure 2).

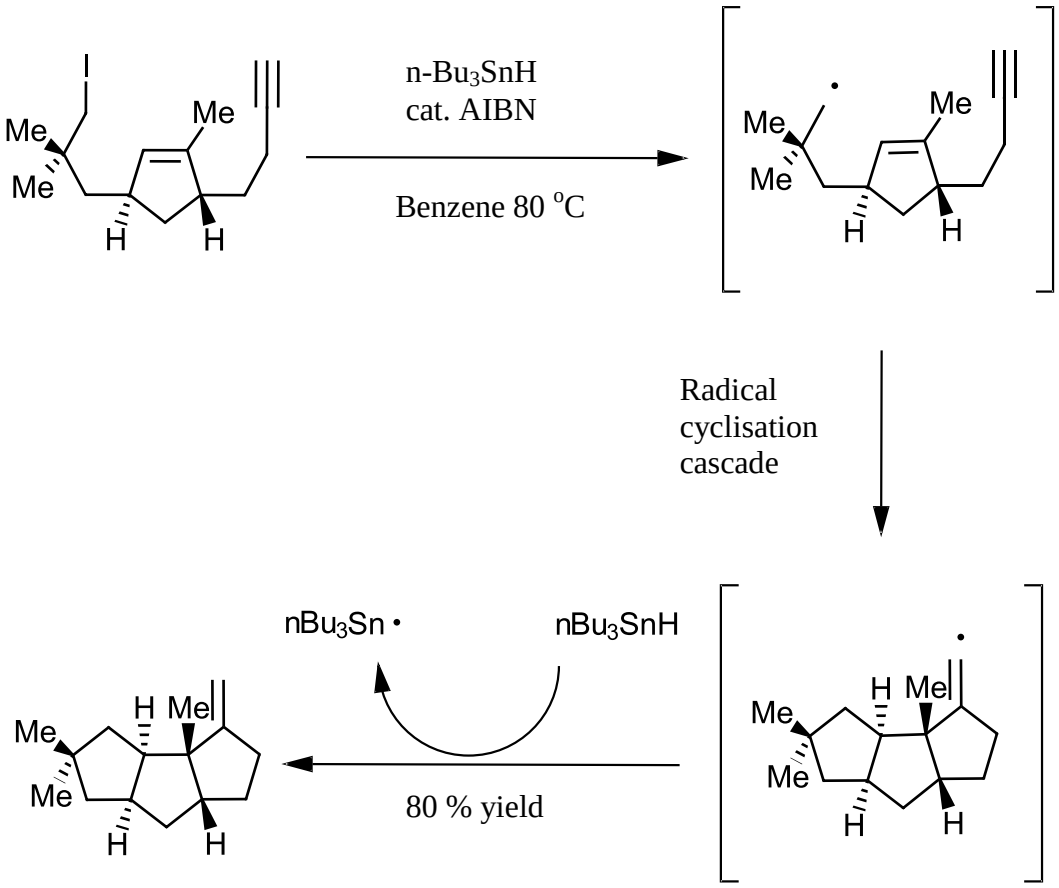


Figure 2 A radical cyclisation cascade in the total synthesis of (±)-hirsutene (Curran and Chen, 1985)

Hirsutene is a tricyclopentanoid natural product, and possesses antibiotic/antitumor activity[14]. The primary iodide is transformed directly into hirsutene. Two carbon-carbon bonds are formed, installing two continuous stereogenic centers (one quaternary) and furnishing two carbocyclic rings. This reaction is very fast, high yielding and stereoselective. In this case a cis-ring junction is formed, this is because 5-membered rings are relatively small; the transition state leading to the cis-ring is relatively free from strain therefore

allowing the SOMO to overlap efficiently with the π^* LUMO, this overlap is not possible in the transition state leading to a trans junction.

This example is one of many that dispelled the perception that free radicals were too reactive to be of any use in the efficient synthesis of small molecules and illustrates what tandem radical cyclisations are especially good for constructing highly hindered carbon-carbon bonds and forming quaternary centers.

Synthetic chemists have a particular interest in constructing a class of compound known as alkaloids. The construction of carbon-carbon bonds adjacent to nitrogen plays an important role in alkaloid chemistry. Alkaloids are of great interest due to their biological activity, two examples being indicine *N*-oxide (Figure 3) which has anti-cancer properties (a pyrrolizidine alkaloid)[15] and castanospermine (Figure 4) a potent glycosidase inhibitor and potential AIDS drug (an indolizidine alkaloid).[16]

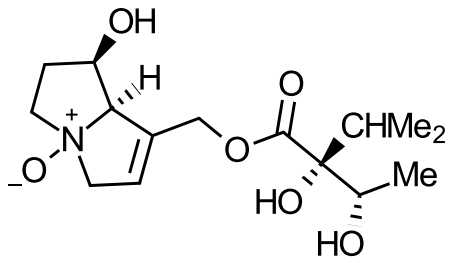


Figure 3 Structure of indicine *N*-oxide

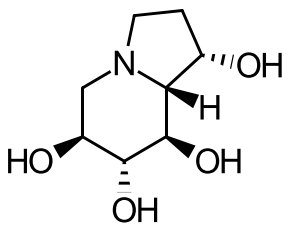
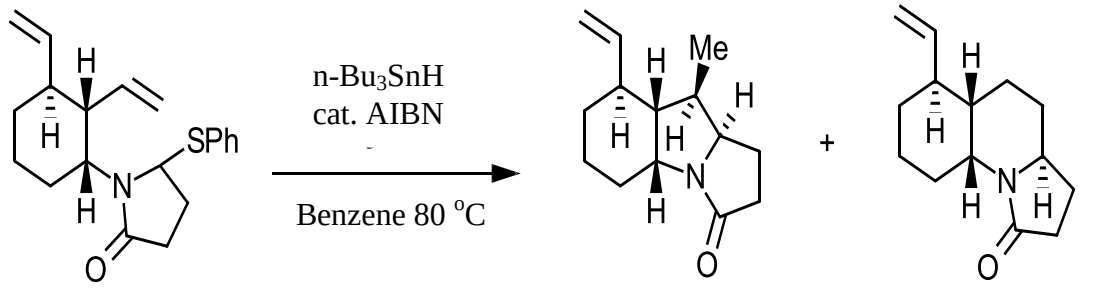


Figure 4 Structure of castanospermine

These molecular architectures can be constructed using radical cyclisations by generating α-amino and α -acylamino radicals using tributyltin hydride.

An early pioneer of this chemistry was David Hart[17], who developed in the 1980's selective routes to these alkaloids using tributlytin hydride, the success of which is demonstrated below (Figure 5).[18]



Exo 51% yield Endo 31% yield

Figure 5 Cyclisation of a thiophenoxylactam with Bu_3SnH (Hart, 1981)

The treatment of a precursor thiophenoxylactam with Bu_3SnH gave an *exo*-cyclisation product and an *endo*-cyclisation product. The *endo*-product is an intermediate in the synthesis of the indolizidine alkaloid gephyrotoxinm (Figure 6). No reduction products were obtained and both cyclisations proceeded with high stereoselectivity

Gephyrotoxin is a naturally occurring natural product that comes from the tropical Harlequin poison dart frog (Colombia). This alkaloid skin secretion has shown interesting neurological activity[19]. Another route to these alkaloids has been developed by Parsons[20] using a tandem radical cascade (Figure 7).

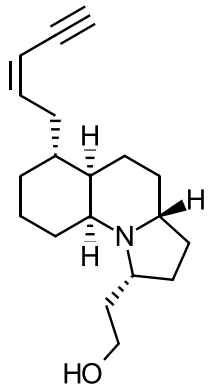


Figure 6 Structure of the natural product gephyrotoxin

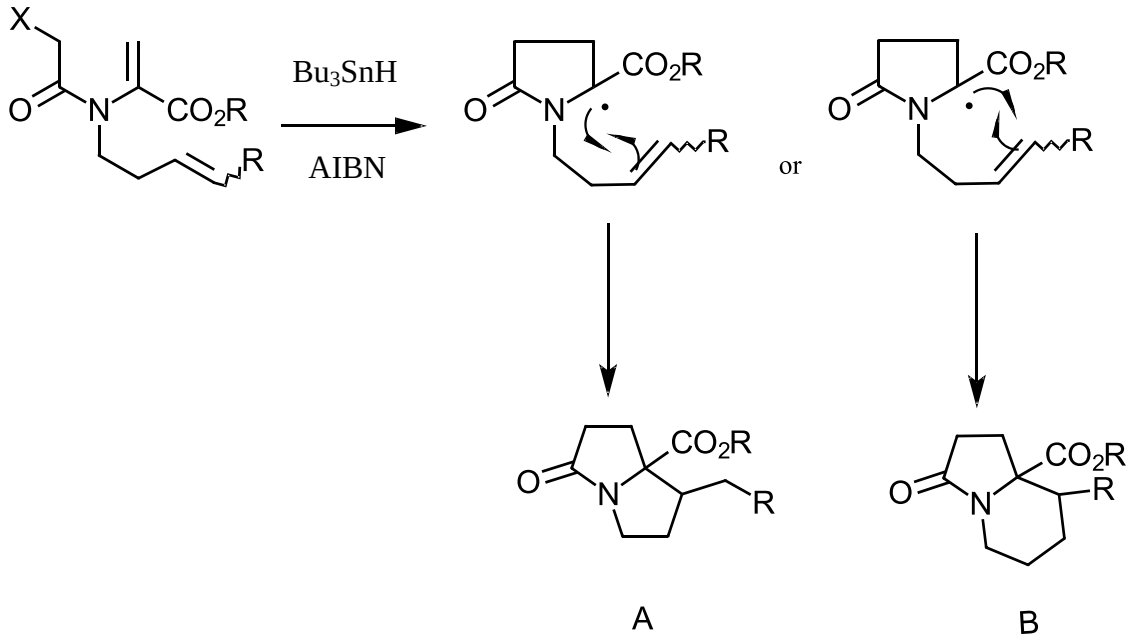


Figure 7 Tandem radical cyclisation leading to indolizidinones and pyrrolizidinones (Parsons, 1998)

This tandem cyclisation approach provides a quick and mild entry to both indolizidine and pyrrolizidine ring systems. The selectivity and high yield of this reaction towards to indolizidine is particularly impressive (Route B, Figure 7). A good example of a high yielding indolizidine reaction is shown below (Figure 8), with a single diastereoisomer of a tricyclic product being isolated in 61% yield.

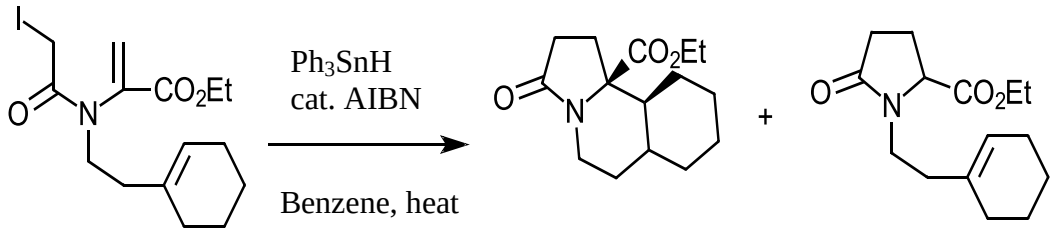


Figure 8 Regioselective tandem radical cyclisation using Ph_3SnH (a 5-endo-6-endo cyclisation sequence)

The reason behind this exclusive 6-*endo*-cyclisation to the tri-substitued double bond is due to steric obstruction. The attraction of this chemistry is not only its high yields or regioselectivity but it can be augmented to give different cyclisation products this time through a 5-*endo*-5-*exo*-cyclisation pathway (Route A, Figure 7). In the next example the pyrrolizidinone product is isolated in a comfortable 55% yield (Figure 9).

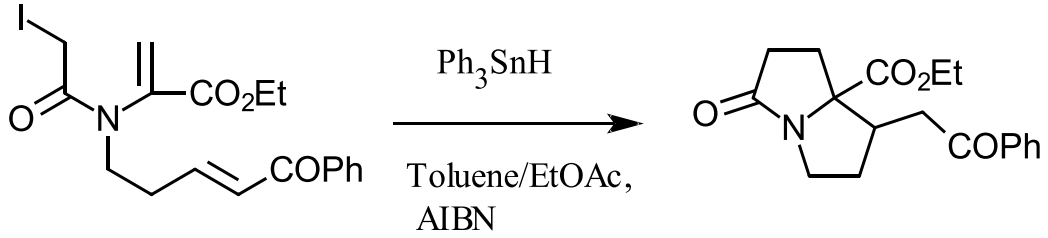


Figure 9 Regioselective tandem radical cyclisation using Ph_3SnH (a 5-endo-5-exo cyclisation sequence)

The regioslectivity can be effectively modulated by the ester substituent which is stabilising the radical in the transition state, seducing it into a 5-*exo* cyclisation.

As elegant as these examples are, the general deployment of these reagents in the synthesis of pharmaceuticals in industry is not likely or desirable due to their

severe toxicity. This presents a challenge and opportunity for interested synthetic chemists to meet this problem. The search for alternative stable, non-metal, free radical species capable of abstracting hydrogen from these compounds is being pursued. One class of compounds that has potential to fill this role are nitroxides.

1.3 Nitroxides And Their Uses In Organic Synthesis

1.3.1 **Nitroxides and their stability**

Nitroxides or nitroxyl radicals are *N*,*N*-disubstituted NO radicals with a delocalised unpaired electron shared between the nitrogen and the oxygen atoms (Figure 10).

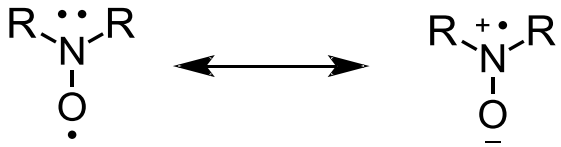


Figure 10 Stability of N-oxy radical owes much to delocalisation of the unpaired electron over N-O bond

Nitroxyl radicals owe their stability to several factors; they have sufficient conjugation with the nitrogen's lone pair. Various conformational advantages aid this conjugation, there is no twisting of the N-O bond and no substiuents are present of the oxygen atom. The stability of nitroxides is influenced by the electron density on the nitrogen, for example aminoxyl radicals (Figure 11) are more stable than imidoxyl radicals (Figure 12) as the alkyl groups donate electron

density towards the nitrogen, while the acyl groups will decrease the spin density on the nitrogen as they are electron withdrawing groups[21].

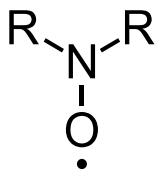


Figure 11 Aminoxyl radical

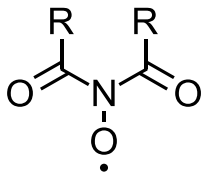


Figure 12 Imidoxyl radical

1.3.2 Synthetic Applications of TEMPO (2,2,6,6-Tetramethylpiperidin-1-yloxyl)

Nitroxides first featured in synthetic procedures with an inorganic nitroxide called Fremy's salt (Figure 13), which has been used as an oxidant in organic synthesis for many years[22], useful for oxidising phenols to quinones (Figure 14)[23].

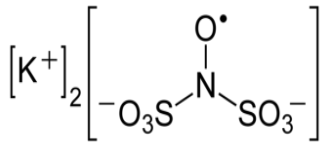


Figure 13 Fremy's salt

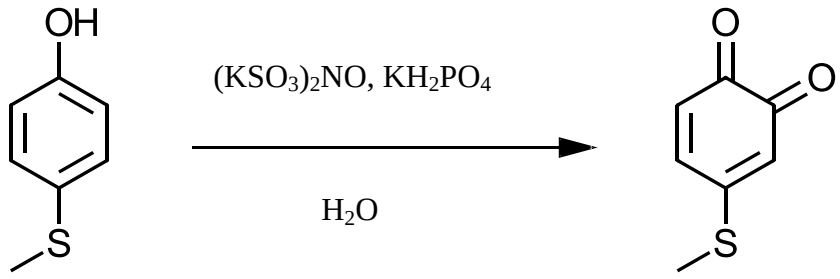
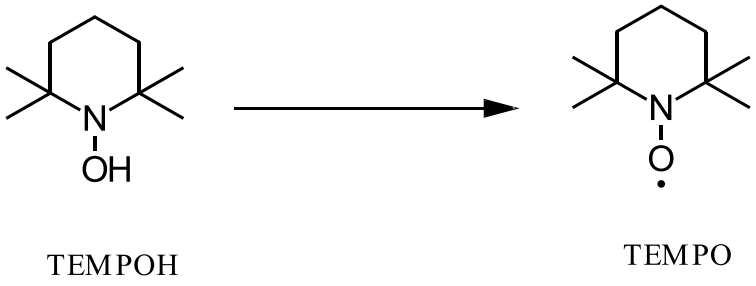


Figure 14 Phenol oxidation to a quinone

But by far the most synthetically successful organic nitroxide is TEMPO (or 2,2,6,6-tetramethylpiperidine-1-oxyl) (Figure 15), which is easily prepared, stable and persistent[24]. TEMPO was first reported by the Russian duo Lebedev and Kazarnovsky back in 1959[25].



TEMPOH TEMPO

Figure 15 Structures of TEMPOH and TEMPO radical

Since TEMPO's debut it has found extensive applications in synthetic chemistry documented in numerous reviews[26], primarily as a catalyst for oxidation reactions, for instance in the oxidation of alcohols. One of the most widely studied TEMPO oxidations are copper-TEMPO catalysis reactions with oxygen, an early example by Semmelhack et al[27], which showed that benzylic or allylic alcohols could be oxidised into aldehydes (Figure 16).

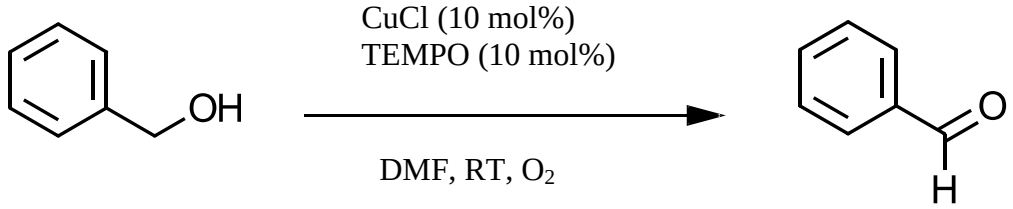


Figure 16 Cu(I)-TEMPO catalysis (Semmelhack, 1984)[27]

Sheldon et al. have studied these systems in great detail and have published many papers and reviews[28] on the exact nature of the reaction mechanism. Sheldon et al.

have also developed new and more selective Cu-TEMPO alcohol oxidations[29]. For example the reaction below has a remarkable selectivity for primary alcohols (Figure 17).

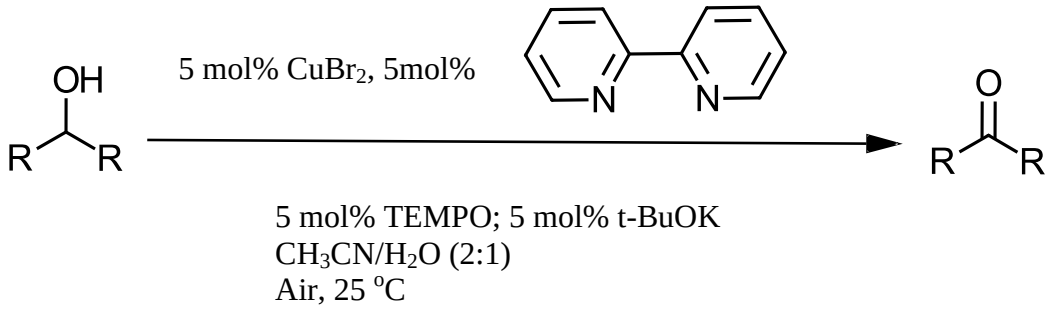


Figure 17 Selective copper-TEMPO oxidation (Sheldon, 2003) [29]

Sheldon has also developed useful ruthenium-TEMPO alcohol oxidation reactions[30] (Figure 18), which can oxidise a broad scope of alcohols and is a useful alternative to traditional metal based oxidation methods.

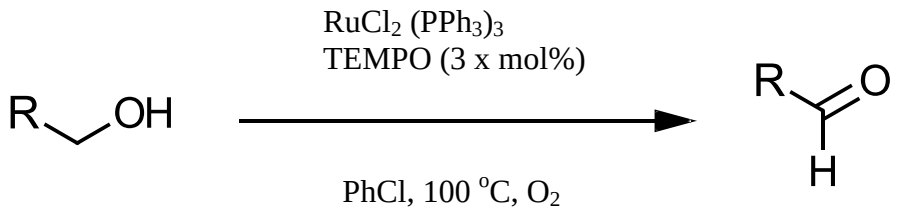
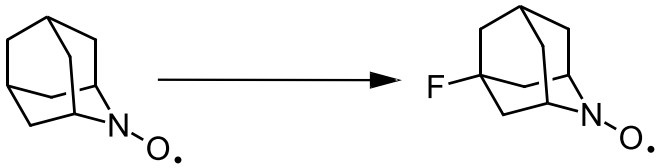


Figure 18 Ruthenium-TEMPO catalysis with O_2 (Sheldon, 2001) [30]

TEMPO however is inefficient for oxidising hindered secondary alcohols; however another nitroxide, the AZADO radical (Figure 19), can be used to oxidise sterically hindered alcohols with greater efficiency than TEMPO.[31]



AZADO 5-F-AZADO

Figure 19 Introduction of fluorine at C_5 position (Iwabuchi, 2011) [31]

Iwabuchi et al.[32] used a fluorinated AZADO radical (Figure 19) for greater efficiency still and can manage a diverse range of hindered alcohols (Figure 20)

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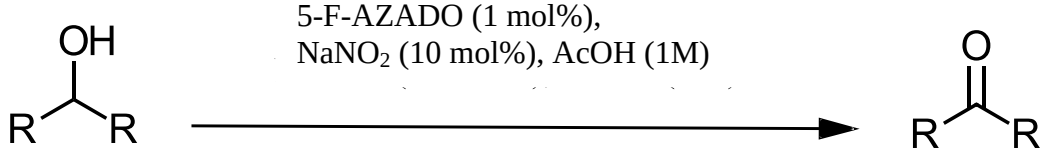


Figure 20 Oxidation of hindered secondary alcohols using 5-F-AZADO radical (Iwabuchi, 2011)[32]

As useful and benign as these TEMPO reactions are, they are of no assistance for radical cyclisations. There are a few examples of TEMPO H-abstraction[33], but the simple truth of it is that TEMPO is not up to the task. This is due to its stability, which is related to the O-H bond dissociation energy (BDE) in the parent hydroxylamine. The alkyl groups in TEMPO donate electron density to the nitrogen which increases conjugation and decreasing the BDE of the O-H and making it limited in its scope with regards to H-abstraction. H-abstraction by TEMPO will be highly endothermic with most substrates.

However, TEMPO is finding new oxidative roles, with a lot of interest in C-H activation, the aspiration of being able to stimulate reactions at C-H bonds rather than having to pre-functionalise a compound is very attractive and a rapidly advancing field of synthetic chemistry. For example Baran et al[34] has found a way to install double bonds into unactivated carbon chains. Trifluoroacetic acid generates a radical on the aryl ring, which abstracts a hydrogen from the nearby carbon to generate a second radical, which is then oxidised to a cation, followed by deprotonation to make an alkene. In this way TEMPO is a radical oxidant, and does not abstract a hydrogen atom but it is a good example of the use of TEMPO expanding into new and exciting areas (Figure 21).

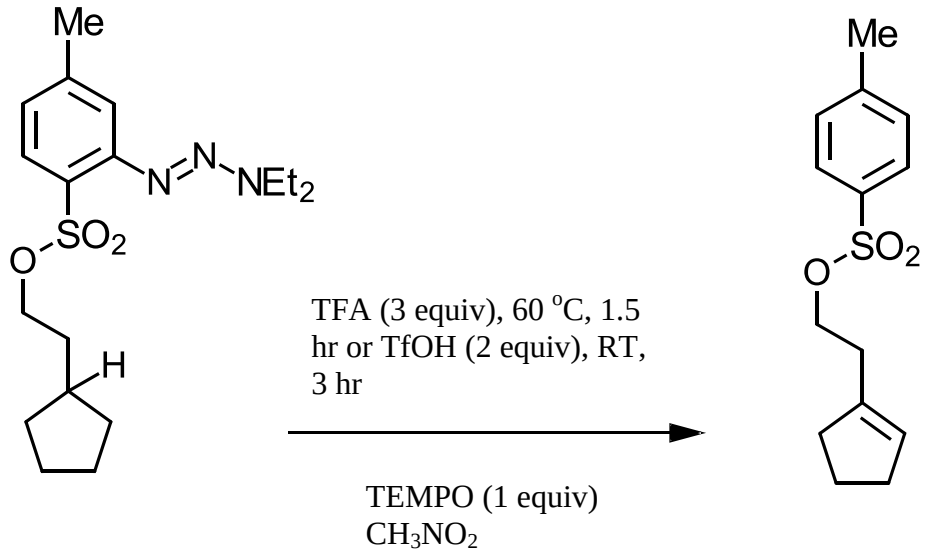
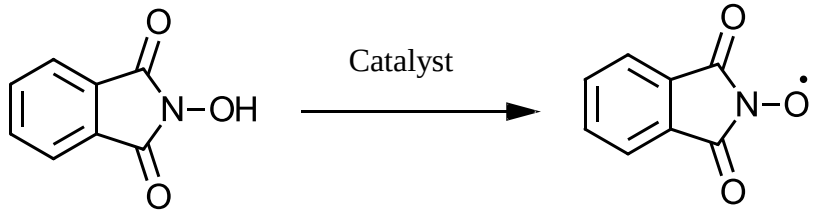


Figure 21 Selective introduction of C=C bonds (Baran, 2012)[34]

1.3.3 Synthetic applications of PINO (phthalimide *N*-oxyl)



NHPI PINO

Figure 22 Structure of NHPI and PINO radical

There is an alternative persistent nitroxide[35] available in the form of phthalimide N-oxyl radical or PINO (Figure 22). This can be generated from NHPI with various oxidants and is far more reactive than TEMPO. The greater reactivity of PINO is due to its relative instability, the acyl groups next to the nitrogen are electron with drawing in nature and therefore decrease electron density on the nitrogen and increasing the BDE of the O-H bond in NHPI which translates to greater reactivity of the nitroxyl radical.

The O-H bond energy in NHPI is very close to the O-H bond in an alkylhydroperoxide, therefore H-abstractions from most organic substrates will be mildly exothermic.

An early example of use of NHPI in synthesis is Grochowski's[36] coupling reaction between ethers and DEAD (diethyl azodicarboxylate) published in 1977 (Figure 23).

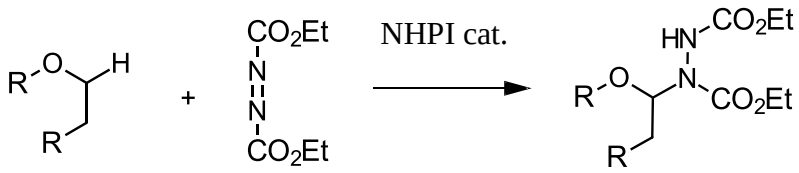


Figure 23 NHPI-mediated coupling between ethers and DEAD (Grochowski, 1977)[36]

One reaction of particular interest is a nitroxide-catalysed methodology developed by Ishii et al.[37] Which is often referred to as the "Ishii system". This system has been shown to oxidise C-H bonds using O_2: potentially providing a green alternative method for the oxidation of bulk chemicals. Ishii has accomplished the remarkable feat of oxidising alkanes[38] (Figure 24), though the conversions fot simple alkanes are low.

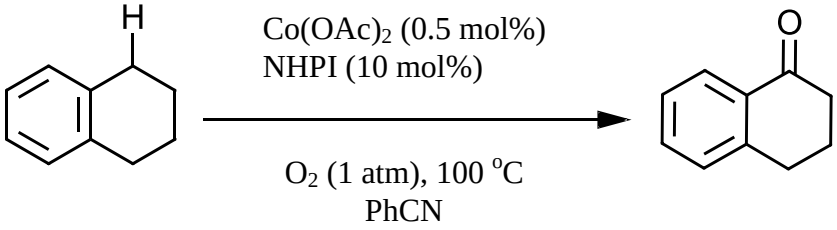


Figure 24 Alkane C(sp^3)-H oxidation catalysed by NHPI (Ishii, 1995) [38]

The methodology can boast the accolade of the first example of catalytic aerobic oxidation of toluene at room temperature[39] (Figure 25).

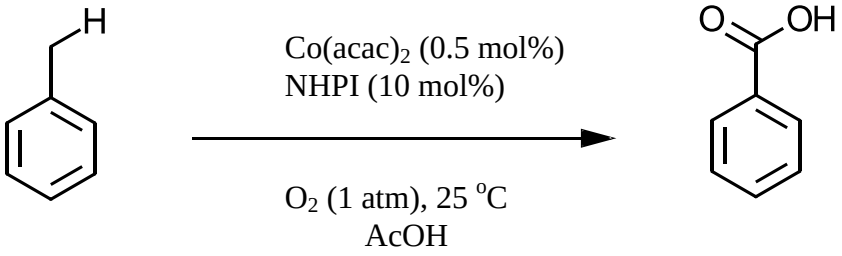


Figure 25 Aerobic oxidation of toluene at room temperature (Ishii, 1997) [39]

But by far the most intriguing accomplishment of Ishii, is the system's ability to perform intermolecular radical additions[40], Radicals derived from dioxolanes can add to electron-poor alkenes to form the corresponding β-hydroxy derivatives (Figure 26).

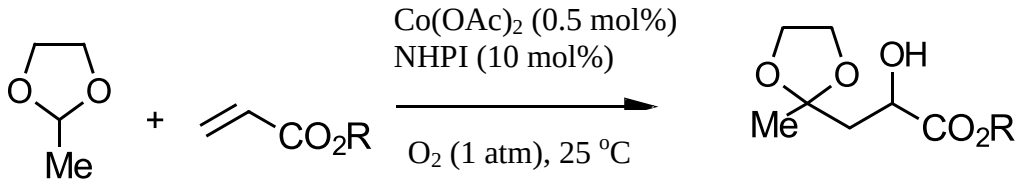


Figure 26 Ishii system's application for C-C bond formation

This carbon-carbon forming reaction is, triggered by H-abstraction from the dioxolane by PINO. If PINO can remove hydrogen from dioxolane could it possibly generate an alpha-acylamino radical, or related radicals that could undergo an intramolecular radical cyclisation?

1.4 Research Objective

Free radical oxidations play an important role in natural processes including ageing[41] and have a wide use in synthesis. However these transformations are often described as "difficult reactions," typically giving numerous products in low yields, with poor selectivity. Many metal-based conventional catalysts are toxic and difficult to separate. Recently organic oxidation catalysts started attracting attention due to the potential for tunable selectivity and cleaner[42], more environmentally friendly chemistry. This is however an emerging area of

synthetic chemistry and only a few catalysts have been successful. One of these successful catalysts is a class of organic radicals called nitroxides.

This thesis is concerned with investigating the viability of nitroxides as a potential alternative in intramolecular carbon-carbon bond forming radical reactions. The Ishii system, which was detailed in the previous section, will be the ideal nitroxide based methodology to exploit for this investigation.

The global aim being developing environmentally benign chemistry, operating at an ambient temperatures. It is envisaged that this chemistry can be exploited in order to perform oxidative intramolecular radical cyclisations, as illustrated in Figure 27. It is hoped that such a technology could offer a viable alternative to trialkyltin reagents. Alternative nitroxide systems and benign alternative radical initiators will also be explored (e.g. N-halosuccinimides and alkylboranes)

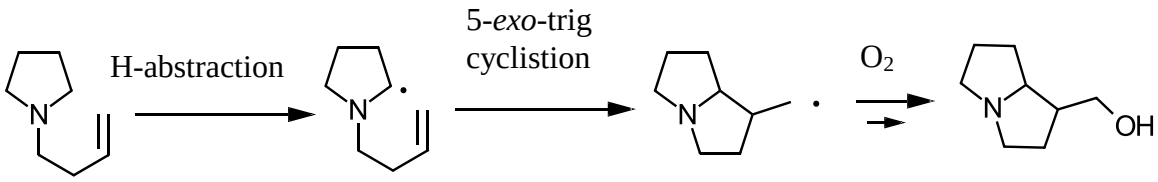


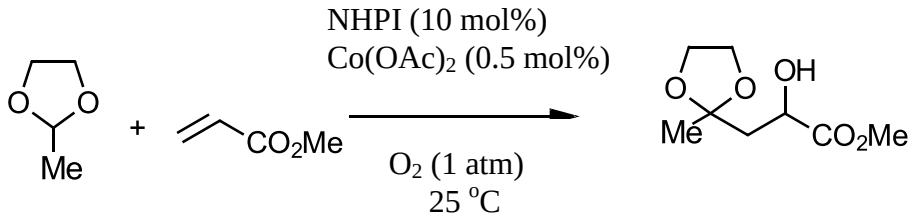
Figure 27 Potential med-chem relevant, oxidative intramolecular radical cyclisation, constructing pyrrolizidinone alkaloid structures.

Lactams bearing unsaturated chains will be synthesised and then subjected to different nitroxides and other stable free radicals and their reactivity explored. The following chapters documents the pursuit of such a cyclisation technology

Chapter Two: Results and Discussion

2.1 Optimisation of Ishii's Nitroxide-catalysed Radical Addition Reaction

As mentioned in the Introduction the project aims to exploit Ishii's nitroxide-catalysed radical addition[40] chemistry to perform some oxidative intramolecular reactions to construct useful alkaloids. Before exploring new radical cyclisation methodology, Ishii's work was replicated. The reaction of interest is shown in Figure 28.



1a **1b** **1c**

Figure 28 Ishii's nitroxide-catalysed radical-addition, between methyl dioxolane and methyl acrylate

The mechanism of the reaction is shown in Figure 29, and starts by hydrogen abstraction from NHPI, using **1g** giving PINO which then abstracts a hydrogen atom from dioxolane **1a** to form a dioxolane radical. The (nucleophilic) radical adds regioselectivly to the acrylate C=C bond, yielding a radical adduct. In the presence of oxygen, the resulting radical is rapidly trapped by O_2 to give a hydroperoxyl radical which then forms hydroperoxide. It is well known that hydroperoxides are subject to redox decomposition by cobalt(II) ions to form an

alkoxyl radical which is eventually converted into the alcohol product **1c**, via hydrogen abstraction from either NHPI or dioxolane **1a**.

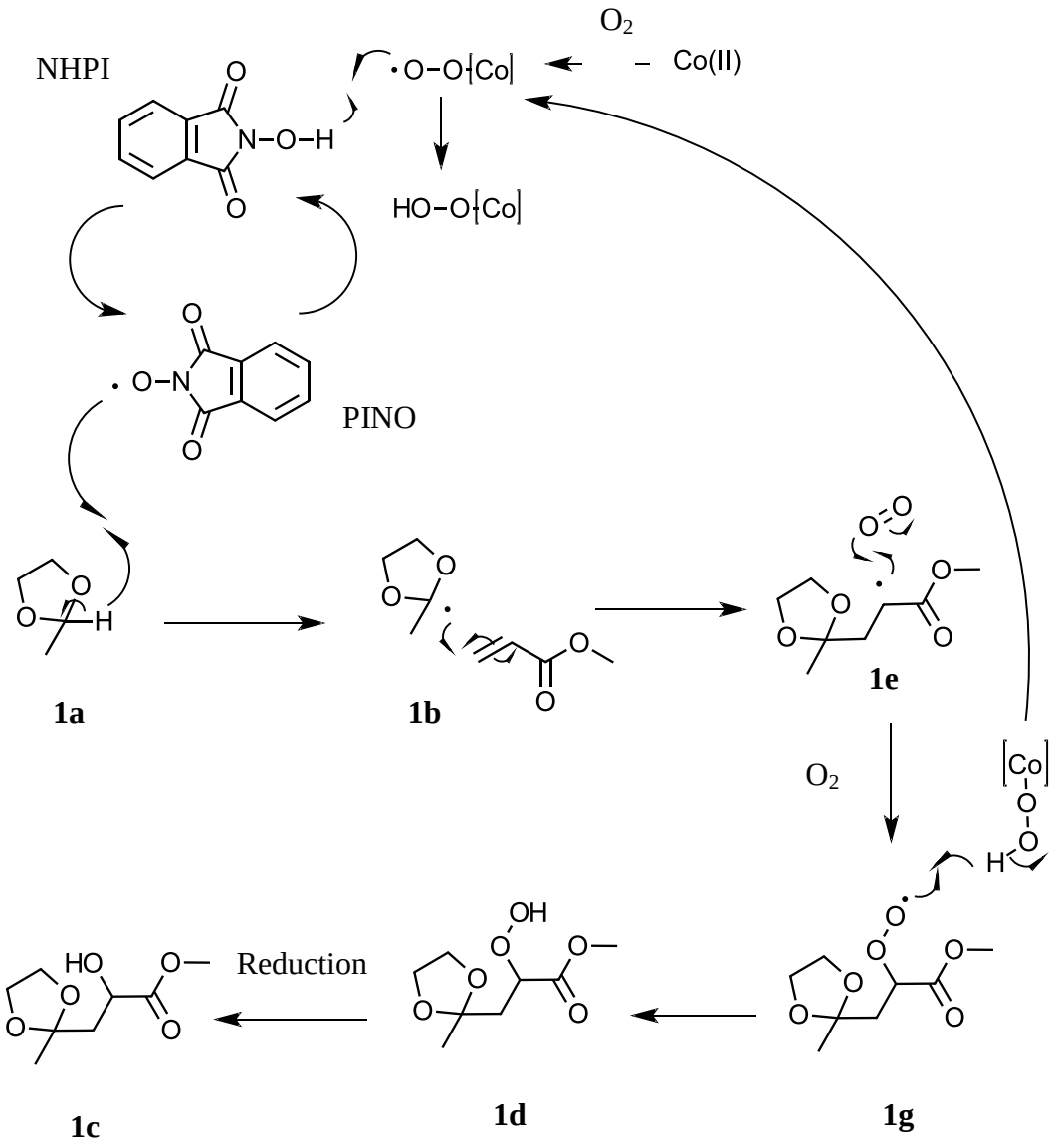


Figure 29 Plausible mechanism for the PINO catalysed radical addition, a Co(III)-dioxygen complex derived from the Co(II) species and O_2 assists the formation of the PINO radical from NHPI.

The Ishii conditions used catalytic amounts of NHPI and $Co(OAc)_2$ and molecular oxygen deployed from a balloon. The first time this reaction was investigated a balloon was not used to deliver the oxygen (air), but the reaction flask was left

open to atmospheric oxygen. The reaction did proceed albeit in low yield which was encouraging. But it was soon found that there were some unwritten intricacies to this reaction (next page).

Ishii reported the desired product **1c** being formed in 81% in 3 hours. On performing the reaction following the exact procedure as outlined in Ishii's paper, an average yield of only 33% was obtained (after column chromatography)

It was noticed that the reaction did not proceed as quickly as stated by Ishii; when worked up after 3 hours the typical yield of **1c** was 27-29%. Even leaving reaction mixture for much longer in later attempts did not increase the yield. However although longer reaction times did not improve the yield of **1c,** the yield of an unreported side product did increase.

It is important to get the delivery of oxygen correct in order to achieve reasonable yield of **1c**. Sticking in a balloon (affixed to a needle) and letting the reaction run its course did not lead to high yields of **1c**. From trial and error, it was found that placing the needle just barely above the surface of the reaction and periodically squeezing (gently) blowing oxygen against the side of the reaction flask causing a gentle bubbling worked well. Placing the needle into the solution and aggressively bubbling oxygen into the solution also works reasonably well, but it is not recommended. If you are attentive with the oxygen you will achieve much better yields of **1c**, although not the reported 81%.

It was envisaged that the side product could shed light on the significantly reduced yield of **1c** and the slow reaction times. Following isolation by column chromatography, the side product appeared as a colourless free flowing liquid, which when developed on a TLC plate using anisaldehyde as a stain appeared red in colour.

After spectroscopic analysis, NMR (^{1}H & ^{13}C) and ESI-MS, the side product was found to be ethylene glycol monoacetate (**1f**), as shown in Figure 30.

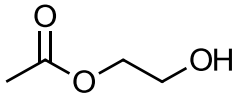


Figure 30 Structure of glycol monoacetate (**1f**)

Acetate **1f** was clearly a fragmentation product of methyl dioxolane **1a.** A plausible sequence leading to the formation of **1f** is shown below (Figure 32), as is the mechanism of dioxolane fragmentation (Figure 31).

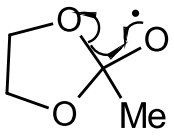


Figure 31 Mechanism of methyl dioxolane fragmentation

The fragmentation of dioxolane from structure **1h** is shown in the following scheme (Figure 32).

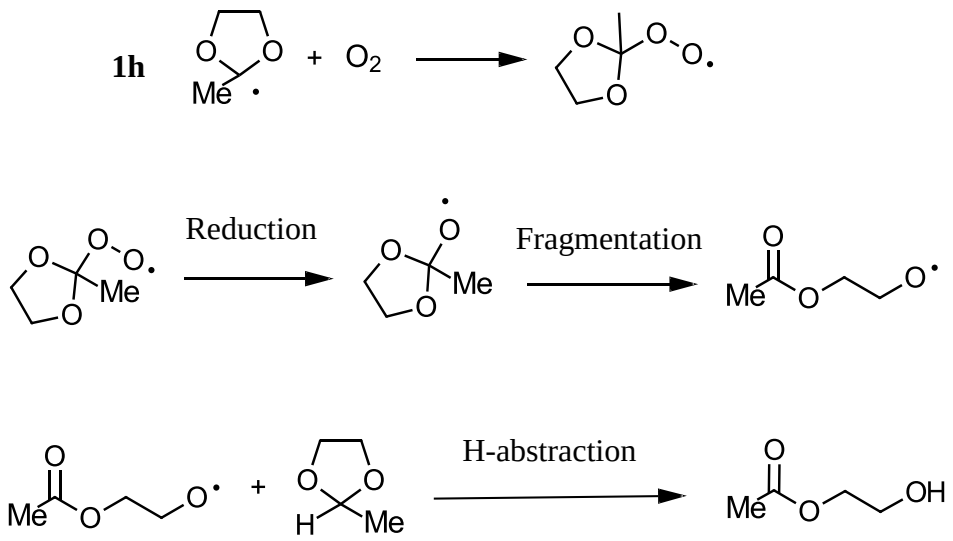


Figure 32 Fragmentation of methyl dioxolane.

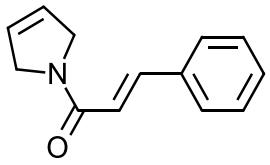
A control reaction was devised to establish what was causing the formation of the side product. The same conditions as before were used except the absence of methyl acrylate from the reaction mixture; after nine hours of vigorous stirring at room temperature, a 45% yield of ethylene glycol monoacetate was obtained, which increased to 86% if the reaction was left overnight. It was rationalised that possibly MEHQ inhibitor present in the acrylates was affecting the selectivity and allowing the radical fragmentation to time to compete effectively with the intended intermolecular radical addition.

To see if the was the case; methyl acrylate (**1b**) was run through a pipette of alumina which removed the inhibitors present. The reaction was performed again with the inhibitor free methyl dioxolane, which gave a vast improvement in the yield of **1c**, after 6-7 hours it was isolated in 60% yield. However efforts to replicate Ishii's yield of 81% for **1c** within the same time frame reported, were unsuccessful.

The reaction successfully showed that PINO is able to abstract a hydrogen atom from dioxolane **1a** and generate a carbon-centred radical. Consequently it was decided to move on and explore the use of this methodology to mediate intramolecular reactions.

2.2 Synthesis of 1-(2,5-Dihydro-pyrrol-1-yl)-3-phenyl-propenone (2a) and Subsequent Cyclisation Attempts

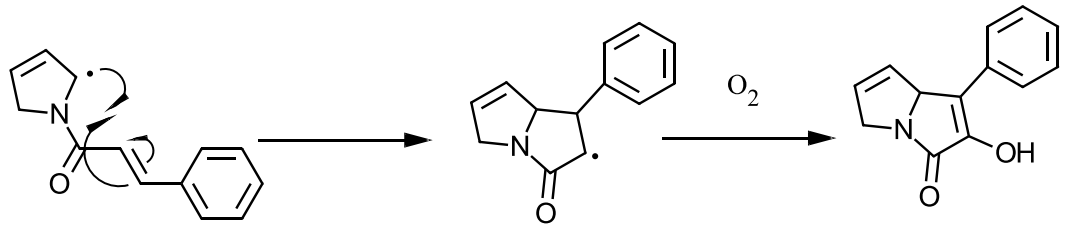
Having confirmed that PINO has potential to be used as an initiator of carbon-centred radical reactions, a model compound was selected (**2a**) to investigate cyclisation reactions (Figure 33).



2a

Figure 33 Structure of 1-(2,5-dihydro-pyrrol-1-yl)-3-phenyl-propenone

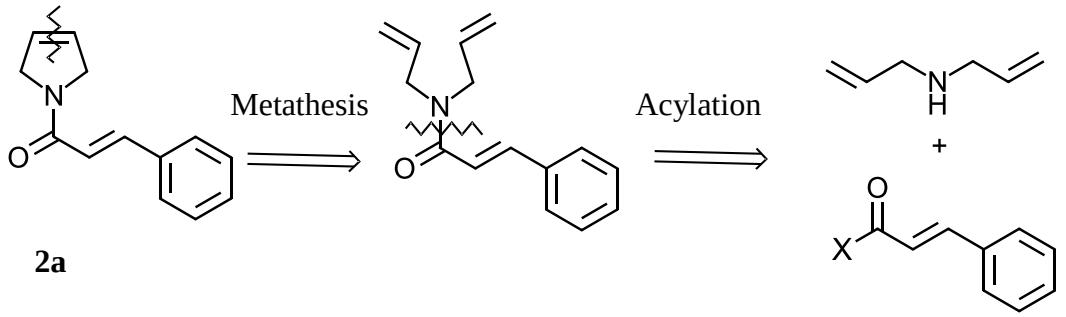
It was envisaged that PINO would abstract a hydrogen atom from the NCH_2C group of **2a** to form a (NCH•C) radical (Figure 34). This resonance-stabilised radical could then undergo an intramolecular cyclisation. A 4-*exo*-trig cyclisation is possible or alternatively a 5-*endo*-trig cyclisation (as shown in **2b**), generating radical species **2c**, which after trapping with molecular oxygen and reduction of the hydroperoxide was expected to give pyrrolizidone like structures **2d**.



2b **2c** **2d**

Figure 34 5-endo-trig cyclisation of **2b**

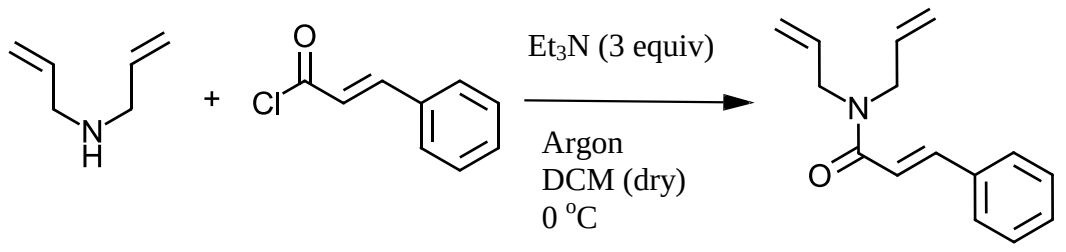
Having selected a suitable model compound to explore this chemistry, it was necessary to first synthesise **2a**. A RSA of the proposed route to **2a** is shown in Figure 35.



2a

Figure 35 Retrosynthetic analysis of **2a**

2.2.1 Synthesis of *N*, *N*-Diallyl-3-phenyl-acrylamide (3c)



3a **3b** **3c**

Figure 36 Acylation of diallylamine with cinnamoyl chloride

The acylation of diallylamine[43] (**3a**) with cinnamoyl chloride (**3b**) was performed under anhydrous conditions (Figure 36). A flame-dried round-bottom flask and an argon atmosphere were used, into which anhydrous DCM was injected followed by diallylamine (**3a**). In a separate oven-dried round-bottom flask, cinnamoyl chloride (**3b**) was dissolved in dry DCM. Triethylamine (dry) was then injected into solution, which was cooled using a water-ice bath. Once the solution was sufficiently cold, the acyl chloride solution was added dropwise (via syringe) into the chilled solution.

After the addition was complete, the ice bath was removed and the solution was allowed to warm to room temperature. After 5 hours, water was added and the mixture worked up. The product (**3c**) was isolated as yellow oil, in an average (62-70%) yield of 67%. The reaction and purification presented no issues; it was a relatively straight-forward procedure.

2.2.2 Synthesis of 1-(2,5-Dihydro-pyrrol-1-yl)-3-phenyl-propenone (2a)

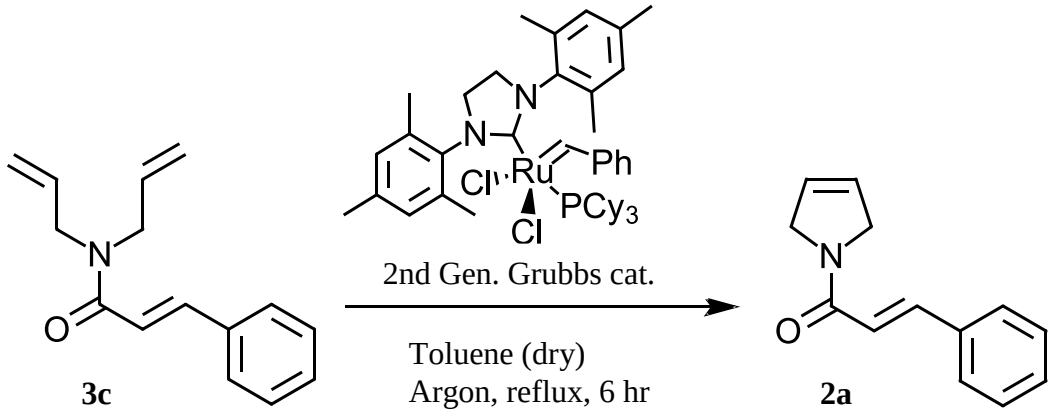
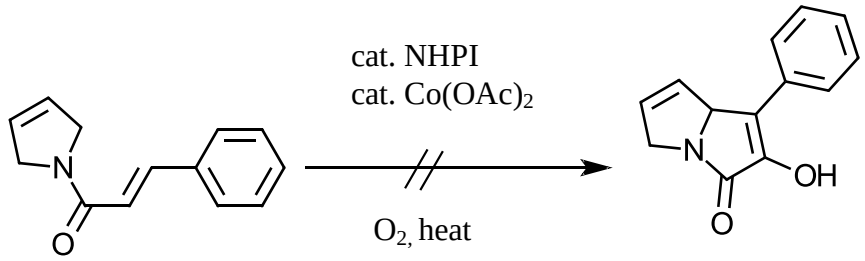


Figure 37 Grubbs metathesis of **3c** to **2a**

After successfully preparing **3c**, a metathesis reaction was used to form **2a** (Figure 37.). The reaction required optimisation to achieve satisfactory yields.

Initially a 2nd generation Grubbs catalyst[44] was used in dry DCM but the yield of **2a** was surprisingly poor. Next, two different solvents, dry MeCN or dry toluene, were investigated. The first performed equally poorly but the toluene performed much better, to give **2a** as a white powder in 62% yield. After purification, it is recommended to store **2a** under argon in a sealed vial in the fridge; it was found that it decomposes slightly over the space of a couple of weeks and turns from a white powder into an orange one.



2a **2d**

Figure 38 Failed cyclisation of **2a** using Ishii system

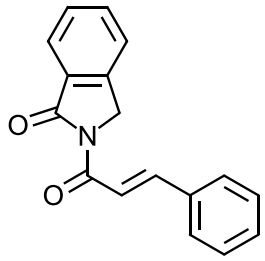
Attempts at using Ishii's methodology[40] to cyclise **2a** (Figure 38), to form **2d,** were not successful. The first problem encountered was the limited solubility of NHPI in various solvents at room temperature. Acetic acid was chosen as solvent, as not only did it dissolve NHPI, but numerous papers claimed it enhanced Ishii's chemistry.[45]

At room temperature, unfortunately, there was no reaction. On increasing the temperature of the reaction nothing was observed until 100 °C; analysis of the

reaction mixture by TLC, however, was extremely complex despite efforts to isolate anything from the mixture using column chromatography. It was apparent that compound **2a** was not reacting in a controllable manner. It was, however, stable in acetic acid at 100 $^{\circ}$C and so it was not degrading under the reaction conditions. It was eventually decided that the model compound **2a** needed to be re-redesigned to increase the reactivity to hydrogen atom abstraction.

2.3 Synthesis of 2-(3-Phenyl-acryloyl)-2,2-dihydro-isoindol-1-one and Subsequent Cyclisation Attempts.

The redesigned compound (**4a**) was chosen as the N-CH_2 hydrogen atoms were anticipated to be particularly susceptible to hydrogen-atom abstraction, due to increased radical stability by the presence of an aromatic ring and an additional carbonyl group (Figure 39).

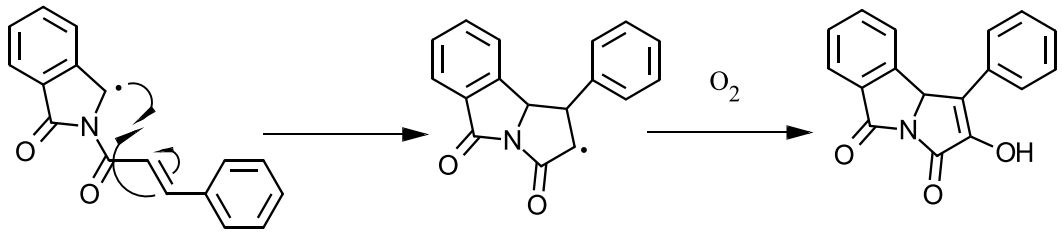


4a

Figure 39 Structure of 2-(3-phenyl-acryloyl)-2, 2-dihydro-isoindol-1-one

It was envisaged that PINO would abstract a hydrogen atom from the NCH_2C group of **4a** to form radical, **4b** (Figure 40). A 4-*exo*-trig cyclisation of **4b** is possible, or alternatively a 5-*endo*-trig cyclisation (as show below), generating

radical species **4c**, which after trapping with molecular oxygen, and reduction of the hydroperoxide was expected to give pyrrolizidinone-like structure **4d**.

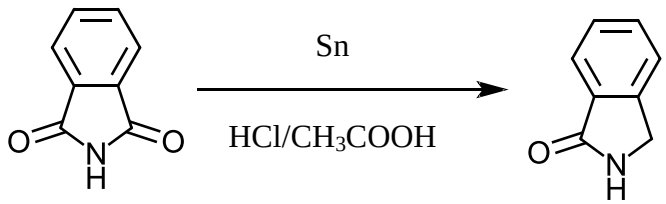


4b **4c** **4d**

Figure 40 5-*endo*-trig cyclisation of **4b**

2.3.1 Synthesis of 2-(3-Phenyl-acryloyl)-2,2-dihydro-isoindol-1-one (4a)

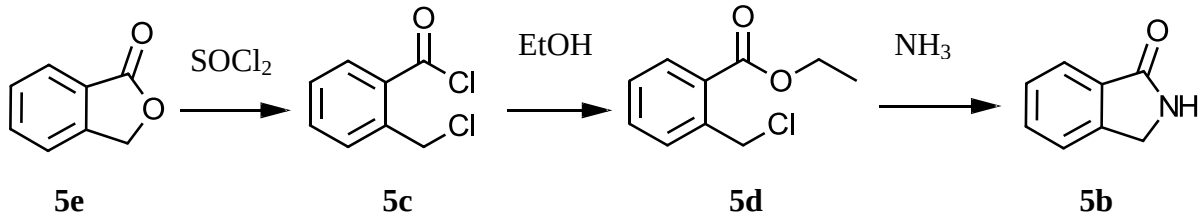
It was envisaged that **4a** could be prepared by *N*-acylation of **5b** (Figure 44). The first route to iso-indolinone **5b** involved reduction of phthalimide **5a** using tin and acid (Figure 41). This old fashioned method[45], involving suspending both phthalimide **5a** and an excess of tin in a 2:1 solution of HCl and acetic acid, and heating to reflux for 2 hours worked well. The yield of **5b** varied but on average was 55%. The compound was (unexpectedly) yellow, but it was not possible to remove the colouration (possibly due to contamination with a tin-containing impurity).



5a **5b**

Figure 41 Phthalimide reduction to iso-indolinone

The requirement for an excess of tin and the impurity causing the yellow colour, caused concern and it was decided to pursue a completely different synthetic route[47] as shown in Figure 42



5e **5c** **5d** **5b**

Figure 42 One-pot synthesis of iso-indolinone

Compound **5c** was manufactured from phthalide (**5e**), which was dissolved in xylene along with benzyltriethylammonium chloride and treated with BF_3-etherate complex. The mixture was refluxed at 100 $^{\circ}$C and thionyl chloride was added very slowly over one hour, and then refluxed at 130 $^{\circ}$C for 9 hours. The excess solvent was distilled off along with residual thionyl chloride under reduced pressure. Purification gave compound **5c** as a clear liquid in 90% yield.

This reaction proved very easy to scale up and gave **5c** in high yields. This was important as the next step was shown to be low-yielding. By manufacturing large quantities of **5c**, it was possible to circumvent this short-coming.

The next step involved the one pot synthesis of iso-indolinone **5b** from **5c**, by first generating an intermediate ester (**5d**), by refluxing **5c** in ethanol for 1 hour and then cooling before adding slowly ammonium hydroxide. Compound **5d** undergoes an intramolecular lactamisation to give **5b** (Figure 43). The solution turned a light orange colour initially then a light yellow when the reaction was complete.

After the reaction had finished the reaction mixture was extracted with dichloromethane. The combined extracts were dried with anhydrous Mg_2SO_4, the solvent was evaporated in vacuo and the residue was recrystallized from benzene (or alternatively toluene) to give iso-indolinone **5b** in 38% yield, as fine clear needle crystals. Although modest, the 38% yield can be increased when using an ammonia gas cylinder, saturating an ethanol solution of **5c** with ammonia gave 80% yield of **5b**. The mechanism of the reaction of **5d** with ammonia, to form iso-indolinone **5b** is shown in Figure 43.

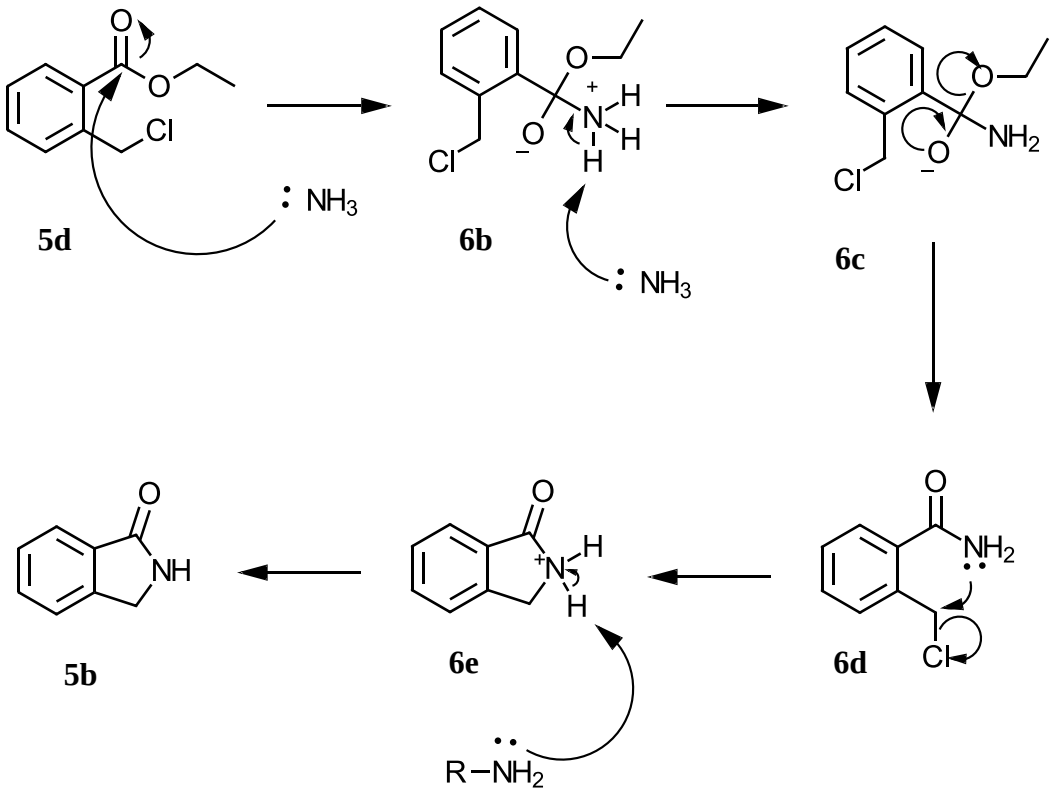
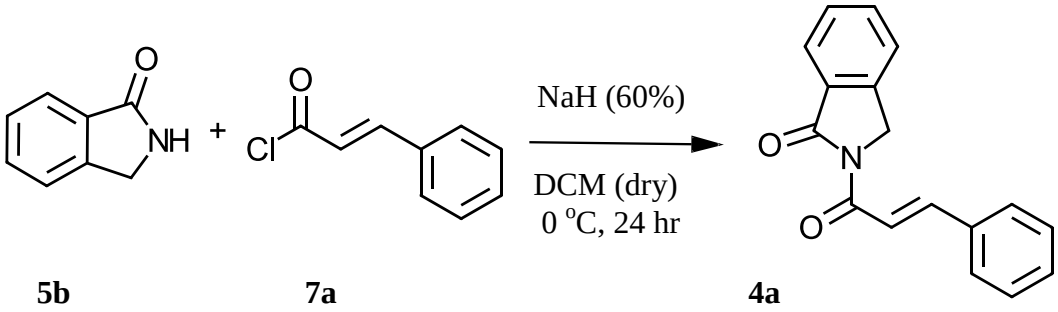


Figure 43 Intramolecular lactamisation mechanism.

2.3.2 Synthesis of 2-(3-Phenyl-acryloyl)-2, 2-dihydro-isoindol-1-one (4a)

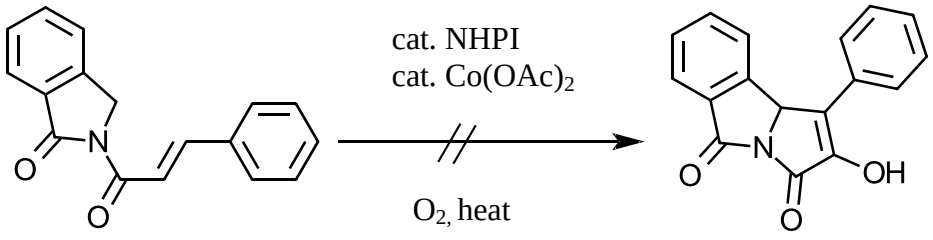
The next step in the synthesis of **4a** was straight-forward[48] (Figure 44).



5b **7a** **4a**

Figure 44 Synthesis of 2-(3-phenyl-acryloyl)-2,2-dihydro-isoindol-1-one

Sodium hydride in anhydrous DCM was added to a solution of iso-indolinone **5b** in dry DCM. The flask was cooled in a water/ice bath, and a solution of cinnamoyl chloride **7a** in DCM was slowly injected into the flask over a period of 30 minutes. The reaction was left to stir for 24 hours, after which a white solid was obtained. Re-crystallisation with benzene gave thin white fluffy needles of **4a** in a 66% yield.



4a **4d**

Figure 45 Failed cyclisation of **4a** using the Ishii system

Treating **4a** with NHPI in acetic acid was investigated at room temperature but surprisingly no reaction was observed (Figure 45). Successive attempts of varying the amount of catalyst, the temperature and the allotted time, did not result in a reaction. The reason for the lack of success is unknown and worthy of further investigation.

The research then moved on from Ishii's work, to investigate the radical cyclisation of **4a** using a different nitroxide-based C-C bond forming reaction. Interestingly, in the literature, TEMPO had been shown to couple nitromethane to acridine (Figure 46).[49]

It was envisaged that an acridine and **4a** would have comparable reactivity to hydrogen abstraction.

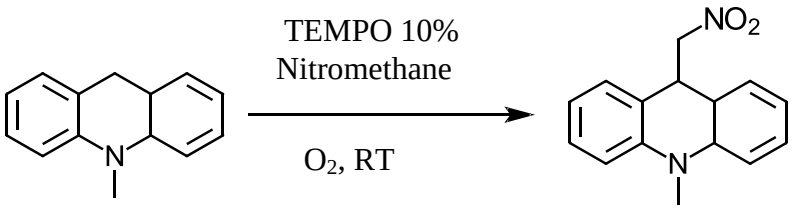
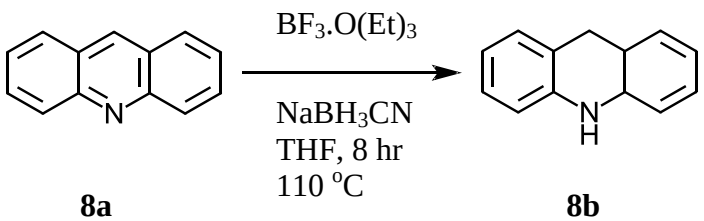


Figure 46 Coupling of nitromethane to an acridine using TEMPO catalyst

Initially the reported chemistry was replicated. This first involved the synthesis of 10-methyl-9,-10-dihydroacridine (**8c**) [50], via **8b**, as shown in Figure 48.

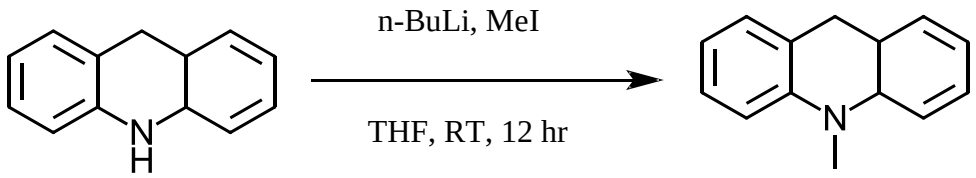


8a **8b**

Figure 47 Quinoline reduction

Compound **8b** was prepared by reacting a solution of quinoline **8a**, sodium cyanoborohydride and boron trifluoride etherate in dry THF at reflux for 8 hours. Purification of the crude product by silica gel column chromatography furnished the desired product in 65% yield (Figure 47).

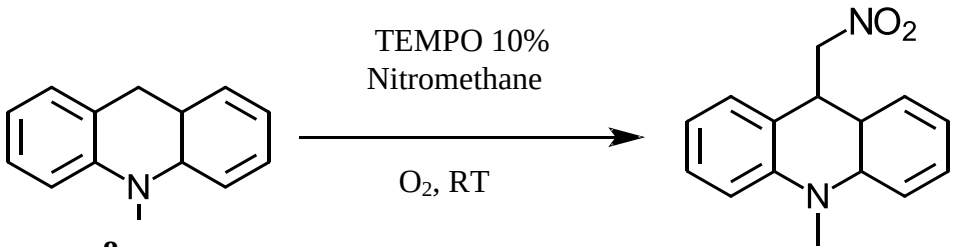
Next acridine **8c** was formed by *N*-methylation of **8b**[51] (Figure 48). Following deprotonation of **8b** using n-butyllithium in dry THF, iodomethane was added to give **8c** in 91% yield as a white solid.



8b **8c**

Figure 48 N-Methylation of **8b**

Next a solution of 10-methyl-9,10-dihydroacridine and TEMPO was stirred at 60 °C under O_2 (1atm) for 18 hours. The solvent was removed and the residue was purified by silica gel column chromatography to afford the desired product in 92% yield as a red solid (Figure 49)



8c **8d**

Figure 49 Successful coupling of nitromethane to **8c**

The ^{1}H NMR spectrum of compound **8d** (Figure 50 and 117) shows a triplet at 7.28 ppm which integrates to two protons (J = 7.8 Hz), a doublet at 7.21 ppm which integrates again to two protons (J = 6.8 Hz) and further along a multiplet at 6.95-6.99 ppm which integrates to four protons. These protons make up collectively the eight aromatic protons. The four protons at 6.95-6.99 ppm are likely to be the protons on the aromatic ring. The triplet at 4.79 ppm (J = 8 Hz) integrates to one, this proton is attached to C1 (31.2 ppm). The doublet at 4.33 ppm (C3, J = 8 Hz) integrates to two, this is the CH_2 directly next to the nitro group. The singlet at 3.40 ppm integrates to three, which is the methyl group.

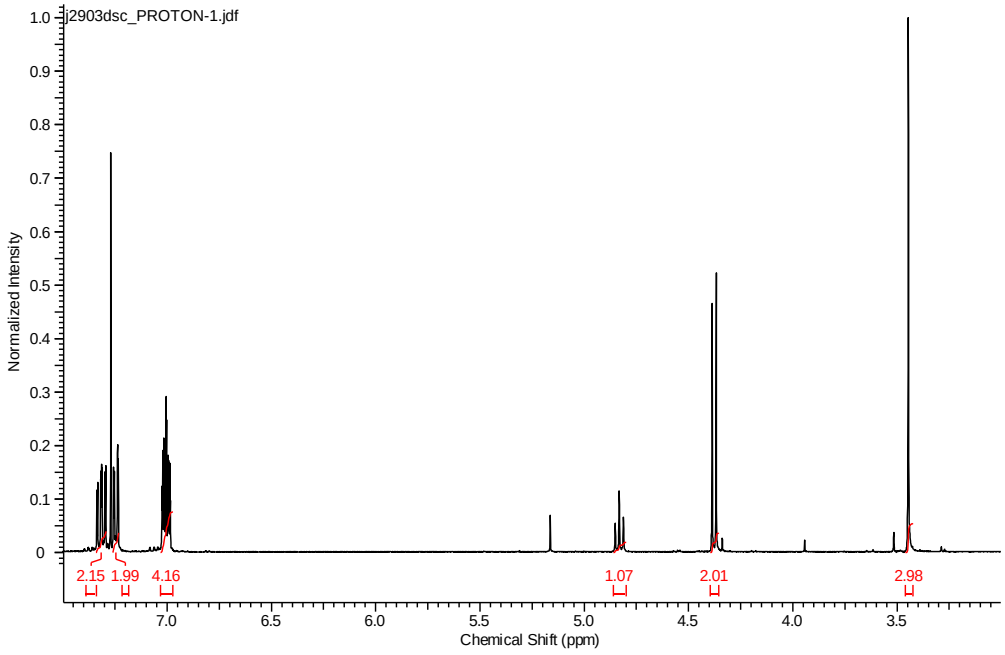
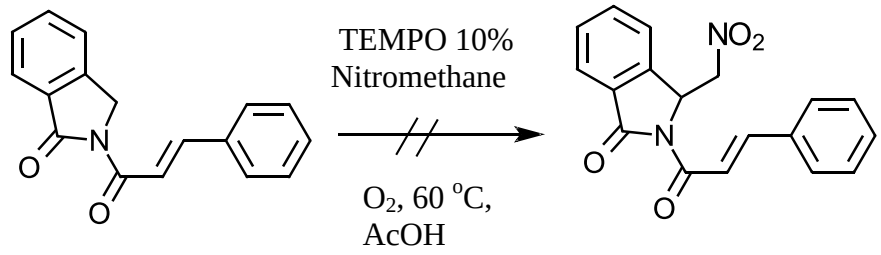


Figure 50 ^{1}H NMR spectrum of (**8d**) at 400 MHz in $CDCl_3$

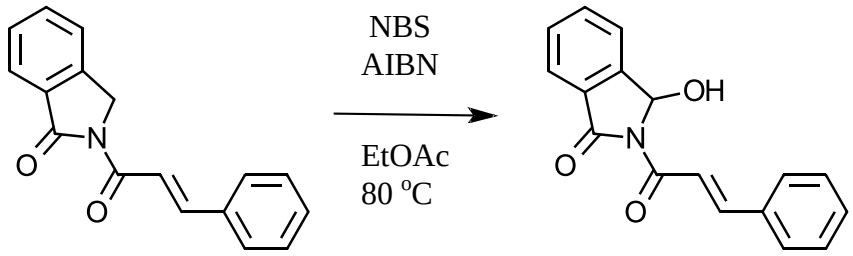
Pleased that the procedure worked as reported, the same reaction conditions were then applied to **4a** (Figure 50). Unfortunately **4a** failed to react, even when stoichiometric amounts of TEMPO were used.



4a **8e**

Figure 51 Attempted reactions of **4a** with mitromethane

After exhausting these options, attention turned to the use of *N*-bromosuccinimide (NBS)[52] to see if it would perform any radical chemistry on the stubborn **4a** (Figure 51). Thankfully for the first time, this combination resulted in some activity.



4a **9b**

Figure 52 Formation of hydroxyl-lactam **9b**

To a solution of **4a** and AIBN in EtOAc, NBS was added and the reaction was refluxed for 12 hours. Purification of the reaction mixture by column chromatography resulted in the formation of **9b** as a white solid in an excellent 80% yield.

NMR spectroscopic analysis showed that the NCH_2 peak in **4a** had vanished, which was great news. A combination of ESI and NMR convincingly showed that the product was **9b**.

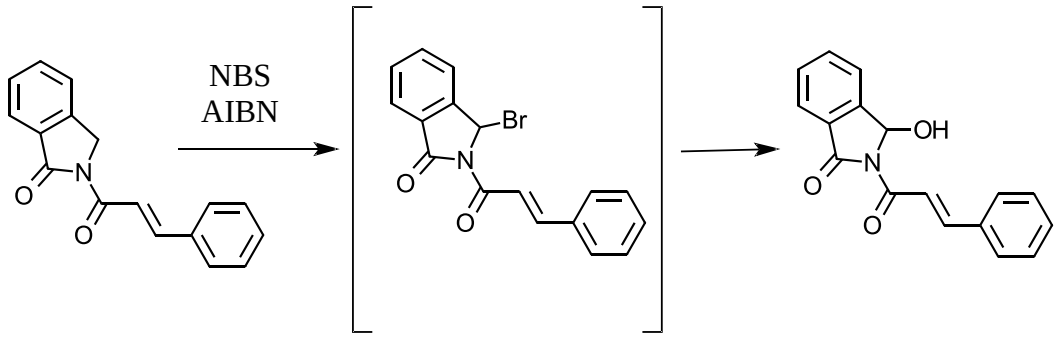


Figure 53 Mechanistic explanations for hydroxyl-lactam formation **9b**

A possible mechanism to form **9b** (Figure 53) involves the formation of bromide **9a**, presumably via a benzylic radical. Bromide **9a** is rapidly hydrolysed into the alcohol on workup. This reaction finally showed that a NCH_2 hydrogen atom could be abstracted, although there was no cyclisation. This led to redesigning the precursor once again, this time extending the carbon chain and removing steric bulk in the hope that the intermediate benzylic radical would cyclise onto the terminal C=C bond of **10a** (Figure 54)

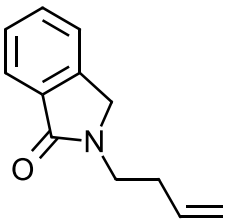
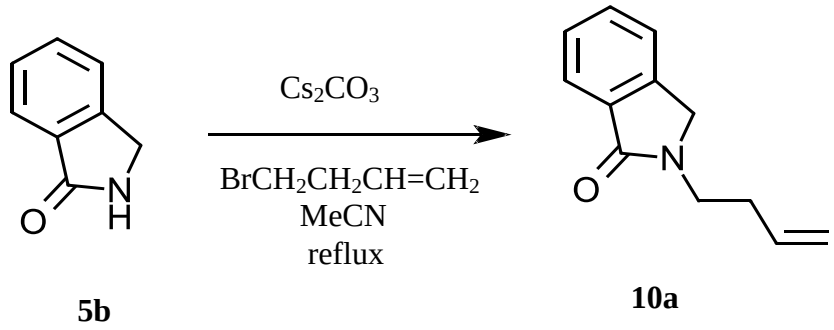


Figure 54 Structure of 2-but-3-enyl-2,3-dihydro-indol-1-one (**10a**)

2.4 Synthesis of 2-But-3-enyl-2,3-dihydro-indol-1-one (10a) and Subsequent Cyclisation Attempts



5b **10a**

Figure 55 N-Alkylation of **5b** using caesium carbonate

To prepare **10a**, iso-indolinone **5b** was *N*-alkylated using caesium carbonate[53] and 4-bromobut-1-ene at 80 °C (Figure 55). Purification by column chromatography afforded **10a** as a yellow oil in 79% yield. The product was analysed by ESI and NMR spectroscopic analysis. The product has the formula $C_{12}H_{13}NO$, which is consistent with the structure of **10a** (Figure 54). The ^{1}H NMR is shown below (Figure 56).

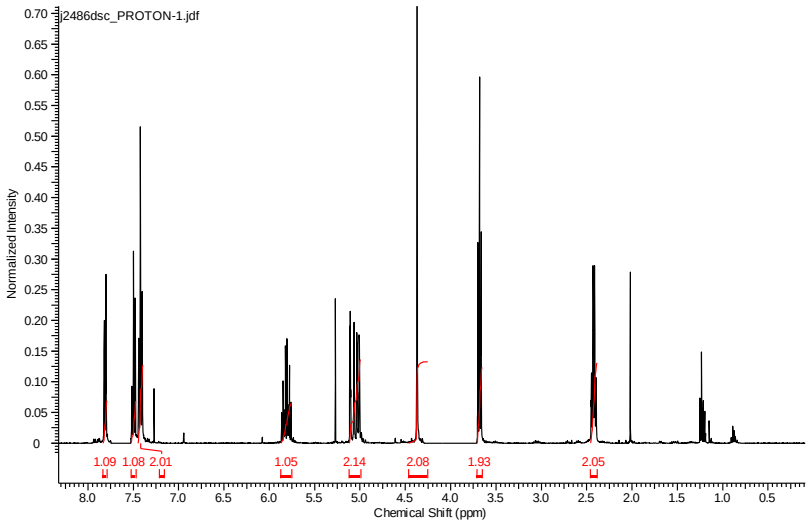


Figure 56 ^{1}H NMR spectrum of compound **10a** (400 MHz, $CDCl_3$)

The aromatic protons of **10a** consist of the doublet at 7.81 ppm which integrates to one (J = 8.34 Hz), the multiplet at 7.47-7.52 ppm integrates to one proton and the multiplet at 7.40-7.44 ppm) which integrates to two protons. The multiplet at 5.75-5.87 ppm integrates to one proton bonded to C11 (141.2 ppm) and is the allylic CH. The multiplet at 5.00-5.11 ppm integrates to two protons which are bonded to C4 (117.2 ppm) and is the terminal allylic CH_2 of **10a**. The singlet at 4.37 ppm integrates to two protons and is bonded directly to C3 (50.2 ppm) and is the CH_2 of the lactam adjacent to the nitrogen. The multiplet at 3.66-3.70 ppm integrates to two protons and is bonded directly at C2 (42 ppm) position, the first carbon of the unsaturated chain bonded to the nitrogen. The multiplet at 2.39-2.45 ppm integrates to two protons which are bonded to C1 (33 ppm).

Now that **10a** was readily available, it was envisaged that reaction with NBS would lead to **10e** by the mechanism shown in Figure 57.

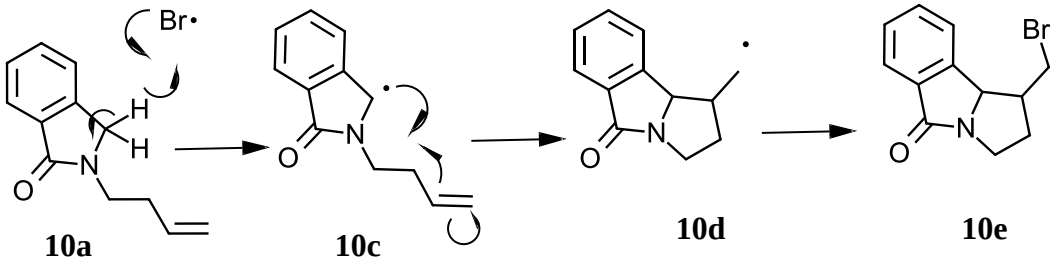
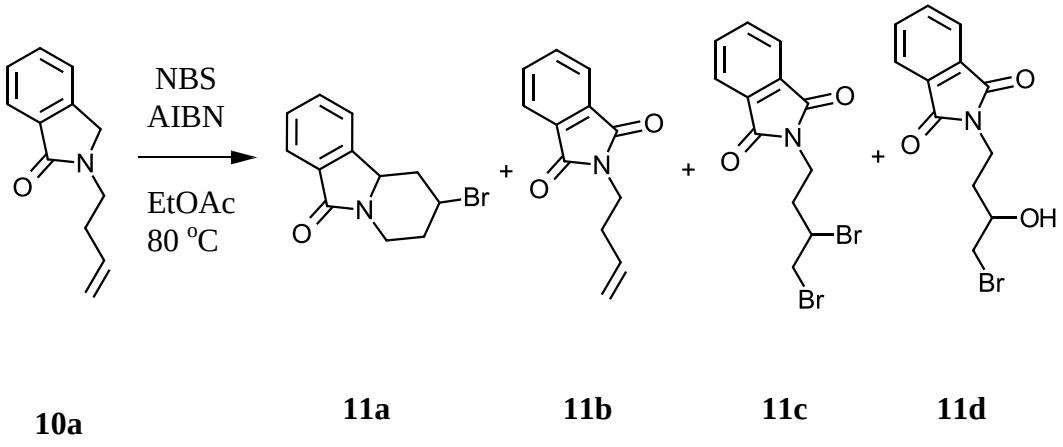


Figure 57 Proposed NBS-mediated cyclisation

First **10a** in EtOAc was reacted with NBS and AIBN; during reflux an orange insoluble gel started to collect on the sides of the flask. The reaction did not reach completion after 5 hours; TLC analysis showed four new products had formed, all

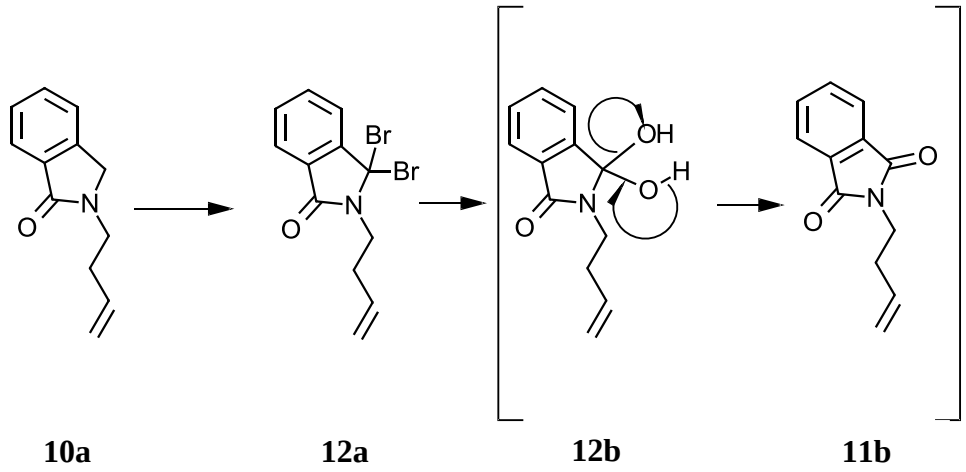
UV active. On cooling the mixture, succinimide precipitated out of the solution. The crude product was subject to column chromatography on silica gel and products **11a-d** were isolated (Figure 58). Unexpectedly, 6-ring compound **11a** was formed.



10a **11a** **11b** **11c** **11d**

Figure 58 Resulting products of NBS reaction, successful cyclisation

Compound **11a** is a light yellow solid isolated in 4-6% yield; **11b** is sticky oil (orange) isolated in 31% yield, **11c** is a yellow crystalline solid isolated in 36% yield; and **11d** is a white solid isolated in 27% yield. Although the yield of **11a was** low, it was very pleasing to see the formation of cyclised product **11a**. A possible mechanism to explain the formation of **11b**, involving double bromination and hydrolysis is shown in Figure 59.



10a **12a** **12b** **11b**

Figure 59 Mechanistic explanations for maleimide formation

The products were analysed using ESI-MS and NMR spectroscopic analysis. Compound **11c** has the formula $C_{12}H_{11}Br_2NO_2$. This suggested the compound had been brominated and had acquired and addition oxygen atom. The ^{1}H NMR spectrum below (Figure 60) suggested a compound that has symmetric aromatic protons and the CH_2 of the starting material (**10a**) was no longer present.

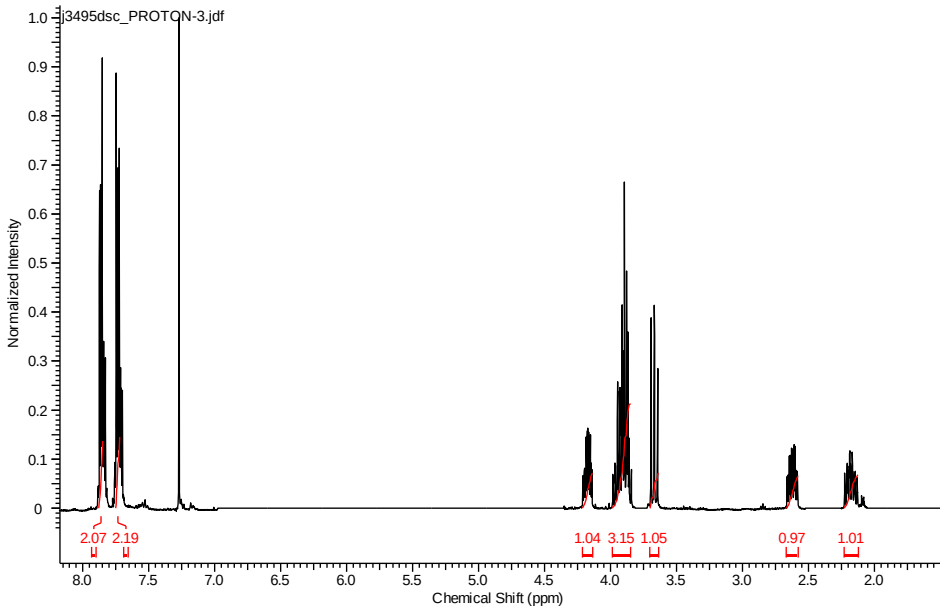


Figure 60 ^{1}H NMR spectrum of compound **11c** (400 MHz, $CDCl_3$)

The ^{1}H NMR spectrum of **11c** shows a multiplet at 7.85-7.88 ppm, which integrates to two protons. Another multiplet which integrates to two protons is found at 7.72-7.74 ppm. The complex multiplet at 4.12-4.21 ppm integrates to one and by using HSQC is bonded to C4 at 48.8 ppm. The complex multiplet at 3.84-3.99 ppm integrates to three, two protons are bonded directly onto C3 (36 ppm) and one to C2 (35 ppm). The triplet at 3.64 ppm integrates to one and is also bonded to C2. The multiplet at 2.53-67 ppm integrates to one, and is bonded directly to C1 (34.9 ppm) the multiplet at 2.13-2.23 ppm is also bonded directly to C1.

This data along with COSY interactions strongly supported the structure of **11c** with the double bond being brominated and the CH_2 being oxidised to a maleimide in the same way **11b** was in Figure 59.

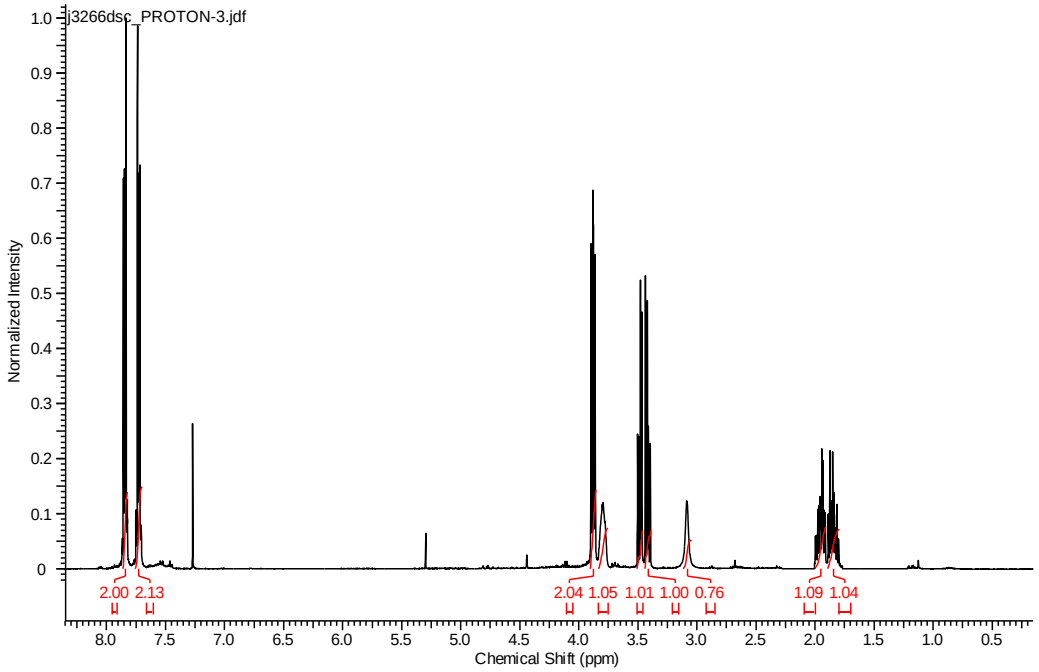


Figure 61 ^{1}H NMR spectrum of compound of **11d**

Spectroscopic analysis of compound **11d** revealed the formula $C_{12}H_{12}BrNO_3$, having one less bromine atom than **11c** and an extra oxygen and hydrogen atom. The ^1H NMR spectrum of compound **11d** is shown (Figure 61), the aromatic region similar to **11c** which indicates it is a maleimide. The double of doublets at 7.82-97 ppm integrates to two protons (J= 3, 8.59 Hz). The double of doublets at 7.70-75 ppm also integrates to two (J= 3, 8.54 Hz). The double of doublets at 3.85-91 ppm integrates to two protons (J= 3, 7.63 Hz), HSQC indicates that one proton is bonded to C1 (34.2 ppm) and the other to C3 (38.9 ppm). The multiplet at 3.80 ppm integrates to one proton and bonded to C4 (68.5 ppm). The multiplet at 3.46-51 ppm integrates to one proton and bonded to C2 (34.7 ppm). The multiplet at 3.39-44 ppm integrates to one proton is also bonded to C2. The multiplet at 3.09 integrates to one proton, does not bond to a carbon suggesting that it is attached to oxygen. The multiplet at 1.91-2.00 ppm integrates to one proton and is bonded to C1. The multiplet at 1.80-1.89 integrates to one proton and is bonded to C3. Compound **11d** therefore has a hydroxyl group at the C4 position. This data along with data from COSY interactions strongly supported the structure of **11d**.

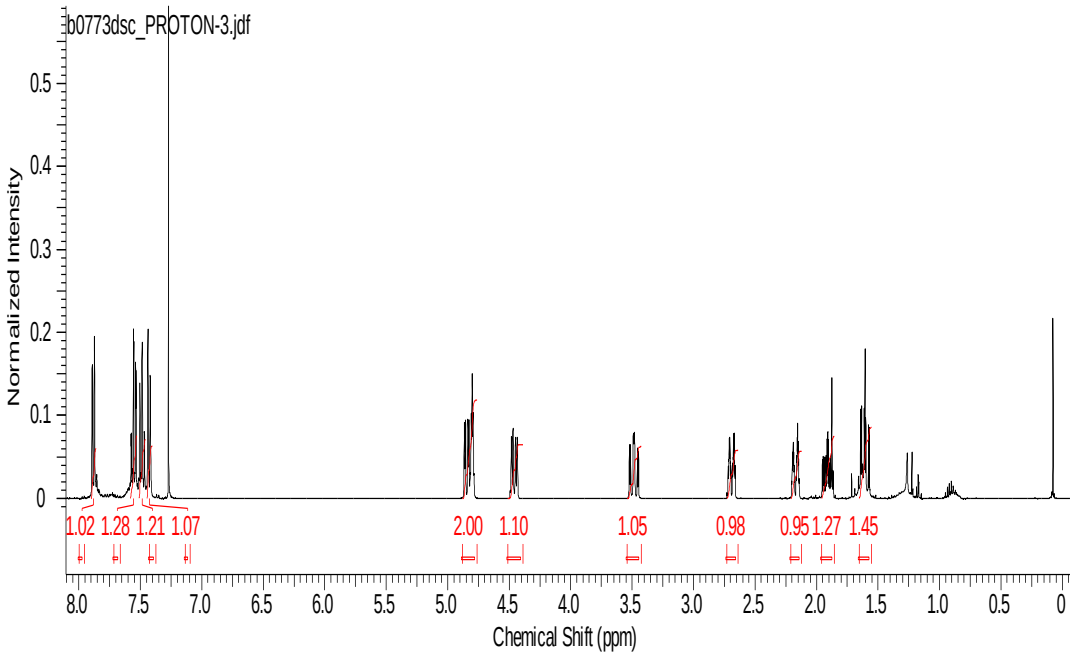


Figure 62 H^1 NMR spectrum of **11a (**400 MHz, $CDCl_3$)

The ^{1}H NMR spectrum of **11a** is shown in Figure 62. The aromatic structure was intact (Figure 63) and the CH_2 singlet (δ 4.35) in **10a** was no longer visible. Integration revealed 12 hydrogens consistent with the molecular structure of **11a**. ESI confirmed the molecular formula as $C_{12}H_{12}BrNO$. Interestingly only a single isomer of **11a** was formed as indicted by single resonances in the spectrum, the stereochemistry of which is unknown. All the protons have been assigned letters, and their chemical shifts and COSY interactions are listed in Table 1. Initially it was not possible to confidently assign the structure of **11a** due to the quality of the 2D NMR spectra, the COSY interactions were only of acceptable quality.

Proton	δ (ppm)	App.	Int.	J(Hz)	COSY
A	7.88	d	1	7	H_C
B	7.55	t	1	7	H_D
C	7.49	t	1	7	H_A
D	7.43	d	1	7	H_B
E	4.84	dd	1	11,3	H_L. H_I
F	4.80	br s	1	-	H_J, H_I
G	4.46	dd	1	14,5	H_K, H_H
H	3.49	td	1	15,3	H_K,H_J, H_G
I	2.69	d	1	13	H_L,H_E(w), H_F(w)
J	2.17	d	1	14	H_K,H_H
K	1.91	m	1	-	H_H, H_G,H_J
L	1.61	ddd	1	14,11,3	H_I, H_E, H_F

Table 1 Tabulated NMR Data for 11a (400 MHz, $CDCl_3$, 20 ^oC)

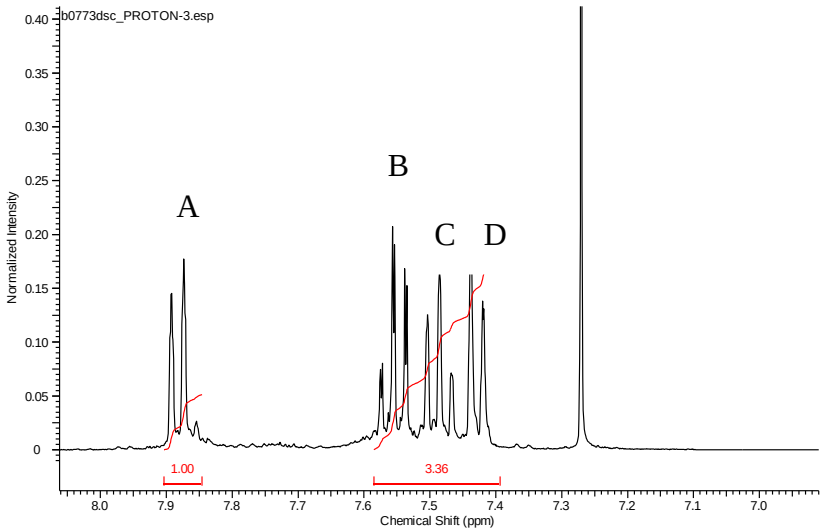


Figure 63 ^{1}H-NMR (400 MHz, $CDCl_3$)

The aromatic protons (A-D) resonate at 7.43-7.88 ppm, and collectively integrate to four (Figure 63). The doublet at 7.88 ppm (proton A, J = 7 Hz) has a COSY cross peak with proton C. The triplet at 7.55 ppm (proton B, J = 7 Hz) has a COSY cross peak with proton D. The triplet at 7.49 ppm (proton C, J = 7 Hz) has a COSY cross peak with proton A. The doublet at 7.43 ppm (proton D, J = 7 Hz) has expected COSY cross peak with proton B.

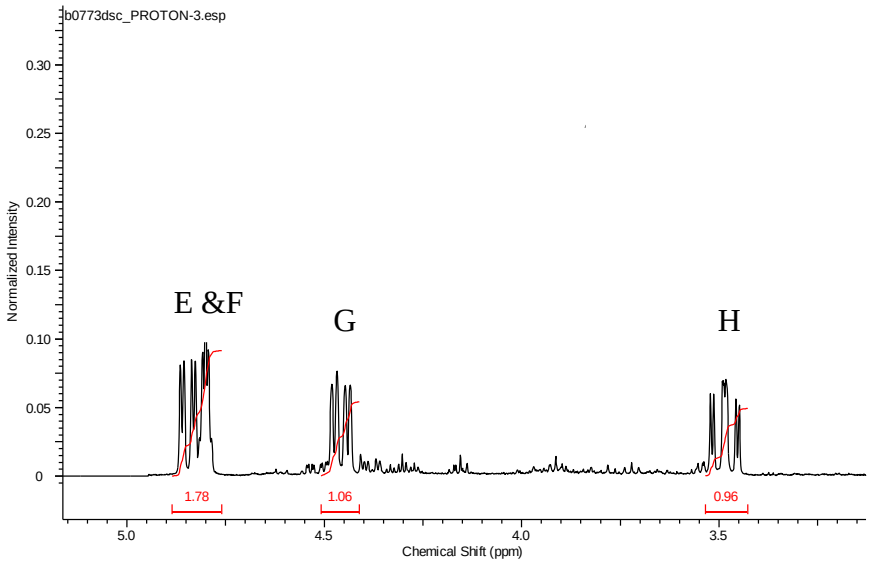


Figure 64 ^{1}H-NMR (400 MHz, $CDCl_3$)

The double of doublets at 4.84 ppm (Figure 64) integrates to one (proton E, J = 11, 3 Hz), COSY cross peaks (see Table 1) suggest it couples to two protons, L (ddd, 1.61 ppm) and I (d, 2.69 ppm). The broad singlet at 4.80 ppm (Figure 64) intergrates to one (proton F) and COSY interactions suggest it weakly couples to protons J (d, 2.17 ppm) and I. The double doublet at 4.46 ppm (Figure 64) integrates to one (proton G, J = 14, 5 Hz) and COSY interactions suggested it couples strongly with proton H (3.49 ppm) and K (1.91 ppm). The triple doublet at 3.49 ppm (Figure 64) integrates to one (proton H, J = 15, 3 Hz) and COSY interactions suggest it couples with protons K (1.91 ppm), J (2.17 ppm) and G

(4.46 ppm). The doublet at 2.69 ppm (Figure 65) integrates to one (proton I, J = 13 Hz) and has a stong COSY interaction with proton L (2.17 ppm) and two weak interactions with protons E (4.84 ppm and F (4.80 ppm). Proton J at 2.17 ppm (Figure 65) integrates to one (J = 14 Hz) has COSY interactions with protons K (1.91 ppm) and H (3.49 ppm). The multiplet at 1.91 ppm (Figure 65) integrates to one (proton K) has COSY interactions with proton H, G and J. Proton L at 1.61 ppm (Figure 65) integrates to one (J = 14, 11, 3 Hz) has COSY interactions with J, E and F.

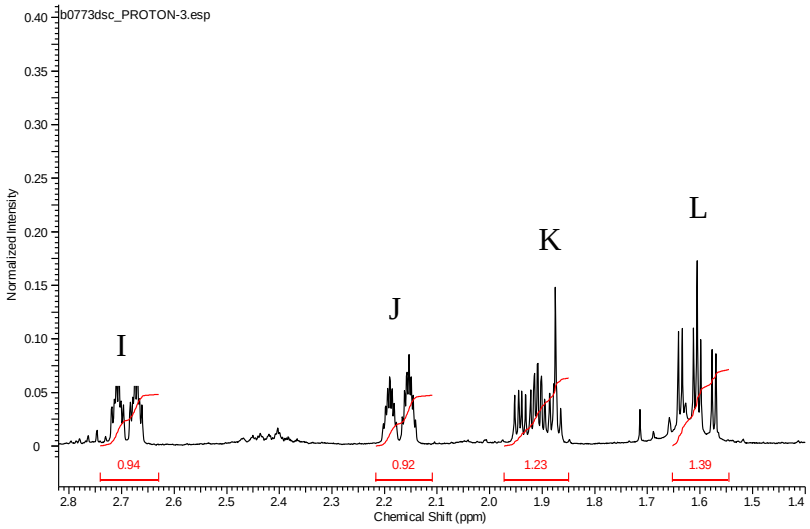
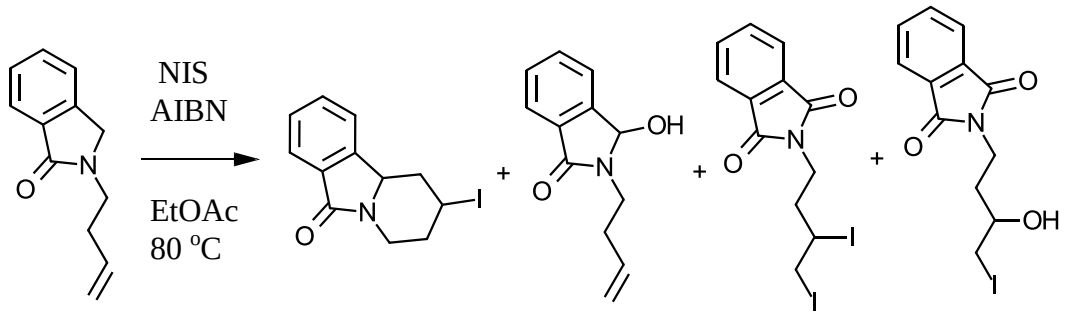


Figure 65 ^{1}H-NMR spectrum of **11a** (400 MHz, $CDCl_3$)

Because the other 2D experiments (HSQC and HMBC) were of poor quality, it was not possible to categorically say what structure was present. But the combination of results of ESI and ^{1}H NMR suggested that a cyclic product had in fact been made.

Encouraged by the success with NBS in producing a cyclic structure it was decided to compare the reactivity of **10a** with NIS (Figure 66). The reaction was

very much the same as before. Purification by column chromatography gave **13a** as a diastereomeric mixture, as a light pink solid in 8-9% yield; **13b** as sticky oil in 39% yield; **13c** as a pink/red solid in 24% yield; and **13d** as a white solid in 29% yield. Pleasingly another cyclic compound was formed, this time as a mixture of diastereomer and in higher yields.



10a **13a** **13b** **13c** **13d**

Figure 66 Resulting products of NIS reaction, successful cyclisation

Running the sample again on 400 MHz spectrometer, produced the H^1 spectrum (Figure 67).

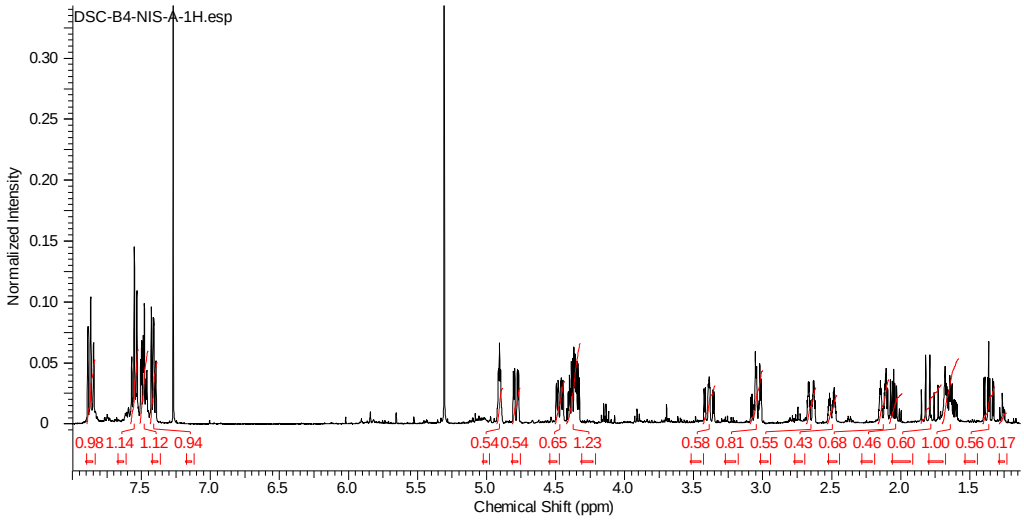


Figure 67 1H NMR spectrum of **11a** (400MHz, $CDCl_3$)

It was clear that there was a diastereomeric mixture of compounds; ESI showed a complementary formula ($C_{12}H_{12}INO$) to compound **11a**. Unfortunately the 2D NMR experiments were not of sufficient quality to tease out the information need for unambiguous assignment. It was decided to run the sample again, this time on a 700 MHz machine, to obtain a higher resolution spectrum.

This proved much more successful, the HSQC data showed which protons were bonded to what carbon and a TOCSY experiment was used to identify which proton belonged to which diastereomer. A TOCSY experiment observes cross-peaks not only nuclei directly coupled (like a COSY) but nuclei connected by a chain of couplings. By identifying the interconnected networks of spin couplings, it was easier to differentiate the protons belonging to each diastereomer.

One diastereomer shared very similar features to the NBS product (Figure 68). As it was not possible to obtain good 2D spectra of the NBS derived product, if the NIS derived product (diastereomer 1) can be assigned the structure of the NBS derived cyclic product could be inferred.

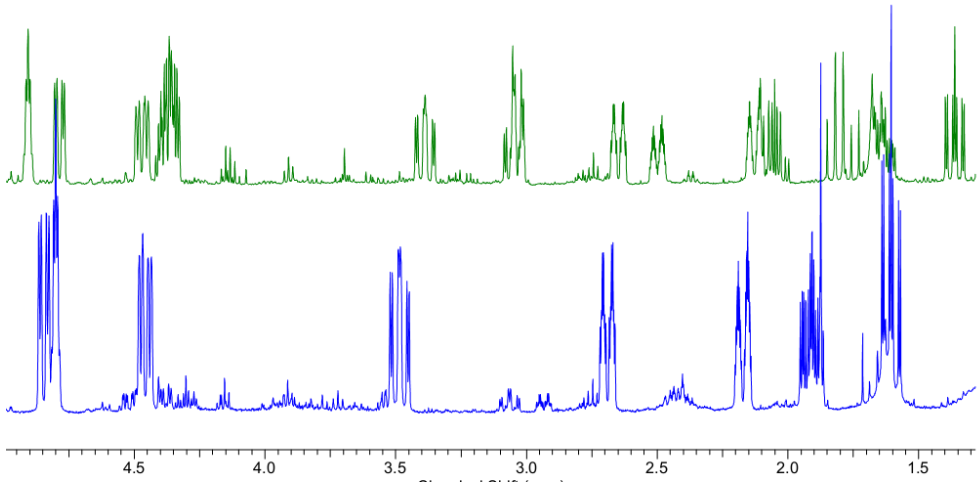


Figure 68 Comparison of **11a** with **13a** (400 MHz)

The COSY, HSQC and HMBC data of each proton and carbon of diastereomer 1 (**13a**) are displayed in Tables 2 and 3.

The COSY interactions for each proton are shown magnified in spectra 43-45, the interactions are virtually identical to the COSY interactions seen in **11a**, just better resolution.

The HSQC data revealed that the molecule consists of three CH_2 groups and two CH groups. C3 is bonded to protons G and H, C2 is bonded to K and J, C4 is bonded to L and I and C5 bonded to F and finally C1 bonded to E. C1 has the lowest chemical shift and is assumed to be linked to iodine. Using the COSY interactions it was possible to determine the locality of the protons to each other and therefore to assign the ring system displayed (Figure 65).

As the 700 MHz spectrometer helped establish the presence three CH_2 groups, this compound cannot possibly be the 5-membered ring (**10e)**. Hence the 6-membered ring is formed as shown in Figure 69.

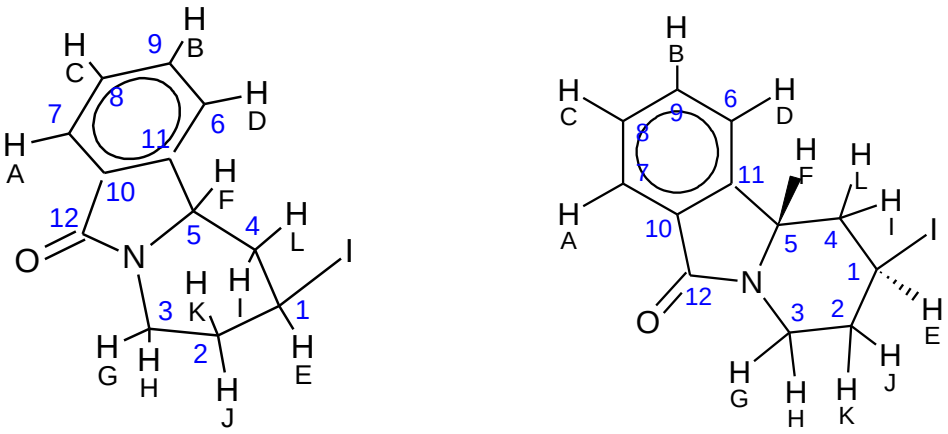


Figure 69 Structure of diastereomer 1 (**13a**)

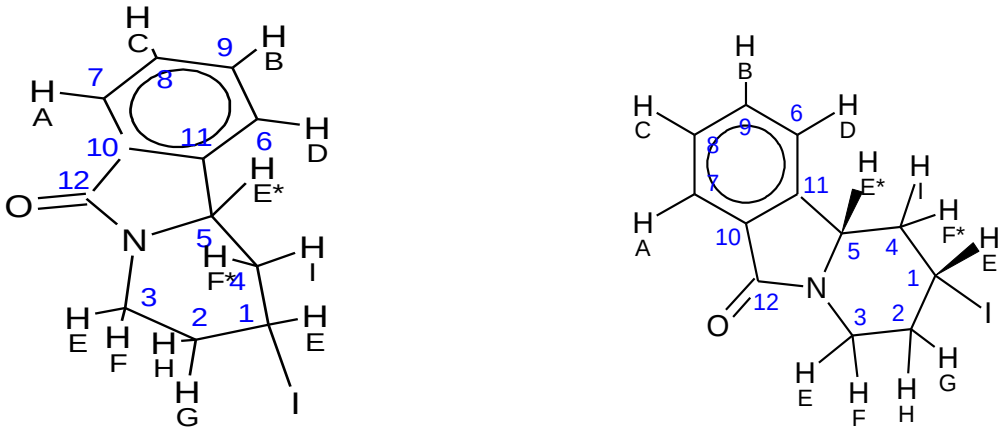


Figure 70 Structure of diastereomer 2 (**13a**)

The tabulated data for diastereomer 2 (Figure 70) can be found in the appendices (Tables 4 and 5).

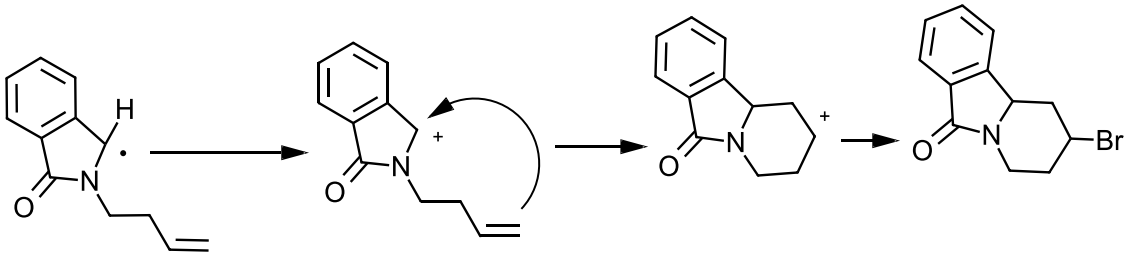


Figure 71 Proposed cyclisation mechanism of **10a** to **11a**.

It appears that the (NCH•) radical does not cyclise but instead gets oxidised to a NCH^{+} cation by single electron transfer with another radical or bromine molecule. This cation adds to the double bond to form a cyclic cation which reacts with Br^{-} to yield the final product (Figure 71).

Proton	δ(ppm)	App.	Int.	J(Hz)	COSY	HSQC	HMBC
A	7.87	d	1	7	H_C	C7	C9, C11, C12
B	7.54	t	1	7	H_D	C9	-
C	7.47	t	1	7	H_A	C8	C10, C6, C12
D	7.41	d	1	8	H_B	C6	C8, C10, C5
E	4.90	br s	1	-	H_I,H_J,H_K,H_L	C1	C2(w)C3, C4, C5
F	4.78	dd	1	11,3	H_L, H_I	C5	C1, C4,C6(w), C10(w), C11, C12
G	4.46	dd	1	14,4	H_K, H_H	C3	C1,C2,C5, C10(w), C12
H	3.38	td	1	15,3	H_K,H_J,H_G	C3	C1,C2,C12
I	2.64	d	1	13	H_L, H_E, H_F	C4	C1,C2,C5(w)
J	2.12	d	1	15	H_L, H_H, H_E	C2	-
K	1.65	m	1	-	H_J, H_H, H_G, H_E	C2	C3(w)
L	1.35	ddd	1	14,12,3	H_I,H_F, H_E	C4	C5(w), C11(w)

Table 2: Tabulated results for diastereomer 1, (13a) (700 MHz, $CDCl_3$, 20 ^oC)

Carbon	δ (ppm)	HSQC	HMBC
1	29.2	H_E	H_F, H_G, H_H, H_I
2	34.7	H_K	H_E(w), H_G, H_H, H_I
3	36.7	H_G, H_H	H_E, H_J(w)
4	41.0	H_I, H_F	H_E, H_F
5	55.9	H_F	H_D, H_E, H_G, H_I(w), H_L(w)
6	121.0	H_D	H_C, H_F(w),
7	124.1	H_A	-
8	128.5	H_C	H_D
9	131.5	H_B	H_A
10	132.4	-	H_C, H_D, H_F(w),H_G(w)
11	144.8	-	H_A,H_F
12	166.0	-	H_A,H_C,H_F,H_G,H_H

Table 3: Tabulated results for diastereomer 1 (13a) (700 MHz, $CDCl_3$, 20 ^oC)

Chapter Three: Concluding Remarks

Although Ishii's chemistry was reproducible it proved to be ineffective as an alternative radical initiator of intramolecular cyclisations, but a new competitive radical fragmentation pathway was identified in the reaction of an acetal under Ishii's reaction conditions.

Other nitroxides such as TEMPO have been shown to be successful performing carbon-carbon bond forming reactions between acridines and nitromethane but unable to couple nitromethane to target lactams **4a** and **10a** or induce intramolecular cyclisations.

Interestingly reactions of lactams bearing unsaturated-chains, with NBS or NIS, were shown for the first time; to afford cyclic products. In competition with cyclisation, was the formation of maleimides and/or hydroxy-lactams derived from oxidation adjacent to nitrogen.

Maybe I was unfortunate with my substrate choice when I initially began exploring the potential of the PINO radical to initiate radical cyclisations. With an alternative and more activated substrate there could have been greater success. But from what I have observed, PINO has been unsuccessful and surprisingly so.

Fortunately a new and unreported cyclisation pathway has been identified, albeit a low yielding pathway. This novel N-halosuccinimide cyclisation technology constructs cyclic architectures of med-chem importance and crucially without the

requirement for tin or other toxic metals. Although currently a low yielding reaction it has revealed a potential, which future researchers could build upon.

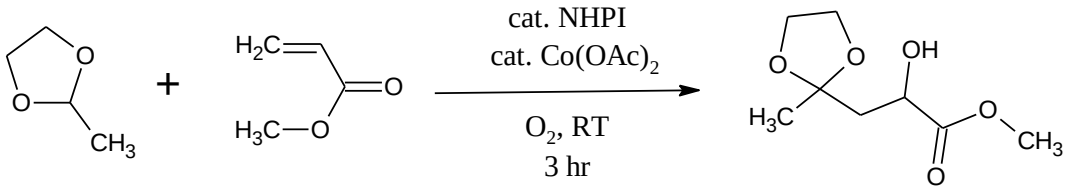
Future work could explore the use of alternative reaction conditions for the NBS/NIS reactions, and alternative substrates bearing different unsaturated side-chains (e.g. electron-poor C=C bonds). Alternative, non-metal oxidants could also be explored, including NCS.

Unfortunately due to time constraints additional lactams that were synthesised (detailed in experimental section), I did not have the opportunity to explore the reactivity. They were synthesised with the intention of developing an intramolecular carbon-carbon bond forming radical reaction. By screening the reactivity of these lactams, it would provide further insight towards developing an intermolecular cyclisation methodology.

However the aim of developing an alternative clean radical cyclisation technology has not been achieved. The search for an environmentally benign alternative to tin radical cyclisation technology continues. I hope in some small way I have contributed to this search and that my findings help others in their future radical endeavours.

Chapter Four: Experimental Section

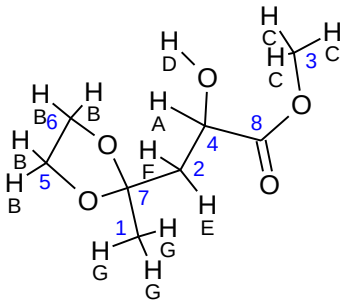
4.1 Synthesis of Methyl-2-hydroxy-3-(2-methyl-1,3-dioxolan-2-yl) propanoate (1c)[40]



A solution of methyl dioxolane (1.32g, 15mmol), NHPI, (25mg, 0.15mmol) and $Co(OAc)_2$ (3mg, 0.0015mmol) in a two necked flask was equipped with a balloon filled with oxygen. To this solution methyl acrylate (258mg, 3mmol), was injected slowly. The acrylate must be run through an alumina column to remove MEHQ inhibitor prior to addition and methyl dioxolane must be thoroughly purged with oxygen. The method of delivery of the oxygen is important; the needle should go into the solution and periodic aggressive bubbling of oxygen over the duration of the reaction is needed to achieve a satisfactory yield of 61% (347mg). Remove the excess dioxolane on a rotary evaporator, leaving a clear liquid after purification using column chromatography (2:1 EtOAc:Hex, rf: 0.37).

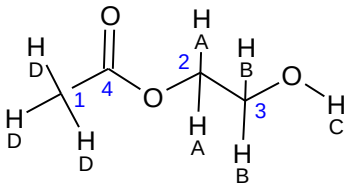
Running the reaction without removing the MEHQ inhibitor reduces the yield of **1c** to 33% (190 mg) and takes significantly longer for the reaction to begin (9hr+) and encourages the significant production of a side product, ethylene glycol monoacetate (0.150 mg, rf: 0.25). High-resolution mass spectroscopy (ESI): $(M+H)^+$: for (**1c**) $C_8H_{14}O_5$, 191.9102; (**1f**) $C_4H_8O_3$, 105.4731.

Methyl-2-hydroxy-3-(2-methyl-1,3-dioxolan-2-yl) propanoate (1c)



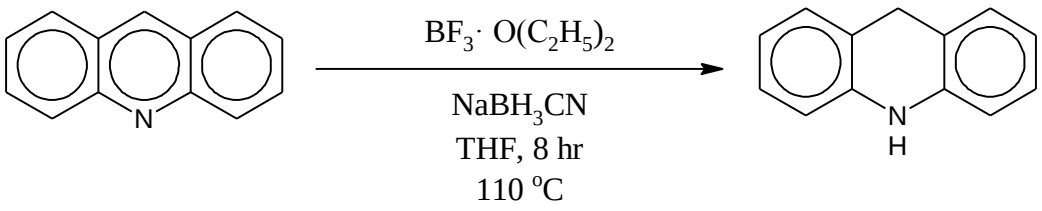
NMR Assignment: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 4.40 (m, 1H, A), 3.99 (m,4H, B), 3.76 (s, 3H, C), 3.69 (br m, 1H, D), 2.28 (1H, E), 2.15 (1H, F), 1.38 (s, 3H, G).^{13}C-NMR (400 MHz, $CDCl_3$): δ = 174.0(7), 109.2(6), 67.7(5), , 64.0(4), 51.8(3), 41.4(2), 24.0(1).

Ethylene glycol monoacetate (1f)

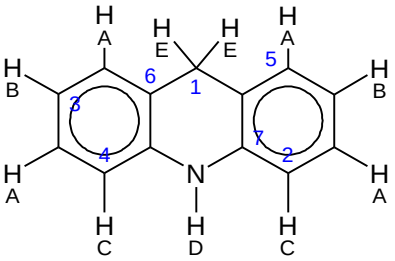


NMR Assignment: ^{1}H-NMR (400 MHz, $CDCl_3$): **δ =** 4.31 (t, 2H, J= 7 Hz, A), 4.18 (t, 2H, J= 7 Hz, B), 2.30 (br, 1H, OH, C), 2.01 (s, 3H, D).^{13}C-NMR (400 MHz, $CDCl_3$): δ = 179.0(4), 72.0(3), 61.92(2), 18.1(1)

4.2 Synthesis of 9,10-Dihydro-acridine (8b) [50]

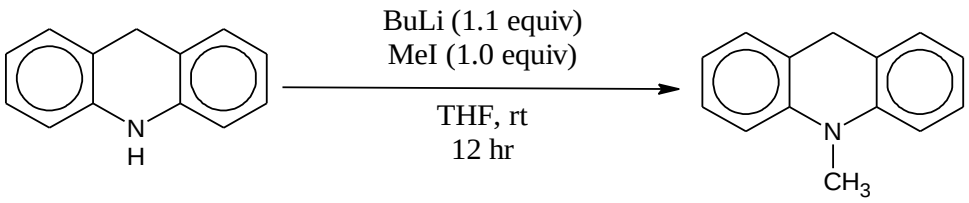


A solution of a quinoline (0.5 mmol), sodium cyanoborohydride (1 mmol) and boron trifluoride etherate (5 mmol) in dry THF (2 ml) was refluxed for 8h. The reaction mixture was cooled, treated with 25 % aqueous ammonia (5 ml) and extracted with diethyl-ether (3 x 5 ml). The ether extract was washed with brine and dried over anhydrous sodium sulfate. Evaporation, of the solvents followed by purification of the residue over a silica gel column (hex:toluene 1:1, Rf:0.34) furnished the product in 60% yield.

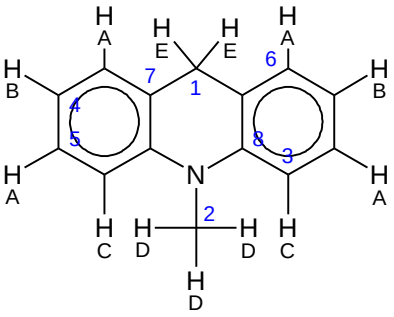


NMR Assignment: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.07-7.13 (m, 4H, A), 6.84-6.89 (m, 2H, B), 6.68 (d, J= 7.9 Hz, 2H, C), 5.96 (br s, 1H), 4.07 (s, 2H). ^{13}C-NMR (400 MHz, $CDCl_3$): δ = 31.5(1), 113.5(2), 120.1(3), 120.7(4), 127.0(5), 128.8(6), 140.2(7).

4.3 Synthesis of 10-Methyl-9,10-dihydro-acridine (8c) [51]

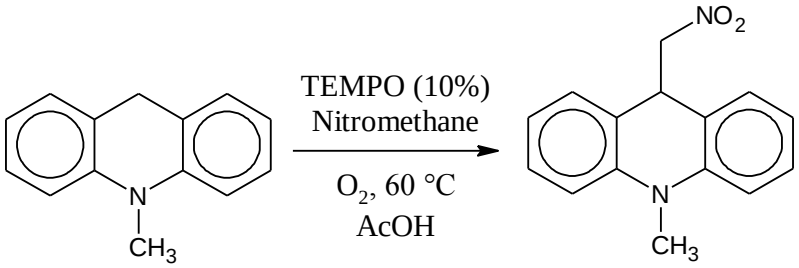


An oven dried round bottom flask equipped with a magnetic stirrer was evacuated and refilled with argon, then charged with a solution of acridine (544mg, 3.0mmol) in THF (20ml). A solution of n-BuLi (2.5M in hexanes, 3.3ml) was added dropwise at 0-5^{0}C for 2 hr and RT overnight. The reaction was then quenched with water (30ml) and the product extracted with EtOAc (3x30ml). The organic layers were combined and washed with brine and dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude was columned on silica (hex:toluene 1:1 v/v) to afford 533 mg (91%) of a white solid.

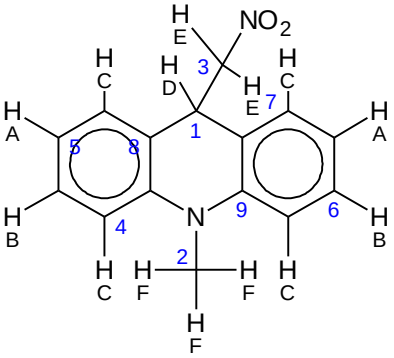


NMR Assignment: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.18-7.26 (m, 4H, A), 6.90-6.98 (m, 4H, B), 3.92 (s, 2H, C), 3.4 (s, 3H, D). ^{13}C-NMR (400 MHz, $CDCl_3$): δ = 33.2(1), 33.3(2), 112.0(3), 120.6(4), 124.4(5), 127.0(6), 127.6(7), 143.8(8).

4.4 Synthesis of 10-Methyl-9-nitromethyl-9,10-dihydro-acridine (8d) [49]

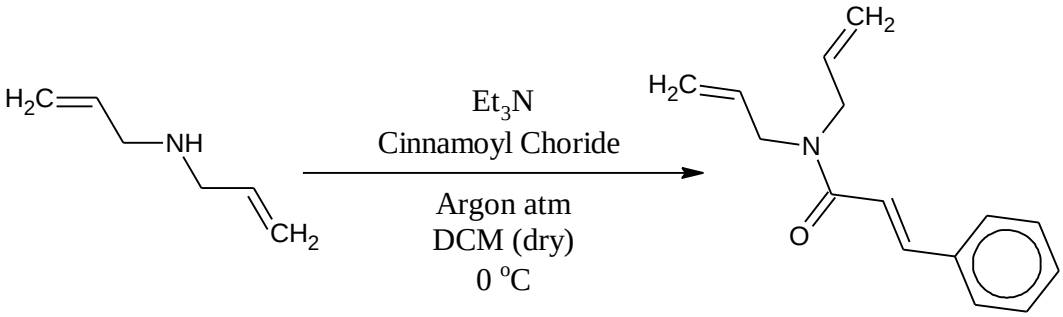


A solution of 10-methyl-9, 10-dihydroacridine (39.5 mg, 0.2 mmol) and TEMPO (3.2 mg, 0.02 mmol) was placed in a 25 mL round bottom flask. Then CH_3NO_2 0.5 mL was added. The reaction mixture was stirred at 60 ℃ under O_2 (1 atm) for 18 h as monitored by TLC. The solvent was removed and the residue was purified by silica gel column chromatography (Pet Ether: Et_2O = 10/1, Rf: 0.28) to afford 46.9 mg (92 % yield) of a red solid. High-resolution mass spectroscopy (ESI): $(M+H)^+$: for $C_{15}H_{14}N_2O_2$, 255.1055. m.p : 89 ^oC (Lit m.p : 88.13 ^oC)

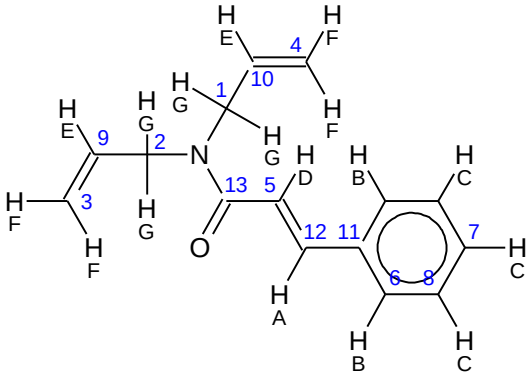


NMR Assignment: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.28 (t, J= 7.8 Hz, 2H), 7.21 (d, J= 6.8 Hz, 2H), 6.99-6.95 (m, 4H), 4.79 (t, J= 8.0 Hz, 1H), 4.33 (d, J= 8.0 Hz, 2H), 3.40 (s, 3H). ^{13}C-NMR (400 MHz, $CDCl_3$): δ = 33.2(1), 43.3 (2), 79.1(3), 99.0(4), 112.7(5), 121.5(6), 128.4(7), 128.6(8), 142.6(9).

4.5 Synthesis of N, N-Diallyl-3-phenyl-acrylamide (3c) [43]



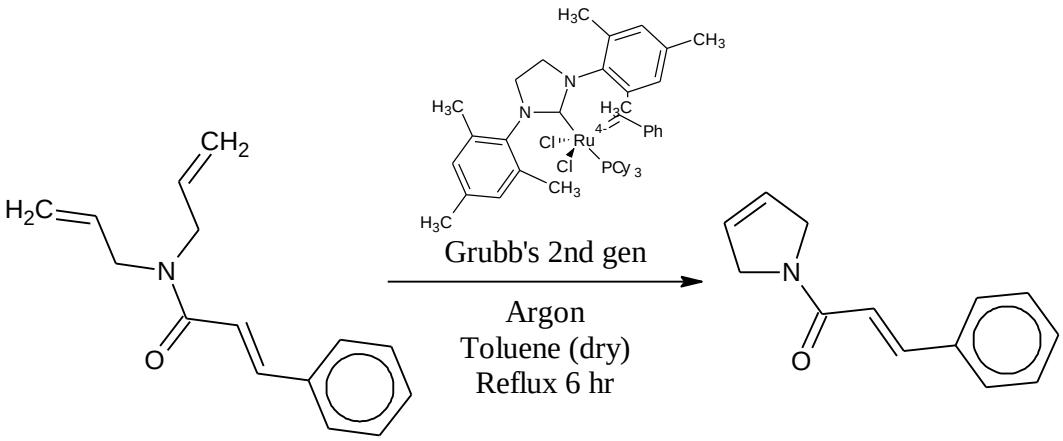
To a stirred solution of diallylamine (972 mg, 10mmol) in anhydrous DCM (15 mL) was added NEt_3 (2.79 mL, 20 mmol). The reaction mixture was cooled to O oC and cinnamoyl chloride (3.5g, 21 mmol) dissolved in 20 ml anhydrous DCM was added slowly. The cooling bath was removed and the reaction mixture was maintained under magnetic stirring overnight. After this period, the reaction mixture was quenched with water (30ml) and extracted with DCM (3x30ml). Combine the organic fractions and wash with brine. Dry with $MgSO_4$, filter and then concentrate. Yellow oil, Purified by silica column chromatography (9:1 DCM:MeOH Rf: 0.32) in an isolated yield of 67%.



NMR Assignment: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, 15.25Hz, 1H, A), 7.47-7.50(m, 2H, B), 7.31-7.37 (m, 3H, C), 6.77 (d, 15.25Hz, 1H, D), 5.76-5.90

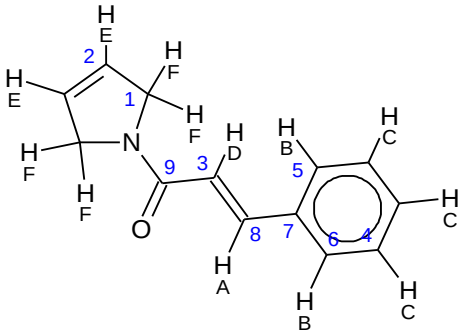
(m, 2H, E), 5.13-5.26 (m, 4H, F), 4.00-4.11(m, 4H G). ^{13}C-NMR (400 MHz, $CDCl_3$): δ = 48.82(1), 49.32(2), 116.89(3), 117.52(4), 117.66(5), 127.9(6), 128.86(7), 129.7(8), 133.28(9), 133.33(10), 135.37(11), 143.05(12), 166.7(13).

4.6 Synthesis of 1-(2,5-Dihydro-pyrrol-1-yl)-3-phenyl-propenone (2a) [44]



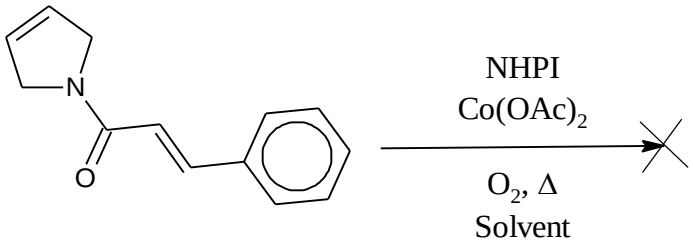
A mixture containing *N*,*N*-diallyl-3-phenyl-acrylamide (400mg 1.2mmol) and 2nd generation Grubb's catalyst (108mg, 0.12mmol) in anhydrous toluene was refluxed for 6hr under argon atmosphere. The mixture was concentrated to yield the crude product which was purified by column chromatography (6:4 EtOAc/Hex, Rf: 0.4). The crude is a dark black gel that eventually solidifies. After column chromatography it was isolated as a white compound (0.245mg, 61% yield).

The compound should be stored in the fridge, under inert conditions (as it degrades over time giving an orange/yellow colour). The reaction was initially performed in dry DCM rather than toluene; this gave a smaller yield 22% on the same time scale. The reaction can also be performed at room temperature in toluene, though in takes considerably longer to achieve comparable yields.



NMR Assignment: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.71 (d, 1H, J= 15 Hz, A), 7.47-49 (m, 2H, B), 7.32 (m, 3H, C), 6.72(d, 1H, 15Hz, D), 5.89(m, 2H, E), 4.44(m, 4H, F)^{13}C-NMR (400 MHz, $CDCl_3$): δ = 52.0(1), 121.7(2), 121.9(3), 125.1 (4), 126.8(5), 127.3(6), 136.2(7), 138.2(8), 177.3(9).

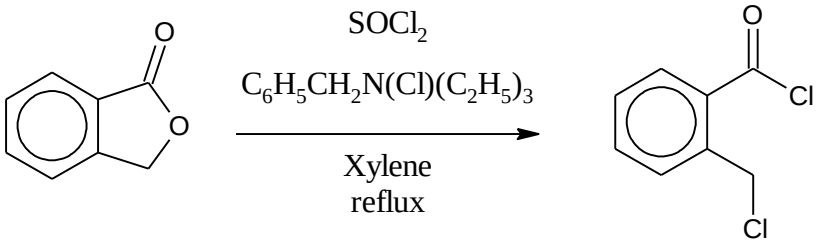
4.7 Failed Cyclisation Attempt of (2a) Using Ishii System



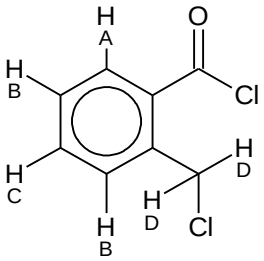
A solution of 1-(2, 5-dihydro-pyrrol-1-yl)-3-phenyl-propenone (100mg, 0.50mmol) and NHPI (25mg, 0.15mmol) and Co (OAc) $_2$ (3mg, 0.0015mmol) was placed in a two necked flask purged with oxygen and equipped with a balloon filled with oxygen. The reaction was run at room temperature in 10ml DCM first, there was no observable reaction. The solvent was changed to acetonitrile and run at 80^{o}C, still to no avail. The solvent was changed again to acetic acid and temperature increased to 100 ^{o}C. There was an observed reaction but a very

complex mixture produced. Attempts to separate and analyse components were unsuccessful. Control reaction was performed to ascertain the stability of the starting material, it was concluded that the compound was stable in acetic acid at 100 ^{o}C.

4.8 Synthesis of 2-chloromethyl-benzoyl chloride (5c)[47a]

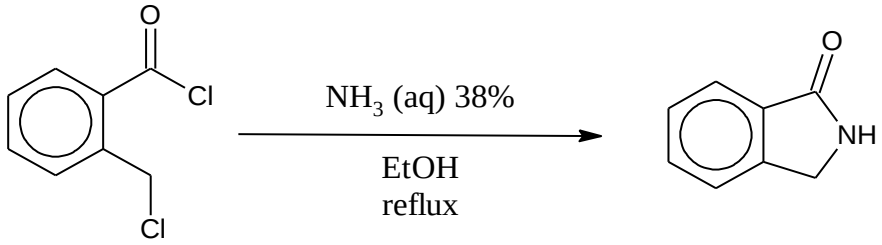


To a 1-L three-necked flask, a solution of xylene (64.3 ml), phthalide (13.41 g 100 mmol), benzyltriethylammonium chloride (1.82 g, 8 mmol), and BF_3- diethyl etherate (0.99 g, 14.6 mmol) were added, and heated to 100°C. Subsequently, thionyl chloride (14.28 g, 1.2 mmol) was added dropwise over 1 h, and stirred at 130°C for 9 h. Xylene and excessive thionyl chloride were distilled off at normal pressure until the internal temperature became 135°C, and xylene was further distilled off under reduced pressure (160°C). Compound should be a thick light green free flowing liquid. The product was taken up in chloroform and left under vacuum several times to remove any residual thionyl chloride, leaving a clear liquid in 90% yield (17g, 90 mmol).

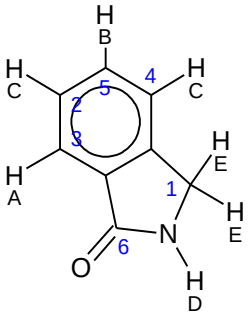


NMR Assignment: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.27 (d, J= 7.32Hz, 1H, A), 7.59-7.72 (m, 2H, B), 7.50-7.56 (m, 1H, C), 4.90 (s, 2H, D).

4.9 Synthesis of 2,3-Dihydro-isoindol-1-one (5b) [47b]

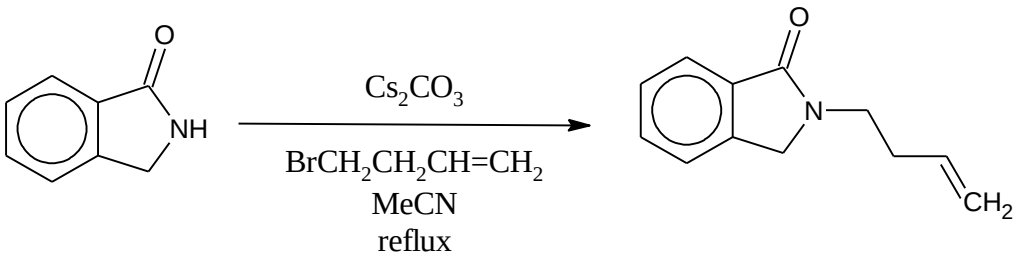


A solution of 2-(chloromethyl) benzoyl chloride (0.94g, 5.00mmol) in ethanol (20mL) was heated under reflux for 1 h forming a subtle pink solution. 38% aqueous ammonia (20mL) was added once the reaction had cooled to room temperature and the reflux was continued for an additional 1 h (the solution should turn a light orange colour initially then a light yellow when the reaction is complete. After the reaction has finished the reaction mixture was extracted with dichloromethane (3 × 30 ml). The combined extracts were dried with anhydrous Na_2SO_4, the solvent was evaporated in vacuo and the residue was recrystallized from benzene (or alternatively toluene), to give fine clear needle crystals of iso-indolinone in 38% (0.25 g); Mp 151 $^{\circ}$C



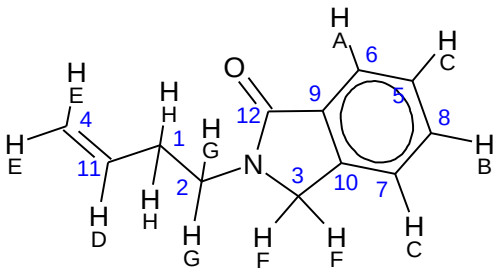
NMR Assignment: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.89 (d, 1H, J= 8.34 Hz, A), 7.61-7.57(m, 1H, B), 7.52-7.49(m, 2H, C), 7.17(brs, 1H, D), 4.48(s, 2H, E).^{13}C-NMR (400 MHz, $CDCl_3$): δ = 171.9(7), 143.7(6), 131.9(5), 128.1(4), 123.9(3.), 123.3(2), 45.7(1)

4.10 Synthesis of 2-But-3-enyl-2,3-dihydro-indol-1-one (10a) [53]



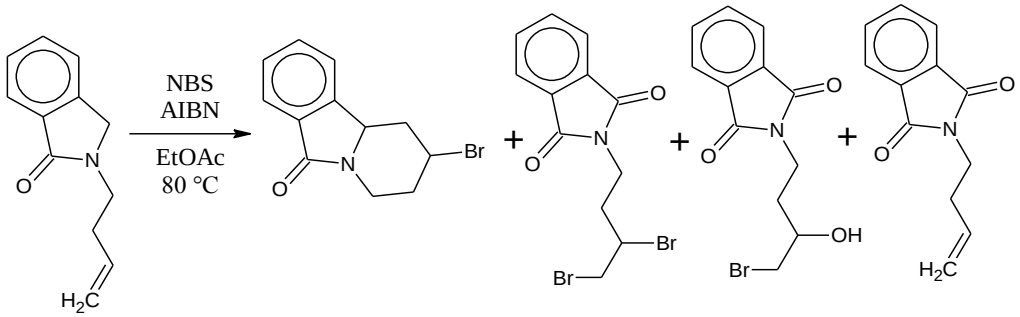
To isoindolinone (250mg, 1.85mmol) in acetonitrile (10ml) was added caesium carbonate (2.4g, 7.39mmol) and the mixture was heated to 80^{o}C. Then 4-bromo-1-ene (518mg, 2.77mmol) in 5ml EtOAc was slowly injected into the reaction mixture over a period of 20 minutes. The reaction was refluxed for 3hr at 80^{o}C. The reaction mixture was partitioned between ethyl acetate and water and the organic layer washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the product was purified by column

chromatography (40%EtOAc/Pet40-60) to afford product as a yellow oil in 79% yield (278mg).



NMR Assignment: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.81 (d, J= 8.34 Hz, 1H, A), 7.52-7.47 (m, 1H, B), 7.40-7.44 (m, 2H. C), 5.75-5.87 (m, 1H, D), 5.00-5.11 (m, 2H, E), 4.37 (s, 2H, F), 3.66-3.70 (m, 2H, G), 2.39-2.45 (m, 2H. H). ^{13}C-NMR (400 MHz, $CDCl_3$): δ = 168.6(12), 141.2 (11), 135.1 (10), 133.0 (9), 131.3 (8), 128.0 (7), 124.0 (6), 122.7 (5), 117.2 (4), 50.2 (3), 42.0 (2), 33.0 (1).

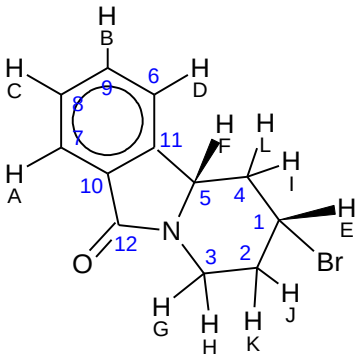
4.11 NBS Cyclisation of 2-But-3-enyl-2,3-dihydro-indol-1-one (10a)



To a solution of 2-but-3-enyl-2, 3-dihydro-indol-1-one (200mg, 1.07mmol) and AIBN (0.018mg, 0.107mmol) in 10 ml EtOAc. NBS (189mg, 1.07mmol) was added and the reaction was refluxed for 2hr. A second equivalent of NBS was

added along with another 0.1 equivalent of AIBN. The reflux was continued for another 2h. The reaction was monitored by TLC. If there was any starting material left, another 0.1 equivalent of AIBN was added repeatedly every hour until the reaction reaches completion. The solution should be a very dark orange colour. There should be four UV active spots visible. The reaction mixture was cooled in a water ice bath and filtered. The filtrate was concentrated on a rotary evaporator. The crude mixture is oil, orange in colour, which was then purified by column chromatography (4:6 EtOAc: Pet Ether 40:60**).** Compound A is a light yellow solid isolated in 6% yield; Compound B is sticky oil (orange) isolated in 31% yield, Compound C is a yellow crystalline solid isolated in 36% yield and Compound D is a white solid isolated in 27% yield.

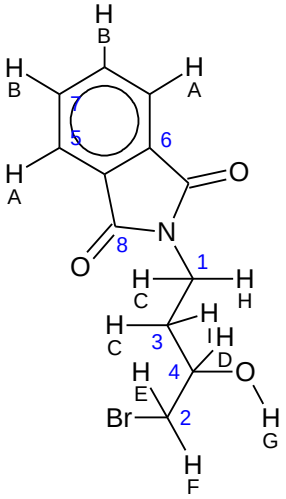
(2*R,10b*S**)-2-Bromo-1,3,4,10b-tetrahydropyrido[2, 1-a]isoindol-6(2H)-one (11a)**



NMR Assignment: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.88 (d, 1H, J= 7.32 Hz, A), 7.55 (t, 1H, J= 7.32 Hz, B), 7.49 (t, 1H, J= 7.32 Hz, C), 7.43(d, 1H, 7.32 Hz, D), 4.84 (dd, 1H, J= 11,3 Hz, E), 4.80, br s, 1H, F), 4.46 (dd, 1H, J= 14, 5, G), 3.49 (td, 1H, J= 15, 3 Hz, H), 2.69 (d, 1H, J= 13 Hz, I), 2.17 (d, 1H, J= 14 Hz, J), 1.91

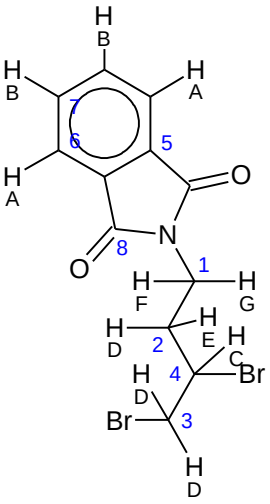
(m, 1H, K), 1.61 (ddd, 1H, J= 3, 11, 14 Hz, L). ^{13}C-NMR (400 MHz, $CDCl_3$): δ = 161.0(12), 145.0(11), 132.4(10), 131.5(9), 128.5(8), 124.1(7), 121.8(6), 54.1(5), 49.3(4), 39.6(3), 34.9(2), 33.4(1).

2-(4-Bromo-3-hydroxybutyl)-1*H*-isoindole-1,3(2*H*)-dione (11d)



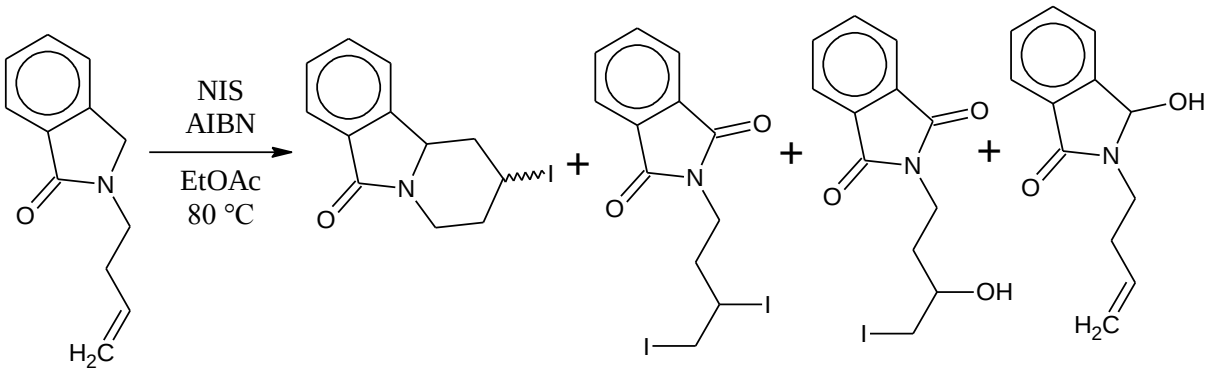
NMR Assignment: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.82-7.97 (dd, 2H, J= 3, 8.59 Hz, A), 7.70-7.75 (dd, 2H, J= 3 Hz, 8.54, B), 3.85-3.91 (dd, J= 3, 7.63 Hz, 2H), 3.80(m,1H), 3.46-3.51(m,1H), 3.39-3.44(m,1H), 3.09(m, 1H), 1.91-2.00(m,1H), 1.80-1.89(m,1H). ^{13}C-NMR (400 MHz, $CDCl_3$): δ = 168.8(8), 134.3(7), 132.0(6), 123.4(5), 68.5(4), 38.9(3), 34.7(2), 34.2(1).

Compound C: 2-(3,4-Dibromobutyl)-1*H*-isoindole-1,3(2*H*)-dione (11c)



NMR Assignment: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.85-7.88 (m, 2H, A), 7.72-7.74 (m, 2H, B), 4.14-4.21(1H), 3.84-3.99(m, 3H, D), 3.64-3.70(m, 1H, E), 2.53-2.67(m, 1H, F), 2.13-2.23(m, 1H, G). ^{13}C-NMR (400 MHz, $CDCl_3$): δ = 168.2(8), 134.2(7), 123.3(6), 121.4(5), 48.8(4), 36.0(3), 35.8(2), 34.9(1).

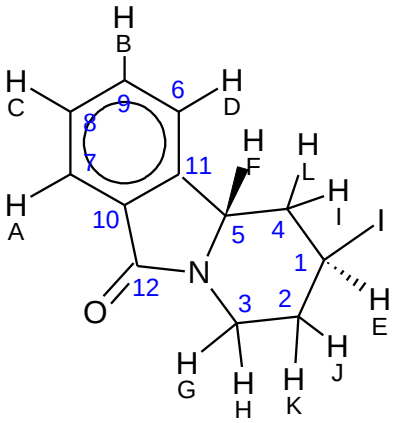
4.12 NIS Cyclisation of 2-But-3-enyl-2,3-dihydro-indol-1-one (10a)



To a solution of 2-but-3-enyl-2, 3-dihydro-indol-1-one (200mg, 1.07mmol) and AIBN (0.018mg, 0.107mmol) in 10ml EtOAc, NIS (189mg, 1.07mmol) was added

and the reaction was refluxed for 2h. A second equivalent of NIS was added along with another 0.1 equivalent of AIBN. The reflux was continued for another 2hrs. The reaction was monitored by TLC. If there was any starting material left, another 0.1 equivalent of AIBN was added repeatedly every hour until the reaction reaches completion. The solution should be a dark pink almost maroon colour. There should be four UV active spots visible. The reaction mixture was cooled in a water ice bath and filtered. The filtrate was concentrated on a rotary evaporator. The crude mixture is oil, black/red in colour, which was then purified by column chromatography (6:4 EtOAc: Pet Ether 40:60**).** Compound 1 is diastereomeric mixture, a light pink solid isolated in 8% yield (Rf: 0.35); Compound 2 is sticky oil isolated in 39% yield (Rf: 0.46), Compound 3 is a pink solid isolated in 24% yield (Rf: 0.53) and Compound 4 is a white solid isolated in 29% yield (Rf: 0.67).

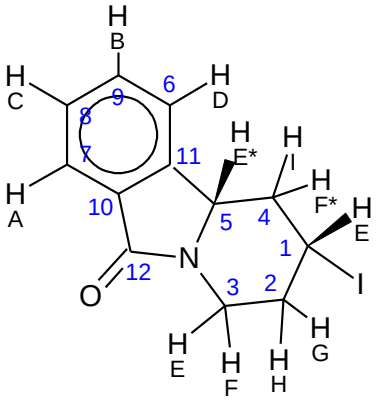
(1): (2*S,10b*S**)-2-Iodo-1,3,4,10b-tetrahydropyrido[2,1-*a*]isoindol-6(2*H*)-one (13a)**



*1: NMR Assignment: ^{1}H-NMR (700 MHz, $CDCl_3$) δ: 7.86(d, 1H, J= 7 Hz, A), 7.54(t, 1H, J= 7 Hz, B), 7.47-48(t, 1H, J= 7 Hz, C), 7.40(d, 1H, J= 8 Hz, D),

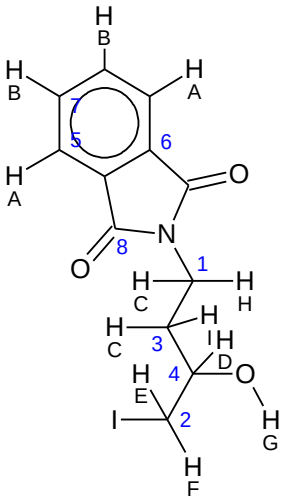
4.90(br s, 1H, E), 4.78(dd, 1H, J= 11, 3 Hz, F), 4.46(dd, 1H, J= 14, 4 Hz, G), 3.38(td, 1H, J= 15, 3 Hz, H), 2.64(d, 1H, J= 13 Hz, I), 2.12(d, 1H, 15 Hz, J), 1.56-1.68(m, 1H, K), 1.35(ddd, J= 14, 12, 3 Hz, L). ^{13}C-NMR (400 MHz, $CDCl_3$): δ = 166.0(12), 144.8(11), 132.4(10), 131.5(9), 128.5(8), 124.1(7), 121.9(6), 55.9(5), 41.0(4), 36.7(3), 34.7(2), 29.2(1).

Compound E (2): (2*R,10bS*)-2-Iodo-1,3,4,10b-tetrahydropyrido[2,1-*a*]isoindol-6(2*H*)-one (13a)**



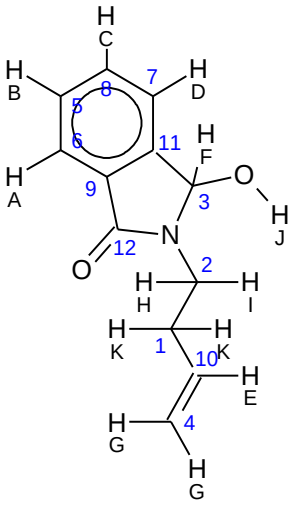
2: NMR Assignment: ^{1}H-NMR (700 MHz, $CDCl_3$) δ: 7.86(d, 1H, J= 7 Hz, A), 7.54(t, 1H, J= 7 Hz, B), 7.47-48(t, 1H, J= 7 Hz, C), 7.40(d, 1H, J= 8 Hz, D), 4.30-4.40(m, 2H, E), .30-4.40(m, 1H, E), 3.00-3.07 (m, 1H, F), 3.00-3.07 (m, 1H, F*), 2.49(br d, J=12 Hz, 1H, G), 2.00-2.08(m, 1H, H), 1.80(q, 1H, J= 12 Hz, I). ^{13}C-NMR (400 MHz, $CDCl_3$): δ = 166.3(12), 143.8(11), 132.0(10), 131.7(9), 128.7(8), 124.0(7), 121.8(6), 60.0(5), 44.8(4), 40.1(3), 38.7(2), 20.0(1).

Compound G: 2-(3-Hydroxy-4-iodobutyl)-1*H*-isoindole-1,3(2*H*)-dione (13d)



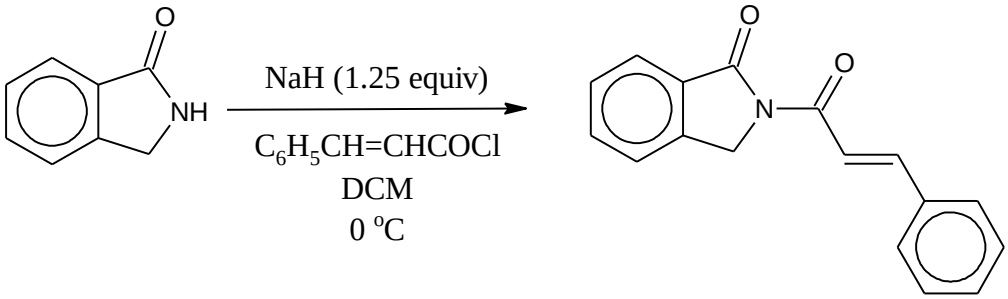
NMR Assignment: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.85 (m, 2H, A), 7.72 (m, 2H, B), 3.88(m, 2H, C), 3.56(m, 1H, D), 3.33 (m, 1H, E), 3.25(m, 1H, F), 3.05(m, 1H, G), 1.98 (m, 1H, H), 1.81(m, 1H, I). ^{13}C-NMR (400 MHz, $CDCl_3$): δ = 168.8(8), 134.3(7), 132.6(6), 123.3(5), 68.4(4), 35.6(3), 34.7(2), 14.0(1).

Compound H: 2-(but-3-en-1-yl)-3-hydroxy-2,3-dihydro-1*H*-isoindol-1-one (13b)



NMR Assignment: ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.63 (m, 1H), 7.60(m, 1H), 7.57(m, 1H), 7.46(m, 1H), 5.78-5.85(m, 1H), 5.73-5.78(m, 1H), 4.99-5.1(m, 1H), 3.55-3.63(m, 1H), 3.35-3.43(m, 1H), 3.22(m, 1H), 2.34-2.45(m, 2H). ^{13}C-NMR (400 MHz, $CDCl_3$): δ = 167.4, 143.4, 138.3, 132.3, 131.6, 129.9, 123.4, 117.2, 82.0, 38.8, 32.8.

4.13 Synthesis 2-(3-Phenyl-acryloyl)-2,2-dihydro-isoindol-1-one (4a)[48]

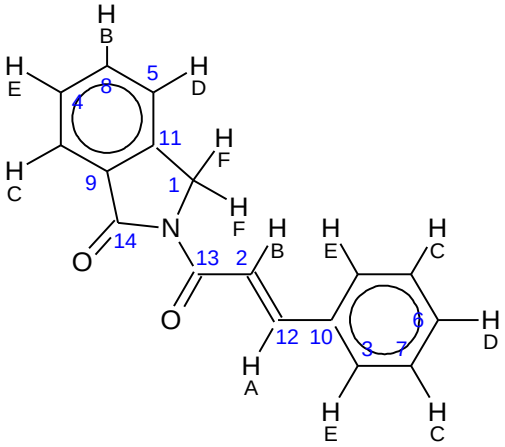


Sodium hydride (1.54g, 1.25 equiv) was placed under N_2 in an oven dried round bottom flask (500ml). Sodium hydride was washed with hexane. Anhydrous DCM (100ml) was added to the sodium hydride. To this grey suspension was added a solution of isoindolinone (5.47g, 0.041mol) in dry DCM (50ml). In a separate oven dried 500ml round bottom flask, cinamoyl chloride (2.5 equivalents) and dry DCM (100ml) were placed.

The flask containing the iso-indolinone/sodium hydride solution was cooled in a water/ice bath, and the cinnamoyl chloride solution was slowly injected into the flask slowly over a period of 30 minutes. The reaction was left to stir for 24 hours. The reaction was quenched with water and extracted with DCM, dry organic layers were dried with $MgSO_4$, filtered and concentrated. White solid was

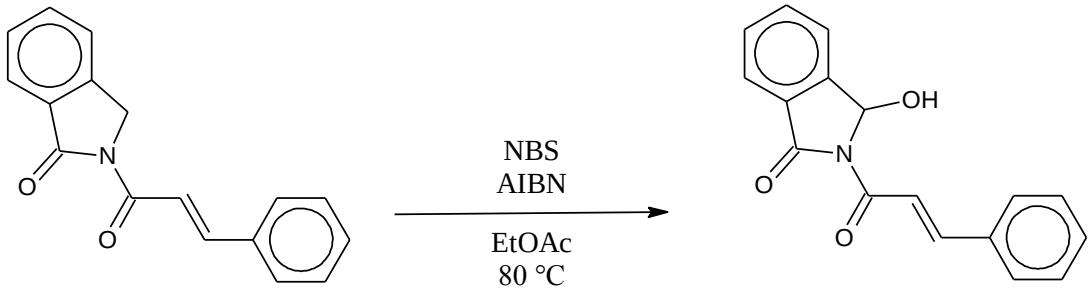
obtained and re-crystallise from benzene; to obtain thin white fluffy needles in 66% yield.

2-(3-Phenyl-acryloyl)-2,2-dihydro-isoindol-1-one (4a)



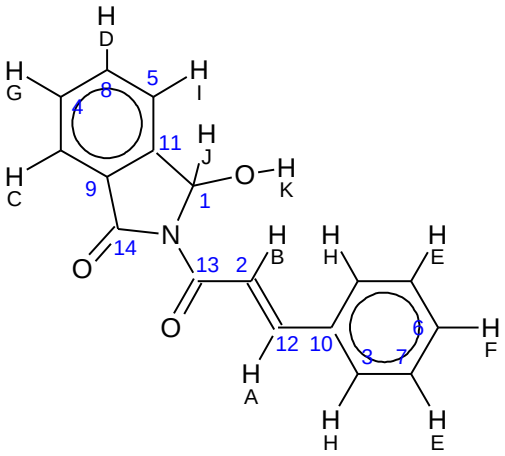
NMR Assignment: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.26 (d, 1H, J= 15.9 Hz), 7.93-7.97 (m, 2H), 7.67-7.71 (m, 3H), 7.52-7.56 (m, 2H), 7.40-7.43 (m, 3H), 4.95 (s, 2H).^{13}C-NMR (400 MHz, $CDCl_3$): δ = 168.0, 166.4, 146.1, 141.4, 135.0, 134.3, 131.6, 130.6, 128.9, 128.8, 125.4, 123.6, 119.2, 48.7.

4.14 Synthesis of 3-hydroxy-2-[(2*E*)-3-phenylprop-2-enoyl]-2,3-dihydro-1*H*-isoindol-1-one (9b)



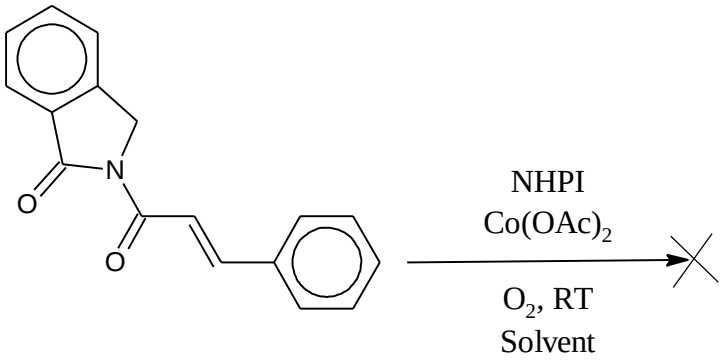
To a solution of 2-(3-phenyl-acryloyl)-2,2-dihydro-isoindol-1-one (350mg, 1.35mmol) and AIBN (0.00215g, 0.0135mmol) in 20ml EtOAc, NBS (235mg, 1.35mmol) was added and the reaction was refluxed for 12hr. The reaction mixture was cooled and filtered then concentrated. The crude (a light brown solid which rapidly turns black when left in sample vial) was purified by column chromatography (EtOAc: Hex 1:1), to afford a white solid (262mg, Rf: 0.43).

3-Hydroxy-2-[(2*E*)-3-phenylprop-2-enoyl]-2,3-dihydro-1*H*-isoindol-1-one (9b)



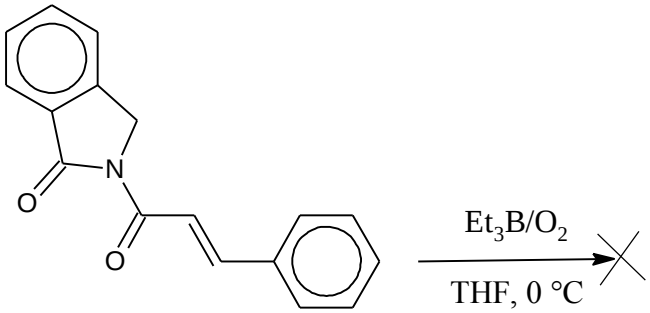
NMR Assignment: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 8.16 (d, 1H, J= 15.7 Hz, A), 7.99 (d, 1H, 15.7 Hz, B), 7.94 (d, 1H, 7.7Hz, C), 7.76 (m, 1H, D), 7.70 (m, 3H, E), 7.63 (m, 2H, F), 7.44 (m, 2H, G), 6.69 (d, 1H. H), 4.74 (d, 1H, I). ^{13}C-NMR (400 MHz, $CDCl_3$): δ = 81.3(1), 118.7(2), 124.2(3), 125.1(4), 128.8(5), 129.0(6), 130.7(7), 130.9(8), 134.7(9), 134.8(10), 142.3(11), 146.9(12), 166.4(13), 167.6(14).

4.15 Failed Cyclisation Attempt of 4a Using Ishii System



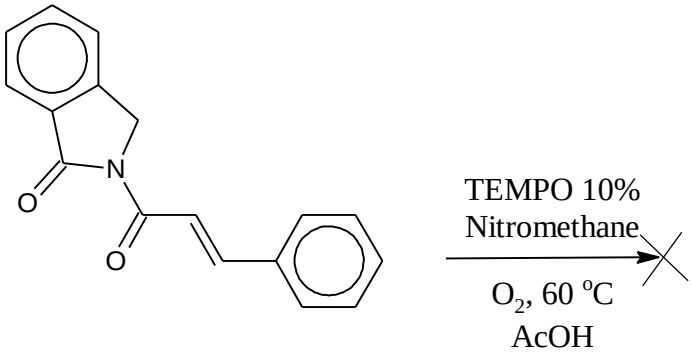
A solution of 2-(3-Phenyl-acryloyl)-2, 2-dihydro-isoindol-1-one (100mg), NHPI (25mg, 0.15mmol) and Co $(OAc)_2$ (3mg, 0.0015mmol) were placed in a two necked flask purged with oxygen equipped with a balloon filled with oxygen. The reaction was run at room temperature in 10ml DCM first, there was no observable reaction. The solvent was changed to acetonitrile and run at 80^{o}C; still no reaction. The solvent was changed again to acetic acid and temperature increased to 110 ^{o}C. There was no observed reaction.

4.16 Failed Cyclisation Attempt of 4a Using Triethylborane as Initiator



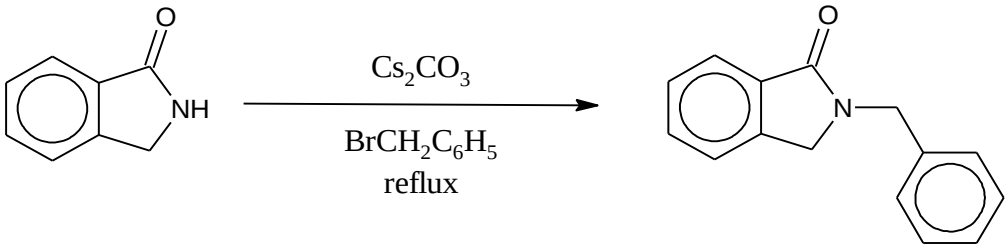
2-(3-Phenyl-acryloyl)-2, 2-dihydro-isoindol-1-one (100mg, 0.38mmol) was dissolved in THF (10mL), purged with oxygen and sealed affixing a balloon filled with O_2 to the sealed vessel. Solution was cooled in a water/ice bath to 0^oC at which point 1 equivalent of triethylborane dissolved in THF was injected into the reaction flask very slowly using an autosyringe over 1 h. No reaction was observed. Injection of two equivalents of Et_3B also did not result in an observable reaction. The reaction was also performed at room temperature, no reaction was observed.

4.17 Failed TEMPO Catalysed Coupling Reaction of 4a to Nitromethane



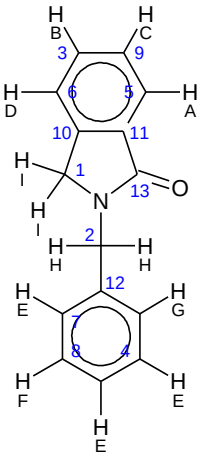
2-(3-Phenyl-acryloyl)-2, 2-dihydro-isoindol-1-one (52.0mg, 0.2mmol) and TEMPO (3.2 mg, 0.02 mmol) were placed in a 25 ml round bottom flask. Then CH_3NO_2 (0.5 mL) was added. The reaction mixture was stirred at 60 °C under O_2 (1 atm) for 24 h, no reaction was observed.

4.18 Synthesis of 2-Benzyl-2,3-dihydro-isoindol-1-one (14a)[53]



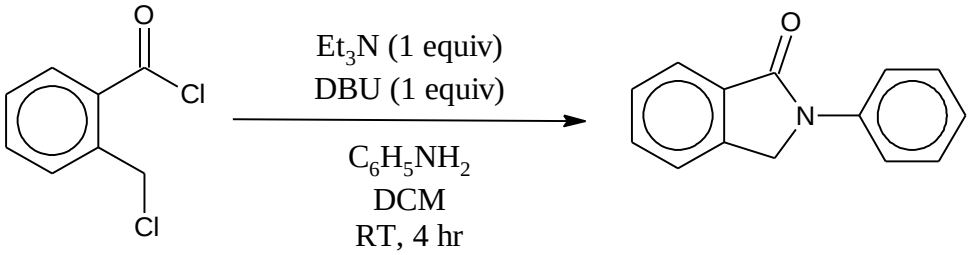
To isoindolinone (250mg, 1.85mmol) in acetonitrile (10ml) was added caesium carbonate (2.4g, 7.39mmol) and the mixture was heated to 80^{o}C. Then benzyl bromide (2.77mmol) in 5ml EtOAc was slowly injected into the reaction mixture over a period of 20 minutes. The reaction was refluxed for 3hr at 80^{o}C. The reaction mixture was partitioned between ethyl acetate and water and the organic layer washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the product was purified by column chromatography (40%EtOAc/Pet40-60) to afford a white solid in 80% yield (Rf 0.26). High-resolution mass spectroscopy (ESI): $(M+H)^+$: for $C_{15}H_{13}NO$, 224.09; m.p: 139.4 ^{o}C

2-Benzyl-2,3-dihydro-isoindol-1-one (14a)



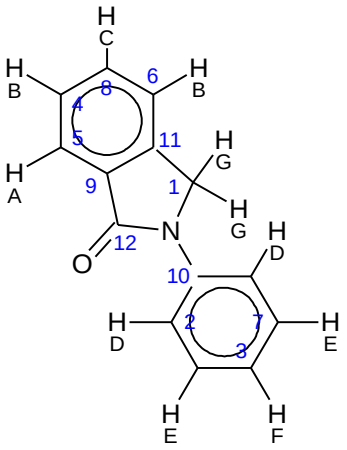
NMR Assignment: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.90 (d, 1H, A), 7.50-7.55 (m, 1H, B), 7.45-7.50 (m, 1H, C), 7.37-7.40 (d, 1H, D), 7.31-7.33 (m, 3H, E), 7.28-7.31 (m, 1H, F), 4.81 (s, 2H, G), 4.27 (s, 2H, H). ^{13}C-NMR (400 MHz, $CDCl_3$): δ = 168.0(12), 141.3(11), 137.1(10), 132.7(9), 128.9(8), 128.3(7), 128.1(6), 127.8(5), 124.0(4), 122.8(3), 49.5(2), 48.5(1).

4.19 Synthesis of 2-Phenyl-2,3-dihydro-isoindol-1-one (15a) [47b]



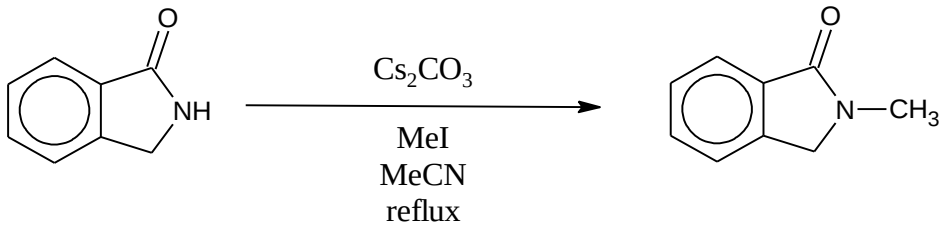
To a stirred solution of aniline (5.50 mmol) and triethylamine (5.50mmol) in dry dichloromethane (30ml) the solution of benzoyldichloride (5.00mmol) in dry dichloromethane (20ml) was added dropwise at room temperature for 30 min. After additional 2 hr DBU (10.10mmol) was added. The reaction was continued for additional 2hr at room temperature. After the reaction was finished, dichloromethane was evaporated in vacuo and the residue was separated by silica gel chromatography (40%EtOAc/Pet40-60). An off white powder was isolated in 63% yield (Rf: 0.3)

2-Phenyl-2,3-dihydro-isoindol-1-one (15a)



NMR Assignment: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.94 (d, 1H), 7.85, (d, 2H), 7.58-7.63 (m, 1H), 7.49-7.54 (m, 2H), 7.41-7.45 (m, 2H), 7.16-7.21 (m, 1H), 4.87 (s, 2H).^{13}C-NMR (400 MHz, $CDCl_3$): δ = 167.6(12), 140.20(11), 139.6(10), 133.33(9), 132.2(8), 129.3(7), 128.6(6), 124.6(5), 124.2(4), 122.7(3), 119.5(2), 50.8(1).

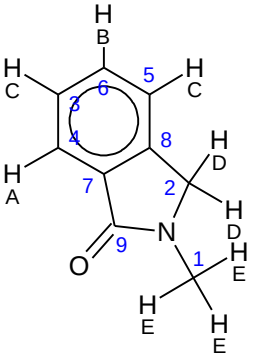
4.20 Synthesis of 2-methyl-2,3-dihydro-isoindol-1-one (16a)[53]



To isoindolinone (250 mg, 1.85 mmol) in acetonitrile (10 ml) was added iodomethane (393 mg, 2.77 mmol) and caesium carbonate(2.4 g, 7.39 mmol) and the mixture was allowed to stir at 80 ^{o}C for 3 h. The reaction mixture was

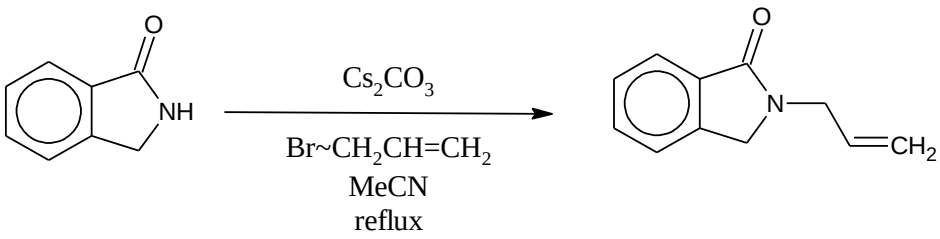
partitioned between ethyl acetate and water and the organic layer washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the product was purified by column chromatography (40%EtOAc/Pet40-60) to afford the product as a white solid (190 mg Rf: 0.38). High-resolution mass spectroscopy (ESI): $(M+H)^+$: for C_9H_9NO, 148.06; m.p: 76.2 ^oC

Methyl-2,3-dihydro-isoindol-1-one (16a)



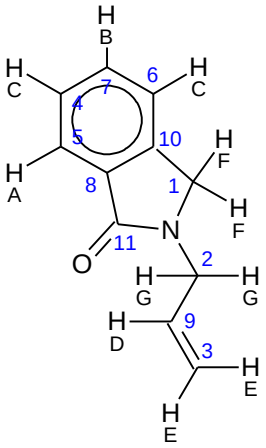
NMR Assignment: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.82 (d, 1H, A), 7.48-7.53 (m, 1H, B), 7.40-7.45 (m, 2H, C), 4.35 (s, 2H, D), 3.18 (s, 3H, E). ^{13}C-NMR (400 MHz, $CDCl_3$): δ = 168.6(9), 144.1(8), 133.0(7), 131.2(6), 128.0(5), 123.6(4), 122.7(3), 52.1(2), 29.5(1).

4.21 Synthesis of 2-Allyl-2,3-dihydro-isoindol-1-one (17a)[53]



To isoindolinone (250mg, 1.85mmol) in acetonitrile (10ml) was added caesium carbonate (2.4g, 7.39mmol) and the mixture was heated to 80^{o}C. Then allyl bromide (518mg, 2.77mmol) in 8ml EtOAc was slowly injected into the reaction mixture over a period of 20 minutes. The reaction was refluxed for 5h at 80^{o}C. The reaction mixture was partitioned between ethyl acetate and water and the organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed under reduced pressure and the product was purified by column chromatography (40%EtOAc/Pet40-60) to afford the title product as yellow oil in 79% yield (278mg, Rf: 0.27). High-resolution mass spectroscopy (ESI): $(M+H)^+$: for $C_{11}H_{11}NO$, 174.08; m.p: 94.5 ^{o}C

2-Allyl-2,3-dihydro-isoindol-1-one (17a)



NMR Assignment: ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 7.73 (m, 1H, A), 7.39-7.44 (m, 1H, B), 7.31-7.36 (m, 2H, C), 5.70-5.80 (m, 1H, D), 5.10-5.16 (m, 2H, E), 4.23 (m, 2H, F), 4.10-4.14 (m, 2H, G). ^{13}C-NMR (400 MHz, $CDCl_3$): δ = 168.3(11), 141.3(10), 134.1(9), 133.0(8), 131.3(7), 128.0(6), 123.6(5), 122.8(4), 117.9(3), 49.6(2), 45.0(1).

Appendices

1. Abbreviations

AcOH: Acetic Acid

AZADO: Azanoradamantane *N*-oxyl

AIBN: Azobisisobutyronitrile

BDE: Bond dissociation energy

BuLi: Butyllithium

PhCl: Chlorobenzene

COSY: Correlation spectroscopy

DBU: 1,8-Diazabicyclo[5.4.0]undec-7-ene

DCM: Dichloromethane

DEAD: Diethyl azodicarboxylate

DMF: Dimethylformamide

ESI: Electrospray ionization

EtOH: Ethanol

EtOAc: Ethyl Acetate

5-F-AZADO: 5-Fluro-2-azaadamantane *N*-oxyl

HMBC: Heteronuclear Multiple-bond Correlation spectroscopy

HSQC: Heteronuclear Single Quantum Coherence spectroscopy

MEHQ: Hydroquinone Monomethyl Ether

Hex: Hexane

LUMO: Lowest unoccupied molecular orbital

MeI: Methyl iodide

NHPI: *N*-hydroxyphthalimide

NBS: *N*-Bromosuccinimide

NCS: *N*-Chlorosuccinimide

NIS: *N*-Iodosuccinimide

NMR: Nuclear magnetic resonance

NOESY: Nuclear Overhauser effect spectroscopy

PINO: Phthalimide-*N*-oxyl

t-BuOK: Potassium tert-butoxide

nBu_3SnH: Tributyltin hydride

Ph_3SnH: Triphenyltin hydride

Rf: Retardation factor

RSA: Retrosynthetic Analysis

RT: Room temperature

SOMO: Singly Occupied Molecular Orbital

THF: Tetrahydrofuran

TLC: Thin layer chromatography

Et_3N: Triethylamine

Et_3B: Triethylborane

TFA: Trifluoroacetic acid

TfOH: Trifluoromethanesulfonic acid

TOCSY: Total correlation spectroscopy

UV: Ultraviolet

2. Tabulated results for diastereomer 2 (13a)

Proton	δ(ppm)	App,	Int.	J(Hz)	COSY	HSQC	HMBC
A	7.85	d	1	7	H_C	C7	C9.C11. C12
B	7.54	t	1	7	H_D	C9	-
C	7.47	t	1	7	H_A	C8	C6,C10
D	7.41	d	1		H_B	C6	C8,C9, C5(w)
E	7.30-40	m	2		H_F,H_H,H_G(w), H_I	C1, C3	C1.C2,C4(w),C5,C12 (w)
E*			1		H_I, H_F	C5	C4,C11,C12()
F	3.00-07	m	1		$H_{E/E}$*,H_G(w), H_H(w)	C3	C1,C2,C12
F*			1		H_I	C4	C5(w)
G	2.49	d	1		H_H, $H_{F/F*}$, $H_{E/E*}$	C2	-
H	2.00-08	m	1		H_G, $H_{F/F*}$, $H_{E/E*}$	C2	C1, C3, C4(w), C12(w)
I	1.80	q	1	12	$H_{F/F*}$, $H_{E/E*}$	C4	C1.C2(w),C5,C11

Table 4: Tabulated results for diastereomer 2, (13a) (700MHz, $CDCl_3$)

Carbon	δ(ppm)	HSQC
1	20.0	HE
2	38.7	HG,HH
3	40.1	HE,HF
4	44.8	HI,HF*
5	60.0	HE*
6	121.8	HD
7	124.0	HA
8	128.7	HC
9	131.7	HB
10	132.0	-
11	143,8	-
12	166.3	-

Table 5: Tabulated results for diastereomer 2, (13a) (700MHz, $CDCl_3$)

3. List of NMR spectra

1. ^{1}H NMR spectrum of 2,3-Dihydro-isoindol-1-one (**5b**) (400 MHz) (**Figure 72**)
2. ^{13}C NMR spectrum of 2,3-Dihydro-isoindol-1-one (**5b**) (400 MHz) (**Figure 73**)
3. ^{1}H NMR spectrum of 2-(3-Phenyl-acryloyl)-2,2-dihydro-isoindol-1-one (**4a**) (400 MHz) (**Figure 74**)
4. ^{13}C NMR spectrum of 2-(3-Phenyl-acryloyl)-2,2-dihydro-isoindol-1-one (**4a**) (400 MHz) (**Figure 75**)

5. ^{1}H NMR spectrum of 3-hydroxy-2-[(2*E*)-3-phenylprop-2-enoyl]-2,3-dihydro-1*H*-isoindol-1-one (**9b**) (**Figure 76**)
6. ^{13}C NMR spectrum of 3-hydroxy-2-[(2*E*)-3-phenylprop-2-enoyl]-2,3-dihydro-1*H*-isoindol-1-one (**9b**) (**Figure 77**)
7. ^{1}H NMR spectrum of 2-Allyl-2,3-dihydro-isoindol-1-one (**17a**) (**Figure 78**)
8. ^{13}C NMR spectrum of 2-Allyl-2,3-dihydro-isoindol-1-one (**17a**) (**Figure 79**)
9. ^{1}H NMR spectrum of 2-But-3-enyl-2,3-dihydro-indol-1-one (**10a**) (**Figure 80**)
10. ^{13}C NMR spectrum of 2-But-3-enyl-2,3-dihydro-indol-1-one (**10a**) (**Figure 81**)
11. ^{1}H NMR spectrum of (2R, 10bS)-2-bromo-1,3,4,10b-tetrahydropyrido [2, 1-a] isoindol-6(2H)-one (**11a**) (**Figure 82**)
12. ^{13}C NMR spectrum of (2R, 10bS)-2-bromo-1,3,4,10b-tetrahydropyrido [2, 1-a] isoindol-6(2H)-one (**11a**) (**Figure 83**)
13. ^{1}H NMR spectrum of (2S & 2R, 10bS)-2-iodo-1,3,4,10b-tetrahydropyrido [2, 1-a] isoindol-6(2H)-one (**13a**) (**Figure 84**)
14. ^{13}C NMR spectrum of (2S & 2R, 10bS)-2-iodo-1,3,4,10b-tetrahydropyrido [2, 1-a] isoindol-6(2H)-one (**13a**) (**Figure 85**)
15. ^{1}H NMR spectrum of 2-Methyl-2,3-dihydro-isoindol-1-one (**16a**) (**Figure 86**)
16. ^{13}C NMR spectrum of 2-Methyl-2,3-dihydro-isoindol-1-one (**16a**) (**Figure 87**)

17. ^{1}H NMR spectrum of 2-Phenyl-2,3-dihydro-isoindol-1-one (**15a**) (**Figure 88**)
18. ^{13}C NMR spectrum of 2-Phenyl-2,3-dihydro-isoindol-1-one (**15a**) (**Figure 89**)
19. ^{1}H NMR spectrum of 2-Benzyl-2,3-dihydro-isoindol-1-one (**14a**) (**Figure 90**)
20. ^{13}C NMR spectrum of 2-Benzyl-2,3-dihydro-isoindol-1-one (**14a**) (**Figure 91**)
21. ^{1}H NMR spectrum of *N*,*N*-Diallyl-3-phenyl-acrylamide (**3c**) (**Figure 92**)
22. ^{13}C NMR spectrum of *N*,*N*-Diallyl-3-phenyl-acrylamide (**3c**) (**Figure 93**)
23. ^{1}H NMR spectrum of 1-(2,5-Dihydro-pyrrol-1-yl)-3-phenyl-propenone (**2a**) (**Figure 94**)
24. ^{13}C NMR spectrum of 1-(2,5-Dihydro-pyrrol-1-yl)-3-phenyl-propenone (**2a**) (**Figure 95**)
25. ^{1}H NMR spectrum of 9,10-Dihydro-acridine (**3b**) (**Figure 96**)
26. ^{13}C NMR spectrum of 9,10-Dihydro-acridine (**3b**) (**Figure 97**)
27. ^{1}H NMR spectrum of 10-Methyl-9,10-dihydro-acridine (**3c**) (**Figure 98**)
28. ^{13}C NMR spectrum of 10-Methyl-9,10-dihydro-acridine (**3c**) (**Figure 99**)
29. ^{1}H NMR spectrum of 10-Methyl-9-nitromethyl-9,10-dihydro-acridine (**3d**) (**Figure 100**)
30. ^{13}C NMR spectrum of 10-Methyl-9-nitromethyl-9,10-dihydro-acridine (**3d**) (**Figure 101**)
31. ^{1}H NMR spectrum of 2-(3,4-dibromobutyl)-1*H*-isoindole-1,3(2*H*)-dione (**11c**) (**Figure 102**)

32. ^{13}C NMR spectrum of 2-(3,4-dibromobutyl)-1*H*-isoindole-1,3(2*H*)-dione (**11c**) (**Figure 103**)
33. ^{1}H NMR spectrum of 2-(3-hydroxy-4-iodobutyl)-1*H*-isoindole-1,3(2*H*)-dione (**13d**) (**Figure 104**)
34. ^{1}H NMR spectrum of 2-(4-bromo-3-hydroxybutyl)-1*H*-isoindole-1,3(2*H*)-dione (**11d**) (**Figure 105**)
35. ^{13}C NMR spectrum of 2-(3-hydroxy-4-iodobutyl)-1*H*-isoindole-1,3(2*H*)-dione (**13d**) (**Figure 106**)
36. ^{13}C NMR spectrum of 2-(4-bromo-3-hydroxybutyl)-1*H*-isoindole-1, 3(2*H*)-dione (**11d**) (**Figure 107**)
37. ^{1}H NMR spectrum of 2-(but-3-en-1-yl)-3-hydroxy-2,3-dihydro-1*H*-isoindol-1-one (**13b**) (**Figure 108**)
38. ^{13}C NMR spectrum of 2-(but-3-en-1-yl)-3-hydroxy-2,3-dihydro-1*H*-isoindol-1-one (**13b**) (**Figure 109**)
39. ^{1}H NMR spectrum of (2S & 2R, 10bS)-2-iodo-1,3,4,10b-tetrahydropyrido [2,1-a] isoindol-6(2H)-one (**13a**) (700 MHz) (**Figure 110**)
40. ^{13}C NMR spectrum of (2S & 2R, 10bS)-2-iodo-1,3,4,10b-tetrahydropyrido [2,1-a] isoindol-6(2H)-one (**13a**) (700 MHz) (**Figure 111**)
41. TOCSY NMR spectrum (2S & 2R,10bS)-2-iodo-1,3,4,10b-tetrahydropyrido [2,1-a] isoindol-6(2H)-one (**13a**) (700 MHz) (**Figure 112**)
42. HMBC NMR spectrum (2S & 2R, 10bS)-2-iodo-1,3,4,10b-tetrahydropyrido [2, 1-a] isoindol-6(2H)-one (**13a**) (700 MHz) (**Figure 113**)

43. COSY NMR diastereomer 1 magnified spectrum protons E-G (**13a**) (700 MHz) (**Figure 114**)
44. COSY NMR diastereomer 1 magnified spectrum protons H-I (**13a**) (700 MHz) (**Figure 115**)
45. COSY NMR diastereomer 1 magnified spectrum protons J-L (**13a**) (700 MHz) (**Figure 116**)
46. ^{1}H NMR spectrum of 10-Methyl-9-nitromethyl-9,10-dihydro-acridine (**8d**) (**Figure 117**)
47. ^{13}C NMR spectrum of 10-Methyl-9-nitromethyl-9,10-dihydro-acridine (**8d**) (**Figure 118**)
48. COSY NMR spectrum of 2-(3,4-dibromobutyl)-1*H*-isoindole-1, 3(2*H*)-dione (**11c**) (**Figure 119**)
49. COSY NMR spectrum of 2-(4-bromo-3-hydroxybutyl)-1*H*-isoindole-1, 3(2*H*)-dione (**11d**) (**Figure 120**)
50. HSQC NMR spectrum of 2-(4-bromo-3-hydroxybutyl)-1*H*-isoindole-1, 3(2*H*)-dione (**11d**) (**Figure 121**)
51. COSY NMR spectrum of (2R, 10bS)-2-bromo-1,3,4,10b-tetrahydropyrido [2,1-a] isoindol-6(2H)-one (**11a**) (**Figure 122**)
52. ^{1}H NMR spectrum of Methyl-2-hydroxy-3-(2-methyl-1,3-dioxolan-2-yl) propanoate (**1c**) (**Figure 123**)
53. ^{1}H NMR spectrum of Ethylene glycol monoacetate (**1f**) (**Figure 124**)

4. NMR Spectra

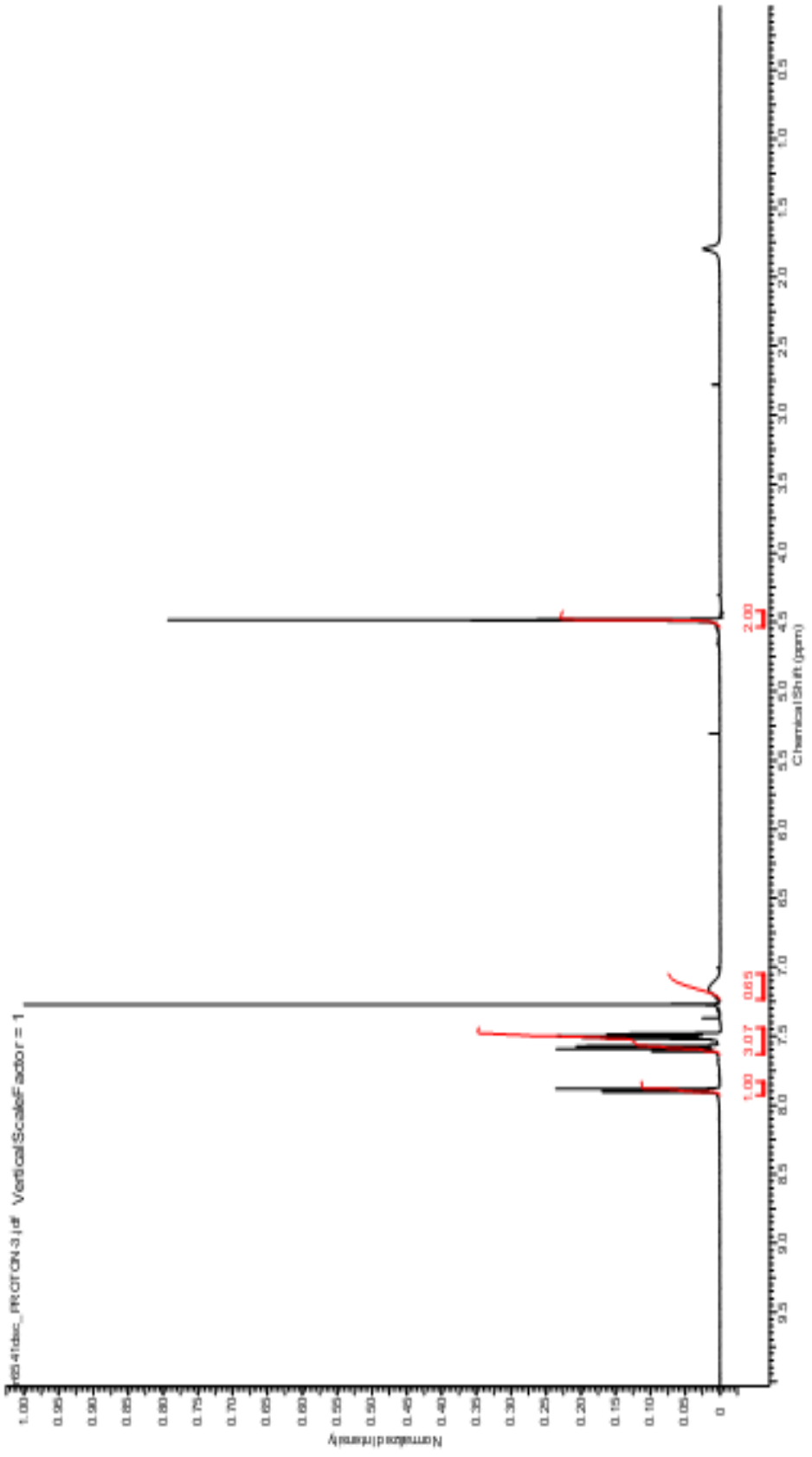


Figure 72: ^{1}H NMR spectrum of 2,3-Dihydro-isoindol-1-one (**5b**) (400 MHz)

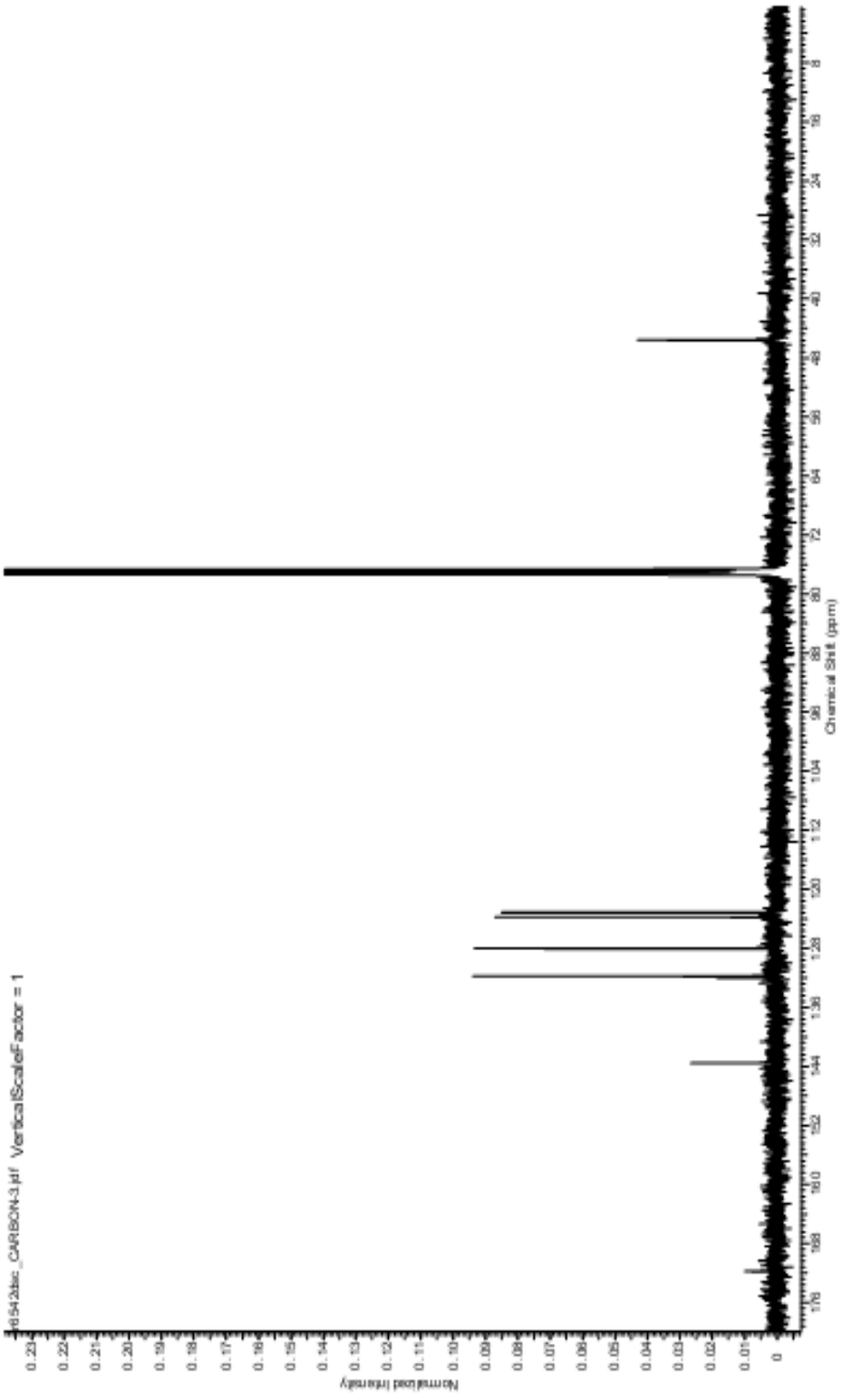


Figure 73: ^{13}C NMR spectrum of 2,3-Dihydro-isoindol-1-one (**5b**) (400 MHz)

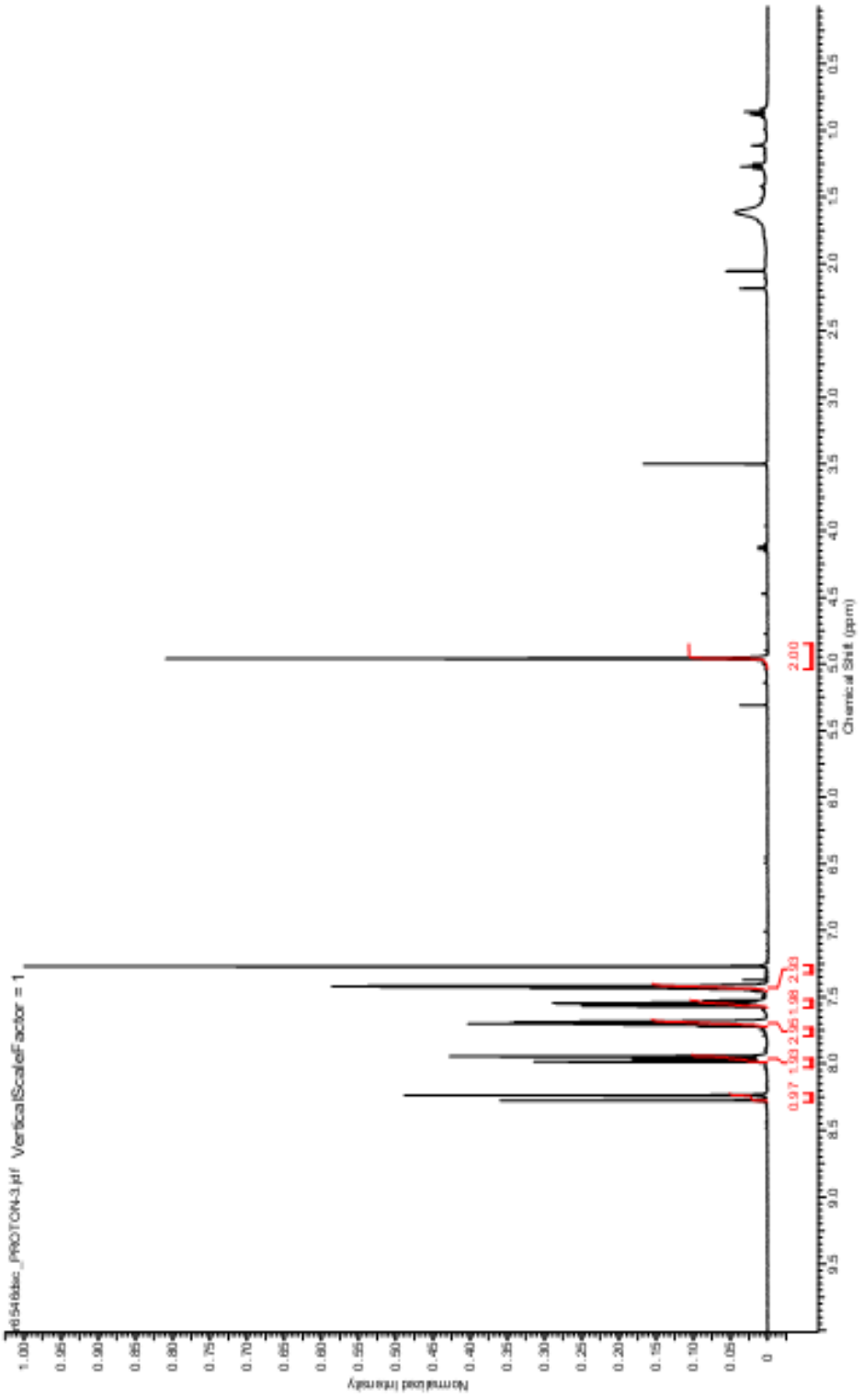


Figure 74 ^{1}H NMR spectrum of 2-(3-Phenyl-acryloyl)-2,2-dihydro-isoindol-1-one (**4a**) (400 MHz)

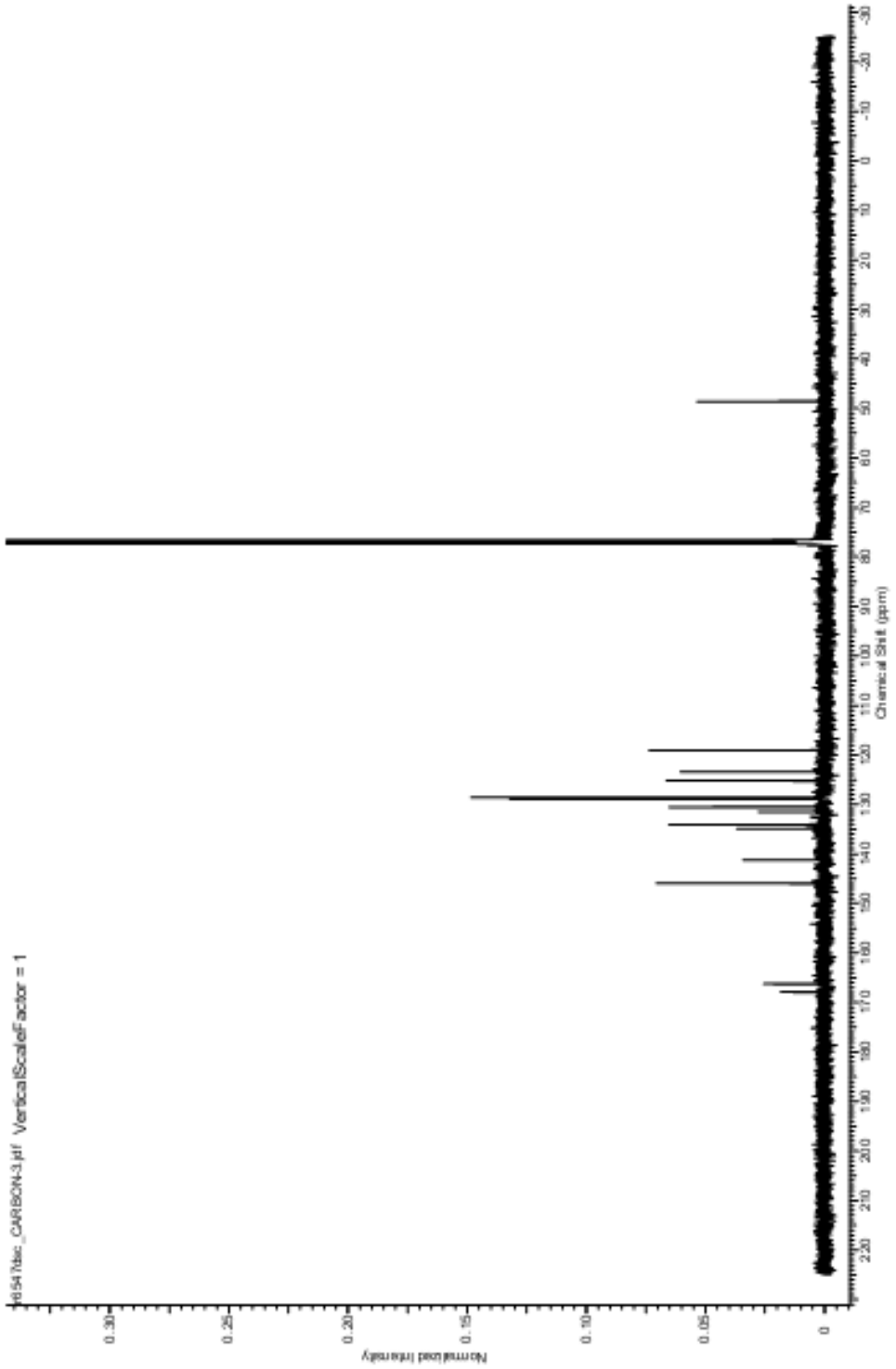


Figure 75 ^{13}C NMR spectrum of 2-(3-Phenyl-acryloyl)-2,2-dihydro-isoindol-1-one (**4a**) (400 MHz)

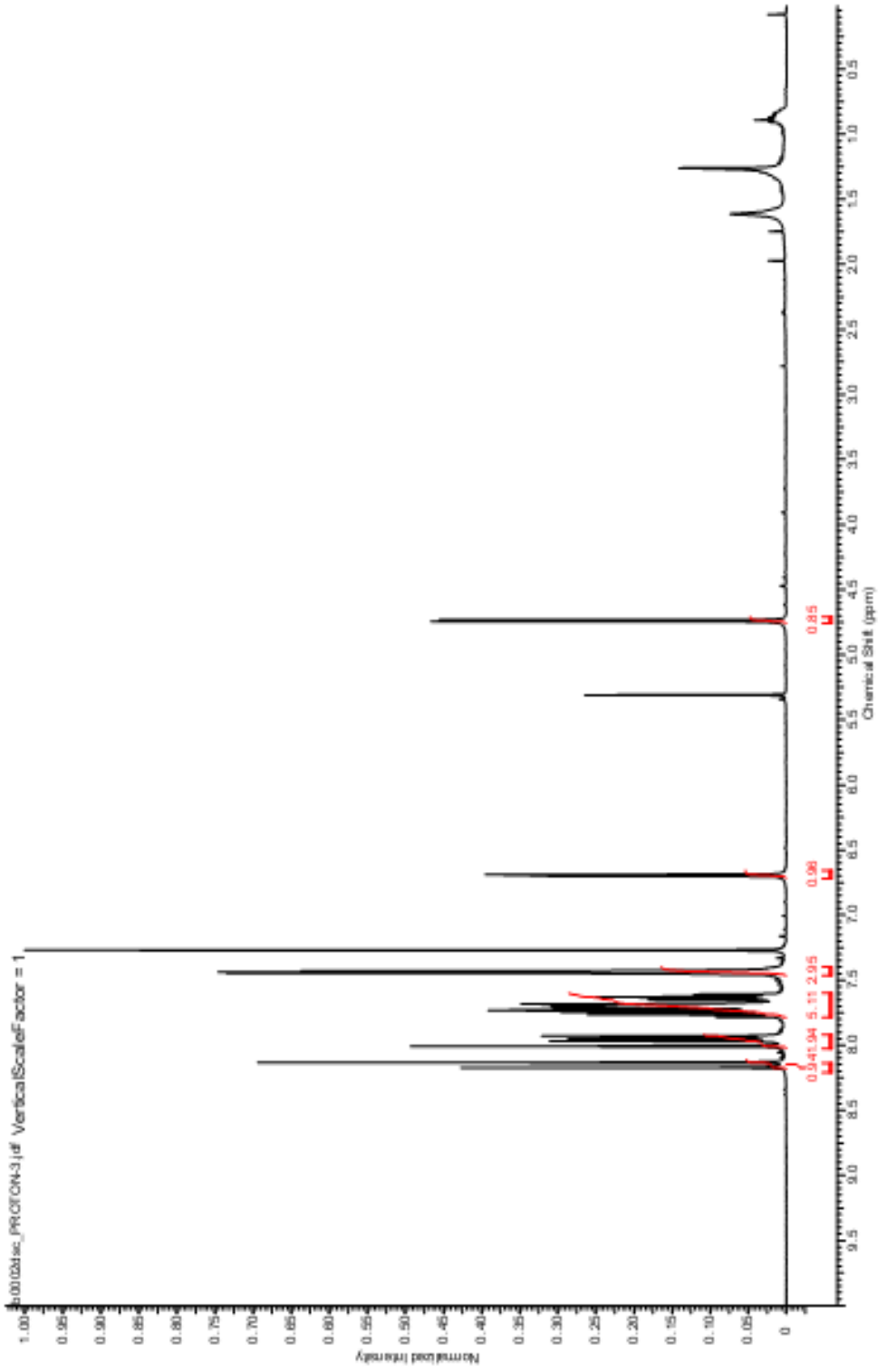


Figure 76 ^{1}H NMR spectrum of 3-hydroxy-2-[(2*E*)-3-phenylprop-2-enoyl]-2,3-dihydro-1*H*-isoindol-1-one (**9b**)

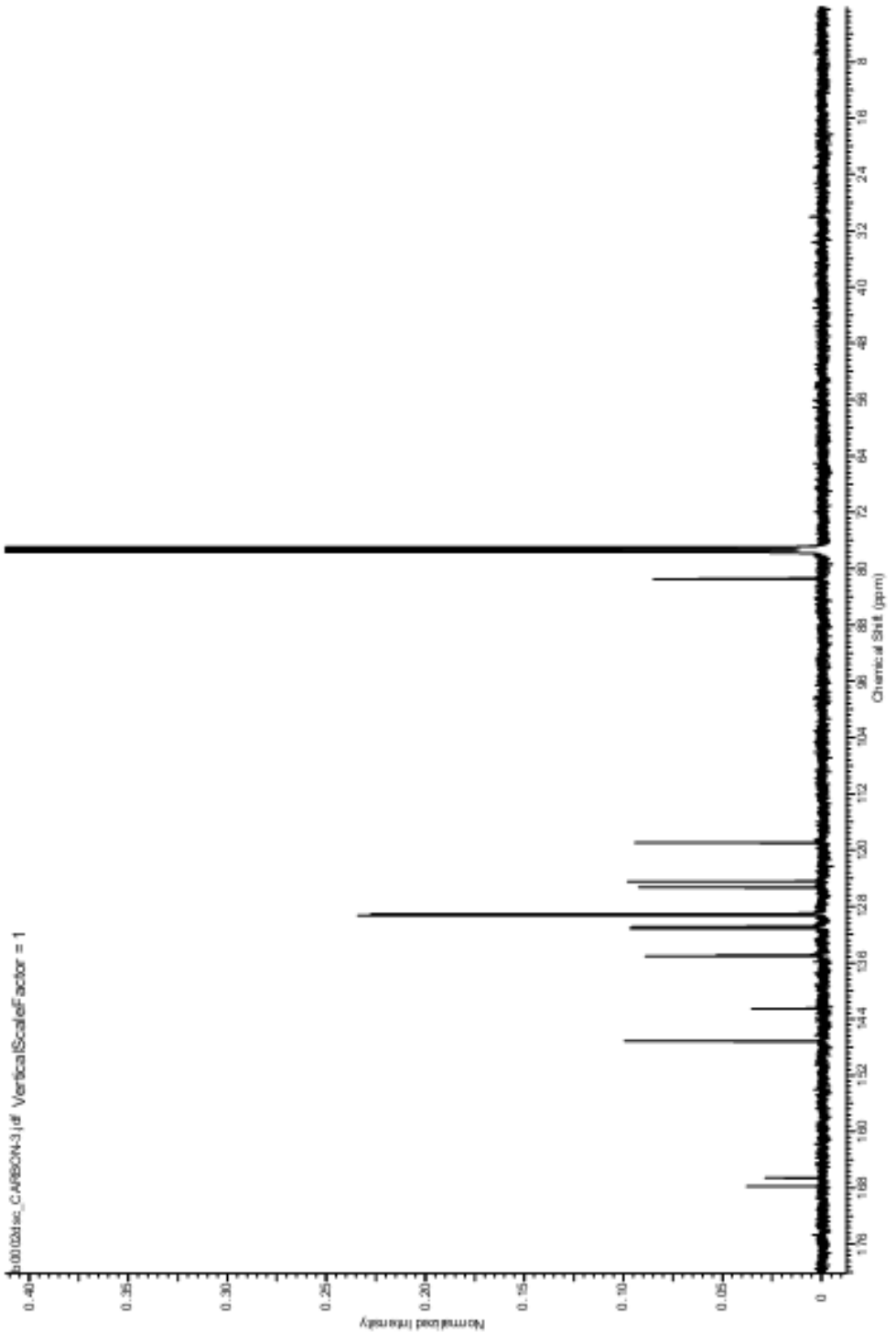


Figure 77 ^{13}C NMR spectrum of 3-hydroxy-2-[(2*E*)-3-phenylprop-2-enoyl]-2,3-dihydro-1*H*-isoindol-1-one (**9b**)

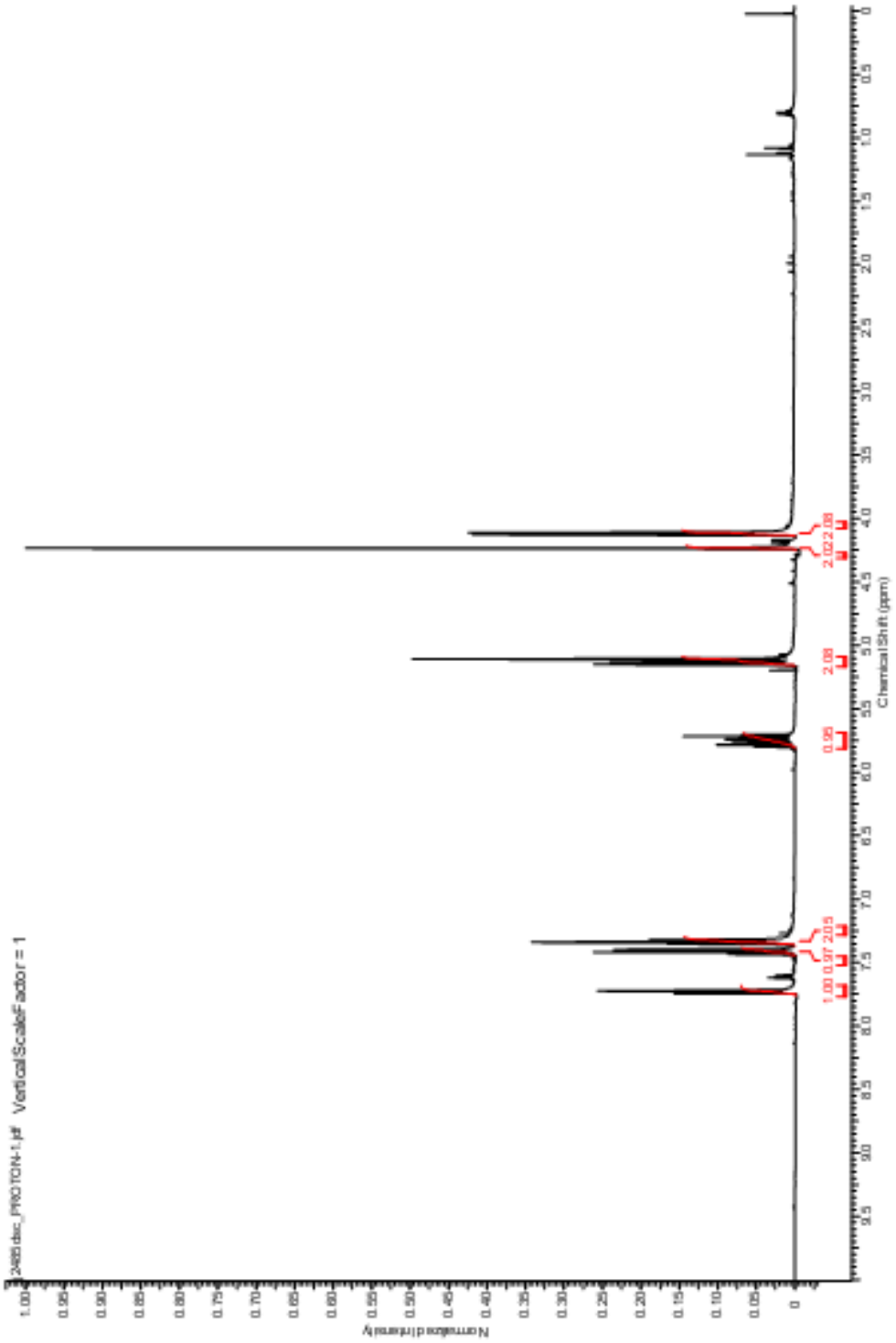


Figure 78 ^{1}H NMR spectrum of 2-Allyl-2,3-dihydro-isoindol-1-one (**17a**)

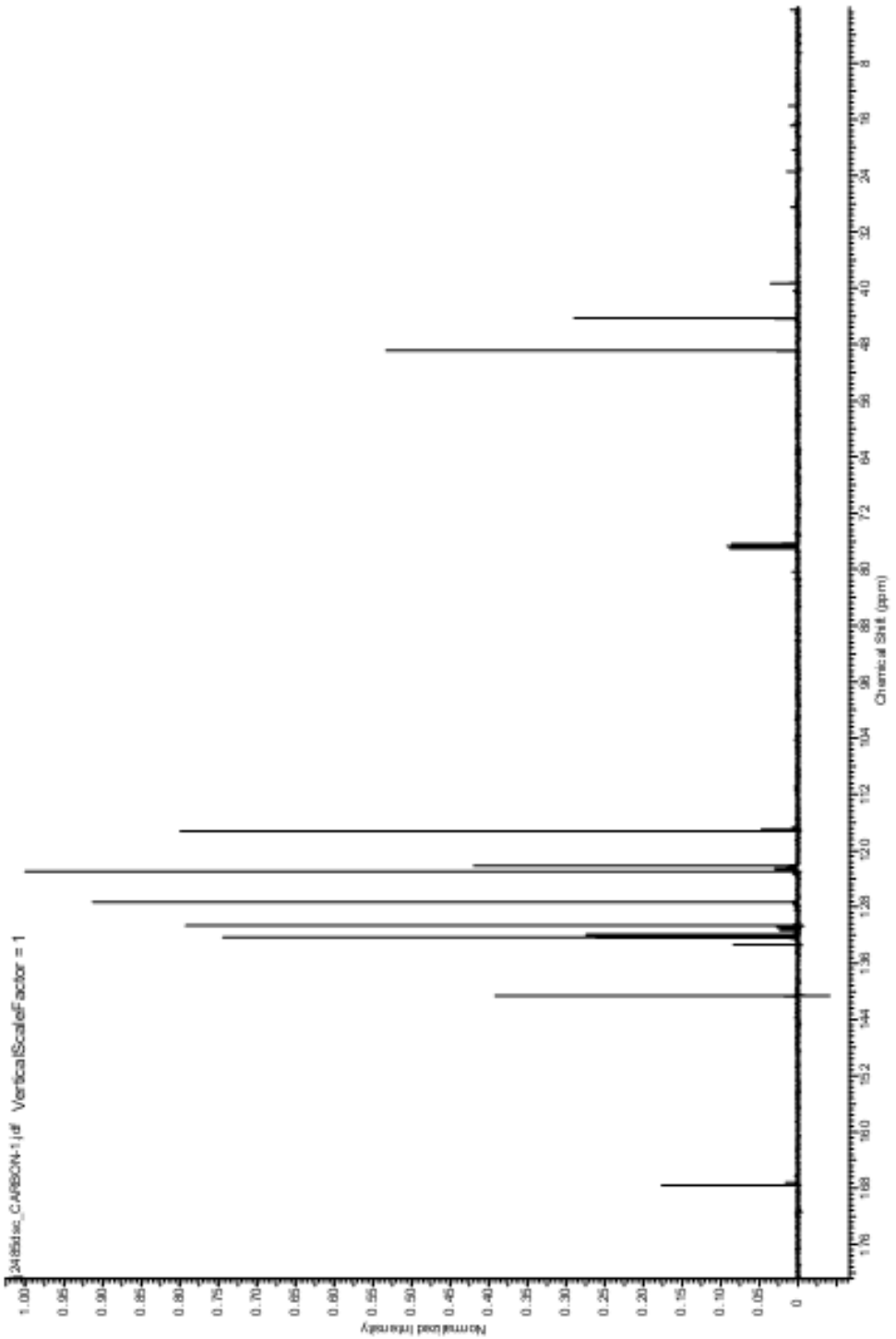


Figure 79 ^{13}C NMR spectrum of 2-Allyl-2,3-dihydro-isoindol-1-one (**17a**)

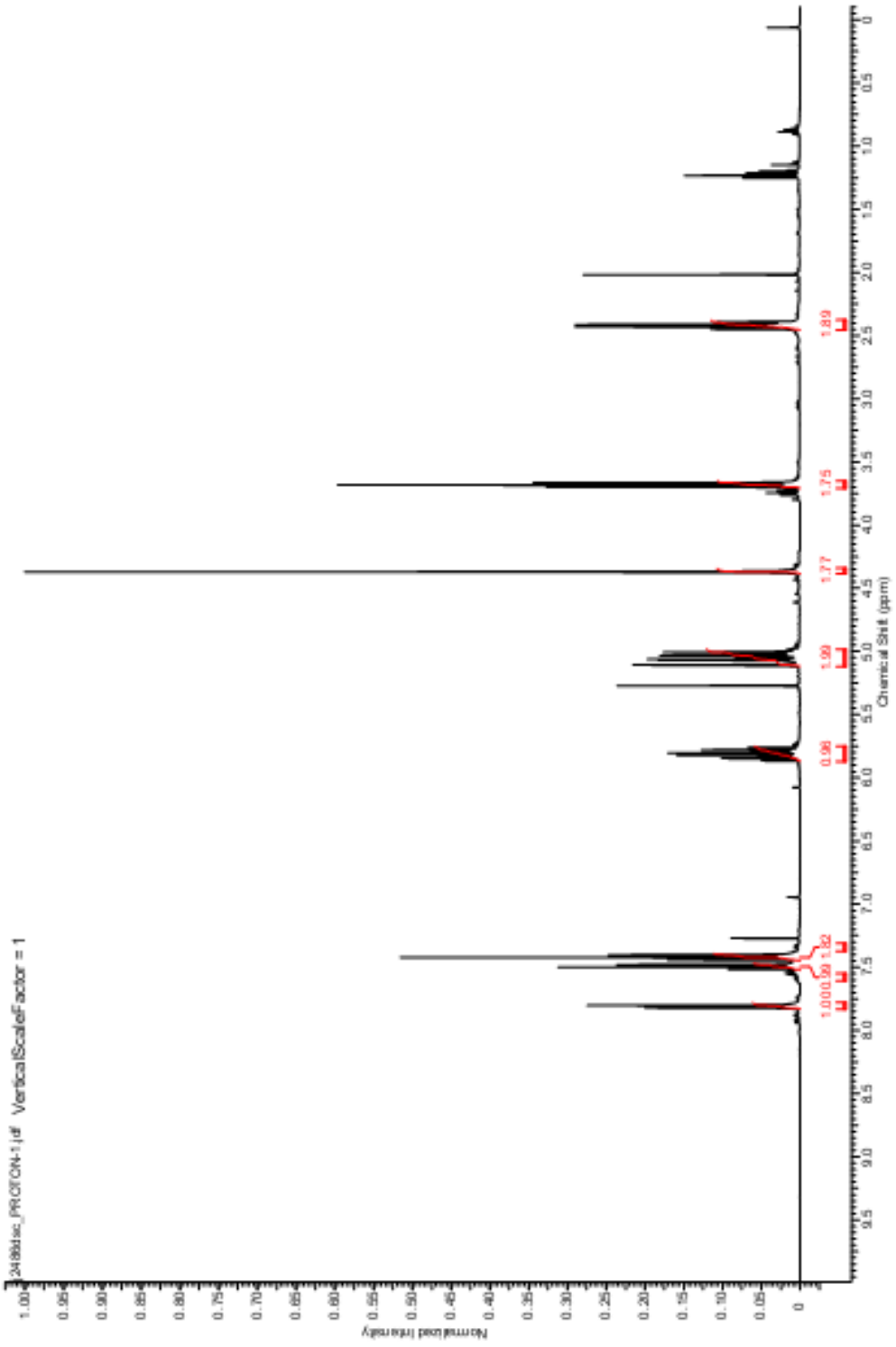


Figure 80 ^{1}H NMR spectrum of 2-But-3-enyl-2,3-dihydro-indol-1-one (**10a**)

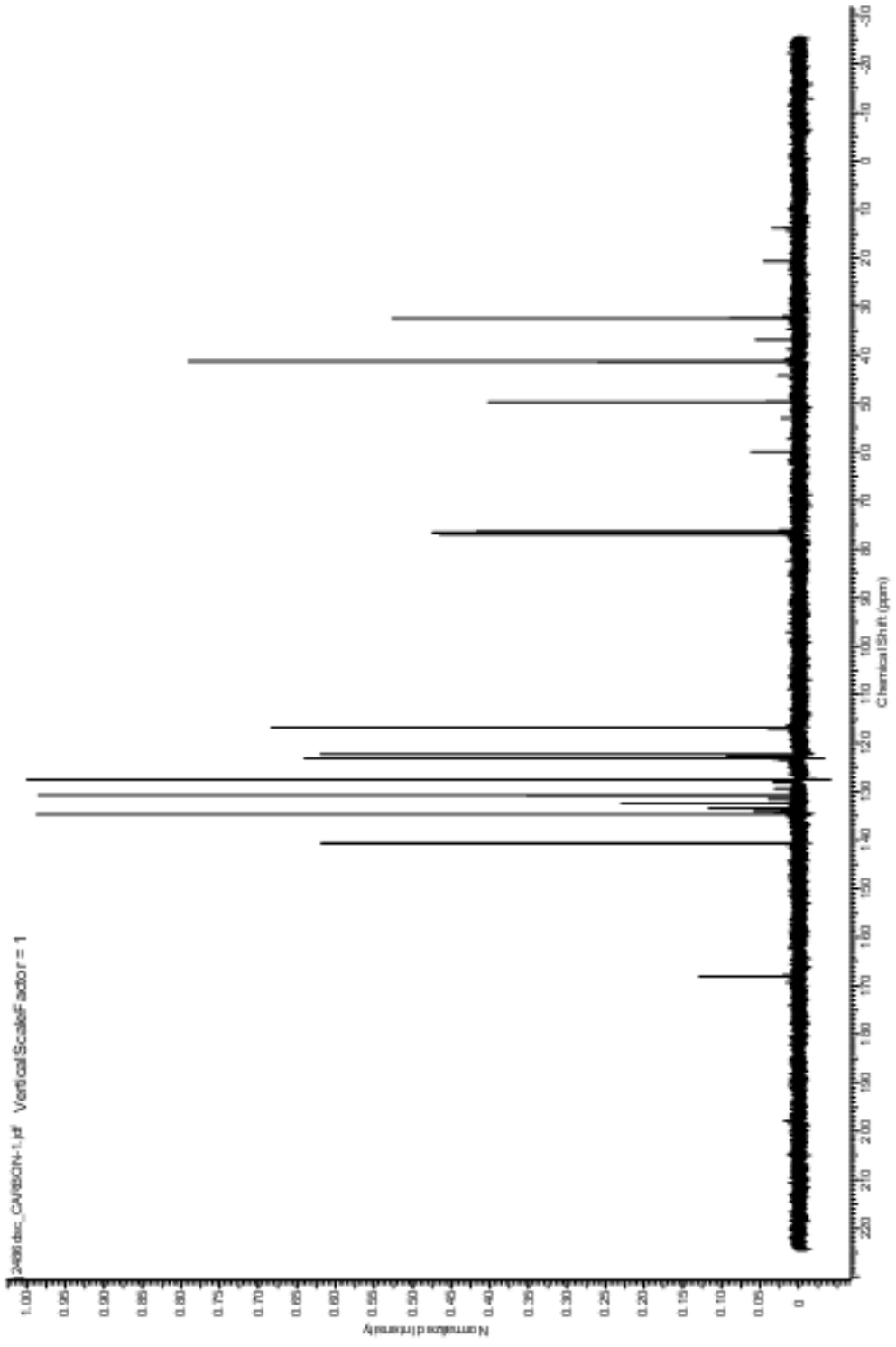


Figure 81 ^{13}C NMR spectrum of 2-But-3-enyl-2,3-dihydro-indol-1-one (**10a**)

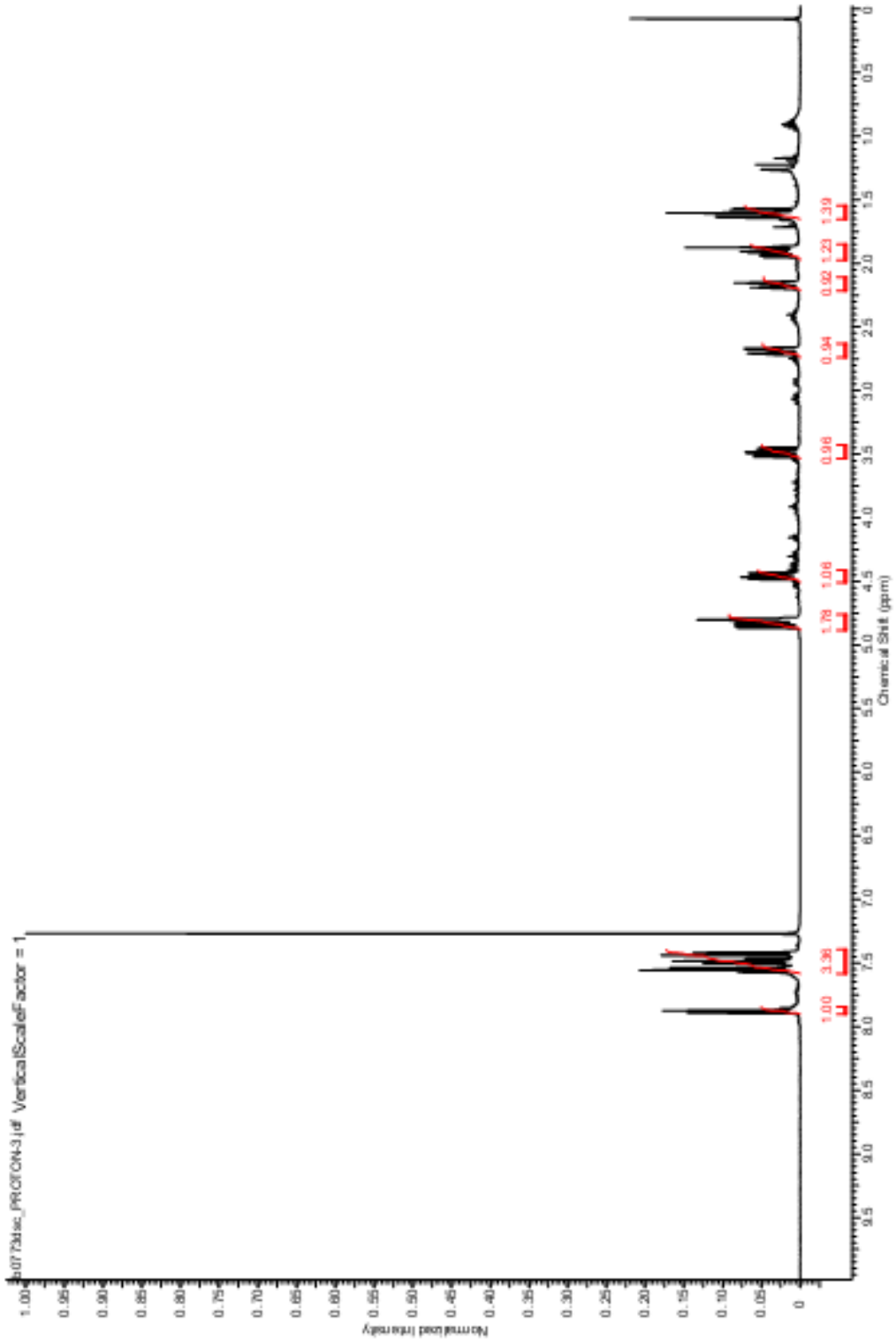


Figure 82 ^{1}H NMR spectrum of (2R, 10bS)-2-bromo-1,3,4, 10b-tetrahydropyrido [2,1-a] isoindol-6(2H)-one (**11a**)

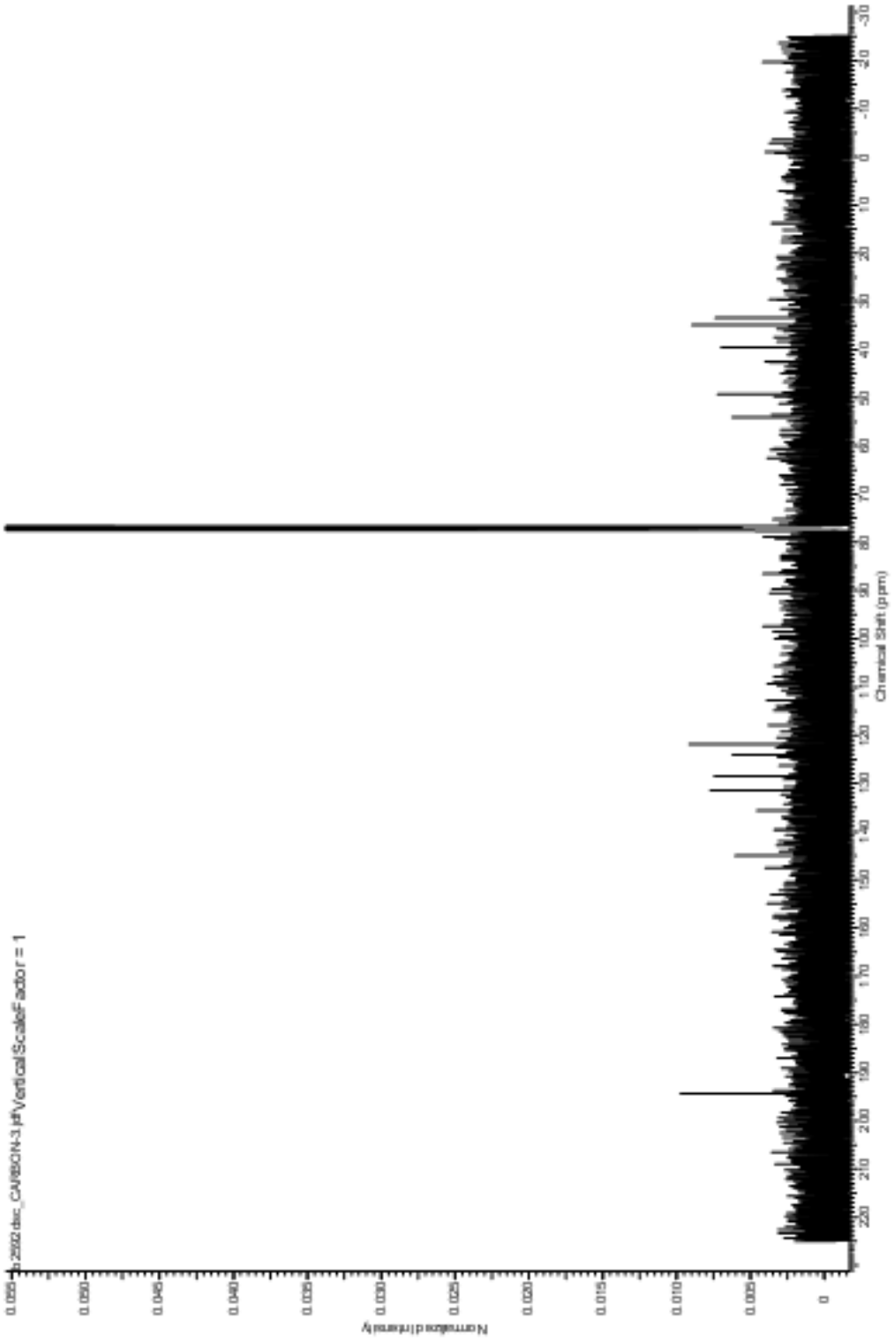


Figure 83 ^{13}C NMR spectrum of (2R,10bS)-2-bromo-1,3,4, 10b-tetrahydropyrido [2,1-a] isoindol-6(2H)-one (**11a**)

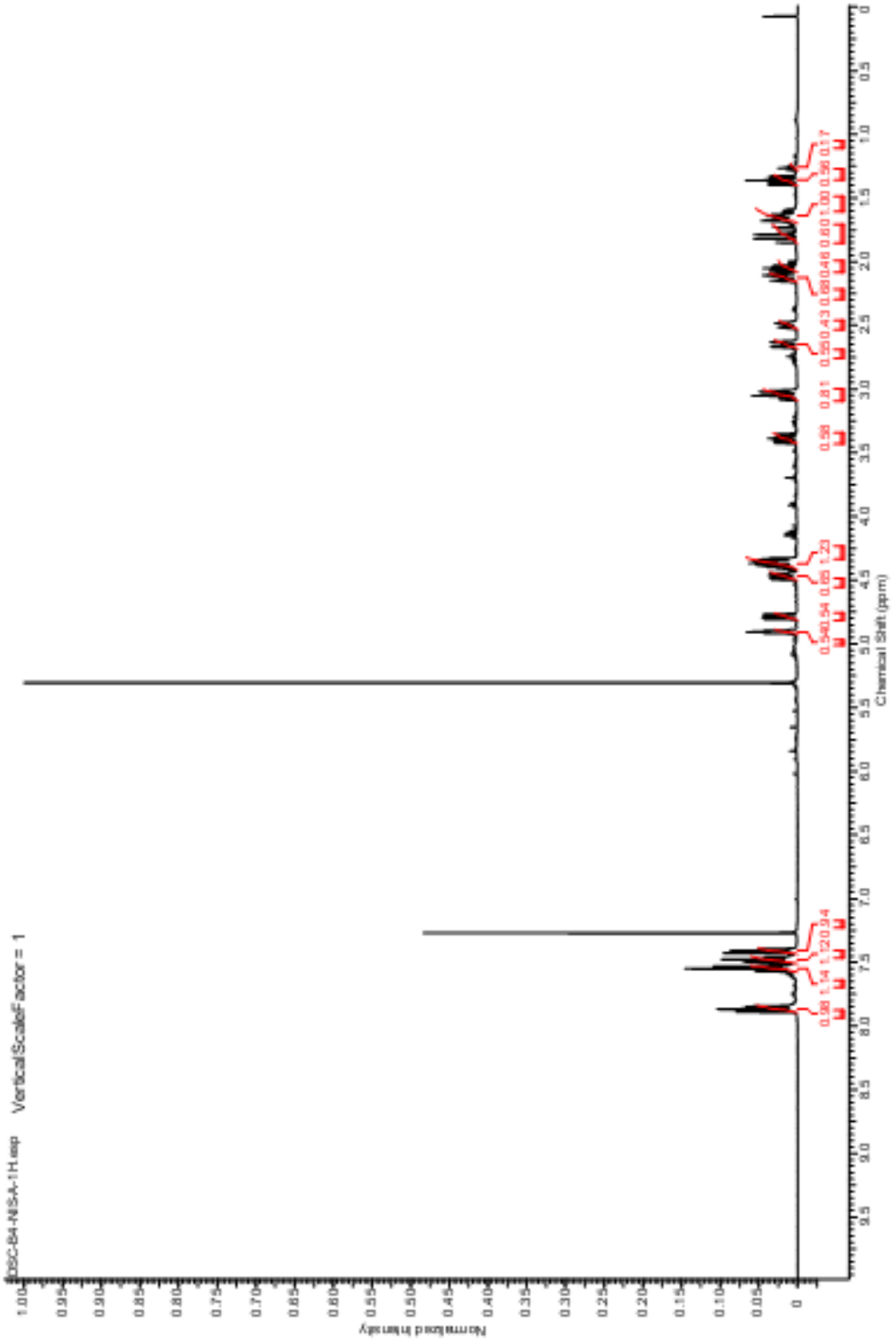


Figure 84 ^{1}H NMR spectrum of (2S & 2R,10bS)-2-iodo-1,3,4,10b-tetrahydropyrido [2,1-a] isoindol-6(2H)-one (**13a**)

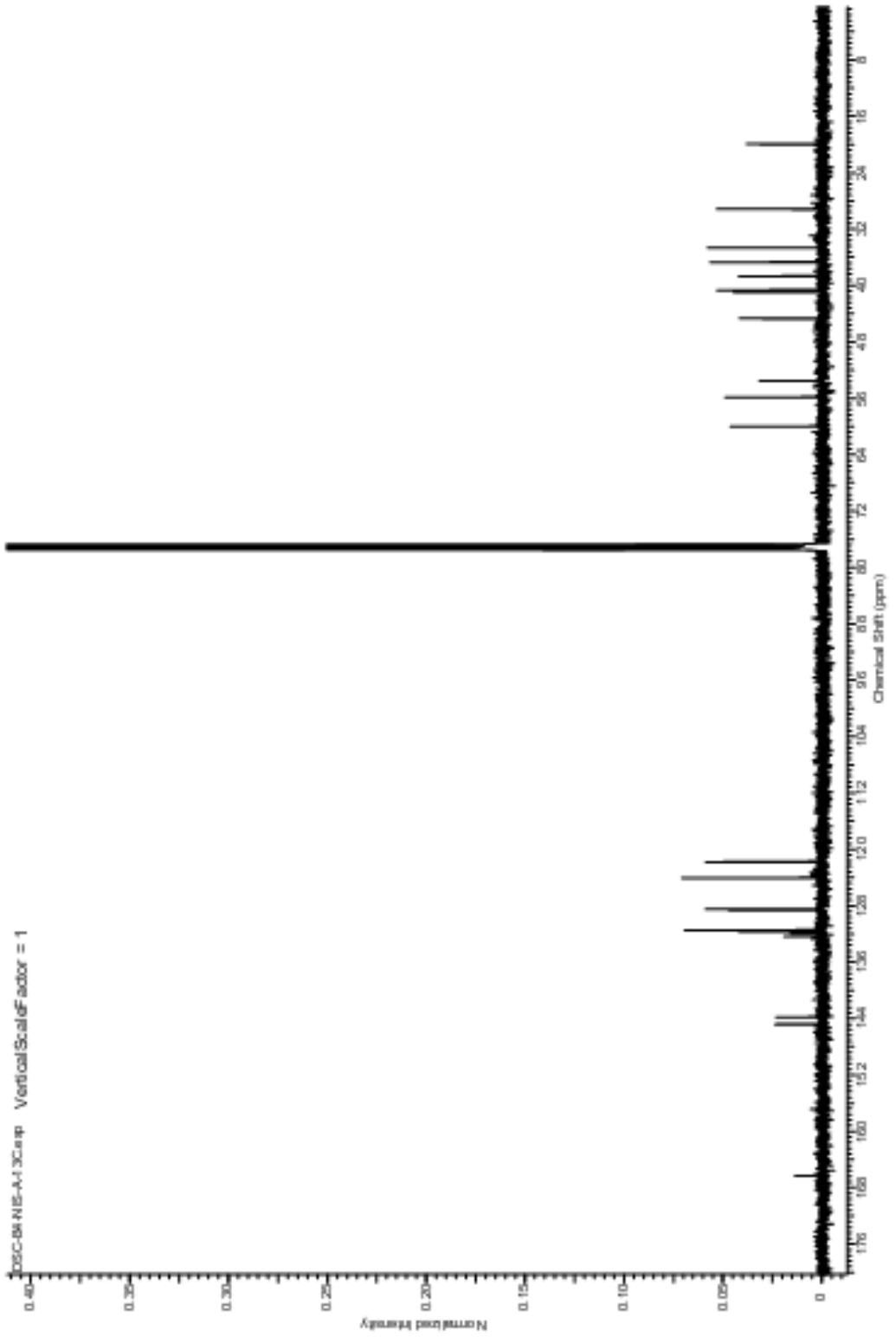


Figure 85 ^{13}C NMR spectrum of (2S & 2R,10bS)-2-iodo-1,3,4,10b-tetrahydropyrido [2,1-a] isoindol-6(2H)-one (**13a**)

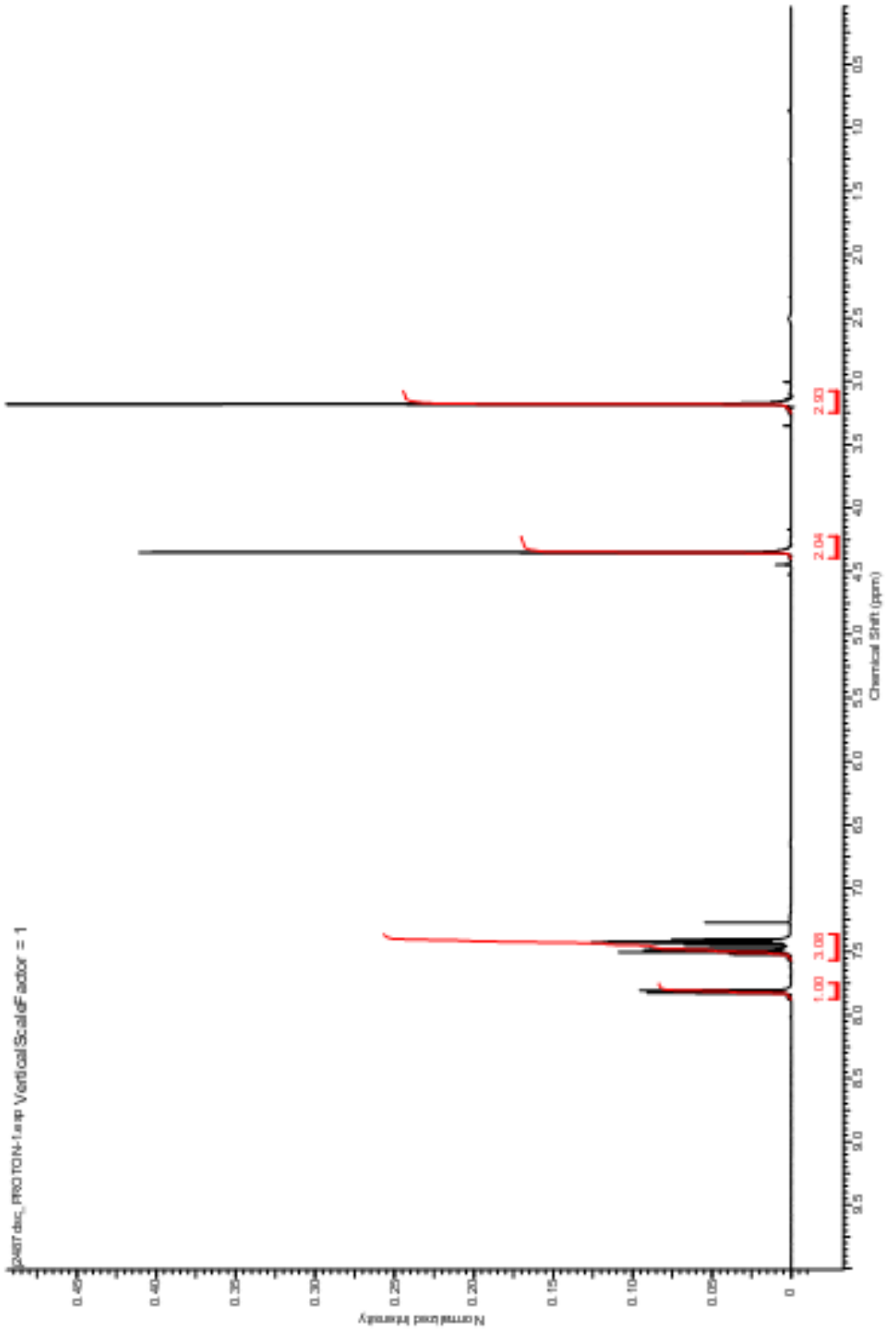


Figure 86 ^{1}H NMR spectrum of 2-Methyl-2,3-dihydro-isoindol-1-one (**16a**)

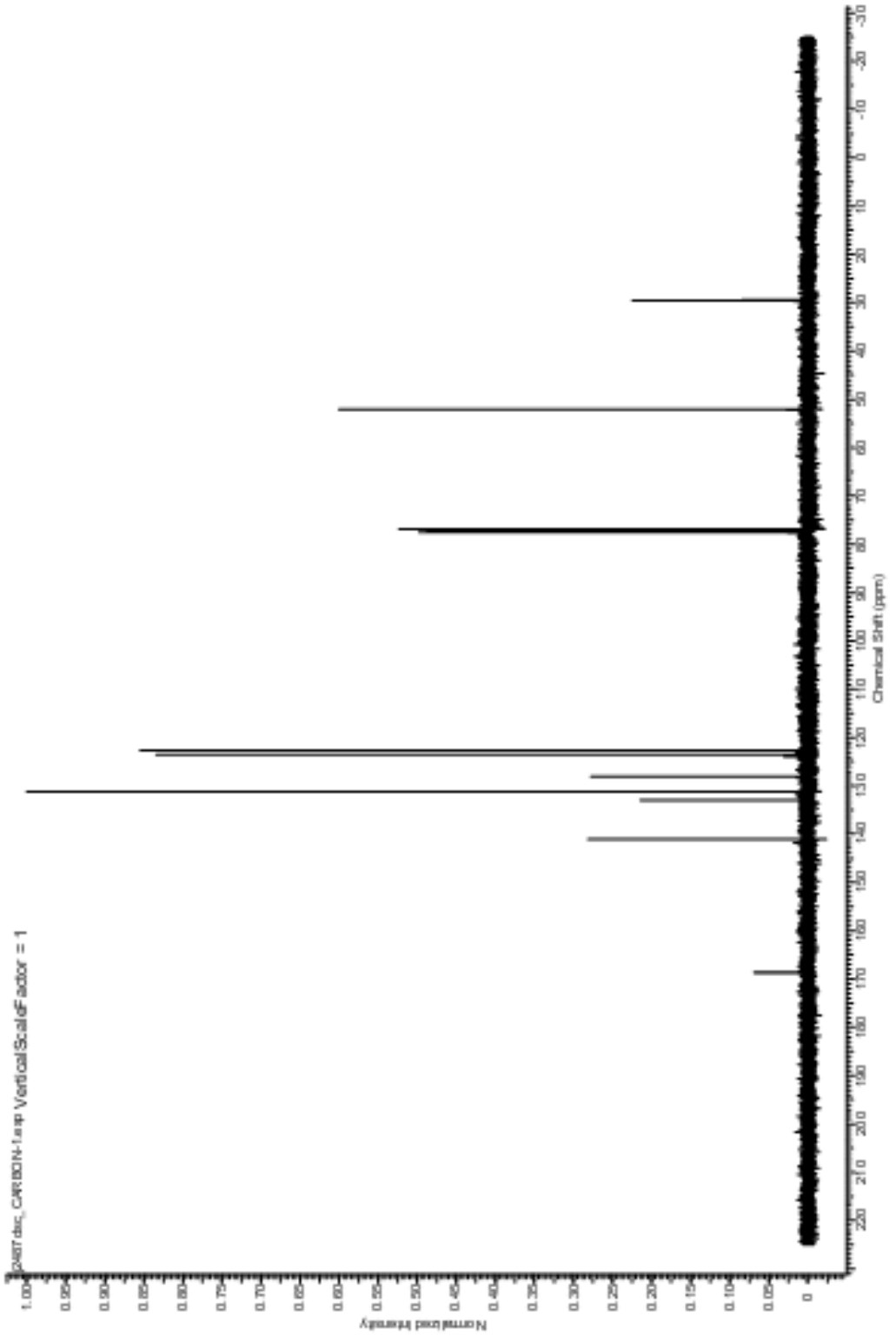


Figure 87 ^{13}C NMR spectrum of 2-Methyl-2,3-dihydro-isoindol-1-one (**16a**)

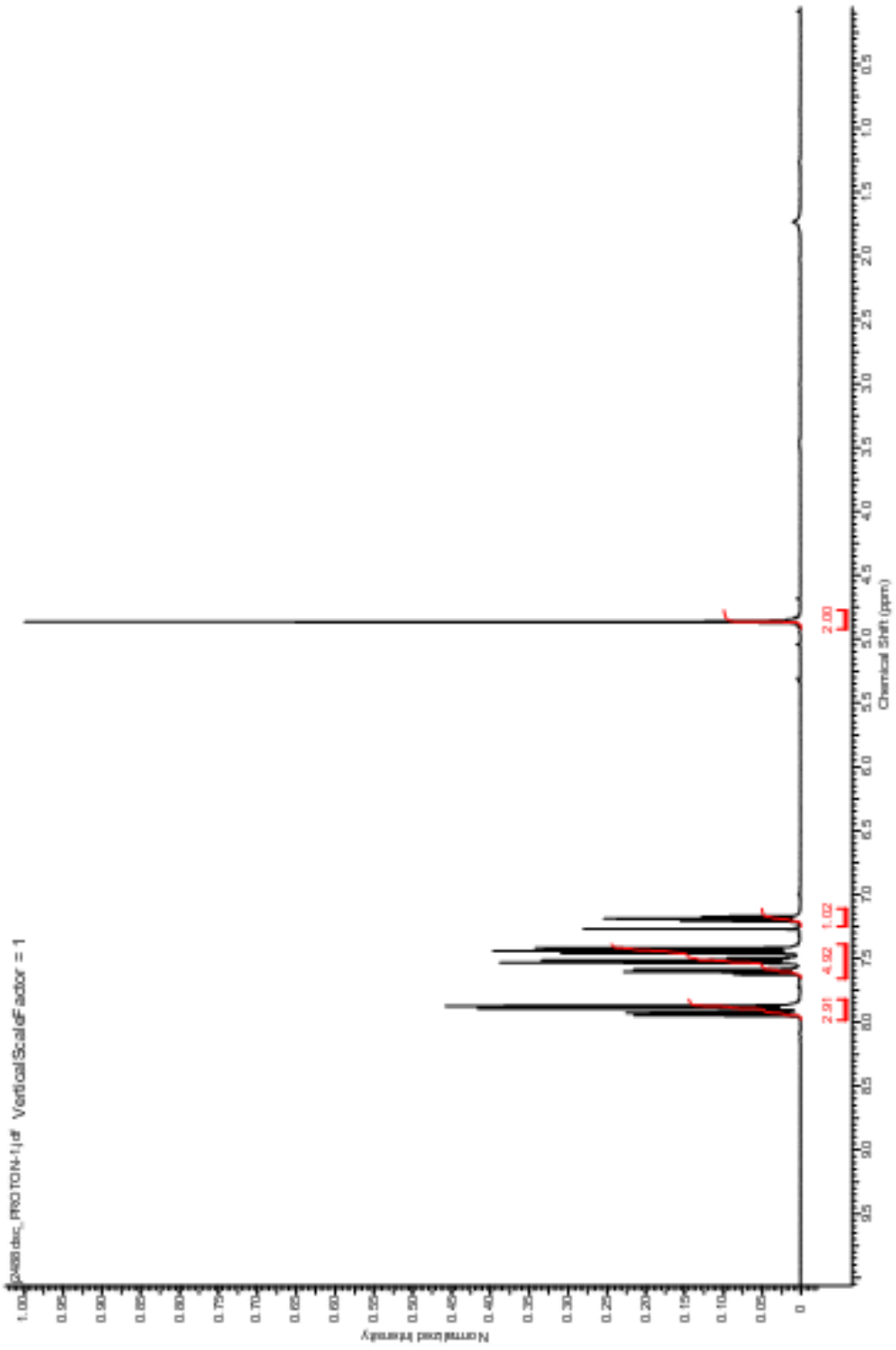


Figure 88 ^{1}H NMR spectrum of 2-Phenyl-2,3-dihydro-isoindol-1-one (**15a**)

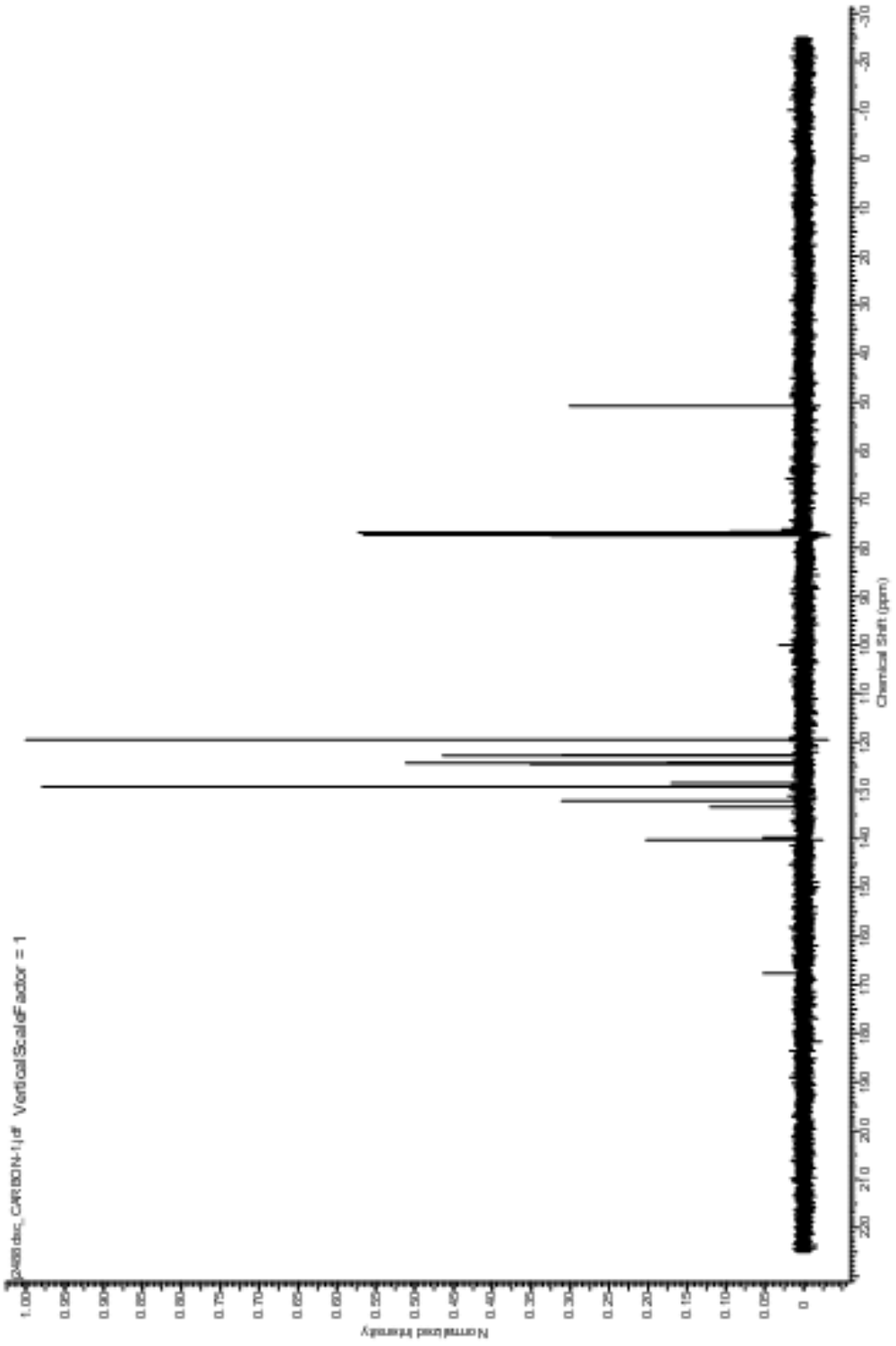


Figure 89 ^{13}C NMR spectrum of 2-Phenyl-2,3-dihydro-isoindol-1-one (**15a**)

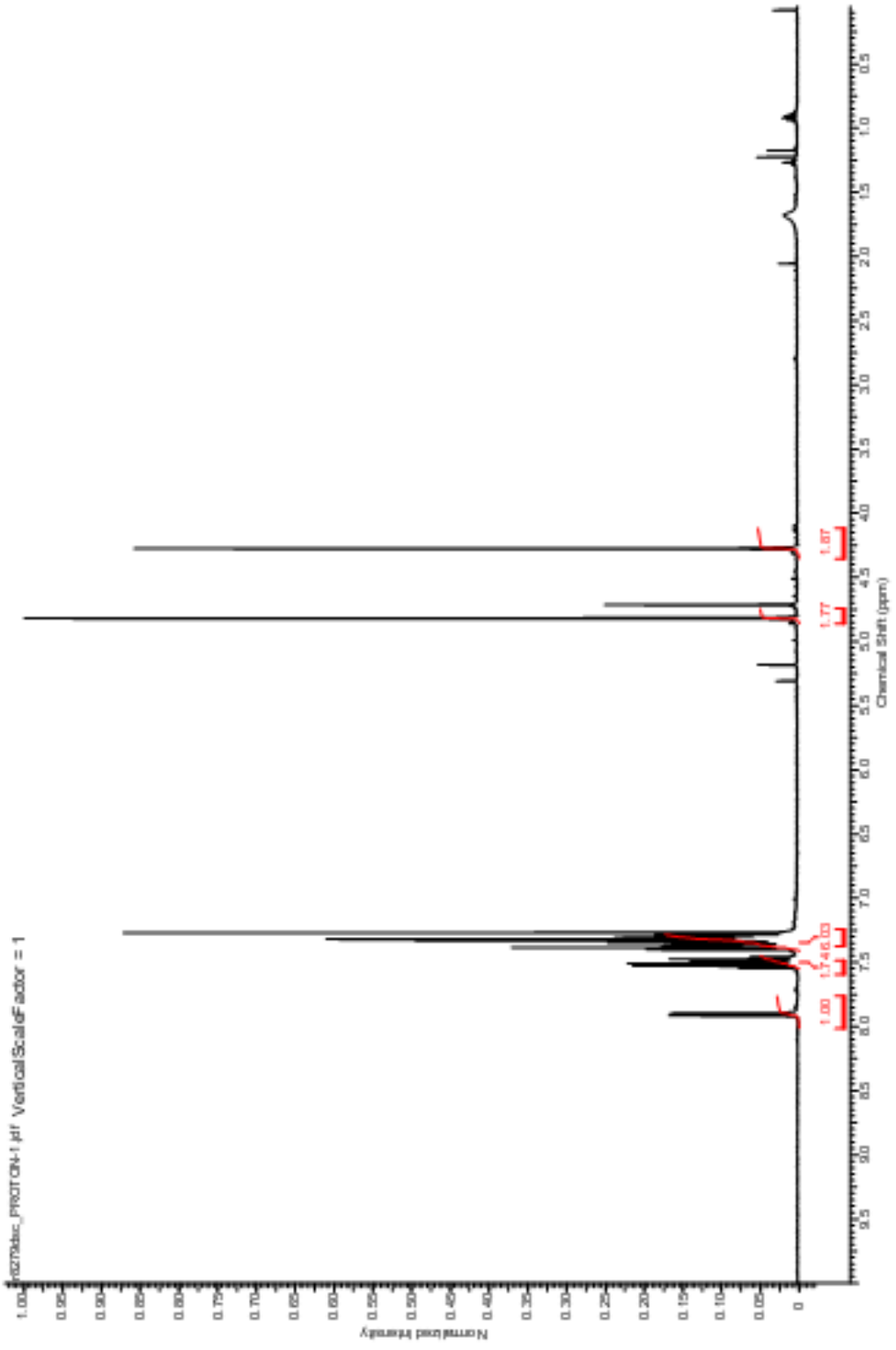


Figure 90 ^{1}H NMR spectrum of 2-Benzyl-2,3-dihydro-isoindol-1-one (**14a**)

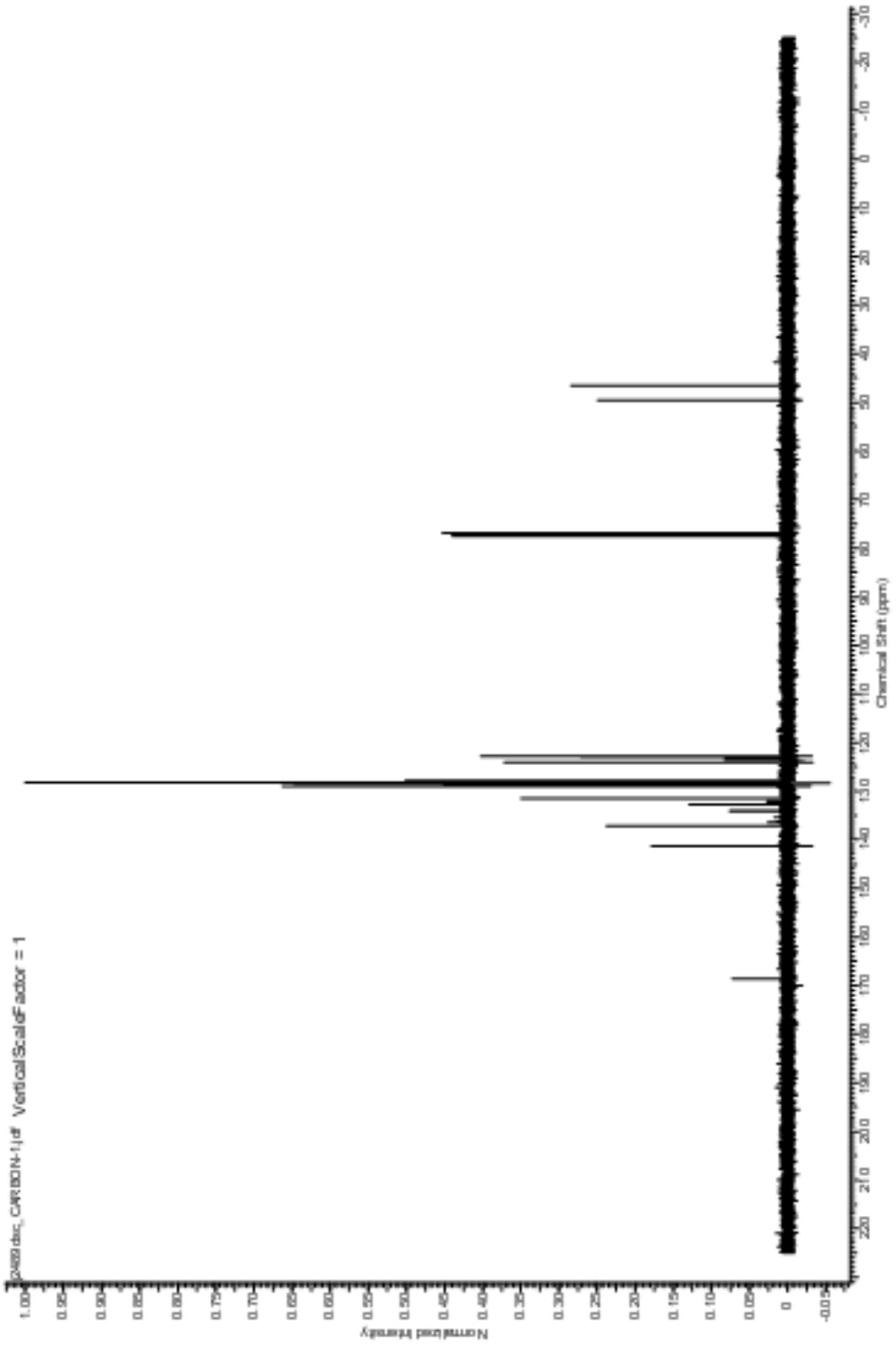


Figure 91 ^{13}C NMR spectrum of 2-Benzyl-2,3-dihydro-isoindol-1-one (**14a**)

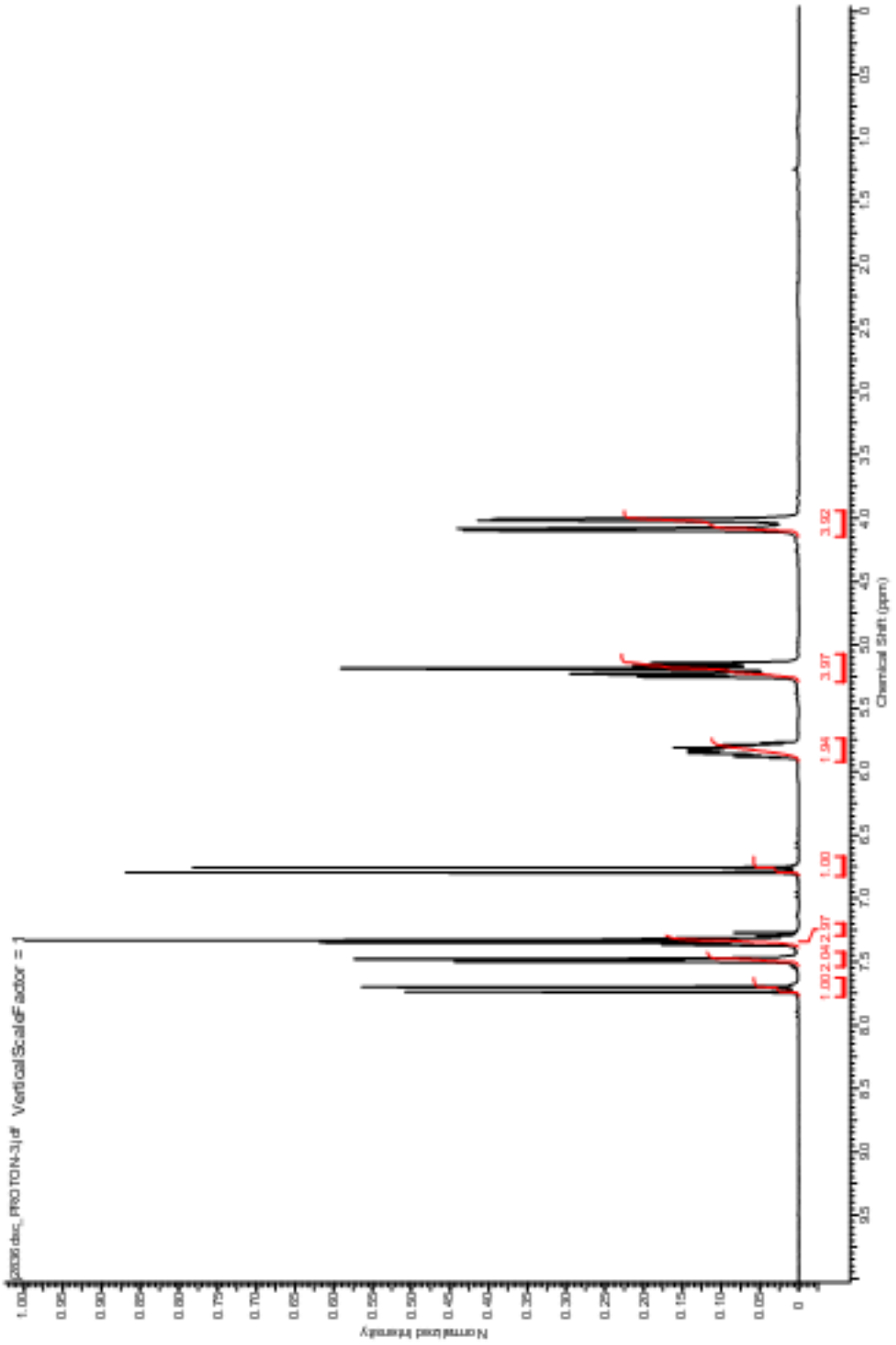


Figure 92 ^{1}H NMR spectrum of *N*,*N*-Diallyl-3-phenyl-acrylamide (**3c**)

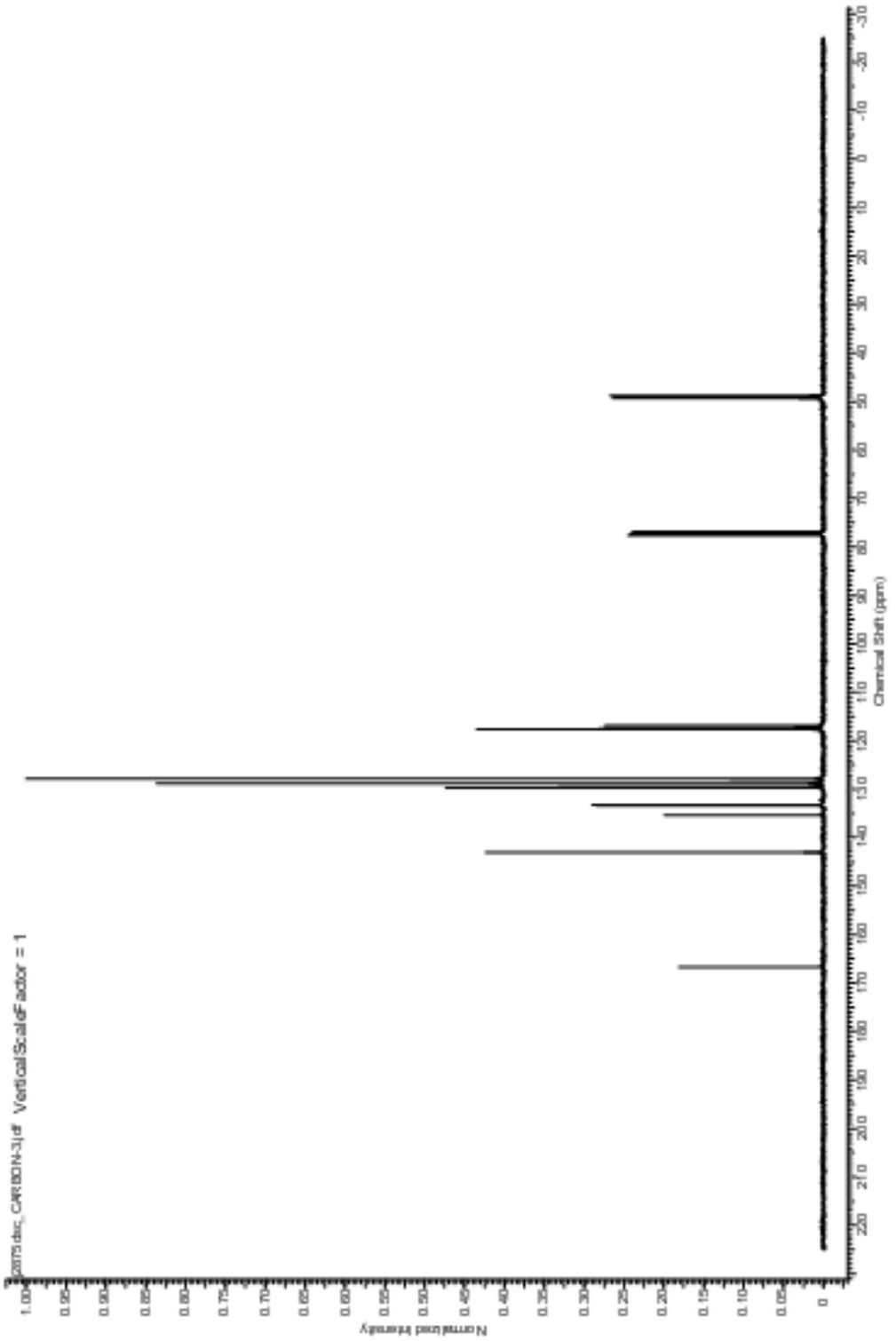


Figure 93 ^{13}C NMR spectrum of *N*,*N*-Diallyl-3-phenyl-acrylamide (**3c**)

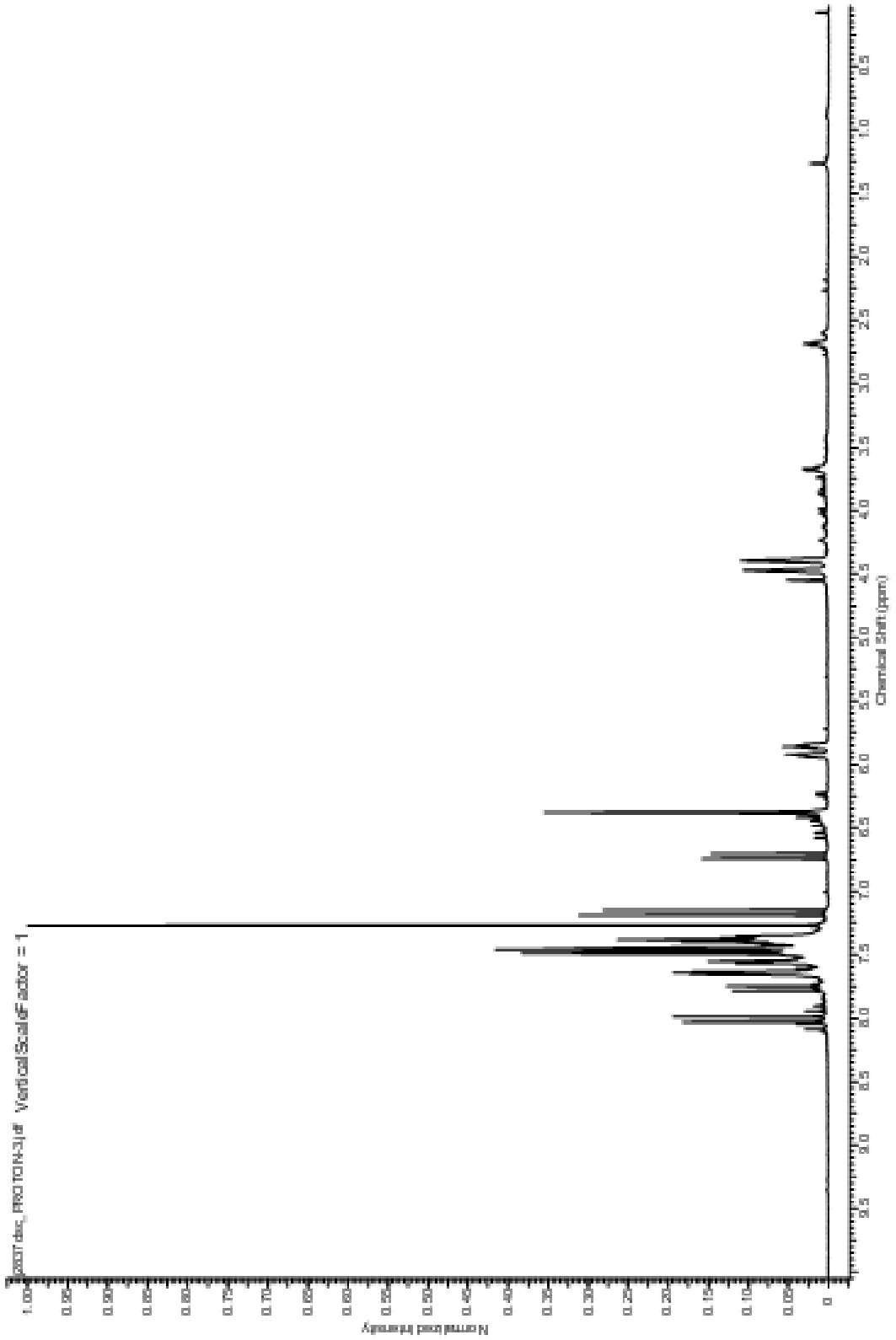


Figure 94 ^{1}H NMR spectrum of 1-(2,5-Dihydro-pyrrol-1-yl)-3-phenyl-propenone (**2a**)

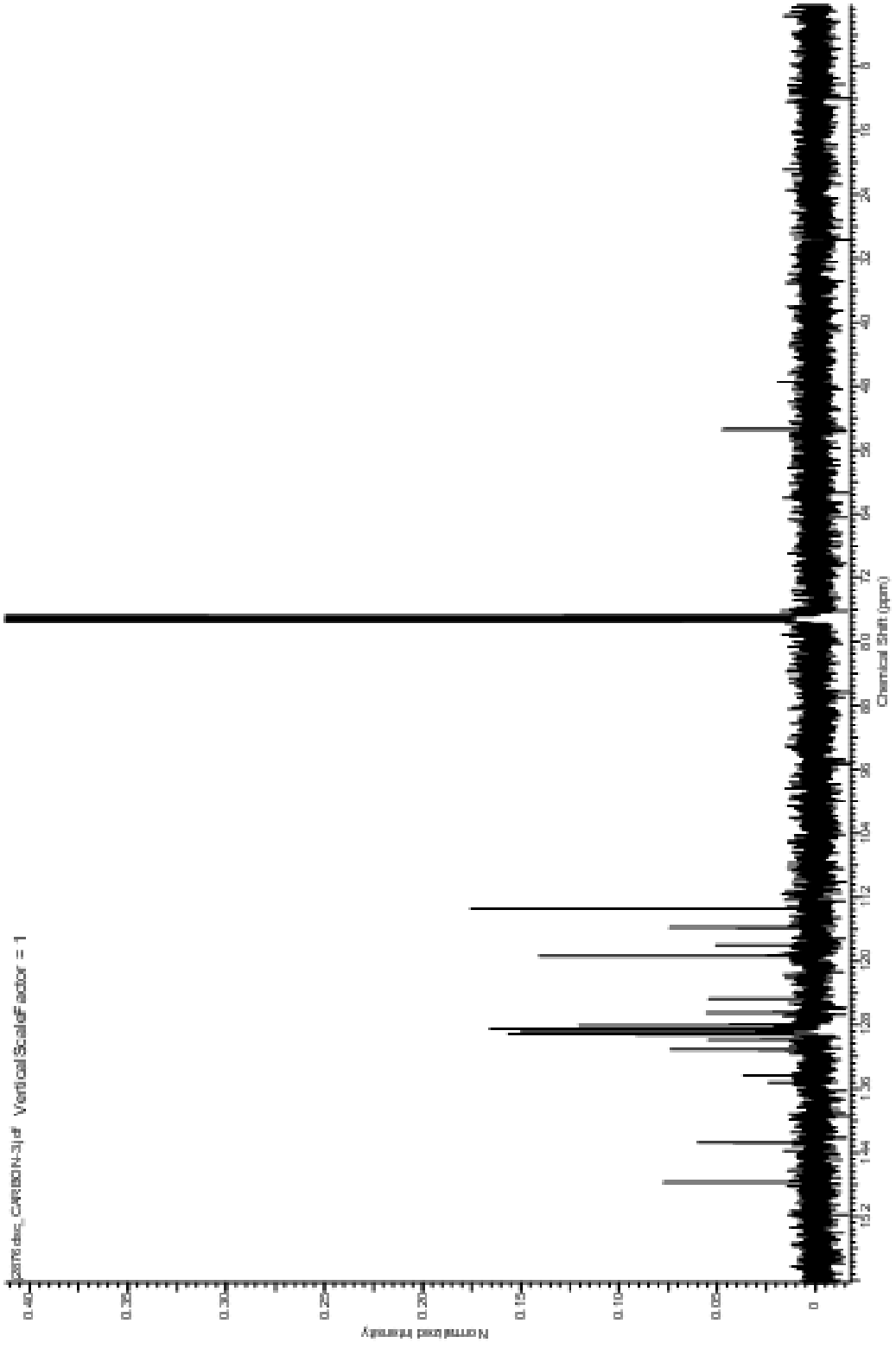


Figure 95 ^{13}C NMR spectrum of 1-(2,5-Dihydro-pyrrol-1-yl)-3-phenyl-propenone (**2a**)

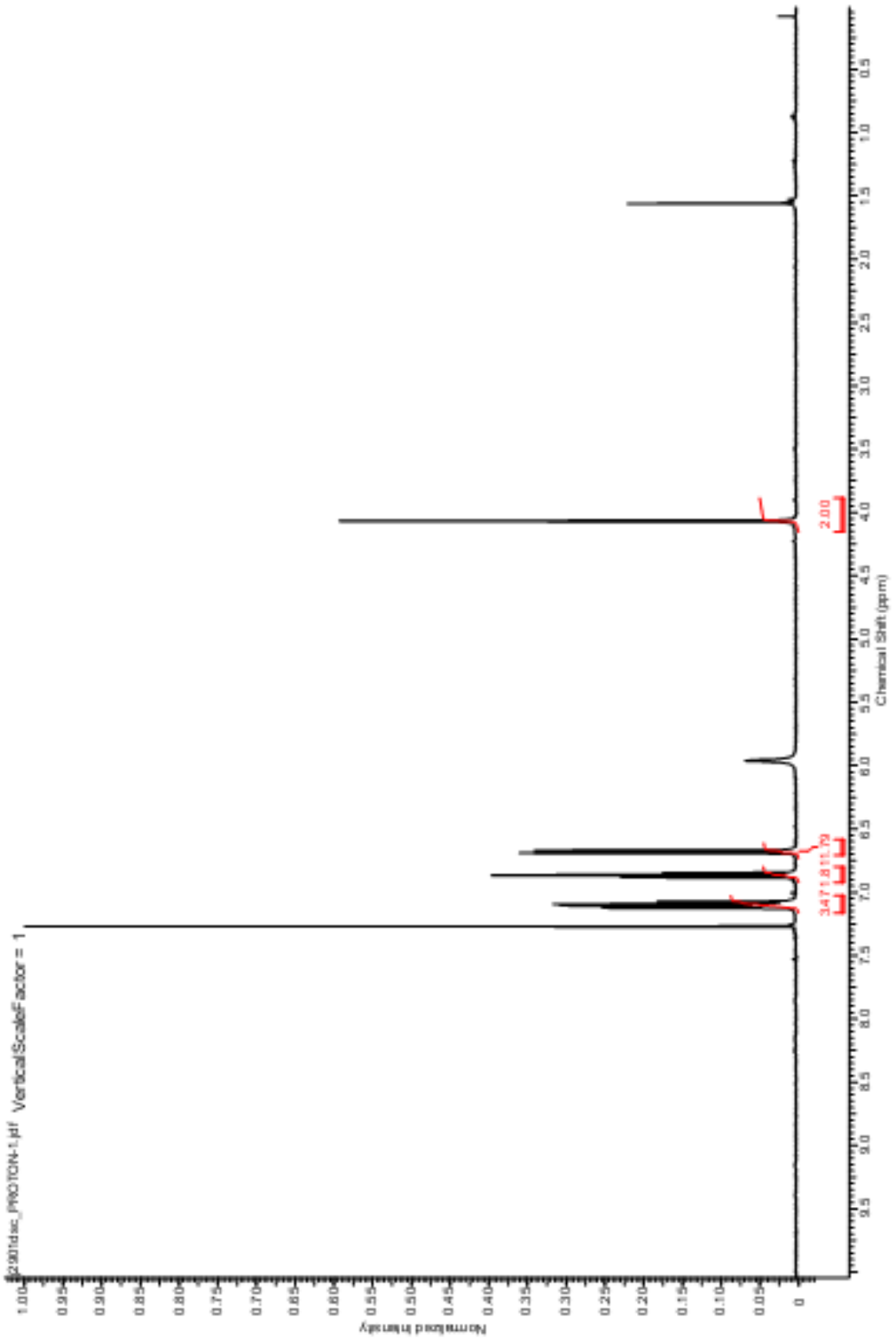


Figure 96 ^{1}H NMR spectrum of 9,10-Dihydro-acridine (**3b**)

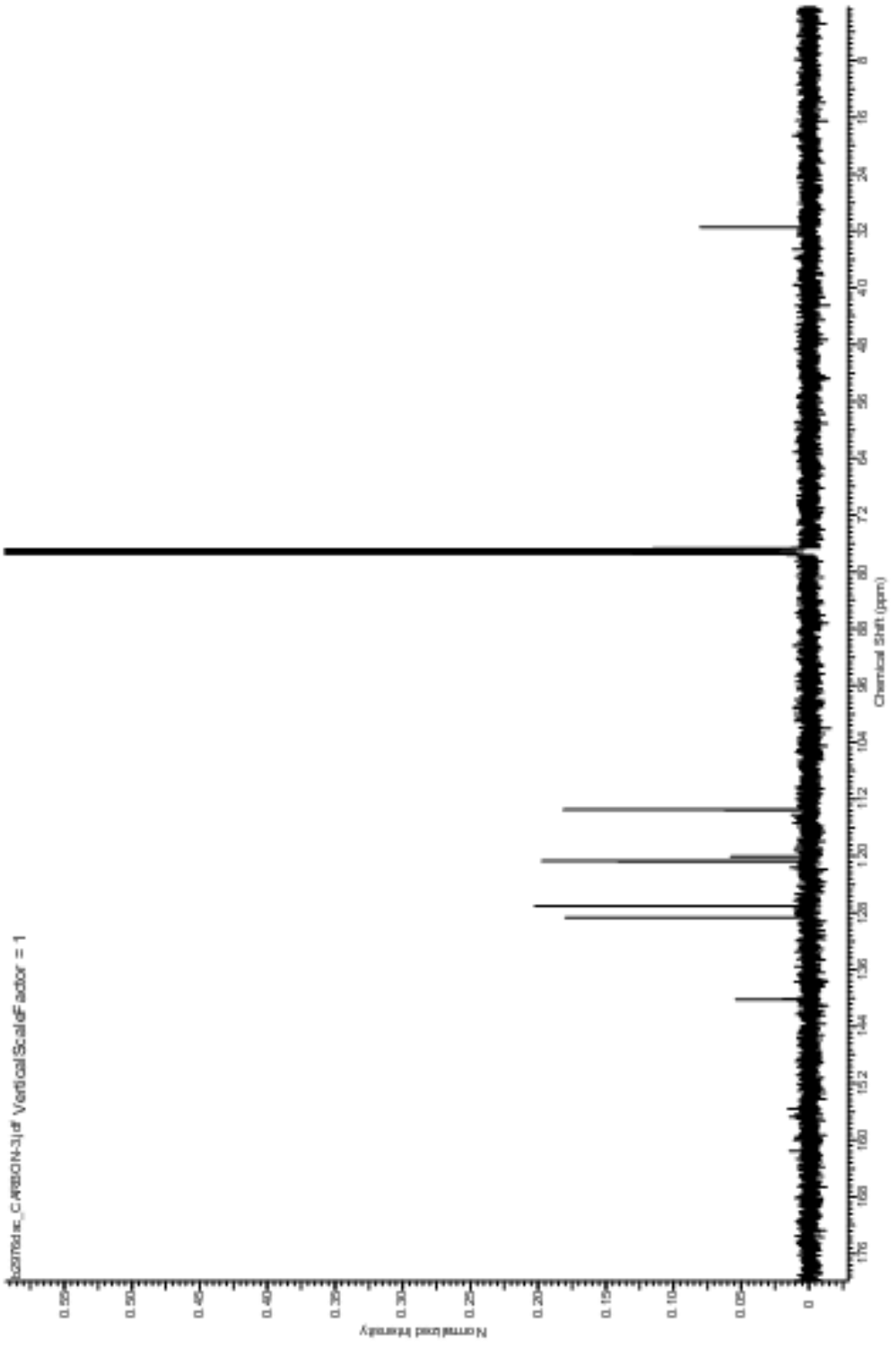


Figure 97 ^{13}C NMR spectrum of 9,10-Dihydro-acridine (**3b**)

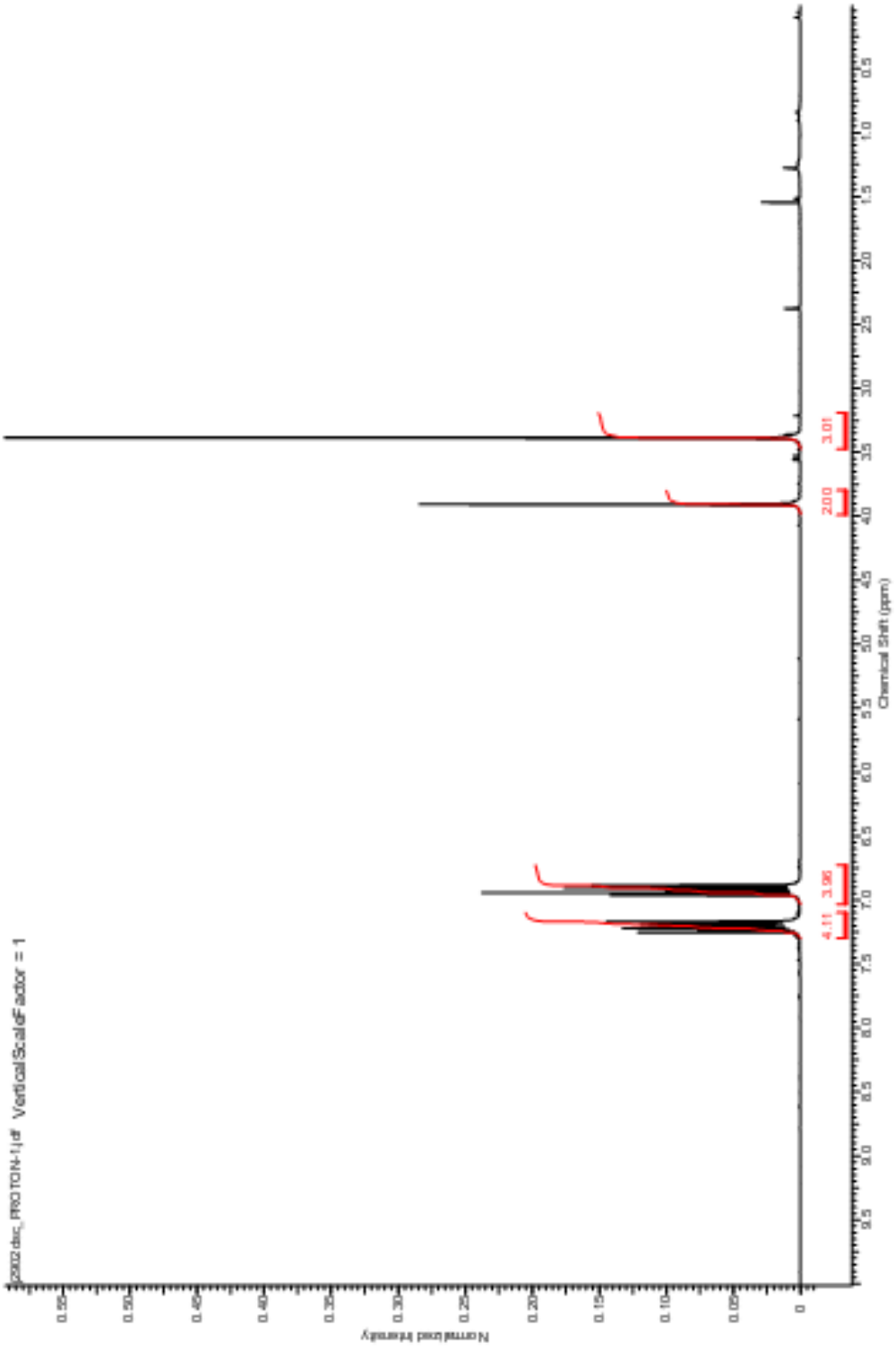


Figure 98 [1]H NMR spectrum of 10-Methyl-9,10-dihydro-acridine (**3c**)

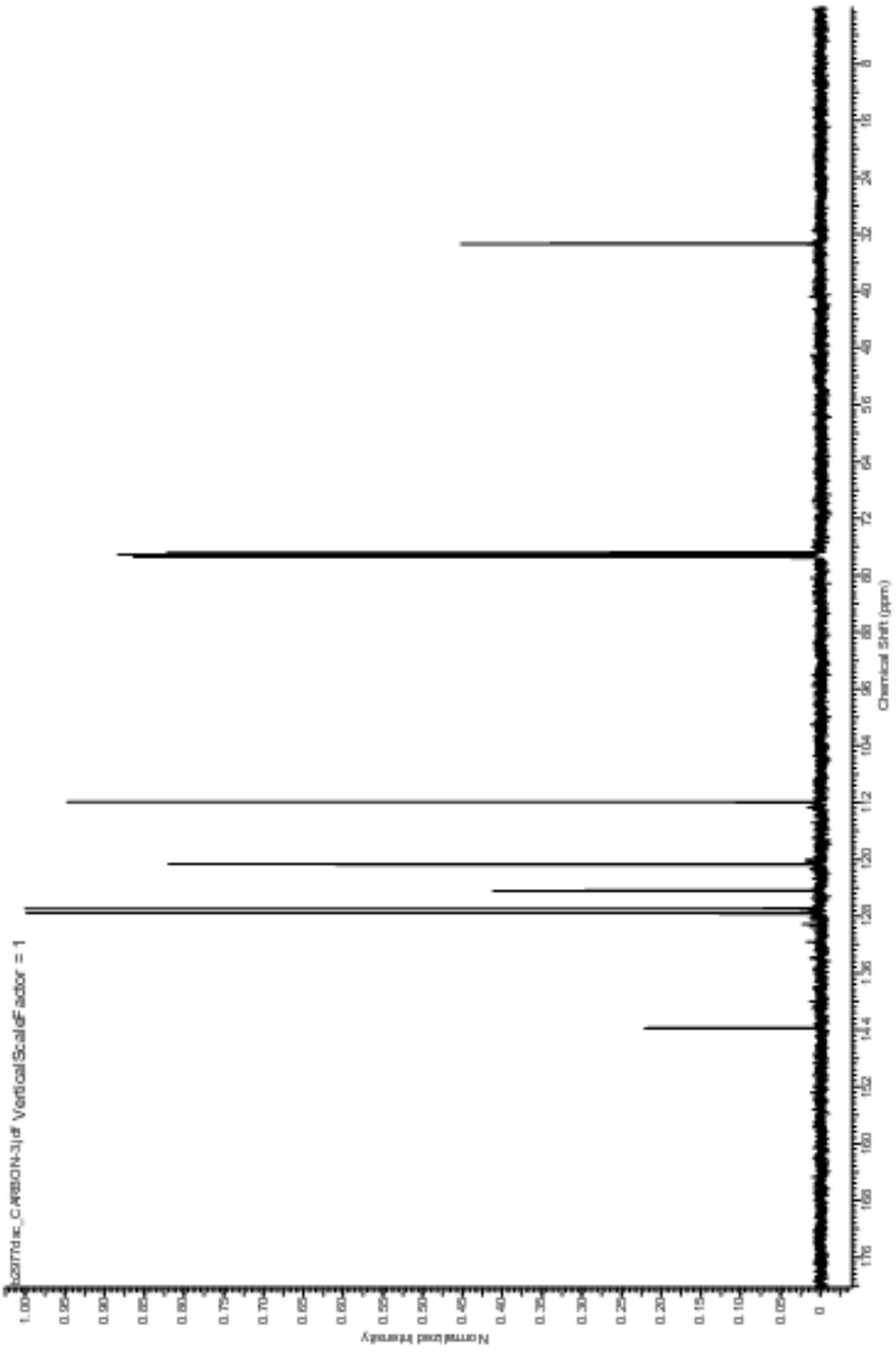


Figure 99 ^{13}C NMR spectrum of 10-Methyl-9,10-dihydro-acridine (**3c**)

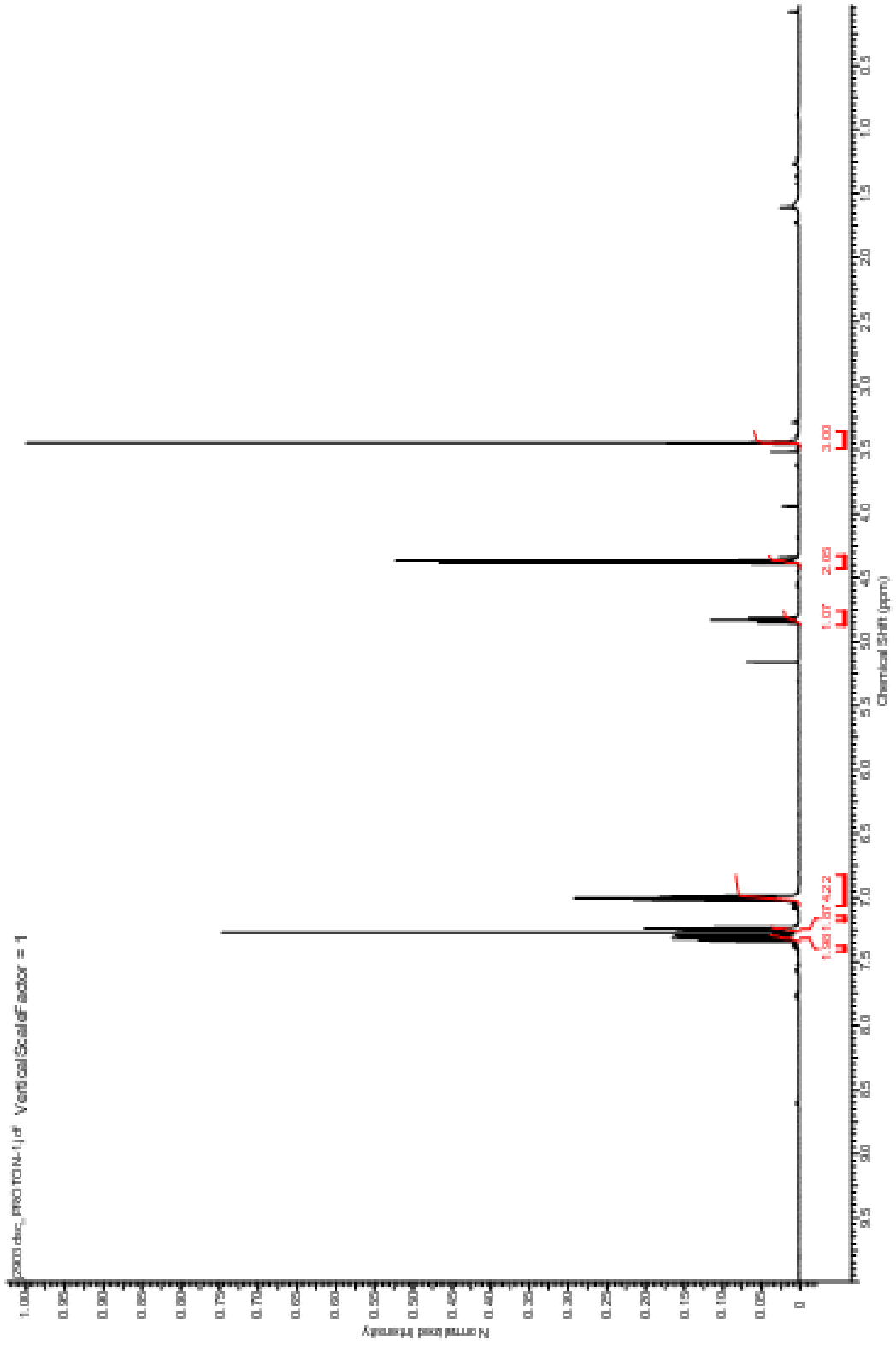


Figure 100 ^{1}H NMR spectrum of 10-Methyl-9-nitromethyl-9,10-dihydro-acridine (**3d**)

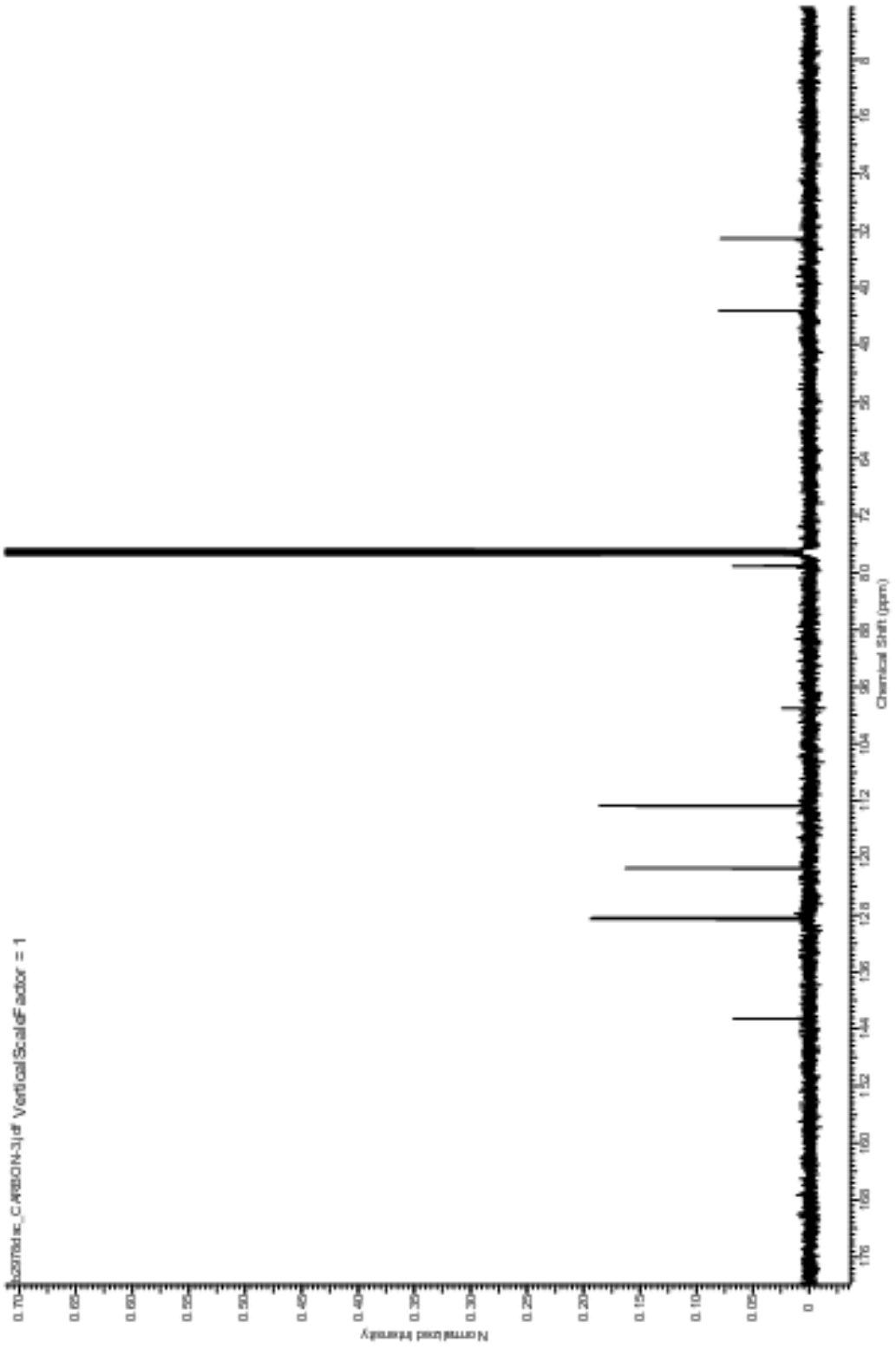


Figure 101 ^{13}C NMR spectrum of 10-Methyl-9-nitromethyl-9,10-dihydro-acridine (**3d**)

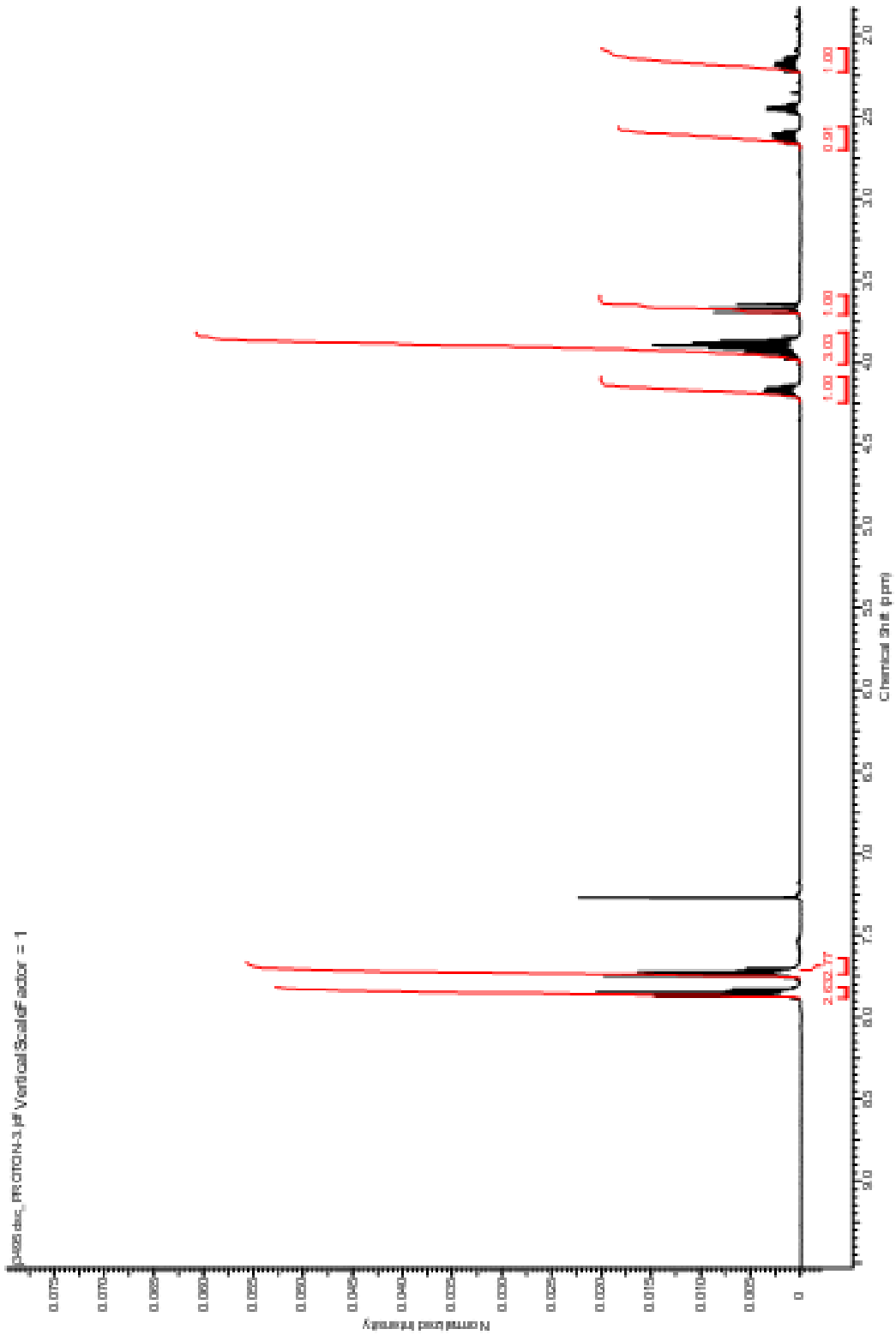


Figure 102 [1]H NMR spectrum of 2-(3,4-dibromobutyl)-1*H*-isoindole-1,3(2*H*)-dione (**11c**)
-

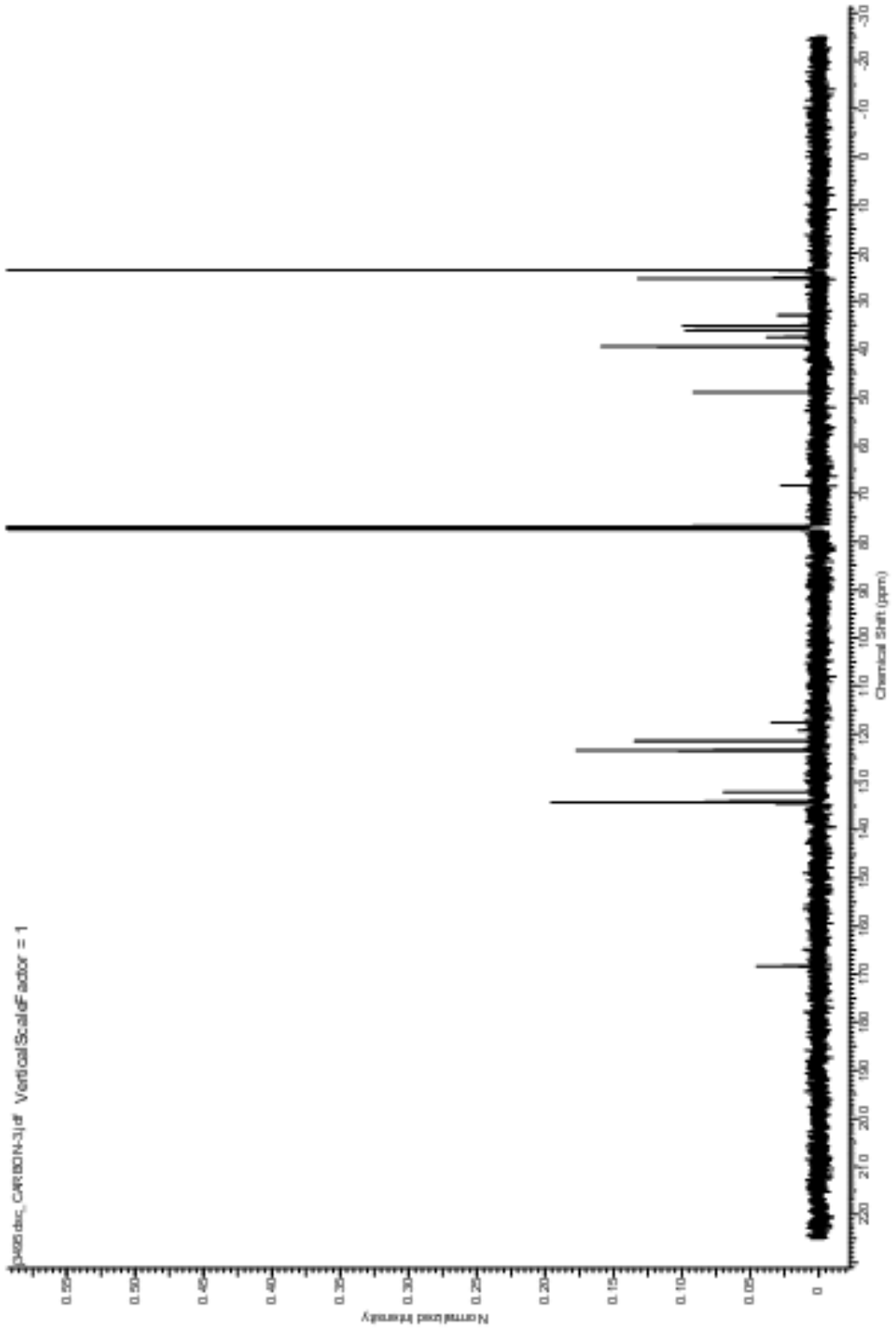


Figure 103 ^{13}C NMR spectrum of 2-(3,4-dibromobutyl)-1*H*-isoindole-1,3(2*H*)-dione (**11c**)

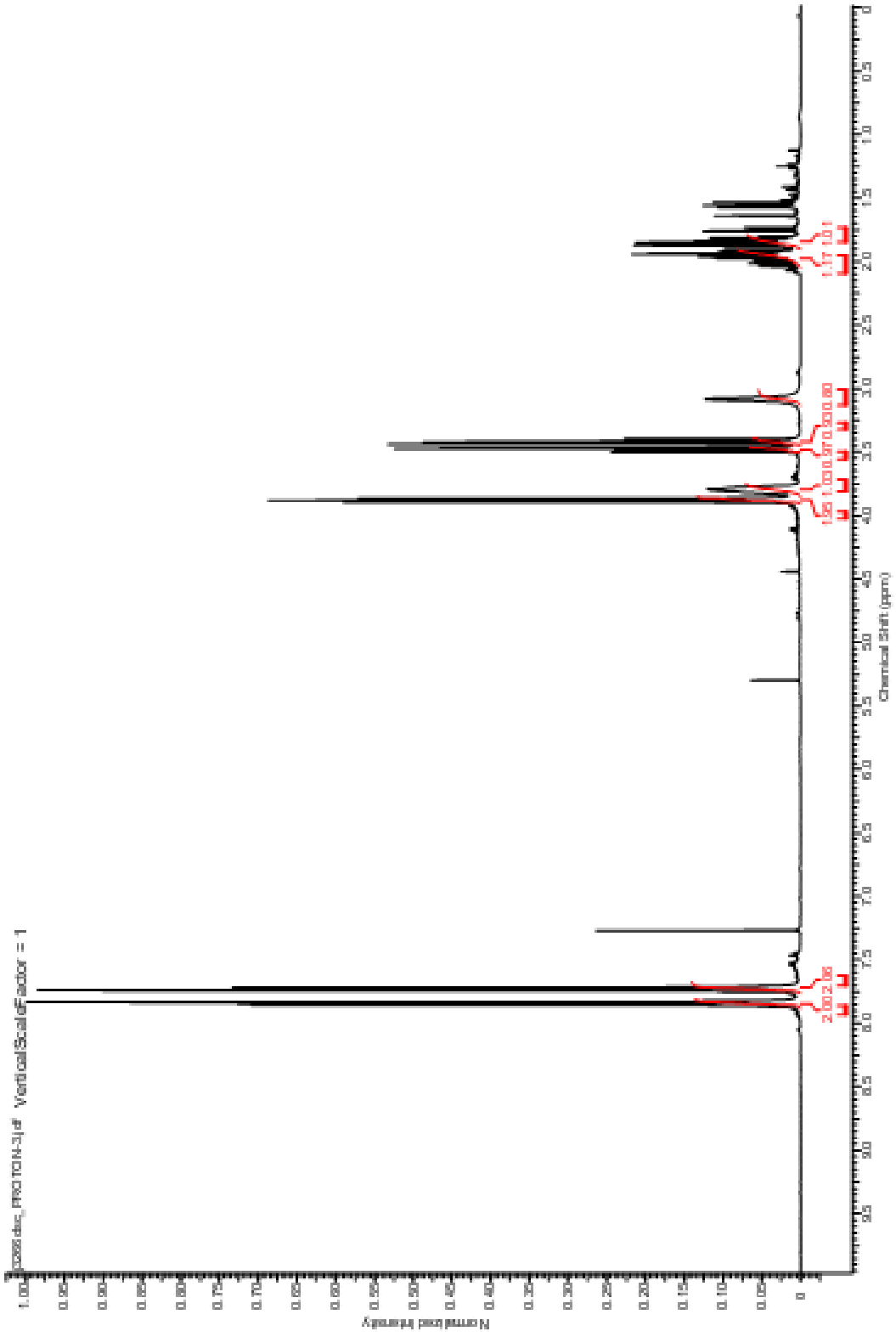


Figure 104 ^{1}H NMR spectrum of 2-(3-hydroxy-4-iodobutyl)-1*H*-isoindole-1,3(2*H*)-dione (**13d**)

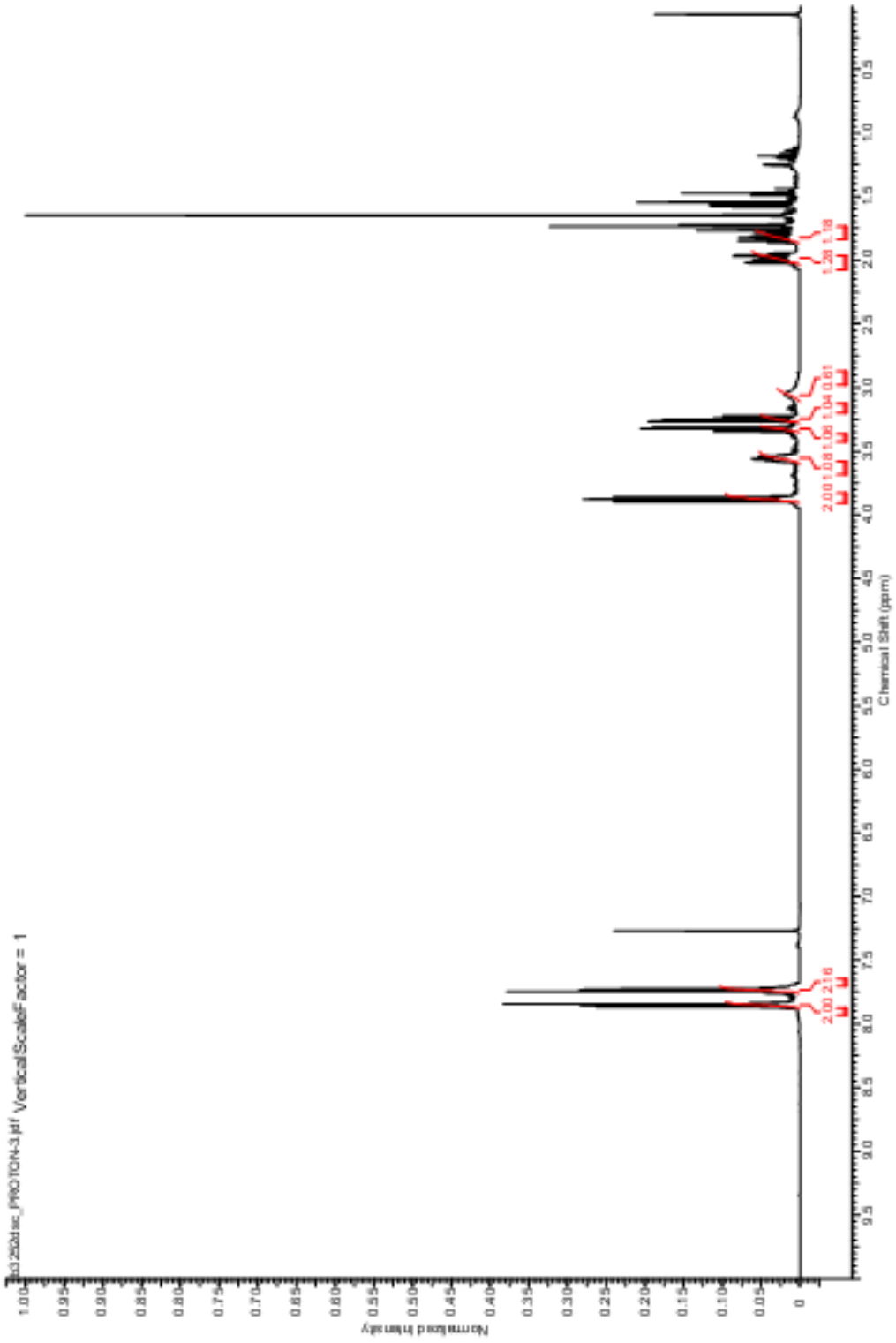


Figure 105 ^{1}H NMR spectrum of 2-(4-bromo-3-hydroxybutyl)-1*H*-isoindole-1,3(2*H*)-dione (**11d**)

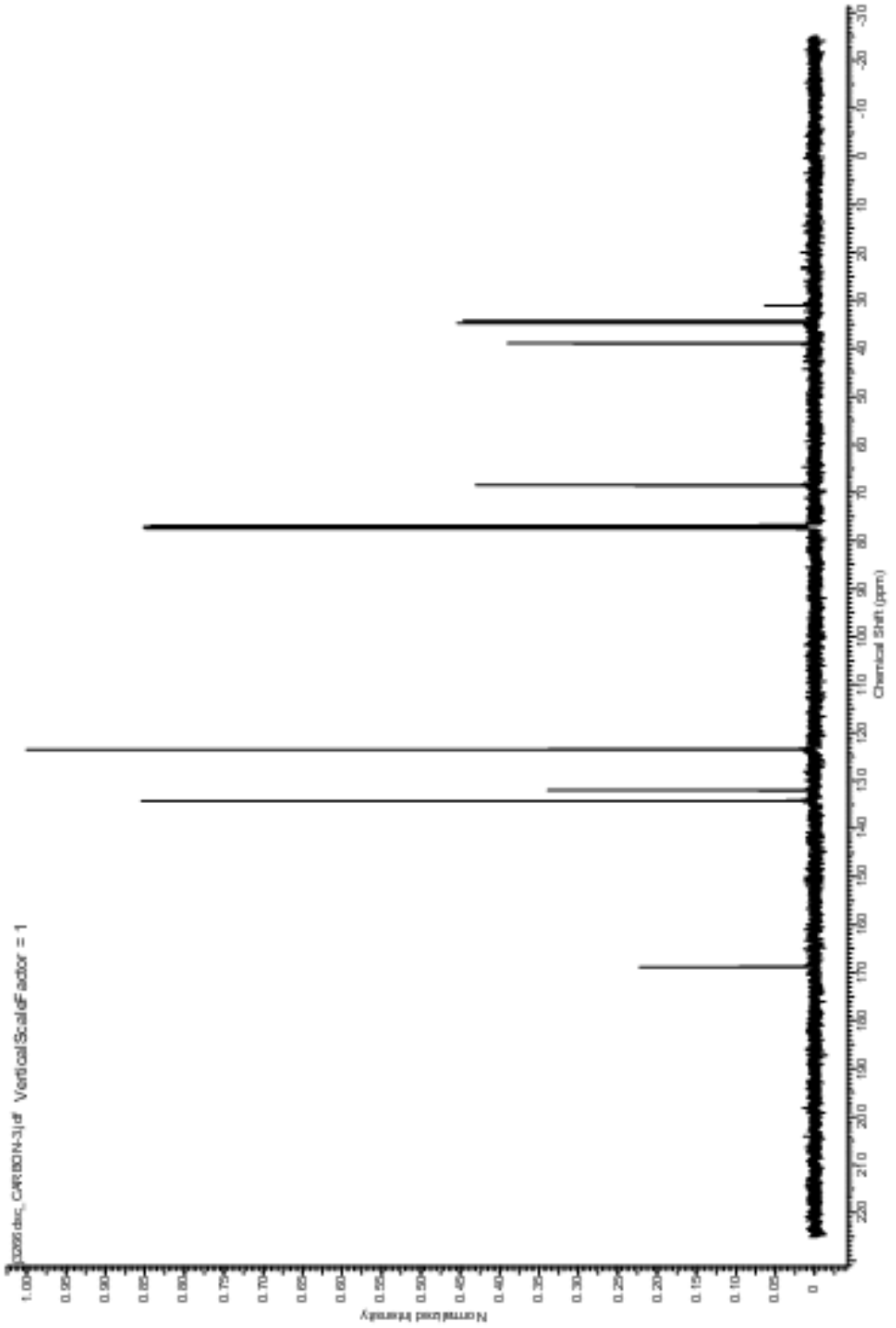


Figure 106 ^{13}C NMR spectrum of 2-(3-hydroxy-4-iodobutyl)-1*H*-isoindole-1,3(2*H*)-dione (**13d**)

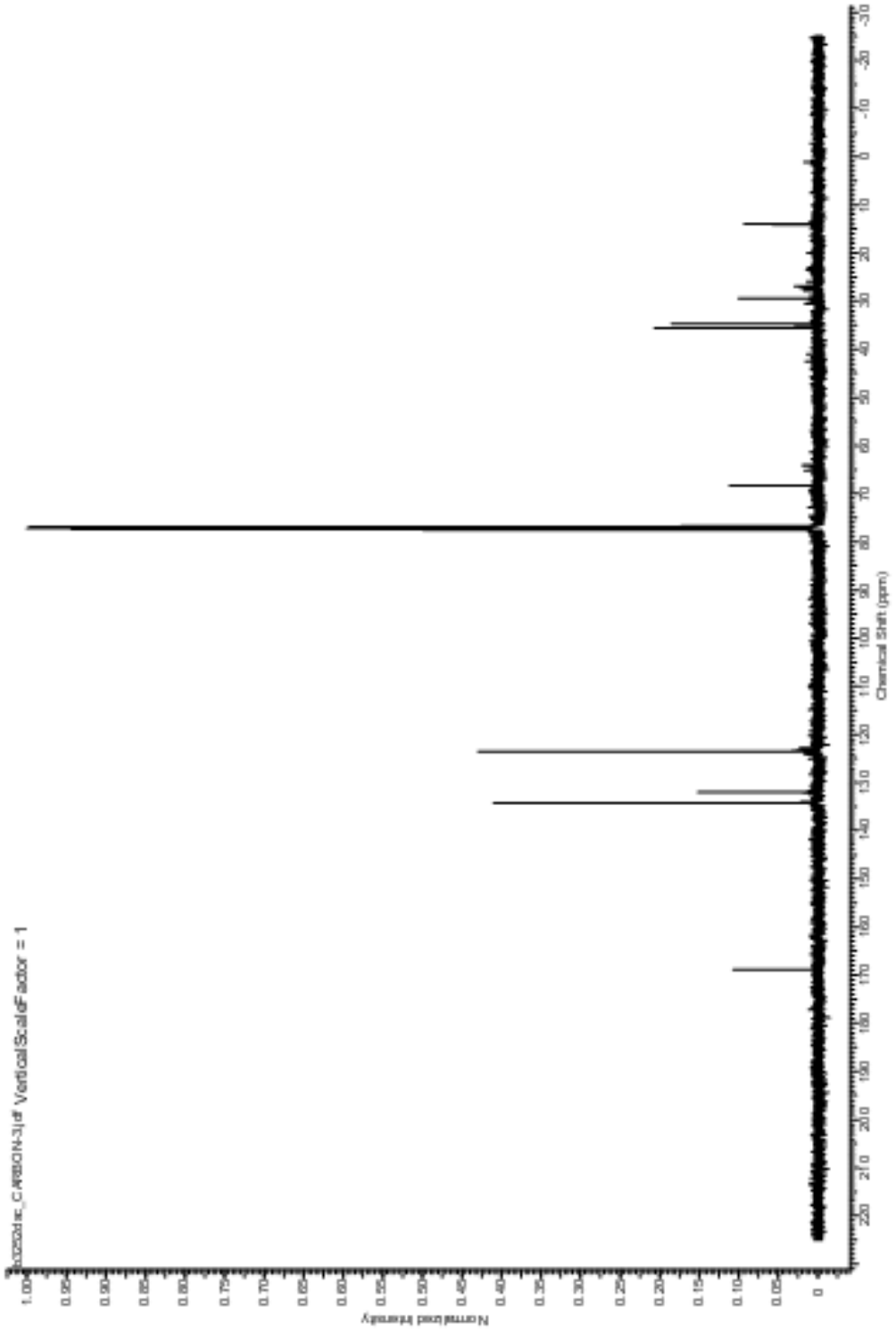


Figure 107 ^{13}C NMR spectrum of 2-(4-bromo-3-hydroxybutyl)-1*H*-isoindole-1,3(2*H*)-dione (**11d**)

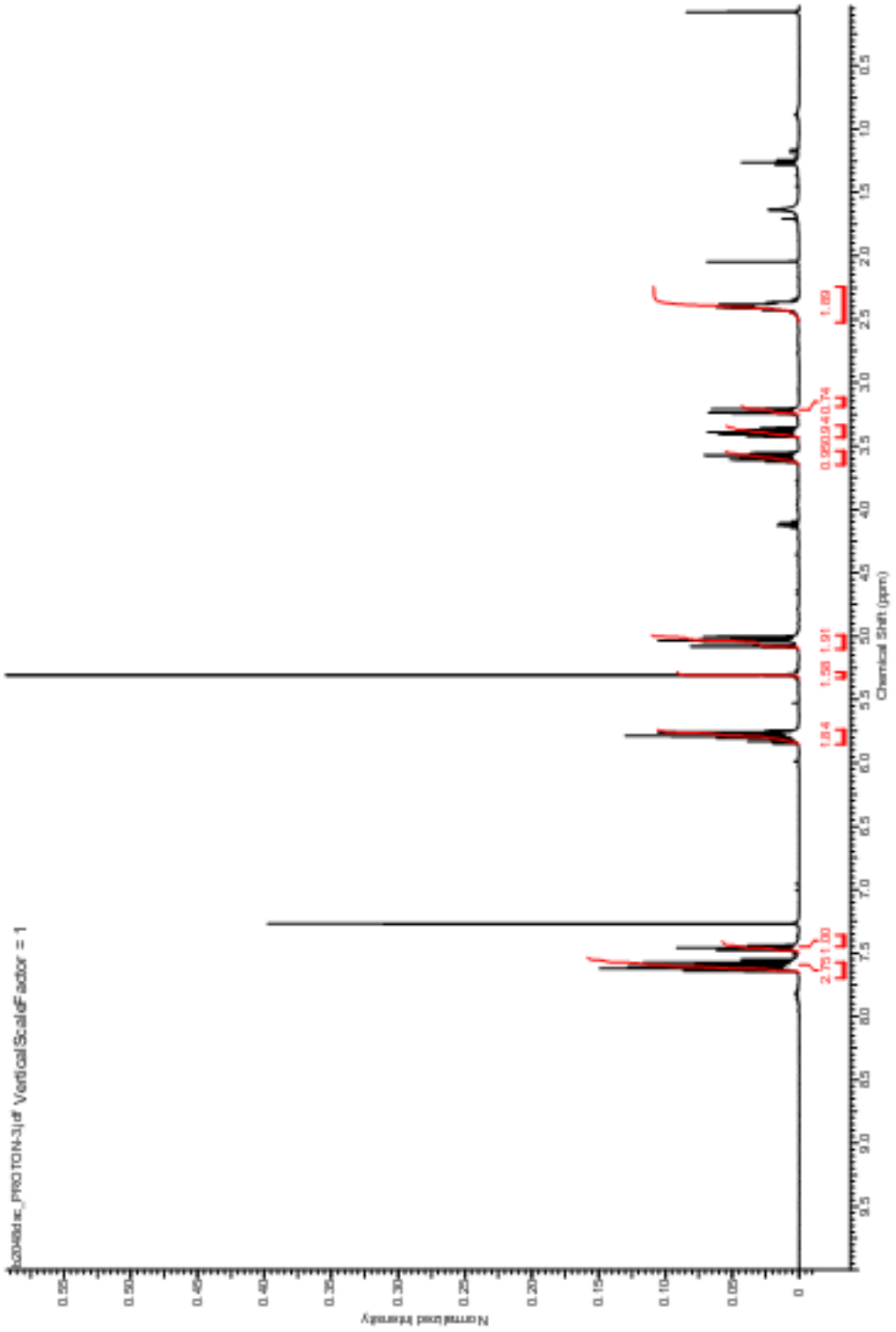


Figure 108 ^{1}H NMR spectrum of 2-(but-3-en-1-yl)-3-hydroxy-2,3-dihydro-1*H*-isoindol-1-one (**13b**)

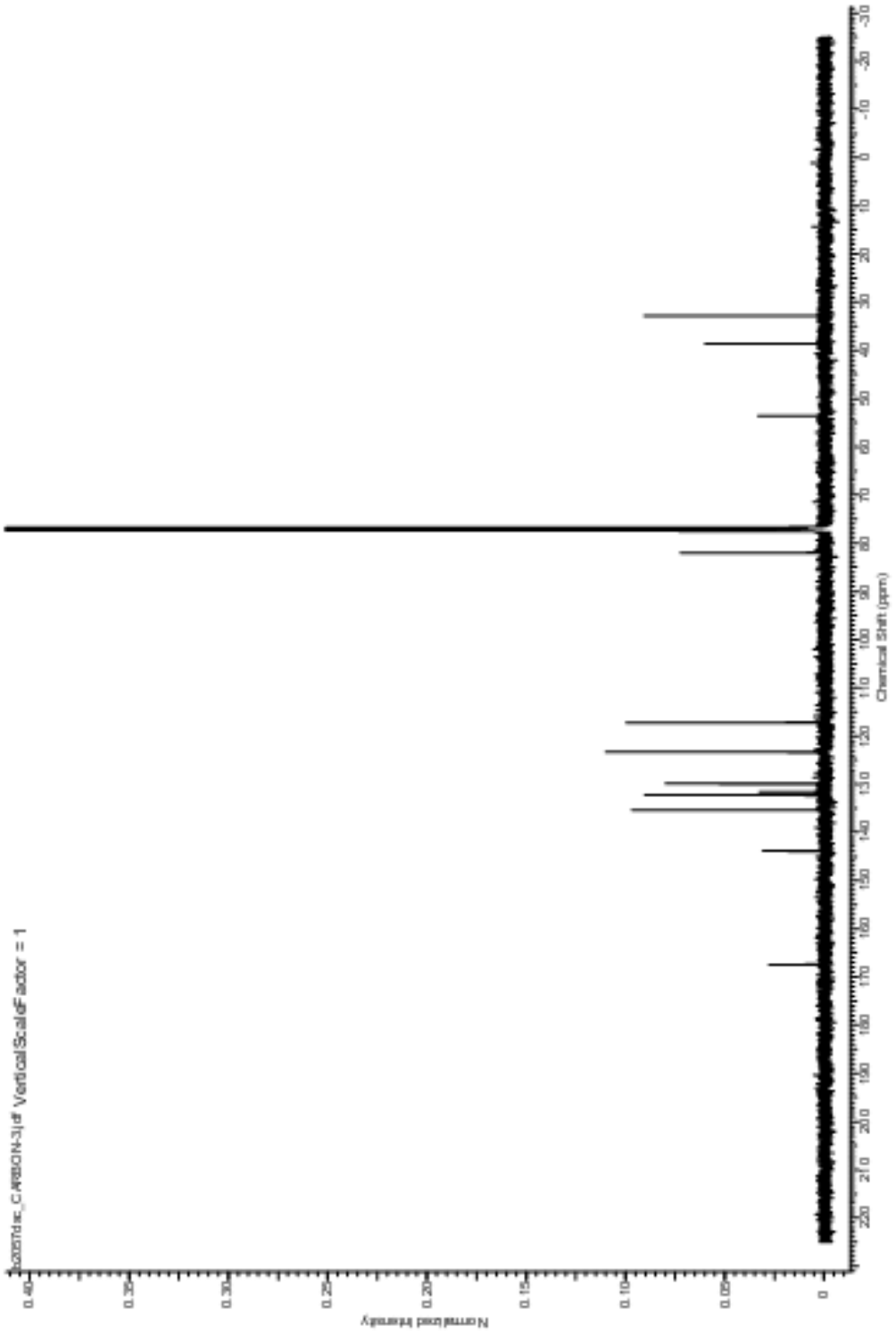


Figure 109 ^{13}C NMR spectrum of 2-(but-3-en-1-yl)-3-hydroxy-2,3-dihydro-1*H*-isoindol-1-one (**13b**)

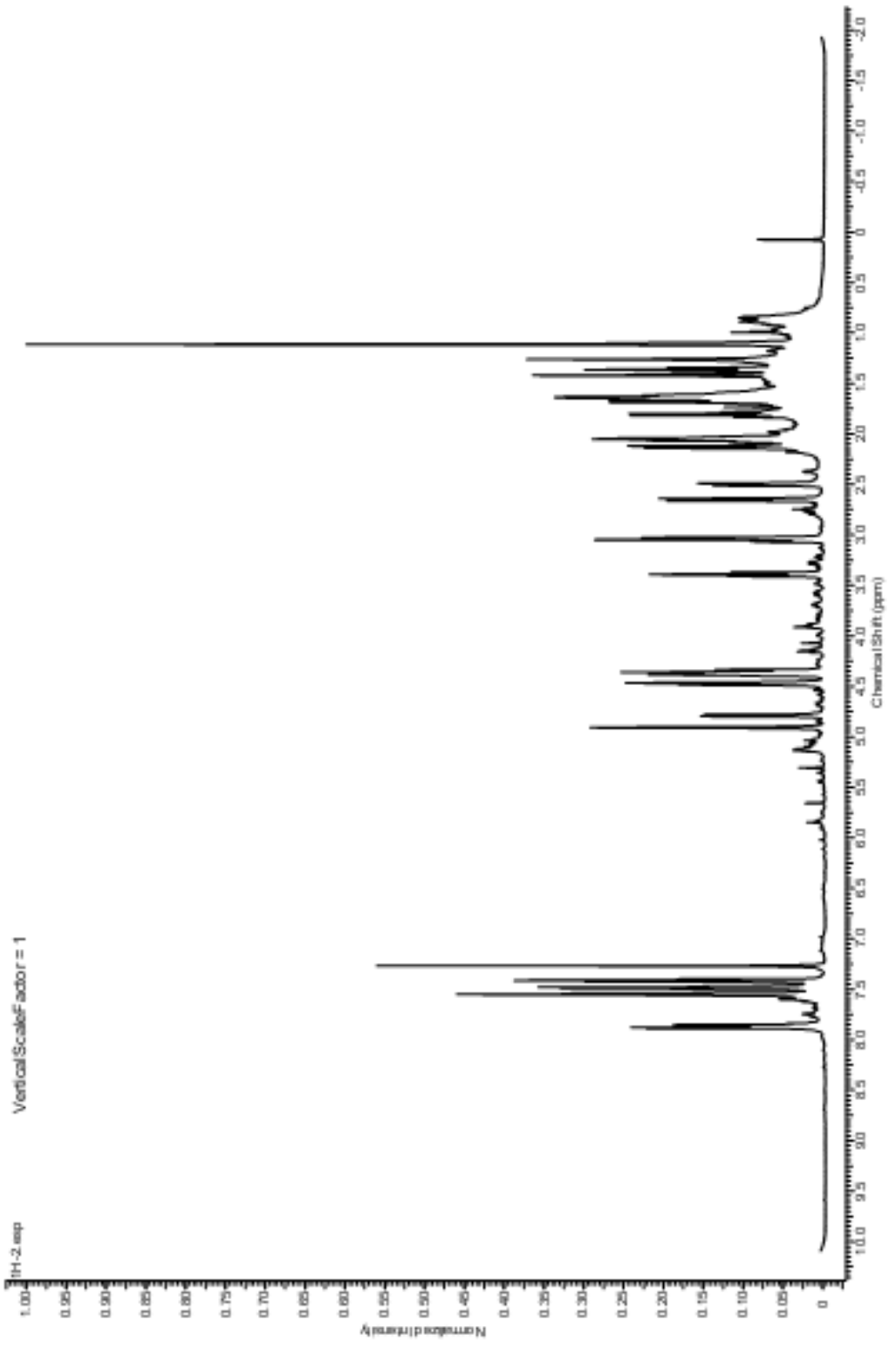


Figure 110 ^{1}H NMR spectrum of (2S & 2R,10bS)-2-iodo-1,3,4,10b-tetrahydropyrido [2,1-a] isoindol-6(2H)-one (**13a**) (700 MHz)

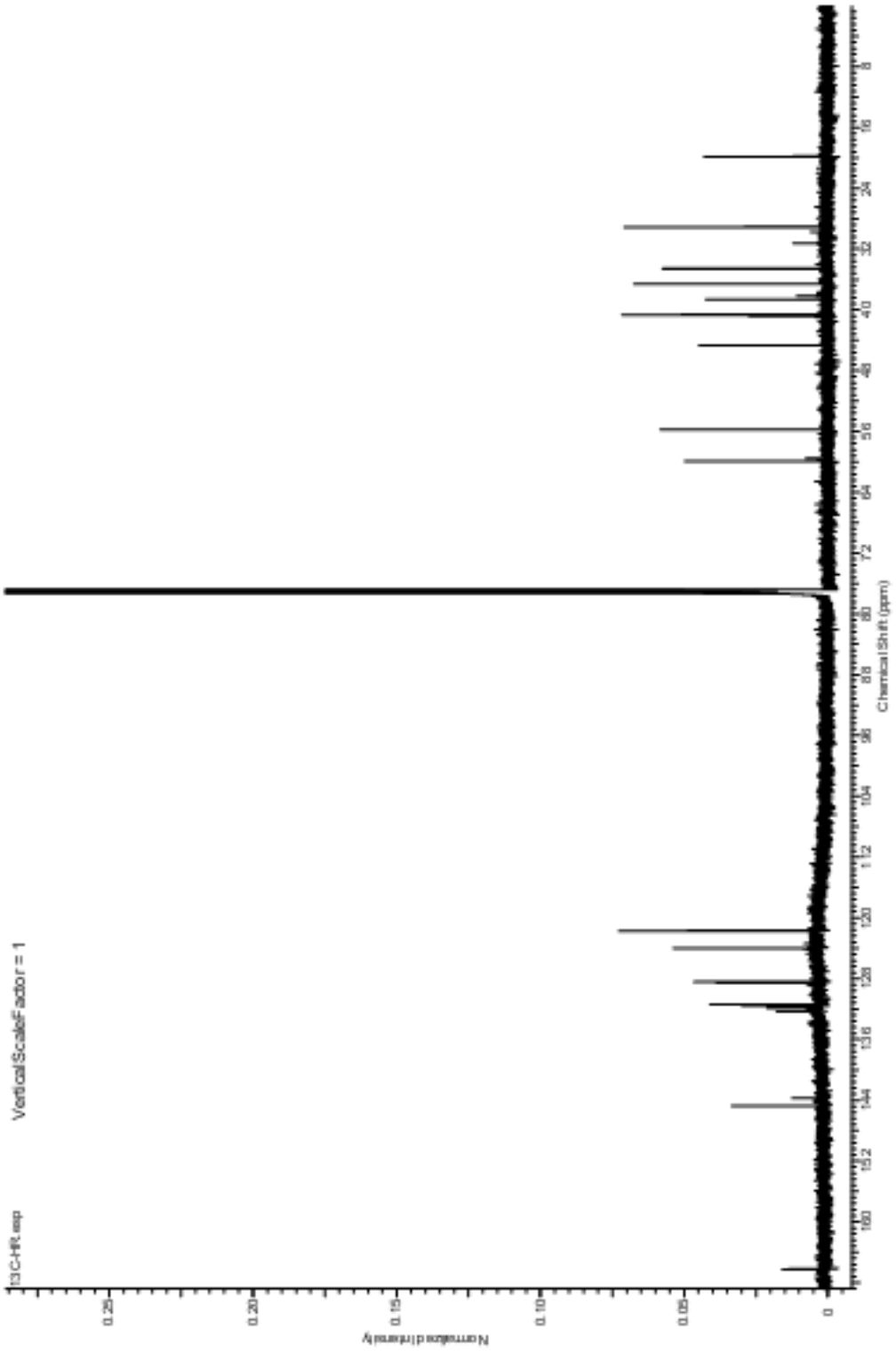


Figure 111 ^{13}C NMR spectrum of (2S & 2R,10bS)-2-iodo-1,3,4,10b-tetrahydropyrido [2,1-a] isoindol-6(2H)-one (**13a**) (700 MHz)

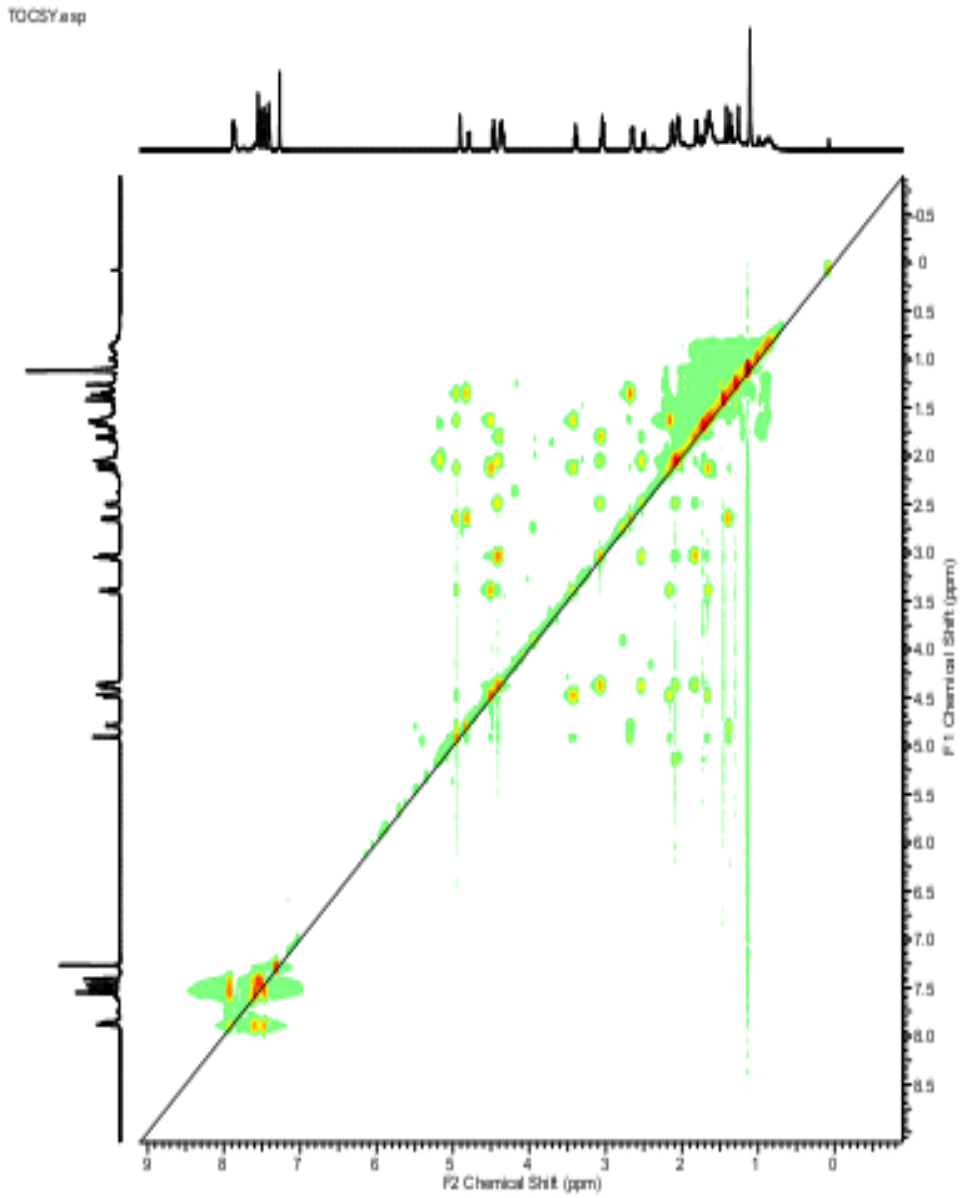


Figure 112 TOCSY NMR spectrum (2S & 2R,10bS)-2-iodo-1,3,4,10b-tetrahydropyrido [2,1-a] isoindol-6(2H)-one (**13a**) (700 MHz)

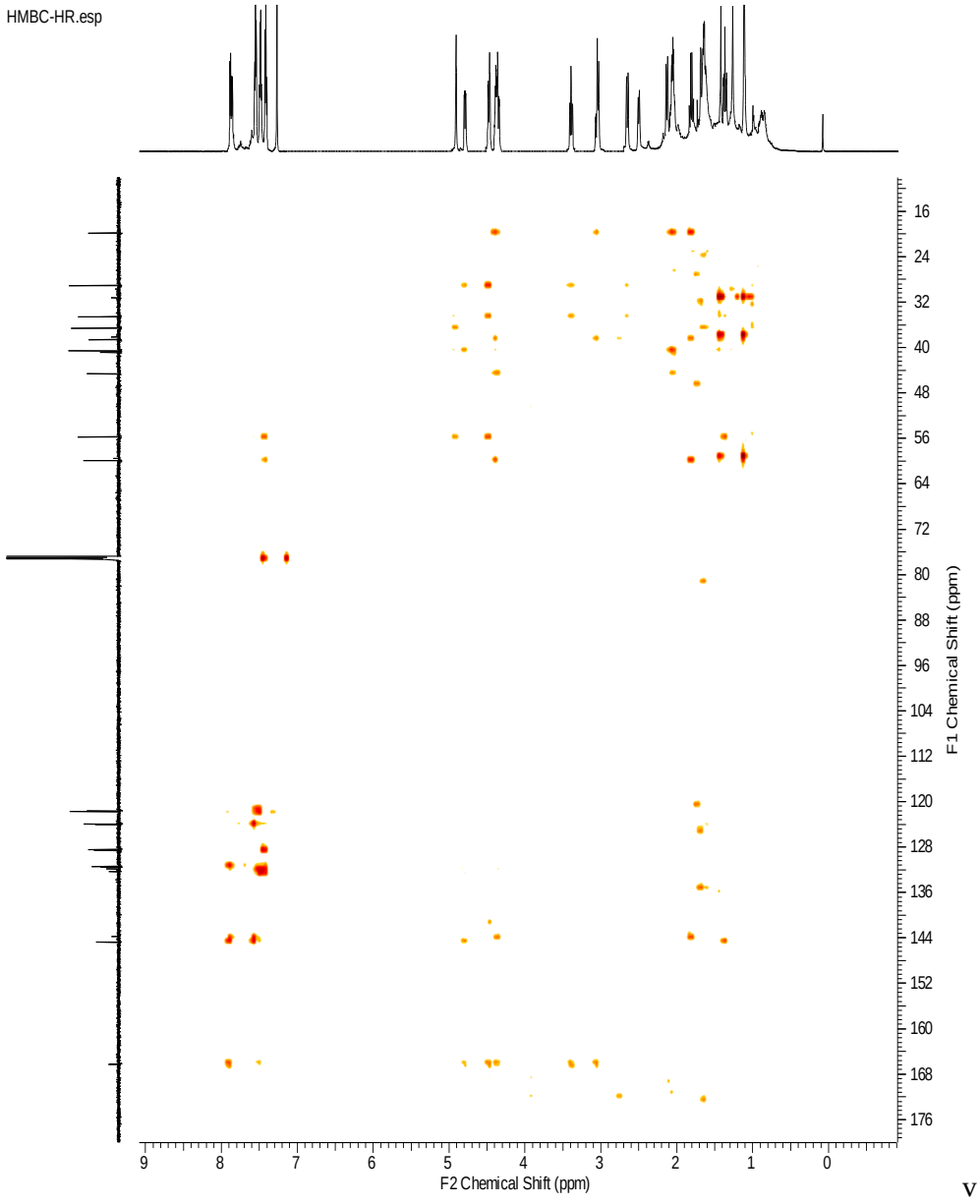
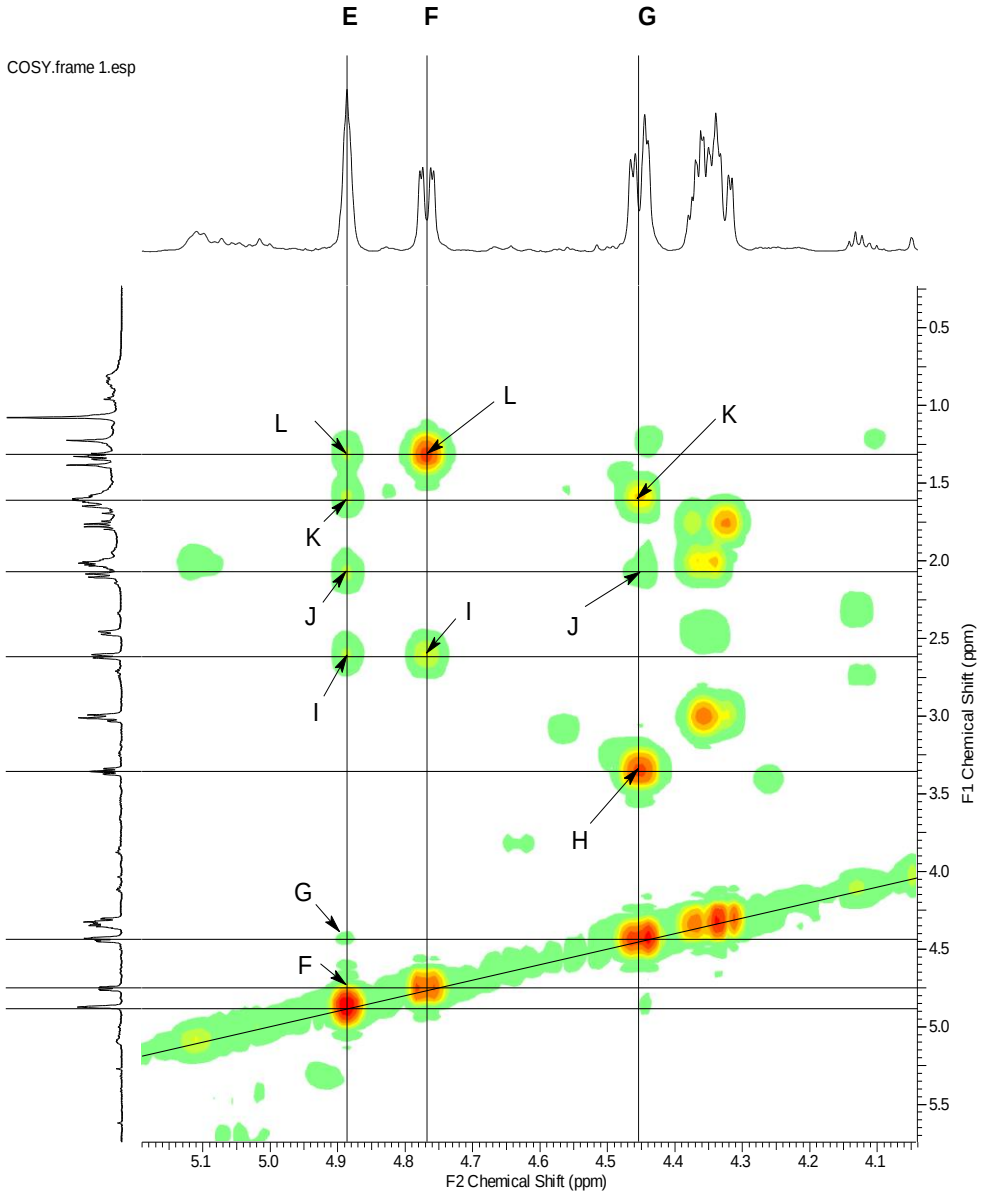
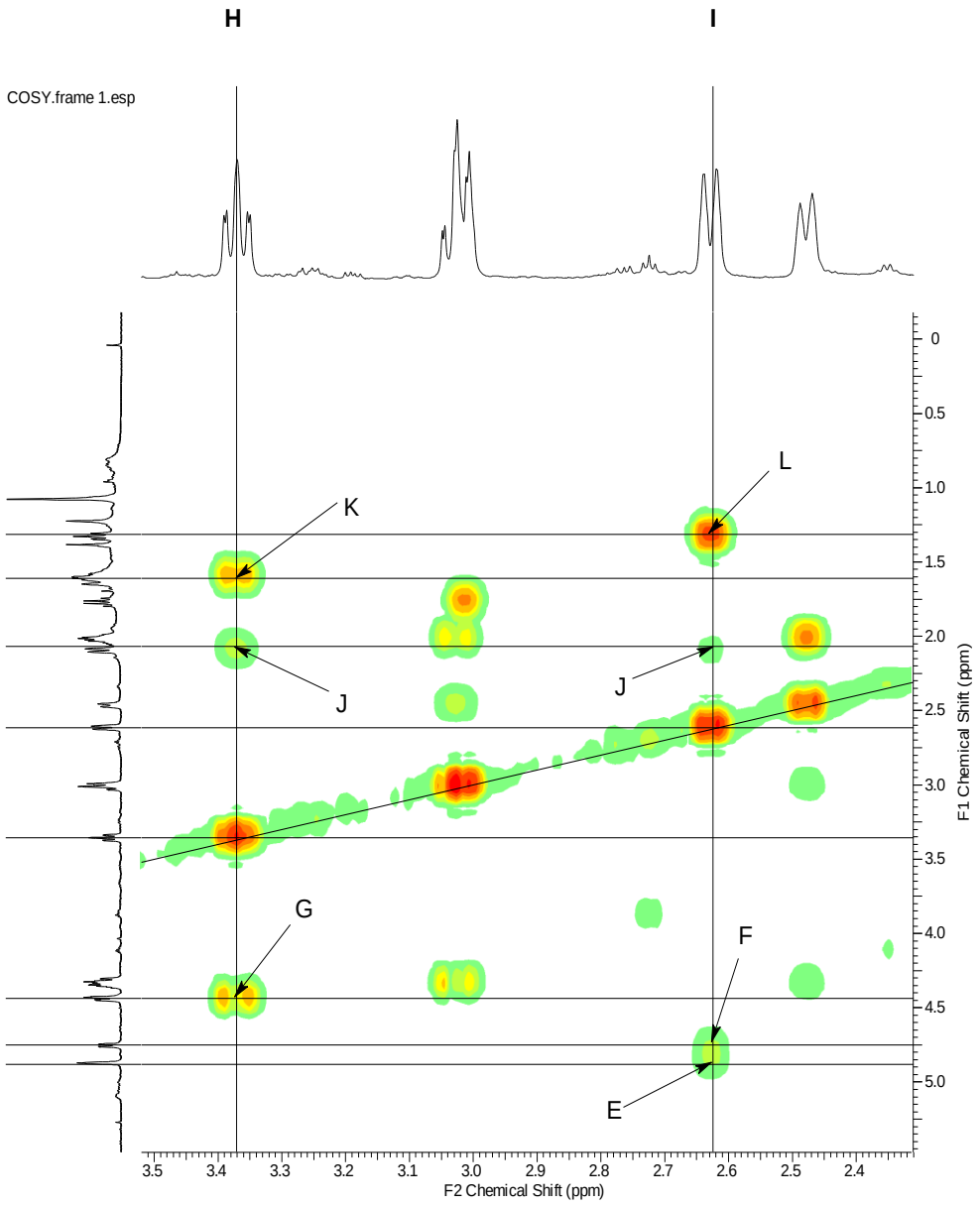


Figure 113 HMBC NMR spectrum (2S & 2R,10bS)-2-iodo-1,3,4,10b-tetrahydropyrido [2,1-a] isoindol-6(2H)-one (**13a**)



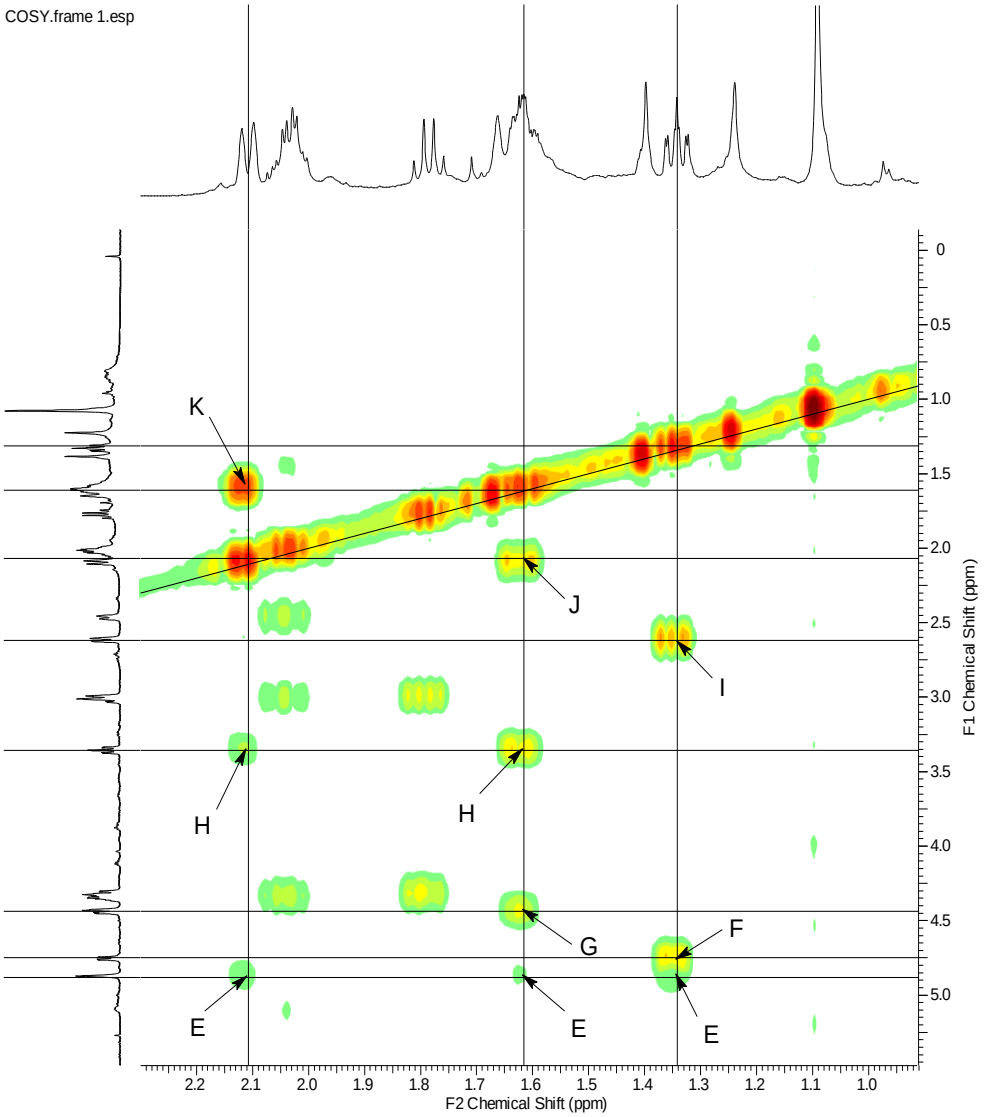
(COSY interaction protons E-G)

Figure 114 COSY NMR diastereomer 1 magnified spectrum protons E-G (**13a**) (700 MHz)



(COSY interaction protons H-I)

Figure 115 COSY NMR diastereomer 1 magnified spectrum protons H-I (**13a**) (700 MHz)



(COSY interaction protons J-L)

Figure 116 COSY NMR diastereomer 1 magnified spectrum protons J-L (**13a**) (700 MHz)

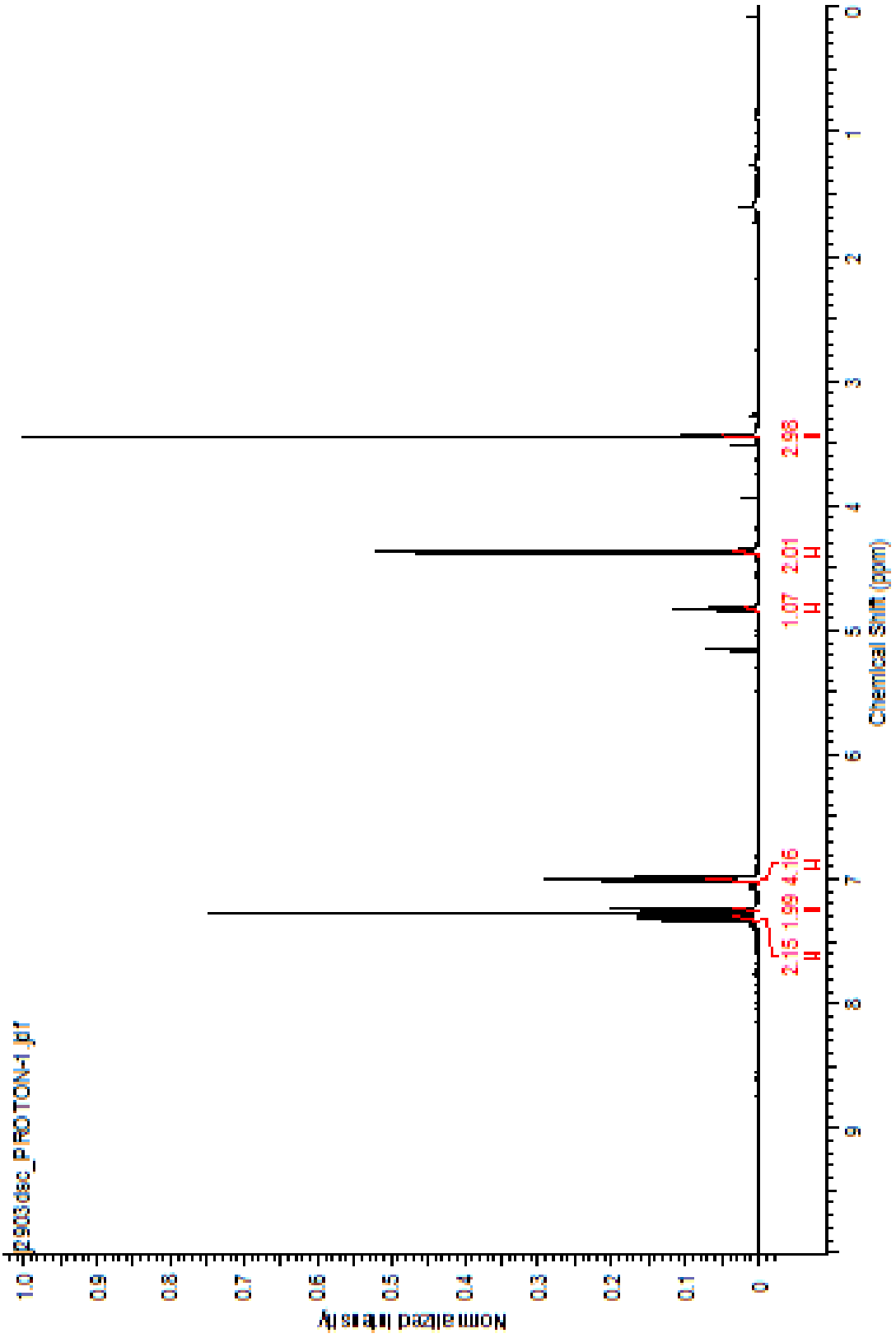


Figure 117 ^{1}H NMR spectrum of 10-Methyl-9-nitromethyl-9,10-dihydro-acridine (**8d**)

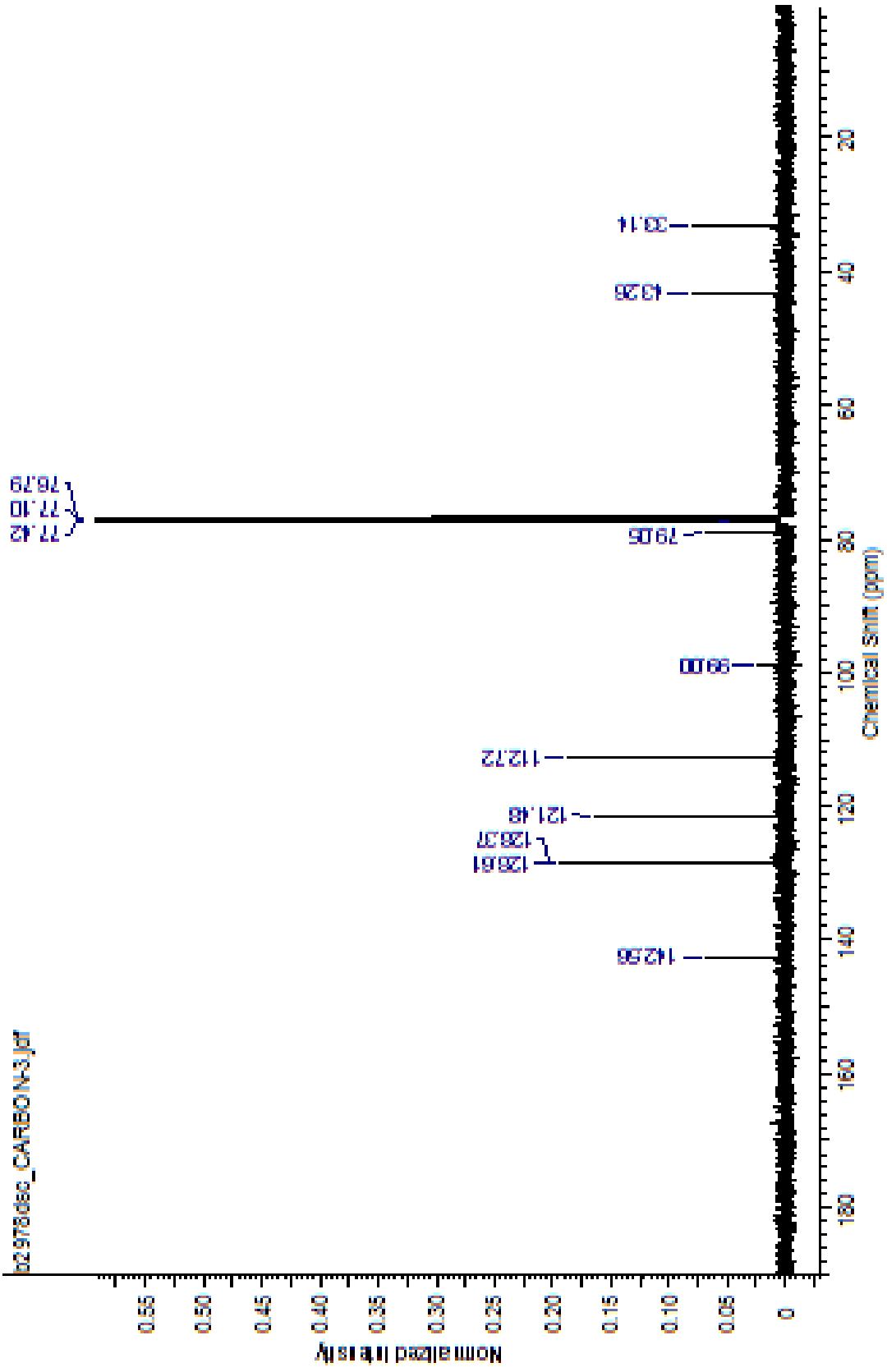


Figure 118 ^{13}C NMR spectrum of 10-Methyl-9-nitromethyl-9,10-dihydro-acridine (**8d**)

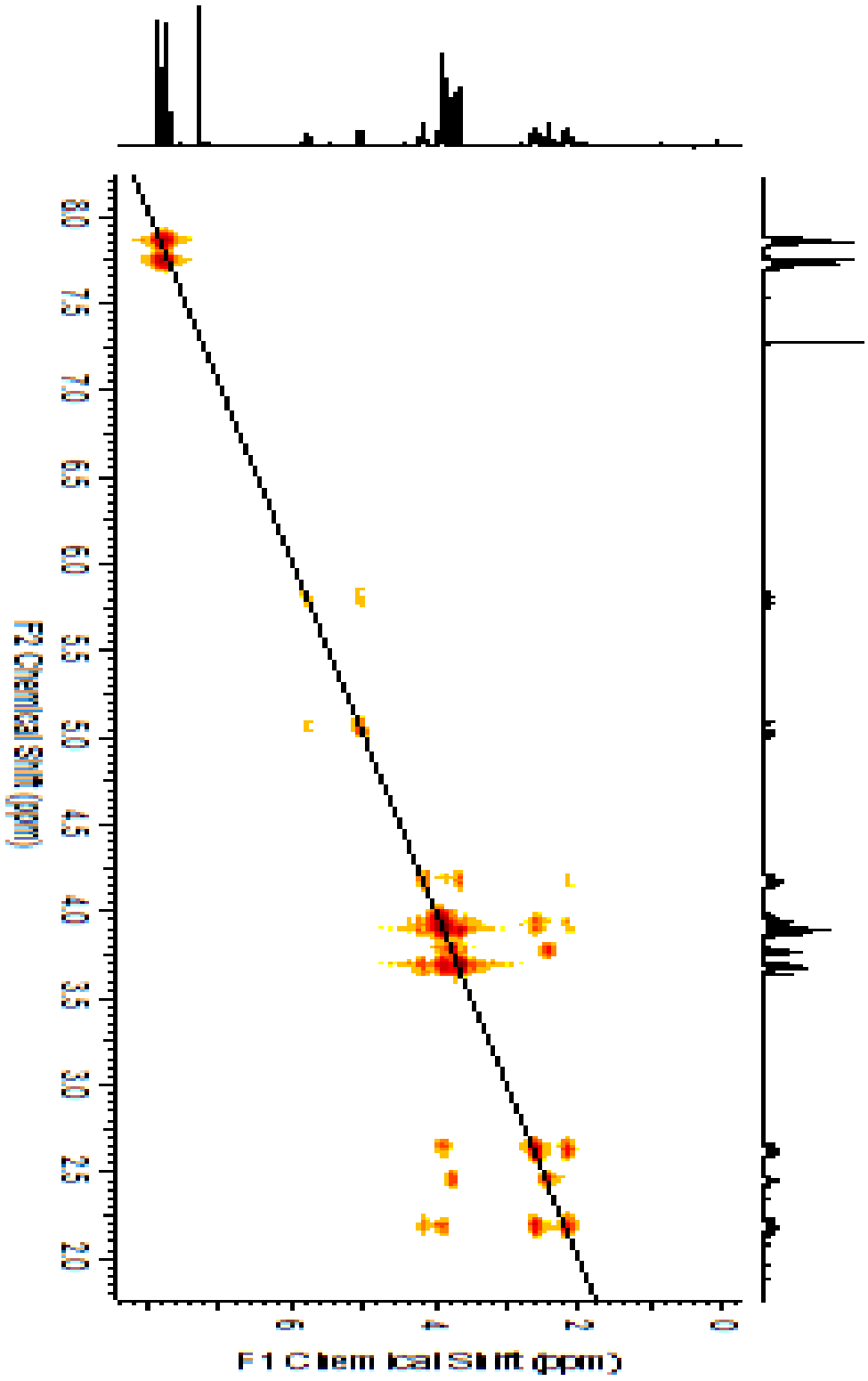


Figure 119 COSY NMR spectrum of 2-(3,4-dibromobutyl)-1*H*-isoindole-1,3(2*H*)-dione (**11c**)

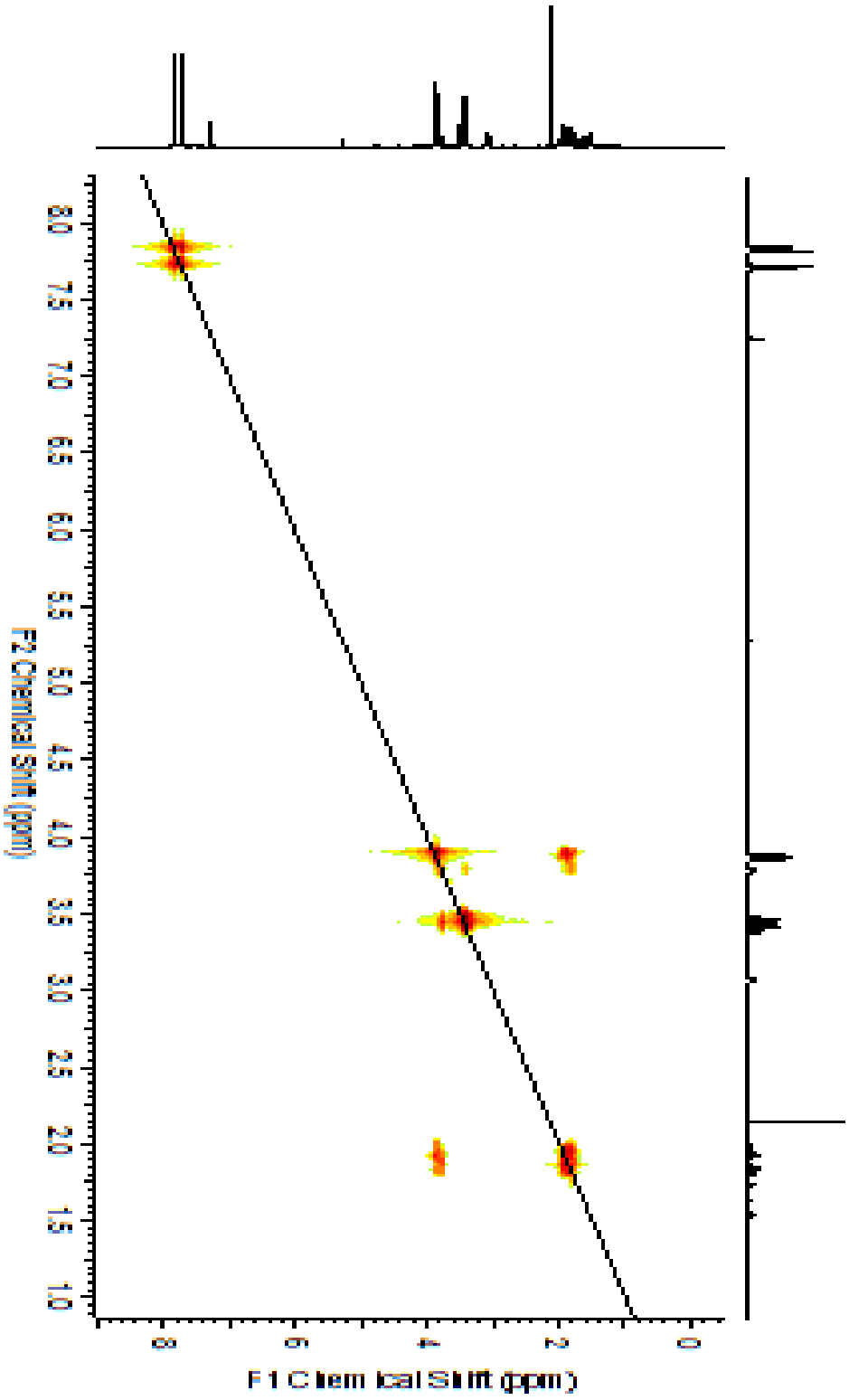


Figure 120 COSY NMR spectrum of 2-(4-bromo-3-hydroxybutyl)-1*H*-isoindole-1, 3(2*H*)-dione (**11d**)

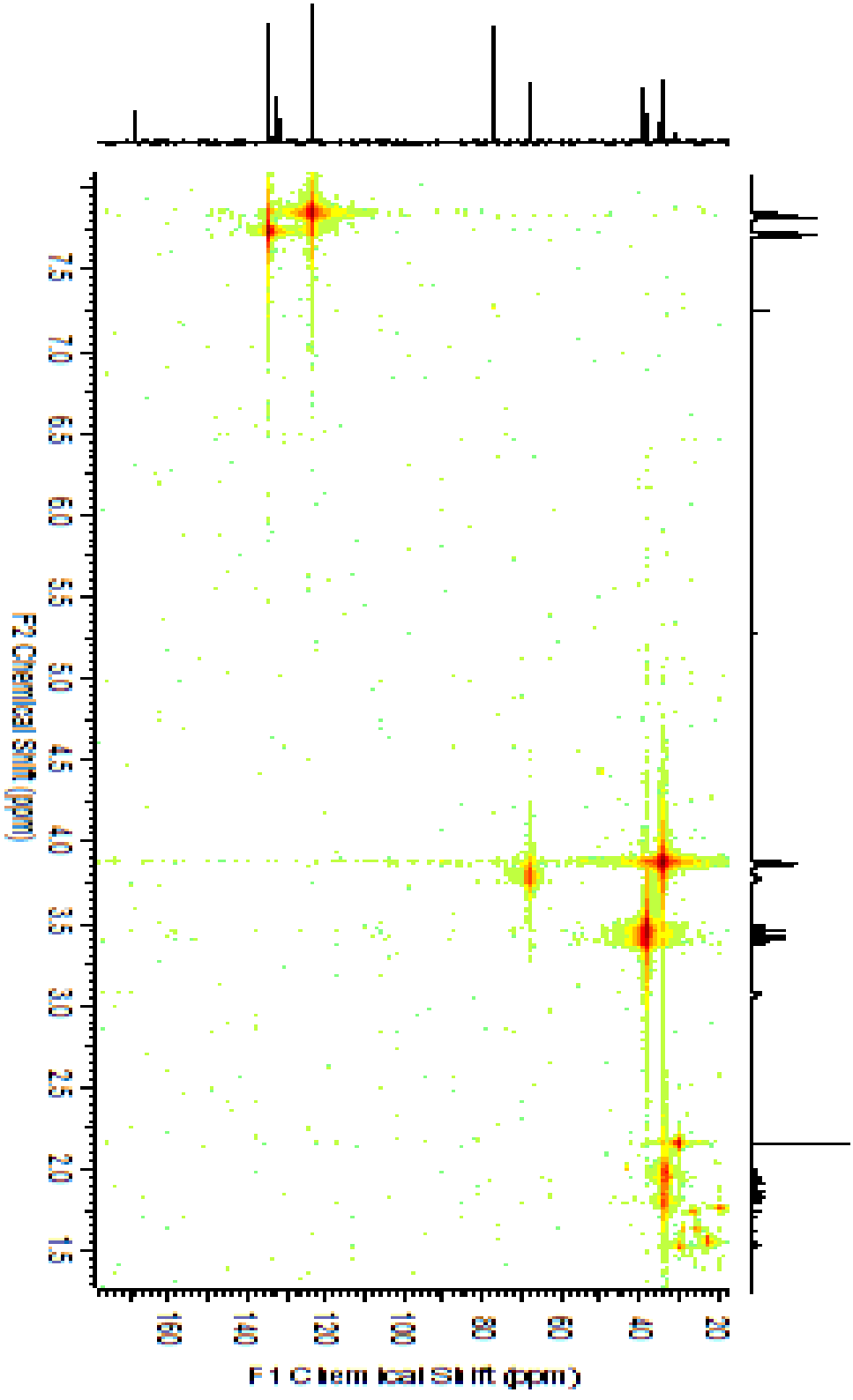


Figure 121 HSQC NMR spectrum of 2-(4-bromo-3-hydroxybutyl)-1*H*-isoindole-1,3(2*H*)-dione (**11d**)

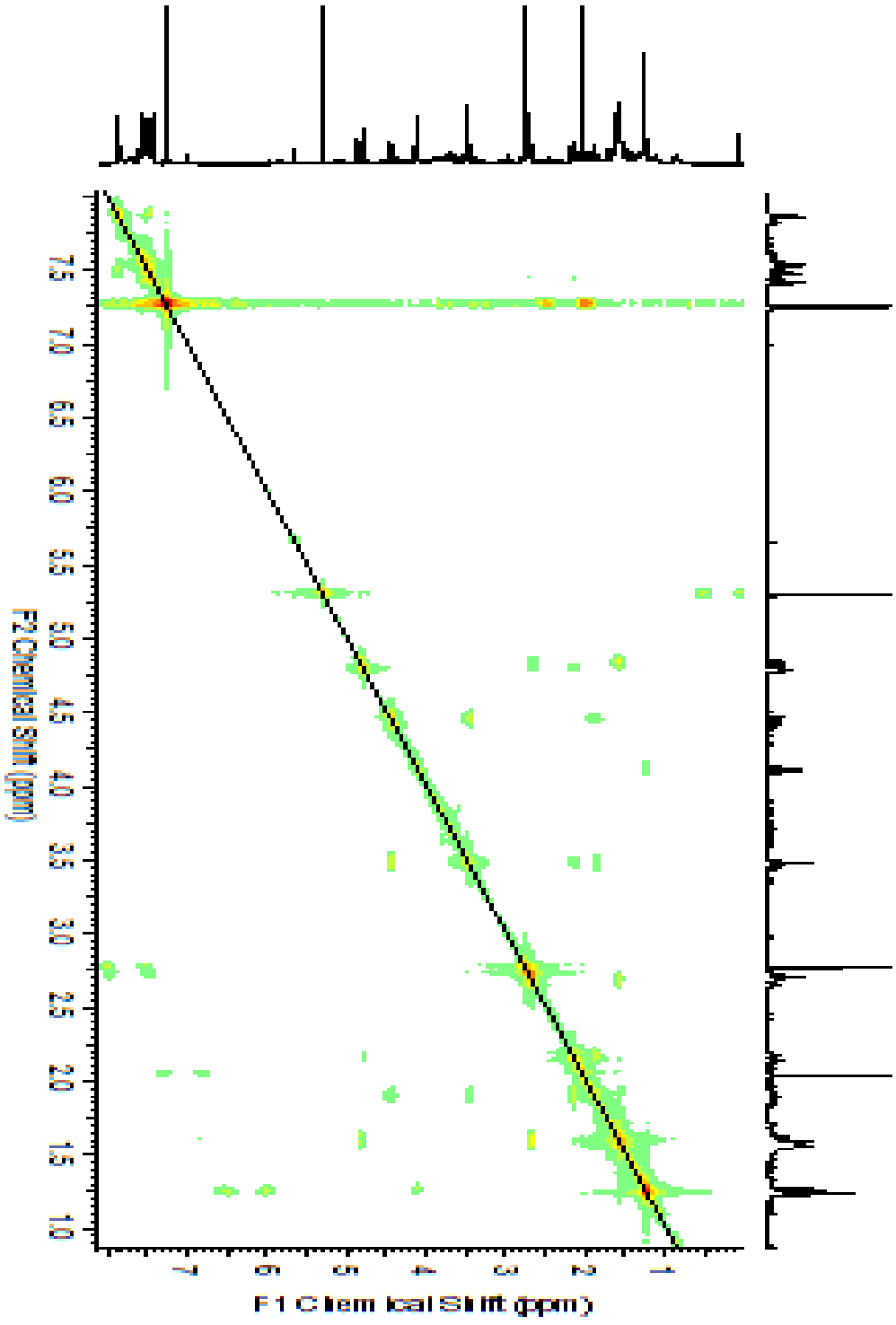


Figure 122 COSY NMR spectrum of (2R, 10bS)-2-bromo-1,3,4,10b-tetrahydropyrido [2,1-a] isoindol-6(2H)-one (**11a**)

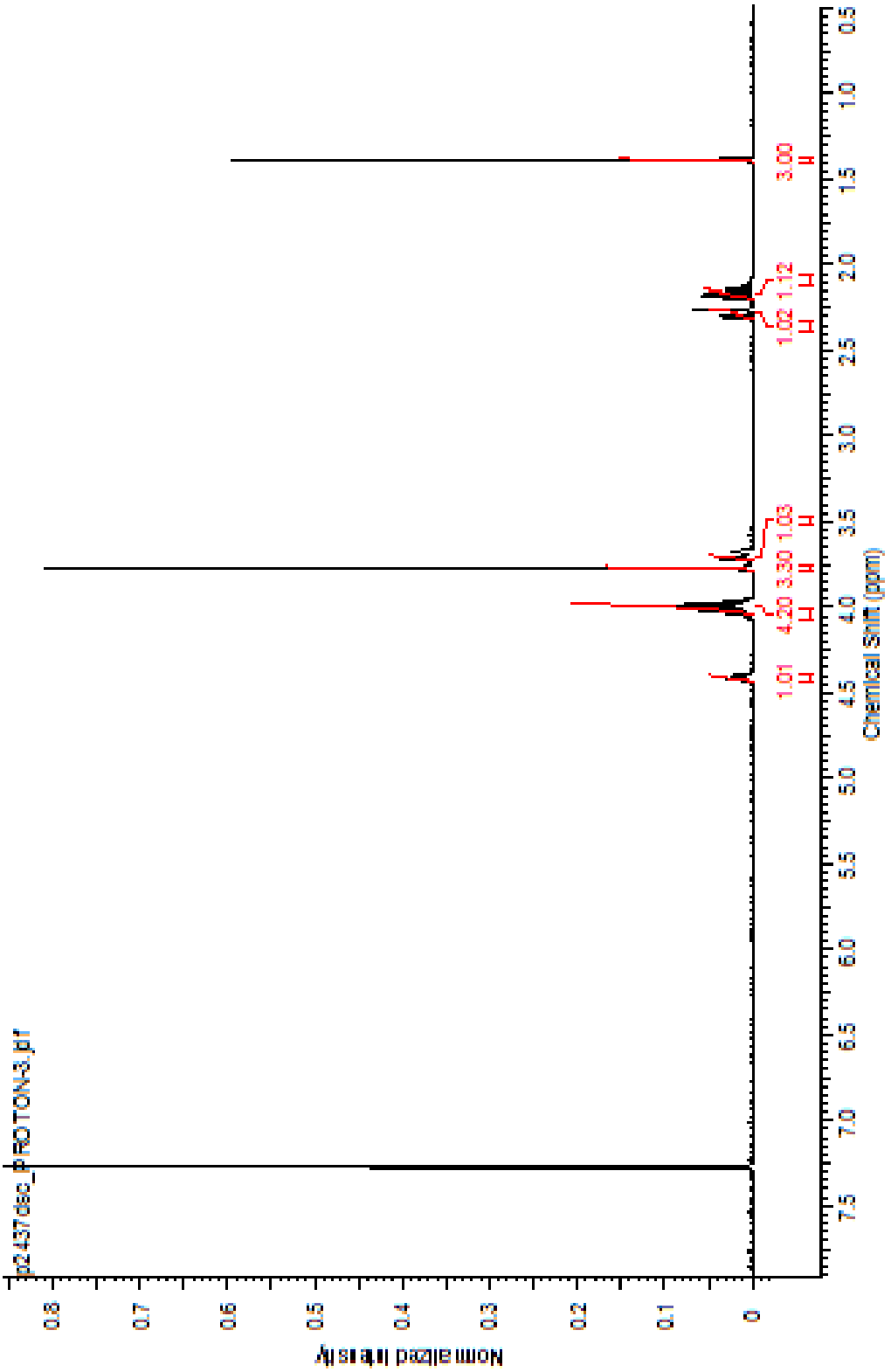


Figure 123 ^{1}H NMR spectrum of Methyl-2-hydroxy-3-(2-methyl-1,3-dioxolan-2-yl) propanoate (**1c**)

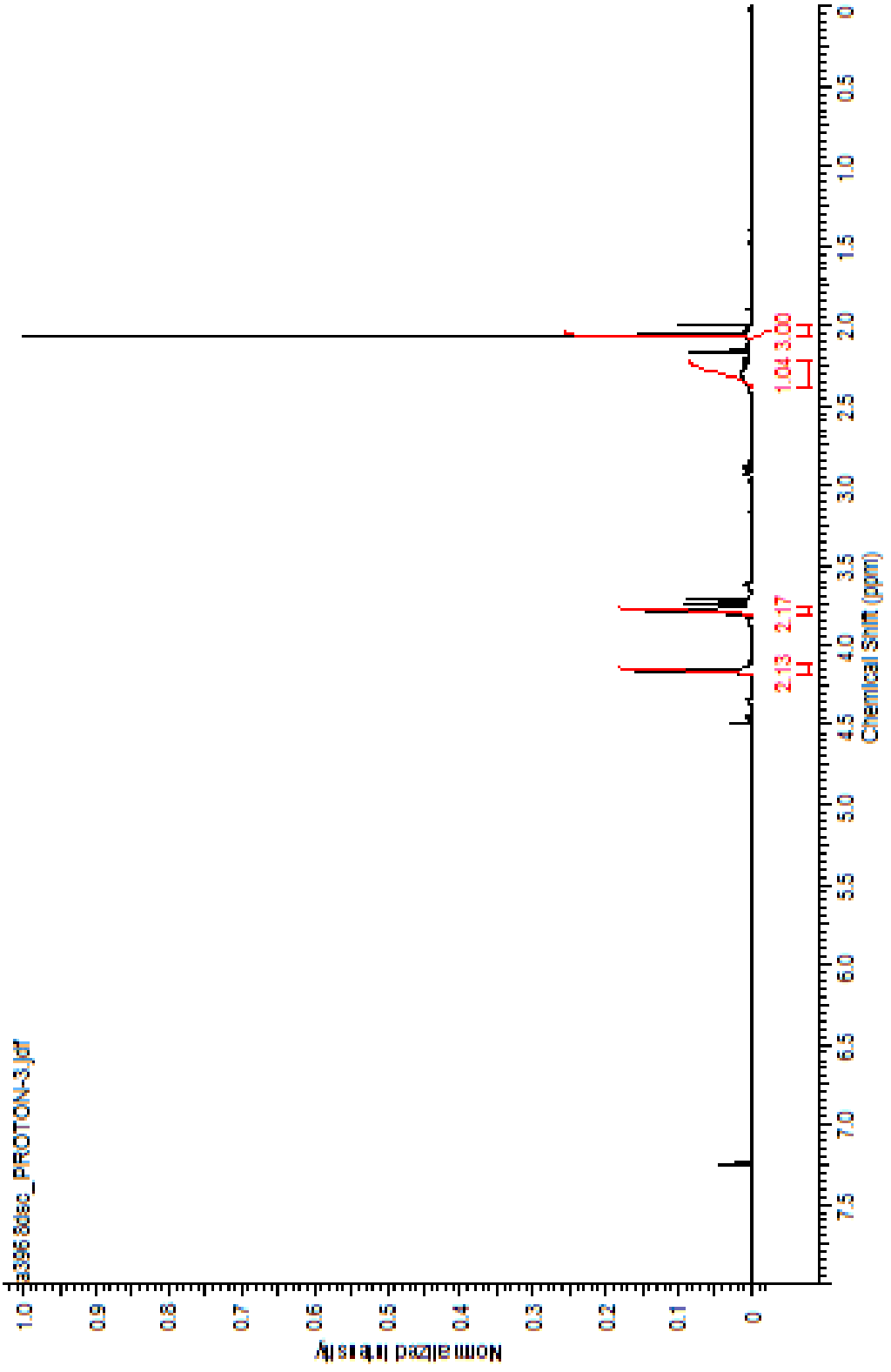


Figure 124 ^{1}H NMR spectrum of Ethylene glycol monoacetate (**1f**)

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